MASARYK UNIVERSITY

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DEGENERATIVE CERVICAL MYELOPATHY: CONTEMPORARY DIAGNOSTIC AND THERAPEUTIC ASPECTS

Habilitation thesis in Neurology

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I hereby declare that I wrote this habilitation thesis on my own, using the relevant resources listed in the references.

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Author’s signature

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Abstract:

Degenerative cervical myelopathy (DCM) is the most common cause of spinal cord dysfunction in adults. It results from narrowing of the spinal canal due to osteoarthritic changes. This narrowing leads to chronic spinal cord compression and neurological disability. Symptoms may range from mild dysfunction, including numbness or decreased dexterity in the upper extremities, to severe dysfunction including quadriparesis and urinary incontinence. This variable pattern of presenting symptoms may lead to a delay in diagnosis. Patients are typically male (3:1 male-to-female ratio), and the average age of presentation is 64 years. The spinal cord, however, is quite resistant to the mechanical compression that may cause DCM. Subjects with cervical cord compression thus may remain completely asymptomatic or develop axial pain or signs of root compression, but without clear signs of symptomatic myelopathy - "non-myelopathic degenerative cervical cord compression" (NMDCCC) – a condition characterised by a mismatch between clinical and imaging data. The current prevalence of cervical stenosis (CS) and NMDCCC is not known and data in the literature differ widely. Definitive diagnosis of DCM requires correlation of physical examination findings with imaging and neurophysiological findings (electromyography, evoked potentials). Magnetic resonance imaging of the cervical spine with and without contrast media is the preferred imaging modality. Cervical spine computed tomography, computed tomography myelography, and plain radiography are helpful in certain situations. Treatment depends on the presence and severity of symptoms. Surgery is recommended for patients with moderate to severe symptoms or rapidly progressive disease. Conservative treatments with monitoring for progression may be considered in patients with mild to moderate disease. This habilitation thesis is conceived as a collection of scholarly works previously published by the author and his colleagues. We present here sixteen manuscripts which could, in our opinion, could be useful in the diagnosis and management of patients with DCM. In the first one we have proved that a standardized 10-meter walk/run test has the capacity to disclose locomotion abnormalities in NMDCCC subjects who lack other clear myelopathic signs, and may provide a means of classifying DCM patients according to their degree of disability. This may be confirmed as another risk factor for progression into symptomatic DCM in future longitudinal studies. The second study targeted predictors of neurological dysfunction in the non-myelopathic patient with degenerative cervical spinal cord compression. We have found that cross section area (CSA) $\leq$ 70.1 mm2, and compression ratio (CR) $\leq$ 0.4 were the only independent significant

predictors for progression into symptomatic myelopathy. It could help the decision-making process for preventive surgical decompression and, more importantly, in defining a subgroup of NMDCCC individuals at higher risk of DCM, among whom a randomized trial evaluating the benefit of such decompression would be justifiable. The third study explored the presence and character of vertigo in patients with DCM, because so called "cervical vertigo" (CV) represents a very controversial entity. We have found that despite a high prevalence of vertigo in patients with DCM, the aetiology could be (in all of them) attributed to causes outside cervical spine and related nerve structures. Clinicians should seek other aetiologies of vertigo in DCM patients, thus avoiding the possibility of overlooking other serious disease.

Four papers present original scientific reports using new MRI techniques ((MR spectroscopy, diffusion tensor imaging and high-resolution 3 T diffusion MRI, Semi-automated detection of cervical spinal cord compression with the Spinal Cord Toolbox). These techniques demonstrated sufficient sensitivity to reveal early changes in cerebral spinal cord, and for the first time, even in NMDCCC participants. This might allow the stratification of non-myelopathic subjects in the future. Introduction of these techniques into radiological evaluations may bring more reliable results to longitudinal and multicentre studies. The approach also saves a great deal of time, perhaps enabling its routine use in the assessment of the natural course of NMDCCC and mild DCM; the rate of progression may well become a valid predictor of whether the patient would benefit from surgery or not The habilitation thesis contains six reviews as well ("Asymptomatic Spondylotic Cervical Cord Compression", "Cervical vertigo – fiction or reality?", "Management of patients with degenerative spondylotic cervical spine compression", "Cervical plexus lesions in clinical praxis", "DCM- clinical manifestation, diagnosis and practical management" and "Asymptomatic Spondylotic Cervical Cord Compression"). One cross-sectional population-based observational study was done to estimate the prevalence of NMDCCC and DCM in a population older than 40 years and to evaluate the MRI characteristics of these conditions. The aim of another study was to retrospectively analyse the risk of symptomatic myelopathy after minor trauma in patients with NMDCCC. Two papers concerning differential diagnosis of degenerative cervical spinal cord compression were added too ("Flexion Cervical Myelopathy (Hirayama Disease) – Reality or Myth?" and "Malignant Peripheral Nerve Sheath Tumour of Cervical Plexus – a Case Report").

We hope that this habilitation thesis helps streamline DCM diagnosis and management, allowing for improved chances of early diagnosis and prevention of further neurological decline among patients.

Key words: degenerative cervical myelopathy; spinal cord stenosis; non-myelopathic degenerative cervical cord compression; magnetic resonance imaging; cervical stenosis; electromyography; evoked potentials; anterior cervical discectomy; laminectomy; laminoplasty.

CONTENT:

1. Introduction

Degenerative cervical myelopathy (DCM) is a neurological condition resulting from spinal cord compression arising out of degenerative narrowing of the cervical spinal canal. It constitutes the leading cause of spinal cord dysfunction in adults worldwide (Rhee et al. 2017; Badhiwala et al. 2020). Early diagnosis and management of DCM are vital to the provision of appropriate care for those living with this condition. Expeditious diagnosis and treatment of DCM are needed to avoid permanent disability. Accurate diagnosis requires agreement between clinical and imaging findings. When DCM is suspected, a detailed history and physical examination should be undertaken first (Badhiwala et al. 2020). Common presenting symptoms include: numb and/or clumsy hand(s), bilateral arm pain and/or paresthesias, gait disturbance, Lhermitte's sign, and urinary urgency, frequency and/or incontinence. Objective physical signs of myelopathy include upper motor neuron signs in the upper and/or lower limbs, flaccid paresis of one or both upper extremities, atrophy of intrinsic hand muscles, sensory involvement in various distributions in upper or lower extremities, and gait ataxia (Harrop et al. 2010; Tracy and Bartleson 2010a; Kalsi-Ryan et al. 2013; Tetreault et al. 2015; Davies et al. 2018). Some of the objective signs of myelopathy required for the diagnosis of DCM, detected in the course of a detailed, although largely qualitative clinical neurological examination, may serve as comparatively late indicators of cervical cord impairment. Further, degenerative compression of the cervical cord may remain free of any of the symptoms or signs of DCM. This condition – known as "presymptomatic" or "non-myelopathic" degenerative cervical cord compression (NMDCCC) is highly prevalent in those above 60 years of age, involving, on average, about 40% of this European/American subpopulation (Kovalova et al. 2016a; Smith et al. 2020). This lies in striking contrast to the prevalence of DCM, estimated at the far lower figure of 2.3% (Smith et al. 2020). Quantitative electrophysiological and MRI methods, however, serve to document functional or microstructural impairment in NMDCCC and DCM patients, indicating that myelopathy precedes the occurrence of commonly detected clinical signs and symptoms. Over the past 10 years, advances in basic science and in translational and clinical research have improved our understanding of the pathophysiology of DCM and helped delineate evidence-based practices for diagnosis and treatment. This habilitation thesis comprises the contemporary state of arts in the diagnosis (with special emphasis on electrophysiology and new MRI techniques), clinical manifestation and management of DCM patients.

2. Epidemiology of degenerative cervical myelopathy

Nontraumatic, degenerative forms of cervical myelopathy represent the commonest cause of spinal cord impairment in the elderly population (Kalsi-Ryan et al. 2013). The epidemiology of DCM is poorly understood, in part because of the difficulties in diagnosis (Nouri et al. 2015). The prevalence of surgically treated DCM is estimated as 1.6 per 100 000 inhabitants (Boogaarts and Bartels 2015). The actual prevalence is likely to be much higher. In North America, the incidence and prevalence was estimated at a minimum of 4.1 and 60.5 per 100,000, respectively (Nouri et al. 2015). In Taiwan, a population-based study reported a hospitalization of 4.04/100,000 person-years (Wu et al. 2013), and in the Netherlands, an incidence based on a fixed referral system of 1.6/100,000 inhabitants was reported (Boogaarts and Bartels 2015). The incidence of DCM is expected to rise with an ageing population. Most patients are first diagnosed in their 50s; DCM is uncommon before the age of 40. Studies in healthy volunteers have shown that incidental cervical cord compression is commonly detected on MRI, and becomes more common with age (Nagata et al. 2012). In a series of randomly selected volunteers aged 40-80, incidental cervical cord compression was detected on MRI in 59% of individuals (108/183, ranging from 31.6% in the fifth decade to 66.8% in the eighth decade). Only two individuals reported related symptoms (Kovalova et al. 2016a). A proportion of individuals with asymptomatic cord compression will go on to develop DCM. The exact figure is unknown. The only prospective study to consider this (n=199) found that 8% of individuals with asymptomatic cord compression will develop DCM after one year and 22% in total over the observation period (median follow-up 44 months, range 2-12 years) (Bednarik et al. 2008a). Many patients with DCM remain undiagnosed. Based on a global cohort of patients derived from the multicentre AO Spine studies on DCM, most patients present with multi-level degeneration (spondylosis) and more than 50% have accompanying ligamentum hypertrophy or in-folding that is contributing to this compression. Ossification of the posterior longitudinal ligament (OPLL) was shown to be present in about 10% of patients, with a significantly higher prevalence in Asia (Nouri et al. 2015). Because of the ageing population, physicians can expect to encounter an increasing number of patients with DCM. This increase is likely to have an important societal impact: people aged 50–65 years are typically still actively working, but degenerative cervical myelopathy can cause patients to lose dexterity, ambulation and urinary sphincter control, resulting in an inability to work, social isolation, and eventual loss of independence (Bartels 2021).

3. Pathophysiology of degenerative cervical myelopathy

3.1. Static and dynamic factors of DCM

The pathophysiology of DCM includes structural and functional abnormalities in the spinal cord that are caused by static factors, such as congenital spinal canal stenosis and cervical spondylosis, and dynamic factors, such as microscopic repetitive spinal cord damage caused by cervical instability. Cervical spondylosis is the most common static pathology that results in spinal cord compression. It is observed in 55% of patients who have cervical myelopathy (Bernhardt et al. 1993). A decrease in disk height induces narrowing of the spinal canal by varying degrees of the herniated intervertebral disk. Additionally, microinstability induces osteophyte formation at the vertebral end plates in the involved segments. Furthermore, hypertrophy in the facet joints accompanying intervertebral disk herniation leads to progressive spinal stenosis, which eventually results in DCM **(Parke** 1988). Other static factors, such as facet cyst, OPLL, and ossification or calcification of the ligamentum flavum, may further diminish the cross-sectional area of the spinal canal, which may aggravate cervical myelopathy.

Dynamic factors of the cervical spine, such as buckling of the ligamentum flavum, may also result in myelopathy. DCM can occur when the dynamic sagittal diameter is <11 mm during extreme flexion or extension (Rao 2002). Cervical spine instability is defined as a translation of >3.5 mm and an angulation of >11° in flexion–extension views of a dynamic radiograph. It affects the narrowing of the spinal canal (White and Panjabi 1987). In addition to mechanical or dynamic compression, increased strain or shear forces induce extensive or localized axonal damage to the spinal cord (Henderson et al. 2005). During physiological flexion of the cervical spine, axial strain and stretching of the spinal cord can increase due to the elongation of the spinal canal (Henderson et al. 2005). Progressive cervical kyphosis can exacerbate cervical myelopathy due to increased intramedullary pressure by compressing the anterior spinal cord and increasing the tension in the spinal cord (Scheer et al. 2013). Shi and Pryor reported that spinal cord elongation increased the temporary membrane permeability, causing a transient electrolyte imbalance and conduction loss in myelinated axons (Shi and Pryor 2002). Moreover, irreversible conduction loss resulted in more severe anatomical membrane damage as the spinal cord was stretched through an in vitro stretch model (Shi and Pryor 2002). Mechanical compression of the cervical spinal cord (CSC) results in cystic cavitation, gliosis, central

grey and medical white matter degeneration, Wallerian degeneration of posterior columns and posterolateral tracts and anterior horn cells (Fehlings and Skaf 1998). Based on work done in acute spinal cord injury (SCI) models, it has been postulated that a similar series of cellular and molecular secondary injury events, including glutamanergic excitotoxicity, free radical generation, lipid peroxidation, inflammation and ischaemia play a key role in the pathobiology of DCM (Kalsi-Ryan et al. 2013). Although it has been thought that histopathological and pathophysiological similarities between DCM and SCI are sufficient to extrapolate from the latter to the former, DCM is unique and its pathomechanisms remain unexplored. Current knowledge related to the pathomechanisms is derived mainly from animal models (Karadimas et al. 2015).

3.2. Chronic interruption of the vascular supply

There is considerable evidence to indicate that chronic interruption of the vascular supply to the spinal cord may be a significant component in the pathophysiology of DCM; post-mortem studies in DCM patients demonstrating abnormal histological findings, such as spinal cord necrosis and grey matter cavitation, have indicated spinal cord ischaemia as a potential mechanism of DCM (Baron and Young 2007). This is supported by the fact that the region of the spinal cord most affected by DCM (C5-7) is also the area of the most vulnerable blood supply (Baron and Young 2007). Several studies have reported evidence of ischaemia in animal models of DCM based on microangiography, autoradiography and hydrogen clearance (Fehlings and Skaf 1998).

A key consequence of DCM is the progressive compression that causes flattening and widening of the spinal cord. This distortion may stretch the intrinsic transverse vessels or terminal branches of the anterior spinal artery (ASA) resulting in endothelial cell loss and dysfunction (Bohlman and Emery 1988). Hypoxia-ischemia-induced endothelial cell death may exacerbate primary tissue damage and contribute to breakdown of the blood-spinal cord barrier (BSCB) leading to increased vascular permeability and vasogenic spinal cord oedema. Following acute neurotrauma, the BSCB remains compromised after the initial damage because of the effects of inflammatory mediators on endothelial cells and loss of endothelial cells; however, this barrier is eventually reformed (Karadimas et al. 2015). Karamidas, in a study using a rat model of DCM, showed that chronic progressive CSC compression causes significant endothelial cell loss (Karadimas et al. 2015).

3.3. Glutamate excitotoxicity

Glutamate is the major excitatory neurotransmitter in the central nervous system (CNS). Research suggest that glutamate excitotoxicity is involved in neuronal and oligodendrocytic death in neurologic diseases including stroke, traumatic SCI and prolonged seizure activity (Fehlings and Skaf 1998). It has also been hypothesized that slow glutamate excitotoxicity plays an important role in initiating neuronal degeneration and promoting the development of neurological deficits under the chronic progressive compression of the CSC (Fehlings and Skaf 1998). In an animal model of DCM, riluzole was administered daily for 5 weeks after the onset of symptoms (Karadimas et al. 2015). The result of the study showed that its administration led to a significant functional improvement, axonal preservation, attenuation of astrogliosis and a decreased level of neuronal apoptosis after chronic progressive compression. This result provided evidence that in the chronic ischaemic state of DCM a slow glutamate excitotoxicity process is activated, which is involved in neuronal degeneration. Furthermore, this study demonstrated the potential use of neuroprotective agents in DCM as an adjuvant to surgical decompression (Karadimas et al. 2015).

3.4. Apoptosis in compressed cervical spine

Apoptosis is programmed cell death, which begins with signal cascades and ends in patterned deoxyribonucleid acid (DNA) fragmentation. The induction of apoptosis in the chronically compressed CSC is well characterised. The technique known as terminal deoxynucleotidyltransferase-mediated deoxyuridine triphosphate nick-end labelling (TUNEL) can be used to find evidence of apoptotic DNA fragmentation. TUNEL-positive neurons and oligodendrocytes and caspase-3 positive neurons and oligodendrocytes were detected in the chronically compressed CSCs of an autopsied patient with DCM and mice exhibiting chronic spinal cord compression (Yu et al. 2009). However, the signal pathway of apoptosis in the chronically compressed CSC remains unclear. Recent work also implicates tumour necrosis factor – α as an external signal in initiating apoptosis (Inukai et al. 2009). Moreover Takenouchi and others demonstrated that the mitogen-activated protein

kinase pathways are activated in neurons and oligodendrocytes during chronic CSC compression (Takenouchi et al. 2008).

3.5. Inflammatory process in DCM

There is compelling evidence that neuroinflammation is a critical player in the pathomechanisms of cell death following neurotrauma (Bomstein et al. 2003). It is now becoming apparent that there are many differences in the innate and adaptive immune responses to acute SCI versus DCM. Beattie and Manley reported that the inflammatory process is unique in DCM and that it is slow and driven by chronic progressive compression (Beattie and Manley 2011). However, little is known regarding the temporal profile of cellular inflammation, the temporal profile of key inflammatory mediators and what aspects of inflammation are beneficial in this unique chronic condition. Yu and others showed that chronic spinal cord compression in patients with DCM causes cellular inflammation and that neutrophils, activated monocytes/macrophages and lymphocytes are recruited to the lesion of human DCM (Yu et al. 2011). Furthermore, the results from Yu suggest that, even in slow progressive injuries of the CSC, a reduction of inflammation leads to less apoptosis and possibly less demyelination and consequent axonal damage (Yu et al. 2011). Matrix metalloproteinase (MMPs) are important for extracellular matrix remodelling and are integral for morphogenesis, inflammation and wound healing. It has been observed that there are a reduced number of neutrophils in the acute injured spinal cord in MMP-9 depleted mice (Noble et al. 2002). Moreover, administration of MMP-9 inhibitors was highly effective in blocking neutrophil administration and tissue damage when administered hours after injury (Noble et al. 2002). This suggest that MMP-9 plays a significant role in the sustained phases of inflammatory cell recruitment. Furthermore, MMP-9 has been implicated in promoting blood-brain barrier disruption and subsequent exaggeration of the inflammatory process in different CNS diseases. A recent study on a rabbit model of DCM revealed that MMP-9 immunoreactivity was significantly higher in spinal cord tissue from rabbits that underwent chronic compression of the CSC for 20 weeks (Karadimas et al. 2015).

3.6. Compensatory changes in the chronically compressed spinal cord

Neurotrophic factors (NFs) are proteins that regulate neuronal survival, axonal growth and synaptic plasticity. NFs have been widely used to promote axonal regeneration in the injured CNS. Some studies report structural regeneration after the administration of the brain-derived neurotrophic factor (BDNF) or neurotrophin 3 (NT-3) (Jones et al. 2001). These findings are consistent with the increased number of neurons and oligodendrocytes rostral and caudal to the injury epicentre and together suggest that BDNF and NT-3 may contribute to neuronal and oligodendrocytes survival in DCM (Yu et al. 2009). Growth-associated protein (GAP) 43 is a protein synthesized in the nerve cell bodies and quickly transported in axons. It is located at the cytoplasmic side of the plasma membrane of axons and growth cones and is a component of the membrane skeleton of such cones. Uchida and others demonstrated increased GAP-43 immunoreactivity in spinal cord tissue coming from mice, which was well correlated with the magnitude and the period of the chronic compression (Uchida et al. 2002). These results suggest that regeneration of axons and the mechanisms involved in axonal repair may occur in the white matter during chronic compression. This evidence collectively reveals that the cervical spinal cord tries to adapt and compensate for chronic, slow and progressive compression (Kalsi-Ryan et al. 2013).

4. Clinical manifestation of degenerative cervical myelopathy

Cervical spondylosis was first clearly defined in 1948 by Brain and colleagues ("Discussion of Rupture of the Intervertebral Disc in the Cervical Region. – London Spine Unit | UK's Best Spinal Clinic | Harley Street" n.d.). Early on, DCM was thought of as a disease causing a variable degree of disability, but one in which the natural tendency was toward a state of arrest or stability (Brain 1951). Lees and Turner provided one of the first accounts of the natural history of DCM (Lees and Turner 1963). This was a retrospective study of 44 patients with clinical evidence of myelopathy followed at St. Bartholomew's Hospital in London, England. The investigators observed and described the course of DCM to contain long or shorter periods of exacerbation, with interspersed long periods of quiescence, without new or worsening symptoms. Exacerbations often left patients worse than they were previously. Few patients deteriorated gradually over several years. At last follow-up, 2 patients (4.5%) had no disability, 3 (6.8%) mild disability, 21 (47.7%) moderate disability, and 18 (40.9%) severe disability. No relation between age and prognosis was found. Despite the seemingly poor outcomes, the investigators concluded that when it came to management of DCM, "a very conservative approach should be the rule," although they acknowledged the need for prospective studies (Lees and Turner 1963). The contemporary literature would suggest anywhere between 20% and 62% of patients with DCM will deteriorate neurologically within 3 to 6 months (Karadimas et al. 2015). Kadanka sr. et al. conducted the only randomized controlled trial on the topic. From 1993 to 1998, 68 patients with mild or moderate DCM (mJOA score 12) were randomized to conservative or operative treatment. Surgery consisted of anterior decompression in 22 patients, corpectomy in 6 patients, and laminoplasty in 5 patients. Conservative strategies included cervical collar, anti-inflammatory medications, and intermittent bedrest for patients with pain, discouragement from participation in high-risk activities, and avoidance of risky environments (eg, physical overloading, movement on slippery surfaces, manipulation therapies, or prolonged flexion of the head). No significant difference was observed in mean mJOA score within or between the conservative and surgical cohorts over a 36-month period. At the 3-year mark, 24.1% of the surgical cohort had improved 2 or more points on the mJOA scale, not significantly different from the corresponding proportion in the conservative cohort (23.3%). At the 10-year mark, mean mJOA score was 15.0 in conservatively and 14.0 in surgically treated patients (Kadaňka et al. 2011). Some papers have been showing that the natural history of

DCM patients consists in an acute worsening, which is followed by a stable phase that may last years, without any worsening. Still, older patients and some patients who have moderate deficits seem to deteriorate more often, justifying though, a surgical procedure in these patients (Lees and Turner 1963) Putting aside the disability when presented, DCM is a known risk factor for developing spinal cord lesion secondary to a minor trauma. For this reason, some authors also indicate surgery even in those patients (Baron and Young 2007) .Regarding outcome, DCM may present in three different manners. In the most common one, 70% of individuals show a stepwise deterioration, with periods of worsening alternated with periods of stabilization. In the second type, 20% experience the progressive evolution of symptoms in a direct way, and lastly 5% of subjects have rapidly evolving progressive disease ("Clair: Natural History of Cervical Spondylotic Myelopathy - Google Scholar" n.d.). Patients with significant spinal compression may present with signs and symptoms of neurological dysfunction. The underlying degenerative spinal pathology may cause localised and radiating neck pain; concomitant radicular pain and weakness may also be present from spinal nerve root compression (Kalsi-Ryan et al. 2013). Pain is a common reason to seek treatment. Musculoskeletal pain might be present in the neck, while neuropathic pain can affect upper and lower limbs and occasionally the trunk. Patients often report neck stiffness, at times without pain (Davies et al. 2018).

No pathognomonic sign exists for DCM. Therefore, clinicians must be cognizant of the constellation of symptoms in this variable presentation. Initially, patients with DCM most commonly present with paraesthesia in one or more extremities. Patients may also report decreased dexterity, often described as "clumsiness" with buttons and zippers or changes in penmanship. Patients may note changes in mobility or frequent falls (Lannon and Kachur 2021). A textbook case would describe gait dysfunction and bilateral hand impairment. Frequently not all symptoms are present. For example, pain might be absent and symptoms can be unilateral and vary in severity, even on a daily basis. Atypical symptoms such as headaches and muscle cramps are also reported (Davies et al. 2018)

The more consistent feature of DCM is the evolution of symptoms. Most patients describe symptoms that have been ongoing for months and getting worse. The rate of progression varies; in some individuals symptoms remain mild over extended periods of time, while in others disease progression accelerates. Functional decline can be insidious, and patients might mistakenly attribute these symptoms to "getting older." Typical features include loss of dexterity (difficulty doing up buttons, using keys, mobile phones, or writing) or mobility

(use of walking aids or frequent falls). Also, at the upper limbs the presence of *melopathic hand* may occur, with the finger escape sign. It consists in the abduction and flexion of the fourth and fifth fingers while maintaining the extended upper limbs for one minute. Also difficulty in holding and releasing the fingers may occur, which consists in failure to hold and extend fingers more than 15 times per 10 seconds (Lavelle and Bell 2007). Additionally, upper limbs may be affected unilaterally or bilaterally, with atrophy of interosseous and thenar muscle along with abolition of the tendinous reflexes, if the compression occurs below C5 level. On the contrary, when the compression takes place above C5, Hoffman sign may appear, and tendinous reflexes are increased (Lees and Turner 1963).

Autonomic symptoms include increased urinary urgency and frequency and urinary incontinence, which are typically not the first symptom noted by the individual, but present in conjunction with other symptoms (Hattori et al. 1990). Non-specific and subtle early features that overlap with other neurological conditions can delay the diagnosis (Tracy and Bartleson 2010b).

Some studies have concluded that a subtle gait disturbance is the common presentation of DCM and that the spastic gait occurs first, followed temporally by upper extremity numbness and loss of fine motor control of the hands (Lunsford et al. 1980). Impaired gait is one of the cardinal symptoms of DCM and frequently its initial presentation. However, gait impairment in DCM can have broad clinical presentation. Quantitative gait analysis is therefore a promising objective tool in the disclosure of early cervical cord impairment in patients with degenerative cervical compression. We have published a cross-sectional observational cohort study in DCM and NMDCCC patients (Kadanka et al. 2021b). The aim of the study was to verify whether an objective (and easily used) walk and run test can detect early gait impairment in a practical proportion of NMDCCC patients, revealing any correlation with severity of disability in DCM. The study group consisted of 45 DCM patients (median age 58 years), 126 NMDCCC subjects (59 years), and 100 healthy controls (HC) (55.5 years), all of whom performed a standardized 10-meter walk and run test. Walking/running time/velocity, number of steps and cadence of walking/running were recorded; analysis disclosed abnormalities in 66.7% of NMDCCC subjects. The DCM group exhibited significantly more pronounced abnormalities in all walk/run parameters when compared with the NMDCCM group. These were apparent in 84.4% of the DCM group and correlated closely with disability as quantified by the modified Japanese Orthopaedic Association (mJOA) scale. We have proven that a standardized 10-meter walk/run test has the capacity to disclose locomotion abnormalities in NMDCCC subjects who lack other clear

myelopathic signs, and may provide a means of classifying DCM patients according to their degree of disability (Kadanka et al. 2021).

Florid spastic paraparesis is the most severe clinical presentation (Kalsi-Ryan et al. 2013). Similarly, the hands can also present with mild sensory deficit that does not affect function or become so severe that dysfunction in the hand does not allow an individual to perform simple tasks such as eating independently (Epstein et al. 1984). Typical features include loss of dexterity (difficulty doing up buttons, using keys, mobile phones, or writing) or mobility (use of walking aids or frequent falls) (Davies et al. 2018).

Sensory symptoms are also frequent, where patients complain of awkward or numb hands (McCormick et al. 2020). Tasks that require motor coordination, such as writing, buttoning up a shirt or undoing a zipper might become challenging (Emery 2001). Moreover, Lhermitte's sign may also occur, indicating a dysfunction of the posterior column. Nonetheless, this sign is not specifically related to DCM, being found in other conditions, such as multiple sclerosis (Baron and Young 2007).

A well-known complication of the pre-existence DCM is the central cord syndrome. It may occur in any patient who suffers a fall or trauma followed by neck hyperextension, which will determine sudden spinal cord compression due to a previous narrowed spinal canal. Clinically, those patients will present different degrees of motor deficits between the superior and inferior limbs, with the upper extremity been more severely affected than the lower one. This may be accompanied by sensory changes below the lesion, along with spasticity and neurogenic bladder (Baron and Young 2007).

There are some authors who believe in the existence of so-called cervical vertigo (CV), but physicians lack sufficient data to form definite opinions and to give clinical guidelines for its diagnosis and treatment. This disorder is over-diagnosed and there is still no laboratory or clinical test to confirm the diagnosis, while none of the possible theories provide fully convincing evidence of a cervical mechanism. We have performed a study with 38 DCM patients from University Hospital Brno. The presence and character of vertigo was explored with a dedicated questionnaire. The cervical torsion test was used to verify the role of neck proprioceptors, and ultrasound examinations of vertebral arteries to assess the role of arteriosclerotic stenotic changes as hypothetical mechanisms of CV. All patients with vertigo underwent a detailed diagnostic work-up to investigate the cause of vertigo. Results were these: symptoms of vertigo were described by 18 patients (47%). Causes of vertigo included: orthostatic dizziness in 8 (22%), hypertension in 5 (14%), benign paroxysmal positional vertigo in 4 (11%) and psychogenic dizziness in 1 patient (3%). No patient responded

positively to the cervical torsion test or showed significant stenosis of vertebral arteries. We found in our own study that, despite a comparatively high prevalence of vertigo in a cohort of DCM patients, it proved impossible to demonstrate that it could be provoked or generated by motions of the cervical spine or related to stenotic changes in the vertebral arteries (Kadanka et al. 2021a). The current gold standard for DCM diagnosis remains any MRI sign of CSC compression (with or without hyperintensity on T2-w) along with clinical signs and symptoms of myelopathy. On the other hand, clinical myelopathic signs and symptoms are not present in all individuals with severe NMDCCC and do not inevitably reflect either the severity of stenosis, or the stenosis duration as they are delayed in chronic compression in comparison with acute compression. Symptoms of DCM might precede objective examination findings. As in focal central nervous system disorders, examination features in DCM have a low sensitivity—that is, a normal finding does not exclude the disease— but high specificity—that is, an abnormal finding is highly suggestive of the disease. Features can be mild and difficult to elicit in the initial stages of disease (Davies et al. 2018). DCM should be suspected in any patient walking with an unsteady gait, many times presenting as a spastic characteristic, due to compression of the corticospinal tract (Karadimas et al. 2015). Concomitant presence of changes in the upper limbs, such as weakness, numbness or loss of manual skills (such as writing), associated with gait changes, should further increase the degree of suspicion of DCM (Amenta et al. 2014).

Clinical examination may reveal the presence of a bilateral (although asymmetric) impairment in lower limbs, with or without spastic hypertonia, Babinski's sign, clonus, paresis and proprioceptive loss (Wang et al. 2016). Iliopsoas and quadriceps femoris are the most affected muscles concerning motor weakness, with distal muscles being affected less commonly (Chiles et al. 1999) Commonly reported symptoms and examination findings in DCM are summarised in this overview (Tracy and Bartleson 2010b).

Tab. 1. Symptoms of DCM

Neck pain/stiffness;
Unilateral or bilateral limb/body pain;
Upper limb weakness, numbness, or loss of dexterity;
Lower limb stiffness, weakness, or sensory loss;
Paraesthesia (tingling or pins and needles sensations);
Autonomic symptoms such as bowel or bladder incontinence, erectile dysfunction, or difficulty passing urine;
Imbalance/unsteadiness;
Falls.

Tab.2. Signs of DCM

Motor signs
Pyramidal weakness (Upper limb; extensors more than flexors. Lower limb: flexors more than extensors) ;
Limb hyperreflexia;
Spasticity (e.g. clasp knife sign);
Clonus, especially Achilles tendon;
Hoffman's sign (thumb adduction/flexion +/− finger flexion after forced flexion and sudden release of a finger, distally);
Babinski's sign;
Segmental weakness (corresponding to the level of compression);
Sensory loss (limb and/or trunk);
Lhermitte's sign (electric shock sensation down the spine, or into the limbs, on neck flexion or extension, present in severe cases);
Gait disturbance.

5. Classification systems used in patients with DCM

A number of classification systems have been generated to assess severity of DCM. The most commonly utilized is the modified Japanese Orthopaedic Association (mJOA) classification, grading motor dysfunction in both upper and lower extremities as well as sensation and bladder control to characterize patients as mild (mJOA 15–17), moderate (12–14), or severe (0–11) (Fehlings et al. 2017).

Category	Score	Description
Upper Extremity Motor Subscore (/5)	0	Unable to move hands
	1	Unable to eat with a spoon but able to move hands
	2	Unable to button a shirt but able to eat with a spoon
	3	Able to button a shirt with great difficulty
	4	Able to button a shirt with mild difficult OR other mild fine motor dysfunction (marked handwriting change, frequent dropping of objects, difficult clasping jewelry, etc.)
	5	Normal hand coordination
Lower Extremity Subscore (/7)	0	Complete loss of movement and sensation
	1	Complete loss of movement, some sensation present
	2	Inability to walk but some movement
	3	Able to walk on flat ground with walking aid
	4	Able to walk without walking aid, but must hold a handrail on stairs
	5	Moderate to severe walking imbalance but able to perform stairs without handrail
	6	Mild imbalance when standing OR walking
	7	Normal walking
Upper Extremity Sensory Subscore (/3)	0	Complete loss of hand sensation
	1	Severe loss of hand sensation OR pain
	2	Mild loss of hand sensation
	3	Normal hand sensation
Urinary Function Subscore (/3)	0	Inability to urinate voluntarily (requiring catheterization)
	1	Frequent urinary incontinence (more than once per month)
	2	Urinary urgency OR occasional stress incontinence (less than once per month)
	3	Normal urinary function

Tab. 3 mJOA classification scale (Fehlings et al. 2017)

Numerous other classification scales have been utilized in the literature, including the Myelopathy Disability Index, Prolo Scale, Cooper myelopathy scale and Nurick Scale. The Nurick Grading Scale focuses primarily on gait assessment, ranging from grade 0 (signs and symptoms of root involvement without evidence of spinal cord disease) to 5 (chairbound or bedridden) (Nurick 1972). Although commonly utilized and frequently correlated with surgical outcome, the Nurick score is considered less sensitive than the mJOA given its focus on lower limb function. One systematic review was unable to find a conclusive association with a number of predictors of outcome for DCM, unlike the more widely utilized mJOA score (Tetreault et al. 2016).

Tab. 4. Nurick grading scale, based on Nurick, 1972

Grade	*Signs and symptoms*
0	Patient has signs and symptoms of root involvement but no spinal cord disease
1	Patient has signs of spinal cord disease with difficulty walking
2	Patient has slight difficulty walking that does not prevent full-time employment
3	Patient has difficulty walking that prevents full-time employment or completion of daily tasks, but does not require assistance with walking
4	Patient is able to walk only with a walker or human assistance
5	Patient is chair bound or bedridden

Tab. 5. Prolo myelopathy scale updated by Vitzthum 2007

Economic status	. Complete invalidity . No gainful occupatioin, including ability to do housework, or continue retirement activities . Able to work but not at previous occupation; able to perform housework and retirement activities . Working at previous occupation part-time or limited status . Able to work at previous occupation with no restriction of any kind
Functional status	. Total incapacity . Difficulty in walking, needing a cane or crutch or persistent moderate motor weakness in upper limb . Slight difficulty in walking, but without help; slight motor weakness in upper limb, moderate pain, persistent paraesthesia . No difficulty in walking, no motor weakness in upper limb, no pain, but persistent paraesthesia . No difficulty in walking, no motor weakness in upper limb, no pain, no paraesthesia, able to perform sports activities

Tab. 6 Cooper myelopathy scale, updated by Vitzthum, 2007

Upper extremity function *(grade)*	
0	Intact
1	Sensory symptoms only
2	Mild motor deficit with some functional impairment
3	Major functional impairment in at least one upper extremity but upper extremities useful for simple tasks
4	No movement or flicker of movement in upper extremities: no useful function
Lower extremity function *(grade)*	
0	Intact
1	Walks independently but nor normally
2	Walks but needs cane or walker
3	Stands but cannot walk
4	Slight movement but cannot walk or stand

El-Zuway et al. suggested that these myelopathic scales are inherently subjective in nature. As a result, they proposed a ten-point myelopathic scale for DCM based on myelopathic signs from clinical examination. Statistically, this scale significantly correlated with postoperative improvement in DCM patients, but was based on a small number of patients (n = 36) and further studies are needed to validate this scale (El-Zuway et al. 2016). Each of the proposed scales provides another aspect of assessment and means to follow patients both pre and postoperatively. However, in general, it is believed that DCM is reasonably well followed with the mJOA in conjunction with objective testing of DCM patients, with examination of myelopathic signs and objective measures of grip strength, dexterity,

balance, and gait (El-Zuway et al. 2016). As such, most recommendations for determining severity of DCM in patients and clinical decision making primarily utilize mJOA.

The Neck Disability Index (NDI) is a ten item self-assessment measure developed to assess disability in patients with neck pain following “whiplash” injury (Vernon and Mior 1991). It is now widely utilized in the evaluation of operative spine patients. The domains assessed in the NDI include pain intensity, personal care, lifting, reading, headache, concentration, work, driving, sleep, and recreation. The challenge in adapting the NDI to DCM patients is that function, not pain, is the primary concern [30].

Tab. 7. Neck disability index, adapted by Vernon, 1991

Section 1 – Pain Intensity

	I have no pain at the moment
	The pain is very mild at the moment
	The pain is moderate at the moment
	The pain is fairly severe at the moment
	The pain is very severe at the moment
	The pain is the worst imaginable at the moment

Section 2 – Personal Care (washing, dressing, etc.)

	I can look after myself normally without causing extra pain
	I can look after myself normally, but it causes extra pain
	It is painful to look after myself, I am slow and careful
	I need some help but manage most of my personal care
	I need help every day in most aspects of self-care
	I do not get dressed; I wash with difficulty and stay in bed

Section 3- Lifting

	I can lift heavy weights without extra pain
	I can lift heavy weights, but it gives me extra pain
	Pain prevents me from lifting heavy weights off the floor, but I can manage, if they are conveniently positioned- for example on the table
	Pain prevents me from lifting heavy weights, but I can manage light to medium weights if they are conveniently positioned
	I can lift only very light weights
	I cannot lift or carry anything at all

Section 4- Reading

	I can read as much I want to with no pain in my neck
	I can read as much I want to with slight pain in my neck
	I can read as much I want to with moderate pain in my neck
	I can´t read as much I want because of moderate pain in my neck
	I can´t hardly read at all because of severe pain in my neck
	I cannot read at all

Section 5- Headaches

	I have no headaches at all
	I have slight headaches that come infrequently
	I have moderate headaches that come infrequently
	I have moderate headaches that come frequently

	I have severe headaches that come frequently
	I have headaches almost all the time

Section 6- Concentration

	I can concentrate fully when I want to with no difficulty
	I can concentrate fully when I want to with slight difficulty
	I have a fair degree of difficulty in concentrating when I want to
	I have a lot of difficulty in concentrating when I want to
	I have a great deal of difficulty in concentrating when I want to
	I cannot concentrate at all

Section 7 – Work

	I can do as much work as I want to
	I can only do my usual work, but not more
	I can only do most of my usual work, but not more
	I cannot do my usual work
	I cannot hardly do any work at all
	I can´t do any work at all

Section 8 - Driving

	I can drive my car without any neck pain
	I can drive my car as long as I want to with slight pain in my neck
	I can drive my car as long as I want to with moderate pain in my neck

	I can´t drive my car as long as I want to because of moderate pain in my neck
	I can´t drive my car as long as I want to because of severe pain in my neck
	I can´t drive my car at all.

Section 9- Sleeping

	I have no trouble with sleeping
	My sleep is slightly disturbed (less than 1 hour sleepless)
	My sleep is mildly disturbed (1-2 hours sleepless)
	My sleep is moderately disturbed (2-3 hours sleepless)
	My sleep is greatly disturbed (3-5 hours sleepless)
	My sleep is completely disturbed (5-7 hours sleepless)

Section 10- Recreation

	I am able to engage in all my recreation activities with no neck pain at all
	I am able to engage in all my recreation activities with some pain in my neck
	I am able to engage in most, but not all of my usual recreation activities because of pain in my neck
	I am able to engage in a few of my recreation activities because of pain in my neck
	I can hardly do any recreation activities because of pain in my neck
	I can´t do any recreation activities at all.

6. Diagnostic imaging

6.1. Plain film (X-rays)

Plain film still remains an inexpensive initial radiological evaluation of the spine in DCM patients. Anteroposterior (AP), lateral and oblique radiographs can be acquired easily at the time of consultation. In the evaluation of spondylosis, plain radiographs are commonly used as the first-line imaging (Mason 1999). This is an indication of the underlying pathology but not diagnostic, as these findings are common in the adult population (Gore et al. 1986). Narrowing of the disc space, facet joint arthrosis, bone spurs, OPLL, and kyphotic alignment may be visualized on a standard lateral plane X-ray. Measurement of the AP diameter is typically determined on a lateral plain film, as the distance from the posterior surface of the vertebral body to the closest point on the spinolaminar line at the pedicle level (Green et al. 2012).

Spondylotic changes often lead to a stiffening of the involved segments. Adjacent segments of the spine may be hypermobile to compensate for the decreased motion at the spondylotic levels. This hypermobility can result in a dynamic compression of the spinal column and may not be seen on routine MRI. Therefore, flexion-extension radiographs should be included in the radiographic evaluation of the patient with DCM. Instability is suggested where translation of >3.5 mm and sagittal plane angulation of >11 degrees are present (White and Panjabi 1987). Additional oblique views are useful for visualizing foraminal narrowing. Comparison of standing radiographs with supine radiographs provides important information about the stability and motion of the cervical spine under a physiological load (Lebl et al. 2011).

In addition to the above-mentioned alterations, the radiographs can be used to estimate the degree of cervical canal stenosis measured by the Pavlov- Torg index (Suk et al. 2009). It is known as the spinal canal to vertebral body ratio and is determined by dividing the sagittal diameter of the spinal canal by the sagittal diameter of the vertebral body (usually at C5 level) (Pavlov et al. 1987). According to Pavlov et al., if the ratio of the sagittal distance of the spinal canal to the anteroposterior diameter of the vertebral body is ≤ 0.82, then cervical spinal stenosis is present (Pavlov et al. 1987).

6.2. Computed tomography (CT)

MRI is currently the best imaging modality to identify the structural causes of a patient's myelopathy and visualize neural tissue and spinal cord abnormalities (Tracy and Bartleson 2010b). CT in isolation lacks the soft tissue detail achieved with MRI scanning. However, CT is still a useful modality when there is a contra-indication to MRI and where a metal artefact is obstructing the anatomy. Similar to radiographs, CT provides an excellent view of bony structures (Waly et al. 2017) Plain radiogram and especially CT are important for verification of cervical spinal stenosis (Kovaľová et al. 2015). Additionally, CT scanning was found to be superior to other radiographic modalities in diagnosing and classifying the type of OPLL (Abiola et al. 2016). CT is widely available, fast and easy to access, allowing primary care physicians to order these investigations without long wait times. The view of soft tissues offered by CT is poor, however, and not sufficient to identify spinal cord compression.

6.2.1. CT myelography

CT myelography is an important imaging modality that combines the advantages of myelography and the high resolution of CT. It provides a detailed delineation of pathological spine conditions, especially those involving the thecal sac and its contents. However, the role of CT myelography has dramatically and appropriately decreased with the advent of MRI, which provides a non-invasive method to demonstrate pathological spine conditions with high signal intensity in soft tissues (Dm et al. 2020). However, there remain some situations in which CT myelography is indicated and plays a critical role in patient treatment. CT myelography is an invasive technique in which contrast dye is injected into the lumbar cistern prior to CT imaging, providing excellent visualisation of the contour of the spinal cord and potentially compressive surrounding structures. CT myelography however involves risks and is an uncomfortable or painful procedure.

6.2.2. CT angiography

CT angiography may be useful to identify anomalous vertebral artery anatomy. This most commonly affects C1 and C2 levels, in which cases CT (or MRI) angiography should be performed, but occasionally subaxial cervical levels have a vertebral artery and foramen transversarium with an abnormally medial position that poses a serious risk of injury (Martin et al. 2018b).

6.3. Magnetic resonance imaging (MRI)

MRI is the crucial imaging modality for DCM diagnosis, because it clearly shows the outline of the spinal cord and nerve roots in relation to surrounding cerebrospinal fluid (CSF). Conventional clinical MRI is primarily acquired in the sagittal orientation to evaluate SC signal abnormalities, such as the presence of T2-w hyperintensities and T1-w hypointensities. Conventional MRI can delineate the nature and degree of degenerative changes, reveal decreases in the diameter of the spinal canal, identify compression of the spinal cord, and detect signal intensity changes within the spinal cord parenchyma (Badhiwala et al. 2020). Any deformation of the spinal cord from its normal shape (flattening, indentation, torsion, or circumferential narrowing due to adjacent tissues) should be considered a type of compression that may cause neurological dysfunction (Martin et al. 2018a). MRI can also differentiate DCM from mimicking conditions or other causes of myelopathy (for example, a tumour, demyelinating plaques or syringomyelia) (Badhiwala et al. 2020) T2-weighted (T2-w) images show the greatest contrast between spinal cord and CSF (Martin et al. 2018b).

Spinal cord compression is a key mechanism for the development of DCM, which along with complex pathophysiological mechanisms leads to a variety of symptoms. While MRI signs of NMDCCC are found in half of randomly examined individuals over the age of sixty (Kovalova et al. 2016b), they are inconsistently associated with myelopathic signs and symptoms. The hyperintensity on T2-weighted scans (which are usually considered “typical” MRI signs of DCM) are only present in less than half of individuals with clinically symptomatic DCM (Matsuda et al. 1991; Matsumoto et al. 2000; Hori et al. 2014). In addition to the conventional clinical description of signal changes, sequences with a sufficient axial in-plane resolution below 1 mm and good contrast between white/grey matter and cerebrospinal fluid (typically 3D isotropic T1-w and 2D axial multi-echo gradient echo

T2*-w sequences) allow for assessing morphometric metrics, in order to further validate the severity of compression (Valošek et al. 2021)

The current gold standard for DCM diagnosis remains any MRI sign of CSC compression (with or without hyperintensity on T2-w) along with clinical signs and symptoms of myelopathy. However, the current clinical MRI protocol can only confirm degenerative aetiology of the stenosis. Abnormalities in signal intensities are insufficient to reflect specific cellular and biochemical pathophysiological processes. The reliable MRI marker that will allow detailed description of microstructural/neurochemical changes, and thus improve prediction of NMDCCC progression to DCM, has not been established yet. To date, studies have not defined a clear-cut quantitative MRI measure of cervical canal stenosis and CSC compression that could be used as a specific indicator of mild CSC compression of "impingement" type in particular. Whereas numerous quantitative MRI parameters quantified severity of compression in patients with symptomatic myelopathy (Nouri et al. 2016), utilizing compression ratio (CR) or maximum CSC compression (MSCC) (Fehlings et al. 1999), the detection of the initial compression stages that lead primarily to microstructural CSC alteration and manifest as a subclinical, preclinical, non-myelopathic condition has not been established. Our studies confirmed that an AP diameter of the cervical spinal canal of <9.9 mm and CR ≤0.5 has the highest discriminative power between NMDCCC and healthy individuals, and the cross-sectional area (CSA) of the cervical spinal cord has the best discriminating ability between DCM and NMDCCC (Kovaľová et al. 2015; Kovalova et al. 2016b; Kadanka et al. 2017). The cross-sectional area (i.e. area of the SC in the axial plane) of ≤70.1 mm^2, and the compression ratio (i.e. the ratio between the anteroposterior diameter and the transverse diameter) of ≤0.4 distinguished NMDCCC patients who developed symptomatic DCM with sensitivities of 66.7 and 82.5 respectively, as well as specificities of 60.0 and 89.7 respectively (Kadanka et al. 2017). Also, the compression-related T_2-w hyperintensities that are preferentially detected in DCM compared to NMDCCC patients have very limited sensitivity for the detection of subtle structural damage to the compressed CSC. Our outcomes confirmed that T_2-w anatomical imaging alone could not confirm NMDCCC or discriminate between NMDCCC and DCM subjects (Kovalova et al. 2016a).

Thus, advanced imaging techniques, that allow quantifying microstructural changes, may offer diagnostic measures and predictors of long-term outcomes. Recently, the importance of dMRI and proton single voxel magnetic resonance spectroscopy (MRS), which can elucidate details of microstructural and neurochemical organization of the CSC, is

highlighted (Stroman et al. 2014). Despite suggested relevance in degenerative CSC alteration, the application of advanced MRI techniques in the CSC is extremely challenging (Stroman et al. 2014). The desirable diagnostic tool will provide high sensitivity for detection of early CSC changes and will overcome the diagnostic uncertainties of standard MRI techniques.

6.3.1. dMRI

Diffusion tensor imaging (DTI) can measure the directionality and magnitude of water diffusion. Based on the principle that the motion of water along the axis of a bipolar magnetic field gradient will induce a phase change causing signal attenuation in MRI, diffusion-weighted images can be collected. These images are sensitised to microscopic, orientation-MR dependent motion of water molecules. Since water diffusion occurs within and outside cellular structures, the degree of water diffusion in the brain or spine depends on the local cellular microstructure. By collecting multiple diffusion-weighted images with different encoding gradient directions, it is possible to characterise the three-dimensional pattern of water diffusion with a diffusion tensor model, incorporating information about the directionality and the magnitude of diffusion at each point in the brain or spine (Le Bihan et al. 2001). The orientation dependence of water diffusion measured with DTI can be quantified with diffusion anisotropy measures calculated from the diffusion tensor such as the fractional anisotropy (FA), which varies in magnitude from a value of 0 (indicating that proton spins in water can diffuse randomly in any direction) to a value of 1 (indicating that water diffusion is restricted only to one direction) (Ressel et al. 2018). FA values show the size of the anisotropy of the analysed structure by taking advantage of the improved directional evaluation of water diffusivity in abnormal areas. They are generally decreased in the presence of local extracellular oedema, or where a reduced number of fibres results in increased extracellular space (Facon et al. 2005). This allows the detection of injury of the axons and myelin in white matter, which tends to have highly directional (anisotropic) diffusivity (Martin et al. 2018b). The other parameter, apparent diffusion coefficient (ADC), is a scalar value reflecting molecular diffusivity under motion restriction. Demyelination and oedema by slow compression result in an increased degree of diffusivity, as indicated by increased ADC values compared to those of normal tissue (Eguchi et al. 2010). ADC maps provide quantitative measures of water diffusion within brain or spine tissue (Le Bihan et al. 2001). Falon et al. concluded that FA is more sensitive than ADC and T2-w imaging in detecting spinal cord abnormalities in patients with acute and slowly progressive cord

compression. This parameter derived from DTI MRI images may be a prognostic factor for the patient's clinical outcome after treatment (Facon et al. 2005). Kara et al showed changes in DTI parametrics at stenotic segments in patients with DCM; while FA values of the spinal cord at the stenotic level showed a statistically significant reduction, there was a statistically significant increase in the measured ADC values (Kara et al. 2011). Budzik et al proved (in 20 symptomatic patients with DCM, matched with 15 volunteers), that FA values were significantly correlated with some of the patients' clinical scores. High signal intensity of the spinal cord on T2 was not correlated either with the DTI parameters or with the clinical assessment, suggesting that FA is more sensitive than T2 imaging (Budzik et al. 2011). In our own study (the study group included 130 patients with NMDCCC confirmed by MRI and 71 control subjects without signs of NMDCCC) significant variations in FA and ADC values emerged when several spinal cord levels were mutually compared in the control group (Keřkovský et al. 2017). FA values correlated significantly with age in the NMDCCC group and sex had a significant influence on ADC values in both groups. The two diffusion parameters in the NMDCCC group differed significantly between patients with clinical signs of mild-to-moderate myelopathy compared with asymptomatic patients, and correlated with measurements of spinal canal morphology (Keřkovský et al. 2017). FA and ADC values enhance the efficacy and accuracy of MRI in the diagnosis of DCM; hence DTI can be used as a non-invasive modality to recognize spondylotic myelopathy changes even in the early stages, which can be helpful in deciding on the appropriate timing of decompression surgery before irreversible chronic changes set in (Nukala et al. 2019).

In another of our studies a new MRI method was used. So-called "high-resolution 3 T diffusion MRI" was acquired for 103 NMDCCC and 21 DCM patients and compared to 60 healthy controls, to reveal diffusion alterations and relationships between tract-specific diffusion metrics and corresponding electrophysiological measures and compression severity. Relationship between the degree of DCM disability, assessed by the mJOA scale, and tract-specific microstructural changes in DCM patients was also explored. The study identified diffusion-derived abnormalities in the grey matter, dorsal and lateral tracts congruent with trans-synaptic degeneration and demyelination in chronic degenerative spinal cord compression with more profound alterations in DCM than NMDCCC. Diffusion metrics were affected in the C3-6 area as well as above the compression level at C3, with more profound rostral deficits in DCM than NMDCCC. Alterations in lateral motor and dorsal sensory tracts correlated with motor and sensory evoked potentials, respectively, whereas electromyography outcomes corresponded with grey matter microstructure. DCM

disability corresponded with microstructure alteration in lateral columns (Valošek et al. 2021).

6.3.2. Intravoxel Incoherent Motion Imaging

Intravoxel incoherent motion (IVIM) imaging measures the microscopic movement of water molecules caused by capillary perfusion, using a dMRI sequence with low b-values (≤300 mm^2/s) to assess flowing blood fraction and pseudo-diffusion coefficient (Le Bihan et al. 2001). Pilot IVIM studies in the human SC at 7T in 6 HC (Lévy et al. 2020) and at 3T in 2 DCM patients, along with 11 HC (Lévy et al. 2020), depicted higher perfusion in GM, compared to white matter in HC, and impaired perfusion in DCM patients at compression levels. However, interpretation is limited, due to the small sample size and possible influence of CSF pulsation (Lévy et al. 2020). IVIM imaging is a promising technique for future DCM and NMDCCC studies, as post-mortem studies showed that degenerative compression results in hypoperfusion and ischemia in specific white matter/grey matter regions (Le Bihan et al. 2001).

6.3.3. MR spectroscopy

Proton magnetic resonance spectroscopy (^{1}H -MRS) quantifies the neurochemical profile within the spectroscopic volume of interest (i.e. spectroscopic voxel) and provides unique information about microstructural or metabolic pathophysiological processes that are inaccessible with conventional imaging methods. It is a technique that can characterize molecular and metabolic changes in the spinal cord, reflecting neuronal loss, gliosis and demyelination (Holly et al. 2017). SC ^{1}H-MRS is challenged by its small transversal area, which is further diminished at the compression level. Therefore, ^{1}H-MRS studies in DCM patients assessed the neurochemical profile only above the stenosis level and observed neurochemical changes rostrally to the compression, likely due to Wallerian degeneration, which manifested as increased levels of total creatine (tCr)/total NAA (tNAA) and total choline (tCho) (Holly et al. 2017). Recent studies have suggested that MRS may be useful for quantitatively assessing subtle biochemical changes within the spinal cord that may precede morphologic changes observed with traditional imaging techniques (Holly et al. 2009). Previous investigations using a 1.5T MRI scanner confirmed the feasibility of accurately performing MRS in symptomatic DCM patients (Holly et al. 2009). Salamon et

al. proved that MRS may capture some of the early and late spinal cord cellular biochemical changes that occur in patients with advanced cervical spondylosis and DCM; the choline/N-acetyl-aspartate (NAA) ratio had a significant correlation with the mJOA score, providing a potentially clinically useful radiographical biomarker in the management of cervical spondylosis patients (Salamon et al. 2013).

We have recently published a study concerning this topic. Proton-MRS data were prospectively acquired from 73 participants with CSC compression and 47 healthy controls (HC). MRS voxel was centred at C2 level. Compression-affected participants were clinically categorized as NMDCCC and DCM, radiologically as mild (MC) or severe (SCo) compression. CSC volumes and neurochemical concentrations were compared between cohorts (HC vs. NMDCCC vs. DCM and HC vs. MC vs. SCo) with general linear models adjusted for age and height ($p< 0.05$) and correlated to stenosis severity, electrophysiology, and myelopathy symptoms ($p< 0.05$). While ratio of total creatine (tCr) to total N-acetylaspartate (tNAA) increased in NMDCCC (+11%) and in DCM (+26%) and SCo (+21%), Myo-inositol/tNAA, glutamate+glutamine/tNAA and volumes changed only in DCM (+20%, +73%, and –14%) and SC (+12%, +46%, and – 8%, respectively) relative to HC. Both tCr/tNAA and myo-inositol/tNAA correlated with compression severity and volume ($–0.376<r<-0.256$). Myo-inositol/tNAA correlated with myelopathy symptoms, whereas CSC volume did not. Short-echo 1H-MRS provided neurochemical signatures of CSC impairment that reflected compression severity and clinical significance. While volumetry only reflected clinically manifest myelopathy, MRS detected neurochemical changes already before the onset of myelopathy symptoms. This study revealed neurochemical changes in CSC above the compression level in subjects with radiological signs of compression and clinical myelopathy and, for the first time, in non-myelopathic participants as well. State-of-the-art MRS demonstrated sufficient sensitivity to reveal early changes in non-myelopathic patients and thus might allow the stratification of non-myelopathic subjects (Horak et al. 2021).

6.3.4. Spinal cord toolbox (SCT)

Although quantitative MRI techniques provide promising predictors of NMDCCC progression, the diagnosis of spinal cord compression (SCC) is still based on conventional structural MRI. Unfortunately, the definition of SCC is vague and varies between studies, leading to bias in meta-analyses derived from global overviews, rendering multi-centre studies difficult (Smith et al. 2020). Further, repeated MRI in longitudinal follow-up of mild

DCM and NMDCCC requires reliable quantitative measures to assess the potential progression of radiological outcomes such as CR and CSA. Personal expert evaluation is time consuming, and investigations of its reliability are currently sparse. In 2016, the Spinal Cord Toolbox (SCT), an open-source software package for the analysis of spinal cord MRI data was introduced (De Leener et al. 2017). Among its plethora of functionalities, SCT includes tools for automated spinal cord segmentation and subsequent morphometric analysis (De Leener et al. 2017). SCT allows one to extract routinely-used radiological measures such as right left diameter (RL), anterior-posterior diameter (AP) and CSA, but also parameters reflecting the indentation and torsion of the spinal cord. SCT is primarily designed for quantitative analysis of the spinal cord, thus the analysis of the surrounding anatomical structures is limited. Martin et al. recently compared automated shape analysis of metrics computed by SCT with expert evaluation and reported excellent results (Martin et al. 2018a). They also proposed an objective definition of SCC as deviation from normal in any of three quantitative parameters that reflect flattening, indentation, and torsion. However, the number of participants in their study was limited—20 healthy controls and 20 NMDCCC patients—while, for some parameters, the cut-off values were defined on the basis of only 3–7 abnormal values (flattening) or 8 abnormal values pooled over different intervertebral levels (torsion).

We have recently published a study, which demonstrated successful semi-automated detection of cervical spinal cord compression based on four SCT-derived morphometric - parameters. The parameters extracted using SCT exhibited lower variability than the experts' manual ratings in RL, AP, CR and CSA. Further, SCT enabled exact quantification of indentation and torsion. Introduction of SCT into radiological evaluations may bring more reliable results to longitudinal and multicentre studies. The approach also saves a great deal of time, perhaps enabling its routine use in the assessment of the natural course of NMDCCC and mild DCM; the rate of progression may well become a valid predictor of whether the patient would benefit from surgery or not (Horáková et al. 2022).

7. Electrophysiological assessment

Many patients with DCM present to primary care physicians or specialists with upper extremity complaints that may be attributable to nerves. While the history, physical examination and diagnostic imaging provide some level of certainty as to the aetiology of a patient's symptoms, it is possible that electrodiagnostic testing further refines the diagnosis. The electrodiagnostic consultation adds considerably to clinical decision-making in patients with upper extremity neurologic complaints. It is also used to monitor the severity of a lesion, to provide prognosis, to map out the exact location of a lesion for surgical intervention, and to provide some estimate of the age of a lesion that may assist in differentiating current from previous complaints in a similar region. With nerve illnesses, EMG can define the type of pathology and thus provide valuable clues as to the aetiology and treatment of the neuropathy. The value of electrophysiological studies in the assessment of DCM is threefold: first, it aids diagnosis and enables longitudinal assessment; second, it enables the coexistence of cervical radiculopathy to be ruled out; and third, it enables neuromuscular diseases such as ALS, peripheral neuropathy and motor neuron disease, which can mimic DCM, to be ruled out (Badhiwala et al. 2020). Nerve conduction studies are useful to rule out peripheral polyneuropathy, peripheral nerve entrapment (for example, carpal tunnel syndrome or cubital tunnel syndrome) and brachial plexopathy (Tetreault et al. 2015). These studies can also indicate extensive damage to anterior horn cells, which causes reductions in the amplitude of compound motor action potentials, although sensory nerve conduction studies sometimes reveal no abnormalities. F-wave recordings allow for the determination of a total peripheral conduction time from the anterior horn cell to the muscle, which thus includes the conduction over the motor root to its exit from the intervertebral foramen. The F-wave is usually normal in mild cases of radiculopathy. Distinct delay of the F-wave or a reduced number of clearly distinguishable F-waves after a given number of supramaximal peripheral stimuli, in association with normal distal motor conduction, is a sign of a proximal lesion (Dvorak et al. 2003).

Needle EMG examines segmentally affected muscles, chosen based upon the clinical investigation. The needle is repositioned on ten different sites in a muscle in order not to miss denervated parts. Increased insertional activity, spontaneous activity (involuntary) such as sharp positive waves, fibrillations, fasciculations and diminished motor unit recruitment are considered signs of denervation due to deterioration of anterior horn cells (myelopathy hands), or due to compression of nerve root. In normal muscles, motor unit action potentials

(MUAPs) are elicited only in response to neural discharges. Denervated muscle fibres become unstable, as they are no longer under neural control, and individual muscle fibres will fire in the absence of neural stimuli. These signs of denervation in EMG can be spotted at the earliest about 8 days after the nerve lesion, and are termed acute signs of denervation (Dvorak et al. 2003). EMG performed with needle concentric electrodes is the oldest neurophysiologic method for diagnosing nerve root compression syndrome. EMG is claimed to have almost no false-positive results (Dvorak et al. 2003). It is a highly sensitive technique for the detection of damage to anterior horn cells, which occurs in DCM as a result of compression and ischaemia. EMG shows degrees of denervation and the number of roots involved, but unfortunately it has no prognostic value (Dvorak et al. 2003). The electrodiagnostician is compelled to perform a study sufficient to confidently identify or exclude cervical radiculopathy. Studies involving a large number of muscles, however, are uncomfortable to the patient. For this reason, delineating an optimal EMG screening examination that allows the examiner to identify a cervical radiculopathy (when one can be electrodiagnostically confirmed) yet minimizes the number of muscles studied to prevent excessive patient discomfort is of great clinical interest. Some radiculopathies cannot be confirmed by needle EMG. Radiculopathies that exclusively cause sensory root involvement, for example, will not produce abnormal EMG findings. If the rate of denervation is balanced by reinnervation in the muscle, then spontaneous activity is less likely to occur. Although EMG findings correlate with spinal imaging (myelography and magnetic resonance imaging) and intraoperative findings, there are some radiculopathies which demonstrate denervation potentials on EMG but show no anatomic structural reasons to explain this muscle denervation. This has been termed chemical or inflammatory radiculitis. Conversely, patients can have a clear structural cause of nerve root compromise and yet have a normal EMG. Dillingham et al published a so- called “concept of a screening EMG” (Dillingham et al. 2001). This concept encompasses detecting the possibility of an electrodiagnostically confirmable radiculopathy. If one of the muscles in the screen is abnormal, the screen must be expanded to exclude other diagnoses, and to fully delineate the radiculopathy level. This screening EMG study involves determining whether the radiculopathy can be confirmed by EMG. If the radiculopathy cannot be confirmed, then presumably no number of muscles can identify the radiculopathy. The process of identification can be conceptualized as a conditional probability. Given that a cervical radiculopathy can be confirmed by needle EMG, what is the minimum number of muscles which must be examined to confidently recognize or exclude this possibility? Despite the

great potential for minimizing the physicians' time and patients' discomfort, the optimal number of muscles for evaluating patients with limb symptoms has received little attention in the literature. Determining how many and which muscles to study to successfully detect a cervical radiculopathy (when one can be electrodiagnostically confirmed) is an important clinical decision. The results of Dillingham's study indicate that if six muscles representing all cervical root levels and including the cervical paravertebral are studied, then the examiner can be confident of detecting a cervical radiculopathy, which can be confirmed by EMG. Adding additional muscles results in only marginal increases in identification, although 100% identification is achieved with several seven muscle screens. Studies involving eight muscles provide no better identification than seven muscles. This study begins to clarify for electrodiagnosticians the point of diminishing returns, beyond which diagnostic certainty for detecting a cervical radiculopathy is not enhanced by examining more muscles. The most commonly investigated muscles in this study were deltoid, biceps, triceps, flexor carpi ulnaris, flexor carpi radialis, extensor digitorum communis, first dorsal interosseous, and pronator teres (Dillingham et al. 2001).

In our EMG laboratory we usually perform conduction studies on six motor nerves (median, ulnar, and tibial nerves bilaterally) and six sensory (median, ulnar and sural nerves bilaterally) using conventional techniques. Needle EMG from four muscles (deltoid, biceps brachii, triceps brachii, and first dorsal interosseous) is usually done bilaterally with assessment of spontaneous activity, motor unit potential parameters, and interference patterns. EMG signs of acute motor axonal neuropathy in one myotome (C5–Th1) corresponding with radicular signs and symptoms are classified as radicular. EMG signs of acute, subacute, or chronic motor axonal neuropathy, established in more than one myotome (C5–Th1) unilaterally or bilaterally, are classified as signs of anterior horn cell lesion resulting from DCM (Kadanka et al. 2017).

DCM is a common ALS mimic syndrome, because both diseases occur at a higher frequency in elderly people and there is a possible overlap when ALS patients lack bulbar signs. Identifying the occurrence of ALS in patients with a clinical and radiological diagnosis of DCM could be challenging. ALS is frequently complicated by cervical spondylosis: indeed, it can be detected in almost half of ALS patients (Yamada et al. 2003). Recognizing ALS in DCM patients is extremely important to prevent the patient suffering from DCM + ALS being subjected to invasive treatments: indeed, ALS patients are at high risk for intraoperative and postoperative complications, and general anaesthesia may exacerbate respiratory failure. Moreover, no improvement has been shown for decompressive spinal

surgery in ALS patients in 86% of cases , and there is evidence that surgical interventions could even accelerate progression of ALS, probably due to surgical stress and anaesthesia (Yoshor et al. 2005). The neurophysiologically based Awaji criteria were developed for use in conjunction with the clinical criteria as set out in the revised El-Escorial criteria, in an attempt to reduce diagnostic delay (de Carvalho et al. 2008). The Awaji criteria proposed that neurophysiological features of lower motor neuron (LMN) dysfunction, including chronic and ongoing neurogenic changes (fibrillation potentials/- positive sharp waves) were equivalent to clinical LMN signs. In addition, fasciculations were deemed to be a biomarker of LMN dysfunction when combined with chronic neurogenic changes. Subsequently, the diagnostic utility of the Awaji criteria was assessed in retrospective and prospective studies, which established an increased or comparable sensitivity when compared to the older El-Escorial criteria.

Hirayama disease (HD) is a rare type of cervical myelopathy related to flexion of the neck characterized by progressive muscular weakness and atrophy of the distal upper limbs, most frequently seen in young males. HD is thought to be secondary to an abnormal anterior displacement of the posterior dura with secondary compression of the lower cervical spinal cord and chronic injury to the anterior grey matter horns. HD has been mainly reported from Asia, with fewer case reports from Europe and North America, including our own case reports (Kadaňka and Mičánková Adamová 2014). Nerve conduction studies and EMG findings is usually consistent with a spinal metameric disorder involving the C7-T1 myotomes (pronator teres, flexor carpi radialis, flexor carpi ulnaris, and abductor digiti minimi muscles etc.). Brachioradialis muscle is typically spared.

Somatosensory evoked potentials (SSEPs) can be used to evaluate the degree of central sensory conduction impairment in DCM, which manifests as latency or low amplitude (Tracy and Bartleson 2010b). Similarly, motor evoked potentials (MEPs) can be used to detect a prolonged central motor latency (Bednarik et al. 2008b). Some clinicians have advocated the use of SSEPs and MEPs in the routine examination of patient with DCM to maximize sensitivity and specificity in making the diagnosis (Dvorak et al. 2003).

SSEPs and MEPs can also be helpful in the setting of asymptomatic (preclinical) degenerative cervical spinal cord compression, as they can detect subclinical involvement of the spinal cord or nerve roots, thereby identifying patients who should be monitored vigilantly for development of myelopathy (Bednarik et al. 2008b)

SSEPs and MEPs are routinely used for intraoperative neurophysiological monitoring (Decruz et al. 2020). Some studies have demonstrated that neurophysiological recording of

spinothalamic pathways (contact heat evoked potentials (CHEPs)) is a feasible and sensitive approach to the assessment of damage to central sensory nerve fibres. This damage usually occurs at the segmental crossings of the spinothalamic pathways, as DCM has a high impact on centromedullary areas of the spinal cord. In this context, CHEPs are more sensitive to damage than SSEPs and enable assessment of individual cervical segments by testing along defined dermatomes (Granovsky et al. 2016).

8. Conservative treatment in degenerative cervical myelopathy

There is a paucity of high-quality studies relating to the optimal management of patients with mild DCM. However, in the absence of robust evidence, Fehlings and colleagues recommend offering a trial of supervised, structured rehabilitative therapy as a conservative treatment measure (Fehlings et al. 2017). If there is no improvement or there is worsening with conservative treatment, surgical treatment is recommended. Conservative treatment might also be indicated owing to patient preference or unacceptable surgical risk. Examples of conservative treatment include structured, careful physiotherapy, a soft neck collar, massage, and medication; however, there is a lack of evidence-based approaches to conservative treatment (Kalsi-Ryan et al. 2013; Tetreault et al. 2016; Rhee et al. 2017). Cervical manipulative therapy and cervical traction should be avoided in order to prevent complications (Sugawara 2018). It is also recommended that patients stay away from activities that have high impact on the neck (contact sports, skydiving, etc).

There are no studies examining the frequency of repeat clinical and imaging examinations for those treated conservatively (Bakhsheshian et al. 2017); however, these patients need education regarding signs and symptoms that represent deterioration, as well as close clinical monitoring and repeat MRI depending on clinical examination findings. Surgical intervention is reserved for those who fail to respond to conservative treatment and whose symptoms progressively worsen.

An important group of patients includes those who are found to have cervical cord compression on MRI but no signs and symptoms of myelopathy. Fehlings and colleagues recommend following these patients with regular clinic visits but no treatment (Fehlings et al. 2017). However, a caveat to this is that if a patient has radiculopathy with evidence of cord compression on MRI, these individuals have a higher risk of progressing to myelopathy; therefore, surgery might be offered. A systematic review by Wilson et al reported that only 8% of patients with evidence of spinal cord compression but who exhibited no myelopathic signs or symptoms had developed myelopathy a year later (Wilson et al. 2013). These patients should be monitored thoroughly and frequently with repeat MRI and physical examination. Owing to the lack of consistent, evidence-based information on the natural history, recommendations for treatment must be largely determined on an individual basis (Karadimas et al. 2015; Fehlings et al. 2017).

9. Operative treatment in degenerative cervical myelopathy

Surgical treatments, such as anterior or posterior decompression accompanying arthrodesis, arthroplasty, or laminoplasty should be considered for patients with chronic progressive cervical myelopathy who are nonresponsive to conservative treatment. Fehlings et al recommend surgical treatment for all patients with severe (mJOA 0-11*)* and moderate (mJOA 12-14) DCM (Fehlings et al. 2017). The goal of surgical treatment is to relieve the mechanical compression of the spinal cord and extend the spinal canal. The selection of the appropriate surgical treatment should be individualized according to levels of involved pathologies, clinical manifestations and radiological factors.

Surgical Procedures

The surgical procedures commonly performed to treat DCM are:

Anterior cervical diskectomy and fusion

- Anterior cervical corpectomy and fusion
- Anterior cervical diskectomy and disk replacement
- Laminectomy and fusion
- Laminoplasty.

The type of selected procedure depends on a number of factors, including the patient's overall health and the type and location of the problem. Studies have not shown one approach to be better than another. Surgery should be individualized. Depending on the procedure, surgery for DCM is performed either from the front of the neck (anterior) or the back (posterior). In some cases, both anterior and posterior approaches may be necessary to address spinal cord compression and instability. Each approach has advantages and disadvantages.

Spinal Fusion

Whether an anterior or posterior approach is used, procedures for DCM often include spinal fusion to help stabilize the spine. Spinal fusion is essentially a welding process. The basic idea is to fuse together the vertebrae so that they heal into a single, solid bone. Fusion eliminates motion between the degenerated vertebrae and takes away some spinal flexibility. The theory is that if the painful spine segments do not move, they should not hurt. Also, degeneration occurs only when there is motion, so by eliminating motion, more degeneration

does not occur. All spinal fusions use some type of a bone graft, to help promote the fusion. The small pieces of bone are placed where disk or bone has been removed. Sometimes larger, solid pieces are used to provide immediate structural support to the vertebrae.

Bone graft sources.

Bone graft material is used to fill in the space left after a disk is removed. It is also placed along the sides of the vertebrae to assist the fusion. A bone graft is primarily used to stimulate bone healing. It increases bone production and helps the vertebrae heal together into a solid bone. The bone graft will come from autograft or from allograft. If an autograft is used, the bone is usually taken from a hip area, but only a small amount is used. Most autografts are harvested from the iliac crest of the hip.

Anterior Approach

Anterior cervical diskectomy and fusion.

During this procedure, the problematic disk and any additional bone spurs are removed, if necessary, then the spine is stabilized through spinal fusion. Typically, a plate with screws is added to the front of the spine for added stability. Plates and screws are used to provide stability and increase the rate of fusion.

Anterior cervical corpectomy and fusion.

This procedure is similar to diskectomy, except that instead of only the disk, more bone (one or more of the vertebrae) is also removed because the compression is caused by a significant bone spur. The difference between a corpectomy and diskectomy is the extent of bony removal. As in diskectomy, the spine is then stabilized through spinal fusion.

In some cases, both the disk and bone may be pressing on the spinal cord. In this situation, a combination of diskectomy and corpectomy may be performed.

Anterior cervical diskectomy and disk replacement.

During this procedure, the problematic disk and any additional bone spurs are removed, if necessary, just as in the anterior cervical diskectomy and fusion. Instead of placing bone, cages, plates, and screws, an artificial disk can be placed to preserve motion. Not every patient is a candidate for a disk replacement.

Posterior Approach

Posterior approaches for decompression include laminectomy (typically with a posterior fusion) and laminoplasty. These procedures are often also accompanied by spinal fusion.

Laminectomy.

In this procedure, the bony arch that forms the backside of the spinal canal (lamina) is removed along with any bone spurs and ligaments that are compressing the spinal cord. Laminectomy relieves pressure on the spinal cord by providing extra space for it to drift backward. Although laminectomy ensures complete decompression of the spinal cord, the procedure makes the bones less stable. For this reason, patients who undergo laminectomy frequently require spinal fusion with a bone graft and possibly screws and rods. Posterior laminectomy is often recommended for people who have very small spinal canals, enlarged or swollen soft tissues at the back of the spine, or problems in more than four spine segments (levels). In a patient with a kyphotic spine, the spinal cord will not float or shift backward — so a combined posterior and anterior approach is used to ensure the best outcome.

Laminoplasty.

In this alternative to laminectomy, instead of removing the bone, the lamina is thinned out on one side and then cut on the other side to create a hinge — much like a door. Using the hinge to open this bony area expands the space available for the spinal cord. Laminoplasty preserves from 30 to 50% of motion at the involved levels of the spine. This is a greater percentage than either laminectomy or anterior surgery. Since neck pain is often related to motion — and some motion still remains after the procedure — patients may still have neck pain after laminoplasty. Another disadvantage is that, in some cases, the lamina that is hinged can inadvertently close.

Combined Approach

Some patients will require combined anterior and posterior approaches to ensure the best outcome. This includes patients who have:

- Fixed or severe kyphosis (abnormal forward cervical spine curvature)
- Severe osteoporosis that has weakened the bone
- Multiple levels of involvement requiring supplemental stabilization

	Advantages	Disadvantages
Anterior Approach	Good relief of neck pain Spine is stabilized with fusion Restores alignment of the spine Direct removal of problem structures	Anterior approach complications (difficulty breathing, injury to esophagus Bone graft complications Loss of motion Swallowing difficulty or hoarseness

	Advantages	Disadvantages
Posterior Approach	Less motion loss (laminoplasty) May address more spine levels Avoids bone graft complications	Wound complications Inadequate decompression possible Cannot be used for kyphotic spines Late instability or deformity (laminoplasty) Inconsistent relief of neck pain (laminoplasty)

10. Commented review of own manuscripts

1. Kadanka Z Jr., Kadanka Z Sr., Skutil T, Vlckova E, Bednarik J. Walk and Run Test in Patients with Degenerative Compression of the Cervical Spinal Cord. *J Clin Med* 2021; 10(5): 927. doi.org/10.3390/jcm10050927. *IF 4,241 Q1*

Impaired gait is one of the cardinal symptoms of DCM and frequently its initial presentation. Quantitative gait analysis is therefore a promising objective tool in the disclosure of early cervical cord impairment in patients with degenerative cervical compression. The aim of this cross-sectional observational cohort study was to verify whether an objective and easily used walk and run test can detect early gait impairment in a practical proportion of NMDCCC patients and of revealing any correlation with severity of disability in DCM. The study group consisted of 45 DCM patients (median age 58 years), 126 NMDCCC subjects (59 years), and 100 healthy controls (HC) (55.5 years), all of whom performed a standardized 10-meter walk and run test. Walking/running time/velocity, number of steps and cadence of walking/running were recorded.

Significant differences were evident in all gait parameters among all the studied groups: analysis disclosed abnormalities in 66.7% of NMDCCC subjects. In comparison with healthy controls, NMDCCC patients took longer to complete the ten meters at a run or walking, moved at lower speeds and required higher numbers of steps. Abnormality within the walking parameters appeared in 46.8% of NMDCCC subjects. Time/velocity exhibited the highest sensitivity (45.2%), followed by number of steps (16.7%), and cadence (4.8%). Similarly, abnormality within the run parameters appeared in 57.1% of subjects, with the highest sensitivity exhibited by time/velocity (42.1%), followed by number of steps (32.5%) and cadence (19.0%).

The DCM group exhibited significantly more pronounced abnormalities in all walk/run parameters when compared with the NMDCCC group. These were apparent in 84.4% of the DCM group and correlated closely with disability as quantified by the mJOA scale. Abnormality of walk parameters appeared in 71.1% of DCM patients, with the highest sensitivity for time/velocity (68.9%), followed by number of steps (31.1%) and cadence (11.1%) All abnormalities were disclosed during investigation of time and number of steps (Table 2B). Similarly, abnormality of run parameters appeared in 79.4% of subjects, with the highest sensitivity for time/velocity (67.6%), followed by number of steps (64.7%) and

cadence (23.5%).

The main benefit of a standardized 10-meter walk/run test in comparison to already used scoring systems such as mJOA score is its objective and quantitative character and sensitivity to mild gait impairment due to myelopathy. It has the capacity to disclose locomotor abnormalities in the early stages of degenerative cervical cord compression that may be confirmed as another risk factor for progression into symptomatic DCM in future longitudinal studies. Furthermore, it may support the clinical diagnosis of DCM in the case of vague clinical myelopathic symptoms and signs and could be employed in routine clinical practice as a tool to evaluate the clinical course or effect of therapy in already diagnosed DCM.

A standardized 10-meter walk/run test has the capacity to disclose locomotion abnormalities in NMDCCC subjects who lack other clear myelopathic signs and may provide a means of classifying DCM patients according to their degree of disability.

Experimental work	Supervision	Manuscript	Research direction
70%	-	80%	30%

2. Kadanka Z Jr, Kadanka Z Sr., Jura R, Bednarik J. Vertigo in Patients with Degenerative Cervical Myelopathy. *J Clin Med* 2021; 10(11): 2496. doi:10.3390/jcm10112496. *IF 4,241 Q1*

Cervical vertigo (CV) represents a controversial entity, with a prevalence ranging from reported high frequency to negation of CV existence; The overall prevalence of CV is not known, because there are not generally accepted clinical or paraclinical tests for CV and therefore it is predominantly a diagnosis by exclusion. Based on these findings and discrepancies, we hypothesized that CV is over-diagnosed due to the absence of detailed diagnostic theory and practice in papers that reported high prevalence of CV. As degenerative cervical myelopathy (DCM) is the most severe symptomatic form of cervical spondylosis (Milligan et al. 2019), we used a well-defined cohort of DCM patients to verify our hypothesis. The aim of the paper was to assess the prevalence and cause of vertigo in these patients. Methods: A study included 38 DCM patients. The presence and character of vertigo was explored with a dedicated questionnaire. The cervical torsion test was used to verify the role of neck proprioceptors, and ultrasound examinations of vertebral arteries to assess the role of arteriosclerotic stenotic changes as hypothetical mechanisms of CV. All patients with vertigo underwent a detailed diagnostic work-up to investigate the cause of vertigo; Results: Symptoms of vertigo were described by 18 patients (47%). Causes of vertigo included: orthostatic dizziness in 8 (22%), hypertension in 5 (14%), benign paroxysmal positional vertigo in 4 (11%) and psychogenic dizziness in 1 patient (3%). No patient responded positively to the cervical torsion test or showed significant stenosis of vertebral arteries; Conclusions: Despite high prevalence of vertigo in patients with DCM, the aetiology in all cases could be attributed to causes outside cervical spine and related nerve structures, thus confirming assumption that the diagnosis of CV is overdiagnosed.

Experimental work	Supervision	Manuscript	Research direction
90%	-	70%	40%

3. Kadanka Z Jr, Adamova B, Kerkovsky M, Kadanka Z, Dusek L, Jurova B, Vlckova E, Bednarik J. Predictors of symptomatic myelopathy in degenerative cervical spinal cord compression. ***Brain Behav*** **2017; e00797. doi.org/10.1002/brb3.797.**
IF 2,219 Q3

A prospective observational follow-up study was performed in a cohort of 112 consecutive NMDCCC subjects (55 women and 57 men; median age 59 years, range 40–79 years), either asymptomatic (40 subjects) - volunteers in whom MRI signs of degenerative cervical cord compression had previously been detected during an epidemiological study focusing on the prevalence of degenerative cervical cord compression in the population of the province of South Moravia - or presenting with clinical signs and symptoms of cervical radiculopathy, moderate-to-severe chronic or intermittent axial cervical pain (72 subjects, who had completed a follow-up of at least 2 years (median duration 3 years) and who had been referred to the Department of Neurology between January 2012 and December 2013. Development of clinical signs of DCM as the main outcome was monitored and correlated with many demographics, clinical, electrophysiological and MRI parameters including DTI established at entry.

Clinical evidence of the first signs and symptoms of DCM was found in 15 patients (13.4%). Development of DCM was associated with several parameters, including the clinical (radiculopathy, prolonged gait, and run-time), electrophysiological (SSEP, MEP, and EMG signs of cervical cord dysfunction), and MRI (anteroposterior diameter of the cervical cord and cervical canal, cross-sectional area, compression ratio, type of compression, T2 hyperintensity). DTI parameters showed no significant predictive power. Multivariate analysis showed that radiculopathy, CSA $\leq$ 70.1 mm2, and compression ratio (CR) $\leq$ 0.4 were the only independent significant predictors for progression into symptomatic myelopathy.

In conclusion, previously and recently identified predictors of DCM development in NMDCCC individuals could help the decision-making process for preventive surgical decompression and, more importantly, in defining a subgroup of NMDCCC individuals at higher risk of DCM, among whom a randomized trial evaluating the benefit of such decompression would be justifiable.

Experimental work	Supervision	Manuscript	Research direction
60%	-	50%	20%

4. Horáková M, Horák T, Valošek J, Rohan T, Koriťáková E, Dostál M, Kočica J, Skutil T, Keřkovský M, Kadaňka Z Jr, Bednařík P, Svátková A, Hluštík P, Bednařík J. Semi-automated detection of cervical spinal cord compression with the Spinal Cord Toolbox. *Quant Imaging Med Surg* 2021; 12(4): 2261–2279. doi: 10.21037/qims-21-782.

IF 3,837 Q 2

A total of 205 participants were enrolled, 68 of them healthy controls (HC) and 137 participants with CSC compression, between May 2018 and May 2020. Healthy controls and CSC compression participants were recruited from a database of individuals at the spinal cord centre of a tertiary university hospital, all of whom had been examined in the course of parallel projects. CSC compression participants fulfilled the radiological imaging criteria for cervical cord compression. All participants with CSC compression were clinically examined by neurological procedures that focused on the detection of symptoms and signs of degenerative cervical myelopathy; this served to distinguish between the DCM and NMDCCC groups. The severity of disability and functional impairment was scored on the mJOA scale. The HCs exhibited no MRI signs of cervical cord compression, were free of any known musculoskeletal disorders and had no acute medical problems. Only participants with sufficient MRI data quality were further analysed, resulting in 66 HC, 102 NMDCCC and 16 DCM. MRI data from these 184 participants were submitted to semi-automated cervical spinal cord compression detection. From this pool of participants, 35 HCs and 30 CSC compression patients were used for a variability analysis of quantitative morphometric parameters. In this analysis, similar parameters than that output by SCT were also quantified manually. Each participant had already been scanned twice, once employing 3T MRI and once employing 1.5 T MRI, as part of parallel projects. For both measurements, multi-echo gradient echo (ME-GRE) sequences were used. Qualitative criteria for cervical spinal cord compression at each level were expert-rater defined as changes in spinal cord contour or shape at the level of an intervertebral disc on axial MRI scan compared with the midpoint level of neighbouring vertebrae. The reported level of spinal cord compression was confirmed on T2 TSE sagittal scan. Visual identification of spinal cord compression was performed consensually by two board-certified radiologists. Compression ratio was calculated as AP:RL diameter, which, together with CSA, reflected flattening of the spinal cord. Eccentricity was defined as the ratio of the focal distance over the major axis length of ellipse with the same second moments as the spinal cord, thus having similar interpretation

as CR. Solidity, which was used to assess indentation of the spinal cord, was expressed as the ratio of CSA to the area of the smallest convex polygon surrounding all positive pixels in the image (13). Torsion was calculated in three variants, based on the extracted orientation (∠).

Results: The parameters extracted using SCT exhibited lower variability than the experts' manual ratings in RL, AP, CR and CSA. Further, SCT enabled exact quantification of indentation and torsion.

This study demonstrated successful semi-automated detection of cervical spinal cord compression based on four SCT-derived morphometric parameters. Introduction of SCT into radiological evaluations may bring more reliable results to longitudinal and multicentre studies. The approach also saves a great deal of time, perhaps enabling its routine use in the assessment of the natural course of NMDCCC and mild DCM; the rate of progression may well become a valid predictor of whether the patient would benefit from surgery or not.

Experimental work	Supervision	Manuscript	Research direction
20%	-	10%	10%

5. Valosek J, Labounek R, Horak T, Horakova M, Bednarik P, Kerkovsky M, Kocica J, Rohan T, Lenglet R, Cohen-Adad J, Hlustik P, Vlckova E, Kadanka Z Jr., Bednarik J, Svatkova A. Diffusion magnetic resonance imaging reveals tract-specific microstructural correlates of electrophysiological impairments in non-myelopathic and myelopathic spinal cord compression. *Eur J Neurol*. 2021; 28(11): 3784-3797. doi.org/10.1111/ene.15027. *IF 6,089 Q1*

NMDCCC frequently occurs throughout aging and may progress to potentially irreversible DCM. Whereas standard clinical MRI and electrophysiological measures assess compression severity and neurological dysfunction, respectively, underlying microstructural deficits still must be established in NMDCCC and DCM patients. The study aims to establish tract-specific diffusion MRI markers of electrophysiological deficits to predict the progression of asymptomatic NMDCCC to symptomatic DCM. High-resolution 3 T diffusion MRI was acquired for 103 NMDCCC and 21 DCM patients compared to 60 healthy controls to reveal diffusion alterations and relationships between tract-specific diffusion metrics and corresponding electrophysiological measures and compression severity. Relationship between the degree of DCM disability, assessed by the modified Japanese Orthopaedic Association scale, and tract-specific microstructural changes in DCM patients was also explored. The study identified diffusion-derived abnormalities in the grey matter, dorsal and lateral tracts congruent with trans-synaptic degeneration and demyelination in chronic degenerative spinal cord compression with more profound alterations in DCM than NMDCCC. Diffusion metrics were affected in the C3-6 area as well as above the compression level at C3 with more profound rostral deficits in DCM than NMDCCC. Alterations in lateral motor and dorsal sensory tracts correlated with motor and sensory evoked potentials, respectively, whereas electromyography outcomes corresponded with gray matter microstructure. DCM disability corresponded with microstructure alteration in lateral columns.

Experimental work	Supervision	Manuscript	Research direction
30%	-	10%	10%

6. Horak T, Horakova M, Svatkova A, Kadanka Z Jr., Kudlicka P, Valosek J, Rohan T, Kerkovsky M, Vlckova E, Kadanka Z, Deelchand D.K., Henry P.G., Bednarik J, Bednarik P. *In vivo* Molecular Signatures of Cervical Spinal Cord Pathology in Degenerative Compression. *J Neurotrauma* 2021; 2999-3010. doi:10.1089/neu.2021.0151.
IF 5,269 Q1

DCM is a severe consequence of CSC compression. The non-myelopathic stage of compression (NMDCCC) is highly prevalent and often progresses to disabling DCM. This study aims to disclose markers of progressive neurochemical alterations in NMDCCC and DCM by utilizing an approach based on state-of-the-art proton magnetic resonance spectroscopy (1H-MRS). Proton-MRS data were prospectively acquired from 73 participants with CSC compression and 47 healthy controls (HC). MRS voxel was centred at C2 level. Compression-affected participants were clinically categorized as NMDCCC and DCM, radiologically as mild (MC) or severe (SCo) compression. CSC volumes and neurochemical concentrations were compared between cohorts (HC vs. NMDCCC vs. DCM and HC vs. MC vs. SCo) with general linear models adjusted for age and height ($p< 0.05$) and correlated to stenosis severity, electrophysiology, and myelopathy symptoms ($p< 0.05$). While ratio of total creatine (tCr) to total N-acetylaspartate (tNAA) increased in NMDCCC (+11%) and in DCM (+26%) and SCo (+21%), Myo-inositol/tNAA, glutamate+glutamine/tNAA and volumes changed only in DCM (+20%, +73%, and –14%) and SC (+12%, +46%, and – 8%, respectively) relative to HC. Both tCr/tNAA and myo-inositol/tNAA correlated with compression severity and volume ($–0.376<r<-0.256$). Myo-inositol/tNAA correlated with myelopathy symptoms, whereas CSC volume did not. Shortecho 1H-MRS provided neurochemical signatures of CSC impairment that reflected compression severity and clinical significance. While volumetry only reflected clinically manifest myelopathy, MRS detected neurochemical changes already before the onset of myelopathy symptoms.

This study revealed neurochemical changes in CSC above the compression level in subjects with radiological signs of compression and clinical myelopathy and, for the first time, in non-myelopathic participants as well. State-of-the-art MRS demonstrated sufficient sensitivity to reveal early changes in non-myelopathic patients and thus might allow the stratification of non-myelopathic subjects. The current work warrants longitudinal studies assessing their risk of myelopathy development. Although MRS markers and the level of

spinal atrophy strongly reflected the severity of stenosis, the volumes were less sensitive to clinical status than MRS.

Experimental work	Supervision	Manuscript	Research direction
30%	20%	20%	10%

7. Kovalova I, Kerkovsky M, Kadanka Z, Kadanka Z Jr, Nemec M, Jurova B, Dusek L, Jarkovsky, Bednarik J. Prevalence and Imaging Characteristics of Nonmyelopathic and Myelopathic Spondylotic Cervical Cord Compression. *Spine* 2016; 41 (24): 1908-1916. doi:10.1097/BRS.0000000000001842. *IF 2,499 Q2*

The aim of the cross-sectional population-based observational study was to estimate the prevalence of NMDCCC and degenerative cervical myelopathy in a population older than 40 years and to evaluate the MRI characteristics of these conditions. The study was performed in a cohort of 183 randomly recruited volunteers; 93 women, 90 men, median age 66 years, range 40-80 years, underwent MRI examination of the cervical spine and spinal cord on a 1.5 T device using conventional sequences from disc levels C2/C3 to C6/C7. The imaging criterion for cervical cord compression was defined as a change in spinal cord contour at the level of an intervertebral disc on axial or sagittal MRI scan.

MRI signs of CSC were found in 108 individuals (59.0%; 95% CI: 51.5%-66.2%); their numbers increased with age from 31.6% in the fifth decade to 66.8% in the eighth. Clinical signs of symptomatic DCM were found in two cases (1.1%), and 75 cases (41.0%) were without compression. An AP cervical canal diameter at the level of intervertebral disc of less than 9.9 mm was associated with the highest probability of NMDCCC-odds ratio (OR)=32.5, followed by a compression ratio of ≤0.5: OR=11.1.

The main benefit of the study is that the prevalence of NMDCCC in a population older than 40 years is higher than previously reported and increases with age. An AP cervical canal diameter at the level of intervertebral disc and compression ratio had the highest capacity to discriminate between subjects with and without asymptomatic compression, and their cut-off values could be used to objectify criteria for cervical cord compression.

Experimental work	Supervision	Manuscript	Research direction
20%	10%	20%	10%

8. Bednarık J, Sladkova D, Kadanka Z, Dusek L, Kerkovsky M, Vohanka S, Novotny O, Urbanek I, Nemec M. Are subjects with spondylotic cervical cord encroachment at increased risk of cervical spinal cord injury after minor trauma? *J Neurol Neurosurg Psychiatry* 2011; 82(7): 779-81. *IF 4,764 Q1*

The aim of the study was to analyse the risk of symptomatic myelopathy after minor trauma in patients with NMDCCC. In a cohort of 199 patients with NMDCCC, previously followed prospectively in a study investigating progression into symptomatic myelopathy, the authors looked retrospectively for traumatic episodes that may have involved injury to the cervical spine. A questionnaire and data file analysis were employed to highlight whatever hypothetical relationship might emerge with the development of symptomatic myelopathy. Fourteen traumatic episodes during a follow-up of 44 months (median) were recorded in our group (who had been instructed to avoid risky activities), with no significant association with the development of symptomatic myelopathy (found in 45 cases). Only three minor traumatic events without fracture of the cervical spine were found among the symptomatic myelopathy cases, with no chronological relationship between trauma and myelopathy. Furthermore, 56 traumatic spinal cord events were found before the diagnosis of cervical cord encroachment was established, with no correlation to either type of compression (discogenic vs osteophytic).

In conclusion, the risk of spinal cord injury after minor trauma of the cervical spine in patients with NMDCCC appeared to be low in our cohort, provided risky activities in these individuals are restricted. Implementation of preventive surgical decompression surgery into clinical practice in these individuals should be postponed until better-designed studies provide proof enough for it to take precedence over a conservative approach.

Experimental work	Supervision	Manuscript	Research direction
20%		20%	20%

9. Keřkovský M, Bednařík J, Jurová B, Dušek L, Kadaňka Z, Kadaňka Z Jr, Němec M, Kovaľová I, Šprláková-Puková A, Mechl M. Spinal Cord MR Diffusion Properties in Patients with Degenerative Cervical Cord Compression. *J Neuroimaging* 2017; 27(1): 149-157. doi:10.1111/jon.12372. *IF 1,953 Q3*

DTI has previously been used as a biomarker of myelopathy in patients with NMDCC. However, many factors may affect the diffusion properties of the spinal cord. This prospective study seeks to identify sources of variability in spinal cord DTI parameters in both NMDCCC patients and healthy subjects.

The study group included 130 patients with NMDCCC confirmed by MRI and 71 control subjects without signs of NMDCCC. DTI data of the cervical spine were acquired in all subjects. FA and ADC values were measured at different levels of the spinal cord (SCLs). Statistical data analysis was then used to determine diffusion parameters in terms of age, sex, SCL, and spinal cord compression.

Significant variations in FA and ADC values emerged when several spinal cord levels were mutually compared in the control group. FA values correlated significantly with age in the NMDCCC group and sex had a significant influence on ADC values in both groups. In conclusion, the two diffusion parameters in the NMDCCC group differed significantly between patients with clinical signs of mild-to-moderate myelopathy compared with asymptomatic patients and correlated with measurements of spinal canal morphology. These findings may be important to the interpretation of DTI measurements in individual patients.

Experimental work	Supervision	Manuscript	Research direction
20%	-	10%	-

10. Kadaňka Z. Jr., Adamová B. Flekční cervikální myelopatie (Hirayamova choroba)-skutečnost, nebo mýtus? Dvě kazuistiky. [Flexion Cervical Myelopathy (Hirayama Disease) – Reality or Myth? Two Case Reports]. ***Cesk Slov Neurol N*** **2014; 77/110(3): 362-367.** *IF 0,157 Q4*

Cervical flexion myelopathy (Hirayama disease, HD) is a rare disease of the cervical spine. This disease was described first by, and named after, Hirayama in 1959 and most cases of this disease have been reported from Japan and India. It is thought to be a kind of cervical myelopathy related to flexion movements of the neck. It is characterized by progressive muscular weakness and atrophy of the distal upper limb (brachioradialis muscle is spared), predominantly affecting male adolescents between 15 and 25 years of age. There is no sensory or deep tendon reflexes involvement. The disease progresses initially, but spontaneous arrest is known to follow several years after the onset, unlike motor neurone disease with which it is commonly confused. HD is characterized by focal ischaemic changes in the anterior horn cells of the lower cervical cord that result in amyotrophy, which is usually unilateral but may also be bilateral. The precise cause of this disorder is still unknown. An assumption of imbalanced growth between the patient's vertebral column and spinal canal contents has been postulated till now. The key to diagnosing this disease during MRI scanning is to obtain images when the neck is flexed. We describe the characteristic findings of flexion MRI suggestive of Hirayama disease. Cervical MRI images show local cord atrophy; T1-weighted images show widened lateral epidural space on flexion that is hyperintense on T2-weighted, especially contrast-enhanced, images. We present two patients with clinical symptoms of this disease and summarize facts about the diagnosis and treatment of Hirayama disease. Although HD is a self-limiting disorder, early diagnosis is necessary because a cervical collar, by preventing neck flexion, may arrest the progression of the disorder. HD should be distinguished from multiple motor neuropathies when the amyotrophy is distally in the upper limb, and in this disease, there is evidence of conduction block in motor nerves, and high serum titers of anti-GM1 ganglioside antibodies.

In conclusion, HD is a rare type of cervical myelopathy related to flexion of the neck characterized by progressive muscular weakness and atrophy of the distal upper limbs most frequently seen in young males.

Experimental work	Supervision	Manuscript	Research direction
80%	30%	70%	80%

11. Kadaňka Z Jr., Hanák J, Gál B. Maligní tumor z pochvy periferního nervu v oblasti cervikálního plexu- kazuistika. [Malignant Peripheral Nerve Sheath Tumour of Cervical Plexus – a Case Report]. *Cesk Slov Neurol N* 2013; 76/109(6): 751-755. *IF 0,159 Q4*

Malignant peripheral nerve sheath tumours (MPNST) are uncommon, biologically aggressive soft tissue sarcomas of neural origin. They are quite rare, especially in the head and neck. They are often asymptomatic, but the presentation of MPNSTs can vary greatly, making diagnosis challenging. For example, patients with intradural spinal MPNSTs usually present with limb pain, motor deficit in upper extremities, (even with progressive central quadriparesis), sensory loss, and bladder/bowel deficits and can resemble degenerative cervical myelopathy.

The prognosis for patients with MPNST is relatively poor, with recurrence rates estimated to range from 20 to 40% and 5-year survival rates ranging from 34 to 52%. A number of factors are known to influence prognosis including tumour size, location, and histological grade, whether removal is en bloc (or not), resection margin, the presence of recurrence, and metastasis. We present the case of a 29-year old patient with neurofibromatosis type 1 with malignant tumour of the cervical plexus. A small resistance in the upper mediastinum was diagnosed (ganglioneurinoma) in 2005 and treated surgically (total exstirpation). A small infiltration in the right supraclavicular area occurred five years later and was also managed surgically (debulking) – histologically MPNST. There was a relapse of this tumour in the same area in 2011; this was treated by en bloc resection, followed by chemotherapy. At present, the patient is in a good clinical status, with no neurological deficit.

MPNSTs of the cervical plexus are very rare. They are usually present with limb pain, motor deficit in upper extremities, (even with progressive central quadriparesis), sensory loss, and bladder/bowel deficits and can resemble DCM.

Experimental work	Supervision	Manuscript	Research direction
60%	90%	80%	70%

12. Kovalová I, Bednařík J, Keřkovský M, Adamová B, Kadaňka Z Jr. Asymptomatická spondylogenní komprese krční míchy. [Asymptomatic Spondylotic Cervical Cord Compression]. *Cesk Slov Neurol N* 2015; 78/111(1): 24-33. doi:10.14735/amcsnn201524. *IF 0,209 Q4*

Degenerative changes in the cervical spine, mainly spondylosis, that lead to cervical spinal canal stenosis, are part of the normal ageing process and are almost omnipresent in the elderly. Cervical spinal stenosis may lead to cervical cord compression and represents the most important mechanical factor in the pathophysiology of cervical spondylotic myelopathy, gwhich along with complex pathophysiological mechanisms leads to a variety of myelopathy symptoms. Medullar tissue is, however, rather resistant to compression and development of symptomatic myelopathy occurs only when higher degree stenosis is present and in combination with other pathophysiological factors, mainly dynamic compression, and trauma. NMDCCC is a quite frequent finding in an older population and found in 50% of randomly examined individuals over the age of sixty. However, the reliability of methods used to verify and quantify cervical stenosis and cervical cord compression is low; clear predictors of the development of symptomatic myelopathy and related indications of potential preventive surgical decompression in NMDCCC have not been determined yet. The overview discusses the most frequently used methods to establish cervical spinal stenosis and cervical cord compression using imaging methods. Radiogram and especially computed tomography are important for verification of cervical spinal stenosis, while MRI is a preferable method to detect cervical cord compression. The cross-sectional spinal cord area and T2 MRI spinal cord hyperintensity are among the parameters considered to be the most closely correlated with clinical manifestation of spinal cord compression. Among newly introduced imaging modalities, MRI diffusion tensor imaging seems to be the most promising one. The presence of symptomatic radiculopathy and abnormality of motor and somatosensory evoked potentials are among generally accepted predictors of symptomatic myelopathy. The importance of imaging methods as predictors of symptomatic myelopathy development, as well as the benefits of preventive surgical decompression in NMDCCC individuals with high risk of developing symptomatic myelopathy, is to be established in future studies.

Experimental work	Supervision	Manuscript	Research direction
20%	80%	30%	40%

13. Kadaňka Z. Jr., Bednařík J. Cervikální vertigo- fikce či realita? [Cervical vertigo – fiction or reality?]. *Cesk Slov Neurol N* 2018; 81/114(5): 1–6.doi: 10.14735/amcsnn2018521. *IF 0,355 Q4*

Cervical vertigo (CV) has long been a controversial entity, a fact which is generally accepted in practice by the medical community. A diagnosis of CV, however, is made too often by many physicians, largely because the simultaneous occurrence of vertigo and cervical spondylosis is very common. In this review we present a summary of contemporary knowledge of the scientific biography of cervical vertigo, its possible aetiology, diagnosis, and treatment. The neck contains mechanisms directly involved in balance control, cardiovascular control (carotid bodies), and purely vascular structures (carotid and vertebral arteries). Neck movements are also invariably associated with head movements. Thus, experiencing unsteadiness or vertigo associated with neck movements could be due to a disorder in the vestibular, visual, vascular, or neurovascular system. Several explanations of the aetiology of cervical vertigo have been published. Disturbed cervical proprioception is suggested by what is probably the most-cited study. A further hypothesis is that CV may arise out of impaired blood circulation in the vertebrobasilar arteries. Cervicogenic dizziness often occurs because of whiplash or head injury and is often seen in conjunction with brain injury or injury to the inner ear. Some authors suggest that migraine-associated vertigo may explain why some patients suffering from cervical pain have vertigo while others do not. In conclusion, CV is overdiagnosed and there is still no laboratory or clinical test to confirm the diagnosis, while none of the possible theories provide fully convincing evidence of a cervical mechanism. Appropriate management is difficult and mostly empirical. All clinical studies on cervical vertigo to date have three weak points: 1. the inability to confirm the diagnosis, 2. the lack of a specific laboratory test, and 3. the unexplained discrepancy between patients with severe neck pain without vertigo and patients complaining of disabling vertigo with moderate neck pain. The debate on the relevance and mechanism of cervical vertigo is more of theoretical interest than of practical relevance.

Experimental work	Supervision	Manuscript	Research direction
90%	70%	90%	-

14. Kadaňka Z Jr., Horák T, Bednařík J. Současný management pacientů s degenerativní kompresí krční míchy. [Current management of patients with degenerative cervical spine compression]. ***Cesk Slov Neurol N*** **2019; 82/115(6): 616-620. doi:10.14735/amcsnn2019632.** *IF 0,377 Q4*

DCM is the most serious consequence of CSC stenosis and NMDCCC. The spinal cord, however, is quite resistant to mechanical compression and subjects with cervical cord compression thus may remain completely asymptomatic (non-myelopathic degenerative cervical cord compression - NMDCCC), and prevalence of this condition in the older population is very high. In patients with moderate and severe DCM, surgical intervention is strongly recommended. However, in patients with mild DCM and NMDCCC, there is no clear, evidence-based agreement on the optimum management and treatment algorithm. It depends upon the development or identification of sensitive and specific clinical, radiological, and/or electrophysiological markers that could reliably predict progression to symptomatic DCM. Currently, many predictors of such involvement have been identified and this has led some surgeons to recommend decompression surgery in these high-risk patients. However, further studies are required to refine our understanding of the frequency, timing, and predictors of myelopathy development in NMDCCC patients. Nevertheless, there are some methodological and ethical aspects that make multicentre randomised studies in NMDCCC and mild DCM patients difficult to realize.

Experimental work	Supervision	Manuscript	Research direction
90%	70%	90%	70%

15. Kadaňka Z Jr., Bednařík J. Klinické syndromy z oblasti cervikálního plexu [Cervical plexus lesions in clinical practice]. ***Cesk Slov Neurol N*** **2019; 82115(6): 632-636. doi:10.14735/amcsnn2019616.** *IF 0,377 Q4*

Cervical plexus lesions are rare and may be overlooked by neurologists. However, several new clinical syndromes centred upon this region have been published in recent years. Herein we present an overview of some possible aetiologies of cervical plexus lesions, their diagnosis and treatment. The most common condition is occipital neuralgia (ON), largely considered idiopathic. It is defined as unilateral or bilateral paroxysmal, shooting, or stabbing pain in the posterior part of the scalp, following the distribution of the greater occipital nerve and/or the lesser occipital nerve. A wide range of treatment options for ON are available. The initial focus should be placed on conservative measures, including rest, hot or cold compresses, postural adjustment, and physical therapy with the aim of reducing neuralgic and muscular pain. We report other rare causes of neuralgia of the head as well, such as considerable auricular neuralgia and red ear syndrome, and neuralgias of Jacobson's and Arnold's nerves (branches of the glossopharyngeal and vagus nerves). Glossopharyngeal neuralgia, also known as vagal glossopharyngeal neuralgia, is characterized by intermittent episodes of shooting sharp pain in the jaw, throat, tongue, and ear that fall within the sensory distribution of the glossopharyngeal nerve. Pharmacotherapy with anticonvulsants, tricyclic antidepressants, and anti-inflammatory agents are effective in relieving paroxysmal pain in most glossopharyngeal neuralgia patients.

Lesions affecting the roots of the cervical plexus can cause syndromes mimicking those typical for degenerative cervical spine diseases. The C3-C4 disc space is the most likely to be involved, but pressure on the C5 root can also produce facial, auricular, or retroauricular pain.

Experimental work	Supervision	Manuscript	Research direction
70%	80%	90%	80%

16. Kadaňka Z Jr, Bednařík J. Degenerativní cervikální myelopatie – klinický obraz, diagnostika a strategie léčby. [Degenerative cervical myelopathy- clinical manifestation, diagnosis and practical management]. ***Neurol Praxi*** **2023; 24(1): 12-16. doi: 10.36290/neu.2022.061.**

We present a contemporary approach to the diagnosis and optimal strategy of treatment in patients with DCM. DCM is a chronic progressive disease of the cervical spinal cord. Osteoarthritic degeneration (spondylosis, facet hypertrophy, and degenerative disc disease), ligament changes (ossification of the posterior longitudinal ligament, hypertrophy of the ligamentum flavum) may lead to spinal cord compression and result in neurological deficits. It is manifested as clumsy hands syndrome, gait impairment, and bladder problems. The latest clinical guidelines recommend surgery for patients with moderate and severe DCM. For patients with mild DCM (or non-myelopathic patients with radiculopathy), the guidelines suggest that either surgery or a supervised trial of structured rehabilitation. The nonoperative treatment with serial clinical follow-up should be reserved for asymptomatic patients with imaging evidence of cervical spinal cord compression.

Experimental work	Supervision	Manuscript	Research direction
80%	90%	90%	70%

11. Literature review

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12. List of abbreviations

ACDF- anterior cervical discectomy and fusion

ACIF- anterior cervical interbody fusion

ADC- apparent diffusion coefficient

AF- anulus fibrosus

ALS- amyotrophic lateral stenosis

AP - anteroposterior

ASA- anterior spinal arteries

ASCCC- asymptomatic spondylotic cervical cord compression

BDNF- brain- derived neurotrophic factor

BMI- body mass index

BMP-2- bone morphogenetic protein-2

BSCB- blood-spinal cord barrier

CHEPs- contact heat evoked potentials

CNS- central nervous system

CS -cervical stenosis

CSA- cross section area

CSC- cervical spinal cord

CSF- cerebrospinal fluid

CR- compression ratio

CV- cervical vertigo

CT- computed tomography

DCM- degenerative cervical myelopathy

dMRI- diffusion MRI

DNA- deoxyribonucleic acid

DTI- diffusion tensor imaging

EMG - electromyography

FA- fractional anisotropy

GAP- growth associated protein

HC- healthy controls

HD- Hirayama disease

HTLV- human T-lymphotropic virus

IL- interleukin

IVD- intervertebral disc

IVIM- intravoxel incoherent motion

LMN- lower motor neuron

MC- mild compression

ME-GRE- multi-echo gradient echo

MEP- motor-evoked potentials

mJOA - modified Japanese orthopaedic association

MMPs- matrix metaloproteinases

MPNST- malignant peripheral nerve sheath tumour

MRI- magnetic resonance imaging

MRS- magnetic resonance spectroscopy

MSCC- maximum cervical spinal cord compression

MUAPs- motor unit action potentials

NAA- N-acetyl-aspartate

NDI- neck disability index

NF- neurotrophic factors

NMDCCC- non-myelopathic degenerative cervical cord compression

NP- nucleus pulposus

NT-3- neurotrophin 3

ON- occipital neuralgia

OPLL -ossification of posterior longitudinal ligament

OR- odds ratio

PLL- posterior longitudinal ligament

RL- right-left

RR- relative risk

SC- spinal cord

SCA- cross-sectional area of the cervical cord

SCC- spinal cord compression

SCI- spinal cord injury

SCL- spinal cord level

SCo- severe compression

SCT- spinal cord toolbgox

SEP- somatosensory evoked potentials

T1-w- T1-weighted

T2-w- T2-weighted

tCho - total choline

tCr- total creatin

TGF-β1- tumour growth factor beta 1

tNAA- total N-acetylaspartate

TNF- tumour necrosis factor

TUNEL- terminal deoxynucleotidyltransferase-mediated deoxyuridine triphosphate nick-end labelling

13. List of author's publications

First or corresponding author, impacted journals

1. Kadanka Z Jr., Kadanka Z Sr., Skutil T, Vlckova E, Bednarik J. Walk and Run Test in Patients with Degenerative Compression of the Cervical Spinal Cord. *J Clin Med* 2021; 10(5): 927. doi.org/10.3390/jcm10050927. *IF 4,964 Q1 Number of citations WoS 2*

2. Kadanka Z Jr, Kadanka Z Sr., Jura R, Bednarik J. Vertigo in Patients with Degenerative Cervical Myelopathy. *J Clin Med* 2021; 10(11): 2496. doi:10.3390/jcm10112496. *IF 4,964 Q1 Number of citations WoS 4*

3. Kadanka Z Jr, Adamova B, Kerkovsky M, Kadanka Z, Dusek L, Jurova B, Vlckova E, Bednarik J. Predictors of symptomatic myelopathy in degenerative cervical spinal cord compression. *Brain Behav* 2017; e00797. doi.org/10.1002/brb3.797. *IF 2,157 Q3 Number of citations WoS 37*

4. Kadaňka Z Jr. Pudendal neuralgia- a case report. Cesk Slov Neurol N 2010, 73/106(5): 555-558. *IF 0, 393 Q4 Number of citations WoS 0*

5. Kadaňka Z Jr. Electrophysiological Examination of the Pelvic Floor. Cesk Slov Neurol N 2013; 76/109(2): 155-161. *IF 0,159 Q4 Number of citations WoS 2*

6. Kadaňka Z Jr., Hanák J, Gál B. Maligní tumor z pochvy periferního nervu v oblasti cervikálního plexu- kazuistika. [Malignant Peripheral Nerve Sheath Tumour of Cervical Plexus – a Case Report]. *Cesk Slov Neurol N* 2013; 76/109(6): 751-755. *IF 0,159 Q4 Number of citations WoS 2*

7. Kadaňka Z. Jr., Adamová B. Flekční cervikální myelopatie (Hirayamova choroba)- skutečnost, nebo mýtus? Dvě kazuistiky. [Flexion Cervical Myelopathy (Hirayama Disease) – Reality or Myth? Two Case Reports]. *Cesk Slov Neurol N* 2014; 77/110(3): 362-367. *IF 0,165 Q4 Number of citations WoS 0*

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9. Gál B, Kadaňka Z Jr, Hložková T, Hanák J, Hložek J. Cesk Slov Neurol N 2015; 78/111(4): 463-467. Syndrom Freyové (aurikulotemporální syndrom) po parotidektomii a jeho prevence. [Frey's Syndrome (Auriculotemporal Syndrome) after Parotidectomy and its Prevention]. *IF 0,209 Q4 Number of citations WoS 0 Corresponding author*

10. Kadaňka Z Jr. H- reflex- jeho role v neurofyziologii a klinice [H-reflex and Its Role in EMG Laboratory and Clinical Practice]. Cesk Slov Neurol N 2017; 80/113(6): 641-646. doi: 10.14735/amcsnn2017641 *IF 0,508 Q4 Number of citations WoS 0*

11. Kadaňka Z Jr. Statiny a jejich vliv na periferní nervový systém. [Statins and their effects on the peripheral nervous system]. Cesk Slov Neurol N 2018; 81/114(1): 98-99. doi: 10.14735/amcsnn201898 *IF 0,355 Q4 Number of citations WoS 0*

12. Kadaňka Z. Jr., Bednařík J. Cervikální vertigo- fikce či realita? [Cervical vertigo – fiction or reality?]. *Cesk Slov Neurol N* 2018; 81/114(5): 1–6.doi:10.14735/amcsnn2018521. *IF 0,355 Q4 Number of citations WoS 0*

13. Gál B., Rottenberg J.,' Talach T.,' Veselý M.,' Kadaňka Z. Jr., Kadaňková E, Horová I., Budíková M., Kostřica R., Hložek J. Efektivita jednostranné kochleární implantace u dospělých pacientů s těžkou poruchou sluchu. [The efficacy of cochlear implantation in adult patients with profound hearing loss]. Cesk Slov Neurol N 2018; 81/ 114(6): 1– 5. *IF 0,355 Q4 Number of citations WoS 1 Corresponding author*

14. Kadaňková E, Kadaňka Z Jr., Lejska M. Postižení sluchu po spinální anestezii. [Hearing loss after spinal anaesthesia]. Cesk Slov Neurol N 2019;82/115(4):456-457 *IF 0,377 Q4 Number of citations WoS 0 Corresponding author*

15. Kadaňka Z Jr., Horák T, Bednařík J. Současný management pacientů s degenerativní kompresí krční míchy. [Current management of patients with degenerative cervical spine compression]. *Cesk Slov Neurol N* 2019; 82/115(6): 616-620. doi:10.14735/amcsnn2019632. *IF 0,377 Q4 Number of citations WoS 0*

16. Kadaňka Z Jr., Bednařík J. Klinické syndromy z oblasti cervikálního plexu [Cervical plexus lesions in clinical practise]. *Cesk Slov Neurol N* 2019; 82115(6): 632-636. doi:10.14735/amcsnn2019616. *IF 0,377 Q4 Number of citations WoS 0*

17. Kadaňka Z Jr., Kadaňka Z, Smrčka M, Bednařík J. Je jasné, kdy operovat výhřez meziobratlové ploténky? [Is it evident when to make a surgery for lumbar disc herniation?] Cesk Slov Neurol N 2020; 83/116(4): 360-363 *IF 0,350 Q4 Number of citations WoS 2*

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Dissertation in the field of neuroscience

Degenerative cervical spinal cord compression: diagnostics, pathophysiology, clinical manifestation and practical management. Brno, 2021.

14. Conclusions of the habilitation thesis

This habilitation thesis concerns the topic of degenerative cervical myelopathy (DCM). DCM is the leading cause of myelopathy in subjects above 55 years old and the major cause of spasticity acquired in the aged population. Regarding the clinical onset, a large number of patients with DCM are asymptomatic at first, but once the symptoms start, most present in a stepwise manner, with periods of stability of the symptoms, alternating with worsening. Clinically, the most characteristic symptoms of DCM are instability of gait, loss of fine motor control of the upper limbs, weakness, and neck pain with reduced range of motion in this region and urinary emergency. Mostly, the diagnosis of DCM is based on the signals observed in the clinical examination supported by radiological studies showing spinal cord compression. However, there is wide variation in diagnosis and symptoms presented by patients suffering criteria.

We have presented here several studies which could, in our opinion, be useful in the diagnosis and management of patients with DCM.

The aim of the first study was to verify whether an objective and easily used walk and run test can detect early gait impairment in a practical proportion of NMDCCC patients and reveal any correlation with severity of disability in DCM. We have proved that a standardized 10-meter walk/run test has the capacity to disclose locomotion abnormalities in NMDCCC subjects who lack other clear myelopathic signs and may provide a means of classifying DCM patients according to their degree of disability. This may be confirmed as another risk factor for progression into symptomatic DCM in future longitudinal studies.

The second (prospective observational follow-up) study targeted predictors of neurological dysfunction in the non-myelopathic patient with degenerative cervical spinal cord compression. Multivariate analysis showed that radiculopathy, CSA $\leq$ 70.1 mm2, and compression ratio (CR) $\leq$ 0.4 were the only independent significant predictors for progression into symptomatic myelopathy. It could help the decision-making process for preventive surgical decompression and, more importantly, in defining a subgroup of NMDCCC individuals at higher risk of DCM, among whom a randomized trial evaluating the benefit of such decompression would be justifiable.

The third study explored the presence and character of vertigo in patients with DCM, because

so-called “cervical vertigo” (CV) represents a very controversial entity. This term is used (and probably overused) very often in clinical practice. We have found that, despite a high prevalence of vertigo in patients with DCM, the aetiology could be (in all of them) attributed to causes outside cervical spine and related nerve structures. Clinicians should seek other (often treatable) aetiologies of vertigo in DCM patients, thus avoiding the possibility of overlooking other serious disease.

Four papers presenting new MRI techniques (MR spectroscopy, diffusion tensor imaging and high-resolution 3 T diffusion MRI, Semi-automated detection of cervical spinal cord compression with the Spinal Cord Toolbox) are included in the thesis. These techniques demonstrated sufficient sensitivity to reveal early changes in the cerebral spinal cord, and for the first time, even in NMDCCC participants. This might allow the stratification of non-myelopathic subjects in the future. Introduction of these techniques into radiological evaluations may bring more reliable results to longitudinal and multicentre studies. The approach also saves a great deal of time, perhaps enabling its routine use in the assessment of the natural course of NMDCCC and mild DCM; the rate of progression may well become a valid predictor of whether the patient would benefit from surgery or not.

The habilitation thesis contains six reviews as well (“Asymptomatic Spondylotic Cervical Cord Compression”, “Cervical vertigo – fiction or reality?”, “Management of patients with degenerative spondylotic cervical spine compression”, “Cervical plexus lesions in clinical praxis“, “DCM - clinical manifestation, diagnosis and practical management”, “Asymptomatic Spondylotic Cervical Cord Compression”). One cross-sectional population-based observational study was done to estimate the prevalence of NMDCCC and DCM in a population older than 40 years and to evaluate the MRI characteristics of these conditions (“Prevalence and imaging characteristics of asymptomatic and symptomatic spondylotic cervical spinal cord compression”). Two papers concerning differential diagnosis of degenerative cervical spinal cord compression were added too (“Flexion Cervical Myelopathy (Hirayama Disease) – Reality or Myth?”, “Malignant Peripheral Nerve Sheath Tumour of Cervical Plexus – a Case Report”).

We hope that our results can help clinicians to improve the diagnostic process in DCM patients. We propose that our findings will have consequences for surgical decision-making in early or mild cases of DCM, and that these findings will help to respond to continuous debate regarding the benefits vs. risks of surgical intervention. Determination of predictors of neurological dysfunction in the non-myelopathic patient with degenerative cervical spinal

cord compression, and the application of advanced MRI techniques in the CSC, are both extremely challenging.

15. Annexes

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Article

Walk and Run Test in Patients with Degenerative Compression of the Cervical Spinal Cord

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Abstract: Impaired gait is one of the cardinal symptoms of degenerative cervical myelopathy (DCM) and frequently its initial presentation. Quantitative gait analysis is therefore a promising objective tool in the disclosure of early cervical cord impairment in patients with degenerative cervical compression. The aim of this cross-sectional observational cohort study was to verify whether an objective and easily-used walk and run test is capable of detecting early gait impairment in a practical proportion of non-myelopathic degenerative cervical cord compression (NMDCC) patients and of revealing any correlation with severity of disability in DCM. The study group consisted of 45 DCM patients (median age 58 years), 126 NMDCC subjects (59 years), and 100 healthy controls (HC) (55.5 years), all of whom performed a standardized 10-m walk and run test. Walking/running time/velocity, number of steps and cadence of walking/running were recorded; analysis disclosed abnormalities in 66.7% of NMDCC subjects. The DCM group exhibited significantly more pronounced abnormalities in all walk/run parameters when compared with the NMDCC group. These were apparent in 84.4% of the DCM group and correlated closely with disability as quantified by the modified Japanese Orthopaedic Association scale. A standardized 10-m walk/run test has the capacity to disclose locomotion abnormalities in NMDCC subjects who lack other clear myelopathic signs and may provide a means of classifying DCM patients according to their degree of disability.

Keywords: degenerative cervical myelopathy; non-myelopathic degenerative cervical cord compression; cervical spinal cord compression; 10-m walk rest; 10-m run test

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1. Introduction

Degenerative cervical myelopathy (DCM) is a neurological condition resulting from spinal cord compression arising out of degenerative narrowing of the cervical spinal canal. It constitutes the leading cause of spinal cord dysfunction in adults worldwide [1,2]. Pathological changes include osteophytosis, intervertebral disc bulging, and ligament ossification and hypertrophy, all leading to static and dynamic injury to the spinal cord [3,4]. Early diagnosis and management of DCM are vital to the provision of appropriate care for those living with this condition. Accurate diagnosis requires agreement between clinical and imaging findings. When DCM is suspected, a detailed history and physical examination should be undertaken first [2]. Common presenting symptoms include: numb and/or clumsy hand(s), bilateral arm pain and/or paresthesias, gait disturbance, Lhermitte's sign, and urinary urgency, frequency, and/or incontinence. Objective physical signs of myelopathy include upper motor neuron signs in the upper and/or lower limbs (for example, hyper-reflexia/clonus, pyramidal Hoffmann's, Trömner's or Babinski's signs, spasticity or spastic paresis of any of the extremities—most frequently spastic lower paraparesis), flaccid paresis of one or both upper extremities, atrophy of intrinsic hand muscles, sensory involvement in various distributions in upper or lower extremities, and gait ataxia with positive Romberg sign [5–9].

Some of the objective signs of myelopathy required for the diagnosis of DCM, detected in the course of a detailed, although largely qualitative clinical neurological examination, may serve as comparatively late indicators of cervical cord impairment. Further, degenerative compression of the cervical cord may remain free of any of the symptoms or signs of DCM. This condition–known as "presymptomatic" or "non-myelopathic" degenerative cervical cord compression (NMDCC) is highly prevalent in those above 60 years of age, involving, on average, about 40% of this European/American subpopulation [10,11]. This lies in striking contrast to the prevalence of DCM, estimated at the far lower figure of 2.3% [10]. Quantitative electrophysiological and MRI methods, however, serve to document functional or microstructural impairment in NMDCC patients, indicating that myelopathy precedes the occurrence of commonly detected clinical signs and symptoms. Thus, a diagnosis of DCM based on standard clinical bedside examination may be too late for adequate proactive treatment to be undertaken [3,12,13].

Impaired gait is one of the cardinal symptoms of DCM. Therefore quantitative gait assessment shows promise as an accurate and objective tool in the diagnosis and classification of DCM, with considerable potential in the evaluation of the impacts of therapeutic interventions [14]. Studies utilizing objective gait assessment have largely concentrated upon comparing the gait parameters of healthy individuals with DCM patients, or analyzing the pre-operative status and post-operative outcomes in DCM patients [5,15,16]. Gait impairment has been reported as a strong indication for surgical intervention and may be used as an index in the assessment of post-operative recovery [17]. Certain studies have concluded that a subtle gait disturbance is the most common and the earliest presentation of DCM [5,18,19]. Promoting this somewhat vague observation to the realm of objective assessment thus has the potential to detect early impairment and facilitate timely diagnosis of DCM [14]. There is evidence that individuals with moderate and severe DCM demonstrate slower gait speed and reduced cadence [15,20]. Correlation between quantitative assessment of gait by means of sophisticated spatiotemporal gait parameters and the degree of disability quantified by the modified Japanese Orthopaedic Association (mJOA) score has also been reported [14]. The aim of this study was, therefore, to verify whether an objective and easy-to-use gait analysis employing a standardized 10-m walk and run test is capable of detecting early gait impairment in a practical proportion of NMDCC subjects and reflecting the severity of disability in DCM patients.

2. Materials and Methods

2.1. Design

Single center, cross-sectional observational cohort study.

2.2. Participants

The study sample consisted of three groups: a group of DCM patients, subjects with NMDCC and a control group of healthy volunteers.

All subjects met the following inclusion criteria:

age $\geq$18 years;
ability to walk at least 10 m without the assistance of another person.

Patients or subjects were excluded if they were affected by any of the following: severe respiratory or cardiac disease hindering walking abilities or safe mobilization;
history of any other neurological disorders with persistent deficit;
symptomatic musculoskeletal problems affecting gait, especially coxarthrosis or gonarthrosis;
symptomatic lumbar spinal stenosis (MRI of the lumbar spine performed only in patients with symptoms or signs suspected of lumbar spinal stenosis);
previous surgical decompression to alleviate DCM.

Approval was granted by the local ethics committee and informed written consent was obtained from all study participants.

DCM patients and NMDCC subjects were recruited from subjects referred between January 2018 and December 2020 to a large tertiary university hospital with a multidisciplinary center specializing in degenerative compressive neurological syndromes.

DCM patients were considered as those exhibiting generally-accepted clinical and imaging diagnostic criteria for DCM, based on the presence of at least one clinical sign and one clinical symptom of myelopathy revealed by magnetic resonance imaging (MRI) signs of degenerative discogenic and/or spondylogenic cervical spinal cord compression [5,21]. The following symptoms and signs were considered as markers of DCM.

Symptoms: gait disturbance; numb and/or clumsy hands; Lhermitte's sign; bilateral arm paresthesias; weakness of lower or upper extremities; urinary urgency or incontinence.

Signs: corticospinal tract signs: hyperreflexia/clonus; spasticity; pyramidal signs (Babinski's, Trömner's or Hoffmann's signs); spastic paresis of any of the extremities (most frequently, lower limb spastic paraparesis); flaccid paresis of one or both upper extremities; atrophy of the hand muscles; sensory involvement in various distributions in the upper or lower extremities; gait ataxia.

NMDCC patients were considered as those with MRI signs of cervical cord compression and may have exhibited one clinical myelopathic symptom, but it was essential that they were free of clinical myelopathic signs and/or lacked the combination of one clinical symptom and one clinical sign of symptomatic myelopathy required for a diagnosis of DCM.

2.3. MRI Examination and Assessment of Cervical Cord Compression

All subjects underwent examination of the cervical spine provided by a 1.5 Tesla MRI device with a 16-channel head and neck coil. The standardized imaging protocol included conventional pulse sequences in sagittal-T1, -T2 and STIR (short-tau inversion recovery) and axial planes (gradient-echo T2). The clinical status of all patients was blinded to the neuroradiologists who examined the cervical spine MRIs. The imaging criterion for cervical cord compression was defined as a change in spinal cord contour at the level of an intervertebral disc on axial or sagittal MRI scan compared with that at the midpoint levels of neighboring vertebrae [11,12,22].

The control group was made up of healthy volunteers without symptomatic lower limb injuries, neurological disorders, or cardiovascular or respiratory impairment that would hinder gait analysis. All volunteers underwent MRI examination of the cervical spine (either as participants in another epidemiological study or for cervical pain or cervical radiculopathy) that disclosed neither signs of degenerative cervical cord compression nor any cervical cord abnormality [11].

2.4. mJOA Score

The degree of disability in DCM patients was assessed in terms of mJOA score, a generally accepted disability scale. This is an investigator-administered tool used to evaluate neurological function in patients with DCM [23]. It is defined on an 18-point scale that addresses upper (5 points) and lower extremities (7 points, JOA–LE) motor function, sensation (3 points) and micturition (3 points).

2.5. Gait Assessment

Gait assessment was performed in standardized fashion for all participants. After a back-and-forth warming-up walk, each subject was asked to walk a 10-m walkway from a standing start, following the instructions: "Once you are given the instruction to start, you should walk as quickly as possible until you are asked to stop. You are not allowed to run". At least one foot per step had always to make contact with the ground in order for the process to be considered "walking" [24]. Distance was calculated using markings on the track. Next, they were asked to run the same 10-m walkway as fast as they could, if possible. For patients who exhibited unstable gait, the supervision of another person was provided to prevent a possible fall. In the case of serious risk of falling, we omitted the running test. The times taken for the walk/run and the number of steps were counted by

an observer and expressed as walking/running time(s), velocity (cm/s), number of steps and cadence (steps/min). No videorecording was performed.

2.6. Statistics

Continuous parameters were summarized as mean (X) ± standard deviation (SD) and/or median (minimum-maximum), or 5th–95th percentiles. Categorical parameters were expressed as absolute and relative frequencies. The normal distribution of continuous variables was investigated by means of graphic tools, the Kolmogorov–Smirnov and the Shapiro–Wilk tests. For assessment of correlation between gait/run parameters and mJOA and mJOA–LE scales in DCM and between gait/run parameters and age in healthy controls, the Spearman's rank sum correlation coefficient and/or the chi-square test were deployed. Differences between the sexes in HC in gait/run parameters were calculated via the Mann–Whitney U test, while differences in gait/run parameters between groups (HC, NMDCC and DCM) were calculated via the Kruskal–Wallis and post-hoc tests with Bonferroni's correction.

3. Results

3.1. Participant Demography

There were 100 healthy volunteers, aged 56.1 ± 13.1 (x ± SD); 55.5 (median); 30–82 (minimum-maximum) years; 52 (52%) were women. The NMDCC group consisted of 126 patients, aged 58.2 ± 9.9; 59; 30–79 years; 65 (51.6%) women. The mJOA score reached 18 points in all healthy volunteers and in vast majority of NMDCC subjects. Slight abnormality of mJOA at the level of 17 points was found in 13 out of 126 NMDCC subjects (10.3%) due to mild lack of stability and/or mild difficulties in attempt to button the shirt. No NMDCC subject had mJOA < 17. Some of them had signs of cervical radiculopathy but in all these 13 NMDCC subjects we found no clear myelopathic signs during routine clinical evaluation including those with subjective gait problems. The DCM group was made up of 45 patients, aged 59.3 ± 11.8; 58; 36–82 years, 20 (45.5%) women. There were no significant differences between the three groups in terms of age or sex proportions ($p > 0.05$). All healthy volunteers and NMDCC subjects were able to perform the 10-m walk and run test, while eleven participants from the DCM group were unable to run and took only the walk test.

3.2. Gait Analysis

3.2.1. Healthy Controls

The values of all parameters displayed normal Gaussian distribution. All parameters correlated highly significantly with age (higher figures with advancing age for time and number of steps, lower values for velocity and cadence for both the walk and the run). They differed between the sexes (higher values of time and number of steps for both walk and run in women, no difference in cadence) (Table 1). Thus, all parameters were assessed independently in four subgroups of healthy controls (men and women aged > 60 and ≤60 years of age) and normal limits were expressed as x + 2SD (time, number of steps) or x-2SD (velocity, cadence). As the values of all the parameters obtained in both groups of patients were distributed non-normally, the 5th and 95th percentiles of values in the HC group were calculated as alternative normal limits (Table 2A).

Table 1. Correlation of walk/run parameters with age and sex in healthy controls.

HC (N = 100)		Correlation with Age: Spearman's Rank Correlation Coefficient: r (p)	Comparison between Sexes: Chi-Square Test: p
		Age	Sex
Time/Velocity (cm/s)	Walk	0.610/−0.610 (<0.001)	0.006 ‡
	Run	0.657/−0.657 (<0.001)	0.001 ‡
Number of steps	Walk	0.497 (<0.001)	<0.001 ‡
	Run	0.353 (<0.001)	<0.001 ‡
Cadence (steps/min)	Walk	−0.268 (0.007)	0.659 †
	Run	−0.564 (<0.001)	0.707 †

HC: Healthy controls; ‡ Significantly higher values in women; † Insignificantly lower values in women.

Table 2. 10-m walking/running test: age- and sex- stratified normal limits (set in the group of healthy controls).

Healthy Controls (*N* = 100): Subgroups	Parameters: 10 m Walk			
	Time (s)/ Velocity (cm/s)		Number of Steps/ Cadence (Steps/min)	
	X ± SD	Normal limits Time: X+2SD/95.perc. Velocity: X-2SD/5.perc.	X ± SD	Normal Limits N.steps: X+2SD/95.perc. Cadence: X-2SD/5.perc.
Men ≤ 60 years *N* = 27	4.2 ± 0.5/ 238.3 ± 30.9	5.2/5.3 176.5/186.9	10.7 ± 1.2 153.6 ± 22.8	13.1/13.0 108.0/125.2
Men > 60 years *N* = 21	5.0 ± 0.8/ 198.8 ± 37.3	6.6/6.4 124.2/145.0	12.8 ± 2.1 158.3 ± 32.3	17.0/16.0 93.7/103.9
Women ≤ 60 years *N* = 31	4.5 ± 0.6/ 221.3 ± 28.6	5.7/5.6 164.1/178.5	12.2 ± 1.3 162.3 ± 25.1	14.8/14.5 112.1/129.4
Women > 60 years *N* = 21	6.1 ± 1.0/ 165.8 ± 30.2	8.1/8.1 105.4/110.0	14.6 ± 2.4 143.8 ± 24.4	19.4/18.0 95.0/101.5
Healthy Controls (*N* = 100): Subgroups	**Parameters: 10 m Run**			
	Time (s)/ Velocity (cm/s)		Number of Steps/ Cadence (Steps/min)	
	X ± SD	Normal Limits Time: X+2SD/95.perc. Velocity: X-2SD/5.perc.	X ± SD	Normal Limits N.steps: X+2SD/95.perc. Cadence: X-2SD/5.perc.
Men ≤ 60 years *N* = 27	2.6 ± 0.3/ 383.7 ± 58.7	3.2/3.3 266.3/304.0	8.7 ± 1.3 199.1 ± 27.6	11.3/11.0 143.9/151.3
Men > 60 years *N* = 21	3.4 ± 0.7/ 296.8 ± 55.8	4.8/4.2 185.2/237.0	9.4 ± 1.0 167.9 ± 29.5	11.4/11.2 108.9/116.9
Women ≤ 60 years *N* = 31	3.0 ± 0.4/ 336.2 ± 40.2	3.8/3.6 255.8/279.0	9.7 ± 1.2 193.6 ± 21.2	12.1/12.0 151.2/158.4
Women > 60 years *N* = 21	4.2 ± 1.0/ 238.2 ± 51.0	6.2/6.3 136.2/158.0	10.6 ± 1.0 155.9 ± 31.2	12.6/12.0 93.5/96.8

X: mean; SD: standard deviation; Perc.: percentile; N: Number.

10 m Walk—Number (Proportion) of Abnormal Values [&]			
Group / Parameter	NMDCC (*N* = 126)	DCM (*N* = 45)	Comparison of the groups: chi-square test (*p*)
Time	57 (45.2%)/60 (47.6%)	31 (68.9%)/32 (71.1%)	0.006/0.007
Velocity	57 (45.2%)/60 (47.6%)	31 (68.9%)/32 (71.1%)	0.006/0.007
Number of steps	21 (16.7%)/22 (17.5%)	14 (31.1%)/23 (51.1%)	0.04/<0.001
Cadence	6 (4.8%)/33 (26.2%)	5 (11.1%)/20 (44.4%)	0.136/0.02
Any abnormality (walk)	59 (46.8%)/66 (52.4%)	32 (71.1%)/34 (75.5%)	0.005/0.007
10 m Run—Number (Proportion) of Abnormal Values [&]			
Group / Parameter	NMDCC (*N* = 126)	DCM (*N* = 34) [#]	Comparison of the groups: chi-square test (*p*)
Time	53 (42.1%)/59 (46.8%)	23 (67.6%)/24 (70.6%)	0.008/0.014
Velocity	53 (42.1%)/59 (46.8%)	23 (67.6%)/24 (70.6%)	0.008/0.014
Number of steps	41 (32.5%)/41 (32.5%)	22 (64.7%)/22 (64.7%)	<0.001/<0.001
Cadence	24 (19.0%)/42 (33.3%)	8 (23.5%)/15 (44.1%)	0.562/0.244
Any abnormality (run)	72 (57.1%)/82 (65.1%)	27 (79.4%)/28 (82.4%)	0.018/0.054
Any abnormality (walk and/or run)	84 (66.7%)/91 (72.2%)	38 (84.4%)/40 (88.9%)	0.024/0.023

NMDCC: Non-myelopathic degenerative cervical cord compression; DCM: Degenerative cervical myelopathy; [&]: number (proportion) of abnormalities calculated for cut-offs set as X ± 2SD/5. or 95.perc.; [#]: eleven DCM patients were not able to run.

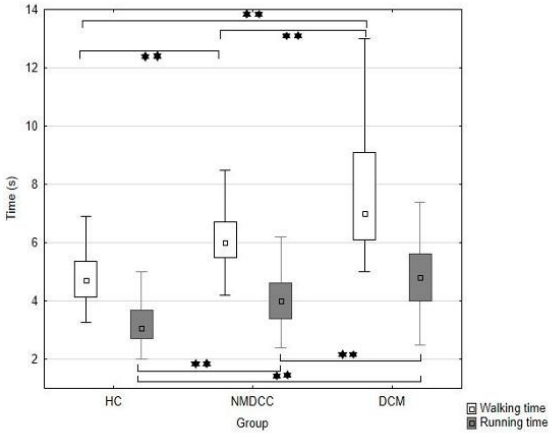
3.2.2. NMDCC

Summaries of gait parameters in NMDCC and DCM patients appear in Table 3 and Figure 1a–c. Significant differences were evident in all gait parameters among all the groups studied ($p < 0.001$; Table 3). In comparison with healthy controls (Table 3), NMDCC patients took longer to complete the ten meters at a run or walking, moved at lower speeds and required higher numbers of steps. Abnormality within the walking parameters appeared in 46.8% of NMDCC subjects. Time/velocity exhibited the highest sensitivity (45.2%), followed by number of steps (16.7%), and cadence (4.8%). All these abnormalities were disclosed in the course of investigation of time and number of steps (Table 2B).

Table 3. Summary statistics of walk/run test parameters in the groups studied.

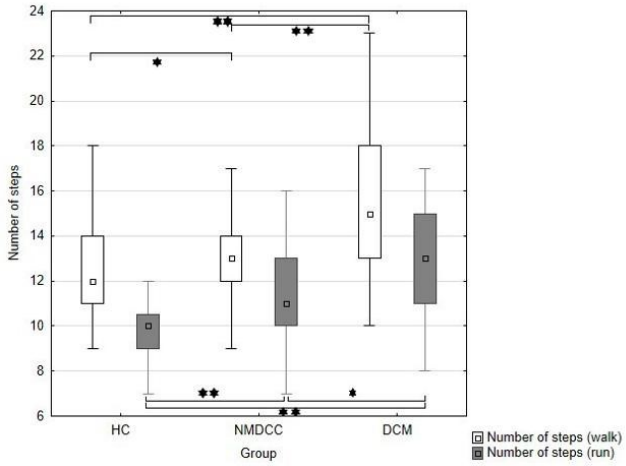
Parameters / Groups	HC	NMDCC	DCM	Kruskal–Wallis *p* Value *
	X (SD); Median (Min.–Max.)			
Walk time (s)	4.9 (1.3); 4.7 (3.3–13.6) [a]	6.2 (1.1); 6.0 (4.2–9.9) [b]	7.2 (2.5); 7.0 (5.0–18.0) [c]	<0.001
Walk velocity (cm/s)	209.0 (42.5); 212.5 (73–306) [a]	165.9 (27.2); 167 (101–238) [b]	139.6 (34.2); 150 (56–200) [c]	<0.001
Walk steps (No.)	12.4 (2.2); 12 (9–23) [a]	13.2 (1.9); 13 (8–18) [b]	14.8 (2.9); 15 (10–23) [c]	<0.001
Walk cadence (steps/min.)	155.2 (29.2); 152.9 (100.0–263.4) [a]	130.7 (20.6); 130 (53.3–228.6) [b]	120.7 (18.0); 120 (63.3–159.4) [b]	<0.001
Run time	3.3 (0.9); 3.1 (2–8) [a]	4.1 (0.9); 4.0 (2.4–6.7) [b]	4.6 (1.4); 4.8 (2.5–9.4) [c]	<0.001
Run velocity (cm/s)	320.1 (74.1); 323.5 (125–497) [a]	255.9 (56.5); 250 (149–416) [b]	219.0 (61.7); 221 (150–400) [c]	<0.001
Run steps (No.)	9.6 (1.4); 10 (6–12) [a]	11.3 (2.4); 11 (7–18) [b]	12.8 (3.0); 13 (8–22) [c]	<0.001
Run cadence (steps/min.)	181.8 (33.3); 182.6 (75.0–264.0) [a]	167.1 (25.9); 169.4 (114.3–266.7) [b]	160.2 (20.0); 161.2 (108.5–200.0) [b]	<0.001

HC: Healthy controls; NMDCC: non-myelopathic cervical cord compression; DCM: degenerative cervical myelopathy; X: mean; SD: standard deviation; * *p*-value represents comparison of all the groups (Kruskal–Wallis test); post hoc tests: a,b,c—same letters marking values of categories within any given row denote groups that are not mutually statistically different.

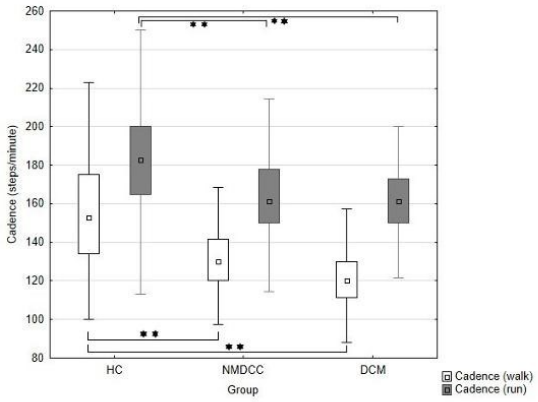


(**a**)

Figure 1. *Cont.*



(**b**)



(**c**)

Figure 1. Box-plots and whisker-plots expressing median, lower and upper quartiles, minimum and maximum (without outliers) of walking/running time (**a**), number of steps taken during walk and run (**b**) and cadence of walk and run (**c**) in healthy controls (HC), non-myelopathic degenerative cervical compression (NMDCC) patients and those with degenerative cervical myelopathy (DCM). * $p < 0.05$; ** $p < 0.01$.

Similarly, abnormality within the run parameters appeared in 57.1% of subjects, with the highest sensitivity exhibited by time/velocity (42.1%), followed by number of steps (32.5%) and cadence (19.0%). Again, all abnormalities were disclosed in the course of investigation of time/velocity and number of steps (Table 2B).

Abnormality of walk and/or run test parameters appeared in 66.7% of NMDCC patients (Table 2B).

3.2.3. DCM

DCM patients exhibited significantly longer times/lower velocities, higher numbers of steps and lower cadence during both the walk and run tests in comparison with both

healthy controls and NMDCC patients (Table 3, Figure 1a–c). Abnormality of walk parameters appeared in 71.1% of DCM patients, with the highest sensitivity for time/velocity (68.9%), followed by number of steps (31.1%) and cadence (11.1%) All abnormalities were disclosed in the course of investigation of time and number of steps (Table 2B). Similarly, abnormality of run parameters appeared in 79.4% of subjects, with the highest sensitivity for time/velocity (67.6%), followed by number of steps (64.7%) and cadence (23.5%). Again, all abnormalities were disclosed in the course of investigation of time/velocity and number of steps (Table 2B). Abnormality of walk and/or run test parameters appeared in 84.4% of DCM patients (Table 2B).

Time/velocity and number of steps as assessed from walk and run tests correlated significantly with both mJOA and mJOA–LE scales (Table 4). In addition, cadence of walk correlated with both mJOA and mJOA–LE scores, although this did not hold true for running (Table 4).

Table 4. Correlation between severity of disability and walk/run parameters in DCM patients.

DCM Patients (N = 45)		Spearman's Rank Correlation Coefficient r (p)	
		mJOA:	mJOA LE
Time (s)	Walk	−0.766 (<<0.001)	−0.790 (<<0.001)
	Run	−0.505 (0.002)	−0.568 (<0.001)
Velocity (cm/s)	Walk	0.766 (<<0.001)	0.790 (<<0.001)
	Run	0.505 (0.002)	0.568 (<0.001)
Number of steps	Walk	−0.589 (<0.001)	−0.649 (<<0.001)
	Run	−0.485 (0.004)	−0.471 (0.005)
Cadence (steps/min)	Walk	0.514 (<0.001)	0.483 (<0.001)
	Run	0.173 (0.329)	0.239 (0.173)

DCM: degenerative cervical myelopathy; mJOA: modified Japanese Orthopaedic Association scale; mJOA LE: modified Japanese Orthopaedic Association subscale for lower extremities; <<0.001: p value less than 10^{-6}.

4. Discussion

This is, to the best of our knowledge, the first study to show that gait analysis utilizing a standardized and simple 10-m walk and run test reflects gait impairment not only in DCM patients, but in a substantial proportion (66.7%) of individuals with NMDCC. Gait impairment constitutes the most prominent clinical manifestation of cervical myelopathy, and thus its amelioration may have a substantial impact on the recovery of patient functionality [25,26].

In routine clinical practice, observational gait analysis is by far the most commonly used approach to evaluating gait disturbance in DCM, including mJOA score. The accuracy and consistency of essentially subjective observation are however, questionable, particularly for subtle gait changes [27]. Timed walk tests are more sensitive to change and are known to be valid and reliable in DCM [28], but they provide no information concerning the underlying gait parameters that have contributed to the measured speed [29]. Recently, there has been a resurgence of research interest in applying quantitative and objective gait analysis to the evaluation of patients with DCM [25,26]. Gait analysis is now largely mostly performed on the basis of a specific movement protocol that includes evaluation of the range of motion of the lower extremities, of muscle strength, and of balance differences [15,25]. An assessment may also be obtained from three-dimensional computer analysis, including a number of spatiotemporal kinetic and kinematic parameters, all of which have been demonstrated as impaired in DCM patients [26,30]. Kalsi-Ryan et al. recently presented a study that found significant differences between control subjects and patients with mild, moderate, and severe DCM, and characterized specific differences in gait parameters between severity subtypes of DCM [14]. These computer analyses, however, are hardly practical in the context

of clinical neurological practice. Thus, this study was based on finding an easy and reliable test, readily available to the clinical neurologist. The protocol employed was simple and easy to reproduce, based on the straightforward instruction "walk as fast as possible, but do not run", and followed by a run test (if possible). This contrasts with other protocols in which the walk has been undertaken at a subject selected pace.

The rationale to evaluate both walking and running abilities in degenerative cervical cord compression subjects is based on the fact that walking and running are generally considered as distinct gait modes, with strikingly different mechanics and energetics. Having the ability to walk does not mean that the individual has the ability to run, as running requires greater balance, muscle strength and greater joint range of movement [31,32]. As expected, 11 out of 45 DCM patients (24.4%) of DCM patients were not able to run, but running test disclosed abnormality in an additional 13% of DCM patients (and in 19.9% of NMDCC subjects) with normal walking test, justifying thus the usefulness of its use.

This study confirms that gait analysis based on a clinically practical and easily administered test is a highly sensitive approach to the disclosure of gait disturbance in DCM patients. The results were in close correlation, especially in terms of walking and running time and the number of steps taken, with the mJOA scale and mJOA–LE, its subscale for the lower extremities, the most widely-employed subjective scale for grading severity of disability. Abnormalities in gait parameters, however, were also found in a substantial proportion of NMDCC patients; further, this cohort exhibited significant differences in all the parameters assessed when compared with age-adjusted healthy controls. A number of reasons for these findings may be suggested. Firstly, DCM diagnosis is based on the presence of clinical symptoms and signs (at least one) of myelopathy, although some patients may complain of a certain degree of gait disturbance in the absence of clear, objective, physical signs of myelopathy [5,6]. In the light of current criteria, a diagnosis of DCM is critically dependent on the clinical expertise of the examining specialist; an objective approach to gait assessment may well serve as an additional clinical tool, enabling timely and reproducible establishment of a DCM diagnosis. Secondly, the approach employed herein based its test protocol of gait analysis on a fast walk and a run where feasible, rather than the usual assessment of a slow walk. The results arising out of a fast walk may be more sensitive than those of a "regular" walk. Of course, a run test is not suitable for DCM patients with moderate-to-severe disability. Nevertheless, in that part of the cohort herein capable of independent locomotion, 75.6% of DCM patients and 100% of those with NMDCC proved able to run, and the running test disclosed additional abnormalities in a quarter (25.5%) of them. Among the parameters assessed, not surprisingly, walking and running times showed the highest sensitivity, followed by number of steps, while cadence of walk/run did not disclose any abnormalities in patients returning normal times and numbers of steps and did not prove immediately useful. Thirdly, the parameters of walk and run correlated closely with age and sex, and therefore normal limits were adjusted for these two demographic parameters. This might have enhanced the sensitivity of the test.

Early recognition and treatment of DCM, before the onset of spinal cord damage, is essential for optimal outcomes. Unfortunately, despite the lack of any study showing a benefit of a prophylactic surgical decompression in NMDCC, some spondylosurgeons recommend and perform such intervention. Recommendations based on expert opinion and longitudinal studies on natural course of NMDCC and risk factors for progression to DCM [12,22,33] generally recommend consideration of surgical treatment in those patients who present with clinical or electrophysiological evidence of cervical radicular dysfunction or central conduction deficits disclosed by electrophysiological examination and are thus at higher risk for developing myelopathy [34,35]. There is also no clear agreement on the conservative treatment of both NMDCC and mild DCM patients. Intermittent immobilization in a cervical collar and "low-risk" activity modification together with close observation of both mild DCM patients and NMDCC subjects with high risk for progression into symptomatic DCM are usually recommended.

Limitations of the Study

Despite the use of age and sex-adjusted normal values and the exclusion of subjects with known tandem lumbar spinal stenosis or musculoskeletal comorbidities that might have interfered with gait, a higher tendency towards degenerative changes in the lumbar spine or hip joints in patients with degenerative cervical cord compression is to be anticipated [36]. This may lead to results indicating more severe impairment in a performance-oriented test of this nature. Moreover, such a test is prone to be influenced by the motivation of the subject tested. Exclusion of patients with symptomatic lumbar spinal stenosis or musculoskeletal comorbidities that are quite frequent in older population and especially in DCM patients eliminates significant proportion of DCM patients in particular and decreases external validity of the test. Our study was performed in the Caucasian (European) population with very low prevalence of the ossification of the posterior longitudinal ligament and the results thus may be of limited value in evaluation of other populations of patients with degenerative cervical cord compression. The methodology to measure the times taken for the walk/run and to count the number of steps manually by an observer is easy to implement in the clinical setting, but might hypothetically serve as a potential source of error.

5. Conclusions

In conclusion, the main benefit of a standardized 10-m walk/run test in comparison to already used scoring systems, such as mJOA score, is its objective and quantitative character and sensitivity to mild gait impairment due to myelopathy. It has the capacity to disclose locomotor abnormalities in the early stages of degenerative cervical cord compression that may be confirmed as another risk factor for progression into symptomatic DCM in future longitudinal studies. Furthermore, it may support clinical diagnosis of DCM in case of vague clinical myelopathic symptoms and signs and could be employed in routine clinical practice as a tool to evaluate clinical course or effect of therapy in already diagnosed DCM.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available.

Conflicts of Interest: The authors declare that they have no conflict of interest.

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Vertigo in Patients with Degenerative Cervical Myelopathy

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Abstract: (1) Background: Cervical vertigo (CV) represents a controversial entity, with a prevalence ranging from reported high frequency to negation of CV existence. (2) Objectives: To assess the prevalence and cause of vertigo in patients with a manifest form of severe cervical spondylosis–degenerative cervical myelopathy (DCM) with special focus on CV. (3) Methods: The study included 38 DCM patients. The presence and character of vertigo were explored with a dedicated questionnaire. The cervical torsion test was used to verify the role of neck proprioceptors, and ultrasound examinations of vertebral arteries to assess the role of arteriosclerotic stenotic changes as hypothetical mechanisms of CV. All patients with vertigo underwent a detailed diagnostic work-up to investigate the cause of vertigo. (4) Results: Symptoms of vertigo were described by 18 patients (47%). Causes of vertigo included: orthostatic dizziness in eight (22%), hypertension in five (14%), benign paroxysmal positional vertigo in four (11%) and psychogenic dizziness in one patient (3%). No patient responded positively to the cervical torsion test or showed significant stenosis of vertebral arteries. (5) Conclusions: Despite the high prevalence of vertigo in patients with DCM, the aetiology in all cases could be attributed to causes outside cervical spine and related nerve structures, thus confirming the assumption that CV is over-diagnosed.

Keywords: cervical vertigo; cervical dizziness; degenerative cervical myelopathy; degenerative cervical spinal cord compression; cervical torsion test

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1. Introduction

Dizziness and vertigo are among the most common complaints that lead patients to visit a physician. The lifetime prevalence in adults is around 20%, reaching 40% in older adults [1]. Vertigo is not a single disease entity but a symptom of a wide range of diseases of varying aetiology. These may arise from the inner ear, the brainstem, and the cerebellum, or they may be of internal, vestibular, or psychosomatic origin.

"Cervical (or cervicogenic) vertigo" (CV) is a term often used in a clinical practice, but physicians lack sufficient data to form definite opinions and to give clinical guidelines for its diagnosis and treatment [2]. The overall prevalence of CV is not known because there are no generally accepted clinical or paraclinical tests for CV, and therefore it is predominantly a diagnosis by exclusion [3]. Colledge et al., in a community-based sample of subjects over 65 years of age, found that cervical spondylosis is the second most frequent cause of dizziness [4]. Takahashi, in an out-patient sample of 1000 patients visiting a general hospital in Japan with a chief complaint of dizziness, estimated a prevalence of CV as high as 90% [5]. These data are in striking contrast to the opinion of several leading experts in the field who doubt the diagnosis of CV entirely [6].

Based on these findings and discrepancies, we hypothesised that CV is over-diagnosed due to the absence of detailed diagnostic theory and practice in papers that reported a high prevalence of CV. As degenerative cervical myelopathy (DCM) is the most severe symptomatic form of cervical spondylosis [7], we used a well-defined cohort of DCM

patients to verify our hypothesis. The aim of this paper was to assess the prevalence and cause of vertigo in these patients with special focus on CV.

2. Materials and Methods

2.1. Design

This study was designed as a cross-sectional, cohort, observational, non-interventional study.

2.2. Participants

The study sample consisted of a cohort of consecutive subjects referred to a large tertiary university hospital between March 2018 and December 2019 in whom a clinical diagnosis of DCM was established, based on the presence of at least one clinical sign and one clinical symptom of myelopathy and magnetic resonance imaging (MRI) signs of degenerative discogenic and/or spondylogenic cervical spinal cord compression [8,9].

Excluded were:

- Patients with previous surgery on the cervical spine (possibly limiting the rotation of the spine);
- Patients with other than degenerative cervical cord compressions or other non-compressive myelopathies.

All subjects gave their written, informed consent to participate in the study.

2.3. Clinical Evaluation

Clinical neurological evaluation was focused on the assessment of clinical signs and symptoms of symptomatic myelopathy (with other possible causes excluded) and possible causes of vertigo. This included a detailed history of the illness, presence of comorbidities (cardiovascular including arterial hypertension, otorhinolaryngological and psychiatric abnormities, etc.), history of significant head or cervical spine trauma, Hallpike manoeuvre and a dedicated vertigo questionnaire (see below).

The following symptoms and signs were sought and/or determined as markers of DCM:

Symptoms

- Gait disturbance;
- Numb and/or clumsy hands;
- Lhermitte's phenomenon;
- Bilateral arm paresthesias;
- Weakness of lower or upper extremities;
- Urinary urgency, or incontinence.

Signs

- Corticospinal tract signs;
- Hyperreflexia/clonus;
- Spasticity;
- Pyramidal signs (Babinski reflex or Hoffman's sign);
- Spastic paresis of any of the extremities (most frequently, lower spastic paraparesis);
- Flaccid paresis of one or two upper extremities;
- Atrophy of the hand muscles;
- Sensory involvement in various distributions in upper or lower extremities;
- Gait ataxia.

The following clinical and demographic data were also noted:

- Age;
- Sex.

Degree of disability was assessed by the modified Japanese Orthopaedic Association (mJOA) score [10].

2.4. Imaging

All subjects underwent examination of the cervical spine on a 1.5 Tesla MRI device with a 16-channel head and neck coil. The standardised imaging protocol included conventional pulse sequences in sagittal-T1, -T2 and STIR (short-tau inversion recovery) and axial planes (gradient-echo T2). The imaging criterion for cervical cord compression was defined as a change in spinal cord contour at the level of an intervertebral disc on axial or sagittal MRI scan compared with that at midpoint level of neighbouring vertebrae [11]. Compression ratio (CR) was calculated by taking the anterior–posterior diameter of the spinal cord divided by the transverse diameter of the cord on the axial image [11]. Lower CR values indicate worse cord deformation. This measurement was taken at the level of maximum spinal cord compression identified as maximum reduction in antero/posterior spinal canal diameter in comparison with other segments. The level of maximal spinal cord compression and signs of myelopathy (signal changes of the spinal cord on T1- and T2-weighted imaging) were also established (Figure 1).

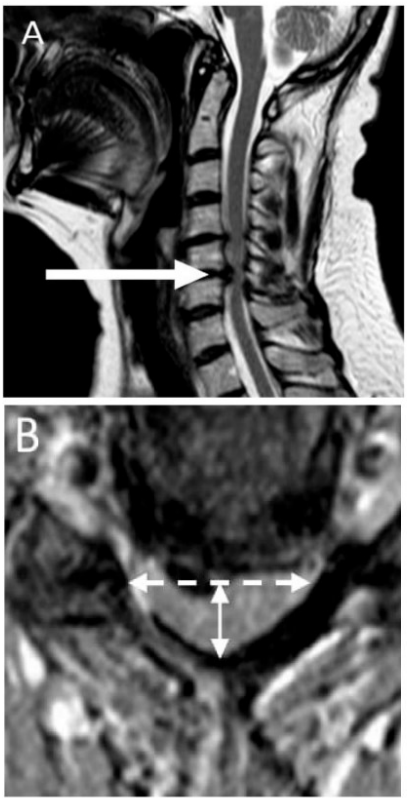

Figure 1. Patient with severe cervical spinal cord compression. (**A**) Sagittal T2-MRI sequence shows a level of maximal compression—C5/6 (arrow); (**B**) Compression ratio: anterior–posterior diameter (solid line double arrow) divided by the transverse diameter (dashed line double arrow) of the spinal cord on the axial T2 MRI image (taken at the level of maximum spinal cord compression; the result is 0.37 in this patient).

2.5. Vertigo Questionnaire

Vertigo/dizziness was defined as an unpleasant disturbance of spatial orientation or to the erroneous perception of movement [12]. An investigator-administered questionnaire originally published by Filippopoulos was administered verbally to all patients [13]. The prevalence, the type of vertigo and the body positions and movements related to the different vertigo types were assessed by a series of questions. The questionnaire is shown in Supplementary Figure S1.

2.6. Uncontrolled Blood Pressure

Patients reporting any dizziness/vertigo were asked to measure their blood pressure at home under basal conditions 3 times daily for 3 consecutive days and the average value was then calculated. Uncontrolled blood pressure was defined as an average value $\geq$140 (systolic)/90 (diastolic) mm Hg. In borderline values 24-h monitoring of blood pressure was performed and the same definition was used for uncontrolled blood pressure.

2.7. Orthostatic Hypotension

Orthostatic hypotension was evaluated in patients reporting dizziness/vertigo by measuring blood pressure after lying flat for 5 min, then 1 min and 3 min after standing. For determination of orthostatic hypotension, we used an updated definition of the American Autonomic Society as a systolic blood pressure decrease of at least 20 mm Hg or a diastolic blood pressure decrease of at least 10 mm Hg within three minutes of standing when compared with blood pressure from the sitting or supine position [14].

2.8. Benign Paroxysmal Positional Vertigo

Diagnostic criteria for benign paroxysmal positional vertigo (BPPV) consisted of vertical–torsional positional nystagmus evoked by the Dix–Hallpike manoeuvre or a predominantly horizontal positional nystagmus after rolling the head sideways from the supine position [15].

2.9. Ultrasound of Carotid and Vertebral Arteries

All ultrasound examinations were performed by an experienced neurosonologist using advanced ultrasound equipment (Philips PureWave HD 15; Massachusetts, USA) with a 3–12 MHz multi-frequency ultrasound probe. Patients were examined in a supine position with the neck slightly extended. Arterial wall thickness was evaluated and any extracranial atherosclerosis and/or occlusive disease was detected, with particular attention to the carotid bifurcation. In the event of carotid stenosis, its severity was measured in B mode and colour mode, with complementary measurements of peak systolic flow velocity and diastolic velocity gauged by Doppler ultrasound, based on the European Carotid Surgery Trial criteria (70–99% stenosis was considered significant) [16]. Vertebral arteries (VAs) were visualised in a longitudinal plane at the sixth cervical vertebra, where the vertebral artery usually enters the transverse foramina. For analysis, the course of the VA was divided into two segments: Vertebral (V1) (from the origin of the vertebral artery until the point where it enters the fifth or sixth cervical vertebra) and V2 (the part of the vertebral artery that courses cranially to the transverse foramina until it emerges besides the lateral mass of the atlas) [17]. Each segment of the VA was studied in B mode and colour-code mode. Any stenotic lesions of the VAs were evaluated according to B mode and flow pattern. Criteria used for grading $\geq$50% stenosis were focal elevated blood flow velocity with a PSV cut-off point at the V1 segment of the vertebral artery of 140 cm/s, and 125 cm/s at the V2 segment [18].

2.10. Cervical Torsion Test

A cervical torsion test was performed in all patients. The procedure was adapted after the work of L'Hereux-Lebeau [19]. Subjects were seated in a rigid but fully rotatable chair that provided support to the entire body. Their legs were flexed with a slight bend

at the knees. They were securely held in the chair with shoulder- and lap-belts. It was requested that their eyes should be closed during the procedure. First, the subject´s trunk was passively turned 70 degrees to the right, with the head still, then returned to centre, followed by turning the trunk 70 degrees to the left, and returning to centre. Each position was held for 30 s with the head stabilised by the observer for all positions. Nystagmus was evaluated with Frenzel goggles. The test was considered positive when nystagmus was found in any of the four positions, or vertigo provoked or increased (Figure 2).

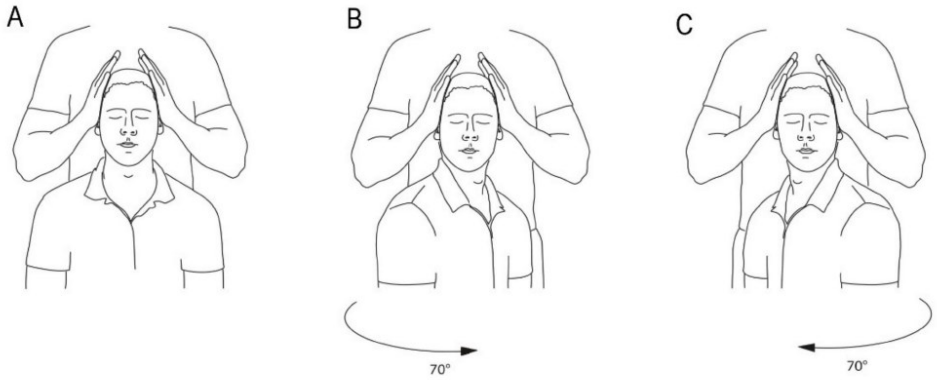

Figure 2. Cervical torsion test. (**A**) Subject seated in a rigid but fully rotatable chair, head fixed. (**B**) The subject´s trunk passively turned 70 degrees to the right, with the head still, then returned to centre. (**C**) Turning the trunk 70 degrees to the left, then returned to centre.

The final diagnosis of DCM, together with the diagnosis of possible causes of vertigo, was defined by a neurologist (ZKJ) and then reviewed and confirmed by two other researchers (ZK and JB). Finally, detailed internal, otorhino-laryngological, neuro-otological or psychiatric examinations were performed according to suspected aetiology and the definite cause of vertigo was additionally verified by a highly qualified specialist. In case of discordance with the cause suspected by a neurologist, the final cause was established by consensus. We always cooperated with the same specialist.

3. Results

3.1. Study Cohort

We screened 51 patients in whom a diagnosis of DCM was established. Eight of them were excluded because of previous cervical spine surgery and five of them were not willing to participate in the study and did not sign informed consent. Thirty-eight patients complied with the DCM diagnosis and exclusion criteria, signed informed consent and completed the study protocol. The study cohort included 17 females (44.7%) with a median age (range) of 59 (41–85) years. The average mJOA score of the evaluated cohort was 16 (median), 9–17 (range). None of them reported significant injury of the head or cervical spine during the last year before inclusion in the study. Detailed demographic and imaging characteristics are summarised in Table 1.

Table 1. Demographic and imaging characteristics.

Patients No	Gender	Age	mJOA Score	Maximum Cervical Cord Compression Level	Signs of Myelopathy on MRI	CR	ICA Stenosis	VA Stenosis
1	F	46	17	C5/6	no	0.31	no	none
2	M	44	17	C4/5	no	0.3	no	none
3	F	60	17	C6/7	yes	0.32	no	none
4	F	60	16	C6/7	no	0.37	no	none
5	F	51	17	C4/5	no	0.44	no	none
6	M	43	16	C4/5	no	0.45	no	none
7	M	71	15	C5/6	yes	0.35	yes	none
8	M	60	17	C4/5	no	0.3	no	none
9	M	65	16	C3/4	yes	0.4	no	none
10	M	51	16	C5/6	yes	0.43	no	none
11	M	65	17	C5/6	no	0.36	no	none
12	F	50	17	C5/6	no	0.36	no	none
13	F	63	11	C5/6	yes	0.36	yes	none
14	F	71	16	C5/6	no	0.41	no	none
15	M	58	16	C4/5	no	0.43	no	none
16	F	69	12	C4/5	yes	0.39	no	none
17	M	60	15	C6/7	yes	0.42	no	none
18	F	59	16	C6/7	no	0.40	no	none
19	M	63	17	C5/6	yes	0.42	no	none
20	M	52	16	C5/6	no	0.28	no	none
21	M	69	15	C5/6	no	0.3	no	none
22	F	57	16	C5/6	yes	0.38	no	none
23	M	82	17	C6/7	no	0.36	no	none
24	F	59	15	C5/6	yes	0.36	no	none
25	M	67	13	C5/6	yes	0.49	yes	none
26	M	64	15	C5/6	no	0.41	no	none
27	M	45	17	C3/4	no	0.37	no	none
28	M	77	9	C4/5	yes	0.41	no	none
29	F	40	17	C5/6	no	0.43	no	none
30	M	59	17	C5/6	yes	0.44	no	none
31	F	51	17	C5/6	no	0.39	no	none
32	M	48	15	C5/6	yes	0.21	no	none
33	F	48	17	C5/6	no	0.23	no	none
34	F	59	17	C5/6	no	0.33	no	none
35	F	48	17	C4/5	yes	0.23	no	none
36	F	52	17	C4/5	no	0.44	no	none
37	M	58	16	C5/6	yes	0.38	no	none
38	M	68	17	C5/6	no	0.39	no	none

mJOA: modified Japanese Orthopaedic Association score; CR: compression ratio; ICA: internal carotid artery; VA: vertebral artery; MRI: magnetic resonance imaging; F: female; M: male.

3.2. Dizziness/Vertigo

Subjective feelings of dizziness/vertigo in the previous six months were reported by 18 patients (47%). Patients characterised dizziness/vertigo as a feeling of impending blackout when rapidly standing up (eight patients), as a spinning vertigo (like in a carrousel) (five patients), as a swaying vertigo (like on a small boat) (four patients) and one patient was not able to specify it. Detailed characteristics of dizziness/vertigo and its aetiology in DCM patients are summarised in Table 2.

Table 2. Detailed characteristics of dizziness/vertigo and its aetiology in DCM patients.

Patients No	Type of Vertigo	Vertigo According to Body Movement	Cervical Torsion Test	Hallpike Test	Drop in BP ≥ 20/10 mmHg after at Least 3 min of Standing	Upright Tilt Table Test	Uncontrolled AH Detection	Final Aetiology of Dizziness
1	none	none	negative	negative	No	NA		NA
2	none	none	negative	negative	No	NA		NA
3	none	none	negative	negative	No	NA		NA
4	none	none	negative	negative	No	NA		NA
5	unspecified dizziness	also present when sitting or lying down	negative	negative	No	NA	24 h monitoring	uncontrolled AH
6	none	none	negative	negative	No	NA		NA
7	spinning	also present when sitting or lying down	negative	negative	No	NA	self-measurement	uncontrolled AH
8	none	none	negative	negative	No	NA		NA
9	none	none	negative	negative	No	NA		NA
10	blackout when standing	triggered by a change of position	negative	negative	Yes	NA		orthostatic vertigo
11	none	none	negative	negative	No	NA		NA
12	blackout when standing	triggered by a change of position	negative	negative	No	positive		orthostatic vertigo
13	swaying	only present when standing or walking	negative	negative	No	NA	24 h monitoring	uncontrolled AH
14	blackout when standing	triggered by a change of position	negative	negative	Yes	NA		orthostatic vertigo
15	none	none	negative	negative	No	NA		NA
16	swaying	also present when sitting or lying down	negative	negative	No	NA		psychogenic vertigo
17	none	none	negative	negative	No	NA		NA
18	swaying	only present when standing or walking	negative	negative	No	NA	self-measurement	uncontrolled AH
19	none	none	negative	negative	No	NA		NA
20	none	none	negative	negative	No	NA		NA
21	blackout when standing	triggered by a change of position	negative	negative	Yes	NA		orthostatic vertigo
22	none	none	negative	positive	No	NA		NA
23	blackout when standing	triggered by a change of position	negative	negative	Yes	NA		orthostatic vertigo
24	spinning	triggered by head movement	negative	positive	No	NA		BPPV
25	blackout when standing	triggered by a change of position	negative	negative	Yes	NA		orthostatic vertigo
26	blackout when standing	triggered by a change of position	negative	negative	Yes	NA		orthostatic vertigo
27	none	none	negative	negative	No	NA		NA

Table 2. *Cont.*

Patients No	Type of Vertigo	Vertigo According to Body Movement	Cervical Torsion Test	Hallpike Test	Drop in BP ≥ 20/10 mmHg after at Least 3 min of Standing	Upright Tilt Table Test	Uncontrolled AH Detection	Final Aetiology of Dizziness
28	spinning	trigered by head movement	negative	positive	No	NA		BPPV
29	none	none	negative	negative	No	NA		NA
30	none	none	negative	negative	No	NA		NA
31	spinning	triggered by head movement	negative	positive	No	NA		BPPV
32	blackout when standing	trigered by a change of position	negative	negative	No	positive		orthostatic vertigo
33	spinning	triggered by head movement	negative	positive	No	NA		BPPV
34	swaying	only present when standing or walking	negative	negative	No	NA	self-measurement	uncompensated AH
35	none	none	negative	negative	No	NA		NA
36	none	none	negative	negative	No	NA		NA
37	none	none	negative	negative	No	NA		NA
38	none	none	negative	negative	No	NA		NA

NA: not attributable; BPPV: benign paroxysmal positional vertigo; AH: arterial hypertension; BP: blood pressure.

The following causes of vertigo were found in these patients: orthostatic dizziness in eight patients (44% of patients with vertigo, 22% of all patients), uncontrolled arterial hypertension in five (28% and 14%, respectively), BPPV in four (22% and 11%, respectively) and psychogenic dizziness in one (6% and 3%, respectively). The presence of uncontrolled arterial hypertension had to be confirmed by 24-h monitoring in two out of five patients (Table 2).

None of the 38 patients studied displayed a positive response to the cervical torsion test, irrespective of the presence or absence of subjectively described vertigo in the previous six months.

Three patients (0.8%) exhibited haemodynamically significant stenosis of the internal carotid arteries (two of them suffered from recently diagnosed, uncontrolled hypertension, while one had orthostatic dizziness). None of the patients studied had significant stenosis of the vertebral arteries (Table 1).

4. Discussion

Our study demonstrated a high prevalence of dizziness/vertigo in a cohort of patients with severe cervical spondylosis. Dizziness/vertigo was reported by 47% of the DCM patients. The aetiology of dizziness/vertigo in all patients in our DCM cohort, however, could be explained by mechanisms other than lesion(s) of the nervous system in the cervical region (i.e., orthostatic dizziness, uncontrolled hypertension, BPPV, psychogenic dizziness) or stenotic changes in the cervical segment of vertebral arteries. We thus have not been able to present any evidence in favour of the high prevalence of cervical dizziness/vertigo attributed either to advanced symptomatic spondylosis of the cervical spine and/or stenotic changes of vertebral arteries reported by other authors [4,5,20].

Vertigo, in general, is a common condition, yet definitions vary and management guidelines are often contradictory [21]. Patients with intrinsic problems (cardiovascular, pulmonary, etc.) are unlikely to suffer from pure rotational vertigo and the severity of this condition is often overrated by their clinicians [6]. Orthostatic dizziness in the adult population has accounted for 42% of all participants with vertigo and for 55% of non-vestibular dizziness diagnoses [22]. These findings correlate with the results of this study—in 44% of symptomatic (vertigo-suffering) patients, orthostatic aetiology was confirmed. Five patients were diagnosed with uncontrolled hypertension, making up 28% of the symptomatic group. In general, hypertension and dizziness are both highly prevalent and significantly associated, highlighting a pressing need for investments in preventive measures [23]. BPPV is the most common of the peripheral types of vertigo. Tan noted that 9% of elderly patients undergoing general geriatric assessment exhibited unrecognised BPPV [24]. This percentage proved even higher in a larger series of patients—approximately 34% [25]. Our study disclosed four patients with BBPV (22% of symptomatic subjects), but the group was too small to draw any definite conclusions. We decided to use the questionnaire by Filippopoulos to determine the prevalence of vertigo [13]. Unfortunately, the questionnaire cannot exactly differentiate between possible underlying pathologies, but it can lead us in a certain direction. A feeling of impending blackout when standing up rapidly is typical for orthostatic dizziness [26]. Vertigo (mostly spinning) triggered by head movements is typical for benign paroxysmal vertigo [27]. Swaying vertigo is often described as a somatoform and/or phobic vertigo [28]. In recent decades, cervical vertigo has emerged as a special category of dizziness, generating considerable controversy. The diagnosis remains debatable; there remains a lack of validated tests to confirm this entity, and exclusion clinical diagnosis appears to be the default standard [3,19]. A diagnosis of CV, however, is made too often by many physicians, largely because the simultaneous occurrence of vertigo and cervical spondylosis is very common [29]. Several explanations of the aetiology of CV have been published. Disturbed cervical proprioception is suggested by probably the most cited study [30]. Neck afferents (nerves) not only assist the coordination of eye, head, and body, but they also affect spatial orientation and control of posture. This implies the theory that stimulation of, or lesions (damage) in, these structures could

produce CV [31]. In experimental studies, vertigo, ataxia, and nystagmus have been induced in animals by injecting local anaesthetics into the neck [32]. Ataxia in healthy human beings, induced by unilateral injection of local anaesthetics in the neck, has also been associated with a broad-based, staggering gait and hypotonia of the ipsilateral arm and leg [32]. According to these findings, some authors have suggested that cervical spinal cord compression is the most frequent cause of cervical vertigo [33]. The cervical torsion test is supposed to be the most useful to distinguish between cervical afferent disturbance and vestibular dysfunction in patients with dizziness/vertigo [19]. It is the reason why it was used in this study to elucidate the role of the cervical proprioceptors in DCM patients. The principle of the test is to achieve stimulation of the proprioceptors of the neck; the trunk of the body is rotated with the head kept stationary. This examination, however, was not able to evoke vertigo in any patient in this cohort. The second most common hypothesis as to the aetiology of CV is that it may arise out of impaired blood circulation in the vertebrobasilar arteries. In 1933, DeKleyn first described a syndrome of vertigo produced by head movement. In post-mortem studies, he noted compromised circulation in the VA with head rotation. Later, stroke accompanying maximum rotation of the head was described in archery [30]. However, because of the collateral blood flow through the contralateral VA and the circle of Willis, VA occlusion does not lead to symptoms in most individual cases. Thus, cases of symptomatic rotational vertebral artery occlusion are very rare [34]. Investigation of the effect of the position of the head on flow rate in the vertebral arteries, as measured by Doppler ultrasound at rotations of 30 degrees up to 60 degrees to either side, revealed no changes in blood flow in healthy subjects, which means that common rotation of the cervical spine cannot elicit vertigo [35]. Thus, in conclusion, the available literature indicates that hypoperfusion in the vertebrobasilar territory has no close correlation with clinical symptoms of cervical vertigo, and should not be raised as the sole reason in explaining CV [36,37]. This finding was also confirmed by this study. Moreover, vertebrobasilar insufficiency remains a controversial clinical entity lacking clear diagnostic criteria [38].

Limitations of the Study

This study has several limitations. The sample size is small. However, we consider a cohort of 30–40 DCM patients large enough to confirm the hypothesis of CV as a prevalent condition; we used robust inclusion/exclusion criteria and an extensive evaluation, including neurological and vestibular clinical assessments. Our results have limited importance only for patients with severe cervical spondylosis and symptomatic cervical myelopathy, not for other conditions or a general population. We used the cervical torsion test to evaluate the role of cervical proprioceptors in the pathophysiology of CV, but there are no generally accepted clinical or paraclinical tests for CV and therefore it is predominantly a diagnosis by exclusion.

5. Conclusions

In conclusion, despite a comparatively high prevalence (47%) of dizziness/vertigo in patients with severe cervical spondylosis, it is primarily necessary to be in doubt about the diagnosis of so-called "cervical vertigo" and to seek other (often treatable) aetiologies, thus avoiding the possibility of overlooking other serious neurological, otorhinolaryngological or circulatory problems.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/jcm10112496/s1, Figure S1: Structured questionnaire assessing the prevalence, the type of vertigo and the body positions and movements related to the different vertigo types.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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Conflicts of Interest: The authors declare that they have no conflict of interest.

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ORIGINAL RESEARCH

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Predictors of symptomatic myelopathy in degenerative cervical spinal cord compression

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Abstract

Objectives: To update a previously established list of predictors for neurological cervical cord dysfunction in nonmyelopathic degenerative cervical cord compression (NMDCCC).

Material and Methods: A prospective observational follow-up study was performed in a cohort of 112 consecutive NMDCCC subjects (55 women and 57 men; median age 59 years, range 40–79 years), either asymptomatic (40 subjects) or presenting with cervical radiculopathy or cervical pain (72 subjects), who had completed a follow-up of at least 2 years (median duration 3 years). Development of clinical signs of degenerative cervical myelopathy (DCM) as the main outcome was monitored and correlated with a large number of demographic, clinical, electrophysiological, and MRI parameters including diffusion tensor imaging characteristics (DTI) established at entry.

Results: Clinical evidence of the first signs and symptoms of DCM were found in 15 patients (13.4%). Development of DCM was associated with several parameters, including the clinical (radiculopathy, prolonged gait and run-time), electrophysiological (SEP, MEP and EMG signs of cervical cord dysfunction), and MRI (anteroposterior diameter of the cervical cord and cervical canal, cross-sectional area, compression ratio, type of compression, T2 hyperintensity). DTI parameters showed no significant predictive power. Multivariate analysis showed that radiculopathy, cross-sectional area (CSA) ≤ 70.1 mm^2, and compression ratio (CR) ≤ 0.4 were the only independent significant predictors for progression into symptomatic myelopathy.

Conclusions: In addition to previously described independent predictors of DCM development (radiculopathy and electrophysiological dysfunction of cervical cord), MRI parameters, namely CSA and CR, should also be considered as significant predictors for development of DCM.

KEYWORDS

cervical radiculopathy, degenerative cervical myelopathy, magnetic resonance imaging, nonmyelopathic degenerative cervical cord compression, predictive model

1 | INTRODUCTION

Degenerative cervical cord compression detected by imaging methods, mostly magnetic resonance imaging (MRI), is a prerequisite for the clinical diagnosis of degenerative cervical myelopathy (DCM). This overarching term is preferred to describe the various degenerative conditions of the cervical spine that cause myelopathy, including most frequent cervical spondylotic myelopathy, but also degenerative disc disease and ossification of the posterior longitudinal ligament and of the ligamentum flavum (Nouri, Tetreault, Singh, Karadimas, & Fehlings, 2015). There is a considerable body of current research related to various aspects of DCM, including prognostic factors (Tetreault, Karpova, & Fehlings, 2015; Tetreault, Nouri, Singh, Fawcett, & Fehlings, 2014). In recent years, studies have demonstrated that asymptomatic degenerative cervical cord compression detected on MRI (Boden et al., 1990; Matsumoto et al., 1998; Teresi et al., 1987) may be of a prevalence that exceeds that of symptomatic myelopathy (Bednarik et al., 2004, 2008; Bednařík et al., 1998; Kovalova et al., 2016; Wilson et al., 2013). Knowledge of the prevalence, as well as the frequency, of myelopathy development, and of risk factors influencing this progression, however, is sparse (Wilson et al., 2013). Such knowledge would be of crucial importance to the practical management of asymptomatic degenerative cervical cord compression, and bear upon the important issue of indications for preventive surgical decompression.

In other studies, we have established that the presence of symptomatic cervical radiculopathy and central conduction deficit in the cervical cord, disclosed by electrophysiological methods—somatosensory (SEP) and/or motor-evoked potentials (MEP)—were independent predictors for the development of symptomatic DCM (Bednarik et al., 2004, 2008; Bednařík et al., 1998). These results tally, in part, with those of an international survey undertaken by the spine care community (Wilson et al., 2013) that identified the presence of radiculopathy together with MRI evidence of intramedullar T2 hyperintensity as important factors influencing the decision to perform preventive decompressive surgery in nonmyelopathic patients with degenerative cervical cord compression.

Our previous study (Bednarik et al., 2008), although extensive, had several limitations. Most importantly, the patients, although lacking any clear myelopathic symptoms and/or signs (i.e., "nonmyelopathic"), were in fact not completely asymptomatic, as our cohort was recruited from consecutive patients referred for radiculopathy and/or cervical axial pain. The term "asymptomatic" degenerative cervical cord compression should be reserved for completely asymptomatic cases, while nonmyelopathic subjects with or without signs/symptoms of radiculopathy or cervical pain should be referred to in terms of "nonmyelopathic degenerative cervical cord compression" (NMDCCC). As one of two alternative criteria for MRI-detected cervical cord compression, we used compression ratio (CR) < 0.4 that might preclude less severe diffuse compression to be included into the study.

Further, spinal cord T2 hyperintensity is considered an important risk factor by the spine care community (Wilson et al., 2013), and diffusion tensor imaging (DTI) parameters have shown the capacity to differentiate cervical myelopathy patients not only from normal individuals (Chen et al., 2016; Guan et al., 2015; Lee et al., 2015) but also from nonmyelopathic cervical cord compression cases (Kerkovsky et al., 2012), and further to correlate with severity of myelopathy (Rajasekaran et al., 2014), the segments of the cervical cord involved (Suetomi et al., 2016), and to predict postsurgical outcome (Arima et al., 2015). A re-evaluation of the predictive model describing the risk of progression of NMDCCC to symptomatic myelopathy (Bednarik et al., 2008) was thus indicated, in a sample also including completely asymptomatic subjects with less severe stages of degenerative cervical cord compression and with the use of DTI parameters to validate the previous model.

2 | MATERIAL & METHODS

The sample size calculation, about 120 patients, was based on an anticipated frequency of DCM development of about 18% over the course of 3 years (derived from the previous study, Bednarik et al., 2008) and the number of evaluated predictors (20).

The study sample here consisted of a cohort of consecutive subjects who had been referred to the Department of Neurology between January 2012 and December 2013 with clinical signs and symptoms of cervical radiculopathy, moderate-to-severe chronic or intermittent axial cervical pain, and volunteers in whom MRI signs of degenerative cervical cord compression had previously been detected during an epidemiological study focusing on the prevalence of degenerative cervical cord compression in the population of the province of South Moravia (Kovalova et al., 2016). The inclusion of volunteers from the epidemiological study, complying with the criteria for the current study into prospective evaluation, had been planned beforehand.

All subjects in the study had to comply with the following inclusion criteria:

- MR signs of degenerative compression of the cervical spinal cord with or without concomitant change in signal intensity from the cervical cord on T2/T1 images (see "Imaging" below)
- Absence of any current myelopathic clinical signs and symptoms that could probably be attributed to cervical cord involvement, from the following list.

Symptoms:

- Gait disturbance
- Numb and/or clumsy hands
- Lhermitte's phenomenon
- Bilateral arm paresthesias
- Weakness of lower or upper extremities
- Urinary urgency, frequency, or incontinence.

Signs:

- Corticospinal tract signs:
  - Hyperreflexia/clonus
  - Spasticity
  - Pyramidal signs (Babinski's or Hoffman's sign)
  - spastic paresis of any of the extremities (most frequently lower spastic paraparesis)
- Flaccid paresis of one or two upper extremities in the plurisegmental distribution
- Atrophy of hand muscles
- Sensory involvement in various distributions in upper or lower extremities (always plurisegmental)
- Gait ataxia with positive Romberg sign.

Originally, 137 NMDCCC subjects were included into the prospective evaluation. Twenty-five subjects were lost during follow-up and the follow-up of at least 2 years was completed by a group of 112 subjects (55 women and 57 men; median age 59 years, range 34–79 years): 72 subjects had nonmyelopathic signs or symptoms probably related to degenerative changes of the cervical spine (namely axial pain and/or symptoms or signs of upper extremity monoradiculopathy), while 40 subjects were completely asymptomatic. The whole study cohort was a completely new sample, and none of these subjects had been included in a previously published prospective study on this topic (Bednarik et al., 2004).

Ethical approval for the study was granted by the Ethical Committee of the University Hospital, Brno.

2.1 | Clinical evaluation

A detailed clinical examination was carried out at the beginning of the study and every 6 months thereafter. Patients were instructed about possible signs and symptoms that might indicate newly developed DCM and encouraged to arrange a consultation with a neurologist from the study group if they suspected a progression to myelopathy. The minimum follow-up period was 24 months (median 30 months; range 24–48 years).

A standardized, timed 10-m walk and run (as quickly as possible) was evaluated, in terms of time taken and number of steps required.

The primary end-point of the study was the detection of development of symptomatic DCM based on the occurrence of at least one symptom and one sign (from the list used as exclusionary criteria—see above), which were probably attributed to degenerative cervical cord compression, were not present at the beginning of the follow-up and had no other topical or etiological explanation.

Clinical evaluation focused on the determination of development of symptomatic myelopathy (as primary outcome) was performed by neurology specialists experienced in the diagnosis and practical management of myelopathic cases (ZK, ZKJ, MN) and the final decision on meeting the outcome, that is, development of symptomatic DCM, was approved by ZK, a senior neurologist with a long-term experience in clinical studies on cervical myelopathy.

2.2 | Imaging

Plain anteroposterior, oblique, and lateral radiograms were obtained in all patients. Their Torg–Pavlov ratio (TPR) at C5 level was calculated from lateral radiograms as the anteroposterior diameter of the spinal canal divided by the anteroposterior diameter of the vertebral body. All subjects underwent MRI examination of the cervical spine on a 1.5 T MR device with a 16-channel head and neck coil. The standardized imaging protocol included conventional pulse sequences in sagittal-T1, T2 and short-tau inversion recovery (STIR) and axial planes (gradient-echo T2) for the purpose of morphological evaluation and a DTI sequence in the axial plane coherently covering five segments of the cervical spine from levels C2/3 to C6/7. The DTI scans were acquired at a slice thickness of 4 mm, with the same geometry settings as those employed for the axial T2 images. The clinical status of patients/volunteers was blinded to the neuroradiologists who examined the cervical spine MRIs. The MRI of every subject was evaluated by two neuroradiologists, who agreed on the assessment of the compression in the majority of cases. Where disagreement existed—seldom—the final decision was based on a cooperative decision.

The imaging criterion for cervical cord compression was defined as a change in spinal cord contour or shape at the level of an intervertebral disc on axial or sagittal MRI scan compared to that at midpoint level of neighboring vertebrae.

Spinal cord compression was further graded as:

- Impingement, that is focal concave, usually anterior, defect of spinal cord contour and with preservation of a major part of subarachnoid space outside of the compression—type I (Figure 1a)
- Flat or circular compression with partially preserved subarachnoid space—type IIa (Figure 1b)—or with lost subarachnoid space—type IIb (Figure 1c).

The following conventional MRI parameters were also measured: Cross-sectional spinal cord area (CSA), anteroposterior (AP) and lateral (LL) spinal cord diameter, compression ratio considered in terms of anteroposterior/laterolateral spinal cord diameter (CR) (Arima et al., 2015; Wilson et al., 2013), circumference of spinal cord (CSC), and anteroposterior diameter of cervical canal (APo). These measurements were taken at the level of maximum spinal cord compression (MCL) identified as maximum reduction of AP spinal canal diameter in comparison with other segments. In patients with multisegmental involvement and a similar degree of spinal canal stenosis, the level with the smallest spinal cord area was chosen. The presence of T2 hyperintensity was also noted.

FiberTrak, Extended MR WorkSpace (release 2.6.3.5, Philips Medical Systems) was used for DTI data analysis. Diffusion data were processed and fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values calculated. Measurements were subjected to region-of-interest (ROI) analysis by placing the ROIs at the level of intervertebral disks over the entire spinal cord area depicted on the axial images of isotropic diffusion. Mean FA and ADC values of the spinal cord cross-sections were recorded at maximum

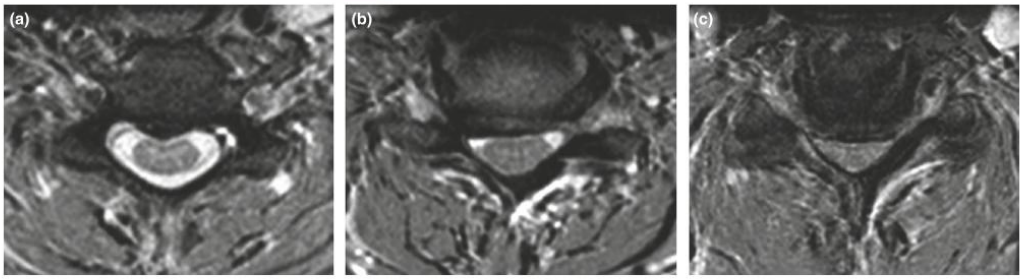

FIGURE 1 (a) Example of the "impingement" type of spondylotic cervical cord compression (type I): focal concave anterior defect of spinal cord contour and with preserved subarachnoid space. (b) Example of a flat compression with partially preserved subarachnoid space (type IIa). (c) Example of a flat compression with lost subarachnoid space (type IIb)

compression level (MCL) in all NMDCCC subjects. FA (ADC) ratios were calculated as FA (ADC) at MCL levels divided by FA (ADC) at C2/3 level.

2.3 | Electrophysiological evaluation

Short-latency SEPs from the median and the tibial nerves were elicited at the beginning of the study by electrical stimulation of mixed nerves at the wrist and the ankle. Similarly, MEPs were elicited by means of transcranial and root magnetic stimulation and recorded from abductor digiti minimi and abductor hallucis muscles on both sides. Details on the methodology of electrophysiological examination and evaluation of results with definition of central conduction abnormality attributable to possible cervical spinal cord lesion are described in previous publications (Bednarik et al., 2004, 2008; Bednařík et al., 1998).

Motor and sensory conduction studies were performed on six motor nerves (median, ulnar, and tibial nerves bilaterally) and four sensory (ulnar and sural nerves bilaterally) using conventional techniques. Needle EMG from four muscles (deltoid, biceps brachii, triceps brachii, and first dorsal interosseous) was performed bilaterally with assessment of spontaneous activity, motor unit potential parameters, and interference patterns. EMG signs of acute motor axonal neuropathy in one myotome (C5–Th1) corresponding with radicular signs and symptoms were classified as radicular. EMG signs of acute, subacute, or chronic motor axonal neuropathy, established in more than one myotome (C5–Th1) unilaterally or bilaterally, were classified as signs of anterior horn cell lesion resulting from degenerative cervical myelopathy.

The following variables were recorded at the entry examination and their association with the predefined end-points (i.e., development of clinically symptomatic DCM and time taken for it) were analyzed.

2.4 | Demographic and clinical data

- Age
- Sex
- Baseline clinical status:
  - Presence of clinical symptoms and signs of cervical radiculopathy (with corresponding CT and/or MR findings and, in the case of motor deficit with corresponding EMG findings, of motor axonal neuropathy in one myotome)
  - Cervical pain
  - Randomly recruited asymptomatic subjects
- 10-m timed walk (time and number of steps)
- 10-m timed run (time and number of steps).

2.5 | Electrophysiological data

- Abnormal SEP interpreted as lesion in either segmental dorsal horn or dorsal column
- Abnormal MEP interpreted as lesion of corticospinal tract
- Abnormal EMG signs of plurisegmental anterior horn cell lesion.

2.6 | Imaging data

- TPR
- AP, LL, CR, CSC, CSA
- FA and ADC at MCL level
- FA and ADC ratios
- T2 hyperintensity
- Type of MRI-detected cervical cord compression
- Maximum stenotic level and number of stenotic levels

2.7 | Statistical analysis

Standard univariate statistical techniques were used to test differences between the chosen subgroups of patients and association between the parameters examined: Fisher's exact test for binary outcomes (or its extension—Fisher–Freeman–Halton exact test for contingency tables larger than 2 × 2) and Mann–Whitney *U* test for continuous variables.

The power of parameters to discriminate between NMDCCC subjects who developed symptomatic DCM and those who remained asymptomatic was evaluated by receiver operating curve (ROC)

analysis and expressed as area under curve (AUC), with sensitivity and specificity based on established cut-off values. The power of parameters to predict development of DCM was calculated using univariate logistic regression. All continuous parameters were also coded as binary predictors on the basis of cut-off points defined in ROC analysis.

Finally, multivariate model—adjusted logistic regression—was used to seek independent predictors for the development of symptomatic DCM. The variables were selected using a forward step-wise selection algorithm.

3 | RESULTS

Clinical evidence of the first signs and symptoms of DCM within the entire follow-up period was found in 15 patients (13.4%): the DCM+ subgroup. DCM developed in seven cases (6.3%) during the first 12 months of the follow-up period. The frequency of myelopathic symptoms and signs in our cohort are summarized in Table 1. Gait disturbance was the most frequent symptom, followed by numb or clumsy hands, while corticospinal tract signs represented dominant initial clinical presentation on neurological examination.

Baseline characteristics for the development of symptomatic cervical myelopathy are summarized in Table 2. Demographic factors (age, sex), maximum compression level, Torg–Pavlov ratio and DTI parameters showed no difference in distribution between DCM+ subgroup and those who did not develop symptomatic DCM (DCM− subgroup). Several clinical (baseline clinical symptoms or signs, parameters of gait and run), electrophysiological (SEP, MEP, EMG), and imaging parameters (type of compression, T2 hyperintensity, APo, AP, CSA, CR), however, displayed differences between DCM+ and DCM− subgroups.

TABLE 1 Frequency of myelopathic symptoms and signs in 15 patients with newly developed DCM

	Frequency (no of patients)
Symptoms	
Gait disturbance	9
Numb and/or clumsy hands	7
Weakness of lower extremity	3
Bilateral arm paresthesias	2
Lhermitte's phenomenon	1
Signs	
Hyperreflexia/clonus	5
Pyramidal signs (Babinski's or Hoffman's sign)	4
Sensory involvement (plurisegmental)	3
Gate ataxia	3
Flaccid paresis of upper extremity (plurisegmental)	3
Spastic paresis of lower extremity, spastic gate	2

Some of these parameters were able to discriminate significantly NMDCCC subjects who developed symptomatic DCM (n = 15) from those who remained asymptomatic (n = 97) (Table 3). Furthermore, the predictive value of parameters to forecast development of DCM using univariate logistic regression and Cox proportional hazard models was evaluated (Table 4). Among significant predictors were the presence of radiculopathy, quantitative gait and run parameters, electrophysiological signs of cervical cord dysfunction detected by SEP, MEP and EMG, and several radiological parameters: type IIB of MRI compression, APo, AP, CSA, CR, and the presence of T2 hyperintensity. DTI parameters showed no significant predictive power.

Multivariate analysis using multivariate-adjusted logistic regression model, however, disclosed radiculopathy, CSA ≤ 70.1 mm^2, and CR ≤ 4.0 as being the only independent predictors (Table 5).

4 | DISCUSSION

This contribution reports the results of a validation study on the predictors for neurological dysfunction in the nonmyelopathic patient with degenerative cervical spinal cord compression. In a sample of subjects with NMDCC that included individuals with no signs and symptoms related to degeneration of the cervical spine, it emerged that cervical radiculopathy is the most important independent predictor for development of DCM. In addition, it established the independent predictive power of certain MRI parameters: CSA < 70.1 mm^2 and CR < 0.4.

In a previous study, with a cohort of 199 NMDCCC individuals followed for 48 months, the authors documented the predictive value of cervical radiculopathy and electrophysiological signs of cervical cord dysfunction detected with SEP and MEP. This cohort, however, included nonmyelopathic but not completely asymptomatic cases, referred to a neurologist for radiculopathy or cervical pain. In this study, 37.5% of nonmyelopathic subjects had the least severe type of compression (type I) and 20.5% the most severe, type IIb. The data from the previous study (Bednařík et al., 1998) were re-evaluated, and the proportions of types I and IIb proved different, with a lower proportion of type I (25.6%) and a higher proportion of type IIb (36.2%). Similarly, CSA < 70 mm^2 was present in 22.3% of individuals in this study compared with 39.7% in the previous one. Thus, subjects in the former study were largely more severe, although still myelopathy-free cases compared with this study, and this probably accounts for the partial discrepancy between the lists of independent predictors in the two studies and for why CSA and CR were disclosed as independent predictors for DCM development. These parameters have been shown to have high reliability in the assessment of cervical cord compression (Karpova et al., 2013; Kovalová, Bednařík, Keřkovský, Adamová, & Kadaňka, 2015). It is not surprising that adding completely asymptomatic subjects to our study group led to a lower proportion of NMDCCC individuals developing DCM in comparison with the former study (13.4% over 3 years and 7.3% during the first year in comparison with 22.6% over 48.4 months and 8.0 during the first year).

TABLE 2 Baseline characteristics in relation to the development of symptomatic cervical myelopathy

Parameter[a]	Total (*n* = 112)	DCM+ (*n* = 15)	DCM− (*n* = 97)	*p*[b]
Sex (male)	57 (50.9%)	8 (53.3%)	49 (50.5%)	.999
Age	59.0 (34.0; 79.0)	58.0 (42.0; 77.0)	59.0 (34.0; 79.0)	.898
Baseline clinical status				
Asymptomatic	40 (35.7%)	2 (13.3%)	38 (39.2%)	**.015**
Cervical pain	50 (44.6%)	6 (40.0%)	44 (45.4%)	
Radiculopathy	22 (19.6%)	7 (46.7%)	15 (15.5%)	
Gait: time (s)	6.0 (3.8; 19.7)	8.8 (4.0; 19.7)	6.0 (3.8; 16.0)	**.015**
Gait: steps	13.0 (6.0; 29.0)	18.0 (10.0; 29.0)	13.0 (6.0; 21.0)	**.002**
Run: time (s)	4.0 (2.2; 13.0)	5.1 (3.0; 13.0)	4.0 (2.2; 8.0)	**.003**
Run: steps	11.0 (7.0; 23.0)	12.0 (8.0; 23.0)	11.0 (7.0; 19.0)	**.143**
EMG signs of myelopathy	7 (6.3%)	3 (20.0%)	4 (4.1%)	**.049**
Abnormal MEP	10 (8.9%)	5 (33.3%)	5 (5.2%)	**.004**
Abnormal SEP	17 (15.2%)	6 (40.0%)	11 (11.3%)	**.011**
Torg–Pavlov ratio	0.9 (0.5; 1.5)	0.9 (0.6; 1.2)	0.9 (0.5; 1.5)	.187
Maximum compression level				
C3/4	15 (13.4%)	2 (13.3%)	13 (13.4%)	.668
C4/5	25 (22.3%)	4 (26.7%)	21 (21.6%)	
C5/6	61 (54.5%)	9 (60.0%)	52 (53.6%)	
C6/7	11 (9.8%)	0 (0.0%)	11 (11.3%)	
Type of compression				
I	42 (37.5%)	1 (6.7%)	41 (42.3%)	**.005**
IIA	47 (42.0%)	7 (46.7%)	40 (41.2%)	
IIB	23 (20.5%)	7 (46.7%)	16 (16.5%)	
APo (mm)	8.0 (4.7; 12.6)	7.5 (5.1; 9.8)	8.3 (4.7; 12.6)	**.015**
AP (mm)	6.7 (4.7; 8.7)	6.1 (4.7; 7.5)	6.7 (4.8; 8.7)	**.015**
LL (mm)	14.6 (12.3; 17.3)	14.6 (13.0; 15.8)	14.6 (12.3; 17.3)	.966
SCC (mm)	36.4 (31.0; 42.9)	35.7 (33.4; 39.0)	36.5 (31.0; 42.9)	.356
CSA (mm^2)	78.7 (53.0; 103.7)	67.1 (53.0; 88.4)	79.4 (54.4; 103.7)	**.001**
CR	0.5 (0.3; 0.6)	0.4 (0.3; 0.5)	0.5 (0.3; 0.6)	**.004**
T2 hyperintensity	11 (9.8%)	5 (33.3%)	6 (6.2%)	**.006**
FA MCL	0.5 (0.3; 0.7)	0.5 (0.4; 0.6)	0.5 (0.3; 0.7)	.620
ADC MCL	1.2 (0.6; 1.6)	1.2 (1.0; 1.4)	1.1 (0.6; 1.6)	.093
FA ratio	0.9 (0.5; 1.6)	0.9 (0.6; 1.1)	0.9 (0.5; 1.6)	.513
ADC ratio	0.9 (0.6; 1.5)	0.9 (0.7; 1.1)	0.9 (0.6; 1.5)	.522

ADC, apparent diffusion coefficient; ADC ratio, ADC at MCL level/C2/3 level; AP, anteroposterior spinal cord diameter; APo, anteroposterior cervical canal diameter; CR, compression ratio; CSA, cross-sectional spinal cord area; DCM, degenerative cervical myelopathy; EMG, electromyography; FA, fractional anisotropy; FA ratio, FA at MCL level/C2/3 level; LL, laterolateral spinal cord diameter; MCL, maximum compression level; MEP, motor-evoked potentials; SCC, spinal cord circumference; SEP, somatosensory-evoked potentials.

[a]Median (minimum–maximum) values were used for continuous variables; absolute and relative frequencies were used for categorical variables. Statistically significant differences are expressed in bold type ($p < .05$).

[b]Mann–Whitney *U* test was used for continuous variables; Fisher's exact test or Fisher–Freeman–Halton exact test was used for categorical variables.

The main limitation of this study is the low number of outcome events in relation to the high number of potential predictors, which weakened the statistical evaluation. In contrast to radiculopathy, which proved a significant predictor in both the current and the previous study (Bednarik et al., 2008) and is generally accepted as such (Wilson et al., 2013), MRI parameters

TABLE 3 Discrimination power of parameters to distinguish between NMDCCC subjects who developed symptomatic DCM (n = 15) and those that remained asymptomatic (n = 97)

Parameter	AUC (95% CI)[a]	p	Cut-off	Sensitivity (%)	Specificity (%)
Sex (male)	0.514 (0.357; 0.672)	.861	–	53.3	49.5
Age	0.510 (0.358; 0.662)	.898	≤59.5	66.7	49.5
Gait: time (s)	0.696 (0.534; 0.858)	**.015**	≥7.35	80.0	66.0
Gait: steps	0.754 (0.601; 0.906)	**.002**	≥17.5	53.3	90.7
Run: time (s)	0.743 (0.584; 0.901)	**.004**	≥4.95	71.4	72.2
Run: steps	0.621 (0.457; 0.784)	.148	≥12.5	50.0	74.4
EMG signs of myelopathy	0.579 (0.410; 0.748)	.324	–	20.0	95.9
Abnormal MEP	0.641 (0.470; 0.812)	.080	–	33.3	94.8
Abnormal SEP	0.643 (0.476; 0.810)	.075	–	40.0	88.7
Torg–Pavlov ratio	0.606 (0.455; 0.757)	.188	≤0.925	73.3	51.5
APo (mm)	0.695 (0.553; 0.838)	**.015**	≤8.4	93.3	42.3
AP (mm)	0.694 (0.546; 0.842)	**.016**	≤5.75	46.7	89.7
LL (mm)	0.503 (0.346; 0.661)	.966	≤15.95	100.0	10.3
SCC (mm)	0.574 (0.431; 0.718)	.356	≤34.35	33.3	84.5
CSA (mm^2)	0.760 (0.624; 0.897)	**.001**	≤70.1	66.7	82.5
CR	0.733 (0.588; 0.877)	**.004**	≤0.40	60.0	89.7
T2 hyperintensity	0.636 (0.466; 0.806)	.092	–	33.3	93.8
FA MCL	0.540 (0.407; 0.673)	.620	≤0.5975	93.3	24.7
ADC MCL	0.635 (0.522; 0.748)	.093	≥1.089	93.3	42.3
FA ratio	0.553 (0.424; 0.681)	.513	≤1.0205	93.3	30.9
ADC ratio	0.552 (0.401; 0.702)	.522	≥0.938	53.3	64.9

ADC, apparent diffusion coefficient; ADC ratio, ADC at MCL level/C2/3 level; AP, anteroposterior spinal cord diameter; APo, anteroposterior cervical canal diameter; CR, compression ratio; CSA, cross-sectional spinal cord area; DCM, degenerative cervical myelopathy; EMG, electromyography; FA, fractional anisotropy; FA ratio, FA at MCL level/C2/3 level; LL, laterolateral spinal cord diameter; MCL, maximum compression level; MEP, motor-evoked potentials; SCC, spinal cord circumference; NMDCCC, nonmyelopathic degenerative cervical cord compression; SEP, somatosensory-evoked potentials.
[a]Area under the curve (95% CI) and its statistical significance, based on ROC analysis. Statistically significant discriminating powers are expressed in bold type (p < .05).

should be considered as preliminary predictors awaiting further confirmation.

Reliable detection of especially early stages of symptomatic DCM is a crucial point of the study. Although previously used diagnostic criteria for DCM were neither standardized nor consistent across published studies, recent and current studies have defined DCM by the presence of at least one neurological sign and at least one neurological symptom in addition to a positive MRI for compression of the cord (Amenta et al., 2014; Kalsi-Ryan, Karamidas, & Fehlings, 2013).

Definition of MRI criteria for degenerative cervical cord compression is essential for reliable and reproducible diagnosis of DCM. In general, spinal cord compression can be described based on the appearance or by measuring a ratio between the anteroposterior diameter at the compressed site and that of a noncompressed site, a ratio between the anteroposterior diameter and the transverse diameter (i.e., CR), or CSA at the region of compression (Nouri, Martin, Mikulis, & Fehlings, 2016). MRI T1/T2 signal changes, although frequently detected in DCM, are neither sensitive nor specific for degenerative cervical cord compression and are invaluable to the diagnosis of DCM (Kalsi-Ryan et al., 2013; Wilson et al., 2013). Regardless of the method used, the objective of especially quantitative measurements is to determine the severity of spinal cord compression rather than to detect especially subtle focal compressions.

The used MRI criterion for cervical cord compression based on subjective evaluation of a spinal cord contour or shape might be considered controversial. In our previous studies on that topic (Bednarik et al., 2004, 2008), we used the presence of impingement (i.e., focal change of contour) and/or CR < 0.4 as MRI criteria for cervical cord compression. However, using these criteria might have prevented less severe circular compressions from inclusion into the study and the compression ratio from showing off its predictive value.

We addressed the issue of an optimal quantitative imaging criterion for cervical cord compression in a recent cross-sectional study of a large cohort of randomly recruited individuals (Kovalova et al., 2016). We used the same qualitative criterion (a change in spinal cord contour) as a gold standard and validated several quantitative MRI parameters for their sensitivity and specificity to discriminate between nonmyelopathic compression and no compression. An anteroposterior diameter of the cervical spinal canal of <9.9 mm was associated with the highest probability of MRI-detected nonmyelopathic cervical cord compression

TABLE 4 Predictive power of parameters to distinguish between NMDCCC subjects who developed symptomatic DCM (n = 15) and those that remained asymptomatic (n = 97) using univariate analysis

	Univariate logistic regression models		Univariate Cox proportional hazard models	
Parameter	**Odds ratio (95% CI)**	***p***	**Hazard ratio (95% CI)**	***p***
Sex (male)	1.120 (0.377; 3.329)	.839	1.102 (0.400; 3.039)	.851
Age	1.004 (0.949; 1.063)	.888	1.005 (0.952; 1.061)	.858
≤59.5	1.959 (0.624; 6.156)	.250	1.791 (0.612; 5.243)	.287
Clinical status at entry				
Asymptomatic	ref.		ref.	
Cervical pain	2.591 (0.494; 13.601)	.260	2.353 (0.000; 0.000)	.296
Radiculopathy	8.867 (1.650; 47.635)	**.011**	6.177 (0.000; 0.000)	**.024**
Gait: time (s)	1.324 (1.112; 1.576)	**.002**	1.235 (1.099; 1.388)	**<.001**
≥7.35	7.758 (2.045; 29.422)	**.003**	6.425 (1.811; 22.796)	**.004**
Gait: steps	1.359 (1.145; 1.613)	**<.001**	1.253 (1.132; 1.388)	**<.001**
≥17.5	11.175 (3.284; 38.022)	**<.001**	7.610 (2.749; 21.067)	**<.001**
Run: time (s)	1.802 (1.249; 2.601)	**.002**	1.368 (1.161; 1.613)	**<.001**
≥4.95	5.760 (1.795; 18.484)	**.003**	4.625 (1.578; 13.553)	**.005**
Run: steps	1.206 (1.017; 1.430)	**.032**	1.154 (1.010; 1.318)	**.035**
≥12.5	2.815 (0.921; 8.603)	.069	2.515 (0.912; 6.939)	.075
EMG signs of myelopathy	5.812 (1.158; 29.171)	**.032**	4.084 (1.151; 14.491)	**.029**
Abnormal MEP	9.200 (2.267; 37.341)	**.002**	6.130 (2.084; 18.030)	**.001**
Abnormal SEP	5.212 (1.556; 17.456)	**.007**	4.114 (1.462; 11.571)	**.007**
Torg–Pavlov ratio	0.084 (0.002; 3.522)	.194	0.105 (0.003; 3.356)	.203
≤0.925	2.926 (0.871; 9.827)	.082	2.623 (0.834; 8.249)	.099
Maximum compression level				
C3/4	ref.		ref.	
C4/5	1.238 (0.198; 7.741)	.819	1.177 (0.215; 6.459)	.851
C5/6	1.125 (0.216; 5.848)	.889	1.049 (0.226; 4.870)	.952
C6/7	—		—	
Type of compression				
I	ref.		ref.	
IIA	7.175 (0.844; 60.989)	.071	6.363 (0.783; 51.715)	.083
IIB	17.937 (2.041; 157.650)	**.009**	14.520 (1.784; 118.149)	**.012**
APo (mm)	0.540 (0.338; 0.864)	**.010**	0.581 (0.390; 0.865)	**.008**
≤8.4	10.250 (1.296; 81.097)	**.027**	9.251 (1.216; 70.398)	**.032**
AP (mm)	0.398 (0.190; 0.835)	**.015**	0.450 (0.238; 0.852)	**.014**
≤5.75	7.612 (2.276; 25.456)	**.001**	5.683 (2.053; 15.730)	**.001**
LL (mm)	0.974 (0.564; 1.680)	.923	0.989 (0.595; 1.645)	.967
≤15.95	—		—	
SCC (mm)	0.912 (0.723; 1.150)	.436	0.928 (0.751; 1.147)	.491
≤34.35	2.733 (0.818; 9.133)	.102	2.310 (0.789; 6.766)	.127
CSA (mm^2)	0.911 (0.859; 0.966)	**.002**	0.925 (0.882; 0.971)	**.002**
≤70.1	9.412 (2.851; 31.071)	**<.001**	7.002 (2.388; 20.529)	**<.001**
CR (0.1 increase)	0.157 (0.051; 0.481)	**.001**	0.217 (0.089; 0.529)	**.001**
≤0.40	13.050 (3.842; 44.329)	**<.001**	8.504 (3.018; 23.962)	**<.001**
T2 hyperintensity	7.583 (1.957; 29.387)	**.003**	5.105 (1.737; 15.000)	**.003**
FA MCL	0.280 (0.000; 320.502)	.723	0.369 (0.001; 254.941)	.765
≤0.5975	4.603 (0.575; 36.861)	.150	4.135 (0.543; 31.474)	.170

(Continues)

TABLE 4 (Continued)

	Univariate logistic regression models		Univariate Cox proportional hazard models	
Parameter	Odds ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*
ADC MCL	8.197 (0.348; 193.260)	.192	6.195 (0.369; 104.003)	.205
≥1.089	10.250 (1.296; 81.097)	**.027**	9.038 (1.188; 68.753)	**.033**
FA ratio	0.334 (0.015; 7.428)	.488	0.392 (0.023; 6.715)	.518
≤1.0205	6.269 (0.788; 49.874)	.083	5.657 (0.744; 43.030)	.094
ADC ratio	2.555 (0.054; 119.886)	.633	2.547 (0.077; 84.577)	.601
≥0.938	2.118 (0.707; 6.341)	.180	2.031 (0.736; 5.606)	.171

ADC, apparent diffusion coefficient; ADC ratio, ADC at MCL level/C2/3 level; AP, anteroposterior spinal cord diameter; APo, anteroposterior cervical canal diameter; CR, compression ratio; CSA, cross-sectional spinal cord area; DCM, degenerative cervical myelopathy; EMG, electromyography; FA, fractional anisotropy, FA ratio, FA at MCL level/C2/3 level; LL, laterolateral spinal cord diameter; MCL, maximum compression level; MEP, motor-evoked potentials; NMDCCC, nonmyelopathic degenerative cervical cord compression; SCC, spinal cord circumference; SEP, somatosensory-evoked potentials.
All continuous parameters were also coded as binary predictors on the basis of cut-off points defined in ROC analysis. Statistically significant predictive powers are expressed in bold type ($p < .05$).

TABLE 5 Predictive power of parameters to distinguish between NMDCC subjects who developed symptomatic DCM ($n = 15$) and those that remained asymptomatic ($n = 97$): multivariate model based on step-wise analysis of data

	Multivariate-adjusted logistic regression models	
Parameter	Odds ratio (95% CI)	*p*
Radiculopathy	5.208 (1.288; 21.057)	**.021**
CR ≤ 4.0	5.613 (1.451; 21.708)	**.012**
CSA (mm^2) ≤ 70.1	6.176 (1.608; 23.719)	**.008**

CR, compression ratio; CSA, cross-sectional spinal cord area; EMG, electromyography; NMDCCC, nonmyelopathic degenerative cervical cord compression. Significant independent predictors are expressed in bold type.

in comparison with CR or CSA, which represent more severe circular compressions and are, on the contrary, more valuable in discrimination between nonmyelopathic compression and symptomatic DCM (Kovalova et al., 2016). We, thus, believe that the use of subjective evaluation of a change in the spinal cord contour or shape compared to that of the neighboring segment and based on agreement of two neuro-radiologist is a legitimate criterion for definition of MRI signs of degenerative cervical cord compression in this study. Quantitative MRI parameters—CR and CSA—proved that especially more severe compressions increase the risk for development of symptomatic DCM and established cut-offs might be used for stratification of a practical management of NMDCCC cases in addition to already known risk factors.

In NMDCCC cases with already detected MRI signs of cervical cord compression, progression into symptomatic myelopathy is based on clinical presentation. Symptoms, especially gait disturbance and loss of sensation, are the most commonly identified presenting symptoms (Kalsi-Ryan et al., 2013), and our findings are similar. Myelopathic signs, although necessary for confirmation of myelopathic origin of otherwise unspecific symptoms, such as gait disturbance, are usually a hallmark of more advanced stage of myelopathy. Assessment tools to better define and document impairment and function quantitatively will be useful in identifying the actual clinical presentation and the impact on independence for these individuals (Kalsi-Ryan et al., 2013). Quantified walk and run are definitely among those assessment tools. Gait or run impairment, however, can have quite a broad range of clinical presentations. We used quantified gait and run not for definition of symptomatic DCM, but as another possible predictor for progression of the disease. Prolonged gait or run proved to be able to discriminate/predict those patients with higher risk of developing symptomatic myelopathy. Lower statistical power of our study due to low number of outcome events in relation to the high number of potential predictors might be the reason why these functional tests, as well as some other predictors, did not prove to be an independent predictors using multivariate analysis. They are, however, promising and worthy further evaluation.

The degenerative compression is certainly a continuum with increased severity of compression and concomitant dysfunction/impairment of spinal cord. As it is not possible to differentiate reliably between symptomatic and nonmyelopathic cervical cord compression cases exclusively on clinical grounds, this limitation could lead to some confusion in terminology. One might speculate whether patients with MRI signs of cervical cord compression and abnormal conduction across spinal cord tracts proved by SEPs or MEP, those with MRI intramedullar signal changes, or those with prolonged time on quantified walk are really nonmyelopathic. Nevertheless, the current concept of symptomatic DCM is based on the presence of clear clinical symptoms and signs, and those "abnormal" or "subclinical" parameters increasing the risk for development of symptomatic myelopathy might define a subgroup of degenerative compressions that might be labeled as high-risk NMDCCC or "presymptomatic myelopathy."

In conclusion, previously and recently identified predictors of DCM development in NMDCCC individuals could help the decision-making process for preventive surgical decompression and, more importantly, in defining a subgroup of NMDCCC individuals at higher risk of DCM, among whom a randomized trial evaluating the benefit of such decompression would be justifiable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Original Article

Semi-automated detection of cervical spinal cord compression with the Spinal Cord Toolbox

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Background: Degenerative cervical spinal cord compression is becoming increasingly prevalent, yet the MRI criteria that define compression are vague, and vary between studies. This contribution addresses the detection of compression by means of the Spinal Cord Toolbox (SCT) and assesses the variability of the morphometric parameters extracted with it.

Methods: Prospective cross-sectional study. Two types of MRI examination, 3 and 1.5 T, were performed on 66 healthy controls and 118 participants with cervical spinal cord compression. Morphometric parameters from 3T MRI obtained by Spinal Cord Toolbox (cross-sectional area, solidity, compressive ratio, torsion) were combined in multivariate logistic regression models with the outcome (binary dependent variable) being the presence of compression determined by two radiologists. Inter-trial (between 3 and 1.5 T) and inter-rater (three expert raters and SCT) variability of morphometric parameters were assessed in a subset of 35 controls and 30 participants with compression.

Results: The logistic model combining compressive ratio, cross-sectional area, solidity, torsion and one binary indicator, whether or not the compression was set at level C6/7, demonstrated outstanding compression detection (area under curve =0.947). The single best cut-off for predicted probability calculated

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using a multiple regression equation was 0.451, with a sensitivity of 87.3% and a specificity of 90.2%. The inter-trial variability was better in Spinal Cord Toolbox (intraclass correlation coefficient was 0.858 for compressive ratio and 0.735 for cross-sectional area) compared to expert raters (mean coefficient for three expert raters was 0.722 for compressive ratio and 0.486 for cross-sectional area). The analysis of inter-rater variability demonstrated general agreement between SCT and three expert raters, as the correlations between SCT and raters were generally similar to those of the raters between one another.

Conclusions: This study demonstrates successful semi-automated compression detection based on four parameters. The inter-trial variability of parameters established through two MRI examinations was conclusively better for Spinal Cord Toolbox compared with that of three experts' manual ratings.

Keywords: Spinal cord compression (SCC); cervical spinal cord; myelopathy; magnetic resonance imaging (MRI); reproducibility

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Introduction

Degenerative cervical spinal cord compression (SCC) is becoming increasingly prevalent as global demographic change tends towards a burgeoning population of ageing people. Up to 40% of the Caucasian American/European population over the age of 60 years show MRI signs of cervical cord compression without neurological symptoms and signs (1,2), a condition termed non-myelopathic degenerative cervical cord compression (NMDC). Around 10% of patients with SCC develop neurological symptoms of compression (1), giving rise to a condition known as degenerative cervical myelopathy (DCM), which has been established as the most common cause of non-traumatic spinal cord dysfunction in adults (3).

Advanced quantitative MRI methods (such as diffusion MRI, magnetization transfer, T_2-weighted white/grey matter signal intensity ratio, and MR spectroscopy) have the capacity to detect cervical spinal cord abnormalities in NMDC patients at much the same order of differences as those that appear when DCM patients are compared with healthy controls (4-8). Several studies have identified parameters that indicate increased risk of progression to symptomatic DCM in the future, among them symptomatic cervical radiculopathy, electrophysiological abnormalities, T_2-weighted MRI hyperintensities, decreased Torg-Pavlov ratio, decreased cross-sectional area (CSA) and compressive ratio (CR) (1,4,9-12).

Although quantitative MRI techniques provide promising predictors of NMDC progression, the diagnosis of SCC is still based on conventional structural MRI. Unfortunately, the definition of SCC is vague and varies between studies, leading to bias in meta-analyses derived from global overviews, rendering multi-centre studies difficult (1). Further, repeated MRI in longitudinal follow-up of mild DCM and NMDC requires reliable quantitative measures to assess the potential progression of radiological outcomes such as CR and CSA. Personal expert evaluation is time-consuming, and investigations of its reliability are currently sparse.

In 2016, the Spinal Cord Toolbox (SCT), an open-source software package for the analysis of spinal cord MRI data was introduced (13). Among its plethora of functionalities, SCT includes tools for automated spinal cord segmentation (14) and subsequent morphometric analysis (13). SCT allows to extract routinely-used radiological measures such as right-left diameter (RL), anterior-posterior diameter (AP) and CSA but also parameters reflecting the indentation, and torsion of the spinal cord. SCT is primarily designed for quantitative analysis of the spinal cord, thus the analysis of the surrounding anatomical structures is limited.

Martin *et al.* (4) recently compared automated shape analysis of metrics computed by SCT with expert evaluation and reported excellent results. They also proposed an objective definition of SCC as deviation from normal in any of three quantitative parameters that reflect flattening, indentation, and torsion. However, the number of participants in their study was limited—20 healthy controls and 20 NMDC patients—while, for some parameters, the cut-off values were defined on the basis of only 3–7 abnormal values (flattening) or 8 abnormal values pooled

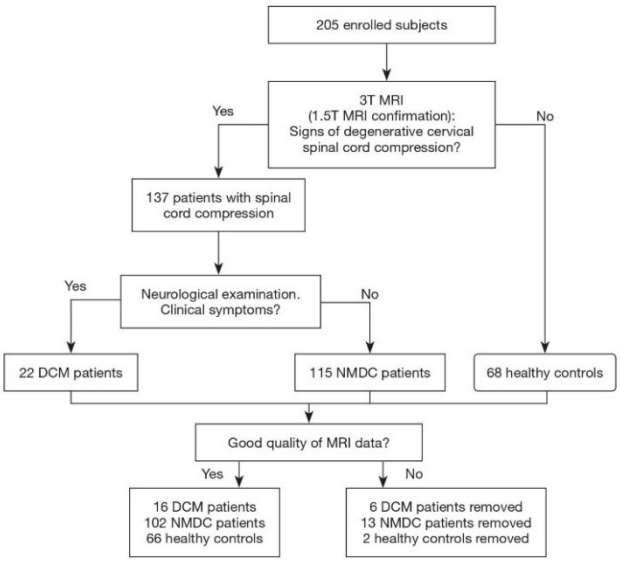

Figure 1 Flowchart of participants' recruitment. DCM, degenerative cervical myelopathy; NMDC, non-myelopathic degenerative cervical cord compression.

over different intervertebral levels (torsion).

The aim of this study is to establish a semi-automated procedure of cervical SCC detection employing the SCT-derived morphometric parameters computed from 3 T MRI data. To establish the variability of the proposed method, the methodology includes investigation of the inter-trial variability of SCT by comparing two (1.5 and 3 T) MRI scanners. A final comparison is then made between the inter-trial and inter-rater variability of experts' manual ratings and the automated assessment.

We present the following article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-21-782/rc).

Methods

Study participants

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All study participants gave written informed consent, and all study procedures received approval from the institutional review board of the University Hospital Brno (No. EKV-2017-055). A total of 205 participants were enrolled, 68 of them healthy controls (HC) and 137 participants with cervical SCC, between May 2018 and May 2020. Healthy controls and SCC participants were recruited from a database of individuals at the spinal cord centre of a tertiary university hospital, all of whom had been examined in the course of parallel projects (7,8,15). SCC participants fulfilled the radiological imaging criteria for cervical cord compression. All participants with SCC were clinically examined by neurological procedures that focused on the detection of symptoms and signs of degenerative cervical myelopathy; this served to distinguish between DCM and NMDC group. The severity of disability and functional impairment was scored on the modified Japanese Orthopaedic Association (mJOA) scale. The HCs exhibited no MRI signs of cervical cord compression, were free of any known musculoskeletal disorders and had no acute medical problems. Only participants with sufficient MRI data quality were further analysed, resulting in 66 HC, 102 NMDC and 16 DCM (see *Figure 1*). MRI data from these 184 participants were submitted to semi-automated cervical spinal cord

compression detection. From this pool of participants, 35 HCs and 30 SCCs were used for a variability analysis of quantitative morphometric parameters. In this analysis, similar parameters to the SCT output were also quantified manually. Data available on request due to privacy/ethical restrictions.

MRI acquisition

Each participant had already been scanned twice, once employing 3T MRI and once employing 1.5 T MR, as part of parallel projects. For both measurements, multi-echo gradient echo (ME-GRE) sequences were used. The 3 T MRI (Prisma, Siemens, Erlangen, Germany) examination used 64-channel head/neck and 32-channel spine coils and contained axial T_2*-w, T_2-w TSE sagittal and diffusion-weighted images (15). For the purpose of this study, the axial T_2*-w MEDIC (Multi-Echo Data Image Combination) sequence covering vertebral levels C3–C7 was used (FOV 180×180 mm^2, matrix size 512×512 voxels after interpolation in Fourier domain, slice thickness 2.5 mm, 42 contiguous slices, interleaved acquisition, TR/TE =778/17 ms, 4 echoes, flip angle 30°, voxel size 0.35×0.35×2.5 mm^3 after interpolation in k-space; original voxel size 0.70×0.70×2.5 mm^3, TA =7 min 51 s).

On 1.5T MRI (Philips Ingenia, Amsterdam, The Netherlands) standard diagnostic imaging of cervical spine was performed. The protocol used 16 channel head/neck coil and included T_1-w TSE sagittal, T_2-w TSE sagittal, T_2-w TSE STIR sagittal, T_2-w TSE transversal (used for creating the report in a routine clinical practice) and the axial T_2*-w multi-echo steady-state sequence (T2 FFE—fast field echo, equivalent of MEDIC) covering C2–C7 levels with 20 contiguous slices, FOV 170×170 mm^2, acquisition matrix size 284×271 voxels, slice thickness 4.0 mm, TR/TE =478/9.2 ms, 1 echo, flip angle 25°, voxel size 0.60×0.63×4.0 mm^3, TA =4 min 37 s. The T2 FFE sequence was used for this study.

Radiological detection of cord compression, image analysis and morphometric parameters

Qualitative criteria for cervical spinal cord compression at each level were expert-rater defined as changes in spinal cord contour or shape at the level of an intervertebral disc on axial MRI scan compared with the midpoint level of neighbouring vertebrae (9,11). The reported level of spinal cord compression was confirmed on T2 TSE sagittal scan. Visual identification of spinal cord compression was performed consensually by two board-certified radiologists (MK, 18 years of practice; TR, 6 years of practice). Qualitative identification of cervical cord compression was largely made on the basis of 3 T data, and only when results were unclear were the corresponding images from the second measurement with the 1.5 T MRI scanner deployed.

Two experts manually selected the slice corresponding to each intervertebral discs C3/4, C4/5, C5/6 and C6/7 on both 1.5 T and 3T, by consensus. The C2/3 intervertebral level was not analysed. Selection of axial slices was performed in correlation with sagittal T2 TSE scans. In the case of a single acquired slice of the intervertebral space, the acquired slice was further analysed. In the case of multiple acquired slices of the intervertebral space, the slice with the lowest compression ratio was further analysed. IntelliSpace Portal Concerto v10.1 software (Philips, Best, The Netherlands) was employed for quantitative assessment of the morphometric parameters by three expert raters (Rater1 = TR, board-certified radiologist, 6 years of practice; Rater 2 = TS, medical student, 1 year of practice; Rater 3 = JK, neurologist, 5 years of practice), who measured CSA, anterior-posterior diameter (AP) and transverse diameter (RL) in these slices.

Both 3T Siemens and 1.5T Philips T2*-w axial images were processed using the SCT v4.1.0 (RRID:SCR_014170) to segment the spinal cord automatically, employing a convolution neural network algorithm (14) automatically to extract morphometric parameters for each participant utilizing the *sct_process_segmentation* function (13). All automated segmentations of the spinal cord provided by SCT were visually inspected using FSLeyes viewer (part of FSL) and spinal cord contour was manually corrected in approximately 5% HC and 30% SCC. Morphometric parameters were extracted for each individual slice, both with and without the integrated angle-correction option. The angle correction stretches the image of spinal cord within the slice on the basis of the angle between the centre-line and the axial plane. The slices corresponding to intervertebral levels were then manually selected. To be more specific, the *area* (cross-sectional area), *diameter_AP*, *diameter_RL*, *eccentricity*, *orientation* and *solidity* functions were used for further analysis.

Compression ratio was calculated as AP:RL diameter, which, together with CSA, reflected flattening of the spinal cord. Eccentricity was defined as the ratio of the focal distance over the major axis length of ellipse with the same second moments as the spinal cord, thus having similar interpretation as CR. Solidity, which was used to assess

indentation of the spinal cord, was expressed as the ratio of CSA to the area of the smallest convex polygon surrounding all positive pixels in the image (13). Torsion was calculated in three variants, based on the extracted *orientation* (∠): (I) the average of absolute differences in orientation between the slice at the intervertebral disc and one slice above and below, (II) similarly, but taking into the account two slices above and below, and (III) finally, taking into account three slices above and three slices below (see *Figure 2*):

$$torsion(v1) = \frac{1}{2}\left(\left|\angle x - \angle x_{-1}\right| + \left|\angle x - \angle x_{+1}\right|\right) \quad [1]$$

$$torsion(v2) = \frac{1}{4}\left(\left|\angle x - \angle x_{-1}\right| + \left|\angle x - \angle x_{+1}\right| + \left|\angle x_{-1} - \angle x_{-2}\right| + \left|\angle x_{+1} - \angle x_{+2}\right|\right) \quad [2]$$

$$torsion(v3) = \frac{1}{6}\left(\left|\angle x - \angle x_{-1}\right| + \left|\angle x - \angle x_{+1}\right| + \left|\angle x_{-1} - \angle x_{-2}\right| + \left|\angle x_{+1} - \angle x_{+2}\right| + \left|\angle x_{-2} - \angle x_{-3}\right| + \left|\angle x_{+2} - \angle x_{+3}\right|\right) \quad [3]$$

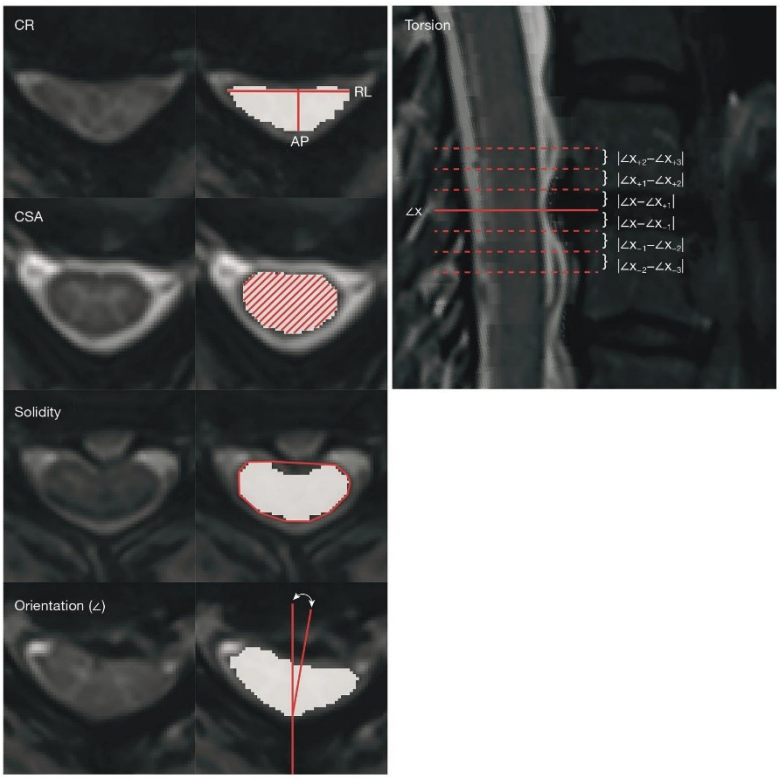

Figure 2 SCT-derived morphometric parameters. CR was calculated as AP:RL ratio. Torsion was calculated as the average of absolute differences in orientation between adjacent slices. RL, right-left diameter; AP, anterior-posterior diameter; CR, compressive ratio; CSA, cross-sectional area; SCT, Spinal Cord Toolbox.

The optimum approach was then selected on the basis of receiver operating characteristic (ROC) analysis with compression as the dependent variable. The results from two slices and three slices above and below proved to be very similar, with the latter variant considered slightly better in the light of the average area under the curve (AUC) (Table S1). Therefore, the torsion used for further analysis was calculated through the three slices with each slice thickness 2.5 mm above and below.

Neither indentation nor torsion was quantified by expert raters. No adjustments were made to defining the compression, selection of slices and experts' manual ratings in consideration of any discrepancies with semi-automated SCT analysis.

Statistical analysis

Data were analysed in SPSS version 25 (Statistical Package for the Social Sciences, IBM, Armonk, New York). All continuous variables were tested for normality by means of the Kolmogorov-Smirnov test. Continuous parameters were summarized as mean (± Standard Deviation, SD) or median (5th–95th percentile range) depending on their distribution. Categorical parameters were expressed as absolute and relative frequencies. Fisher´s exact test (for binary variables) Chí-square test for nominal variables, and the Kruskal-Wallis test and Mann-Whitney U test (for continuous variables) were employed to test differences between selected groups. Repeated measures ANOVA were employed to assess differences in morphometric parameters across the intervertebral levels and between different raters. Paired *t*-tests and Wilcoxon signed ranks sum tests were used to test differences between data with and without angle correction. Pearson/Spearman correlations were used to analyse the relationship between continuous variables, depending on their distributions. There were no missing data.

Angle correction

All morphometric parameters derived from SCT were extracted twice, once with angle correction and once without. The differences between corrected and uncorrected values were calculated and the parameters with and without correction were compared by means of paired *t*-test and Wilcoxon signed ranks test, depending on their distribution. The results of angle correction analyses appear in the Table S2. The values with angle correction were employed for the main analysis. A summary of data without angle correction appears in the Tables S3,S4.

Relationship between CR and eccentricity

Interestingly, but in agreement with the definition of eccentricity as the ratio of the focal distance over the major axis length of ellipse with the same second moments as the spinal cord, the value of the Spearman correlation between CR and eccentricity was 1 in all analyses. A scatter-plot of the relationship appears in the Appendix 1 (Figure S1). There was no significant difference between usage of CR and eccentricity throughout the study and CR was chosen only because it is easier to interpret, as well as being in more frequent use in other studies.

Normative data

The normative data of SCT-derived morphometric parameters with angle correction were expressed as mean (± SD) or median (5th–95th percentile range) depending on their distribution. ROC with AUC was plotted to assess the detection capability of morphometric parameters with angle correction in the establishment of cervical cord compression at each intervertebral level determined by the consensus of two experts. The best cut-offs were determined by Youden's index.

Semi-automated compression detection

Parameters with an AUC of >0.7 (the ability to detect compression) and a mutual correlation of less than 0.7 (due to collinearity) were used in multivariate logistic regression (for binary-coded presence of compression as an outcome) with backward stepwise removal of factors. CR was chosen as one parameter representing both AP and RL. Age and height were also included as confounding factors.

Four multivariate logistic regression model were calculated, one for each intervertebral level C3/4, C4/5, C5/6, C6/7. Further, a multivariate logistic regression pooled over all intervertebral levels was performed. The base was set to level C5/6 due to the highest number of compressions in this level and all other levels (C3/4, C4/5 and C6/7) were included in the pooled model as categorical (dummy) variables. The models were constructed over data from HC and data in levels with compression in the SCC group. Therefore, the levels without compression in SCC were not used. The approach, including levels without compressions from the SCC group as "healthy levels", appears in the Table S6. ROC analysis of the predicted probabilities of final multivariate logistic regressions was performed and three diagnostic thresholds determined: the first by maximising the Youden's index (the sum of sensitivity and specificity), the second defined

as the maximal value with sensitivity of over 90% and the third as the minimal value with specificity of over 90%. The latter two values were used to establish a borderline interval. Cross-validation of this approach was performed with random assignment of each level with compression and levels from healthy participants to six groups. Six models were then constructed, each over 5/6 of the data. ROC analysis was performed, defining the best cut-off for predicted probability employing the Youden's index. The predicted probability, and consequently sensitivity and specificity of compression detection, were then calculated in the remaining 1/6 levels.

Inter-trial and inter-rater variability of morphometric parameters

The analysis of variability took into account the RL, AP, CR and CSA from a subset of 35 HCs and 30 NMDCs, parameters obtained from both the MRI measurements employing SCT, together with the assessments from all three expert raters. The variability of solidity was also analysed, in SCT only. The differences between the two MRI measurements were calculated for SCT and each expert rater, with the equation stated as the values from 1.5 T minus the values from 3T. Intraclass correlation coefficients (ICC, two-way random, absolute agreement, single measurements) were used to compare each parameter and each rater over the two MRI measurements. Further, visualization of inter-rater and inter-trial variability was performed with multidimensional scaling. A correlation matrix (Pearson coefficients) was calculated for both CR and CSA for all raters and SCT. Then, the distances between each pair were defined as 1 minus the Pearson correlation coefficient and matrix of distances was generated. Finally, these distances were visualized in common space using two dimensions employing the multidimensional scaling.

Results

Participant characteristics

Participant characteristics appear in *Table 1*. There were 66 healthy controls and 118 participants with SCC, 102 (86.4%) of whom were asymptomatic (NMDC) and 16 (13.6%) exhibited clinical symptoms of myelopathy (DCM). The median age was 3.5 years higher in both NMDC and DCM groups. There were no statistically significant differences in sex, height, and weight. There were no significant correlations between age, weight, and any of the morphometric parameters in HC, although there was a significant correlation between height and RL diameter ($0.436<r<0.513$), CR ($-0.183<r<0.336$) and CSA ($0.340<r<0.445$) at each level. Similarly, in the variability subset, the median age was higher in the NMDC group, although significance could not be established due to the low number of participants. Age and height were therefore considered confounding factors in multivariate analysis. The median interval between the two MRI examinations was 11 days and there was no significant difference between the groups.

Normative data and proposed thresholds

Table 2 summarizes the SCT-derived morphometric parameters of HC (normative data) and of SCC participants with compression at given intervertebral levels. All individual parameters showed moderate capacity to detect compressions based on ROC analysis of each metric in relation to the presence of compression. However, the cut-offs were close to one standard deviation (SD) from the mean and within the 5th–95th percentile for solidity and torsion. Both sensitivity and specificity exceeded 80% for only a few parameters. Repeated measures ANOVA with Bonferroni corrections in HC showed significant differences ($P_{corr}<0.003$) between intervertebral levels in CR (except for C4/5 compared with C6/7) and CSA (except levels C4/5 and C5/6 compared with C6/7). In contrast, only a borderline significant difference emerged between solidity at C3/4 compared with other levels ($0.030<P_{corr}<0.043$); otherwise, solidity did not differ between levels. Finally, there was no difference in torsion between levels C3/4, C4/5 and C5/6, but all of them differed from level C6/7 ($P_{corr}<0.002$).

Compression detection

The variables included in the multivariate logistic model were age, height, CR, CSA, solidity, and torsion for each intervertebral level. The pooled model included CR, CSA, solidity, torsion, and intervertebral level (expressed as dummy variables with the base set at level C5/6). At each level (except C3/4) four factors remained significant: CR, CSA, solidity, and torsion. At level C3/4, only CR and CSA remained significant; this, however, was attributed to the low number of compressions at this level and used the same four factors to retain consistency of results. For the pooled model, CR, CSA, solidity, torsion, together with whether or not compression set at level C6/7 remained significant. The

Table 1 Characteristics of all participants and the subset of participants used for reliability analysis

Characteristics	HC, n=66	NMDC, n=102	DCM, n=16	P value
All participants				
Age (years)	53.5 (41.0, 70.7)	57.0 (42.2, 72.9)	57.0 (35.0, 76.8)	0.042*
Sex	Female: 42 (63.6%); male: 24 (36.4%)	Female: 57 (55.9%)	Female: 9 (56.3%)	0.595
Height (cm)	170 (156, 186)	170 (156, 186)	170 (147, 181)	0.422
Weight (kg)	80 (51, 105)	79 (55, 110)	79 (62, 102)	0.996
Number of patients with compression at level				
C3/4		19	5	
C4/5		55	10	
C5/6		76	13	
C6/7		39	3	
mJOA score		18 (18, 18)	15 (9, 17)	
Variability subset	HC, n=35	NMDC, n=30		
Age (years)	51.3 (40.5, 71.5)	58.8 (41.6, 72.2)		0.060
Sex	Female: 21 (60.0%); male: 14 (40.0%)	Female: 16 (53.3%); male: 14 (46.7%)		0.623
Height (cm)	174 (158, 193)	171 (157, 183)		0.282
Weight (kg)	80 (52, 100)	78 (61, 113)		0.828
Interval between MRIs (days)	10.0 (2.0, 75.0)	13.5 (1.0, 84.2)		0.683
Number of patients with compression at level				
C3/4		4		
C4/5		14		
C5/6		22		
C6/7		15		

Expressed as count, median (5th–95th percentile) or percentage. Kruskal-Wallis test used for continuous variables for comparison of all participants, Mann-Whitney test for reliability subset. Chí-square test was used for nominal variables for all participants, Fisher's exact test for reliability subset. HC, healthy controls; NMDC, non-myelopathic degenerative cervical cord compression; DCM, degenerative cervical myelopathy.

results are summarized in *Table 3*.

The parameters of each model were very similar, and the pooled model demonstrated outstanding compression discrimination (AUC = 0.947). The latter model explained 73.6% of data variability (Nagelkerke R^2 =0.736). The probability for each participant can be calculated by means of:

$$p = \frac{e^{(57.501-0.273*CR-0.102*CSA-0.408*solidity+2.168*torsion-2.729*C6/7)}}{1+e^{(57.501-0.273*CR-0.102*CSA-0.408*solidity+2.168*torsion-2.729*C6/7)}} \quad [4]$$

The thresholds for compression detection were defined by ROC analysis. The borderline interval of predicted probabilities (with the boundaries defined as a maximum value of sensitivity of over 90% and the minimum value with a specificity of over 90%) was 0.345–0.451. All cut-offs of predicted probability under 0.345 exhibited a sensitivity of 90% or more, and all cut-offs above 0.451 exhibited a specificity of 90% or more. The best single cut-off was determined by Youden index at 0.451, with sensitivity 87.3%, specificity 90.2%, positive predictive value

Table 2 Normative data and data from levels with compression for parameters extracted with SCT with angle correction

	Healthy controls	Levels with compressions	Cut-off	AUC (95% CI)	Sensitivity (%)	Specificity (%)
RL (mm)						
C3/4	12.6±1.1	13.1±1.2				
C4/5	13.3±1.1	13.7±1.2				
C5/6	13.2±1.1	13.3±1.5				
C6/7	12.1±1.2	12.3±1.1				
AP (mm)						
C3/4	7.3±0.5	6.0±0.8				
C4/5	7.3±0.6	6.2±0.8				
C5/6	7.0±0.6	6.1±0.7				
C6/7	6.6±0.6	5.7±0.6				
CR (%)						
C3/4	58.7±6.3	46.0±6.2	52.0	0.943 (0.894, 0.992)	87.5	90.9
C4/5	55.1±6.4	45.7±6.8	51.1	0.854 (0.791, 0.918)	83.1	75.8
C5/6	53.4±6.2	46.1±6.5	49.6	0.792 (0.723, 0.862)	68.5	77.3
C6/7	54.8±6.1	46.7±5.6	50.2	0.844 (0.768, 0.92)	78.6	81.8
CSA (mm^2)						
C3/4	71.7±8.2	59.5±11.1	65.7	0.874 (0.782, 0.966)	87.5	81.8
C4/5	75.4±8.6	64.4±10.1	68.4	0.807 (0.732, 0.882)	70.8	81.8
C5/6	71.4±9.3	60.7±10.8	61.0	0.781 (0.71, 0.853)	56.2	90.9
C6/7	62.3±8.9	53.4±8.2	56.7	0.778 (0.687, 0.87)	71.4	78.8
Solidity (%)						
C3/4	96.8 (95.1–98.3)	94.4 (88.4–98.0)	95.5	0.857 (0.753, 0.961)	70.8	95.5
C4/5	96.4 (94.1–97.8)	94.8 (87.8–97.8)	95.9	0.744 (0.658, 0.83)	72.3	71.2
C5/6	96.3 (94.0–98.0)	94.6 (85.8–97.2)	94.7	0.773 (0.701, 0.845)	55.1	90.9
C6/7	96.4 (93.8–98.3)	94.7 (91.1–97.5)	95.1	0.754 (0.658, 0.849)	64.3	77.3
Torsion (degree)						
C3/4	0.81 (0.45–2.01)	1.48 (0.49–3.61)	1.23	0.737 (0.607, 0.868)	62.5	86.4
C4/5	0.75 (0.25–1.61)	1.25 (0.49–2.87)	0.78	0.764 (0.683, 0.844)	83.1	60.6
C5/6	0.88 (0.44–1.65)	1.37 (0.61–3.18)	1.09	0.774 (0.701, 0.847)	75.3	71.2
C6/7	1.18 (0.53–2.76)	2.10 (0.52–3.84)	2.03	0.719 (0.615, 0.824)	54.8	87.9

Data are presented as mean ± SD where normally distributed, median (5th–95th percentile) for data without normal distribution. The values are calculated from 66 HC: 24 compressions at C3/4 level, 65 at C4/5 level, 89 at C5/6 level and 42 at C6/7 level. ROC analysis served to compare the quantitative parameters with expert qualitative assessment of the presence of compression. For data without angle correction, see Table S3. AUC, area under curve; CI, confidence interval; RL, right-left diameter; AP, anterior-posterior diameter; CR, compressive ratio; CSA, cross-sectional area; SCT, Spinal Cord Toolbox.

Table 3 Models for semi-automated compression detection employing morphometric parameters with angle correction (for data without angle correction see Table S4)

	Coefficients	OR (95% CI)	P value (factors)	P value (model)	Nagelkerke R^2	AUC (95% CI) of predicted probabilities
C3/4				<0.0005	0.843	0.979 (0.952, 1.000)
Constant	58.300		0.061			
CR (%)	−0.530	0.588 (0.413, 0.838)	0.005			
CSA (mm^2)	−0.167	0.846 (0.721, 0.992)	0.038			
Solidity (%)	−0.233	0.792 (0.392, 1.598)	0.308			
Torsion (degree)	2.369	10.690 (0.434, 263.133)	0.188			
C4/5				<0.0005	0.725	0.943 (0.904, 0.982)
Constant	54.361		0.003			
CR (%)	−0.268	0.765 (0.673, 0.869)	<0.0005			
CSA (mm^2)	−0.108	0.898 (0.831, 0.970)	0.006			
Solidity (%)	−0.375	0.687 (0.476, 0.992)	0.045			
Torsion (degree)	2.629	13.853 (3.534, 54.303)	<0.0005			
C5/6				<0.0005	0.706	0.939 (0.903, 0.975)
Constant	67.088		0.002			
CR (%)	−0.191	0.826 (0.739, 0.923)	0.001			
CSA (mm^2)	−0.069	0.933 (0.880, 0.989)	0.020			
Solidity (%)	−0.593	0.553 (0.356, 0.857)	0.008			
Torsion (degree)	3.506	33.314 (7.500, 147.973)	<0.0005			
C6/7				<0.0005	0.800	0.964 (0.930, 0.997)
Constant	90.540		0.002			
CR (%)	−0.464	0.629 (0.509, 0.777)	<0.0005			
CSA (mm^2)	−0.199	0.819 (0.734, 0.915)	<0.0005			
Solidity (%)	−0.620	0.538 (0.310, 0.934)	0.028			
Torsion (degree)	1.989	7.311 (2.349, 22.752)	0.001			
Pooled model				<0.0005	0.736	0.947 (0.928, 0.966)
Constant	57.501		<0.0005			
CR (%)	−0.273	0.761 (0.712, 0.813)	<0.0005			
CSA (mm^2)	−0.102	0.903 (0.868, 0.939)	<0.0005			
Solidity (%)	−0.408	0.665 (0.535, 0.826)	<0.0005			
Torsion (degree)	2.168	8.744 (4.809, 15.900)	<0.0005			
Level C6/7 (yes or no)	−2.729	0.065 (0.026, 0.162)	<0.0005			

Models were constructed over data from HC and from levels with compression in SCC. OR, odds ratio; CI, confidence interval; AUC, area under curve.

88.1% and negative predictive value 89.5%. The cross-validation of this approach appears in Table S5. The overall sensitivity of compression detection in validation data (i.e., participants that were not used for model construction) was 0.836, specificity 0.905, positive predictive value 0.880 and negative predictive value 0.869.

The minimum predicted probability of any compression in the DCM group was 0.484, each DCM patient had at least one compression at a probability of over 0.764, and the median of maximal probabilities in the DCM group was 0.985.

The approach including levels without compressions from the SCC group as "healthy levels" appears in the Table S6. The AUC for predicted probability in the pooled model using this approach was 0.906.

The odds ratios (ORs) for CR, CSA and solidity were consistently below 1 for all models, while the OR of torsion was significantly higher than 1. Depending on the exact model, a drop of 1% in CR increases the risk of compression by 1.2–1.7×, a drop in CSA of 10 mm^2 increases risk of compression 2.0–7.3×, a drop in solidity of 1% increases the risk of compression 1.3–1.9× and an increase in torsion of one degree increases the risk of compression 7.3–33.3 times. The categorical predictor, compression situated at level C6/7, significantly decreases the risk compared with other levels, which accords with the fact that the normal values of CSA and torsion at level C6/7 would be abnormal at other levels. *Figure 3* shows examples of morphometric parameters and the resulting predicted probability of compression in healthy control and participants with various severity of compressions.

Analysis of DCM compared to NMDC group

There were 16 (13.6%) DCM patients in the SCC group. The percentage of DCM in the SCC group bore an approximate resemblance to the estimated prevalence of DCM (1). The comparison of morphometric parameters and predicted probabilities calculated from the pooled model between the compression in NMDC and DCM group is shown in Table S7. There was no significant difference between these two groups, except for CSA at levels C3/4 (62.7 *vs.* 47.1 mm^2) and C4/5 (65.5 *vs.* 58.0 mm^2), however, this significance did not pass the correction for multiple testing and the number of subjects with compression was very low in both groups. The ROC analysis of all parameters and predicted probability did not find any well performing discriminating parameter to distinguish between NMDC and DCM. The only AUC > 0.7 were for CSA in C3/4 and C4/5 already mentioned and for solidity and predicted probability in C3/4. None of the compressions in DCM were undetected and the median of maximal predicted probabilities in DCM patients was 0.985.

Inter-trial and inter-rater variability of morphometric parameters

The differences in morphometric parameters for each expert rater and SCT with and without angle correction between the two MRI examinations appear in *Table 4* and *Figure 4*. Based on these results, SCT performed better than any of the three expert raters. The differences between SCT values with angle correction were generally slightly smaller, and ICC slightly better. The relevant table, divided into HC and SCC, appears in the Table S8.

Comparison of the inter-trial variability relative to inter-rater variability using multidimensional scaling is shown in *Figure 5*. It should be viewed as a map of distances; the higher the distance between each pair, the lower the Pearson correlation coefficient between the pair. *Figure 5* provides an approximate illustration of the agreement of SCT with expert raters since the former lay in quite close proximity to the cluster of expert raters. It also demonstrated that, in general, the values from each measurement correlated more closely in SCT compared with expert raters. Further, it shows very close correlation between SCT values with and without angle correction. The complete correlation matrices are shown in Table S9.

Discussion

Summary of findings

This study introduced semi-automated detection of compression in the cervical spinal cord, employing an open-source SCT software package. It demonstrated lower inter-trial variability of quantitative morphometric parameters extracted with SCT than that established by expert manual ratings. This approach, therefore, could well prove ideal for consistency across longitudinal and multi-centre studies, something that is acutely lacking in current research. The results indicated outstanding compression discrimination, combining four radiological parameters extracted with SCT from conventional MRI (CR, CSA, solidity, torsion) and one binary indicator of being the level C6/7 or not, into the logistic model.

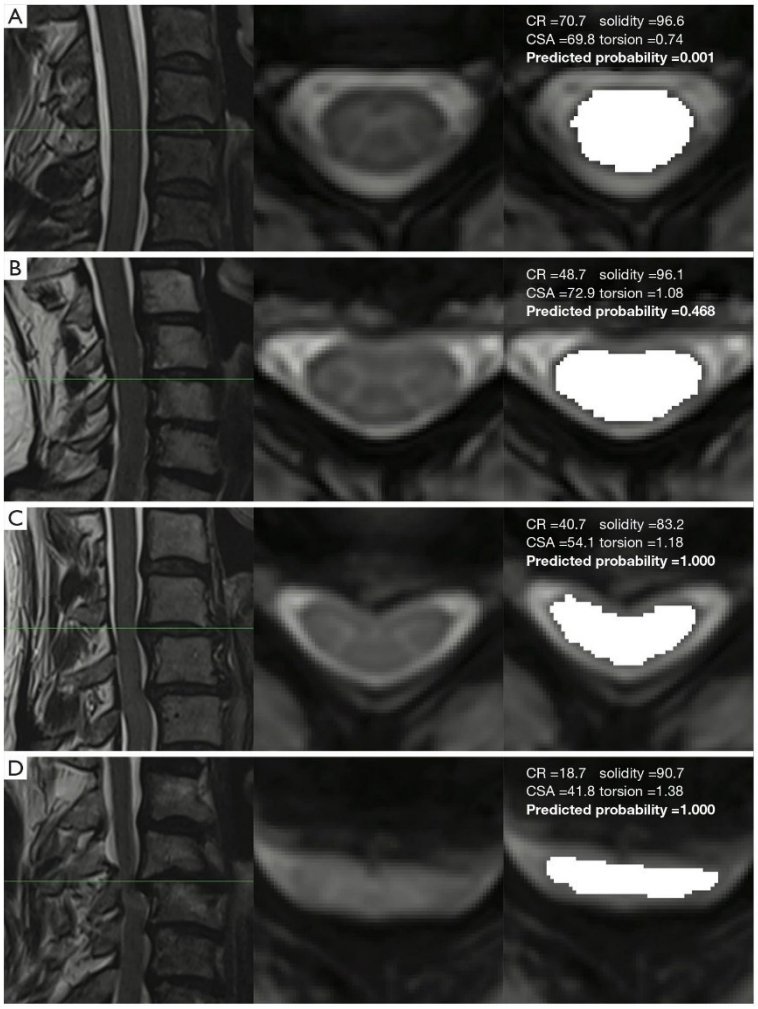

Figure 3 Examples of relation between morphometric parameters and predicted probability of compression in healthy control and various compressions. (A) Healthy control with normal parameters and low predicted probability of compression, (B) NMDC participant, (C) DCM participant with extremely low solidity, (D) DCM participant with extremely low CR. NMDC, non-myelopathic degenerative cervical cord compression; DCM, degenerative cervical myelopathy; CR, compressive ratio.

Table 4 Differences in morphometric parameters between the two MRI examinations (3 and 1.5 T) in 35 HCs and 30 SCCs

	SCT (without angle correction)	SCT (with angle correction)	Rater 1	Rater 2	Rater 3
RL (mm)					
C3/4	0.52 (–0.34, 1.18)	0.50 (–0.35, 1.17)	1.00 (0.30, 1.70)	0.34 (–0.64, 1.09)	0.76 (0.02, 1.56)
C4/5	0.61 (–0.38, 1.43)	0.60 (–0.37, 1.46)	1.00 (0.43, 1.57)	0.32 (–0.64, 1.27)	0.68 (–0.42, 2.99)
C5/6	0.45 (–0.37, 1.46)	0.42 (–0.37, 1.46)	0.80 (–0.37, 1.70)	0.17 (–0.66, 1.1)	0.62 (–1.03, 2.11)
C6/7	0.5 (–0.23, 1.34)	0.48 (–0.22, 1.33)	0.8 (–0.2, 1.6)	0.2 (–0.79, 1.16)	0.54 (–1.25, 2)
ICC	0.832 (0.289, 0.935)	0.832 (0.290, 0.935)	0.678 (–0.055, 0.883)	0.815 (0.751, 0.862)	0.631 (0.264, 0.795)
AP (mm)					
C3/4	0.58 (–0.4, 1.17)	0.57 (–0.38, 1.19)	1.40 (0.63, 2.14)	0.53 (–0.55, 1.34)	0.75 (–0.28, 1.84)
C4/5	0.25 (–0.23, 1.01)	0.27 (–0.23, 1)	1.20 (0.46, 1.9)	0.60 (–0.36, 1.30)	0.92 (–0.70, 2.10)
C5/6	0.37 (–0.29, 0.99)	0.33 (–0.29, 0.97)	1.10 (0.43, 1.97)	0.41 (–0.54, 1.27)	0.73 (–0.45, 1.74)
C6/7	0.46 (–0.17, 1.44)	0.37 (–0.18, 1.14)	1 (0.33, 2.27)	0.4 (–0.63, 1.3)	0.64 (–0.72, 2.44)
ICC	0.722 (0.169, 0.879)	0.731 (0.191, 0.882)	0.356 (–0.067, 0.706)	0.677 (0.311, 0.826)	0.459 (0.014, 0.698)
CR (%)					
C3/4	2.09 (–4.22, 7.10)	2.22 (–3.83, 7.15)	6.46 (0.65, 11.48)	1.82 (–5.5, 9.06)	2.46 (–3.71, 10.00)
C4/5	0.67 (–5.45, 4.25)	0.66 (–5.76, 4.20)	6.14 (0.51, 10.85)	2.91 (–2.75, 7.23)	3.55 (–5.15, 10.95)
C5/6	0.66 (–4.75, 7.2)	0.66 (–4.82, 7.25)	5.56 (1.37, 11.03)	2.69 (–4.09, 9.4)	2.73 (–8.01, 12.77)
C6/7	0.87 (–3.85, 10.13)	0.83 (–4.05, 8.21)	6.86 (–1.95, 13.77)	2.32 (–4.35, 9.11)	2.59 (–6.9, 14.44)
ICC	0.851 (0.801, 0.888)	0.858 (0.814, 0.891)	0.647 (–0.079, 0.876)	0.817 (0.627, 0.898)	0.703 (0.527, 0.804)
CSA (mm^2)					
C3/4	8.5 (–4.8, 15.4)	8.3 (–4.8, 15.4)	15.0 (8.0, 24.7)	4.0 (–4.7, 14.0)	10.0 (–3.4, 21.0)
C4/5	6.4 (–2.3, 15.3)	6.5 (–2.5, 15.3)	13.0 (4.3, 24.0)	5.0 (–5.0, 13.7)	11.0 (–12.7, 31.8)
C5/6	6.8 (–4.7, 13.7)	6.3 (–4.6, 13.6)	12.0 (–1.7, 22.1)	2.0 (–15.7, 13.7)	10.0 (–10.5, 25.1)
C6/7	7.3 (–0.9, 14.9)	6.7 (–0.6, 14.1)	12.0 (0.3, 26.4)	3.0 (–11.4, 14)	10.0 (–13.0, 34.8)
ICC	0.725 (0.021, 0.896)	0.735 (0.042, 0.900)	0.367 (–0.088, 0.702)	0.717 (0.610, 0.792)	0.373 (–0.018, 0.620)
Solidity (%)					
C3/4	–0.54 (–3.79, 2.53)	–0.63 (–3.75, 1.91)			
C4/5	–0.36 (–4.15, 1.40)	–0.55 (–4.07, 1.65)			
C5/6	–0.75 (–4.25, 2.24)	–0.84 (–4.04, 2.16)			
C6/7	–0.76 (–4.42, 3.21)	–0.88 (–4.23, 2.81)			
ICC	0.536 (0.412, 0.635)	0.552 (0.406, 0.660)			

The equation was stated as the values from 1.5 T minus the values from 3T. Data are summarized as median (5th–95th percentile). ICCs (two-way random, absolute agreement, single measures) with 95% CI compare each parameter pooled per all intervertebral levels between the two examinations (P<0.0005 in each parameter and rater). ICC, intra-class correlation coefficient; SCT, Spinal Cord Toolbox; RL, right-left diameter; AP, anterior-posterior diameter; CR, compressive ratio; CSA, cross-sectional area.

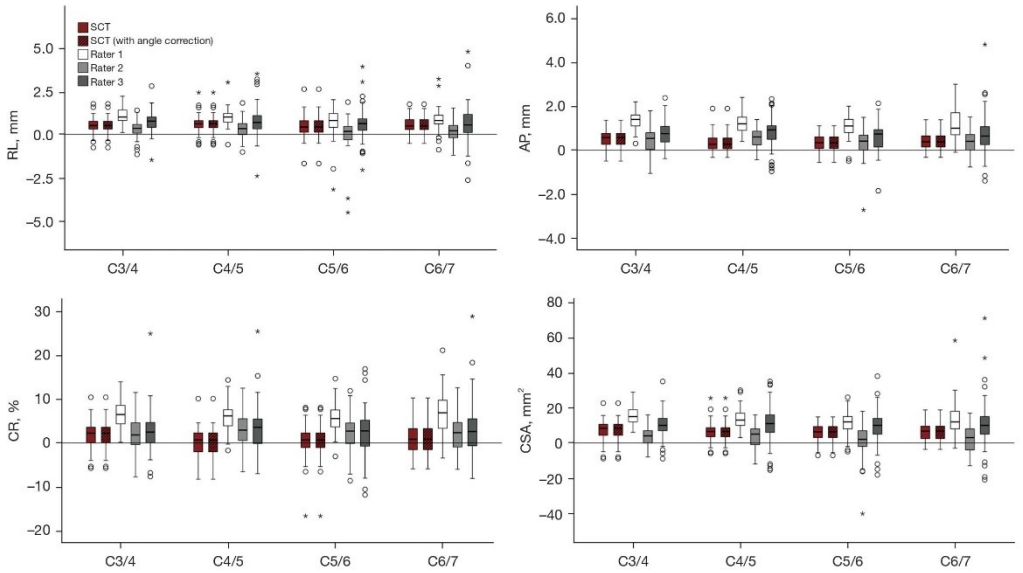

Figure 4 Differences in morphometric parameters between the two MRI examinations (3 and 1.5 T). Data pooled for HC and SCC. The bars represent 25th–75th percentiles, whiskers denote the lowest and the highest values, excluding mild outliers, which appear as dots (values greater than 1.5 times the interquartile range) and extreme outliers that appear as asterisks (values greater than 3 times the interquartile range). Medians appear as horizontal lines within the bars. RL, right-left diameter; AP, anterior-posterior diameter; CR, compressive ratio; CSA, cross-sectional area.

Further, the variability between the two MRI examinations was conclusively smaller in SCT compared with the three expert raters. The ICCs showed excellent inter-trial variability of CR (0.858) and good in CSA (0.735). There were surprising discrepancies in variability between the raters; one was very close to the standard of SCT, while the other two made systematic errors of either overestimation of the measures in 1.5T MRI or underestimation of the measures in 3T MRI.

The degree of agreement between the results extracted with SCT and the results of expert raters also became evident, as the correlations between SCT and expert raters were generally similar to those of the raters between one another.

Previous studies

To the best of our knowledge, only a few similar studies have been performed (4,16,17). Martin *et al.* (4), covered a much lower number of participants (20 HC and 20 NMDC, compared to the 66 HC and 102 NMDC and 16 DCM herein). They also addressed compression detection in a different way, as they defined compression as deviation from normal in flattening, indentation and/or torsion, and the ROC analysis was performed over these parameters separately. In contrast, our study did not assess flattening, indentation, and torsion manually, deploying only one binary indicator—the presence of compression. Thus, the data herein does not show the discriminating powers of individual parameters separately. All four parameters (CR, CSA, solidity, and torsion) in our data showed good ability to detect compression with AUCs around 0.8. However, the cut-offs were close to one SD from normal. Therefore, we combined the four parameters in a multivariate logistic model receiving excellent results. Further, the data herein did not replicate the Martin *et al.* finding that rostral CSA was significantly higher in SCC; our results indicate a C3/4 CSA mean of 72.6 mm^2 in HC, 67.4 mm^2 in NMDC and

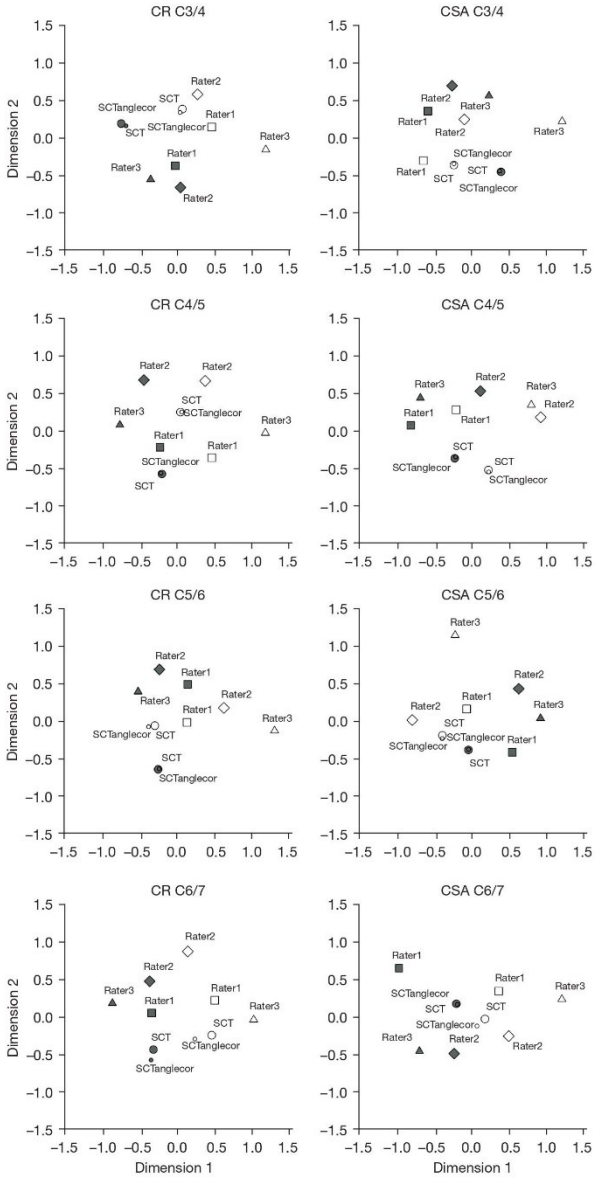

Figure 5 Inter-trial variability and inter-rater variability of morphometric parameters. The distance is defined as 1 minus r (Pearson correlation coefficient) in two-dimensional space. Empty symbols signify 1.5 T MRI measurements, filled symbols signify 3 T. CR, compressive ratio; CSA, cross-sectional area.

55.8 mm^2 in DCM. The findings herein accord with reports of spinal cord atrophy above the level of compression (18-20). Papinutto (16) investigated the reliability of CSA in 12 healthy volunteers in three different 3T MR scanners and the ICCs were in range of 0.79–0.95. Ost *et al.* (17) demonstrated that most of the SCT derived metrics lack the sufficient differentiation across mJOA score severity in DCM; however, the means of CSA, solidity and eccentricity extracted from the entire spinal cord volume were significantly related to mJOA.

Other minor findings

The normative data herein corresponded with the physiological anatomy of the spinal cord, including increases in CSA at levels C4/5 and C5/6 due to cervical enlargement and an increase in torsion at level C6/7 arising out of cervical lordosis. The substantial decline in CSA and increase in torsion at level C6/7 is probably strong justification for the inclusion of the binary C6/7 factor in the pooled logistic model.

We did not find any well performing discriminating parameter to distinguish NMDC and DCM participants. Neither the predicted probability calculated from the pooled model showed any significant differences in DCM compared to NMDC group, even though none of the compressions in DCM were undetected.

The *angle-corr* function available in SCT is a useful tool, lending further slight improvements to the inter-trial variability of SCT-derived morphometric parameters between the two MRI examinations, but the differences between corrected and uncorrected values are very small compared with those of inter-rater or inter-trial variability.

The estimates for RL, AP and CSA were generally larger in 1.5 T scanner compared to 3T scanner. The exact reason for this effect is unknown but might be attributed to the higher in-place resolution of the 3 T MEDIC sequence and usage of 4 echoes compared to 1 echo in 1.5 T FFE sequence, resulting in smaller partial volume effect between SC and CSF and better contrast for 3 T sequence, paradoxically leading to "smaller" values. The systematic error in different manufacturers and different protocols has already been published previously (21).

Limitations

The main limitation of this study is the general lack of a gold standard for compression detection that might have otherwise served for comparison with its results. This study is therefore based on qualitative determination of compression presence reflected in changes in spinal cord contour or shape. We tried to overcome this limitation by using the consensus ratings of two experienced radiologists and further, two MRI measurements from two different MRI scanners were available in the event of doubt.

Second, the approach herein is not fully automated, as the slices corresponding to intervertebral levels were chosen in person rather than by automated labelling of vertebrae. We opted for this approach after discovering the need for manual correction of the automated labelling in 20% of the first sample. Nevertheless, this limitation could be overcome in future developments in SCT that may feature an improved version of the algorithm for spinal cord labelling. It may even be possible that there exists no necessity for precise selection of intervertebral level, as the software could mark all slices with possible compressions and the expert rater would then check only these slices.

Since SCT is a tool primary designed for quantitative analysis of the spinal cord, assessment of the surrounding structures (such as vertebrae, intervertebral discs, cerebrospinal fluid) is limited. This is a limitation compared to expert raters, who might include the surrounding anatomy in their decision. However, even though the only input of the compression detection via SCT was the shape of segmented spinal cord (and manually chosen slices corresponding to intervertebral levels), the agreement between SCT and experts was excellent. Further, since both 1.5 and 3 T protocols were primarily designed for other projects (7,15), we did not acquire isotropic 3D T1w and T2w image that would be also suitable for SC segmentation.

The inter-trial variability analyses were performed over two different MRI scanners with two different protocols: on 3 T with 42 slices and 1.5 T with 20 slices. The correlation coefficients could further improve if two matching MRI scanners were employed with the same protocols. The different scanners also limited torsion calculation in 1.5 T MR; the slices were too thick (4 mm) in this protocol; at the same time, similar variants of torsion calculation to those used in 3T did not demonstrate the ability to discriminate between HC and compression (AUC within a range of 0.415–0.586). Performance of the same compression detection via 1.5 T data therefore proved impossible. Nevertheless, this approach better represents the reality of multicentre studies, and this study showed that SCT is

more reliable than expert raters, even in this situation. The ICC of solidity in the data herein was also low (0.636 in SCC group but minus 0.040 in the HC group), but it could also arise out of the low variability of solidity values in the healthy controls.

As already pointed out in the Results section, levels without compression in the SCC group were not used in the model construction shown in main text. The reason for this was possible atrophy and changes in the spinal cord even above or below the level of compression. However, an alternative approach, including levels without compressions as "healthy", appears in the Table S6 and the results remain very promising (with AUC of the pooled model at 0.906).

The number of DCM in our study was very small and the vast majority of DCM participants had compressions at multiple levels and there was no way to determine which one had been responsible for clinical myelopathy. We could not, therefore, investigate separately the parameters of compressions causing neurological symptoms. We also did not investigate the difference in Torg-Pavlov ratios between these groups.

We did not include the intervertebral level C2/3 in the analysis due to the fact, that the 3T sequence covered vertebral levels C3–C7, as it was primarily designed for other parallel projects (8,15), however, there was only one participant with compression in level C2/3 based on the 1.5 T MRI examination covering C2–C7.

Only one of the three expert raters manually measuring RL, AP and CR was board-certified radiologist. However, all raters completed training of spinal cord measurement. Further, based on the result of inter-trial variability, Rater 2 (TS, medical student) had the highest values of ICCs.

Conclusions

This study demonstrated successful semi-automated detection of cervical spinal cord compression based on four SCT-derived morphometric parameters. The parameters extracted using SCT exhibited lower variability than the experts' manual ratings in RL, AP, CR and CSA. Further, SCT enabled exact quantification of indentation and torsion. Introduction of SCT into radiological evaluations may bring more reliable results to longitudinal and multi-centre studies. The approach also saves a great deal of time, perhaps enabling its routine use in the assessment of the natural course of NMDC and mild DCM; the rate of progression may well become a valid predictor of whether the patient would benefit from surgery or not.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of University Hospital Brno (No. EKV-2017-055) and informed consent was taken from all individual participants.

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ORIGINAL ARTICLE

Diffusion magnetic resonance imaging reveals tract-specific microstructural correlates of electrophysiological impairments in non-myelopathic and myelopathic spinal cord compression

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Abstract

Background and purpose: Non-myelopathic degenerative cervical spinal cord compression (NMDC) frequently occurs throughout aging and may progress to potentially irreversible degenerative cervical myelopathy (DCM). Whereas standard clinical magnetic resonance imaging (MRI) and electrophysiological measures assess compression severity and neurological dysfunction, respectively, underlying microstructural deficits still have to be established in NMDC and DCM patients. The study aims to establish tract-specific diffusion MRI markers of electrophysiological deficits to predict the progression of asymptomatic NMDC to symptomatic DCM.

Methods: High-resolution 3 T diffusion MRI was acquired for 103 NMDC and 21 DCM patients compared to 60 healthy controls to reveal diffusion alterations and relationships between tract-specific diffusion metrics and corresponding electrophysiological measures and compression severity. Relationship between the degree of DCM disability, assessed by the modified Japanese Orthopaedic Association scale, and tract-specific microstructural changes in DCM patients was also explored.

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Results: The study identified diffusion-derived abnormalities in the gray matter, dorsal and lateral tracts congruent with trans-synaptic degeneration and demyelination in chronic degenerative spinal cord compression with more profound alterations in DCM than NMDC. Diffusion metrics were affected in the C3-6 area as well as above the compression level at C3 with more profound rostral deficits in DCM than NMDC. Alterations in lateral motor and dorsal sensory tracts correlated with motor and sensory evoked potentials, respectively, whereas electromyography outcomes corresponded with gray matter microstructure. DCM disability corresponded with microstructure alteration in lateral columns.

Conclusions: Outcomes imply the necessity of high-resolution tract-specific diffusion MRI for monitoring degenerative spinal pathology in longitudinal studies.

KEYWORDS
diffusion magnetic resonance imaging, diffusion tensor imaging, spinal cord compression

INTRODUCTION

The relative resilience of the cervical spinal cord (CSC) to degenerative changes might delay the development of clinically manifest myelopathy and result in non-myelopathic degenerative cervical spinal cord compression (NMDC) [1,2]. The prevalence of NMDC progressively increases throughout aging affecting up to 40% of Caucasian individuals over 60 years of age [3-5]. Over time, a portion of NMDC patients progress into potentially irreversible degenerative cervical myelopathy (DCM) [2,6], which is the most common non-traumatic cause of CSC dysfunction. Delineation of risk factors of NMDC progression to the DCM remains an unsolved challenge [2,6,7]. Whilst radiological measures such as cross-sectional area (CSA), anteroposterior diameter or compression ratio (CR) together with electrophysiological abnormalities might be useful in predicting DCM development [6], standard clinical magnetic resonance imaging (MRI) protocols fail to describe microstructural CSC abnormalities in NMDC and DCM. Hyperintensity on T_2-weighted scans, considered as a radiological correlate of myelopathy, is not inevitably observed even in the most severe DCM patients with clinical myelopathic signs [8]. Yet, it remains a critical factor influencing decision-making in decompressive surgery [9]. Thus, quantitative MRI markers are urgently needed to detect early microstructural NMDC changes and predict progression into symptomatic DCM.

Whereas previous studies demonstrated the ability of diffusion MRI (dMRI) to depict profound microstructural CSC alteration in DCM patients [10-15], NMDC reports provided inconclusive outcomes [6,16-18]. However, all previous studies utilized single-shell dMRI protocols that limited estimation of the high-order diffusion models and exclusively quantified the diffusion tensor imaging (DTI) model [19]. Whereas DTI metrics are sensitive to microstructural integrity (i.e., fractional anisotropy [FA]) and axonal, myelin or membrane density deficits (i.e., axial [AD], radial [RD] and mean diffusivity [MD], respectively), the single tensor per voxel does not account for axonal, glial and extracellular compartments within the tissue and remains nonspecific [20]. To address this issue, optimized multi-shell high angular resolution diffusion imaging (HARDI) sequence with reduced field of view, so-called HARDI-ZOOMit [21], were utilized to estimate critical microstructural information from single-compartment DTI and the more advanced multi-compartment ball-and-sticks model [22]. The ball-and-sticks model indeed better fits dMRI data than DTI [20] and more reliably captures the microstructural tissue property in each voxel.

High-resolution multi-shell diffusion and anatomical sequences were combined with state-of-the-art postprocessing [23-26] to achieve selective tract-specific CSC analyses. Capability of the microstructural dMRI metrics to reliably reflect histopathological studies, which previously demonstrated tract-specific distinctions in CSC integrity in degenerative compression [1,27] was also investigated.

Thus, tract-specific alterations in degenerative spinal cord compression at the compression level and also above the compression were hypothesized with more severe deficits in DCM patients than NMDC patients. Relationships between tract-specific dMRI metrics and corresponding electrophysiology and compression severity, previously confirmed as risk factors of DCM development [6] were further hypothesized. Relationship between the degree of DCM disability assessed by the modified Japanese Orthopaedic Association (mJOA) scale [28] and tract-specific diffusion-informed microstructure was also explored.

MATERIALS AND METHODS

Participants

The ethical committee approved the study, and all participants signed an informed consent form. Healthy controls (HC) between 40 and 80 years of age had to be physically healthy with no history of any neurological or other somatic disorder. DCM and NMDC patients were recruited from the database of a spinal center of a tertiary university hospital. The requirements on subjects are shown in Figure 1a.

All subjects underwent a neurological examination to rule out DCM symptoms/signs in HC and NMDC individuals. The degree of DCM disability was assessed by an mJOA scale [28]. All participants underwent standard clinical MRI on a 1.5 T scanner to evaluate radiological signs of degenerative compression and estimate the maximal compression level (MCL), CSA and CR (see Supplementary Materials and Methods).

Non-myelopathic degenerative cervical spinal cord compression patients and DCM patients underwent electrophysiological examination performed by experienced neurologists to detect abnormalities of dorsal columns and/or dorsal gray matter (GM) horns (i.e., somatosensory evoked potentials, SEP), dysfunction in lateral columns (i.e., motor evoked potentials, MEP) and lesions of ventral GM horns (i.e., electromyography, EMG) as described previously [2,29]. Three DCM and 13 NMDC patients did not agree with electrophysiological examination. A detailed description of electrophysiological measures as well as the definition of MEP, SEP and EMG abnormalities is provided in the Supplementary Materials and Methods.

Magnetic resonance imaging acquisition

All participants were scanned on a 3 T Siemens Prisma scanner (Siemens Healthcare, Erlangen, Germany) using 64-channel head/neck and 32-channel spine coils. Lordosis, which could introduce a partial volume effect from the surrounding cerebrospinal fluid and negatively influence field homogeneity, was minimized by keeping the spinal cord as straight as possible. An optimized multi-shell diffusion protocol with reduced field of view [21] with total acquisition time (TA) of 12 min, 46 s covering C3-6 levels with 21 gradient waveform directions with $b_1 = 550$ s/mm^2, 42 directions with $b_2 = 1000$ s/mm^2 and seven b_0 images with anterior–posterior phase encoding, voxel size 0.65 × 0.65 × 3 mm^3 after interpolation in

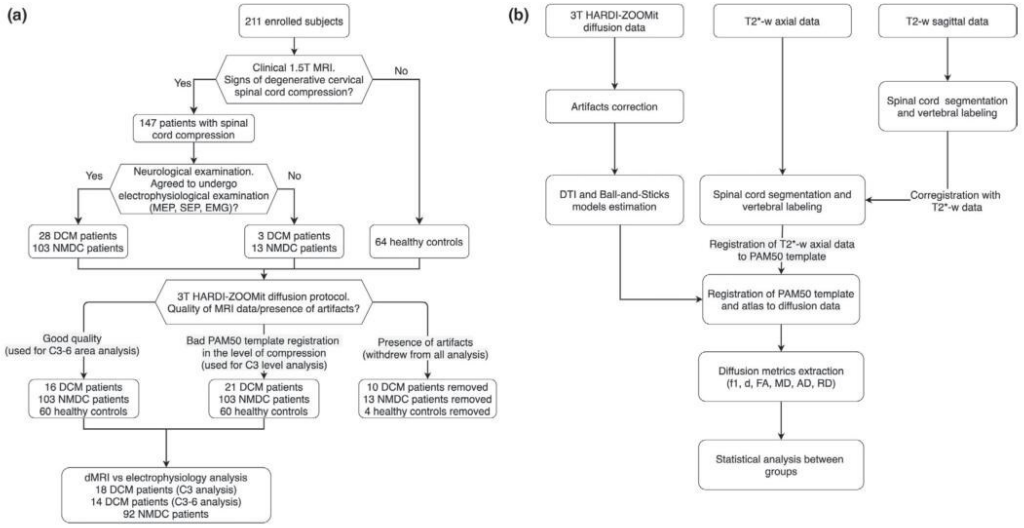

FIGURE 1 Flowcharts of (a) participants' requirements and (b) MRI data analysis

Fourier space, original voxel size 1.30 × 1.30 × 3.00 mm^3 was acquired. An additional five b_0 images with reversed posterior–anterior phase encoding were collected. All gradient waveforms were uniformly sampled over a *q*-space sphere [30]. Axial T_2*-weighted MEDIC images with high grey/white matter contrast using interleaved acquisition (voxel size 0.35 × 0.35 × 2.5 mm^3 after interpolation in Fourier space, original voxel size 0.70 × 0.70 × 2.5 mm^3, TA ≈ 8 min) and T_2-weighted sagittal turbo spin-echo images (voxel size 0.28 × 0.28 × 1.3 mm^3 after interpolation in Fourier space, original voxel size 0.56 × 0.56 × 1.3 mm^3, TA ≈ 9 min) were also collected. Detailed sequence parameters are listed in the Supplementary Materials and Methods.

Image analysis

Images were visually inspected by two independent observers to ensure data quality. Data were analyzed using the Spinal Cord Toolbox [26] v3.2.3 and FMRIB Software Library [31] v5.0.10 (Figure 1b). T_2*-w and T_2-w data were corrected for MR field induced intensity non-uniformities using the N4 bias-field correction tool, and interleaved T_2*-w axial data were additionally slice-by-slice corrected utilizing affine registration between even and odd slices followed by additive image fusion. Spinal cord segmentation and vertebral labeling of T_2-w sagittal data was performed and co-registered with T_2*-w axial data. Then spinal cord segmentation using convolution neural network [23] of T_2*-w axial was performed and vertebral levels were defined [32] using initial information from T_2-w sagittal labeling. Finally, the T_2*-w spinal cord was registered to the PAM50 template [24] using C3 and C6 as labels. Diffusion data were corrected for motion, susceptibility and eddy current artifacts. A conventional DTI [19] model and a multi-compartment ball-and-sticks [22] model were estimated to extract FA, MD, AD and RD as well as f_1 and *d* metrics. The PAM50 template was registered to diffusion data using the initial transformation from the T_2*-w axial image, and the probabilistic spinal cord atlas [25] was warped into diffusion data.

Metric extractions

Diffusion metrics were extracted per subject from all regions of interest (ROIs) utilizing the *sct_extract_metric* function [26] with use of the *maximum a posteriori* optimizing approach [25,26] to eliminate partial volume effect and variability in tract size. ROIs included the GM, ventral, lateral, dorsal columns, fasciculus gracilis, fasciculus cuneatus, lateral corticospinal tracts, spinal lemniscus (i.e., spinothalamic and spinoreticular tracts), dorsal GM horns and ventral GM horns (Figure 2a). Diffusion metrics for individual ROIs were averaged from the whole C3-6 area and from C3 above the compression vertebral level (Figure 2d).

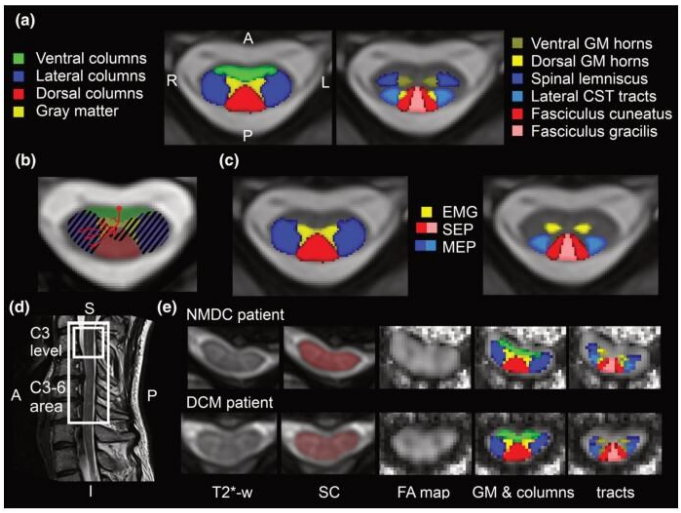

FIGURE 2 (a) Individual ROIs masks from probabilistic PAM50 atlas. (b) Lesion distribution caused by compressed anterior spinal artery. Filled areas are affected by the compression, that is, lateral columns, anterior part of dorsal columns and ventral GM horns. Adapted from Mair and Druckman [27]. (c) Individual ROIs related to electrophysiological measures: EMG, electromyography; SEP, somatosensory evoked potentials; MEP, motor evoked potentials. (d) Two analyzed areas, the C3-6 area and C3 above the compression level. (e) Representative slices from the C4/5 disc from NMDC and DCM patients. From the left: T2*-w axial image, CSC segmentation used for PAM50 registration, fractional anisotropy (FA) map, white matter columns, and gray matter (GM) and individual tracts registered into an FA map

Mean CSA at the C3 level was calculated to quantify atrophy above the compression level from high-resolution T_2^*-w data using the *sct_process_segmentation* function [26].

Statistical analysis

Statistical analysis was performed using Matlab R2019b (The Mathworks Inc.), Python 3.7 and SPSS 25 (IBM). Data normality was examined using the Shapiro–Wilk test. Comparison between groups in age, height, weight, body mass index (BMI) and CSA at C3 were tested by the Kruskal–Wallis *H* test, and sex by Fisher's exact test.

Between-group differences in dMRI metrics from the C3-6 area and above the compression (i.e., C3) level were analyzed per individual tract and column using ANCOVA with age and BMI as covariates using Tukey–Kramer post hoc tests. Analyses were corrected using the Holm–Bonferroni correction.

Associations between dMRI metrics from the C3-6 area, age and BMI in 60 controls as well as between CSA and CR at MCL and dMRI metrics from the C3-6 area and C3 above the compression level in DCM and NMDC together with the relationship between the degree of myelopathy (mJOA scale) and dMRI metrics at C3 in DCM were examined using the Spearman correlation. Relationships between electrophysiological abnormalities, reported as categorical and dMRI metrics, were quantified in NMDC and DCM patients by the Mann–Whitney rank tests with Holm–Bonferroni correction. MEPs were related to dMRI from motor tracts, that is, lateral columns and lateral corticospinal tracts. SEPs were correlated with sensory tracts, that is, the dorsal column, fasciculus cuneatus, fasciculus gracilis and dorsal GM horns. Relationships between EMG and dMRI from GM and ventral GM horns (Figure 2c) were examined. Finally, post hoc correlation analysis between quantitative electrophysiological parameters and dMRI metrics was performed (see the Supplementary Materials and Methods).

RESULTS

Participant characteristics

A total of 116 NMDC patients, 31 DCM patients and 64 HC were enrolled in the study. Ten DCM, 13 NMDC patients and four HC were initially excluded due to the presence of motion artifacts, low CSC/cerebrospinal fluid contrast in T2*-w axial images preventing proper CSC segmentation, sub-optimal fat saturation, and dMRI signal dropouts caused by excessive cardiac pulsatile motion.

The final group consisted of 103 NMDC patients, 21 DCM patients and 60 HC. Analyses did not reveal any statistically significant differences in age, height, weight, BMI or sex between groups (Table 1).

None of the 60 HC had MR signs of degenerative CSC compression, whilst all 103 NMDC and 21 DCM patients had MR signs of compression varying from focal impingement to flat compressions with partially preserved or lost subarachnoid space [2,6]. The majority of patients (93.6%) had MCL at the C4/5 level and/or lower. Thus, level C3 was selected as a reference level above the compression to evaluate rostral microstructural changes.

Non-myelopathic degenerative cervical spinal cord compression patients had no radiological signs or neurological symptoms/signs of DCM. Hyperintensities on T_2-w scans were found in one cervical level in 12 DCM patients and two cervical levels in two DCM patients. The mean mJOA scale in the DCM group was 14.5.

Five out of 21 DCM patients were excluded from C3-6 analysis due to imperfect PAM50 atlas registration caused by severe compression, and these subjects were used only in the analysis of the C3 level. The accuracy of CSC segmentation and labeling was verified and corrected if necessary.

Detailed results for the relationship between dMRI metrics and compression measures are described in the Supplementary Results.

Cross-sectional area at the C3 above the compression level

The Kruskal–Wallis *H* test detected a significant between-group difference between groups in CSA above the compression level. Subsequent Dunn's post hoc tests showed significant ($p_{FWEcorr} < 0.05$) CSA reduction between HCs and NMDC patients (−5.0%, $p = 0.007$), HCs and DCM patients (−18.4%, $p < 0.0001$) and NMDC and DCM (−14.1%, $p < 0.0001$) (Table 1, Figure S1).

Correlations between dMRI metrics and demographic characteristics

Analyses revealed significant decreases ($p_{uncorr} < 0.05$) in f_1, FA, *d* and AD in the whole C3-6 area with age, whilst the opposite relationship was found between RD and age in HC (Figure S2). FA, MD, AD and *d* showed significant negative correlations with BMI (Figure S3). Correlation outcomes proved age and BMI as confounding variables, which were thus included as covariates to test between-group differences.

Distinctions between healthy controls and NMDC patients

Analysis of the C3-6 area revealed significantly ($p_{FWEcorr} < 0.05$) lower f_1 and FA in NMDC patients in dorsal and lateral tracts, that is, the fasciculus gracilis, lateral corticospinal tracts, spinal lemniscus and fasciculus cuneatus, compared to HC. Higher *d*, MD, AD and RD in NMDC patients relative to HC were observed in dorsal and lateral tracts and GM horns. Alterations in ventral columns were only revealed by the ball-and-sticks model, and NMDC patients showed higher *d* compared to HC.

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TABLE 1 Characteristics of 184 participants

Characteristic	Healthy controls ($n = 60$)	NMDC patients ($n = 103$)	DCM patients ($n = 21$)	p value
Age (years)	53.7 ± 8.7	56.5 ± 9.8	58.2 ± 10.8	0.084
Sex (females/males)	38/22	59/44	12/9	0.711
Height (cm)	172.4 ± 9.8	170.0 ± 8.7	167.0 ± 10.5	0.227
Weight (kg)	78.9 ± 16.5	81.2 ± 16.7	81.7 ± 13.3	0.880
Body mass index (BMI)	26.5 ± 4.8	28.0 ± 4.6	28.8 ± 4.1	0.073
Cross-sectional area (CSA) at C3 level (mm^2)	69.7 ± 7.6	66.0 ± 7.4	56.7 ± 7.1	<0.001*
mJOA	18.0 ± 0.0	18 ± 0.0	14.5 ± 2.6	
Maximally compressed level (MCL)				
C3/4	–	5 (4.8%)	3 (14.3%)	
C4/5	–	28 (27.2%)	4 (19.0%)	
C5/6	–	49 (47.6%)	14 (66.7%)	
C6/7	–	21 (20.4%)	-	
Compression ratio (CR) at MCL	–	0.41 ± 0.07	0.35 ± 0.08	
Cross-sectional area (CSA) at MCL	–	60.71 ± 11.3	52.14 ± 13.84	
Number of stenotic levels				
1 compression	–	39 (37.9%)	6 (28.6%)	
2 compressions	–	33 (32.0%)	8 (38.1%)	
3 compressions	–	25 (24.3%)	4 (19.0%)	
4 compressions	–	6 (5.8%)	3 (14.3%)	
Electrophysiological measurements				
Abnormal MEP	–	11 patients from 87 (12.6%)	12 patients from 18 (66.7%)	
Abnormal SEP	–	28 patients from 87 (32.2%)	13 patients from 18 (72.2%)	
Abnormal EMG	–	24 patients from 92 (26.1%)	11 patients from 17 (64.7%)	

Note: Asterisk (*) indicates significance ($p < 0.05$).

Abbreviations: DCM, degenerative cervical myelopathy; EMG, electromyography; MEP, motor evoked potentials; mJOA, modified Japanese Orthopaedic Association; NMDC, non-myelopathic degenerative cervical spinal cord compression; SEP, somatosensory evoked potentials.

Lower f_1 values at C3 above the compression level were found in lateral columns, specifically in spinal lemniscus, in NMDC patients in comparison to HCs (Figures 3 and 4, Table S1).

Differences between healthy controls and DCM patients

Degenerative cervical myelopathy patients showed significantly lower f_1 and FA ($p_{FWEcorr} < 0.05$) in dorsal and lateral tracts, that is, fasciculus cuneatus, fasciculus, lateral corticospinal tracts and spinal lemniscus, in the C3-6 area compared to HC. The ball-and-sticks model demonstrated lower f_1 values in DCM patients relative to HC in ventral columns and ventral and dorsal GM horns. Higher MD and RD values in DCM patients in comparison to HC were detected in dorsal and lateral tracts, whilst higher RD in DCM patients was also observed in ventral columns. In contrast, higher d and AD in DCM patients were solely revealed in dorsal tracts. Ventral and dorsal GM horns exhibited higher d, MD, AD and RD in DCM patients compared to HC.

Lower f_1 in DCM patients relative to HC above the compression level was detected in dorsal and lateral tracts, that is, the fasciculus cuneatus, fasciculus, lateral corticospinal tracts, spinal lemniscus and dorsal GM horns, whilst lower FA affected identical areas but spared the dorsal GM. Higher MD and RD were found in dorsal and lateral columns and GM, higher d and AD were observed only in ventral GM horns and the GM of DCM patients compared to HCs. No changes were detected in dMRI metrics at the C3 level in ventral columns (Figures 3 and 4 and Table S1).

Comparisons between NMDC and DCM patients

Degenerative cervical myelopathy patients exhibited significantly lower f_1 and FA compared to NMDC patients in dorsal and lateral tracts, that is, the fasciculus cuneatus, fasciculus, lateral corticospinal

tracts and spinal lemniscus, with lower f_1 values also in the dorsal GM horns of DCM patients at the C3-6 level. Higher MD and RD were detected in the dorsal and lateral tracts as well as ventral and dorsal GM horns with higher *d* and AD in GM horns in DCM patients relative to NMDC patients.

Above the compression level, lower f_1 and FA and higher MD and RD were detected in the fasciculus cuneatus, fasciculus, lateral corticospinal tracts and spinal lemniscus, and the dorsal GM horns in DCM relative to NMDC. Higher *d* and AD were observed in GM, specifically in ventral GM horns in DCM compared to NMDC (Figures 3 and 4 and Table S1).

Relationship between dMRI and electrophysiological measures

Patients with abnormal MEP findings exhibited significantly lower f_1 and FA in lateral columns and lateral corticospinal tracts ($p_{FWEcorr} < 0.05$) and lower AD in lateral columns compared to patients with normal MEP findings in the C3-6 area. Similarly, patients with altered SEPs demonstrated significantly lower FA in the dorsal columns, fasciculus gracilis, fasciculus cuneatus and dorsal GM horns compared to unaffected patients. Abnormal EMG was also reflected by higher RD in GM and ventral GM horns comparing patients with abnormal and normal EMG (Figure 5 and Table S2).

A comparison of dMRI metrics at the C3 above the compression level revealed significantly lower f_1 and FA and higher RD in the lateral columns and lateral corticospinal tracts ($p_{FWEcorr} < 0.05$) in patients with abnormal versus normal MEP. Also, lower *d* and AD were detected in the lateral columns in patients with abnormal MEP. Altered SEP measurements were associated with lower f_1 and FA in dorsal columns, fasciculus gracilis and fasciculus cuneatus, as well as lower FA and *d* in dorsal GM horns compared to patients with normal SEP. Lower f_1, FA and RD were detected in the GM in patients with abnormal EMG compared to individuals with unaffected EMG (Figure 5 and Table S2).

Overall, patients with abnormal electrophysiological measurements showed significantly lower f_1, FA, *d* and AD values, and higher RD values, in corresponding anatomical areas in comparison to patients with normal electrophysiological findings at the compression level but also above at C3 (Figure 5 and Table S2).

Results of post hoc correlation analysis between quantitative electrophysiological parameters and dMRI metrics are shown in the Supplementary Results.

Relationship between dMRI and clinical mJOA scale at the C3 level in DCM

Exploratory correlation analysis revealed significant positive correlations between mJOA and f_1, FA, *d* and AD from the C3 level in lateral columns in DCM patients. FA, AD and *d* in the spinal lemniscus and FA in ventral columns showed significant positive correlations with the mJOA scale. A negative relationship was identified between the mJOA scale and RD in lateral columns (Figures 6 and S6).

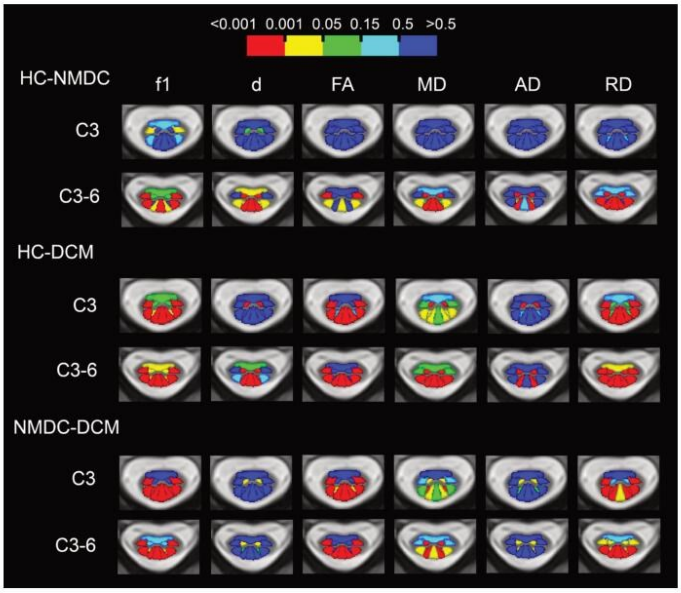

FIGURE 3 Between-group differences in diffusion metrics for tract-specific ROIs from C3 above the compression level and C3-6 area color coded by their *p* values ($p_{FWEcor} < 0.05$)

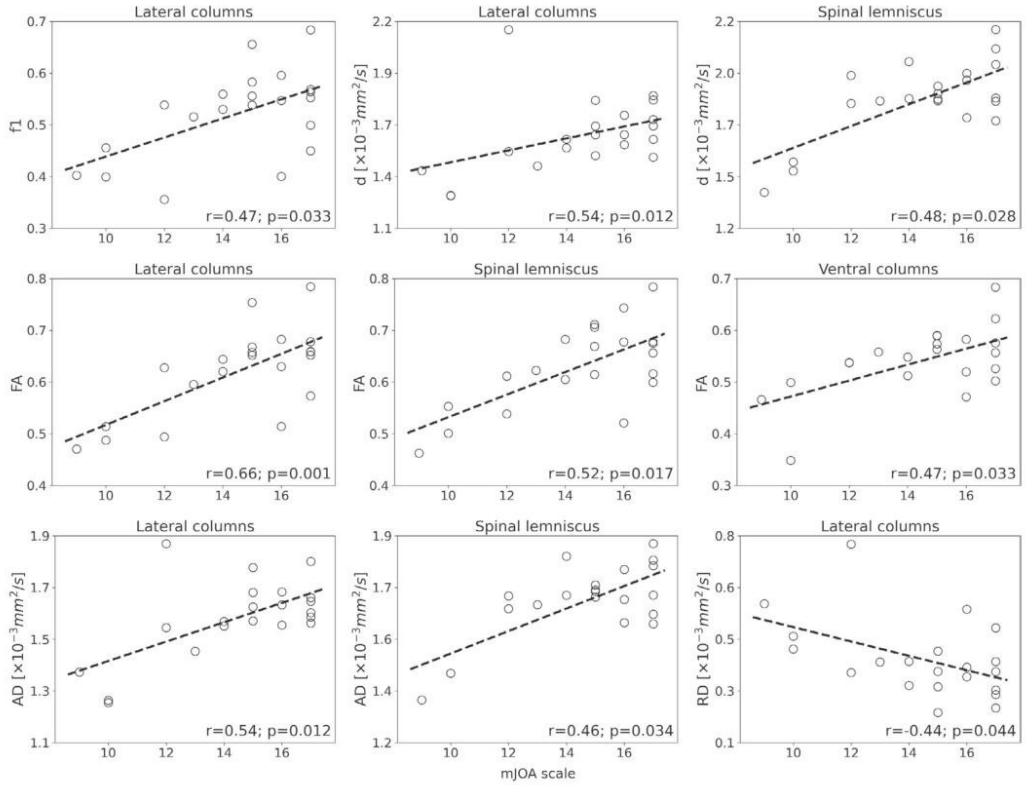

FIGURE 6 Correlations between dMRI metrics from C3 above the compression level and the modified Japanese Orthopaedic Association (mJOA) scale in DCM patients

DISCUSSION

Our study detected tract-specific distinctions in diffusion metrics between NMDC and symptomatic DCM patients compared to HC in the GM and dorsal columns, that is, fasciculus gracilis, fasciculus cuneatus, and in the lateral columns composed of lateral corticospinal tracts and spinal lemniscus. DCM patients also showed additional alterations in the ventral columns compared to HC. Diffusion changes were found in the C3-6 area as well as above the compression level at C3, and were accompanied by reduced cord cross-sectional area at the C3 level in both NMDC and DCM relative to HC. Importantly, diffusion metrics in the GM and motor and sensory tracts correlated with relevant electrophysiological abnormalities and clinical mJOA scale, implying the critical importance of tract-specific measures for future longitudinal studies.

Differences in dMRI metrics in the C3-6 area in NMDC patients compared to HC confirmed incipient CSC damage in the early stages of degenerative compression in the dorsal and lateral tracts. The findings align with post-mortem histopathological studies, in which chronic CSC compression led to damage of the lateral pial plexus resulting in limited blood flow and axonal degeneration of lateral corticospinal tracts and dorsal areas [1]. Malperfusion through the compressed anterior spinal artery initially affects GM, lateral columns and the anterior part of the dorsal columns and can ultimately result in progressive demyelination [1,27]. Indeed, lower f_1 and FA and higher diffusivity metrics in the lateral and dorsal tracts and GM observed in our study in NMDC and DCM patients compared to HC suggest ongoing demyelination [13]. Differences in f_1 in the lateral and dorsal tracts separated DCM from NMDC with more profound deficits found in DCM than NMDC patients. Thus, dMRI alterations corroborate post-mortem studies, which reported lesions of the anterior GM horns, the lateral tracts and the anterior part of the dorsal tracts but showed no changes in the ventral columns in the early stages of degenerative compression [13,33]. Additional f_1 and RD deficits occur in ventral columns as the compression progresses from NMDC to symptomatic DCM. Our findings thus align with histopathological samples when revealing alterations in diffusion metrics in ventral columns in DCM but not in NMDC. Direct comparison between NMDC and DCM groups showed profound changes in dorsal and lateral columns as well as GM that further confirmed the influence of gradual alteration

of arterial flow on the compression-related deficits and myelopathy [34,35]. Whilst lower FA corroborates previous DTI studies in DCM patients [10,14,36-38], asymptomatic patients with CSC compression [16] and patients with slowly progressing CSC compression [39], to date no study showed tract-specific changes in a large sample of both NMDC and DCM patients. Spatial distinctions in alterations between DCM and NMDC further emphasize the necessity of tract-specific analysis in CSC studies.

Our findings also demonstrate malicious effects of the compression on microstructural CSC integrity above the compression level at the C3 level. Deficits at C3 in NMDC were limited to the spinal lemniscus and were depicted solely using the ball-and-sticks f_1 metric pointing to incipient remote degeneration in NMDC patients in the early stages of degenerative CSC compression. As the compression progressed to DCM, additional f_1, FA and RD alterations in dorsal and lateral columns occurred. The ball-and-sticks f_1 demonstrated higher discrimination when showing changes in the spinal lemniscus that were not detected using the DTI model. Significantly lower f_1 and FA above the compression level in DCM patients compared to HC point to progressive anterograde and retrograde axonal degeneration of dorsal sensory pathways such as fasciculus gracilis, cuneatus and spinal lemniscus as well as lateral motor corticospinal tracts, respectively [1,13,14]. Alterations of FA at the C3 level are in agreement with a recent study from Seif et al. [14] which demonstrated a remote FA decrease in the lateral corticospinal and spinothalamic tracts at the C2/3 level in DCM patients and patients with traumatic spinal cord injury compared to HC. Changes in GM along with spinal cord CSA reduction above the compression level in DCM patients compared to NMDC patients and HC point to trans-synaptic degeneration and GM atrophy above the stenosis level in patients with myelopathy [13]. Direct comparison between symptomatic DCM and NMDC patients demonstrated more severe deficits in DCM patients in the dorsal and lateral columns, as well as in the ventral and dorsal GM horns. Whereas remote degeneration in DCM patients compared to HC corroborates previous reports [13,14,38,40,41], tract-based approaches also delineated gradual changes between NMDC and symptomatic DCM patients. Alterations above the compression level further endorse brain studies [42-44] that reported changes in motor and somatosensory cortex in symptomatic DCM patients with degenerative CSC compression. A decrease of CSA at the C3 level in DCM compared to HC corresponds with previous studies [10,13,14,40] and further points to remote degeneration rostrally to MCL. A smaller yet significant CSA deficit was also found in the NMDC group, suggesting more profound changes in DCM than in NMDC compared to HC.

Tract-specific analysis also revealed a relationship between the degree of disability (i.e., mJOA scale) and diffusion metrics in lateral columns and spinal lemniscus comprising motor and sensory pathways in DCM patients. DCM patients with lower mJOA scale (worse DCM disability) exhibited a decrease of f_1, FA and AD and an increase of RD compared to NMDC patients and HC. These findings correspond to more severe demyelination and axonal damage in DCM patients with profound motor and sensory disability.

Most importantly, significant dMRI changes in individual tracts between patients with and without electrophysiological deficits point to a crucial relationship between functional impairments and microstructural dMRI degeneration. Patients with abnormal electrophysiology findings showed lower values of f_1, FA, d and AD metrics and higher values of RD and MD compared to those with normal electrophysiological findings. Microstructural changes in sensory and motor tracts were related to SEP and MEP, respectively, with altered GM found in patients with EMG changes. Whilst previous studies also examined the relationship between dMRI and electrophysiology, they failed to detect dMRI distinctions between patients with and without electrophysiological deficits [18], or detected FA alterations in DCM patients with normal SEP [38]. Whereas electrophysiological measures serve as essential predictors of DCM development [2,6], optimized spatially selective tract-based measures of the CSC overcome previous unselective dMRI analyses of the whole axial spinal cord volumes. Thus, the proven significant relationship between electrophysiology and tract-based dMRI metrics suggest that tract-specific analysis might provide an objective tool to examine the relationship between diffusion-informed microstructural changes and functional electrophysiological impairments. Tract-specific dMRI should be explored as a potential predictor in future longitudinal studies utilizing current high-resolution methods. Also, dMRI is a non-invasive tool that is easier to perform than electrophysiological measures.

Our outcomes imply the importance of novel dMRI models in CSC analysis. The multi-compartment ball-and-sticks model, which incorporates intra-axonal restriction and better explains the data than DTI [20], has not been utilized in a large sample of NMDC or DCM patients yet. The ball-and-sticks f_1 metric indeed revealed additional between-group alterations at the C3-6 area in GM as well as ventral columns and fasciculus cuneatus, which were not revealed by FA. Lemniscal alterations between NMDC patients and HCs at C3 above the compression level were also exclusively revealed by the ball-and-sticks f_1 metric.

Our study was limited by spatial coverage of dMRI data (i.e., the C3-6 area). Caudal vertebral levels were not explored due to scanning time constraints and possible signal loss at the C7 level caused by the character of the HARDI-ZOOMit protocol [21]. Semi-automatic analyses also required time-consuming manual adjustment of segmentations, mainly in patients with severe CSC compression. Severe compression further limited proper white matter atlas registration in five DCM patients. Although the atlas-based approach provides higher accuracy and less propensity to susceptibility distortions than tractography-based methods [45], future studies may benefit from subject-specific tractography approaches, which are not yet fully developed.

In conclusion, the combination of conventional DTI and the multi-compartment ball-and-sticks model allowed to reveal tract-specific dMRI changes congruent with previous histopathological studies. Compression-caused demyelination, atrophy and axonal degeneration in white matter tracts and GM progressed from less severe NMDC to symptomatic DCM. Tract-specific diffusion abnormalities

correlated with clinical deficits and abnormal electrophysiology in relevant anatomical tracts. Thus, our study demonstrated that high-resolution tract-specific dMRI is a sensitive microstructural marker of CSC alterations for longitudinal trials aiming to provide early predictors of progression into symptomatic myelopathy and potentially can be translated also for patients with traumatic spinal cord injury.

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CONFLICT OF INTEREST

No authors disclosed any relevant relationships.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Supplementary Material

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In vivo Molecular Signatures of Cervical Spinal Cord Pathology in Degenerative Compression

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Abstract

Degenerative cervical myelopathy (DCM) is a severe consequence of degenerative cervical spinal cord (CSC) compression. The non-myelopathic stage of compression (NMDC) is highly prevalent and often progresses to disabling DCM. This study aims to disclose markers of progressive neurochemical alterations in NMDC and DCM by utilizing an approach based on state-of-the-art proton magnetic resonance spectroscopy (^{1}H-MRS). Proton-MRS data were prospectively acquired from 73 participants with CSC compression and 47 healthy controls (HCs). The MRS voxel was centered at the C2 level. Compression-affected participants were clinically categorized as NMDC and DCM, radiologically as mild (MC) or severe (SC) compression. CSC volumes and neurochemical concentrations were compared between cohorts (HC vs. NMDC vs. DCM and HC vs. MC vs. SC) with general linear models adjusted for age and height ($p_{FWE} < 0.05$) and correlated to stenosis severity, electrophysiology, and myelopathy symptoms ($p < 0.05$). Whereas the ratio of total creatine (tCr) to total *N*-acetylaspartate (tNAA) increased in NMDC (+11%) and in DCM (+26%) and SC (+21%), myo-inositol/tNAA, glutamate + glutamine/tNAA, and volumes changed only in DCM (+20%, +73%, and −14%) and SC (+12%, +46%, and −8%, respectively) relative to HCs. Both tCr/tNAA and myo-inositol/tNAA correlated with compression severity and volume ($-0.376 < r < -0.259$). Myo-inositol/tNAA correlated with myelopathy symptoms ($r = -0.670$), whereas CSC volume did not. Short-echo ^{1}H-MRS provided neurochemical signatures of CSC impairment that reflected compression severity and clinical significance. Whereas volumetry only reflected clinically manifest myelopathy (DCM), MRS detected neurochemical changes already before the onset of myelopathy symptoms.

Keywords: cervical spinal cord, compression, degenerative; magnetic resonance; myelopathy; spectroscopy

Introduction

Degenerative changes in the spine develop with aging and frequently give rise to degenerative compression of the cervical spinal cord (CSC).[1] Magnetic resonance imaging (MRI) has revealed signs of CSC compression in 50% of randomly examined persons >60 years of age.[2] Prolonged compression often leads to clinically manifest degenerative cervical myelopathy (DCM).[3,4] However, in some patients, signs and symptoms of clinical myelopathy remain unexpressed, constituting a highly prevalent

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condition known as non-myelopathic degenerative compression (NMDC),[2] characterized by a variety of subclinical dysfunctional or microstructural impairments detectable by electrophysiological[5] or advanced MRI methods.[6,7] Unlike conventional MRI, proton magnetic resonance spectroscopy (^{1}H-MRS) quantifies neurometabolite levels and tracks changes in the cellular and biochemical composition of CSC tissue.[6–9] Thus, ^{1}H-MRS can provide markers specific to pathophysiological processes, such as gliosis, axonal/neuronal loss, and demyelination, resulting from mechanical compression.

Although only a few MRS studies have reported remote metabolic changes in the primary sensorimotor cortex arising out of CSC compression through Wallerian/Wallerian-like degeneration,[10,11] others have confirmed metabolic changes in the cranial CSC above the lesion level.[12–16] Increased levels of total creatine (tCr)/total N-acetylaspartate (tNAA)[11,12,15,17] and total choline (tCho)/tNAA[12,15,16] in DCM have also been reported. Higher spinal myo-inositol (myo-Ins)/tNAA and tCho/myo-Ins have been demonstrated in chronic CSC injury in diplegia and quadriplegia.[14] Studies to date have not included more than 35 participants[8,13,15] and often encountered technical challenges that compromised spectral quality. Metabolite changes have yet to be shown in the non-myelopathic stage.

We hypothesized that metabolite changes might be detected in NMDC by means of sensitive ^{1}H-MRS. More pronounced neurochemical impairment in DCM than in NMDC, and in severe compression (SC) than in mild compression (MC), could be anticipated. Given that SC is a condition with a greater risk that DCM will develop, the fact that MRS can distinguish between SC and MC becomes highly relevant to clinical practice.[18]

In view of this, MRS data were acquired from the cranial part of the CSC in the proximity of the stenosis in a large cohort (120 participants), using a fine-tuned 3 Tesla (T) MRS semi-LASER 3T sequence. The intention was to identify markers of CSC compression that might reflect progressive neurochemical deficits in groups defined by clinical (NMDC and DCM) or radiological (MC and SC) criteria when compared to healthy controls (HCs). The objective was to quantify the relationships between metabolite concentrations and CSC volume, and stenosis severity, together with electrophysiological and clinical outcomes.

Methods

Participant classification

Seventy-three participants with degenerative CSC compression and 47 HCs were enrolled between May 2018 and September 2019. All gave written informed consent. The local ethics committee approved the study (EKV-2017-055). Compression-affected participants were recruited by the University Hospital database. All participants underwent a clinical 1.5T MR scan (Philips-Achieva; Philips, Best, The Netherlands; Supplementary Materials S1.1.1) and the results were specialist screened for signs of CSC compression (Supplementary Materials S1.1.2)[2] and myelopathy.

Subjects without compression, cervical cord intensity changes on T_1- and T_2-weighted images, or any neurological symptoms or other illnesses were classified as HCs. Healthy persons were recruited to frequency match the age and sex of participants with compression. Expert neurological examination focused on clinical symptoms and signs of symptomatic myelopathy (Supplementary Materials S1.2). Participants with CSC compression were classified as non-myelopathic (NMDC) or exhibiting at least one clinical symptom and/or sign of myelopathy corresponding with a clinical diagnosis of DCM (Supplementary Table S1). Degree of disability and functional impairment was scored on the modified Japanese Orthopedic Association (mJOA) scale (3–18 points).[19]

Further, to detect functional abnormalities, electrophysiological measurements (Supplementary Materials S1.3) were taken of all participants with compression. Posterior columns or segmental lesions of the posterior horns were assessed with somatosensory-evoked potentials (SEP), dysfunction of the corticospinal tracts with motor-evoked potentials (MEP), and segmental lesions of the anterior horns with electromyography (EMG).[20,21]

Maximum compression level (MCL) was consensually determined by two specialists (T.R., M.H.); compression was quantified at MCL as both cross-sectional CSC area (CSA) and compression ratio (CR). The C4/5 level was used as a reference in HCs. Groups were established on the basis of the radiological severity of CSC compression at MCL: MC (CR $\geq$0.4 or CSA $\geq$70.1 mm^2) and SC (CR $<$0.4 and CSA $<$70.1 mm^2).[22]

Magnetic resonance data acquisition at 3 Tesla

MRS data were acquired on a 3T scanner (Siemens-Prisma; Siemens Healthcare, Erlangen, Germany) with a standard 64-channel head-neck coil, in separate sessions. The subject's neck was fixed with a memory foam collar.[23] High-resolution ($0.6\times0.6\times3$ mm, repetition time [TR] = 3500 ms, and echo time [TE] = 106 ms) T_2 turbo spin echo (TSE) images were obtained to center the 3.2-mL ($8\times9\times45$ mm) MRS voxel posterior to vertebra C2 (Fig. 1), that is, above the compression level in subjects with CSC compression. Magnetic field inhomogeneities were minimized by means of fast, automatic shimming technique by mapping along projections.[24] MRS data were acquired with a cardiac-triggered sLASER (256 single shots; TR = 5 sec, TE = 28 ms, acquisition time $\sim$21 min, scanner sofware version: syngo VE 11C, number of complex points: 2048, frequency offset of MRS acquisition: - 2 ppm, sweep width: 6000 Hz, location of outer volume suppression [OVS] bands: X, Y, Z, the width of OVS slabs 120 mm); water was suppressed with frequency-selective variable pulse power and

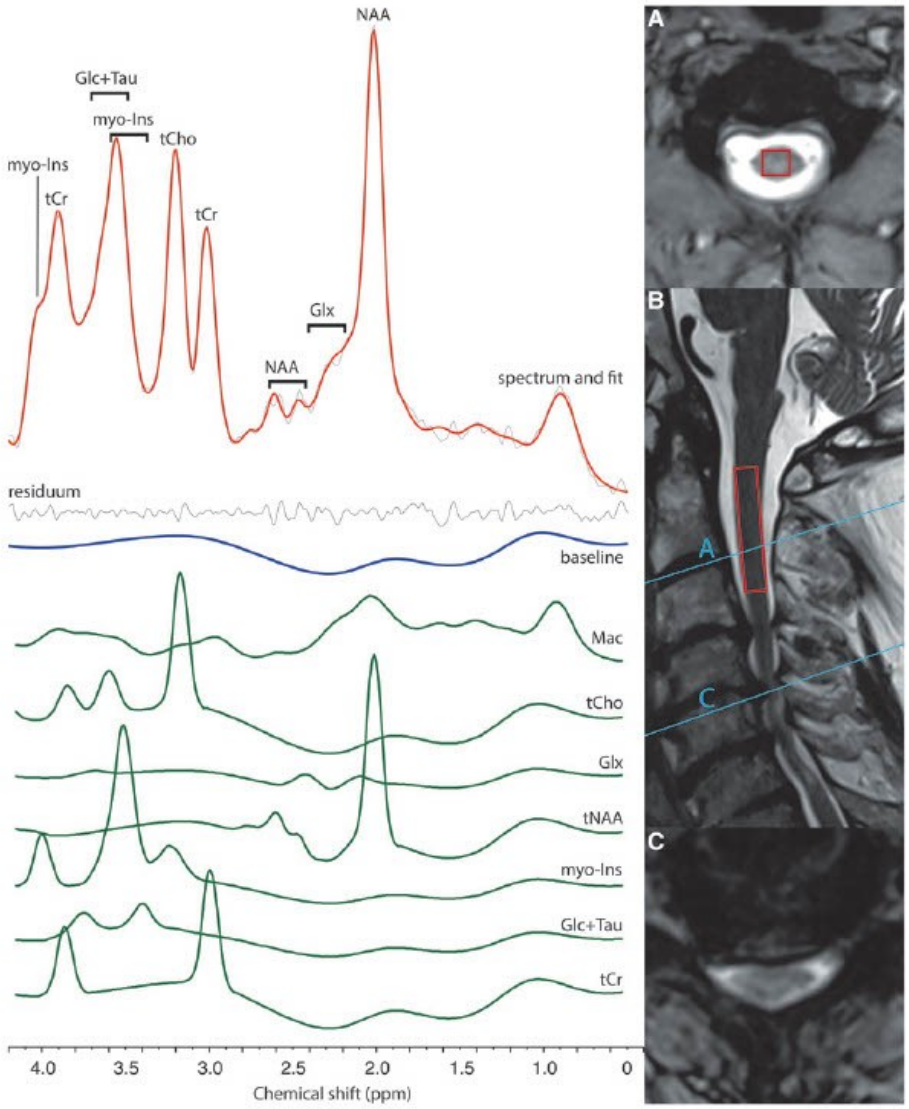

FIG. 1. Example of an MR spectrum and its quantification in LCmodel. Data were obtained from the cervical spinal cord of 1 healthy volunteer. Voxel position is shown on a sagittal T_2-weighted MR image (inset). Blue A and C letters on (**B**) represent the positions of axial/transverse slices of (**A**) and (**C**). MR, magnetic resonance; Mac, macromolecules; Cr, creatine; Glc, glucose; Glx, glutamate + glutamine; myo-Ins, myo-inositol; Lac, lactate; NAA, N-acetylaspartate; Tau, taurine; tCho, total choline; tCr, total creatine; tNAA, total N-acetylaspartate. Color image is available online.

optimized relaxation delays water suppression,[25] and fat and water signals originating outside the MRS voxels were suppressed by the OVS.[23]

Hyperbolic secant adiabatic pulses[26] were replaced by frequency-offset corrected inversion (bandwidth 50 kHz) refocusing pulses for improved semi-LASER localization performance.[27]

Magnetic resonance imaging/magnetic resonance spectroscopy data processing

T_2-TSE images were segmented automatically using Spinal Cord Toolbox v3.2.3[28] to create CSC masks for volumetry and cerebrospinal fluid (CSF) fraction calculations, both measured in the segment covered by the MRS voxel.

MR spectra were saved as single shots and processed in MRspa (Magnetic Resonance signal processing and analysis, Center for Magnetic Resonance Research, University Of Minnesota, USA). Metabolite spectra were summed in blocks of 8 (32×8 per subject), corrected for frequency and phase drifts and the residual effects of eddy currents, and summed to obtain spectrum for single-subject analysis. MR spectra from each subject were pooled and summed to obtain one group-averaged spectrum with high signal-to-noise ratio (SNR) for each of the cohorts. Spectral SNR and linewidths were provided by LCmodel based on metabolite spectra analysis.

Single-subject and group-averaged spectra were analyzed in LCmodel v6.3-0G[29] utilizing a basis set, which included a measured spectrum of macromolecules (Mac)[30] and simulated spectra of 18 metabolites.[31] Metabolites were quantified as ratios to tNAA. Although the pulsatile flow of the CSF can be partially compensated by ECG trigger,[32–34] absolute quantification through internal water referencing is rendered unreliable by biased quantification of the water spectrum in CSC.[14] Quality-control criteria based on Cramér-Rao lower bounds (CRLB) and correlation coefficients provided by LCmodel (R_L) served to select reliably-quantifiable metabolites (Supplementary Materials S1.4).[23]

Statistical analysis

Data were analyzed in SPSS software (v25; IBM Corp., Armonk, NY). Based on the Kolmogorov-Smirnov test, continuous variables with normal and non-Gaussian distribution are presented as means ± standard deviation (SD) and medians (5th–95th percentile), respectively. Demographic and physical parameters were compared between groups by means of the parametric *t*-test/analysis of variance (ANOVA) or the non-parametric Mann-Whitney/Kruskal-Wallis for continuous variables, with chi-square tests for categorical variables. Spearman's correlations assessed relationships between selected continuous variables.

General linear models corrected for the effects of age and height, with *post hoc* tests, were used for between-group comparison of single-subject metabolite ratios and CSC volumes. The Bonferroni correction was applied to correct type 1 errors in *post hoc* group comparisons. Uncertainty intervals of metabolite ratios obtained from the quantification of group-averaged MR spectra were propagated from the CRLB of each metabolite as fractional uncertainties. Thus, between-group differences were considered significant when intervals given by propagated errors did not overlap.

Partial correlations, controlled for age and height, were performed separately for HCs and subjects with compression to assess the relationship between metabolite ratios, CSC volumes, CSA, and CR.

Results

Demographics, physical characteristics, confounding variables

Age, sex, height, weight, and body mass index did not differ significantly within HC, NMDC, and DCM, nor between HC, MC, and SC. However, patients with DCM were, on average, 4 years older than those with HC (Table 1). Analysis revealed that height was a factor that influenced MRS and volumetry outcomes (Supplementary Materials S2.1). Different spinal segments were involved, to a variable extent, in MRS and volumetry assessment, a trend arising out of variable subject height

Table 1. Basic Characteristics of Study Cohort

Group	N	Sex	Age: women (years)	Age: men (years)	Height (cm)	Weight (kg)	Body mass index (kg/m²)	Linewidth (Hz)	Signal-to-noise ratio
HC	47	F 57.4%	53.6±10.5	53.1±7.8	173.3±10.4	80.1±15.7	26.6±4.3	12.1 (8.5, 18.7)	13.0 (9.4, 16.6)
NMDC	60	F 51.7%	54.9±10.8	55.2±9.7	171.5±9.0	81.4±16.3	27.5±3.9	12.6 (6.6, 17.1)	13.0 (9.0, 19.0)
DCM	13	F 46.2%	57.4±7.5	57.9±16.2	169.8±7.0	82.1±15.7	28.4±4.9	11.9 (9.6, 17.6)	14.0 (10.0, 17.6)
Sig.			$p=0.720$	$p=0.696$	$p=0.516$	$p=0.405$	$p=0.887$	$p=0.302$	$p=0.812$	$p=0.570$
MC	41	F 41.5%	55.9±9.9	56.6±8.9	172.4±8.2	82.9±15.3	27.7±3.8	12.7 (6.6, 17.8)	13.0 (8.1, 18.0)
SC	32	F 62.5 %	54.8±10.9	54.0±14.7	169.6±9.2	79.8±17.1	27.5±4.5	11.6 (8.5, 19.0)	14.0 (9.7, 19.7)
Sig.			$p=0.160$	$p=0.761$	$p=0.485$	$p=0.213$	$p=0.635$	$p=0.384$	$p=0.394$	$p=0.731$

Values are presented as mean ± SD or median (5th, 95th percentile interval), except where indicated as percentage (%). The *p* values are derived from the chi-square test for sex and ANOVA/Kruskal-Wallis tests for continuous variables.

HC, healthy controls; NMDC, non-myelopathic degenerative compression; DCM, degenerative cervical myelopathy; Sig, significance; MC, mild compression; SC, severe compression; F, female; SD, standard deviation; ANOVA, analysis of variance.

and the constant length of the MRS voxel.[35] Because it was considered impossible to rule out the effects of bias intrinsic to age and height in the between-group differences in metabolite levels and volumes, age and height were introduced as covariates. Because there was no between-subject difference ($p > 0.15$) in metabolite ratios with MCL at C3/4 ($N = 5$), C4/5 ($N = 20$), C5/6 ($N = 35$), and C6/7 ($N = 13$; Table 2), MCL was not considered a confounding factor.

Magnetic resonance spectroscopy data quality

Linewidth of unsuppressed water spectra measured in MRSpa software was 12.4 (8.2, 17.8) Hz. The LCmodel provided linewidth and SNR of 13.7 (9.7, 19.6) and 13.0 Hz (9.1, 18.0), respectively, as measured on metabolite spectrum. These parameters did not differ between groups (Table 1). The LCmodel quantified metabolites with CRLB medians below 10% for Mac, myo-Ins, tCho, tCr, and tNAA, and below 30% for glucose (Glc) + Tau and combined glutamate/glutamine (Glx) in single-subject spectra analysis, whereas the CRLB of group spectra were 5% for Mac, 3–4% for tCr, 11–15% for Glc + Tau, 10–13% for Glx, 2% for myo-Ins, 4–5% for tCho, and 2–3% for tNAA.

Single-subject magnetic resonance spectra quantification

Between-group differences and their significance appear in Figure 2A (groups based on clinical terminology) and in Figure 2B (groups based on radiological terminology), whereas their averages appear in Table 3. NMDC patients showed altered myo-Ins/tNAA compared to DCM ($p = 0.009$) and tCr/tNAA compared to HCs ($p = 0.003$). Further, tCr/tNAA ($p < 0.001$), Glx/tNAA ($p = 0.010$), and myo-Ins/tNAA ($p = 0.001$) were higher in DCM than in HCs. Differences in tCr/tNAA between the two patient groups (NMDC vs. DCM) and any tCho/tNAA deficits that appeared between patients and HCs did not pass Bonferroni's correction.

Single-subject spectra analyses also revealed differences in tCr/tNAA ($p < 0.001$), Glx/tNAA ($p = 0.001$), and myo-Ins/tNAA ($p = 0.001$) between HC and SC as well as between MC and SC in tCr/tNAA ($p < 0.001$), Glx/tNAA ($p = 0.004$), and myo-Ins/tNAA ($p = 0.006$). Distinctly different tCho/tNAA ($p = 0.011$) levels were found between HC and SC. Alterations in Mac/tNAA and Glc + Tau/tNAA between groups based on compression severity did not pass correction for type 1 error (Supplementary Table S2).

Group-averaged magnetic resonance spectra

High-SNR group averages of MR spectra served for visual comparison of the distinctive spectral patterns that appear in Figure 3, whereas their quantification yielded concentrations with higher accuracy than that of lower-SNR single-subject spectra (Fig. 2). Comparison with HC revealed significantly higher tCr/tNAA and myo-Ins/tNAA in both NMDC and DCM, whereas Glx/tNAA and Glc + Tau/tNAA were only elevated in DCM, as was tCho/tNAA in NDCM. Significant differences in tCr/tNAA, Glx/tNAA, myo-Ins/tNAA, and tCho/tNAA were detected in both groups defined by compression severity, with more profound deficits in SC compared to MC, whereas differences between MC and SC patients emerged in Mac/tNAA (Table 3).

Segmentation outcomes

Significant reductions in CSC volume in DCM compared to HC ($-412\,mm^3$; -14%) and compared to NMDC ($-363\,mm^3$; -12%) were observed (Fig. 4). In contrast to metabolite ratios, differences in volumes between HC and NMDC were not significant. CSC volumes were also significantly lower in SC than in HC ($-250\,mm^3$; -8%) and in SC than in MC ($-213\,mm^3$; -7%), whereas differences between MC and HC were non-significant (Table 2). The within-voxel CSF fraction was significantly higher in DCM (38.5% [27.4, 57.7]) compared to HC (27.3% [14.5, 33.5]; $p < 0.0001$) and NMDC (27.3% [16.0, 39.2]; $p < 0.0001$) and in SC (31.5% [19.0, 54.3]) compared to HC ($p < 0.0001$) and MC (25.2% [16.2, 43.8]; $p < 0.0001$).

Table 2. Radiological Characteristics of the Study Cohort

Group	*CR*	*CSA (mm^2)*	*Volume (mm^3)*	*MCL at C3/4*	*MCL at C4/5*	*MCL at C5/6*	*MCL at C6/7*
HC	0.52 (0.41, 0.64)	72 (61, 85)	3024 (2501, 3693)	n.a.	n.a.	n.a.	n.a.
NMDC	0.41 (0.28, 0.54)	62 (43, 88)	2975 (2448, 3480)	4 (7%)	17 (28%)	26 (43%)	13 (22%)
DCM	0.36 (0.24, 0.48)	53 (26, 74)	2612 (1096, 2953)	1 (8%)	3 (23%)	9 (69%)	0 (0%)
Sig.	$p = 0.009$*	$p = 0.013$*	$p < 0.001$*		—		
MC	0.45 (0.38, 0.59)	68 (43, 88)	2987 (2524, 3636)	3 (7%)	10 (24%)	21 (51%)	7 (17%)
SC	0.35 (0.24, 0.39)	54 (28, 67)	2774 (1777, 3367)	2 (6%)	10 (31%)	14 (44%)	6 (19%)
Sig.	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*		—		

Compression ratio (CR) and cross-sectional areas (CSA) measured at maximum compression level (MCL), as well as spinal cord volumes measured above the compression level, are presented as medians (5th, 95th percentile intervals). The p values are derived from Kruskal-Wallis tests for continuous variables and chi-square tests for MCL. An asterisk (*) indicates $p < 0.05$. The number of participants with different MCLs and their proportional representation within the groups compared are summarized in the left part of the table.

HC, healthy controls; NMDC, non-myelopathic degenerative compression; DCM, degenerative cervical myelopathy; Sig, significance; MC, mild compression; SC, severe compression; n.a., not applicable.

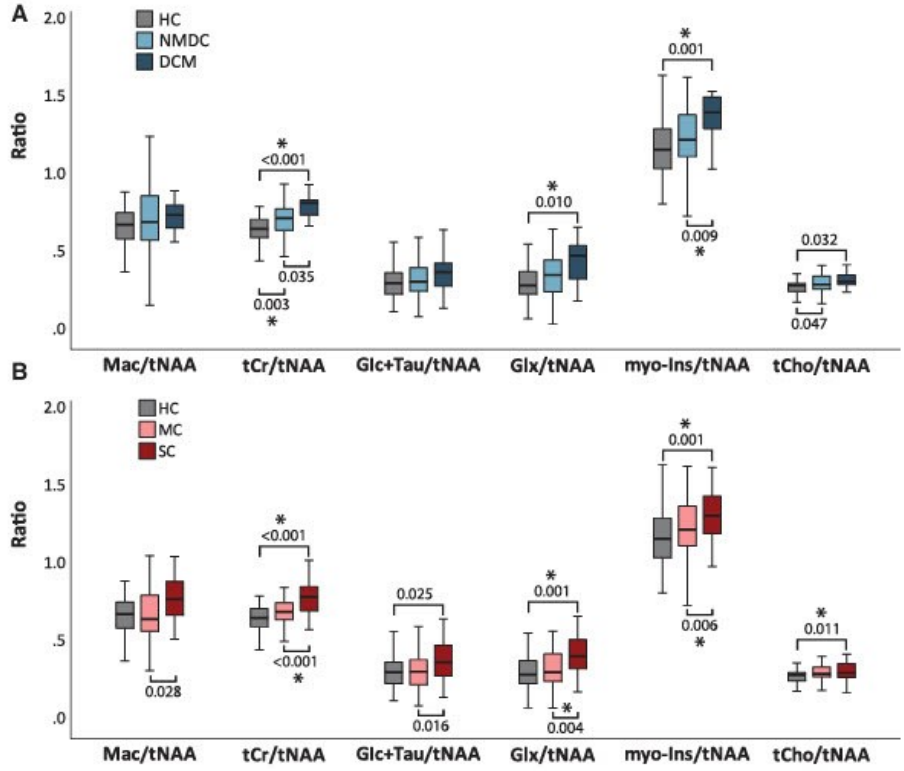

FIG. 2. Single-subject MR spectra quantification. Between-group comparison (general linear model corrected for age and height) of metabolite ratios in healthy controls (HC; $N=47$) and subjects with non-myelopathic degenerative compression (NMDC; $N=60$) and degenerative cervical myelopathy (DCM; $N=13$; **A**) and HC and subjects with mild compression (MC, $N=41$) and severe compression (SC; $N=32$) (**B**). Numbers represent p values uncorrected for multiple comparisons. Asterisks indicate significant differences that passed Bonferroni's correction. Bars represent 25th–75th percentiles; whiskers denote the lowest and highest values, excluding outliers (values >1.5 times the interquartile range). Medians appear as horizontal lines within the bars. MR, magnetic resonance. Color image is available online.

Relationship between neurochemistry, compression severity, cervical spinal cord volumes, and electrophysiology

The relationships between CR and CSA (at MCL), volume, and selected neurochemical levels appear in Table 4 and Supplementary Figure S2. Physiological correlations in HCs are shown together with correlations in compression-affected subjects. Whereas correlations of tCr/tNAA, Glx/tNAA, and myo-Ins/tNAA with volume, CSA, and CR were consistently negative in compression, opposite, positive, relationships between tCr/tNAA, myo-Ins/tNAA, and radiological measures were observed in HCs.

Although significant correlations ($p<0.0001$) between CSC volume and CSA were found in both HCs ($r=0.643$) and compression-affected subjects ($r=0.681$), the correlation between CSC volume and CR significance was confined to subjects with compression ($r=0.363$, $p=0.002$), but was not attained in HCs ($r=-0.156$, $p=0.306$). The relationship between neurochemistry and

Table 3. Between-Group Differences from LCmodel Analysis of Single-Subject (Single-SUBJ) and Group-Averaged (Group-AVG) Spectra

Metabolite	Mac/tNAA (%)		tCr/tNAA (%)		Glc + Tau/tNAA (%)		Glx/tNAA (%)		myo-Ins/tNAA (%)		tCho/tNAA (%)	
Difference	Single-subject	Group-avg.	Single-subject	Group-avg.	Single-subject	Group-avg.	Single-subject	Group-avg.	Single-subject	Group-avg.	Single-subject	Group-avg.
NMDC - HC	3.2	1.2	11.0	12.6	3.1	12.5	31.6	13.8	5.6	6.9	3.7	13.1
DCM - HC	10.9	8.0	25.6	14.4	24.0	33.9	72.9	32.9	19.9	11.3	10.0	6.4
DCM - NMDC	7.5	6.8	13.2	1.6	20.2	19.0	31.4	16.8	13.5	4.1	6.1	–5.9
MC - HC	–5.3	–3.3	8.0	11.0	1.4	6.6	11.2	4.3	5.7	6.7	4.1	11.2
SC - HC	15.5	9.6	21.0	9.6	22.2	29.8	45.7	39.6	12.4	8.0	4.8	9.1
SC - MC	22.0	13.0	12.1	–1.2	20.5	21.8	31.1	33.8	6.3	1.2	0.7	–1.9

Average differences from single-SUBJ data analysis are compared with differences resulting from the analysis of group-AVG spectra. Whereas light red indicates that significance that did not pass correction for multiple comparison, dark red highlights differences significant after multiple comparison correction. Statistical comparison was performed with a general linear model corrected for age and height effects and *post hoc* tests. In group-averaged MR spectra, the significance of the differences was assessed by means of the intervals given by estimated quantification errors (Cramer-Rao lower bounds). Gray cells mark differences lying where error intervals did not overlap. Color table is available online.

HC, healthy controls; NMDC, non-myelopathic degenerative compression; DCM, degenerative cervical myelopathy; MC, mild compression; SC, severe compression; Mac, macromolecules; tNAA, total *N*-acetylaspartate; tCR, total creatine; Glc, glucose; Glx, combined glutamate/glutamine; myo-Ins, myo-inositol; tCho, total choline; MR, magnetic resonance.

electrophysiology can be found in the Supplementary Materials (Supplementary Materials section S2.3 and Supplementary Fig. S1), together with electrophysiological characteristics of the study cohorts (Supplementary Table S3). For relationship between radiological characteristics and neurometabolites, see Supplementary Figure S2.

Relationship between neurochemistry, volumetry, and myelopathy symptoms

According to the mJOA[19] score, with a median of 16 (9, 17), most of the DCM patients (8 of 13) were classified within mild myelopathy. A significant correlation between mJOA and myo-Ins/tNAA ($r=-0.665$, $p=0.013$) appeared (Fig. 5). Because of the relatively low number of DCM patients ($N=13$), the correlation between mJOA and neurochemicals was not corrected for height. The observed significant correlations between mJOA and Mac/tNAA ($r=-0.623$, $p=0.023$) might therefore be a consequence of the height effect on Mac/tNAA levels (Supplementary Materials S2.1). Correlation between volumes and mJOA was not significant ($r=0.192$, $p=0.531$).

Discussion

Our study identified metabolic alterations in spinal neurochemical profiles of distinct compression phenotypes. Revealed distinctions in metabolite fingerprints between subclinical degenerative compression and HCs imply high sensitivity of the methodology. Sensitive metabolic markers are required for longitudinal studies to estimate risk of the development of myelopathy and reveal potential candidates for preventive decompressive surgery among patients without myelopathy symptoms. Such predictors may well revolutionize clinical practice in terms of anticipative protocols; however, longitudinal studies are needed to verify the assumption. This MRS study benefited from the full-signal-intensity semi-LASER pulse sequence, fine-tuned by implementing broadband frequency-offset corrected inversion pulses, leading to a reduction in undesired lipid signals from vertebrae. Further, this approach minimized chemical shift displacement error and attenuated J-evolution/T_2-relaxation relative to point-resolved spectroscopy (PRESS).[27] Spectral quality consistent across the study facilitated the reliable quantification of 10 metabolites, in similar fashion to recent outcomes with metabolite-cycled PRESS.[14]

High spectral quality facilitated the capture of early alterations in tCho/tNAA and tCr/tNAA in NMDC, and more profound differences in tCr/tNAA, myo-Ins/tNAA, Glx/tNAA, and tCho/tNAA in DCM, when compared to HCs. These outcomes prevail over clinical MRI findings, which are unable to distinguish between NMDC and DCM and adequately to reflect clinical status in CSC compression.[36] Total Cr/tNAA, myo-Ins/tNAA, Glx/tNAA, and Glc + Tau/tNAA ratios differed significantly between subjects with MC and SC, likely because NMDC subjects with SC are at higher risk of DCM development.[2] Thus, the distinctions in tCr/tNAA and tCho/tNAA found between NMDC and HC arose out of more-severe compressions in certain subjects.

LCmodel analysis of single-subject spectra was corroborated by the quantification of spectral sums by group. The resulting values were compared while accounting for quantification errors, that is, LCmodel-provided CRLBs of individual metabolites propagated to the ratios. Despite the intrinsic statistical distinctions between the two comparison approaches, the higher SNR of group averages improved quantification accuracy for the metabolites and confirmed the key findings of single-subject spectra analyses. Both comparisons clearly show the dependence of tCr/tNAA, myo-Ins/tNAA, and tCho/

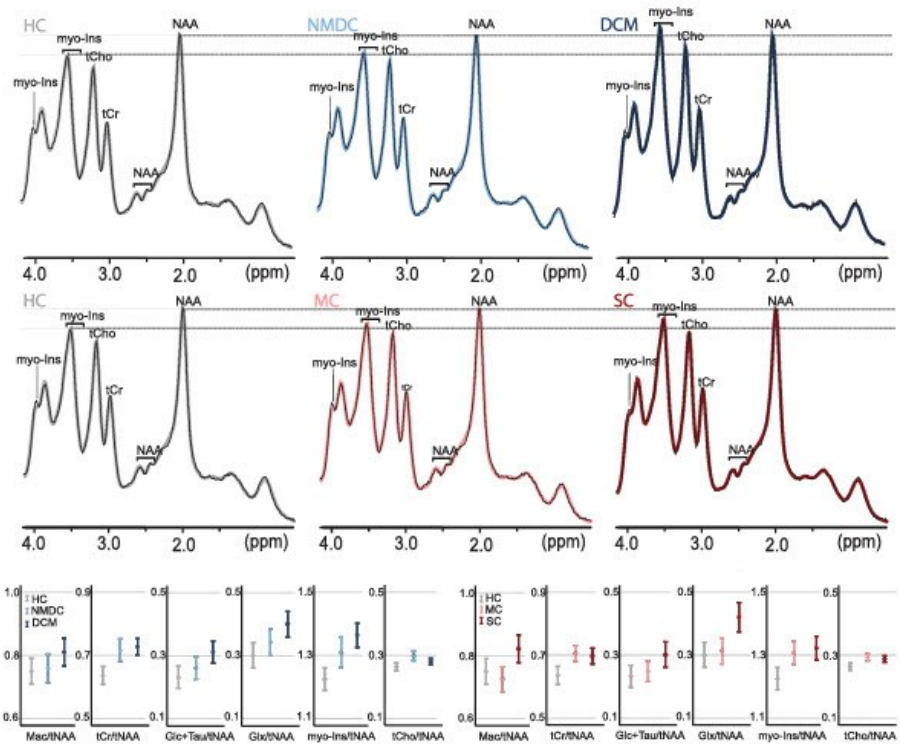

FIG. 3. Group-averaged MR spectra and their quantification in LCmodel. Spectra of individual subjects were pooled and summed, whereas group averages for healthy controls (HC; $N=47$) were compared to spectra representing non-myelopathic degenerative compression (NMDC; $N=60$) and degenerative cervical myelopathy (DCM; $N=13$; **A**) and to spectra representing mild compression (MC; $N=41$) and severe compression (SC; $N=32$; **B**). The spectra (black line) and their LCmodel fits (in color) are scaled using NAA-methyl resonance at 2 ppm. Horizontal lines indicate height of 2 ppm NAA-methyl peak (upper), 3.56 ppm myo-Ins peak, and 3 ppm Cr-peak in HC to facilitate visual comparison. Outcomes of quantification in LCmodel are shown in plots (**C**), where error bars represent Cramer-Rao lower bounds propagated to the ratio of metabolites. MR, magnetic resonance; myo-Ins, myo-inositol; NAA, *N*-acetylaspartate. Color image is available online.

tNAA on the radiological severity of compression and clinical impairment. Both methods disclosed differences in tCr/tNAA and tCho/tNAA between HC and NMDC, largely driven by SC subjects. Therefore, early signatures of spinal neurochemical impairment merit future longitudinal studies to improve the stratification of patients with cervical compression and their subsequent management.

Although degenerative stenosis precluded consistent voxel placement at the compression level, metabolite changes propagate rostrally from the CSC lesion up to the brain through Wallerian/Wallerian-like neurodegeneration.[11,17,37] Myo-Ins/tNAA elevation, which reflects neuronal/axonal loss or demyelination (tNAA)[38] and gliosis or inflammation (myo-Ins), accords with recent MRS work on chronic spinal cord injury[14] and other studies of neurodegeneration.[39–41] Elevated tCho and tCho/tNAA have indicated increased membrane turnover arising out of ongoing neurodegeneration/demyelination[39] and have been associated with the duration of spinal cord injury.[14] Increased tCr/tNAA and Glx/tNAA ratios attributable to compression might relate to various pathophysiological processes.

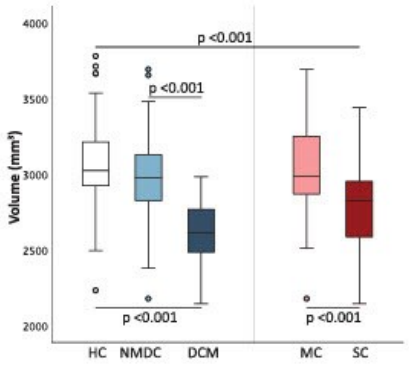

FIG. 4. Volumes of cropped individual spinal cord masks calculated above the level of stenosis, beginning with the slice corresponding to the bottom edge of vertebra C3, taking 90 cranial slices into account. The *p* values are derived from general linear models corrected for age and height. The bars represent the 25th–75th percentiles; whiskers denote the lowest and highest values, with the exception of outliers (values >1.5 times the interquartile range), which are marked as circles. Medians appear as horizontal lines within the bars. NAA, *N*-acetylaspartate. Color image is available online.

Although exact interpretation is challenging, particularly because individual metabolites (e.g., creatine and phosphocreatine) cannot be reliably separated, the changes might be driven by decreased tNAA and related to neurodegeneration/demyelination. Both tCr and tCho were quantified with relatively high accuracy, leading to low SDs in tCr/tNAA and tCho/tNAA, reflecting early reduction in tNAA. In contrast, tCho/myo-Ins was not significantly altered in patients with chronic CSC injury,[14] probably attributable to limited, not fully developed neurochemical changes in substantially milder CSC impairment. The contrasting relationship between neurochemicals and volume in HCs and subjects with compression implies that neurochemical levels reflect altered CSC composition rather than atrophy. The CSF fraction did not bias metabolite ratios within the MRS voxel; the relevant metabolites (except for Glc) are not measurable in CSF. In accord with earlier publications,[7,42] the degree of rostral CSC atrophy correlated with the degree of compression.[11] In contrast to the situation with neurochemicals, CSC volume was not significantly different between HC and NMDC. This suggests that volumetry reflects more-severe CSC impairment and is less sensitive than MRS to early changes.

The significant correlation between mJOA and myo-Ins/tNAA highlights the capacity of MRS to reflect the degree of clinical severity and serve as a potential predictor of DCM development.[17,36]

The current work was limited by the relatively low number of participants in the DCM group; this condition is relatively rare compared with NMDC,[2] and DCM patients are difficult to recruit because urgent surgery often takes priority. Further, given that degenerative changes advance with age, the age differences between

Table 4. Partial Correlations between Metabolite Ratios and Radiological Parameters Controlled for Age and Height Effects

	HC group			*Patient group*		
	Volume	*CSA*	*CR*	*Volume*	*CSA*	*CR*
Mac/tNAA	–0.038 $p=0.403$	0.281 $p=0.031$	–0.047 $p=0.380$	–0.154 $p=0.100$	**–0.254** **$p=0.016$***	**–0.275** **$p=0.010$***
tCr/tNAA	**0.329** **$p=0.014$***	**0.302** **$p=0.022$***	0.127 $p=0.203$	**–0.259** **$p=0.014$***	**–0.343** **$p=0.002$***	**–0.376** **$p=0.001$***
Glc + Tau/tNAA	0.002 $p=0.495$	0.085 $p=0.292$	0.213 $p=0.082$	–0.039 $p=0.375$	**–0.199** **$p=0.049$***	–0.145 $p=0.115$
Glx/tNAA	-0.173 $p=0.129$	-0.168 $p=0.135$	-0.002 $p=0.494$	**–0.277** **$p=0.001$***	**–0.234** **$p=0.026$***	**–0.205** **$p=0.044$***
myo-Ins/tNAA	0.226 $p=0.039$	**0.415** **$p=0.002$***	0.054 $p=0.361$	**–0.277** **$p=0.001$***	**–0.339** **$p=0.002$***	**–0.278** **$p=0.009$***
tChol/tNAA	0.260 $p=0.043$	0.243 $p=0.054$	0.033 $p=0.414$	0.093 $p=0.220$	–0.078 $p=0.259$	–0.122 p=0.154
CSA	**0.642** **$p=0.000$***	n.a.	0.208 $p=0.085$	**0.684** **$p=0.000$***	n.a.	**0.600** **$p=0.025$***
CR	–0.156 $p=0.153$	0.208 $p=0.085$	n.a.	**0.363** **$p=0.001$***	**0.600** **$p=0.025$***	n.a.

The asterisk represents the statistically significant result.

Mac, macromolecules; tNAA, total *N*-acetylaspartate; tCr, total creatine; Glc, glucose; Glx, combined glutamate/glutamine; myo-Ins, myo-inositol; tChol, total choline; CSA, cross-sectional area; CR, compression ratio; n.a., not applicable.

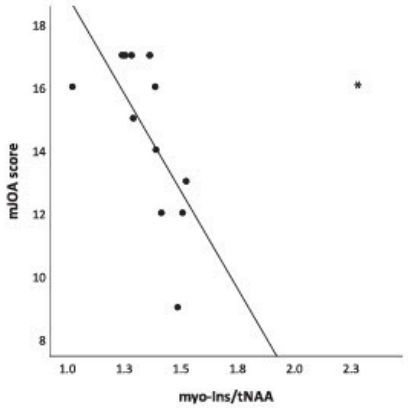

FIG. 5. Relationship between myo-Ins/tNAA and mJOA score, assessing the severity of degenerative cervical myelopathy ($N = 13$). The outlier (asterisk) was not included in the regression fit line. myo-Ins, myo-inositol; mJOA, modified Japanese Orthopedic Association (scale); tNAA, total *N*-acetylaspartate.

HC and DCM often appear in the literature.[14,17] Although the 4-year age difference between HC and DCM in this study did not reach the level of significance, the single-subject level analysis was corrected for the age effect. Age differences also declined when subjects were divided into groups according to compression severity. Despite the utilization of standard clinical MR hardware, there is still a need for operators trained in MRS data acquisition, post-processing, and relatively long acquisition times. These factors limit the use of the methodology herein at non-specialized centers. However, spinal MRS will gain from progress toward automatic MRS acquisition in the brain (e.g., user-independent voxel placement and power calibrations).[27]

Conclusion

In conclusion, the current study revealed neurochemical changes in CSC above the compression level in subjects with radiological signs of compression and clinical myelopathy and, for the first time, in non-myelopathic participants as well. State-of-the-art MRS demonstrated sufficient sensitivity to reveal early changes in non-myelopathic patients and thus might allow the stratification of non-myelopathic subjects. The current work warrants longitudinal studies assessing their risk of myelopathy development. Although MRS markers and level of spinal atrophy strongly reflected the severity of stenoses, volumes were less sensitive to clinical status than MRS.

Data availability statement

The data sets generated during the current study are not publicly available because of ethical reasons, but are available from the authors (petr.bednarik@meduniwien.ac.at, ts.horak@gmail.com) on reasonable request.

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Authors' Contributions

P.B., J.B., and T.H. are guarantors of the entire study. P.K. and P.B. set up the MR protocol. P.K. acquired the data. T.H. and P.B. analyzed the data. M.H., P.B., and A.S. performed the statistical analyses. T.H. and M.H. wrote the manuscript draft. Z.K. and Z.K.J. conducted the neurological assessment. J.V. processed the MRI data. T.R. and M.K. evaluated 1.5T MRI. E.V. carried out the electrophysiological evaluation. D.D. and P.G.H. provided technical expertise and adapted the sLASER pulse sequence (Oz and Tkac)[26] for spinal cord MRS. J.B., P.B., and T.H. coordinated the study. J.B., A.S., and P.B. designed the study. All authors contributed to interpreting the data, read and revised the manuscript, and agreed upon the final version.

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Author Disclosure Statement

No competing financial interests exist.

Supplementary Material

Supplementary Table S1
Supplementary Table S2
Supplementary Table S3
Supplementary Figure S1
Supplementary Figure S2
Supplementary References

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DIAGNOSTICS

Prevalence and Imaging Characteristics of Nonmyelopathic and Myelopathic Spondylotic Cervical Cord Compression

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Study Design. Cross-sectional population-based observational study.

Objective. To estimate the prevalence of nonmyelopathic spondylotic cervical cord compression (NMSCCC) and cervical spondylotic myelopathy (CSM) in a population older than 40 years and to evaluate the magnetic resonance imaging (MRI) characteristics of these conditions.

Summary of Background Data. The prevalence of neither NMSCCC nor CSM is known and there exists no commonly accepted quantitative MRI definition of cervical cord compression.

Methods. A group of 183 randomly recruited volunteers, 93 women, median age 66 years, range 40–80 years, underwent MRI examination of the cervical spine and spinal cord on a 1.5 T device using conventional sequences from disc levels C2/C3 to C6/C7. The imaging criterion for cervical cord compression was defined as a change in spinal cord contour at the level of an intervertebral disc on axial or sagittal MRI scan.

Results. MRI signs of cervical cord compression were found in 108 individuals (59.0%; 95% CI: 51.5%–66.2%); their numbers increased with age from 31.6% in the fifth decade to 66.8% in the eighth. Clinical signs of symptomatic CSM were found in two cases (1.1%), and 75 cases (41.0%) were without compression. An anteroposterior cervical canal diameter at the level of intervertebral disc (CD_{disc}) of less than 9.9 mm was associated with the highest probability of NMSCCC—odds ratio (OR) = 32.5, followed by a compression ratio of ≤0.5: OR = 11.1.

Conclusion. The prevalence of NMSCCC in a population older than 40 years is higher than previously reported and increases with age. CD_{disc} and compression ratio had the highest capacity to discriminate between subjects with and without asymptomatic compression, and their cut-off values could be used to objectify criteria for cervical cord compression.

Key words: anteroposterior diameter of cervical canal, cervical spondylotic myelopathy, compression ratio, epidemiology, magnetic resonance imaging, nonmyelopathic cervical cord compression, prevalence.

Level of Evidence: 2

Spine 2016;41:1908–1916

Stenosis of the cervical spinal canal due to degenerative spondylotic changes is a key factor in the development of symptomatic cervical spondylotic myelopathy (CSM). Experimental findings, however, indicate a certain resistance of the spinal tissue to chronic compression and also a delay in the development of symptomatic myelopathy.[1–3] Magnetic resonance imaging (MRI) is able to detect even subtle compressions leading to changes in spinal cord contour, shape and, in more advanced compression, even giving rise to decreases in the volume of the spinal cord and signal intensity abnormalities.[4] The influence of compression on the development of symptomatic myelopathy, however, varies among individuals, and MRI findings overlap significantly between individuals with CSM and those with nonmyelopathic compression, leading to a "clinical-radiological mismatch." Nonmyelopathic (presymptomatic or asymptomatic) spondylotic cervical cord compression (NMSCCC) has become a well-documented entity.[5,6] The prevalence of neither NMSCCC nor CSM is known; the

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data in the literature differ widely. Cervical cord impingement or compression has previously been found in 27% of subjects incidentally examined with MRI; in individuals older than 64 years the prevalence reached 30%.[7] There is, however, no clear and, in particular, quantitative definition of cervical cord compression. Symptomatic CSM is the most frequent cause of cervical cord dysfunction in individuals older than 55 years,[8] but no epidemiological report on the prevalence of CSM emerged from the authors' literature search.

The aim of the present study was to estimate the prevalence of both NMSCCC and CSM in a general population older than 40 years and to investigate the capacity of MRI characteristics to discriminate between individuals with and without compression, and between nonmyelopathic and myelopathic compression.

MATERIALS AND METHODS

An optimized estimate method was employed to calculate the extent of the sample required to investigate the prevalence of NMSCCC.[9] The presumed prevalence was set at 2.5%–5%–7.5%–10% in the fifth to eighth decades. It emerged that the estimated quota of subjects to be examined to confirm such a prevalence at 95% confidence interval (CI) and 5% range was 181 subjects. Personal recruitment by experienced staff was used to gather volunteers from the Caucasian population of the province of South Moravia (south-eastern Czech Republic). Their guidelines included an established quota of subjects, intended to obtain a proportional representation of the four age decades, both sexes, type of domicile (urban *vs.* rural) and type of work (manual *vs.* nonmanual labor).

A total of 183 randomly chosen volunteers, recruited irrespective of the presence of signs of symptomatic myelopathy or radiculopathy, but with no history of cervical spine surgery or trauma, 93 women and 90 men, median age 66, age range 40 to 80 years, agreed to participate. Of these, 94 were of urban domicile and 90 reported nonmanual labor.

All underwent MRI examination on a 1.5 T device (Philips Achieva, Philips Medical Systems, Eindhoven, the Netherlands) using conventional sequences, including T1, T2, and STIR (short-tau inversion recovery) images in the sagittal plane and axial T2-weighted gradient-echo scans coherently covering five segments of cervical spine from levels C2/C3 to C6/C7. Detailed MRI parameters are summarized in Table 1. The clinical status of patients/volunteers was blinded for the neuroradiologists who examined the cervical spine MRIs. The MRI of every subject was evaluated by two neuroradiologists, who agreed on the assessment of the compression in the majority of cases. Where disagreement existed—seldom—the final decision was based a cooperative decision.

The imaging criterion for cervical cord compression was defined as a change in spinal cord contour at the level of an intervertebral disc on axial or sagittal MRI scan compared with that at midpoint level of neighboring vertebrae. We did not observe any case with other than degenerative cervical cord compression (*i.e.*, tumorous or traumatic) or a significant cervical cord deformity causing cervical cord compression.

Spinal cord compression was further graded as

- Impingement, that is, focal concave, usually anterior defect of spinal cord contour and with preservation of a major part of subarachnoid space outside the compression—type I (Figure 1A)
- Flat or circular compression with partially preserved subarachnoid space—type IIa—or with lost subarachnoid space—type IIb (Figure 1B, C). Combined types of distinct cord compression with complete loss of subarachnoid space would be classified as grade IIb.

The following conventional MRI parameters at the level of intervertebral disc with maximum compression were also measured: cross-sectional spinal cord area (CSA) (Figure 2B), anteroposterior (AP) and laterolateral (LL) spinal cord diameter, compression ratio (CR) considered in terms of AP/LL spinal cord diameter (CR) (Figure 2A), AP diameter of cervical canal (CD_{disc}) representing the space available for the dural sac (excluding osteophytes, disc herniations and ligaments, and the presence of spinal cord T2 hyperintensity). Correlation of quantitative MRI parameters with age and sex was evaluated.

TABLE 1. Parameters of Magnetic Resonance Imaging Protocol

Sequence	Imaging Plane	Slice Thickness (mm)	In-plane Resolution (mm)	FOV (mm)	TR (ms)	TE (ms)	Other
T1 TSE	Sagittal	3	0.92 × 1.23	250 × 250 × 36	400	7.8	
T2 TSE	Sagittal	3	0.92 × 1.23	250 × 250 × 36	3500	120	
STIR	Sagittal	4	0.9 × 1.25	300 × 300 × 52	5000	80	TI 120 ms
T2 FFE	Axial	4	0.65 × 0.67	170 × 170 × 80	479	9.2	
DTI	Axial	4	1.25 × 1.25	170 × 170 × 80	3549	83	b 900 s/mm^2

b indicates b-value setting; DTI, diffusion tensor imaging; FFE, fast field echo; FOV, field of view; STIR, short-tau inversion recovery; TE, echo time; TI, inversion time; TR, repetition time; TSE, turbo spin echo.

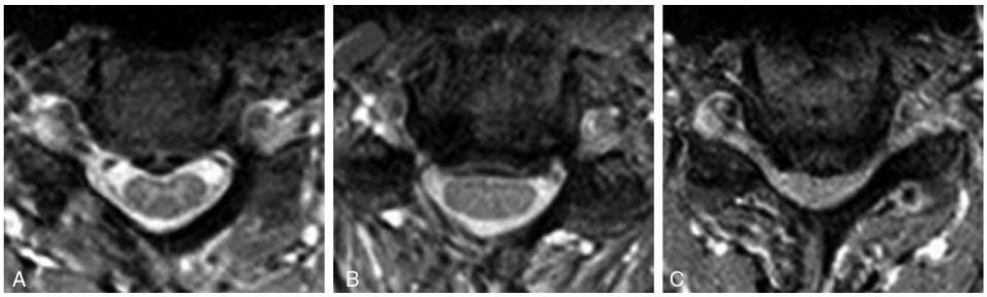

Figure 1. A, Example of the "impingement" type of spondylotic cervical cord compression (type I): focal concave anterior defect of spinal cord contour and with preserved subarachnoid space. **B**, Example of a flat compression with partially preserved subarachnoid space (type IIa). **C**, Example of a flat compression with lost subarachnoid space (type IIb).

In patients with multisegmental involvement the level of maximum compression was identified by the grade of cervical cord compression (type IIb>IIa>I) and in case with two or more similar grades the maximal reduction of CD_{disc} diameter was used as an additional criterion.

Subjects with MRI signs of cervical cord compression underwent thorough formal neurological examination by a neurologist, with special attention paid to the usual first clinical symptoms and/or signs of symptomatic cervical myelopathy: gait disturbance, clumsy hand syndrome, Lhermitte sign, spastic paresis of any of the extremities (most frequently lower spastic paraparesis), flaccid paresis of one or two upper extremities in a plurisegmental distribution, and sensory involvement in various distributions (always plurisegmental).

For comparison with NMSCCC, the two CSM cases were supplemented with a further 35 CSM cases recruited from our database (group C). The demographic and MRI characteristics of all three groups of individuals without compression, with NMSCCC, and with CSM are summarized in Table 2. Subgroups differed in age, with NMSCCC patients slightly older. The lower age of CSM cases was biased by their not being recruited randomly.

Statistical Methods

Standard descriptive statistics were applied to describe the data. Median values supplemented with minimum and maximum ranges were used for continuous data and absolute and relative frequencies for categorical data. The Kruskal-Wallis test for continuous data assessed the statistical significance of differences between patient groups and the Fisher exact test addressed categorical data. Relations between continuous variables were described in terms of Spearman rank correlation coefficient and its statistical significance. Interobserver reliability was calculated using Pearson correlation and intraclass correlation in continuous data (quantitative MRI parameters) and kappa statistics in categorical data (assessment of the presence and type of compression). The power of individual characteristics (demographic and continuous MRI parameters) required to discriminate between compared groups of patients (with definition of groups based on qualitative criterion standards—presence of compression and myelopathy) was analyzed by Receiver Operating Characteristics curve and described by a standard set of characteristics (area under curve, sensitivity, specificity, positive and negative predictive values, overall accuracy, true- and

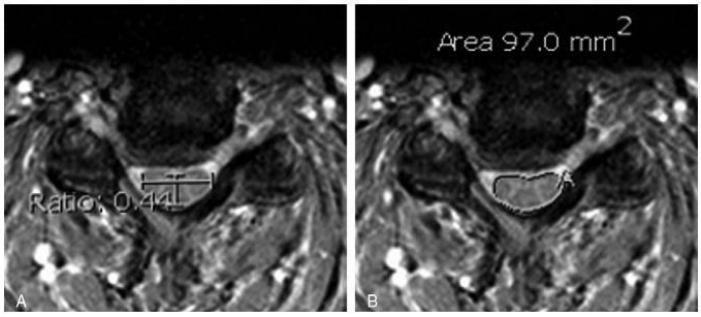

Figure 2. A, Assessment of compression ratio (anteroposterior/laterolateral spinal cord diameter): 0.44. **B**, Assessment of cross-sectional spinal cord area: 97 mm^2.

TABLE 2. Comparison of Demographic and Magnetic Resonance Imaging Characteristics of Patient Groups

Parameter*	(A) No compression (N = 75)	(B) NMSCCC (N = 106)	(C) CSM (N = 37)	P†
Age	63 (41;86)[a]	67 (40;81)[b]	58 (42;78)[a]	<0.001
Men	33 (44.0%)	56 (52.8%)	20 (54.1%)	0.470
Urban domicile	38 (50.7%)	55 (51.9%)	–	0.881
Nonmanual labor	36 (48.0%)	53 (50.0%)	–	0.880
CD_{disc}	11.4 (9.1;15.0)[a]	9.1 (5.9;12.6)[b]	7.6 (3.8;10.5)[c]	<0.001
AP	7.5 (5.5;9.1)[a]	6.7 (5.1;8.7)[b]	6.0 (3.0;9.3)[c]	<0.001
LL	14.2 (12.2;16.2)[a]	14.6 (12.5;16.6)[b]	14.6 (11.8;16.9)[a,b]	0.017
CSA	87.5 (65.0;106.8)[a]	82.4 (64.0;103.7)[a]	63.7 (37.4;86.6)[b]	<0.001
CR	0.54 (0.36;0.66)[a]	0.47 (0.34;0.62)[b]	0.42 (0.19;0.68)[c]	<0.001

*Median (minimum; maximum) values were used for continuous variables; absolute numbers (proportional representation) were used for categorical variables.

†Kruskal-Wallis test was used for continuous variables; Fisher exact test was used for categorical variables.

[a,b,c]Identical letters indicate homogeneous (mutually not statistically significantly different) groups of patients (post hoc test).

AP indicates anteroposterior spinal cord diameter; CD_{disc}, anteroposterior diameter of cervical canal at the level of intervertebral disc; CR, compression ratio; CSA, cross-sectional spinal cord area; CSM, cervical spondylotic myelopathy; LL, laterolateral spinal cord parameter; NMSCCC, nonmyelopathic spondylotic cervical cord compression.

false-positive/negative cases). The definition of cut-off values with the highest predictive power was based on the highest sum of sensitivity and specificity. The predictive power of patient characteristics was subsequently evaluated by logistic regression, and described by odds ratios and their CIs. The analysis was performed in one-dimensional terms for each characteristic, and with a multidimensional model for age adjustments. For comparison of subgroups with and without compression, MRI parameters measured at the level of maximum compression were compared with those obtained at C4/5 level in a subgroup without compression (C4/5 disc level was an arbitrary choice). The analysis was performed with SPSS 22.0.0.1 software (IBM Corporation, Chicago, IL, 2013).

RESULTS

Interobserver Reliability

Assessment of the presence and type of compression displayed high interobserver reliability (kappa 0.949 and 0.643, respectively; $P < 0.001$—Table 3).

Similarly, assessment of quantitative MRI parameters showed high interobserver correlation and consistency ($P < 0.01$; Table 4).

MRI signs of cervical cord compression were found in 108 individuals (59.0%; 95% CI: 51.5%–66.2%) and increased with age from 31.6% in the fifth decade to 66.8% in individuals older than 69 years. Clinical signs of symptomatic CSM were found in two cases (1.1%), whereas 106 cases (57.9%) displayed no myelopathic signs (NMSCCC—group B), and 75 cases (41.0%) were without compression at all (group A).

The level of maximum compression was most frequently located at C5/6 level (n = 61; 56.5% of all compressions), followed by C4/5 level (n = 27; 25.0%), C3/4 level (n = 11; 10.2%), and C6/7 level (n = 9; 8.3%).

No significant difference appeared in the prevalence of NMSCCC between the sexes, or types of domicile and work (Table 2).

Some quantitative MRI parameters correlated weakly with age, but not with sex. Age adjustment was thus applied in calculation of the predictive power of MRI parameters. All subgroups differed significantly in all the conventional MRI parameters evaluated (Table 2).

The discriminative power of MRI parameters to distinguish between individuals without compression and with nonmyelopathic compression appears in Table 5 and between individuals with asymptomatic and symptomatic

TABLE 3. Interobserver Reliability Analysis of the Assessment of Type of Cervical Cord Compression According to Magnetic Resonance Imaging Using Kappa Statistics

Compression Type	Observer 2				Kappa (95% CI)	P
	1	2a	2b	Total		
Observer 1						
1	4 (20.0%)	2 (10.0%)	0 (0.0%)	6 (30.0%)	0.643 (0.333; 0.952)	<0.001
2a	0 (0.0%)	10 (50.0%)	2 (10.0%)	12 (60.0%)		
2b	0 (0.0%)	0 (0.0%)	2 (10.0%)	2 (10.0%)		
Total	4 (20.0%)	12 (60.0%)	4 (20.0%)	20 (100.0%)		

TABLE 4. Intraclass Correlation Coefficient of the Measurement of Quantitative Magnetic Resonance Imaging Parameters

ICC (95% CI)—Consistency	Single Measures	Average Measures
CD_{disc}	0.942 (0.860; 0.977)*	0.970 (0.925; 0.988)*
AP	0.879 (0.720; 0.950)*	0.936 (0.837; 0.974)*
LL	0.881 (0.725; 0.951)*	0.937 (0.841; 0.975)*
CR	0.877 (0.717; 0.950)*	0.935 (0.835; 0.974)*
CSA	0.936 (0.846; 0.974)*	0.967 (0.916; 0.987)*
ICC (95% CI)—Absolute Agreement	**Single Measures**	**Average Measures**
CD_{disc}	0.925 (0.763; 0.973)*	0.961 (0.866; 0.986)*
AP	0.748 (0.015; 0.924)*	0.856 (0.030; 0.961)*
LL	0.882 (0.730; 0.951)*	0.937 (0.844; 0.975)*
CR	0.784 (0.169; 0.931)*	0.879 (0.288; 0.964)*
CSA	0.780 (−0.059; 0.945)*	0.877 (−0.126; 0.972)*

Two-way random effects model in which both people effects and measures effects are random.

**Correlation is significant at the 0.01 level (F-test with true value 0).*

AP indicates anteroposterior spinal cord diameter; CD_{disc}, anteroposterior diameter of cervical canal at the level of intervertebral disc; CR, compression ratio; CSA, cross-sectional spinal cord area; LL, laterolateral spinal cord parameter.

compression in Table 6, both using cut-off values calculated by ROC analysis.

A comparison of the value of calculated cut-off values for MRI parameters, expressed as odds ratios, in the prediction of cervical cord compression in asymptomatic individuals based on changes in spinal cord contour appears in Table 7, and the power of prediction of the presence of symptomatic myelopathy in subjects with cervical cord compression in Table 8. An anteroposterior diameter of the cervical spinal canal of <9.9 mm was associated with the highest probability of MRI-detected nonmyelopathic cervical cord compression—an odds ratio (95% CI) of 32.5 (13.5–8.2) followed by CR ≤0.5: 11.1 (5.4–22.9), whereas CSA ≤88.3 mm^2 showed only low predictive value: 2.3 (1.2–4.4) for nonmyelopathic cervical cord compression.

In contrast, CSA ≤74.8 expressed the highest value in predicting CSM: odds ratio (95% CI), at 36.2 (11.8–111.1).

Investigation of type and degree of NMSCCC revealed isolated focal impingement (type I) in 45 cases (41.7% of all cases with MRI-detected compression), wide compression (type IIa) in 39 subjects (36.1%), and type IIb in 24 subjects (22.2%) including the two cases with CSM. In further evaluation of the capacity of MRI parameters to discriminate between subjects with impingement and flat compression, it emerged that in CR (cut-off ≤0.483; $P = 0.001$) and CD_{disc} (cut-off: ≤9.45; $P = 0.002$), ROC analysis had the highest discriminative power.

The prevalence of T2 hyperintensity was significantly higher in the CSM subgroup (17 individuals—45.7%, subgroup C) in comparison with both subgroup A (no case with hyperintensity) and subgroup B (four cases, 3.7%); $P < 0.001$.

DISCUSSION

In this cross-sectional descriptive study of a population older than 40 years, it emerged that the prevalence of cervical cord compression, based on qualitative assessment of changes in spinal cord contour on MR images, was higher than that has previously been reported and increased with age. Quantitative MRI parameters and cut-off values that could be used for the definition of cervical cord compression on MRI images, and for prediction of development of symptomatic myelopathy in subjects with cervical cord compression, were identified.

Descriptions of the prevalence of spondylotic cervical cord compression are influenced by the MRI criteria considered for compression. Definitions and classification of MRI-detected cervical cord compression vary widely among published studies to date. Teresi *et al*[7] (1987) differentiated between "spinal cord impingement" (considered as a concave defect in the spinal cord adjacent to a site of disc bulging/protrusion or posterior osteophytosis without obliteration of the subarachnoid space posterior to the cord) and "cord compression" (defined as a concave defect associated with obliteration of the posterior subarachnoid space). The reported prevalence of 27% (impingement + compression) in a group older than 45 years, half that of the proportion determined by the present study, could have been influenced by the lower resolution of the 0.3 T MR device used, in comparison to the 1.5 T device employed here. A further reason for the higher prevalence of NMSCCC in the present study may lie in the use of prospective MRI examinations with a standardized protocol dedicated to cervical spine imaging in all subjects. Shimomura *et al*[10] defined two categories of MRI signs of cervical cord compression: "partial compression" with the ventral surface of spinal cord compressed by a combination of osteophytes and disc bulging with preserved dorsal subarachnoid space, and "circumferential spinal cord compression and deformity" with the surface of the spinal cord compressed and deformed by a combination of osteophytes, disc bulging, and ligamentum flavum infolding, with obliterated dorsal subarachnoid

TABLE 5. Discriminative Power of Parameters to Distinguish Between (A) Patients Without Compression (N = 75) and (B) Patients With Nonmyelopathic Compression (N = 106)

Parameter	AUC (CI)*	P*	Cut-off	TN†	FN†	FP†	TP†	Specificity	Sensitivity	PPV	NPV	Accuracy
Age	0.606 (0.52;0.691)	0.016	≥66.5	50 (27.6%)	51 (28.2%)	25 (13.8%)	55 (30.4%)	0.667	0.519	0.688	0.495	0.580
Men	0.544 (0.459;0.629)	0.312	–	33 (18.2%)	56 (30.9%)	42 (23.2%)	50 (27.6%)	0.440	0.472	0.543	0.371	0.459
CD_{disc}	0.903 (0.861;0.945)	<0.001	≤9.9	67 (37.0%)	21 (11.6%)	8 (4.4%)	85 (47.0%)	0.893	0.802	0.914	0.761	0.840
AP	0.799 (0.734;0.864)	<00.001	≤6.8	67 (37.0%)	47 (26.0%)	8 (4.4%)	59 (32.6%)	0.893	0.557	0.881	0.588	0.696
LL	0.613 (0.529;0.697)	0.010	≥13.9	32 (17.7%)	20 (11.0%)	43 (23.8%)	86 (47.5%)	0.427	0.811	0.667	0.615	0.652
CSA	0.590 (0.503;0.676)	0.040	≤88.3	35 (19.3%)	27 (14.9%)	40 (22.1%)	79 (43.6%)	0.467	0.745	0.664	0.565	0.630
CR	0.830 (0.768;0.891)	<0.001	≤0.5	60 (33.1%)	27 (14.9%)	15 (8.3%)	79 (43.6%)	0.800	0.745	0.840	0.690	0.768

**Area under the curve (95% CI) and its statistical significance, based on receiver operating curve analysis.*

†Absolute number (proportional representation).

AP indicates anteroposterior spinal cord diameter; CD_{disc}, anteroposterior diameter of cervical canal at the level of intervertebral disc; CR, compression ratio; CSA, cross-sectional spinal cord area; FN, false negative; FP, false positive; LL, laterolateral spinal cord parameter; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive.

TABLE 6. Discriminative Power of Parameters to Distinguish Between (B) Patients With Nonmyelopathic Compression (N = 106) and (C) Patients With Symptomatic Compression (N = 37)

Parameter	AUC (IS)*	P*	Cut-off	TN†	FN†	FP†	TP†	Specificity	Sensitivity	PPV	NPV	Accuracy
Age	0.708 (0.607;0.809)	<0.001	≤61.5	78 (54.5%)	14 (9.8%)	28 (19.6%)	23 (16.1%)	0.736	0.622	0.451	0.848	0.706
Men	0.506 (0.398;0.614)	0.912	–	56 (39.2%)	20 (14.0%)	50 (35.0%)	17 (11.9%)	0.528	0.459	0.254	0.737	0.510
CD_{disc}	0.798 (0.715;0.881)	<0.001	≤8.3	74 (51.7%)	8 (5.6%)	32 (22.4%)	29 (20.3%)	0.698	0.784	0.475	0.902	0.720
AP	0.737 (0.632;0.842)	<0.001	≤6.3	91 (63.6%)	16 (11.2%)	15 (10.5%)	21 (14.7%)	0.858	0.568	0.583	0.850	0.783
LL	0.519 (0.401;0.637)	0.735	≥14.7	69 (48.3%)	19 (13.3%)	37 (25.9%)	18 (12.6%)	0.651	0.486	0.327	0.784	0.608
CSA	0.917 (0.863;0.971)	<0.001	≤74.8	92 (64.3%)	6 (4.2%)	14 (9.8%)	31 (21.7%)	0.868	0.838	0.689	0.939	0.860
CR	0.701 (0.594;0.808)	<0.001	≤0.4	99 (69.2%)	19 (13.3%)	7 (4.9%)	18 (12.6%)	0.934	0.486	0.720	0.839	0.818

**Area under the curve (95% CI) and its statistical significance, based on ROC.*

†Absolute number (proportional representation).

AP indicates anteroposterior spinal cord diameter; CD_{disc}, anteroposterior diameter of cervical canal at the level of intervertebral disc; CR, compression ratio; CSA, cross-sectional spinal cord area; FN, false negative; FP, false positive; LL, laterolateral spinal cord parameter; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive.

TABLE 7. Predictive Power of Parameters to Distinguish Between (A) Patients Without Compression (N = 75) and (B) Patients With Nonmyelopathic Compression (N = 106)

Parameter	One-Dimensional Model*		Age Adjustment*	
	Odds Ratio (95% CI)	*P*	Odds Ratio (95% CI)	*P*
Age	1.039 (1.006;1.073)	0.021	–	–
Age ≥ 66.5	2.157 (1.169;3.981)	0.014	–	–
Men	1.425 (0.787;2.583)	0.242	1.351 (0.739;2.473)	0.329
CD_{disc}	0.299 (0.212;0.421)	<0.001	0.302 (0.215;0.425)	<0.001
CD_{disc} ≤ 9.9	33.899 (14.131;81.320)	<0.001	32.495 (13.510;78.157)	<0.001
AP	0.172 (0.095;0.310)	<0.001	0.179 (0.098;0.326)	<0.001
AP ≤ 6.8	10.513 (4.597;24.044)	<0.001	9.856 (4.288;22.655)	<0.001
LL	1.603 (1.145;2.245)	0.006	1.617 (1.147;2.280)	0.006
LL ≥ 13.9	3.200 (1.641;6.241)	0.001	3.501 (1.762;6.957)	<0.001
CSA	0.965 (0.935;0.997)	0.032	0.970 (0.939;1.002)	0.067
CSA ≤ 88.3	2.560 (1.364;4.806)	0.003	2.306 (1.211;4.389)	0.011
CR	0.782 (0.725;0.844)	<0.001	0.786 (0.728;0.849)	<0.001
CR ≤ 0.5	11.704 (5.726;23.921)	<0.001	11.077 (5.359;22.895)	<0.001

*Logistic regression.

AP indicates anteroposterior spinal cord diameter; CD_{disc}, anteroposterior diameter of cervical canal at the level of intervertebral disc; CR, compression ratio; CSA, cross-sectional spinal cord area; LL, laterolateral spinal cord parameter.

space. These two types correspond to the "boomerang" and "triangular" types described by Kameyama *et al.*[11] Our classification is a combination of these suggested classification systems, reflecting location (impingement is focal and usually anterior), extent, and spinal cord deformity (impingement causing boomerang-type deformity with preserved posterior subarachnoid space). Still more sophisticated systems for grading cervical stenosis and deformity of the dural sac and spinal cord have been proposed.[12] One limitation of all these definitions and classifications is that they reflect static compression only, whereas dynamic compression is not represented.

The major strength of the present study lies in its evaluation of an ethnically homogenous population sample using random recruitment performed with specific consideration of age, sex, type of domicile, and work.

In this randomly chosen population older than 40 years, the prevalence of compression based on change of spinal cord contour was higher than that has been previously reported; as expected, it rose with age. The prevalence of

TABLE 8. Predictive Power of Parameters to Distinguish Between (B) Patients With Nonmyelopathic Compression (N = 106) and (C) Patients With Symptomatic Compression (N = 37)

Parameter	One-Dimensional Model*		Age Adjustment*	
	Odds Ratio (95% CI)	*P*	Odds Ratio (95% CI)	*P*
Age	0.923 (0.882;0.965)	<0.001	–	–
Age ≤ 61.5	4.577 (2.072;10.108)	<0.001	–	–
Men	1.050 (0.496;2.225)	0.898	1.263 (0.567;2.812)	0.568
CD_{disc}	0.399 (0.274;0.580)	<0.001	0.381 (0.252;0.574)	<0.001
CD_{disc} ≤ 8.3	8.383 (3.457;20.327)	<0.001	9.158 (3.555;23.593)	<0.001
AP	0.330 (0.201;0.543)	<0.001	0.295 (0.173;0.504)	<0.001
AP ≤ 6.3	7.962 (3.406;18.617)	<0.001	9.196 (3.633;23.278)	<0.001
LL	1.142 (0.770;1.693)	0.509	1.095 (0.721;1.663)	0.671
LL ≥ 14.7	1.767 (0.828;3.771)	0.141	1.571 (0.704;3.504)	0.270
CSA	0.807 (0.748;0.871)	<0.001	0.798 (0.733;0.869)	<0.001
CSA ≤ 74.8	33.952 (12.008;95.999)	<0.001	36.216 (11.810;111.056)	<0.001
CR	0.881 (0.829;0.937)	<0.001	0.870 (0.814;0.931)	<0.001
CR ≤ 0.4	13.398 (4.921;36.479)	<0.001	14.433 (4.906;42.461)	<0.001

*Logistic regression.

AP indicates anteroposterior spinal cord diameter; CD_{disc}, anteroposterior diameter of cervical canal at the level of intervertebral disc; CR, compression ratio; CSA, cross-sectional spinal cord area; LL, laterolateral spinal cord parameter.

different types of cervical cord compression decreased from highest for cervical cord impingement (41.7% of all compressions) to more extensive, mostly circular, cervical cord compression with partially preserved subarachnoid space (36.1%) and finally loss of it (22.2%), including two cases of CSM. These MRI-defined types of cervical cord compression are successive stages of a degenerative cervical spine process leading to cervical stenosis, asymptomatic (nonmyelopathic) cervical cord compression, and finally to symptomatic cervical myelopathy. In contrast to the high prevalence of NMSCCC, the prevalence of CSM is far lower. The prevalence of 1.1% in this sample should, however, be considered as only indicative and must be investigated by a much larger study. Knowledge of the prevalence and exact definition of the different types of cervical cord compression is essential to the assessment of their prognostic significance.

A major limitation of most cervical cord compression definitions, one that bears upon differences in the reported prevalence of cervical cord compression, is their qualitative, or semiquantitative character, prone to subjective bias. Despite a significant overlap in the standard quantitative MRI parameters that describe the characteristics of the spinal cord canal and the morphological characteristics of cervical spinal cord in individuals with and without cervical cord compression, some of these parameters, however, showed high discriminative and predictive power for the presence of NMSCCC. Decreased CD_{disc} ($\leq$9.9 mm) and CR ($\leq$0.5) could thus be used for verification of MRI-detected cervical cord compression based on subjective descriptive judgment.

The parameters that may discriminate between symptomatic and nonmyelopathic compression (especially CSA and T2 hyperintensity)[13,14] do not appear applicable to defining criteria for NMSCCC. Although there exists a significant overlap in all MRI parameters for subjects with NMSCCC and CSM, the present study suggested that CSA (cut-off $\leq$74.8 mm^2) has the highest discriminative and predictive power of the routine MRI parameters, followed by CR (cut-off $\leq$0.4). The presence of T2 hyperintensity is another useful parameter for discriminating between subjects with symptomatic and asymptomatic myelopathy.

A limitation of the present study is the fact that the estimate of the extent of the sample required to assess the prevalence of cervical cord compression with acceptable accuracy was much lower than that eventually disclosed. Nevertheless, the high prevalence of NMSCCC revealed acceptable 95% CI (between 51.5% and 66.2%). We were not able to monitor MRI parameters (especially those that showed significant predictive power, *i.e.*, CD_{disc}, CR, and CSA) for bony dimensions using parameters such as the Torg-Pavlov ratio. These parameters were, however, able to discriminate clearly between NMSCCC and no compression, and between NMSCCC and CSM. As the study population was ethnically homogenous, expansion of the results to other ethnicities should only be undertaken with caution.

Our grading system of severity of cervical cord compression is less comprehensive than it might be, as it does not take into consideration direction of focal compressions. We, however, did not observe any case with isolated posterior focal compression in our study group.

In conclusion, the present study reveals that the prevalence of spondylotic cervical cord compression in a population older than 40 years is higher than that has been previously reported. In most cases, compression is nonmyelopathic, less severe, and not accompanied by significant decrease of CSA or presence of T2 hyperintensity compared with findings in subjects without compression. CD_{disc} and CR showed the highest power to discriminate between subjects with and without asymptomatic compression and between impingement and wide compression, and their cut-off values could be used to objectify criteria for cervical cord compression. The risk of development of symptomatic CSM in different types and degrees of NMSCCC remains to be established in future prospective evaluation of larger groups of subjects.

➢ Key Points

- ❑ The prevalence of neither NMSCCC nor that of symptomatic cervical myelopathy is known and there exists no commonly accepted or, in particular, quantitative MRI definition of cervical cord compression.
- ❑ The prevalence of nonmyelopathic spondylotic cervical cord compression in a randomly recruited cohort of 183 volunteers older than 40 years reached 57.9%, and 1.1% displayed signs of symptomatic CSM.
- ❑ Among MRI parameters, the highest capacity to predict nonmyelopathic cervical cord compression, and to discriminate subjects with this condition from those without compression is shown by AP diameter of the cervical spinal canal and the spinal cord (SC) compression ratio (AP/LL SC diameter).

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Are subjects with spondylotic cervical cord encroachment at increased risk of cervical spinal cord injury after minor trauma?

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ABSTRACT

The aim of the study was to analyse the risk of symptomatic myelopathy after minor trauma in patients with asymptomatic spondylotic cervical spinal cord encroachment (ASCCE). In a cohort of 199 patients with ASCCE, previously followed prospectively in a study investigating progression into symptomatic myelopathy, the authors looked retrospectively for traumatic episodes that may have involved injury to the cervical spine. A questionnaire and data file analysis were employed to highlight whatever hypothetical relationship might emerge with the development of symptomatic myelopathy. Fourteen traumatic episodes in the course of a follow-up of 44 months (median) were recorded in our group (who had been instructed to avoid risky activities), with no significant association with the development of symptomatic myelopathy (found in 45 cases). Only three minor traumatic events without fracture of the cervical spine were found among the symptomatic myelopathy cases, with no chronological relationship between trauma and myelopathy. Furthermore, 56 traumatic spinal cord events were found before the diagnosis of cervical cord encroachment was established, with no correlation to either type of compression (discogenic vs osteophytic). In conclusion, the risk of spinal cord injury after minor trauma of the cervical spine in patients with ASCCE appeared to be low in our cohort provided risky activities in these individuals are restricted. Implementation of preventive surgical decompression surgery into clinical practice in these individuals should be postponed until better-designed studies provide proof enough for it to take precedence over a conservative approach.

INTRODUCTION

Degenerative changes in the cervical spine are part of the normal ageing process and are almost omnipresent in older people.[1] They may lead to the development of clinical symptoms in some individuals if the discs and/or osteophytes impinge on neural structures such as the nerve root or spinal cord. Spondylotic cervical cord encroachment (SCCE) detected by imaging methods, mostly MRI, is a prerequisite for the clinical diagnosis of cervical spondylotic myelopathy (CSM). However, SCCE can also be asymptomatic with regard to myelopathy.[1 2]

CSM develops insidiously, but it has been reported to occur after trauma.[3–6] Some authors have suggested that individuals who have asymptomatic spondylotic cervical cord encroachment (ASCCE) on the cervical spinal cord are at increased risk of acute myelopathy if they experience minor trauma.[7 8] This has led some surgeons to recommend decompression surgery for the purpose of preventing this trauma-induced myelopathy in individuals presumed susceptible,[9 10] and this topic became a matter of controversy.[11]

The aim of our study was to retrospectively analyse all traumas of the cervical spine in our cohort of 199 individuals with ASCCE followed for the median period of 44 months, and investigate any relationship to clinical manifestation of myelopathy and type of cervical spinal cord compression.

METHODS

Group

The study sample consisted of a cohort of 199 subjects (94 women and 105 men; median age 51 years, range 28–82 years) recruited consecutively between January 1993 and January 2005, and followed up to July 2007, who completed at least a 2-year follow-up. MRI examination of the cervical spine and spinal cord was performed in all patients who exhibited clinical signs and symptoms of cervical radiculopathy or moderate to severe chronic or intermittent axial cervical pain. All included patients had to meet the following inclusion criteria:

- MR signs of spondylogenic or discogenic compression of the cervical spinal cord with or without concomitant change in signal intensity from the cervical cord on T2/T1 images;[12]
- Axial pain or clinical signs and/or symptoms of radiculopathy that could be controlled by conservative treatment;
- Absence of any current clinical signs and symptoms that could be possibly attributed to cervical cord involvement.

During the follow-up period (median 44 months) progression in symptomatic myelopathy was found in 45 patients (22.6%); the 25th percentile time to clinically manifested myelopathy was 48.4 months.

Further details of the clinical, imaging and electrophysiological evaluation and algorithm of the study that centred upon risk factors predicting clinical manifestation of myelopathy have been published elsewhere.[12] The presence of any trauma, both before inclusion of a patient into the study and during the follow-up period, was detected with

a questionnaire administered at the end of the follow-up period, and focused on:

- Date and mechanism of trauma;
- Short-term sequelae (including loss of consciousness, fracture, weakness of extremities, disturbance of sensitivity or sphincters, therapy including surgery);
- Long-term sequelae (including disturbances of gait, loss of self-support, permanent disability, chronic pain.

Further, the patient case histories and a database containing complete relevant data on all patients included into the study were retrospectively analysed with respect to the occurrence and characteristics of any trauma. All traumatic episodes were subsequently classified as possibly relevant or irrelevant to cervical spinal cord injury. The following traumatic episodes were classified as possibly relevant:

Traumas of the head, spine, trunk and shoulder region, if at least one of the following characteristics was present:

- Any fall;
- High-energy accident (according to Advanced Trauma Life Support principles, a high-energy (vehicle) accident is defined as initial speed >64 km/h, major car-deformity, intrusion into passenger compartment >30 cm, extrication time from vehicle >20 min, falls >6 m, roll over, auto–pedestrian accidents, or motorcycle crash >32 km/h or with separation of rider and bike[13]);
- Unconsciousness;
- Fracture;
- Necessity for surgical treatment;
- Probable transient neurological deficit;
- Permanent disability.

Traumatic episodes before the beginning of the follow-up period were correlated with the type of spinal cord compression (discogenic vs osteophytic) classified from MRI and CT scans, while traumatic episodes during the follow-up period were correlated with clinical manifestation of spondylotic cervical myelopathy.

Statistics

Univariate logistic regression models predicting probability of CSM were used for trauma as a potential risk factor, and the OR was estimated with 95% confidence limits.

RESULTS

During the follow-up period, 14 relevant traumatic events were recorded. None of them was of a serious degree with fracture of the cervical spine and/or followed by immediate neurological deficit after the trauma. In terms of mechanism, there were six falls (all from height <6 m), four sports injuries, three traffic accidents and one occupational injury. Among 45 patients (22.6%) who developed symptomatic myelopathy during the follow-up period, potentially relevant traumatic episodes were found in three patients: in two cases, myelopathy became symptomatic 6 months before trauma and in one case manifestation developed 4 years after the trauma. There was no statistically significant association between traumatic events and subsequent development of symptomatic myelopathy (OR 0.935; 95% CI: 0.247 to 3.535; p=0.921).

We found 56 potentially relevant traumatic episodes before the beginning of the follow-up with possible relationships to the cervical disc herniation. In terms of mechanisms, 21 were falls (two from height >6 m), 12 sports injuries, 11 traffic accidents, 11 occupational injuries and one injury caused by a falling object.

The type of cervical spinal cord compression (herniation, osteophytes or both) was evaluated and classified as discogenic (due to disc herniation) in 50 patients (25.1%), osseous (due to osteophytes) in 67 patients (33.7%) and mixed (herniation +osteophytes) in 82 patients (41.2%).[12] We found no statistical association between traumatic events and discogenic (OR 1.281; 95% CI 0.636 to 2.582; p=0.484) or mixed type of compression (OR 1.767; 95% CI 0.879 to 3.549, p=0.106).

DISCUSSION

In a cohort of 199 patients with ASCCE who progressed into symptomatic myelopathy, we detected only three traumas of the cervical spine in those who became symptomatic, but without a direct chronological relationship. Furthermore, traumatic events before detection of cervical spinal cord encroachment showed no impact on the type of spinal cord compression.

Increased risk of cervical spinal cord injury in patients with ASCCE presumed sufficient to justify preventive surgical decompression is based on case reports, case series or retrospective cross-sectional studies.[7–10] Moreover, risks involved in surgery to the cervical spine in asymptomatic spinal cord encroachment have not been reported.[11]

Some authors have reported an increased risk of spinal cord injury in patients with cervical spondylosis. Regenbogen *et al*,[5] in a group of 88 retrospectively analysed patients over the age of 40 with spinal cord injury resulting from trauma, found 25 cases with no bony or ligamentous injury but with signs of severe spondylosis as compared with 35 younger spinal cord injury patients (below 37 years of age) who showed severe bony or ligamentous injury in all but one case. Kang *et al*,[14] in a retrospective analysis of 288 spinal injury patients, found a significantly lower sagittal diameter of the spinal canal and Pavlov canal/body ratio at both compressed and uncompressed levels in patients with complete and incomplete spinal injury compared with those with no nerve or spinal cord injury. Yoo *et al*,[15] among a series of 200 cases with cervical spondylosis or ossification of posterior longitudinal ligament, and symptomatic myelopathy, detected retrospectively minor trauma of the cervical spine in 63 cases, and deterioration of pre-existing myelopathy or development of new myelopathy in 31 of them. Most of these cases (25) had narrow spinal canal (diameter <10 mm).

Murphy *et al* [11] addressed the question of whether patients with ASCCE are at increased risk of spinal cord injury after minor trauma and may thus warrant early decompression. They found none of the case–control or prospective cohort studies that are essential to drawing the firm conclusion that risk of spinal cord injury from minor trauma is increased in ASCCE.

Lauryssen *et al*,[10] combining data from several databases, estimated the 'worst case scenario' risk of myelopathy in the ASCCE population at 1:2100. This low-risk estimate is largely consistent with our own findings.

Furthermore, Murphy *et al* found no relevant study reporting the outcome of surgery in asymptomatic patients with cervical cord spondylotic encroachment.[11] The reported frequency of serious complications or mortality in surgical series of patients with symptomatic CSM is generally well above 1%. As reported postsurgical complications generally relate to the surgery itself rather than to myelopathy, it is not likely that the complication rate would be substantially different in asymptomatic individuals as compared with patients with symptoms.

The major limitation of our study was its retrospective design, which could have had an influence on the exact timing of trauma in some individuals. However, significant traumatic episodes were found in only three cases with symptomatic myelopathy, and the timing of their traumas correlated with

records found in their case histories. The low frequency of traumas in our cohort may have resulted, at least in part, from our recommendation to all patients with diagnosed ASCCE that they avoid risky activities, such as certain sports (skiing, climbing, etc), walking on slippery surfaces and so on. As we detected no severe trauma of the cervical spine in our cohort, we were not able to assess the hypothesis that stenosis of the cervical spinal canal (both degenerative and congenital) could worsen neurological sequelae of such a trauma.

We also investigated the possibility that disc herniation as a cause of spinal cord compression might more frequently be the result of preceding trauma but found no such association.

In conclusion, the risk of spinal cord injury after minor cervical spine trauma in patients with asymptomatic spondylotic cervical cord encroachment appeared to be low in our cohort, provided risky activities in these individuals are restricted. Implementation of preventive surgical decompression surgery into clinical practice in these individuals should be postponed until better-designed studies show justification for giving it precedence over the conservative approach.

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Competing interests None.

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Spinal Cord MR Diffusion Properties in Patients with Degenerative Cervical Cord Compression

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ABSTRACT

BACKGROUND AND PURPOSE: Diffusion tensor imaging (DTI) has previously been used as a biomarker of myelopathy in patients with degenerative cervical cord compression (DCCC). However, many factors may affect the diffusion properties of the spinal cord. This prospective study seeks to identify sources of variability in spinal cord DTI parameters in both DCCC patients and healthy subjects.

METHODS: The study group included 130 patients with DCCC confirmed by magnetic resonance imaging and 71 control subjects without signs of DCCC. DTI data of the cervical spine were acquired in all subjects. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values were measured at different levels of the spinal cord (SCLs). Statistical data analysis was then used to determine diffusion parameters in terms of age, sex, SCL, and spinal cord compression.

RESULTS: Significant variations in FA and ADC values emerged when several spinal cord levels were mutually compared in the control group. FA values correlated significantly with age in the DCCC group and sex had a significant influence on ADC values in both groups. The two diffusion parameters in the DCCC group differed significantly between patients with clinical signs of mild-to-moderate myelopathy compared with asymptomatic patients, and correlated with measurements of spinal canal morphology.

CONCLUSIONS: Diffusion parameters of the cervical spinal cord were thus shown to respond significantly to spinal cord compression, but were subject to interaction with several other factors including sex, age, and SCL. These findings may be important to the interpretation of DTI measurements in individual patients.

Keywords: Magnetic resonance imaging, diffusion tensor imaging, degenerative cervical myelopathy, degenerative cervical cord compression.

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Introduction

Diffusion tensor imaging (DTI) has recently emerged as a sensitive marker of structural abnormalities of the brain and spinal cord, enabled by measurements of the scalar parameters that characterize the diffusion properties of tissue.[1] The prospects for its application to degenerative cervical myelopathy (DCM) appear promising, since asymptomatic spinal cord compression is frequent,[2] and in some patients, it appears difficult to link the clinical manifestation with the finding of cervical cord compression. Thus, a reliable diagnostic tool capable of sensitive detection and quantification of the spinal cord structural abnormality is desirable.

Several authors have described significant changes in DTI parameters in patients with degenerative cervical cord compression (DCCC).[3–5] However, certain recent reports indicate an apparent physiological variability in scalar diffusion parameters between cervical spinal cord levels (SCLs)[6,7] and these parameters may also correlate significantly with age.[8] It has become relevant to investigate the extent to which DTI parameters may relate to such physiological variables and to establish the real contribution of spinal cord compression in patients with DCCC, because it may be important for evaluation of cervical cord abnormalities by means of DTI analysis in patients suspected of having DCM. The main purpose of this prospective study is therefore to evaluate the influences of age, sex, level within the spinal cord (SCL), and the presence of spinal cord compression, together with clinically manifest myelopathy, on the diffusion characteristics of the cervical spinal cord in a group of patients with DCCC. Furthermore, analysis of DTI data in a group of controls without signs of spinal cord compression provides normative data and enables study of physiological variability in diffusion parameters.

Materials and methods

Subjects

DCCC group

The group consisted of 130 prospectively examined patients (77 men, 53 women, and mean age 62 years) with various clinical signs of cervical spine degenerative disease (cervical

Table 1. Demographic Features of the Study Subjects

		N	Mean Age	SD	Range
DCCC group	Total	130	62.2	9.5	39-82
	Male	77	63.3	8.9	39-82
	Female	53	60.6	10.2	40-78
Control group	Total	71	62.6	10.4	43-87
	Male	31	62.4	12.0	43-87
	Female	40	62.7	9.2	44-83

N= number of subjects; SD = standard deviation; DCCC = degenerative cervical cord compression.

pain, radiculopathy, or myelopathy). Detailed demographic data of the study group appear in Table 1. The inclusion criterion was the finding of spinal cord compression arising out of intervertebral disc herniation and/or osteophytes confirmed by magnetic resonance imaging (MRI). Spinal cord compression was defined as a change of spinal cord contour visible on axial and sagittal MRI scans at the level of the intervertebral disc. The MRI of every subject was evaluated by two radiologists who agreed on the assessment of the compression in the majority of cases. In debatable cases, the final decision was based on group discussion. Signs of DCM were sought by standardized clinical examination in all subjects in the DCCC group and 37 patients with symptoms and signs of DCM (20 men, 17 women, mean age 59 years) were identified, with decreased modified Japanese Orthopaedic Association scale (mJOA)[9] of <18 (mean score 15, SD 1.7, range 12–17)—the DCM subgroup.

The remaining 93 individuals (57 men, 36 women, mean age 63 years) formed the asymptomatic DCCC (ADCCC) subgroup. Clinical signs of radiculopathy were observed in 4 patients (3 from the DCM subgroup and 1 from the ADCCC subgroup). Patients with other confirmed or suspected neurological disease that might mimic DCM were not included in the study.

Control group

The control group consisted of 71 subjects (31 men, 40 women, mean age 63 years) without cervical spinal cord compression and with no history of significant neurological disorder. They were recruited from a prospectively examined cohort of volunteers, selecting only those who were free of MRI signs of DCCC according to the criteria described above. For more information about the demographic features of the subjects, see Table 1.

Informed consent was obtained from all patients and volunteers and the study was approved by the institutional ethics board.

MRI Examination and Image Analysis

All subjects enrolled into the study underwent MRI examinationofthecervicalspineona1.5TMRdevicewitha16-channel head and neck coil (Philips Achieva, Best, the Netherlands). The standardized imaging protocol included conventional pulse sequences in sagittal (T1-weighted, T2-weighted, and short tau inversion recovery (STIR) images) and axial planes (T2-weighted gradient-echo) for the purpose of morphological evaluation and a DTI sequence in the axial plane giving comprehensive coverage of spinal cord segments C2/3-C6/7 (Figs 1 and 2). The DTI scans were acquired with a slice thickness of 4 mm, with the same geometry settings as those employed for the axial T2 images. Single-shot echo planar imaging was used for the DTI sequence (TR 3549 ms, TE 83 ms, flip angle 25°, in-plane resolution 1.25 × 1.25 mm), applying 15 directions of diffusionsensitizing gradient with 900 s/mm^2 as the value of *b*-factor.

In the DCCC group, morphological parameters measured on axial T2 scans included anteroposterior (AP) spinal canal diameter, spinal cord cross-sectional area and compression ratio (AP divided by laterolateral diameter of the spinal canal), using Impax software (release 6.6.0.145, Agfa HealthCare, Mortsel, Belgium). These measurements were taken at the level of maximum spinal cord compression (MCL), which was identified by maximum reduction of AP spinal canal diameter in comparison with other segments. In patients with multisegmental involvement and a similar degree of spinal canal stenosis, the level with the smallest spinal cord area was chosen.

A diffusion registration tool (Philips Medical Systems, Best, the Netherlands) was employed to remove misalignments and distortions arising out of head motion and eddy currents. FiberTrak application, Extended MR WorkSpace (release 2.6.3.5, Philips Medical Systems) was used for DTI data analysis. The diffusion data were processed and fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values calculated. Measurements were subjected to region-of-interest (ROI) analysis by placing the ROIs at the level of intervertebral disks over the entire spinal cord area depicted on the axial images of isotropic diffusion. Special care was taken to avoid the surrounding cerebrospinal fluid and data contamination by susceptible artifacts, by avoiding the borderline zone at the margins of the spinal cord cross sections, and abnormal signal intensities from susceptible artifacts at the spinal cord margins, if visible on the isotropic diffusion images. Mean FA and ADC values of the spinal cord cross sections were recorded at MCL in the DCCC group and at all cervical levels (C2/3 to C6/7) in the control group. Interobserver variability of FA and ADC values had already been tested in a previous study of ours, where the same technique of DTI data analysis had been used; the reproducibility of all parameters tested proved acceptable.[3]

Data Analysis

DCCC group. Subjects from the DCCC group were classified into subgroups according to level of maximum spinal cord compression. Comparisons were made up of FA values between different SCLs, and the same done for ADC. The statistical significance of differences in paired measurements between SCLs was assessed by repeated application of the ANOVA model. ADC and FA values were compared between subgroups defined by sex, presence, or absence of T2 hyperintensity and clinical manifestation of myelopathy using the *t*-test for independent samples. Both diffusion parameters were correlated with age and morphological measurement by means of Pearson correlation coefficient. ADC and FA values at individual SCLs were also mutually compared between the control group and DCCC group using Mann-Whitney U test.

The repeated-measures ANOVA model was applied to identify and quantify sources of interindividual variability in ADC and FA

values; particular factors (age, sex, SCL, morphological parameters, presence of myelopathy, and spinal cord T2 hyperintensity) were assessed using the relative sum of squares related to the total experimental sum of the square.

Results

Control Group

A summary of morphological parameters measured at different SCLs appears in Table 2. Significant differences of FA and ADC values were found between SCLs, with a decrease of FA values from C2/3 level to C6/7 level. The ADC values decreased from level C2/3 to C5/6, while at C6/7, they were comparatively higher. ADC values differed significantly between men and women in most of the SCLs (except C2/3 level), with higher values in women (Table 3); the FA values were not significantly different (data not shown). Neither ADC nor FA values correlated significantly with age.

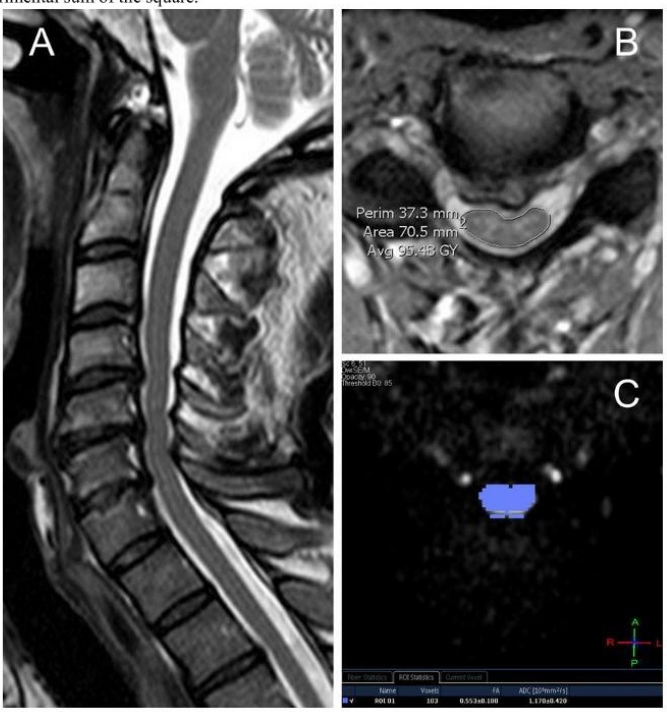

Fig 1. Conventional and DTI MR examination of a patient with multisegmental narrowing of the spinal canal. (A) T2-weighted image in sagittal plane. (B) T2-weighted image in axial plane at C4/5 level depicting spinal cord impingement by intervertebral disk herniation; an example of spinal cord area measurement is also shown. (C) Isotropic diffusion-weighted image at the same level calculated from multidirectional diffusion data in FiberTrak application, diffusion parameters measured within the region-of-interest placed over the spinal cord cross section.

Control group. ADC and FA values were compared between different SCLs using the repeated measures ANOVA model and the Tukey HSD post hoc test. Both diffusion parameters were compared between males and females using the *t*-test for independent samples and correlated with age by means of Pearson correlation coefficient.

The repeated-measures ANOVA model was applied to identify and quantify sources of interindividual variability in ADC and FA values; age, sex, SCL, and their mutual interactions were evaluated using the relative sum of squares related to the total experimental sum of the square.

Finally, post hoc analysis was performed to disclose potential relations between spinal cord area, sex, and ADC values. Thus, the spinal cord area was compared between males and females at individual SCLs using Mann-Whitney U test and the interactions of spinal cord area and sex with ADC values were addressed by univariate and multivariate linear regression models.

The statistical analyses were performed with SPSS 22 (IBM Corporation, Armonk, New York, United States 2014) and Statistica 12 (Statsoft Inc., Tulsa, OK, USA 2014)

The interindividual variability in ANOVA analysis was relatively high and only partially explained by the factors investigated. The most important predictor was SCL, which emerged as by far the strongest source of variability of FA values, less conspicuously of ADC values. Sex contributed significantly to ADC values (Table 4).

The spinal cord area was significantly lower in women compared to men at most SCLs (Table 5). Sex of subject emerged as a significant predictor of ADC values independent of spinal cord area according to multivariate regression analysis at SCLs C4/5, C6/7, and C6/7 (Table 6). Significant interactions between sex and ADC also appeared in the univariate regression model at the above-mentioned SCLs; however, interactions with spinal cord area were

not significant (data not shown). Both spinal cord area and sex significantly predicted ADC values at C3/4 level according to the univariate regression model (P = .033 and .018, respectively), but these interactions in the multivariate model were not significant. No significant interactions between spinal cord area, sex, and ADC values were found at C2/3 level.

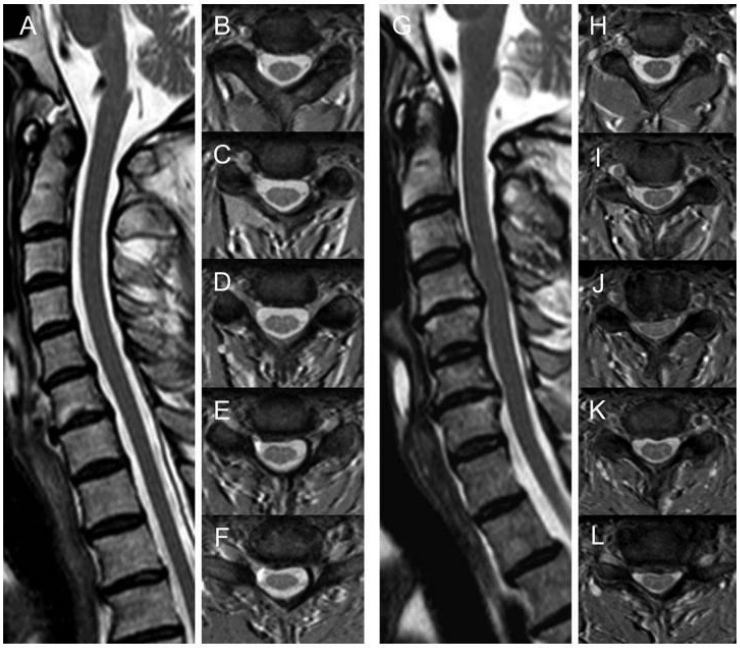

Fig 2. Example of MR examination of a cervical spine in a subject without spinal cord compression and in a patient with present spinal cord compression. (A)-(F) Subject without spinal cord compression. (G)-(L) Patient with present spinal cord compression. (A,G) T2-weighted images in sagittal plane. (B)-(F) and (H)-(L) T2-weighted gradient echo images in axial plane at spinal cord levels C2/3 to C6/7, respectively. Mild disk protrusions can be seen in a control subject at the levels C5/6 and C6/7 without any signs of cord compression. Conversely, severe degenerative changes are present in a patient with flat spinal cord compression at the level of maximal spinal canal stenosis C4/5 (J).

DCCC Group

Maximum spinal cord compression appeared most often at C5/6 level (67 subjects, 51.5%). Maximum spinal cord compression did not occur at C2/3 level in any of the subjects. Mean AP spinal canal diameter measured for all patients with spinal cord compression at all MCLs was 8 mm (SD 1.7 mm), spinal cord area 74 mm^2 (SD 14.3 mm^2), and compression ratio .45 (SD .081). The morphological measurements at individual SCLs appear in Table 2.

Analysis of DTI parameters revealed a statistically significant decrease in FA values and an increase in ADC values in the DCM subgroup compared with the ADCCC subgroup. Significant differences were also found in comparison of FA and ADC values in the subgroup of patients with T2 hyperintensity (mean values .45 and 1.33, respectively) compared with those with normal spinal cord T2 signal (.54 and 1.15, respectively). FA values correlated significantly with age according to analysis of continuous predictors (r =−.227, P = .009). ADC values were significantly lower in men compared to women, although differences in FA values were not significant here. Details of DTI parameters and comparisons between selected subgroups appear in Tables 7A and 7B.

Table 2. Morphological Measurements of the Spinal Canal and Spinal Cord in Control Group and DCCC Group

Group	SCL	*N*	AP (mm)	CR	CSA (mm^2)
Control group	C2/3	71	13.1 (1.4)	.67 (.07)	85.4 (9.1)
	C3/4	71	12.3 (1.2)	.59 (.06)	88.5 (9.1)
	C4/5	71	11.8 (1.8)	.54 (.05)	90.1 (9.4)
	C5/6	71	11.6 (1.5)	.54 (.05)	87.3 (10.1)
	C6/7	71	12.2 (2.1)	.59 (.07)	83.0 (12.3)
DCCC group	C3/4	16	8.3 (1.3)	.46 (.08)	73.3 (11.9)
	C4/5	35	8.4 (2.0)	.43 (.09)	75.8 (15.2)
	C5/6	67	8.3 (1.8)	.44 (.08)	74.7 (15.0)
	C6/7	12	8.5 (.7)	.5 (.04)	70.1 (9.7)

The values of measurements are given as mean and standard deviation. SCL = spinal cord level; *N* = number of subjects; AP = anteroposterior diameter of the spinal canal; CR = compression ratio; CSA = cross-sectional area of the spinal cord; DCCC = degenerative cervical cord compression.

When all MCLs were analyzed altogether, significant positive correlations of FA values were found in all the morphological parameters measured (AP canal diameter, spinal cord area, and compression ratio). Such correlations were also found separately at C3/4 level and FA correlated positively with AP canal diameter at C4/5 level. For ADC values, there was a significant negative correlation with AP canal diameter and spinal cord area in overall analysis of all MCLs. Analysis at individual SCLs revealed significant negative correlations of ADC values with values (Table 8). The presence of clinical manifestation of myelopathy had a borderline significant influence on both FA and ADC values.

Comparison of the diffusion parameters between the DCCC group and the control group revealed significant decreases of FA values at C3/4 and C5/6 levels in the DCCC group compared with the control group (P = .004 and .030, respectively). At C4/5 level, the ADC values were significantly lower in the DCCC group compared to the control group (P = .041). No significant differences in diffusion parameters were found at C6/7 level.

Table 3. FA and ADC According to Age, Sex, and Spinal Cord Level in Control Group

Group[1]	N	FA C2/3	FA C3/4	FA C4/5	FA C5/6	FA C6/7	P_2
Total	71	0.58 (.57; .60)[a]	0.59 (.57; .60)[a]	0.56 (.55; .57)[b]	0.54 (.53; .56)[b]	0.51 (.50; .53)[c]	<.001
Group[1]	**N**	**ADC C2/3**	**ADC C3/4**	**ADC C4/5**	**ADC C5/6**	**ADC C6/7**	**P_2**
Total	71	1.29 (1.25; 1.33)[a]	1.24 (1.21; 1.28)[ab]	1.23 (1.20; .26)[b]	1.17 (1.13; 1.21)[c]	1.24 (1.19; 1.29)[ab]	<.001
female	40	1.31 (1.25; 1.36)[a]	1.28 (1.23; 33)[ab]	1.28 (1.24; .32)[ab]	1.21 (1.16; 1.27)[b]	1.3 (1.23; 1.36)[ab]	0.035
Sex	31	1.27	1.19	1.17	1.1	1.17	
male		(1.20; 1.34)[a]	(1.15; 1.24)[ab]	(1.13; 1.21)[bc]	(1.05; 1.15)[c]	(1.11; 1.23)[bc]	<.001
	P_3	0.44	0.018	<.001	0.005	0.011	

[1]measures ANOVA.Mean and 95% confidence interval. N = number of subjects; FA[a, b, c, d]mark statistical significance of differences within rows—categories marked with the same letter are not= fractional anisotropy; ADC = apparent diffusion coefficient; P = statistical significance. [2]Repeated

[3]t-test for two independent samples.

mutually significantly different (tested by Tukey HSD post hoc test; P < .05).

Table 4. Sources of FA and ADC Variability in the Control Group

Model FA Explained	ADC Explained parameters[a]	variance (%)	P variance (%)	P
Sex		.03%	.796	6.21%	.004
Age		.07%	.712	.14%	.646
Sex × Age		.00%	.960	.65%	.332
SCL		17.03%	<.001	5.06%	<.001
SCL × Sex		.81%	.321	.53%	.457
SCL × Age		1.26%	.124	.99%	.153
SCL × Sex × Age		.75%	.367	1.84%	.015
	Residual variability (error)	80.05%		4.58%	

[a]Based on repeated measures ANOVA. SCL = spinal cord level; FA = fractional anisotropy; ADC = apparent diffusion coefficient; P = statistical significance.

spinal cord area at C3/4 and C4/5 levels. No significant correlations of morphological parameters with either FA or ADC values were found at C5/6 and C6/7 levels.

There were no significant differences in ADC and FA between MCLs (Tables 7A and 7B), but SCL explained some of the variability of ADC in ANOVA analysis. Other significant predictors were sex and T2 hyperintensity for ADC values and age, T2 hyperintensity, and AP spinal canal diameter for FA

Discussion

This study systematically analyzes the influence of several factors (age, sex, and segmental level) upon DTI parameters (ADC and FA values) of the cervical cord in patients with asymptomatic and symptomatic DCCC and a control group.

Anumberofstudieshaveinvestigatedtheinfluenceofageon cervical spinal cord diffusion parameters; their findings have, however, been somewhat variable. Mamata et al[10] report a

Table 5. Comparison of Cross-Sectional Area of the Spinal Cord Values between Men and Women in Control Group

Spinal Cord Level	Men (N= 31) CSA Mean ± SD (mm²)	Women (N= 40) CSA Mean ± SD (mm²)	P
C2/3	88.7 ± 8.6	82.9 ± 8.7	.015
C3/4	92.1 ± 8.8	85.7 ± 8.4	.009
C4/5	94.2 ± 9.3	86.9 ± 8.2	.002
C5/6	90.9 ± 10.5	84.5 ± 9.0	.007
C6/7	86.1 ± 12.5	80.5 ± 11.7	.083

Statistical significance (P) was tested by Mann-Whitney U test. CSA = crosssectional area of the spinal cord.

significant positive correlation of ADC values and a negative correlation of FA with age, both measured at only the upper spinal cord in groups of patients with cervical spondylosis. A recent study by Wang et al[8] reported significant age-dependent changes in both ADC and FA values in a group of healthy volunteers by measuring those parameters selectively in spinal cord gray matter and in various white-matter funiculi. A further study found significant age-dependent FA and mean diffusivity (MD) changes using novel automatic segmentation methods.[11] Agosta et al[12] performed a study analyzing a comparatively large group of 96 healthy subjects, and reported a significant decrease of cervical cord mean FA associated with age, but nothing similar for MD values. Brandner et al,[13] in a recent study, found no correlation between DTI metrics and age.

This study reveals no significant relation between diffusion parameters and age in the control group. Contrasting and variable results elsewhere may be explained in part by differences in modes of measurement and approaches to data analysis employed in particular studies, eg, ROI analysis versus tractography-based segmentation[11] or histogram analysis.[12] Further, this study did not include subjects younger than 43 years. Thus, the findings herein do not actually contest a general dependency of spinal cord DTI parameters on age; however, it does appear that the a priori age-related modification of DTI parameters is not substantial in individuals between approximately 40 and 80 years of age. On the other hand, age was identified as the most important predictor of FA values in the DCCC group. As it may be assumed that the period of spinal cord compression is longer in elderly patients, we may hypothesize that the duration of spinal cord

Table 6. Prediction of ADC Values by Multivariate Linear Regression Model in Control Group

SCL	β (95% CI)				
C2/3Constant	1.427 (.953; 1.902)				
Spinal cord area (mm^2)				−.002 (−.007; .004)	.508
Women		Women		.025 (−.071; .121)	.606
	C3/4	Constant		1.470 (1.084; 1.856)	
C3/4Constant					
Spinal cord area (mm^2)				−.003 (−.007; .001)	.153
Women		Women		.067 (−.008; .143)	.079
	C4/5	Constant		1.223 (.905; 1.540)	
C4/5Constant					
Spinal cord area (mm^2) Women	Women		−.001 (-.004; .003) .104 (.042; .167)	.739 .001	17.2%
C5/6Constant	1.244 (.867; 1.622)				
Spinal cord area (mm^2) Women	Women		−.002 (−.006; .003) .103 (.020; .187)	.447 .016	11.4%
C6/7Constant	1.231 (.873; 1.590)				
Spinal cord area (mm^2) Women	Women		−.001 (−.005; .003) .123 (.023; .223)	.726 .017	9.2%

β (95% CI) = regression coefficient and 95% confidence interval; *P* = statistical significance; R^2 = coefficient of determination; SCL = spinal cord level; ADC = apparent diffusion coefficient.

Table 7A. FA at Maximum Compression Level According to Level of Compression and Presence of Clinically Manifest Myelopathy in the DCCC Group

Group[1]	FA Total				FA C3/4		
Total	*N* = 130; .52 (.51; .53)	(.48; .56)	(.52; .57)	(.50; .54)	*N* (.51; .53)	= 16; .52 (.48; .56)	(.52; .57)
Myelopathy					*N*		
no	*N* = 93; .54 (.52; .55)				(.52; .55)	= 12; .54 (.50; .58)	(.53; .59)
yes	*N* = 37; .48 (.46; .51)				*N* = 4; .47 (.38; .56)		
P[3]	<.001				0.109		

DCCC = degenerative cervical cord compression.[2]ANOVA. [3][1]Independent samplesSample size;mean supplemented by 95% confidence interval. FA*t*-test. = fractional anisotropy; ADC = apparent c

Table 7B. ADC at Maximum Compression Level According to Level of Compression, Sex, and Presence of Clinically Manifest Myelopathy in the DCCC Group

Group[1]	ADC total	ADC C3/4	ADC C4/5	ADC C5/6	ADC C6/7	*P*[2]
Total	*N* = 130; 1.18 (1.14; 1.21)	*N* = 16; 1.27 (1.18; 1.36)	*N* = 35; 1.17 (1.11; 1.22)	*N* = 67; 1.16 (1.11; 1.21)	*N* = 12; 1.18 (1.06; 1.30)	0.217
Sex female	*N* = 53; 1.24 (1.19; 1.28)	*N* = 2; 1.43 (1.15; 1.70)	*N* = 10; 1.24 (1.16; 1.33)	*N* = 35; 1.22 (1.17; 1.27)	*N* = 6; 1.27 (1.14; 1.40)	0.255
male	*N* = 77; 1.14 (1.09; 1.18)	*N* = 14; 1.25 (1.15; 1.34)	*N* = 25; 1.14 (1.07; 1.20)	*N* = 32; 1.10 (1.02; 1.17)	*N* = 6; 1.09 (.91; 1.27)	0.129
P[3]	0.003	0.215	0.046	0.011	0.143	
Myelopathy no	*N* = 93; 1.14 (1.10; 1.17)	*N* = 12; 1.23 (1.13; 1.32)	*N* = 27; 1.14 (1.08; 1.19)	*N* = 45; 1.12 (1.07; 1.17)	*N* = 9; 1.13 (1.00; 1.27)	0.291
yes	*N* = 37; 1.27 (1.21; 1.34)	*N* = 4; 1.40 (1.19; 1.60)	*N* = 8; 1.26 (1.14; 1.39)	*N* = 22; 1.24 (1.15; 1.33)	*N* = 3; 1.33 (1.16; 1.50)	0.531
P[3]	<.001	0.118	0.06	0.013	0.162	

DCCC = degenerative cervical cord compression.[1]Sample size;mean supplemented by 95% confidence interval. FA = fractional anisotropy; ADC = apparent diffusion

coefficient; *P* = statistical significance. [2]ANOVA. [3]Independent samples *t*-test.

compression could be a more important determinant of FA values than the age of the subjects themselves. However, in the light of the assumption that at least a substantial proportion of compressions remain asymptomatic at onset, it was not possible to establish retrospectively the duration of spinal cord compression in our study group. Further data provided by long-term prospective studies would be required to quantify the matter accurately.

The influence of sex on DTI parameters may be assumed to parallel DTI studies of the brain; some authors indicate significant differences in FA values between men and women within certain areas of brain white matter.[14,15] Nevertheless, Takao et al[15] suggest that the differences in FA may be partly related to the fact that total brain volume is different in men and women. There are only few reports of sex-related changes in DTI parameters of the cervical spinal cord, and no significant

Table 8. Sources of FA and ADC Variability in DCCC Group

	FA Explained		ADC Explained	
Model Parameters[1]	Variance (%)	*P*	Variance (%)	*P*
SCL	4.23%	.082	5.66%	.039
Sex	1.42%	.131	10.63%	<.001
Age	9.62%	<.001	.24%	.548
Myelopathy	2.09%	.068	2.08%	.078
T2 hyperintensity	5.07%	.005	3.13%	.031
Channel diameter	3.35%	.021	.01%	.920
Spinal cord area	.24%	.532	.11%	.687
Compression ratio	.66%	.301	.00%	.959
Error	73.31%		78.15%	

DCCC = degenerative cervical cord compression. [1]Based on ANOVA model. SCL = spinal cord level; FA = fractional anisotropy; ADC = apparent diffusion coefficient; *P* = statistical significance.

correlations have emerged.[13,16] This study, with a comparatively large population of healthy volunteers, demonstrated no differences in FA values between males and females, but such differences in ADC values were significant in both the DCCC group and in the control group. The association of these differences with spinal cord volume may raise questions similar to those generated by Takao's brain study.[15] Papinutto et al[17] reported sex-related differences in the total cross-sectional and gray matter area at upper cervical level, while this study found lower values of total cord area at most SCLs in women compared to men. However, sex was identified as a significant predictor of ADC values at C4/5-C6/7 SCLs independent of spinal cord area, the influence of which upon ADC values was not significant here. Although the measurement of cross-sectional area is not equivalent to volumometry of the spinal cord calculated from isotropic data, a relation between spinal cord volume and diffusivity appears improbable. Interestingly, the independent influence of sex on ADC values was observed below C4/5 level, which corresponds approximately with the location of the cervical enlargement that is characterized by a greater amount of gray matter.[18] The sex-related changes of ADC may therefore arise largely out of differences in gray-matter diffusivity. Further studies using separate gray and white matter segmentations based on DTI data with higher image resolution may provide important data to support such a hypothesis.

Brain structural sex dimorphisms have been linked to hormonal differences between the sexes. Herting et al[19] reported differences in FA and MD in various regions of the brain white matter and demonstrated significant correlations between diffusion parameters and sex hormones. Menzies et al[20] found a significant decrease in MD values (not FA values) of the brain white matter in adolescent boys correlating with salivary testosterone levels. Although these conclusions may not easily be applied to the entire central nervous system, it can be assumed that sex hormones have a certain influence on spinal cord diffusivity. Our findings of significant differences in ADC without changes of FA suggest changes in the directionally independent magnitude of diffusion within the spinal cord tissue. This may be related, in part, to differences in the extracellular water content or in overall tissue density, quite apart from differences in directional structure; further studies are necessary to explain these findings in relation to the spinal cord microstructure. To the best of our knowledge, this is the first study to report sexrelated differences in diffusion parameters measured within the
cervical spinal cord.

The findings of this study indicate that in the group of subjects without spinal cord compression, DTI parameters depend strongly on the level at which measurements are taken. Previously published data on this topic are not consistent; Song et al,[7] in agreement with our findings, found differences in FA values between cranial and caudal spinal cord segments, but observed no differences in ADC values. Their group of volunteers was comparatively small. Brandner et al[13] report a decrease in FA and increase in ADC in a craniocaudal direction from C2 to C7, results similar to those that appear here. Conversely, other authors have reported no significant differences in DTI parameters in a group of healthy controls.[21] The variation in diffusion properties between levels of the spinal cord may be related to differences in the anatomical structure of the cervical spine. Wheeler-Kingshott et al[18] suggested that a decline in FA values in the lower SCL may be due to the brachial plexus nerve roots entering and leaving the lower cervical spinal cord, something that leads to a degree of disruption of the directional coherence of the fibers at voxel scales. Another reason may lie in the relatively higher volume of spinal cord gray matter within the ROIs at segments of cervical enlargement,[18] since it is established that diffusion parameters within gray matter are different from those measured in white matter.[8,16]

Technical considerations and variable image quality of the diffusion data may also be responsible for SCL-dependent differences. Vedentam et al[16] have demonstrated a decrease in the signal-to-noise ratio (SNR) in the lower spinal cord segments (C4-Th1) compared with the upper segments (C1-3). It is known that low SNR may lead to overestimation of FA values at *b*-factors approaching 1,000 s/mm^2[,22,23] so signal quality may influence DTI metrics. Although this alone does not explain the decrease of FA in a craniocaudal direction, some influence of SNR variation on measurements is possible. Further experimental studies, using multiple acquisitions with different acquisition settings and SNR,

would be required to evaluate reliably the influence of SNR, and other technical aspects, on diffusion measurements.

Spinal cord compression in patients with cervical spondylosis is important to any determination of DTI parameters. This study disclosed significant differences in both FA and ADC values between patients with clinical findings of symptomatic myelopathy compared with ADCCC patients. These findings are in agreement with existing reports[6,24] and with our own previously published data.[3] Some authors stress the role of DTI as a more sensitive biomarker of myelopathy than conventional T2-weighted images.[3,25] From this perspective, it is not surprising that the finding of spinal cord T2 hyperintensity had a significant influence on both FA and ADC values.

According to the findings herein, the reactivity of diffusion parameters to spinal cord compression is greater at the upper cervical levels (C3/4 and C4/5), as FA and ADC values measured at these segments correlated well with the degree of spinal canal stenosis, in contrast to segments C5/6 and C6/7. The explanation for this phenomenon is not straightforward, although it may be related to the above-described level-dependent differences in anatomical structure of the spinal cord or technical aspects, mainly differences in SNR. Nevertheless, sensitivity of DTI to clinically manifest myelopathy is preserved even at lower cervical segments, where this study found significant changes of ADC values measured at C5/6 level. On the other hand, the general influence of myelopathy findings (mostly mild-to-moderate represented in this study group) on the diffusion parameters was comparatively low among other variables considering the influence of the particular factors investigated through variability of ADC and FA values. Thus, the potential of DTI to discriminate myelopathy at the early stage seems to be reduced by the influence of physiological or technical factors that contribute to variability of diffusion parameters.

Variations in diffusion parameters between SCLs were not significant in the DCCC group. This is probably due to the modification of the values measured near the spinal cord compression itself, and also to the varying reactivity of parameters measured at different SCLs.

Direct comparison of the two diffusion parameters between the DCCC group and the control group revealed significant differences in either ADC or FA values at several SCLs. These results are not fully consistent with the aforementioned correlation analyses of diffusion and morphological parameters within the individual groups. At C4/5 level, there was a mild but statistically significant decrease in ADC values in the DCCC group compared to the control group, which contrasts with the finding of increasing ADC values in correlation with the reduction of spinal cord area. It can be surmised that a certain degree of spinal cord compression may generally lead to mild decrease of ADC values by reduction of the extracellular compartment and increase in relative cellularity. Increasing compression of the spinal cord documented by the reduction of the spinal cord area, which would cause structural damage to the spinal cord tissue, may then be reflected in an increase of ADC values.

A limitation of this study may lie in the selection of the scalar parameters available for the quantification of diffusion within ROIs in FiberTrak software, which is limited to ADC and FA. There are other scalar parameters, eg, axial diffusivity (AD) and radial diffusivity (RD), which may be used in the investigation of diffusivity characteristics. All these parameters may be calculated from the eigenvectors that represent the magnitude of the three main axes of the ellipsoid characterizing diffusion anisotropy.[26] Some studies use MD instead of ADC for the quantification of total diffusivity; however, both of these parameters represent measures of total direction-independent
diffusivity.[24]

ADC and FA are the most commonly employed parameters in studies using DTI in CSM research.[24] This study therefore centered around them, with consequent effects upon the extent of the study and its main objective, which was to discriminate those factors that might have some general influence upon the diffusivity of the spinal cord in terms of DCCC. More specific analysis of other parameters may provide additional information, as it is known that AD and RD may be helpful in differentiation between axonal injury and demyelination.[27] AD, RD, and particular eigenvalues of the ellipsoid have been evaluated by only a few studies of patients with CSM.[5,28,29] Changes in their values were more or less followed by changes in ADC or FA values. Rajasekaran et al[5] have recorded a significant increase of all three eigenvalues in a myelopathy group compared to healthy volunteers, together with an increase in ADC and a decrease in FA. Other authors report increases in AD, RD, and FA in CSM patients, but they point out that regional differences between spinal cord tracts exist; while AD and RD changed in similar fashion in all spinal columns, a decrease in FA was more pronounced in the lateral and dorsal columns.[28,29] Rajasekaran et al[5] considered the FA pattern of the myelopathic cord more compatible with histopathological features appearing in previously published studies than AD and RD. Thus, the evaluation of AD and RD in terms of CSM currently seems to play comparatively minor role.

It should be noted that the analyses indicating level-specific results in the DCCC group may have been influenced by the different numbers of subjects in the subgroups, which were classified according to MCL, thus modifying the power of the statistical analyses. Another possible source of bias may lie in the selection of MCL. Li et al[30] correlated DTI measurements with detailed neurological examination in patients with multilevel DCM and found the capacity of DTI to identify the level of spinal cord pathology higher than that of conventional morphological measurements. As dynamic factors may play an important role in this matter,[31] it may be assumed that diffusivity changes might correlate better with clinical presentation at other SCLs than at MCL identified at rest position if the spinal cord is compressed and damaged, eg, by a shear mechanism at these levels more markedly than at MCL. Thus, further investigation combining DTI with dynamic studies may prove productive.

To conclude, DTI is a valuable tool for the evaluation of structural abnormalities of the cervical spinal cord caused by the degenerative compression, correlating with clinical manifestation of myelopathy and with degree of spinal canal stenosis. However, it appears that the diffusion properties of the cervical spinal cord are dictated by the interaction of several other factors beyond the cord compression itself, mainly sex of the patient and segmental level of measurement. These may not have a substantial effect on the results of various group studies, if males and females and various stenotic levels are represented proportionally throughout the study groups, but may be highly important for evaluation of the diffusion parameters in individual patients with DCCC in clinical settings. Such interpretations require robust, normative data reflecting the aforementioned variables.

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Flekční cervikální myelopatie (Hirayamova choroba) – skutečnost, nebo mýtus? Dvě kazuistiky

Flexion Cervical Myelopathy (Hirayama Disease) – Reality or Myth? Two Case Reports

Souhrn

Flekční cervikální myelopatie (Hirayamova choroba) je vzácné onemocnění krční míchy. Manifestuje se asymetrickou, velmi pomalu progredující atrofií a slabostí svalů ruky a předloktí (s ušetřením m. brachioradialis) a postihuje většinou mladé muže mezi 15 a 25 lety. Nebývají přítomny změny reflexologické ani poruchy senzitivity. Na MR krční páteře je typicky popisována lokální atrofie míchy, ve flexi v T1 vážených obrazech dochází k rozšíření zadního epidurálního prostoru, který je hyperintenzní v T2 vážených obrazech a zvýrazňuje se po aplikaci kontrastní látky. Existence choroby samotné je mnohými autory zpochybňována. Autoři popisují kazuistiky dvou pacientů, které svým průběhem připomínaly tuto chorobu, a shrnují dosavadní poznatky o diagnostice a léčbě této sporné nozologické jednotky.

Abstract

Cervical flexion myelopathy (Hirayama disease) is a rare disease of the cervical spine. It is characterized by progressive muscular weakness and atrophy of the distal upper limb (brachioradialis muscle is spared), predominantly affecting male adolescents between 15 and 25 years of age. There is no sensory or deep tendon reflexes involvement. Cervical MRI images show local cord atrophy, T1-weighted images show widened lateral epidural space on flexion on that is hyperintense on T2-weighted, especially contrast-enhanced, images. The existence of the Hirayama disease is disputed by many authors. We present two patients with clinical symptoms of this disease and summarize facts about the diagnosis and treatment of Hirayama disease.

Autoři deklarují, že v souvislosti s předmětem studie nemají žádné komerční zájmy.
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Klíčová slova

Hirayamova choroba – cervikální myelopatie – segmentální spinální muskulární atrofie – amyotrofie

Key words

Hirayama disease – cervical myelopathy – segmental spinal muscular atrophy – amyotrophy

Úvod

Flekční cervikální myelopatie (Hirayamova choroba) je vzácné onemocnění krční míchy (synonyma: monomelická amyotrofie – MMA, juvenilní asymetrická segmentální spinální muskulární atrofie – JASSMA, juvenilní distální amyotrofie horní končetiny – JMADUE). Choroba byla poprvé popsána v roce 1959 [1]. Jde o onemocnění, jehož existence bývá zpochybňována [2]. Vyskytuje se zejména v asijských zemích, ale byly popsány případy i v Evropě a Severní Americe [3–6]. Postihuje nejčastěji mladé muže mezi 15 a 25 lety [7].

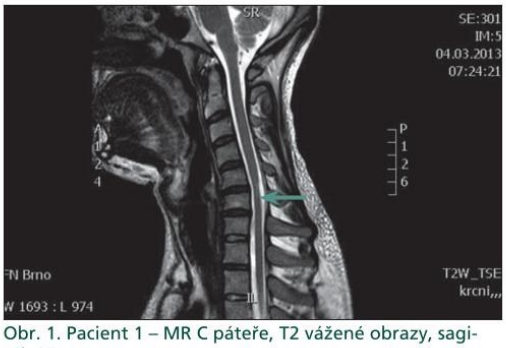
Onemocnění má tyto základní charakteristiky:

1. svalové atrofie jsou omezeny na svaly předloktí a ruky (mimo m. brachioradialis),
2. výskyt je obvykle sporadický, vzácně familiární,
3. vyskytuje se zejména u mladých mužů (15–25 let) – většinou jednostranně,
4. není porucha čití nebo změna reflexů na končetinách,
5. pomalá progrese (roky),
6. přítomna ztráta uchycení mezi zadní částí durálního vaku a laminami (v oblasti dolní krční páteře) a charakteristický obraz na MR (zvětšení zadního epidurálního prostoru ve flexi krční páteře).

Nejčastěji uváděná patogenetická hypotéza je mechanické a ischemické poškození cervikálních spinálních motoneuronů [8,9], ale poukazuje se rovněž na neurodegenerativní či autoimunitní příčinu [3]. Histopatologické nálezy ukazují na změnu pružnosti tkáně durálního vaku jako základní příčinu vedoucí k opakovaným míšním kompresím a myelopatii [10]. Při pitvě bývá zjišťována atrofie, nekróza a glióza v předních rozích míšních C5–Th1 (obzvláště v C7–8), ale bez poškození intra- i extramedulárních cév [11]. Léčba Hirayamovy choroby je pouze empirická. Na základě postulované hypotézy o patogenezi choroby a jejím průběhu a vzhledem k tomu, že v prvních letech onemocnění progreduje, se doporučuje intermitentní nošení měkkého límce po dobu 3–4 roků [12]. V některých případech se zvažuje i operační léčba, která je však stále považována za kontroverzní. Uvádíme kazuistiky dvou mladých pacientů, jejichž příznaky byly velmi podobné tomuto onemocnění.

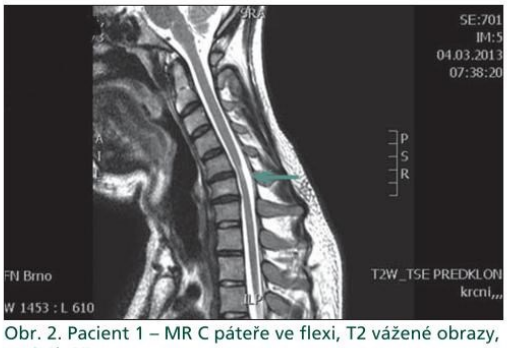
Kazuistika 1

Muž, 37 let, od roku 1996 (od 20 let věku) pozoruje hubnutí svalstva a neobratnost levé horní končetiny s maximem akrálně. Rozvoj potíží byl pozvolný a progrese v dalších letech velmi pomalá. Pracuje jako technik u počítače, léky trvale žádné neužívá. Pacient je bývalý kuřák (přestal kouřit v roce 2008). V anamnéze neuvádí úrazy páteře, nemá další subjektivní problémy jako bolesti hlavy, bolesti páteře, parestezie končetin a jiné poruchy senzitivity. EMG provedené již v roce 1997 vykazovalo známky subakutní až chronické motorické axonopatie v myotomech C7–Th1 vlevo s maximem v distribuci kořene C8. MR vyšetření krční páteře bylo provedeno v roce 1999 s nálezem diskrétní spondylózy C5–6, drobné paramediální pravostranné protruze C6–7 a náznakem myelopatického ložiska (tehdy však ložisko nebylo radiologem zaznamenáno). Od roku 1999 již pacient nikde nebyl neurologicky vyšetřován ani sledován, až v roce 2009 se znovu rozhodl navštívit neurologa. Na kontrolním EMG vyšetření z HKK byl nález subakutní až chronické motorické axonopatie ve svalech myotomů C7–8 vlevo, bez průkazu bloku vedení motorických vláken. EMG z DKK bylo jen lehce abnormní, resp. byla přítomna lehká prolongace latencí F-vln n. tibialis a n. peroneus, subjektivně pacient nemá žádné potíže z dolních končetin. Klinicky dominuje atrofie a paréza svalů inervovaných z myotomu C7–8 vpravo, bez poruchy senzitivity, jinak je ložiskový neurologický nález v normě. Bylo provedeno genetické vyšetření, které nesvědčí pro HNPP (tomakulozní neuropatie), Charcot-Marie-Tooth typ Ia, hereditární motorické neuropatie (mutace genu kódujícího protein HSP 22 a HSP 27). Celá baterie testů včetně likvorologického vyšetření nepodporovala diagnózu zánětlivého onemocnění nervového systému. Antigangliozidové protilátky anti-GM 1, 2, 3, GD1A, GD1B, GQ1B byly v séru negativní. MR brachiální plexu je bez patologického nálezu. Na základě průběhu a klinického obrazu onemocnění vzniklo podezření na flekční cervikální myelopatii. Provedené kontrolní MR krční páteře prokázalo lokální míšní atrofii ve výši meziobratlového prostoru C5/6 a lehčí rozšíření zadního epidurálního prostoru při flexi (obr. 1–3). Diferenciálně diagnosticky by se však mohlo jednat o HMN5 (distální SMA s postižením horních končetin, lokus 7p15). Stav pa-



Obr. 1. Pacient 1 – MR C páteře, T2 vážené obrazy, sagitální řez.

Šipkou označena míšní atrofie v etáži C5/6.



Obr. 2. Pacient 1 – MR C páteře ve flexi, T2 vážené obrazy, sagitální řez.

Šipkou označeno rozšíření zadního epidurálního prostoru při flexi.

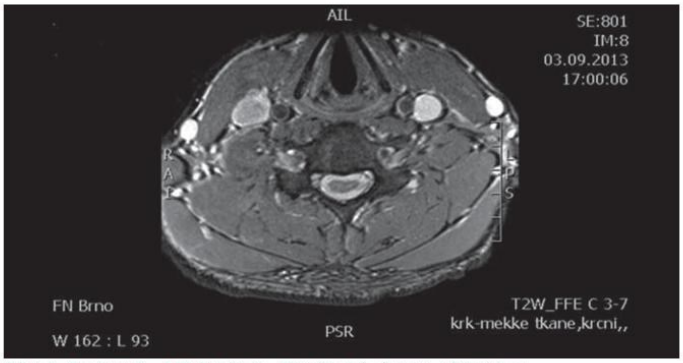
cienta zůstává prakticky stacionární, objektivně je pozorována jen zcela mírná progrese atrofií.

Kazuistika 2

Muž, 21 let, vysokoškolský student, dosud zdravý, v anamnéze bez traumatu krční páteře. Od 17 let věku se u něj postupně pomalu rozvíjela neobratnost a slabost pravé horní končetiny. Nebyla přítomna bolest ani jiné senzitivní příznaky. Výše uvedené potíže progredovaly velmi pomalu tři roky, poslední rok je stav stacionární. Ve 20 letech podstoupil deliberaci n. ulnaris v lokti vpravo, která neměla klinický efekt. Operace byla provedena patrně na základě chybné interpretace potíží a EMG nálezu, ve kterém bylo vysloveno podezření na fokální lézi n. ulnaris v lokti (dominovalo postižení ulnarisových svalů). Pro nejasnou diagnózu byl pacient odeslán k vyšetření na naši kliniku. V objektivním neurologickém obraze dominovala hypotrofie akrálních svalů na PHK, byla přítomna periferní paréza s oslabením svalů inervovaných z myotomů C8–Th1 (svalová síla dle MRC scale: m. abductor pollicis brevis 3, m. abductor digiti minimi 3, m. extensor indicis 3, m. brachioradialis 5). Nebyl přítomen senzitivní deficit na PHK. Objektivní neurologický nález na LHK a obou dolních končetinách byl v normě. EMG vyšetření prokazovalo známky čistě motorické axonální subakutní až chronické neuropatie v myotomech C8–Th1 vpravo. EMG z LHK a obou DKK bylo v normě, bez známek periferně neurogenní léze, bloky vedení motorických vláken nebyly prokázány, stimulace na HKK byla provedena až do Erbova bodu (tab. 1). Magnetická rezonance krční páteře vykazovala známky atrofie míchy v etážích C6–7, přičemž mícha byla bez známek patologického signálu (obr. 4, 5). Při flexi krční páteře v místě atrofie míchy byl vrchol kyfotického ohybu a docházelo k rozšíření dorzálního arachnoidálního a epidurálního prostoru (obr. 6). Lumbální punkci pacient odmítl. Na základě klinického obrazu, EMG nálezu a MR krční páteře je zvažována diagnóza Hirayamovy choroby. Pacientovi byla doporučena pouze režimová opatření s vyvarováním se úrazů krční páteře, klinicky nedochází k progresi neurologického deficitu.

Diskuze

Hirayamova choroba je vzácné onemocnění, v literatuře bylo dosud popsáno

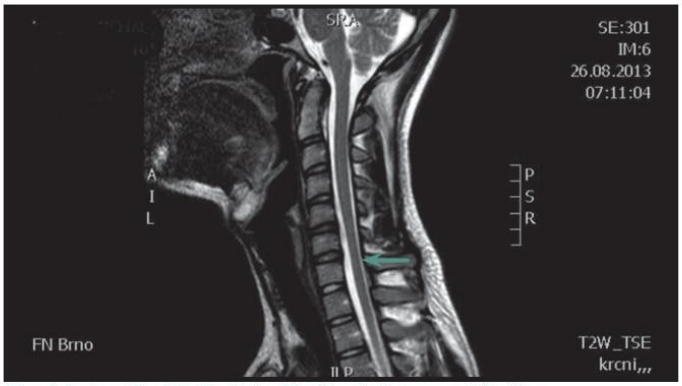


Obr. 3. Pacient 1 – MR C páteře, T2 vážené obrazy, příčný řez.
Na příčném průřezu je v etáži C5/6 zřejmá atrofie míchy.

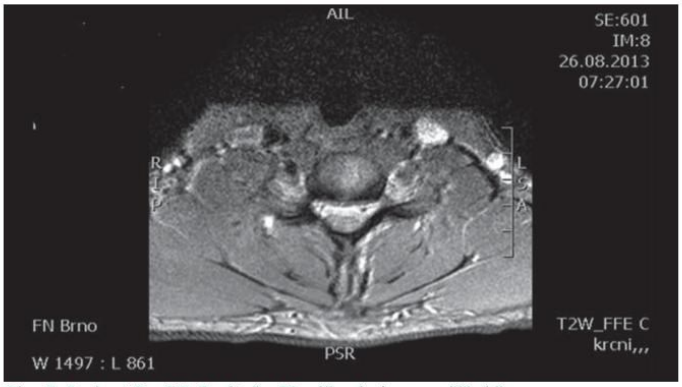
Tab. 1. Kondukční studie z horních končetin.

Motor Nerves	dLat	SD	dAmp	SD	CV	Amp %	SD	F–M	SD
pravý medianus								30,9	6,6
zápěstí–loket	4,3	1,7	4,7	–1,9	52,7	–7	–0,5		
loket-paže	8,0		4,4		58,3	–2	–0,1		
paže–axilla	9,8		4,3		55,9	8	0,6		
axilla–Erbův bod	11,5		4,6		69,2	17	1,2		
Erbův bod–APB	14,1		5,4						
levý medianus								23,3	–0,5
zápěstí–loket	3,9	0,6	9,7	–0,1	50,0	6	0,4		
loket-paže	7,5		10,2		73,3	–5	–0,4		
paže–axilla	9,0		9,7		79,2	–1	–0,0		
axilla–Erbův bod	10,2		9,6		58,1	–3	–0,2		
Erbův bod–APB	13,3		9,4						
pravý ulnaris								–	
zápěstí–pod loktem	3,7	1,6	3,4	–3,5	53,2	–1	–0,1		
pod loktem–nad loktem	6,8		3,4		61,4	3	0,2		
nad loktem–axilla	9,0		3,5		48,0	0	0,0		
axilla–Erbův bod	11,5		3,5		53,1	–18	–1,2		
Erbův bod–ADM	14,7		2,9						
levý ulnaris								26,5	1,5
zápěstí–pod loktem	3,2	0,0	10,5	–0,6	63,5	–15	–1,0		
pod loktem–nad loktem	5,8		8,9		56,0	–5	–0,3		
nad loktem–axilla	8,3		8,5		51,9	–1	–0,1		
axilla–Erbův bod	11,0		8,4		60,0	1	0,0		
Erbův bod–ADM	14,0		8,4						

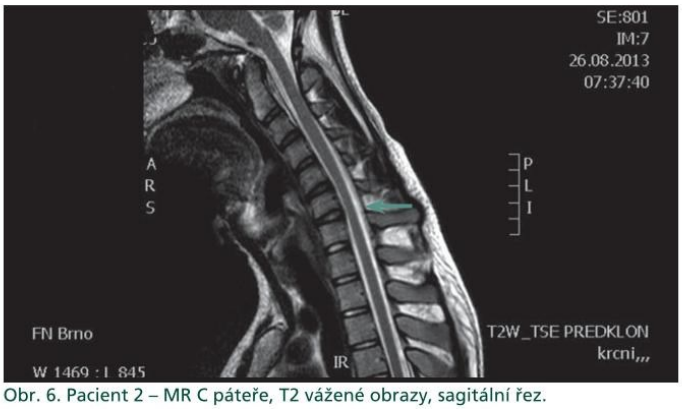
Prokazují nižší amplitudy sumačního svalového akčního potenciálu nervus medianus a n. ulnaris vpravo ve srovnání s levou stranou, dále je přítomna prolongace latence F vlny n. medianus vpravo a nevýbavnost F vlny n. ulnaris vpravo. Rychlosti motorického vedení jsou na obou horních končetinách v normě, bloky vedení motorických vláken neprokázány. APB – musculus abductor pollicis brevis, ADM – musculus abductor digiti minimi, Lat – latence, Amp – amplituda, SD – směrodatná odchylka, CV – rychlost vedení, Amp % – změna amplitudy (%), F-M – minimální latence F-vlny – distální motorická latence.



Obr. 4. Pacient 2 – MR C páteře, T2 vážené obrazy, sagitální řez.
Šipkou označena míšní atrofie v etáži C6/7.



Obr. 5. Pacient 2 – MR C páteře, T2 vážené obrazy, příčný řez.
Na příčném průřezu je v etáži C6/7 zřetelná atrofie míchy.



Obr. 6. Pacient 2 – MR C páteře, T2 vážené obrazy, sagitální řez.
Šipkou označeno rozšíření zadního epidurálního prostoru při flexi.

zhruba 200 případů, zejména v asijských zemích [13]. Nejčastěji se uvádí tato etiopatogeneze nemoci: při flexi krční páteře dochází k abnormálnímu ventrálnímu posunu zadní části durálního vaku a sekundární míšní kompresi. Tento patologický posun je vysvětlován disproporcí mezi růstem páteřního kanálu (větší růst) a jeho obsahu (menší růst) zejména během růstového spurtu, který bývá rychlejší u mužů než u žen [14], tím dochází k relativnímu „poklesu durálního vaku", resp. ke ztrátě jeho uchycení. Jiný mechanizmus předpokládá, že tento posun je způsoben zahuštěním a změnou počtu elastických vláken durálního vaku, což vede ke ztrátě elasticity vaku a též k mechanickému míšnímu postižení [10]. Další autoři předpokládají ztrátu „ukotvení" mezi zadní částí dury a ligamentum flavum způsobenou snížením počtu epidurálních ligament [15]. Výše popsané pojetí patogeneze bývá ale zpochybňováno z následujících důvodů: nevysvětluje, proč udávaná dynamická komprese krční míchy poškozuje exkluzivně motoneurony a nepostihuje dlouhé dráhy, proč je neprogresivní a tak často přísně jednostranná. V jedné studii např. nebyl zjištěn rozdíl předozadního rozměru míchy u nemocných a kontrol, což by ukazovalo na to, že se jedná o primární degeneraci motoneuronů [16]. Podobně zpochybňuje flekční mechanizmus jako příčinu amyotrofie další práce, ve které mírnou redukci páteřního kanálu ve flexi našli jak u nemocných, tak i u pěti zdravých kontrol. Předozadní rozměr míchy byl stejný u pacientů jako u kontrol a u žádného z nemocných nedošlo k úplné obliteraci zadního subarachnoidálního prostoru [2]. Hirayamovu chorobu někteří považují spíše za formu MND (Motor Neuron Disease) [2]. Ostatní práce však oproti kontrolám a nemocným s amyotrofickou laterální sklerózou nacházejí u Hirayamovy choroby posun dury ventrálně a míšní kompresi [17]. Na MR krční páteře se u nich charakteristicky zadní epidurální prostor zvětšuje ve flexi a je možno pozorovat zvyšující se intenzitu signálu tohoto prostoru na T2 vážených obrazech [18]. Je též prokázáno, že extenze krční páteře signifikantně zvyšuje míru komprese míchy ve srovnání se standardním postavením při CT či NMR vyšetření [19]. Epidurální prostor je vyplněn zmoženými cévami venózního plexu. Uniformní enhancement tohoto epidu-

rálního prostoru se pak ještě zvýrazní po aplikaci kontrastní látky [9]. U některých jedinců s tímto postižením se však patologický posun durálního vaku krční míchy ventrálně nezjistil, což bývá vysvětlováno tím, že postupem času (tedy v pozdějším věku nemocných) již laxita vaku plen mizí a typický MR nález se neprokáže. Chybění posunu durálního vaku ventrálně v pozdních a neprogresivních stadiích choroby ukazuje na to, že dynamická komprese má patogenetický význam v počátku choroby [20]. Diferenciální diagnostika Hirayamovy choroby je široká. Mezi další příčiny jednostranné amyotrofie horní končetiny patří amyotrofická laterální skleróza, a to zejména v počátečních stadiích onemocnění, kdy postižení může být výrazně lateralizováno, dále zánětlivé či kompresivní postižení krční míchy a kořenů, brachiální neuritida (amyotrofická neuralgie brachiálního plexu), multifokální motorická neuropatie anebo spinální svalová atrofie. Spinální svalová atrofie (SMA) je heterogenní skupina geneticky podmíněných chorob s různou distribucí postižení čistě dolních motoneuronů s pomalou progresí. Přes předpokládaný hereditární základ se však objevují i zcela sporadické případy, i když lze těžko v těchto případech vyloučit autozomálně recesivní dědičnost. Zvláštní formou je dominantně hereditární distální SMA, u které se prokázalo, že vzniká na podkladě mutace genu glycyl-tRNA syntetázy (HMN V), a která má predilekci postižení na horních končetinách. Kolem roku 1983 byly některé případy asymetrických atrofií na HKK označovány jako chronická asymetrická spinální svalová atrofie [21]. Je možné, že v některých případech šlo o Hirayamovu chorobu. Je též nutno vyloučit i kompresivní mononeuropatie – zvláště lézi n. medianus a ulnaris.

Vzhledem k vzácnému výskytu bývají klinické a radiologické nálezy u Hirayamovy choroby popisovány na jednotlivých případech, souhrnnější obraz o nálezech podává jedna studie, která zahrnuje skupinu 11 nemocných s tímto postižením. Bylo zjištěno, že 10 pacientů mělo méně než 25 let, jeden nemocný měl 53 let. Všichni pacienti měli šikmou amyotrofii předloktí (ušetřený m. brachioradialis), 36 % chladovou parézu, 27 % mělo fascikulace. EMG vykazovalo chronickou denervaci v myotomech C7–Th1, u 82 % pacientů byla atrofie dolní části krční míchy, asymetrické oploštění míchy bylo přítomno ve 100 %, míšní hyperintenzity u 18 %, v 90 % byl zachycen ventrální posun dury a ztráta úponů durálního vaku. Léčba límcem zpomalila progresi ve většině případů [22]. Rovněž Hirayama popisuje, že léčba choroby v progresivním stadiu měkkým límcem se jeví jako účinná [20]. Nicméně přirozený průběh nemoci není spolehlivě dokumentován.

Oběma našim pacientům byla doporučena terapeuticky pouze režimová opatření s vyvarováním se přetěžování a poranění krční páteře. Rovněž z retrospektivních studií vyplývá, že většina nemocných je léčena konzervativně [23].

Jelikož patofyziologie cervikální flekční myelopatie není zcela objasněna, tak i v literatuře doporučovaná chirurgická léčba zůstává kontroverzní. Přední dekomprese a fúze bývá užívána jako metoda první volby [24]. Podle některých autorů duroplastika a laminoplastika může být užitečná v časné fázi nemoci, šlachově svalový transfer ve fázi pozdní. Někteří chirurgové provádějí laminektomii a duroplastiku bez spinální fúze a popisují zástavu progrese nemoci i po dvou letech po operaci – tyto chirurgické metody ovšem nejsou v této indikaci obecně přijímány [25]. Je také otázka, zda zástava progrese choroby byla na podkladě operace či je dána přirozeným vývojem nemoci.

Závěr

Hirayamova choroba (flekční cervikální myelopatie) je jednotka, která je sporná a bývá mnohými autory zpochybňována, což je dáno zejména nejasností v etiopatogenezi choroby. Měli bychom na její existenci pomýšlet u mladých jedinců (zejména mužů) s asymetrickou atrofií ruky a předloktí, která nevykazuje známky výraznější progrese. U těchto pacientů je indikována MR krční páteře ve flexi, při níž jsou změny nejvýraznější a v případě jasné komprese masou v zadním epidurálním prostoru přichází v úvahu i operační řešení. Nicméně stále jde o jednotku, která dosud nebyla definitivně zařazena mezi onemocnění krční páteře a míchy a jejíž léčba je pouze empirická.

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Maligní tumor z pochvy periferního nervu v oblasti cervikálního plexu – kazuistika

Malignant Peripheral Nerve Sheath Tumour of Cervical Plexus – a Case Report

Souhrn

Maligní tumory z pochvy periferního nervu jsou vzácná neoplazmata, obzvláště v oblasti hlavy a krku. Bývají často asymptomatická. Popisujeme případ 29letého pacienta s neurofibromatózou 1. typu s maligním tumorem v oblasti cervikálního plexu. V roce 2005 u něj bylo diagnostikováno ložisko v oblasti horního mediastina, které bylo následně chirurgicky odstraněno a diagnostikováno jako ganglioneurinom. Po pěti letech se objevila rezistence v pravém nadklíčku, dle CT a CT angiografie byla prokázána infiltrace v horním hrudním mediastinu vpravo, jež byla chirurgicky řešena (debulking). Histologicky byl verifikován maligní tumor z pochvy periferního nervu. Roku 2011 došlo k recidivě tumoru v této lokalizaci, nádor byl v bloku resekován a podána chemoterapie. V roce 2013 je pacient v dobrém klinickém stavu, bez neurologického deficitu.

Abstract

Malignant peripheral nerve sheath tumours are rare neoplasms, especially in the head and neck. They are often asymptomatic. We present a case of 29-years old patient with neurofibromatosis type 1 with malignant tumour of the cervical plexus. A small resistance in the upper mediastinum was diagnosed (ganglioneurinoma) in 2005 and treated surgically (total exstirpation). A small infiltration in the right supraclavicular area occurred five years later and was also managed surgically (debulking) – histologically MPNST. There was a relapse of this tumour in the same area in 2011; this was treated by en bloc resection, followed by chemotheraphy. At present, the patient is in a good clinical status, with no neurological deficit.

Podpořeno MZ ČR – RVO (FNBr, 65269705).

Autoři deklarují, že v souvislosti s předmětem studie nemají žádné komerční zájmy.
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The Editorial Board declares that the manuscript met the ICMJE "uniform requirements" for biomedical papers.

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Klíčová slova

maligní tumor z pochvy periferního nervu – cervikální plexus – maligní schwannom – neurofibromatóza 1. typu

Key words

malignant peripheral nerve sheath tumour – cervical plexus – malignant schwannoma – neurofibromatosis type 1

Úvod

Maligní tumory z pochvy periferního nervu (MPNST) jsou vzácná neoplazmata.

Nejčastěji bývají lokalizovány v oblasti trupu a končetin (cca v 80 % případů), jak již bylo popsáno i českými autory [1,2]. V oblasti hlavy a krku však bývají tyto malignity většinou jen ojediněle popisovany v literatuře. Jedná se ale o jedny z nejzhoubnějších nádorů, které často recidivují a metastazují [3]. Lokalizace v cervikálním plexu je vzácná a mnohdy bývá spojena s absencí senzitivních či motorických příznaků [4]. MPNST se vyskytují buď sporadicky, či jsou spojeny s neurofibromatózou, zejména 1. typu. U části pacientů bývá popisována v anamnéze radiační expozice [4]. Uvádíme případ maligního tumoru z pochvy periferního nervu v oblasti cervikálního plexu u 29letého pacienta s neurofibromatózou 1. typu. Jedná se pravděpodobně o první případ MPNST v této lokalizaci publikovaný u nás.

Kazuistika

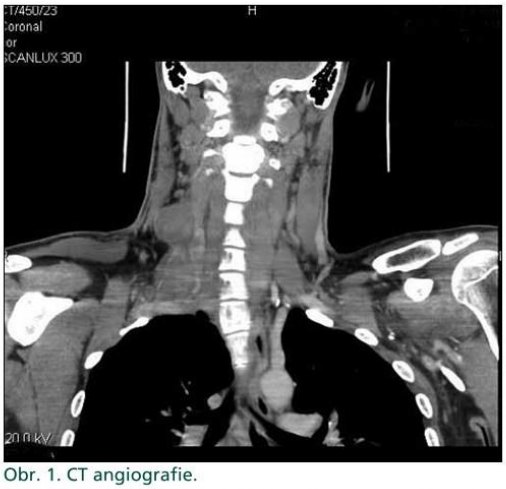
Pacient (29 let) s diagnostikovanou neurofibromatózou 1. typu (morbus von Recklinghausen) a typickým klinickým nálezem mnohočetných kutánních a subkutánních tumorózních uzlíků. Onemocnění zůstávalo dlouhodobě stacionární.

V roce 2005 bylo provedeno v rámci vstupní prohlídky do zaměstnání RTG plic a bylo popsáno ložisko v oblasti horního mediastina. Na MR hrudníku byla zjištěna postkontrastně se sytící tumorózní formace vysoko paramediastinálně a paravertebrálně velikosti 67 × 40 × 5,5 mm, zasahující až do hrotu hemithoraxu. Dle FNAB (aspirační biopsie tenkou jehlou) byl histologicky verifikován ganglioneurinom. Následně bylo indikováno radikální odstranění tumoru, které histologicky diagnózu potvrdilo.

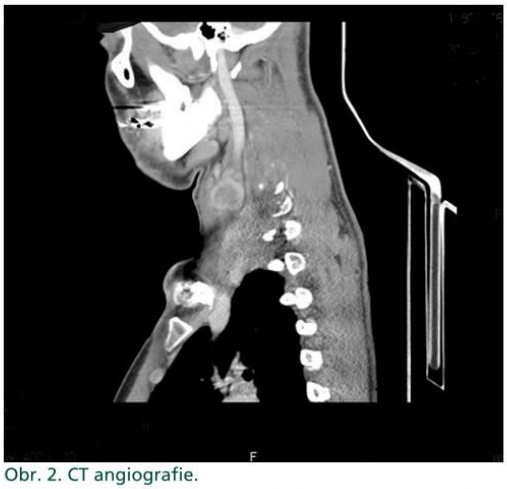
Po pěti letech byla zjištěna rezistence v oblasti pravého nadklíčku. Podle CT a CT angiografie v květnu 2010 byl prokázán infiltrát v oblasti horní hrudní apertury vpravo velikosti 61 × 64 × 98 mm, přerůstající do měkkých tkání supraklavikulárně. Do něj byla zavzata i pravá vertebrální tepna a a. subclavia. Infiltrát dosahoval až k laterálnímu okraji trachey a k pravému laloku štítné žlázy. Hrudním multidisciplinárním chirurgickým týmem byla provedena operační revize, při níž byl nalezen multicentrický tumor v oblasti pravého nadklíčku vycházející z nervových kmenů plexus cervicalis. Byla provedena subtotální resekce nádoru a histologicky verifikován maligní tumor periferní nervové pochvy G2 (grading FNCLCC, Fédération Nationale des Centres de Lutte Contre le Cancer), proliferační frakce (Ki-67/MIB-1) – 23 %. Pooperační průběh byl komplikován zánětlivým procesem v supraklavikulární krajině, avšak byl úspěšně zvládnut antibiotickou léčbou.

V dubnu 2011 byla s pomocí zobrazovacích vyšetření (MR, CT angiografie) zjištěna recidiva tumoru a indikována chirurgická revize (obr. 1, 2). Peroperačně byl ověřen multicentrický tumor formovaný z kuželovitě ztluštělých nervových kmenů cervikální pleteně a n. vagus (obr. 3). Hlavní masa tumoru vyplňovala supraklavikulární oblast, uzavírala vnitřní jugulární žílu, obkružovala a.carotis communis, distálně naléhala k a. subclavia a dorzálně se zanořovala do skalenických svalů. Po subadventiciální preparaci a uvolnění společné krkavice byl tumor v bloku s vnitřní jugulární žílou a postiženými nervovými kmeny resekován (obr. 4). Histologicky byla opět potvrzena recidiva maligního tumoru periferní nervové pochvy s invazí do stěny vnitřní jugulární žíly a pozitivní distální okrajovou excizí v oblasti horního mediastina (obr. 5, 6). Pooperační CT angiografie je na obr. 7 a 8.

S výsledkem histologického vyšetření byl stav zhodnocen na indikační mezioborové onkologické komisi pro léčbu tumorů hlavy a krku a indikována pooperační chemoterapie. Ta byla aplikována v měsíčních intervalech, doposud 15 sérií, režim: ifosfamid v kombinaci s doxorubicinem (od 8. série monoterapie ifosfamidem). Stav je od operace stabilizovaný. Po celou dobu je objektivní neurologický nález pacienta bez ložiskových projevů, je přítomna pouze lehčí hypestezie na pravém rameni.



Obr. 1. CT angiografie.
Kulovité ložisko v oblasti cervikálního plexu vpravo – koronární řez.



Obr. 2. CT angiografie.
Kulovité ložisko v oblasti cervikálního plexu vpravo – sagitální řez.

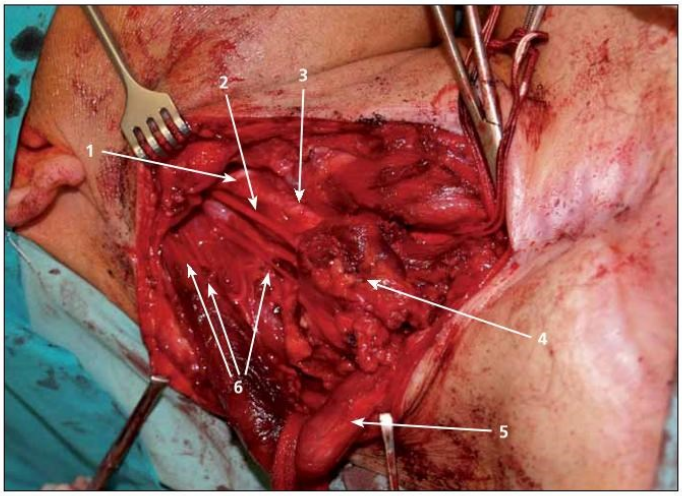
Diskuze

Maligní tumor z pochvy periferního nervu (MPNST) byl poprvé popsán A. P. Stoutem v roce 1935 jako „maligní neurilemmom" [5]. Tento typ nádoru byl následně v literatuře nazýván různými popisnými názvy jako neurogenní sarkom, maligní schwannom, neurofibrosarkom. Z těchto důvodů byl Světovou zdravotnickou organizací zaveden termín „maligní tumor z pochvy periferního nervu" (MPNST), aby nahradil výše uvedené zavádějící názvy [6].

MPNST jsou sarkomy, které pocházejí z periferních nervů nebo z buněk souvisejících s pochvou periferního nervu (Schwannovy buňky, perineurální buňky nebo fibroblasty). Představují asi 10 % všech sarkomů měkkých tkání [7]. Vyskytují se buď sporadicky, nebo ve spojení s neurofibromatózou 1. typu, a to až v 50 % případů [6].

Neurofibromatóza typu 1 je dědičný syndrom spojený s dysregulací v systému proteinů Ras [8]. Predispozice ke vzniku nádoru se vytváří mutací genu pro neurofibromin (280 kDa protein lokalizovaný na 17. chromozomu), který působí jako negativní regulátor systému proteinů Ras. NF1 deficientní buňky jsou hypersenzitivní na některé růstové faktory, jež vedou signál systémem Ras [9]. Ačkoliv byl neurofibromin typu 1 izolován před více než 20 lety, naše znalosti, jak ovlivňuje růst, metabolizmus a apoptózu buněk jako klíčový supresorový gen, zůstávají neúplné. V poslední době se zdá, že klíčovou roli v tumorigenezi hraje aktivace Heat Shock Proteinu 1 (HSP1), který byl ve velkém množství prokázán u pacientů s MTPPN. Neurofibromin typu 1 působí jako silný regulátor hladiny HSP1 a jeho aktivity [10]. U pacientů s MTPPN bývají též často popisovány mutace supresorového genu *p53* [11] a dále v lokusu 9p21 [12], což vede k předpokladu, že k maligní transformaci je zapotřebí ještě druhá genová mutace.

MPNST se vyskytují zhruba ve stejném procentu u obou pohlaví. Jsou lokalizovány zejména na končetinách a trupu, cca v 80 % případů, v oblasti hlavy a krku – dle různých autorů v 10–20 % [3,4,13]. Typicky se objevují v sedmé dekádě života, u pacientů s neurofibromatózou však podstatně dříve – nejčastěji ve třetím až čtvrtém deceniu [6]. U pacientů s NF1 je riziko rozvoje MPNST 8–13% [7].



Obr. 3. Operační pole před výkonem.

1 – n. hypoglossus, 2 – n. vagus, 3 – a. carotis interna, 4 – tumor, 5 – m. sternocleidomastoideus, 6 – větve cervikálního plexu.

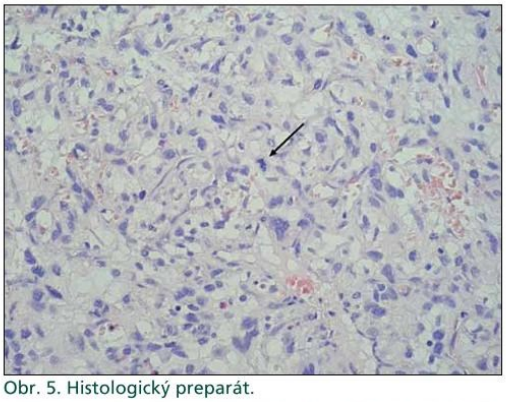
Obr. 4. Operační pole po odstranění tumoru.

1 – pahýl n. vagus, 2 – a. carotis, 3 – pahýl n. větve cervikálního plexu.

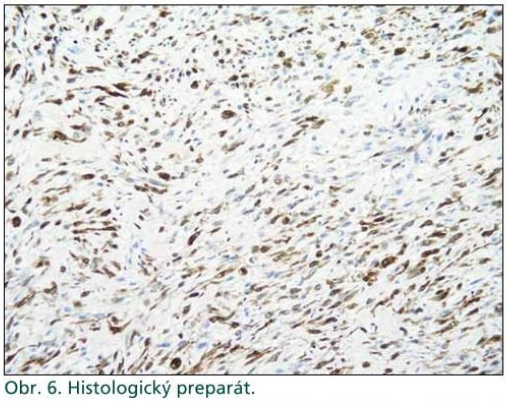
Příčina genové mutace není známa. Byla však popsána vyšší incidence tohoto nádoru u pacientů s anamnézou radiační expozice [14], u našeho pacienta ale přítomna nebyla.

Diagnostika těchto tumorů bývá často nesnadná a zavádějící, neboť se i přes značnou agresivitu tumoru často jedná o léze, které nepůsobí větší klinické obtíže, a bývají proto považovány za benigní.

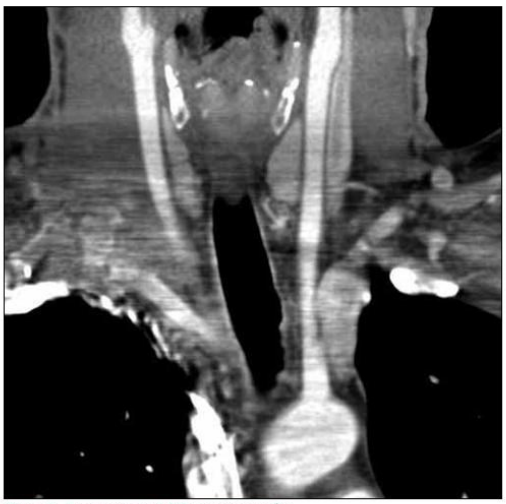
Nejčastějším příznakem MPNST u dospělých je rychle se zvětšující útvar v příslušné oblasti, který bývá obvykle asymptomatický [15]. Nejinak tomu bylo i u našeho pacienta. Mnohem vzácněji se může MPNST manifestovat celou škálou



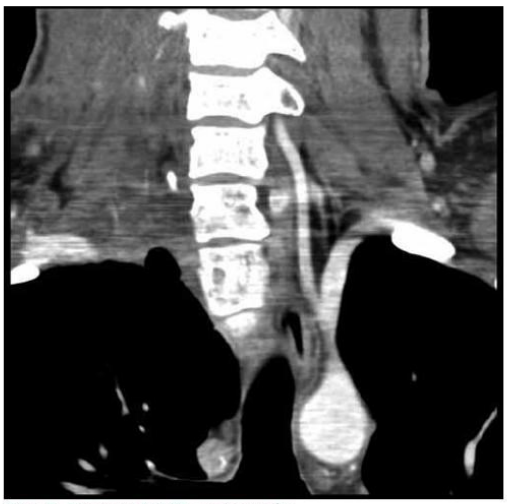
Obr. 5. Histologický preparát.
Barvení hematoxilin + eozin, zvětšení 400×. V nádorovém infiltrátu výrazná nukleární pleomorfie, šipkou označena atypická mitóza.



Obr. 6. Histologický preparát.
Zvětšení 200× – IHC (imunohistologické vyšetření). V nádorových buňkách intenzivní exprese S-100 proteinu (hnědočerná barva).



Obr. 7. Pooperační CT angiografie.
Stav po odstranění tumoru – koronární řez.



Obr. 8. Pooperační CT angiografie
Stav po odstranění tumoru – koronární řez.

neurologických příznaků zahrnujících radikulární bolesti, parestezie a eventuálně i parézy – vše v závislosti na lokalizaci léze.

Radiologicky a ultrasonograficky se MPNST u dospělých manifestuje jako kulovitý útvar, který většinou přesahuje 5 cm v průměru [16], zejména u pacientů s neurofibromatózou [4].

Magnetická rezonance bývá u MPNST metodou volby a je považována za značně senzitivní a specifické vyšetření k odlišení benigních a maligních tumorů, se specificitou až 81 % pro benigní tumory [17]. Typický je zejména hyperintenzní okraj s centrálním poklesem intenzity na T2 vážených sekvencích, homogenně izodenzní nebo mírně hyperintenzní ke svalu na T1 vážených sekvencích. Zejména rozsah tumoru (nad 5 cm), invaze do tukových tkání, heterogenita, neostré okraje a perifokální edém budí podezření na maligní typ nádoru [18].

FDG (fludeoxyglukóza) PET se ukazuje jako přínosné v detekci metastáz či relapsu choroby [19], ačkoliv jeho role v odlišení benigního a maligního nádoru se původně považovala za spornou [20], nicméně dle recentních studií je velmi přínosná [21].

Histopatologické zhodnocení je pro stanovení definitivní diagnózy zásadní. Typicky bývají popisovány vřetenovité buňky uspořádané do fasciklů, kdy histologický vzorec je podobný fibrosarkomu. Jsou přítomny četné mitózy, celulární atypie, zvýšená celularita a infiltrované, špatně definované buněčné okraje. Imunohisto-

chemické stanovení pozitivity S100 proteinu ukazuje na neuronální původ nádoru, negativita však MPNST nevylučuje. Přítomnost proteinu S ale může být negativní až v 10–50 % MPNST [21].

CT hrudníku bývá preferované pomocné vyšetření při pátrání po vzdálených metastázách, scintigrafie skeletu odhalí eventuální kostní postižení.

Resekce nádoru je univerzálně přijímána jako základní metoda léčby [19,22,23]. Cílem je kompletní odstranění tumoru se širokými (histologicky negativními) okraji, bez vynětí regionálních mízních uzlin. Ty bývají postiženy jen extrémně vzácně [4]. Kompletní resekce tumoru však není často možná – zejména v oblasti trupu a hlavy (na rozdíl od končetin), což samozřejmě výrazně zhoršuje další prognózu.

Role přídatné radio- a chemoterapie zůstává nejasná. D'Agostino předpokládá, že chirurgické řešení je jediné vhodné pro pacienta, další autoři rovněž zdůrazňují, že přídatná radio- a chemoterapie nezmění výrazně prognózu onemocnění [5,24]. Léčba sarkomů měkkých tkání adjuvantní radioterapií totiž sice vedla ke statisticky nižšímu počtu lokálních recidiv, nevedla však k poklesu počtu metastáz nebo k prodloužení mediánu dlouhodobého přežití [25]. Někteří autoři se naopak domnívají, že adjuvantní radioterapie by měla být vždy použita spolu s co možná nejradikálnější resekcí tumoru [3]. Přídatná chemoterapie zůstává ještě kontroverznější. Dle některých autorů nemá vůbec smysl [3,4], jiní ji doporučují pouze u nádorů s vysokým stupněm malignity, u nichž je pravděpodobný rozvoj metastáz [8]. Onkologickou komisí pro tumory hlavy a krku byl u našeho pacienta při recidivě tumoru zvolen tento způsob léčby, prozatím s uspokojivým efektem. Radioterapie indikována nebyla.

Prognóza MPNST je velmi závažná, zejména v oblasti hlavy a krku a u pacientů s von Recklinghausenovou nemocí [4]. Většina MPNST jsou sarkomy vysokého stupně malignity, s velkou tendencí k lokální recidivě i k tvorbě metastáz. Ve velkých sériích byla lokální recidiva popsána mezi 40 a 65 % a metastázy v 40–68 % [19]. Nádory metastazují nejčastěji do plic, následně pak do kostí a pleury. Pětiletá doba přežití je uváděna od cca 15 do 20 % u pacientů s NF1 a 50–55 % u pacientů bez této nemoci [4,15,19,23]. Delší doba přežití je dokumentována u pacientů s totální excizí tumoru, menší velikostí tumoru (pod 5 cm) a u tumorů nižšího stupně [19].

Závěr

Maligní tumor z pochvy periferního nervu v oblasti cervikálního plexu je vzácný. Stejně jako ostatní MPNST je velmi zhoubný a má špatnou prognózu. Léčba spočívá především v subtotální až totální resekci, přičemž role přídatné aktino- a chemoterapie zůstává kontroverzní. Mělo by se na něj myslet u rychle rostoucí kulovité podkožní expanze bez neurologických příznaků, a to především u nemocných s neurofibromatózou 1. typu.

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Asymptomatická spondylogenní komprese krční míchy

Asymptomatic Spondylotic Cervical Cord Compression

Souhrn

Stenóza cervikálního kanálu může vést ke kompresi krční míchy a představuje nejvýznamnější mechanický faktor v patofyziologii cervikální spondylogenní myelopatie. Míšní tkáň je však vůči kompresi poměrně odolná a k rozvoji manifestní myelopatie dochází až při vyšším stupni komprese a v kombinaci s dalšími patofyziologickými faktory, zejm. dynamickým faktorem a zevním traumatem. Asymptomatická spondylogenní komprese krční míchy (ASCCC) je velmi častým nálezem zvláště v populaci vyššího věku nad 50 let. Objektivizace a kvantifikace cervikální stenózy a komprese krční míchy jsou však nejednotné a nejsou jasně stanoveny prediktory progrese do manifestní myelopatie a s tím související indikace případné preventivní chirurgické dekomprese. Přehled obsahuje nejčastěji používané metody stanovení cervikální stenózy a cervikální míšní komprese pomocí zobrazovacích metod. Nativní radiogram a výpočetní tomografie mají význam v objektivizaci cervikální stenózy, zatímco dominantní metodou objektivizace míšní komprese je magnetická rezonance (MR). Z parametrů, které nejvíce korelují s klinickou manifestací komprese, jsou uváděny příčná plocha míchy v místě komprese a přítomnost intenzitních změn míšního signálu. Z novějších zobrazovacích modalit je nejcitlivější MR zobrazení tenzorů difúze. Z prognostických faktorů rozvoje manifestní myelopatie u ASCCC jsou obecně akceptovány přítomnost manifestní radikulopatie a abnormita motorických a senzomotorických evokovaných potenciálů. Význam zobrazovacích metod v predikci rozvoje manifestní myelopatie a benefit provedení preventivní dekomprese ve skupině nemocných s asymptomatickou kompresí a vyšším rizikem rozvoje manifestní myelopatie bude nutné ověřit dalšími studiemi.

Abstract

Cervical spinal stenosis may lead to cervical cord compression and represents the most important mechanical factor in pathophysiology of cervical spondylotic myelopathy. Medullar tissue is, however, rather resistant to compression and development of symptomatic myelopathy occurs only when higher degree stenosis is present and in combination with other pathophysiological factors, mainly dynamic compression and trauma. Asymptomatic spondylotic cervical cord compression (ASCCC) is a quite frequent finding in older population above the age of fifty. However, reliability of the methods used to verify and quantify cervical stenosis and cervical cord compression is low and clear predictors of development of symptomatic myelopathy and related indication of potential preventive surgical decompression in ASCCC have not been determined yet. The overview discusses the most frequently used methods to establish cervical spinal stenosis and cervical cord compression using imaging methods. Radiogram and especially computed tomography are important for verification of cervical spinal stenosis, while magnetic resonance imaging (MRI) is a preferable method to detect cervical cord compression. The cross-sectional spinal cord area and T2 MRI spinal cord hyperintensity are among the parameters considered to be the most closely correlated with clinical manifestation of spinal cord compression. Among newly introduced imaging modalities, MRI diffusion tensor imaging seems to be the most promising one. The presence of symptomatic radiculopathy and abnormality of motor and somatosensory evoked potentials are among generally accepted predictors of symptomatic myelopathy. The importance of imaging methods as predictors of symptomatic myelopathy development as well as benefits of preventive surgical decompression in ASCCC individuals with high risk of developing symptomatic myelopathy is to be established in future studies.

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Klíčová slova

cervikální stenóza – cervikální spondylogenní myelopatie – asymptomatická komprese krční míchy – magnetická rezonance – zobrazení tenzorů difúze – výpočetní tomografie

Key words

cervical spinal stenosis – cervical spondylotic myelopathy – asymptomatic spondylotic cervical cord compression – magnetic resonance imaging – diffusion tensor imaging – computed tomography

Úvod

Cílem přehledu je poukázat na existenci asymptomatické netraumatické spondylogenní komprese krční míchy a možnosti zobrazovacích metod při její detekci a predikci dalšího vývoje a prognózy.

Prevalence degenerativního onemocnění páteře narůstá s věkem, postihuje predilekčně krční a bederní páteř a ve vyšším věku je výskyt degenerativních změn prakticky ubikvitární [1]. Degenerativní změny postihují meziobratlové disky, intervertebrální klouby, kostní a vazivové struktury páteře a mohou vést ke zúžení spinálního kanálu a kořenových kanálů a tím i k potenciální kompresi nervových struktur.

Nativní RTG zobrazí pouze změny obratlů, nepřímé známky degenerace meziobratlového disku (obr. 1) a umožní kvantifikovat některé rozměry spinálního kanálu, zejm. anteroposteriorní průměr.

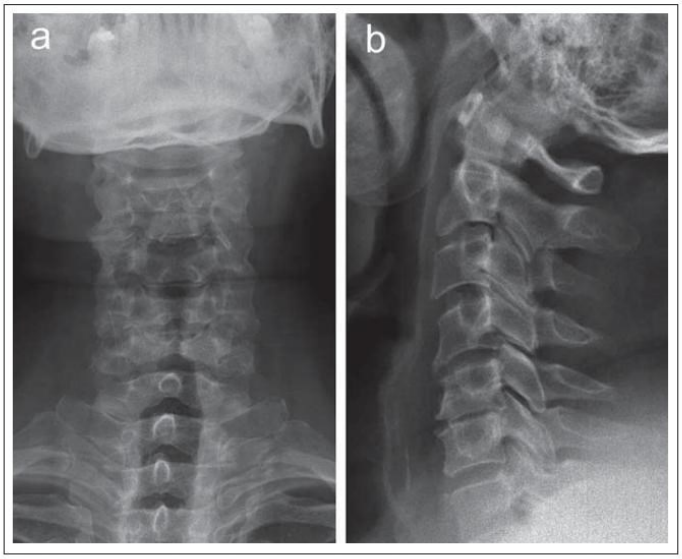
Výpočetní tomografie (CT) dokáže zobrazit detailně tvar a rozměry kostěného spinálního i kořenového kanálu, durální vak a orientačně i míchu, avšak pomocí CT nelze spolehlivě objektivizovat míšní či kořenovou kompresi i změny struktury míchy (obr. 2).

Magnetická rezonance (MR) dokáže zobrazit i vazivové struktury (ligamenta longitudinalia, ligamenta flava, meningy), míchu a kořeny, umožní objektivizovat míšní kompresi i změnu struktury míšní tkáně. Současná diagnostika klinicky manifestní cervikální spondylogenní myelopatie (CSM) jako nejzávažnějšího následku krční spondylózy je založena na klinické detekci subjektivních a především objektivních příznaků míšní léze v krčním úseku a MR známkách míšní komprese (obr. 3).

CSM byla popsána Stookeym již v roce 1928 [2], ale její patofyziologie není detailně známa. Zahrnuje statické faktory (cervikální spinální stenózu) a faktory dynamické vedoucí k opakovanému míšnímu poranění. Tyto mechanické faktory sekundárně indukují ischemii, zánět a apoptózu. Histologicky se nacházejí cystické kavitace a glióza v centrální šedi míšní a demyelinizace v mediálních částech dlouhých míšních drah. Wallerova degenerace postihuje zadní provazce a posterolaterální ascendentní dráhy kraniální od místa komprese, a přední provazce a kortikospinální trakty v místě komprese a kaudálně [3].

Z experimentálních prací je známo, že míšní tkáň je poměrně odolná vůči kompresi a neurologický deficit se může manifestovat s významným zpožděním po vzniku komprese [4–6]. Vzniká tak klinicko-radiologická disociace („mismatch"), kdy radiologické známky komprese nejsou do určitého stupně provázeny klinickými projevy myelopatie – tzv. presymptomatická spondylogenní komprese krční míchy (PSCCC) [7,8]. Protože termín „presymptomatická komprese" implikuje, že musí dojít ke klinické manifestaci komprese, což naše nálezy nepotvrzují, je v těchto případech přesnějším termínem asymptomatická komprese (Asymptomatic Spondylotic Cervical Cord Compression or Encroachment; ASCCC, ASCCE) [1,8–10].

Následující přehled shrnuje současné možnosti diagnostiky cervikální stenózy a cervikální míšní komprese, poznatky o korelaci mezi zobrazovacími a klinickými nálezy a prediktory rozvoje cervikální míšní komprese a symptomatické cervikální myelopatie.



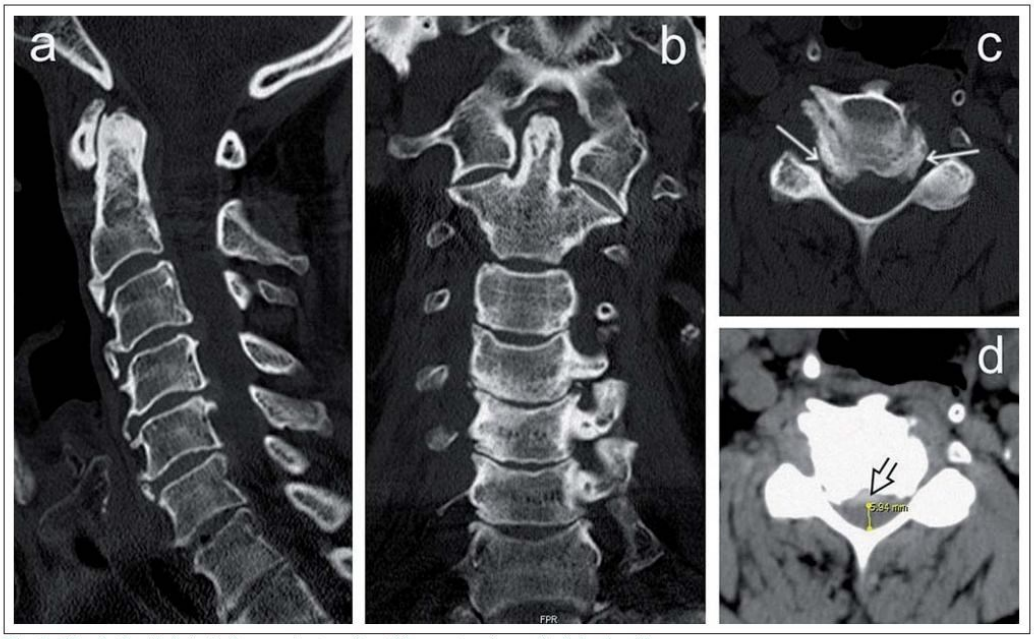
Obr. 1. RTG snímek v předozadní (a) a laterální projekci (b) u pacienta s osteochondrózou v segmentech C4–C6, zvláště pokročilou v etáži C5/6.

Zde je patrné výrazné snížení meziobratlového prostoru při degeneraci ploténky a reaktivní osteofyty na okrajích krycích ploch, které dorzálně působí mírné sekundární omezení páteřního kanálu. Primární šíře páteřního kanálu je normální (index Torg-Pavlovové = 0,97).

Diagnostika cervikální stenózy

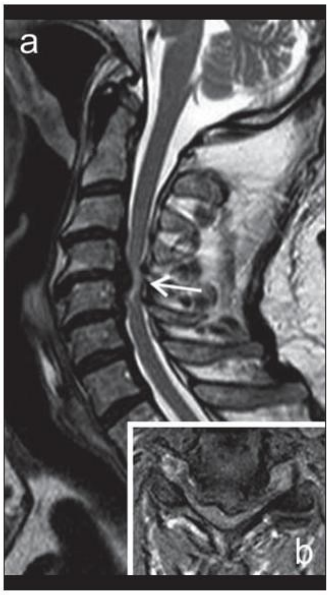
Zúžení spinálního kanálu v krčním úseku páteře je označováno jako **cervikální spinální stenóza** (CS). Může vést nejprve k obliteraci subarachnoidálního prostoru a teprve později ke kompresi nervových struktur – kořenů a krční míchy. Toto zúžení může být buď vrozené (primární stenóza) nebo získané (sekundární stenóza).

Normální uváděné hodnoty nejdelšího anteroposteriorního průměru kostěného spinálního kanálu, hodnoceného vzhledem k projekčnímu zkreslení při nativním RTG optimálně ze sagitálního či axiálního CT skenu v místě středu obratlového těla (Canal Diameter Midvertebral; $CD_{mitvertebral}$) [11], vyjádřené v absolutních hodnotách, jsou kolem 17–18 mm (ve výši obratlů C3–C6) [12]. Za stenózu jsou považovány hodnoty < 10 mm, hodnoty 10–13 mm jsou považovány za hraniční [13]. Podle jiných autorů signalizují stenózu již hodnoty < 12 mm [14]. Dalším parametrem je průměr kanálu v úrovni disku (CD_{disc}) [11]. Daleko častěji je ke kvantifikaci anteroposteriorního průměru spinálního kanálu používán Index Pavlovové (nebo také Index Torga-Pavlovové; TPR [15]), protože jde o relativní poměr, který eliminuje zkreslení dané zvětšením či zmenšením radiologického obrazu nebo mohutnosti kostěných struktur páteře. Jde o poměr anteroposteriorního průměru kanálu a obratlového těla měřený původně ve výši středu obratlového těla C5 z nativního bočního



Obr. 2. CT vyšetření krční páteře u pacienta s víceetážovou stenózou páteřního kanálu.

a – sagitální rekonstrukce, b – koronální rekonstrukce, c – axiální zobrazení v přepočtu s vysokým rozlišením dobře demonstruje oboustrannou spondylogenní forminostenózu (šipky), d – axiální zobrazení s použitím „měkkotkáňového" rekonstrukčního algoritmu demonstruje stenózu páteřního kanálu způsobenou osteofyty i dorzální protruzí ploténky (šipka).



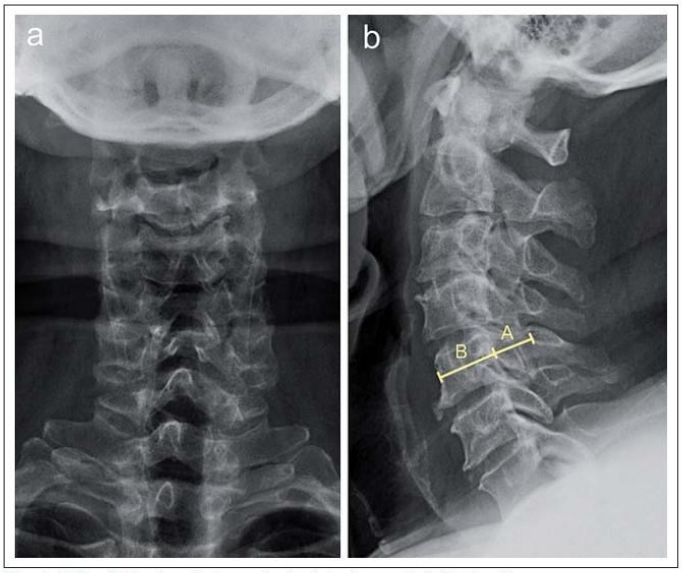
Obr. 3. MR zobrazení krční páteře v T2 obraze v sagitální (a) a axiální (b) rovině u pacienta s klinickými známkami myelopatie.

Mícha je výrazně stištěna v etáži C4/5 v důsledku sekundární stenózy páteřního kanálu, v míše je zde patrný okrsek zvýšeného T2 signálu (šipka).

RTG snímku, nověji však i ze sagitálního CT či MR skenu (obr. 4) [11,16]. Za normální byly označeny hodnoty > 1,0 a jako stenóza hodnoty TPR < 0,82 [15]. Absolutní či relativní zúžení nejdelšího anteroposteriorního průměru v centrální oblasti kanálu (tzv. **centrální typ stenózy**) je indikátorem stenózy dominantně **vrozeného (vývojového)**, nikoliv získaného, zejm. degenerativního původu. TPR byl v řadě prací použit jako možný prediktor rozvoje míšní komprese i její tíže a prognózy, včetně efektu operační dekomprese, a to s nejednoznačnými výsledky – viz dále. Lindberg et al [17] zjistili u pacientů s CSM korelaci mezi TPR a parametry zobrazení tenzorů difúze (DTI) v MR obraze.

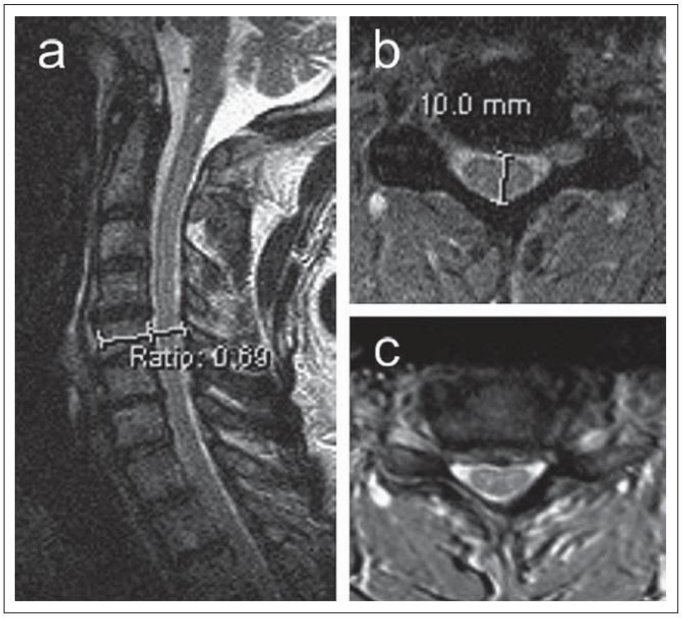
Degenerativní cervikální stenóza je nejčastější příčinou **získané CS.** Na rozdíl od vývojové stenózy, která je typicky centrálního typu, vede degenerativní cervikální stenóza k hypertrofii unkovertebrálních kloubů a zúžení laterálních recesů **(laterální stenóza**) a proximální části kořenového kanálu. Degenerace však vede i k protruzi disků a jejich komplexů s osteofyty, dorzálně dochází k osifikaci zadního longitudinálního ligamenta a ligamenta flava a tím i k zúžení v centrální části spinálního kanálu. Cervikální spinální kanál ztrácí při výrazné laterální stenóze na průřezu typický oválný tvar včetně konvexity ventrálního okraje a v pokročilejším stadiu nabývá tvaru třírohého klobouku nebo trojlístku („trefoil"). (obr. 5a,b).

Ke kvantifikaci rozměrů cervikálního kanálu se používá kromě anteroposteriorního průměru kanálu i **transverzální průměr** a zejm. **transverzální plocha kostěného kanálu** (Osseous Spinal Canal Area; OSCA)



Obr. 4. RTG vyšetření pacienta s primární stenózou páteřního kanálu.

a – anteroposteriorní projekce; b – laterální projekce se znázorněním měření indexu Torg-Pavlovové, který představuje podíl nejdelšího průměru páteřního kanálu (A) a obratlového těla (B) při měření v úrovni středu obratlového těla C5. U tohoto pacienta byla naměřena hodnota 0,67 značící primárně úzký páteřní kanál. Kromě obrazu primární stenózy jsou přítomny i známky degenerativních změn zejm. v etáži C3/4.



Obr. 5a,b) MR zobrazení u pacienta s primární stenózou páteřního kanálu v sagitální (a) a axiální (b) rovině T2 zobrazení.

Index Torg-Pavlovové činí pouze 0,69 (a), předozadní rozměr 10 mm při zúžení centrální části páteřního kanálu (b). Pro porovnání je ukázán též axiální MR obraz jiného pacienta se sekundární (degenerativní) stenózou páteřního kanálu (c), kde je výraznější zúžení laterální části páteřního kanálu.

a transverzální plocha durálního vaku (Dural Sac Area; DSA) (obr. 6a–c) [14].

Zvláštním subtypem degenerativní stenózy je osifikace zadního podélného ligamenta (OPLL), která se vyskytuje převážně u Asiatů. Porovnáním CT/myelografie a MR Naganawa et al [18] zjistili, že rozměry durálního vaku jsou při měření CT myelografií lehce větší v porovnání s fast spin echo T2 MR obrazem, zatímco rozměry míchy zjištěné pomocí MR jsou naopak větší. Lze předpokládat, že při použití MR T2* gradientního echa by tento rozdíl mezi MR a CT myelografií byl ještě větší. Další studie prokázala vyšší validitu CT/myelografie v detekci foraminální stenózy a rozlišení kostěných a měkkotkáňových struktur, zatímco MR lépe detekuje přímou kompresi kořene [19] a zvláště míchy.

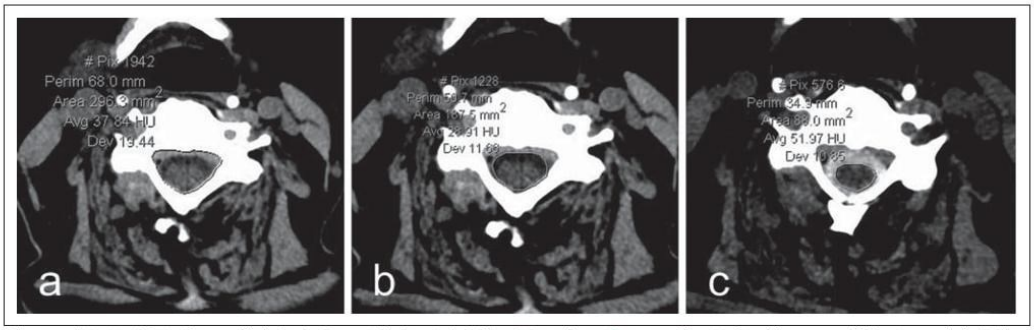
Dalšími parametry navrženými ke kvantifikaci cervikální stenózy jsou rozměry měřené ze sagitálního MR skenu:

- prostor dostupný pro míchu – **Space Available for Cord** (SAC) vypočítaný jako AP průměr cervikálního kanálu (CD_{disc}) minus AP průměr míchy ve výši disku;
- podíl AP průměru kanálu k AP průměru míchy – **Canal to Cord Ratio** (CCR) = (CD_{disc}) / AP průměr míchy ve výši disku (obr. 7a,b) [11].

Definice a diagnostika míšní komprese

Spolehlivá detekce míšní komprese je možná pouze pomocí MR. Hodnocení komprese provádí většina autorů v T2 vážených obrazech, které poskytují výborný kontrast mezi míchou, mozkomíšním mokem a strukturami ohraničujícími páteřní kanál, a to z transverzálních (axiálních) řezů nebo ze sagitálního řezu ve střední čáře. Sagitální řez umožní rychlé orientační zhodnocení ve všech etážích, axiální řezy mají výhodu detailnějšího posouzení tíže a směru komprese.

Byla navržena řada způsobů a algoritmů, jakým způsobem definovat a kvantifikovat míšní kompresi.



Obr. 6a–c) Nativní CT zobrazení krční páteře v axiální rovině (a,b) a CT myelografie po aplikaci jodové kontrastní látky intratekálně (c).
Na těchto obrazech je znázorněno měření plochy kostěného páteřního kanálu (a), plochy durálního vaku (b) a plochy míchy (c).

Anteroposteriorní průměr míchy (obr. 7b) hodnocený jak ze sagitálního, tak transverzálního T2 MR skenu je u dospělých jedinců poměrně konstantní a ve výši obratlů C3–C7 se pohybuje kolem 8 mm [12].

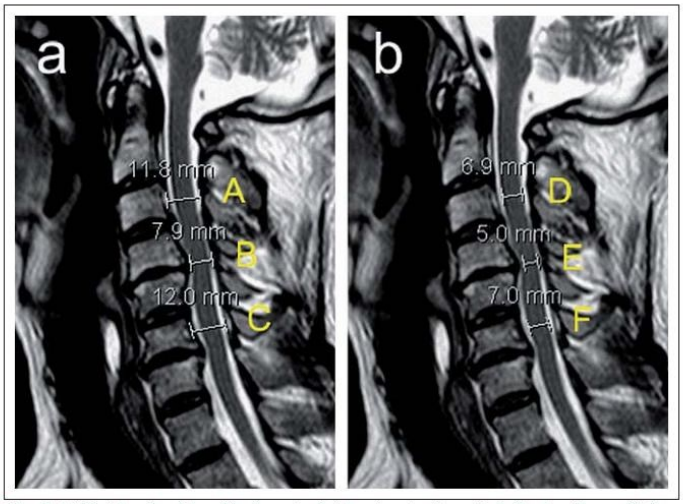
Plocha míchy na příčném řezu (Cross-Sectional Area; CSA; nebo Spinal Cord Area) asi nejlépe odráží případnou atrofii míchy. Z téhož řezu lze hodnotit kompresivní poměr (Compression Ratio; CR) jako poměr předozadního a laterolaterálního průměru míchy (obr. 8a,b).

Fehlings et al [20] navrhli hodnocení cervikální stenózy a komprese krční míchy ze sagitálních CT a MR skenů pomocí indexů **„Maximum Canal Compromise"** (MCC) a **„Maximum Spinal Cord Compression"** (MSCC), které se hodnotily podle následujícího vzorce:

$$1 - \left(\frac{d_i}{(d_a + d_b)/2}\right) \times 100\ \%,$$

kde d_i je anteroposteriorní průměr míchy v místě maximální komprese, d_a a d_b průměr míchy ve výši nejbližšího kraniálního a kaudálního segmentu bez komprese (měřeno ze sagitální T2 MR skenů). V případě výpočtu MCC se do vzorce dosadí anteroposteriorní průměry kostěného spinálního kanálu měřené ze sagitální CT nebo T1 MR skenů (obr. 7a,b). Karpová et al [21] zjistili vysokou intra- a interobserver reliabilitu CR, CSA, MCC a MSCC.

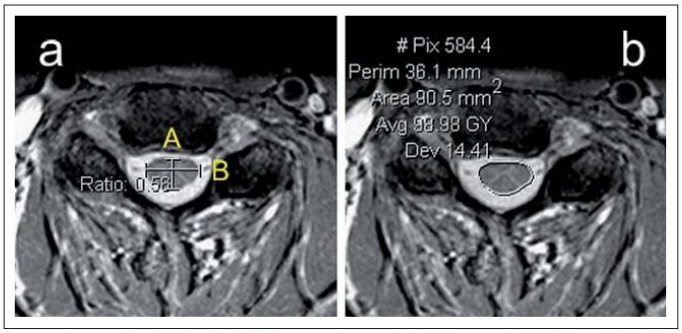
Teresi et al [9] rozlišili **„impingement"** jako konkávní defekt v míšním signálu související s protruzí disku a/nebo osteofytem bez obliterace subarachnoidálního prostoru a míšní kompresi jako konkávní defekt s obliterací subarachnoidálního prostoru. Současně kvantifikovali tíži komprese vyjádřenou pomocí CSA jako relativní podíl hodnoty CSA v úrovni maximální komprese na hodnotě zjištěné z nejbližší normální etáže nad kompresí.



Obr. 7a,b) Ukázka různých měření popisujících míru stenózy páteřního kanálu a míšní komprese u pacienta se sekundární spinální stenózou s maximem v etáži C4/5 znázorněné na sagitálních T2 vážených skenech MR zobrazení (a,b).
Rozměry A–C udávají ventrodorzální šíři páteřního kanálu, rozměry D–E šíři míchy. Z těchto rozměrů lze vypočítat následující parametry: prostor pro míchu – Space Available for Cord: SAC = B – E; podíl AP průměru kanálu k AP průměru míchy – Canal to Cord Ratio: CCR = B/E; relativní kvantifikace maxima stenózy páteřního kanálu vůči sousedním segmentům bez stenózy kraniálněji a kaudálněji – Maximal Canal Compromise: MCC = (1 – (B/((A + C)/2))) × 100 %; obdobný výpočet lze použít pro kvantifikaci míry maximální míšní komprese – Maximal Spinal Cord Compression: MSCC = (1 – (E/((D + F)/2))) × 100 %.

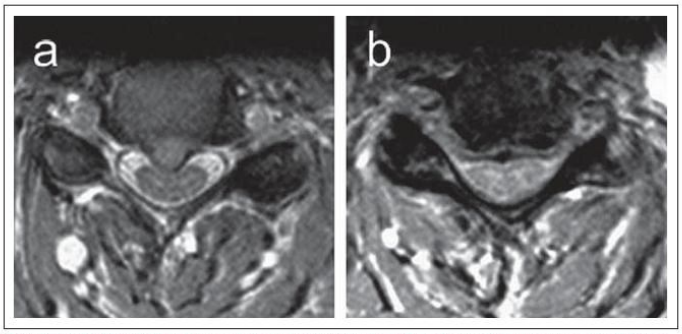
Shimomura et al [22] rozlišovali typ „P" („Partial") s kompresí míchy ventrálně protrudovaným diskem a/nebo osteofytem a zachovaným zadním subarachnoidálním prostorem; a typem „C" („Circumferential") s cirkulární kompresí diskem, osteofyty a ligamentum flavum a zašlým subarachnoidálním prostorem. Kameyama et al [23] označili typ „P" jako „boomerang" a typ C jako triangulární (obr. 9a,b).

Byly však navrženy i komplexnější způsoby kvantifikace stupně cervikální stenózy a komprese durálního vaku a míchy [16]:



Obr. 8a,b) Axiální T2 zobrazení MR krční páteře s ukázkou měření kompresního poměru (a) a plochy míchy (b).

Kompresní poměr představuje podíl předozadního (A) a laterálního průměru míchy (B).



Obr. 9a,b) Axiální MR zobrazení dvou pacientů s cervikální spinální stenózou s odlišným typem míšní komprese.

a – fokální imprese (impingement) ventrální kontury míchy mediální herniací ploténky, subarachnoidální prostor páteřního kanálu je z převážné části zachován; b – sekundární stenóza páteřního kanálu s plošnou kompresí míchy a s povšechnou redukcí subarachnoidálního prostoru; mícha při tomto typu spinální stenózy na průřezu nabývá postupně triangulárního tvaru.

Index komprese krční míchy (Cervical Cord compression Index; CCI):

Skóruje se tíže přední a zadní komprese:

Přední komprese (body):

0 bez komprese
1 protruze disku, ale zachovaný subarachnoidální prostor (intaktní signál mozkomíšního moku; CSF)
2 zašlý subarachnoidální prostor bez signálu CSF, ale bez míšní komprese
3 míšní komprese

Zadní komprese (body):

0 bez komprese
1 mírná komprese žlutým vazem, ale zachovaný subarachnoidální prostor
2 zašlý subarachnoidální prostor bez signálu CSF, ale není míšní komprese
3 míšní komprese

CCI = součet bodů přední a zadní komprese

Stupeň 0: 0 bodů
Stupeň 1: 1–2 body
Stupeň 2*: 3–4 body
Stupeň 3: 5–6 bodů

Signifikantní kompresi představuje stupeň 3, tj. musí být přítomna komprese míšní alespoň zepředu nebo zezadu, případně obojí.

Dynamická komprese krční míchy

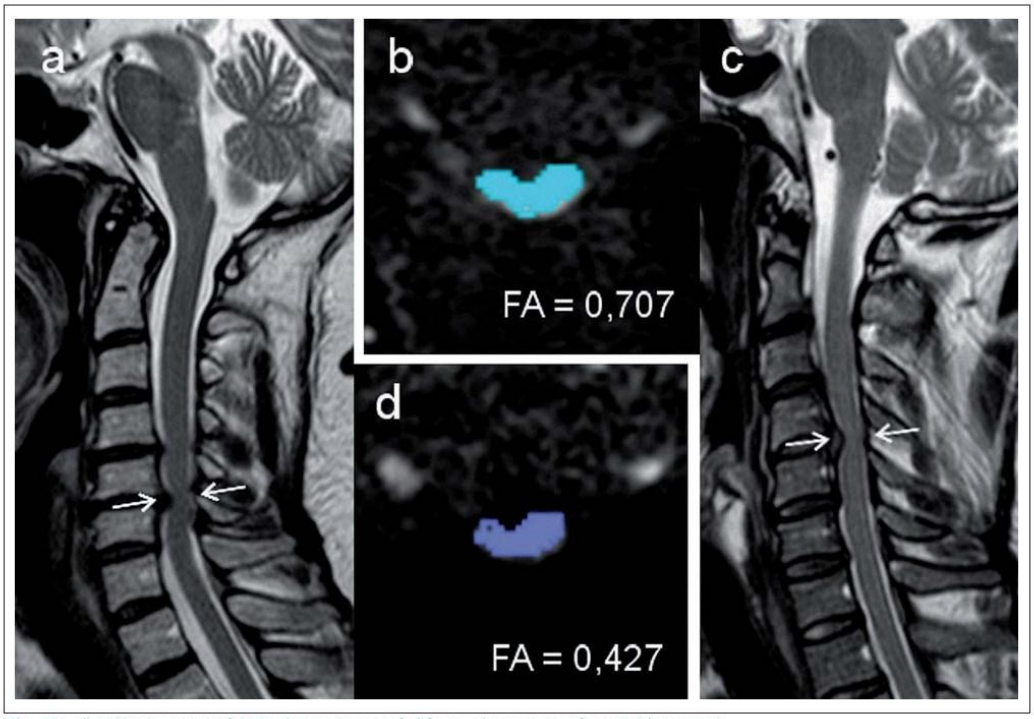
Dynamická MR u pacientů s CSM zjistila, že CSA byla největší v neutrální poloze, zmenšila se ve flexi a ještě více v extenzi. Impingement krční míchy byl poněkud v rozporu s CSA zaznamenán jen u 12 % nemocných ve flexi, avšak u 34 % v neutrální pozici a u 74 % v extenzi [24]. Muhle et al [25] zjistili progresi cervikální stenózy při změně z neutrální pozice do extenze o 48 % a progresi míšní komprese o 20 %, zatímco stejný pohyb do flexe vedl k progresi CS o 24 % a míšní komprese o 11 %. Kromě mechanické komprese a distenze míchy může přispívat k lézi míchy i ischemie, především při ventrální kompresi.

Korelace mezi zobrazovacími nálezy a klinickou manifestací míšní komprese

U **cervikální stenózy** byla popsána určitá, i když nevýrazná a nekonstantně prokazovaná korelace s klinicky manifestní míšní kompresí. Edwards a LaRocca [13] zjistili nepřímou úměru mezi anteroposteriorním průměrem cervikálního kanálu a rozvojem myelopatie. Aebli et al [26] zjistili, že pacienti s vývojovou (vrozenou) cervikální stenózou, vyjádřenou TPR < 0,7, mají vyšší riziko míšního poranění po lehkém traumatu krční páteře. Iizuka et al [27] u pacientů s LSS a současnou CSM (8,86 %) nalezli nižší TRP ve srovnání s jedinci bez CSM (cut-off hodnota 0,78). Existuje však nepříliš těsná korelace mezi hodnotou TPR a prostorem pro míchu v cervikálním kanále [28].

Významnější korelace s klinickou manifestací míšní komprese byla ilustrována u **CSA míchy a intenzitních změn míšní tkáně** v MR obraze. Okada et al zjistili korelaci mezi absolutní hodnotou CSA i mezi podílem mezi transverzální plochou cervikálního kanálu a míchy a klinickou manifestací [29]. Kadaňka et al srovnávali dvě skupiny nemocných s míšní kompresí – s manifestní myelopatií a bez klinických známek myelopatie. Kritickou hodnotou CSA v místě komprese bylo 50–60 mm^2, avšak pouze při současné přítomnost MR T2 hyperintenzity, zatímco u nemocných bez intenzitních změn nebylo možno nalézt spolehlivou korelaci mezi CSA a klinickou manifestací komprese [30].

Intenzitní změny míšního signálu v MR obraze jako předpokládané známky myelopatie mohou mít různý patologicko-anatomický korelát, zejm. v závislosti na stadiu komprese (obr. 3). Izolovaná T2 hyperintenzita může být podmíněna edémem v akutním stadiu myelomalcie [31], zvláště pokud je hyperintenzita nevýrazná a přechodná, nebo odpovídá glióze či cystické nekróze,



Obr. 10a–d) Měření parametrů MR zobrazení tenzorů difuze u dvou pacientů s míšní kompresí.

a,d – pacient s klinickými známkami myelopatie s nízkými hodnotami frakční anizotropie (FA = 0,426) v místě max. komprese v úrovni C5/6; b,c – pacient s kompresí míchy v úrovni C4/5 na podkladě herniace ploténky, u nějž nebyly zjištěny klinické známky myelopatie. Naměřená hodnota FA je zde vyšší (0,707). Šipky na sagitálních obrazech (a,c) označují úroveň, ve které byla provedena měření na obrazech v axiální rovině (b,d).

především pokud je dobře ohraničená a permanentní. Kombinace T2 hyperintenzity s T1 hypointenzitou odráží přechod myelomalacie do ireverzibilního stadia cystické nekrózy a tvorbu dutin [12,32].

Enhancement gadolinia byl přítomen u pacientů s CSM vždy v oblasti T2 hyperintenzity, vymizel u většiny nemocných do jednoho roku po chirurgické dekompresi a predikoval horší pooperační průběh [33]. PET studie prokázala u části pacientů s CSM zvýšené vychytávání ^{18}fluorodeoxyglukózy v místě komprese, které korelovalo s kratším trváním symptomů, rychlejším poklesem funkce před operací a predikovalo zlepšení po operaci ve srovnání s pacienty bez zvýšeného vychytávání [34].

Existuje řada studií, které potvrzují, že zobrazení tenzorů difúze (Diffusion Tensor Imaging; DTI), konkrétně parametry frakční anizotropie (FA), jež vyjadřuje míru směrové závislosti difúze, a „Apparent Diffusion Coefficient" (ADC) nebo také „Mean Diffusivity" (MD) vyjadřující celkovou difuzivitu vody v tkáni bez ohledu na směrovou predilekci, by mohly odlišit pacienty se symptomatickou a asymptomatickou kompresí krční míchy lépe než MR intenzitní změny [12,35]. Kara et al [36] prokázali u skupiny 16 nemocných s CSM, avšak bez intenzitních MR změn v míše snížení FA a zvýšení ADC v místě komprese oproti kontrolám. Snížení FA v úrovni komprese u pacientů s CSM ve srovnání s kontrolami prokázali i Budzik et al [37]. Hodnoty FA korelovaly s funkčním stavem pacienta, nikoli však s přítomností T2 hyperintenzity. U pacientů s T1 hypointenzitou byly přítomny velmi nízké hodnoty FA. Podobné snížení hodnot FA, ale také zvýšení hodnot ADC bylo nalezeno u pacientů s CSM v místě maximální komprese [38] a parametry DTI ukázaly vyšší diskriminační schopnost v odlišení od skupiny nemocných s ASCCC než standardní radiologické parametry – CSA a přítomnost intenzitních změn v míše (obr. 10).

DTI tak představuje slibný parametr pro identifikaci pacientů s kompresí míchy v riziku klinické manifestace a je citlivějším parametrem míšního postižení lépe korelujícím s klinickou symptomatikou. Může přispět k výběru vhodných pacientů pro chirurgickou dekompresi.

Epidemiologie ASCCC a CSM

Přibližně 14 % populace udává chronické bolesti v krční páteři trvající déle než šest měsíců, avšak prevalence asymptomatické či symptomatické míšní komprese (SCM) není přesně známa, resp. údaje v literatuře se značně liší [39].

Symptomatická CSM je nejčastější příčinou míšní dysfunkce u jedinců starších 55 let [3].

Lee et al [40] udávají přítomnost cervikální stenózy u 4,9 % zdravé populace a u 9 % populace ve věku > 70 let. Hayashi et al [41] nalezli asymptomatické zúžení cervikálního kanálu s anteroposteriorním průměrem < 13 mm u 10 % populace nad 60 let věku.

Teresi et al [9] nacházejí ve skupině jedinců vyšetřených pomocí MR pro jinou diagnózu známky protruze disku u 57 % jedinců a impingement míchy bez obliterace subarachnoidálního prostoru u 27 % jedinců nad 64 let. Míšní komprese s obliterací subarachnoidálního prostoru byla nalezena u 7 % souboru ve věku 45–82 let, nelze však zjistit, jaká byla prevalence tohoto typu komprese ve vyšší věkové skupině. Procentuální redukce CSA ve výši komprese byla v průměru 7 % a nikdy nepřesáhla 16 %.

Matsumoto et al [1] zjistili ve skupině 497 asymptomatických jedinců degeneraci krčních meziobratlových disků v rozsahu C2/3–C6/7 u 17 % disků u mužů a 12 % disků u žen ve věku do 30 let a u 86 % disků u mužů a 89 % disků u žen nad 60 let věku. Kompresi míchy protruzí disku nalezli u 7,6 % jedinců studovaného souboru, většinou ve věku nad 40 let, bez bližší definice metodiky hodnocení či věkového složení jedinců s míšní kompresí.

Naše předběžné výsledky [42] ukazují, že ve věku nad 40 let je prevalence cervikální míšní komprese vyšší, než bylo původně referováno a přesahují 50 %, i když jde o asymptomatické komprese lehkého stupně, charakteru impingementu nebo ploché komprese bez obliterace subarachnoidálního prostoru a bez klinické manifestace.

Predikce rozvoje CSM u ASCCC

Existuje řada prací popisující prognostické faktory ovlivňující výběr pacientů s CSM k chirurgické dekompresi i prognózu po operaci. Souhrnně míšní T2 hyperintenzita zhoršuje prognózu, a to více dobře definovaná a ohraničená hyperintenzita, víceúrovňová hyperintenzita a zvětšení rozsahu hyperintenzity po operaci, zatímco vymizení hyperintenzity po dekompresi je příznivým prognostickým faktorem [12]. Míšní T1 hypointenzita nebo její objevení po dekompresi výrazně zhoršuje prognózu pacientů s CSM. Enhancement gadolinia zhoršuje prognózu, kdežto zvýšené vychytávání fluorodeoxyglukózy je příznivým faktorem. Přetrvávající známky komprese po dekompresi a chybění zvětšení CSA jsou negativními prognostickými faktory [11].

Predikce rozvoje CSM u ASCCC však není dosud známa [43] a byla studována opakovaně naší skupinou [7,8,44] a její výsledky bude třeba potvrdit. Nicméně v r. 2013 publikovala v časopise Spine expertní skupina severoamerických spondylochirurgů za podpory AO Spine North America přehled problematiky asymptomatické netraumatické spondylogenní komprese krční míchy na terénu cervikální spinální stenózy a/nebo osifikace zadního longitudinálního ligamenta (OPLL) se zaměřením na otázku indikace operačního řešení, a výsledky naší skupiny jsou hodnoceny jako významné [45]. Autoři přehledu si položili tři základní otázky, které současně řešíme v našem článku:

- Jaká je u ASCCC prevalence a časový rámec rozvoje klinické manifestace (tj. manifestní myelopatie)?
- Jaké jsou u ASCCC klinické, zobrazovací a elektrofyziologické prediktory klinické manifestace?
- Jaké klinické a zobrazovací parametry ovlivňují rozhodnutí o léčbě ASCCC? (Odpověď na tuto otázku hledali pomocí dotazníku rozeslaného 19 750 členům AO Spine International, která reprezentuje mezinárodní komunitu profesionálů zabývajících se onemocněním páteře včetně spondylochirurgů).

Z původně identifikovaných 388 prací blíže analyzovali pět prací, které splňovaly vstupní kritéria, a výsledky byly z hlediska síly průkazu hodnoceny čtyřmi stupni (I–IV – I. stupeň představoval nejvyšší sílu průkazu) na základě doporučení AHRQ a pracovní skupiny Grade [46,47]. Tři japonské práce se věnovaly problematice OPLL a jediné dvě hodnocené práce zabývající se problematikou ASCCC u cervikální stenózy byly naše vlastní práce, jež byly z hlediska síly průkazu hodnoceny stupněm II [8], resp. III [10]. Jako odpověď na první dvě otázky autoři přejímají výsledky naší práce [8], která zjistila rozvoj symptomatické CSM do jednoho roku u 8 % nemocných s ASCCC a průměrná doba, do níž dojde u 25 % jedinců s ASCCC k rozvoji CMS, je 48,4 měsíců. Významnými prediktory časného rozvoje symptomatické CSM (do jednoho roku) byla klinicky manifestní radikulopatie, abnormální somatosenzitivní a motorické evokované potenciály a chybění míšní MR hyperintenzity.

Zajímavé výsledky přinesla i přes nízkou návratnost (3,9 %, avšak 774 respondentů) dotazníková akce. V případě chybění manifestní radikulopatie se mírně nadpoloviční většina (53,9 %) respondentů domnívala, že ASCCC zůstane stabilní, zatímco v případě klinicky manifestní radikulopatie předpokládala stabilní vývoj bez rozvoje manifestní myelopatie významně nižší část respondentů (27,3 %). Na základě hodnocení modelových případů by operační řešení indikovalo u jedince s ASCCC, míšní hyperintenzitou v MR obraze a bez manifestní radikulopatie 67,8 % respondentů, u obdobného případu s manifestní radikulopatií již 85,9 % respondentů a u jedince se známkami míšní komprese v MR obraze bez hyperintenzity a s klinickými známkami lehké myelopatie pouze 65,1 % respondentů. Na základě zhodnocení dostupných vědeckých důkazů a převažujícího klinického názoru autoři doporučují, že jedinci se známkami ASCCC v důsledku cervikální spinální stenózy, kteří vykazují známky manifestní radikulopatie a abnormální vedení somatosenzitivní a motorickou dráhou prokázanou pomocí SEP a MEP, mají vyšší riziko rozvoje manifestní CSM a je nutné u nich zvážit operační řešení. Sílu průkazu tohoto tvrzení hodnotí jako středně silnou a sílu doporučení jako silnou [45].

Nedávno publikované výsledky studií s použitím DTI [36,38,48] ukazují, že parametry DTI v MR obraze korelují s klinickými známkami manifestní myelopatie těsněji než tradiční zobrazovací a elektrofyziologické prediktory rozvoje CSM a bude nezbytné doplnit posouzení rizika rozvoje manifestní myelopatie u ASCCC za použití těchto parametrů.

Predikce rozvoje CSM u ASCCC po lehkém traumatu

Řada autorů popisuje vznik cervikální myelopatie akutně po lehkém úrazu krční páteře [49–51]. Aebli et al prokázali, že u pacientů s akutně vzniklou lézí krční páteře po traumatu ve srovnání s těmi, kteří prodělali úraz bez následků, je významně nižší hodnota řady parametrů odrážejících rozměry cervikálního kanálu, nejvyšší predikční hodnotu měla CD_{disc} < 8 mm [11] a TPR < 0,7 [26]. Tato asociace je považována některými autory za důkaz, že pacienti s cervikální stenózou a zejm. ASCCC mají vyšší riziko vzniku akutní myelopatie po často lehkém poranění páteře [52,53], což vedlo u řady spondylochirurgů k provádění preventivní dekompresní operace s cílem zabránit rozvoji myelopatie [54,55]. Tato otázka se stala jedním z kontroverzních spondylochirurgických témat v posledních letech [10,43]. Přehledná práce z roku 2009 našla dvě práce, které prokazují toto zvýšené riziko, avšak šlo o práce retrospektivní [51,56], a proto autoři uzaví-

rají, že neexistuje dostatek důkazů k provádění dekompresní operace u pacientů s ASCCC [43].

V naší práci z roku 2011 [10] jsme retrospektivně analyzovali epizody traumatu krční míchy u naší kohorty 199 jedinců s ASCCC jak během téměř čtyřletého prospektivního sledování (medián 44 měsíců), tak retrográdně před sledováním analýzou dokumentace a pomocí dotazníku. Identifikovali jsme 14 relevantních traumatických epizod během sledování a nenašli jsme korelaci s rozvojem manifestní CSM, kterou jsme zaznamenali u 45 jedinců (RR: 0,95; p > 0,05). Validitu této studie snižuje její retrospektivní charakter, pro nějž ji Wilson et al hodnotí stupněm III dle AHRQ a Grade [46,47], avšak současně ji identifikovali jako jedinou relevantní studii řešící tento problém [45]. Výsledky mohly být ovlivněny faktem, že kohorta našich pacientů s ASCCC byla poučena o nutnosti minimalizovat rizikové aktivity, u kterých hrozilo riziko poranění krční páteře.

Závěr

Degenerativní onemocnění krční páteře vede zejm. ve vyšším věku k časté cervikální stenóze a následné kompresi nervových struktur – míšních kořenů a míchy. Komprese může zůstat asymptomatická, ale vést i k závažnému neurologickému deficitu. Vzhledem k vysoké prevalenci ASCCC ve vyšším věku, variabilnímu klinickému průběhu cervikální spondylózy a nepříliš uspokojivému efektu dekompresivních operací prováděných u nemocných se signifikantním neurologickým deficitem je zásadní potřeba najít biomarkery časných stadií zvláště míšního postižení a zvýšeného rizika přechodu do klinicky významného symptomatického stadia. U těchto rizikových jedinců pak bude nutné ověřit provádění dekompresí v časném presymptomatickém stadiu stenózujícího degenerativního onemocnění krční páteře.

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Cervikální vertigo – fikce či realita?

Cervical vertigo – fiction or reality?

Souhrn

Cervikální vertigo je již řadu let značně kontroverzní jednotka, která je však v praxi široce akceptována odbornou veřejností. Podáváme souhrn o současných poznatcích týkající se možné etiologie, diagnostiky a léčby této nozologické jednotky. Cervikální vertigo je značně přediagnostikované, stále neexistuje žádný laboratorní nebo klinický test specifický pro tuto diagnózu a žádná z možných teorií nevysvětluje plně etiologii možných potíží. Léčba je obtížná a spíše empirická.

Abstract

Cervical vertigo has long been a controversial entity, which is generally accepted in practice by the medical community. We present the summary of contemporary knowledge of the scientific biography of cervical vertigo, possible etiology, diagnosis and treatment. This disorder is overdiagnosed and there is still no laboratory or clinical test to confirm the diagnosis, while none of the possible theories provide fully convincing evidence of a cervical mechanism. Appropriate management is difficult and mostly empirical.

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Klíčová slova
vertigo – cervikální vertigo – vertebrobazilární insuficience – cervikookulární reflex – vestibulookulární reflex – závratě

Key words
vertigo – cervical vertigo – vertebrobasilar insufficiency – cervicoocular reflex – vestibuloocular reflex – dizziness

Úvod

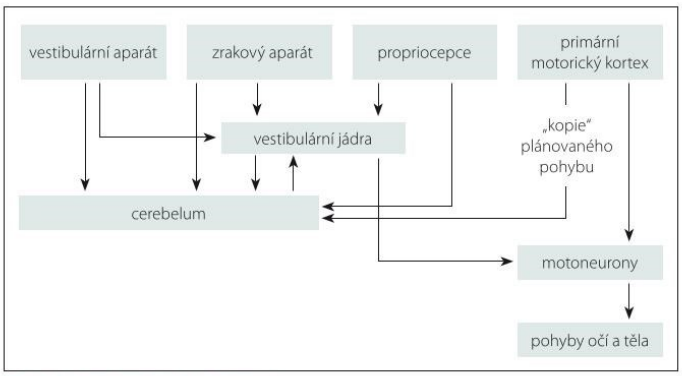
Pocity vertiga a nevolnosti patří mezi 20 nejčastějších příčin návštěv u lékaře v celosvětovém měřítku [1]. Celková prevalence v populaci bývá odhadována na 5–10 %, u pacientů nad 50 let na více než 50 % a bývá příčinou až 25 % pádů u pacientů starších 65 let [1]. Zprávy z pracovišť urgentního příjmu v USA z let 1995–2004 uvádějí, že vertigo a pocity nevolnosti bývají cca v 2,5 % příčinami akutního vyšetření [2]. Cervikální vertigo je stále považováno za značně kontroverzní a problematickou entitu, která bývá velmi často přediagnostikována, a neurolog musí nezřídka čelit situaci, kdy je nucen odmítnout či potvrdit tuto diagnózu stanovenou jiným lékařem. U většiny pacientů, kteří jsou takto primárně diagnostikováni, se totiž po podrobnějším prošetření nalezne jiná vysvětlující příčina (až v 90 %) [3].

Etiologie vertiga

Pocity nejistoty v prostoru či závratí mají často multifaktoriální a komplikovanou příčinu. V praxi to znamená, že poměrně velké procento závrativých stavů zůstává etiologicky neobjasněno (zejména při absenci detailního vyšetření). Pro udržení správného pocitu tělesné rovnováhy je nezbytná:

1. správná prostorová orientace (v klidu i při pohybu);
2. neporušená fixace pohledu při pohybech hlavy i celého těla;
3. neporušená zpětná vazba mezi svalovým tonem a CNS k udržení správné tělesné postury.

Tyto systémy jsou mezi sebou propojeny velmi složitým způsobem a pocity závratí znamenají dysfunkci ne pouze jednoho, ale celé řady kontrolních mechanizmů současně. Například senzorická dysfunkce u starších lidí – potíže se zrakem (např. katarakta), se sluchem (presbyakuze), ischemické kme-



Obr. 1. Schéma senzorické integrace.
Fig. 1. Scheme of sensory integration.

nové léze či zhoršená propriocepce (např. polyneuropatie) – se mohou projevovat pocity vertiga či celkové nejistoty. Závrativost též vyvolává silný emoční doprovod – na jedné straně nepříjemné (domnělé či skutečné) pocity nekontrolovaného pádu, na straně druhé pozitivní emoce z pocitů rotací (např. při tanci či turistických a pouťových atrakcích). Vertigo bývá často spojeno s nauzeou a zvracením, což svědčí o těsném vztahu k vegetativním centrům. Pocity vertiga mohou být vyvolány i u jinak zcela zdravého jedince (např. výšková závrať, při rychlé jízdě automobilem apod.). Vertigo bývá často i projevem různých interních onemocnění (arteriální hypotenze a hypertenze, srdeční arytmie, hypoglykemie) nebo psychiatrických onemocnění. Nezřídka se jedná o účinek mnoha užívaných léků [4].

Krční vertigo

Krční páteř jako možný zdroj vertiga byla dlouho v odborné literatuře zcela ignorována. První reference se objevují až v roce 1955 [5]. Již tato pilotní práce s sebou však nese výrazné kontroverze, které jakoby předurčily další osud této nozologické jednotky. Ryan et al totiž popsali kazuistiky pěti pacientů, z nich však čtyři měli velmi pravděpodobně příznaky benigního paroxyzmálního polohového vertiga (BPPV) spolu s radikulární krční symptomatikou (jak bylo zjištěno později), a nazvali je cervikálním vertigem [5]. Někteří autoři tuto jednotku od počátku zcela popírají [3], jiní její existenci hájí [6].

Krční oblast obsahuje několik struktur, které se mohou teoreticky spolupodílet na mechanizmu řízení rovnováhy – krční aferentace ze svalových vřetének, čistě cévní struktury (karotické a vertebrální arterie) a svalové struktury, které se podílejí na udržení správné postury jedince, dále pak karotická tělíska, která se však účastní selektivně v procesu regulace kardiovaskulárního systému.

Pohyby krční páteří jsou za fyziologických podmínek asociovány i s pohybem hlavy, takže pocity vertiga mohou být teoreticky způsobeny porušením vestibulárního, zrakového, cévního či krčního proprioceptivního mechanizmu. Termín cervikální vertigo bývá většinou rezervován pro případy se suspektním porušením proprioceptivní složky [7], někteří však pojem cervikálního vertiga asociují spíše s lézemi nervového systému ve vertebrobazilárním (VB) povodí, což se již jeví poněkud diskutabilní – viz níže. Vestibulární aparát vnitřního ucha detekuje jakýkoli pohyb hlavy v prostoru. Vstupy do vestibulárního systému zahrnují cervikální proprioceptivní aferentaci, zrakové vjemy a informace o korekci plánovaných pohybů z cerebela (do mozečku vstupují tyto motorické povely „jako kopie plánovaných pohybů", které jsou vysílány z primární motorické kůry) [8]. Všechny tyto vstupy jsou vyhodnocovány vestibulárním nukleárním komplexem, který vydává příkazy k pohybu očí a těla. Tento systém je velmi přesný a je kontrolován a řízen mozečkem – obr. 1.

Již prvním problémem je samotná definice cervikálního vertiga. Yahia et al je popisují takto: chronická krční bolest spojená s vertigem po rotaci krční páteře (avšak bez nystagmu) s nálezem krční osteoartritidy a degenerativních změn meziobratlových disků [9]. Furman et al je charakterizují jako neurčitý pocit změny rovnováhy a prostorové orientace, který vzniká abnormální aktivitou krčních aferentních drah [10]. Wristley et al uvádí, že diagnóza cervikálního vertiga závisí na korelujících symptomech nerovnováhy a závratí ve spojitosti s bolestmi krční páteře a při vyloučení jiné vestibulární patologie [11]. Lewit se zmiňuje o tom, že cervikogenní závrať je polymorfní skupina krátce trvajících závratí vyvolaných určitým postavením (pohybem) hlavy proti trupu, při kterém nemocný udává pocit náhlého tahu ke straně, dopředu nebo dozadu s představou, že se musí bránit. Nauzea a zvracení zpravidla chybí [12]. Vidíme tedy, že jednoznačná definice cervikálního vertiga neexistuje, autoři si často pomáhají různými popisnými syndromologickými pojmy a vylučovacími formulacemi, které působí poněkud kostrbatě a komplikovaně.

Teoretické předpoklady možných příčin cervikálního vertiga

V průběhu posledních 60 let se objevila celá řada studií a různých teorií, které měly vysvětlovat možnou příčinu vzniku cervikálního vertiga. U žádné z nich však neexistuje spolehlivý důkaz o její platnosti. Podáváme rozbor těch nejvíce užívaných a citovaných.

Krční aferentace

Cervikální propriocepce je závislá zejména na krátkých hlubokých krčních svalech, které jsou bohatě zásobeny svalovými vřeténky a které hrají důležitou roli v řízení správné tělesné postury [13]. Dle recentně publikovaných údajů se uvažuje i o roli Ruffiniho tělísek, která fungují též jako mechanoreceptory a jejichž zvýšený počet byl nalezen v krčních meziobratlových discích u pacientů s krční spondylózou a vertigem [14]. Krční proprioceptory zprostředkovávají dva typy reflexů – posturální krční reflexy a cervikookulární reflex (COR). Tonické krční reflexy nejvíce studoval Magnus [15]. U lidí jsou výbavné pouze u novorozenců (např. ipsilaterální flexe a kontralaterální extenze končetin spojená s rotací hlavy – tzv. „pozice šermíře"), v průběhu zrání nervového systému však vymizí. COR interferuje s vestibulookulárním reflexem (VOR), jenž se též podílí na stabilizaci hlavy v prostoru [16].

První demonstroval cervikookulární reflex Bárány u králíků [17]. De Jong et al prokázali, že blokováním aferentních cervikálních drah (bez současné vestibulární stimulace) lze vyvolat nystagmus u celé řady zvířat [18]. U lidí je však tento reflex klinicky výbavný pouze u novorozenců [19] či u pacientů s těžkým postižením CNS, event. u pacientů s výrazně porušeným vestibulárním aparátem [20]. Cervikookulární reflex totiž výrazně interfe-

ruje s reflexem vestibulookulárním, který jej u zdravého jedince prakticky zcela inhibuje. Abychom vyloučili vliv vestibulárního a zrakového aparátu, musel by být pacient vyšetřen s hlavou fixovanou, v zatemněné místnosti. Byla tak provedena celá řada studií s použitím elektronystagmografie se zaměřením na porovnání výbavnosti COR a VOR. Při těchto experimentálních modelech skutečně došlo u vyšetřovaných jedinců při rotaci trupu k subjektivním pocitům rotace hlavy [21] a i u zdravých (tj. zcela asymptomatických) jedinců se podařilo vybavit COR s nystagmem (reflex byl však velmi potlačen a nystagmus měl pomalou frekvenci) [22]. Pokud však byla hlava fixována pevně či za normálních zrakových podmínek, rotace trupu žádné pocity pohybů hlavy či vertiga nevyvolaly [23]. Dále se zjistilo, že COR je zvýšen u pacientů s nespecifickými bolestmi krční páteře [24], stejně tak u pacientů s omezenými krčními pohyby (blokáda apod.) [25] a u starších jedinců [26] – též ve specifických experimentálních podmínkách odlišných od běžné klinické praxe. Je prokázáno, že COR a VOR fungují jako „spojité nádoby", že existuje korelace mezi hodnotami VOR a COR, tj. že při útlumu VOR dochází ke zvýšení COR, který tak přebírá jeho funkci [27]. Hluboká stimulace krčních svalů vibrací (tj. aktivace svalových vřetének) způsobuje pocity náklonu hlavy a iluzi pohybujícího se obrazu, přičemž se zjistilo, že ta je zapříčiněna minutovou pomalou fází očních pohybů [23]. De Jong et al dokumentovali, že lokální anestezie hlubokých krčních svalů u člověka vyvolá zvýšený ipsilaterální a snížený kontralaterální tonus extenzorů, což vede k poruchám chůze s tendencí k pádu k umrtvené straně [18]. Nicméně u pacientů, u kterých byla (za fyziologických podmínek) provedena krční blokáda anestetikem v etáži C2, nebyl prokázán žádný nález na elektronystagmografii, statické posturografii, nebyly zaznamenány ani subjektivní pocity pohybu zrakového pole [28]. Brand prokázal, že lze za specifických podmínek (v zatemnělé místnosti) vyvolat nystagmus dokonce i pasivní rotací paže [29], Hinoki et al jej vybavili i prokainizací v lumbální oblasti [30]. Některé studie předpokládají, že za udržení svalového tonu a postury jsou odpovědné zejména proprioceptivní informace z horních tří dorzálních kořenů (C1–C3) [18]. Hülse zjistil, že 50 % krčních proprioreceptorů se skutečně nachází v kloubních pouzdrech C1–C3 [31]. Klinicky však bývají nervové kořeny postiženy v drtivé většině ze segmentů kaudálnějších (C5/6, C6/7), kraniální segmenty bývají postiženy vzácně, což je opět v kontrastu s výše uvedenou hypotézou [32]

Co tedy z výše uvedeného vyplývá? Krční aferentace se zcela prokazatelně podílí na stabilizaci polohy hlavy a trupu, avšak u zdravého jedince (resp. u člověka s nepostiženým periferním vestibulárním aparátem či bez difuzního těžkého postižení CNS) je klinicky výrazně utlumena a v roli „stabilizátora polohy hlavy" dominuje vestibulární ústrojí. Vliv krční aferentace též nelze „separovat" od vlivu vestibulárního či zrakového aparátu a termín cervikální vertigo se nám proto nejeví jako ideální. Vybavení nystagmu ve specifických podmínkách (zatemnělá místnost s fixací hlavy) je fyziologické a jistě není průkazem existence cervikálního vertiga. Propriocepce však nepochází pouze z oblasti krční, ale samozřejmě i z hrudní, bederní a potažmo ze všech končetin. Pokud tedy uznáváme tuto teorii, nebylo by logičtější užívat termín „vertigo proprioceptivní"? Pak se ovšem nabízí otázka, jestli je vertigo proprioceptivní synonymem pro vertigo cervikální. Dle našeho názoru nikoli.

Whiplash injury

Často se v literatuře uvádí, že krční vertigo vzniká následkem úrazu krční páteře: tzv. whiplash injury – jedná se o poranění vzniklé při prudkém a nečekaném pohybu hlavy, zejména vlivem působení velké síly při vnějším nárazu [33]. Nejčastějšími symptomy u těchto pacientů však nejsou závratě, ale bolesti krční páteře, bolesti hlavy, následované zrakovou symptomatikou (rozmazaný vizus), kognitivními a emočními potížemi [34]. Pouze u poloviny pacientů jsou přítomny závratě a poruchy rovnováhy [35]. Nejčastěji zvažovaným mechanizmem, který má vysvětlovat etiologii tohoto posttraumatického vertiga, je porucha koordinace mezi vestibulárním, zrakovým a proprioceptivním vstupem do vestibulárních jader, tedy v podstatě tytéž mechanizmy, které se zvažují v etiologii cervikálního vertiga – viz výše [36]. Významnou roli zde však zcela jistě hrají i psychosociální a forenzní důvody [37] a finanční kompenzace [38]. V případech krčního traumatu je však obtížné odlišit současné postižení vestibulárního labyrintu nebo vestibulárních jader a drah od postižení krční páteře, protože prakticky vždy s traumatem páteře dochází i k traumatu hlavy a možnému postižení rovnovážných center (tj. posttraumatické BPPV, postižení utriculu a sacculu nebo vznik perilymfatické fistuly) [39,40].

Někteří autoři vysvětlují etiologii vertiga u poranění typu whiplash injury VB insuficiencí či posttraumatickou lézí v oblasti mozkového kmene. Endo et al ve své studii (20 pacientů po whiplash injury, 13 zdravých kontrol) prokázali abnormální nález na MRA vertebrálních tepen (okluze, stenóza či redukce průtoku) v 77 % případů v kontrolní (tj. „zdravé") skupině a v 60 % případů ve skupině pacientů. Zjistili však větší mezistranovou (pravo/levou) diferenci při měření krevního průtoku ve skupině pacientů (6,1 ± 3,0 cm/s) v porovnání se skupinou kontrolní (3,5 ± 2,5 cm/s). Z těchto dat vyvozují postulát, že pacienti s perzistujícím vertigem či nevolností po whiplash injury mají častější příznaky VB insuficience [41].

Co se týče studií funkce mozku, tak ty prokázaly (na funkčním MR a jednofotonové emisní výpočetní tomografii [SPECT]) reflexní hypoperfuzi a hypometabolizmus u pacientů s whiplash injury v různých oblastech (frontální, temporální lalok, inzula, bazální ganglia, talamus) [34,42].

S další možnou etiologií vzniku vertiga přichází japonští autoři, kteří zjistili, že až 80 % pacientů (po poranění typu whiplash) má známky cerebrospinální hypovolémie na radioizotopové cisternografii. Tito pacienti pak byli vyšetřeni elektronystagmograficky a posturograficky s abnormálním nálezem a byla u nich provedena MR, která prokázala pokles mozečkových tonzil a zploštění Varolova mostu, což jsou charakteristické známky cerebrospinální hypovolémie nazývané „brain sagging" (čili mozkový pokles či průvěs). Z toho vyvozují teorii, že vertigo je způsobeno tímto mechanizmem, čili se jedná vlastně o syndrom nitrolební hypotenze [43].

Dalším možným etiologickým faktorem může být i vestibulární migréna, která prokazatelně může být též spuštěna poraněním krční páteře [44].

Z výše uvedeného tedy vyplývá, že whiplash injury vyvolává difuzní postižení v oblasti mozku a krční míchy. Jedná se spíše o sdruženou symptomatologii než o izolované postižení krční páteře s projevy cervikálního vertiga.

Vaskulární teorie (komprese vertebrálních tepen)

Teorie vaskulární komprese vychází z hemodynamických studií, které byly prováděny v 60. letech na kadáverech. Toole et al zjistili, že rotace hlavy je spojena s kompresí vertebrální tepny (AV) na protilehlé straně, a postulovali teorii, že tento mechanizmus může být příčinou cervikálního vertiga [45]. Pokud by tato teorie platila, pak by musela být komprese

AV spojena i s další symptomatikou ze zadní cirkulace (diplopie, poruchy zorného pole, dropp attacks, vomitus atd.), a nevysvětluje též příčinu bolestí krční páteře. Epizody symptomatiky z VB povodí bychom též museli definovat spíše jako tranzitorní ischemické ataky (TIA) v zadní cirkulaci (s riziky, etiologií a léčbou s nimi spojenými) a nikoliv jako cervikální vertigo. Navíc novější studie s digitální subtrakční angiografií (DSA) potvrdily, že klinicky významná arteriální komprese (při pouhé rotaci hlavy) není v podmínkách *in vivo* prakticky vůbec možná [46]. Nicméně výjimku z výše uvedeného přehledu představuje tzv. Bow Hunterův syndrom, což je ovšem velmi vzácná příčina přechodné ischemie v zadní mozkové cirkulaci vzniklá kompresí AV. V literatuře bylo prozatím popsáno cca 200 pacientů s tímto syndromem [47]. Symptomy zahrnují paroxyzmální vertigo, nystagmus, tinnitus, synkopy, rozostření vidění, nauzeu a zvracení [47]. Vzniká při kompresi dominantní AV kostními strukturami při rotaci či náklonu hlavy. Etiologicky se jedná o velké osteofyty nebo atlantookcipitální hypermobilitu. Patologie je často spojena s hypoplazií či stenózou nedominantní AV. Symptomy odezní po návratu hlavy do neutrální polohy [48]. Syndrom musí být potvrzen radiologicky, metodou volby je dynamická DSA, která prokáže uskřinutí AV. Léčba je chirurgická [49].

Je třeba navíc dodat, že Choi et al ve své práci následně potvrdili, že ischemie a pocity vertiga ve VB povodí jsou způsobeny ischemií v oblasti vnitřního ucha, nikoliv v oblasti kmene [50].

Neurovaskulární hypotéza – syndrom zadního krčního sympatiku (Barré-Lieou)

Tuto teorii poprvé publikovali v roce 1926 Jean-Alexander Barré a Young-Choen Lieou [51]. Předpokládali, že plexus sympaticus, který obklopuje vertebrální tepny, může být mechanicky drážděn degenerativními změnami krční páteře, a iritace sympatiku tak způsobí reflexní vazokontrikci ve VB povodí. Experimentální data však prokázala, že sympatická denervace nezpůsobuje vazodilataci ani u zvířat, stejně jako iritace sympatiku nezpůsobuje vazokonstrikci [52]. Syndrom Barré-Lieou je tedy dnes jednoznačně považován za obsolentní jednotku, přesto se s ním občasně i nadále v neurologické literatuře setkáme [53].

Teorie komprese krční míchy

Někteří autoři udávají příčinnou souvislost cervikálního vertiga s kompresí ascendentních a descendentních míšních drah, které jsou ve spojení s vestibulárními jádry nebo vestibulospinálními projekcemi. Podle jejich názoru je diskogenní komprese míchy dokonce nejčastější příčinou cervikálního vertiga [54]. Jako průkaz této hypotézy bývají nezřídka uváděny dobré efekty různých invazivních výkonů na krční páteři, jako např. pozitivní efekt transkutánní laserové dekomprese disku [55] či zlepšení subjektivních potíží po přední krční diskektomii a fúzi obratlů [56]. Mechanizmus účinku a etiopatogeneze tohoto subjektivního zlepšení však i nadále zůstává na úrovni výše diskutovaných teorií – tj. že např. chirurgická dekomprese kořene nebo míchy umožní lepší přenos proprioceptivních signálů do CNS a tím zlepší i řízení postury [56], či zcela opačný postulát – tj., že po odstranění aberantních mechanoreceptorů (po náhradě postiženého intervertebrálního disku) dojde k úpravě abnormální propriocepce, která jinak způsobuje „mismatch" ve vestibulárních jádrech CNS [14]. Musíme si však uvědomit, že efekt chirurgického či jakéhokoliv jiného invazivního zákroku (zejména u pacientů s nespecifickými potížemi) je obecně velmi často výrazný [57]. Nenašli jsme v literatuře studii, která by se zabývala tzv. shame operacemi v oblasti krční páteře, ale zajímavé jsou např. práce, které byly provedeny u pacientů s osteoporotickou frakturou obratlů, kdy v podstatě placebové zákroky (povrchová kožní anestezie) měly srovnatelný efekt v úlevě bolesti jako reálně provedená vertebroplastika [58]. Musíme též vzít do úvahy prozatím nevysvětlitelnou diskrepanci mezi pacienty s těžkou blokádou a bolestí krční páteře (dokonce i s myelopatií) bez vertiga a pacienty s prakticky imobilizujícím vertigem a pouze mírnou bolestí páteře [7]. Dále je třeba si uvědomit, že spojení páteře s vestibulárním systémem je bilaterální – tj., že chronická primárně vestibulární léze vede k asymetrickému napětí šíjových svalů, a tím k sekundárním potížím s krční páteří.

Teorie vestibulární migrény

V roce 2013 Yacovino a Hain „oživili" hypotézu migrénou navozeného cervikálního vertiga. Tímto způsobem se snaží vysvětlovat diskrepanci mezi pacienty, kteří mají bolesti krční páteře s vertigem, a mezi těmi, kteří mají pouze bolesti bez vertiga, a domnívají se, že právě migréna by měla být pojítkem mezi krční bolestí a krčním vertigem [59]. Již předtím byly publikovány četné práce o této problematice [60,61]. U třetiny pacientů s migrénou bývá skutečně přítomno vertigo, na druhou stranu bolesti za krkem až ztuhlost jsou typickými znaky migrény [62]. Předpokládaným mechanizmem vzniku cervikálního vertiga je konektivita mezi vestibulárními jádry a jádrem n. trigeminus. Předpokládá se, že stimulace vestibulárních jader vede k aktivaci nucleus spinalis n. trigemini, která sekundárně spouští ataku migrény s bolestí krční páteře a vertigem [59]. Dominují pocity rotační závrati, jejichž intenzita se však dá modifikovat změnou polohy hlavy, mohou být přítomny i jiné neurologické příznaky, i když ty jsou méně časté (dysartrie, diplopie, brnění či hypestézie rukou a obličeje). Co se týče léčby vestibulární migrény, data jsou relativně chudá [63]. Celá tato teorie však také potřebuje ještě daleko širší a podrobnější výzkum.

Diagnostika

Pokud jde o cervikální vertigo, tak se v podstatě vždy jedná jen o diagnostiku *per exclusionem*, kdy vylučujeme všechny možné (zejména vestibulární, oční či periferně neurogenní) příčiny závratových stavů. Neexistuje žádný specifický test pro diagnostiku cervikálního vertiga. Pokud pacient nemá bolesti krční páteře, ale pouze vertigo, tak je tato diagnóza již od počátku vyloučena [7]. Samozřejmostí je podrobné základní neurologické vyšetření, při kterém musíme provést i Dix-Hallpikův test k vyloučení BPPV, které se často mylně považuje za cervikální vertigo [7]. RTG vyšetření krční páteře je bez významu. Zobrazovací vyšetření jako je CT či MR slouží k zobrazení anatomických poměrů (např. malformace), expanzivních lézí (např. tumory mostomozečkového koutu), traumatických změn (kontuzní ložiska mozku a míchy, diskopatie), degenerativní změny (spinální cervikální stenóza) [59]. K diferenciaci od rotačního vertebrálního arteriálního syndromu (Bow Hunterův syndrom) je vhodná MRA nebo CTA, v nejasných případech i DSA s rotací hlavy k postižené straně [59].

Někteří autoři se snažili monitorovat vliv cervikálního podílu na okohybných funkcích pomocí elektrookulografie. Jak však bylo uvedeno výše, vybavení COR je ve specifických podmínkách možné i u zcela zdravých jedinců, nemůžeme jej pokládat za průkaz cervikálního vertiga. Navíc se tento test jeví málo senzitivní i málo specifický [59].

Při vyšetření plynulých sledovacích očních pohybů (smooth pursuit eye movement test) zůstává hlava pacienta ve stejné poloze, pouze sleduje očima pohyby ruky vyšetřujícího. Test je však komplexem

Tab. 1. Diferenciální diagnostika cervikálního vertiga.

Benigní paroxyzmální polohové vertigo	objevuje se pouze při změnách polohy hlavy, většinou trvá několik vteřin; vertigo a nystagmus vybavíme při polohových manévrech (Dix-Hallpike)
Neuronitis vestibularis	jednotlivé ataky vertiga, většinou s těžkým počátečním průběhem, které trvají několik dnů až týdnů
Ménierova choroba	opakující se epizody vertiga, které trvají několik hodin a jsou doprovázeny poruchou sluchu (event. tinnitem); pozitivní nález při audiologickém vyšetření
Bilaterální vestibulopatie	dominují spíše poruchy rovnováhy než vertigo; neurootologické vyšetření odhalí oboustrannou periferní vestibulární afekci
Arnold-Chiariho malformace (typ 1)	může být provázena bolestí hlavy, pocity ztuhnutí krku, nerovnováhy a pozičního vertiga
Multisenzorické vertigo (presbyvertigo)	porucha rovnováhy min. dvou následujících faktorů – periferní neuropatie, poruchy zraku, vestibulární poruchy
Centrální vertigo	pozitivní nález při objektivním neurologickém vyšetření (centrální nystagmus, ložiskové příznaky)
Interní příčiny	arteriální hypertenze/hypotenze, intoxikace, nežádoucí účinky léků, srdeční arytmie, hypoglykemie
Psychogenní příčiny	nutná psychologická, event. psychiatrická intervence
Disekce arteria vertebralis	bývá spojena s úrazem krční páteře, bolesti hlavy/krční páteře, parestezie obličeje, mozečkové příznaky
Cerebelární či spinální ataxie	hemoragické či ischemické cerebelární ikty, mozečkové tumory, degenerativní postižení, hypovitaminóza B12, karenční syndromy

mnoha vjemů, závislý i na kognici, věku, sedaci pacienta a slouží především jako jedno ze zásadních vyšetření k posouzení funkce cerebela [59].

Existuje dále celá baterie různých testů k vyšetření vestibulárního aparátu (elektronystagmografie, testy na rotačním křesle, posturografie atd.), jejichž popis však přesahuje rozsah tohoto textu, jsou však detailně popsány v jiných monografiích [4].

Diferenciální diagnostika je uvedena v tab. 1.

Léčba

Terapie cervikálního vertiga je samozřejmě komplikovaná, protože zdroj obtíží v drtivé většině případů nelze identifikovat.

Někteří autoři navrhují manuální léčbu jako metodu volby [64]. Pokud však byly provedeny systematické analýzy literatury zabývající se manuální terapií pacientů s cervikálním vertigem, tak se zjistilo, že naprostá většina provedených prací byla metodologicky velmi nedokonalá (např. chyběly kontrolní skupiny zdravých jedinců, nekvalitní randomizace, chybně provedené statistické zpracování, chybělo zaslepení atd.) [65]. Na základě výše uvedených poznatků dospěli Reid et al k závěru, že existují jen omezené důkazy (úroveň průkazu 3) pro efekt manipulační léčby v terapii cervikálního vertiga [66]. Neexistují též žádná spolehlivá data o intenzitě, četnosti či jiné specifikace manuální léčby v této indikaci [65].

Další možností je užití „vestibulární rehabilitace", která zahrnuje mentální cvičení, fyzická cvičení s cílem obnovení správného vnímání pozice kloubů, zlepšení koordinace pohybů, oční trénink – vše s cílem posílení VOR [67]. Stejně jako u manuální léčby však v této indikaci spolehlivý důkaz efektu chybí, vestibulární rehabilitace je prokazatelně účinná jen u periferních vestibulárních lézí [68].

Co se týče léčby poranění typu whiplash injury, tak nejsilnější důkazy jsou v případě léčby akutního postižení. Možná poněkud překvapivě se častěji doporučují fyzioterapie a lehká mobilizační cvičení než úplná imobilizace krční páteře a absolutní klidový režim [68]. Trakce není účinná [69]. Neexistuje žádná studie, která by prokázala efekt klidového režimu a imobilizace měkkým krčním límcem oproti jiné léčbě [69]. Dokonce jsou i důkazy, že pokud pacientovi řekneme, aby se „choval jako normálně", může být výsledný stav stejně efektivní jako při aktivní léčbě [70]. U pacientů s chronickými potížemi je léčba většinou multioborová a velmi komplikovaná. Může být ovlivněna (a často prodloužena) mnoha sociálními, ekonomickými i psychologickými faktory. Současná literatura předpokládá, že časná mobilizace a brzký návrat k běžné aktivitě mají nejlepší šanci na úspěch. Avšak absence jasných diagnostických a léčebných možností svědčí pro to, že další široký výzkum na tomto poli je nadále potřebný [71].

Závěr

Cervikální vertigo zůstává i nadále kontroverzní klinickou jednotkou, jejíž existence není jednoznačně prokázána. Neexistuje žádná přesná ani jednotná definice cervikálního vertiga.

Nejsou k dispozici žádná relevantní epidemiologická data o této jednotce (či data z populačních registrů). Neexistuje žádný test specifický pro cervikální vertigo. Není jasný patofyziologický podklad vzniku cervikálního vertiga. Cervikální vertigo je silně přediagnostikované (při správné diagnostice se odhalí jiná příčina až u 90 % případů). Léčba je komplikovaná, často víceoborová a empirická, nemáme k dispozici kvalitní randomizované studie, které by prokázaly efekt nejčastěji poskytované terapie. Při absenci bolestí krční páteře je tato diagnóza vyloučena.

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Současný management pacientů s degenerativní kompresí krční míchy

Current management of patients with degenerative cervical spine compression

Souhrn

Degenerativní cervikální myelopatie (DCM) je nejzávažnější komplikací spinální cervikální stenózy (CS) a degenerativní krční míšní komprese. Mícha je však značně rezistentní zejména k pozvolnému, chronickému útlaku. Asymptomatická degenerativní komprese krční míchy (asymptomatic degenerative cervical cord compression; ADCCC), která je charakterizována přítomností prokázané cervikální míšní komprese pomocí zobrazovacích metod, avšak bez klinických známek myelopatie, je tak velmi častá. V případě prokázané těžké či středně těžké formy DCM je jednoznačně preferováno operační řešení. U lehčích forem DCM a u ADCCC však neexistuje jasný, vědecky podložený konsenzus managementu a léčebného algoritmu. V současnosti byla identifikována řada prediktorů vyššího rizika progrese ADCCC do stadia klinicky manifestní DCM a část spondylochirurgických pracovišť považuje časnou chirurgickou dekompresi u těchto rizikových pacientů s ADCCC za indikovanou. K lepšímu pochopení významu těchto prediktorů jsou však potřeba další studie. Navíc existují určité metodologické a etické aspekty, které brání provedení multicentrické randomizované studie u pacientů s ADCCC a lehkou formou DCM.

Abstract

Degenerative cervical myelopathy (DCM) is the most serious consequence of cervical spinal stenosis (CS) and degenerative cervical spinal cord compression. The spinal cord, however, is quite resistant especially to gradual, chronic mechanical compression. Asymptomatic degenerative cervical cord compression (ADCCC), which is characterized by cervical cord compression in medical imaging techniques, but without clinical signs of myelopathy, is therefore very common. In patients with moderate and severe DCM, surgical intervention is strongly recommended. However, in patients with mild DCM and ADCCC, there is no clear, evidence-based agreement on the management and treatment algorithm. Currently, a lot of predictors of ADCC progression to symptomatic DCM have been identified and this has led some surgeons to recommend early decompression surgery in these high-risk patients. However, further studies are required to refine our understanding of the importance of these predictors. Moreover, there are some methodological and ethical challenges that make multicentre randomized study in ADCCC and mild DCM patients difficult to realize.

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Key words
degenerative cervical myelopathy – asymptomatic degenerative cervical cord compression – spinal cervical stenosis

Úvod

Degenerativní cervikální myelopatie (DCM) je nejzávažnější komplikací spinální cervikální stenózy (CS) a degenerativní krční míšní komprese. Je nejčastější příčinou paraparézy dolních končetin u dospělých jedinců nad 50 let a nejčastější příčinou míšního postižení vůbec [1]. Patofyziologie DCM je komplexní, ale klíčovým faktorem jejího vzniku je mechanická komprese krční míchy. Mícha je však značně rezistentní, zejména k pozvolnému, chronickému útlaku. Pacienti s míšní kompresí tak mohou být kompletně asymptomatičtí nebo mohou mít jen projevy lokálních segmentových bolestí či známky kořenové komprese, avšak bez jasných známek myelopatie. U těchto jedinců užíváme termín asymptomatická degenerativní kom-

prese krční míchy (asymptomatic degenerative cervical cord compression; ADCCC) či lépe nemyelopatická degenerativní komprese krční míchy (non-myelopathic degenerative cervical cord compression; NMDCCC), která přesněji vystihuje výskyt radikulární iritace u některých pacientů.

Současná prevalence ADCCC není známa a literární údaje se značně liší. Míšní cervikální komprese byla nalezena u 27 % pacientů, kteří byli náhodně vyšetřeni na MR; u pacientů starších 64 let v 30 % [2]. Naše data prokázala výskyt ADCCC dokonce ještě vyšší, ve vzorku populace nad 40 let dosahovala 50 % [3,4]. Vzhledem k jejímu vysokému výskytu je v současné době důležitou klinickou výzvou vytipování těch pacientů, u kterých můžeme předpokládat rozvoj symptomatické myelopatie. Bohužel i v případě, kdy se je podaří najít, neexistuje žádný jednotný postup, jak by tito rizikoví pacienti měli být léčeni; zda by měla být preferována konzervativní léčba s observací klinického stavu, či zda by měla být provedena odložená operace (při event. rozvoji míšních příznaků), event. zda by měli být profylakticky léčeni již v presymptomatické fázi, abychom se tak vyhnuli budoucím myelopatickým komplikacím.

V této práci podáváme přehled současných doporučení managementu pacientů s různým stupněm degenerativního krčního míšního postižení, od zcela asymptomatických až po pacienty s těžkou formou DCM.

Etiopatogeneze degenerativní míšní komprese

Základním patofyziologickým mechanizmem CS a DCM je věkově vázaná degenerace tkání páteřního kanálu a opakované dynamické zatížení při páteřní hypermobilitě [5]. Strukturální změny zahrnují:

- degeneraci intervertebrálních disků, obratlových těl a facetových kloubů;
- hypertrofii ligamentum flavum;
- osifikaci zadního podélného ligamenta.

Tyto změny zužují páteřní kanál a mohou vést až k míšní kompresi. Ta může nastartovat řadu patologických procesů, které mohou zhoršit neurologický deficit a způsobit nevratné cytologické, biochemické a histologické změny:

- ischemii a změny cévní architektury;
- postižení endoteliálních buněk a porušení hematoencefalické bariéry;
- zánětlivé změny;
- apoptózu neuronů a oligodendrocytů [6].

Klinické projevy degenerativní míšní komprese

Pacienti s míšní kompresí mohou vykazovat celou škálu neurologických příznaků. Někteří mohou být zcela asymptomatičtí, jiní trpí velmi těžkou paretickou a senzitivní symptomatikou a poruchou sfinkterů. Příznakům míšní komprese často předcházejí lokalizované bolesti krční páteře či příznaky komprese míšních kořenů, event. se s nimi kombinují (cervikální radikulomyelopatie) [7]. Vlastní komprese míchy se v iniciálním stadiu manifestuje nejčastěji poruchami chůze s nejistotou a pády, neobratností rukou s dominujícím postižením drobných pohybů ruky a pozitivními či negativními senzitivními symptomy [7]. K převážně subjektivním obtížím se při pokračující tíži komprese přidávají výpadové motorické příznaky charakteru spastické paraparézy dolních končetin a chabé či smíšené paraparézy horních končetin, poruchy senzitivity charakteru hypestezie na končetinách a trupu a sfinkterové poruchy [8]. DCM je diagnostikována v případě, kdy klinické známky myelopatie korelují s průkazem míšní komprese pomocí zobrazovacích metod (dnes prakticky výhradně pomocí MR) [9]. V současnosti je standardem pro stanovení klinické diagnózy přítomnost alespoň jednoho subjektivního a jednoho objektivního klinického příznaku míšní komprese [8].

Subjektivní příznaky:

- porucha chůze;
- neobratnost rukou;
- Lhermitteův příznak;
- bilaterální parestezie horních končetin;
- slabost horních nebo dolních končetin;
- močová urgence nebo inkontinence.

Objektivní příznaky:

- poruchy kortikospinální dráhy:
- hyperreflexie/klonus;
- spasticita;
- pozitivní pyramidové příznaky (Babinského nebo Hoffmanův příznak);
- spastická paréza jakékoliv končetiny (nejčastěji spastická paraparéza dolních končetin);
- chabá paréza jedné nebo dvou horních končetin v plurisegmentální distribuci;
- atrofie svalů ruky;
- porucha senzitivity v různé distribuci na horních či dolních končetinách (vždy plurisegmentální);
- ataxie chůze.

K hodnocení klinického stavu (u pacientů s již manifestní DCM) se používají různé škály. Nejčastěji je to škála Japonské ortopedické asociace modifikovaná Benzelem pro země s evropskou kulturou (mJOA), která hodnotí hybnost horních a dolních končetin, poruchu senzitivity horních končetin a sfinkterovou dysfunkci [10]. Někdy se užívá Nurickova škála neschopnosti a celá řada dalších testů [11].

Vývoj doporučení managementu pacientů se spondylogenní kompresí krční míchy

V historicky prvních publikacích o predikci vývoje DCM byl přirozený průběh choroby považován za téměř uniformní postupné zhoršování neurologického deficitu. V roce 1955 Clarke a Robinson [12] popsali typický průběh onemocnění zařazením pacientů do několika možných „vzorců": 5 % pacientů mělo mít prudký nástup symptomů, následovaný dlouhým obdobím remise; 20 % pacientů postupný funkční pokles klinického stavu a u 75 % mělo být zhoršení skokové. V průběhu let však řada prací prokázala, že přirozený průběh choroby je velmi individuální a variabilní a že řada pacientů zůstává stabilních i po mnoho let. Naopak poměrně velké množství z nich progreduje, pokud není včas léčeno.

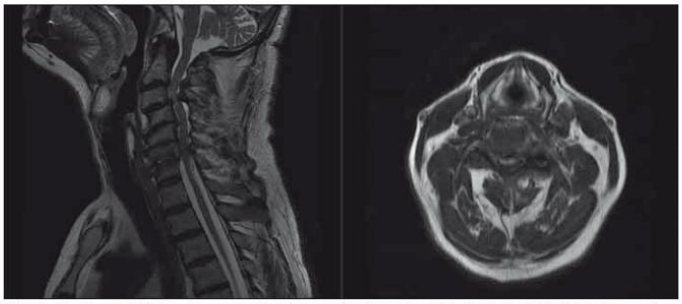
Na sympoziu Cervical Spine Research Society (CSRS) v roce 1988 byla formulována následující doporučení léčby pacientů s DCM:

1. operační řešení předním či zadním přístupem vede k míšní dekompresi a záleží na anatomických poměrech každého nemocného, které metodě dát přednost;
2. optimální načasování operace není známo, ale obecně se soudí, že by se mělo operovat v případě progresivního průběhu;
3. není jasné, zda pouhá přítomnost myelopatie je indikací k operaci, protože není přesně znám přirozený průběh choroby [13].

V roce 2009 se chopila iniciativy Kloubní sekce Americké asociace neurochirurgů na Kongresu o postižení míchy a periferních nervů (Disorders of The Spine and Peripheral Nerves) s cílem vytvořit doporučení pro léčbu degenerativních onemocnění krční páteře. Panel expertů vydal doporučení stran managementu těchto pacientů a přiřadil k nim jednotlivou sílu důkazů [9].

S narůstajícím povědomím o frekventním výskytu nemyelopatických stadií míšní komprese publikovala expertní skupina severoamerických spondylochirurgů za podpory AOSpine North America [14] meta-analýzu potenciálně relevantních 388 prací

týkajících se této problematiky. Bylo identifikováno pouhých 5 publikací, které splňovaly stanovená metodologická inkluzní kritéria. Tři z nich zahrnovaly asijskou populaci a zabývaly se převážně osifikací zadního podélného ligamenta, zbývající dvě práce pocházely z našeho pracoviště [15,16]. Studovali jsme v nich kohortu 199 jedinců se spondylogenní či diskogenní kompresí krční míchy se změnou nebo beze změny signálu na MR krční míchy, se segmentovými bolestmi či známkami krční radikulopatie (která však byla zvládnuta konzervativně), bez přítomnosti jakýchkoliv známek míšního postižení. Na začátku studie byli pacienti klinicky vyšetřeni, absolvovali elektrofyziologické a radiologické vyšetření. První 2 roky byli prospektivně sledováni každých 6 měsíců, následně pak jednou ročně. Na začátku studie mělo 70,9 % pacientů (141/199) ve škále mJOA 18 bodů a 29,1 % jedinců (58/199) 16 nebo 17 bodů. Myelopatie byla definována jako rozvoj klinických známek či symptomů DCM s poklesem skóre mJOA alespoň o jeden bod. Klinické známky prvního rozvoje DCM byly nalezeny u 22,6 % pacientů (45/199), s mediánem sledování 44 měsíců (rozsah 24–144 měsíců). V univariantní analýze bylo zjištěno, že EMG známky léze předních rohů míšních (RR: 2,4; 95% CI: 1,5–3,9), prolongované somatosenzitivní evokované potenciály (SEP; RR: 2,9; 95% CI: 1,7–5,1), prolongované motorické evokované potenciály (MEP; RR: 3,2; 95% CI: 1,9–5,6), hyperintenzita na MR (RR: 1,7; 95% CI: 1,0–2,7) a klinicky symptomatická radikulopatie (RR: 3,0; 95% CI: 2,0–4,4) byly spojeny s rozvojem myelopatie. Potenciální rizikové faktory, které nebyly spojeny s rozvojem DCM, zahrnovaly věk, pohlaví, typ komprese (osteofyty a/nebo herniace disku), počet stenotických rovin, Pavlovův index pod 0,8, kompresní poměr 0,4 či méně a příčná plocha míchy ≤ 70 mm^2. Navíc se u 8 % jedinců (16/199) rozvinula symptomatická myelopatie během 12 měsíců od začátku studie a doba, ve které 25 % jedinců progredovalo do klinicky manifestní myelopatie, byla 48,4 měsíců. Multivariantní Coxův proporcionální regresní model pak odhalil, že prolongované SEP ($p = 0,007$) a MEP ($p = 0,033$), klinicky symptomatická radikulopatie ($p = 0,007$) a nepřítomnost hyperintenzity na MR ($p = 0,036$) byly spojeny s časným (≤ 12 měsíců) rozvojem CSM. V další naší studii z roku 2011, která se zaměřila na vliv menšího traumatu krční páteře na rozvoj DCM u pacientů s ASCCC [16], jsme nenašli statisticky signifikantní asociaci



Obr. 1. Pacient s těžkou degenerativní cervikální myelopatií, klinicky těžká kvadruparéza s poruchami čití a sfinkterů, dle mJOA 8; indikováno operační řešení, pacient souhlasil. T2-vážené sekvence, vlevo sagitální řez, vpravo axiální řez v úrovni maximální komprese.

mJOA – modifikovaná škála Japonské ortopedické asociace

Fig. 1. Patient with a severe degenerative cervical myelopathy, clinically severe quadriparesis with sensory loss and bladder dysfunction, mJOA 8; surgical intervention was recommended, patient consented. T2-weighted sagittal scan on the left side, axial scan at the level of maximal compression on the right side.

mJOA – the modified Japanese Orthopaedic Association scale

(RR: 0,9; 95% CI: 0,3–3,2) mezi traumatem a rozvojem DCM.

Na základě výše uvedených výsledků publikovala severoamerická expertní skupina v roce 2013 přehled doporučení managementu pacientů s cervikální míšní kompresí, která klasifikovala jako „silná" [14]:

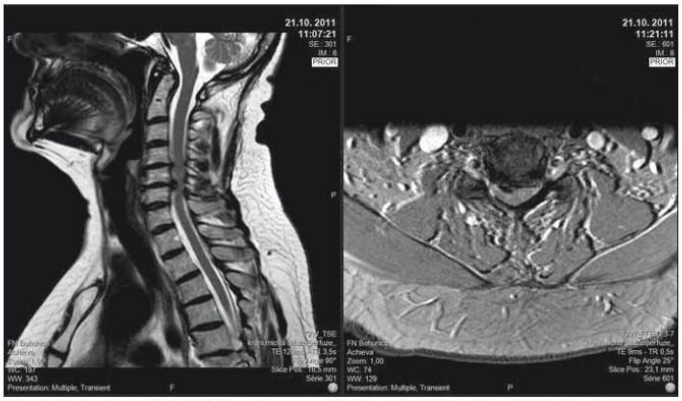
Bod 1: Podle současných poznatků u pacientů s CS a spondylogenní míšní kompresí bez známek myelopatie přibližně v 8 % (v průběhu jednoho roku) a v 23 % (v průběhu 44 měsíců) dojde k rozvoji klinických známek myelopatie.

Bod 2: U pacientů s CS a spondylogenní míšní kompresí, bez klinických známek myelopatie, absence T2 hyperintenzity na MR predikuje rozvoj časné myelopatie (do 12 měsíců sledování) a přítomnost této hyperintenzity predikuje rozvoj myelopatie pozdní (průměrně 44 měsíců sledování). Vzhledem k této diskrepanci nemůže být stanoveno jasné doporučení (ohledně tohoto radiologického parametru) v predikci rozvoje myelopatie.

V současné době jsme aktualizovali náš prediktivní model rozvoje DCM u ADCCC: použili jsme reprezentativnější vzorek jedinců s ADCCC, který zahrnoval jedince kompletně asymptomatické s lehkou míšní kompresí a zapracovali jsme též nové radiologické parametry jako MR DTI (diffusion tensor imaging) [17,18]. Identifikovali jsme příčnou plochu míchy < 70,1 mm^2 a kompresní poměr < 0,4 jako nezávislé signifikantní radiologické prediktory rozvoje ADCCC do DCM [19]. Na základě těchto výsledků je tedy nyní možné lépe odhadnout míru rozvoje symptomatické DCM u jedinců s ADCCC a vyselektovat podskupinu pacientů s vyšším rizikem nepříznivého vývoje.

V roce 2017 výše uvedená severoamerická expertní skupina doplnila svoje doporučení jednak ve vztahu k současným metodologickým standardům, dále doplnila názory odborníků z oblasti chirurgie páteře, rehabilitace, neurologie, revmatologie a v neposlední řadě zahrnula i pacientovy preference, rizika a benefity prováděných operací i ekonomický dopad jednotlivých způsobů léčby. Vydala tato doporučení [9]:

1. pacient s těžkou DCM (mJOA 0–11): doporučuje se chirurgická intervence (doporučení: silné; průkaz: střední) (obr. 1);
2. pacient se středně těžkou DCM (mJOA 12–14): doporučuje se chirurgická intervence (doporučení silné; průkaz střední) (obr. 2);
3. pacient s mírnou DCM (mJOA 15–17): doporučuje se nabídnout chirurgickou intervenci nebo strukturovanou rehabilitaci s monitorací klinického stavu. Pokud neproběhne v iniciálním stadiu operace, tak se doporučuje chirurgická intervence v případě, že se stav pacienta neurologicky horší či se po konzervativní léčbě nelepší (doporučení slabé; průkaz velmi nízký) (obr. 3);

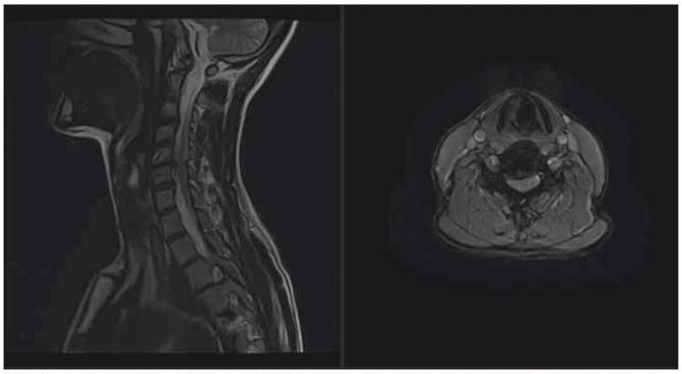


Obr. 2. Pacient se středně těžkou degenerativní cervikální myelopatií, klinicky lehká kvadruparéza (lehce neobratné ruce, parestézie rukou, lehce nejistá chůze), dle mJOA 12; pacient sám již řadu let stabilní, operaci odkládá. T2-vážené sekvence, vlevo sagitální řez, vpravo axiální řez v úrovni maximální komprese.

mJOA – modifikovaná škála Japonské ortopedické asociace

Fig. 2. Patient with moderate degenerative cervical myelopathy, clinically mild quadriparesis (clumsy hands, paresthesias of the hands, light gait ataxia), mJOA 12; surgical intervention offered, patient prefers conservative treatment, neurologic status is stable for years. T2-weighted sagittal scan on the left side, axial scan at the level of maximal compression on the right side.

mJOA – the modified Japanese Orthopaedic Association scale



Obr. 3. Pacient s lehkou degenerativní cervikální myelopatií, klinicky pouze lehká neobratnost rukou, dle mJOA 16; navrhováno operační řešení, které pacient odkládá. T2-vážené sekvence, vlevo sagitální řez, vpravo axiální řez v úrovni maximální komprese.

mJOA – modifikovaná škála Japonské ortopedické asociace

Fig. 3. Patient with mild degenerative cervical myelopathy, clinically only discrete clumsy hands, mJOA 16; surgical intervention was recommended, patient postpones the surgery. T2-weighted sagittal scan on the left side, axial scan at the level of maximal compression on the right side.

mJOA – the modified Japanese Orthopaedic Association scale

4. pacient s míšní kompresí bez známek radikulopatie: nedoporučuje se profylaktická operace. Pacient by měl být poučen o potenciálních rizicích a symptomech myelopatie a měl by být klinicky sledován (doporučení slabé; průkaz žádný – založeno na expertním názoru autorů doporučení) (obr. 4);
5. pacient s míšní kompresí s klinickými a/nebo radiologickými známkami radikulopatie: jsou se vyšším riziku rozvoje myelopatie, měla by být zvážena možná rizika. Doporučuje se nabídnout chirurgickou intervenci nebo neoperativní léčbu sestávající z časných kontrol a strukturované rehabilitace. V případě rozvoje myelopatie by měl být pacient léčen podle výše uvedených doporučení (doporučení: slabé; průkaz nízký).

Vidíme tedy, že i nadále neexistuje přesvědčivý a jasný konsenzus ohledně algoritmu managementu vysoce rizikových pacientů s ADCCC. Někteří autoři předpokládají, že jedinci s CS či ADCCC mají zvýšené riziko rozvoje akutní myelopatie v případě, že prodělají i menší trauma [20,21]. To vedlo některé chirurgy k doporučení provádět dekompresní operace za účelem prevence traumatem navozené myelopatie u ohrožených jedinců [22], což je ovšem názor značně kontroverzní. Murphy et al si položili otázku, zda jsou pacienti s ADCCC ve zvýšeném riziku míšního postiženi po menším traumatu krční páteře a zda mohou profitovat z preventivní dekompresní operace [23]. Nenašli však žádnou prospektivní studii, která by jasně prokázala, že riziko míšního postižení je u pacientů s ADCCC vyšší. Nenašli též žádnou relevantní práci, která by zhodnotila efekt chirurgické intervence u asymptomatických pacientů se spondylogenní cervikální míšní kompresí. Zjistili, že frekvence vážných komplikací či mortalita u chirurgicky léčených pacientů se symptomatickou myelopatií je obecně cca 1 %. Postoperační komplikace byly komplikacemi zákroků samotných, nikoliv projevy myelopatie, není tedy pravděpodobné, že by škála komplikací byla jiná u pacientů asymptomatických v porovnání se symptomatickými.

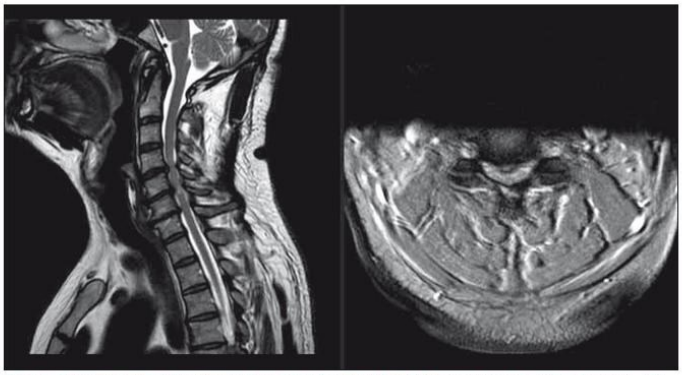
Nicméně jiní autoři jsou ještě radikálnější a přímo doporučují, aby pacienti s jakoukoliv formou DCM byli operováni co nejčasněji, jednak jako prevence budoucích komplikací, jednak i proto, abychom poskytli pacientům co nejdelší potenciál k uzdravení [24]. Zhang et al prokázali zlepšení ve všech chirurgicky léčených věkových skupinách, a to jak cca týden, tak i půl roku po zákroku. Nenašli též rozdíl mezi věkovými skupinami ve frekvenci pooperačních komplikací [25]. Na druhou stranu však v plánování chirurgických výkonů musíme brát do úvahy

i možná rizika pooperačních komplikací. Tetrault et al v dosud nejrozsáhlejší metaanalýze dokumentovali, že jedinými významnými prediktory méně příznivého výsledku operační dekomprese DCM s vyšším procentem pooperačních komplikací jsou vyšší věk a delší trvání operačního výkonu (vč. zákroků ve dvou a více etážích) [26]. Potřeba vědeckého průkazu dlouhodobého klinického benefitu chirurgické dekomprese u lehkých forem DCM a vysoce rizikových pacientů s ADCCC však naráží na řadu metodologických i etických úskalí realizace multicentrické randomizované studie.

Závěr

Podle současných doporučení jsou k chirurgické intervenci jednoznačně indikováni pacienti s těžkou (mJOA 0–11) a středně těžkou formou (mJOA 12–14) DCM.

Přestože existují některá data, která monitorují četnost a rizikové faktory progrese ADCCC do symptomatické DCM, neexistuje jasný, vědecky podložený konsenzus managementu a léčebného algoritmu zejména u pacientů s mírnou myelopatií či asymptomatickou cervikální míšní kompresí, který by zahrnoval i eventuální prospěšnost chirurgické dekomprese u vysoce rizikových pacientů s ADCCC. Jsou potřeba další studie, aby bylo možno definovat načasování chirurgického zákroku a nalézt další prediktory rozvoje DCM u prozatím asymptomatických jedinců.



Obr. 4. Pacient s míšní kompresí bez klinických známek myelopatie či radikulopatie, dle mJOA 18; pacient poučen o možných rizicích a klinicky sledován. T2-vážené sekvence, vlevo sagitální řez, vpravo axiální řez v úrovni maximální komprese.

mJOA – modifikovaná škála Japonské ortopedické asociace

Fig. 4. Patient with cervical spine compression with no signs of myelopathy or radiculopathy, mJOA 18; patient was educated about possible risks and is followed clinically. T2-weighted sagittal scan on the left side, axial scan at the level of maximal compression on the right side.

mJOA – the modified Japanese Orthopaedic Association scale

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doi: 10.14735/amcsnn2019616

Klinické syndromy z oblasti cervikálního plexu

Cervical plexus lesions in clinical practice

Souhrn

Léze v oblasti cervikálního plexu jsou relativně vzácné a mohou uniknout pozornosti klinického neurologa. V posledních letech bylo publikováno několik nových syndromů z této lokalizace. Podáváme aktuální přehled možných postižení krční pleteně, jejich diagnostiky a léčby. Jedná se o okcipitální neuralgii, která je relativně nejčastější a většinou bývá považována za idiopatickou. Dále o neuralgie v oblasti ucha, jako jsou léze n. auricularis magnus a syndrom červeného ucha. Popisujeme i postižení Jacobsonova a Arnoldova nervu, které jsou klinicky velmi podobné, i když se jedná o léze n. glossopharyngeus, resp. n. vagus. Zabýváme se i postižením n. phrenicus, které bývá většinou jednostranné a asymptomatické, při bilaterální paréze jím inervované bránice však může vyústit až do respiračního selhání s nutností umělé plicní ventilace.

Abstract

Cervical plexus lesions are relatively rare and may be overlooked by clinical neurologists. Several new clinical syndromes centered upon this region have been published in recent years. Herein we present an overview of possible etiologies of cervical plexus lesions, their diagnosis and treatment. Relatively the most common condition is occipital neuralgia, which is largely considered idiopathic. We report considerable auricular neuralgia and red ear syndrome, and neuralgias of Jacobson's and Arnold's nerves (branches of the glossopharyngeal and vagus nerves). We deal also with phrenic nerve lesion, which is usually unilateral and asymptomatic. Nevertheless, bilateral diaphragmatic palsy may result in disabling dyspnea requiring mechanical ventilation.

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The Editorial Board declares that the manuscript met the ICMJE "uniform requirements" for biomedical papers.

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Klíčová slova
plexus cervicalis – okcipitální neuralgie – neuralgie n. occipitalis magnus – syndrom červeného ucha – postižení nervus phrenicus

Key words
cervical plexus – occipital neuralgia – great auricular neuralgia – red ear syndrome – phrenic nerve palsy

Úvod

Léze v oblasti cervikálního plexu zůstávají někdy stranou v diferenciálně diagnostických úvahách klinického neurologa, což může být dáno jednak jejich malou četností, ale i tím, že mohou imitovat příznaky jiných (např. interních či otorinolaryngologických) chorob [1]. Často též bývají mylně považovány za vertebrogenní v rámci cervikokraniálního syndromu [2]. V posledních letech bylo publikováno několik nových (i když vzácných) klinických jednotek z této lokalizace. Podáváme aktuální přehled syndromů lézí cervikálního plexu, jejich diagnostiky a terapie.

Anatomie plexus cervicalis

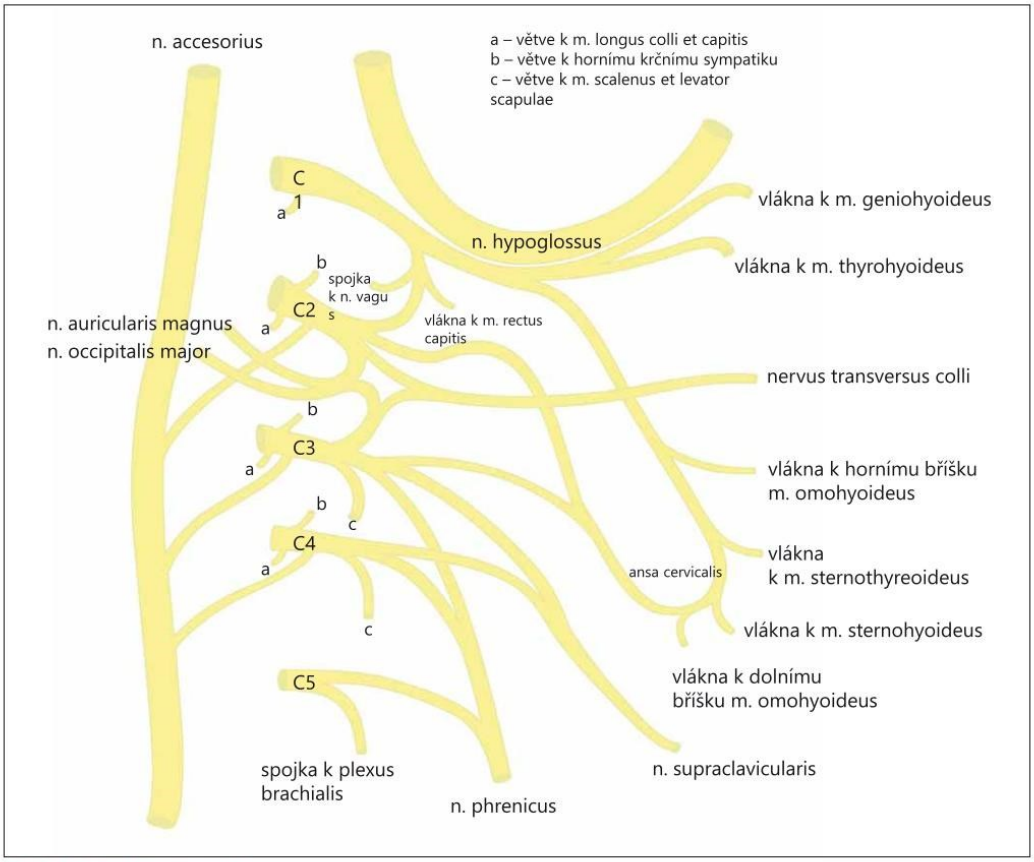
Cervikální plexus je tvořen ventrálními větvemi prvních čtyř krčních nervů (C1–C4) a jejich spojkami. Tato pleteň se nachází nad m. scalenus medius a m. levator scapulae pod m. sternocleidomastoideus (SCM). Je kryta hlubokou krční fascií (lamina praevertebralis). Z krční pleteně vychází nervy senzitivní i motorické pro svaly a kůži krku a pro bránici (obr. 1).

Plexus cervicalis (rami ventrales spinálních nervů)

Senzitivní nervy

N. occipitalis minor (C2, 3) – obtáčí n. accesorius, stoupá kraniálně podél zadního okraje m. SCM. Terminální kožní větévky inervují horní část dorzolaterální strany krku, horní část ušního boltce a malou část skalpu (za ušním boltcem a nad ním). Inervační oblast nervu dorzálně sousedí s n. occipitalis major a ventrálně s inervační oblastí n. auricularis magnus.

N. auricularis magnus (C2, 3) – běží po povrchu m. SCM vzhůru pod boltec, vydává dvě větve:



Obr. 1. Schéma plexus cervicalis.
Fig. 1. Cervicalis plexus scheme.

- r. anterior – inervuje kůži nad příušní žlázou a části přední plochy boltce (mívá spojku s n. facialis);
- r. posterior – senzitivně zásobuje kůži zadní plochy boltce a regio mastoidea.

N. transversus colli (C3) – vystupuje mediálně dopředu přes m. SCM pod kožní sval krční (m. platysma) a dělí se na dvě větve:
- r. superior – inervuje kůži v regio suprahyoidea;
- r. inferior – inervuje kůži v regio infrahyoidea.

N. supraclaviculares (C3,4)
- mediales – probíhají kaudálně a mediálně, inervují kůži ve fossa jugularis a nad manubrium sterni;
- intermedii – sestupují kaudálně a inervují kůži v dolní části krku a v klavikulární a infraklavikulární krajině (v rozsahu m. pectoralis major);
- laterales – sestupují kaudálně a dorzálně, inervují kůži akromiální krajiny.

Motorické nervy

Rami musculares – samostatné svalové větve pro svaly pre- a intervertebrální, m. scalenus medius, m. SCM (C2–4 + n. accesorius), m. trapezius (C2–4 + n. accessorius) a m. levator scapulae (C4, 5 + n. dorsalis scapulae z brachiálního plexu).

Ansa cervicalis (prof.) C1–3: (ansa n. hypoglossi) – vlákna pro infrahyoidní svaly, m. thyrohyoideus
- radix sup. (C1, 2) – spojí se s n. hypoglossus (inervuje m. geniohyoideus);
- radix inf. (C2, 3) – inervuje m. sternohyoideus, m. omohyoideus;

N. phrenicus (C4, méně i C3 a C5) – smíšený, ale převážně motorický nerv. Na krku probíhá na m. scalenus ant., vstupuje do hrudníku, probíhá předním mediastinem k bránici, kterou inervuje. Senzitivní vlákna vydává k perikardu a pleuře.

Funkčně bývají do cervikálního plexu řazeny i rami dorsales spinálních cervikálních nervů (i když se anatomicky samozřejmě o krční pleteň nejedná):
1. **N. suboccipitalis (C1)** – čistě motorický nerv, který inervuje m. rectus a m. obliquus capitis (zajišťují drobné pohyby hlavy);

2. **N. occipitalis major (C2)** – jeho počáteční úsek je smíšený (inervuje m. semispinalis capitis a m. longissimus capitis), v konečném úseku je nervem kožním. Po výstupu z páteřního kanálu se zatáčí kolem dolního okraje m. obliquus capitis inf., prostupuje přes m. semispinalis capitis a m. trapezius do krajiny týlní a inervuje kůži až po tzv. čáru interaurikulární, kde se stýká se senzitivními větvemi n. trigeminus;
3. **N. occipitalis tertius (C3)** – často se spojuje s n. occipitalis major, ale může probíhat i samostatně, senzitivně inervuje úzký pruh kůže šíjové krajiny při střední rovině (mediálně od inervační oblasti n. occipitalis major).

Klinické syndromy při lézích cervikálního plexu

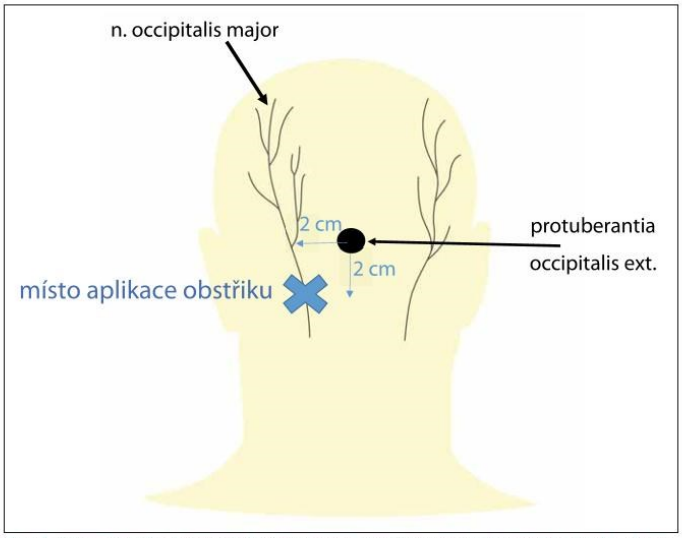
Okcipitální neuralgie (C2 neuralgie, Arnoldova)

Okcipitální neuralgie (ON) je definována jako paroxyzmální vystřelující nebo bodavá bolest v dermatomu n. occipitalis major či minor [3]. Bolest vychází ze subokcipitální oblasti, vystřeluje přes týl a temeno až za oči a může být provázena hypestezií či dysestezií v příslušné distribuci. Incidence onemocnění je cca 3/100 000 [4]. Etiologicky je většinou považována za idiopatickou [5], může mít však příčinu:

- cévní – arteriovenózní malformace [6], bulbocervikální kavernom [7], útlak aberantní větví a. cerebelli inferior posterior (posterior inferior cerebellar artery, PICA) [8];
- neurogenní – schwannom [9], C2 myelitis [10] či roztroušená skleróza [11];
- osteogenní – artróza C1/2 [12], osteolytické léze kranía [13].

Spouštěcím mechanizmem může být komprese v průběhu n. occipitalis major (90 %) či n. occipitalis minor (10 %) [3].

Diagnostika ON je založena na těchto kritériích: bolestivost lokalizovaná ve výše uvedené oblasti, citlivost v průběhu postiženého nervu a alespoň krátkodobá úleva od bolesti při lokálním obstřiku příslušného nervu [2]. Místa provedení obstřiku jsou různá – např. 2 cm laterálně a 2 cm pod protuberantia occipitalis externa [2] (obr. 2). Existuje celá řada možností léčby ON. Imobilizace krku límcem, fyzioterapie a kryoterapie se neprokázaly být účinnější než placebo [14]. Nesteroidní antirevmatika, tricyklická antidepresiva, inhibitory zpětného vychytání serotoninu a antikonvulziva mohou ulevit od bolesti, stejně jako lokální obstřiky – nejlépe pod UZ kontrolou [15]. Pulzní nebo termická radiofrekvenční ablace může přinést dé-



Obr. 2. Místo obstřiku n. occipitalis major pro okcipitální neuralgii (modrý křížek) – 2 cm laterálně a 2 cm pod protuberancia occipitalis externa.

Fig. 2. Great occipitalis nerve block for occipital neuralgia (blue cross) – 2 cm lateral and 2 cm inferior to the external occipital protuberance.

letrvající úlevu od bolesti, podobný efekt má i chemická neurolýza alkoholem nebo fenolem [15]. Chemická neurolýza však není všeobecně akceptovanou léčebnou metodou. Neexistují doporučení či jasná indikační kritéria jejího použití [16]. Měla by být rezervována pouze pro pacienty s perzistující a jinak neovlivnitelnou bolestí. Pacienti by měli být pečlivě vyselektováni s podrobným celkovým vyšetřením vč. psychologického profilu, měl by předcházet lokální anestetický blok nervu alespoň s krátkodobým efektem [16]. Další alternativní metodou léčby je neuromodulace okcipitálního nervu se stimulačními elektrodami v oblasti baze lební [2]. Chirurgická dekomprese je preferována u nejvíce refrakterních případů [13]. Další alternativou invazivní léčby je gangliotomie C2 [14].

Neuralgie v oblasti ucha

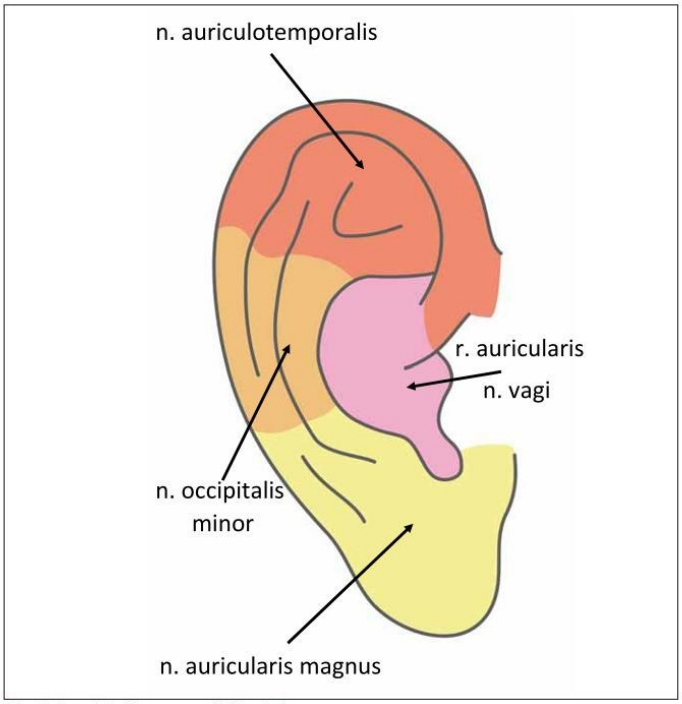
Patří sem zejména neuralgie n. auricularis magnus a syndrom červeného ucha, vzhledem ke značné klinické podobnosti uvádíme i neuralgii Arnoldova a Jacobsonova nervu, které jsou však větvemi hlavových nervů (n. X., resp. n. IX.).

Senzitivní inervace ucha

Zadní a dolní část ušního boltce inervují n. auricularis magnus a n. occipitalis minor (z cervikálního plexu). Přední a horní část boltce senzitivně zásobuje n. auriculotemporalis (větev n. mandibularis z n. trigeminus). Okolí tragu, antitragu, cavitas conchae, dolní stěny zvukovodu a dolní část bubínku z vnější strany inervuje r. auricularis n. vagi (tzv. Arnoldův nerv) (obr. 3). Střední ucho (vnitřní strana bubínku, středoušní dutina, kostěná část sluchové trubice) je senzitivně zásobována z n. tympanicus (Jacobsonův nerv), který je větví n. glossopharyngeus. Vnitřní ucho nemá vlastní senzitivní inervaci.

Neuralgie n. auricularis magnus

Jedná se o velmi vzácnou klinickou jednotku. Velký ušní nerv probíhá vertikálně po povrchu m. SCM, senzitivně inervuje spodní část ušního boltce, spodní část obličeje a horní část krku. Neuralgie je charakterizována intermitentní elektrizující, vyčerpávající bolestí ve výše uvedené oblasti, přičemž může být provokována rotací hlavy na opačnou stranu. Etiopatogeneze je nejasná, někdy bývá dávána do souvislostí se stavy po traumatu hlavy a krku či při déletrvajícím útlaku v krční oblasti, v posledních letech i po kosmetických plastických operacích (liftingu krku) [17]. Diagnostika je značně obtížná, obvykle per exclusionem, může nám však pomoci elektrofyziologické vy-



Obr. 3. Senzitivní inervace ušního boltce.
Fig. 3. External ear-innervation.

šetření nervu, které bylo v roce 2018 poprvé popsáno korejskými autory [17]. Postižení je často velmi nepříjemné a má tendenci k chronickému průběhu. V léčbě bývají zkoušena analgetika, antikonvulziva, antidepresiva, dobrý efekt může mít blokáda nervu pod UZ kontrolou [18]. Často je však nutná operační revize s neurolýzou, obvykle s dobrým efektem [19].

Syndrom červeného ucha (red ear syndrome)

Jedná se o další, velmi vzácné postižení (doposud bylo v literatuře popsáno asi 100 případů) poprvé publikované v roce 1996 [20]. Typické jsou jednostranné (62 %) či oboustranné ataky pálivých bolestí a zčervenání zevního ucha (nejvíce v lalůčku), které mohou vystřelovat do tváře a dolní čelisti [21]. Doba trvání záchvatu bývá vteřiny až hodiny. Patofyziologie není známa. Lance et al předpokládali periferní příčinu, kdy při iritaci kořene C3 s následnou bolestivostí dochází k uvolnění vazodilatačních peptidů a zarudnutí ucha [20]. Vzhledem k časté asociaci s migrénou, zejména u mladých lidí, se v etiologii syndromu zvažuje i aktivace trigeminovaskulárního komplexu [22]. V současné době se uznávají dva subtypy syndromu červeného ucha, a to:

- primární – častěji u dětí a dospívajících, až v 80 % bývá asociován s migrénou;
- sekundární – vyskytuje se spíše u starších jedinců a bývá spojován s postižením v oblasti horní krční páteře, s bolestmi temporomandibulárního kloubu a čelisti.

Oba subtypy se však mohou vyskytovat v jakémkoli věku [23]. Syndrom je obvykle refrakterní na léčbu, zkouší se gabapentin, amitriptylin, imipramin, flunarizin, propranolol, verapamil či pregabalin [24].

Neuralgie Jacobsonova nervu

Jacobsonův nerv (n. tympanicus) je první (smíšenou) větví n. glossopharyngeus po výstupu z foramen jugulare. Senzitivně inervuje střední ucho a processus mastoideus. Klinicky je neuralgie tohoto nervu charakterizována jako nesnesitelná bolest lokalizovaná hluboko v uchu. Diagnostika je možná prakticky pouze *per exclusionem* (je nutno vyloučit otorinolaryngologickou, zubní etiologii, provést CT temporální kosti, CT krku, MR hlavy – se zaměřením na kořeny IX. a X. hlavového nervu) [25]. Léčba je shodná jako u jiných neuralgií. V refrakterních případech přichází do úvahy neurektomie plexus tympanicus, které jsou v posledních letech v této indikaci prováděny [25].

Neuralgie Arnoldova nervu

Je extrémně vzácná. Arnoldův nerv je aurikulární větví n. vagus. Senzitivně inervuje ušní boltec v oblasti konchy, meatus acusticus externus (tragus, antitragus) a vnitřní povrch zevního zvukovodu. V roce 2016 byly popsány dva případy pacientů s torpidními bolestmi v oblasti zevního zvukovodu, které perzistovaly i po mikrovaskulární dekompresní léčbě neuralgie trigeminu, která byla původně zvažována jako příčina bolestí; peroperačně však byl prokázán těsný kontakt PICA s nervus vagus a významná komprese vláken aurikulární větve tohoto nervu. Následující, tj. druhý mikrovaskulární zákrok s odstraněním neurovaskulárního konfliktu (mezi n. X. a PICA) bolesti zcela eliminoval [26].

Léze v oblasti ansa cervicalis

Neexistuje žádný specifický syndrom postižení nervů z oblasti ansa cervicalis. Jazylka se spolupodílí na procesu polykání, žvýkání, ale tyto pohyby jsou ve značné míře závislé na svalech orofaryngu (např. m. cricothyreoideus) a fungují normálně dokonce i při průkazu úplné denervace infrahyoidních svalů [27]. Z tohoto důvodu bývá ansa cervicalis využívána v transplantologii např. k náhradě postiženého n. laryngeus recurrens [28] či n. facialis [29].

Léze n. phrenicus

Bránice je primární respirační sval a její postižení může vést až k selhání vitálních funkcí. Klinické projevy jsou závislé na etiologii parézy a značně variabilní – od zcela asymptomatických jedinců až po pacienty s nutností trvalé mechanické ventilace. Převažuje jednostranné postižení nervu. Eventuální bilaterální paréza bránice se projevuje nejčastěji ortopnoí a paradoxním dýcháním [30]. Etiologie je značně různorodá. Nejčastějším onemocněním, které se může projevit izolovanou lézí obou bráničních nervů axonálního typu, je bolestivá neuralgická amyotrofie [30]. Brániční nerv bývá nezřídka postižen

během chirurgických hrudních operací – zejména srdečního bypassu [31]. Jakékoliv ložiskové procesy plic či mediastina mohou vyústit do postižení bráničního nervu, dokonce byla popsána i komprese phrenicu těžkými degenerativními změnami krční páteře [31]. Brániční nerv může být narušen metabolickým postižením (diabetes mellitus) [32], infekčním agens (Lymeská borelióza a herpes zoster) [33,34], roztroušenou sklerózou či při Guillain-Barrého syndromu [35]. Asi 90 % jednostranných postižení bránice je diagnostikováno náhodně pomocí nativního RTG vyšetření plic, kde se prokáže typicky jednostranná elevace na postižené straně [36]. Lze využít i UZ vyšetření bránice, které zhodnotí i její funkční stav [37]. CT hrudníku by měla být provedena u každého pacienta s lézí n. phrenicus k vyloučení ložiskových změn plic a mediastina. EMG vyšetření bývá někdy obtížné a hůře interpretovatelné vzhledem k technickým limitům a možným komplikacím [38], nicméně na specializovaných pracovištích se rutinně provádí jehlová EMG bránice a jsou stanovena normativní data u kondukčních studií [39,40]. Většina pacientů s asymptomatickou unilaterální parézou bránice nevyžaduje léčbu [41]. Pokud se nám podaří identifikovat základní příčinu, tak ji budeme řešit – např. kompresi nervu ložiskovým procesem. V případech idiopatického postižení léčíme symptomaticky – existují dva způsoby: plikace svalu či stimulace n. phrenicus. Plikace se preferuje zejména u pacientů s jednostranným postižením, bez známek výraznější obezity [41]. Stimulace nervu se provádí u pacientů s intaktním nervem a po vyloučení myopatie [31].

Závěr

Léze v oblasti cervikálního plexu jsou relativně vzácné a někdy opomíjené, často diagnostikované až *per exclusionem*. Měli bychom na ně však v diferenciálně diagnostických úvahách pomýšlet, protože zejména v poslední době se objevily nové terapeutické možnosti, které mohou přinést zvláště úlevu od bolestí u postižených pacientů.

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Degenerativní cervikální myelopatie – klinický obraz, diagnostika a strategie léčby

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Degenerativní cervikální myelopatie (DCM) je chronické, progresivní onemocnění krční míchy. Degenerativní procesy (spondylóza, hypertrofie facetových kloubů, výhřezy plotének) včetně postižení vazů (osifikace zadního podélného vazu, hypertrofie ligamentum flavum) vedou k míšní kompresi a rozvoji možného neurologického deficitu. Ten se projevuje zejména syndromem neobratných rukou, zhoršením chůze a sfinkterovou insuficiencí. Podle současných doporučení by měli být nemocní se střední a těžkou formou DCM léčeni operativně. U pacientů s lehkou formou DCM a pacientů bez klinických známek myelopatie, avšak s projevy radikulopatie, by měla být navržena buď operační léčba, či cílená rehabilitace. Jedinci s průkazem významné míšní komprese (avšak bez klinických známek myelopatie či radikulopatie) by měli být pravidelně klinicky sledováni.

Klíčová slova: degenerativní krční myelopatie, spinální cervikální stenóza, nemyelopatická degenerativní cervikální míšní komprese, syndrom neobratných rukou.

Degenerative cervical myelopathy – clinical manifestation, diagnosis and practical management

Degenerative cervical myelopathy (DCM) is a chronic progressive disease of the cervical spinal cord. Osteoarthritic degeneration (spondylosis, facet hypertrophy, and degenerative disc disease), ligament changes (ossification of the posterior longitudinal ligament, hypertrophy of the ligamentum flavum) may lead to the spinal cord compression and result in neurological deficits. It is manifested as clumsy hands syndrome, gait impairment, and bladder problems. The latest clinical guidelines recommend surgery for patients with moderate and severe DCM. For patients with mild DCM (or non-myelopathic patients with radiculopathy), the guidelines suggest that either surgery or a supervised trial of structured rehabilitation. The nonoperative treatment with serial clinical follow-up should be reserved for asymptomatic patients with imaging evidence of cervical spinal cord compression.

Key words: degenerative cervical myelopath, cervical spinal stenosis, non-myelopathic degenerative cervical spinal cord compression, clumsy hand syndrome.

Úvod

Degenerativní cervikální myelopatie (DCM) je závažné onemocnění, které vzniká (většinou postupně progredující) kompresí krční míchy. Ta je vyvolána rozvojem degenerativních změn a vede ke statickému i dynamickému útlaku míchy a jejích cév. Toto onemocnění je i v současné době prozatím nedostatečně diagnostikováno, přestože se jedná o nejčastější netraumatické míšní postižení u lidí starších 14 let (častější než roztroušená mozkomíšní skleróza či nádory míchy). Pokud není adekvátně léčeno, tak může vést k nevratnému postižení nervových struktur a manifestovat se těžkou poruchou hybnosti až úplnou imobilizací pacienta.

Patofyziologie vzniku DCM

Na vzniku onemocnění se podílejí statické a dynamické faktory. Mezi statické faktory patří veškeré strukturální změny, které vedou k postupnému zužování páteřního kanálu. Patofyziologická kaskáda rozvoje DCM začíná změnami na meziobratlovém disku (Fehlings et Skaf, 1998). Ten se při degenerativním procesu postupně zmenšuje, tvoří se trhliny v jeho pevném pouzdře, které mohou pokračovat až k periferii. Skrze tyto trhliny dochází k vyklenutí měkkého jádra ploténky. Současně se mění tvar krycích destiček a tvoří se okrajové osteofyty přilehlých obratlů, zbytňují facetové klouby. Dochází ke zkrácení délky celé páteře a ke změnám jejích biome-

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chanických parametrů. Na příčném zúžení páteřního kanálu se může podílet (kromě výše uvedeného) i patologicky ztluštělé a nařasené ligamentum flavum a osifikace zadního podélného vazu (Fehlings et Skaf, 1998). Degenerativní změny mohou vést ke zhoršení hybnosti postižených páteřních segmentů a ke kompenzatorní hypermobilitě přilehlých struktur (Lebl et al., 2011).

Dynamické faktory se podílí na vzniku myelopatie zejména opakovanou flexí a extenzí krční páteře, které zhoršují míšní útlak. Ten je primárně zapříčiněn výše zmíněnými degenerativními změnami (Fehlings et Skaf, 1998). Hyperextenze páteře též může přispívat k míšní kompresi – ventrálně obratlovými těly a dorzálně zbytnělým žlutým vazem (Lebl et al., 2011).

Postupně progredující míšní komprese vede k histopatologickým změnám. Způsobuje vznik cystických míšních dutinek, projevy gliózy a degenerace šedé i bílé hmoty, walleriánskou degeneraci zadních míšních provazců, posterolaterálních drah a předních rohů míšních. Chronické narušení cévního zásobení míchy je též významnou komponentou rozvoje DCM. Vede k ischemiím a poškození endotelu. Endoteliální dysfunkce následně zhoršuje tkáňové postižení, což vede k vazogennímu míšnímu edému (Lebl et al., 2011). Dochází k zánětlivým změnám, které hrají kritickou roli **v patofyziologii** buněčného úmrtí nervových buněk (apoptózy) (Kalsi-Ryan et al., 2013).

Stupeň míšního postižení závisí na tíži komprese a je odpovědný za rozvoj klinických projevů DCM, které jsou popsány níže.

Klinické projevy DCM

Klinické projevy DCM jsou velmi pestré, což vyplývá z míšního útlaku na jedné, dvou nebo více úrovních krční páteře, a navíc z možné kombinace s kompresí jednoho či několika míšních kořenů. První příznaky se většinou objevují po 40. roce věku, často mezi 50.–70. rokem života. Muži bývají postiženi častěji než ženy – v poměru 3 : 2 (Milligan et al., 2019). Příznaky jsou typicky postupné a plíživé, jen v menším procentu případů akutní či subakutní (např. po úrazu hlavy či páteře).

Počáteční diagnostika DCM bývá většinou založena na přítomnosti těchto příznaků: bolesti (či pocity ztuhlosti) krční páteře, pocity slabosti a zhoršené obratnosti horních končetin, oboustranné parestezie horních končetin, poruchy chůze a Lhermitteův příznak (Tracy et Bartleson, 2010). Méně často jsou přítomny příznaky autonomní dysfunkce – tj. častější močení (urgence) a močová inkontinence, které však typicky nebývají prvními příznaky choroby, ale bývají spojeny s jinými symptomy DCM (Hattori et al., 1990). Nespecifické a pouze diskrétní časné příznaky DCM mohou být překryty symptomy jiných neurologických onemocnění a mohou značně oddálit stanovení diagnózy (Tracy et Bartleson, 2010).

Segmentové bolesti krční páteře

Prevalence segmentových bolestí krční páteře u pacientů s DCM bývá uváděna okolo 60 % (Milligan et al., 2019). Je nutné zdůraznit, že bolest v krční páteři může být důležitým diagnostickým příznakem, a naopak její chybění může od diagnózy odvádět. **Absence bolesti** v krční páteři (30–50 % nemocných) tedy **nesvědčí proti diagnóze DCM,** stejně jako normální funkční nález na krční páteři. Bolesti často vyzařují z krční páteře do ramen a horních končetin (41 %), mezi lopatky (51 %) a do hlavy (30 %) (Bednarik et al., 2008). Pacienti si nezřídka stěžují i na nebolestivou ztuhlost krční páteře (Davies et al., 2018).

Radikulární bolesti

Kořenové bolesti bývají popisovány až u 86 % pacientů s DCM (Milligan et al., 2019). Nejčastěji zasaženými kořeny jsou C6 a C7. Pacienti mají bolesti krční páteře, parestezie a bolesti horních končetin, ale i algie v oblasti lopatky i hrudníku. Radikulární bolest je pravděpodobně způsobena kompresí zaníceného či drážděného kořene (Milligan et al., 2019).

Syndrom neobratných rukou (clumsy hand syndrom)

Typickými klinickými projevy DCM jsou **ztráta obratnosti a jemné motoriky rukou** (potíže se zapínáním knoflíčků u košile, s používáním klíčů, mobilního telefonu či problémy se psaním) (Davies et al., 2018). Ono et al. popsali skupinu nemocných s DCM s charakteristickým obrazem, který nazvali „syndromem myelopatické ruky" (Ono et al., 1987). Ta se projevovala oslabením addukce a extenze III.–V. prstu paretické ruky a neschopností provést střídavou rychlou extenzi a flexi prstů téže ruky. Obraz myelopatické ruky však není pro DCM specifický (Ono et al., 1987). Ebara et al. proto v následující práci odlišují tzv. „amyotrofický a myelopatický typ ruky" (Ebara et al., 1988). Amyotrofický typ se vyznačuje slabostí a atrofiemi svalů (zejména drobných ručních), ale bez poruch cítivosti a není spojena s poruchou chůze. Histopatologicky převažuje postižení šedé hmoty předních míšních rohů ve výši míšních segmentů C7–Th1. Oproti tomu u myelopatického typu převažuje spasticita, jsou přítomné poruchy cítivosti a histologicky průkazné postižení kortikospinálního traktu a zadních míšních provazců (Ebara et al., 1988). V naší studii jsme zjistili neobratnost rukou v 84 % případů, sníženou svalovou sílu horních končetin v 54 % a slabost jen akrálně (stisk ruky, abdukce a addukce prstů) v 16 % (Bednarik et al., 2008). Senzitivní postižení rukou může být jen mírné, nemusí být klinicky vůbec patrné. Motorické postižení naopak může být tak výrazné, že pacientovi dokonce neumožnuje samostatně jíst (Epstein et al., 1984).

Postižení chůze

Poruchy chůze jsou velmi častým (80–100 %) a zároveň časným příznakem (Malone et al., 2012). Chůze je neobratná, nešikovná, nejistá, ataktická, zpočátku jen nenápadně (Kalsi-Ryan et al., 2020). Projeví se především při náročnějších typech chůze (rychlá, v nerovném terénu, při rychlé změně směru) a zejména při běhu, a to již u nemocných bez jasných klinických známek spasticity (Kadanka et al., 2021). Někteří autoři uvádí, že lehká porucha chůze bývá nejčasnějším příznakem DCM, následovaná zhoršením jemné motoriky horních končetin (Lunsford et al., 1980). Etiopatogeneze není ještě zcela vyjasněna a je předmětem řady studií, nejspíše však klíčovou roli hraje postižení kortikospinálního traktu s postupně nastupující spasticitou, v kombinaci s poruchou propriocepce (Malone et al., 2012). Zhoršení chůze může mít poměrně široký klinický obraz, v nejtěžších případech až těžké spastické paraparézy (Kalsi-Ryan et al., 2013).

Tab. 1. *Subjektivní příznaky DCM (dle Tracy et Bartleson, 2010)*

- Bolesti (či ztuhlost) krční páteře
- Jednostranná/oboustranná bolest horních končetin
- Slabost, ztráta obratnosti a jemné motoriky horní končetiny
- Ztuhlost dolních končetin, slabost či porucha senzitivity
- Močová inkontinence či urgence
- Nejistota při chůzi, pády
- Lhermitteův příznak

Tab. 2. *Objektivní příznaky DCM (dle Tracy et Bartleson, 2010)*

- Spastická paréza jakékoliv končetiny (nejčastěji spastická paraparéza dolních končetin)
- Hyperreflexie na končetinách/klonus nohy
- Hoffmanův příznak
- Babinského a/nebo Chaddockův příznak
- Chabá paréza jedné nebo obou horních končetin (korespondující s místem komprese)
- Ztráta senzitivity (končetin či trupu)
- Porucha chůze, zejména při podezření ze spasticity

Tab. 3. *mJOA škála (modifikovaná podle Benzela et al., 1991)*

Body	Definice
	Skóre poruch hybnosti horních končetin
0	neschopnost pohybu rukama
1	neschopnost se najíst lžící, ale možnost pohybu rukama
2	neschopnost zapnutí knoflíků u košile, ale schopnost se najíst lžící
3	schopnost zapnout knoflíky u košile s velkými potížemi
4	schopnost zapnout knoflíky u košile s malými potížemi
5	žádná porucha funkce
	Skóre poruch hybnosti dolních končetin
0	úplná ztráta motorických a senzitivních funkcí
1	čití zachováno, ale nemožnost pohnout dolními končetinami
2	schopnost pohnout dolními končetinami, ale neschopnost chůze
3	schopnost chůze po rovné podlaze s pomocí hole nebo berle
4	schopnost chůze po schodech nahoru i dolů za přidržování zábradlí
5	střední až významná porucha stability, ale schopen chůze po schodech – bez přidržování zábradlí
6	střední porucha stability, ale schopnost chůze bez hole, plynulým střídáním dolních končetin
7	bez poruchy funkce
	Skóre poruchy senzitivity horních končetin
0	úplná ztráta čití na horních končetinách
1	těžká ztráta čití nebo bolest
2	mírná porucha čití
3	bez poruchy čití
	Skóre poruch sfinkterových funkcí
0	neschopnost volního spouštění mikce
1	značné obtíže při močení
2	mírné až středně těžké obtíže při močení
3	normální močení

Vyšetření chůze (a event. i běhu) a monitorace eventuálního zhoršení těchto parametrů by mělo být součástí rutinního vyšetření každého pacienta s DCM.

Poruchy močení

Vyskytují se u relativně malého počtu pacientů s DCM – zhruba u 20 % (Hilton et al., 2018). Vzhledem k tomu, že DCM postihuje především starší muže, tak mohou připomínat (či bývají kombinovány s) projevy onemocnění prostaty. Pacienti si obvykle stěžují na urgenci (nebo naopak opožděné močení a menší frekvenci), jen zřídka na inkontinenci (Kelly et al., 2012). Různý stupeň postižení svalového napětí močového měchýře (často subklinický) bývá dokonce popisován až u 44 % pacientů (McCormick et al., 2020).

Další klinické známky myelopatie

Klonus nohy: může být projevem zvýšené spasticity při postižení kortikospinální dráhy. Tento klinický projev má v diagnostice DCM nízkou senzitivitu (11 %), ale vysokou specificitu (96 %) (Cook et al., 2009). **Lhermitteův příznak:** je charakterizován pocity elektrických výbojů dolů podél páteře a do končetin po předklonu (méně často po záklonu) hlavy. Je způsoben lézí zadních míšních provazců krční nebo kaudální části prodloužené míchy. Je velmi specifický pro krční myelopatii (jakékoliv příčiny), ale jeho senzitivita není u DCM příliš velká – bývá uváděna asi v 27 % (Milligan et al., 2019). **Hoffmannův příznak:** při něm uchopíme pacientovu ruku a druhou rukou krátce cvrnkneme do nehtu třetího prstu držené ruky. Odpovědí je krátká flexe palce nebo prstů. Tento iritační pyramidový jev má v běžné populaci prevalenci 2 %. V případě DCM má pozitivní prediktivní hodnotu 68 % a negativní prediktivní hodnotu 70 %, což jej činí užitečným nástrojem v její diagnostice (Fogarty et al., 2018). **Babinského příznak:** pozitivní Babinského reflex, typický pro centrální postižení, má vysokou specificitu (100 %), avšak nízkou senzitivitu (McCormick et al., 2020).

Diagnostika DCM

Současný zlatý standard diagnostiky DCM je průkaz míšní komprese na MR krční páteře (s nebo bez hyperintenzity na T2-vážených obrazech) a přítomnost alespoň jednoho objektivního a jednoho subjektivního příznaku myelopatie. Ty jsou shrnuty v následujícím přehledu (Tracy et Bartleson, 2010) (Tab. 1 a 2).

Ke zhodnocení klinického stavu pacientů s DCM se používají různé škály (Nurickova, Cooper myelopathy scale, European myelopathy scale apod.). Klinicky nejpraktičtější a nejvíce citovanou je tzv. mJOA (modified Japanese Orthopaedic Association) škála. Byla vytvořena Japonskou ortopedickou asociací v roce 1974. Pro celosvětové používání však musela být upravena, původní škála totiž hodnotila i schopnost pacientů jíst japonskými jídelními hůlkami (Benzel et al., 1991). Tato škála velmi dobře odráží poruchu hybnosti horních končetin, postižení chůze, hodnotí i poruchu cítivosti na horních končetinách a potíže s močením (Tab. 3). Maximum bodů je 18, které bývá stanoveno u pacientů bez jakýchkoliv klinických známek myelopatie, minimum bodů je 0, které značí již extrémně těžké funkční omezení (prakticky kvadruple-

gii). Fehlings et al. definovali tíži myelopatie na lehkou (mJOA ≥ 15), středně těžkou (mJOA 12–14) a těžkou (mJOA < 12) (Fehlings et al., 2017).

Zobrazovací a pomocná vyšetření

MR krční páteře je podle současných kritérií základním radiologickým vyšetřením pro stanovení diagnózy DCM, zobrazení míchy a jejích kořenů. Hyperintenzita signálu v T2-vážených obrazech v místě komprese, která bývá často považována za klasický projev DCM, však bývá přítomna v méně než 50 % případů (Matsumoto et al., 1998). Jakákoliv deformita krční míchy (vyklenutí, zploštění či zúžení přilehlými strukturami (zejména vyklenutím meziobratlové ploténky)) by měla být posuzována jako typ komprese, který může způsobit neurologické postižení (Obr. 1). Krční míšní komprese je však velmi častá a je přítomna i u zcela asymptomatických jedinců. Nazýváme ji pak asymptomatickou míšní degenerativní kompresí či lépe nemyelopatickou degenerativní míšní kompresí (NMDCC). U bělošské euroamerické populace nad 60 let dosahuje její prevalence dokonce až 40 % (Kovalova et al., 2016).

CT a nativní rtg snímky (včetně funkčních) poskytují důležité informace zejména o dynamice páteře a kostních změnách, které mohou být vodítkem pro zvolení správného typu operace (Martin et al., 2018). CT též poskytuje užitečné informace v případě kontraindikace MR či při přítomnosti kovových artefaktů, které znekvalitňují MR obraz. CT může být přínosnou metodou v diagnostice a klasifikaci typu osifikace zadního podélného vazu (Abiola et al., 2016).

Elektrofyziologické vyšetření umožňuje hodnotit funkční stav nervových struktur (kořenů, míchy, resp. jednotlivých jejích drah). Přispívá tak k rozhodnutí o významnosti radiologických nálezů degenerativních změn, které vykazují v klinické praxi vysokou prevalenci, často však bez jasného klinického korelátu. Elektrofyziologické metody mohou odhalit subklinická postižení příslušných struktur, objektivizují a zpřesňují klinický nález a mohou poskytnout bližší informaci o lokalizaci postižení v případech, kdy to klinický nález neumožňuje. U pacientů s DCM provádíme kondukční studie z horních končetin (n. medianus, ulnaris a radialis) a jehlovou EMG se zaměřením na radikulopatii C5–8 na obou horních končetinách.

Nedílnou součástí diagnostického algoritmu u pacientů s míšní kompresí či myelopatií jsou kromě elektromyografie také motorické a somatosenzorické evokované potenciály. Motorické evokované potenciály (MEP) umožňují hodnocení rychle vedoucích kortikospinálních drah. Jsou odpovědí na magnetickou stimulaci motorických drah transkraniálně v oblasti primárního motorického kortexu a dále v oblasti míchy. Podstatou této stimulace je indukce proudu ve vodivé tkáni pulzním magnetickým polem. Odpovědí je aktivace odpovídajících svalových skupin snímaná na periferii, tedy nad cílovým svalem s využitím stejných elektrod a zapojení, jaké jsou užívány v běžných kondukčních studiích. Snímáme motorické odpovědi z m. abductor digiti minimi na horních končetinách a m. abductor hallucis či m. tibialis anterior na dolních končetinách. Somatosenzitivní evokované potenciály (SEP) vznikají jako odpověď struktur periferního nervového systému (brachiálního nebo lumbálního plexu), míchy a mozku na elektrickou stimulaci periferních nervů. Tím nás informují o funkci zadních provazců a tractus spino-bulbo-thalamo-corticalis/lemniscus medialis. Na horních končetinách nejčastěji vyšetřujeme SEP n. medianus při stimulaci v zápěstí, na dolních končetinách SEP n. tibialis při stimulaci za vnitřním kotníkem, v obou případech repetitivní elektrickou stimulací nízké intenzity. Evokované potenciály nás informují o stupni postižení periferní i centrální části senzitivní a motorické dráhy. Nabývají na významu při průkazu subklinických změn, při sledování průběhu nemoci, efektu terapie a při diferenciální diagnostice. Působí však i jako prediktory rozvoje DCM u pacientů s NMDCC (Kadanka et al., 2017). Elektrofyziologické vyšetření je důležité i pro vyloučení jiné neurologické etiologie potíží (např. periferní mononeuropatie, amyotrofická laterální skleróza, roztroušená skleróza apod.).

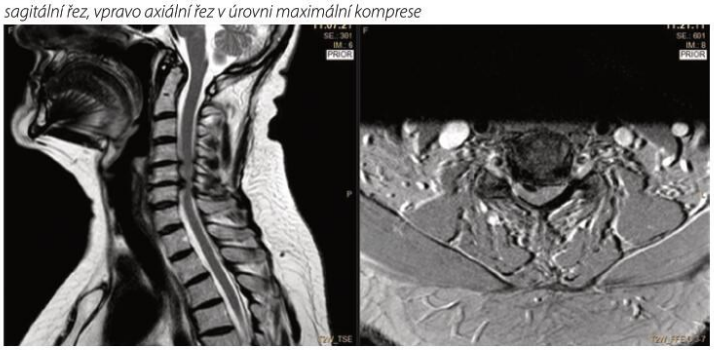
Strategie léčby DCM

V průběhu let řada prací prokázala, že klinický vývoj onemocnění je velmi individuální a variabilní a že mnoho pacientů zůstává stabilních i po řadu let. Naopak poměrně velké množství z nich se klinicky horší, pokud není včas léčeno. Postupně docházelo k průběžné úpravě doporučení léčby pacientů s DCM i nemyelopatickou degenerativní míšní kompresí. Přestože existují některá data, která sledují rizikové faktory progrese NMDCC do symptomatické DCM, neexistuje jasný, vědecky podložený konsenzus léčebného postupu zejména u pacientů s mírnou myelopatií či NMDCC, který by zahrnoval i eventuální prospěšnost chirurgické dekomprese u vysoce rizikových pacientů s NMDCC.

Konzervativní léčba DCM spočívá v první řadě v úpravě životosprávy a změně životního stylu. K tomu patří především odstranění všech rizikových faktorů, které mohou progresi nemoci urychlit:

- těžká fyzická námaha,
- úprava lůžka tak, aby krční páteř nedosahovala během spánku krajních poloh,
- omezení takové aktivity, která by mohla vést k poranění páteře (pohyb na kluzkém teré-

Obr. 1. *Pacient se středně těžkou DCM, mJOA 12; klinicky lehká kvadruparéza; T2-vážené sekvence, vlevo sagitální řez, vpravo axiální řez v úrovni maximální komprese*



Tab. 4. *Strategie léčby pacientů s DCM (dle Fehlings et al., 2017)*

1. Pacient s těžkou DCM (mJOA 0–11): doporučuje se chirurgická intervence (*doporučení: silné; průkaz: střední*)
2. Pacient se středně těžkou DCM (mJOA 12–14): doporučuje se chirurgická intervence (*doporučení silné; průkaz střední*)
3. Pacient s mírnou DCM (mJOA 15–17): doporučuje se nabídnout buď chirurgickou intervenci, nebo cílenou rehabilitaci se sledováním klinického stavu; pokud neproběhne operace v počátečním stadiu, tak se doporučuje provést v případě, že se stav pacienta neurologicky horší či se po konzervativní léčbě nelepší (*doporučení: slabé; průkaz: velmi nízký*)
4. Pacient s míšní kompresí, bez známek myelopatie, avšak s projevy radikulopatie: mají vyšší riziko rozvoje DCM; doporučuje se nabídnout buď chirurgickou intervenci, nebo cílenou rehabilitaci se sledováním klinického stavu; v případě rozvoje DCM pokračovat podle výše uvedených doporučení (*doporučení: slabé; průkaz: žádný – založeno na expertním názoru autorů*)
5. Pacient s míšní kompresí bez známek myelopatie či radikulopatie: nedoporučuje se profylaktická operace; pacient by měl být poučen o potenciálních rizicích a příznacích myelopatie a měl by být dlouhodobě klinicky sledován (*doporučení: slabé; průkaz: žádný – založeno na expertním názoru autorů*)

nu, na žebříku, práce ve výškách, extrémní sportovní aktivity),
- omezení takových činností, které zhoršují funkci páteře (jednostranná statická i dynamická zátěž), vibrace (práce s vibračními nástroji), dlouhodobá fyzická nečinnost, dlouhodobá fixace páteře, prochlazení, vyloučení krajních poloh hlavy (u kadeřníka, při operacích), násilný předklon i záklon hlavy,
- pečlivá léčba diabetu,
- zákaz kouření,
- denně dostatek chůze,
- přechodná fixace krční páteře měkkým límcem v době nezbytné zátěže.

V obdobích period bolestí doporučujeme přechodný klid na lůžku a nošení měkkého krčního límce. Podáváme nesteroidní antiflogistika a myorelaxancia, výjimečně u těžkých případů krátkodobě kortikoidy. Je možná též epidurální injekce anestetika a kortikoidů. Do úvahy přichází i fyzikální terapie, i když její efekt též nebyl dostatečně prokázán, je kontraindikovaná manipulace krční páteře (Toto, 1986).

V roce 2017 vydala expertní skupina severoamerických spondylochirurgů za podpory AOSpine North America svoje doporučení, které dále doplnila názory odborníků z oblasti chirurgie páteře, rehabilitace, neurologie, revmatologie a v neposlední řadě zahrnula i pacientovy preference, rizika a benefity prováděných operací i ekonomický dopad jednotlivých způsobů léčby (Fehlings et al., 2017). Tato kritéria charakterizují současný pohled na indikace operační léčby pacientů s DCM a NMDCC (Tab. 4).

Závěr

DCM je potenciálně závažné onemocnění, které je značně poddiagnostikované a může vést až k výrazné imobilizaci pacientů. Správná a včasná diagnostika a strategie léčby včetně ideálního načasování operace může výrazně zlepšit kvalitu života postižených jedinců. Podle současných doporučení by měli být nemocní se střední (mJOA 12–14) a těžkou (mJOA 0-11) formou DCM léčeni operativně. U pacientů s lehkou (mJOA 15–17) formou DCM a pacientů bez klinických známek myelopatie, avšak s projevy radikulopatie, by měla být navržena buď operační léčba, či cílená rehabilitace. Jedinci s průkazem významné míšní komprese (avšak bez klinických známek myelopatie či radikulopatie) by měli být pravidelně klinicky sledováni.

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