PAINFUL SENSORY NEUROPATHIES IN THE ELDERLY

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ABSTRACT

Introduction: Painful sensory neuropathies are frequently encountered in elderly individuals. The pathophysiology of peripheral nerve dysfunction as well as the clinical picture and applicable diagnostic methods in senescence may be at least partly different from those in the general neuropathy population with respect to the potential role of age-related neurodegeneration as well as to some specific features of the elderly population in general.

Patients and methods: Thermal quantitative sensory testing (T-QST), evaluation of intra- (IENFD) and subepidermal nerve fibre densities in skin biopsy samples, nerve conduction studies, autonomic nervous system testing, and clinical neurological examination including detailed assessment of neuropathic symptoms and pain intensity were performed in a group of 25 elderly (≥65 years) and 74 non-elderly patients with painful sensory neuropathy. For comparison, data from 37 age-matched healthy individuals (10 elderly and 27 non-elderly) were used.

Results: The involvement of small nerve fibres documented by T-QST or IENFD was almost invariably found in both elderly and non-elderly patients and the sensitivity as well as applicability of both these methods was similar between the age groups. Nevertheless, an obvious trend to decrease in nerve fibre counts with age was observed in the healthy control group. The dysfunction of large nerve fibres (assessed by nerve conduction studies or clinical examination) as well as of the autonomic ones was significantly more frequent in elderly neuropathy patients compared to younger age groups. Moreover, evaluation of the autonomic nervous system could frequently not be performed in elderly patients with respect to associated heart diseases or medication.

Conclusions: Painful neuropathy patients almost invariably display involvement of small nerve fibres regardless of the patient's age. In elderly painful neuropathy patients, however, a more frequent and more extensive dysfunction of large myelinated fibres and autonomic fibres was found suggesting the increasing role of age-related neurodegeneration in the development of peripheral neuropathies in old age and

implying the need of age-stratified reference data of most of the diagnostic tests of small- and large-fibre dysfunction in peripheral neuropathies.

ABBREVIATIONS USED

AUDIT – alcohol use disorders identification test
IENFD – intraepidermal nerve fibre density
MNSI – Michigan neuropathy screening instrument questionnaire (subscales i and ii)
NDS – neuropathy disability score
NSS – neuropathy symptom score
PGP – protein gene product
T-QST – thermal quantitative sensory testing
SENPD – subepidermal nerve plexus density
SNAP – sensory nerve action potential
VAS – visual analogue scale

INTRODUCTION

Painful sensory neuropathies are frequently encountered in elderly individuals and may have an important impact on their sleep and quality of life. Besides an increasing incidence of neuropathy risk factors in senescence, degeneration of the peripheral nervous system in old age has repeatedly been shown in humans as well as in animal models of nervous system aging, and seems to play a role in the development of peripheral neuropathies in the elderly [1, 2]. Both the age-related degeneration and the involvement of peripheral nerves by some pathological processes may involve various types of nerve fibres, and the pattern and proportion (and probably also the time sequence) of the fibres affected are crucial for the clinical picture of peripheral neuropathy. Experimental models [1, 2, 3] suggest that, in contrast to e.g. metabolic neuropathies, where initial and more pronounced involvement of so-called small non-myelinated and low myelinated nerve fibres of the classes A-delta and C is usually described, the age-related degeneration process affects predominantly large myelinated fibres of A-beta class. The suggested different pattern of the affected nerve fibres in the elderly therefore indicates that the resulting clinical picture and diagnostic methods of peripheral neuropathies in senescence may be at least partly different from those in younger age groups.
Besides more frequent affection of large nerve fibres in senescence, age-related loss of small nerve fibres has also been described in rodents [2, 3] as well as in some of the human studies on epidermal innervation reflecting the age-related changes of small nerve fibre status [4, 5]. The involvement of these fibres (mediating pain and temperature, and also serving autonomic functions) has repeatedly been shown to play an important role in the pathophysiology of neuropathic pain [6, 7], and their dysfunction has been found in most of the painful neuropathies [8, 9, 10]. A-delta and C fibres can even be the only nerve fibres affected in some of the painful neuropathy patients (so-called small fibre neuropathies) [8, 9, 10]. Their involvement, however, is usually underdiagnosed in clinical practice, because common clinical examination and nerve conduction studies fail in the verification of their dysfunction [8], and special diagnostic methods (e.g. examination of thermal and/or pain sensation on quantitative sensory testing (T-QST) or quantification of intraepidermal nerve fibre density (IENFD)) have to be used for this purpose [8]. Both of these methods, however, may have some limitations, particularly in elderly patients. Together with some specific characteristics of senescence in general, all these facts point out the possibility that the pathophysiology, the clinical picture and applicable diagnostic methods of neuropathies in the elderly are at least partly different from the general neuropathy population, in particular when pain is a leading clinical symptom. Only few studies, however, deal with clinical, neurophysiological, and morphological characteristics of painful peripheral neuropathies in senescence.
The aim of our study was therefore to evaluate selected clinical, morphological, and electro- and psychophysical findings in older adults with painful sensory neuropathy compared to younger patients to reveal possible specific features of this diagnostic unit in the elderly and to assess the diagnostic validity of several methods used to confirm a peripheral nerve dysfunction in these patients.

PATIENTS AND METHODS

Twenty-five elderly patients (older than 65 years) with painful sensory neuropathy and a prominent complaint of "burning feet" were included in the study (Table 1). For comparison, data from seventy-four non-elderly individuals with painful neuropathy complying with the same inclusion and exclusion criteria (see below) were used (Table 1). All the patients from both these groups were prospectively recruited from the Peripheral Neuropathy Outpatient Clinic of the Brno Faculty Hospital between September 1999 and March 2005. The protocol was approved by the institutional ethics committee of the University of Brno; written informed consent was obtained from all patients and volunteers before inclusion into the study.
The following inclusion criteria had to be met: [1] Positive sensory symptoms (pain or painful dysesthesias described as electric shock-like, burning, cold, prickling, tingling, or itching) in a distal symmetrical distribution in the lower extremities for more than 3 months and with an intensity of at least 3 on a visual analogue scale (VAS) of 0–10. [2] Abnormal thresholds for at least one thermal modality as assessed by T-QST.

Table 1
Clinical characteristics of patients and controls. Abbreviations are defined in the text

Demographic characteristics	Neuropathy group		Controls	
	Elderly	Non-elderly	Elderly	Non-elderly
Number of subjects studied	25	74	10	27
Males	13	45	6	11
Signs of large fibre affection	17	24		
Age				
Median (min/max) (years)	71 (65/83)	55 (25/64)	70 (67/86)	54 (27/64)
Symptom duration				
Median (min/max) (years)	1.50 (0.25/6)	2.00 (0.25/13)		
Associated relevant diseases (number of subjects)				
Diabetes mellitus or impaired glucose tolerance	5	27		
Alcohol abuse	2	13		
Others[1]	7	14		
Undetermined	11	20		

[1]Others: potential aetiological factors or co-factors include toxins (anticancer chemotherapy or antituberculous drugs), paraneoplastic syndromes, monoclonal gammopathy, hyperlipidaemia, and amyloidosis

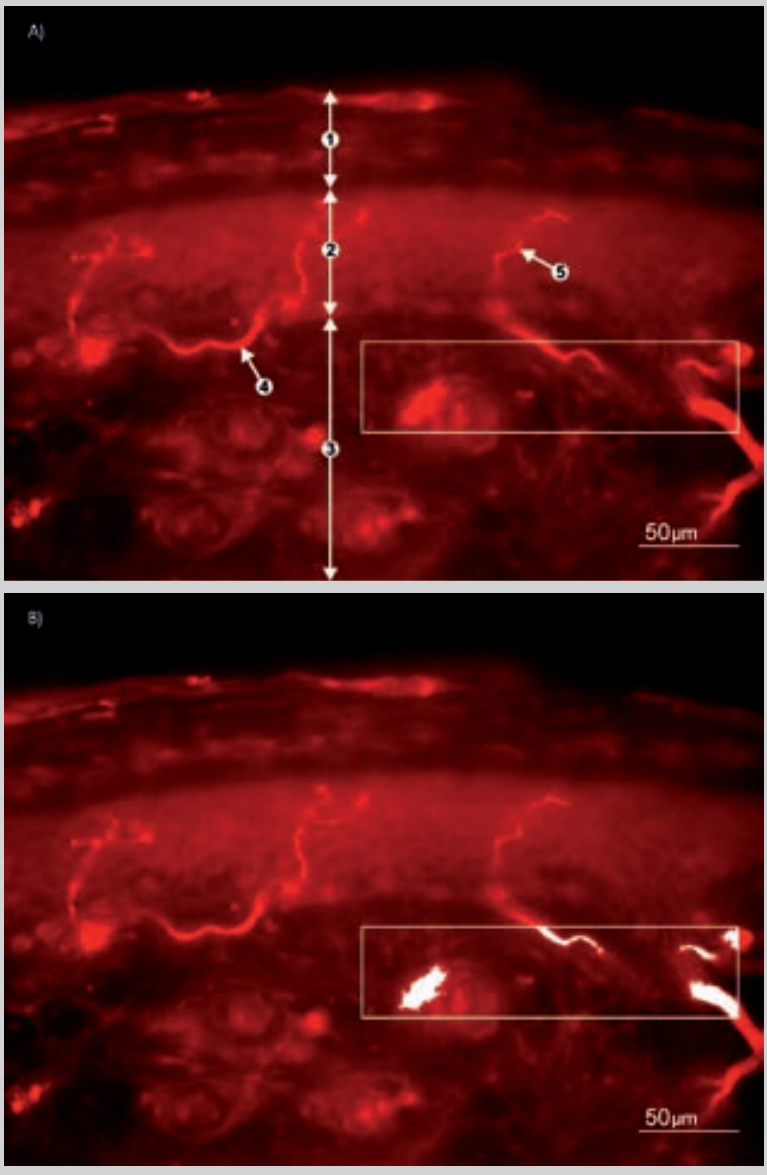
Exclusion criteria were signs of central (brain or spinal cord) involvement and any overt clinical motor signs (weakness, distal muscle atrophy, fasciculations). Other diseases or conditions leading to foot pain (both neuropathic and non-neuropathic) such as plantar fasciitis, Charcot's joints, osteoarthritis, peripheral vascular disease, central nervous system dysfunction, tarsal tunnel syndrome, and other peripheral mononeuropathies were excluded by history and clinical examination.

For comparison of skin nerve fibre densities with the non-neuropathy population, data from a group of thirty-seven healthy volunteers matched for age and body mass index (10 elderly and 27 non-elderly subjects) were used (Table 1). These individuals were recruited at the Brno Faculty Hospital, mainly from among hospital employees and their relatives, and the details about their history and clinical status as well as their laboratory findings of the parameters with a potential aetiological relation to peripheral neuropathies were published previously in detail [9, 10].

Data from the patients and controls included into the present study were reported in part in a previous study evaluating in detail the diagnostic value of skin biopsy (including a newly validated parameter – subepidermal nerve plexus density) [9]. The previous study, however, dealt mainly with morphological findings and was focused neither on the specifications of painful neuropathies in the elderly nor on the differences between elderly patients and those of younger age groups. In contrast, the current study deals only with characteristic features of painful peripheral neuropathy in senescence, which are suggested to be partly different from the general neuropathy population.

A detailed medical history was taken from all patients, who underwent a thorough clinical neurological examination, including assessment of tendon reflexes, muscle strength, trophism, sensation to touch, pinprick, warm and cold stimuli, proprioception, and vibration sense. Associated diseases with potential aetiological relevance were explored by history and routine biochemical, haematological, and immunological blood tests including thyroid hormones, triglycerides, vitamin B_{12} and folate levels, serum protein electrophoresis, carbohydrate-deficient transferrin, and a set of autoantibodies (ANA, anti-Ro, anti-La, anti-DNA). Diabetes mellitus was confirmed by fasting plasma glucose levels and oral glucose tolerance tests. Quantification of alcohol consumption as well as further confirmation of harmful alcohol use and possible alcohol dependence was performed according to the WHO AUDIT (Alcohol Use Disorders Identification Test) manual [11].

For quantification of the presence and severity of clinical symptoms and neurological impairment, the Neuropathy Symptom Score (NSS) [12], the Neuropathy Disability Score (NDS) [12], and the Michigan Neuropathy Screening Instrument Questionnaire (MNSI) [13] were employed. The mean intensity of neuropathic pain during the week before clinical



Figures 1a, b
Images depicting the method for evaluation of the intraepidermal nerve fibre density (IENFD) and subepidermal nerve plexus density (SENPD) on PGP 9.5 immunoreacted 40-µm cryosections of the skin. SENPD was measured using a density threshold for PGP 9.5 immunoreactive structures and expressed as a percentage of the whole subepidermal area analysed (200 x 50 µm adjacent to the dermoepidermal junction in each optical field)

A: Original digitised image. Bar = 50 µm
1 + 2 = epidermis (1 = stratum corneum, 2 = stratum basale, spinosum, granulosum, and lucidum)
3 = dermis
4 = subepidermal nerve plexus
5 = intraepidermal nerve fibre

B: Density threshold set for morphometric determination of nerve fibre area. Bar = 50 µm

and electrophysiological testing was assessed using a 10-cm VAS, in which 0 cm represented "no pain" and 10 cm "the worst pain I can imagine". All the clinical and electrophysiological tests were performed at the time of admission to the clinic and no specific treatment for neuropathic pain had been delivered to these patients previously.

Quantitative sensory thermal threshold testing (T-QST) was performed using thermal sensory analyser software (Medoc Thermal Sensory Analyser 2001). Thermal thresholds were examined on the dorsum of the right foot; both the method of limits and levels were used. For evaluation we used our own normal limits [14]. The methodology was described elsewhere in detail [9, 14].

Electrophysiological examinations, sympathetic skin response, and cardiovascular tests based on heart rate variability examination were performed using a Keypoint type II electromyograph system (Dantec, Skovlunde, Denmark), following the published recommendations [15]. The results were processed according to the reference values related to age and height at the Brno laboratory.

Skin punch biopsies were taken from the distal calf. The details of skin specimen removal and further processing were published previously [9, 16] and follow standard recommendations [17, 18]. Sections of 40 µm thickness were immunostained with rabbit polyclonal antibodies to human protein gene product (PGP) 9.5 (Ultraclone, Wellow, UK; 1:800) as a primary antibody and goat anti-rabbit IgG labelled with a cyanine fluorescent probe as a secondary antibody (Amersham, Biosciences, Piscataway, NJ; 1:100). Using Image-Pro Plus 4.0 software (Media Cybernetics, Leiden, The Netherlands), the intraepidermal nerve fibre density (IENFD) was quantified by counting the nerve endings within an accurately measured length of epidermis [17, 18] (Figure 1).

Subepidermal nerve plexus density (SENPD) was measured using a density threshold for PGP9.5 immunoreactive structures and expressed as a percentage of the whole subepidermal area analysed (200 x 50 µm adjacent to the dermoepidermal junction in each optical field) [9] (Figure 1). The IENFD was defined as abnormal if lower than the cut-off value of 8.8 fibres/mm [9]. Similarly, the SENPD was defined as abnormal if lower than the cut-off value of 7.25 % [9]. The normal limits were established from the skin biopsy results in the group of normal individuals and the method settings were described in our previous publication [9].

Standard descriptive statistics were used to summarise the distribution of the data. Comparison of continuous data between both the subgroups was performed by a univariate t-test, while categorical data were compared using a chi-square test. The Pearson's correlation coefficient was used in correlation analyses. The value $\alpha < 0.05$ was taken as the universal limit for statistical significance.

RESULTS

As a matter of course, the age of elderly patients was higher in comparison with non-elderly ones ($p<0.001$), while the other demographic characteristics (i.e. sex and duration of symptoms) did not differ between the groups (Table 1). Prominent aetiological factors of both groups represented impaired glucose metabolism and chronic harmful alcohol use or possible alcohol dependence. The incidence and proportion of the particular aetiological factors did not differ significantly between the groups, though a trend towards lower incidence of glucose dysmetabolism ($p=0.12$) and a higher proportion of patients with undetermined (i.e. idiopathic) aetiology in elderly patients ($p=0.11$) was found (Table 1).

Clinically, impaired proprioception and vibration sense as signs of large-fibre sensory dysfunction were significantly more frequent in elderly patients ($p=0.001$ and 0.002, respectively; data not shown). For other sensory modalities, a trend towards higher incidence of abnormities in the elderly group was also found, though without statistical significance ($p= 0.07$, 0.05, and 0.10 for sensation to pinprick and pain and thermal perception, respectively; data not shown). In accordance with these findings, higher values and higher sensitivity of NDS and a second part of the MNSI questionnaire (as the scales reflecting the presence of clinical abnormities and in particular large-fibre function) were found in our group of elderly patients, while only less obvious and less significant differences were found in the Neuropathy Symptom Score values (reflecting both the small and large nerve fibre function) (Table 2).

The intensity of neuropathic pain as assessed by VAS as well as the presence of clinical symptoms of sensory dysfunction (evaluated either as particular items or as a summary score reflecting mainly the dysfunction of small nerve fibres, i.e. the first part of the MNSI questionnaire) were similar in both groups of neuropathy patients (Table 2). Accordingly, the sensitivity of this questionnaire was also comparable in elderly and non-elderly individuals.

Absolute values of cold and warm detection thresholds, the number of abnormities of thermal sensation found by the particular testing algorithms using the age-related normal values, and also the variability of the responses did not differ significantly between the groups (Table 2). The results obtained by the three T-QST methods were consistent and values did not differ significantly between the methods.

The reduction of sensory nerve action potential (SNAP) amplitudes represented the most significant difference of nerve conduction studies between the groups (Table 2). In general, electrophysiological signs of large fibre sensory neuropathy were more frequent in elderly patients ($p = 0.002$) (data not shown).

The elicitability of sympathetic skin response was similar in both groups of patients. In the elderly group, however, slightly

Table 2

Absolute values and number of abnormities (if applicable) revealed by selected psychophysical, neurophysiological, and clinical tests in elderly and non-elderly neuropathy patients. Values are mean ± standard deviation. Abbreviations are defined in the text

Test	Absolute values			Number of abnormities revealed		
	Elderly	Non-elderly	p-value (t-test)	Elderly	Non-elderly	p-value (chi²-test)
Thermal thresholds (dorsum of the right foot, °C)						
MLI – R CS	20.2 ± 10.4	21.5 ± 8.8	0.54	14	37	0.60
WS	47.0 ± 3.4	46.8 ± 2.8	0.73	22	56	0.19
MLE – CS	22.3 ± 10.6	23.3 ± 9.3	0.66	13	38	0.96
WS	44.4 ± 4.1	44.2 ± 3.5	0.76	22	67	0.72
Nerve conduction studies						
Sural SNAP amplitude (μV)	3.7 ± 3.3	8.7 ± 5.5	< 0.001	16	20	< 0.001
Sympathetic skin response (lower extremities)						
Mean latency (ms)*	2.23 ± 0.28	2.11 ± 0.22	0.04			
Mean amplitude (mV) *	0.41 ± 0.25	0.73 ± 0.72	0.04			
Elicitability (%)	58	66	0.27	4	8	0.50
Heart rate variability						
Heart-rate variability to						
deep breathing (%)	11.9 ± 5.8	18.8 ± 10.3	0.04	8	22	0.04
Clinical findings						
VAS*	6.14 ± 2.56	6.38 ± 2.0	0.62			
MNSI 1	7.60 ± 2.00	7.93 ± 2.29	0.52	19	57	0.91
MNSI 2	2.48 ± 1.41	1.35 ± 1.33	< 0.001	20	26	< 0.001
NSS*	2.56 ± 1.16	2.04 ± 0.83	0.02			
NDS*	15.7 ± 13.7	6.9 ± 7.9	< 0.001			

*No limit data for discrimination of normal and abnormal findings of this parameter are available

MLI – Method of Limits, MLE – Method of Levels, CS – cold sensation, WS – warm sensation, R – random variant of the test); other abbreviations are defined in the text

higher latencies and lower amplitudes of the response were found in the lower extremities (Table 2).

The heart rate variability testing could not be performed or evaluated in more than a half of the elderly group because of associated heart disease or medication with potential influence on the heart rate (56 % compared to 24 % of non-elderly individuals, p = 0.003). From the evaluable tests, the vast majority was abnormal in elderly patients, while in the non-elderly group abnormal results were much less frequent (72 and 36 %, respectively, p = 0.02). In most of the tests performed, significantly lower heart rate variability values were thus obtained were thus obtained in elderly individuals in comparison to younger ones (Table 2).

In the group of healthy individuals, a non-significant trend to the correlation of the IENFD and SENPD values with age as well as to higher values in the subgroup of elderly controls compared to non-elderly ones was found (Table 3). Comparison of healthy individuals and painful neuropathy patients demonstrated a clear reduction in both intra- and subepidermal nerve fibre/plexus density in both the elderly and non-elderly subgroups of patients with neuropathies compared to the particular age-related subgroups of healthy controls (Table 3). In neuropathy patients, lower values of the SENPD were found in elderly patients than in non-elderly ones, while the IENFD values did not differ significantly between the age groups (Table 3). A clear correlation of the IENFD values with warm thresholds in T-QST examination and with the scales reflecting particularly small nerve fibre involvement (i.e. MNSI I) and lower intraepidermal nerve fibre counts in the presence of clinical signs of small fibre dysfunction were found in both the age subgroups of neuropathy patients, while the SENPD correlated better with SNAP amplitude and MNSI II and NDS (as the scales showing mainly large nerve fibre function) in both elderly and non-elderly individuals (p from 0.02 to <0.001; data not shown).

DISCUSSION

The principal finding of this prospective study is that the involvement of small nerve fibres is almost invariably present in elderly patients with painful neuropathies. Despite this fact,

Table 3

Skin biopsy findings. IENFD (fibres/mm) and SENPD (% of the subepidermal area of the size 200 x 50 µm adjacent to the dermoepidermal junction): basic summary statistics, comparison of the neuropathy and control groups and elderly and non-elderly individuals, and correlation with age in the control group of healthy individuals. Abbreviations are defined in the text

	Groups of patients		Comparison of the groups	Correlation with age in control group	
	Elderly	Non-elderly	p_1-value	r	p-value
IENFD (fibres/mm)					
Group of patients	4.95 ± 3.02	5.69 ± 4.08	0.40		
Healthy individuals	9.81 ± 1.61	11.80 ± 3.30	0.08	–0.325	0.06
Comparison of the groups (p_2-value)	< 0.001	< 0.001			
SENPD (%)					
Group of patients	3.19 ± 1.91	4.88 ± 2.75	0.006		
Healthy individuals	8.20 ± 1.31	9.76 ± 2.76	0.10	–0.237	0.16
Comparison of the groups (p_2-value)	< 0.001	< 0.001			

p_1-value – comparison of nerve fibre density between elderly and non-elderly individuals in a group of patients (first row) or in a group of healthy individuals (second row)

p_2-value – comparison of nerve fibre density between elderly neuropathy patients and controls (first column) or non-elderly patients and controls (second column)

a partly different pattern of involvement of the particular nerve fibre types with a more severe and more frequent dysfunction of large nerve fibres compared to younger age groups was found in these individuals showing a probable role of age-related neurodegeneration in the development of peripheral neuropathies in the elderly. These findings imply an increasing significance of clinical examination and nerve conduction studies in the diagnostic algorithm of painful neuropathies in senescence. Almost all the elderly painful neuropathy patients however present an involvement of small nerve fibres and in a remarkable part of them (about 1/3) these fibres were shown to be the only affected ones. Appropriate diagnostic methods of small nerve fibre involvement (i.e. thermal quantitative sensory testing and examination of intraepidermal nerve fibre density) thus still play a pivotal role in the battery of diagnostic tests of painful neuropathies in the elderly, and our findings prove their applicability in older adults as well as their similar diagnostic validity compared to younger age groups, though some particularities (e.g. the need of age-related normal limit data) should be taken into account.

Painful sensory neuropathies are frequently encountered in older adults. As in the other types of peripheral nerve affections, both the clinical picture and applicable diagnostic methods of painful neuropathies in senescence depend in particular on the pattern and proportion of the affected types of nerve fibres. In accordance with the observations in the general painful neuropathy population [9, 19], dysfunction of small nerve fibres was almost invariably present in our group of elderly painful neuropathy patients. A comparison of the age groups showed a similar extent of small-fibre affection (proved both by examination of IENFD and T-QST) as well as an almost identical spectrum of corresponding clinical symptoms and pain intensity (as assessed by VAS) in elderly and non-elderly patients in our study. These findings suggest that, regardless of the patients' age, a similar extent of small fibre damage leads to a similar clinical picture, and thus indirectly confirm the role of small nerve fibre dysfunction in the development of pain and appropriate clinical symptoms of painful neuropathies.

In contrast to these findings, most of the diagnostic methods (in particular clinical examination and nerve conduction studies) proved a more severe and more frequent affection of large myelinated nerve fibres in our group of elderly neuropathy patients compared to the younger ones. A similar pattern of nerve fibre involvement was repeatedly shown in animal models of age-related degeneration of the peripheral nervous system [1, 2]. In aging rats, more symptoms of disturbed mechanosensation compared to disturbed nociception were found [2], and a more severe loss of large and myelinated fibres compared to smaller ones was shown in sural nerve studies of peripheral nervous system aging [1]. Our data thus confirm the observation of more severe age-related degeneration of large and myelinated fibres compared to smaller ones and imply that neurodegeneration plays an important role in the development of painful peripheral neuropathies in the elderly.

Despite these facts, age-related loss of epidermal and dermal innervation, involving both sensory and autonomic

components, was also described in rodents [2, 3]. In humans, some of the studies [4, 5] suggest a similar decrease of intraepidermal innervation with age, but there is no clear agreement on this field and not all the studies show such a significant negative correlation [20], probably due to the considerable interindividual variability of epidermal nerve counts in normal humans. Despite such controversial findings, only few studies are focused on normal skin innervation in senescence and provide separated limit data of intraepidermal nerve fibre counts in the elderly [21], which may complicate the evaluation and the validity of skin biopsy examination in older adults.

In our control group of healthy individuals, an obvious trend to inversed correlation of IENFD/SENPD with age was observed, as well as a trend to lower fibre counts in the subgroup of elderly controls compared to the younger ones. Both of these trends were apparent, but none of them was statistically significant, probably with respect to the small size of our control group and in particular to the small number of elderly individuals among our healthy controls (10 out of 37). Our findings nevertheless seem to confirm the age-related degeneration of intra- and subepidermal nerve fibres and suggest the need of setting particular normal limits for elderly and non-elderly individuals. An increased number of healthy controls and in particular a higher proportion of elderly individuals are therefore needed in future studies.

In comparison with the age-related subgroups of healthy controls, a highly significant decrease in IENFD/SENPD values was found in both the elderly and non-elderly painful neuropathy patients, confirming the high sensitivity of this method, regardless of the patients' age. The examination was well tolerated by all the individuals and no complications of wound healing were observed in any one of the elderly or non-elderly patients. Together with a good correlation of the IENFD with warm thermal thresholds in T-QST examination and with MNSI I as the methods reflecting mainly small fibre dysfunction, these findings show that the examination of the IENFD from skin biopsy is an applicable method in the evaluation of small fibre damage in older adults, and we can recommend the inclusion of this method to the diagnostic algorithm of painful neuropathies in the elderly.

Another method of evaluation of the small nerve fibre dysfunction involved in our study was the examination of thermal thresholds on quantitative sensory testing [8, 22]. In contrast to the morphological character of the previous test, T-QST is a psychophysiological method and therefore requires concentration, attention, and the ability of fast response [22], which may be decreased in the elderly. However, when using the age-stratified reference data, the number of abnormities revealed by the T-QST and the response variability of the methods used did not differ between younger and older neuropathy patients and the results obtained by the three T-QST methods were consistent and values did not differ significantly between the particular algorithms. These findings suggest that when using the age-stratified reference data, psychophysiological methods are useful in elderly patients and provide reliable and reproducible results, fully comparable with younger individuals.

Besides the methods evaluating sensory small nerve fibres, assessment of autonomic nervous system functions can also be used for the evaluation of small nerve fibre status in polyneuropathy patients. Our previous findings [9], however, suggest that the autonomic nervous system testing is less sensitive compared to T-QST and skin biopsy in the evaluation of painful neuropathies in general. In elderly patients, the use of these methods (in particular examination of heart rate variability) is furthermore complicated by the increasing number of patients with coincidental heart rate abnormalities (e.g. atrial fibrillation) and those with implanted pacemakers or using antiarrhythmics (e.g. beta-blockers) in their regular medication. Due to these conditions, the heart rate variability testing could not be performed or evaluated in up to 60 % of elderly patients in our study (but only in about 1/4 of younger individuals). Among the evaluable tests, a significantly higher proportion of abnormalities was found in older patients, suggesting that the autonomic nerves are more frequently involved in painful neuropathies in the elderly as compared with younger age groups. Despite this fact, the sensitivity of autonomic nervous system assessment did not reach the value of the T-QST or the IENFD examination and autonomic tests thus still remain only complementary methods in the diagnostic algorithm of painful neuropathies in senescence and we recommend their use in particular for the verification of autonomic dysfunction in patients with relevant clinical symptoms. The signs of more severe dysfunction of autonomic fibres in our elderly neuropathy patients compared to younger age groups are in agreement with the observation of a significant age-related degeneration of autonomic nerve fibres in experimental models of nervous system aging [3] and may again support the hypothesis of the important pathophysiological role of age-related degeneration in the development of peripheral neuropathies in the elderly, which is also corroborated by the diverse pattern of large and small nerve fibre affection and by the higher proportion of idiopathic neuropathies in senescence. Thus, in younger patients the development of peripheral nerve dysfunction seems to be in particular the result of peripheral nerve damage caused by various aetiological factors, while in the elderly, age-related nerve degeneration is suggested to play an increasing role in the development of peripheral neuropathies.

Finally we conclude that painful neuropathies in the elderly display a slightly different pattern of involvement of the

particular nerve fibre types with a more frequent and more extensive involvement of large myelinated fibres as well as of the autonomic ones in comparison with younger age groups, suggesting the increasing role of age-related neurodegeneration in the development of peripheral neuropathies in senescence. The involvement of small nerve fibres, however, represents the most frequent and most remarkable abnormality in elderly painful polyneuropathy patients, confirming the role of small nerve fibre dysfunction in the development of painful neuropathy symptoms regardless of the patient's age. The assessment of thermal thresholds on the T-QST and the examination of the IENFD on skin biopsy as methods of evaluation of small fibre status proved to be applicable and sensitive in older adults and continue to play a key role in the diagnostic algorithm of painful neuropathies in senescence, despite the increasing sensitivity of nerve conduction studies and autonomic nervous system testing in these age groups.

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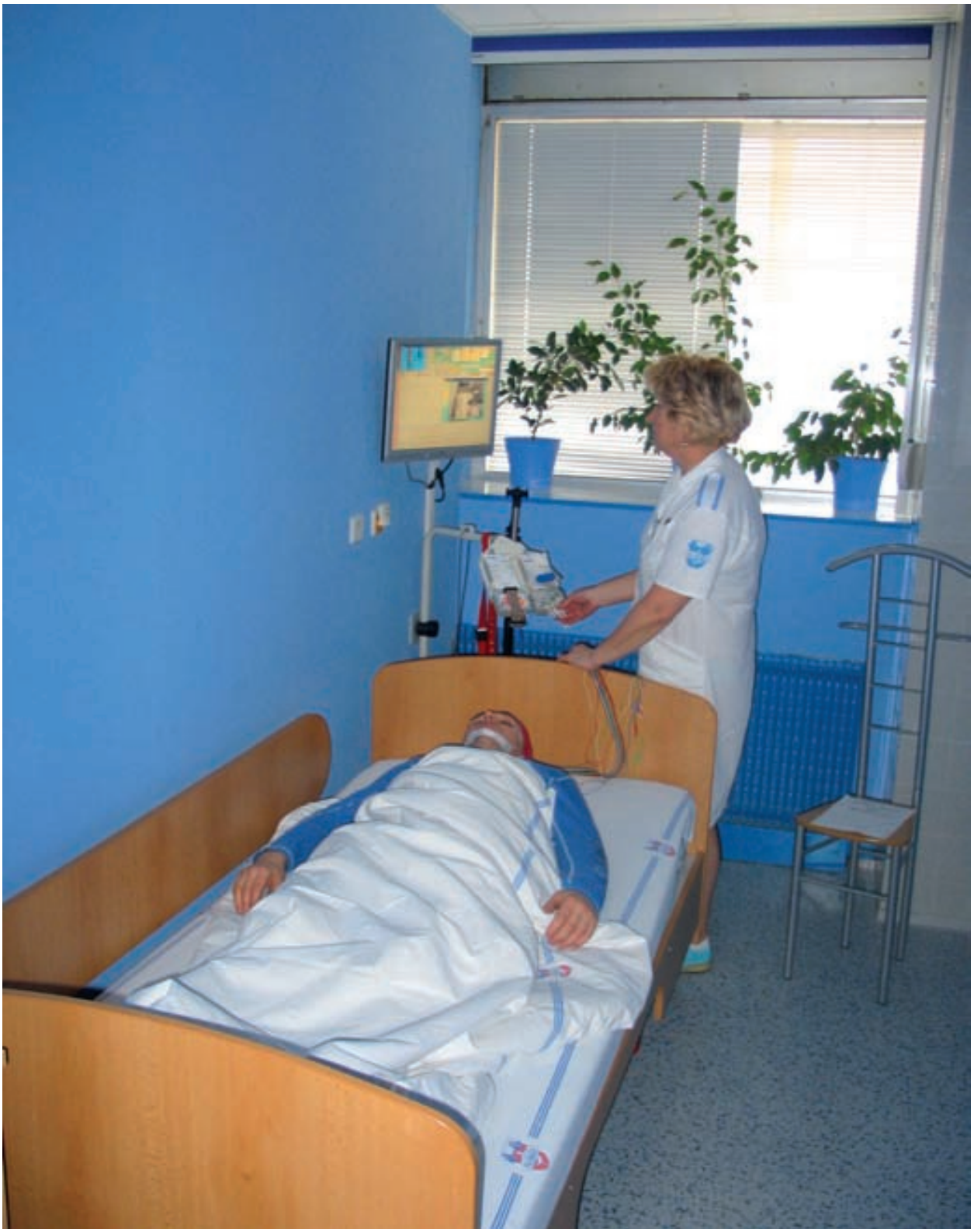

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