Autoimmune (immune-mediated) neuropathies

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ETIOLOGY OF POLYNEUROPATHIES

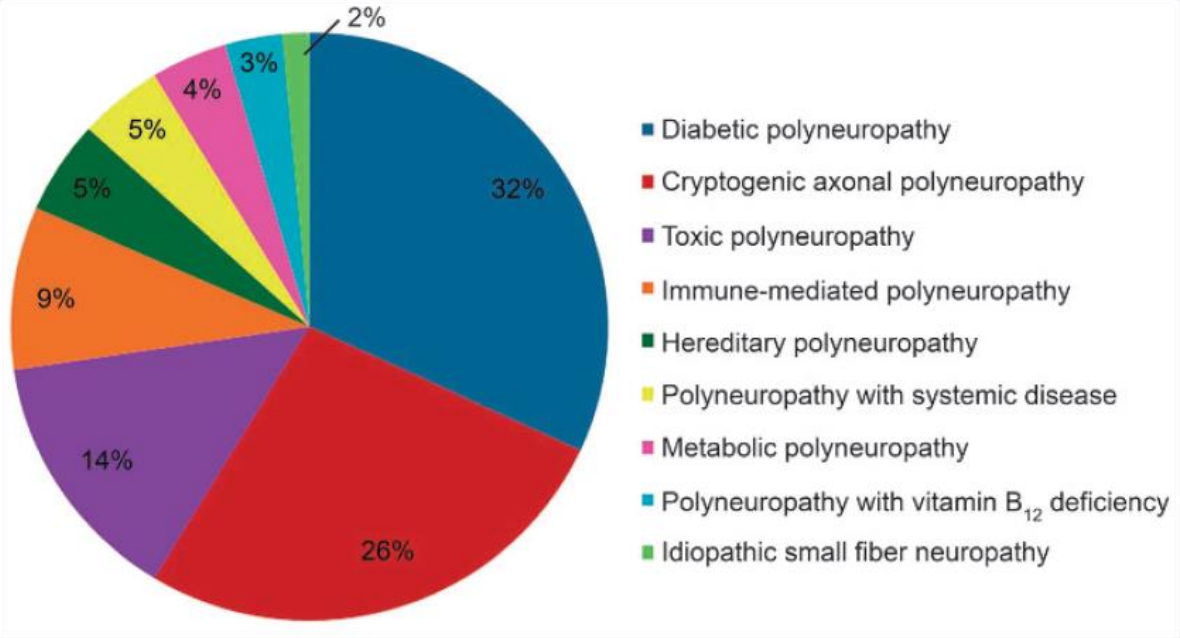


FIGURE 1-2 Estimated prevalence of common polyneuropathy categories.

Modified with permission from Visser NA, et al, Neurology.[1] © 2014 American Academy of Neurology. *neurology.org/content/84/3/259.full*.

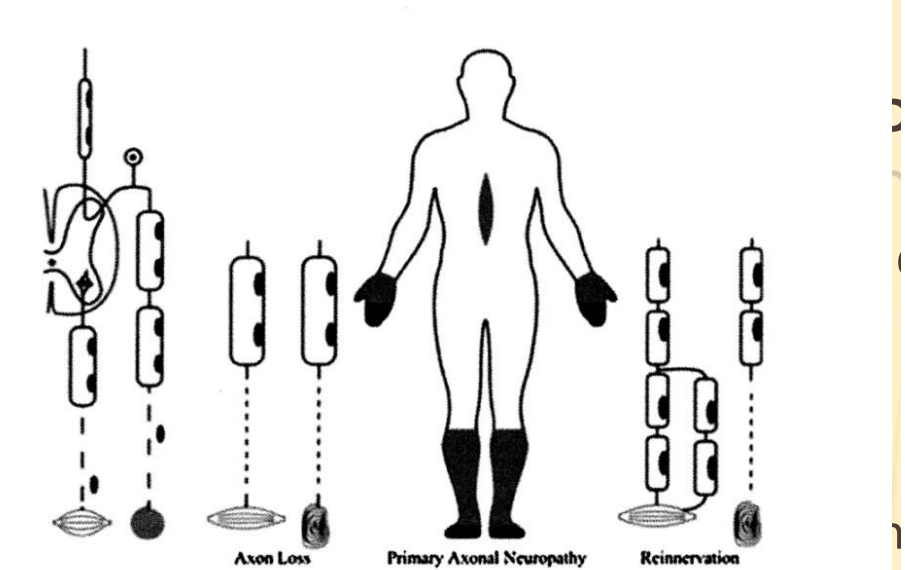


Fig. 5. Primary axonal neuropathy (primary axonal neuropathy). The distribution of sensory loss is demonstrated, with mild involvement in legs in stocking distribution loss, more severe involvement in legs and arms in stocking-glove distribution loss, and very severe involvement with shield distribution loss.

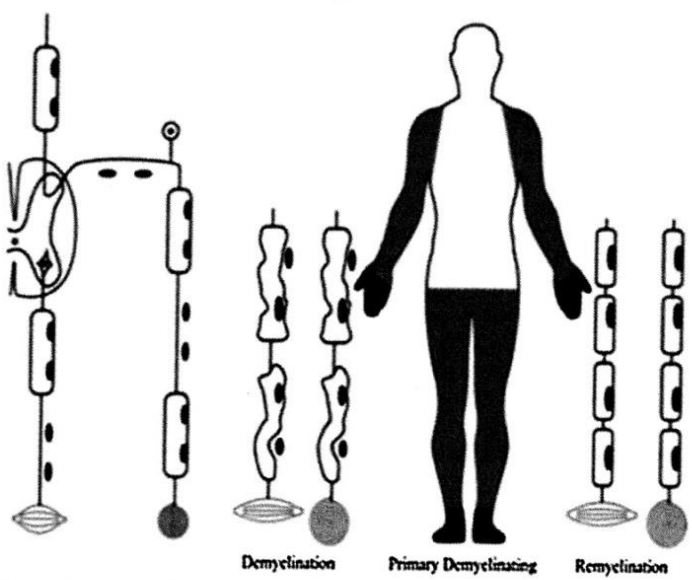
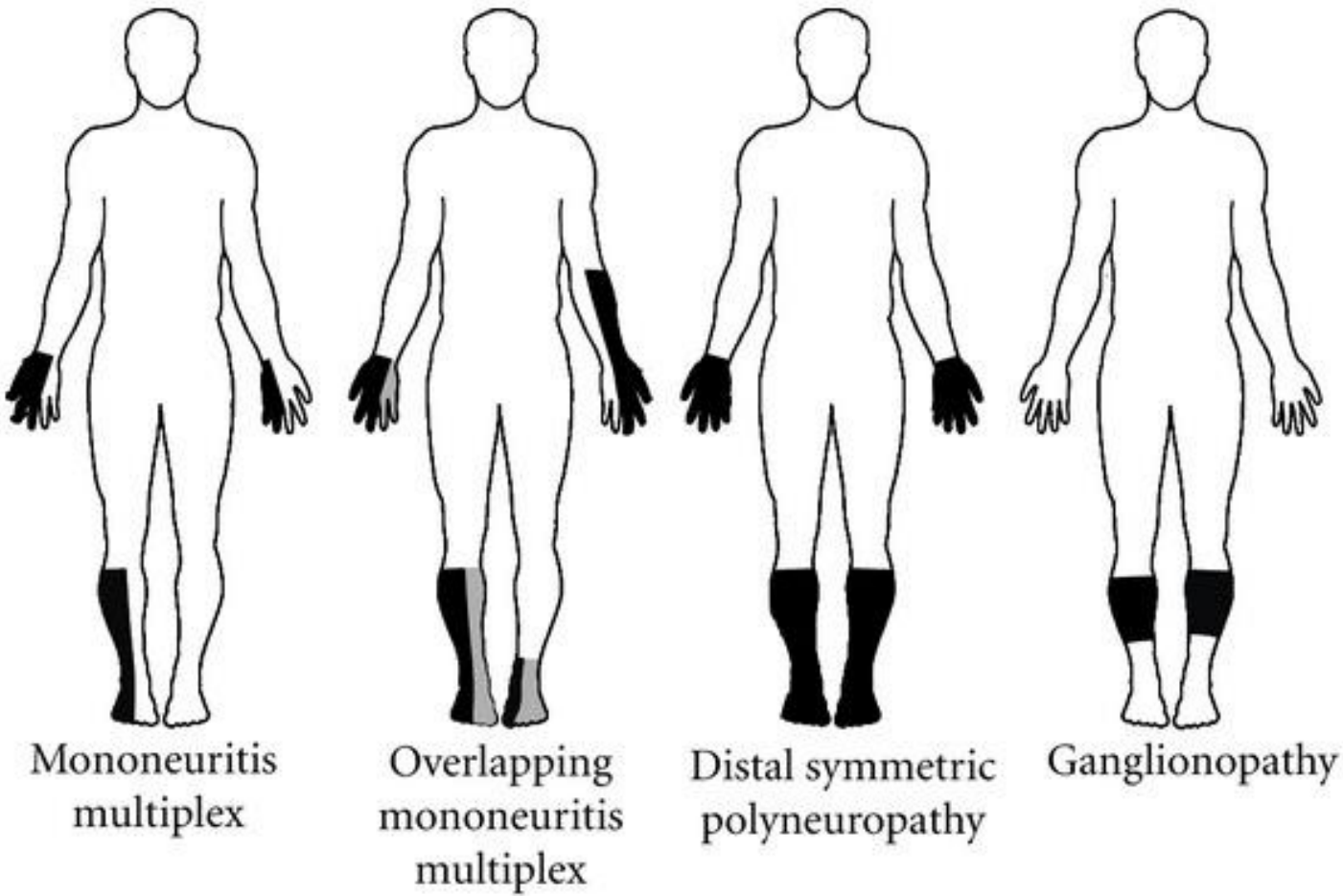


Fig. 6. Primary demyelinating neuropathy (primary demyelinating neuropathy). The distribution of sensory loss resulting from multifocal demyelination involving nerve and spinal root fibers is shown. Sensory loss involves both legs and arms, both distally and proximally, with distal predominance.

- Mixed neuropathies
- Symmetry of involvement
  - Symmetrical
    - Distal (length-dependent, „dying-back“)
    - Diffuse (non-length dependent)
  - Multifocal (mononeuropathy multiplex)

- Pat
  - +
  - +
- Typ
  - +
  - +
  - +
  - +
- Syn
  - +
  - +


Mononeuritis multiplex
Overlapping mononeuritis multiplex
Distal symmetric polyneuropathy
Ganglionopathy

IDIOPATHIC INFLAMMATORY (MOSTLY DEMYELINATING) NEUROPATHIES

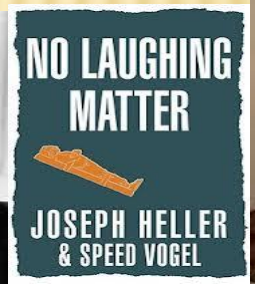
- Acute (monophasic) form: Guillain-Barré syndrome
  - Several clinical and pathogenetic variants

GBS: HISTORY

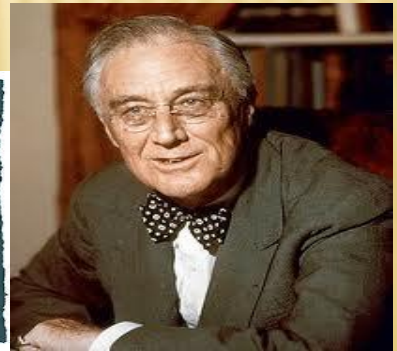
- First description: Landry 1859
- Description of typical proteino-cytological dissociation: Guillain, Barré, Strohl 1916

Andy Griffith

Joseph Heller



FD Roosevelt



GBS: EPIDEMIOLOGY

- incidence 0.5% – 2.0/100.000/year;
- slightly higher prevalence in men
- any age
- 2/3 of cases is preceeded by infection, especially Campylobacter jejuni (4-66%), EBV (2-10%), cytomegalovirus (5-15%) a Mycoplasma pneumoniae (1-5%), further by vaccination, surgery.

GBS: CLINICAL MANIFESTATION

Demyelinative form:

- acute inflammatory demyelinative polyradiculoneuropathy (AIDP)

Axonal form:

- acute axonal motor-sensory neuropathy (AMSAN)
- acute axonal motor neuropathy (AMAN)

GBS variants:

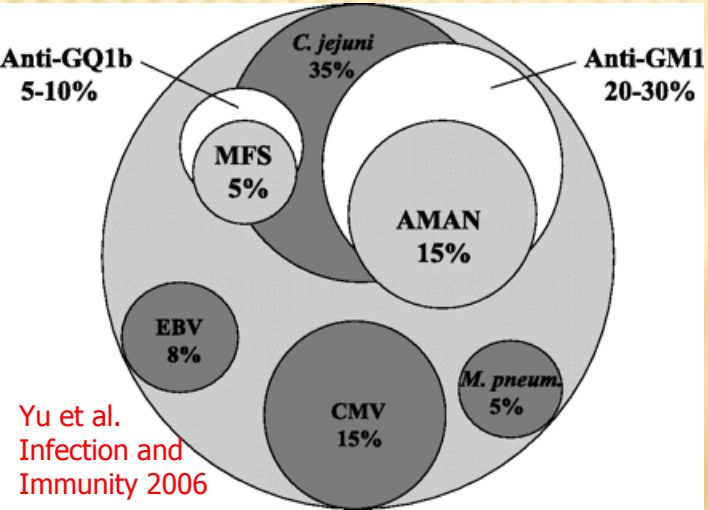
- Miller-Fisher syndrome (MFS)
- acute pandysautonomia
- sensory form
- facial diplegia
- oropharyngeal form

GBS: CLINICAL MANIFESTATION

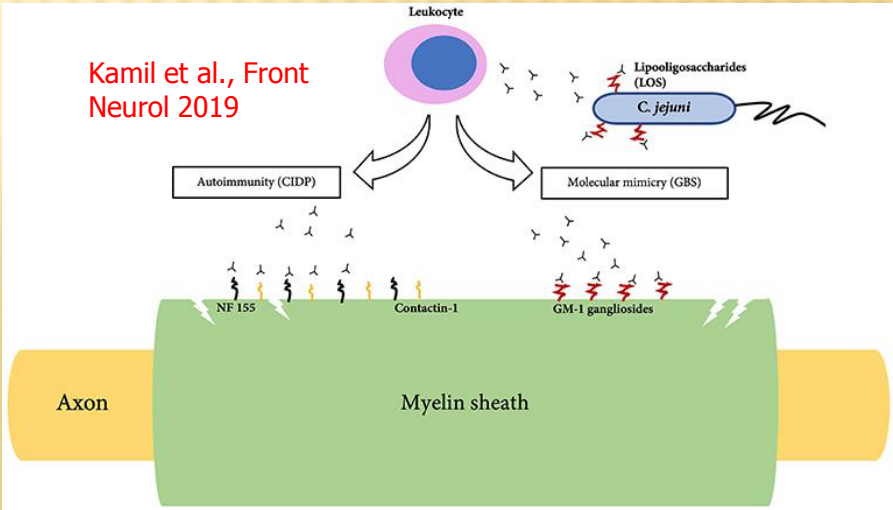
- Self-limited course with progression of clinical signs up to 4 weeks (90%)
- Cranial nerves frequently involved (facial diplegia in 50% of cases)
- Extraocular muscles (with the exception of MFS) and bowel and bladder are spared
- Motor involvement (weakness) is dominant
- Pain is sometimes prominent (mimicking root lesion) - in 30-50% of cases)
- Autonomous dysfunction (especially orthostatic hypotension, cardiac arrhythmias) in 2/3 of cases

GBS: ETIOPATHOGENESIS

- Axonal form (AMAN) is often preceeded by **Campylobacter jejuni** infection, whose cells has similar structure as GM1 gangliosides – „molecular mimicry“ hypothesis;
- **anti-GM1 antibodies** are present in 15-40% of GBS cases
- Miller-Fisher syndrome is associated with **anti-GQ1b a GT1a antibodies** in 90% of cases



Yu et al. Infection and Immunity 2006



Kamil et al., Front Neurol 2019

GBS: DIAGNOSIS

CSF: typically proteino-cytological dissociation

BUT:

- 10% have pleocytosis up to 50 cells/ml
- Hyperproteinorrhachia is common during the 2nd week, not earlier

GBS: DIAGNOSIS

EMG: typically multifocal demyelinative neuropathy with conduction blocks, temporal dispersion, conduction slowing; early signs of axonal involvement indicate unfavourable prognosis

BUT:

- In axonal forms (AMAN, AMSAN) signs of demyelinative involvement are lacking
- EMG abnormalities arel lacking during first days especially in MFS

ELECTRODIAGNOSIS

Main electrophysiological signs of demyelinative neuropathy

- ➔ Conduction slowing
- ➔ Temporal dispersion
- ➔ Conduction block

ELECTRODIAGNOSIS: MULTIFOCAL TEMPORAL DISPERSION, CONDUCTION SLOWING AND BLOCK

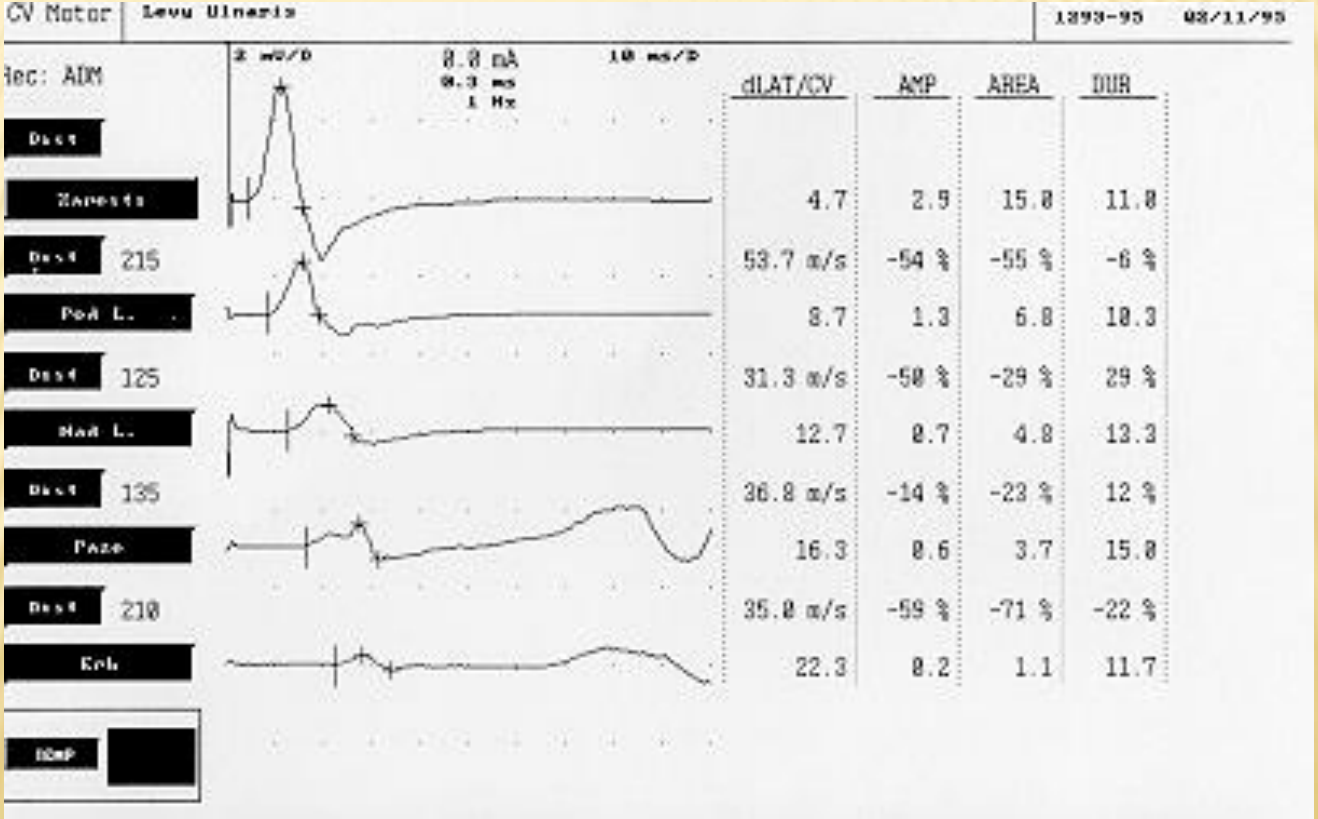


TABLE 4-2 Diagnostic Criteria for Guillain-Barré Syndrome[a]

- Progressive weakness in the legs and arms[b]
- Areflexia or hyporeflexia[b]
- Progression of symptoms lasting up to 4 weeks
- Relative symmetry of weakness and sensory loss
- Sensory symptoms and signs, if present, less impressive then weakness
- Pain is common, often in the back and legs
- Autonomic dysfunction common
- Absence of fever
- Albuminocytologic dissociation in the CSF by 3 weeks
- Postgadolinium enhancement of peripheral nerve roots and cauda equina

[a] Data from Willison HJ, et al, Lancet,[1] *thelancet.com/journals/lancet/article/PIIS0140-6736(16)00339-1/fulltext*; Esposito S, Longo MR, Autoimmun Rev,[2] *sciencedirect.com/science/article/pii/S1568997216302178*; and Asbury AK, Cornblath DR, Ann Neurol,[10] *onlinelibrary.wiley.com/doi/10.1002/ana.410270707/abstract*.

[b] Required for the diagnosis.

TABLE 4-4 Features Casting Doubt or Eliminating a Dia Guillain-Barré Syndrome[a]

- Features That Cast Doubt on a Diagnosis of Guillain-Barré Synd
  - Marked persistent asymmetry of weakness
  - Bowel or bladder dysfunction at onset
  - Presence of greater than 50 polymorphonuclear leukocytes in
  - Sharp sensory level
  - Severe pulmonary dysfunction with little or no limb weakness
  - Fever at onset
  - Slow progression of weakness more than 4 weeks
- Features That Eliminate the Diagnosis of Guillain-Barré Syndror
  - Current history of hexacarbon abuse
  - Abnormal porphyrin metabolism, particularly acute intermittent
  - Recent diphtheric infection
  - Exposure to lead
  - A purely sensory presentation

CSF = cerebrospinal fluid.

[a] Data from Esposito S, Longo MR, Autoimmun Rev,[2] *sciencedirect.com/science/a S1568997216302178*, and Asbury AK, Cornblath DR, Ann Neurol,[10] *onlinelibrary.wiley.com/doi/10.1002/ana.410270707/abstract*.

TABLE 4-5 Disorders That Mimic Guillain-Barré Syndrome[a]

- Critical illness neuropathy and myopathy
- Neurotoxin poisoning: tick paralysis, snake bite, marine toxins, buckthorn, pyrinuron, organophosphates, *n*-hexane
- Acute intermittent porphyria, hepatic porphyrias
- Heavy metal poisoning, particularly arsenic
- Infectious: poliomyelitis, West Nile encephalomyelitis, human immunodeficiency virus (HIV), cytomegalovirus, Lyme disease, diphtheria, botulism
- Myasthenia gravis
- Amyotrophic lateral sclerosis
- Transverse myelitis
- Wernicke encephalopathy
- Vitamin B_{12} deficiency (severe)
- Acute/subacute compressive myelopathy
- Metabolic abnormalities: hypermagnesemia, hypophosphatemia
- Drug adverse effect: amiodarone, cytarabine, streptokinase, suramin
- Vasculitis

GBS: COURSE AND PROGNOSIS

Indicators of unfavourable prognosis:

- Electrophysiological signs of axonal neuropathy (spontaneous activity, decreased CMAP amplitude)
- Rapid progression, assisted ventilation
- Preceeding gastrointestinal infection, cytomegalovirus infection, age >50 let, generalized severe weakness

GBS: COURSE AND PROGNOSIS

- Mortality is 3-8%;
- Moderate to severe residual involvement in 5-10%;
- Spontaneous improvement after 2 years is no probable;
- Relapses in 3% of patients.

GBS: TREATMENT

Pathogenetic treatment

- therapeutic plasmapheresis
- intravenous human immunoglobulin

Symptomatic treatment

- Pain
- Depression, anxiety
- Infections

Prevention of complications

- Respiratory failure (early intubation)
- Cardiovascular failure
- dysphagia (nasogastric feeding, gastrostomia)
- nosocomial infections (pneumonia, urinary infections)
- Pressure sores

TABLE 4-6 Management of Guillain-Barré Syndrome[a]

- ▶ Frequent monitoring of respiratory function
- ▶ Monitoring for autonomic dysfunction
- ▶ Deep venous thrombosis prophylaxis
- ▶ Treatment of constipation/ileus
- ▶ Nonopioid management of neuropathic pain
- ▶ Psychosocial support
- ▶ Physical, occupational, and speech therapy
- ▶ Immunologic treatment with IV immunoglobulin (IVIg) or plasma exchange
- ▶ Corticosteroid treatment not indicated

[a] Data from Willison HJ, et al, Lancet,[1] *thelancet.com/journals/lancet/article/PIIS0140-6736(16)00339-1/fulltext*; Esposito S, Longo MR, Autoimmune Rev,[2] *sciencedirect.com/science/article/pii/S1568997216302178*; and van den Berg B, et al, Nat Rev Neurol,[3] *nature.com/nrneurol/journal/v10/n8/full/nrneurol.2014.121.html*.

CHRONIC AUTOIMMUNE DEMYELINATING POLYNEUROPATHIES

- Chronic
- Immune (dříve Inflammatory)
- Demyelinating
- Polyneuropathy
  - Including „multifocal CIDP“ (Lewis-Sumner syndrome) and CIDP variants
  - CIDP associated with other disorders (MGUS, DM, HIV, lupus, CNS demyelinization)
    - ✓ Uncertain differentiation againts other autoimmune neuropaties with auto-antibodies (POEMS, GALOP, anti-sulfatidy, anti-MAG) – „nodopathies“;
- Multifocal motor neuropathy (MMN)

EPIDEMIOLOGY

Rare disorders:

- MMN: prevalence 0.6-2.0/100 tis.
- CIDP: prevalence 1.2-8.9/100 tis.

CIDP: DIAGNOSIS
(EFNS/PNS REVISED CRITERIA CIDP 2010)

Table 4. Clinical diagnostic criteria.

(1) Inclusion criteria
- (a) Typical CIDP
  Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected; and
  Absent or reduced tendon reflexes in all extremities
- (b) Atypical CIDP (still considered CIDP but with different features) One of the following, but otherwise as in (a) (tendon reflexes may be normal in unaffected limbs):
  Predominantly distal (distal acquired demyelinating symmetric, DADS) or
  Asymmetric [multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), Lewis-Sumner syndrome] or
  Focal (e.g., involvement of the brachial or lumbosacral plexus or of one or more peripheral nerves in one upper or lower limb)
  Pure motor or
  Pure sensory (including chronic immune sensory polyradiculopathy affecting the central process of the primary sensory neuron)

CIDP: DIAGNOSIS
(EFNS/PNS REVISED CRITERIA CIDP 2010)

Exclusion criteria

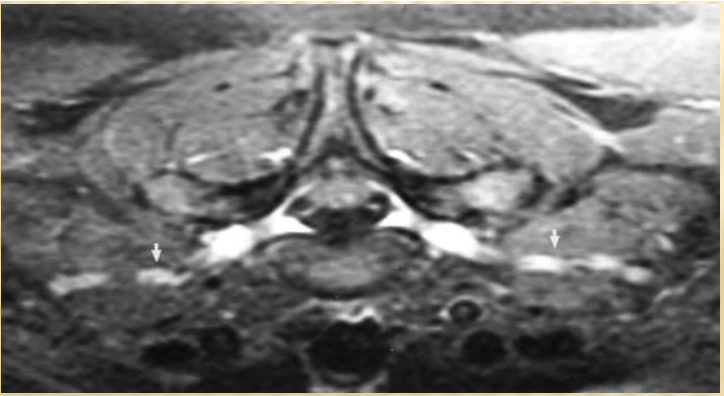
Borrelia burgdorferi infection (Lyme disease), diphtheria, drug or toxin exposure probably to have caused the neuropathy
Hereditary demyelinating neuropathy
Prominent sphincter disturbance
Diagnosis of multifocal motor neuropathy
IgM monoclonal gammopathy with high titre antibodies to myelin-associated glycoprotein
Other causes for a demyelinating neuropathy including POEMS syndrome, osteosclerotic myeloma, diabetic and non-diabetic lumbosacral radiculoplexus neuropathy. PNS lymphoma and amyloidosis may occasionally have demyelinating features

CIDP: DIAGNOSIS

(EFNS/PNS REVISED CRITERIA CIDP 2010)

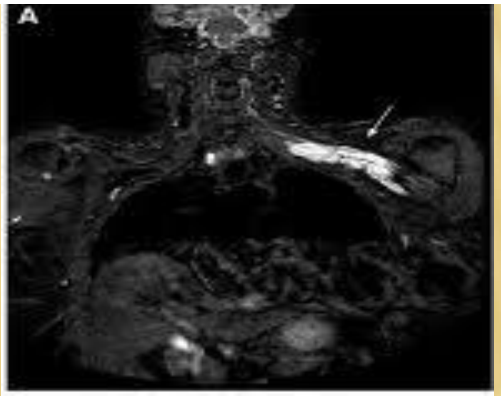
Supportive criteria

1. Elevated CSF protein with leukocyte count $<10/mm^3$ (level A recommendation)
2. MRI showing gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses (level C recommendation)
3. Abnormal sensory electrophysiology in at least one nerve (Good Practice Points):
   a. Normal sural with abnormal median (excluding median neuropathy at the wrist from carpal tunnel syndrome) or radial sensory nerve action potential (SNAP) amplitudes; or
   b. Conduction velocity <80% of lower limit of normal (<70% if SNAP amplitude <80% of lower limit of normal); or
   c. Delayed somatosensory evoked potentials without central nervous system disease
4. Objective clinical improvement following immunomodulatory treatment (level A recommendation)
5. Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy or teased fibre analysis (Good Practice Points)

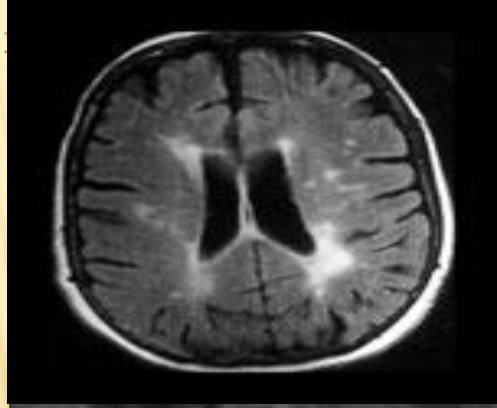


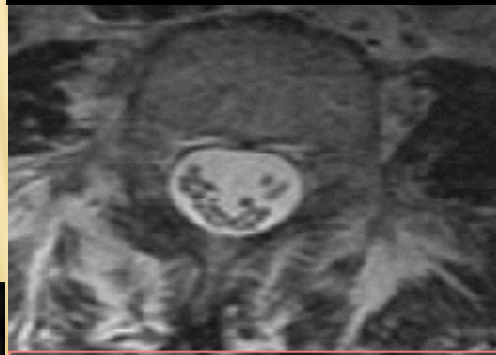
CIDP

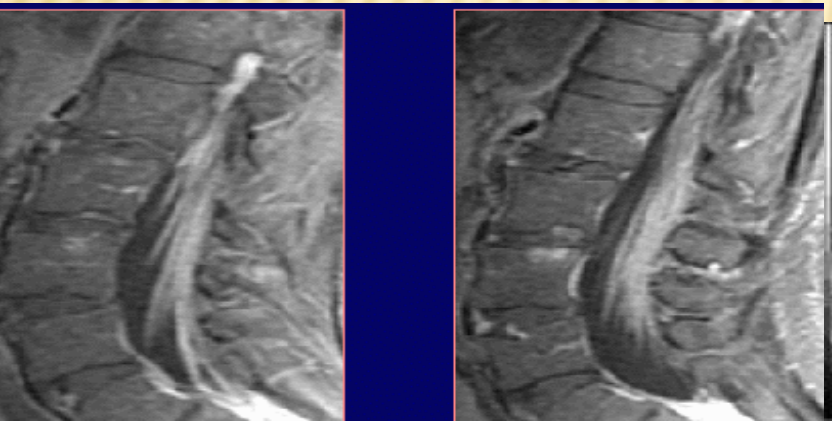
MMN

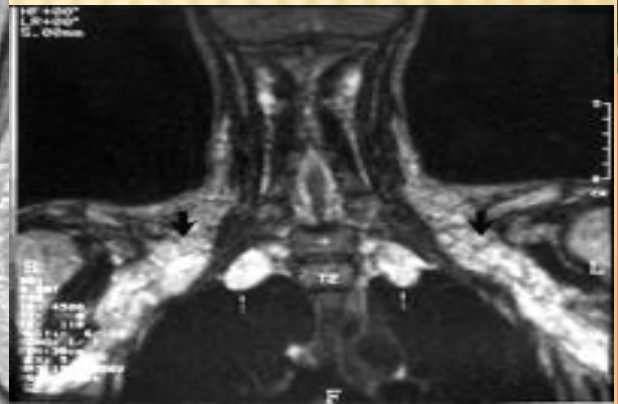


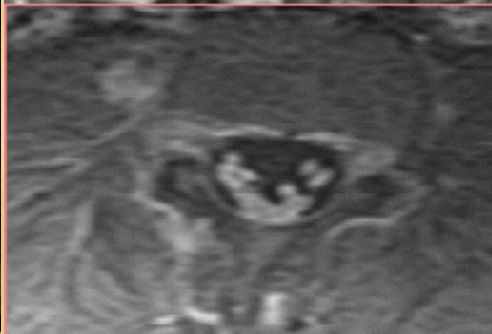
CIDP: MRI FINDINGS











DISEASES ASSOCIATED WITH CIDP

- Diabetes mellitus
- MGUS (IgG, IgA)
- Monoclonal gamapathy IgM non-anti-MAG
- Lupus erytematosus or other vasculitis or collagenosis
- HIV
- Chronic active hepatitis
- Sarkoidosis
- Thyreopathy
- Colitis
- Bone marrow or organ transplantation

CIDP TREATMENT

Induction (initial) treatment:

- CIDP with sensory-motor involvement:
  - 1st choice = corticosteroids or IVIG
  - 2nd choice: Plasma exchange (less tolerated)
- CIDP with predominantly motor involvement
  - 1st choice = IVIG

IVIG VS. CORTIKOSTEROID IN CIDP

	IVIG	Corticosteroids
Efficacy	++	+
Latency of the onset of effect	+	±
Duration of remission	±	+
Side effects	+	-
Patient‘s preference	+	±
Cost	-	+

CIDP TREATMENT

Maintenance treatment:

- Continue with treatment of 1st choice, if effective, to maximum effect, than decrease the dose to minimum effective
- Try 2nd choice treatment, if 1st choice is ineffective or not tolerated

CIDP TREATMENT: IMUNOSUPRESANT AND IMUNOMODULATORS

Evidence of effectiveness is lacking, but it is used:

- Alemtuzemab
- Azathioprine
- Cyklofosfamid
- Cyklosporin
- Etanercept
- Interpheron alfa a beta1a
- Mycofenolate mofetil
- Methotrexate
- Rituximab
- Transplantation of haemopoetic stem cells

DIAGNOSTIC CRITERIA FOR MMN
(VAN SCHAIK ET AL. ENS 2006)

Table 1 Clinical criteria for MMN

Core criteria (both must be present)

1. Slowly progressive or stepwise progressive, asymmetric limb weakness, or motor involvement having a motor nerve distribution in at least two nerves, for more than 1 month[a]
2. No objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs

Supportive clinical criteria

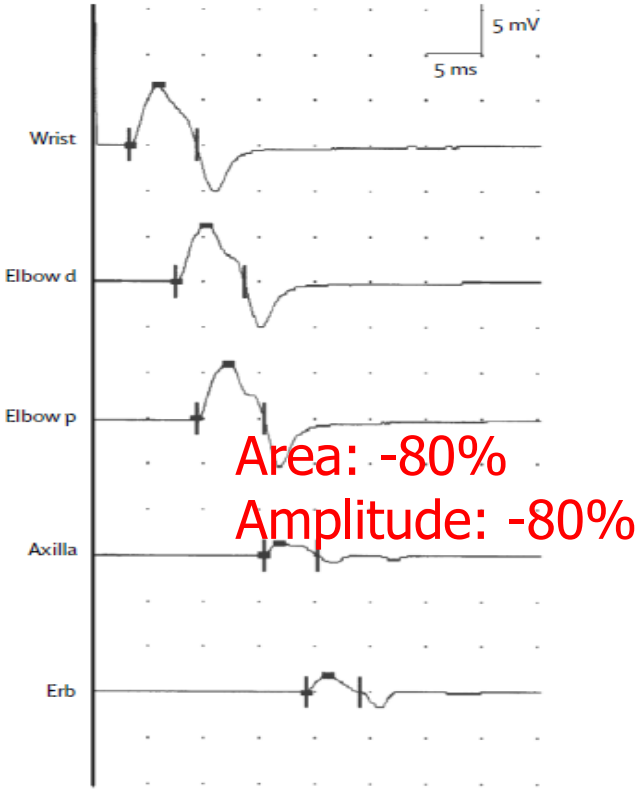
3. Predominant upper limb involvement[b]
4. Decreased or absent tendon reflexes in the affected limb[c]
5. Absence of cranial nerve involvement[d]
6. Cramps and fasciculations in the affected limb

Exclusion criteria

7. Upper motor neuron signs
8. Marked bulbar involvement
9. Sensory impairment more marked than minor vibration loss in the lower limbs
10. Diffuse symmetric weakness during the initial weeks
11. Laboratory: CSF protein >1 g/l

Table 2 Electrophysiological criteria for conduction block[a]

1. Definite motor CB[a]: negative CMAP area reduction on proximal versus distal stimulation of at least 50% whatever the nerve segment length (median, ulnar and peroneal). Negative CMAP amplitude on stimulation of the distal part of the segment with motor CB must be >20% of the lower limit of normal and >1 mV (baseline negative peak) and an increase of proximal negative peak CMAP duration must be ⩽30%
2. Probable motor CB[a]: negative CMAP area reduction of at least 30% over a long segment of an upper limb nerve with an increase of proximal negative peak CMAP duration ⩽30%; or negative CMAP area reduction of at least 50% (same as definite) with an increase of proximal negative peak CMAP duration >30%
3. Normal sensory nerve conduction in upper limb segments with CB and normal sensory nerve action potential amplitudes (see exclusion criteria)



	Duration (ms)	Amplitude (mV)	Area (mV/ ms)	Distal motor latency (ms) Motor conduction velocity (m/s)
Wrist	6·2	6·7	23·3	3·2
Elbow d	6·3	6·2	21·9	55
Elbow p	6·0	6·4	21·6	55
Axilla	4·8	1·4	4·4	23
Erb	4·8	1·9	4·9	58

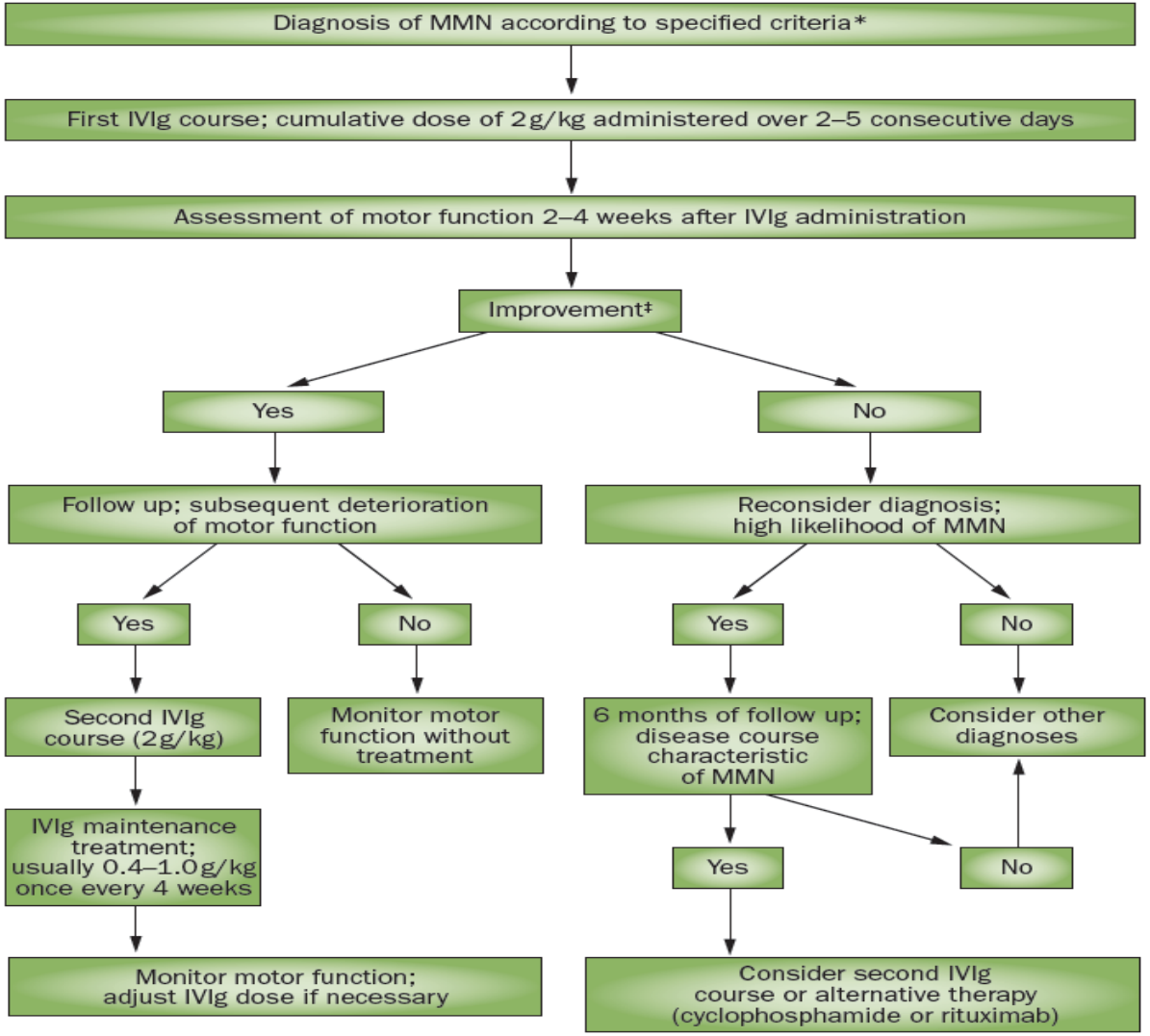
DIAGNOSTIC CRITERIA FOR MMN:

(VAN SCHAIK ET AL.. 2006,

Definite conduction block

MMN TREATMENT

IVIG treatment is the only treament modality with proved effectiveness – 1st choice and the only option



Therapeutic scheme in MMN

Vlam et al.
Nat Rev Neurol 2011

NEW THERAPEUTIC TRENDS

- Patient-tailored IVIG treatment (personalized therapy)
- Subcutaneous (ScG) immunoglobulin
- Complement blockade:
  - Eculizumab – monoclonal antibody against C5 – blocks MAC synthesis
  - Other drugs blocking activation of complement
- Blockade of antoantibodies formation by B lymphocytes:
  - Rituximab – monoclonal antoantibody against CD20

DIFFERENTIAL DIAGNOSIS AMONG CHRONIC DYSIMMUNE NEUROPATHIES

Symptom/diagnosis	MMN	CIDP	MADSAM
Distribution of weakness - symmetry	assymetrical	symmetrical	assymetrical
Distribution of weakness – upper > lower extremities	yes	no	yes
Distinctive sensory syptoms	**no**	yes	yes
Tendon reflexes in a territory of weak muscles	normal or diminished	diminished or unelicited	diminished
Course of the disease	slow progression	progressive or relapsing	progressive or relapsing
Hyperproteinorachia >1g/	**no**	yes	rarely
Anti-GM1 IgM	**yes (50%)**	rarely	rarely
Abnormal MRI of the brachial plexus	asymmetrically	symmetrically	asymmetrically
Effect of IVIG	yes	yes	yes
Effect of corticosteroids	**no**	yes	yes
Motor conduction block	yes	yes	yes