Disorders of Peripheral Nerves

35

Gian Maria Fabrizi and Giampietro Zanette

Abbreviations

AAN, American Academy of Neurology; A-CIDP, acute-onset CIDP; AD, autosomal dominant; AIDP, acute inflammatory demyelinating polyradiculoneuropathy; AIP, acute intermittent porphyria; AL, amyloidosis light-chain; ALS, amyotrophic lateral sclerosis; AMAN, acute motor axonal neuropathy; APOA1, apolipoprotein A1; AMSAN, acute motor-sensory axonal neuropathy; AR, autosomal recessive; BBE, Bickerstaff's brain-stem encephalitis; BMI, body mass index; C, campylobacter; CAN, cardiovascular autonomic neuropathy; CB, conduction block; CDAS, CIDP disease activity status; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CMAP, compound motor action potential; CMT, Charcot-Marie-Tooth (CMTX = X-dominant CMT, CMT1 = demyelinating subtypes, CMT2 = axonal subtypes); CMT-NS, CMT-neuropathy score; CMV, cytomegalovirus; CNS, central nervous system; CB, conduction block; cPAN, cutaneous polyarteritis nodosa; CSA, cross-sectional area; CSF, cerebrospinal fluid; CTS, carpal tunnel syndrome; CV, conduction velocity; DM, diabetes mellitus; DML, distal motor latency; dSMA, distal spinal muscular atrophy; DSP, distal symmetric polyneuropathy; EFNS, European Federation of Neurological Societies; EDX, electrodiagnosis; EMG, electromyography; ENG, electroneurography; ERT, fibrillation potentials, enzyme replacement therapy; FAP, familial amyloid polyneuropathies; FP, fibrillation potential; GBS, Guillain-Barré syndrome; GSN, gelsolin; HMSN, hereditary motor sensory neuropathies; HNA, hereditary neuralgic amyotrophy; HNPP, hereditary neuropathy with liability to pressure palsies; HRV, heart rate variability; HSAN, hereditary sensory and autonomic neuropathies; HSCT, allogenic hematopoietic stem cell transplantation; HSP, hereditary spastic paraplegias; IVIg, intravenous immunoglobulin; LLN, lower limit of normal; LSRP, radiculoplexopathy; MAG, myelin associated glycoprotein; MFS, Miller-Fisher syndrome; MGUS, monoclonal gammopathy of undetermined significance; MNGIE,

G.M. Fabrizi (✉)
Department of Neurological and Movement Sciences,
University of Verona, Ospedale Policlinico
G.B. Rossi, P.le L.A. Scuro 10, Verona 37134, Italy

Neurology Section, Pederzoli Hospital,
Peschiera del Garda, Verona, Italy
e-mail: gianmaria.fabrizi@univr.it

G. Zanette
Neurology Section, Pederzoli Hospital,
Peschiera del Garda, Verona, Italy

A. Sghirlanzoni et al. (eds.), *Prognosis of Neurological Diseases*,
DOI 10.1007/978-88-470-5755-5_35

mitochondrial neurogastrointestinal encephalopathy; MRC, Medical Research Council; MRI, magnetic resonance imaging; MU, motor unit; NCV, nerve conduction velocities, (M = motor, S = sensory); NSAIDs, non-steroidal anti-inflammatory drugs; NSVN, non-systemic vasculitic neuropathy; PE, plasma exchange; OLT, orthotopic liver transplantation; PNI, peripheral nerve injury; PNS, peripheral nervous system; POEMS, peripheral neuropathy, organomegaly, endocrinopathy, M-protein, and skin changes; QSART, quantitative sudomotor axon reflex testing; QST, quantitative sensory testing; SAP, *sensory* action *potentials*; SC, Schwann cell; SFN, small-fiber-neuropathy; SNAP, sensory nerve action potential; SW, sharp waves; SVN, systemic vasculitic neuropathies; T1DM and T2DM, type 1 DM and type2 DM; TTR, transthyretin; ULN, upper limit of normal; US, ultrasonography; VEGF, vascular endothelial growth factor; WM, Waldenström macroglobulinemia

35.1 Title: Hereditary Neuropathies

Key Facts

- **Definition**
  Heritable genetic defects that affect selectively the peripheral nervous system (PNS) [myelin sheath, Schwann cell (SC), axon] or the PNS plus the central nervous system (CNS) and/or other organs [1]
- **Demographics**
  Rare disorders with prevalence less than 1:2000 when considered singly. All ages may be affected from birth to late adulthood.
- **Clinical features and terminology** (Table 35.1)
  (1) *Chronic length-dependent polyneuropathies*: hereditary motor-sensory neuropathies (alias CMT); distal hereditary motor neuropathies [(dHMN), alias spinal CMT or distal spinal muscular atrophy (dSMA)]; hereditary sensory and autonomic neuropathies (HSAN). (2) *Relapsing/progressive motor-sensory polyneuropathies* (Refsum disease). (3) *Chronic*, *progressive*, *motor-sensory polyneuropathies* with early small-fiber involvement (e.g., familial amyloid polyneuropathies). (4) *Painful neuropathies* (Fabry disease). (5) *Acute generalized polyneuropathies* (porphyrias). (6) *Chronic sensory neuronopathies* associated with hereditary ataxias. (7) *Chronic sensory* (and motor) neuropathies due to mitochondrial disorders [2]. *Recurrent focal neuropathies/plexopathies*: hereditary neuropathy with liability to pressure palsies (HNPP); hereditary neuralgic amyotrophy (HNA).
- **Diagnostic markers**
  - Clinical picture; neurophysiology; DNA testing; other laboratory tests in selected disorders: blood biochemical tests; MRI and or ultrasonography (US); CSF analysis; nerve biopsy.
- **Top differential diagnosis**
  Phenotypically convergent acquired neuropathies.
- **Prognosis**
  - **Principles of treatment** – Rehabilitation; symptomatic treatments (e.g., pain). Disease-modifying therapies available for selected forms, e.g., FAP (liver transplantation; pharmacotherapy; gene therapy); Fabry disease [Enzyme replacement therapy (ERT)]; acute intermittent porphyria [(AIP): hematine, glucose]; Refsum disease [diet; plasma exchange (PE); mitochondrial neurogastrointestinal encephalopathy [MNGIE: ERT, allogenic hematopoietic stem cell transplantation (HSCT)]. Disease-modifying therapies under investigation for many forms, e.g., CMT.
  - **Outcome and disability** – Variable, from minor disability throughout life (e.g., CMT) to relentless fatal course over years if untreated (e.g., FAP).

Table 35.1 Overview of hereditary neuropathies

Disease (inheritance)	Onset	PNS syndrome	Pathologal nerve process	Additional neurological features	Other signs	Laboratory tests	Therapy	Prognosis
CMT (AD, AR. X-l)	1st–2nd decade (birth-adult)	Chronic motor-sensory polyneuropathy	De-remyelinating or axonal or intermediate			DNA: >30 genes known	Rehabilitation ± othosis ± foot surgery	Variable spectrum of severity even within specific subtypes Typical: usually poorly and slowly progressive without relevant functional impairment Early onset: usually slowly progressive, with relevant functional impairment
dHMN (AD, AR. X-l)	1st–2nd decade (birth-adult)	Chronic distal motor neuropathy	Axonal	(± Pyramidal syndrome)		DNA: >10 genes known	Rehabilitation ± othosis ± foot surgery	Variable spectrum of severity even within specific subtypes Typical: usually poorly and slowly progressive without relevant functional impairment Early onset: usually slowly progressive, with relevant functional impairment
HSAN (AD, AR)	1st–2nd decade (birth-adult)	Chronic sensory (autonomic) neuropathy	Axonal			DNA: >10 genes known	HSAN1 (SPTLC1 mutations): oral L-serine	Usually progressive, morbidity and mortality variable within different subtypes
HNPP (AD)	1st–3rd decade (all decades)	Acute recurrent multifocal neuropathies	Demyelinating + tomacula			DNA (17p12 deletion or PMP22 mutations)	Rehabilitation ± othosis	Palsies may recur lasting for days to weeks (rarely months) usually without significant residual impairment Carriers may be asymptomatic
HNA (AD)	2nd–3rd decade (all decades)	Acute recurrent brachial (rarely lumbar) plexopathies	Axonal		Facial dysmorphisms	DNA: *SEPT9*e[)	Symptomatic treatment	Intense pain lasts for up two weeks and may result in chronic aching pain Long-term prognosis is favorable with functional recovery in more than 90 % patients after 4 years

(continue)

Table 35.1 (continue)

Disease (inheritance)	Onset	PNS syndrome	Pathologal nerve process	Additional neurological features	Other signs	Laboratory tests	Therapy	Prognosis
GAN (AR)	1st decade (typical: early childhood)	Motor-sensory polyneuropathy	Axonal, giant axons	Optic atrophy, nystagmus, cerebellar ataxia, pyramidal syndrome	Curled hair and eyelashes	DNA: *GAN* ± sural nerve biopsy	Rehabilitation ± othosis	Typical: slowly progressive with death by late adolescence
FAP (AD)	Adult, (from 3rd–4th to 7th decade)	Motor-sensory-autonomic polyneuropathy	Axonal, focal amyloid deposits	(± Leptomeningeal amyloidosis)	Weight loss, cardiomyopathy, vitreus opacity, nephropathy	DNA: *TTR* ± fat periumbilical and/or sural nerve biopsy	First-line: orthotopic liver transplantation Second-line: tafamidis, diflunisal, si-RNA, doxycycline + TUDCA Symptomatic treatment	Relentless progression if untreated with death 10–15 years after onset
Refsum (AR)	1st–5th decade (usually 1st–2nd)	Relapsing/remitting (or progressive) generalized polyneuropathy ± increased CSF proteins	Demyelinating	Pigmentary retinopathy, pupillary abnormalities, hearing loss, anosmia, cerebellar ataxia	Heart, skeletal deformities, ichthyosis, cataract	Blood: phytanic acid DNA: *PHYH*, *PEX7*	Dietary restriction (avoid phytol-containing fish oils, dairy products, ruminant fats) Plasma exchange for exacerbations	Early diagnosis and continuative treatment lead to significant restoration of neurological function but cranial nerve dysfunction does not regress
MLD (AR)	1st decade	Motor-sensory polyneuropathy	Demyelinating, metachromatic inclusions	Progressive psychomotor regression, dysarthria, aphasia, blindness, nistagmus, ataxia, spasticity		Brain NMR Blood: ARSA activity DNA: *ARSA* gene	HSCT	Usually fatal with variations depending on presentation's age (late-infantile, juvenile, adult)
KRABBE (AR)	1–2 years	Motor-sensory polyneuropathy	Demyelinating, globoid macrophages	Progressive psychomotor regression, blindness, ataxia, spasticity		Brain NMR Blood: GALC activity DNA: *GALC* gene ± sural nerve biopsy	HSCT	Early-infantile: fatal Late-onset slower progression with peripheral neuropathy and spasticity as the only manifestations

AMN (X-l)	2nd–3rd decade	Motor-sensory polyneuropathy	Axonal (± demyelination) CS lamellar inclusions	Spastic paraparesis	Adrenal insufficiency	Brain NMR Blood: VLCFA DNA: *ABCD1* gene	Dietary restriction of VLCFA; "Lorenzo's oil." Corticosteroid replacement	Slowly progressive
AIP (AD)	2nd decade-adulthood	Generalized acute polyneuropathy	Axonal	Psychosis, convulsions, coma, SIADH	Photosensitivity	Urine: ALA, PGB and stool: copro-/uroporphyrins Blood: PBG activity DNA: *PBG deaminase*	Prevention of acute attacks (be aware of precipitating drugs) For attacks: i.v. Glucose (10–20 g/h) or i.v. hematin 1–5 mg/kg/d for 3–5 days	Neuropathy improves with treatment Avoid precipitants factors
FABRY (X-l)	1st–2nd decade	Painful neuropathy	Axonal, small fibers Lamellated ultrastructural inclusions in perineurial, endothelial, perithelial cells	Strokes	Angiokeratoma, heart, kidney, corneal opacities, cataract	Brain NMR Blood: α-GLA activity DNA: *GLA*	ERT therapy is beneficial for nephropathy and pain control	Course is slowly progressive Death may occur by the 5th decade due to strokes or systemic complications
TANGIER (AR)	2nd decade-adulthood	Pseudo-syringomyelic syndrome (or multifocal mononeuropathies)	Axonal, small fibers (demyelination) CS lipid vacuoles		Large orange tonsils, ischemic cardiomyopathy, corneal opacity, hepatosplenomegaly, decreased cholesterol and HDL levels	Blood: cholesterol, VLDL DNA: *ABC1*	Specific treatment unavailable	Progressive course influenced by systemic complications (premature myocardial infarction (30 % of cases), stroke, thrombocytopenia
FRIEDREICH (AR)	1st–2nd decade	Sensory neuronopathy	Axonal, no clusters of regenerating fibers	Pyramidalism, dysarthria, nistagmus	Cardiomyopathy, diabetes (consider diabetes neuropathy) Skeletal deformities	DNA: *FRDA*	No proven effective disease modifying therapies. Idebenone is given to slow progression of cardiomyopathy	Relentless progressive Cardiomyopathy is a frequent cause of premature mortality Several therapeutic strategies under investigation

(continue)

Table 35.1 (continue)

Disease (inheritance)	Onset	PNS syndrome	Pathologal nerve process	Additional neurological features	Other signs	Laboratory tests	Therapy	Prognosis
Ataxia-Vitamin E Deficit (AR)	1st–2nd decade	Sensory neuronopathy	See above		Cardiomyopathy, diabetes Skeletal deformities Retinitis pigmentosa	Blood: vitamin E DNA: *TTPA* gene	Treatment with vitamin E slow progression	Onset (childhood or adult) and natural history influenced by residual TTP activity
ABETA-LYPO Proteinemia (AR)	1–2 decade	Sensory neuronopathy	See above		Retinitis pigmentosa, acanthocytosis, malabsorption, hypocholesterolemia deficits, liposoluble vitamins	Blood: vitamin E, cholesterol, acanthocytosis DNA: *MTP*		Slowly progressive
MNGIE (AR)	1st decade-adulthood	Chronic motor-sensory CIDP or CMT1-like evolution and features	Demyelinating	± ptosis, ophthalmoparesis, leukoencephalopathy Myopathy with RRF, mtDNA deletion and/or depletion	Severe gastrointestinal dysmotility (pseudo-obstruction), cachexia	Blood: reduced TYMP activity; increased urinary and plasma dThd, dUrd DNA: TYMP mutations. Muscle: RRF and COX-fibers, mtDNA deletions	Continuous peritoneal dialysis. HSCT Erythrocyte-entrapped enzymatic therapy Platelet infusion Caution with liver primary metabolizing drugs	Variable from rapid, often lethal course between 20–40 years to late-onset and slower forms [2]
SANDO/ SCAE (AR)	Juvenile-to-adult	Sensory neuronopathy	Axonopathy or axonal-demyelinating	± dysarthria, ophthalmoparesis Hearing loss, migraine, myopathy with RRF and mtDNA depletion		DNA: *POLG DNA*: *C10ORF72*		POLG1: moderate-to-severe C10ORF72: mild or subclinical, rarely severe
NARP (matrilinear mtDNA)	1–3 decade	Sensory neuronopathy	Axonopathy (may be the unique feature)	± epilepsy	Retinitis pigmentosa Developmental delay	DNA: mtDNAATP6		Moderate to severe

CMT Charcot-Marie-Tooth, *dHMN* distal hereditary motor neuropathy, *HSAN* hereditary sensory-autonomic neuropathy, *HNPP* hereditary neuropathy with liability to pressure palsies, *HNA* hereditary neuralgic amyotrophy, *GAN* giant axonal neuropathy, *FAP* familial amyloidotic polyneuropathy, *MLD* metachromatic leukodystrophy, *AMN* adrenomyeloneuropathy, *AIP* acute intermittent porphyria, *SANDO* sensory ataxic neuropathy, dysarthria, ophthalmoparesis, *SCAE* spinocerebellar ataxia and epilepsy, *MNGIE* mitochondrial neurogastrointestinal encephalopathy, *NARP* neurogenic muscle weakness, ataxia, retinitis pigmentosa, *AD* autosomal dominant, *AR* autosomal recessive, *X-l* X–linked, *SIADH* syndrome of inappropriate ADH secretion, *RRF* ragged-red fibers, *SEPT9* septin 9, *GAN* gigaxonina, *TTR* trasntiretina, *PHYH* phytanoyl-CoA 2-hydroxylase, *PEX7* peroxisome biogenesis factor 7, *ARSA* arylsulfatase A, *GALC* galactosylceramidase, *VLCFA* very-long-chain fatty acids, *ABCD1* ATPase-binding cassette-D1, *ALA* acido δ-aminolevulinico, *PBG* porfobilinogeno, *GLA* a-galactosidade A, *ABC1* ATP-binding cassette transporter 1, *FRDA* Friedreich ataxia gene, *TTPA* α-tocopherol transfer protein, *MTP* microsomal triglyceride transfer protein, *POLG* DNA polymerase gamma, *mtDNA* mitochondrial DNA, *ATP6* ATP synthase subunit 6, *HSCT* allogenic hematopoietic stem-cell transplantation, *ERT* enzyme replacement therapy

35.1.1 Charcot-Marie-Tooth Disease (CMT)

35.1.1.1 Terminology

Alias: Hereditary Motor and Sensory Neuropathy (HMSN) or peroneal muscular atrophy.

35.1.1.2 Demographics

The most frequent hereditary neuromuscular disorder with a general prevalence of about 1:2500. All modes of Mendelian inheritance are possible. In most European and US populations, 90 % of cases are autosomal dominant or X-dominant (CMTX), while 10 % are autosomal recessive. Autosomal dominant CMT: demyelinating subtypes (CMT1) more common (60 %) than the axonal subtypes (CMT2) (40 %), but the true prevalence of CMT2 is unknown and approximately 70 % of the CMT2 genes remain unidentified [3].

35.1.1.3 Clinical Features

Common Phenotype associated to CMT1, CMTX, and CMT2: onset in infancy or childhood, difficulty in running, twisting of ankles, pes cavus (planus at onset) and hammertoes, progressive peroneal atrophy with steppage gait, foot drop, mild sensory ataxia, weakness/wasting of hand intrinsic muscles, stocking-glove multimodal sensory loss.

Clinical clues: positive family history, presentation in the first-second decade, long and slow progression, foot deformities, paucity of positive sensory symptoms, degree of functional impairment milder than neurophysiological involvement. Postural tremor may be prominent independently of genetic subtypes (Roussy-Lévy syndrome).

Caveats: truly isolated cases may occur, caused by de novo dominant mutations. Dominant forms may be associated to age-independent intrafamilial phenotypical variability, from asymptomatic to severe disease. CMTX may be suggested by pedigree analysis (no male-to-male transmission; males affected, females asymptomatic or mildly affected) but a few CMTX females may be severely affected.

Early-Infantile Phenotype with perinatal onset, hypotonia, and breathing difficulties, or with delay of motor milestones. Severe weakness and wasting of distal and proximal muscles, sensory ataxia, foot and spine deformities, possible cranial involvement (mild ophthalmoparesis, facial weakness, neurosensorial hearing loss, vocal cord paralysis). Inheritance may be autosomal dominant with most cases isolated due to de novo mutations (demyelinating CMT3 alias Dejerine-Sottas disease), or autosomal recessive (demyelinating CMT4, or axonal AR-CMT2).

Adult Onset Phenotype Associated to CMT1B, CMTX women, CMT2. Symptoms develop after 40–50 years.

Special phenotypes CMTX may be suggested by marked involvement of abductor pollicis brevis; exceptional CMTX cases may present acute transitory leukoencephalopathies. Adult onset CMT2 may be associated with pupillary abnormalities, hearing loss and/or paresthesias/pain (CMT2I/J). CMT2 may be associated with optic neuritis/optic atrophy (CMT2-VI) or with brisk reflexes in the upper and proximal lower limbs (CMT2-V). Some genetic subtypes of CMT2 have a prevalent motor (CMT2F) or sensory involvement (CMT2B) that may affect prevalently the arms (CMT2D), or cause vocal cord paralysis (CMT2C).

35.1.1.4 Diagnostic Markers

Blood No biochemical markers available.

DNA Causal genes have been increasingly identified (more than 50 genes known, updated database at http://www.molgen.ua.ac.be/CMTMutations/). Many genes are tested currently by Sanger sequencing using a single-gene approach based on mutational frequencies; high throughput mutational analysis done by next-generation-sequencing techniques is becoming available for diagnostic purposes. Approximately 80–90 % of CMT1 have the duplication of chromosome 17p12 (*PMP22* gene), the remaining have mutations (mostly point mutations) in *GJB1*/*Cx32* (CMT1X, 6–20 %), *MPZ*/*P0*

(CMT1B, 5 %), *EGR2*, *PMP22*, *LITAF*/*SIMPLE*. Only 25–30 % of CMT2 receive a molecular diagnosis having mutations of *MFN2* (CMT2A, 10–20 % of all cases), *GJB1*/*Cx32* (CMTX), *MPZ*/*P0* (CMT2J), *NEFL* (CMT2E), *GDAP1* (CMT2K), *HSPB1* (CMT2F), *TRPV4* (CMT2C), *GARS* (CMT2D), or even other rarer genes. Dominant intermediate CMT is most frequently reported to be associated with *GJB1* (CMTX), *NEFL* (CMT2E), and *DNM2* (CMT2M). Autosomal recessive CMT is most frequently associated with mutation of *SH3TC2* (CMT4C, early, prominent kyphoscoliosis), *GDAP1* (CMT4A, AR-CMT2, AR- CMT intermediate), *HINT1* (predominant motor ± neuromyotonia).

CSF Is not analyzed with exception of the differential diagnosis with acquired neuropathies, when molecular investigations are negative, or for the diagnosis of an acquired disorder superimposed onto a known genetic neuropathy. Mildly increased protein content is occasionally found in CMT1 and CMT3, without any clear-cut boundary levels with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Imaging In CMT1-CMT3 inversion recovery (STIR)-MRI neurography may disclose hypertrophy ± MRI contrast enhancement of spinal roots, cauda equina, plexuses and/of median and ulnar nerves; ultrasound (US) discloses marked and diffuse increase of the cross-sectional area (CSA).

Neurophysiology Autosomal dominant CMT1 and CMT3, and autosomal recessive CMT4: uniformly slow nerve conduction velocities (NCV) with median and ulnar motor NCV (MNCV) < 38 m/s (below 12 m/s in CMT3) and proportionate delay in distal motor latencies and F-wave latencies. There is a relative preservation of CMAP while SAP decreases or is absent. In CMT1, NCV changes are fully penetrant independently of the clinical status. Autosomal dominant CMT2 and autosomal recessive AR-CMT2: NCV is preserved or mildly decreased (usually median or ulnar MNCV > 38 m/s), while CMAP and SAP are reduced. In CMT2, the electrodiagnostic changes may have incomplete penetrance. CMT1X male and rare autosomal dominant intermediate DI-CMT: median or ulnar MNCV between 25 and 45 m/s; MNCV is normal or slightly reduced in CMT1X women. In CMT1X, nerve conduction abnormalities may be non-uniform between and within nerve trunks with excessive temporal dispersion and conduction blocks.

35.1.1.5 Pathology

A sural nerve biopsy is no longer indicated unless for a differential diagnosis with other inherited neuropathies or with various, eventually superimposed, acquired neuropathies.

Besides demonstrating hypertrophic de-remyelination (CMT1, CMT4), hypo-amyelination (CMT3), or a chronic axonal neuropathy (CMT2), nerve biopsy may disclose additional pathological abnormalities of peculiar genetic forms: outfoldings and myelin uncompaction in CMT1B; prominent myelin outfoldings and/or basal-lamina SC onion bulbs in some CMT4 subtypes; giant axons in CMT2E.

35.1.1.6 Top Differential Diagnoses

CMT1: CIDP, anti-MAG neuropathy, familial amyloid polyneuropathies (FAP).
CMT3: metachromatic leukodystrophy, hereditary ataxias, Refsum disease, mitochondrial encephalomyopathies (MNGIE).
CMT2: acquired axonal neuropathies, FAP, distal myopathy, dHMN, HSAN, spinal dysraphism, mitochondrial encephalomyopathies (MNGIE, POLG1 mutations), GAN.
CMT5: hereditary spastic paraplegias (HSP).

35.1.1.7 Therapy

There are no specific medical therapies for any of the genetic subtypes. Treatment is supportive with rehabilitation and orthotics. Mild-to-moderate exercise is safe and likely effective. Effects of high-resistance training are controversial because it could result in overwork-weakness. Passive stretching is advised to prevent and counteract tendon retractions. Plantar and/or custom-fitted

ankle-foot orthoses are prescribed to correct foot position and to overcome foot drop.

Different surgical interventions for foot deformities.

Symptomatic therapy of neuropathic pain, joint/bone pain, paresthesias, cramps, fatigue, and restless leg syndrome is done as for other neuropathies.

35.1.1.8 Prognosis

Genetic counseling of probands and families is mandatory for diagnostic, predictive, prenatal, and pre-implantation testing.

Independently of the primary demyelinating or axonal process, evolution is associated with axonal loss. CMT-neuropathy score (CMT-NS), a composite clinical and neurophysiological score, is a validated tool for natural-history studies; patients are classified as mild (≤10), moderate (11–20), or severe (>20); in CMT1A the mean annual progression is 0.69 points/year. Most patients with CMT1A and CMT1X do not require ambulation aids beyond ankle-foot orthoses. CMT3 patients may require above-the-knee bracing, walkers, or wheelchairs by 20 years of age.

Periods of self-limiting worsenings may be related to growth in childhood and adolescence. Acute or subacute worsenings should prompt to exclude a superimposed, treatable, acquired neuropathy (e.g., GBS, CIDP, diabetic neuropathy).

Guillain-Barré syndrome or GBS-like syndromes have been reported after chemotherapy; cancer in CMT should be treated with less neurotoxic chemotherapeutic agents.

Some patients report faster deterioration during pregnancy, usually but not always, with recovery.

Anesthetics are well tolerated but regional anesthesias are considered somewhat contraindicated.

35.1.2 Hereditary Neuropathy with Liability to Pressure Palsy (HNPP)

35.1.2.1 Terminology and Definitions

HNPP (alias tomaculous neuropathy) is an autosomal dominant demyelinating polyneuropathy manifesting most frequently with acute/subacute painless palsies at common entrapment sites, caused by haploinsufficiency of *PMP22* (commonly associated to the 1.4 Mb deletion of chromosome 17p12).

35.1.2.2 Demographics

Prevalence is theoretically similar to CMT1A. Up to 25 % of the carriers of the 17p12 deletion may be asymptomatic, having a subclinical polyneuropathy. All ages are involved; the first episode is usually in the second-third decade, occasionally in childhood.

35.1.2.3 Clinical Features

Typical Presentation (Approximately Two-Thirds of Patients) episodic, painless, recurrent focal, and motor palsies affecting variably the median, ulnar, peroneal nerves or brachial plexus often preceded by minor compression or trauma at vulnerable sites (wrist, elbow, knee, shoulder). Palsies may be debilitating and last for days or weeks (or rarely months). Besides episodes, patients often complain of positional acroparesthesias and disclose reduced or absent deep tendon reflexes and mild pes cavus.

Atypical Presentations may occur in up 30 % of patients and include: chronic sensory polyneuropathies, CMT1-like polyneuropathies, chronic ulnar neuropathies, acute syndromes with multiple limbs involved, carpal tunnel syndromes.

35.1.2.4 Pathophysiology

Haploinsufficiency associated to the common deletion of *PMP22* (90–95 % of cases) or to rare micromutations cause a mild chronic demyelinating polyneuropathy marked by sausage-like "tomaculous" focal thickenings of the myelin sheath. Focal constrictions of axons segments enclosed by tomacula may predispose to mechanically induced CB and acute clinical deficits.

35.1.2.5 Diagnostic Markers

Blood DNA The most common molecular lesion is the 1.4 Mb 17p12 (*PMP22*) deletion. A minority

of cases (approximately 5 %) have micromutations of *PMP22* (nonsense or frameshifting mutations).

Imaging US may disclose nerve enlargements at multiple sites of entrapment but its sensitivity and specificity is still limited.

Neurophysiology Neurophysiological testing provides a reliable picture even in asymptomatic cases. Distal motor latencies (DML) are prolonged in median, ulnar nerves, and peroneal nerves with only mild slowing in the distal segments (median MNCV usually above 38 m/s); SAPs are diffusely reduced; coNduction blocks CB over entrapment sites are characteristic in symptomatic nerves.

35.1.2.6 Pathology

Sural nerve biopsy has full specificity and almost complete sensitivity but is no longer indicated. It discloses a chronic demyelinating polyneuropathy with a variable number of *tomacula* (sausage-like myelin thickenings) in semithin and ultrathin sections and in teased fibers.

35.1.2.7 Top Differential Diagnoses

Entrapment neuropathies. Vasculitic neuropathies. Familial carpal tunnel syndrome (CTS). Idiopathic and hereditary neuralgic amyotrophy (HNA).

HNA is an autosomal dominant disorder caused by mutations or intragenic duplications of the septin 9 (*SEPT9*) gene that manifests with recurrent attacks of pain, weakness, and sensory disturbance with predilection for the brachial plexus. It progresses 2–3 weeks after the onset of pain and involves, in some cases, the phrenic nerves and/or cranial nerves VII and X. Associated features include: short stature, hypotelorism, long nasal bridge, cleft palate, epicanthal folds, facial asymmetry, and partial syndactyly. HNA may develop in all ages (most commonly in the second-third decade), possibly triggered by periods of physical (partum), immunological, or emotional stress.

35.1.2.8 Prognosis and Therapy

Management is mainly preventive: employment or recreational activities which increase the risk of nerve compression should be avoided. Obstetricians and surgeons should be informed of the diagnosis, to avoid prolonged positioning of the body and limbs. Peripheral regional anesthesia is somewhat contraindicated. Surgery is sometimes offered for nerve entrapment release but any benefit tends to be short-lived.

Life expectancy is normal and most patients have a good quality of life. About 10 % of patients make an incomplete recovery from episodes of nerve palsy due to persistent CBs. Age-related irreversible motor axonal damage may ensue at entrapment sites [4].

Management is mainly preventive: employments or recreational activities with increased risk of nerve compression should be avoided. Obstetricians and surgeons should be informed of the diagnosis to avoid prolonged positioning of the body and limbs.

35.1.3 Familial Amyloid Polyneuropathies (FAP)

35.1.3.1 Terminology and Definitions

Autosomal dominant disorders associated with the extracellular deposition of amyloid fibrils made of the mutated proteins: transthyretin (TTR), apolipoprotein A1 (APOA1), or gelsolin (GSN). TTR is a plasma transporter for thyroxine and vitamin A produced predominantly by liver.

35.1.3.2 Demographics

TTR-FAP variants are world widely distributed: incidence in the USA is 1:100,000 individuals; the Val30Met variant is endemic in some areas of northern Portugal (incidence 1 in 538 individuals), northern Sweden, Japan, and Brazil. GSN-FAP has some clusters in southeastern Finland and it is very rare in other European countries, USA, and Japan. APOA1-FAP, described in an Iowa kindred with British extraction, was also reported in rare families with different ancestries [5].

35.1.3.3 Clinical Features

TTR-FAP Val30Met in endemic areas: onset in third-fourth decade, relentless sensory-motor-

autonomic polyneuropathy with superimposed CTS, cardiac and kidney dysfunction.

Clues to diagnosis: stabbing lancinating pain, gastrointestinal motility disturbances, erectile dysfunction, orthostatic hypotension, neurogenic bladder, bulbar involvement, cardiomyopathy with thickened ventricular walls, advanced atrioventricular block, cotton-wool inclusions of vitreous body, glaucoma, albuminuria, hyperazotemia.

Val30Met in non-endemic areas and other molecular variants: reduced penetrance (less than 50 %), later adult onset (up to seventh decade, mean age 55–60 years), lack of familiarity, CIDP or *Amyotrophic Lateral Sclerosis* (ALS)-like evolution with fasciculations, lack of pain or dysautonomia, much later multi-system involvement, isolated CTS preceding polyneuropathy of several years. A minority of TTR mutations may lead to selective oculo-leptomeningeal amyloidosis (stroke, seizures, hydrocephalus, spinal cord infarction, vitreous opacities) or cardiac amyloidosis (restrictive cardiomyopathy).

GSN-FAP Onset in third-fourth decades. Corneal lattice dystrophy, multiple cranial neuropathies (facial and bulbar weakness), cutis laxa. Late generalized polyneuropathy. Symptoms generally worsen with age.

APOA1-FAP Onset in the third-fourth decades. Painful, autonomic, sensorimotor polyneuropathy. Early renal involvement, peptic ulcer disease.

35.1.3.4 Diagnosis

In non-endemic areas the mean interval from onset to diagnosis of TTR-FAP is 3–4 years.

35.1.3.5 Laboratory

Blood DNA Mutational analysis of involved genes.

CSF Analysis is not indicated; when done may be misleading revealing an increased protein content.

Blood *TTR-FAP* Some serum variants of TTR may be detected by mass spectrometry (not routinely); plasma NT-proBNP, high sensitivity troponin, creatinine clearance and albuminuria (for evaluating cardiac and renal progression).

Neurophysiology *TTR-FAP*: NCV studies consistent with an axonal polyneuropathy ± CTS, sometimes with a demyelinating polyneuropathy [6]. EMG: denervation. Autonomic tests: sympathetic skin reflex, quantitative sensory testing (QST), beat-to-beat heart rate variability (HRV: ECG rate monitoring while breathing in-and-out at six breaths per minute).

ECG and Two-Dimensional Echocardiography *TTR-FAP*: cardiac assessment and non-invasive diagnosis of amyloidotic cardiomyopathy.

Imaging *TTR-FAP*: *cardiac magnetic resonance* (delayed gadolinium enhancement to detect amyloid in the myocardial interstitium).

Scintigraphy with ^{99m}Tc-DPD to image amyloid in the myocardium. Scintigraphy with ^{123}I-MIBG to reveal loss of sympathetic nerve endings in heart. Scintigraphy with ^{123}I-SAP to evaluate extent and distribution of amyloid deposits in soft tissues and visceral organs except heart.

Biopsies *TTR-FAP*: demonstration of amyloid deposits by Congo red staining (green birefringence under polarized light) and electron microscopy is essential for eligibility for liver transplantation. Sensitivity is as follows: subcutaneous fat approximately 60 % (repeatable); sural nerve or gastrointestinal mucosa approximately 80 %. Immunohistochemistry with anti-TTR antibodies is mandatory to characterize the biochemical nature of the amyloid fibrils. Liquid chromatography-tandem mass spectrometry may also identify precursor proteins of amyloid fibrils, including variant TTR.

35.1.3.6 Top Differential Diagnoses

TTR-FAP AL (amyloid light chain)-amyloidosis. Diabetic, alcoholic neuropathies. CIDP. Paraneoplastic neuropathies. CMT2. Fabry disease. ALS.

35.1.3.7 Therapy

Disease-Modifying Treatments

Orthotopic liver transplantation (OLT) is the first line therapy, removing approximately 95 % of mutant blood TTR. OLT is indicated in early stages with bioptically proven amyloidosis [7]; [see also Familial Amyloidotic Polyneuropathy world Transplant Registry and Domino Liver Transplant Registry (www.fapwtr.org)].

Life expectancy is better in Val30Met patients (10-year survival approximately 74 % compared with 44 % in non-Val30Met patients), in patients transplanted earlier in the disease, in patients <50 years. Low modified body mass index (<600) is a negative predictor. Besides life expectancy, some Val30Met patients reported improvement of gastrointestinal, autonomic, peripheral-nerve symptoms, but recovery of nerve function does not occur. Patients in later stages and some non-Val30Met patients disclose progression after transplantation due to continued deposition of wild type TTR and/or of the mutant TTR in heart (progressive restrictive cardiomyopathy, cardiac autonomic denervation) and PNS.

OLT is not indicated in predominantly leptomeningeal amyloidosis.

Combined heart and liver transplant is indicated in severe heart failure due to amyloidotic cardiomyopathy in patients without advanced neurologic involvement. Liver transplant is also an option for non-Val30Met candidates with echocardiographic evidence of cardiomyopathy.

Domino liver transplant of FAP-livers in patients with liver failure is an accepted procedure but it may lead to TTR-FAP in the recipients after 8–10 years.

The following pharmacotherapies are a second line option for patients not eligible for OLT or waiting for OLT in early stages of disease [8]: kinetic stabilizers (tafamidis, authorized for marketing in Europe for early stages of disease; diflunisal); fibril disruptors (oxycycline/tauroursodeoxycholic acid). Gene-therapy approaches are becoming available including antisense oligonucleotides (ASO) and RNA interference-based molecules vehicled by lipid nanoparticles.

Symptomatic Treatments

Neuropathic pain (see Chap. 27) and autonomic dysfunction are treated as in other neuropathies (see Chap. 24).

35.1.3.8 Prognosis

TTR-FAP is relentlessly progressive. Untreated patients with the classical Portuguese phenotype die 10–15 years after onset because of malnutrition, cardiac or renal failure, or cardiac arrhythmias (Transthyretin Amyloidosis Outcomes Survey –THAOS – www.thaos.net).

Follow-up should be done every 6 months including neurological disability scores, full neurophysiological and cardiological laboratory tests, and evaluation of the modified body mass index (BMI) (BMI multiplied by serum albumin level). Degrees of clinical involvement: 0 = no symptoms, variant TTR form, evidence of amyloid deposits; I = unimpaired ambulation; mostly mild sensory, motor, and autonomic neuropathy in the lower limbs; III = assistance with ambulation required; mostly moderate impairment progression to the lower limbs, upper limbs, and trunk; III = wheelchair-bound or bedridden; severe sensory, motor, and autonomic involvement of all limbs.

35.1.4 Porphiric Neuropathy

35.1.4.1 Terminology and Definitions

Acute neuropathy resembling Guillain-Barré syndrome (GBS), associated to dysfunction of the autonomic and central nervous systems. Neuropathic porphyrias are caused by the following autosomal dominant enzymatic defects in the hepatic biosynthesis of heme: porphobilinogen (PBG) deaminase (acute intermittent porphyria – AIP); copro oxidase (hereditary coproporphyria – HCP); proto oxidase (variegate porphyria – VP).

35.1.4.2 Demographics

Carriers of the genetic defect are estimated to be 1/80.000 people; prevalence was 20-times higher in the psychiatric hospital populations in the USA. Ten to forty percent of carriers may develop neuropathy. Attacks are five times more frequent

in women and manifest usually in the third and fourth decades.

35.1.4.3 Pathophysiology

Predominantly proximal motor axonal damage with Wallerian degeneration and secondary demyelination. Peripheral and central neuronal involvement might result from impaired energy metabolism due to heme deficiency and/or toxicity by the common precursor δ-aminolevulinic acid (ALA).

35.1.4.4 Clinical Features

Acute attacks are often triggered by fasting, porphyrinogenic treatments (estrogen/progesterone contraceptives, barbiturates, sulfonamides, antiepileptics, any drug that is metabolized by the P450 system), sepsis or alcohol (possibly misinterpreted as acute intoxication). Attacks feature the classic triad of abdominal pain, psychosis, and neuropathy. They manifest as an autonomic neuropathy (resting tachycardia, papillary abnormalities, abdominal pain, nausea, vomiting, and severe constipation mimicking a surgical abdomen) and neuropsychiatric changes (anxiety, insomnia, seizures, hallucinations, sudden changes in behavior; the recurrence during the luteal phase may be misdiagnosed as a bipolar disorder). Motor neuropathy manifests subacutely 3–75 after onset (within 1 month in 80 % of cases) and progresses symmetrically for over 1 month; at nadir total quadriplegia and respiratory insufficiency may ensue requiring ventilatory support; facial and bulbar weakness are common. Evolution may be descendent from arms to legs with rapid muscle wasting. Sensory symptoms may be associated or not to distal sensory loss; tendon reflexes are diminished or absent, rarely retained. Atypical presentations include progressive motor neuropathies, mostly affecting the upper limbs, without abdominal pain.

Patients with HCP and VP may develop cutaneous photosensitivity in adult life.

35.1.4.5 Top Differential Diagnosis

GBS, vasculitis, heavy metal intoxication, poliomyelitis.

35.1.4.6 Diagnostic Markers

CSF Proteins can be normal or mildly elevated.

Blood and Urine The diagnosis of porphiric attack is made revealing a marked elevation of PBG and ALA in blood, urine, and stool. During an attack, urine may be brown reflecting high concentration of porphyrin metabolites. Enzymatic assays may identify and distinguish among hepatic porphyrias, but the results may be misleading.

Neurophysiology NCV studies show an axonal neuropathy with decreased amplitudes of motor responses and possible slowing of conduction velocities secondary to large-fiber loss, without CB or abnormal temporal dispersion; sensory function is relatively or completely spared. EMG demonstrates prominent fibrillation potentials within weeks of onset, most prominent in proximal muscles.

35.1.4.7 Prognosis and Therapies

Once aborted, the prognosis of a single attack is generally good with rapid resolution of the autonomic and psychiatric symptoms. Recovery of neuropathy is slower, often occurring over many months (approximately 10 months for proximal muscles and 20 for distal muscles), usually with incomplete recovery. Sixty-eighty percent of patients have a single acute attack of porphyria. Since cumulative fixed deficits may ensue after repeated attacks, the long-term prognosis depends on successful prevention of attacks.

The prognosis of AIP is good even in severe, acute attacks. Anyway, AIP carries a potentiality fatal outcome due to motor and autonomic involvement with respiratory and bulbar paralysis and/or cardiac arrhythmias.

Prevention is based by awareness and avoidance of precipitating drugs and situations. During an attack abortive therapies include IV glucose (10–20 g/h) followed, if there is no improvement, by IV hematin (1–5 mg/kg/day infused over 30–60 min); supportive therapies are discussed in the following section of GBS. **

35.2 Title: Immunomediated Neuropathies

Key Facts

- **Terminology and definitions**
  - **Acute forms** – *GBS*: acute inflammatory polyradiculoneuropathies reaching their maximal severity within 4 weeks. Variants AIDP, AMAN, acute motor-conduction-block neuropathy, AMSAN, acute sensory neuronopathy, MFS, GBS-MFS overlaps, acute panautonomic neuropathy. *MFS*: acute ataxia, with ophthalmoplegia and areflexia.
  - **Chronic forms** *CIDP* = Acquired demyelinating neuropathy reaching maximal severity in at least 8 weeks.:
  - *MMN* = Peripheral neuropathy with slowly progressive or remitting asymmetric distal weakness and persistent motor conduction blocks, without significant sensory loss.
- **Clinical features**
  - **Acute forms** – Incidence: 1.8/100,000 for *GBS*; 0.1/100,000 for *MFS*. Gastrointestinal or respiratory upper-tract infection before onset in 66 % of patients. Progressive weakness of both legs and arms with areflexia characterize AIDP, AMSANm AMAN. In *MFS* ophthalmoparesis may develop asymmetrically but often becomes complete; pupillary involvement is uncommon.
  - **Chronic forms** – *CIDP* prevalence: 1.97–4.77/100,000. Typical forms (80 % of cases) are characterized by symmetrical distal and proximal weakness, sensory loss and paresthesias, absent deep tendon reflexes with progressive or relapsing/remitting course. *MMN* prevalence: 1–2/100,000. MMN show weakness developing over months or years with a multifocal asymmetric distribution in individual nerves and usually prominent in the distal arms.
- **Diagnostic markers**
  - **Blood** – Ig auto-Ab anti-GM1 in: *AMAN*, *AMSAN*, and acute motor-conduction-block neuropathy. *MFS*: Ab anti-GQ1b in 95 % of patients.
  - **MMN** – IgM auto-Ab anti-GM1 in 40–50 % of patients.
  - **CSF** – Albumin-cytologic dissociation. Normal in MMN.
  - **MRI** – Possible enhancement and/or hypertrophy of the cauda equina, lumbosacral nerve roots, brachial and lumbosacral plexuses.
  - **Neurophysiology** – Demyelination and CBs in *AIDP* and *CIDP*; axonopathy in *AMAN*.
- **Top Differential Diagnoses**
  - **Acute forms** – Polymyositis, myasthenia gravis, CIDP. *MFS*: Brainstem ischemia, Wernicke's encephalopathy.
  - **Chronic form***s* – *CIDP*: Polyneuropathies of different cause; Myopathies.
  - **MMN**: Motor neuron disorders. CIDP. Myopathies.
- **Prognosis and Principles of treatment**
  - **Acute forms** – PE or IVIg within the first 2–4 weeks from onset.
  - **Chronic forms** – *CIDP*: Steroids, PE and IVIg. *MMN*: IgIV are effective in 79–86 % of patients. Steroids are contraindicated in MMN.
- **Disability**
  - **Acute forms** – *GBS*: 5 % of patients die, 5–10 % remain disabled or severely fatigued, 15 % are asymptomatic 1–2 years after onset. *MFS*: mostly benign. Recovery takes a median of 1–3 months. By 6 months, most patients are free from ataxia and ophthalmoparesis.
  - **Chronic forms** – *CIDP*: age <45 years predicts a better outcome; axonal loss is associated with poorer prognosis. In the long term, mortality ranges from 1.3 to 9 %; 40 % of patients have no or non-disabling symptoms, 75 % are able to work, 24 % carry severe handicap.
  - **MMN**: very uncommon spontaneous remissions. In the long term, 1/3 of patients improves, 1/3 is IgG dependent, and 1/3 continues to be non-responsive.

35.2.1 Guillain-Barré Syndrome (GBS)

35.2.1.1 Definition and Terminology

GBS is an acute, inflammatory, areflexic paralysis with variable degree of weakness that reaches maximal severity within 4 weeks, usually with an ascending progression from lower to upper limbs and cranial nerves, and albuminocytologic dissociation [9].

Clinical and/or electrophysiological variants:

1. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)
2. Acute motor axonal neuropathy (AMAN)
3. Acute motor-conduction-block neuropathy
4. Acute motor-sensory axonal neuropathy (AMSAN)
5. Acute sensory neuronopathy
6. Miller-Fisher syndrome (MFS)

7. GBS-MFS overlaps
8. Acute panautonomic neuropathy

35.2.1.2 Demographics

Worldwide mean annual incidence is 1.8 per 100,000 for GBS (ranging from 0.8 for age <18 years to 3.2 for age >60 years) and 0.1 per 100,000 for MFS. Males are affected more frequently than females (1.5:1). AIDP accounts for 90 % of cases in North America and Europe; AMAN accounts for 30–47 % of cases in Asia and Central and South America and 5 % of cases in Western countries. AIDP is non-seasonal; AMAN may occur in summer epidemics in northern China affecting children and young adults and is likely associated with *Campylobacter* (*C.*) *jejuni* infections.

Two-thirds of patients report an event 1–4 weeks before onset, most frequently symptoms or signs of gastrointestinal or respiratory upper-tract infection: *C. jejuni* (30 %), cytomegalovirus (CMV) (10 %), Epstein-Barr virus, Varicella-zoster virus, HIV, *Mycoplasma pneumoniae*, *Haemophilus influenzae*.

Incidence of GBS is 0.25–0.65 per 1000 cases of *C. jejuni* infection and 0.6–2.2 per 1000 cases of primary CMV infection. Less frequent antecedents: vaccinations (only brain-derived rabies vaccines have been associated with elevated risk above the background incidence), drugs (heroin, streptokinase, suramin, gangliosides), or surgical procedures.

35.2.1.3 Pathophysiology

Immune-mediated disorders resulting from generation of autoimmune antibodies and/or inflammatory cells which cross-react with epitopes on peripheral nerves and roots, leading to demyelination or axonal damage or both. Molecular mimicry may involve ganglioside epitopes of myelin (AIDP) or axonal membranes (AMAN) and lipopolysaccharide epitopes of infectious agents. Antiganglioside antibodies that cross-react with *C. jejuni* are common in AMAN and AMSAN (anti-GM1 in 65 % of patients); MFS (anti-GQ1b in more than 90 % of patients) and acute sensory neuronopathy (anti-GD1B).

In AIDP anti-myelin antibodies directed against epitopes on the abaxonal SC membrane may lead to demyelination with activation of complement and recruitment of macrophages, followed by secondary axonal degeneration. In AMAN anti-GM1 antibodies react against epitopes at nodes of Ranvier and along the axolemma of motor fibers; activation of complement and recruited macrophages lead to Wallerian degeneration.

35.2.1.4 Diagnosis

Diagnosis is based on clinical characteristics and ancillary laboratory investigations [10]. New criteria to better identify patients for vaccine safety studies are under validation [11].

Clinical Criteria

AIDP Required features: progressive weakness of both legs and arms; areflexia. Supportive features: progression over days to 4 weeks (more often with ascending evolution); relative symmetry of symptoms and signs; mild sensory symptoms or signs (distally decreased vibration sense); moderate-severe pain in extremities, interscapular area or back (in up 89 % of patients in the acute phase); bifacial palsies (45–75 % of patients, whereas involvement of extraocular muscles and lower cranial nerve is less common); autonomic instability (in up to 65 % of patients); monophasic evolution pattern with recovery beginning 2–4 weeks after progression ceases.

AMSAN and AMAN overlap clinically with AIDP (AMAN have non-sensory signs or symptoms) but diverge in electrodiagnostic features and prognosis.

35.2.1.5 Diagnostic Markers

Supportive Criteria

CSF elevated protein with <10 cells/μl in 80 % of patients after 2 weeks (pleocytosis >10 lymphocytes/μl should prompt to consider Lyme disease, recent HIV infection, sarcoidosis, and poliomyelitis).

Neurophysiology Electrodiagnostic (EDX) is aimed at detecting signs of multifocal demyelination (AIDP) or axonopathy (AMAN), showing signs of polyneuropathy in the arms when weakness is only in the legs, excluding other diagnoses.

AIDP EDX criteria are at least one of the following in each of at least two nerves, or at least two of the following in one nerve, if all others are inexcitable and CMAP is >10 % of lower limit of normal (LLN): MNCV <90 % LLN (85 % if dCMAP <50 % LLN). DML >110 % of upper limit of normal (ULN) (>120 % if dCMAP <100 % LLN). pCMAP/dCMAP (ratio between CMAP obtained after proximal and distal stimulation) <0.5 and CMAP >20 % LLN. F-response latency >120 % ULN. Sensory conduction studies: sural SAPs are frequently normal in spite of reduced or absent SAPs in the upper limbs. Needle EMG is mostly complementary showing decreased motor unit recruitment; fibrillation potentials appear 2–4 weeks after onset if axonal degeneration occur.

AMSAN: none of the features of AIDP except one demyelinating feature allowed in one nerve if dCMAP <10 % LLN. SAPs < LLN.

AMAN: none of the features of AIDP except one demyelinating feature allowed in one nerve if dCMAP <10 % LLN. SAPs normal. dCMAP absent in all nerves or present in only one nerve with dCMAP <10%LLN.

Serial recordings are indicated for proper diagnosis and prognosis. In the very early course electroneurography (ENG) may be normal in up to 15 % of patients and may not distinguish different electrophysiological subtypes. In AIDP delayed DML, delayed or absent F waves and temporal dispersion may be more sensitive indicators than conduction slowing and CB in the intermediate nerve segments; the nadir of conduction slowing is 3–6 weeks after onset, corresponding to the clinical recovery stage and remyelination. AMAN may disclose transient conduction slowing and block within 3 weeks after onset and rapid normalization in parallel with clinical recovery; CMAP amplitudes have a rapid progressive decrement and gradually improve with clinically recovery without prolongation of DML, conduction slowing or excessive temporal dispersion. In acute motor-conduction-block neuropathy, an aborted form of AMAN, CBs rapidly resolve without excessive temporal dispersion or conduction slowing.

Other Laboratory Features

Antiganglioside antibodies are not specific or prognostic and not always suitable clinically. Ig anti-GM1 antibodies may be detected in the majority (64 %) of AMAN patients and in AMSAN as well as in AMSAN and acute motor-conduction-block neuropathy.

Liver function tests are often elevated.

35.2.1.6 Top Differential Diagnoses

Muscle: critical illness myopathy, polymyositis, rabdomyolysis, hypokalemia, hypophosphatemia.

Neuromuscular junction: myasthenia gravis (crisis), botulism, organophosphate poisonings, tick paralysis.

Polyneuropathies: AIP, critical illness polyneuropathy, vasculitis, diphtheria, heavy metals, or drug intoxications.

Polyradiculopathies: inflammatory or neoplastic meningoradiculopathies, CMV lumbosacral radiculomyelopathy.

Central Nervous System: West Nile and enterovirus poliomyelitis, transverse myelitis.

35.2.1.7 Therapy

Immunotherapy

In all patients, even if only mildly affected and able to walk with or without assistance, plasma exchange (PE) or IVIg (preferred in many centers because of greater convenience and availability) should be started early, preferably within the first 2 weeks. They are equally effective in improving the disability grade after 4 weeks as well as the duration of mechanical ventilation, mortality, and residual disability. PE: four to six alternate-day

exchanges (2–4 L each). IVIg: 2.0 g/kg body weight infused over 5 days.

In patients who continue to worsen, a repeated course of IVIg might be effective (not proven, trials and observational studies ongoing); combination of PE followed with IVIg is not superior compared to PE or IVIg alone. Combination of IVIg and intravenous methylprednisolone is no more effective than IVIg alone.

In patients who deteriorate after initial improvement (treatment-related clinical fluctuations in 5–10 % of cases), a second IVIg is given (2 g/kg in 2–5 days).

Three or more episodes of deterioration after 9 weeks from onset suggest Acute-onset CIDP (A.CIDP), which should be treated accordingly.

Indications for ICU Admission
Rapidly progressive severe weakness often with impaired respiration. Need for artificial ventilation (elective intubation if forced vital capacity less than 15 ml/kg or negative inspiratory force less than –20/–30 cm H_2O). Severe autonomic dysfunction (cardiac arrhythmias, marked fluctuations of blood pressure).

Supportive Care

35.2.1.8 Prognosis
Maximal weakness is reached within 4 weeks (at least 50 % of patients reach a nadir by 2 weeks). About 5 % of patients initially diagnosed with GBS have longer progression over 8 weeks (A-CIDP). Following the plateau phase, which lasts from several days to weeks, most patients recover a satisfactory function over several months, but only about 15 % of patients are asymptomatic 1–2 years after onset and 5–10 % remain persistently disabled or severely fatigued. GBS is potentially fatal: about 25 % of patients require artificial ventilation during a period of days to months, about 5 % die due to respiratory failure or distress syndrome, aspiration pneumonia, pulmonary embolism, cardiac arrhythmias, or sepsis related to acquired infections.

AIDP tend to have a longer progression and later nadir (18 vs 11.5 days), facial weakness (71 % vs 9 %), and more frequent need of artificial ventilation (27 % vs 9 %) in comparison to AMAN.

Risk Predictors for Artificial Ventilation The risk was found to be relatively lower (less than 2.5 %) in patients without CB of the common peroneal nerve and with a vital capacity of more than 81 % [12]. Days between onset of weakness and admission, Medical Research Council (MRC) sum score, and presence of facial and/or bulbar weakness were the main predictors of mechanical ventilation in the Erasmus GBS Respiratory Insufficiency Scale (EGRIS) [13].

Outcome Predictors The modified Erasmus GBS Outcome scale (mEGOS) takes into account the patient's age, presence or absence of preceding diarrhea, and disease severity; advanced age, preceding diarrhea, and low MRC sum score, calculated at admission and at 1 week, are independently associated with inability to walk at 1, 3, and 6 months [14].

35.2.2 Miller-Fisher Syndrome (MFS)

35.2.2.1 Definition
Acute syndrome of ataxia, ophthalmoplegia, areflexia with median peak at 1 week after onset.

35.2.2.2 Demographics
Incidence estimated at 0.09 per 100,000. More frequent in eastern Asia (20 % and 25 % of GBS in Taiwan and Japan) with male predominance (2 to 1) and mean age of onset in early forties. Onset is most common in spring. Most patients have an antecedent respiratory or gastrointestinal infection 1–3 weeks before onset (*C. jejuni* 20 %, *Haemophilus influenzae* 8 %). MFS is also anecdotally associated with autoimmune and neoplastic conditions.

35.2.2.3 Pathophysiology
Anti-GQ1b antibodies raised through molecular mimicry are detectable in most patients and may interact with GQ1b ganglioside concentrated in the oculomotor, trochlear, and abducens nerves

as well as in limb muscle spindles. Primary pathological changes of the uncomplicated form are unclear but early sensory nerve conduction studies are consistent with nerve demyelination or conduction failure along the axons rather than axonal loss. Sensory ataxia may be caused by selective involvement of muscle-spindle afferents.

35.2.2.4 Diagnosis

Clinical Features

Ophthalmoparesis may develop asymmetrically but becomes often complete; pupillary involvement is uncommon. Diplopia is the most frequent symptom at onset (39 %). Ataxia is evident in 21 % of patients at onset. Areflexia is detectable in 82 % of patients. Associated features may be facial diparesis (57 %), dysphagia (40 %), and dysarthria (13 %), distal paresthesias. Some patients may have MFS-AIDP overlap with limb weakness and respiratory involvement or incomplete forms with various combinations of ophthalmoplegia, facial or bulbar palsy, and sensory neuropathy. Overlap of MFS with Bickerstaff's brain-stem encephalitis (BBE) may have additional features of CNS involvement such as drowsiness and extensor plantar responses.

35.2.2.5 Top Differential Diagnosis

Other anti-GQ1b antibody syndromes: acute ophthalmoparesis, acute ataxic neuropathy, pharyngeal-cervical-brachial weakness, and BBE (ophthalmoplegia, ataxia, hypereflexia, and disturbed consciousness, associated to Ig anti-GQ1b antibodies in 66 % of cases). Brainstem stroke. Wernicke's encephalopathy, myasthenia gravis, botulism.

35.2.2.6 Diagnostic Markers

Blood IgG anti-GQ1b antibodies are detectable in up to 95 % of patients but are not specific or prognostic; they are not always suitable clinically.

CSF Most patients have elevated CSF proteins without significant pleocytosis; normal CSF proteins do not exclude the diagnosis.

MRI Imaging is unremarkable in most cases. Singleton cases may disclose brainstem abnormalities.

Neurophysiology SNAPs are initially reduced alone or out of proportion to prolongation of DML or slowing of sensory conduction velocities and return to normal with clinical improvement. CMAPs in arms and legs are usually normal. *Blink reflex* may be abnormal and reduced facial CMAP coincides with loss or mild delay of R1 and R2 responses. In some cases, abnormalities of visual, auditory, somatosensory, and motor-evoked potentials suggest a combined central and peripheral involvement. Anti-GQ1b antibody-positive MFS patients may have abnormal jitters that improve with clinical recovery and may have evidence of presynaptic neuromuscular transmission defect at high-frequency repetitive nerve stimulation up to 3 months after onset.

35.2.2.7 Therapy

There are no randomized, double-blind, placebo-controlled trials. Anecdotal patients are treated with IVIg or PE similarly to GBS.

35.2.2.8 Prognosis

Peak is at a median of 1 week. Median interval between onset and the beginning of recovery is 12–15 days. Recovery from ataxia and from ophthalmoplegia takes a median of 1 and 3 months. By 6 months, most patients are free from ataxia and ophthalmoparesis. The pure form is mostly self-limiting and benign. MFS-GBS or MFS-BBE overlap forms are described, particularly in children, and may require mechanical ventilation or lead to serious complications such as coma, ballism, cardiomyopathy from dysautonomia, lactic acidosis, and pain. Recurrences are rare but documented.

35.2.3 Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

35.2.3.1 Definition

Acquired demyelinating neuropathy of presumed autoimmune origin.

35.2.3.2 Demographics

Prevalence: from 1.97/100,000 (American Academy of Neurology – AAN research criteria) to 4.77/100,000 (European Federation of Neurological Societies and the Peripheral Nerve Society – EFNS/PNS diagnostic criteria). Incidence: 0.35/100,000 (AAN research criteria) – 0.70/100,000 (EFNS/PNS diagnostic criteria). Although all ages may be involved (including infancy), CIDP is most common after 40-years. Other possibly associated diseases: IgG or IgA MGUS (monoclonal gammopathy of undetermined significance), IgM MGUS without anti-MAG antibodies, HIV infection, various inflammatory or immunomediated systemic disorders. There are no clear-cut differences between idiopathic CIDP and CIDP associated with others disorders.

35.2.3.3 Pathophysiology

Both cellular and humoral immunity are implicated in the pathogenesis with variable mechanisms. No pathogenic antibody or definite triggering antigen have been identified. Demyelination is caused by macrophages recruited by activated T-cells and by complement-fixing immunoglobulins.

35.2.3.4 Clinical Features

Typical CIDP (80 % of cases) Symmetrical distal and proximal weakness, sensory loss and paresthesias, decreased or absent deep tendon reflexes; rare involvement of cranial nerves, respiratory insufficiency and dysautonomia. Disease course is steadily progressive or relapsing/remitting over at least 8 weeks. In the GBS-like presentation (A-CIDP) deterioration occurs for more than 8 weeks after onset or relapse at least three times; A-CIDP should be suspected with prominent sensory involvement at presentation.

Atypical CIDP *Asymmetric CIDP* or Lewis-Sumner syndrome or multifocal demyelinating neuropathy with persistent CBs: slowly progressive, asymmetric sensorimotor involvement in the distribution of two or more peripheral nerves, usually first in the upper, later in lower limbs and, rarely, cranial nerves.

Focal CIDP: localized to brachial or lumbosacral plexus or one or more peripheral nerves in an upper or lower limb.

Pure motor CIDP: selective involvement of motor fibers.

Pure sensory CIDP: gait ataxia and paresthesias (MNCV slowing and CBs may be present despite absence of motor symptoms).

Distal Acquired Demyelinating Symmetrical neuropathy (DADS): mainly sensory neuropathy associated in 2/3 of cases with anti-MAG antibodies (see paraproteinemic neuropathies); cases without anti-MAG antibodies respond to immunotherapy similarly to typical CIDP.

Other features: subclinical signs of CNS involvement may occur in up to 50 % of cases (prolonged central motor conduction times, periventricular white matter MRI hyperintensities). Multiple Sclerosis-like syndrome may rarely occur.

35.2.3.5 Diagnostic Markers

CSF Increased CSF protein content with blood cell count less than 10/mm^3 occurs in approximately 90–95 %.

Imaging MRI discloses gadolinium enhancement and/or hypertrophy of the cauda equina and lumbosacral nerve roots, and of brachial and

lumbosacral plexuses; STIR images are more sensitive (66.7 %) than T1-weighted images or gadolinium enhancement. US may reveal normal, mildly, or regionally enlarged nerves.

Neurophysiology Sensitivity for motor nerves may be improved by exhaustive studies of the four limbs including proximal stimulation in the upper limbs; somatosensory-evoked potentials may be useful to demonstrate abnormal proximal sensory conduction.

The EFNS/PNS diagnostic criteria have 81.3 % sensitivity and 96.2 % specificity [15].

Definite CIDP Criteria for definite CIDP include at least one of the following in two nerves: at least 30 % reduction of MNCV; at least 50 % prolongation of DML; at least 30 % prolongation of F-wave latency; CB with at least 50 % reduction of the proximal negative peak CMAP relative to distal; abnormal temporal dispersion (at least 30 % increase between the proximal and distal negative peak CMAP); prolongation of distal CMAP duration (median nerve 6.6 ms, ulnar 6.7 ms, peroneal 7.6 ms, tibial 8.8 ms).

Probable CIDP At least 30 % amplitude reduction of the proximal negative peak CMAP relative to distal.

Possible CIDP One the abovementioned findings is detectable in only one nerve.

In probable and possible CIDP, supportive criteria may come from other laboratory tests and from objective clinical improvement after immunotherapy [16].

Nerve biopsy Sural or superficial peroneal nerves are analyzed, if affected. Positive findings are not specific and negative findings (normal nerve or chronic axonal degeneration) do not exclude the diagnosis. Supportive features include: hypertrophic de-remyelination with onion-bulb formations (possible overlap with CMT1), variations between fascicles, endoneurial edema, and endoneurial mononuclear infiltration.

35.2.3.6 Therapy

Patients with very mild symptoms who are not functionally impaired may be monitored without treatment. Up to 80 % of patients with adulthood or childhood typical CIDP respond to one of the three first-line therapies: IVIg, corticosteroids or PE; whether a combination of IVIg and steroids may offer additional benefit and greater chance of remission remains to be proven. IVIg should be the first choice for motor CIDP; if steroids are used, patients should be monitored closely for deterioration. As a general rule, if the first-line treatment is effective, continuation should be considered until the maximum benefit is achieved and then the dose reduced to find the lowest effective maintenance dose. IVIg is most often used because of its safer profile and better short-term efficacy.

IVIg may represent an ideal first-line choice in severely disabled patients who need rapid improvement provided that there are no absolute (IgA deficiency) or relative (renal failure, hyperviscosity syndrome) contraindications [17]. A first course is done by giving 2 g/kg intravenously in 5 days. Long-term management is empiric: IVIg can be maintained in doses over 1 g/kg over 1–2 days every 3 weeks but the appropriate dose and/or frequency is individualized (0.4–1.2 g/kg every 2–6 weeks). Once recovery is complete or stable (usually within 2–4 months) the therapy should be tapered and eventually discontinued as patients may have a monophasic course without relapse for months or years.

Corticosteroids represent an ideal first-line choice in patients with milder disease and without contraindications due to the higher likelihood of long-term remission. In long-term maintenance therapy, patients should be monitored for steroid-related side effects and complications. There is no consensus about whether to use oral daily or alternate-day regimens or intermittent pulsed intravenous or oral regimens. Prednisone 1–1.5 mg/kg is given daily as a single oral dose; once improvement begins, usually within 2–4 weeks, tapering the daily to alternate-day treatment (1–1.5 mg/kg every other day until complete or stable recovery) will lessen potential side-effects; further tapering, usually after

6 months, may be done by decreasing the dose by 5 mg every 2–3 weeks. Pulsed oral dexamethasone is given at a dosage of 40 mg daily for 4 days repeated at 4 weekly intervals for 6 months and then tapered over another 6 months [18]. Intermittent intravenous methylprednisolone is used at a dosage of 1000 mg daily for 3–5 days and then 1000 mg monthly.

Plasma-exchange (*PE*). Because the response is transient and CIDP may worsen after stopping it, PE needs to be combined with other treatments for stabilization or may be considered as a second-line temporary measure in the treatment of IVIg and steroid-unresponsive CIDP. A regimen of five to six exchanges over 2 weeks (total exchanged plasma 200–250 mL/kg) may be beneficial over the short term (1–2 months) in inducing a rapid remission in patients without contraindications.

If the response of the first-line treatment is inadequate or the maintenance doses of the initial treatment result in adverse effects, therapy should be shifted to another first-line treatment. Second or third-line immunosuppressive therapies should be reserved for severely affected patients refractory to any of the first-line treatments; the efficacy of these therapies has yet to be proven (see Chap. 25).

35.2.3.7 Prognosis

Onset is progressive (symptoms develop for more than 8 weeks) in the majority of patients (~80 %), acute (symptoms develop within less than 4 weeks), or subacute (symptoms develop within 4–8 weeks). The course is relapsing-remitting ("two episodes with remission and relapse unrelated to therapeutical changes") in ~ 15 % of patients and progressive in the remaining cases [19].

Progressive course, CNS involvement, pathologically active demyelination, and severe axonal loss are associated with poorer long-term prognosis and disability [20]. Significant disability may result also from symptoms such as fatigue (severe in up to three quarters of patients), pain (up to one third), and refractory tremor (more than half of patients). Mild autonomic genitourinary or gastrointestinal symptoms are relatively common, but severe autonomic dysfunction should raise doubts about the diagnosis of CIDP.

In a recent retrospective series, approximately 40 % of patients had no or non-disabling symptoms, 75 % were able to work and walk, and 24 % had a severe handicap (Rankin score >2). Long-term mortality due to neurological deficits (bulbar involvement and respiratory failure) ranged from 1.3 to 9 %. Ventilatory involvement was relatively rare, but abnormal phrenic nerve conductions were evident in the majority of patients [21]. A-CIDP may have had a higher risk of ventilatory failure with a mortality rate similar to GBS.

Around 80 % of patients are responders to therapies but 40 % of treated patients remain treatment-dependent in the long term [19]; 1 year after initiating IVIg, up to 60 % patients need regular courses of therapy. Treatment-dependence may be associated with IVIg responsiveness and corticosteroids resistance, longer delay from onset to effective therapy, and with multifocal clinical presentation; steroids might be associated with more frequent treatment withdrawal [17, 22]. IVIg is less often discontinued due to inefficacy, adverse events, or intolerance when compared with IV methylprednisolone.

Patients responding to IV methylprednisolone have fewer relapses after discontinuation of treatment compared to responders to IVIg. By evaluating the CDAS (CIDP Disease Activity Status) score in more than 100 patients, the long-term (mean duration = 6.4 years) outcome was as follows: 11 % of patients were "cured" (off treatment for ≥5 years with a stable examination), 20 % "in remission" (stable and off treatment with a follow up <5 years), 44 % had a "stable active disease" (requiring ongoing therapy for at least 1 year), 7 % had an improvement after recent initiation of therapy (for at least 3 months but less than 1 year), 18 % had an unstable active disease (treatment naïve or treatment refractory) [23].

CDAS may be a useful tool in order to identify patients with long-term inactive disease off therapy (CDAS 1 and 2) and those who are treatment refractory (CDAS 5B and CDAS 5C) as well as to avoid overtreatments.

CIDP variants may have different courses and sometimes response to treatment compared to typical CIDP.

Pure sensory CIDP (up to 35 % of CIDP cases, the most frequent atypical CIDP), which includes CISP (chronic inflammatory sensory polyradiculoneuropathy with predominant sensory ataxia in lower limbs) may be either progressive or monophasic and respond either to IVIg or corticosteroids. *Pure-motor CIDP* (~10 % of CIDP cases) has a good response to IVIg and may deteriorate after corticosteroid treatment.

Asymmetric CIDP (15 % of CIDP cases) has frequent involvement of cranial nerves (25 % of cases) and progressive course (~ three quarters of cases). Despite treatment (corticosteroids and IVIg seem to be equally effective), the course is more often slowly progressive.

Focal CIDP has a slowly progressive course over one to several years, without progression to other limbs and is equally responsive to IVIg or corticosteroids.

A relatively small subgroup of treatment-resistant patients mostly affected by a rapidly progressive course with predominantly motor involvement and/or disabling tremor, were associated recently with immunoglobulin G4 (IgG4) immune reactivity and serum Ab against neurofascin 155, contactin1 (CNTN1) and contactin1-associated protein-1 (CASPR1) which bind paranodes and are detectable by immunocytochemistry and ELISA. Rituximab was an effective rescue therapy in those patients [24].

In childhood, the majority of patients (60 %) have a chronic onset and a relapsing course (70 %), and respond similarly (approximately 80 %) to corticosteroids or IVIg (most frequently used first-line monotherapy). Childhood CIDP usually has a favorable course [25].

35.2.4 Multifocal Motor Neuropathy (MMN)

35.2.4.1 Definition

A treatable immune-mediated peripheral neuropathy which frequently mimics a motor neuron disease, characterized by slowly progressive asymmetric distal weakness without significant sensory loss, persistent motor CB, evidence of IgM anti-GM1 in about 50 % of cases, and response to IVIG in up to 90 % of patients.

35.2.4.2 Demographics

Prevalence: 1–2 per 100,000 with male-to-female ratio of approximately 2.6:1. Median age of onset: around 40 years with the majority of cases presenting between 20 and 50 years. Children may be exceptionally affected. In some cases, MMN co-occurs with celiac disease and Hashimoto's thyroid disease. First-degree family members also have higher incidence of type 1 diabetes, celiac disease and Hashimoto's thyroid disease.

35.2.4.3 Pathophysiology

A nodo-paranodopathy likely caused by an immune attack against the node of Ranvier (e.g., IgM to GM1) with formation of membrane attack complexes, which disrupts and displaces ion channels and paranodal structures, and compromises nerve conduction, resulting finally into axonal degeneration [26].

35.2.4.4 Diagnosis

Current criteria rely upon clinical and electrophysiological features reviewed by the Task Force of EFNS/PNS; the diagnosis may be supported by laboratory and imaging data [27].

35.2.4.5 Clinical Features

Slow or stepwise progressive weakness developing over months or years with a multifocal asymmetric distribution in individual nerves, usually starting and remaining prominent in the distal arms. Cramps and fasciculations are frequent in the affected motor nerves with no or slight amyotrophy in the early stages, reflecting the clinical expression of CB. Decreased muscle bulk may develop over time due to secondary axonal degeneration. Weakness is often exacerbated by cold. Predominant lower limb involvement at onset accounts for only 10 % of cases. Deep tendon reflexes are usually depressed or absent in affected territories but may be normal or even brisk in rare cases. Sensory examination should be normal except for minor vibration sense abnormalities in the lower limbs. In some cases, MMN may have a progressive stepwise course; a few cases may have an AIDP-mimicking acute onset but further course and response to treatment are typical of classical MMN.

35.2.4.6 Laboratory Features

Immunology The most typical finding, detected in 40–50 % of cases, is significant titers of serum IgM autoantibodies binding to ganglioside GM1 and, less frequently, to other glycolipids including asialo-GM1, GD1A, or GM2. Serum IgM against NS6S heparin disaccharide have the same positivity as that of anti-GM1 antibodies, suggesting that concomitant tests for both antibodies would increase the seropositivity to 64 %, but anti-NS6S antibodies may be detected also in sensory neuropathies [28]. The accuracy of antibodies has limitations and their absence does not exclude the diagnosis.

CSF Normal or <1 g/L protein content is a supportive criteria for diagnosis.

MRI Although non-specific, MRI of the brachial plexus may be a supportive criterion showing increased signal intensity on T2-weighted scans or contrast-enhancement on T1 sequences.

Electrophysiology CB in motor nerve fibers outside the usual sites of entrapment/compression with normal SNCV in the same limb segments are the disease hallmark. Criteria for definite and probable CB have been revised by EFNS/PNS [27]. Some patients with typical MMN have no detectable CB probably because CBs are activity dependent or located in segments not assessed by the routine electrophysiological tests. More sensitive techniques such as transcranial magnetic stimulation, triple stimulation, and transcutaneous cervical root stimulation may be useful to detect CB located in the proximal segments of motor nerves. EMG reveals reduced recruitment in weak muscles and, once secondary axonal loss has established, positive sharp waves and fibrillation potentials.

Other Laboratory Features may be helpful to discover or rule out concomitant diseases or alternative causative disorders.

35.2.4.7 Top Differential Diagnosis

Motor neuron disorders. CIDP. Myopathies. Disorders of nerve roots and plexus.

35.2.4.8 Therapy

IVIg are the first-line treatment and are effective in 79–86 % of patients resulting in an improvement of muscle strength, sometimes accompanied by disappearance of partial CB but without correlations with anti-GM1 positive patients.

IVIg are given at the initial dose of 2 g/kg given in 5 consecutive days; most responders require long-term maintenance with varying intervals and doses. A single course is not sufficient to establish responsiveness to IVIg.

In patients who do not respond to IVIg, in patients with a declining response to IVIg, in patients in whom IVIg are contraindicated, alternative therapies are available. IV cyclophosphamide was reported to be effective in more than 70 % of patients; experts do not recommend it because of short- and long-term toxicity and lack of clear evidence of efficacy. Rituximab can be administered at a dose of 375 mg/m^2 every week to achieve peripheral B cell depletion.

35.2.4.9 Prognosis

The extent of axonal degeneration may be a valuable prognostic factor regarding clinical course and response to treatment. An elevated titer of anti-GM1 antibodies and definite CB may be associated with IVIg responsiveness. Some rare patients achieve spontaneous remission but more than two-thirds of patients are IVIg-dependent.

Long-term efficacy of IVIg has been addressed by numerous retrospective studies of patients who were under treatment for several years. After years the effectiveness of IVIg often declines due to axonal degeneration [29]. When given at high doses every month, IVIg improve muscle strength and functional disability, decrease the number of CB and the extent of axonal degeneration [30]. Early initiation of IVIg followed by a maintenance treatment is the only intervention that may prevent axonal loss and a more severe outcome; IVIg non-responders have often a longer duration of disease before the first treatment [31].

35.2.5 Paraproteinemic Neuropathies

Key Facts

- **Terminology and definitions** – Clinically and pathogenetically heterogeneous neuropathies sharing the presence of an abnormal spike of β-γ serum proteins.
- **Clinical features** –
  MGUS prevalence: 3.2 % in the population above 50 years and 7.5 % above 80 years. CIDP may be related to MGUS in 15 % of cases.
  POEMS: severe predominantly motor and sensory polyneuropathy most frequently associated with IgG or IgA monoclonal proteins bearing λ light chains.
  Anti-MAG IgM-Ab: prevalence of 20–40/100,000 in older than 50 years. Anti-Mag is a chronic slowly progressive, mainly sensory and distal demyelinating neuropathy with tremor (sometimes disabling).
- **Diagnostic markers**
  - **Blood**
    POEMS: IgG or IgA monoclonal proteins bearing λ light chains.
    Anti-MAG neuropathy: IgM antibodies against the MAG glycoprotein.
  - **CSF** – *POEMS* increased CSF proteins.
  - **Imaging** – *POEMS*: osteosclerotic bone lesions.
  - **Neurophysiology** – *Anti-MAG* shows reduced CV with disproportional delay of DML.
    POEMS – has diffuse demyelinating neuropathy with early decrease of CMAP.
- **Top differential diagnoses** – Hereditary and inflammatory demyelinating neuropathies.
- **Prognosis**
  - **Principles of treatment**
    Anti-MAG: no evidence of efficacy and safety of any long-term therapy.
    POEMS – Rx-therapy in the presence of sclerotic plasmacytoma. Alkylating-agents. Steroids.
  - **Disability**
    Anti-MAG: most patients have a favorable functional prognosis with only 25 % of patients becoming disabled after 10 years and 50 % after 15–20 years.
    POEMS: is chronic and invalidating; 50 % of patients are bedridden; mean survival ranges from 12–33 to 165 months. VEGF correlate with the activity of disease and response to therapy.

35.2.5.1 Definition

Paraproteinemic neuropathies are a clinically and pathogenetically heterogeneous group of neuropathies sharing the presence of an abnormal spike in the β-γ region of serum protein electrophoresis and/or by serum immunofixation. The monoclonal gammopathy may indicate an underlying clonal B-cell expansion, which may appear in the context of an hematological malignancy [multiple myeloma; heavy chain disease; primary amyloidosis (amyloidosis light-chain – AL); Waldenström macroglobulinemia (WM), B cell lymphoma or chronic lymphocytic leukemia] or, in more than two thirds of patients, may be not associated with a lymphoproliferative disorder [monoclonal gammopathy of undetermined significance (MGUS)]. MGUS may evolve into a malignant form after several years (around 1 %/year of MGUS cases may progress to malignancy).

35.2.5.2 Demographics

MGUS occurs in 3.2 % in the population above 50 years and in 7.5 % of those above 80 years. In those individuals the neuropathy is often the only clinical manifestation and may be symptomatic in up to 35 % of cases; the prevalence of neuropathy is higher in patients with IgM than with IgG or IgA MGUS. In hematological malignancies, neuropathy may occur in up 50 % of patients with WM (in which it may be the only manifestation of the disease in up to one third of cases), 15 % of those with multiple myeloma, 20 % with AL, 8 % with lymphoma [32].

35.2.5.3 Pathophysiology

The mechanisms are heterogeneous and may be related to infiltration of neoplastic cells, specific immunoreactivities of the circulating paraproteins, hyperviscosity, cryoglobulinemia, or

upregulation of proinflammatory cytokines and growth factors.

35.2.5.4 Clinical Features

Heterogeneous presentations correlate with different disease mechanisms. Major syndromes are recognizable.

The most frequent presentation is related to IgM antibodies reacting against Myelin Associated Glycoprotein (MAG) with a highly stereotyped clinical picture of a chronic slowly progressive, mainly sensory, demyelinating neuropathy.

CIDP may be related to IgG or IgA immunoglobulins (monoclonal gammopathy can be detected in up 15 % of CIDP cases).

A rare syndrome of chronic sensory ataxic neuropathy, ophthalmoplegia and bulbar dysfunction may be also related to IgM MGUS with antibodies against disialosyl group shared by several gangliosides (CANOMAD: chronic ataxia neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, disialosyl antibodies).

A progressive motor-sensory and autonomic neuropathy with early involvement of small fibers (painful dysesthesias, diminished pain, and temperature sensation) is associated with AL amyloidosis or amyloidosis occurring in the setting of WM, multiple myeloma, or other lymphoproliferative disorders.

35.2.6 POEMS

POEMS [*P*eripheral neuropathy, *O*rganomegaly, *E*ndocrinopathy, *M*onoclonal gammopathy, and *S*kin changes (rusty hyperpigmentation, white nails, hypertrichosis)] is a severe, subacute, predominantly motor neuropathy. Demyelinating polyradiculoneuropathy, sclerotic bone lesions, elevated vascular endothelial growth factor (VEGF), and the occurrence of Castleman disease are the major criteria for the diagnosis.

POEMS manifests as a neuropathy with early decrease of CMAP and increased CSF proteins, possibly related to the upregulation of proinflammatory cytokines (markedly increased levels of VEGF correlate with the activity of disease and response to therapy). Pulmonary hypertension, renal failure, thrombotic events, and congestive heart failure may be also syndromic features.

35.2.6.1 Therapy

Rx-therapy is first line in the presence of sclerotic plasmacytoma. Corticosteroids may be useful, but alkylating agents are the basis of medical treatment.

35.2.6.2 Prognosis

POEMS is a chronic and invalidating disease and many patients (50 %) are bedridden due to the neuropathy. In available studies the mean survival ranged from 12 to 33 months [33] to 165 months in a more recent series [34]. Nail clubbing and extravascular fluid overload were associated with shorter survival. Management depends on treatment of the underlying plasma cell dyscrasia and may include radiation therapy, chemotherapy and/or hemopoietic cell transplantation. VEGF level correlates with the activity of the disease.

35.2.7 Neuropathy with Anti-MAG IgM

35.2.7.1 Definition

Demyelinating neuropathy associated with IgM antibodies against the MAG glycoprotein mostly concentrated in uncompact myelin.

35.2.7.2 Demographics

Prevalence in the population above 50 years may be at least 20–40 per 100,000. Almost 80 % of patients with anti-MAG IgM have IgM MGUS while most remaining patients have WM which is frequently indolent.

35.2.7.3 Pathogenesis

Complement mediated demyelination triggered by anti-MAG IgM M-proteins

35.2.7.4 Clinical Features

Chronic, slowly progressive, symmetric, distal predominantly sensory demyelinating neuropathy with paresthesias, hypo-dysesthesia, cramps of the lower limbs, unsteadiness of gait, often associated with intentional and postural tremor in the upper limbs. Examination discloses signs of large-fiber involvement with ataxia, decreased distal vibration sense, Romberg's sign, with minor distal motor deficit. Tremor may be the presenting symptom and may be disabling. Onset is most frequently in the sixth-seventh decade.

35.2.7.5 Diagnostic Markers

Blood Sera anti-MAG IgM are detectable by commercially available ELISA systems or by cumbersome western blot assays against home-made isolated myelin. Indirect immunofluorescence may detect deposition of IgM, IgG, IgA heavy and light chains in control bioptic nerves thus suggesting an immunomediated attack event in patients with uncharacterized reactivity to nerve [35]. A careful survey should be done to rule out hematological malignancies.

CSF CSF analysis is unnecessary in typical cases. In almost all patients it discloses increased proteins in a CIDP-overlapping range of 80–100 mg/dl. Cytofluorimetry may investigate malignant cells in atypical cases.

Neurophysiology Reduced SNCV and MNCV with disproportional delay of DML. CBs are rare and should raise the suspicion of CIDP. Relevant reduction of NCV (slowing of MNCV, often in the range of 15–25 m/s) diverges from mild clinical impairment.

Nerve biopsy is unnecessary in typical cases. It discloses a demyelinating neuropathy with typical ultrastructural widening of outer myelin lamellae in 90 % of cases; direct immunofluorescence discloses deposits of IgM at the periphery of residual myelinated fibers.

35.2.7.6 Therapy

Patients unimpaired in their daily life: symptomatic therapy for tremor and paresthesias, neurological and hematological follow-up. Some patients with significant functional impairment may benefit from rituximab (4 weekly infusions of 375 mg/m^2), but placebo control trials failed to provide any clear evidence of efficacy, even for a 1-year follow-up [36] and indications to treatment should consider potential side-effects including progressive multifocal leukoencephalopathy (PML). Evidence of long-term term efficacy and safety are lacking also for other immune therapies.

35.2.7.7 Prognosis

Anti-MAG neuropathy is a prognostically favorable disease: patients with neuropathy, IgM paraprotein, and anti-MAG have a lower risk of evolution into malignancy than patients without neuropathy or without anti-MAG reactivity. The neuropathy is slowly progressive and most patients have a long-term favorable functional prognosis with only 25 % of patients becoming disabled after 10 years and 50 % after 15–20 years. A minority of patients have a CIDP-like faster progression with severe ataxia or motor involvement.

35.2.8 Non-systemic Vasculitic Neuropathy (NSVN)

Key Facts

- **Terminology and definitions** – Vasculitides are due to secondary ischemic injury of peripheral nerves caused by inflammatory infiltration and destruction of the afferent vessel walls.
- **Clinical features**
- PNS vasculitides annual incidence is 0.6–1.2/100,000; incidence of NSVN is 5/million. Vasculitic neuropathies cause subacute or slowly progressive, sometimes stepwise, multifocal, asymmetric peripheral neurological deficits. They may appear as painful multiple mononeuropathy (45 % of cases), asymmetrical polyneuropathy (30 %), and distal symmetrical polyneuropathy (25 %).
- **Diagnostic markers**
  - **Blood** to assess non-neurological organ dysfunction.
  - **CSF** may demonstrate pleocytosis (5 %), elevated CSF proteins (30 %), and oligoclonal bands in NSVN.
  - **Nerve biopsy** – '*Definite*' vasculitic neuropathy shows inflammation within the vessel wall and vascular damage in the epineurium. Perivascular inflammation and signs of chronic vascular injury identify definite but inactive vasculitis.
  - **Neurophysiology** consistent with a primary axonal, sensory-motor process; "pseudo-CB" occur in 10–25 %.
- **Top differential diagnoses** – CIDP variants, HNPP, amyloidosis, lymphomatosis; different forms of vasculitides (Churg-Strauss, PAN, etc.)
- **Prognosis**
  - **Principles of treatment** – First-line therapy: steroids alone or associated with cyclophosphamide.
  - **Disability** usually not fatal, NSVN may become systemic in 10 % of patients. Most patients remain independent in daily activities; 60 % have chronic pain. Mortality rates: 4–15 % in NSVN (21–31 % in SVN); 5-year survival: 85 % (75 % in SVN). Relapse rate: 32 % in NSVN.

35.2.8.1 Definition

"Vasculitides" are characterized histologically by an inflammatory infiltration and destruction of the vessel walls with secondary ischemic injury to the involved tissues.

Peripheral nerve vasculitis may occur in up to 60–70 % of patients with systemic vasculitides which may manifest either as primary diseases or as secondary disorders related to various diseases ranging from rheumatological conditions to infections, malignancies, or inflammatory bowel diseases [37]. Peripheral nerve vasculitides may also occur as non-systemic or localized vasculitides, which are restricted to PNS over a prolonged follow-up. Localized vasculitides encompass: non-systemic vasculitic neuropathy (NSVN) which includes non-diabetic radiculoplexopathy and some cases of Wartenberg's migrant sensory neuritis; diabetic radiculoplexus-mononeuropathies; localized cutaneous vasculitides such as the cutaneous form of polyarteritis nodosa (cPAN).

35.2.8.2 Demographics

Incidence and prevalence are not estimated. It was claimed that PNS vasculitides have an annual incidence of 0.6–1.2 per 100,000 and NSVN of five cases per million. In certain series, NSVN was the most frequent PNS vasculitis, equivalent to PAN and microscopic polyangiitis [38]. Onset is around 60 years and women seem to be preferentially affected.

35.2.8.3 Pathophysiology

NSVN is mainly a microvasculitis of the smallest arterioles (< 40 μm), endoneurial microvessels (capillaries), and venules. Occasionally NSVN affect large arterioles and small arteries. Vasculitis is an axonopathy affecting mixed (sensory-motor) and purely sensory cutaneous nerves.

Pathogenesis implies a cell-mediated autoimmune disorder.

35.2.8.4 Clinical Features

Presentation is similar to systemic vasculitic neuropathies (SVN) developing subacute or slowly progressive, sometimes stepwise, multifocal asymmetric neurological deficits. Reported presentations include: 45 % multiple mononeuropathy, 30 % asymmetrical polyneuropathy (overlapping multifocal neuropathy), and 25 % distal symmetrical polyneuropathy. Both motor and sensory nerves are affected but 15 % of cases have predominantly sensory findings. Pain occurs in up to 80–96 % of patients. Systemic symptoms are uncommon and mild but 30 % of patients have weight loss and 10–15 % suffer fever. Affected nerves derive frequently from the lumbosacral plexus (common peroneal nerve or peroneal division of the sciatic); in the upper limbs the ulnar nerve is more commonly affected than median, radial and more proximal nerves.

Among clinical variants, cPAN affects the small-to-medium-sized arteries in the deep dermis and panniculus resulting in characteristic, painful, recurrent, often ulcerated nodes in the skin of the lower limbs; skin manifestations include also livedo racemosa, gangrene, urticaria, and bullae. Multifocal neuropathies in the lower limbs follow closely the distribution of the skin lesions. Other variants are represented by diabetic lumbosacral radiculoplexopathy (LSRP) and the analogous "non-diabetic LSRP" which is distinguished by its progressive evolution from the rare acute, painful, idiopathic, monophasic lumbosacral plexopathy syndrome (a regional variant of brachial neuralgic amyotrophy).

35.2.8.5 Diagnosis

The interval between onset and diagnosis is usually longer in NSVN (6 months) than in SVN. Painful, stepwise progressive, distal predominant, asymmetrical multifocal neuropathies suggest vasculitis, even if the clinical course is of several years.

Electrodiagnostic studies should be extensive in order to assess for asymmetries and non-length-dependent signs. Neurophysiology is consistent with a primary axonal, sensory-motor process; "pseudo-CBs" occur in 10–25 % of cases reflecting axonal degeneration; persistent, ischemia-induced, demyelinating partial motor CBs are rare.

Laboratory tests are done to assess non-neurological organ dysfunction, measure systemic inflammation, and investigate specific causes of multifocal neuropathy or vasculitis.

CSF Lumbar puncture should be considered in patients with proximal involvement to rule out malignancies or meningeal infections; in NSVN it may demonstrate pleocytosis (5 %), elevated CSF proteins (30 %), and oligoclonal bands.

Nerve or nerve/muscle biopsy is mandatory. The sural nerve or the superficial peroneal nerve plus the peroneus brevis muscle are biopsied most commonly, provided that they are clinically and neurophysiologically affected. Pathological criteria for active *definite vasculitic neuropathy* are as follows [39]: evidence of inflammation within the vessel wall and signs of vascular damage (fibrinoid necrosis, endothelial loss/disruption, loss/fragmentation of internal elastic lamina, acute thrombosis, hemorrhage), usually in the epineurium. Perivascular inflammation and signs of chronic vascular injury identifies definite but inactive vasculitis. Sensitivity of a definite nerve biopsy is 50–60 %; yield of muscle biopsies are similar. Pathological criteria for *probable vasculitic neuropathy* are not uniform [39].

35.2.8.6 Top Differential Diagnoses

Prior to biopsy: other causes of asymmetrical/multifocal neuropathy (e.g., CIDP variants, HNPP, amyloidosis, lymphomatosis).

Pathologically definite/probable vasculitis: primary (e.g., Churg-Strauss syndrome, essential mixed non-HCV cryoglobulinemia, PAN) or secondary (connective tissue disease, e.g., rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome; infection-related vasculitis, e.g., HBV, HCV, HIV, CMV, leprosy, Lyme disease; malignancy-related vasculitis).

35.2.8.7 Therapy and Prognosis

Natural history of untreated NSVN is unknown, but approximately 10 % of cases may evolve into systemic vasculitis.

Therapy is mandatory with the exception of improving and stable patients without recent pathological evidence of active vasculitis. Clinical trials are lacking [39]. First-line immunosuppressive therapies: oral prednisone 1 mg/kg/day or pulse IV methylprednisolone in severe, rapidly progressive NSVN. Combination therapy with IV cyclophosphamide, methotrexate, or azathioprine is advised in rapidly progressive NSVN and patients non-responders to monotherapy. Maintenance therapy by low-dose prednisone (5–7.5 mg daily) or azathioprine (1–2 mg/kg/day) or methotrexate (20–25 mg/week) for 18–24 months is advisable; probable remission is considered in the absence of clinical worsening after a 6-month follow-up.

At presentation most patients are still independent in activities of daily living. Approximately 50 % can walk without assistance, 35 % require walking aids, 15 % are non-ambulatory. NVSVN is usually not fatal: Most patients remain independent in daily activities and ambulation, although up to 60 % have chronic pain. Mortality rates of NSVN range from 4 to 15 % (21–31 % in SVN); 5-year survival is approximately 85 % (75 % in SVN). Relapse rate is approximately 32 % in NSVN; relapses (median interval = 15 months after onset of treatment) may occur either after discontinued therapy and in maintenance therapy.

35.2.9 Diabetic Neuropathies

Key Facts

- **Terminology and definitions** – Neuropathies associated with diabetes DM or prediabetes.
- **Clinical features** – Ten percent present with neuropathy at initial diagnosis of DM and 50 % after 20 years.
- **Diagnostic markers** – Diabetic neuropathies may occur as: 1 – Symmetrical neuropathies (DSP; SFN; autonomic neuropathy); 2 – Radiculoplexopathy; 3 – Cranial neuropathies; 4 – Limb mononeuropathy; 5 – Truncal radiculopathy.
  - **Blood** – Uncontrolled, or long lasting hyperglycemia.
  - **Neurophysiology** – Routine electrodiagnostic tests may be normal in SFN and in autonomic neuropathy.
  - **Autonomic tests** – Sympathetic skin reflex, quantitative sensory testing (QST), beat-to-beat HRV.
  - **Skin biopsy** – Can demonstrate the reduction of intraepidermal nerve fiber density in affected regions in *SFN*, and in *autonomic neuropathies.*
- **Top differential diagnoses** – Mono-plexo and polyneuropathies of different origin.
  Autonomic Neuropathy: Hereditary amyloidosis; Idiopathic immune-mediated and Paraneoplastic autonomic neuropathy.
- **Prognosis**
  - **Principles of treatment** – Prevention and treatment require an optimum glycemic control. Supportive and symptomatic medical measures.
  - **Disability**
    DSP is slowly progressive; can stabilize or improve with tight control of diabetes.
    Autonomic neuropathy increases the risk of adverse cardiovascular events. *LSRP* has a monophasic, self-limiting evolution.

35.2.9.1 Definition

Neuropathies associated with diabetes mellitus (DM) or prediabetes (impaired fasting glucose or impaired glucose tolerance) after the exclusion of other causes.

35.2.9.2 Demographics

Approximately two-thirds of patients with type 1 DM (T1DM) and with type 2 DM (T2DM) diabetes have symptoms and/or signs of neuropathy. The percent of patients with neuropathy is up to 10 % at the time of initial diagnosis of DM and up to 50 % after 20 years. The prevalence of neuropathy increases with poor glycemic control and age. Half of diabetics have a distal symmetric polyneuropathy (DSP), a quarter have carpal tunnel syndrome (CTS), 5 % have an autonomic neuropathy, and 1 % have an asymmetrical proximal neuropathy. Neuropathic pain occurs in about 10–20 % of the diabetic population, and in about 40–60 % of patients with documented neuropathy [40].

35.2.9.3 Clinical Features and Terminology

Symmetrical Neuropathies DSP; small-fiber-neuropathy (SFN); autonomic neuropathy. Episodic symmetrical neuropathies: treatment-induced neuropathy; diabetic neuropathic cachexia (DNC). Asymmetrical/focal and multifocal neuropathies; lumbosacral radiculoplexopathy (LSRP alias Bruns–Garland syndrome; diabetic amyotrophy); truncal radiculopathy; cranial neuropathies; limb mononeuropathies; multiple mononeuropathies.

Distal Symmetric Polyneuropathy (DSP) represents a continuous clinical spectrum influenced by the prevalent or mixed involvement of large or small fibers. It may be silent or manifest, usually with decreased feeling or tingling in toes, and evolves according to a stock-and-glove pattern with burning dysesthesias, allodynia, hyperalgesia, and electrical or shooting neuropathic pain. Thermal sensibility can be reduced in isolation or combination with diminished muscle stretch reflexes, light touch sensation, sensibility to pressure and vibration, and decreased joint position sense with postural instability and, rarely, ataxia. Distal weakness and wasting are a late event.

Small Fiber Neuropathy (SFN) manifests with spontaneous pain of a deep, burning, stinging, aching type, and allodynia to light touch. It is often accompanied by autonomic neuropathy.

Autonomic Neuropathy ranges from subclinical functional impairment of cardiovascular reflexes and sudorimotor function to severe cardiovascular, gastrointestinal, and genitor-urinary dysfunctions (see Chap. 24).

Radiculoplexopathy (LSRP) affects the lumbosacral or, rarely, the cervical plexus. LSRP is unrelated to the duration of disease; most patients are middle or old aged and have mild T2DM and concomitant weight loss. Onset is acute or subacute with burning or lancinating pain in the anterior thigh followed by days or weeks of difficulty in walking and climbing stairs with wasting and weakness of the quadriceps, iliopsoas, gluteus and, to a lesser extent, hamstring and anterior tibialis muscles; knee and ankle jerks are usually lost. The opposite leg may become affected is some cases after days or months. Progression may be steady or stepwise and may continue for many months before the disease stabilizes. Up to 60 % of cases overlap with DSP, disclosing a more gradual onset.

Cranial Neuropathies Unilateral palsies of the third and sixth cranial nerves often heralded by transient frontal pain, with acute onset and progression over 1–2 days. Third nerve palsy is usually nearly or fully complete but spares the pupillary reflex.

Limb Mononeuropathy Entrapment neuropathies of the median, ulnar, or peroneal nerves are common. Rarer mononeuropathies with abrupt painful onset followed by weakness and atrophy are caused by nerve infarction from occlusion of *vasa nervorum*; two or more nerves may be involved sequentially (multiple mononeuropathies, alias mononeuritis multiplex).

Truncal Radiculopathy is usually unilateral, may affect spinal roots from T4 through T12 and manifests with pain and dysesthesias possibly associated with bulging of abdominal muscles and focal anhidrosis.

- *Pathophysiology* of DSP and SFN remains controversial and the dysmetabolic process (hyperglycemia leading to production of pro-inflammatory advanced glycation products and to accumulation of polyols and reactive oxygen species with oxidative stress; dyslipidamia) may prevail on the ischemic damage. For LSRP an ischemic damage of the nerves due to an immune-mediated epineurial microvasculitis has been hypothesized (based on nerve biopsies) but not proven. Cranial neuropathies are supposed to be due to microvascular infarcts.

35.2.9.4 Diagnosis

According to the American Diabetes Association, all patients should be screened for DSP at diagnosis of T2DM and 5 years after the diagnosis of T1DM, and at least annually thereafter [41].

DSP Should not be diagnosed on the basis of one symptom, sign, or tests alone. At least two tests [symptoms/signs, nerve conduction studies, quantitative sensory testing (QST) should be done]. The diagnosis is made with a Neurological Disability Score ≥3 and/or a Vibration Perception ≤4/8 at the first metatarsal head by the Rydel-Seiffer tuning fork. NCS demonstrates a generalized, symmetric sensory > motor polyneuropathy that is primarily axonal.

SFN Routine electrodiagnostic tests are normal but should be done to rule out subclinical involvement of large fibers. Quantitative sudomotor axon reflex testing (QSART) assesses the sudomotor autonomic function. Skin biopsy is more sensitive (sensitiveness 88 %) than QSART evidencing the reduction of intraepidermal nerve fiber density [42].

Autonomic Neuropathy History and examination may be ineffective for early detection of cardiovascular autonomic neuropathy (CAN). CAN may be suggested by resting tachycardia (> 100 bpm) and orthostatic hypotension (fall in systolic blood pressure >20 mmHg upon standing) without appropriate heart response. At least three relatively easy tests are recommended to assess CAN at the diagnosis of T2DM and 5 years after the diagnosis of T1DM: postural blood pressure testing; heart rate response (HRV) to the Valsalva maneuver with analysis of the R-R intervals. Gastroparesis should be investigated in patients with erratic glucose control. Bladder function should be investigated in patients with recurrent urinary infections, incontinence, palpable bladder. *LSRP* – EMG discloses low femoral-nerve CMAP, prominent fibrillation potentials in thoracic and lumbar paraspinal muscles, and active denervation in affected muscles. CSF proteins are usually mildly increased. Erythrocyte sedimentation rates (ESR) may be increased. MRI of lumbar spine and lumbosacral plexus may rule out structural radiculoplexopathies and demonstrate signs of inflammation.

35.2.9.5 Top Differential Diagnosis

Neuropathies not-related to DM may include: CIDP, systemic vasculitides, alcoholic neuropathies, and other miscellaneous polyneuropathies, mononeuropathies, or radiculopathies [43].

Most frequent non-diabetic causes of DSP after prediabetes and DM (prediabetes and DM account for more than half of DSP cases) include vitamin B12 deficiency, thyroid dysfunction, alcohol, chemotherapy. Even after careful tests, DSP remains "idiopathic" in more than one-fourth of cases [44].

Non-diabetic length-dependent SFN: connective tissue disease, dysthyroidism, vitamin B12 deficiency, paraproteinemia, HIV infection, hepatitis C virus infection, celiac disease, neurotoxic drug exposure; idiopathic.

Autonomic neuropathy: Hereditary amyloidosis. AL amyloidosis. Sjögren syndrome [test for anti-Ro (SSA) and anti-La (SSB) antibodies; autonomic neuropathy may be present with normal serological tests]. Idiopathic immune-mediated autonomic neuropathy (test for nicotinic ganglionic acetylcholine receptor antibodies, present in some patients). Paraneoplastic autonomic neuropathy (test for the most prevalent anti-Hu antibodies and type 2 Purkinje-cell antibodies and collapsing response mediator protein 5). HSAN.

Other asymmetrical/focal and multifocal radiculo-neuropathies: entrapment neuropathies, systemic or non-systemic localized vasculitides, traumatic radiculopathies, neoplastic or infectious polyradiculoneuropathies, compressive radiculopathies, idiopathic plexopathies. Spinal stenosis is common in diabetic patients and should be distinguished from LSRP.

35.2.9.6 Prognosis and Therapy

DSP is slowly progressive and can stabilize or improve with tight control of diabetes.

Neuropathic pain occurs in about 40–60 % of patients, representing one of the most disabling symptoms. Neuropathy is one of the three major risk factors for falls in diabetic patients (together with retinopathy and vestibular dysfunction).

Trophic changes of the distal lower limbs and foot ulcers are a common, potentially severe, complication which is both neuropathic and ischemic in nature, related to unperceived trauma. Foot ulcer decreases the quality of life and increases the risk of lower-extremity amputations and mortality; its prevalence ranges from 2 to 15 %.

Neuropathic osteoarthropathy is a complication of long-standing diabetic neuropathy, characterized by painless fractures of the metatarsal bones and disruption of the metatarsophalangeal joints. Infection of the neuropathic ulcers can lead to chronic osteomyelitis.

Prevention and treatment require an optimum glycemic control. Pancreas transplantation may stabilize or improve the underlying neuropathy. Symptomatic treatment is devoted to pain control. Prevention and treatment of "diabetic foot" is important and usually administered in "foot clinics." Commonly used oral antioxidant agents such as α-lipoic acid demonstrated limited efficacy on neuropathic symptoms and neurophysiological parameters; other available drugs ("pathogenetic treatments") such as aldose reductase inhibitors gave inconclusive results in clinical trials.

Treatment-Induced Neuropathy is an apparently rare, acute, painful neuropathy with allodynia, which may be precipitated by poor metabolic control (ketoacidosis) or by initiation of treatment with insulin and sudden achievement of glycemic control ("insulin neuritis"). In young adults with T1DM it may be associated with cachexia and depression. Pain has marked nocturnal exacerbations and may persist for weeks or months before spontaneous resolution.

Autonomic Neuropathy CAN may limit exercise capacity and increase the risk of adverse cardiovascular events during exercise. Patient with CAN may have difficulties with thermoregulation and should be advised to avoid exercise in hot or cold environments and stay hydrate. CAN gives an increased risk of silent myocardial ischemia and mortality [45]. If the first evaluation is negative for CAN, the screening tests should be repeated annually; if positive, additional cardiovascular tests and symptomatic treatments should be ensured.

LSRP After progressing over several weeks or months, LSRP stabilizes (monophasic, self-limiting evolution); spontaneous pain may decrease rapidly, but prolonged morbidity often ensues. Long-term prognosis seems not to be influenced by glycemic control [46]. There is no evidence from any trial to show whether immunotherapies (IVIg, oral prednisone, or intravenous steroids) are effective [47], but small retrospective studies indicated that IVIg, oral prednisone, or intravenous methylprednisolone are effective, particularly in pain control allowing physical therapy. IVIg should be weighed with the increased risk of renal failure in diabetics. Insulin/oral hypoglycemic drugs should be adjusted during short courses with steroids.

Cranial Neuropathies Usually resolve over several months.

35.2.10 Carpal Tunnel Syndrome (CTS)

Key Facts	
• **Terminology and definitions** – CTS: mono-neuropathy due to median nerve compression in the wrist. • **Clinical features** – Pain, paresthesias, and late atrophy in the median nerve distribution of the hand. • **Diagnostic markers** – **Neurophysiology** – Prolonged median distal sensory and/or motor latencies.	• **Top differential diagnoses** – Cervical radiculopathies, proximal median nerve lesions. • **Principles of treatment** – **Conservative**: wrist splints, FANS, oral or locally injected steroids. – **Surgery**: section of transverse carpal ligament • **Disability** – Spontaneous improvement in 30 % of patients; surgery may obtain almost complete healing in 80–95 % of CTS.

35.2.10.1 Definition

Carpal tunnel syndrome (CTS) is a mononeuropathy due to median nerve compression in the wrist.

35.2.10.2 Epidemiology

With a prevalence of 1/1,000 CTS is the most frequent entrapment mono-neuropathy. The risk of developing CTS is higher in women aged 50–55 years. Usually mild and self-limited forms of CTS affect 20 % of pregnant women. Diabetes, obesity, thyroid, kidney diseases, rheumatoid arthritis, and hand stress are further risk factors.

35.2.10.3 Clinical Features

Pain, tingling, sensory deficits over the median nerve distribution of the hand, provoked or worsened by sleep, alleviated by changing posture or by shaking of the hand, are typical. Atrophy of the thenar eminence is a late sign. Notwithstanding a high proportion of false positive and false negative results, Tinel and Phalen tests are very useful clinical tools for the diagnosis.

35.2.10.4 Diagnostic Markers

Neurophysiology – Median-ulnar palmar sensory latency difference >0.5 msec (distance of 8 cm), or prolonged median nerve Distal Motor Latency >4 msec (mean value + 2 SD).

Ultrasound (US) – besides supporting the diagnosis of idiopathic CTS [increased cross sectional area (CSA) proximal to the compression point where the nerve suddenly flattens (notch sign), and changes of echotexture], US may help individuate causes of secondary CTS often susceptible to therapeutic options.

35.2.10.5 Differential Diagnosis

Cervical radiculopathy, proximal median nerve lesions, brachial plexopathies

35.2.10.6 Therapy

Conservative Opinion differs as to conservative treatment of CTS. Wrist splints reduce hand stress and can give some improvement. There is no evidence that non-steroidal anti-inflammatory drugs are useful. Oral steroids are not as effective as their local injections. Injections of a local anesthetic can relieve symptoms in the short term.

Surgery The section of transverse carpal ligament is the most appropriate therapy if pain and sensory impairment persist after conservative treatment.

35.2.10.7 Prognosis

CTS symptoms and pain tend to decrease with time. One-third of patients have spontaneous improvement.

Fifty-one to 94 % of patients respond initially to a single local steroid injection but after 1 year the percentage of symptom-free patients drops to only 6.5–33 %, whereas over 80–95 % of surgically treated patients result asymptomatic. Pain and weakness usually disappear within 2 months after operation, but it may take 6 months to a year to recover [48].

The prognosis of CTS is worse in the presence of muscle atrophy.

Duration of symptoms, bilateral CTS, positive Phalen test, age (the odds of improvement are reduced by 30 % for each 10 additional years) all are negative prognostic factors [49].

On the contrary, the duration of symptoms is inversely related to improvement of pain notwithstanding a possible progressive worsening of the electrophysiological pattern, symptoms and pain do not increase as the neurophysiological severity progresses.

The presence of hand stress at onset is associated with higher odds of improvement, due to its relief.

35.2.11 Bell Palsy

Key Facts

- **Terminology and definitions** – peripheral, unilateral facial palsy of subacute onset.
- **Clinical features** – subacute, unilateral weakness of an upper and lower emi-face.
- **Diagnosis**
  - **Genetics** – Autosomal dominant transmission is detected in some families.
  - **Imaging** – May show seventh nerve contrast enhancement.
  - **Neurophysiology** – Denervation of affected muscles.
- **Top differential diagnoses** – *central palsies*; *autoimmune neuropathies.*
- **Prognosis**
- **Principles of treatment** – Steroids.
- **Disability** – Healing occurs within 6 months in 80 % of patients; 15 % of cases display moderate or severe residual deficits.

35.2.11.1 Definition

Bell palsy (syn.: facial/seventh nerve palsy, paralysis a frigore) is a peripheral, unilateral facial palsy of subacute onset (2–5 days).

35.2.11.2 Epidemiology

Incidence: 20–30 per 100,000 per year that peaks at age 40–49 years [50].

35.2.11.3 Clinical Features

Unilateral weakness of an upper and lower emi-face with widening of the palpebral fissure, drooping of corner of mouth, inability to smile and close the eye on the affected side. Palsy is complete in 70 % of patients, pain is present in 60 %, taste changes in 30–50 %, and hyperacusis in 15–30 %.

Herpes simplex virus (HSV) infection is the most common cause.

Laboratory Non-significant in isolated palsy

Genetic Autosomal dominant transmission is detected in some families.

Neurophysiology EMG: denervation of affected muscles. The ipsilateral blink reflex is abnormal

Brain MRI May show seventh nerve contrast enhancement and excludes central causes.

Differential Diagnosis Seventh nerve palsy of different origin.

Therapy

Corticosteroids (prednisone 1 mg/kg for 5 days) should be started in the first 72 h from the onset and tapered within 10 days.

Antivirals are usually considered in severe and moderate cases (7-day cycle of: valaciclovir 1 g×2/day, or famciclovivir 750 mg×3/ day, or acyclovir 400 mg 5×/day), but acyclovir, added to corticosteroids, does not provide additional benefit [51].

35.2.11.4 Surgery

Its efficacy is queried. Seventh nerve decompression may be performed in severe palsies that do not make progress. To avoid irreversible nerve degeneration, patients should be operated on within the first 2 weeks from the onset.

35.2.11.5 Prognosis

Bell palsy is a self-limited, monophasic disorder that may recur in 8 % of cases. Healing occurs within 6 months in 80 % of patients; 15 % of cases display moderate or severe residua. Onset of improvement usually takes from 10 days to 2 months and reaches its plateau between 6 weeks and 9 months. Nerve regeneration may require more than 6 months so 15 % of remissions occur in 3–6 months. Facial emispasm is a residual disorder in 17 % of cases.

Weakness has better evolution in patients with: 1 – incomplete paralysis, 2 – early improvement, 3 – younger age, and 4 – timely treatment ($\leq$ 3 days).

Poor prognostic factors include A – age over 60 years, B – hypertension, C – impairment of taste, and D – complete palsy.

Moreover: 1 – absence of improvement at 3 weeks *carries poor prognosis*. 2 – About 90 % of patients fully recover if nerve excitability is maintained at 3 weeks. 3 – Only 20 % recover if nerve excitability has been lost within the same period of time [50]; 4 – from 80 to 100 % of patients regain optimal facial mobility if nerve degeneration is lesser than 90 %. This percentage drops to 50 % if nerve degeneration is equal or greater than 90 %.

35.2.12 Peripheral Nerve Injury (PNI)

Key Facts

- **Terminology and definitions** PNI is a disruption of anatomo-functional integrity of the nerve.
- **Clinical features** PNI occurs in 2–5 % of patients admitted to Level I trauma centers.
- **Diagnostic markers**
  - **Laboratory** – Non-significant.
  - **Imaging** – Ultrasonography and MRI have a role in the diagnostic work-up.
  - **Neurophysiology** – Provides essential information in the diagnosis and management of PNI.
- **Top differential diagnoses** – Acute inflammatory demyelinating polyradiculoneuropathy; cervical spondylosis; diabetic neuropathies.
- **Prognosis**
  - **Principles of treatment** – Symptomatic; surgical repair.
  - **Disability** – *Neurapraxic* lesions usually recover within a few months. In complete *axonotmesis,* recovery is determined by axonal regeneration; in *2nd degree axonotmesis* recovery is complete; in *3rd and 4th* degrees prognosis for spontaneous regrowth is worse.
- **After surgery**: the sooner the nerve is repaired the better the functional recovery will be; recovery is better in young people.

Key Facts

35.2.12.1 Definition and Basic Injury Types

Peripheral Nerve Injury is a total or partial disruption of anatomo-functional integrity of the nerve resulting from kinetic energy applied to the nerve or limb, as in stretch-related injury, laceration and penetrating trauma, or direct compression of a nerve.

Stretch-related injuries are the most common type. Elongation more than 10–15 % produces nerve ischemia and, beyond the limit of elasticity, a complete loss of continuity may occur. *Compression* is also common and includes acute compression as in 'Saturday Night palsy' and chronic compression as in entrapment neuropathies. A dose–response relationship between the duration of compression and neural injury was noted.

35.2.12.2 Demographics

PNI occurs in 2–5 % of patients admitted to Level I trauma centers [52]. In peacetime, young men are mainly affected (range 15–45 years, ratio M/F = 3:1). PNI commonly results from vehicle accidents (about 50 %); iatrogenic factors account for 10–15 % of cases.

PNI classification (Table 35.2)

The extent to which the axons and the connective sheaths of a nerve are disrupted by injury is fundamental to make the prognosis and treatment strategy.

Seddon (1943) proposed three main grades of nerve injury (see Table 35.2) [53]

Sunderland (1978) added two subclasses to Seddon's axonotmesis grade, depending on the degree of connective tissue involvement (see Table 35.2) [54].

In *grade 3* lesions there is endoneurial disruption, while perineurium and epineurium are preserved. Endoneurial discontinuity prevents full spontaneous reinnervation, rarely to more than 60–80 % of normal function. Surgical repair is required in patients with poor functional recovery.

In *grade 4* lesions the internal structure (axons and connective) is completely disrupted, nerve continuity is maintained by epineurium and scar tissue. The internal scarring blocks the regenerating axons (*neuroma in continuity*). Reinnervation occurs only with surgical repair.

35.2.12.3 Nerve Response to Injury

Remyelination: is the early and faster mechanism to promote recovery

Collateral sprouting: in partial axonotmesis, muscle strength may recover thanks to collateral sprouting from distal intact axons.

In 4th and 5th degree injuries (Table 35.2) the scar tissue prevents the regenerating axons from reaching the distal routes, leading to the formation of a *neuroma-in-continuity* in 4th degree injury and an *amputation neuroma* in 5th degree injury.

35.2.12.4 Neurophysiology

It provides essential information in the diagnosis and management of PNI by:

Table 35.2 PNI classification

Seddon	Sunderland Grade	Pathology	Prognosis	Electrophysiological correlate
Neuroapraxia	1	Myelin injury and/or ischemia usually secondary to compression	Excellent recovery in weeks to months	Conduction block complete or partial ± conduction slowing across the site of lesion
Axonotmesis	2	Axon loss; stromal derangement; endoneurium, perineurium, and epineurium intact	Good spontaneous regeneration	FP; mild reduction to absence of SNAP and CMAP in relation to the degree of axonal loss ± varying degree of slowing and block of conduction
	3	Loss of continuity of axons and endoneurium; perineurium and epineurium intact	Variable reinnervation, axonal misdirection, surgery may be required.	FP, absent SNAP and CMAP
	4	Loss of continuity of axons, endoneurial tubes, perineurium and fasciculi; epineurium intact	Internal scar tissue blocks regenerating axons (neuroma in continuity). Surgery required	FP, absent SNAP and CMAP
Neurotmesis	5	Loss of continuity of entire nerve trunk	No spontaneous recovery, need of surgical repair	FP, absent SNAP and CMAP

FP fibrillation potential, *SNAP* sensory nerve action potential, *CMAP* compound muscle action potential

1. *Localizing the site of nerve injury*. The site of nerve conduction failure may be detected within the first week, then it is lost in the case of axonal discontinuity. Persistence of SAP in the face of sensory loss invariably means that the lesion is proximal to the dorsal root ganglion.
2. *Discriminating neuroapraxia from axonotmesis and quantifying the degree of axonal loss* (after 2–3 weeks post-injury).
3. *Recognition and measurement of reinnervation* (after 3–4 months post injury). Early reinnervation may be detected in the muscle proximal to the lesion site by recording the voluntary recruitment of a few small MU, before clinical evidence.

Ultrasound (*US*) *and magnetic resonance* (*MRI*) imaging have a role in the diagnostic work-up in PNI.

High-resolution US may strongly modify the diagnostic process and therapeutic strategies in patients with PNI [55].

Magnetic resonance (*MRI*) is uniquely informative in the diagnosis of avulsions that frequently occur in closed traction injury of the brachial plexus [56].

35.2.12.5 Prognosis

Factors affecting prognosis are:

- *Clinical severity of PNI*. Complete loss of temperature-pain detection and of autonomic responses invariably indicates a severe PNI. The Medical Research Council (MRC) method of recording muscle power and sensibility offers a practical tool to make a grading of the PNI and to measure the progress.
- *Type of PNI. Neurapraxic lesions* have a good prognosis for recovery within a few months. *Mixed nerve injuries* typically have two phases of recovery: the neurapraxic component resolves quickly, but the axonal component is slower, because it depends upon axonal sprouting and the distance to reach the target. With lesions involving less than 20–30 % of the axons, recovery occurs over 2–6 months predominantly by collateral sprouting from intact axons.
- In *complete axonotmesis,* recovery is determined uniquely by axonal regeneration, which occurs depending upon the degree of PNI. In 2nd degree injury, recovery is complete and can be planned considering the rate of axonal growth (about 1–5 mm/day). The CMAP amplitude provides some guide to prognosis. In the 3rd and 4th degrees, prognosis for spontaneous regrowth is worse. Extensive scarring reduces the growth rate of regenerating axons and their ability to cross the lesion to reach the end organs. Since it is not possible to know the degree of axonotmetic lesions on the basis of preoperative data, it is necessary to look for reinnervation in proximal muscles after 2–4 months. Lesions with some spontaneous recovery are usually treated conservatively, while absence of reinnervation requires operative exploration. *Neurotmesis* requires surgical repair.
- *Level of injury*: distance from the lesion site to the end organs determines the functional outcome. Proximal lesions such as root avulsion, lumbar-sacral plexus and sciatic nerve injury have bad prognosis. Root avulsion cannot be surgically repaired.
- *Delay in diagnosis and surgery*: the sooner the nerve is repaired the better the functional recovery will be. Muscle reinnervation must occur within 12–18 months (before fibrotic replacement), while sensory recovery may continue for a longer period of time.
- *Age*: recovery is better in young people; older patients are more likely to develop pain.
- *Abnormal Reinnervation*: muscle co-contraction is particularly common in brachial plexus injury.
- *Vascular injuries*, *post-ischemic contracture*, *tendon retraction and muscle fibrosis*, *stiffness of joints* all are negative prognostic factors.

35.2.12.6 Therapy

Symptomatic management. Control of *neuropathic pain* [57]:

- Mild pain (VAS <5) can be treated with NSAIDs.
- Topical lidocaine patches are very useful in localized cutaneous pain

- In severe pain (VAS more than 5–6) use low-dose tricyclic agents such as nortriptyline or antiepileptic drugs (gabapentin/pregabalin, lamotrigine, and carbamazepine).
- Patients unresponsive to these agents may require narcotic analgesia. First, it may be used tramadol, and if ineffective, oxycodone with increasing doses for not more than 3–4 months (studies on long-term efficacy, safety and effects on quality of life are lacking).
- Spinal cord or nerve stimulators may be useful for patients with segmental neuropathic pain.

Patients with weakness and deformity should be considered for physical and occupational therapy evaluation. Use appropriate assistive devices such as cock-up wrist splints for radial nerve injuries and AFO splints for foot drop. Consider muscle and tendon transfer to improve residual function in selected cases.

Surgical nerve repair is indicated in 4th or 5th degree injury. *Primary repair* is performed immediately or within 1 month (delayed primary repair) and *secondary repair* is performed at between 3 weeks and 3 months after injury [58].

Immediate end-to-end repair is performed in nerve transection due to sharp lacerations. Delayed primary repair in blunt trauma or avulsion requires nerve grafting, as the nerve ends are usually retracted and/or scars need to be resected. Nerve autografts (sural nerve) remain the gold standard.

Secondary repair is preferred when the degree of injury has not yet been ascertained. Surgical procedure is recommended in absence of reinnervation in the proximal muscles within 3–4 months from injury, as the quality of motor recovery decreases steadily after a 6-month delay of repair.

Late nerve reconstruction, beyond 6 months, is generally carried out for pain control, such as neuroma resection.

References

1. Klein CJ, Duan X, Shy ME. Inherited neuropathies: clinical overview and update. Muscle Nerve. 2013;48:604–22.
2. Pareyson D, Piscosquito G, Moroni I, et al. Peripheral neuropathy in mitochondrial disorders. Lancet Neurol. 2013;12:1011–24.
3. Rossor AM, Polke JM, Reilly MM. Clinical implications of genetic advances in Charcot-Marie-Tooth disease. Nat Rev Neurol. 2013;9:562–71.
4. Koike H, Hirayama M, Yamamoto M, et al. Age related associated axonal features in HNPP with 17p11.2 deletion in Japan. J Neurol Neurosurg Psychiatry. 2005;76:1109–14.
5. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013;8:31.
6. Cappellari M, Cavallaro T, Ferrarini M, et al. Variable presentation of TTR-related familial amyloid polyneuropathy in seventeen patients. J Peripher Nerv Syst. 2011;16:119–29.
7. Benson MD. Liver transplantation and transthyretin amyloidosis. Muscle Nerve. 2013;47:157–62.
8. Obici L, Merlini G. An overview of drugs currently under investigation for the treatment of transthyretin-related hereditary amyloidosis. Expert Opin Investig Drugs. 2014;23:1239–51.
9. Wakerley BR, Uncini A, Yuki N for the GBS Classification Group. Guillain-Barré and Miller-Fisher syndromes – new diagnostic classification. Nat Rev Neurol. 2014;10:537–44.
10. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. Ann Neurol. 1990;27(Suppl):S21–4.
11. Fokke C, van den Berg B, Drenthen J, et al. Diagnosis of Guillain-Barré syndrome and validation of Brighton criteria. Brain. 2014;137:33–43.
12. Durand MC, Porcher R, Orlikowski D, et al. Clinical and electrophysiological predictors of respiratory failure in Guilla-Barré syndrome: a prospective study. Lancet Neurol. 2006;5:1021–8.
13. Walgaard C, Lingsma HF, Ruts L, et al. Prediction of respiratory insufficiency in Guillain-Barré syndrome. Ann Neurol. 2010;67:781–7.
14. Van Koningsveld R, Stevenberg EW, Hughes RA, et al. A clinical prognostic scoring system for Guillain-Barré syndrome. Lancet Neurol. 2007;6:589–94.
15. Rajabally YA, Nicolas G, Piéret F, et al. Validity of diagnostic criteria for chronic inflammatory demyelinating polyneuropathy: a multicentre European study. J Neurol Neurosurg Psychiatry. 2009;80:1364–8.
16. Van den Bergh PYK, Hadden RDM, Bouche P, et al; European Federation of Neurological Societies; Peripheral Societies. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Society – First revision. Eur J Neurol. 2010;17:356–3.
17. Nobile-Orazio E, Cocito D, Jann S, et al. Intravenous immunoglobulin versus intravenous methylprednisolone for chronic inflammatory demyelinating polyradiculoneuropathy: a randomised controlled trial. Lancet Neurol. 2012;11:493–502.

18. van Schaik IN, Eftimov F, van Doorn PA, et al. Pulsed high-dose dexamethasone versus standard prednisolone treatment for chronic inflammatory demyelinating polyradiculoneuropathy (PREDICT study): a double-blind, randomised, controlled trial. Lancet Neurol. 2010;9:245–53.
19. Viala K, Maisonobe T, Stoikovic T, et al. A current view of the diagnosis, clinical variants, response to treatment and prognosis of chronic inflammatory demyelinating polyradiculoneuropathy. J Peripher Nerv Syst. 2010;15:50–6.
20. Bouchard C, Lacroix C, Planté V, et al. Clinicopathological findings and prognosis of chronic inflammatory demyelinating polyneurpathy. Neurology. 1999;52:498–503.
21. Živković SA, Peltier AC, Iacob T, Lacomis D. Chronic inflammatory demyelinating polyneuropathy and ventilatory failure: report of seven new cases and review of the literature. Acta Neurol Scand. 2011;124:59–63.
22. Rabin M, Mutlu G, Syojkovic T, et al. Chronic inflammatory demyelinating polyradiculoneuropathy: search for factors associated with treatment dependence or successful withdrawal. J Neurol Neurosurg Psychiatry. 2014;85:899–904.
23. Gorson KC, van Schaik IN, Merkies IS, et al. Chronic inflammatory demyelinating polyneuropathy disease activity status: recommendations for clinical research standards and use in clinical practice. J Peripher Nerv Syst. 2010;15:326–33.
24. Huijbers MG, Querol LA, Niks EH, et al. The expanding field of IgG4-mediated neurological autoimmune disorders. Eur J Neurol. 2015;22:1151–61.
25. McMillan HJ, Kang PB, Jones HR, Darras BT. Childhood chronic inflammatory demyelinating polyradiculoneuropathy: combined analysis of a large cohort and eleven published series. Neuromuscul Disord. 2013;23:103–11.
26. Uncini A, Susuki K, Yuki N. Nodo-paranodopathy: beyond the demyelinating and axonal classification in anti-ganglioside antibody-mediated neuropathies. Clin Neurophysiol. 2013;124:1928–34.
27. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of multifocal motor neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society – first revision, Joint Task Force of the EFNS and the PNS. J Peripher Nerv Syst. 2010;15:295–301.
28. Pestronk A, Chuquillin M, Choksi R. Motor neuropathies and serum IgM binding to NS6S heparin disaccharide or GM1 ganglioside. J Neurol Neurosurg Psychiatry. 2010;81:726–60.
29. Terenghi F, Cappellari A, Bersano A, et al. How long is IVIg effective in multifocal motor neuropathy? Neurology. 2004;62:666–8.
30. Vucic S, Black KR, Chong PS, Cros P. Multifocal motor neuropathy: decrease in conduction blocks and reinnervation with long-term IVIg. Neurology. 2004;63:1264–9.
31. Cats EA, van der Pol WL, Piepers S, et al. Correlates of outcome and response to IVIg in 88 patients with multifocal neuropathy. Neurology. 2010;75:818–25.
32. Nobile Orazio E. Neuropathy and monoclonal gammopathy. Handb Clin Neurol. 2013;115:443–59.
33. Driedger H, Pruzanski W. Plasma cell neoplasia with peripheral polyneuropathy: a study of five cases and a review of the literature. Medicine. 1980;59:301–10.
34. Dispenzieri A, Kyle RA, Lacy MQ, et al. Definitions and long-term outcome. Blood. 2003;101:2496–506.
35. Monaco S, Bonetti B, Ferrari S, et al. Complement-mediated demyelination in patients with IgM ömonoclonal gammopathy and polyneuropathy. N Engl J Med. 1990;322:649–52.
36. Léger JM, Viala K, Nicolas G, et al; RIMAG study group. Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein neuropathy. Neurology. 2013;80:2217–25.
37. Gwathmey KG, Burns TM, Collins MP, Dyck PJB. Vasculitic neuropathies. Lancet Neurol. 2014;13:67–82.
38. Collins MP, Periquet MI. Isolated vasculitis of the peripheral nervous system. Clin Exp Rheumatol. 2008;26:S118–30.
39. Collins MP, Dyck PJB, Gronseth GS, et al. Peripheral Nerve Society Guideline on the classification, diagnosis, investigation, and immunosuppressive therapy of non-systemic vasculitic neuropathy: executive summary. J Peripher Nerv Syst. 2010;15:176–84.
40. Callaghan BC, Cheng HT, Stables CL, et al. Diabetic neuropathy: clinical manifestations and current treatments. Lancet Neurol. 2012;11:521–34.
41. Boulton AJM, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, Malik RA, Maser RE, Sosenko JM, Ziegler D. Diabetic neuropathies. Diabetes Care. 2005;28:956–62.
42. Lauria G. Small fibre neuropathies. Curr Opin Neurol. 2005;18:591–7.
43. Lozeron P, Nahum L, Lacroix C, et al. Symptomatic diabetic and non-diabetic neuropathies in a series of 100 diabetics patients. J Neurol. 2002;249:569–75.
44. Callaghan BC, Kerber KA, Lisabeth LL, et al. Role of neurologists and diagnostic tests on the management of distal symmetric polyneuropathy. JAMA Neurol. 2014;71:1143–9.
45. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy (technical review). Diabetes Care. 2003;26:1553–79.
46. Coppack SW, Watkins PJ. The natural history of diabetic femoral neuropathy. Q J Med. 1991;79:307–13.
47. Chan YC, Lo YL, Chan ES. Immunotherapy for diabetic amyotrophy. Cochrane Database Syst Rev. 2012;6:CD006521. doi: 10.1002/14651858.CD006521.
48. Hui AC, Wong S, Leung CH, et al. A randomized controlled trial of surgery vs steroid injection for carpal tunnel syndrome. Neurology. 2005;64:2074–8.
49. Padua L, Padua R, Aprile I, et al; Italian CTS Study Group. Carpal tunnel syndrome. Multiperspective follow-up of untreated carpal tunnel syndrome: a multicenter study. Neurology. 2001;56(11):1459–66.

50. Gilden DH. Clinical practice. Bell's Palsy. N Engl J Med. 2004;351:1323–31.
51. Sullivan FM, Swan IR, Donnan PT, et al. Early treatment with prednisolone or acyclovir in Bell's palsy. N Engl J Med. 2007;357(16):1598–607.
52. Kouyoumdjian JA. Peripheral nerve injuries: a retrospective survey of 456 cases. Muscle Nerve. 2006;34:785–8.
53. Seddon HJ. Three types of nerve injury. Brain. 1943;66:237–88.
54. Sunderland S. Nerves and nerve injuries. 2nd ed. New York: Churchill Livingston; 1978. p. 133–8.
55. Padua L, Di Pasquale A, Liotta G, et al. Ultrasound as a useful tool in the diagnosis and management of traumatic nerve lesions. Clin Neurophysiol. 2013;124(6):1237–43.
56. Gasparotti R, Lodoli G, Meoded A, Carletti F, Garozzo D, Ferraresi S. Feasibility of diffusion tensor tractography of brachial plexus injuries at 1.5 T. Invest Radiol. 2013;48(2):104–12.
57. Magrinelli F, Zanette G, Tamburin S. Neuropathic pain: diagnosis and treatment. Pract Neurol. 2013;13(5):292–307.
58. Birch R. Surgical disorders of the peripheral nerves. 2nd ed. London/New York: Springer Science and Business Media; 2011. p. 77–114.