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Peripheral neuropathies

1. Definition

Peripheral neuropathy, a result of damage to your peripheral nerves, often causes weakness, numbness and pain affecting various areas of the body.

2. Classification

2.1. Etiology:

Hereditary forms

- Charcot-Marie-Tooth neuropathy (CMT)
- Hereditary Neuropathy with Pressure Palsy (HNPP)
- Familiar amyloid polyneuropathy

Acquired forms

- Diabetic neuropathy
- Toxic neuropathy
- Dysimmune neuropathy
- Autoimmune disease
- Vasculitis
- Paraneoplastic syndrome
- Metabolic cause

2.2. Involved nerves:

Number of involved nerves

- Mononeuropathy (only one nerve)
- Multiplex mononeuropathy (couple of nerves)
- Polyneuropathy (many nerves)

Type of neuropathy

- Motor neuropathy
- Sensory neuropathy
- Sensorimotor neuropathy

Regarding the distribution

- Symmetric or asymmetric
- Proximal or distal

2.3. Characteristic of neuropathy

Demyelinating

- Uniform slowing
- Non-uniform slowing with conduction blocks

Axonal

Intermediate

2.4. Course of disease

Acute (hours, days)
Subacute (weeks, months)
Chronic (months, years)

3. Evaluation of neuropathy

3.1. Medical history

- Age at onset, first symptoms, course of progression
- Familial anamnesis
- Exposition of toxic substances (alcohol, chemotherapeutics, medications, toxins)
- Infectious diseases (Lyme disease – tick bites, HIV, HCV, HBV)
- Other medical conditions, especially: malignant neoplasm, lymphoma, multiple myeloma, amyloidosis, autoimmune disease, thyroid dysfunction, uremia

3.2. Clinical assessment

Symptoms occur primarily in the regions of nerve damage.

Motor symptoms

- Paresis, atrophy and hypotonia (impaired tip toe and heel walking, paretic gait, problem with but, difficulty using zippers and buttons, clumsiness in manipulating small objects)
- Decreased or absent tendon reflexes
- Fasciculation, cramps, pes cavus, shortening of Achilles tendon

Sensory symptoms

- Paraesthesia, hypaesthesia, anaesthesia or pain (starts usually distal and progress proximal)
- Impaired autonomic innervation (urine and/or stool incontinence and/or retention)
- Spinal ataxia

To follow the progression, the weakness of muscles and affected regions should be given exactly parallel with the distribution and the type of sensory impairment.

3.3 Nerve conduction study

Demyelinating neuropathy can be diagnosed if the distal latency and/or F-latency was prolonged and/or the conduction velocity was reduced. Increased temporal dispersion shows demyelination as well. Diffuse amplitude-reduction indicate axonal loss. Nerve lesion can be diagnosed as intermediate or mixed type if both axonal and myelin loss was present. Normal ranges can

3.4 Lab tests

- se. glucose (fasting glu., oral glucose tolerance test) HgbA1C
- sediment rate, Ca^{2+}, CK, LDH, TSH, B12 vitamin levels

} *First round (family doctor)*

- ganglioside profile (GM1, GD1b, GQ1b) IgG and IgM,
- postinfectious panel (B. burgerdorfii, HIV, HBV és HCV, C. jejuni) } *Second round*
- Ig electrophoresis, ANA/ANCA, paraneoplastic s. markers } *Third round / suspicion*

3.5 Further investigations

- Liqour punction: CIDP, GBS
- Nerve biopsy: vasculitis
- Rectum or skin biopsy: amyloidosis
- Muscle biopsy: mitochondrial dysfunction (multiple organs are affected)
- Bone marrow biopsy: multiple myeloma
- CT or MRI: radiculopathia or myelolysis
- Head MRI: CNS involvement or myelon lesio
- Nerve ultrasound: mononeuropathy, CMT1

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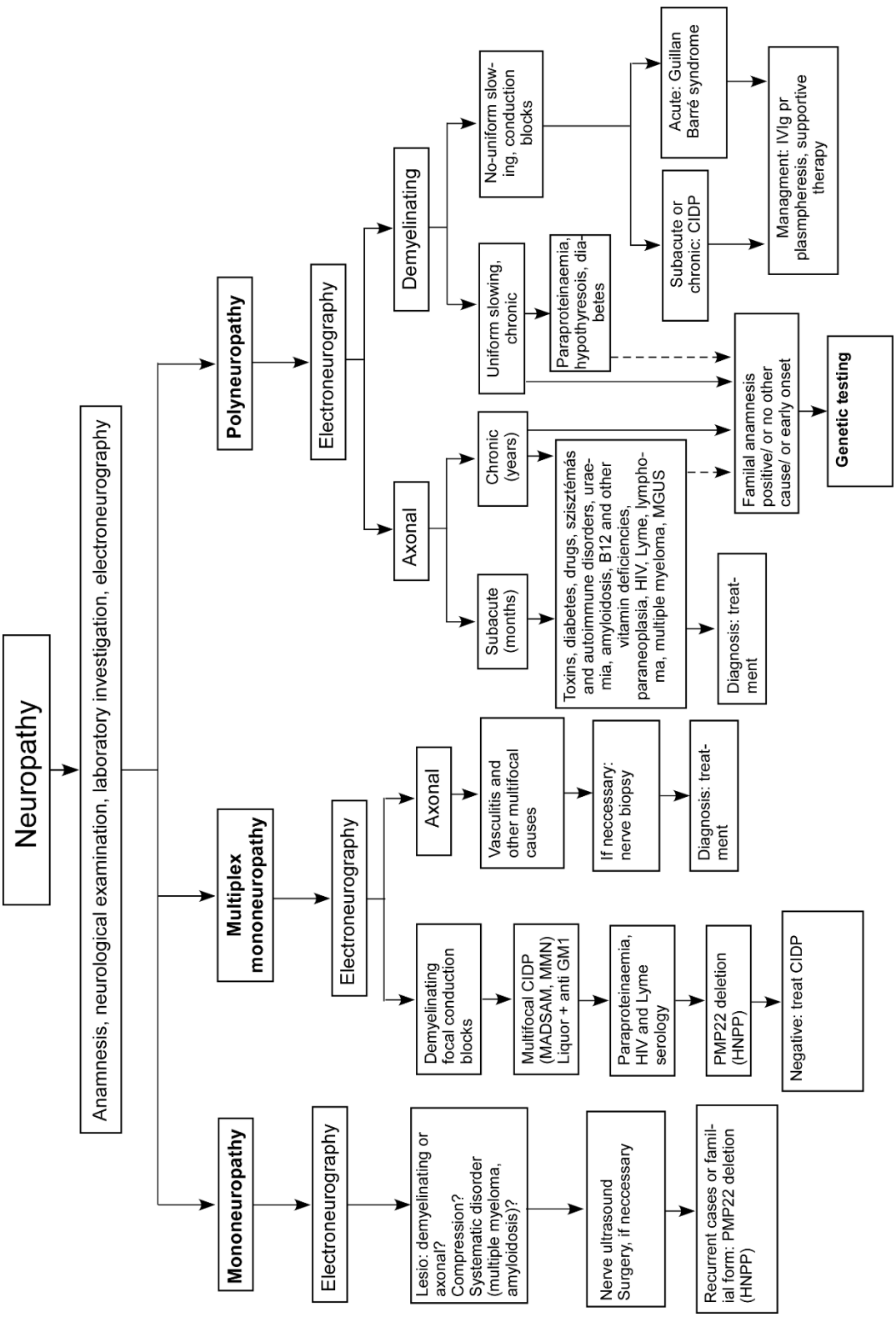


4. Hereditary motor and sensory neuropathy – classification and clinical evaluation

A Charcot-Marie-Tooth disease (CMT) is one type of hereditary motor and sensory polyneuropathy. It is one of the most common hereditary neurological disorders.

4.1. CMT classification

According to the type of neuropathy, two main groups of CMT can be separated: (1) demyelinating type or CMT1 (NCV <38 m/s) and (2) axonal type or CMT2 (NCS >38 m/s, decreased amplitudes). Intermediate form (ICMT) both type are present and cannot be distinguished. CMT starts usually in the first two decades. (CMT1: 10-20 ys; CMTII – 20-30 ys).

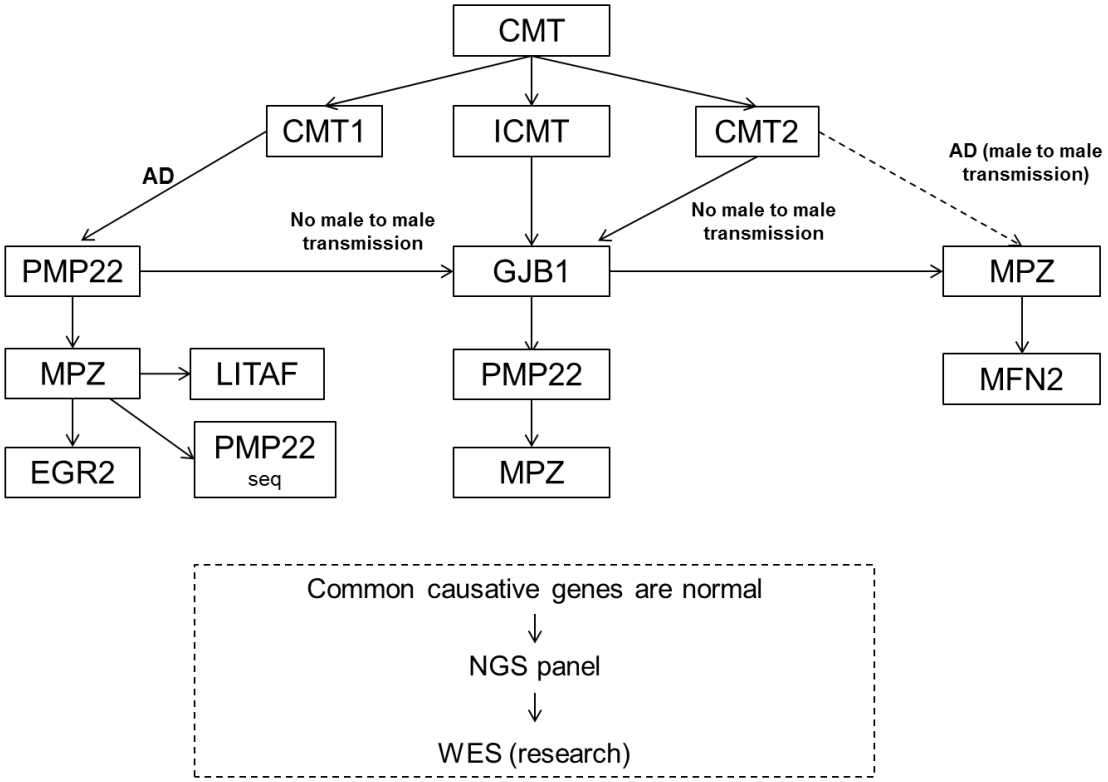
4.2 Genetic background

Hereditary neuropathy shows the following inheritance patterns: autosomal dominant (CMT1, CMT2, ICMT), recessive (CMT4) or X-linked (CMTX).

There are more than 70 known genes causing CMT and this number increase permanently.

Abbreviation	***Gene***	***Distribution***
CMT1A	PMP22*dupl*	37.2%
CMTX1	Cx32	6.5%
CMT2A	MFN2	4.2%
CMT1B	MPZ	4.1%
CMT1E	PMP22	1.0%
CMT1D	EGR2	0.06%
CMT1C	LITAF	0.12%

Percentages of gene distribution [Fridman et al. 2014]



Algorithm of CMT genetic evaluation [Friedman et al and own data]

4.3 Clinical appearance

The symptoms show distal symmetric neuropathy phenotype. CMT Neuropathy Score-t (CMTNS) is recommended to evaluate the severity and to follow up (see p. 6). CMTNS is consisted by nine different scores: symptoms (3), signs (4) and neurophysiology (2). Each score is rated from 0 to 4 regarding the severity (0 – normal, 4 – severe). Severity is ranked as follows: ≤10 mild, 11-20 moderate, >20 severe.

Certain *GJB1* mutations can cause CNS involvement (spasticity, corticospinal tract involvement, cortical lesion, cerebellar ataxia) as well. Furthermore, early onset hearing impairment and acute florid attacks can be also observed sometimes. *GJB1* mutations cause milder clinical signs and symptoms in females compared to males. *MFN2* can appear with mitochondrial deletion or depletion, cerebellar ataxia or CNS involvement. DNM2 mutations can be associated with mitochondrial deletion, centronuclear myopathy (seen in muscle biopsy) or rarely with cardiomyopathy

Suspicion of hereditary neuropathy usually comes up if relatives are also affected and the disorders starts in first decades. However, sporadic cases are also relatively common. Acquired neuropathies must be ruled out.

4.4 Management of CMT

There is no cure for CMT but symptoms and signs can be treated. These aim the improvement of life quality and the slower progression.

- vitamins – C-vitamin 1000 mg, Milgamma 1-3 pills
- neuropathic pain – Lyrica 1-2x 75mg / Cymbalta 30-60mg/ Teperin-EP 25-50mg
- musculosceletal pain – COX2 inhibitors (Xefo 8mg)
- physiotherapy
- Mobility aids – surgery, peroneus orthesis, Toe-OFF, wheel chair, crutches
- depression – neuropsychological examination, antidepressants, psychotherapy
- control and treat of diabetes mellitus
- avoiding the neurotoxic agents (alcohol, industrial toxins, certain medications)

4.5 Differential diagnostic

Inherited disorders accompanied with polyneuropathy:

- Mitochondrial disorders (systematic involvement, elevated lactate, muscle biopsy, mitochondrial deletio, hotspot mutation);
- Familiar amyloid polyneuropathy (heart, kidney, vascular involvement, V30M mutation)
- Hereditary Neuropathy with Pressure Palsy (HNPP) if multifocal motor neuropathy is present (PMP22 deletion)

References:

Harrison's Neurology in Clinical Use 1st Edition
Murphy et al 2011; Journal of Peripheral Nervous System 16:191-198
Fridman V et al 2014; J Neurol Neurosurg Psychiatry 2014;0;1-6