Neurophysiological diagnosis of polyneuropathies

Definition of polyneuropathy
- Diffuse disorder of peripheral nerves
- Often all types of axons are involved
  - Motor
  - Sensory
  - Autonomic
- Usually distal nerves more affected than proximal
- Symmetric

Etiology
- Toxic
  - Drugs, solvents....
- Metabolic and endocrine
  - Diabetes, uremia
- Immune mediated
  - AIDP, CIDP, MMN, MGUS
- Hereditary
  - CMT, HNPP
- Infectious
  - Leprous, HIV, Borrelia
- More than 300 different causes for PNP

Affected types of axons
- Sensory
  - Pyridoxine
- Motor
  - Lead
- Sensory and motor
  - MoOst PNP's
  - Diabetes
- Thin fibre
  - Fabry disease

Patophysiology
- Axonal 80-90%
- Demyelinating 10-20%
  - Without conduction block
  - With conduction block

Polyneuropathy - Site of primary defect
- Axonopathies
  - Central-peripheral axonopathy
  - Axon transport
  - Cumulative effect of pathology along the nerve
- Neuronopathies
  - Primary events in the perikaryon
- Myelinopathies
- The precise site and mechanism is not always known
Polyneuropathy – time course

- Acute (days to weeks)
  - Acute polyradiculitis
  - Critical illness
  - Polyarteritis nodosa
  - Toxic polyneuropathies
  - Porphyria
- Chronic (months to years)
  - HMSN
  - Diabetes
- Relapsing
  - Chronic polyradiculitis

Distribution

- Distal symmetric
  - By far most common
  - Related to axon length
  - Legs>arms
- Proximal symmetric
  - Intermittent porphyria
  - Tangier disease
  - Sometimes polyradiculitis

Polyneuropathy - Multifocal neuropathy

- Multifocal mononeuropathies may superficially look like a polyneuropathy
- In many polyneuropathies there is susceptibility for local neuropathies
  - Diabetes
  - Hereditary liability to pressure neuropathies

Distribution

- Upper limb predominant
  - Lead
  - Dapsone
- Complex distributions
  - Lepromatous leprosy (skin temperature)
- Cranial nerve involvement
  - Miller-Fisher syndrome
  - Borreliosis
  - Sarcoidosis
  - Sjögren’s syndrome

Epidemiology of PNP

- 2.4% of the population have PNP
- 8% of >65 year olds have PNP
- In the western world diabetes most common
- In developing world leprous neuropathy is most common

Generation of symptoms

- Loss of function (negative symptoms)
  - Axonal loss
  - Conduction block
- Abnormal excitability (positive symptoms)
  - Hyperexcitability
  - Abnormal spreading of impulses
  - Abnormal pathways
Polyneuropathy - motor symptoms

- Loss of neural function
  - weakness
- Increased abnormal neural function
  - fasciculation
  - myokymia
  - muscle cramps

Polyneuropathy - sensory symptoms

- Loss of neural function
  - decreased sensation
  - touch
  - pain
  - temperature
- Increased abnormal neural function
  - paresthesia
  - dysesthesia
  - neuropathic pain

Polyneuropathy - autonomic symptoms

- Loss of neural function
  - Horner’s syndrome
  - Loss of sweating
  - Cardiovascular symptoms
    - Orthostatic hypotonia
  - Genitourinary function
- Abnormal neural function
  - cardiovascular symptoms (vagal overactivity)

Polyneuropathy - clinical findings

- Decreased tendon reflexes
- Decreased or altered sensation
  - Vibration
  - Pain
  - Temperature
- Loss of muscle strength
- Muscle atrophy
- Trophic skin changes
- Joint deformities

Polyneuropathy - skeletal deformity

- Pes cavus
  - HMSN
  - Indicates onset in childhood
- Rarely pes planus
- Scoliosis
- Neuropathic joint deformity

Symptom chart
Pes cavus in CMT1a

Neuropathic arthropathy

Polyneuropathy - nerve thickening

- Lepromatous neuropathy
  - greater auricular nerve
  - supraclavicular nerves
  - radial nerve at the wrist
  - etc
- Amyloidosis
- CMT 1 and 2
- Neurofibromatosis

Monofilament (10 g)

Monofilament test

Diagnosis of polyneuropathies
Diagnosis and treatment of PNP

- Does the patient have PNP?
  - Exposure, diseases
  - Symptoms
  - Clinical findings
  - EMG

- PNP etiology?
  - Exposure, deprivation
  - Clinical chemistry
  - Genetics
  - Other

- Treatment
  - Is the underlying condition treatable?
  - Symptomatic treatment

Polyneuropathy - Neurophysiological criteria

- The diagnosis is not always clear
- Normal aging causes alterations to the peripheral nerves
  - Reduced CV with age
  - SCS amplitude reduced with age
- How many abnormal findings are required for the diagnosis??
- Cumulative effects of lifestyle and aging

Methods available

- History
- Clinical examination
- Neurography
- Psychophysiological methods
  - Vibration sensation thresholds
  - Thermal sensation thresholds
- EMG
- Tests of the autonomic nervous system
- Intraepidermal axon density
- Nerve biopsy

N. medianus

Axonal neuropathy

- Normal median nerve neurography

- Axonal neuropathy
Axonal neuropathy

- Reduced motor and sensory amplitudes
- Conduction velocity normal or slightly reduced
  - Median motor > 40 m/s
- Distal latency normal or slightly prolonged
- No decay

Axonal PNP

- Diabetic polyneuropathy
  - May show features of demyelination
- Hereditary motor and sensory polyneuropathy type 2 (HMSN 2)
- Amyloidosis
- Renal insufficiency

Conduction in abnormal nerves

- Saltatory nerve conduction depends on the innermost myelin layers
- Prolonged internodal conduction time from 20 us to 500 us
- Conduction blocks arise due to local inexcitability
- Non-saltatory conduction requires reorganization of the axolemma

Demyelinating neuopathy

- CV reduced >30%
  - Median nerve CV < 40 m/s
- Distal latency > 7 ms
- Normal or reduced amplitudes
Conduction block

Definition of conduction block

- > 20% amplitude or area decay and less than 15% dispersion
- >50% amplitude or area decay
- Both criteria are equally sensitive, but the latter is more specific

Ad hoc committee of the American Academy of Neurology AIDS taskforce, Neurology; 41: 617-618

Practical criteria of conduction block

- Motor decay abnormal without dispersion
  - Upper extremities >25% decay and <15% dispersion
  - Lower extremities >40% decay and < 20% dispersion
- Reduced number of F waves

Polyneuropathies with conduction block

- Acute polyradiculitis (AIDP)
- Chronic polyradiculitis (CIDP)
- Multifocal motor neuropathy with conduction blocks (MMN)
- Diphtheria
- Polyneuropathies in gammopathies

Demyelinating no conduction block

- Inherited polyneuropathies
  - CMT 1
  - Hereditary liability to pressure palsies
  - conduction blocks are limited to sites of local nerve lesions

Demyelinating with conduction block

- Acquired demyelinating polyneuropathies show conduction blocks
  - Acute polyradiculitis
  - Chronic polyradiculitis
  - Diphtheria
  - MMN
  - Polyneuropathy associated with gammopathy
F-WAVE LATENCY, THE MOST SENSITIVE NERVE CONDUCTION PARAMETER IN PATIENTS WITH DIABETES MELLITUS

Hedvig Jersjens, MD, PhD, Ulrika Sjöberg, MD, PhD, and
Stina Nilsson, MD, PhD

1 Department of Clinical Neurophysiology, University Hospital, Uppsala, Sweden
2 Department of Neurology, Vallila Central Hospital, BMH, Uppsala, Sweden

ABSTRACT: In the study we examined the diagnostic sensitivity of nerve conduction velocity, F-wave latency, F-wave persistence, motor nerve conduction velocities, and amplitude of compound muscle action potentials (CMAPs) of the median, radial, ulnar, and sciatic nerves of diabetic patients. F-wave latencies were significantly longer in median (7.5 ± 1 ms), radial (8.2 ± 1 ms) and sciatic nerves (15.3 ± 2 ms) in diabetic patients than in the normal control group (median 6.2 ± 0.9 ms, radial 6.9 ± 1 ms, sciatic 13.1 ± 2 ms). F-wave latencies were significantly longer than those of the control group with a CMAP amplitude of 8.4 nA/cm and an F-wave threshold of 40% of the maximum compound muscle action potential (CMAP) amplitude. The median nerve F-wave latency was significantly longer than those of the ulnar, radial, and sciatic nerves, and the ulnar nerve F-wave latency was significantly longer than those of the median and sciatic nerves.

F-wave latencies were significantly longer than those of the control group with a CMAP amplitude of 8.4 nA/cm and an F-wave threshold of 40% of the maximum CMAP amplitude. The median nerve F-wave latency was significantly longer than those of the ulnar, radial, and sciatic nerves, and the ulnar nerve F-wave latency was significantly longer than those of the median and sciatic nerves.

EMG

- May be helpful in providing information about the involvement of alpha motor axons
- Distribution
- Time course
  - Fibrillation potentials
  - MUP abnormalities
- Differential diagnosis
  - Spinal stenosis

Diabetic neuropathies

Classification of diabetes

- Type 1 diabetes
  - Immune, cell mediated destruction of β-cells 90%
  - Idiopathic 10%
- Type 2 diabetes
  - Multiple causes
  - Defective insulin secretion
  - Insulin resistance
  - Genetic predisposition
- Other specific types
  - Genetic defects of β-cell function
  - Genetic defects of insulin action
  - Diseases of exocrine pancreas
  - Endocrinopathies
- Gestational diabetes mellitus
- Prediabetes (Impaired glucose tolerance)

Epidemiology of DM

- 1.3% of population has DM
- 27% DM type 1
- 73% DM type 2
Definition of diabetic neuropathy

“Diabetic neuropathy is is a descriptive term meaning a demonstrable disorder, either clinically evident or subclinical, that occurs in the setting of diabetes mellitus without other causes for peripheral neuropathy. The neuropathic disorder includes manifestations in the somatic and/or autonomic parts of the peripheral nervous system.”


Definition of diabetic polyneuropathy


“.....confirmed definite clinical neuropathy also required the finding of unequivocal abnormality on nerve conduction studies or autonomic nervous system testing....”

Types of diabetic neuropathy

- Mononeuropathies
  - Entrapment neuropathies
  - Acute mononeuropathies (Parsonage-Turner syndrome)
- Diabetic lumbosacral radiculoplexus neuropathy
  - Bruns-Garland syndrome
- Sensory-motor axonal polyneuropathy
  - Usually high correlation between affection of different types of axons
  - Thin fiber neuropathy
  - Autonomic neuropathy
- Acute painful diabetic neuropathy
  - Diabetic neuropathic cachexia
- Hyperglycemic polyneuropathy
  - Transient neuropathy related to hyperglycemia, especially in patients with newly diagnosed diabetes

Staging of diabetic neuropathy

- Stage 0
  - No neuropathic symptoms
  - ≤ 2 abnormalities on neurophysiological tests
- Stage 1 (Asymptomatic neuropathy)
  - No neuropathic symptoms
  - ≥ 2 abnormalities on neurophysiological tests
- Stage 2
  - Neuropathic symptoms not disabling
  - ≥ 2 abnormalities on neurophysiological tests
- Stage 3
  - Neuropathic symptoms disabling
  - ≥ 2 abnormalities on neurophysiological tests


Polyneuropathy in newly diagnosed diabetes

- Patients are rarely investigated at this stage
- Usually no subjective symptoms
- Reduced conduction velocities
- Reversible within a few months

Predisposing factors

- Duration of diabetes
- Age
- Glycemic control as measured by GHB
- Height
- Other diseases or exposure to toxins
  - Alcohol
  - Uremia
  - B12
- Type of diabetes? Probably type2 > type1
Epidemiology of diabetic polyneuropathy

- 8% have polyneuropathy at the time of diagnosis
  - type 2 > type 1
- Overall 30% of diabetics have PNP
- > 20 years of diabetes 50% have PNP
  - type 1 > type 2

Pathology of diabetic polyneuropathy

- Loss of myelinated and unmyelinated axons distally
- Loss of anterior horn cells and sensory ganglion cells in some cases
- Segmental and paranodal demyelination (both primary and secondary)
- In patients with treated diabetes, axonopathy predominates

Pathogenesis

- Formation of glycosylation end products
- Altered polyol metabolism
- Altered neurotrophic factors
- Oxidative stress
- Altered essential fatty acid metabolism
- Vascular factors

Complications more severe in Type 1

- Polynuropathy
  - N0
  - N20a
  - N20b
- Retinopathy
  - R0
  - R1
  - R2
  - R3

PNP and retinopathy go hand in hand

Diabetes not the only cause of PNP

Additional causes for distal sensory polyneuropathy in diabetic patients

K C Gomaa, A H Ropper
Diabetes not the only cause of PNP

- If diabetes patient with significant PNP does not have retinopathy ➔ look for other causes of PNP

Strategy in patients with diabetes

- Assess polyneuropathy
  - Severity
  - Pathophysiology (axonal-demyelinating)
  - Distribution (distal-proximal, symmetry)
  - Types of axons involved (sensory, motor, thin fibers, autonomic nervous system)
- Assess local nerve lesions
  - Carpal tunnel syndrome in all patients
  - If clinically symptoms other nerves

Neurography in diabetes

- Sensory neurography
  - Superficial peroneal nerve
  - Sural nerve
  - Median nerve
  - Ulnar nerve

- Motor neurography
  - Peroneal nerve
  - Tibial nerve
  - Median nerve

Depending on the clinical symptoms other nerves may be investigated

Sensitivity of different tests

<table>
<thead>
<tr>
<th>Test</th>
<th>% abnormal findings in 180 diabetes patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve conduction (NC)</td>
<td>69 %</td>
</tr>
<tr>
<td>Neuropathy symptom score (NSS)</td>
<td>54 %</td>
</tr>
<tr>
<td>Neuropathy disability score (NDS)</td>
<td>48 %</td>
</tr>
<tr>
<td>Neuropathy symptom score (NSC)</td>
<td>47 %</td>
</tr>
<tr>
<td>Vibratory detection threshold (VDT)</td>
<td>44 %</td>
</tr>
<tr>
<td>Cooling detection threshold (CDT)</td>
<td>35 %</td>
</tr>
</tbody>
</table>


Treatment

- Hyperglycemic control
- Aldose reductase inhibitors
- Myo-inositol administration
- α-lipoic acid
- Neurotrophic factors
- Pancreatic transplantation

Controversial issues

- Does prediabetes cause PNP?
- Do diabetic patients have an increased frequency of CIDP?
Prediabetes (Impaired glucose tolerance)

- Fasting blood glucose 100-125 mg/dL
- 2 hour glucose level after oral glucose test 140-199 mg/dL.

Does prediabetes cause PNP?

- Singleton et al (Diabetes care 2001) found in 107 patients with PNP of undetermined cause prediabetes in 34%
  - No control group
  - In 30% of >65 year olds prediabetes
- Hughes et al (Brain 2004) looked at similar PNP patients with a control group and found prediabetes equally common in both groups

CIDP in diabetes patients

- Some reports indicate increased frequency of CIDP in diabetes patients
- Not substantiated by epidemiologic studies (Muscle nerve 2006:34:512)

Further reading

The Spectrum of Diabetic Neuropathies
Jennifer A. Tracy, MD, P. James B. Dyck, MD
*Peripheral Neuropathy Research Laboratory, Mayo Clinic College of Medicine, 200 First Street Southwest, Rochester, MN, USA
Department of Neurology, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, USA

History

- 1886 Charcot J and Marie P (France)
- 1886 Tooth H (UK)
- 1893 Dejerine H and Sottas J
- 1926 Roussy G and Levy G
Jean-Martin Charcot 1867-1936


Pierre Marie 1853-1940

Howard Henry Tooth 1856-1925

Dissertation
University of Cambridge
“The peroneal type of muscle atrophy” 1886

CMT

- Hereditary sensory and motor polyneuropathies (PNP)
- Primary affection is PNP
- No or little CNS symptoms
- Fairly homogenous group
- Hundreds of different mutations affecting several different genes related with myelin
- Most are autosomal dominant (AD)
- A few are autosomal recessive
- Also x-linked forms exist

CMT terminology

- CMT
- HSMN (hereditary sensory and motor polyneuropathy)
  - Introduced by Peter Dyck
  - Currently less used
- Usually in classifications CMT = HSMN
  - CMT4 ≠ HMSN4
  - HMSN3=Dejerine Sottas
Main clinical features

- Onset in the first or second decade of life
- Symptoms mainly motor
- Foot deformity
  - Pes cavus
  - Digitus malleus
- Little subjective sensory abnormalities
  - Unpleasant neuropathic symptoms rare
  - Pain due to deformity of the foot may cause pain
- Slowly progressive
- Do not reduced life expectancy
- Rarely wheelchair bound

Pes cavus in CMT1a

CMT prevalence

- All CMT 30/100000
- CMT1 15/100000
- CMT1A 10/100000
- CMT2 7/100000

CMT classification

- CMT1 (demyelinating)
- CMT2 (axonal)
- CMT DI (dominant intermediate)
- CMT 3 (severe early onset, demyelinating)
- CMT 4
- HNPP (hereditary liability to pressure palsies)

Myelin proteins

Extracellular
- PMP22
- P0
- Connexin
- MAG

Intracellular
CMT1 – demyelinating, dominant

<table>
<thead>
<tr>
<th>Gene</th>
<th>Location</th>
<th>Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMT1A</td>
<td>PMP22</td>
<td>17q11</td>
</tr>
<tr>
<td>CMT1B</td>
<td>P0</td>
<td>1q22</td>
</tr>
<tr>
<td>CMT1C</td>
<td>LITAF</td>
<td>16p13</td>
</tr>
<tr>
<td>CMT1D</td>
<td>EGR-2</td>
<td>10q21</td>
</tr>
</tbody>
</table>

CMT1A

- Most common CMT, 70% of all
- AD, Linked to chromosome 17p11.2
- Peripheral myelin protein 22 (PMP-22)
- Duplication or point mutations
- Genetic testing available
- Male:female 1:1
- Family history in 60%, 30% de novo mutations
- Complete penetrance

Abnormal crossing over

CMT1A variants

- Roussy-Levy
  - Ataxia and tremor

CMT1A

- Reduced CV
  - <39 m/s in median nerve
  - Note increased stimulation threshold
  - No conduction blocks
- Present from 2 years of age
  - Demyelination not detectable at birth
- EMG
  - In young patients no signs of axonal involvement
  - Later varying degrees of axonal degeneration
- Axonal degeneration cause of handicap

CV in children with CMT1a

Garcia et al. CMT type 1a disease with duplication 17a duplication in infancy and childhood. Neurology 1998;50:1061-
**CMT1B**
- Autosomal dominant inheritance
- Linked to chromosome 1q21-23
- Peripheral myelin protein P₀ (PNPO)
- Gene mutations > 95
- Sporadic cases common
  - 50%
- 1B is less common
- CSF protein elevated

**P₀ protein**
- 28kD
- 219 amino acids
- Most abundant peripheral nerve protein
  - 50%
- Compact myelin
- Not present in CNS
- Required for normal myelin function

**CMT1C**
- LITAF – lipopolysaccharide-induced tumor necrosis factor-α
  - Stimulates monocytes and macrophages
  - May play a role in protein degradation
- Autosomal dominant
- Chromosome 16p13
- Three families described
- Similar to other CMT1

**CMT1D**
- Zinc-finger transcription factor EGR2/Krox20
- Autosomal dominant
- Overexpression of EGR2 leads to increased expression of several myelin proteins
- Neurophysiologically like other CMT1

**CMT2 – axonal, dominant**

<table>
<thead>
<tr>
<th>CMT2A1</th>
<th>KIFB1β</th>
<th>10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMT2A2</td>
<td>Mitofusin 2</td>
<td>10 years</td>
</tr>
<tr>
<td>CMT2B</td>
<td>RAB8</td>
<td>3q13</td>
</tr>
<tr>
<td>CMT2C</td>
<td>12q23-q24</td>
<td>1 decade</td>
</tr>
<tr>
<td>CMT2D</td>
<td>GARS</td>
<td>7p14</td>
</tr>
<tr>
<td>CMT2E</td>
<td>NF-68</td>
<td>8p21</td>
</tr>
<tr>
<td>CMT2F</td>
<td>HSPB1</td>
<td>7q11</td>
</tr>
<tr>
<td>CMT2G</td>
<td>12q12</td>
<td>15-25</td>
</tr>
<tr>
<td>CMT2H</td>
<td>HSPB8</td>
<td>12q24</td>
</tr>
</tbody>
</table>

**CMT2A1**
- Kinesin family number 1Bβ (KIF1B)
- Chromosome 1p36.2
- Dominant
- Described in Japan
Mitofusin 2 (MFN2)
- Autosomal dominant
- Most CMT2A
- MFN2 mitochondrial fusion protein
  - Outer membrane of mitochondria
  - Regulates OXPHOS expression

Onset 1-52 years
- Distal weakness
- Sensory loss
- Sometimes painful
- Intention tremor
- Hearing loss in 60%
- Wheelchair may be needed on 5th decade

CV
- >40 m/s in median nerve
- Reduced amplitudes

EMG
- Axonal involvement

Severe
- Infantile onset
- Slowly
- Autosomal dominant
  - Most cases are sporadic
  - Few become ambulatory
  - Hypotonia, areflexia
  - Pes cavus
- CSF proteins elevated

Overlap with CMT1
- Is the eponym warranted?
- Genetically heterogeneous
  - PMP22
  - P0
  - Connexin-32
Dejerine-Sottas (HSMN3)

- **CV**
  - <10 m/s
  - No sensory responses
- **EMG**
  - Signs of active denervation

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**CMTX**

<table>
<thead>
<tr>
<th>CMTX</th>
<th>Connexin-32</th>
<th>Xq13</th>
<th>2 decade</th>
</tr>
</thead>
</table>

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**CMTX**

- Connexin-32
- Chromosome Xq13
- Semidominant
- >240 point mutations
  - Phenotype depends on mutation
- Connexin function
  - Gap junction
  - Uncompacted myelin

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**CMTX**

- **Males**
  - Onset < 20 years
  - Distal weakness
- **Females**
  - Asymptomatic
  - May have slight slowing of CV

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**Family history**

- I. Autosomal dominant inheritance
- C. Isolated cases
  - incomplete penetrance
  - de novo mutations

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Guidelines for diagnosis of hereditary neuropathy with liability to pressure palsies

Odielle Deboutte
Philippe Moutet
Alexis Broc
Erie LeGuern
Pierre Bocche

Service d’Electrodiagnostic, Neurologie, Hôpital La Salpétrière, 47 bd de l’Hippodrome, 75015 Paris, France

12800 NIMH and University of Toronto, Toronto, Ontario, Canada

Revised 4 August 1999
Age at onset
- I. Usually during second or third decade
- C. Vide variability from birth to old age

Clinical manifestations
- I. Acute recurrent peripheral nerve lesions, usually with good recovery
- I. Acute deficits both sensory and motor
- I. Precipitating factors (trauma, pressure or stretching) usually identified
- I. Some mutation carriers remain asymptomatic
- C. Deficit may be purely sensory or motor
- C. Number of nerve lesions vary from one to many
- E. Presence of pain before or during episodes

Location of nerve palsies
- C. Peroneal nerve, ulnar nerve and brachial plexus often affected
- C. Median and radial nerves may be affected
- C. Other nerves, including cranial nerves may exceptionally be affected
- C. Several nerves may be simultaneously affected

Clinical findings
- C. Tendon reflexes may be diminished or abolished, ankle jerk most often affected
- C. General areflexia may be noted
- C. Pes cavus may be present
- C. Scoliosis may be present
- C. Muscle weakness and wasting may be present in areas previously affected
- C. Muscle weakness and wasting may be observed in areas not previously affected
- E. Predominant CNS involvement including pyramidal tract or cerebellar signs

Course and severity
- I. Absence of deficits between palsy episodes
- I. Complete recovery occurs within days to months
- C. Recovery may be incomplete

Neurophysiological criteria
- I. Presence of diffuse neurography abnormalities in all mutation carriers, symptomatic or not, age >15 years
  - delayed median nerve MDL bilaterally
  - reduced median nerve CV palm to wrist
  - reduced CV or delayed DL in one peroneal nerve
- C. Ulnar nerve CV often reduced at the elbow
- C. Motor CV reduced in lower limbs
- C. Sensory nerve action potentials reduced, especially in upper limbs
**Molecular genetics**

- I. Deletion in 17p11.2 detected in 85-90% of HNPP
- I. Some point mutations in PMP22 cause HNPP
- E. Absence of HNPP deletion in 17p11.2 or point mutation

**Prevalence**

- In south western Finland prevalence is at least 16/100,000 (Meretoja et al., Neuromusc Disord 1997;7:529-32)

**Acute polyradiculitis**

- Guillain-Barré Syndrome, GBS
- Acute inflammatory demyelinating polyneuropathy, AIDP

**Clinical features**

- In most patients distal and ascending
- The presentation may be descending in a portion of patients
- Pain in 15-50% of patients
- Facial nerve is often involved
- Autonomic nervous system may be affected, especially in patients with severe motor deficits
- Tendon reflexes are decreased or absent

**GBS – time course**

- Most patients worsen over 1-2 weeks, some for up to 4 weeks
  - Axonal: reach quicker maximal weakness than demyelinating
- After plateau subsequent recovery over 6-12 months
- Patients that worsen for more than 8 weeks probably have chronic polyradiculitis
GBS - Strategy
- Demonstrate acute motor and sensory neuropathy
- In the acute stage the motor nerves are more affected than sensory nerves
- Typically demyelinating with conduction block
- Axonal forms are also common
- Proximal demyelination and distal axonopathy
- Most prominent findings are often in the proximal parts of the nerves – sometimes the findings are distal
- Sometimes the neuropathy is predominantly axonal, especially if associated with Campylobacter jejuni
- Assess: severity, pathology, distribution

GBS - Abnormal findings
- Motor
  - Conduction block
  - F waves delayed and few
  - DL prolonged
  - Reduced MCV, sometimes normal initially
  - Distal amplitude may be initially normal - low amplitude with normal DL indicates severe axonal involvement
- Sensory
  - Reduced SCV is not necessarily seen during the first weeks
  - Reduced amplitude is seen in the presence of axonal loss

GBS - Abnormal EMG findings
- < 10-18 days from onset of symptoms: only reduced interference pattern
- > 10-18 days from onset: signs of acute neurogenic EMG findings

GBS - Procedure
- Neurography
  - MCS: n.medianus, n.ulnaris, n.tibialis, n.peroneus unilaterally
  - SCS: n.radialis, n.surals unilaterally.
- EMG
  - < 10 days from onset of symptoms not necessarily informative, but may reveal earlier onset and confirm peripheral cause of weakness
  - > 10 days from onset,
- Autonomic tests (optional)
  - RR-interval
  - SSR
- Sensory thresholds (optional)
  - temperature
  - vibration

CIDP - Course
- Occurs in all age groups from 2 years
- May begin as a typical acute polyradiculitis
- May start with subacute symptoms
- Course
  - chronic progressive (slowly or stepwise) course
  - relapsing
    - progression > 6 weeks followed by episodes of improvement and worsening for at least 3 months
**CIDP - Symptoms**
- Bilateral relatively symmetric weakness - distal and proximal
- Paresthesias in toes and fingers
- Facial muscles may be affected (10-15% of patients)

**CIDP - Prognosis**
- Patients with a relapsing course often resolve after a few years and they tend to have a better prognosis than those with chronic progressive course

**CIDP - Other investigations**
- Elevated CSF protein concentration during deterioration
- MRI shows increased signals on T2 weighted images at the sites of conduction blocks
- Nerve biopsy not useful

**CIDP - Abnormal neurography findings**
- Motor neurography
  - Reduced CV
  - Conduction block
  - F waves delayed and few
  - Distal latency prolonged
  - Distal ampl may be initially normal - low amplitude with normal dist.lat. indicates severe axonal involvement
- Sensory neurography
  - Reduced SCV
  - Reduced amplitude

**CIDP Abnormal EMG findings**
- Distal muscles and proximal muscles show neurogenic findings
- Depends on severity

**CIDP - Abnormal findings**
- Autonomic nervous system tests
  - RR-interval often abnormal
  - SSR may be abnormal
CIDP - Procedure

- Neurography
  - Motor: n.medianus, n.ulnaris, n.tibialis, n.peroneus unilaterally
  - Sensory: n.radialis, n.suralis unilaterally.
- EMG
  - one proximal and distal muscle in the upper and lower extremities
- Autonomic tests (optional)
- Sensory thresholds (optional)

Miller-Fisher syndrome


Listen to podcast with interview at AANEM website

Miller-Fisher syndrome - Clinical features

- External ophthalmoplegia, ataxia and areflexia
- Diplopia and unsteadiness of gait, either of these symptoms may be the initial sign
- Other muscles innervated by cranial nerves may show weakness

Miller-Fisher syndrome - Clinical

- Acute onset within days
- Peak of symptoms in one to two weeks
- Mild weakness and sensory symptoms may be present
- Usually the course is monophasic and relatively benign
- Recurrences have been described
- CSF protein is elevated
- Antibodies against GQ1b

Miller-Fisher syndrome - Neurography

- Motor
  - F waves delayed and few due to conduction block
  - DL may be prolonged
  - Mildly reduced MCV, sometimes normal initially
  - Distal amplitude reduced, especially in facial muscles
- Sensory
  - Reduced amplitude dominates over reduced CV

Miller-Fisher syndrome - Blink reflex

- Absent or mildly prolonged R1 components
- R2 may be absent, but latency is usually normal
**Miller-Fisher syndrome**

- **Neurography**
  - Motor: n.medianus, n.ulnaris, n.tibialis, n.peroneus unilaterally, the branches of n.facialis bilaterally
  - Sensory: n.radialis, n.suralis unilaterally
- **EMG**
  - > 10 days from onset
  - Facial muscles should be studied
- **Blink reflex**
- **Autonomic tests (optional)**
  - RR-interval
  - SSR
- **Sensory thresholds (optional)**
  - Temperature and vibration

**Utility of neurophysiological tests in the diagnosis of PNP**

**Role of neurophysiological tests**

- Diagnose PNP
- Characterize PNP
  - Axonal-demyelinating-conduction blocks
  - Motor-sensory-autonomic
  - Myelinated-unmyelinated axons
  - Severely
- Prognosis
  - Small M wave amplitude in the acute stage may be related with a poor recovery
- Follow-up

**Timing of electrodiagnosis**

- In acute PNP ENMG immediately!!!
  - Neurography shows abnormalities early
  - Needle EMG shows abnormalities after 2-3 weeks
  - In the early stages it is not possible to distinguish between distal conduction block and axonal damage (pseudo block)

**Characterization**

- Pathophysiology
  - Axonal
  - Demyelinating (with or without conduction blocks)
- Severity
  - Mild
  - Moderate
  - Severe
- Distribution
  - Distal>proximal
  - Proximal>distal
  - Proximal=distal
- Time course
  - Acute
  - Chronic

**Examples of characterization**

- Mild, chronic, symmetric, distal sensory-motor axonal polyneuropathy
- Moderate, acute, demyelinating, distal sensory-motor-autonomic polyneuropathy with conduction blocks
Strengths

- Guides the diagnostic etiological evaluation
- Objective and reliable in the diagnosis of symmetric sensory motor polyneuropathy
- Quantitative
- Sensitive
- Most methods are non-invasive
- Cost is relatively low

Weaknesses

- Routine methods do not measure function of thin myelinated and unmyelinated axons
- Variability of repeated measurements for some of the methods is relatively high
- Routine methods measure only loss of neural function

Diagnostic difficulties

- Aging
  - Normal aging causes mild neuropathic changes
- Mononeuritis multiplex
- False positive diagnosis
  - Spinal stenosis in older subjects
  - Distal myophy
  - ALS
- False negative diagnosis
  - Mild sensory neuropathies
  - Thin fibre neuropathy