Neurophysiological testing in the diagnosis of polyneuropathies

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No disclosures

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Goals

- Have knowledge of the methods used in the diagnosis
- Understand different types of polyneuropathies
- Be able to characterize polyneuropathies

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Outline 1

- General aspects of polyneuropathy
  - Epidemiology
  - Pathophysiology
  - Types of PNP
  - Etiology
  - Significance

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Diagnosis

- Symptoms
- Clinical findings
- Neurography
- EMG
- QST (quantitative sensory thresholds)
- IENFD (intraepidermal nerve fiber density)
- Autonomic nerveous system testing
- Nerve excitability measurements
- Ultrasound

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Definition of polyneuropathy

- Generalized disorder of peripheral nerves
- Different types of axons may be involved,
  - Motor
  - Sensory
  - Autonomic
  - Large axons: motor and sensory
  - Thin axons: pain, temperature, autonomic
- Often distal nerves more affected than proximal
- Symmetric (not perfectly)

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EMG findings during one year Turku University Hospital

	Total		Men		Women	
	number	%	number	%	number	%
No abnormalities	2360	48.3	858	40.3	1502	54.4
Focal neuropathy	1931	39.5	907	42.7	1024	37.1
Polyneuropathy	443	9.1	285	13.4	158	5.7
Myopathy	78	1.6	34	1.6	44	1.6
Motorneuron dis.	32	0.7	34	1.8	28	1.0
Myasthenia	9	0.2	4	0.2	5	0.2
Spinal cord	2	<0.1	1	<0.1	1	<0.1
Other	2	<0.1	0	<0.1	2	<0.1
Total	4891		2129		2762	

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Causes of PNP

- Metabolic ja endocrine: Diabetes, uremia....
- Toxic: Drugs, solvents….
- Immune mediated: GBS, CIDP, MMN, MGUS....
- Genetic: Charcot-Marie-Tooth…....
- Infectious: HIV, Leprosy....
- Systemic diseases: Rheumatoid arthritis, collagenosis, myeloma
- Idiopathic: often a combination of causes
- **More than 300 different causes for PNP**

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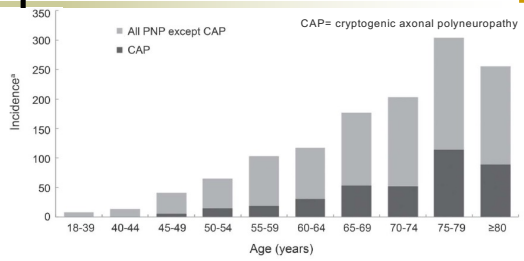
Age stratified incidence of PNP



Visser et al, Incidence of polyneuropathy in Utrecht, the Netherlands. Neurology 2015::84:259-

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Epidemiology of PNP

- 2.4% of the population have PNP
- 8 % of >65-year-olds have PNP
- Incidence in adults 80/100000 per year
  - Diabetes 32%
  - Cryptogenic axonal 24%
  - Toxic 14%
  - Immune mediated 9%
  - Hereditary 5%

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Affected types of axons

- Sensory and motor
  - Most PNPs
  - Diabetes
- Sensory
  - Platinum derivates, cisplatin
  - Paclitaxel
  - Pyridoxine
- Motor
  - Lead
  - Dapsone, drug used in dermatology
- Thin fiber
  - Fabry disease

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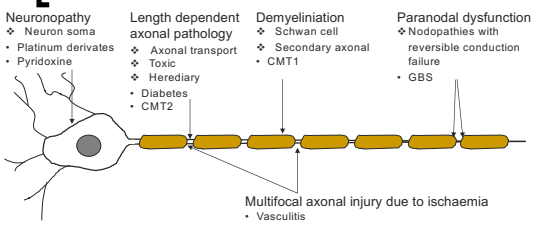
Pathophysiology of PNP



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Site of primary defect

- Neuronopathies
  - Primary events in the perikaryon
- Axonopathies
  - Central-peripheral axonopathy
  - Axon transport
  - Cumulative effect of pathology along the nerve
- Myelinopathies - demyelinating
- The precise site and mechanism is not always known
- Often a combination

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Patophysiology

- Axonal 85-90%
- Demyelinating 10-15%
  - Without conduction block (hereditary)
  - With conduction block (immune mediated)

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Polyneuropathy – time course

- Acute (days to weeks)
  - Guillan-Barré syndrome
  - Critical illness PNP
  - Polyarteritis nodosa
  - Toxic polyneuropathies
  - Porphyria
- Chronic (months to years)
  - CMT
  - CIDP
  - Diabetes
- Relapsing
  - Chronic inflammatory demyelinating PNP (CIDP)

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Distribution 1

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

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Distribution 2

- Upper limb predominant
  - Lead
  - Dapsone® (dermatitis herpetiformis, leprosy, toxoplasmosis)
- Complex distributions
  - Lepromatous leprosy (cold skin areas)
- Cranial nerve involvement
  - Miller-Fisher syndrome
  - Sjögren's syndrome
- Sensory ganglionopathy
  - All sensory nerves evenly affected
  - Platinum derivates, taxols, thalidomide…..
  - Pyridoxine PNP

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Multifocal neuropathy

- Multifocal mononeuropathies resemble a polyneuropathy when it progresses to involve multiple overlapping nerves
- In polyneuropathies there is susceptibility for focal neuropathies
  - Diabetes
  - Hereditary liability to pressure neuropathies

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Generation of symptoms

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

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Motor symptoms

- Loss of neural function
  - Weakness
- Increased abnormal neural function
  - Fasciculation
  - Myokymia, neuromyotonia
  - Muscle cramps

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Sensory symptoms

- Loss of neural function
  - Decreased sensation
    - Touch
    - Pain
    - Temperature
- Increased abnormal neural function
  - Paresthesia
  - Dysesthesia
  - Allodynia
  - Hyperesthesia

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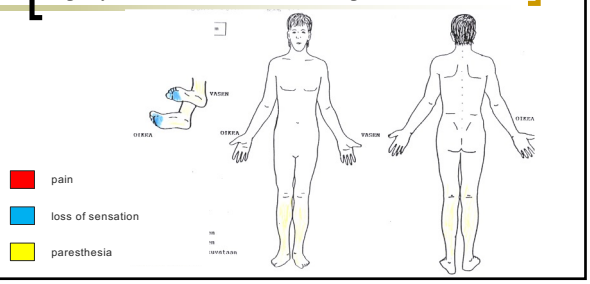
Symptom chart in a distal symmetric PNP



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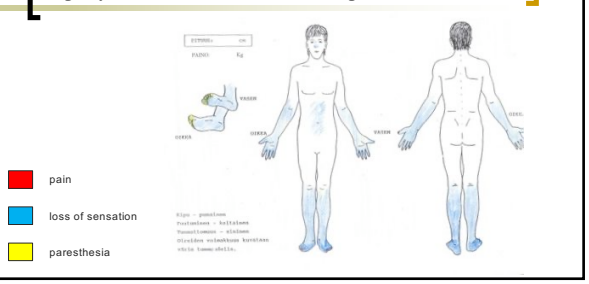
Symptom chart in a distal symmetric PNP



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Autonomic symptoms

- Loss of function
  - Loss of sweating
  - Horner's syndrome
  - Cardiovascular symptoms
    - Orthostatic hypotonia
  - Genitourinary function
    - Impotence
- Abnormal neural function
  - Cardiovascular symptoms (vagal overactivity)
  - Eating provokes sweating

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Importance of polyneuropathies

- Unpleasant sensation, pain – poor sleep quality
- Weakness
- Unstable gait, falls
- Impairment of daily activities
- Depression
- Elevated risk for dementia
- Increased mortality
- Reduced quality of life

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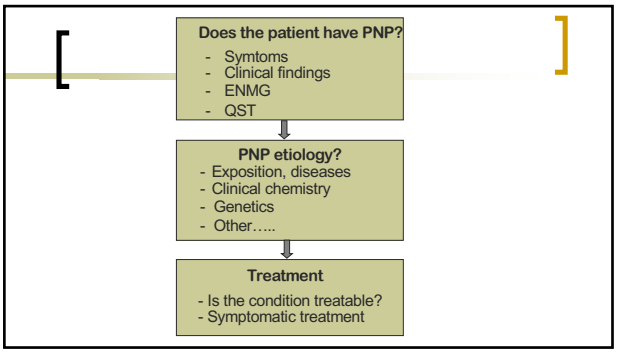

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Polyneuropathy – diagnostic criteria

- The diagnosis is not always simple
- Aging causes alterations in peripheral nerves
  - Reduced conduction velocity with age
  - Sensory amplitudes reduced with age
- How many abnormal findings are required??
- Cumulative effects of lifestyle and aging

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History

- Chronic disorders
  - Diabetes
  - Rheumatoid arthritis
- Time course
  - When did it start
  - Progression
- Distribution of symptoms
  - Distal, proxmal
  - Symmetry
  - Level (toes, ankle…hands..)

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History

- Type of sensory abnormality
  - Hypoestehesia
  - Pain
- Timing of maximum symptoms
  - PNP symptoms usually troubling at rest
  - Often alleviated by activity
- Weakness
- Autonomic symptoms
  - Lack of sweating
  - Impotence
  - Gastrointestinal symptoms
  - Orthostatic intolerance (hypotension)

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Sensory abnormalities

- **Hypoestesia** = Reduced sensation
- **Parestesia** = Numbness, tingling
- **Allodynia** = Normally painless sensation painful
- **Hyperestesia** = Increased sensation
- **Hypoalgesia** = Reduced pain sensation
- **Hyperalgesia** = Increased pain sensation
- **Dysestesia** = Altered sensation
- **Hyperpatia** = Stimulus causes an increased level and duration of pain

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Clinical findings

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

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Skeletal deformity

- Pes cavus
  - Charcot-Marie-Tooth (CMT)
  - Indicates onset in childhood
- Scoliosis
- Neuropathic joint deformity

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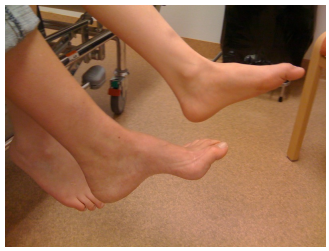
Pes cavus in CMT1A



Daughter

Mother

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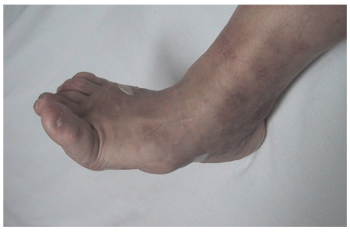
Neuropathic arthropathy (Charcot joint)



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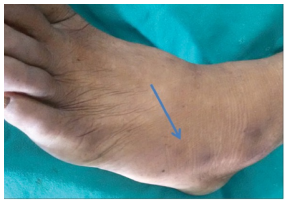
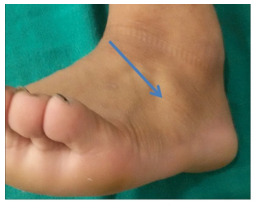
Muscle atrophy

Atrophy of extensor digitorum brevis



Normal



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Nerve thickening

- Amyloidosis
- Sometimes CMT 1A and CIDP
- Neurofibromatosis
- Lepromatous neuropathy
  - Greater auricular nerve
  - Supraclavicular nerves
  - Radial nerve at the wrist

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Monofilament

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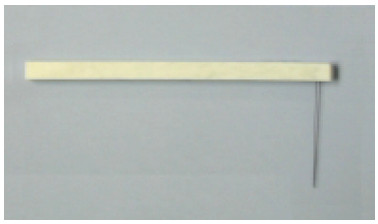
Monofilament (10 g)



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Monofilament testing

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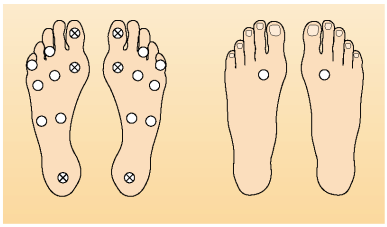
Monofilament test



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Semmers-Weinsten monofilament test

- 10 g filament
- 3 points, >=1 abnormal
  - For screening
- 10 points
  - Takes 1 minute per foot
  - > 3 abnormal points
  - Sensitivity 50%
  - Specificity 100%

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Neurography

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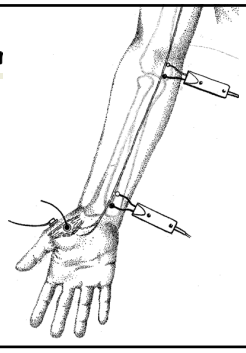
N. Medianus - motor



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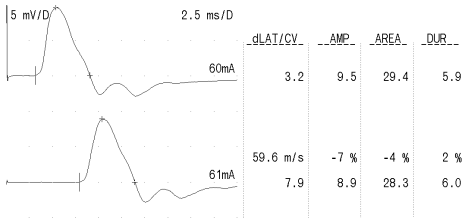
Normal median nerve motor



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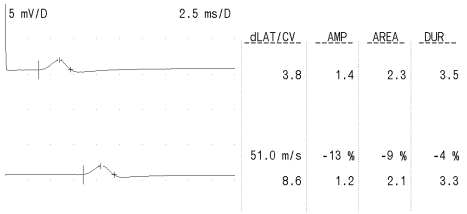
Axonal neuropathy



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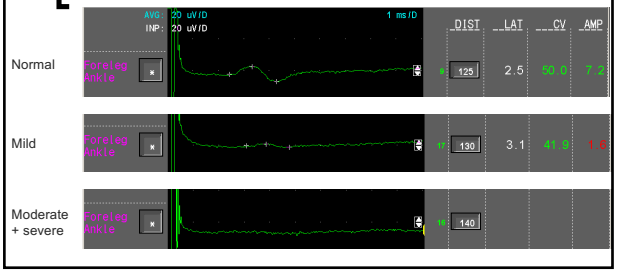
Sural nerve sensory – axonal neuropathy



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Axonal neuropathy

- Reduced motor and sensory amplitudes
- Conduction velocity normal or slightly reduced
  - Median nerve motor CV > 38 m/s
- Distal latency normal or slightly prolonged
- No decay
- Normal or slightly prolonged F latencies
- Reduced number of F waves

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Axonal PNPs

- Most polyneuropathies
- Diabetes
- Uremia
- CMT2
- Amyloidosis
- Renal insufficiency
- Many drug related PNPs
  - Vinca alcaloids
- B^{12} vitamin deficiency

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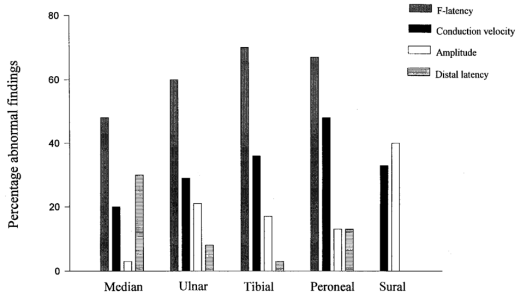

Andersen, Stålberg, Falck. F-wave latency, the most sensitive nerve conduction parameter in patients with diabetes mellitus. Muscle Nerve 1997:20:1296–1302

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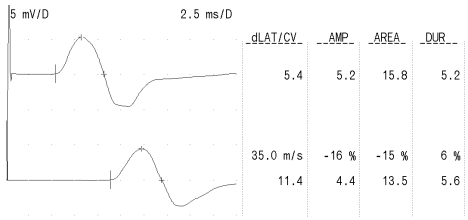
Demyelinating neuropathy



Median nerve in a patient with CMT1B

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Demyelinating neuropathy

- CV reduced >30%
  - median nerve CV < 38 m/s
- Motor nerve distal latency prolonged
- Normal or reduced amplitudes
- Often combined with secondary axonal involvement
- Moderately prolonged F latencies

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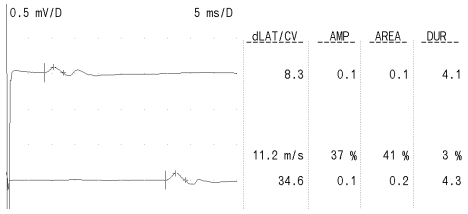
Demyelinating with secondary axonal involvement



CMT1A

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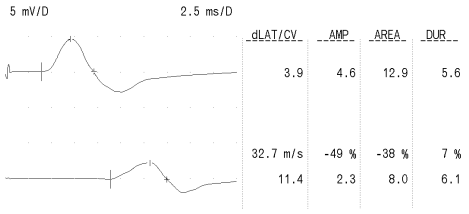
Conduction block



median nerve, multifocal motor neuropathy with conduction blocks

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Conduction block definition

- > 20% amplitude or area decay and < 15% dispersion
- >50% amplitude or area decay
- Both criteria are equally sensitive, latter more specific

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

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Practical criteria – 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**
- Tibial nerve sometimes difficult to interpret due to submaximal stimulation at the knee

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Demyelinating - no block

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

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PNP with conduction block

- Immune mediated
  - Acute inflammatory demyelinating polyneuropathy (AIDP)
  - Chronic inflammatory demyelinating polyneuropathy (CIDP)
  - Multifocal motor neuropathy with conduction blocks (MMN)
  - Many types of MGUS
  - Levis-Sumner syndrome (MADSAM)

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Nerves tested in PNP

- Motor
  - Peroneal nerve bilateral
  - Tibial nerve bilateral
  - Median nerve one side
- Sensory
  - Sural bilateral
  - Superficial peroneal bilateral
  - Radial unilateral

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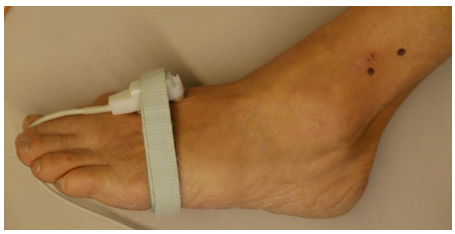
Superficial peroneal nerve



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Axonal PNP - Motor nerves

MOTOR NERVES:	Lat [ms]	SD	Amp [mV]	SD	CV [m/s]	SD	Amp% [%]	SD	F-M [ms]	SD
Right Medianus									25.2	0.5
Wrist - APB	3.2	-0.5	6.1	-0.9						
Ab Elb - Wrist	9.0		5.4		43.1	-4.1	-12	-1.2		
Right Ulnaris									29.3	3.5
Wrist - ADM	2.5	-1.3	5.5	-1.4						
Be Elb - Wrist	7.4		5.8		49.0	-2.4	4	2.6		
Ab Elb - Be Elb	9.7		5.5		43.5	-2.4	-4	0.1		
Left Tibialis									--	
Ankle - AHB	9.8	6.6	0.1	-2.0						
Knee - Ankle	19.9		0.1		42.6	0.0	67	6.2		
Right Tibialis									55.3	5.7
Ankle - AHB	7.8	3.9	0.2	-1.9						
Knee - Ankle	18.5		0.2		41.6	-0.2	14	2.7		
Left Peroneus									61.7	5.2
Ankle - EDB	4.8	0.4	0.3	-2.4						
Be knee - Ankle	13.5		0.3		34.5	-2.5	9	1.6		
Right Peroneus									--	
Ankle - EDB	5.2	0.9	0.6	-2.2						
Be knee - Ankle	13.5		0.5		37.3	-1.7	-14	-0.7		

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Axonal PNP - Sensory nerves

SENSORY NERVES:	Lat [ms]	SD	Amp [uV]	SD	CV [m/s]	SD	Amp% [%]	SD
Right Medianus								
Palm - Wrist	1.42		16	-2.1	49.3	-1.2		
Dig III - Wrist	2.6		3.8	-0.8	48.1	-1.1		
Dig IV - Wrist	2.9		1.2	-3.4	44.8	-2.3		
Right Ulnaris								
Palm - Wrist	1.35		5.8	-1.3	48.1	-1.8		
Dig IV - Wrist	2.3		0.8	-2.7	50.0	-1.9		
Dig V - Wrist	1.73		3.0	-0.2	54.9	-0.4		
Right Radialis								
Forearm - 10D 1	2.5		7.4	-1.5	56.0	-0.9		
Left Peroneus super								
Foreleg - Ankle	--		--		--			
Right Peroneus super								
Foreleg - Ankle	--		--		--			
Left Suralis								
Foreleg - Ankle	--		--		--			
Right Suralis								
Foreleg - Ankle	--		--		--			

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Neurography PNP

- 40-50 measured parameteres
- Statistical evaluation
- Common sense
- Overdiagnosis should be avoided
  - *"If in doubt say no"*
  - *"If in doubt say so"*

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Using Z-score to predict abnormality

	% of population observed	
Z-score	one-tailed	two-tailed
1	15,87	13,36
2	**2,28**	4,55
2,5	0,62	1,24
3	0,13	0,27

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Probability of Z score > 2 or < -2

number of tests	number of abnormal findings (> 2 sd)			
	1	2	3	5
1	0,023			
2	0,045	0,001		
5	0,110	0,005	0,000	0,000
10	**0,208**	0,021	0,001	0,000
25	0,441	**0,112**	0,019	0,000
50	0,688	0,320	**0,108**	0,006

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Neurography in PNP

- 3 or more abnormal parameters
- In classic distal axonal neuropathy abnormalities mainly in leg nerves
- In axonal PNP median nerve CV > 38 m/s
- In demyelinating PNP median nerve < 38 m/s
- Specific criteria for different types of GBS

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What is needed

- Composite score of all neurography results
  - Amplitude - axonal involvement
  - Conduction velocity - myelin function
  - Conduction block/failure nodal/myelin function/
- Mahalanobis distance

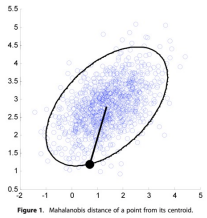

Figure 1. Mahalanobis distance of a point from its centroid.

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Interpretation of findings

- Number of tests performed
- Magnitude of abnormality
- Clinical situation
- Pattern of abnormal findings

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EMG

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EMG

- Optional
  - Not necessary for confirmation of a suspected PNP
- Provide information about involvement of motor nerves
- Distribution
  - Distal > proximal
  - Symmetry
- Time course
  - Fibrillation potentials
  - MUP abnormalities
- Differential diagnosis
  - Spinal stenosis in lumbar region

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Axonal sensory-motor PNP severity grading

	Mild	Moderate	Severe	Very severe
Per.sup sensory	abnormal	no response	no response	no response
Sural sensory	normal/slight	no response	no response	no response
Radial sensory	normal	normal/slight	moderate	no response
Peroneal motor	slight/normal	moderate	no response	no response
Tibial motor	slight/normal	moderate	no response	no response
Median motor	normal	slight	moderte/severe	no response
EMG tib ant	normal	slight	moderate/severe	total
EMG vast lat	normal	normal	slight	moderate/severe

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Quantitative sensory thresholds (QST)

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Quantitative sensory thresholds (QST)

- Sensory pathways from receptors, nerve terminals to cortex
- Quantify sensory deficit
- Information of Aβ, Aδ and C fiber function

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QST — advantages

- Quick
  - Method of limits
- Non-invasive
- Hypo-phenomena
- Hyper-phenomena may be quantified
  - Hyperalgesia
  - Hyperesthesia

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QST — disadvantages

- Dependent on patient co-operation
- Quiet environment - no distractions
- Do not define the level of disturbance
  - Abnormalities may be caused peripheral or central disorders

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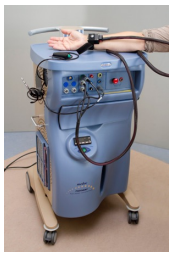
Equipment



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Thermode

- Peltier-element
- Large thermode
  - 50 x 25 mm
  - Hand, foot
- Small thermode
  - 10*10 mm
  - Face, tongue

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QST - Comparison of algorithms

- **Method of limits**
  - Increasing stimulus until subject perceives stimulus
  - Reaction time, cognitive capacity and motor performance included
  - Higher than real thresholds
- **Forced choice**
  - Patient has to tell does he feel stimulus or not
  - Accurate
  - Time consuming, especially if threshold is abnormal
  - Non-compliance (boredom, fatigue)
  - Not practical

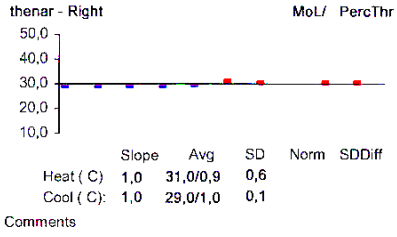
80

Proctocol QST

- **Vibratory (VDT)**
- **Thermal**
  - **Cold (CDT)**
  - **Warm (WDT)**
- Heat-pain (PDT)
- Method of limits, 5 repeated ascending series with linear ramps

81

QST measurement - hand



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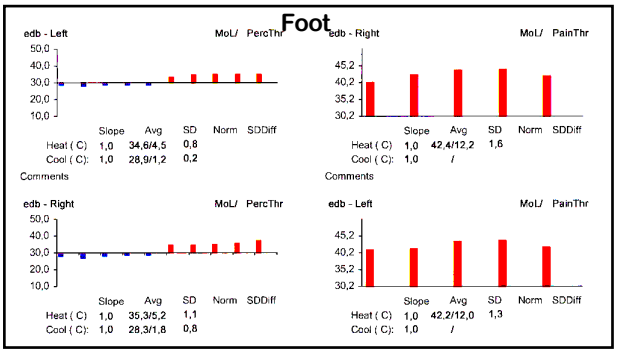

84

Indication for QST

- Suspicion of thin fiber neuropathy
  - Unpleasant neuropathic symptoms
  - Normal neurography
- Quantification of thin fiber function

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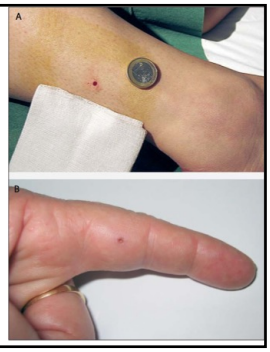
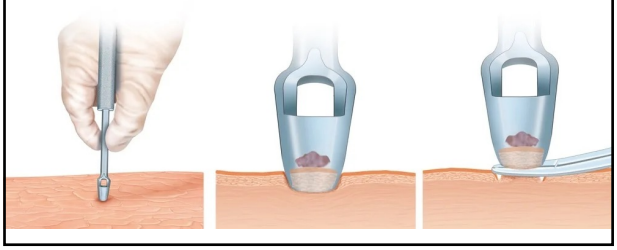
Punch biopsy of skin



88

Punch biopsy



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Method

- 3 mm punch biopsy from skin
  - Distal leg: 10 cm above lateral malleolus
  - Proximal thigh: 20 mm below iliac spine
- 50 µm sections
- Stained with pan-axonal marker
  - PGP 9.5 (protein gene product)
- Intraepidermal axon density calculated

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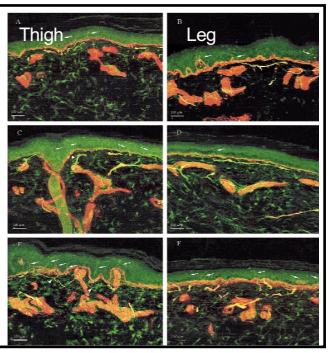
Ganglionopathy

Distal PNP

Control



Muscle Nerve **24:** 1034–1039, 2001

94

Indication for IENFD

- Combined with QST
- Objective
- In thin fiber neuropathy IENFD and QST should be similar

95

Sympathetic skin response - SSR

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SSR - Physiology

- Sweat glands have sympathetic cholinergic innervation
  - SSR can be abolished with atropine
  - Botulinum toxin can be used for hyperhidrosis
- Psychogenic sweating has considerable CNS representation
- The spontaneous fluctuations in the skin of the limbs is synchronous

98

SSR - physiology

- Negative offset during secretion of sweat
- The positive offset during reabsorption of sweat
- SSR is the sum of these two stages

99

SSR – Recording environment

- Quiet, warm and dimmed room
- Limb temperature 30 C
- 10 min rest before recording
- 30 sec rest between stimuli
- 3-5 repeated recordings

101

SSR - Recording

- Filter settings **0,2 Hz** - 50 Hz
- Time window 5 - 10 sec
- Gain 100 - 500 µV/div

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SSR - recording

- Ag/AgCl plate electrodes or disposable electrodes
- Good cleaning of the skin
  - Active electrode
    - Palm of the hand
    - Sole of the foot
  - Reference electrode
    - Dorsum of the hand
    - Dorsum of the foot

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SSR - stimulation

- Electric shock
  - stimulus duration 0,5 ms
  - stimulus intensity 10 - 20 mA
  - Should be unpleasant
- Sudden sound
- Touch
- Immersion of face or hand into cold water
- Deep inhalation

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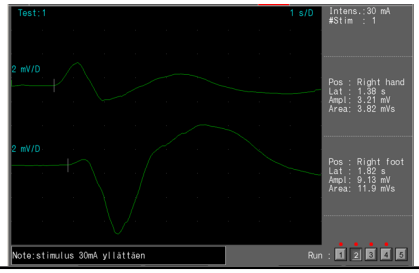
Normal finding – electric shock



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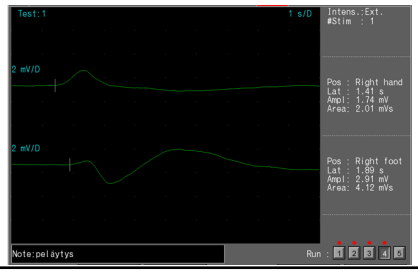
Normal finding – loud sound



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SSR – reference values

		normal	abnormal
latency	hand	1,5 sec	> 2,0 sec
	foot	2,0 sec	> 3,0 sec
ampl	hand	500 uV	
	foot	100 uV	

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SSR – reference values

- Large interindividual variability
- Large intraindividual variability to different stimuli
- Always obtainable in subjects < 60 years
- Only missing response abnormal with certainty
- Repeated prolonged latency (unusual)
- Reduced amplitude
- Marked side difference

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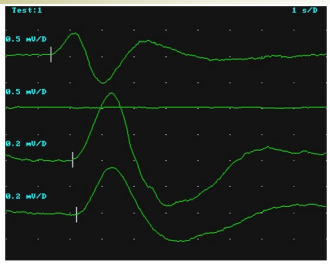
SSR – left sided brachial plexopathy



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Heart rate variation (HRV)

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Heart rate variability (HRV)

- Vagal stimulation – decreased heart rate
- Sympathetic stimulation – increased heart rate

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HRV

- ”Beat to beat” variation
- Short recordings (1-5min)
- Long recordings (24h ambulatory)

113

HRV testing

- 15 min of rest before study
- Quiet room
- Sinus rythm
  - Automatic and manual control of ectopic beats
- If there is no sinus rythm, analysis cannot be made

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Time-domain measures

Statistical measures

- Mean RR interval duration
- Standard deviation of RR (SDNN)
- Difference betveen longest and shortest interval
- RR4 = (RRmax - RRmin) X lOO/RRmean

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Vagal provocation

- Deep breathing 6/min
  - 5 sec inspiration and 5 sec expiration
- Carotic massage
- Diving reflex
  - Immersion of face in cold water
  - Ice pack over face and no breathing for 30 sec
  - HR decreases

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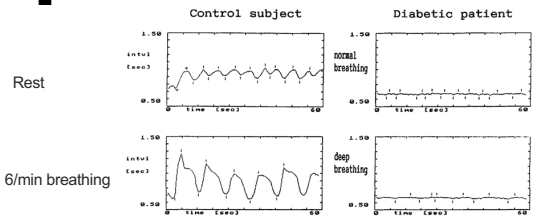
HRV at rest and 6/min breathing



E. Stålberg and M. Nogues. Automatic analysis of heart rate variation 1. Method and reference values in heathy controls. Muscle & Nerve 1989:12:993-1000 1989

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Sympathetic provocation tests

- Mental
  - Arithmetic tasks, reaction time
  - HR, BP
- Hand grip
  - 30% of maximal strength 3 min.
  - BP, HR
  - Normal diastolic BP increase > 16 mmHg

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Provocation tests

- Mixed sympathetic and parasympathetic
  - Valsalva
  - Tilt
  - Stand up
  - Cold-pressor

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Nerve biopsy

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Nerve biopsy

- Often fascicular biopsies from the sural nerve
- Limited utility in the diagnosis of PNP
- May be helpful in the diagnosis of etiology
  - Vasculitic neuropathy

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Motor nerve excitability testing

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Research paper

The additional diagnostic value of motor nerve excitability testing in chronic axonal neuropathy

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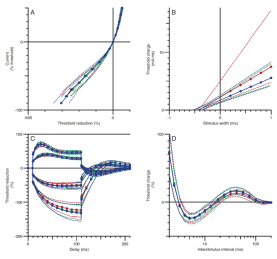
Motor nerve exctibility testing



Red - PNP

Blue - Controls

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Motor nerve exctibility testing (NET)

- Significance: Motor NET does not seem to offer any additional diagnostic value in chronic mixed etiology neuropathy.

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Ultrasound

127

Muscle Nerve 2018:57: 716–728

NERVE ULTRASOUND IN POLYNEUROPATHIES

JOHAN A. TELLEMAN, MD [1,3] ALEXANDER GRIMM, MD,[2] STEPHAN GOEDEE, MD,[3] LEO H. VISSER, MD,[1] and CRAIG M. ZAIDMAN, MD[4]

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Accepted 30 November 2017

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Sonographic parameters measured

- Caliber - Enlargement of nerves
  - Diffuse
  - Regional
- Fascicle size
- Fascicle echogenicity
  - Increased
  - Decreased
- Vascularization
  - Increased

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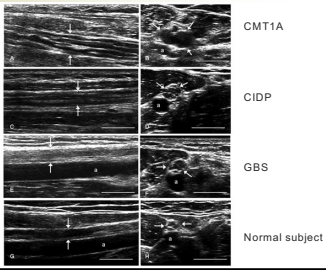
Diffuse enlargement



Telleman et al. Nerve ultrasound in polyneuropathies. Muscle Nerve 57: 716–728, 2018

130

Ultrasound enlargement of nerves

- Diffuse
  - GBS
  - CIDP
  - CMT1A
  - CMTX
  - Amyloidosis
- Regional
  - CIDP
  - MMN
  - MADSAM
  - Leprosy
  - HNPP (at compression sites)

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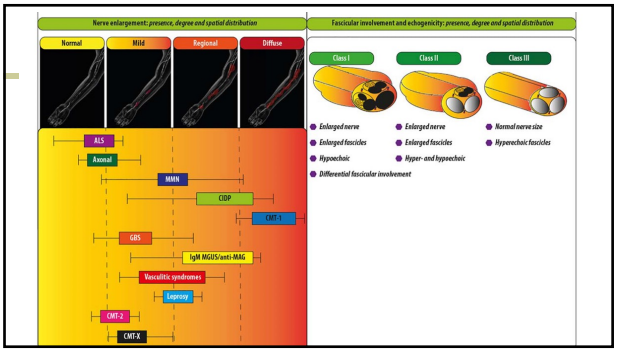

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Summary - Characterization of findings

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Characterization of a PNP 1

- Severity
  - Mild
  - Moderate
  - Severe
- Pathophysiology
  - Axonal
  - Demyelinating (with or without conduction blocks)
  - Types of axons (sensory, motor, thin fiber)

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Characterization of a PNP 2

- Distribution
  - Distal > proximal
  - Proximal > distal
  - Proximal = distal
  - Random
- Time course
  - Acute
  - Chronic
  - Inactive

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Examples of characterization

- Mild, chronic, symmetric, distal sensory-motor-autonomic axonal polyneuropathy (diabetes)
- Moderate acute, demyelinating, distal sensory-motor polyneuropathy with conduction blocks (GBS)

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Timing of electrodiagnosis

- In acute PNP testing on day one!!!
  - 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)

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Role of neurophysiological tests

- Diagnose PNP
- Characterize PNP – helps to find etiology
- Prognosis
- Follow-up

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Strengths of neurophysiological testing

- Objective and reliable diagnosis of PNP
- Guides the diagnostic etiological evaluation
- Quantitative
- Sensitive
- Most methods are non-invasive
- Cost is relatively low

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Weaknesses

- ENG and EMG do not measure function of thin myelinated and unmyelinated axons
- Variability of repeated measurements for some of the methods is relatively high
  - Neurography amplitudes
  - QST
- Routine methods measure only loss of neural function
  - Unpleasant sensations due to altered neuronal activity

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Diagnostic difficulties

- **Aging**
  - **Normal aging causes mild neuropathic changes**
- Mononeuritis multiplex
  - Later stages
- False positive diagnosis
  - Spinal stenosis in older subjects
- False negative diagnosis
  - Mild sensory neuropathies
  - Thin fiber neuropathy

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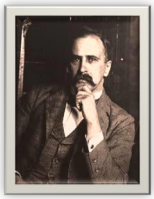
William Osler 1849-1919



"Medicine is a science of uncertainty and an art of probability."

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