Neurophysiological testing in the diagnosis of polyneuropathies

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Outline

- General aspects of polyneuropathy
  - Epidemiology
  - Pathophysiology
  - Types of PNP
  - Etiology
- Diagnosis
  - Symptoms
  - Clinical findings
  - Neurography and EMG
  - QST
  - IENFD

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Definition of polyneuropathy

- Generalized disorder of peripheral nerves
- Different types of axons be involved,
  - Motor
  - Sensory – think fibers
  - Autonomic
- Distal nerves often more affected than proximal
- Symmetric (not perfectly)

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EMG findings 2007 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
  - CMT...
- Infectious
  - HIV, Leprosy....
- More than 300 different causes for PNP

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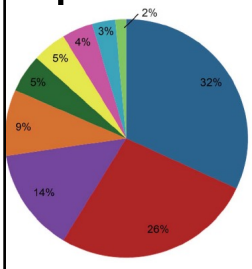
Visser et al, Incidence of polyneuropathy in Utrecht, the Netherlands. Neurology 2015::84:259-

Distribution of causes of PNP



	Mean age (±SD)[a]	% Men[b]
Diabetic polyneuropathy	66.4 (±12.3)	60
Cryptogenic axonal polyneuropathy	70.5 (±11.1)	54
Toxic polyneuropathy[c]	62.0 (±9.7)[d]	66
Immune-mediated polyneuropathy[e]	55.5 (±18.1)[d]	76
Hereditary polyneuropathy	54.9 (±14.9)[d]	59
Polyneuropathy with systemic disease[f]	68.3 (±13.9)	38
Metabolic polyneuropathy[g]	69.8 (±11.7)	54
Polyneuropathy with vitamin B_{12} deficiency[h]	67.9 (±14.9)	58
Idiopathic small fiber neuropathy	53.4 (±9.8)	20

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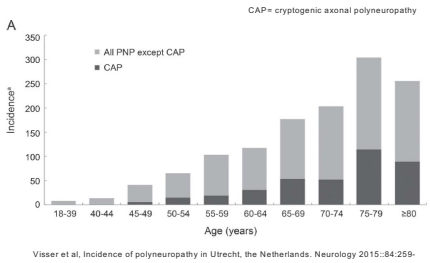
Age stratified incidence of PNP



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

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Journal of the Peripheral Nervous system 2112:17:43-

Idiopathic neuropathy: new paradigms, new promise

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Abstract Idiopathic neuropathy, now designated as chronic idiopathic axonal polyneuropathy (CIAP), is a major public health problem in the United States. The disorder affects an estimated 5–8 million Americans, comprising about one-third of patients with neuropathy, based on data from referral centers. Typically, patients develop symptoms in the sixth decade or older. The onset is insidious, with numbness, paresthesias, and pain appearing over months to years. Although strength is generally preserved, the sensory loss and pain can be disabling. The clinical approach to this condition has evolved in important ways over the years, enabling improved diagnosis and characterization of this population. Current work has focused on identifying modifiable risk factors that may be associated with idiopathic neuropathy. The results may suggest that an underlying mechanism such as oxidative stress contributes to the development of CIAP.

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Chronic idiopathic axonal polyneuropathy (CIAP)

- In 30% of PNP patients no definite etiology is found
- Typically, onset 50-60 years
- Sensory > motor, all sensory modalities affected
- Axonal
- Distal, symmetric
- Usually no weakness
- Slow progression

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Chronic idiopathic axonal polyneuropathy

- Risk factors
  - Hypertension
  - Dyslipidemia
  - Obesity
  - Obstructive sleep apnea syndrome
- Etiology
  - Age
  - Oxidative stress

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Epidemiology of PNP

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

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Affected types of axons

- Sensory and motor, usually including thin fibre
  - Most PNPs
  - Diabetes
- Sensory
  - Pyridoxine
  - Platinum derivates, cisplatin
  - Paclitaxel
- Motor
  - Lead
  - Dapsone
- Thin fibre
  - Fabry disease

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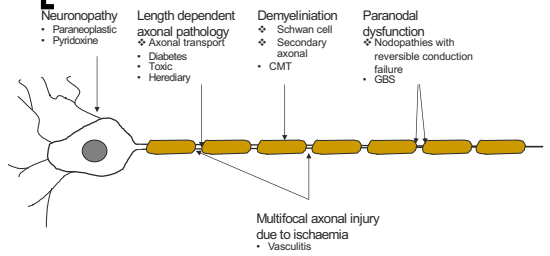
Pathophysiology of PNP



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Site of primary defect

- Axonopathies
  - Central-peripheral axonopathy
  - Axon transport
  - Cumulative effect of pathology along the nerve
- Neuronopathies
  - Primary events in the perikaryon
- 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 polyradiculitis

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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
  - Borreliosis (bilateral facial palsy) (+polyradicultisi)
  - Sjögren's syndrome
- Sensory ganglionopathy
  - All sensory nerves evenly affected
  - Pyridoxine PNP
  - Platinum derivates, taxols, thalidomide…..

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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
  - Muscle cramps

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Sensory symptoms

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

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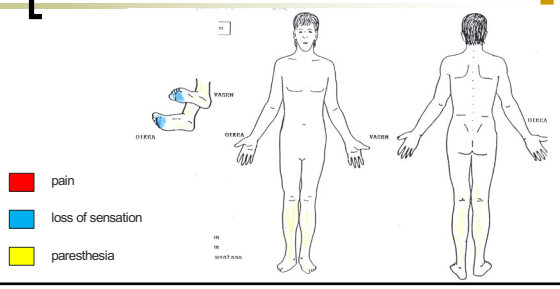
Symptom chart in a distal symmetric PNP



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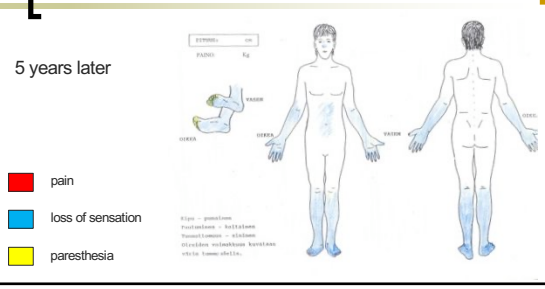
Symptom chart in a distal symmetric PNP

5 years later



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Autonomic symptoms

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

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Importance of polyneuropathies

- Unstable gait, falls
- Unpleasant sensation, pain
- Weakness
- Impairment of daily activities
- Autonomic nervous system dysfunction
- Depression
- Increased mortality

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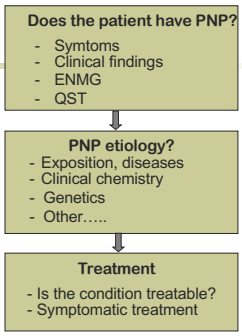

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Polyneuropathy – diagnostic criteria

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

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Methods

- History
- Clinical examination
- Neurography
- Quantitative sensory thresholds (QST)
  - Vibration sensation thresholds
  - Thermal sensation thresholds
  - Pain sensation thresholds
- EMG
- Tests of the autonomic nervous system
- Intraepidermal axon density
- Imaging
- Nerve biopsy

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History

- Chronic underlying 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 troubling at rest
  - Often alleviated by activity
- Weakness
- Autonomic symptoms
  - Impotence
  - Orthostatic intolerance (hypotension)
  - Lack of sweating
  - Gastrointestinal symptoms

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Sensory abnormalities

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

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Clinical findings

- Decreased tendon reflexes
- Decreased/altered sensation
  - Vibration
  - Pain
  - Temperature
- Loss of muscle strength
- Muscle atrophy
- 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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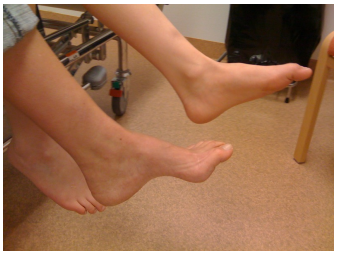
Pes cavus in CMT1A



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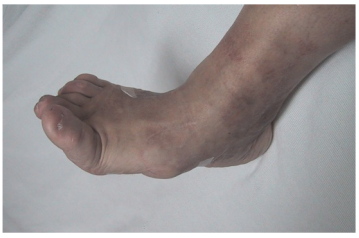
Neuropathic arthropathy (Charcot joint)



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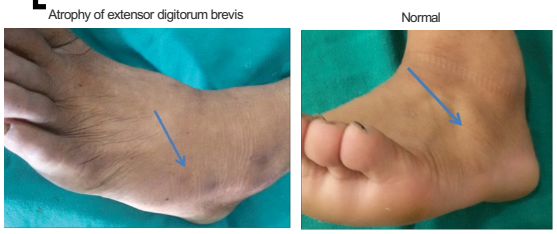
Muscle atrophy



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Nerve thickening

- Amyloidosis
- Sometimes CMT 1 and CMT2
- Neurofibromatosis
- Lepromatous neuropathy
  - Greater auricular nerve
  - Supraclavicular nerves
  - Radial nerve at the wrist

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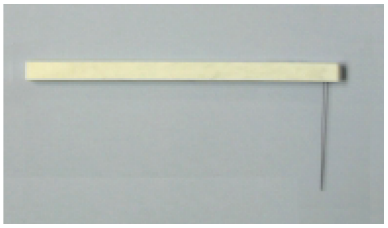
Monofilament (10 g)



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Monofilament testing

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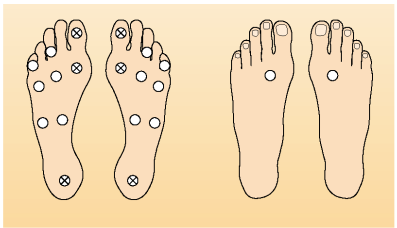
Monofilament test



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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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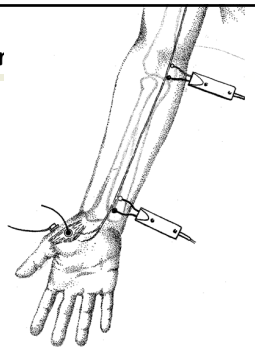
N. Medianus - motor



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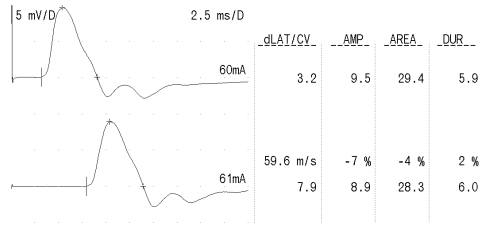
Normal median nerve motor



	dLAT/CV	AMP	AREA	DUR
	3.2	9.5	29.4	5.9
	59.6 m/s	-7 %	-4 %	2 %
	7.9	8.9	28.3	6.0

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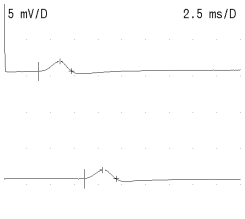
Axonal neuropathy



	dLAT/CV	AMP	AREA	DUR
	3.8	1.4	2.3	3.5
	51.0 m/s	-13 %	-9 %	-4 %
	8.6	1.2	2.1	3.3

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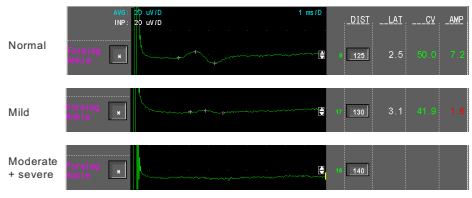
Sural nerve sensory – axonal neuropathy



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Axonal neuropathy

- Reduced motor and sensory amplitudes
- Conduction velocity normal or slightly reduced
  - median motor > 38 m/s
- Distal latency normal or slightly prolonged
- No decay

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Axonal PNPs

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

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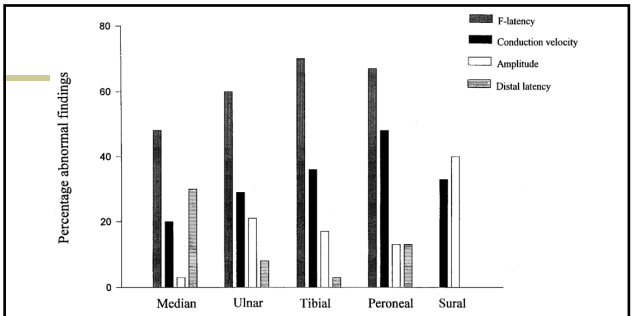

Andersen, Stålberg, Falck. F-wave latency, the most sensitive nerve conduction parameter in patients with diabetes mellitus. Muscle Nerve 1997:20:1296–1302

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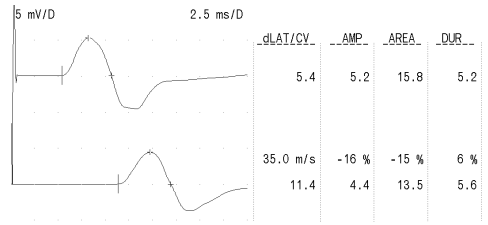
Demyelinating neuropathy



Median nerve in a patient with CMT1B

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Demyelinating neuropathy

- CV reduced >30%
  - median nerve CV < 38 m/s
- Median nerve distal latency > 7 ms
- Normal or reduced amplitudes

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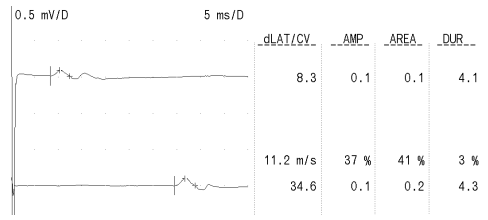
Demyelinating with secondary axonal involvement



CMT1A

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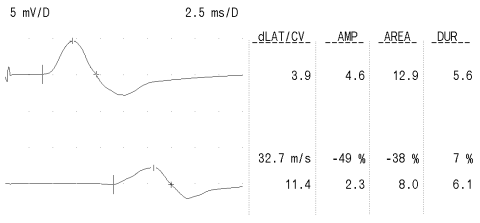
Conduction block



median nerve, multifocal motor neuropathy with conduction blocks

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Conduction block definition

- > 20% amplitude or area decay and 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

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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

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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

- Aquired - 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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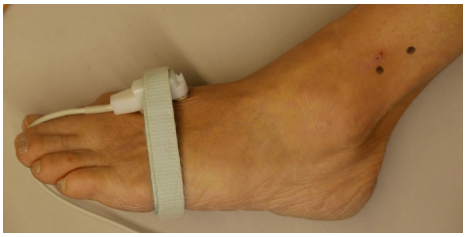
Superficial peroneal nerve



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Neurography PNP

- 40-50 measured parameteres
- Statistical evaluation
- Common sense
- Overdiagnosis should be avoided
  - *"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 are 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

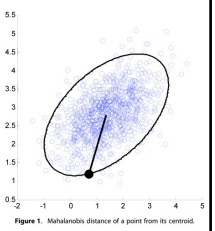

Figure 1. Mahalanobis distance of a point from its centroid.

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Interpretation of findings

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

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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									65.3	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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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 - IOD 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	--		--		--			

70

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

72

PNP severity

	Mild	Moderate	Severe	Very severe
Per.sup sensory	abnormal	no response	no response	no response
Sural sensory	normal/slight	no response/severe	no response	no response
Radial sensory	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

75

QST — advantages

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

76

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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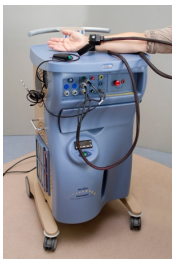
Equipment – Medoc Pathway



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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

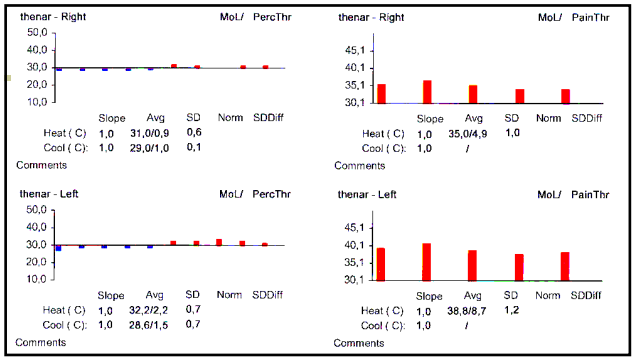
- **Method of limits**
  - Increasing stimulus until subject perceives stimulus
  - 'Reaction time, cognitive capacity and motor performance included
  - Higher than real thresholds
- **Forced choice**
  - Patient has to tell does he feel stimulus or not
  - Accurate
  - Time consuming, especially if 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



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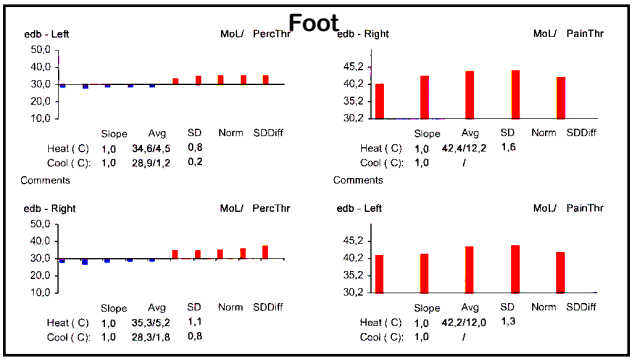
Foot



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QST in clinical practice

- Inter-session variability
  - 50% to 200 %
- Clinical trials
  - Inter-examiner differences
- Pain threshold measurements
  - Method of limits is recommended

84

Indication for QST

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

85

Intraepidermal nerve fiber density (IENFD)

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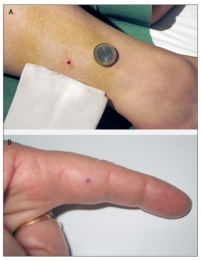
Punch biopsy of skin



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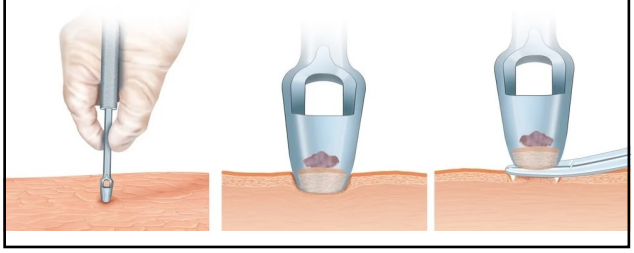
Punch biopsy



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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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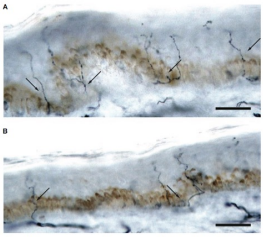
Control subject

Thigh

Leg



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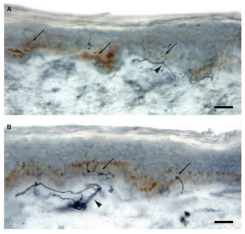
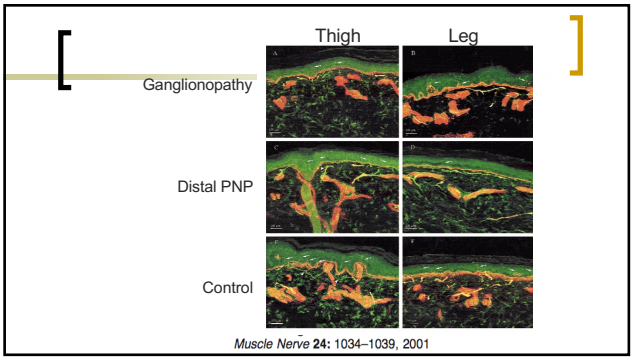
Diabetic thin fiber neuropathy



Thigh

Leg

91



Muscle Nerve **24:** 1034–1039, 2001

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Indication for IENFD

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

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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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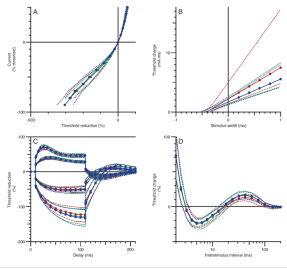
Motor nerve exctibility testing (NET)



Red - PNP

Blue - Controls

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Motor nerve exctibility testing

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

98

Sympathetic skin response - SSR

99

SSR - Physiology

- Electric response from the skin due to activation of the sympathetic nervous system
- Closely associated with sweating
  - Emotional sweating
  - Change in the potassium permeability of sweat glands
- Part of the orienting response

100

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

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SSR - physiology

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

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SSR - Anatomy

- Stimulus ⇨ afferent pathway (peripheral nerve and spinal cord) ⇨ Posterior hypothalamus ⇨ ventrolateral medulla (RAS) ⇨ Spinal cord (lateral column) ⇨ preganglionary sudomotor neurons (intermediolateral column) ⇨ preganglionic axons to sympathetic ganglions ⇨ synapses to cholinergic postganglionic neurons (unmyelinated axons; CV 0.5-2 m/s)
- Skin vasoconstriction is mediated over other pathways
  - Vasoconstriction changes SSR

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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

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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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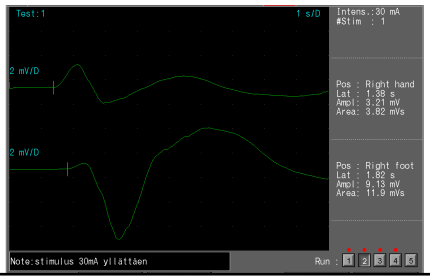
Normal finding – electric shock



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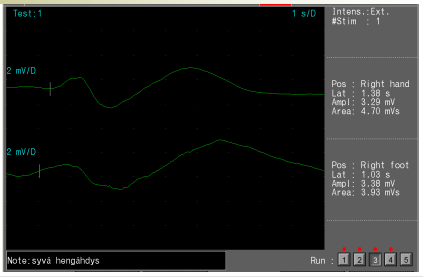
Normal finding – inhalation



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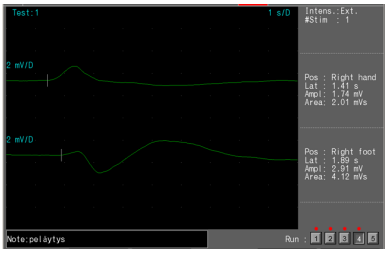
Normal finding – loud sound



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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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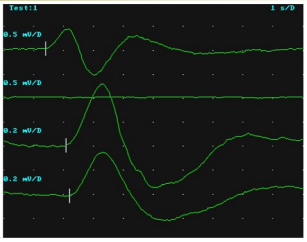
SSR – left sided plexopathy



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Heart rate variation (HRV)

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Heart rate variability (HRV)

- Vagal activity – low heart rate
- Sympathetic stimulation – increased heart rate

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HRV

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

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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

117

Time-domain measures

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

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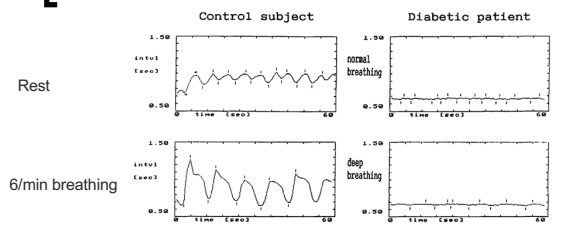
HRV at rest and 6/min breathing



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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Vagal provocation

- Deep breathing 6/min
  - 5 sec inspiration and 5 sec expiration
- Carotic massage
- Diving reflex
  - Imnmersion of face in water
  - Ice pack over face and no breathing for 30 sec
  - HR decreases 70->45

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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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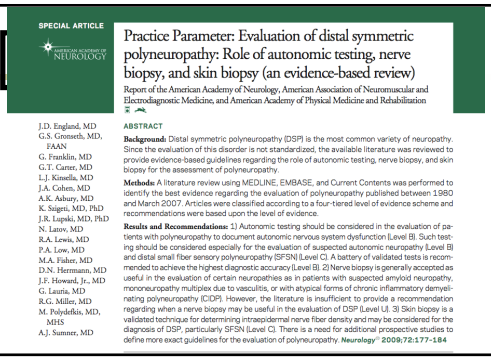

SPECIAL ARTICLE

Practice Parameter: Evaluation of distal symmetric polyneuropathy: Role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review)

Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation

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A.J. Sumner, MD

ABSTRACT

Background: Distal symmetric polyneuropathy (DSP) is the most common variety of neuropathy. Since the evaluation of this disorder is not standardized, the available literature was reviewed to provide evidence-based guidelines regarding the role of autonomic testing, nerve biopsy, and skin biopsy for the assessment of polyneuropathy.

Methods: A literature review using MEDLINE, EMBASE, and Current Contents was performed to identify the best evidence regarding the evaluation of polyneuropathy published between 1980 and March 2007. Articles were classified according to a four-tiered level of evidence scheme and recommendations were based upon the level of evidence.

Results and Recommendations: 1) Autonomic testing should be considered in the evaluation of patients with polyneuropathy to document autonomic nervous system dysfunction (Level B). Such testing should be considered especially for the evaluation of suspected autonomic neuropathy (Level B) and distal small fiber sensory polyneuropathy (SFSN) (Level C). A battery of validated tests is recommended to achieve the highest diagnostic accuracy (Level B). 2) Nerve biopsy is generally accepted as useful in the evaluation of certain neuropathies as in patients with suspected amyloid neuropathy, mononeuropathy multiplex due to vasculitis, or with atypical forms of chronic inflammatory demyelinating polyneuropathy (CIDP). However, the literature is insufficient to provide a recommendation regarding when a nerve biopsy may be useful in the evaluation of DSP (Level U). 3) Skin biopsy is a validated technique for determining intraepidermal nerve fiber density and may be considered for the diagnosis of DSP, particularly SFSN (Level C). There is a need for additional prospective studies to define more exact guidelines for the evaluation of polyneuropathy. *Neurology*® 2009;72:177–184

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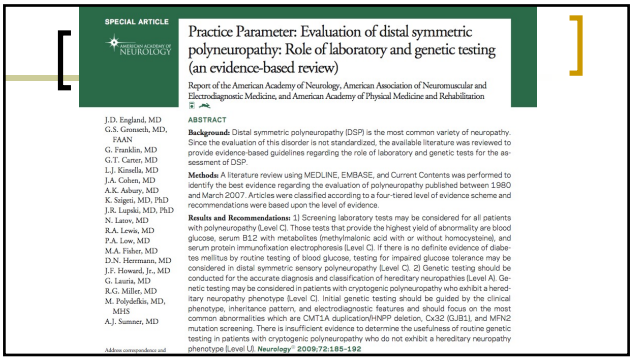

SPECIAL ARTICLE

NEUROLOGY

Practice Parameter: Evaluation of distal symmetric polyneuropathy: Role of laboratory and genetic testing (an evidence-based review)

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Results and Recommendations: 1) Screening laboratory tests may be considered for all patients with polyneuropathy (Level C). Those tests that provide the highest yield of abnormality are blood glucose, serum B12 with metabolites (methylmalonic acid with or without homocysteine), and serum protein immunofixation electrophoresis (Level C). If there is no definite evidence of diabetes mellitus by routine testing of blood glucose, testing for impaired glucose tolerance may be considered in distal symmetric sensory polyneuropathy (Level C). 2) Genetic testing should be conducted for the accurate diagnosis and classification of hereditary neuropathies (Level A). Genetic testing may be considered in patients with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype (Level C). Initial genetic testing should be guided by the clinical phenotype, inheritance pattern, and electrodiagnostic features and should focus on the most common abnormalities which are CMT1A duplication/HNPP deletion, Cx32 (GJB1), and MFN2 mutation screening. There is insufficient evidence to determine the usefulness of routine genetic testing in patients with cryptogenic polyneuropathy who do not exhibit a hereditary neuropathy phenotype (Level U). **Neurology® 2009;72:185–192**

Address correspondence and

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Characterization of a PNP

- Pathophysiology
  - Axonal
  - Demyelinating (with or without conduction blocks)
  - Types of axons (sensory, motor, thin fiber)
- Severity
  - Mild
  - Moderate
  - Severe
- Distribution
  - Distal>proximal
  - Proximal > distal
  - Proximal=distal
  - Random
- Time course
  - Acute
  - Chronic

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Examples of characterization

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

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Timing of electrodiagnosis

- In acute PNP 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
- Prognosis
- Follow-up

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Strengths

- 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 increased neuronal activity

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Diagnostic difficulties

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

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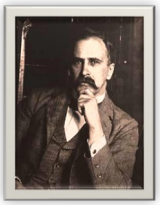
William Osler 1849-1919



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

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