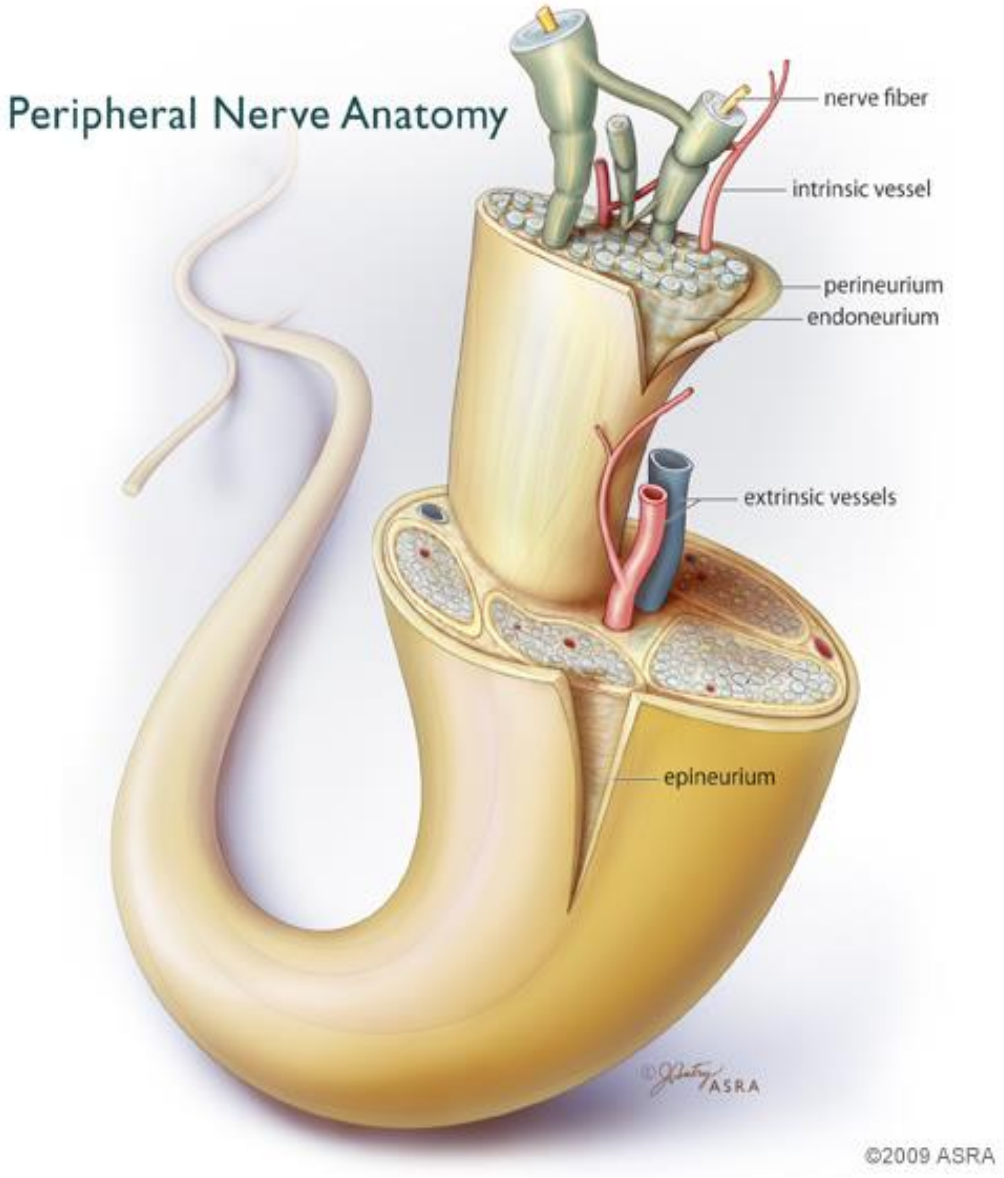


Seminari specializzandi 2016

Neuropatie Periferiche

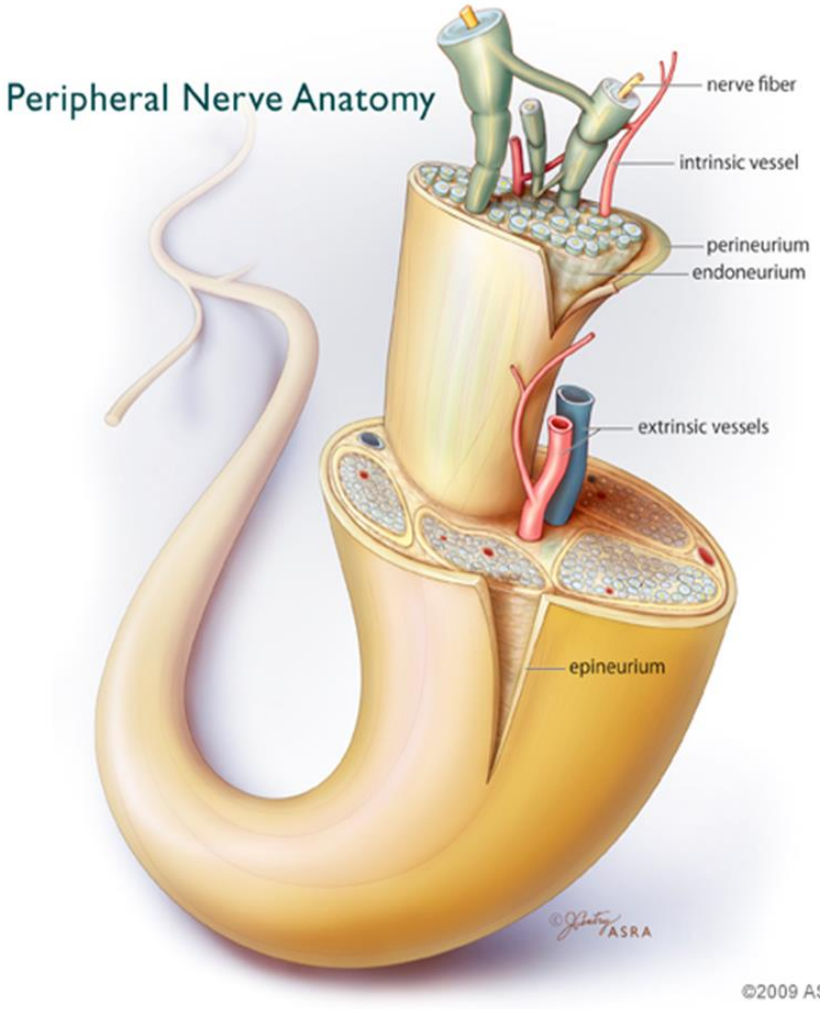
Aspetti classificativi, neurofisiologici e altre tecniche diagnostiche

21 marzo 2016

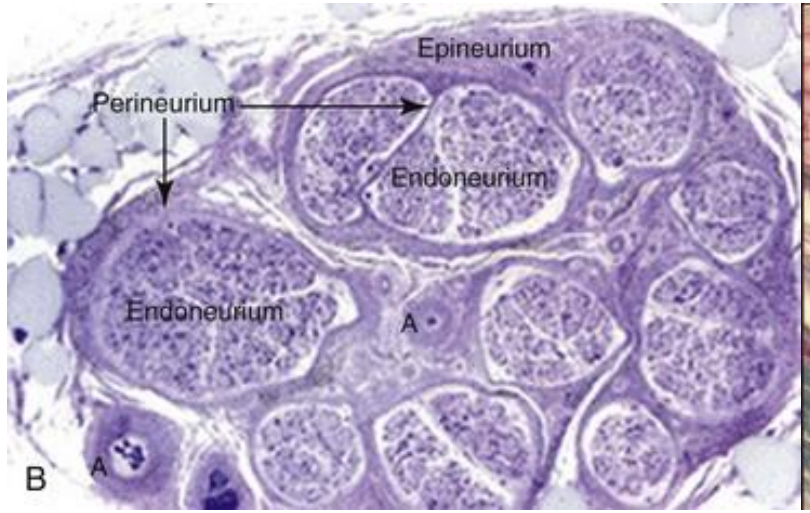
Daniele Cazzato

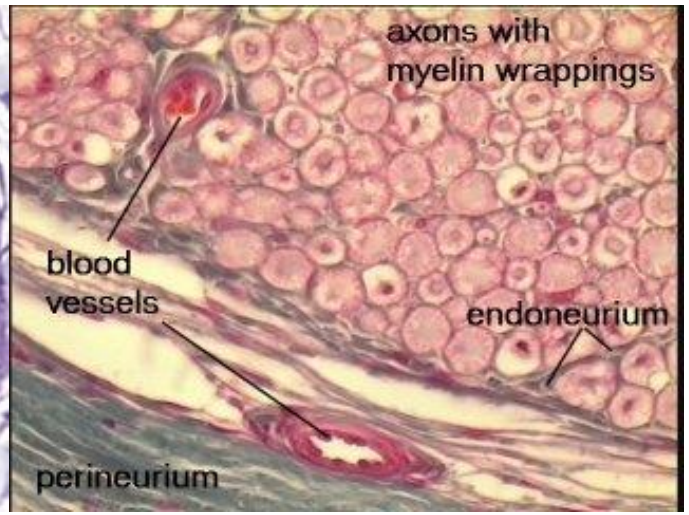
Scuola di Specializzazione di Neurologia
Università di Ferrara
Coordinatore: Enrico Granieri

Anatomia del nervo periferico

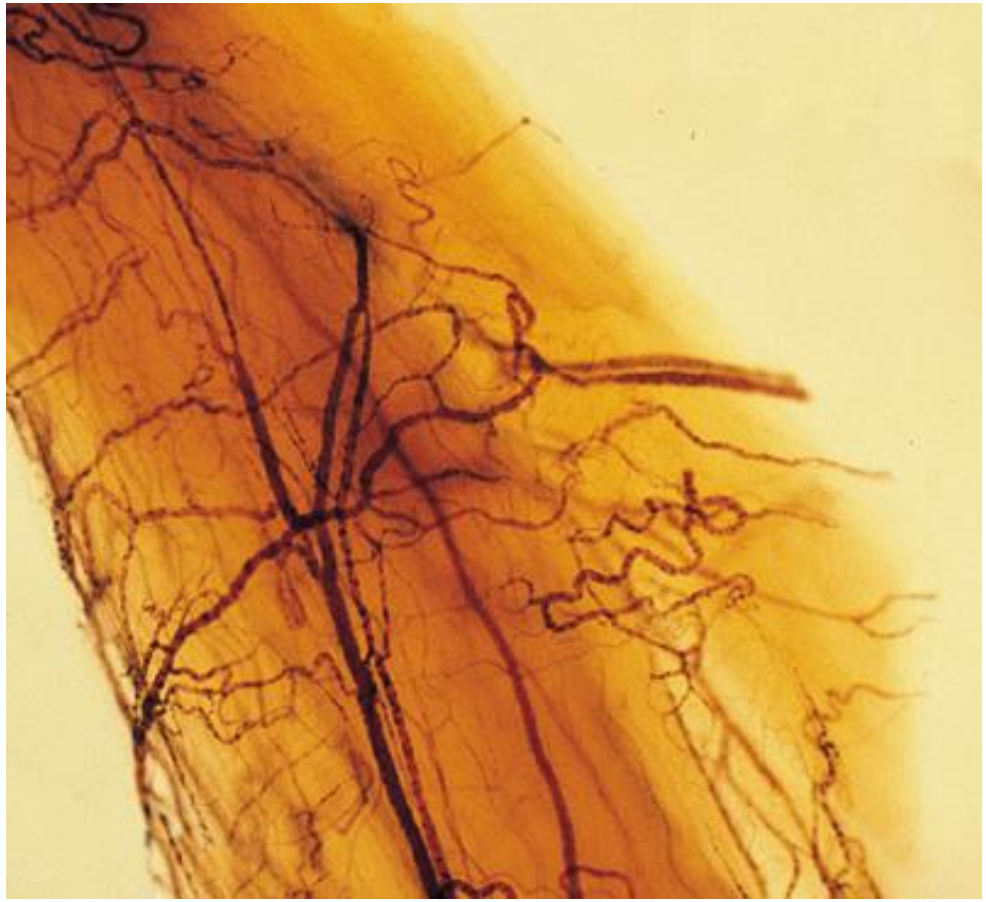


- Assoni mielinici o amielinici → endonevrio
- Fascicoli nervosi → perinevrio
- Nervo → epinevrio

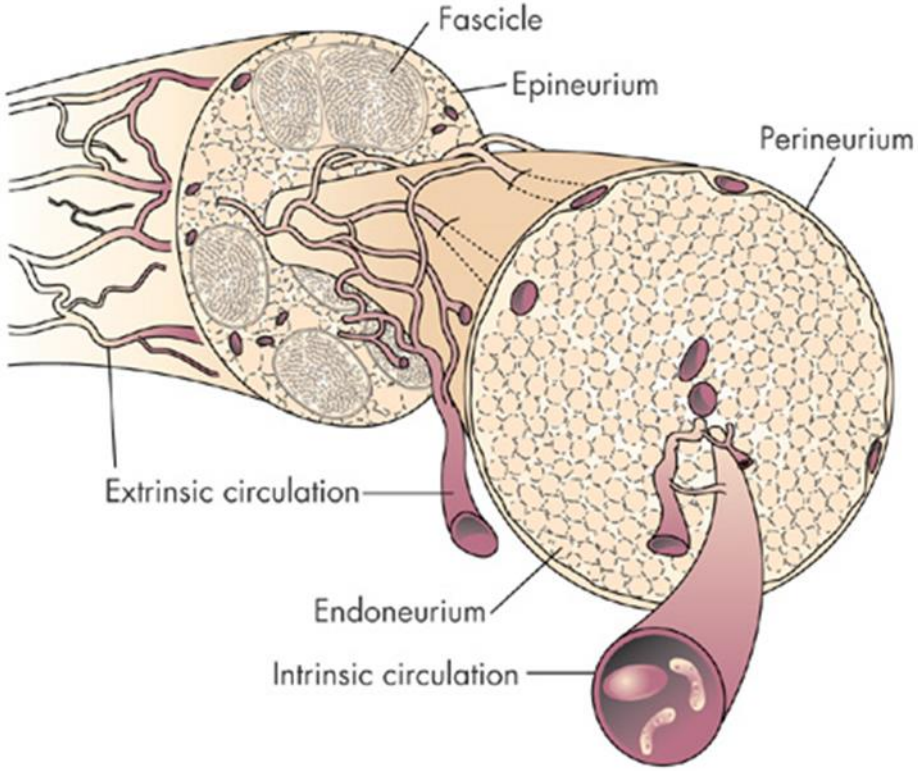




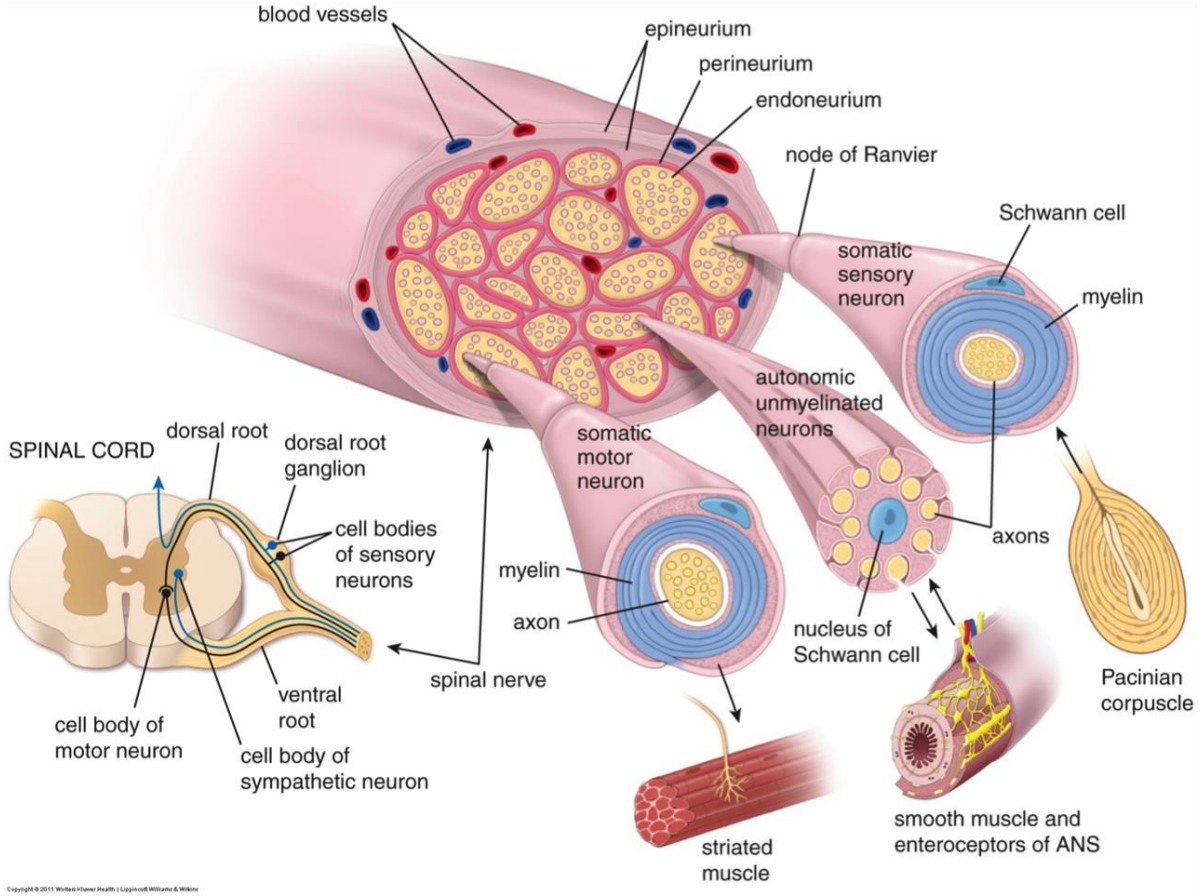
Anatomia del nervo periferico

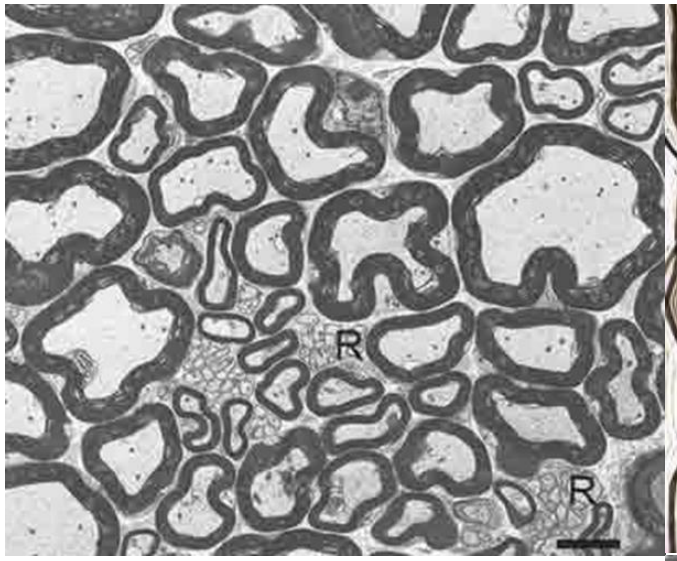


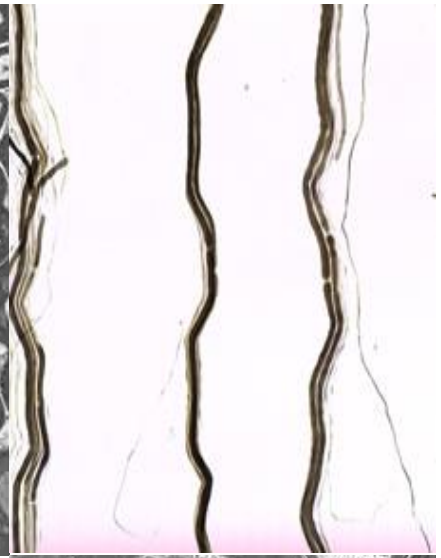
Vascolarizzazione: Vasa Nervorum



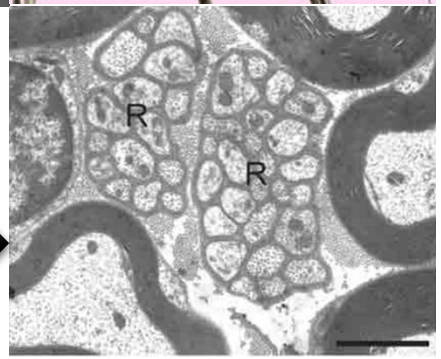
Anatomia del nervo periferico



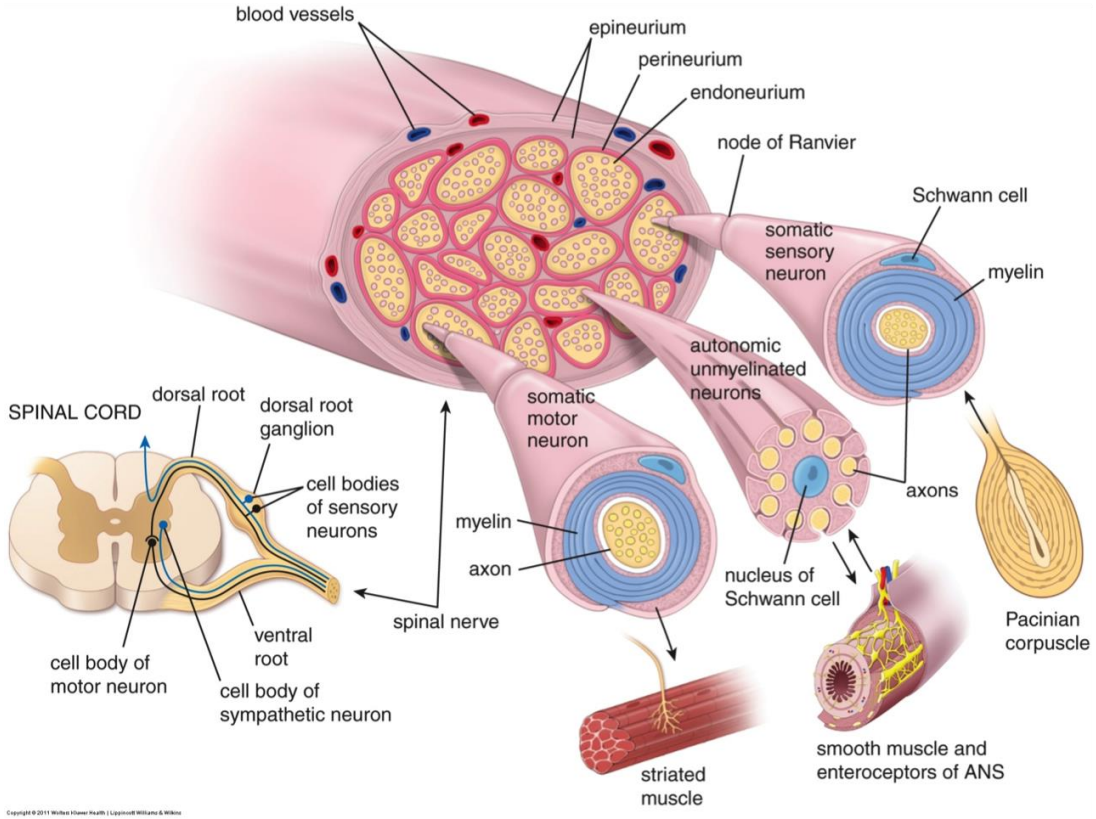




Remak bundle



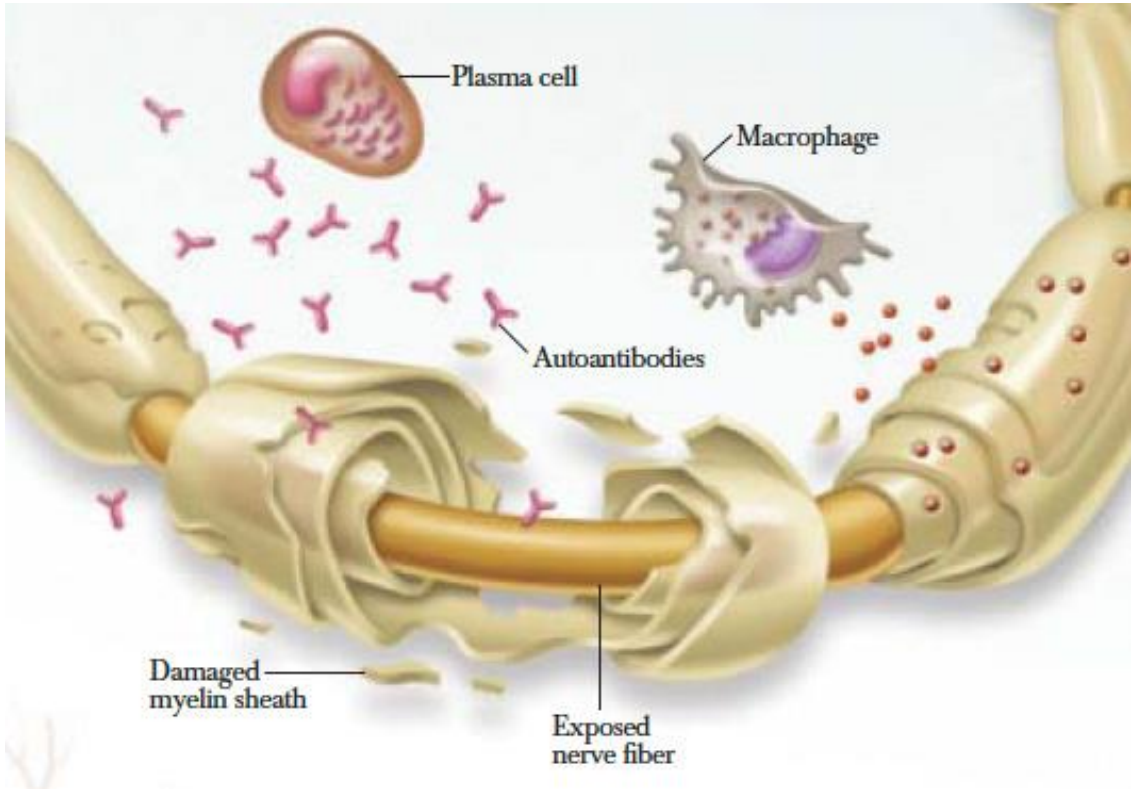
Meccanismi patogenetici: Classificazione Eziopatogenetica



Possibili siti coinvolti nel processo patogenetico:

- Corpo cellulare
  - (Corna ventrali)
  - Gangli radici dorsali
- Assone
- Mielina (Schwann Cells)
- Vasa nervorum
- Connettivo

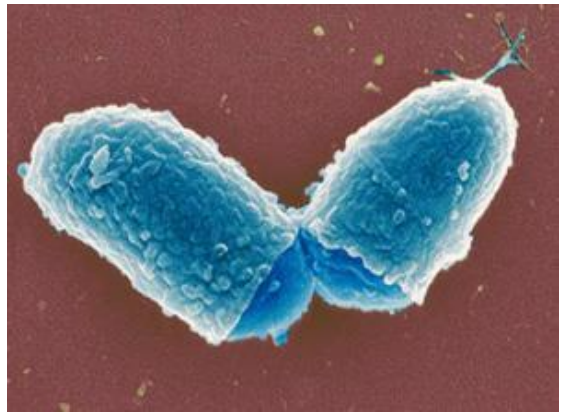
Meccanismi patogenetici



Immuno-mediato:

- Risposta umorale e cellulo-mediata verso i componenti della mielina, regioni paranodali.

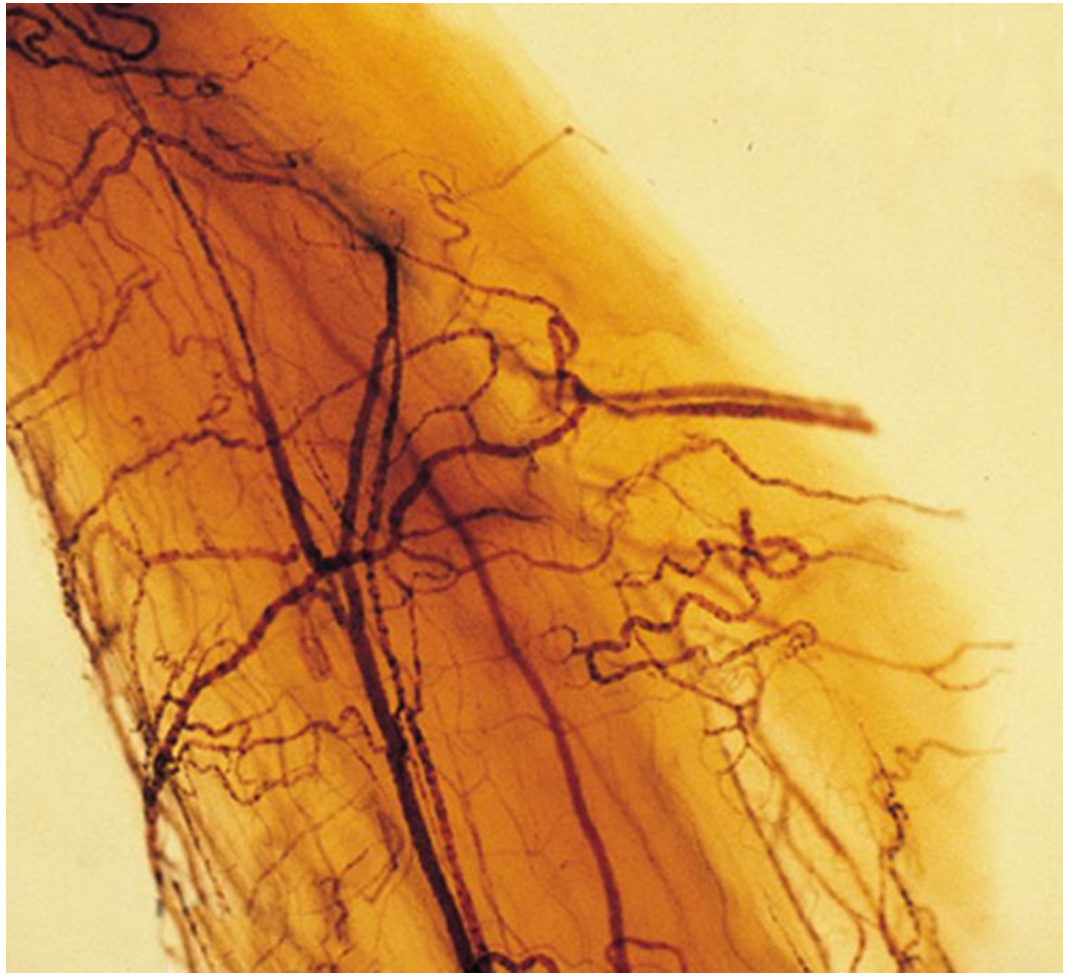
Meccanismi patogenetici



Sostanze neurotossiche:

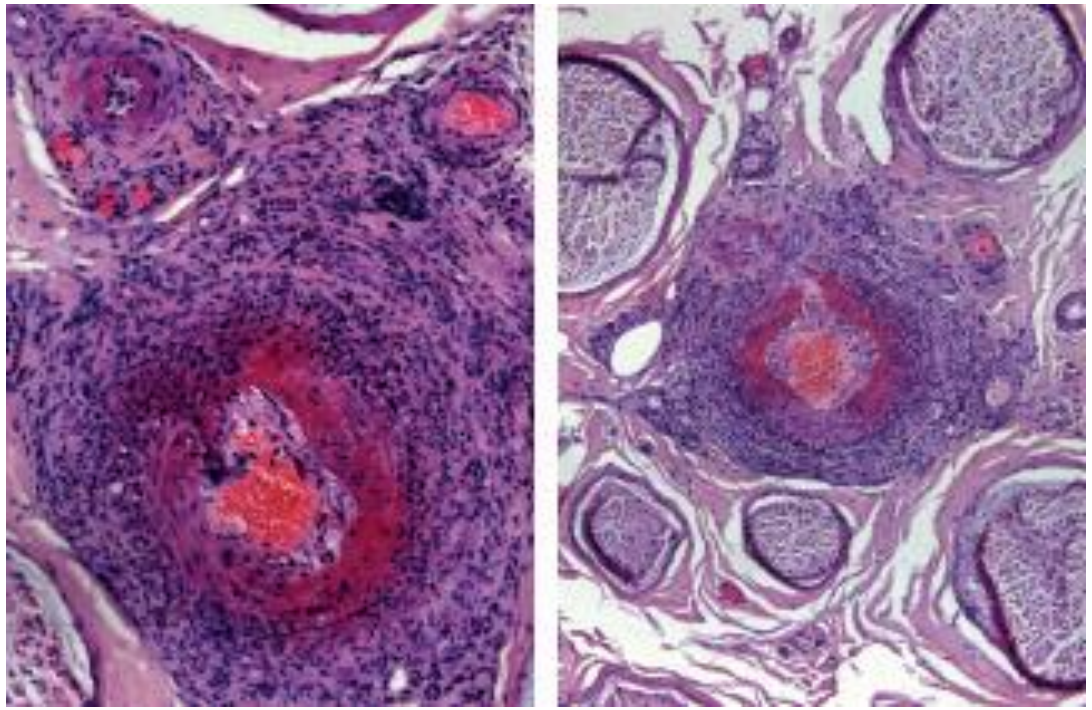
- Tossina difterica
  - Inibizione sintesi proteica nelle cellule di Schwann (radici sensitive e motorie e nervi cranici, simula GBS)
- Metalli pesanti
  - Alterazioni mitocondriali e fosforilazione ossidativa danno assonale
- Chemioterapici
  - Alterazione mitocondrio, canali ionici, trasporto assonale cellule dei gangli delle radici dorsali

Meccanismi patogenetici



Vasculite vasa nervorum:

- Es. Poliarterite nodosa



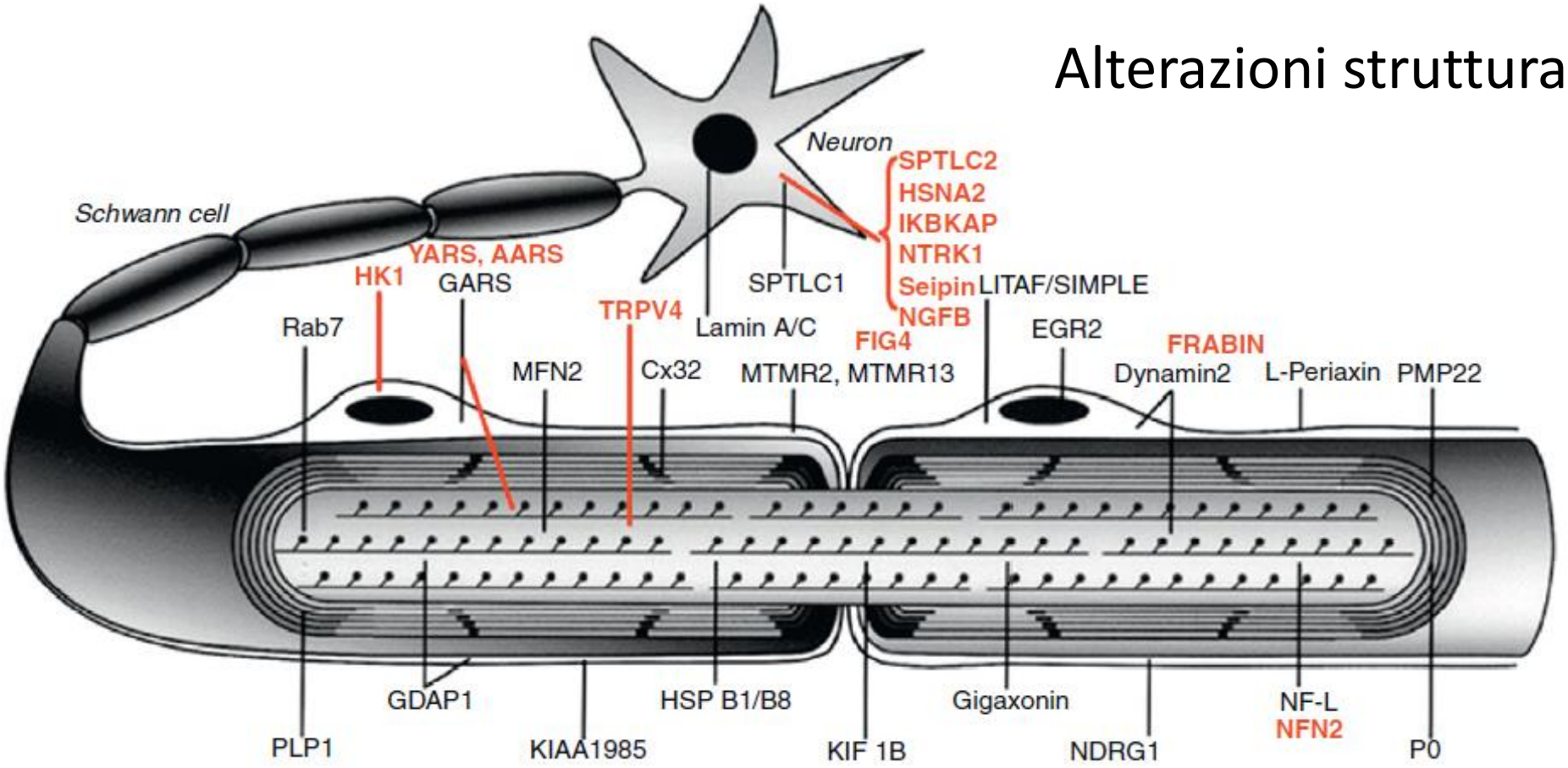
Meccanismi patogenetici

Metabolico:

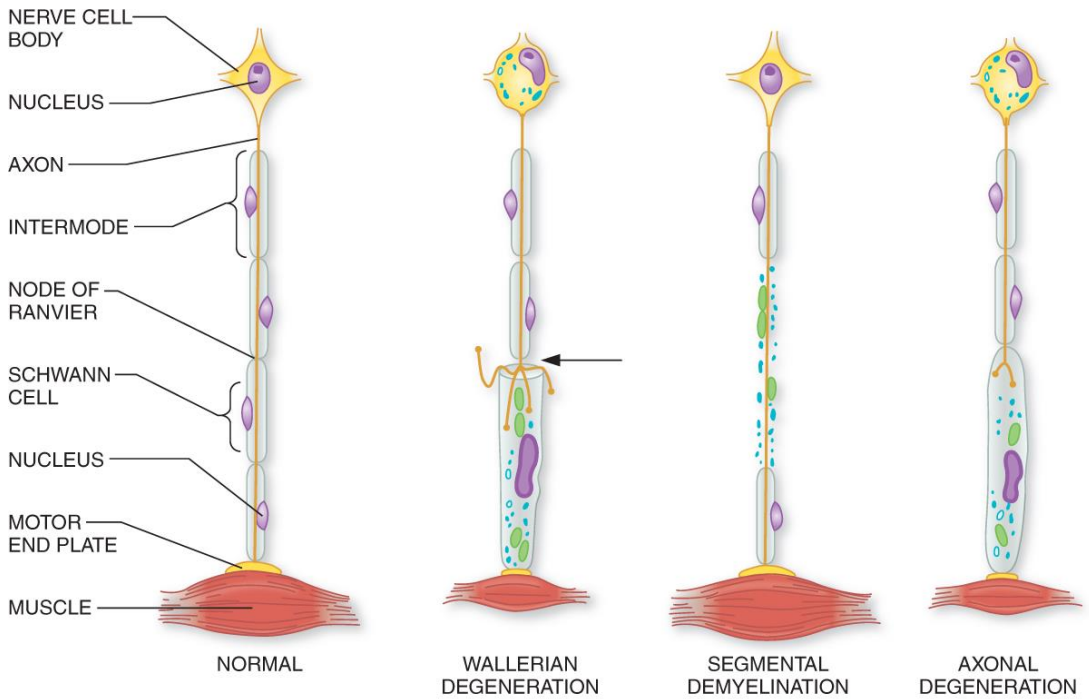
- alterazione delle funzioni cellulari
  - Es Polineuropatia diabetica, polineuropatia uremica..

Meccanismi patogenetici

Alterazioni strutturali congenite



Alterazioni patologiche del nervo periferico: Classificazione Neuropatologica



- Degenerazione Walleriana (dying forward):
  - degenerazione del moncone distale al sito di lesione in seguito a interruzione assonale (recupero lento)
- Demielinizzazione segmentaria:
  - alterazione del rivestimento mielinico in una segmento nervoso di dimensioni variabili (recupero potenzialmente rapido)
- Degenerazione assonale (dying back):
  - alterazioni delle funzioni cellulari es. del trasporto assonale causano una progressiva degenerazione assonale in senso disto-prossimale

Aspetti semeiologici: Classificazione Clinico-Semeiologica

Le neuropatie periferiche si presentano con un corteo variabile di sintomi che possono comprendere:

- Deficit motori
- Deficit sensitivi, alterazioni della sensibilità, dolore
- Disfunzione autonomica
- Alterazione dei riflessi
- Alterazioni trofiche

Aspetti semeiologici: disfunzione motoria

MRC - Valutazione della funzione motoria

0 – Nessun movimento, nessuna contrazione muscolare

1 – Contrazione visibile ma nessun movimento

2 – Movimento attivo possibile solo in assenza di gravità

3 – Movimento attivo possibile contro gravità

4 – Movimento attivo possibile contro resistenza ma più debole del normale

5 – Forza normale

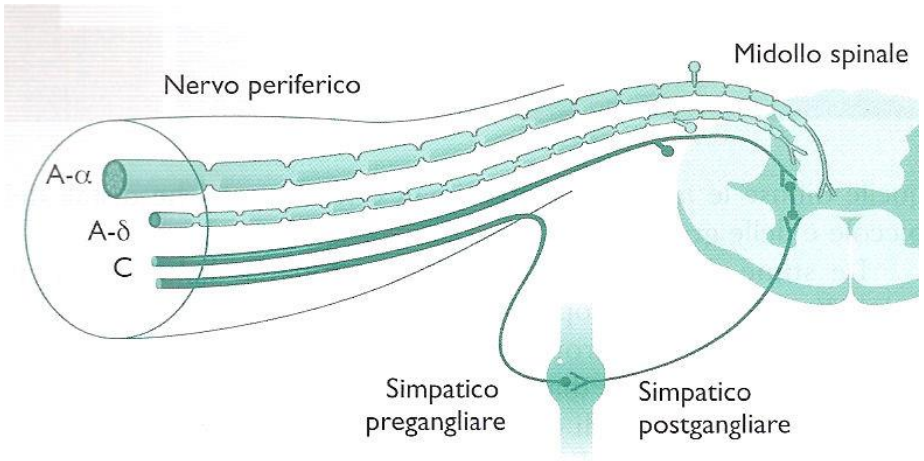
Martin Vigorimeter - Grip strength

Sintomi positivi:

- Fascicolazioni
- Crampi
- Spasmi

Aspetti semeiologici: disfunzione sensitiva

Fibre nervose sensitive



Sintomi negativi

Grosso calibro A-beta:

- Ipoestesia tattile
- Ipopallestesia e propriocezione
- Iporeflessia
- Atassia sensitiva

Piccolo calibro A-delta e C:

- Ridotta sensibilità termodolorifica

Aspetti semeiologici: disfunzione sensitiva

Monofilmenti di Von Frey – Valutazione sensibilità tattile

Monofilament Size	Target Force (Grams)
1.65	0.008
2.36	0.02
2.44	0.04
2.83	0.07
3.22	0.16
3.61	0.4
3.84	0.6
4.08	1
4.17	1.4
4.31	2
4.56	4
4.74	6
4.93	8
5.07	10
5.18	15
5.46	26
5.88	60
6.10	100
6.45	180
6.65	300

Aspetti semeiologici: disfunzione sensitiva

Diapason Rydel Seiffer 64 Hz – Valutazione pallestesia (Fibre grande calibro)

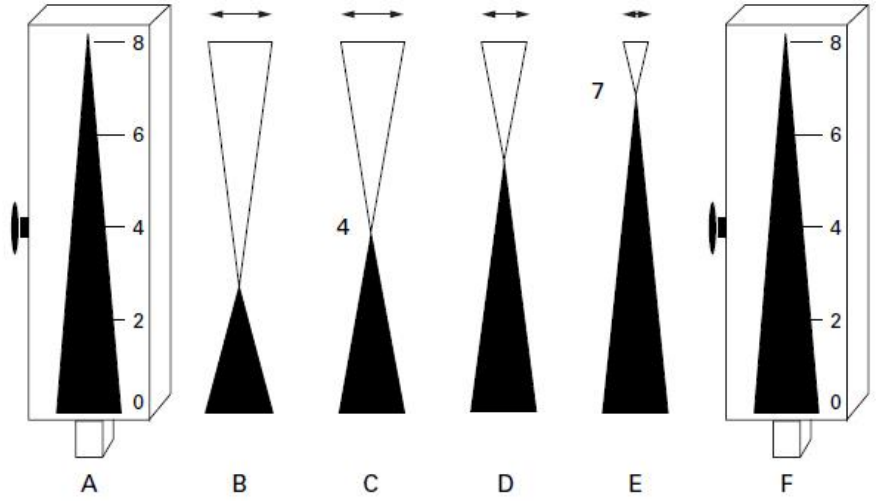


Figure 1 Extremities of the graduated tuning fork at rest (A) and during vibration (B→F). Intersection between lower and upper triangles moves from 0 (minimum score) to 8 (maximum score) with decreasing vibration amplitude (↔).

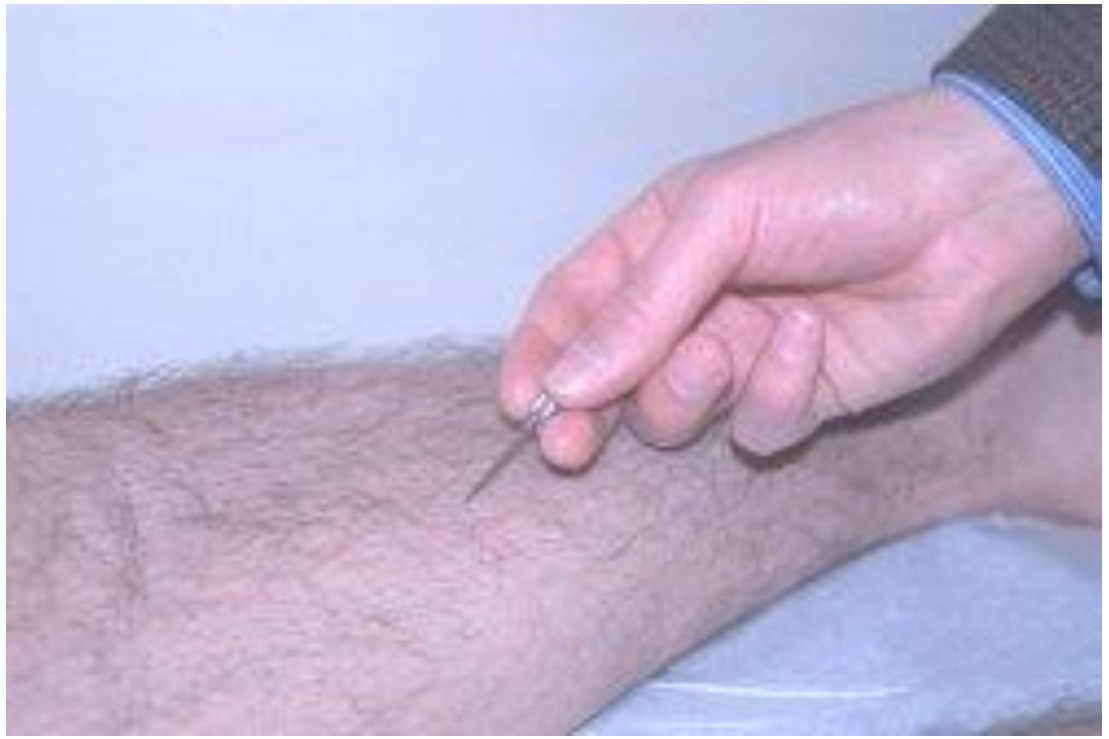
Table 1 Normal vibration threshold values (5% lower limit) in healthy controls (with the Rydel-Seiffer tuning fork)

For the upper extremities		*For the lower extremities*	
Age (y)	*Values*	*Age (y)*	*Values*
≤40	≥6.5	≤40	≥4.5
41–85	≥6.0	41–60	≥4.0
>85	≥5.5	61–85	≥3.5
		>85	≥3.0

Sites of examination: dorsum of the distal interphalangeal joint of the index finger, the ulnar styloid process, dorsum of the interphalangeal joint of the hallux ,and the internal malleolus. Values are 0–8; the vibration threshold values are presented in rounded numbers.

Aspetti semeiologici: disfunzione sensitiva

Valutazione sensibilità puntoria/dolorifica (pin prick) (Fibre piccolo calibro)

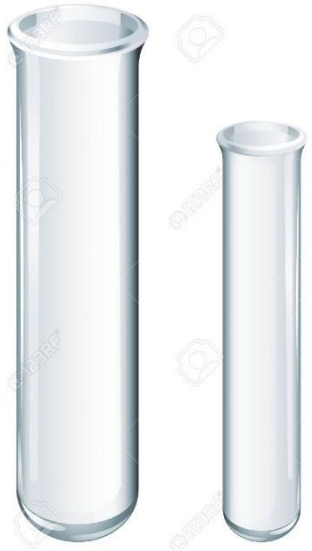


Aspetti semeiologici: disfunzione sensitiva

Esame sensibilità termica (Fibre piccolo calibro)

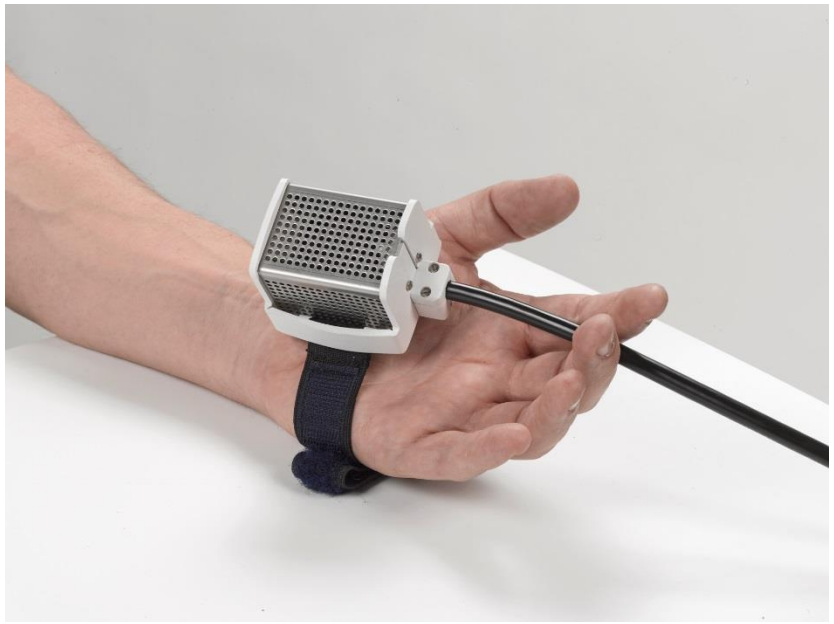
Due provette di vetro riempite con:

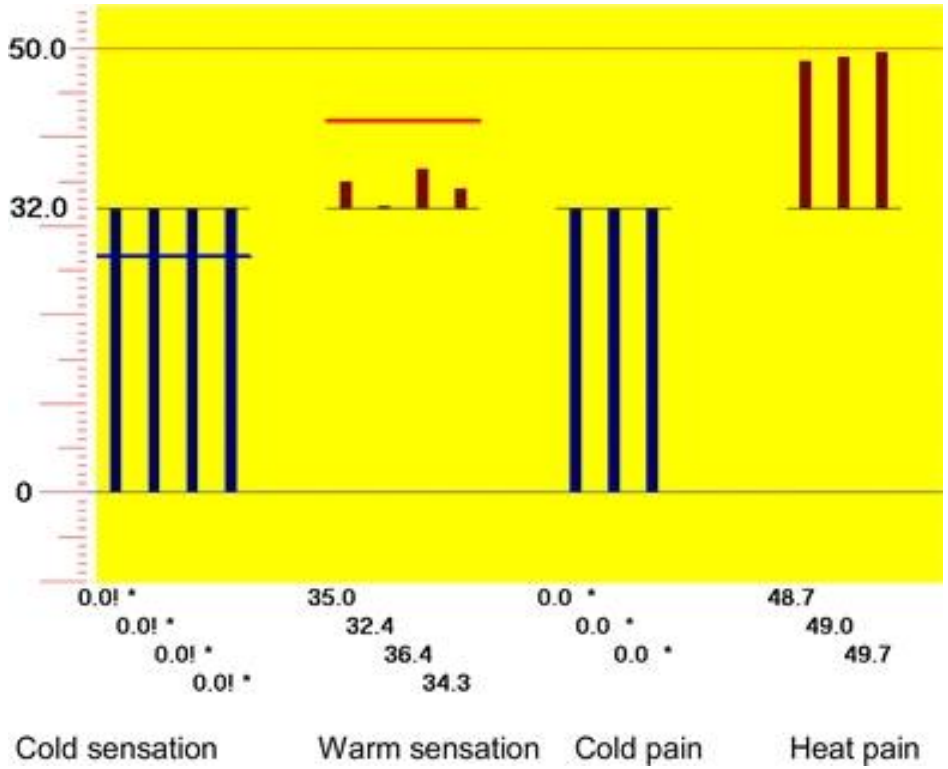
- Ghiaccio
- Acqua calda 40°C



Aspetti semeiologici: disfunzione sensitiva

Quantitative sensory testing QST (Fibre piccolo calibro)





Aspetti semeiologici: disfunzione sensitiva

Sintomi sensitivi positivi

- **Parestesie** *(percezioni sensitive anomale spontanee)*
- **Allodinia** *(dolore evocato da stimoli normalmente non dolorosi)*
  - Meccanica statica (contatto)
  - Meccanica dinamica (pressione lieve)
  - Termica (caldo o freddo non intensi)
- **Iperalgesia** *(risposta dolorosa incrementata a stimoli dolorosi)*
  - *Wind up like pain (incremento del dolore con stimolo costante)*
  - *Aftersensation (dolore che persiste anche dopo la fine dello stimolo)*

Aspetti semeiologici: disfunzione sensitiva

Atassia sensitiva e tremore

Deficit di propriocezione nelle neuropatie delle grandi fibre o nelle ganglionopatie, tabe dorsale, varianti GBS (Miller Fisher)

-Atassia sensitiva: marcia scalciata, movimenti bruschi degli arti inferiori

-Pseudoatetosi: movimenti irregolari di segmenti articolari slatentizzati dalla soppressione visiva. Es. movimenti tentacolari delle dita delle mani

-Tremore: tremore d'azione ad alta frequenza, tipico in alcune neuropatie (anti-MAG, CIDP)

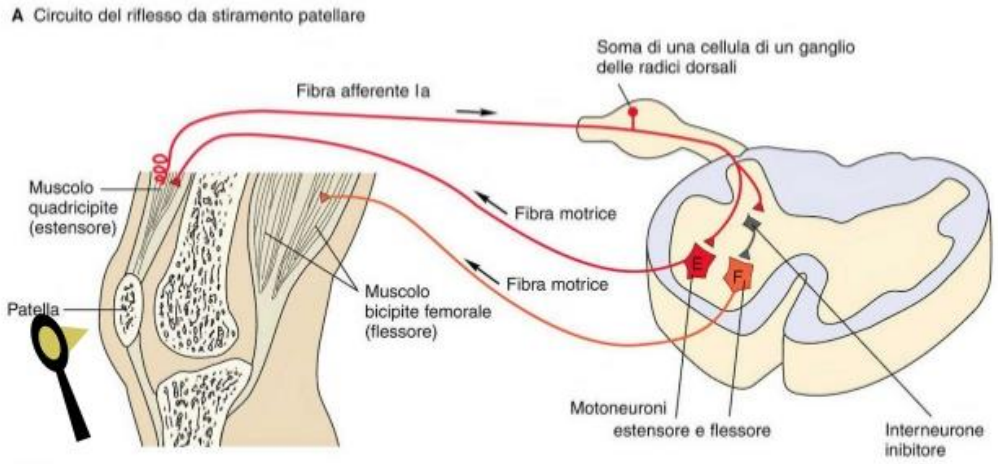
Aspetti semeiologici: Riflessi

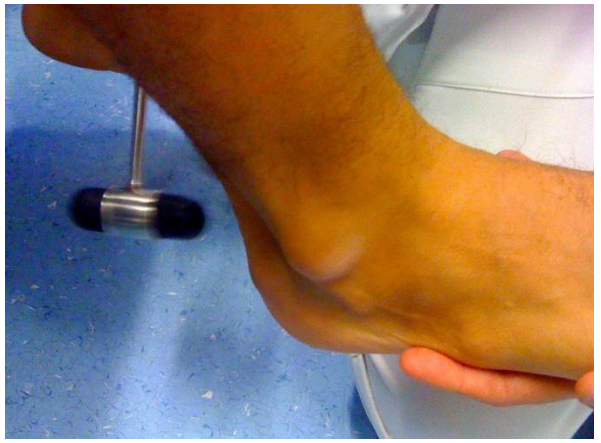
Riflessi profondi

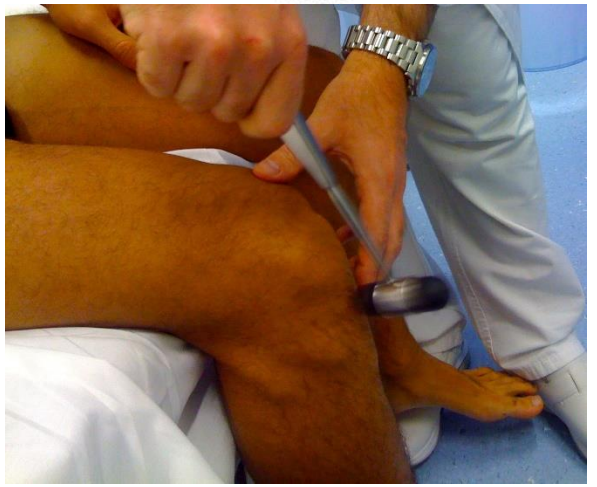
- Normali
- Elicitabili con rinforzo (Jendrassik)
- Assenti

La riduzione o abolizione dei riflessi profondi è un segno di disfuzione del nervo periferico

Possono essere normali nelle neuropatie delle piccole fibre



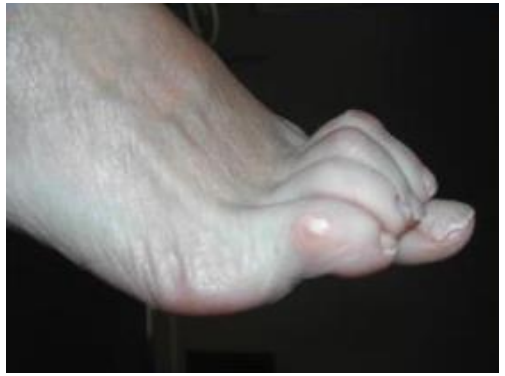


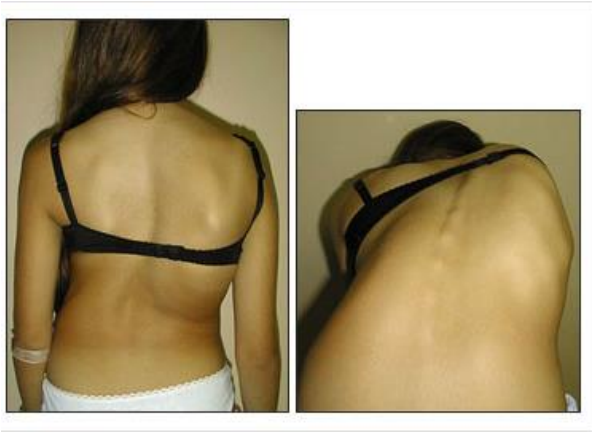


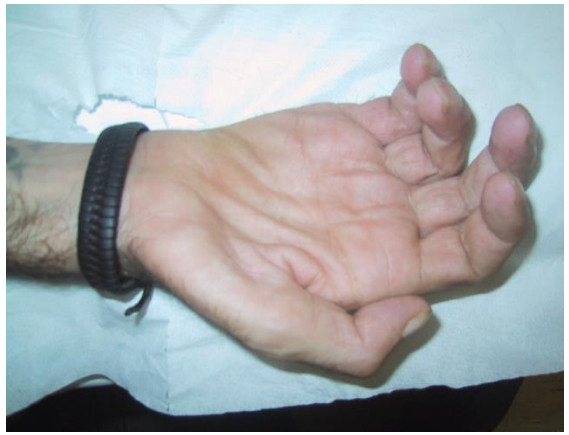
Aspetti semeiologici: Deformità e Alterazioni trofiche

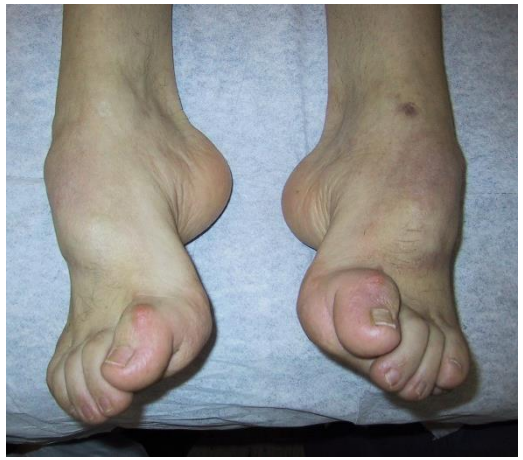
Neuropatie congenite

- Scoliosi *(CMT4C)*
- Piede cavo
- Dita a martello
- Retrazioni tendinee
- Mano ad artiglio
- Decubiti, callosità, disturbi della marcia conseguenti



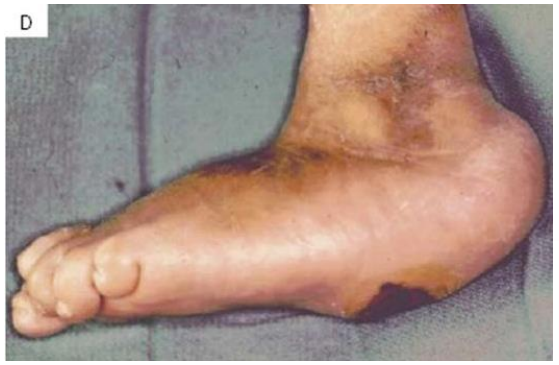


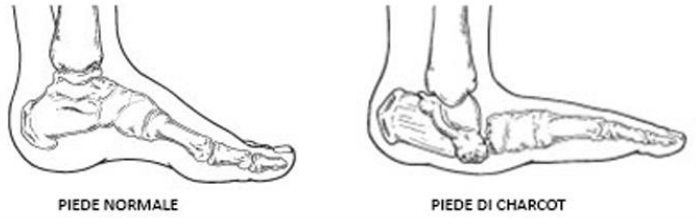


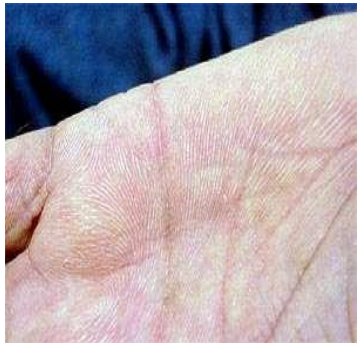


Aspetti semeiologici: Deformità e Alterazioni trofiche

- Neuro-osteoartropatia di Charcot (crollo articolare alla caviglia)
- Complex regional pain syndrome
- Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS – Crow Fukase)







Cute secca e spessa

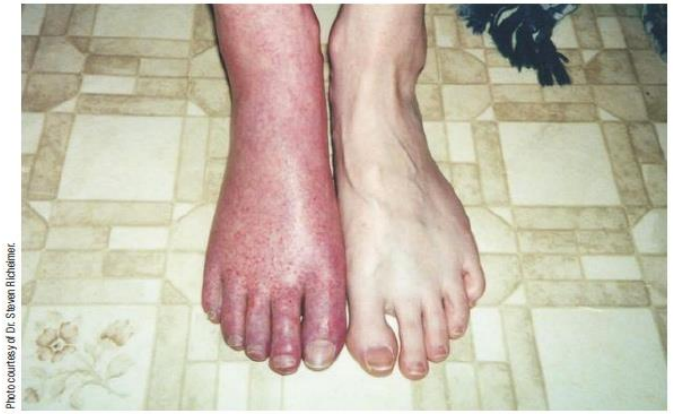
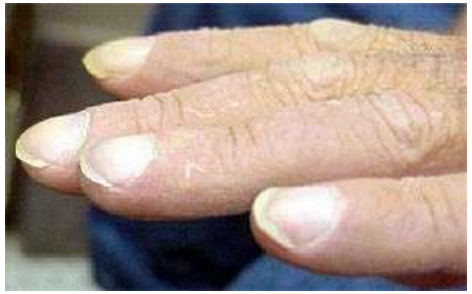


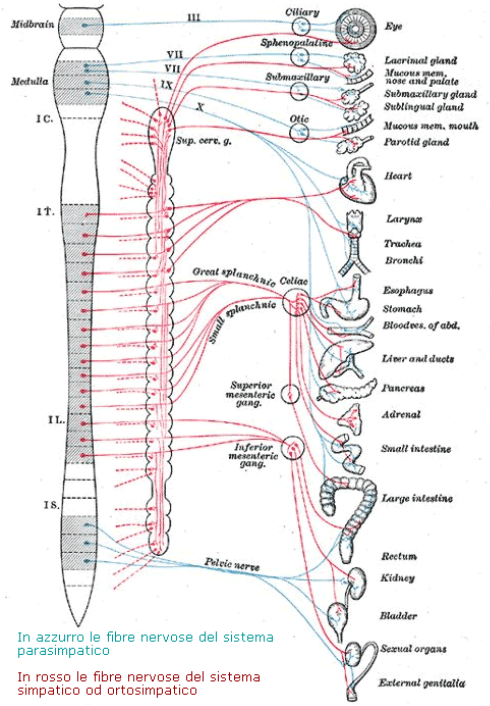
Photo courtesy of Dr. Steven Richheimer.

Figure 1. Image of a patient with lower extremity complex regional pain syndrome.



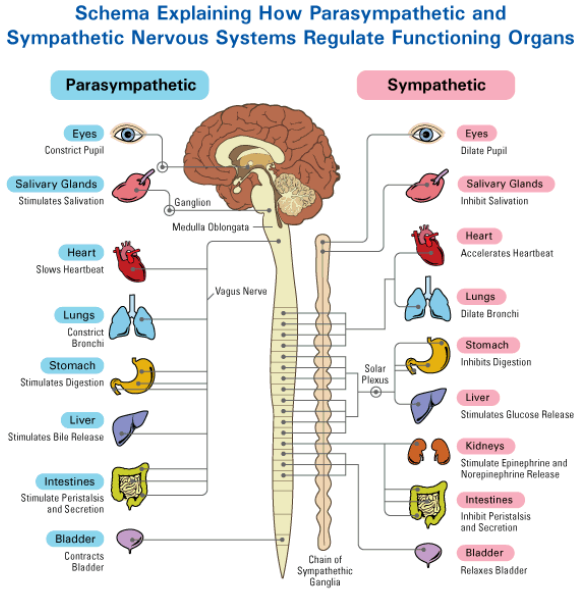
Dita a bacchetta

Aspetti semeiologici: Disturbi Autonomici



In azzurro le fibre nervose del sistema parasimpatico

In rosso le fibre nervose del sistema simpatico od ortosimpatico



SINTOMI DI INTERESSAMENTO AUTONOMICO

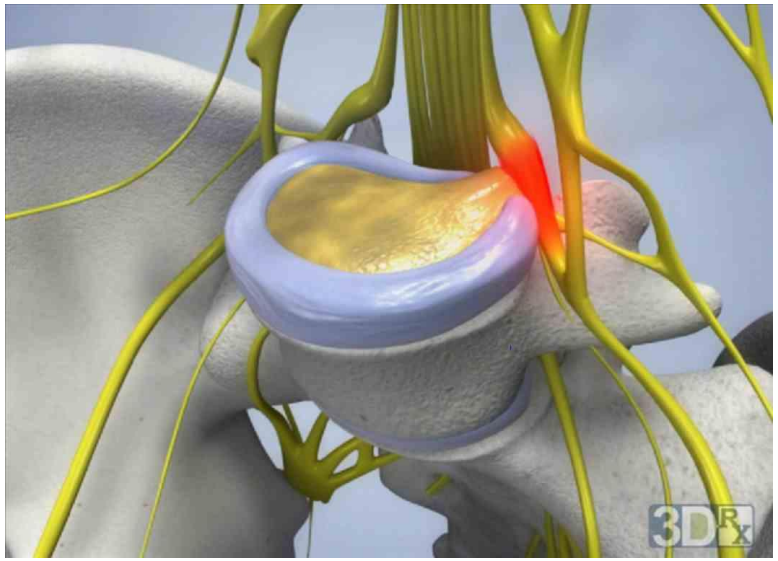
- Cardiovasculare
  - Tachicardia a riposo
  - Ipotensione ortostatica
  - Scompenso cardiaco
- Genitourinario
  - Disfunzione della minzione (esitazione o incontinenza)
  - Disturbi di erezione ed eiaculazione
- Gastrointestinale
  - Gastroparesi
  - Diarrea
  - Stipsi
- Periferici
  - Alterazioni della sudorazione
  - Alterazione dei riflessi pupillari
  - Edema
  - Alterazione del flusso ematico capillare

Classificazione Topografica

- **Mononeuropatie / radiculopatie:** lesione di un singolo nervo o radice nervosa
- **Poliradiculoneuropatie:** neuropatie con coinvolgimento di più radici nervose (es. Guillain-Barré, CIDP)
- **Multineuropatie:** interessamento di più nervi in maniera asimmetrica (es. vasculiti)
- **Polineuropatie:** interessamento neuropatico diffuso prevalentemente distale e simmetrico (es. neuropatie metaboliche, tossiche, disimmuni)
- **Ganglionopatie:** interessamento dei neuroni sensitivi dei gangli delle radici dorsali (paraneoplastiche, disimmuni, idiopatiche)

Classificazione Topografica: mononeuropatie / radiculopatie

- Radiculopatia isolata:
  - prevalentemente da compressione spondilogena di una radice nervosa che si presenta con dolore, disturbi sensitivi, motori e alterazione dei riflessi nel territorio radicolare coinvolto
- Mononeuropatie:
  - Possono essere coinvolti tutti i nervi
  - Prevalentemente coinvolti nervi che attraversano regioni delimitate da strutture rigide (sindromi da intrappolamento)

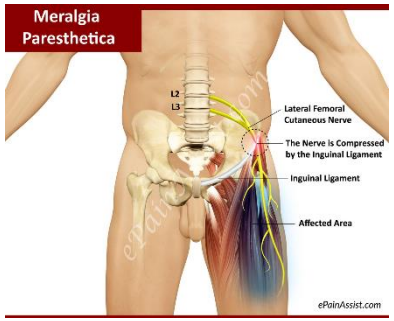


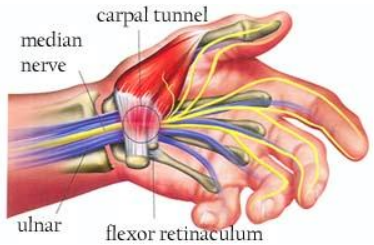
Classificazione Topografica: Mononeuropatie

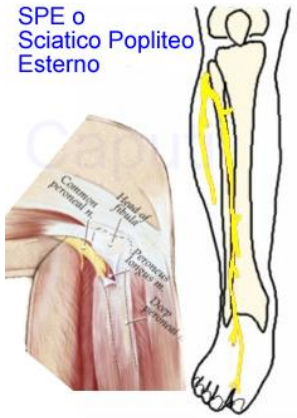
Tabella V - Neuropatie da intrappolamento.

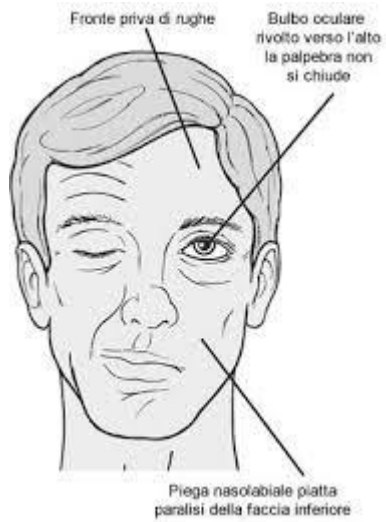
Nervo	Sito di intrappolamento	Fattori predisponenti	Aspetti clinici
Lesioni comuni			
Mediano	Tunnel carpale	Sesso femminile Piccolo tunnel Gravidanza Recente aumento di peso Tenosinoviti Malattia reumatica Precedenti fratture Ipotiroidismo Acromegalia	Parestesie notturne
Ulnare	Gomito	Sesso maschile Pesante occupazione manuale Aumento dell'angolo di sollevamento Pregresse fratture Osteoartrite del gomito	Parestesie di IV e V dito, debolezza dei muscoli innervati da questo nervo, particolarmente gli interossei
Tronco inferiore del plesso brachiale	Costa cervicale o fascia	Varianti anatomiche	Dolore al braccio e alla mano Ipotrofia e ipostenia di tutti i muscoli della mano e dei muscoli mediali dell'avambraccio
Nervo cutaneo laterale della coscia (meralgia parestesica)	Legamento inguinale	Sesso maschile Esercizio prolungato Recente aumento di peso Pantaloni bermuda	Parestesie nella regione anteriore e laterale della coscia
Lesioni meno comuni			
Interosseo mediano o anteriore	Sotto il gomito dai tendini del pronatore rotondo e del flessore superficiale delle dita	Varianti anatomiche	Dolore e gonfiore dell'avambraccio Ipostenia del flessore lungo del pollice e dell'indice
Ulnare	Canale ulnare costretto tra l'osso pisiforme e l'uncino	Ganglio al polso Occupazione manuale Pregresse fratture	Dolore al polso, ipostenia dei piccoli muscoli della mano innervati dalla branca profonda dell'ulnare
Interosseo posteriore	Membrana dell'interosseo, dal tendine del muscolo supinatore	Varianti anatomiche Lipoma o ganglioma in questa sede	Ipostenia del flessore ulnare del carpo, estensore comune delle dita e dell'indice, abduttore ed estensore lungo del pollice
Peroneale	Tra tibia e testa del perone	Varianti anatomiche Pregresse fratture	Ipostenia del tibiale anteriore, estensore comune dell'alluce, talora dei muscoli peroneali
Tibiale posteriore	Tunnel tarsale, sotto e dietro il malleolo laterale	Varianti anatomiche	Dolore urente sotto la pianta del piede, talora ipoestesia nell'area mediale plantare

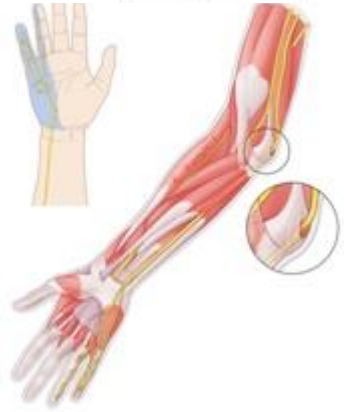
Il diabete mellito, o una lieve neuropatia generalizzata sottostante, predispone per lo sviluppo della neuropatia da intrappolamento. Questa ipotesi dovrebbe essere sempre tenuta presente in caso di neuropatia da intrappolamento.



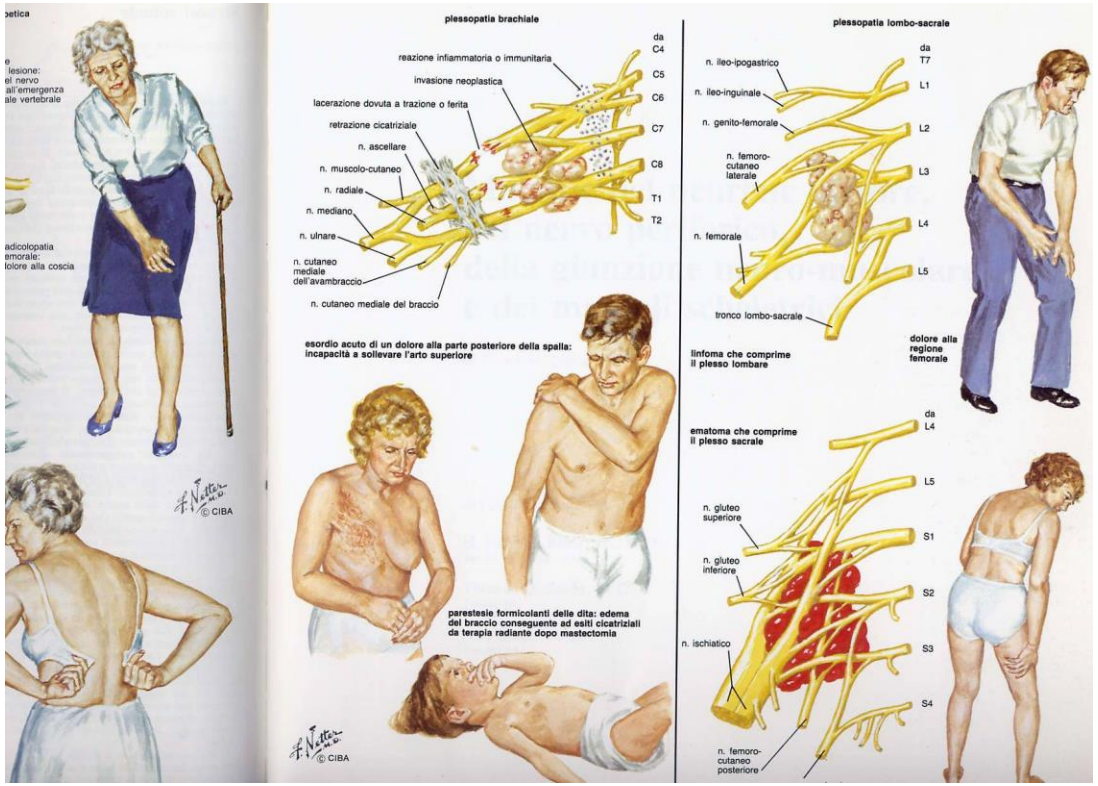








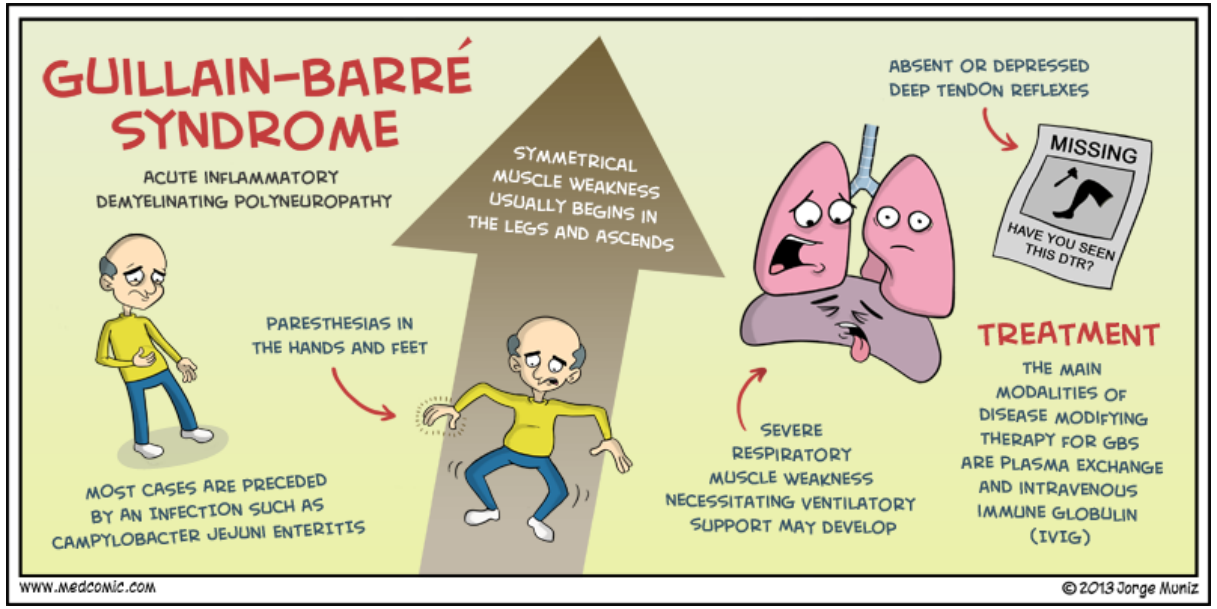
Classificazione Topografica: Plessopatie



- Lesione completa è rara
- Più spesso il deficit incompleto ricalca il danno di uno o più tronchi nervosi o dei singoli nervi del plesso

Classificazione Topografica: Poliradicoloneuropatie

- Coinvolgimento di più radici nervose con sintomi sensitivi e motori nella sede di pertinenza delle radici e nervi coinvolti
- Possono coinvolgere distretti sia distali che prossimali e nervi cranici
- Esempi:
  - GBS
  - CIDP



Classificazione Topografica: Poliradicoloneuropatie

Table 1 Major phenotypic variants of CIDP

CIDP phenotypic variant	Estimated prevalence within CIDP	Onset	Clinical symptoms	Distribution	References
Typical CIDP	51%	Chronic	Sensory and motor	Symmetrical, proximal and distal	8–10
Sensory CIDP	4–35%	Chronic	Sensory predominant; motor involvement may develop	As per typical CIDP	5, 9–11
Chronic immune sensory polyradiculopathy	5–12%	Chronic	Sensory ataxia	As per typical CIDP	8, 9, 12, 13
Lewis-Sumner syndrome/ MADSAM	6–15%	Chronic	Sensory and motor	Asymmetrical; often upper limb onset	5, 8, 9, 14
Focal CIDP	1%	Chronic	Sensory and motor	Focal; may progress to diffuse CIDP over time	9, 15
DADS	2–17%	Chronic	Sensory predominant, but may include motor involvement	Symmetrical, distal	5, 9, 10
Acute onset CIDP	2–16%	Acute onset	As per typical CIDP	As per typical CIDP	9, 16–18
Motor CIDP	4–10%	Chronic	Motor predominant	As per typical CIDP	5, 8, 9, 13

CIDP, Chronic inflammatory demyelinating polyradiculoneuropathy; DADS, distal acquired demyelinating symmetric; MADSAM, multifocal acquired demyelinating sensory and motor neuropathy.

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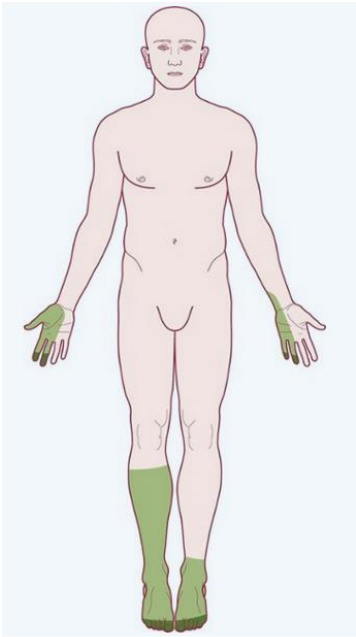
Classificazione Topografica: Multineuropatie

- Lesione di due o più nervi
  - Asimmetrica
  - Asincrona (in tempi differenti)
  - Nervi anche distanti tra loro



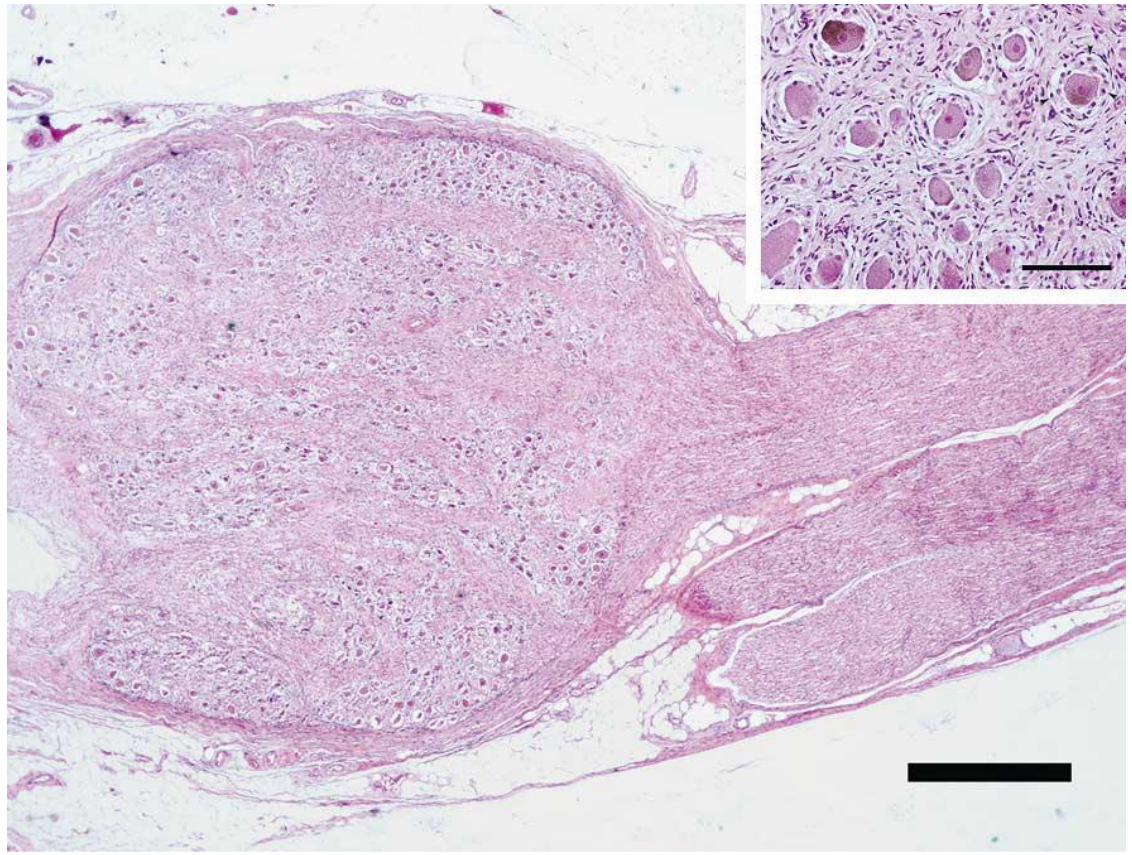
Cause più comuni:

- Vasculiti e malattie reumatologiche (Granulomatosi di Wegener, Sindrome di Churg Strauss, panarterite nodosa, LES, artrite reumatoide, S. di Sjogren)
- Diabete
- Malattie granulomatose (sarcoidosi, lebbra)
- Forme ereditarie HNPP
- Disimmuni atipiche (es. Lewis Sumner, MMN)

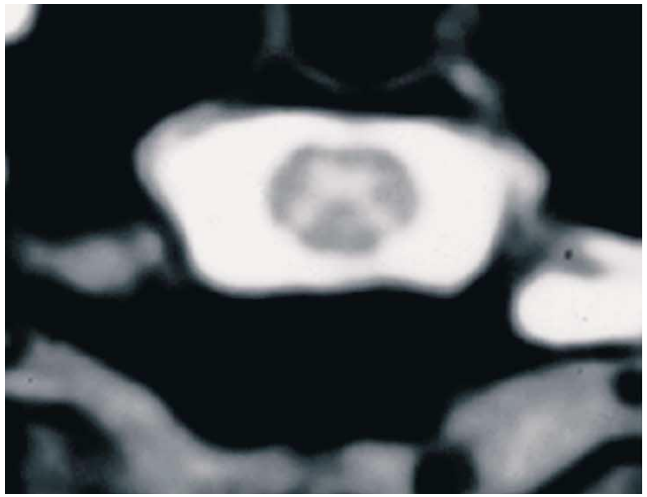
Classificazione Topografica: Ganglionopatie

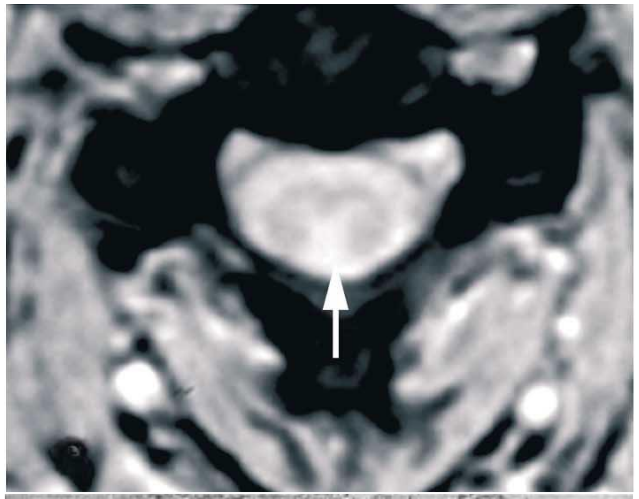
- Neuronopatia sensitiva
  - Lesione a carico del corpo cellulare del 1° neurone sensitivo a livello del ganglio delle radici dorsali

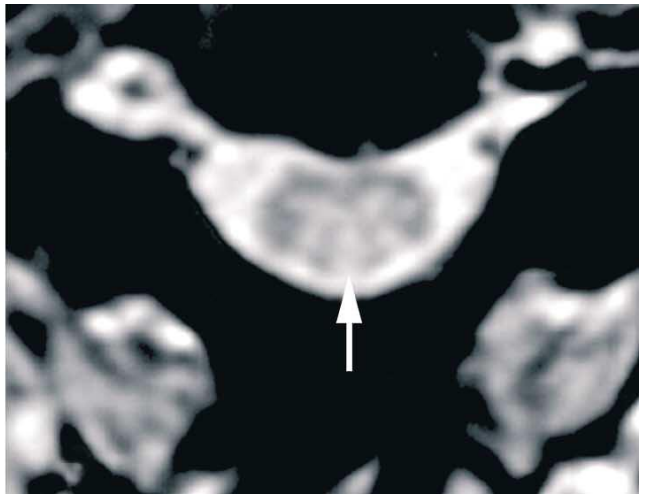
  Sintomi e segni
  - Atassia sensitiva
  - Deficit sensitivo irregolare a chiazze
  - Areflessia generalizzata
  - Disturbi autonomici

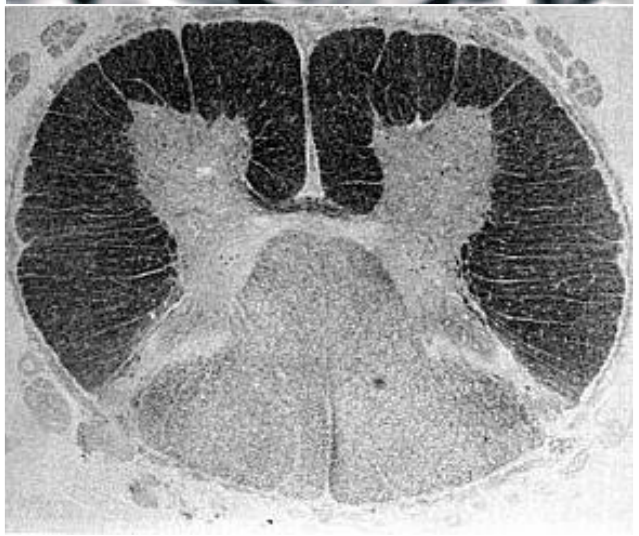


Classificazione Topografica: Ganglionopatie









Degenerazione dei cordoni posteriori in corso di neuronopatia sensitiva in pz con S. di Sjogren

Lancet Neurol 2005; 4: 349–61

Classificazione Topografica: Ganglionopatie Acquisite

	Onset	Aetiology	Laboratory findings	
			Serum	CSF
Paraneoplastic	Subacute>chronic	Bronchial carcinoma, SCLC, Hodgkin's lymphoma, neuroendocrine tumours, breast cancer, ovarian cancer, sarcoma	Hu antibodies, CRMP-5 antibodies	Possible increase in protein concentration and pleocytosis; rarely oligoclonal IgG bands; Hu antibodies
Immune-mediated	Subacute>chronic	Sjögren's syndrome	SSA/SSB antibodies; inflammatory infiltrates in small salivary glands on lip biopsy	Mild increase in protein concentration; normal cell count; rarely oligoclonal IgG bands
		Unclassified connective disorders	RF, ANA, ASMA, others autoAb	
		Chronic autoimmune hepatitis	Hyperglobulinaemia, RF, ANA, ASMA, hepatitis B core antibodies	
		MGUS	Monoclonal gammopathy; GD1b antibodies	
Infective	Subacute	AIDS	HIV antibodies; low CD4 count	Increased protein concentration and pleocytosis in the acute phase
		Epstein-Barr virus, varicella-zoster virus, measles, HTLV-1	Increased IgM concentration in the acute phase	
Iatrogenic	Subacute>chronic	CDDP, carboplatin, oxaliplatin, doxorubicin, suramin sodium, bortezomid, thallium, penicillin	Typically normal	Typically normal
Vitamin-related	Subacute>chronic	Pyridoxine intoxication	High 5-pyridoxal phosphate concentration	
		Nicotinic acid deficiency	Low nicotinic acid concentration; low tryptophan and erythrocyte NAD and NADP; low urinary excretion of metabolites	
		Vitamin-E deficiency	Low vitamin-E concentration; abetaliproteinaemia	
		Riboflavine deficiency	Low riboflavine concentration in red blood cells and urine	
Idiopathic	Chronic	Unknown	Typically normal	Typically normal

SCLC=small-cell lung carcinoma; CRMP-5=collapsin response-mediator protein-5; RF=rheumatoid factor; ANA= nuclear antibodies; ASMA=smooth-muscle antibodies; HTLV-1=human T-cell lymphotropic virus type I; MGUS=monoclonal gammopathy of undetermined significance; CDDP=cis-diammine-dichloro-platinium.

Table 1: Acquired sensory neuronopathies

Classificazione Topografica: Gangliopatie Ereditarie

Disease	Inheritance	Locus; gene	Clinical features
Hereditary sensory and autonomic neuropathy (HSAN)[85]			**Pure sensory and autonomic neuronopathies**
HSAN I	Autosomal dominant	9q22.1-q22.3; *SPTLC1*	Preferential small-fibre loss; early algothermal anaesthesia; recurrent ulcers, acromutilation, Charcot joints, ± lancinating pain, occasional deafness.
HSAN II	Autosomal recessive	12p13.33; *HSN2*	All-size fibre loss; early onset, ulcers, acromutilation, Charcot joints.
HSAN III	Autosomal recessive	9q31; *IKBKAP*	All-size fibre loss; dysautonomia, absence of tongue fungiform papillae, late sensory loss.
HSAN IV	Autosomal recessive	1q21; *TRKA*	Small-myelinated fibre and unmyelinated-fibre loss; congenital insensitivity to pain with anhydrosis.
HSAN V	Autosomal recessive	1q21; *TRKA* 1p13.1; *NGFB*	Small-fibre loss; loss of pain and temperature perception.
CMT2B	Autosomal dominant	3q21; *RAB7*	Similar to HSAN I; motor nerves may be affected.
Other neuropathies[86]			
Fabry's disease	X-linked	Xq22; α-*Galactosidase A*	Episodic lancinating pain, acroparaesthesias, autonomic involvement; angiokeratomas; heart, kidney, respiratory tract, cornea, lens, brain vessel involvement.
Tangier's disease	Autosomal recessive	9q22-q31; *ABC1*	Algo-thermal sensory loss (may be pseudosyringomyelic); motor involvement; orange tonsils; involvement of liver, spleen, cornea, coronaries; low serum cholesterol.
Pure posterior column ataxia[87,88]			**Sensory ataxia**
Biemond's ataxia	Autosomal dominant or autosomal recessive-pseudodominant	..	Loss of vibration and position sense (± optic atrophy and Purkinje cell degeneration).
PCARP (posterior column ataxia and retinitis pigmentosa)	Autosomal recessive	1q31-q32; ..	Sensory ataxia and retinitis pigmentosa.
Hereditary ataxias[89,90]			**Spinocerebellar ataxia**
Friedreich's ataxia	Autosomal recessive	9q13; *FRDA*	Loss of large sensory neurons, deep sensory loss, spinocerebellar ataxia, cardiomyopathy, diabetes, skeletal deformities.
Ataxia with vitamin-E deficiency	Autosomal recessive	8q13.1-q13.3; *TTPA*	Friedreich-like ataxia ± pigmentary retinopathy, low vitamin E.
Abetalipoproteinaemia	Autosomal recessive	4q22-q24; *MTP*	Fat malabsorption, Friedreich-like ataxia, pigmentary retinopathy; acanthocytosis; low serum cholesterol, vitamin-E deficiency.
Ataxia teleangectasia	Autosomal recessive	11q22.3; *ATM*	Cerebellar ataxia, ocular apraxia, choreoathetosis, deep sensory loss, peripheral neuropathy, skin and ocular teleangiectases, immunodeficiency, tumour susceptibility; high concentration of α-fetoprotein.
Spinocerebellar ataxias	Autosomal dominant	Several loci and genes identified	Cerebellar ataxias plus variable involvement of other neuronal systems including sensory neurons.
Mitochondrial disorders[91–93]			**Different phenotypes, with sensory neuronopathy**
SANDO	Autosomal recessive	15q25; *POLG*	Sensory ataxic neuropathy, dysarthria, opthalmoparesis.
NARP syndrome	Maternal mtDNA	mtDNA; ATP synthase subunit 6 gene	Sensory neuropathy, ataxia, retinitis pigmentosa, neurogenic muscle weakness.

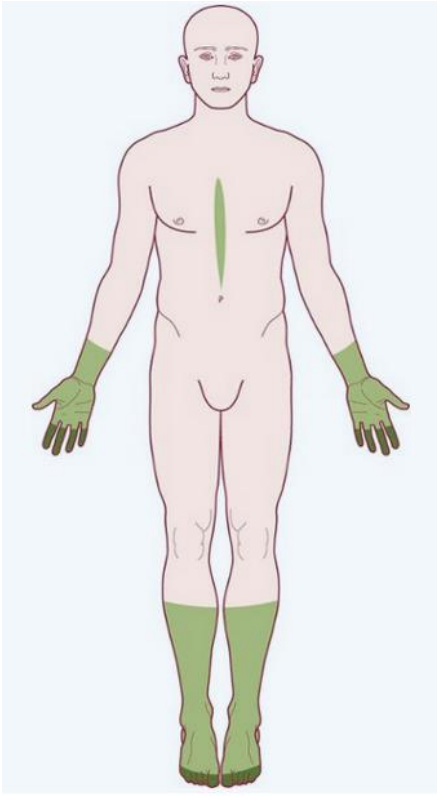
HSAN=Hereditary sensory and autonomic neuropathy; *SPTLC1*=Serin palmitoyltransferase, long chain base subunit-1; *IKBKAP*=Inhibitor of kappa light polypeptide gene enhancer in B cells, kinase complex-associated protein; *HSN2*=Hereditary sensory neuropathy 2 gene; *TRKA*=Tyrosine kinase A receptor for nerve growth factor; *NGFB*=Nerve growth factor, beta subunit; CMT=Charcot-Marie-Tooth neuropathy; *RAB7*=small GTP-ase late endosomal protein RAB7; *ABC1*=ATP-binding cassette transporter 1 gene; PCARP=Posterior column ataxia and retinitis pigmentosa; *FRDA*=Friedreich ataxia gene, frataxin gene; *TTPA*=α-tocopherol transfer protein; *MTP*=Microsomal triglyceride transfer protein; *ATM*=Ataxia-telangiectasia mutated gene; SANDO=Sensory ataxic neuropathy, dysarthria, opthalmoparesis; *POLG*=DNA polymerase gamma; NARP=Neurogenic muscle weakness, ataxia, retinitis pigmentosa.

Table 2: **Hereditary diseases with sensory neuronopathy**

Classificazione Topografica: Polineuropatie

<u>Lesione di più nervi:</u>

- Coinvolgimento distale
- Simmetrico
- Sincrono
- Lunghezza dipendente (meccanismo neuropatologico «Dying-back»)
- Distribuzione a guanto e calza



<u>Sintomi:</u>

- Disturbi sensitivi in genere prevalenti su quelli motori
- Possono associarsi disturbi trofici per interessamento neurovegetativo
- Areflessia distale AAII

Classificazione Topografica: Polineuropatie

Table 2 Clinical version of the Total Neuropathy Score (TNSc)

TNSc					
	0	1	2	3	4
Sensory symptoms	**None**	**Limited to fingers or toes**	**Extend to ankle or wrist**	**Extend to knee or elbow**	**Above knees/elbows**
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require help/assistance	Disabled
Autonomic symptoms (n)	0	1	2	3	4 or 5
Pin sensation	Normal	Reduced in fingers or toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced above elbow/knee
Vibration sensibility	Normal	Reduced in fingers or toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced above elbow/knee
Strength	Normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
Tendon reflexes	Normal	Ankle reflex (AR) reduced	AR absent	AR absent and others reduced	All reflexes absent

J Neurol Neurosurg Psychiatry 2013;0:1–7

Polineuropatie: Classificazione eziologica

Disease*	Sensory (S), motor (M), or sensori-motor (SM)	Axonal (A) or demyelinating (D)	Comment
Diabetes mellitus (very common)	S, SM, rarely M	A and D	Commonest cause of chronic polyneuropathy
Renal insufficiency	SM	A	Controllable with dialysis; curable with renal transplantation
Nutritional deficiency (mainly B vitamin deficiencies); often exists with chronic alcoholism	SM	A	Deficiency of thiamine, pyridoxine, folic acid, pantothenic acid, and probably others
Vitamin B-12 deficiency	S	A	Neuropathy may be overshadowed by myelopathy (subacute combined degeneration)
Chronic liver disease	S or SM	A and D	Polyneuropathy usually mild
Porphyria (rare)	M or SM	A	Often acute; might be proximal rather than distal, with arms affected more than legs; distinguish from Guillain-Barré syndrome
Malabsorption (inflammatory bowel disease, short bowel syndrome)	S or SM	A	Some have deficiency of vitamins (especially vitamin E or B-12); in others, the basis is unknown
Coeliac disease	S or SM	A	Rarely due to vitamin deficiency; might have an autoimmune basis
Primary systemic amyloidosis (rare)	SM; might have prominent small fibre component	A	Most have serum paraprotein. Some have multiple myeloma, Waldenstrom's macroglobulinaemia, or lymphoreticular malignancy
Acromegaly (rare)	S	A	Carpal tunnel syndrome frequent
Chronic obstructive pulmonary disease (rare)	S or SM	A	Only seen with severe pulmonary insufficiency
Leprosy (tuberculoid, dimorphous, and lepromatous)	S; less often SM	A	Most often involves cutaneous nerves in coolest parts of body
Lyme disease (occasionally)	S>M	A	Focal or multifocal radiculoneuropathy. Facial neuropathy also common
HIV infection	S>M	A	Chronically causes distal mainly sensory polyneuropathy. Other types of neuropathies occur, especially with early infection
Sarcoidosis	S or SM	A	Mononeuropathy multiplex or polyneuropathy. Facial neuropathy common.
Carcinoma (pure sensory) (rare, but distinctive)	Pure S	A	Paraneoplastic ganglionitis mostly with small cell lung or breast cancer; might have positive paraneoplastic antibodies in serum
Carcinoma (sensori-motor)	SM	A	Mainly with lung carcinoma; might have positive paraneoplastic antibodies in serum
Lymphoma (Hodgkin's and non-Hodgkins)	SM	A and D	Usually axonal, but sometimes demyelinating polyneuropathy
Multiple myeloma	S, M, or SM	A	Uncommon and usually axonal
Myeloma (osteosclerotic)	SM	D	Usually demyelinating; might be associated with POEMS syndrome
Monoclonal gammopathy of unknown significance (MGUS)			
IgM	S or SM	D	IgMκ most common; may bind to myelin associated glycoprotein; usually demyelinating predominantly sensory polyneuropathy.
IgG	SM	A	Usually axonal polyneuropathy
IgA	SM	A	Usually axonal polyneuropathy
Cryoglobulinaemia (rare)	SM	A	May be mononeuropathy multiplex; sometimes associated with chronic hepatitis C infection

Polineuropatie: Classificazione eziologica

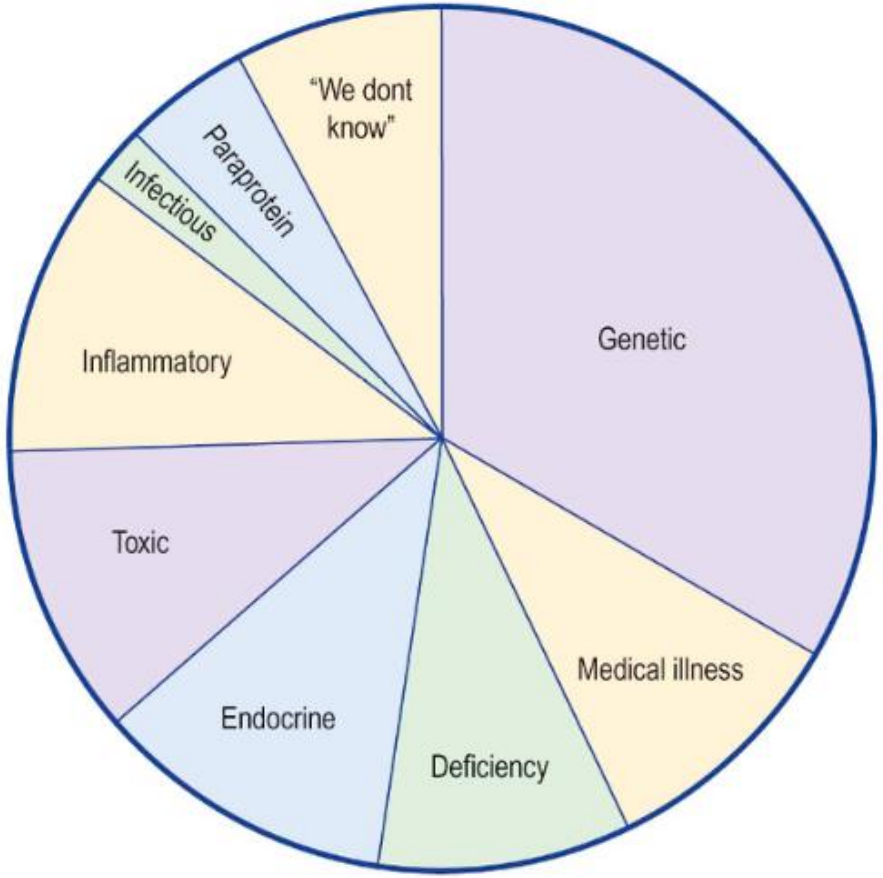
Drug*	Sensory (S), motor (M), or sensori-motor (SM)	Axonal (A) or demyelinating (D)	Comments
Amiodarone (antiarrhythmic)	SM	D and A	Prominent demyelination; also tremor, optic neuropathy; dose related
Chloramphenicol (antibiotic)	SM	A	Rare; usually reversible
Chloroquine (antimalarial)	SM	A and D	Mild demyelination; principal toxicity is myopathy
Colchicine (anti-gout)	S or SM	A	Neuropathy overshadowed by myopathy
Dapsone (dermatological agent; also for leprosy, pneumocystis pneumonia)	M	A	Nearly pure motor with predominant arm, hand weakness
Disulfiram (anti-alcohol)	SM	A	Usually occurs after months to years of treatment
Ethambutol (anti-tuberculous)	S	A	Mild and reversible
Hydralazine (anti-hypertensive)	S>M	A	Pyridoxine antagonist; avoid by co-administration of pyridoxine
Isoniazid (anti-tuberculous)	SM	A	Pyridoxine antagonist; slow acetylators more susceptible; avoid by co-administration of pyridoxine
Metronidazole (antibiotic)	S or SM	A	Mainly large fibre; dose related
Misonidazole (radiosensitiser)	S or SM	A	Congener of metronidazole; neurotoxicity is the dose-limiting factor
Nitrofurantoin (antibiotic)	SM	A	Rapidly progressive; renal failure increases toxicity
Nitrous oxide (inhalational anaesthetic)	S	A	Usually inhalational abuse; often presents with ataxia and is associated with myelopathy and megaloblastic anaemia; interferes with vitamin B-12 metabolism
Nucleosides (ddC, ddI, d4T) (anti-retroviral)	S>M	A	Painful; dose-limiting; "coasting"† can occur; must distinguish from HIV-induced neuropathy
Phenytoin (anti-epileptic)	S>M	A	Rare and only after decades of use
Platinum (cisplatin) (anti-neoplastic)	S	A	Severe large-fibre sensory neuropathy; dose related; coasting can occur; also ototoxicity and nephrotoxicity
Pyridoxine (vitamin B-6)	S	A	Sensory neuronopathy; occurs with high doses (>200 mg per day)
Suramin (anti-parasitic, anti-neoplastic)	M>S	D and A	Prominent demyelination; resembles Guillain-Barré syndrome; related to maximal plasma levels >350 μg/mL
Taxol (anti-neoplastic)	S>M	A	Occurs with doses >200 mg/m^2; often begins suddenly
Thalidomide (sedative-hypnotic; anti-inflammatory, immunomodulatory)	S>M	A	Initial symptoms always sensory often with profound insensitivity to pain and touch; sensory nerve conduction studies useful for detecting subclinical neuropathy
Vincristine (anti-neoplastic)	S>M	A	Onset with sensory symptoms in hands more so than in feet; if weakness occurs, medication should be stopped; autonomic neuropathy (gastroparesis, constipation, urinary retention) frequent

Polineuropatie: Classificazione eziologica

Toxin*			
Acrylamide monomer (grouting and flocculation agent). Acrylamide polymer is non-toxic	S>M	A	Large fibre neuropathy with diffuse areflexia; gait ataxia; high doses can cause CNS dysfuntion (encephalopathy); sensory nerve conduction studies useful for detecting subclinical neuropathy
Arsenic (insecticide, herbicide; also from smelting and wood preservative industries); might be given with suicidal or homicidal intent	SM	A; acutely may have D	Onset with painful sensory symptoms followed by weakness; prominent systemic effects (gastrointestinal symptoms, anaemia) and skin/nail changes (Mees lines); acute intoxication may cause a Guillain-Barré-syndrome-like polyneuropathy with proximal nerve demyelination; however, most acute and chronic intoxications cause a distal symmetrical axonal polyneuropathy
Carbon disulphide (solvent used in manufacture of rayon fibre and cellophane film)	S>M	A	Sensory symptoms followed by motor deficits; primary central distal axonopathy; neurofilamentous swelling of axons causes retraction of paranodal myelin and slowing of nerve conduction
Diphtheria toxin (protein exotoxin from *Corynebacterium diphtheriae*)	SM	D	Rare; begins 8–12 weeks after infection; may be confused with Guillain-Barré syndrome; toxin inhibits myelin synthesis causing demyelination
Ethylene oxide (gas sterilisation)	SM	A	Usually inhalational exposure; inprovement follows termination of exposure
Hexacarbons (n-hexane and methyl n-butyl ketone) (solvents)	SM	A and D	Exposure via inhalation such as inhalational abuse of gasoline or glue; neuropathy might be severe; coasting could last 2 to 4 months; neurofilamentous swelling of axons causes retraction of paranodal myelin and slowing of nerve conduction
Lead (inorganic) (industrial uses in batteries, smelting)	Pure M or M>S	A	Primarily motor neuropathy; arms (wrist drop) affected more than legs; occurs with systemic effects (gastrointestinal symptoms, anaemia)
Mercury (metallic and vapour)	M>S	A	Predominantly motor neuropathy; can mimic Guillain-Barré syndrome; might occur with CNS effects (lethargy, emotional lability, and tremor)
Organophosphates (insecticides, petroleum additives)	M>S	A	Neuropathy is delayed by 10–20 days after exposure; also myelopathy with lower limb spasticity and loss of proprioception
Thallium (rodenticides)	S>M	A	Painful sensory symptoms prominent; occurs with systemic effects (gastrointestinal symptoms, anaemia); alopecia is hallmark but does not occur until 2–3 weeks after exposure

Lancet 2004; **363:** 2151–61

Approccio diagnostico alle neuropatie periferiche



Overview of polyneuropathy

Neuropatie periferiche: gli strumenti a supporto della diagnosi

- Anamnesi ed esame obiettivo neurologico
- Neurofisiologia: EMG, Elettroneurografia, Potenziali evocati somatosensoriali (PESS), Valutazione del Sistema Nervoso Vegetativo
- Studio del liquor cerebro-spinale (dissociazione albumino-citologica, anticorpi)
- Biopsia del nervo periferico
- Studio delle piccole fibre nervose
- Neuroimaging
- Genetica molecolare

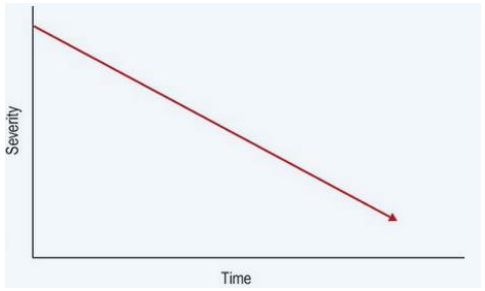
L’esame neurofisiologico a supporto dell’inquadramento clinico

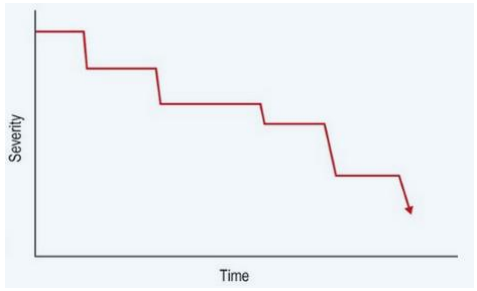
1-ESORDIO

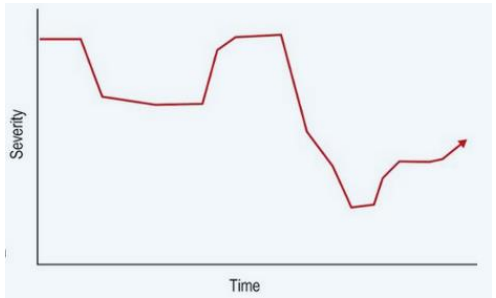
- acuto
- subacuto
- cronico

2-EVOLUTIVITA’

- monofasico
- progressivo
- recidivante/remittente
- progressivo a step



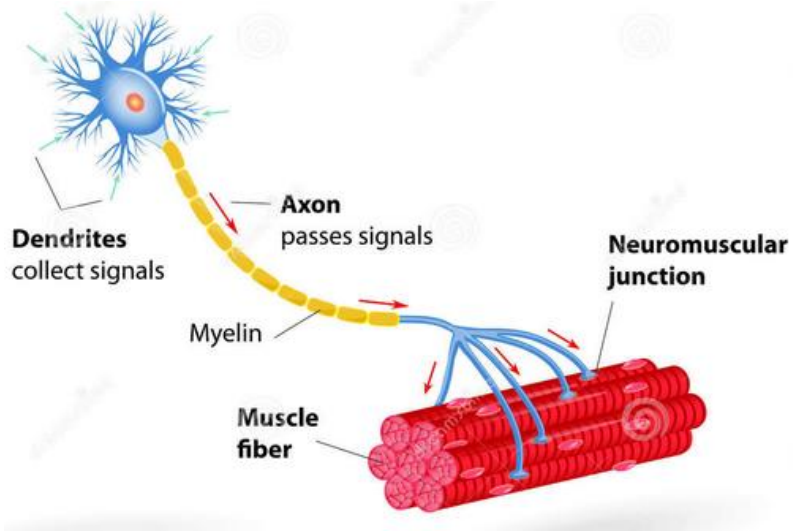


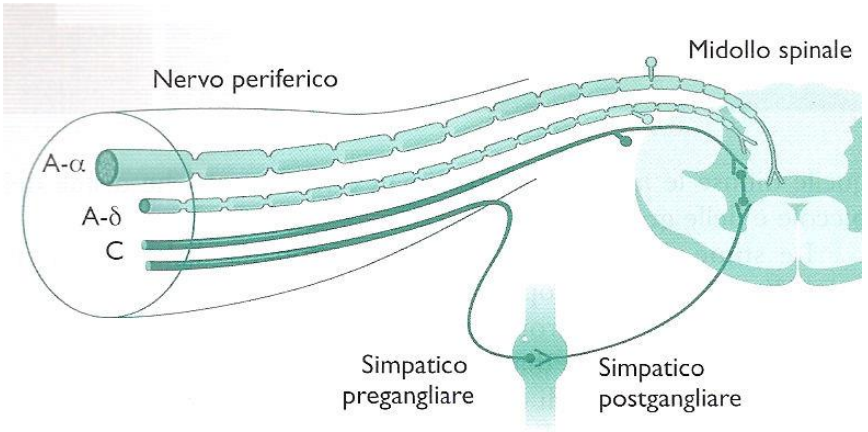


L’esame neurofisiologico a supporto dell’inquadramento clinico

3-FIBRE NERVOSE COINVOLTE

- motorie
- sensitive di grade diametro
- sensitive di piccolo diametro
- autonomiche

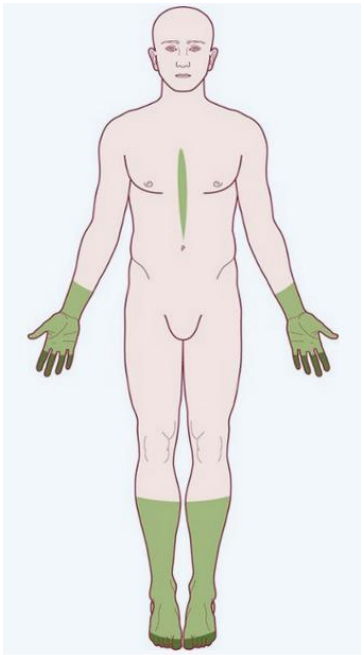


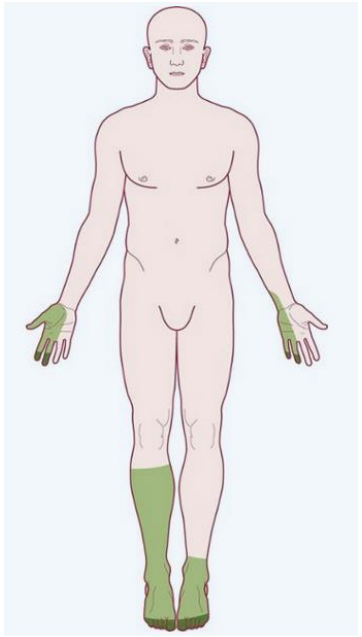


L’esame neurofisiologico a supporto dell’inquadramento clinico

4-PATTERN DI DISTRIBUZIONE

- Simmetrico / Asimmetrico
- Gradiente disto-prossimale (dying back)
- Multineuropatia

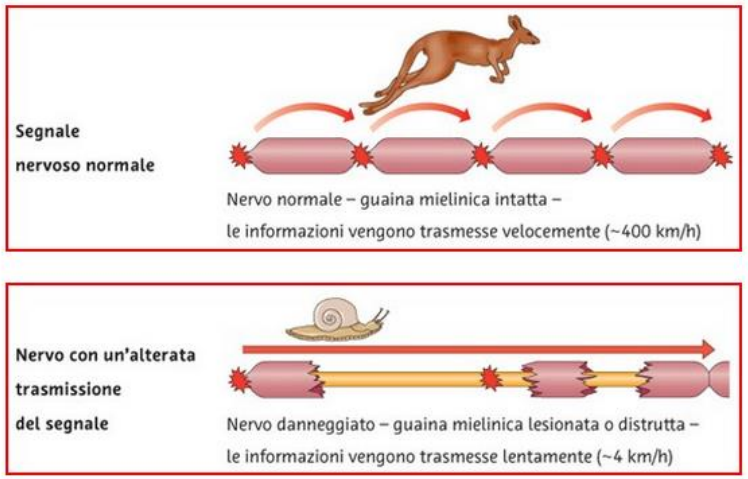


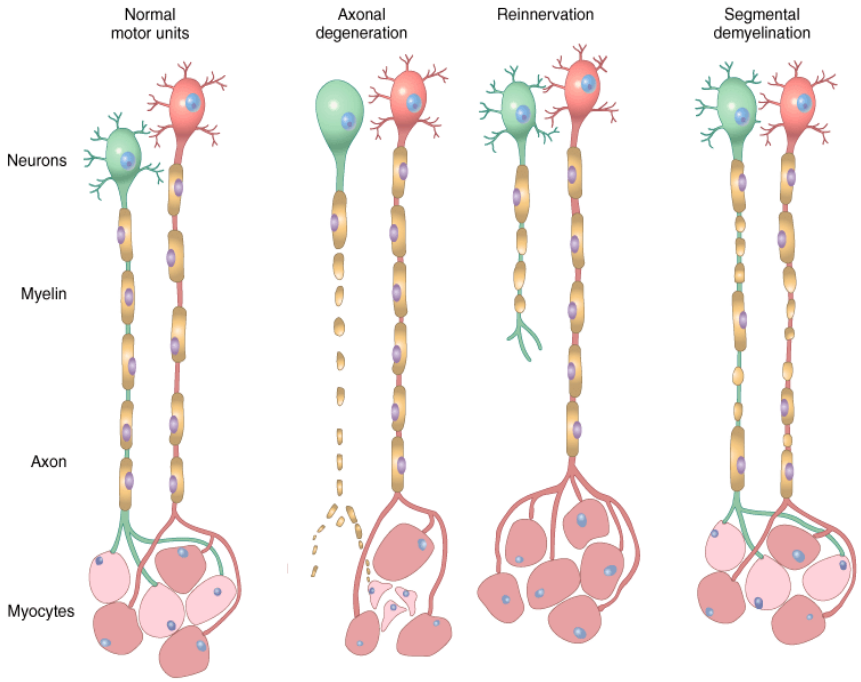


L’esame neurofisiologico a supporto dell’inquadramento clinico

5-PROCESSO PATOLOGICO SOTTOSTANTE

- Demielinizzazione
- Perdita assonale
- Danno misto





L’esame neurofisiologico a supporto dell’inquadramento clinico

6-ANAMNESI FAMILIARE

- Storia familiare di «polio», «reumatismi», «artrite» (forme lievi di neuropatie genetiche?)
- Nota neuropatia in familiari

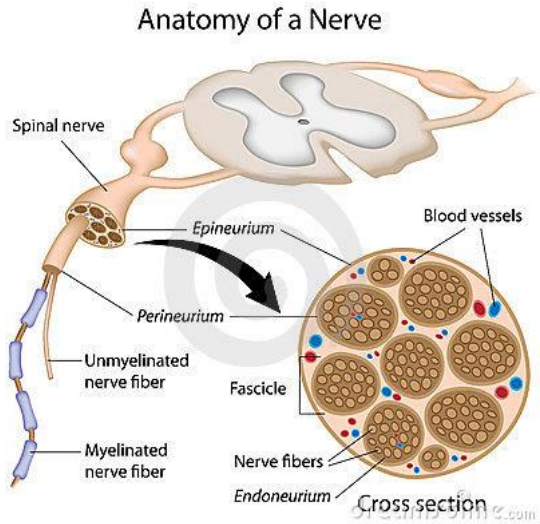
7-ESPOSIZIONE A FARMACI O TOSSICI

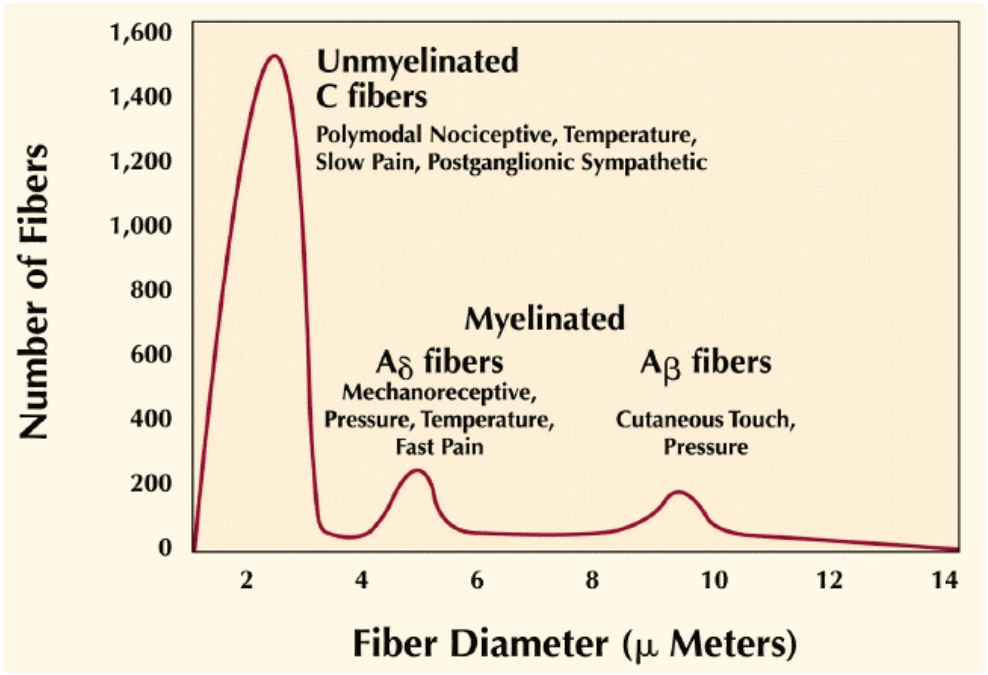
- Esposizione a farmaci (es. antitubercolari, chemioterapici, ecc…)
- Metalli pesanti (alluminio, piombo, arsenico, mercurio), solventi industriali, fosfati organici

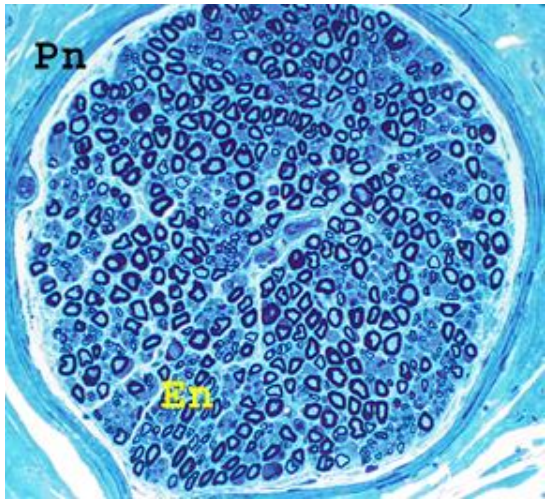
UTILITA' DELL'ESAME NEUROFISIOLOGICO

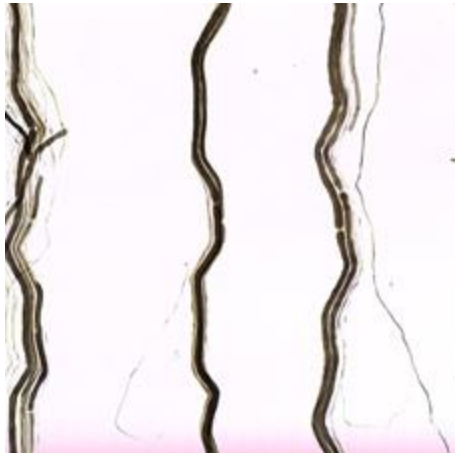
- **Confermare** la presenza di una polineuropatia
- Stabilire se l'interessamento è **motorio, sensitivo o misto**
- Definire la sottostante patofisiologia: perdita **assonale** / **demielinizzazione**
- Identificare il **pattern di distribuzione**
- Stabilirne la **gravità**

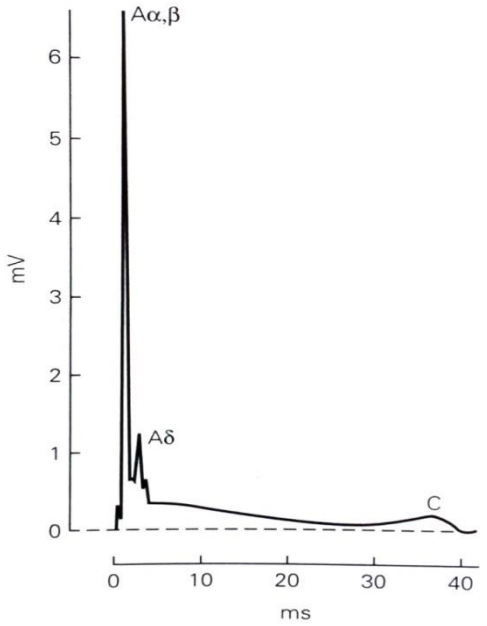
ENG per lo studio delle le fibre di grosso calibro





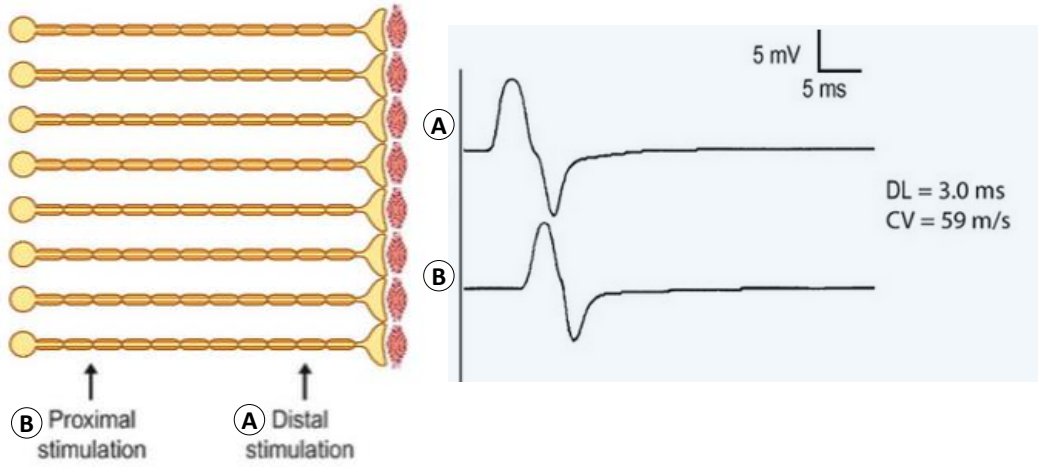


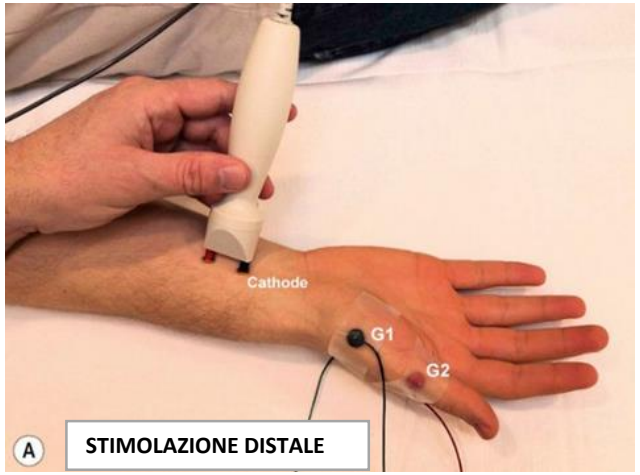


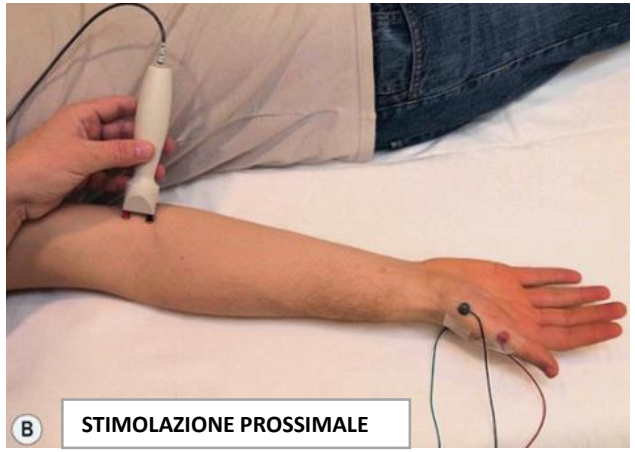


L'ELETTRONEUROGRAFIA

STUDIO CONDUZIONE MOTORIA (es. NERVO MEDIANO)



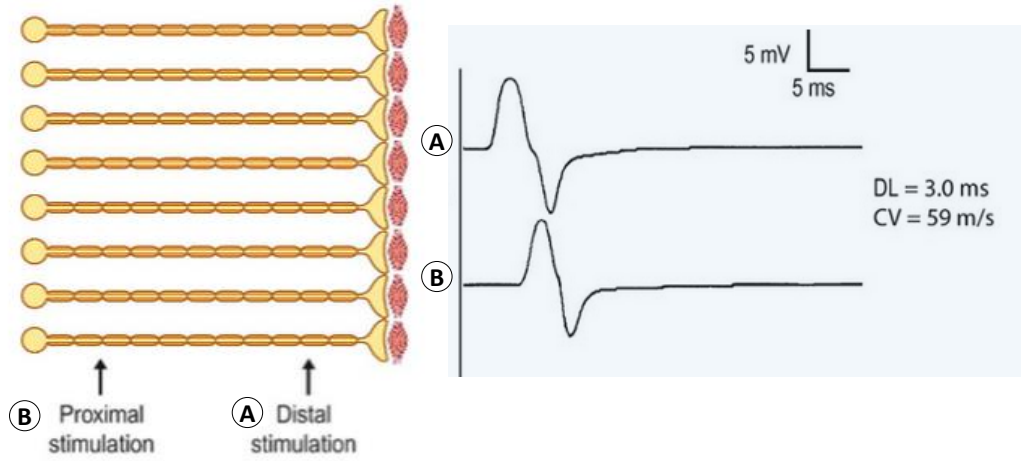


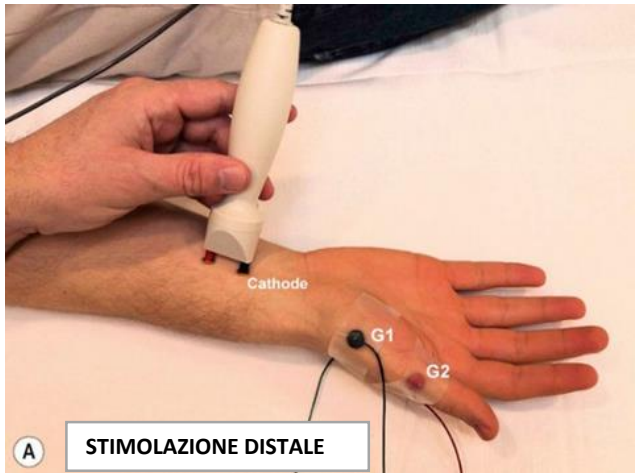


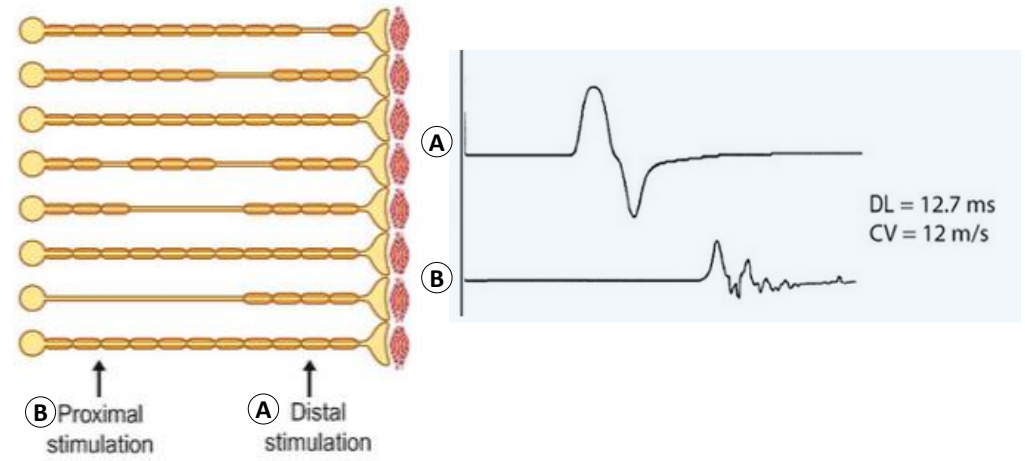
PARAMETRI ESSENZIALI

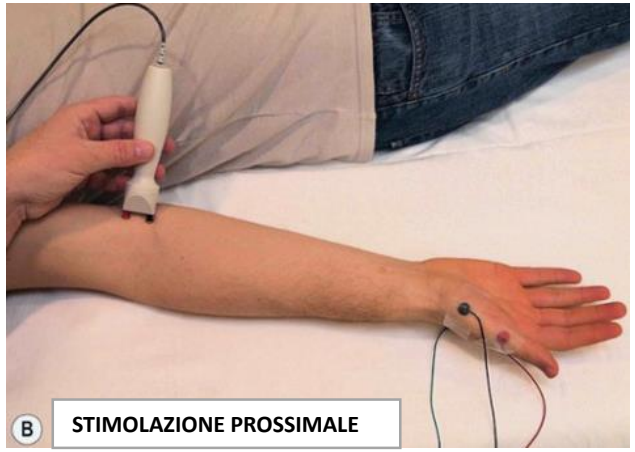
- Latenza motoria distale (ms)
- Ampiezza del potenziale d'azione motorio (mV)
- Velocità di conduzione motoria (m/s)

PATTERN DEMIELINIZZANTE (neuropatie acquisite)

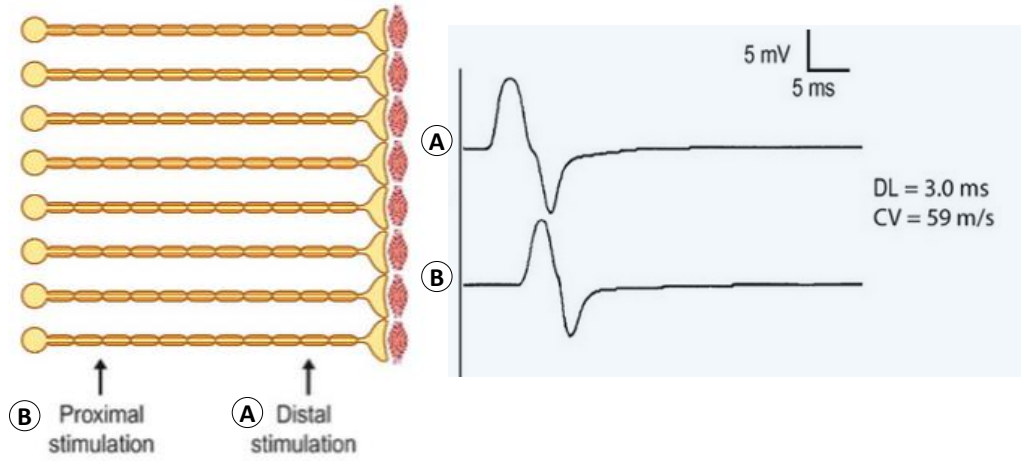


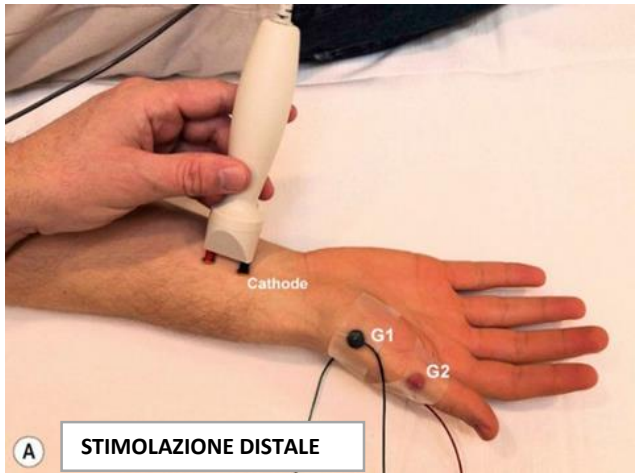


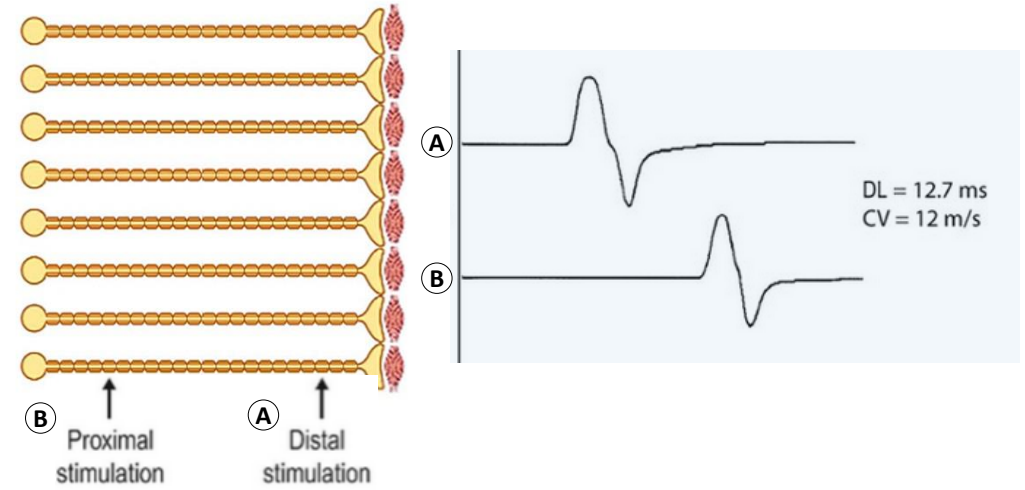


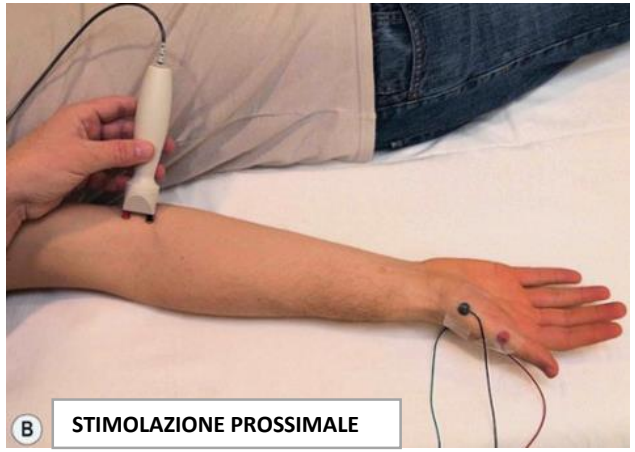


PATTERN DEMIELINIZZANTE (neuropatie genetiche)

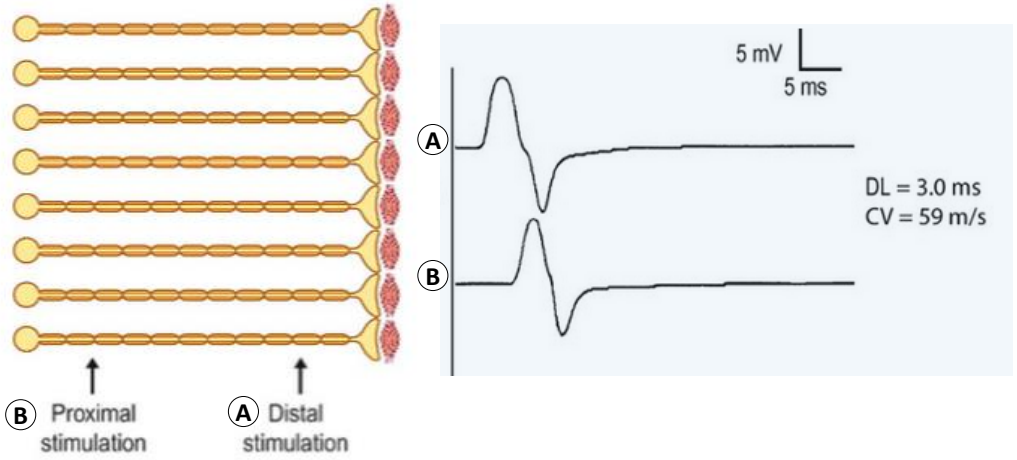


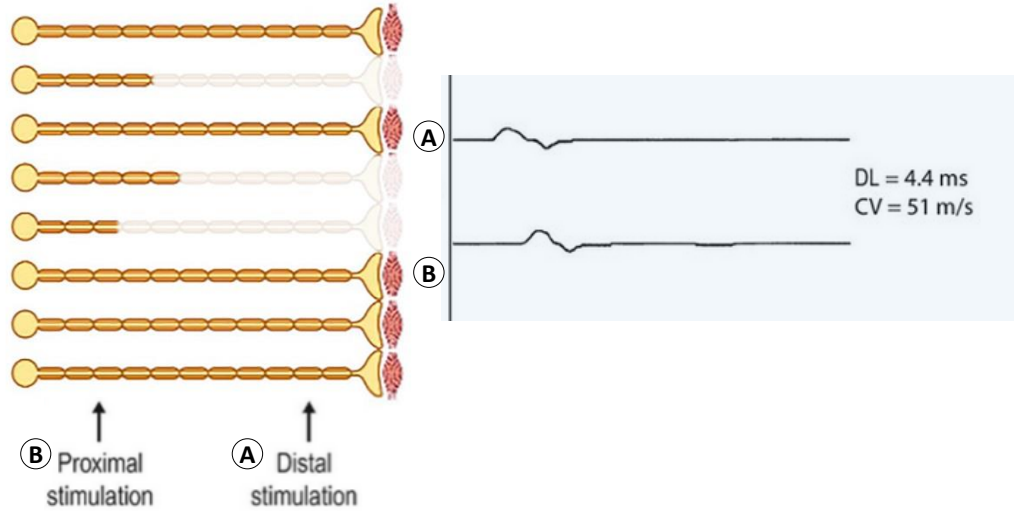


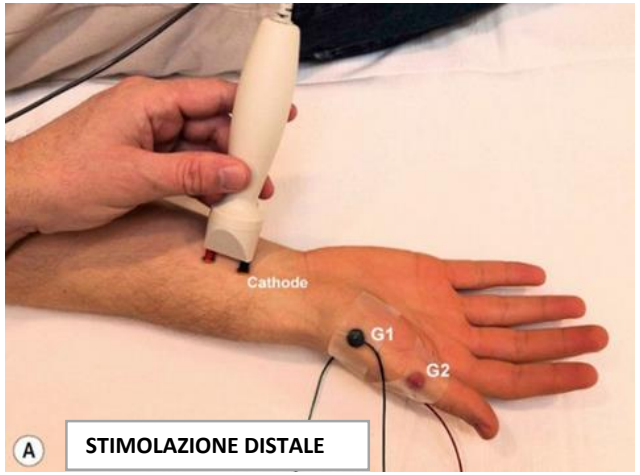


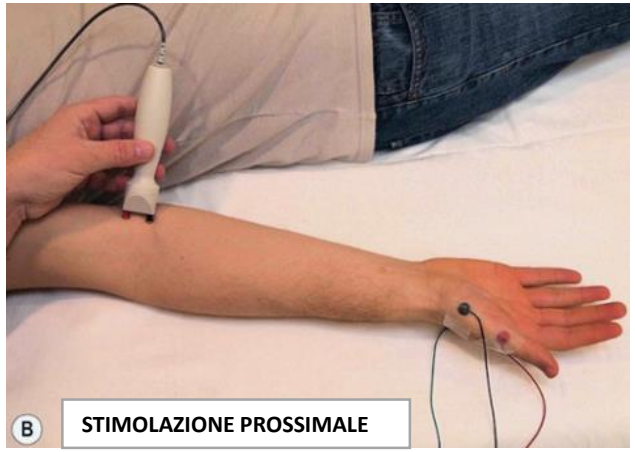


DANNO ASSONALE

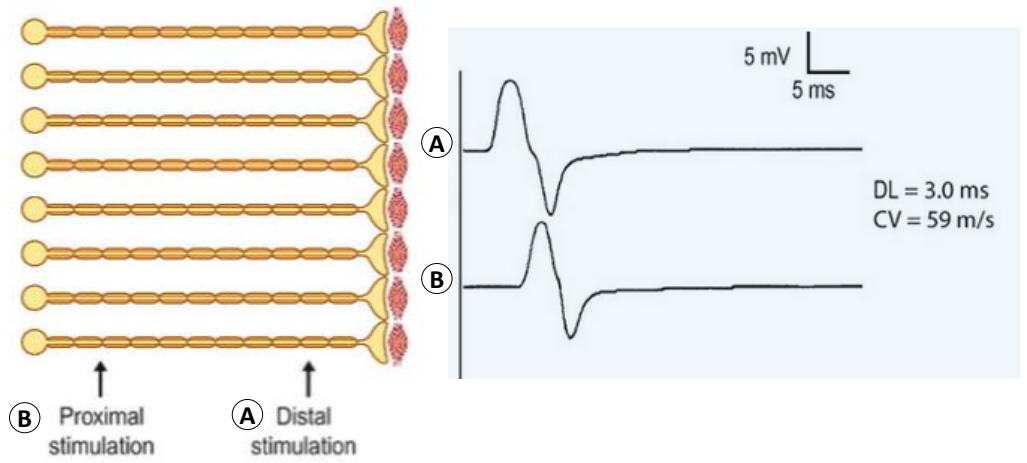


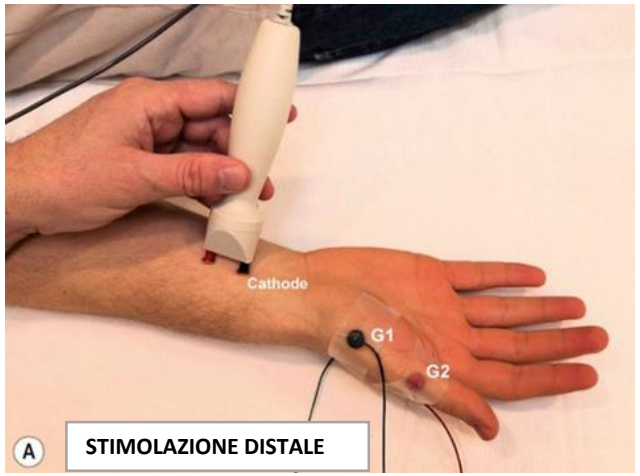


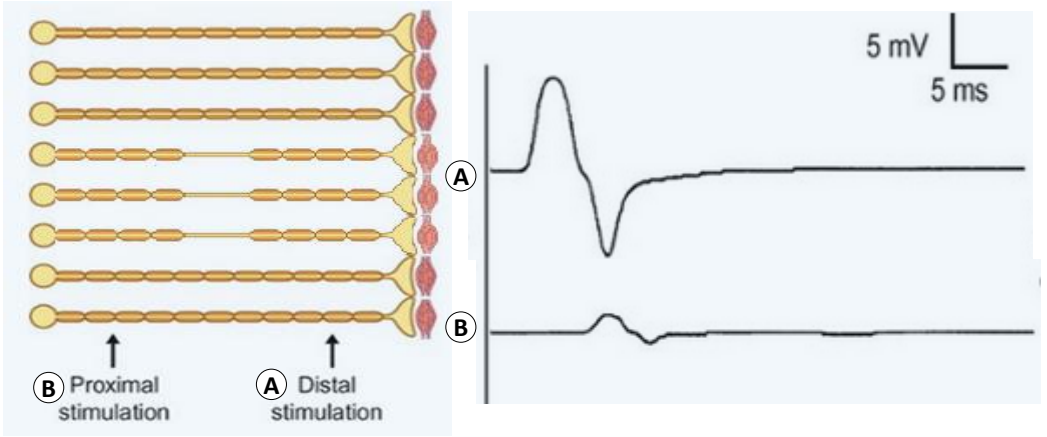


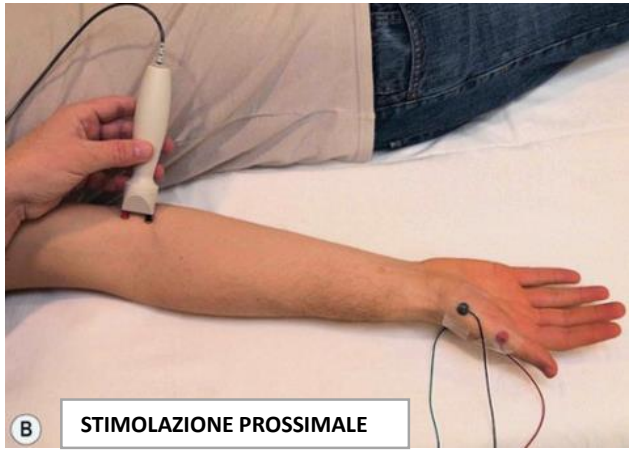


BLOCCO DI CONDUZIONE

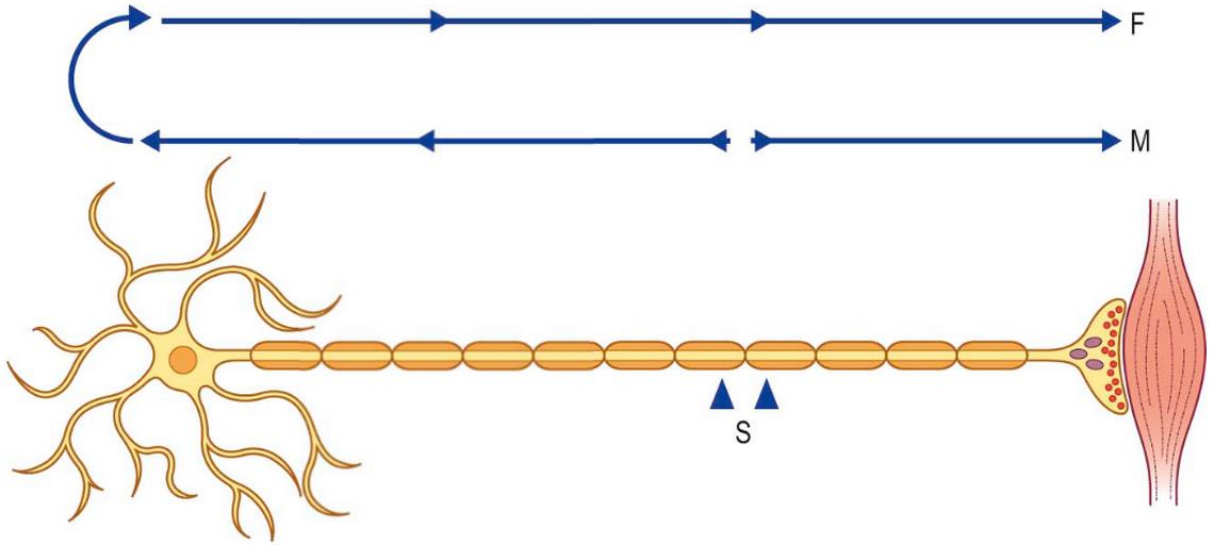


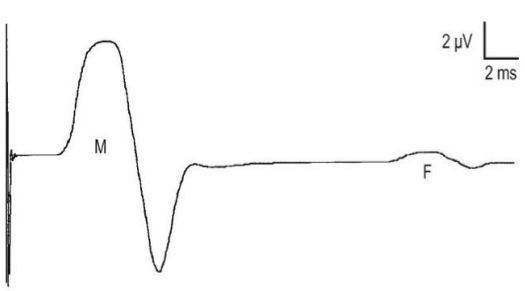


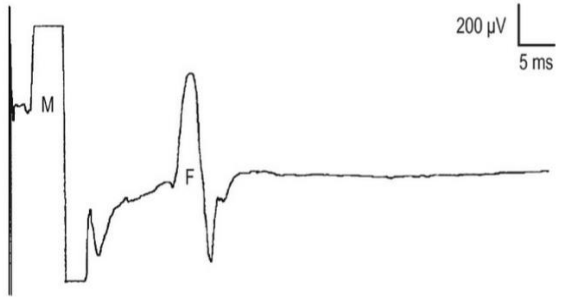


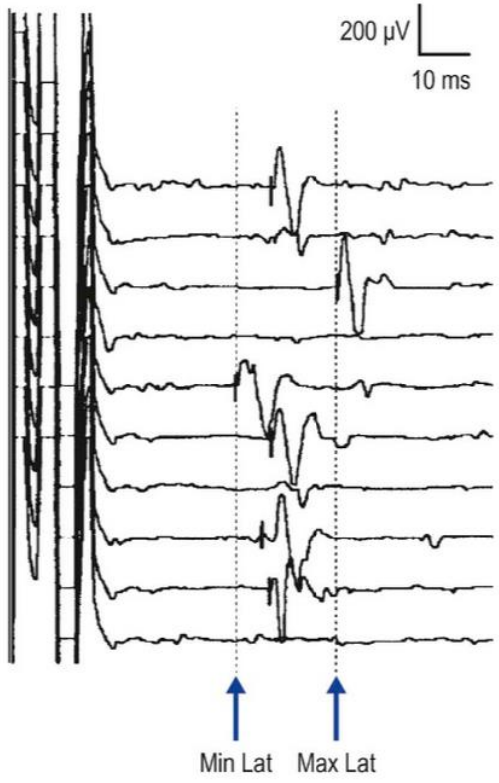


ONDA F



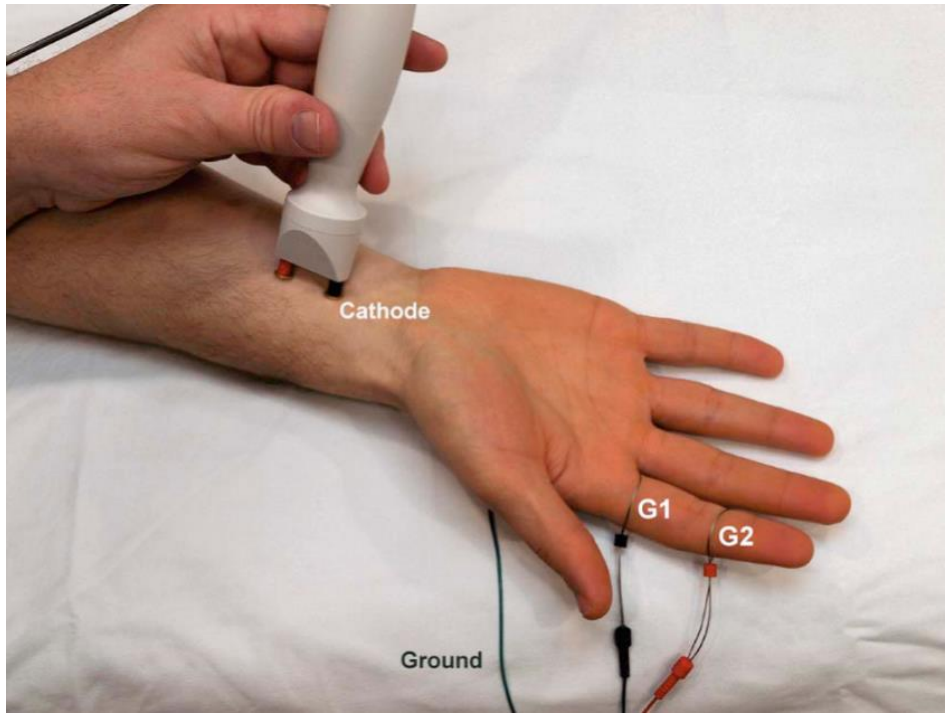


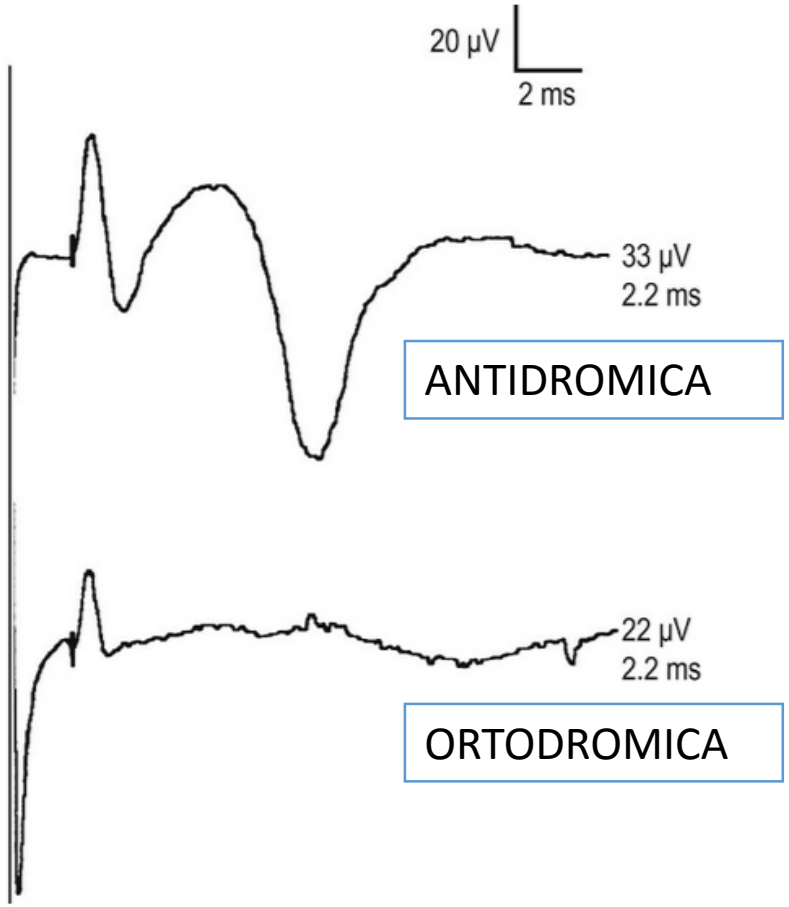




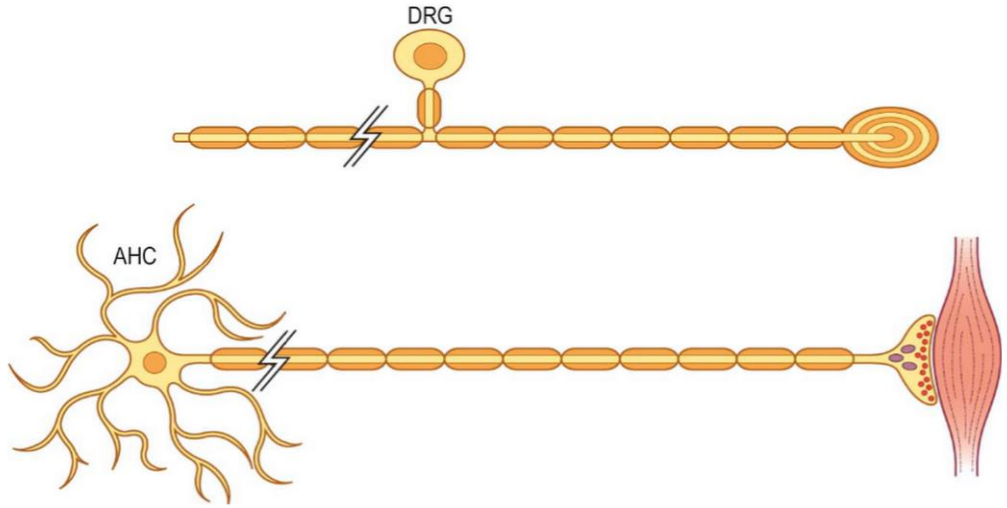
Da valutare sempre in relazione alla risposta M

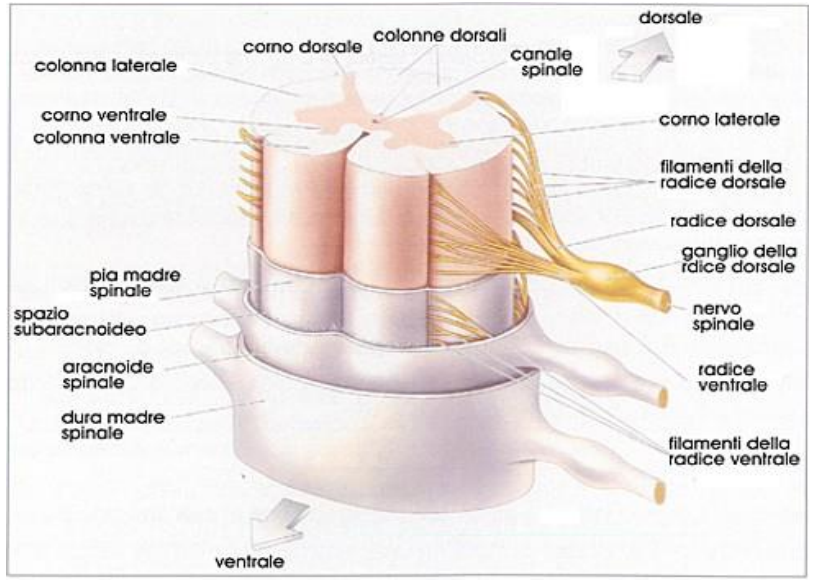
STUDIO CONDUZIONE SENSITIVA





Conduzione sensitiva e sede di lesione

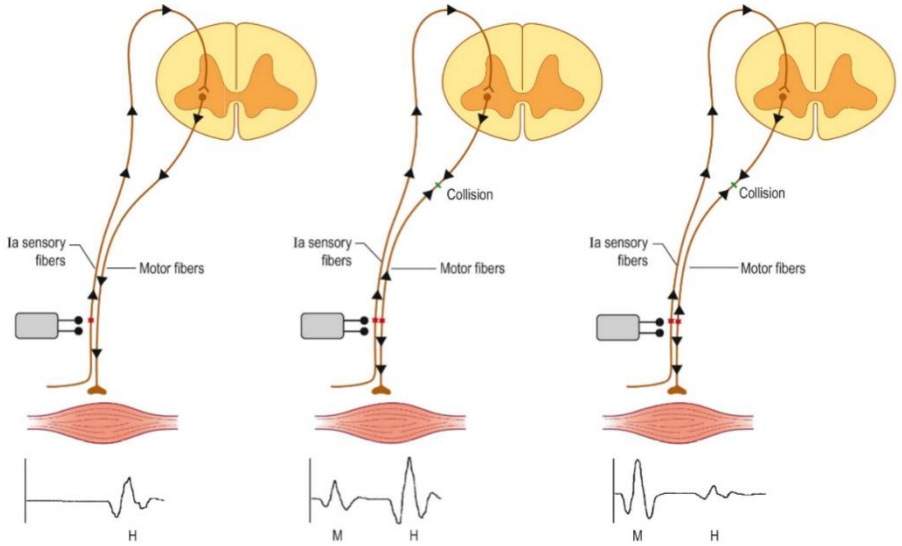


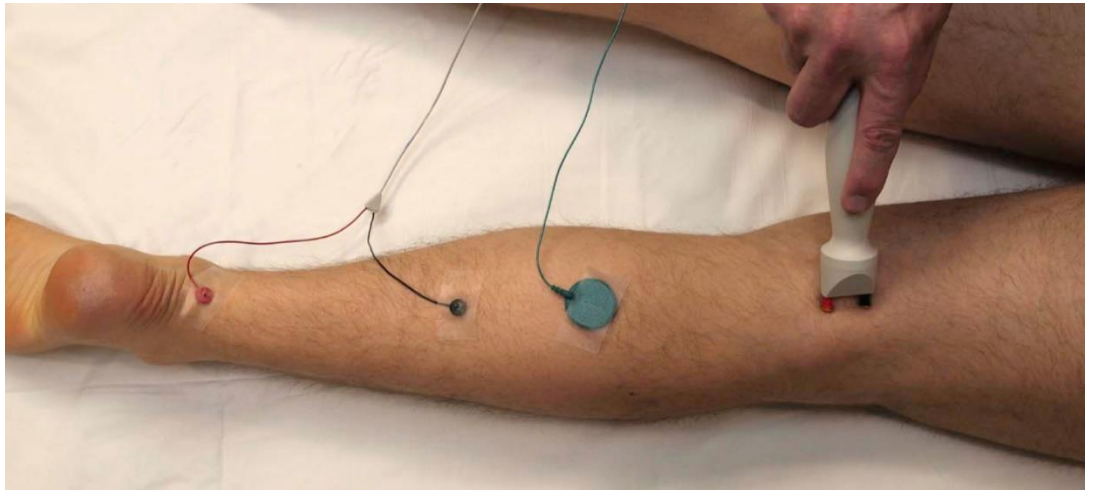


Conduzione sensitiva periferica → normale

Conduzione motoria periferica → alterata

Riflesso H e studio radicolare pre-gangliare





M. Soleo (n. tibiale)→ radice S1

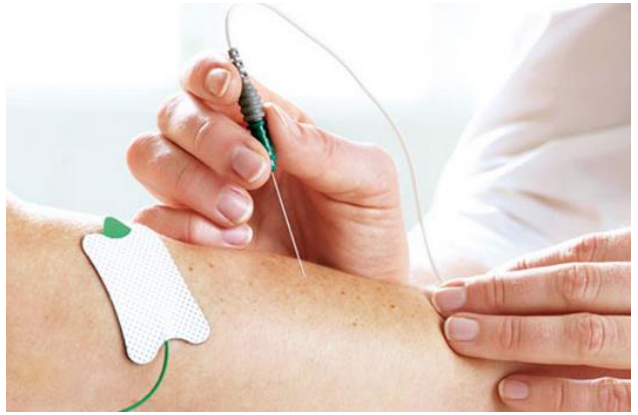
M. flessore radiale del carpo (n. mediano) → radice C7

ESAME ELETTROMIOGRAFICO

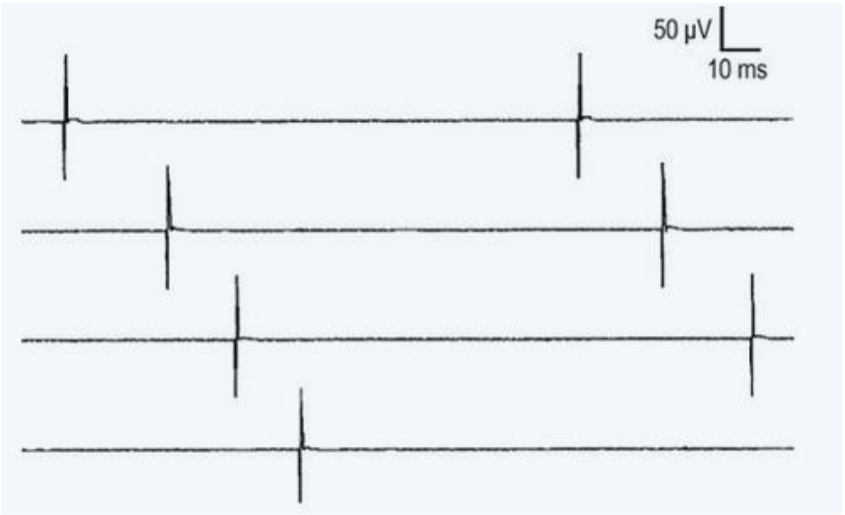
Utilizza un elettrodo ad ago per valutare l'attività bioelettrica muscolare:

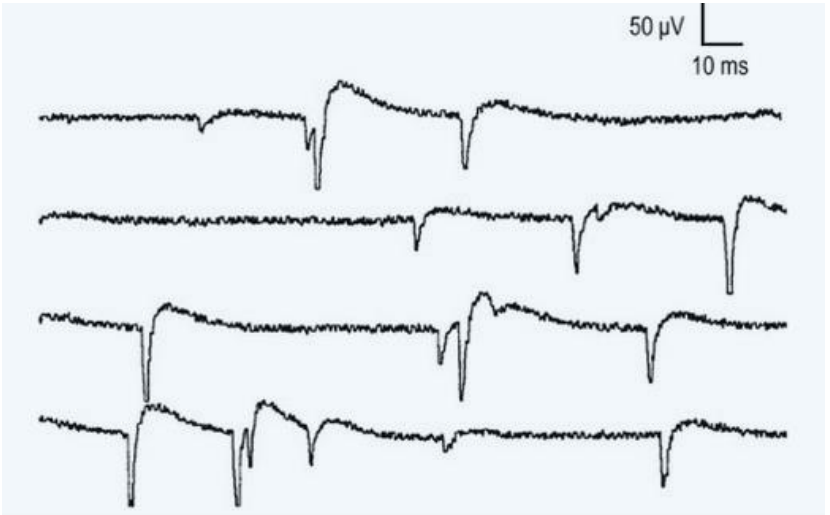
- *In condizione di riposo*
  - Attività muscolare spontanea (denervazione acuta 3-4 settimane)

- *Durante attivazione muscolare*
  - Potenziali di unità motoria (PUM)
  - Reclutamento



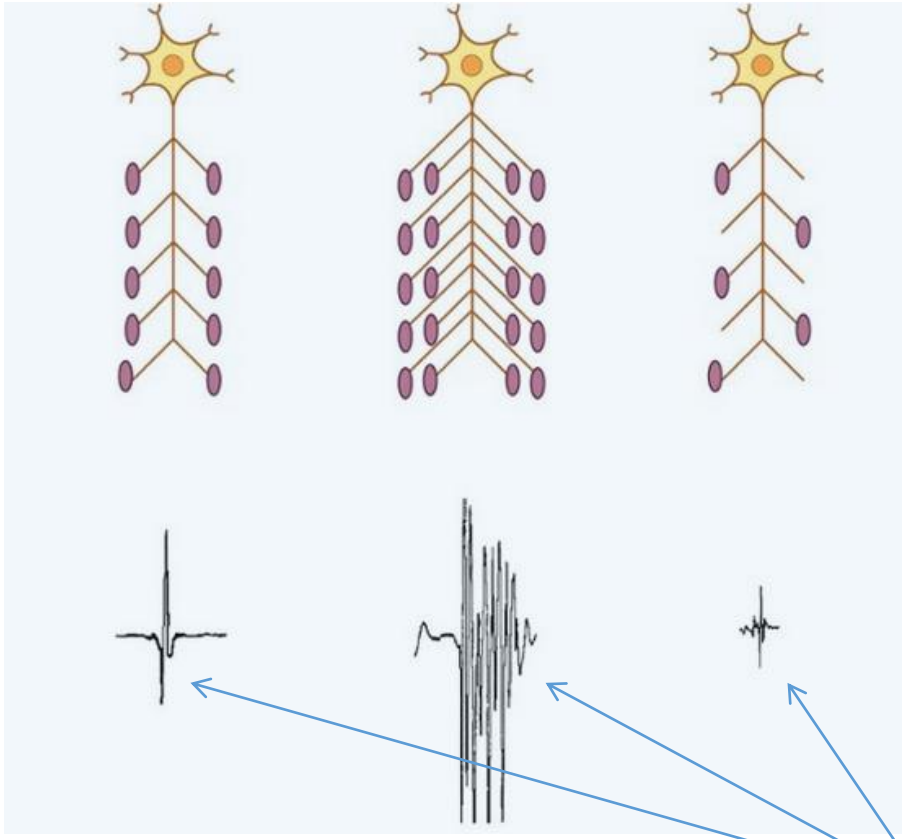
ESAME ELETTROMIOGRAFICO A RIPOSO



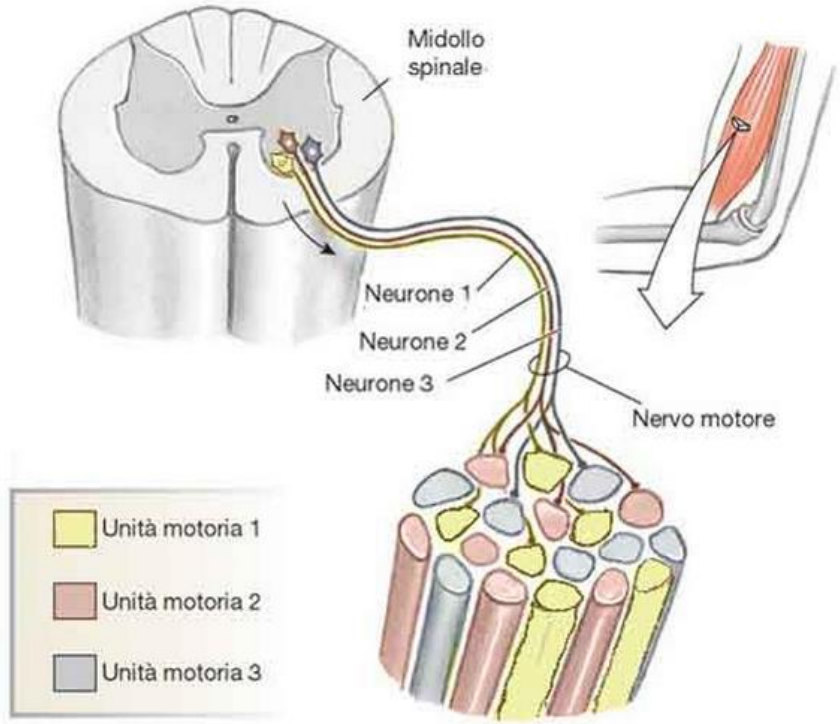


Attività elettrica muscolare spontanea da denervazione

Esame elettromiografico in attivazione muscolare



NORMALE NEUROPATIA MIOPATIA



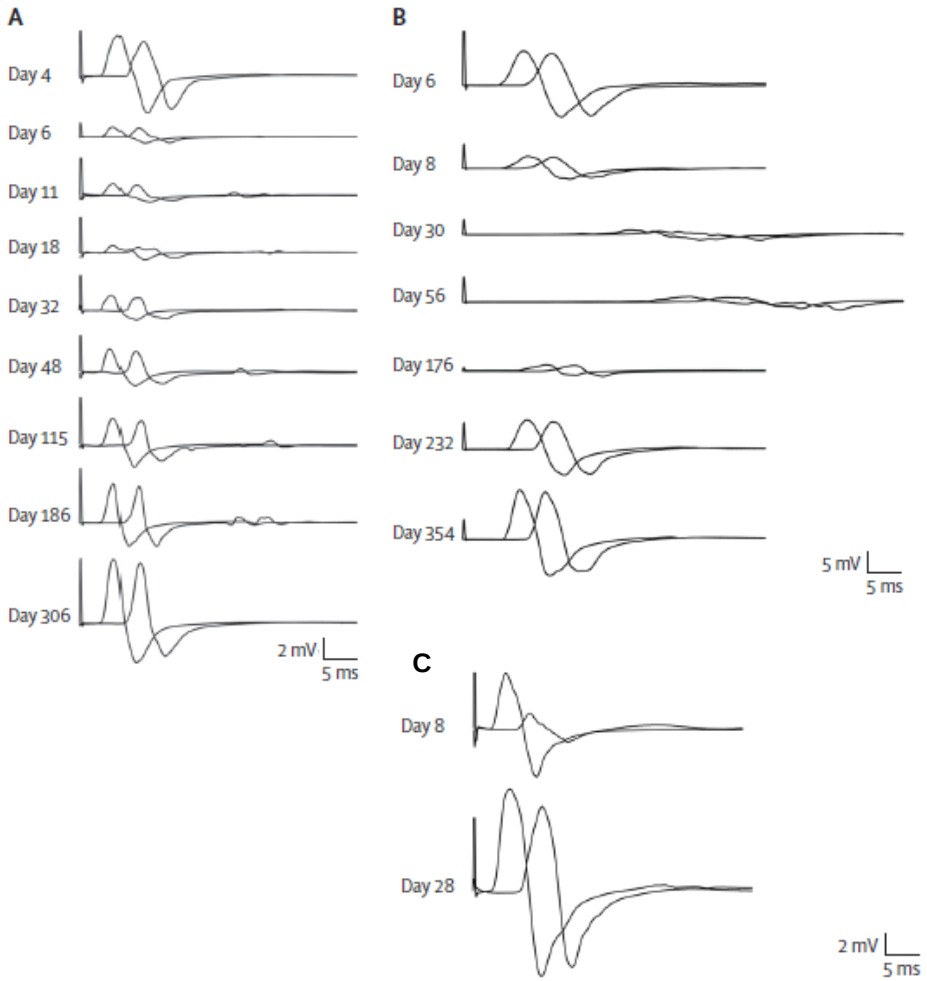
Registrazione potenziali di unità motoria (PUM)

ESAME ELETTROMIOGRAFICO

- Fornisce informazioni sulla evoluzione del processo neuropatico → acuto-attivo / cronico
- Da informazioni sulla severità
- Importante nella localizzazione di lesione soprattutto nei territori più difficilmente esplorabili con l'elettroneurografia → distretti prossimali
- Distribuzione del danno neuropatico motorio

PATTERN NEUROFISIOLOGICI

Neuropatie infiammatorie acute

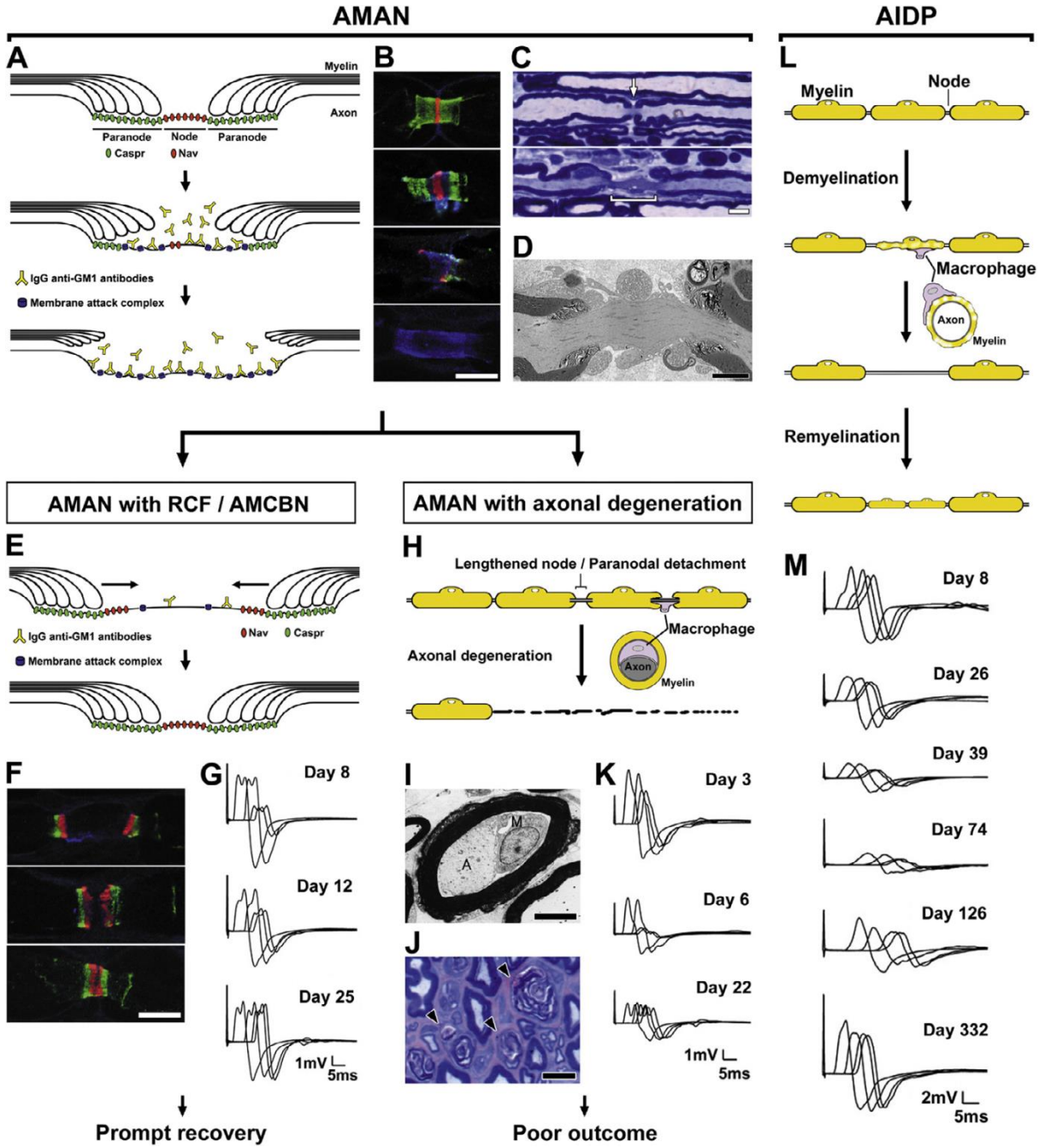


A) AMAN neuropatia assonale motoria acuta

B) AIDP poliradiculoneuropatia demielinizzante infiammatoria acuta

C) AMAN con blocco di conduzione reversibile

***Lancet Neurol* 2013; 12: 1180–88**



Lancet Neurol 2013; 12: 1180–88

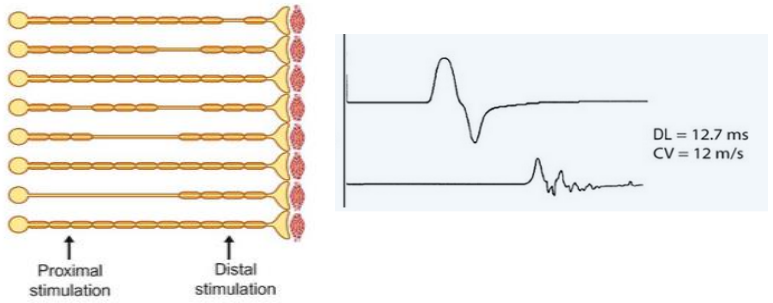
PATTERN NEUROFISIOLOGICI

Criteri diagnostici elettrofisiologici per CIDP

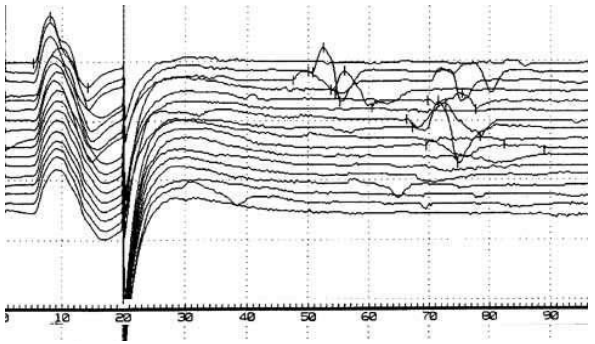
(1) Definite: at least one of the following
(a) Motor distal latency prolongation ≥50% above ULN in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome), or
(b) Reduction of motor conduction velocity ≥30% below LLN in two nerves, or
(c) Prolongation of F-wave latency ≥30% above ULN in two nerves (≥50% if amplitude of distal negative peak CMAP <80% of LLN values), or
(d) Absence of F-waves in two nerves if these nerves have distal negative peak CMAP amplitudes ≥20% of LLN + ≥1 other demyelinating parameter[a] in ≥1 other nerve, or
(e) Partial motor conduction block: ≥50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parameter[a] in ≥1 other nerve, or
(f) Abnormal temporal dispersion (>30% duration increase between the proximal and distal negative peak CMAP) in ≥2 nerves, or
(g) Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in ≥1 nerve (median ≥ 6.6 ms, ulnar ≥ 6.7 ms, peroneal ≥ 7.6 ms, tibial ≥ 8.8 ms)[b] + ≥1 other demyelinating parameter[a] in ≥1 other nerve

(2) Probable
≥30% amplitude reduction of the proximal negative peak CMAP relative to distal, excluding the posterior tibial nerve, if distal negative peak CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parameter[a] in ≥1 other nerve

(3) Possible
As in (1) but in only one nerve



Conduzione nervosa motoria

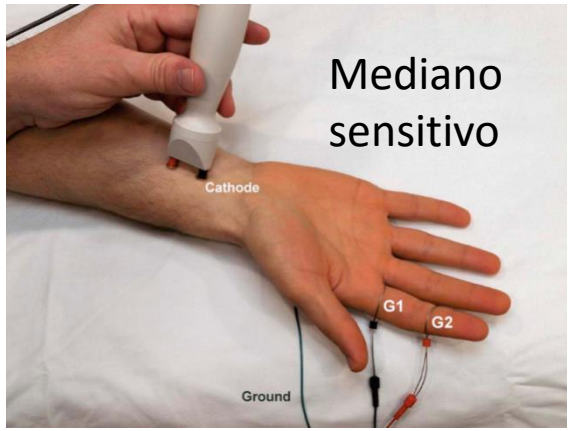


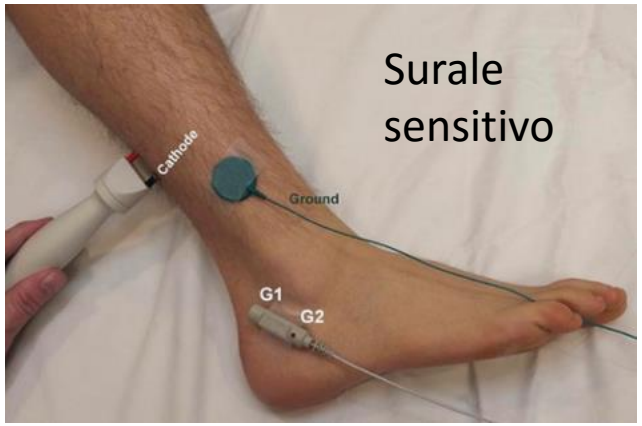
Onde F

Poliradiculoneuropatia infiammatoria demielinizzante cronica (CIDP)

Criteri di supporto alla diagnosi

1. Elevated CSF protein with leukocyte count $<10/mm^3$ (level A recommendation)
2. MRI showing gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses (level C recommendation)
3. Abnormal sensory electrophysiology in at least one nerve (good practice points):
   a. Normal sural with abnormal median (excluding median neuropathy at the wrist from carpal tunnel syndrome) or radial sensory nerve action potential (SNAP) amplitudes; or
   b. Conduction velocity $<80\%$ of lower limit of normal ($<70\%$ if SNAP amplitude $<80\%$ of lower limit of normal); or
   c. Delayed somatosensory evoked potentials without central nervous system disease
4. Objective clinical improvement following immunomodulatory treatment (level A recommendation)
5. Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy or teased fibre analysis (good practice point)





Neuropatia motoria multifocale con blocchi di conduzione

- Presentazione clinica simile alla variante di SLA con coinvolgimento solo del II motoneurone (atrofia muscolare progressiva)
- Presenza di anticorpi anti-GM1 (nel 50-80% dei casi)
- Interessamento asimmetrico e prevalente agli arti superiori
- Mancata risposta al cortisone

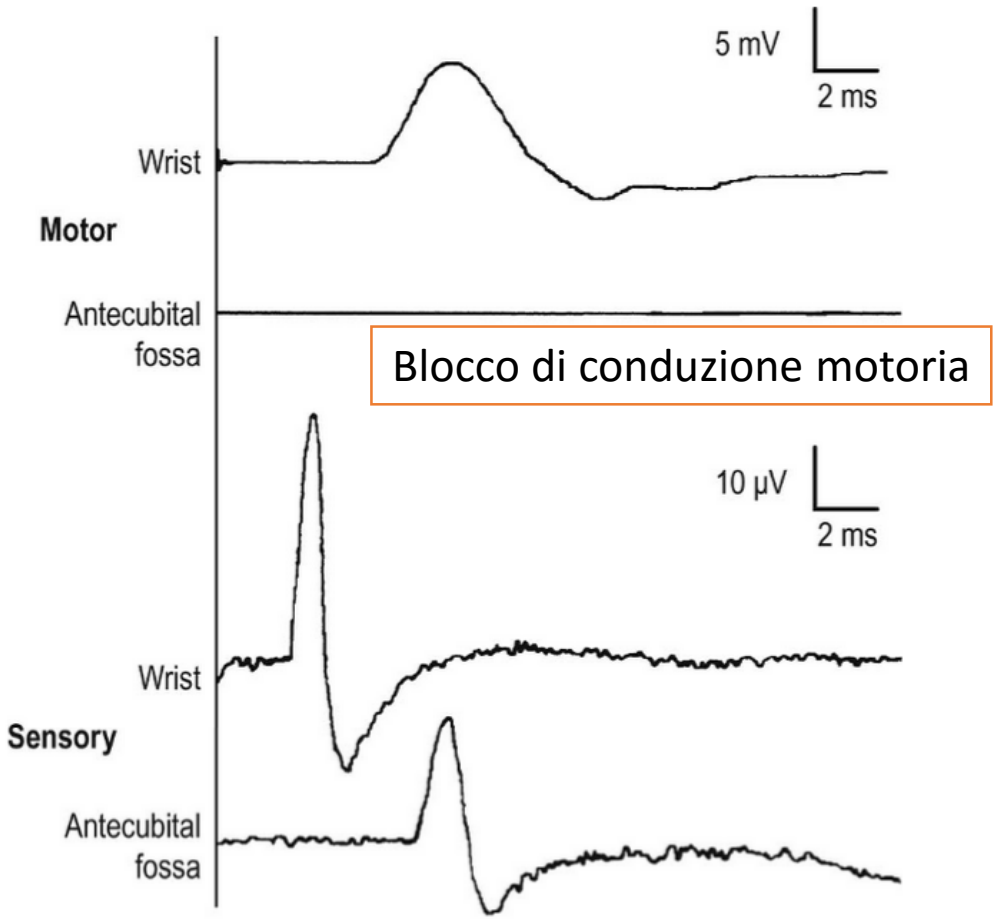
MMN Caratteristiche neurofisiologiche

Elementi suggestivi di demielinizzazione:

- Ridotta VCM
- Incremento latenza motoria distale
- Incremento latenza onde F

Elementi caratterizzanti

- Presenza di BLOCCHI DI CONDUZIONE MOTORIA
- Possono essere anche solo prossimali
- Conduzioni sensitive risparmiate



NEUROPATIE DEMILINIZZANTI ASSOCIATE A DISCRASIE EMATICHE

- Macroglobulinemia di Waldenström
- Linfoma
- Mieloma multiplo e osteosclerotico
- Amiloidosi
- Crioglobulinemia
- Gammopatie monoclonali di significato non determinato (MGUS) IgG/IgA
- MGUS IgM-Kappa con anticorpi anti-MAG

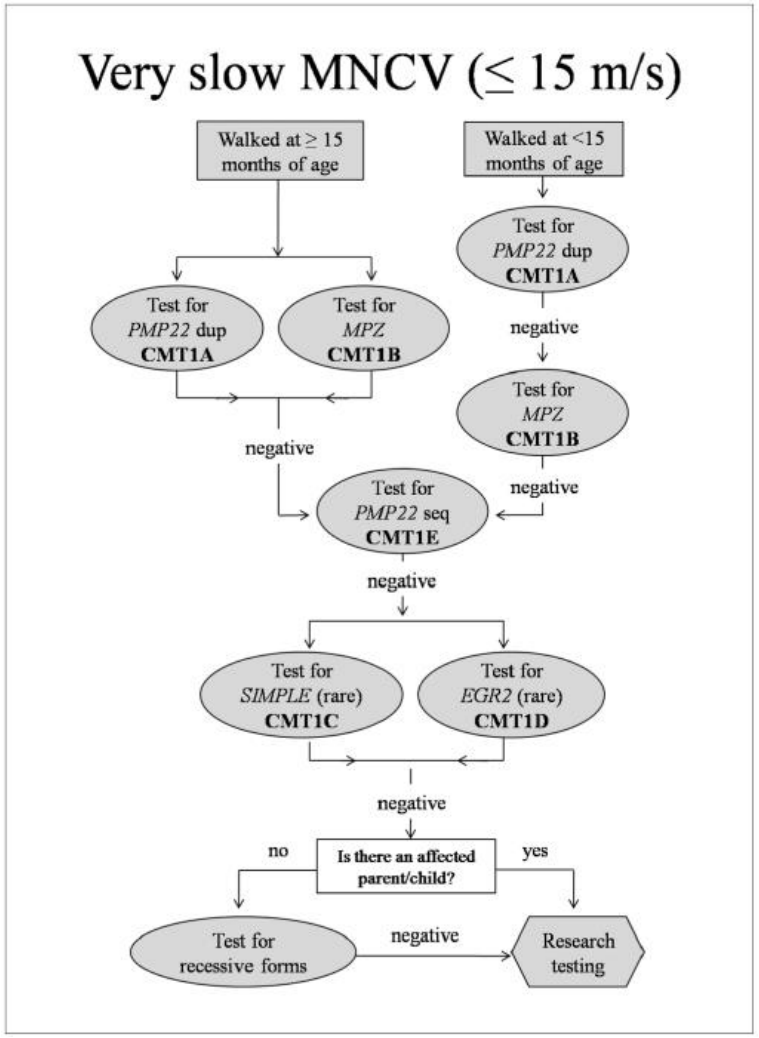
Neuropatia anti-MAG

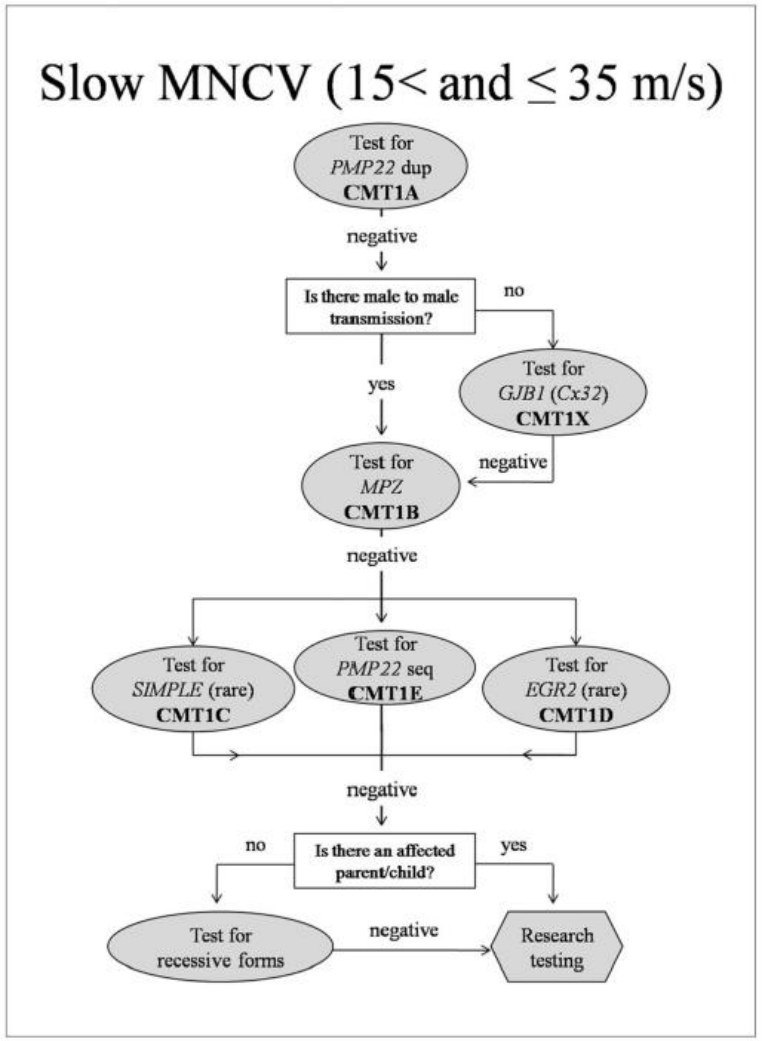
- Evoluzione lentamente progressiva
- Prevalentemente sensitiva
- Atassia, apallestesia (fibre sensitive di grosso calibro), tremore fine delle mani

Aspetti neurofisiologici:

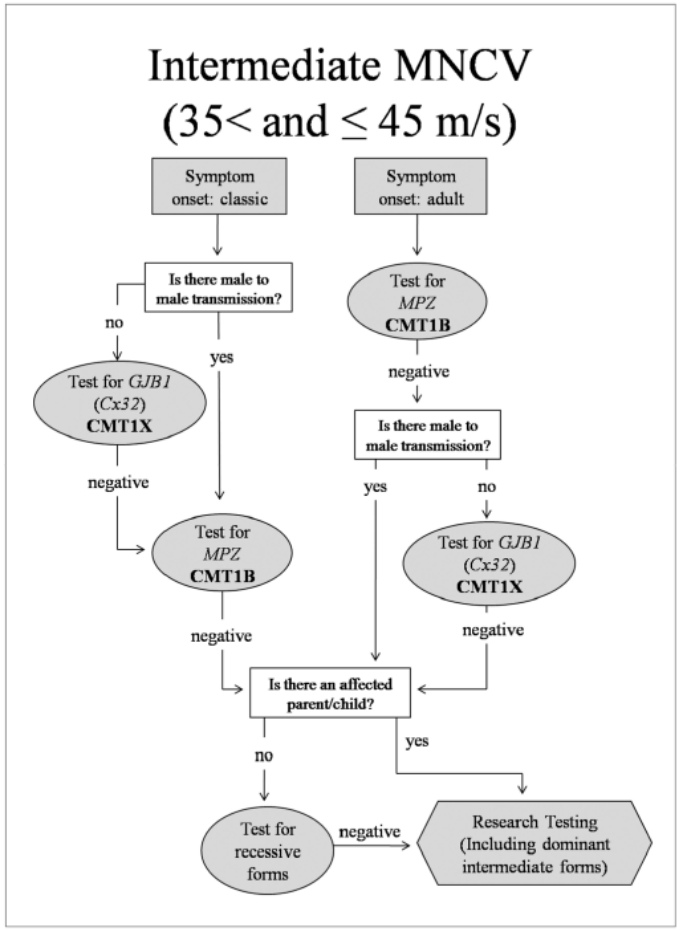
- Evidenza di demielinizzazione acquisita, sensitivo –motoria
- Incremento marcato delle latenze motorie distali!

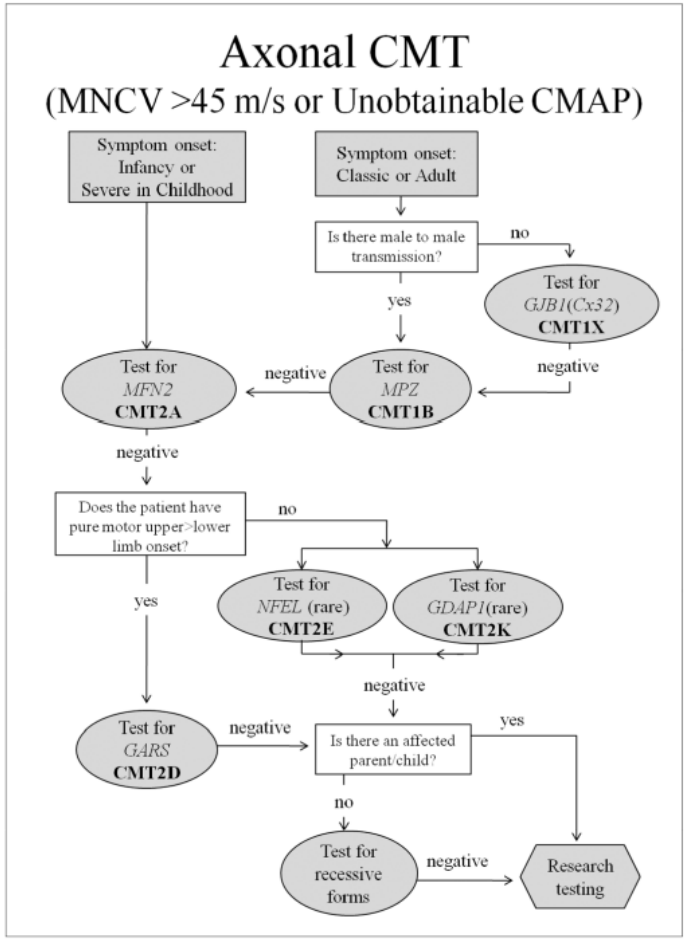
Neuropatia demielinizzante genetica





Neuropatia demielinizzante genetica

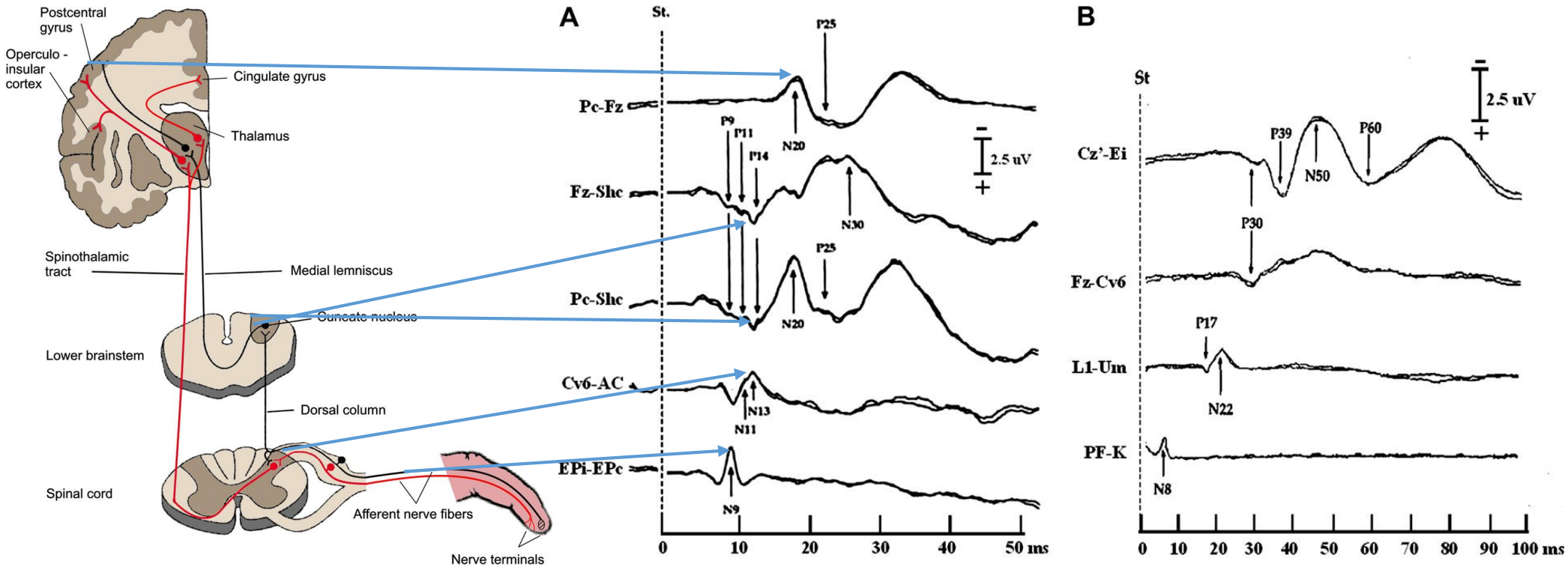




Scarsa correlazione tra entità del rallentamento e sintomi clinici!

Potenziali evocati somatosensoriali

- Permettono di esplorare tutta la via somatosensoriale (cordoni posteriori / lemnisco mediale)

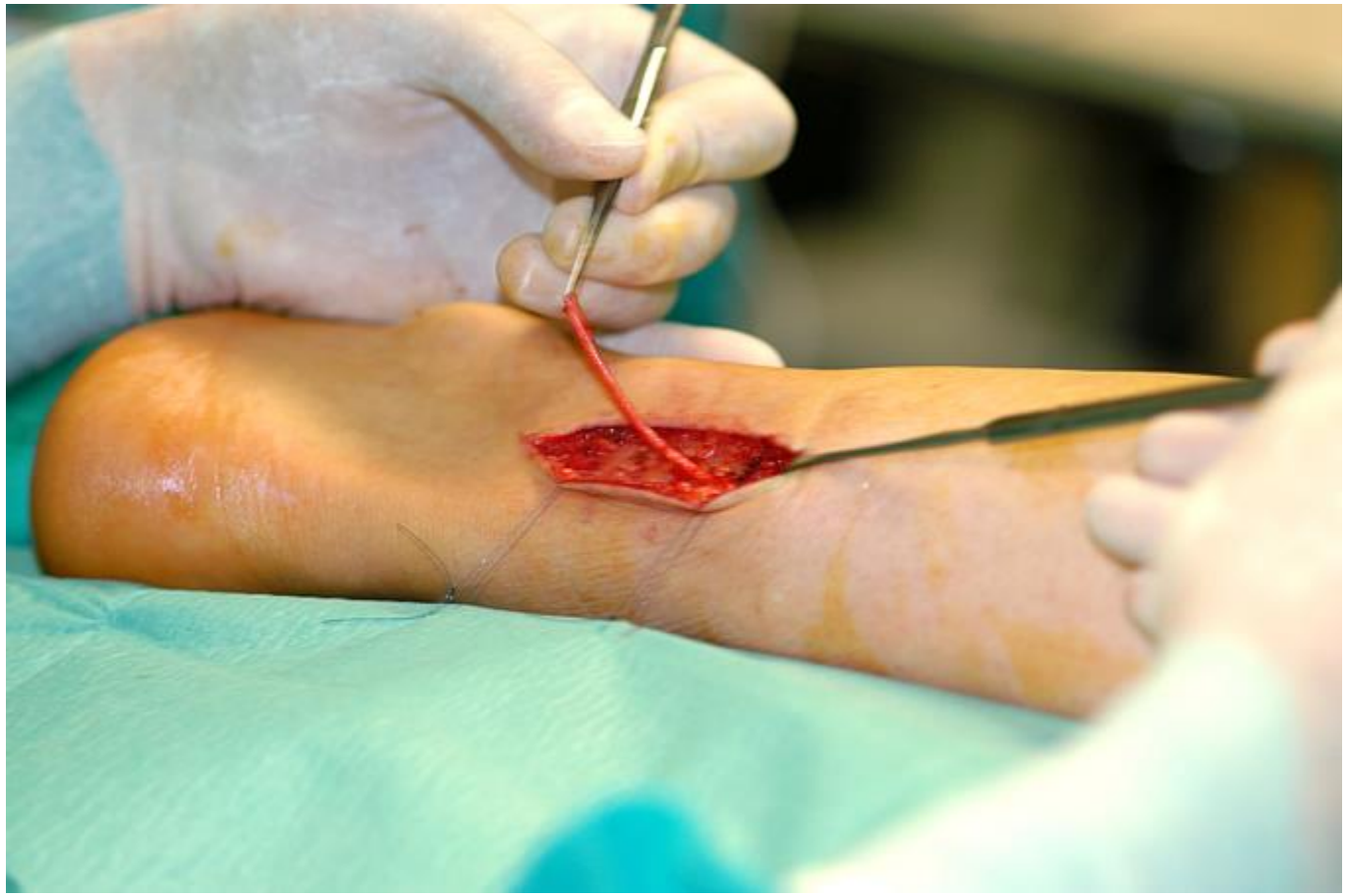


Biopsia di nervo surale (sensitivo)

INDICAZIONI

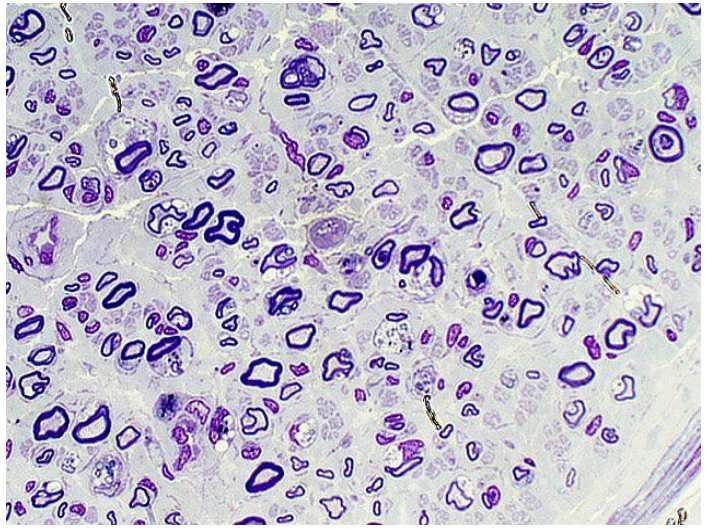
Supporto alla diagnosi di:

- Neuropatie vasculitiche
- Neuropatie demielinizzanti
- Neuropatie genetiche, es.:
  - N. giganto assonale
  - N. con inclusioni
- Neuropatie in patologie sistemiche, es.:
  - Amiloidosi
  - Lebbra
  - Sarcoidosi



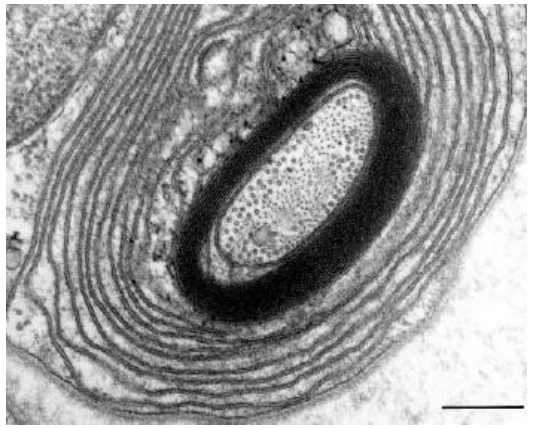
Biopsia di nervo surale (sensitivo)

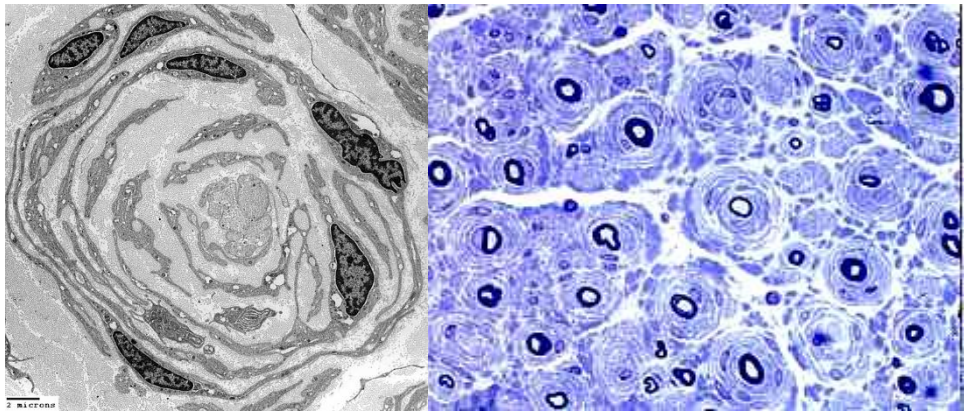
Demielinizzazione



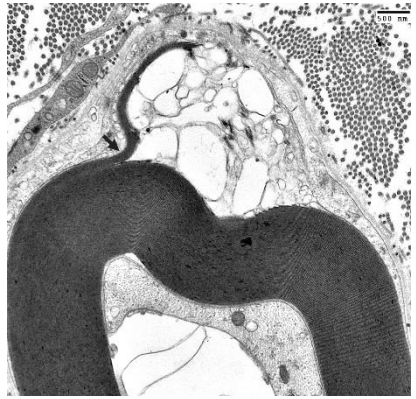
Ridotto spessore mielina

Mielina non compatta





Molteplici tentativi di rimielinizzazione (CIDP)→ Onion bulbs

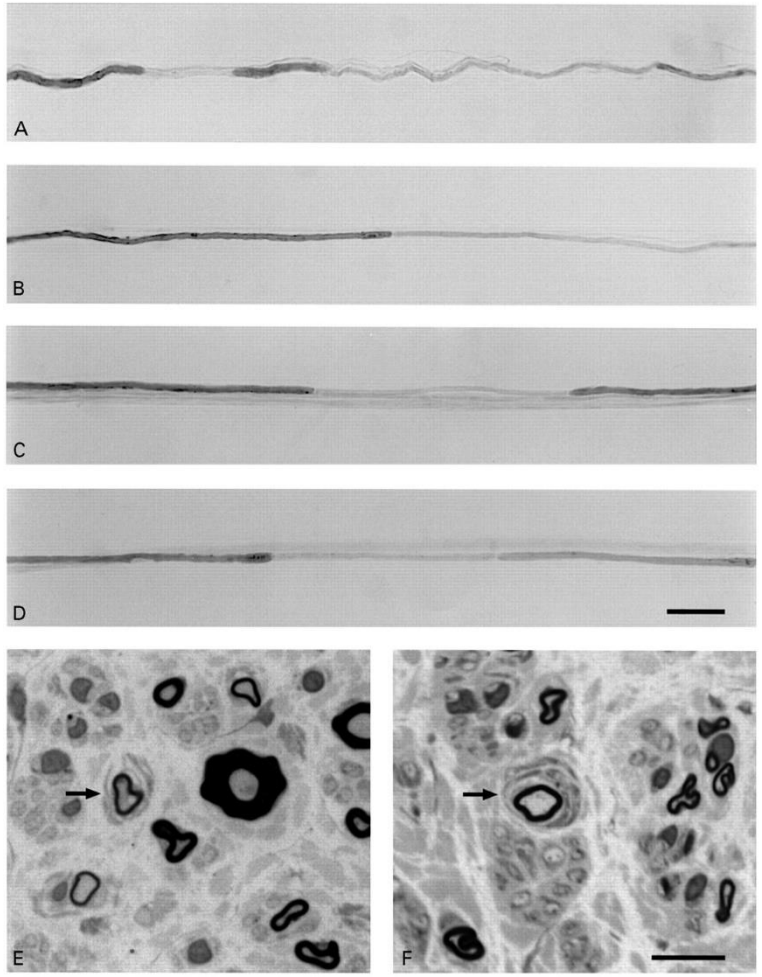


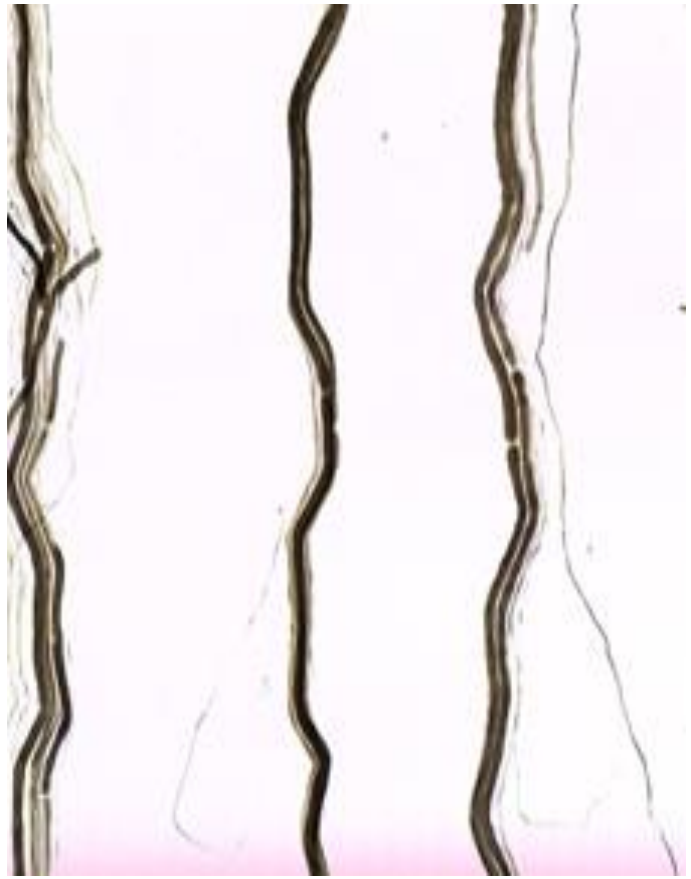
Autoimmunità cellulo mediata - macrofagi

Biopsia di nervo surale (sensitivo)

Demielinizzazione

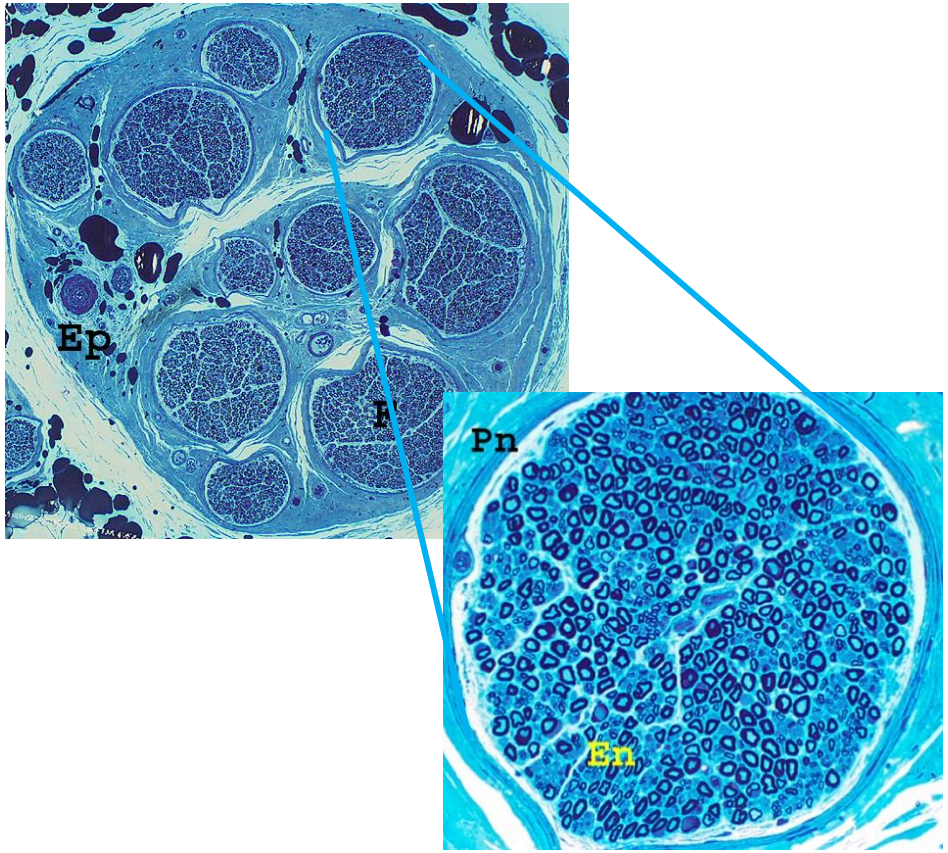
Fibre isolate (Teasing)



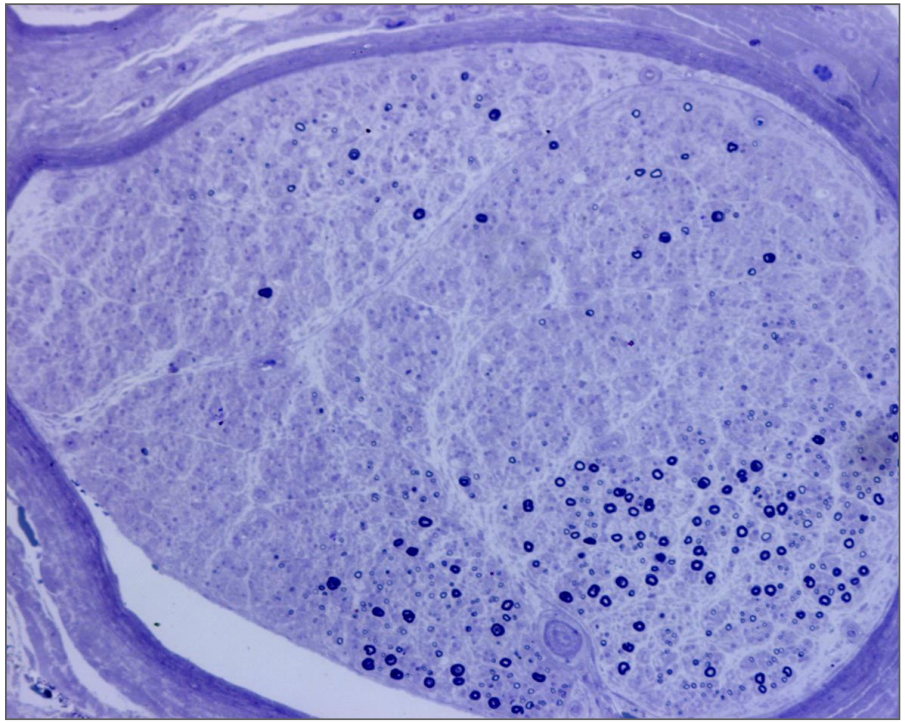


Biopsia di nervo surale (sensitivo)

Nervo normale

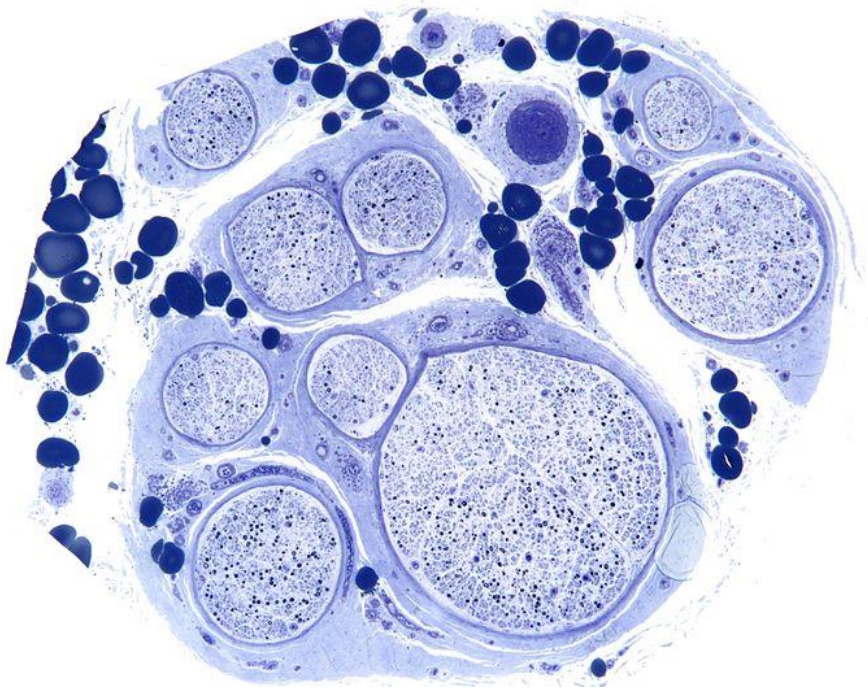


Danno assonale



Biopsia di nervo surale (sensitivo)

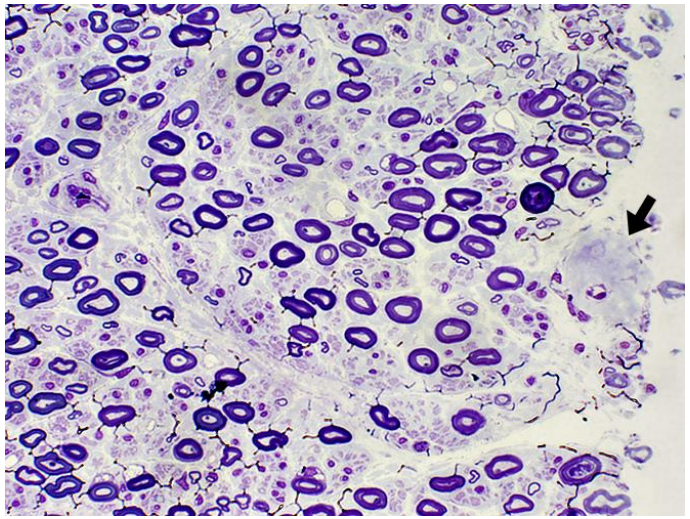
Vasculite

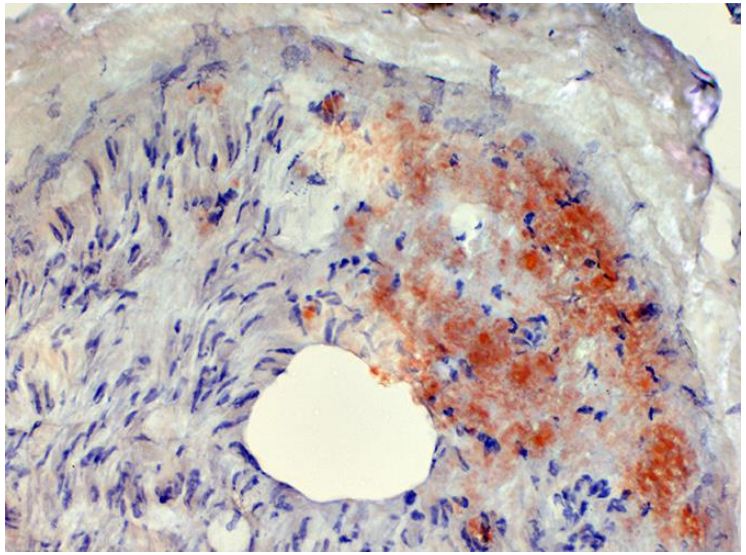


Danno fascicolare

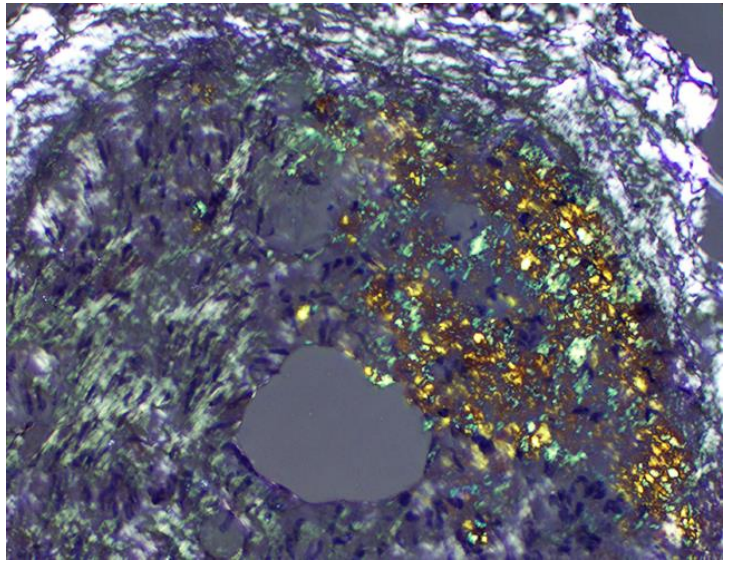
Biopsia di nervo surale (sensitivo)

Amiloidosi





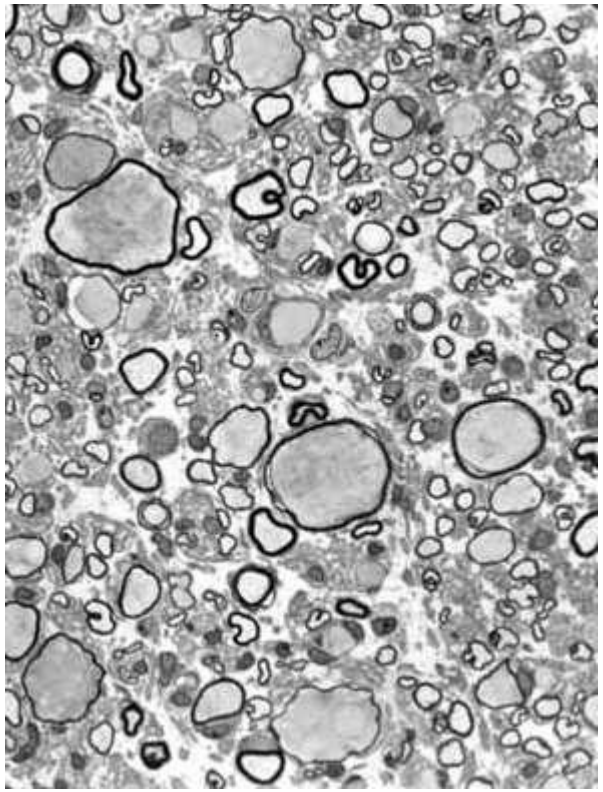
Congo Rosso

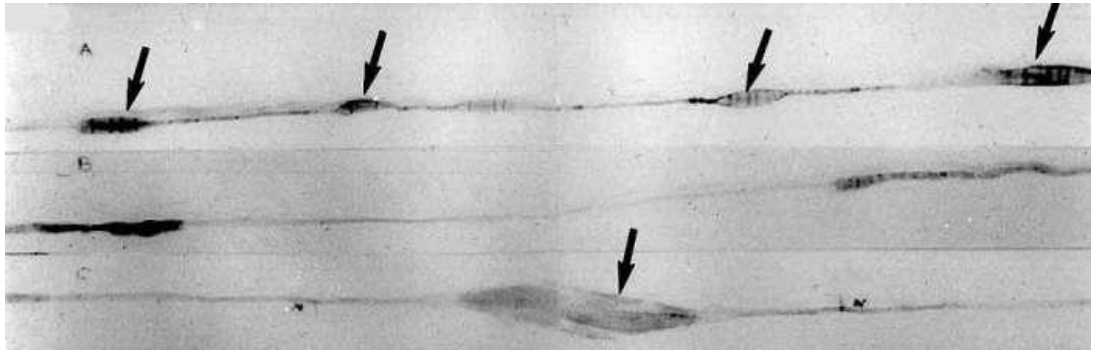


Congo Rosso – birifrangenza verde mela a luce polarizzata

Biopsia di nervo surale (sensitivo)

Neuropatia giganto assonale

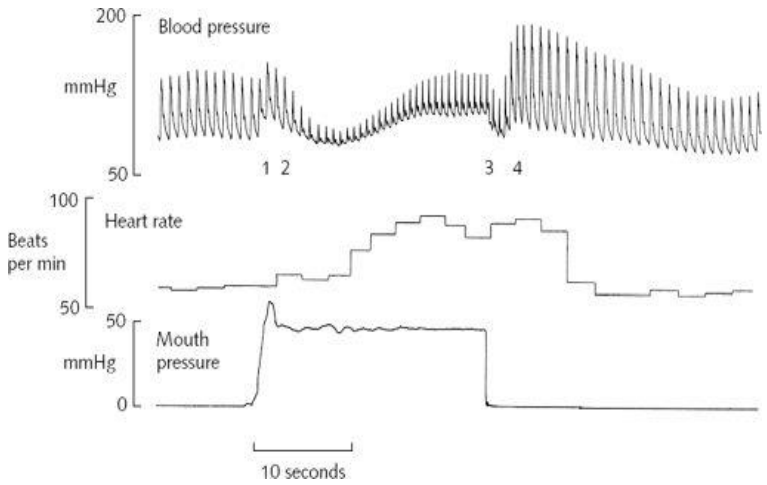




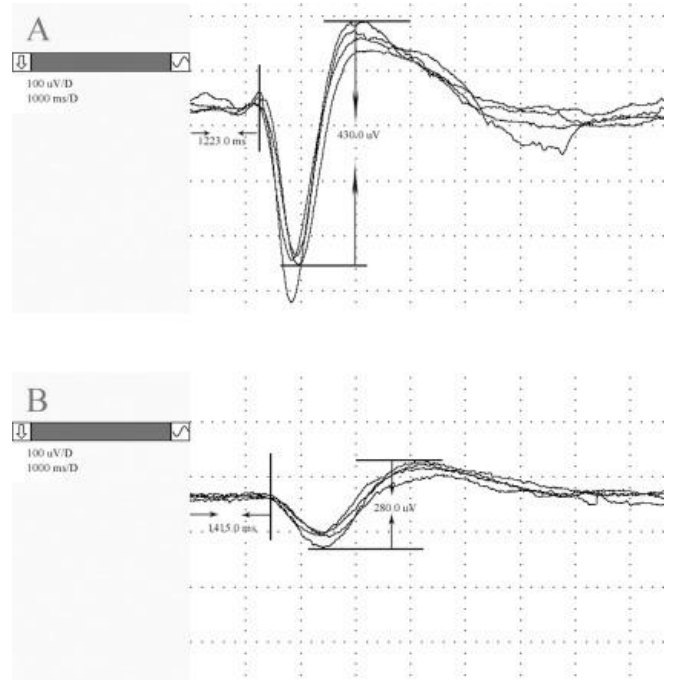
Rigonfiamenti (swelling) assonali focali

Neuropatia delle piccole fibre

- Fibre sensitive
  - Sensibilità termica
  - Sensibilità dolorifica
- Fibre autonomiche
  - Colinergiche
  - adrenergiche



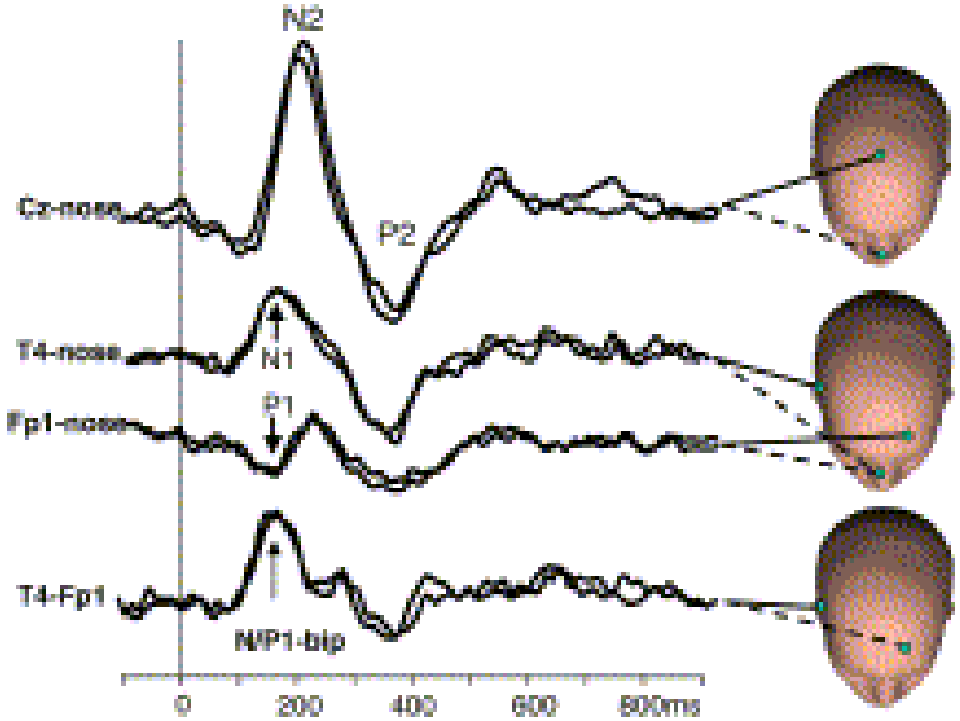
Prova di Valsalva - Autonomico



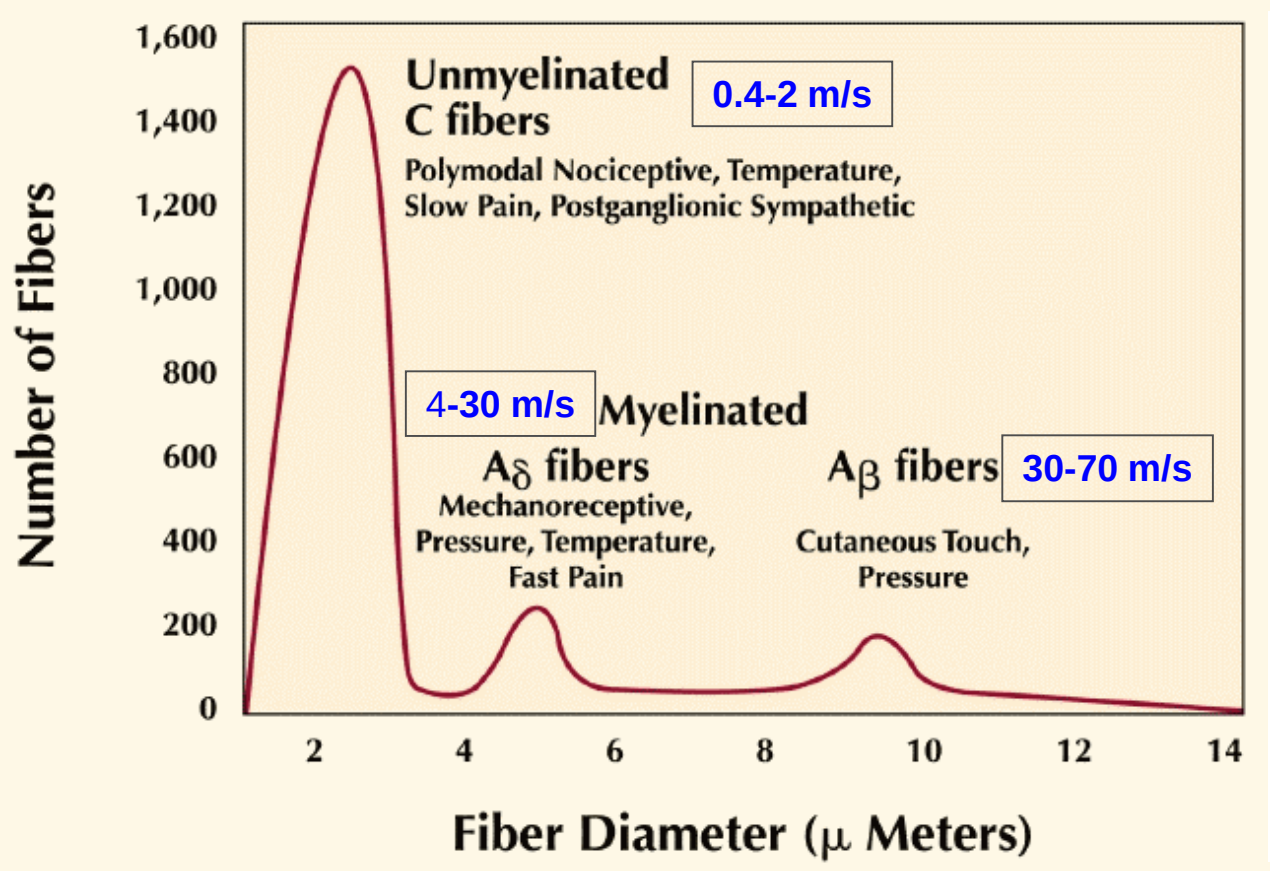
Sympathetic Skin response – simpatico colinergico (ghiandole sudoripare)

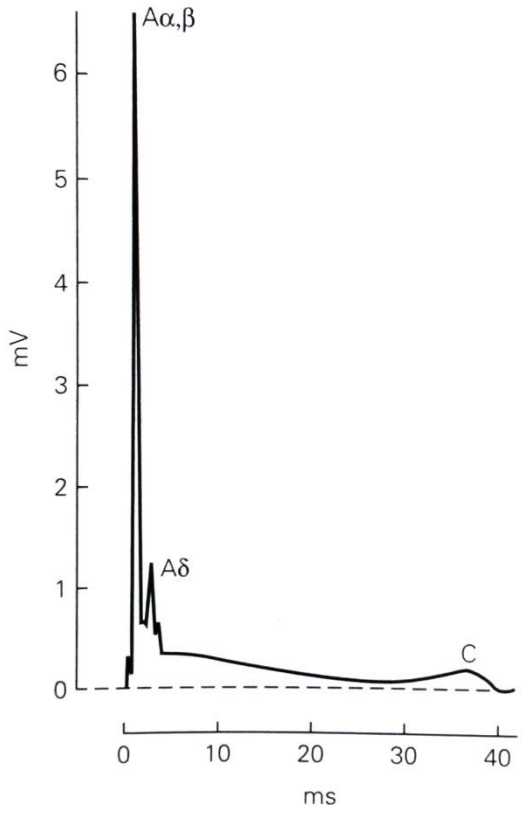
Neuropatia delle piccole fibre

LEP – Potenziali evocati laser



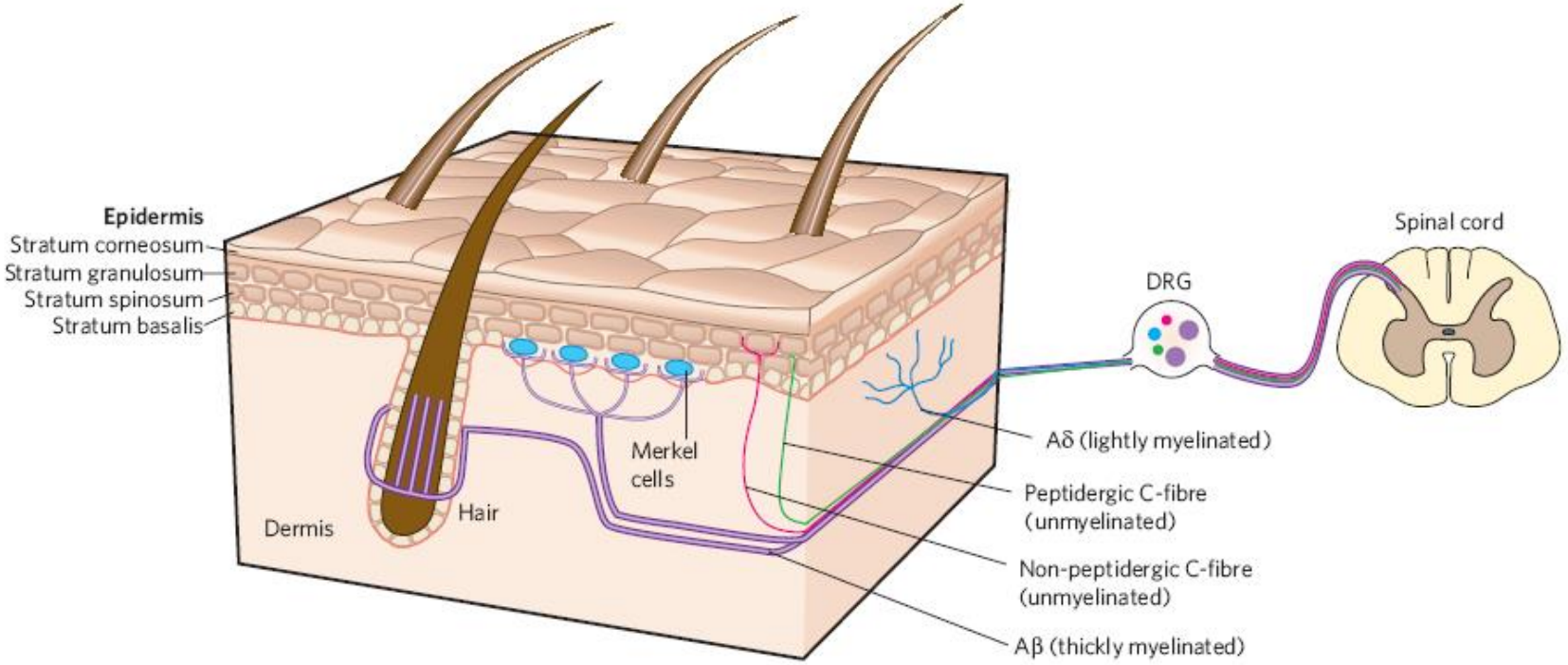
Neuropatia delle piccole fibre: Limiti neurofisiologia



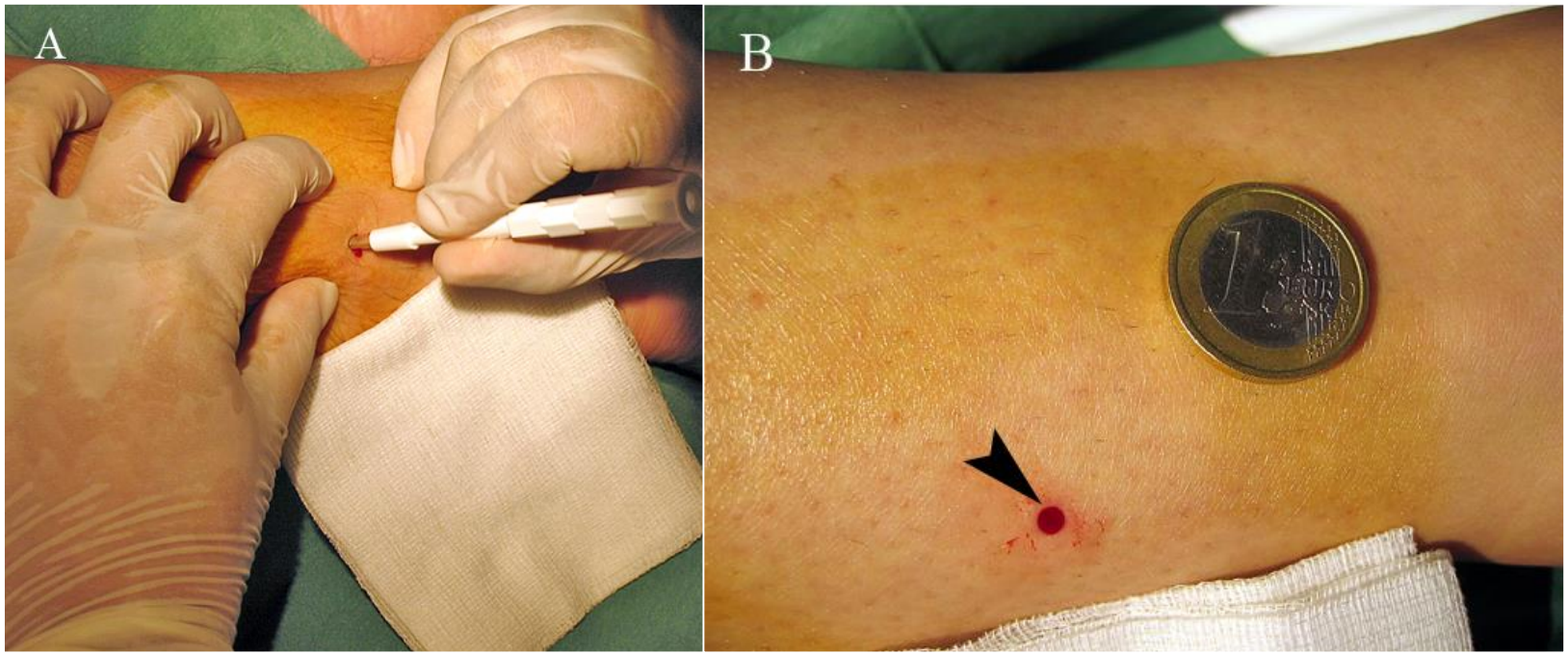


Neuropatia delle piccole fibre: Biopsia Cutenea

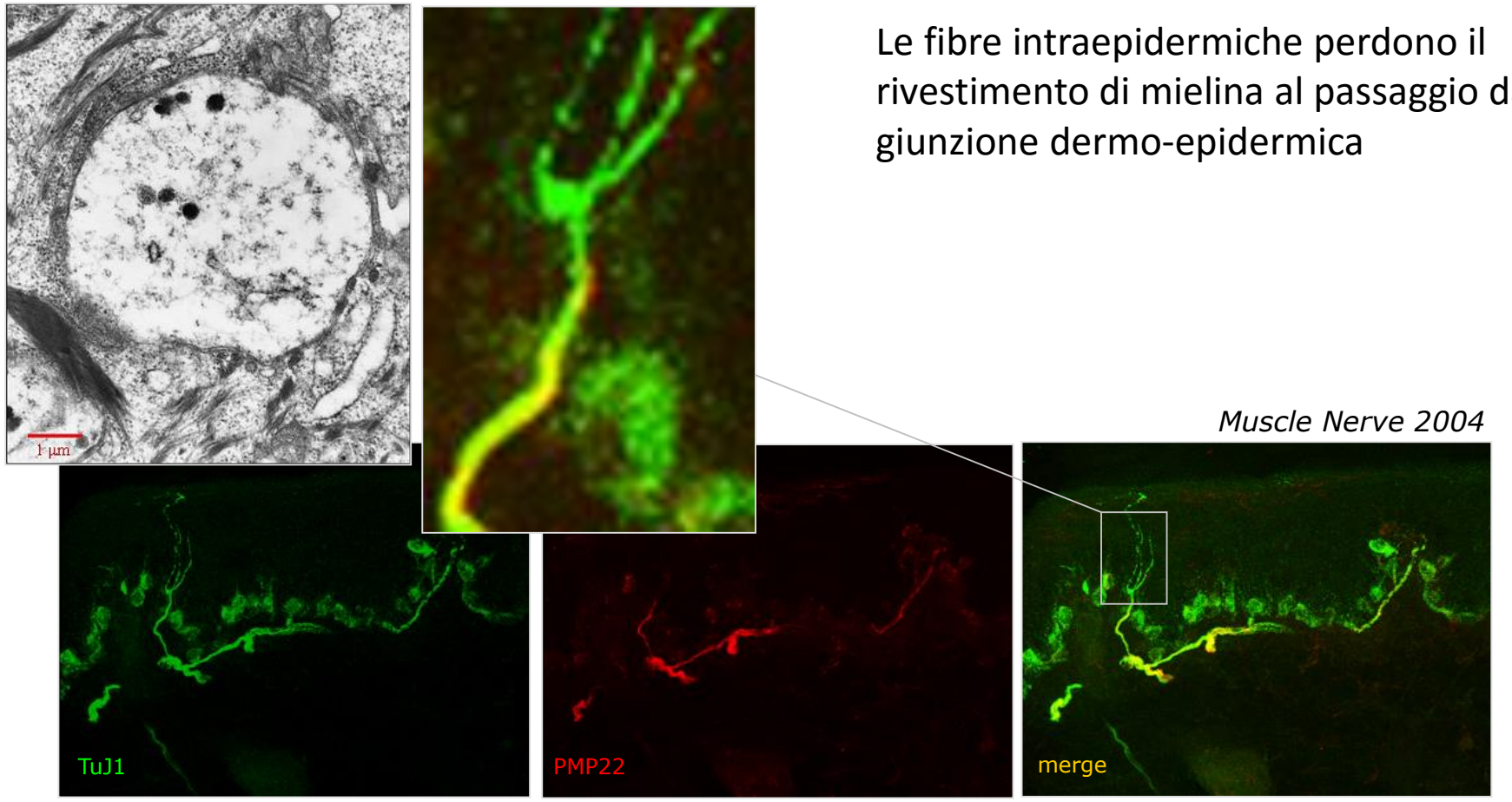
Gold standard nella diagnosi della neuropatia della piccole fibre



Neuropatia delle piccole fibre: Biopsia Cutenea



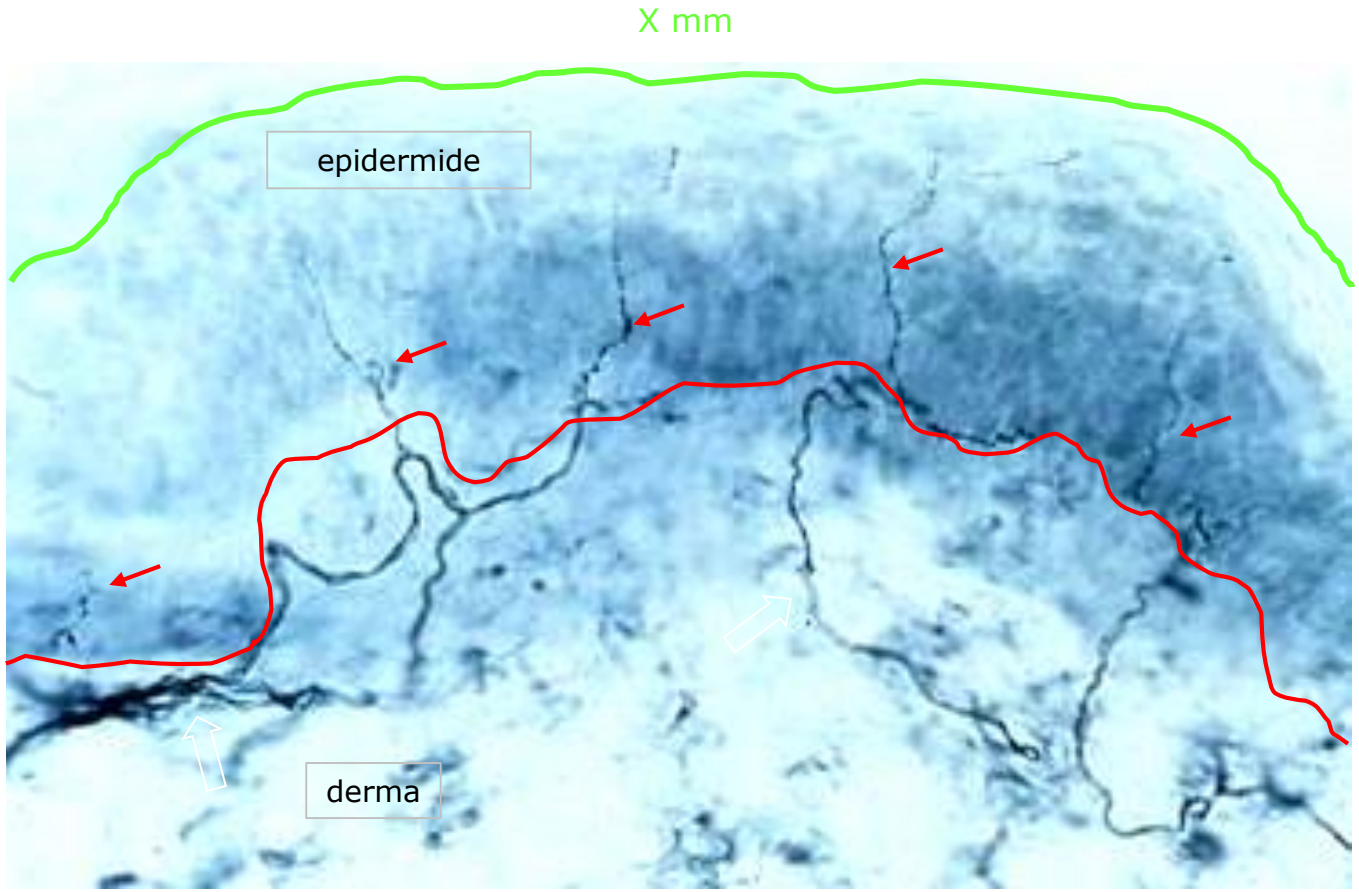
Neuropatia delle piccole fibre: Biopsia Cutenea



Le fibre intraepidermiche perdono il rivestimento di mielina al passaggio dalla giunzione dermo-epidermica

Muscle Nerve 2004

Neuropatia delle piccole fibre: Biopsia Cutenea



Quantificazione dell'innervazione intraepidermica

Neuropatia delle piccole fibre: Biopsia Cutenea

	Females (n=285)			Males (n=265)		
Age (years)	Number of Subjects	0.05 quantile IENFD values per age span	median IENFD values per age span	Number of Subjects	0.05 quantile IENFD values per age span	Median IENFD values per age span
20 – 29	57	8.4	13.5	36	6.1	10.9
30 – 39	47	7.1	12.4	40	5.2	10.3
40 – 49	70	5.7	11.2	62	4.4	9.6
50 – 59	59	4.3	9.8	53	3.5	8.9
60 – 69	32	3.2	8.7	43	2.8	8.3
70 – 79	16	2.2	7.6	22	2.1	7.7
≥ 80	4	1.6	6.7	9	1.7	7.2

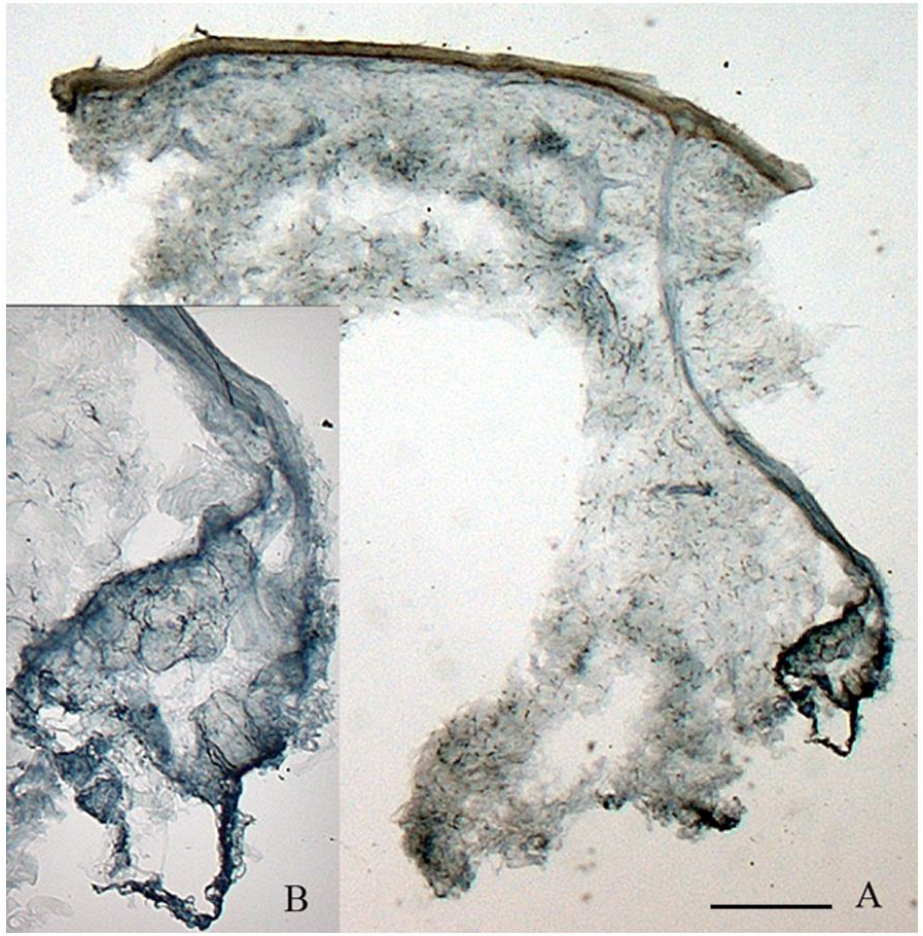
Valori normativi IENFD (numeri di fibre/mm)

Journal of the Peripheral Nervous System 15:202–207 (2010)

Neuropatia delle piccole fibre: Biopsia Cutenea

Valutazione qualitativa sistema nervoso autonomo:

Innervazione ghiandole sudoripare



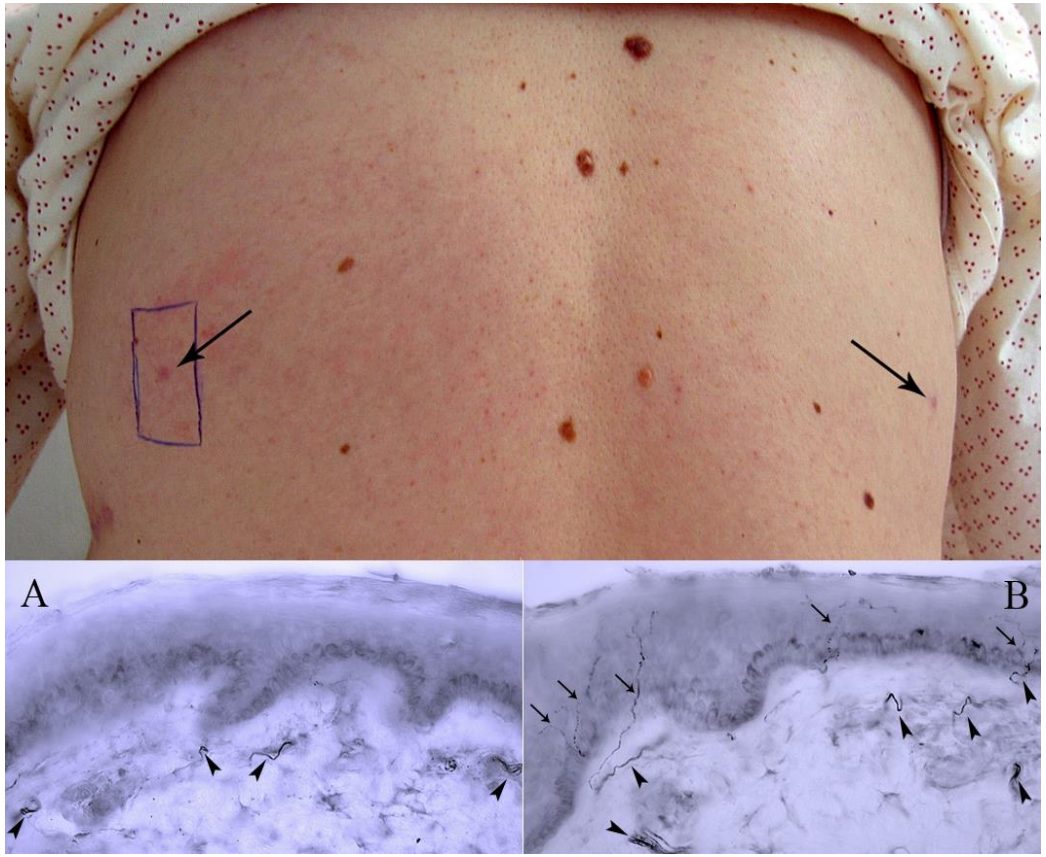
Neuropatie delle piccole fibre

	Cause	Length-dependent	Non-length-dependent
Metabolic	Diabetes	+	
	Impaired glucose tolerance	+	
	Rapid glycaemia control in diabetes	+	
	Hypothyroidism	+	+
	Vitamin B_{12} deficiency		+
Infectious disease	HIV	+	
	Influenza		+
	Hepatitis C	+	+
Drugs and toxics	Antiretroviral drugs	+	
	Metronidazole	+	
	Bortezomib	+	
	Statin	+	
	Nitrofurantoin		+
	Flecainide	+	
	Linezolid	+	
	Chronic alcohol abuse	+	
Immune-mediated	Celiac disease		+
	Sarcoidosis	+	
	Sjögren's syndrome	+	+
	Systemic lupus erythematosus	+	
	Rheumatoid arthritis		+
	Inflammatory bowel diseases	+	+
	Paraneoplastic syndrome	+	+
	Monoclonal gammopathy	+	+
	Complex regional pain syndrome type 1		+
Genetic	HSAN type IV		+
	Fabry's disease	+	+
	Familial amyloidosis	+	
	Hemochromatosis	+	
	Familial burning feet syndrome	+	
	Sodium channel mutations (*SCN9A*)	+	
Idiopathic	Unknown	+	+

Curr Opin Neurol 2012, 25:542–549

Neuropatia delle piccole fibre: Biopsia Cutenea

NOTALGIA



Area Notalgica

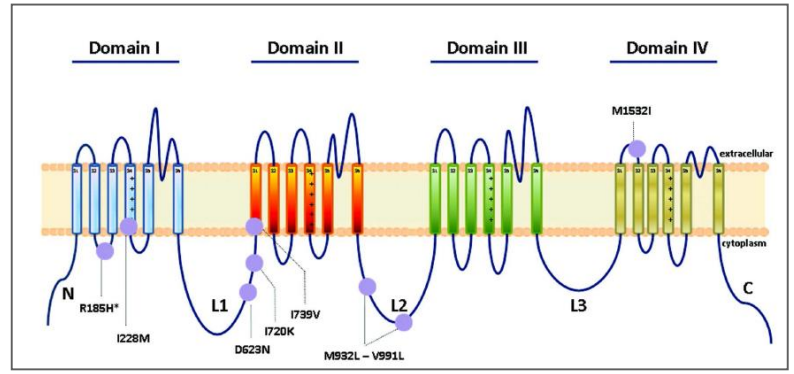
Innervazione normale

BMJ 2007;334;1159-1162

Neuropatia delle piccole fibre: genetica

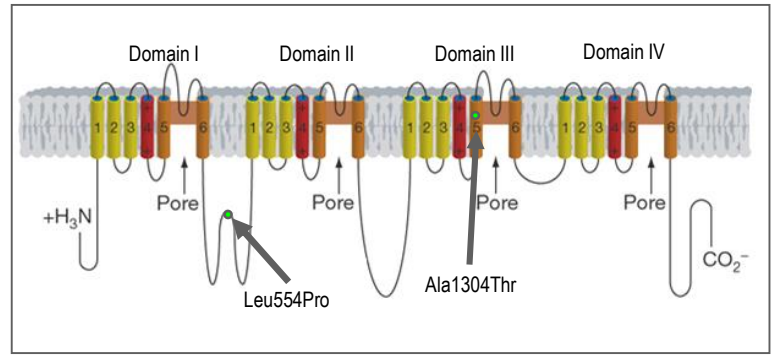
Gain of Function $Na_V1.7$ Mutations in Idiopathic Small Fiber Neuropathy

ANN NEUROL 2012;71:26–39



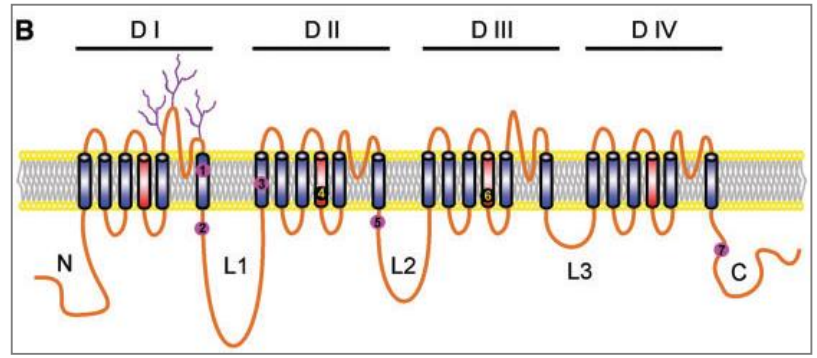
Gain-of-function $Na_V1.8$ mutations in painful neuropathy

PNAS | November 20, 2012 | vol. 109 | no. 47



Gain-of-function mutations in sodium channel $Na_V1.9$ in painful neuropathy

Brain 2014: 137; 1627–1642



Grazie a tutti per l'attenzione!