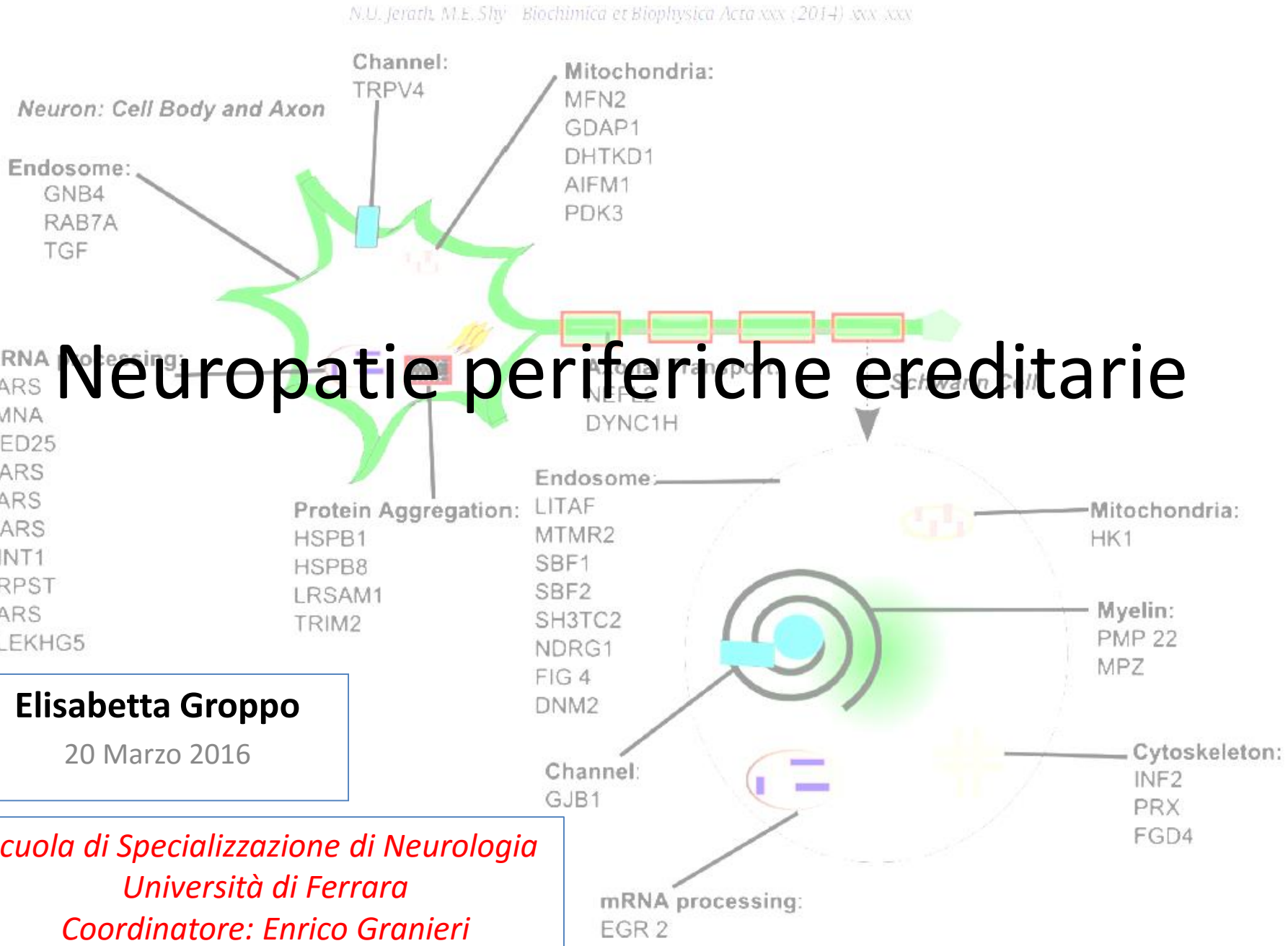

Neuropatie periferiche ereditarie

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20 Marzo 2016

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Concetti generali

- Aspetti classificativi: caratteristiche cliniche, tipo di ereditarietà/trasmissione, caratteristiche NFS, difetto metabolico, markers genetici specifici
- Forme “primarie”: conivolgimento predominante o esclusivo del SNP → segni e sintomi di disfunzione del nervo periferico
- Forme “sintomatiche/plus”: coinvolgimento SNP e SNC, altri organi/sistemi; segni e sintomi da coinvolgimento del SNP +/-

Concetti generali.

Neuropathies in which the neuropathy is the sole or primary part of the disorder

Charcot-marie-tooth disease (CMT)

Hereditary neuropathy with liability to pressure palsies (HNPP)

Hereditary sensory and autonomic neuropathies/hereditary sensory neuropathies (HSAN/HSN)

Distal hereditary motor neuropathies (dHMN)

Hereditary neuralgic amyotrophy (HNA)

Neuropathies in which the neuropathy is part of a more widespread neurological or multisystem disorder

Familial amyloid polyneuropathy (FAP)

Disturbances of lipid metabolism (e.g., adrenoleukodystrophy)

Porphyrias

Disorders with defective DNA (e.g., ataxia telangiectasia)

Neuropathies associated with mitochondrial diseases

Neuropathies associated with hereditary ataxias

Miscellaneous

Le più comuni

Concetti generali

- La diagnosi genetica è sempre più possibile
- Identificati oltre 30 geni causativi
- Molti geni ricercabili: quale il migliore approccio diagnostico?
- Lo sviluppo di terapie geniche renderà ancora più importante la diagnosi genetica

Concetti generali

- In termini «funzionali»:
  - Motorie
  - Sensitivo-autonomiche
  - Sensitivo-motorie

Concetti generali

Reilly MM, Neurology. 2009;12(2):80-88.

- In termini «funzionali»: motorie

ALS: Hereditary & Familial

Recessive SMA (es. SMA1: SMN 5q)

Dominant, Proximal

X-linked SMA (Recessive) (es. Bulbospinal (Kennedy): AR; Xq12)

Bulbar syndromes

AAA syndrome: Aladin; 12q13;

Recessive (Brown-Vialetto-van Laere; Fazio-Londe; Kennedy (BSMA): Androgen Receptor, Xq12; PLS, Juvenile: Alsin, 2q33)

HMN e distal SMA (DSMA; dHMN)

CMT 2N: AARS; 16q22; CMT 2O: DYNC1H1; 14q32

dHMN + (Recessive) others features (Ataxia telangectasia/Macular deg,…)

Mitochondrial

Sporadic (es. Hirayama)

Multisystem disorders

Recessive (es. Chediak-Higashi; Hexosaminidase A; Leukoencephalopathy: CP2, 1p32; MPAN: c19orf12, 9q12)

Dominant (es. Machado-Joseph: Ataxin-3, 14q32; Myopathy + Paget: HNRNPA2B1, 7p15; DDPAC: MAPT; 17q21)

X-linked (es. Polyglucosan body: GBE1, 3p12)

Mitochondrial

Sporadic

Concetti generali

- In termini «funzionali»: Sensitivo-autonomiche

Neuropatie ereditarie con ulcere mutilanti

Acro-mutilazioni
Ulcere cutanee
Amutazioni
Osteoartropatia neurogena (articolazioni di Charcot)

- HSAN
  - Es: HSAN3 (Riley-Day): IKBKAP; 9q31; recessive; Congenital absence of pain perception: SCN11A; 3p22; Dominant; Sensory
- HMSN
- Hereditary Sensory > Motor Neuropathy with Ulcero-mutilation
- Congenital insensitivity to pain (PRDM12: 9q33; Recessive)
- Hereditary sensory neuropathy with spastic paraparesis (Es. SPG 61: ARL6IP1; 16p12)
- Other: occasional patients with CMT 1A,

Concetti generali

- In termini «funzionali»: Sensitivo-autonomiche

Hereditary sensory neuropathy with

- **α-galactosidase (Fabry's)**
- **An-α-lipoproteinemia (Tangier's)**
- Anosmia
- **Ataxia telangectasia**
- Ataxia, thermoanalgesia & loss of fungiform papillae
- Deafness & Global delay
- Deafness - X-linked
- **Friedreich's ataxia**
- Gastroesophageal reflux & Cough
- Gyrate atrophy of choroid & retina with hyperornithinemia
- Minifascicles & 46,XY Gonadal dysgenesis
- Mitochondrial disorder
  - Maternal: NARP
  - Recessive: Cytopathy
- Multiple symmetrical lipomatosis
- Optic atrophy & Deafness: 8q24.22-ter
- Posterior column ataxia + Retinitis pigmentosa
- Scoliosis & deafness
- Spastic paraparesis

Concetti generali

- In termini «funzionali»: Sensitivo-motorie

CMT & HMSN: demielinizzanti (1)

dominanti

1A (PMP-22; 17p12), 1B (P_0 protein, 1q23), 1C (LITAF, 16p13), 1D (EGR2, 10q21), 1E (Deafness, PMP-22, 17p12; P_0, 1q23), 1F (NEFL, 8p21), CMT1 (FBLN5, 14q32);
HNPP (PMP-22; KARS, 16q23)
HMSN 3 (Dejerine-Sottas; PMP-22; P_0; 8q23; EGR2)
Thermosensitive
PNS & CNS hypomyelin (SOX10, 22q13)
Sensory PN + Hearing loss (GJB3, 1p34)
ypomyelination (ARHGEF10, 8p23)
CMT-DIF (GNB4, 3q26)
HMSN (HARS, 5q31; PMP2, 8q21)

recessive

4A (GDAP1, 8q21), 4B1 (MTMR2, 11q22), 4B2 (SBF2, 11p15), 4B3 (SBF1, 22q13), 4C (SH3TC2, 5q32), 4D (NDRG1, 8q24), 4E (EGR2, 10q21), 4F (Periaxin, 19q13), 4G (HK1, 10q22), 4H (FGD4, 12q12), 4J (FIG4, 6q21), 4K (SURF1, 9q34), HMSN 3 (Dejerine-Sottas; P_0;PMP-22, EGR2, Periaxin), HMSN + Juvenile glaucoma, Cataracts (CTDP1, 18qter), Cockayne's, Congenital hypomyelinating (P_0, PMP-22, EGR-2), Farber lipogranulomatosis (ASAH, 8p22), CDG1a (PMM2, 16p13), Krabbe (GALC, 14q31), MLD (ARSA, 22q13), PMP-22 point mutations; Refsum's disease; HMSN + CNS Heterogeneous, Neurodegeneration (DNAJC3, 13q32)

X-linked

1 (GJB1-CX32, Xq13), Pyramidal signs

Concetti generali

- **In termini «funzionali»: Sensitivo-motorie**

CMT & HMSN: assonali (2), dominanti

2A2 (MFN2, 1p36), 2A1 (KIF1B, 1p36),2B (RAB7, 3q21), 2C (TRPV4, 12q24), 2D (GARS, 7p14), 2E (NEFL, 8p21), 2F (HSPB1, 7q11), 2G (12q12), 2I ($P_{0,}$ 1q22), 2J (P_0), 2K (GDAP1, 8q21), 2L (HSPB8, 12q24), 2M (DNM2, 19p13), 2N (AARS, 16q22), 2O (DYNC1H1, 4q32), 2P (LRSAM1, 9q33), 2Q (DHTKD1, 10p14), 2T (DNAJB2, 2q35), 2U (MARS, 12q13), 2V (NAGLU, 17q21), 2W (HARS, 5q31), 2Y (VCP, 9p13), 2Z (MORC2, 22q12), 2 (TFG, 3q12); giant axonal 2 (DCAF8, 1q22); proximal (TFG, 3q12);

CMT2 + pyramidal/optic atrophy/deafness/ulcero-mutilation;
HSAN I (SPTLC1 e C2);
HMSN (SPTLC3, 20p12), HSMN + Ataxia (IFRD1, 7q31);
HMN 5B (BSCL2, 11q13);

CFEOM3 (TUBB3, 16q24)

Concetti generali

- **In termini «funzionali»: Sensitivo-motorie**

CMT & HMSN: assonali, recessive

2→A (B1; lamin A/C; 1q22), B (B2; MED25; 19q13.3), F/Distal HMN (HSPB1; 7q11-q21), H/Pyramidal signs (8q21.3), K/Hoarseness (GDAP1; 8q21), P (LRSAM1; 9q33), R (TRIM2; 4q31), S (IGHMBP2; 11q13), X (SPG11; 15q21), HSJ1 (2q35), PNKP (19q13), Acrodystrophy (ATSV; 2q37), Andermann (KCC3; 15q13), Ataxia + Neuropathy (Cough + Sensory; Hepato-Cerebellar; SCAN1);

Early onset (Lethal Neonatal, Neuroaxonal dystrophy-PLA2G6, Ouvrier, Optic, Respiratory failure,Severe);
Giant axonal (Gigaxonin; 16q23);
Neuromyotonia (HINT1; 5q31);
Optic neuropathy (HMSN ± Deaf; HMSN6B);
Syndromes: HMSN+Childhood onset/CNS/Deafness

X-linked

1 (GJB1(CX32), Xq13), 6 (PDK3, Xp22); 2 (Xp22.2), 3 (Xq26), 4 (AIFM1, Xq26), 5 (PRPS1, Xq22), Sensory PN + Deaf (Xq23)

Mitochondriali: MT-ATP6

Concetti generali

- **In termini «funzionali»: Sensitivo-motorie**

CMT + Intermediate NCV

Dominanti	Recessive
CMT DIA: 10q24	**CMT RIA**: GDAP1; 8q21.1
CMT DIB: DNM2; 19p13	**CMT RIB**: KARS; 16q23
CMT DIC: YARS; 1p35	**CMT RIC**: PLEKHG5; 1p36
CMT DID: P_0; 1q22	**CMT RID**: COX6A1; 12q24
CMT-DIE: INF2; 14q32	**CMT XI**: DRP2; Xq22
CMT-DIF: GNB4; 3q26	
CMT-X (Semi-dominant)	
CMT 2E: NEFL; 8p21	
Hypomyelination: ARHGEF10; 8p23	

Altre neuropatie non meglio classificate: malattie del SNC e dei nervi cranici, sd cliniche complesse, ipomielinizzazione congenita, **condizioni ricorrenti (plessopatia brachiale, paralisi da pressione (HNPP; PMP-22))**

…

Concetti generali

Inheritance	Pathophysiology	Type	Example gene associations
Autosomal dominant	Demyelinating	CMT1	*PMP22, MPZ, LITAF/SIMPLE, EGR2, NEFL, FBLN5*
	Axonal	CMT2	*KIF1B, MFN2, RAB7, TRPV4, GARS, NEFL, HSPB1, MPZ, GDAP1, HSPB8, DNM2, AARS, DYNC1H1, LRSAM1, DHTKD1, DNAJB2, HARS, MARS, MT-ATP6, TFG*
	Intermediate	CMTDI	*DNM2, YARS, MPZ, IFN2, GNB4*
Autosomal recessive	Demyelinating	CMT4	*GDAP1, MTMR2, MTMR13 (SBF2), SBF1, SH3TC2, NDRG1, EGR2, PRX, HK1, FGD4, FIG4, SURF1*
	Axonal	CMT2	*LMNA, MED25, GDAP1, MFN2, NEFL, HINT1, TRIM2, IGHMBP2, GAN*
	Intermediate	CMTRI	*GDAP1, KARS, PLEKHG5, COX6A1*
X-linked	Intermediate or axonal	CMTX	*GJB1, AIFM1, PRPS1, PDK3*

Other hereditary considerations	Clinical clues
Hereditary sensory neuropathy	Sensory predominant, autonomic features, ulcerations
Distal hereditary motor neuropathy	Minimal or no sensory involvement
Leukodystrophy	Confluent white matter changes on MRI of the brain
Familial amyloidosis	Cardiomyopathy, autonomic dysfunction, neuropathic pain, carpal tunnel, or nephropathy
Fabry disease	Periodic pain crises in the limbs (acroparesthesias), angiokeratomas on the skin, unexplained renal disease, or unexplained stroke
Refsum disease	Retinitis pigmentosa, deafness, ataxia, and icthyosis (scaly skin)
Tangier disease	The presence of enlarged orange tonsils, a low HDL, or a syrinx-like pattern of sensory loss
Mitochondrial disorders	Diabetes, myopathy, ptosis, external ophthalmoplegia, sensorineural deafness, optic atrophy, pigmentary retinopathy, and short stature

Concetti generali

- I tipi più frequenti sono CMT, HSAN e dHMN
- Conoscenze patogenesi SNP
- Classificabili in due grandi gruppi:
  - neuropatia è il solo/primario disturbo
  - neuropatia è parte di un disordine neurologico generalizzato o multisistemico
- Maggiori conoscenze e avanzamenti nella dgn e tp del II gruppo

Classification of the genetic neuropathies

Neuropathies in which the neuropathy is the sole or primary part of the disorder

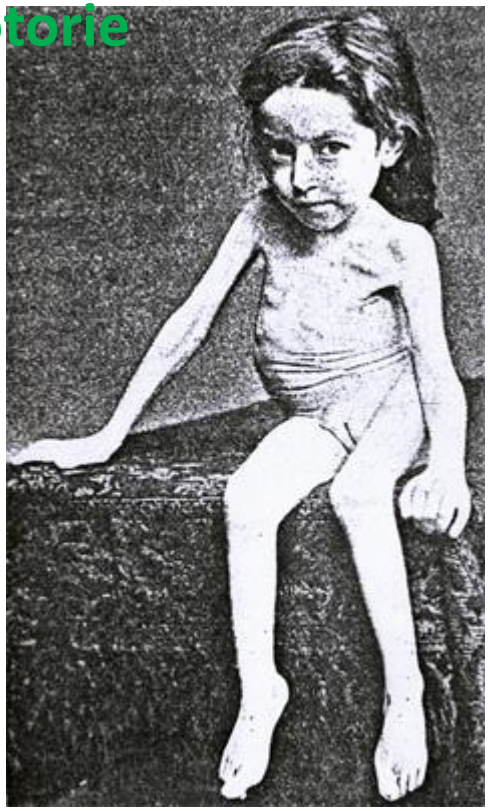
- Charcot–Marie–Tooth disease (CMT)
- Hereditary neuropathy with liability to pressure palsies (HNPP)
- Hereditary sensory and autonomic neuropathies/ hereditary sensory neuropathies (HSAN/HSN)
- Distal hereditary motor neuropathies (dHMN)
- Hereditary neuralgic amyotrophy (HNA)

Neuropathies in which the neuropathy is part of a more widespread neurological or multisystem disorder

- Familial amyloid polyneuropathy
- Disturbances of lipid metabolism
- Porphyrias
- Disorders with defective DNA
- Neuropathies associated with mitochondrial diseases
- Neuropathies associated with hereditary ataxias
- Miscellaneous

Charcot-Marie-Tooth

In termini «funzionali»: Sensitivo-motorie



- Raggruppabili in:
  - CMT1: AD demielinizzanti (classicamente HMSN I)
  - CMT2: AD assonali (classicamente HMSN II)
  - CMT3 (o HSMN III): AR, bambini gravemente affetti; definiti anche CHN o DSN

Charcot-Marie-Tooth

Table 1 Classification of Charcot–Marie–Tooth disease

Type	Gene/locus	Specific phenotype
Autosomal dominant CMT1 (AD CMT1)		
CMT 1A	Dup 17p (PMP22) PMP22 (point mutation) MPZ LITAF EGR2 NEFL	Classic CMT1 Classic CMT1/DSN/CHN/HNPP CMT1/DSN/CHN/intermediate/CMT2 Classic CMT1 Classic CMT1/DSN/CHN CMT2 but can have slow MCVs in CMT1 range +/– early onset severe disease
CMT 1B		
CMT 1C		
CMT 1D		
CMT 1		
Hereditary neuropathy with liability to pressure palsies (HNPP)	Del 17p (PMP-22) PMP-22 (point mutation)	Typical HNPP Typical HNPP
HNPP		
X linked CMT1 (CMT 1X)	GJB1	Intermediate +/– patchy MCVs/male MCVs < female MCVs
CMT 1X		
Autosomal recessive demyelinating (CMT4)	GDAP1	CMT1 or CMT2 usually early onset and severe/vocal cord and diaphragm paralysis described/rare AD CMT2 families described
CMT4A		
CMT4B1	MTMR2	Severe CMT1/facial/bulbar/locally folded myelin
CMT4B2	MTMR13	Severe CMT1/glaucoma/locally folded myelin
CMT4C	KIAA1985 (SH3TC2)	Severe CMT1/scoliosis/cytoplasmic expansions
CMT4D (HMSNL)	NDRG1	Severe CMT1/gypsy/deafness/tongue atrophy
CMT4E	EGR2	Classic CMT1/DSN/CHN
CMT4F	PRX	CMT1/more sensory/locally folded mydin
CMT4H	FGD4	CMT1
CMT4J	FIG4	CMT1/gypsy/cataracts/dysmorphic features
CCFDN	CTDP1	CMT1
HMSN Russe	10q22-q23	Classic CMT1/DSN/CHN/HNPP
CMT1	PMPZ2 (point mutation)	CMT1/DSN/CHN/intermediate/CMT2
CMT1	MPZ	
Autosomal dominant CMT2 (AD CMT 2)		Classic CMT2
CMT2A	KIF1Bβ	CMT2/usually severe/optic atrophy
CMT2A	MFN 2	CMT2 with predominant sensory involvement and sensory complications
CMT2B	RAB7	CMT2 with vocal cord and respiratory involvement
CMT2C	12q23-q24	CMT2 with predominant hand wasting/weakness or dHMN-V
CMT2D	GARS	CMT2 but can have slow MCVs in CMT1 range +/– early onset severe disease
CMT2E	NEFL	Classic CMT2 or dHMN-II
CMT2F	HSP27 (HSPB1)	Classic CMT2
CMT2G	12q12-q13.3	Classic CMT2 or dHMN-II
CMT2L	HSP22 (HSPB8)	CMT1/DSN/CHN/intermediate/CMT2
CMT2	MPZ	CMT2 with proximal involvement
CMT2 (HMSNP)	3q13.1	
Autosomal recessive CMT 2 (also called CMT4)	LMNA	CMT2 proximal involvement and rapid progression described/also causes muscular dystrophy/cardiomyopathy/lipodystrophy
AR CMT2A		
AR CMT2B	19q13.1–13.3	Typical CMT2
AR CMT2	GDAP1	CMT1 or CMT2 usually early onset and severe/vocal cord and diaphragm paralysis described/rare AD CMT2 families described
Dominant intermediate CMT (DI-CMT)		
DI-CMTA	10q24.1–25.1	Typical CMT
DI-CMTB	DNM2	Typical CMT
DI-CMTC	YARS	Typical CMT
Hereditary neuralgic amyotrophy (HNA)		
HNA	SEPT9	Recurrent neuralgic amyotrophy

AD, autosomal dominant; AR, autosomal recessive; CHN, congenital hypomyelinating neuropathy; CMT, Charcot–Marie–Tooth; CTDP1, CTD phosphatise subunit 1; Dal, deletion; DMN2, dynemin 2; DSN, Dejerine Sottas neuropathy; Dup, duplication; EGR2, early growth response 2; FGD4, FYVE, RhoGEF and PH domain containing 4; FIG4, FIG 4 homologue; GARS, glycyl tRNA synthetase; GDAP1, ganglioside induced differentiation associated protein 1; GJB1, gap junction protein beta1; HNPP, hereditary neuropathy with liability to pressure palsies; HSPZ2, heat shock 22 kDa protein 8; HSP27, heat shock 27 kDa protein 1; KIF1Bβ, kinesin family member 1B-β; LITAF, lipopolysaccharide induced tumour necrosis factor; LMNA, lamin A/C; MCV, motor conduction velocity; MFN2, mitofusin 2; MPZ, myelin protein zero; MTMR2, myotubularin related protein 2; MTMR13, myotubularin related protein 13; NDRG1, N-myc downstream regulated gene 1; NEFL, neurofilament, light polypeptide 68 kDa; PMPZ2, peripheral myelin protein 22; PRX, periaxin; RAB7, RAB7, member RAS oncogene family; SEPT9, septin 9; SH3TC2, SH3 domain and tetratricopeptide repeats 2; YARS, tyrosyl tRNA synthetase.

Charcot-Marie-Tooth

Table 2 Classification of the hereditary sensory and autonomic neuropathies

Type	Inheritance	Gene/locus	Specific phenotype
HSAN I	AD	SPTLC1	Mainly sensory, sensory complications, motor involvement variable, males may be more severe
CMT2B	AD	RAB7	Sensorimotor, sensory complications, no pain
HSAN 1B	AD	3p22–p24	Sensory, cough, gastro-oesophageal reflux
HSAN II	AR	HSN2	Severe sensory complications, mutilations, onset first 2 decades
HSAN III	AR	IKBKAP	Familial dysautonomia or Riley-Day syndrome, prominent autonomic, absence fungiform papillae of the tongue
HSAN IV		NTRK1	Congenital insensitivity to pain with anhydrosis(CIPA), severe sensory, anhydrosis, mental retardation, unmyelinated fibres mainly affected
HSAN V	AR	NTRK1	Congenital insensitivity to pain with mild anhydrosis, no mental retardation, small myelinated fibres mainly affected
HSAN V	AR	NGFB	Congenital insensitivity to pain, minimal autonomic, no mental retardation, mainly unmyelinated fibres affected
Channelopathy associated insensitivity to pain	AR	SCN9A	Congenital insensitivity to pain

AD, autosomal dominant; AR, autosomal recessive; CMT, Charcot–Marie–Tooth; HSN2, hereditary sensory neuropathy type II gene; IKBKAP, Inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein; NGFB, nerve growth factor beta polypeptide; NTRK1, neurotrophic tyrosine kinase receptor type 1; SCN9A, sodium channel, voltage gated, type IX, alpha subunit; RAB7, RAB7, member RAS oncogene family; SPLTC1, serine palmitoyltransferase, long chain base subunit-1.

Table 3 Classification of the distal hereditary motor neuropathies

Type	Inheritance	Gene/locus	Specific phenotype
HMN I	AD	Unknown	Juvenile onset dHMN
HMN II	AD	HSP27(HSPB1)	Adult onset typical dHMN/CMT2F
HMN II	AD	HSP22(HSPB8)	Adult onset typical dHMN/CMT2L
HMN III	AR	11q13	Early onset, slowly progressive
HMN IV	AR	GARS	Juvenile onset, diaphragmatic involvement
HMN V	AD	BSCL2	Upper limb onset, slowly progressive/CMT2D
HMN V	AD	IGHMBP2	Upper limb onset, +/−spasticity lower limbs/Silver syndrome
HMN VI	AR	2q14	Spinal muscle atrophy with respiratory distress (SMARD1), infantile onset respiratory distress
HMN VIIA	AD	DCTN1	Adult onset, vocal cord paralysis
HMN VIIB	AD	SETX	Adult onset/vocal cord paralysis/facial weakness
HMN/ALS4	AR	9q21.1–p12	Early onset, pyramidal signs
HMN-J	AD	12q23–12q24	Juvenile onset, pyramidal features, Jerash
Congenital distal SMA			Antenatal onset, arthrogryposis

AD, autosomal dominant; AR, autosomal recessive; BSCL2, Berardinelli-Seip congenital lipodystrophy 2 (Seipin); CMT, Charcot–Marie–Tooth; dHMN, distal hereditary motor neuropathy; DCTN1, dynactin1; HSP22, heat shock 22 kDa protein 8; HSP27, heat shock 27 kDa protein 1; GARS, glycyl tRNA synthetase; IGHMBP2, immunoglobulin mu binding protein 2; SETX, sentaxin; SMA, spinal muscular atrophy.

Charcot-Marie-Tooth

•La caratterizzazione genetica non è comunque specifica: nell'ambito di alcune forme cliniche, diverse anomalie genetiche sottostanti o viceversa (HSAN1 e CMT2B clinicamente identiche); certi geni per dHMN anche causa di CMT assonale (GARS, HSP27, HSP22)

Primo passo: "Is the neuropathy genetic (CMT/HNPP/HSAN/dHMN)?"

•Parente affetto? Probabile AD o X-linked o AR se storia di consanguineità tra genitori di fratelli affetti
•Ma se non c'è storia familiare o questa è difficilmente ricostruibile, diagnosi CMT complessa

Elementi di supporto e indirizzo diagnostico: esordio infanzia, progressione, deformità piedi, assenza sintomi sensitivi positivi (adulti) in presenza di chiari deficit sensitivi

Charcot-Marie-Tooth

Table 3. Genetic epidemiology of CMT in the general population

Country	Affected individuals, n	Families, n	CMT prevalence/ 100,000 population	CMT1, % (prevalence/ 100,000) (n)	CMT2, % (prevalence/ 100,000) (n)	Others, % (n)
Norway	245	116	82.3	37.6 (–) (92)	35.9 (–) (88)	2.9 (intermediate CMT: 7) 23.6 (unknown neurophysiological phenotype: 58)
Sweden	104	52	20.1	81 (16.2) (84)	15 (–) (16)	4 (4)
UK	133	49	18.1	56 (10.9) (69)	12 (2.7) (15)	31 (CMT3: 1; CMT5: 7; spinal CMT: 9; not classified: 22)
Italy	58	13	17.5	64 (–) (37)	25 (–) (15)	1 (6)
Turkey		33	16	52 (–) (18 families)	33 (–) (11 families)	15 (intermediate CMT: 4 families)
Egypt	5	–	12	–	–	–
Iceland	37	18	12	84 (10) (31)	16 (2) (6)	–
England	352	275	11.8	56.7 (–) (126)	17.6 (–) (39)	25.8 (57)
Japan	19	11	10.8	–	–	–
Serbia	161	–	9.7	73 (7.1) (119)	23 (2.3) (37)	4 (5)
Germany	776 (589*)	–	–	60 (–) (355)	26 (–) (151)	14 (HNPP: 83)
Italy	100	30	–	– (9.37) (100)	–	–
Total	1,990	597				

Norvegia Ovest prev: AD 36/100,000, X-linked 3.6/100,000, AR 1.4/100,000

* Five hundred eighty nine patients with nerve conduction studies.

- Prevalenza di 1:2500
- In UK/nord Europa/USA: 90% AD o X linked; Paesi con consanguineità AR CMT 40%.

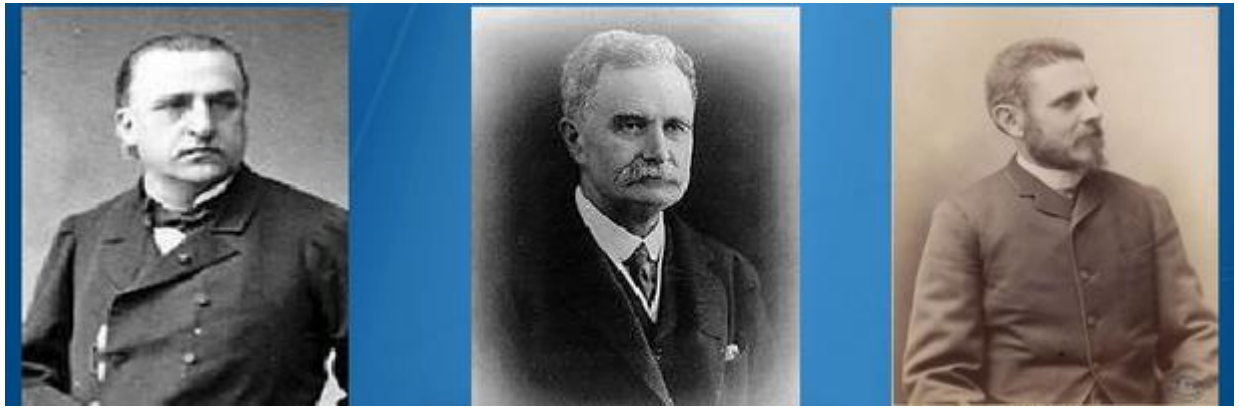
- Approccio diagnostico diverso a seconda della provenienza geografica

- Forme sporadiche: di solito mutazioni nei geni AD (de novo) o AR

Charcot-Marie-Tooth

120 aa fa, descrizione contemporaea di una sindrome familiare, l'atrofia muscolare peroneale, da Charcot e Marie a Parigi, e Tooth in Inghilterra (Charcot and Marie, 1886; Tooth, 1886).

(1893) Déjèrine e Sottas: due fratelli affetti da una neuropatia più grave, a esordio precoce e ipertrofia nervi



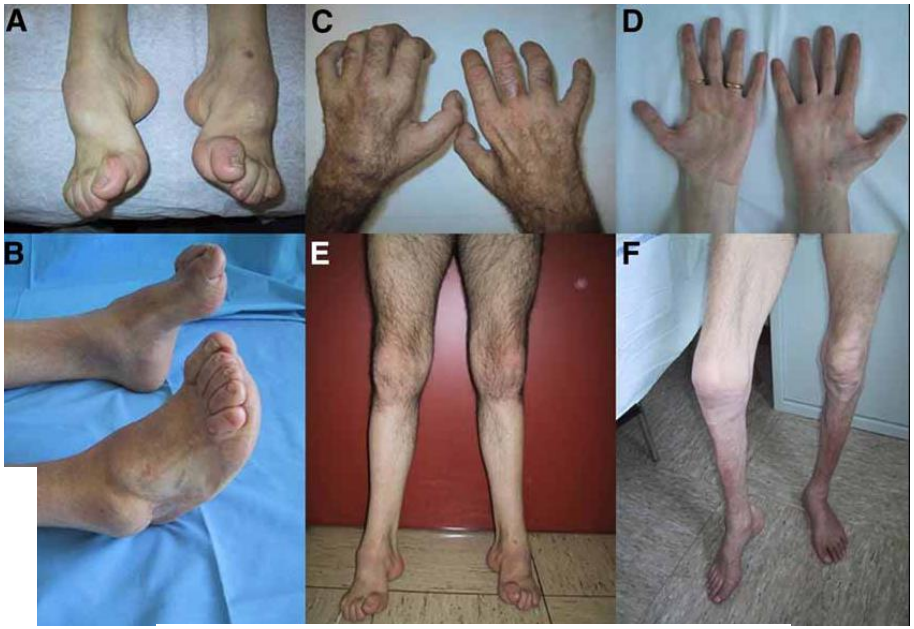
HMSN I e II (introdotte '60-'80 da Dyck, Lambert, Harding, Thomas):

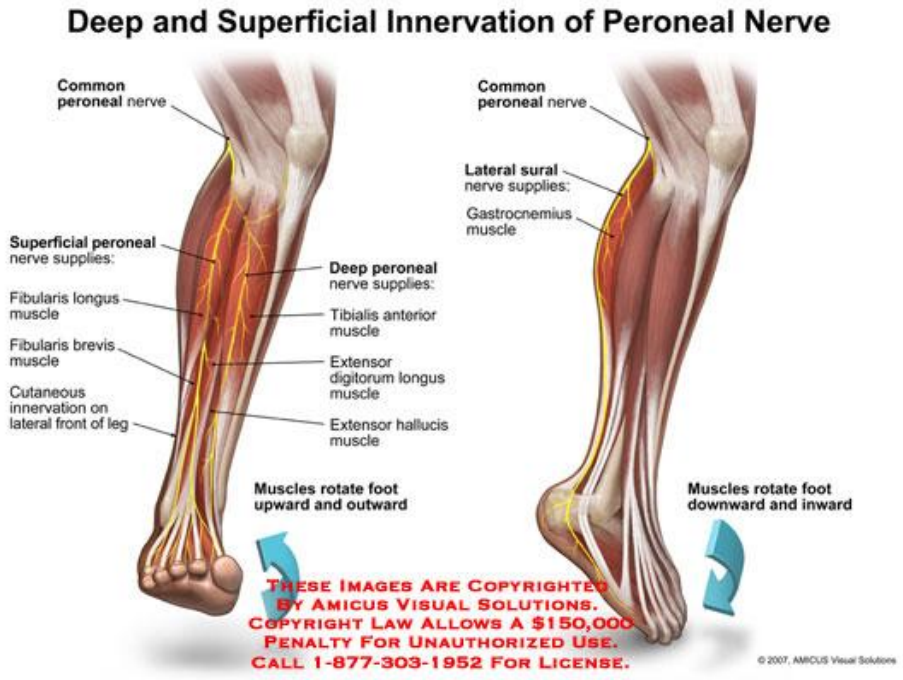
- AD, "ipertrofica" con basse VC, demielinizzazione e remielinizzazione segmentale HNPP;
- AD, VC conservata/poco rallentata, con degenerazione e rigenerazione assonale

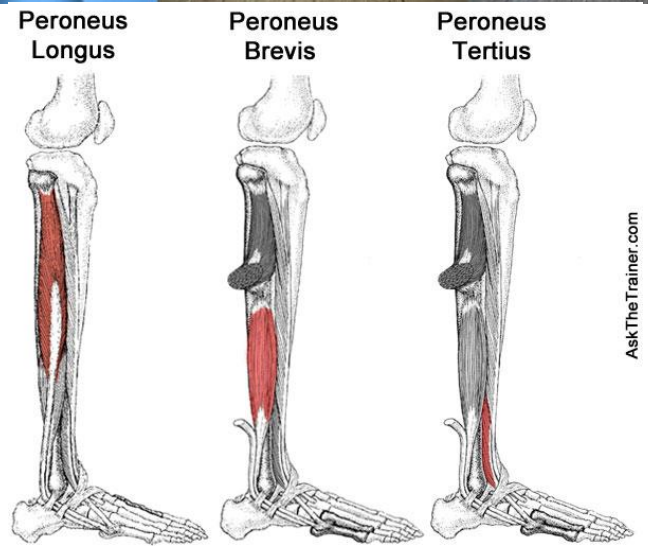
Charcot-Marie-Tooth

Diagnostic approach

1) definizione fenotipo clinico
2) identificazione ereditarietà
3) esame NFS
4) analisi molecolare
5) biopsia di nervo (cute?)





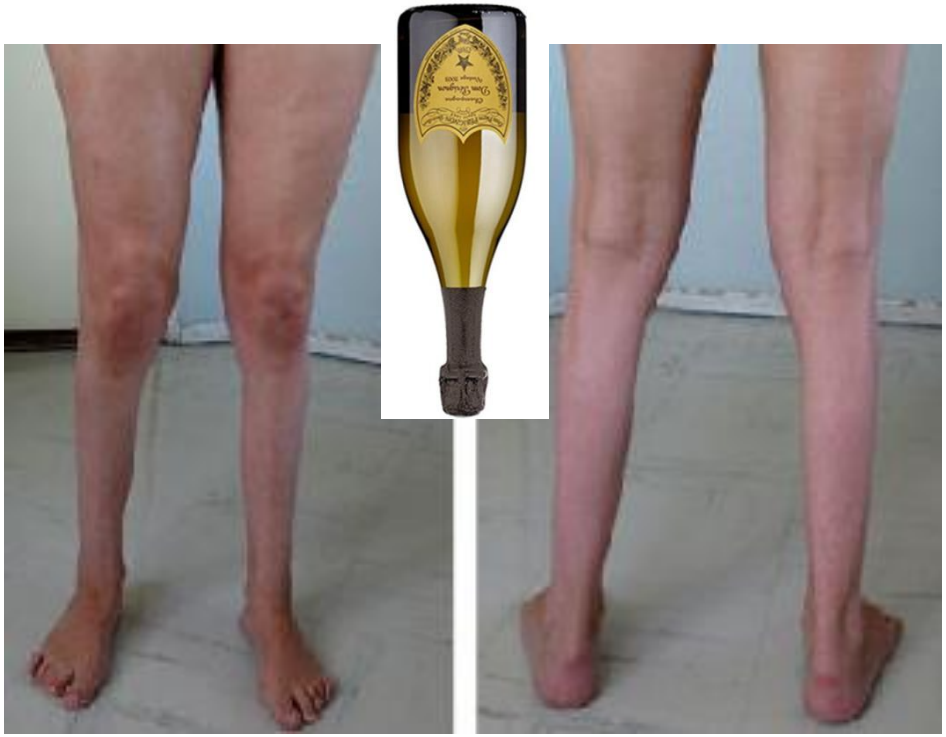


Charcot-Marie-Tooth

Fenotipo clinico simile per mutazioni geni diversi (struttura mielina, proteine gap-junction, citoscheletro, enzimi, TF,…)

Fisiopatologia: danno primario mielina o degenerazione assonale lunghezza-dipendente

Evoluzione motoria: deficit distali AAII → mani → porzione distale cosce.
Evoluzione sensitiva: deficit distali AAII → prox AAII → mani;



Fenotipo clinico: sospetto di CMT

neurofisiologia

genetica

DIAGNOSI (?)

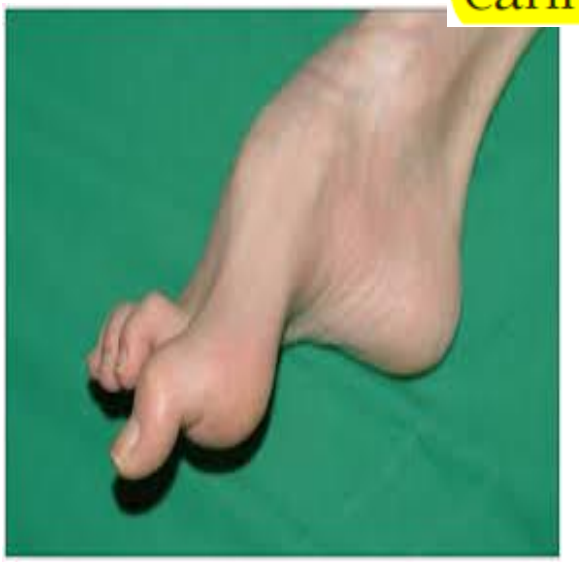
Charcot-Marie-Tooth

Gravità ed evoluzione variabile, anche tra gemelli affetti dal medesimo difetto genetico

- Esordio infantile (prima decade) con “walking toe”
- Decorso lentamente progressivo
- Raramente esordio precoce con ipotonia “floppy child” o ritardo nello S(P)M
- Forme anche a esordio tardivo

Equilibrio

worse in a crowd at night, when vision cannot overcome proprioceptive loss.



•Deformità scheletriche (66% in totale e 70-95% in CMT1); >% pes cavus e dita a martello(<<scoliosi)
•A volte esordio con pes planus → cavus

Da squilibrio nell’attività muscoli gamba piede

Charcot-Marie-Tooth

•Più suggestivi/di sospetto: difficoltà corsa con steppage/piede cadente in bambini/adolescenti con pes cavus, nel ruotare caviglie, manipolazione

- Muscle loss in feet and calves
- Cannot lift toes high enough when walking naturally
- Compensate by lifting leg from thigh

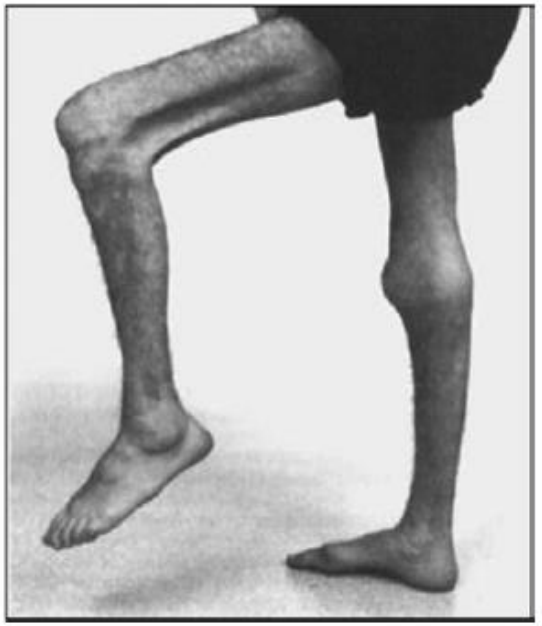


FIGURE 5-2 An example of steppage gait is shown in a patient with an unusual amount of leg wasting.

Reprinted from Charcot J, Marie P. Sur une forme particulière d'atrophie musculaire progressive, souvent familiale, débutant par les pieds et les jambes et atteignant plus tard les mains. Rev Med Paris 1886;6:97–138.

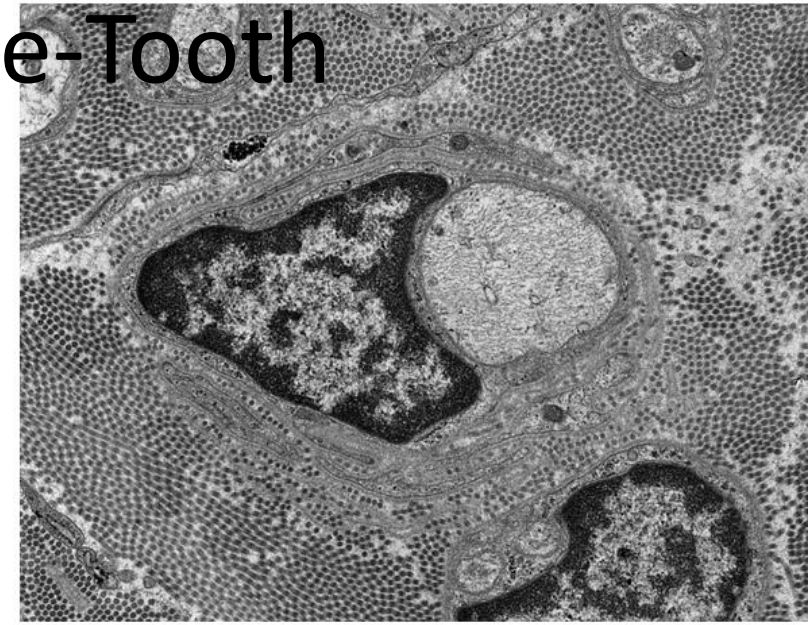
Charcot-Marie-Tooth

rule of thumb is that sensory symptoms in the hands begin about the time sensory symptoms in the lower extremities have progressed to the knee.

modalities. Cold, erythematous, or bluish discolored feet suggest a loss of small fiber function. Large fiber sensory

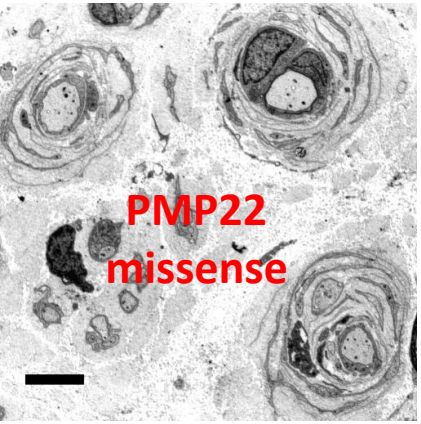
Charcot-Marie-Tooth

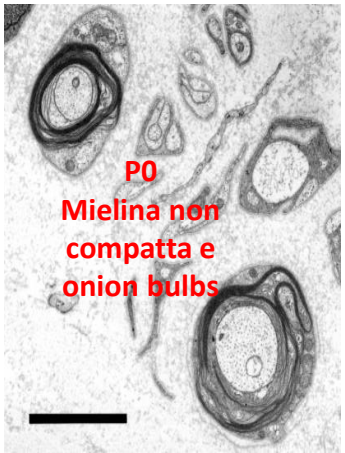
for DSS have included the following: (1) onset by age 2 years with delayed motor milestones; (2) severe motor, sensory, and skeletal deficits with frequent extension to proximal muscles, sensory ataxia, and scoliosis; (3) markedly abnormal NCVs with either slowing in the range of 10 m/s or severe reductions in motor and sensory amplitudes; and (4) evidence of severe demyelination or axonal loss on nerve biopsy.



Congenital hypomyelinating neuropathy. The Schwann cell touches the axon but makes no myelin. There are rings of basement membrane.

CH are usually hypotonic in the first year of life, have developmental delays in walking, and, in some cases, have swallowing or respiratory difficulties. Patients with CH often appear as "floppy" infants. Patients classified as having either CH or DSS have shown the same severe pathologic changes on sural nerve biopsies, and both diseases are associated with very slow NCVs (less





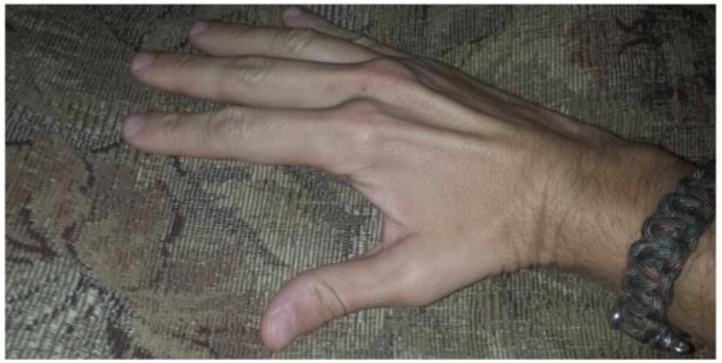
Charcot-Marie-Tooth

esordio tardivo: NO deformità scheletriche

Muscoli intrinseci piede

↓

Muscoli gamba → steppage → Deficit flex plantare



↓

Terzo inferiore coscia

↓

Muscoli mano → en griffe, tremore

↓

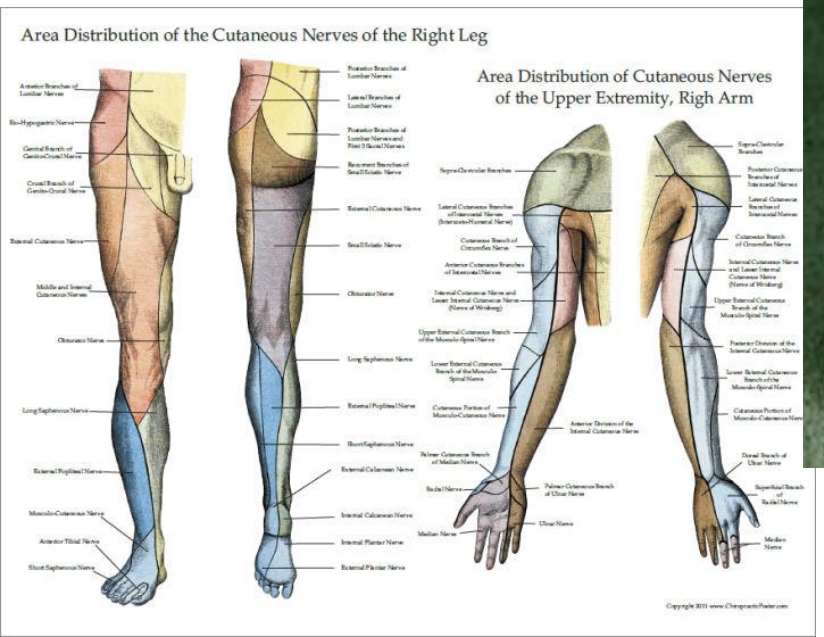
Muscoli avambraccio

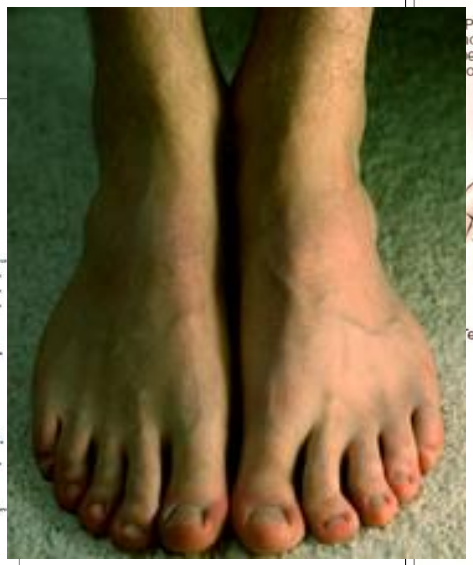
Charcot-Marie-Tooth

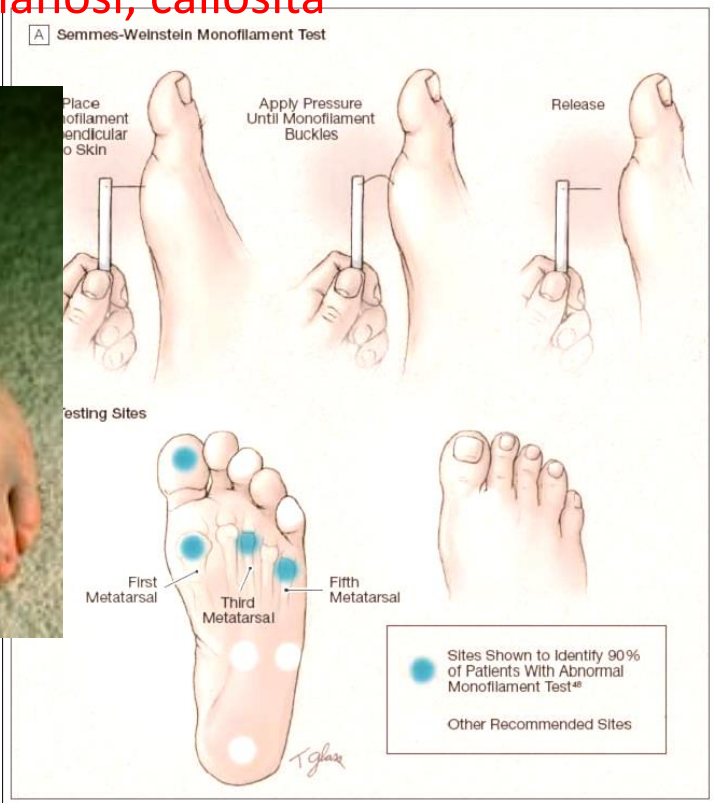
sintomi sensitivi < sintomi motori (anche subdoli)

- Deficit sensitivo tattile, dolorifica, pallestesia > propriocezione (ATASSIA)
- Possibili parestesie e disestesie
- Risparmio fibre sensitive nelle forme dHMN
- RP ipoelicitabili/assenti in CMT1; ipo-/nella norma in CMT2 e dHMN

Frequenti: crampi, piedi freddi, acrocianosi, callosità







Charcot-Marie-Tooth

Alcuni sintomi molto utili nel guidare l'approfondimento diagnostico (molecolare)

CMT1D (10q21.1–q22.1; *EGR2; <1%):* ***grave*** *fenotipo, coinvolti* ***nervi cranici***
CMT1F (8p21; *NEFL; rare): esordio* ***precoce, atassia e tremore cerebellare*** *in alcuni*

CMTX1 (Xq13.1; G*JB1/Cx32; 7–12%):* **SNC subclinico, anche transitori** *(segni clinici lievi*, anomalie ai PE multimodali; anomalie RM sostanza bianca)

Case reports: transient cerebral WM lesions of CMXT1 + acute or subacute ataxia, dysarthria, hypoesthesia, aphasia, hemiplegia or quadriplegia etc., which can be alleviated in several hours or several days, or maybe attack repeatedly.

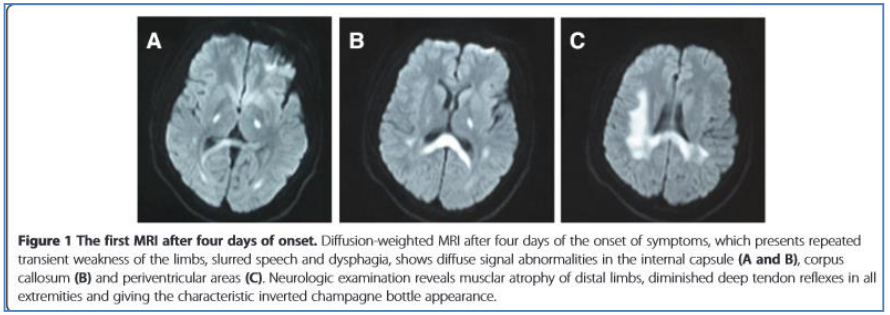


Figure 1 The first MRI after four days of onset. Diffusion-weighted MRI after four days of the onset of symptoms, which presents repeated transient weakness of the limbs, slurred speech and dysphagia, shows diffuse signal abnormalities in the internal capsule **(A and B)**, corpus callosum **(B)** and periventricular areas **(C)**. Neurologic examination reveals muscular atrophy of distal limbs, diminished deep tendon reflexes in all extremities and giving the characteristic inverted champagne bottle appearance.

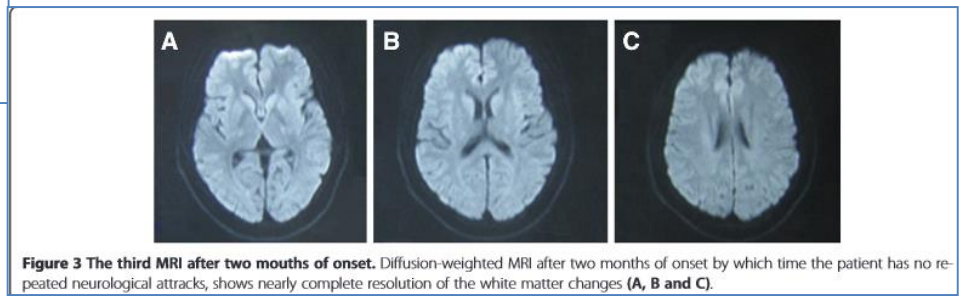


Figure 3 The third MRI after two mouths of onset. Diffusion-weighted MRI after two months of onset by which time the patient has no repeated neurological attracks, shows nearly complete resolution of the white matter changes **(A, B and C)**.

Charcot-Marie-Tooth

Alcuni sintomi molto utili nel guidare l'approfondimento diagnostico (molecolare)

CMTX4 (Xq24–q26): severa neuropatia, **ritardo mentale, sordità** (Cowchock syndrome)
CMTX5 (PRPS1); *2 famiglie: esordio precoce; neuropatia lieve-moderata;* **atrofia ottica e sordità**

CMT2A (*MFN2*): *fino al 20% of CMT2; anche grave; atrofia ottica, ipoacusia, piramidalismo, anomalie sostanza bianca cerebrale*

CMT2B (*RAB7*): *prominente deficit sensitivo, ipercheratosi e gravi ulcere piedi*

CMT2C (12q23–q24): rara; esordio precoce; coinvolgimento **corde vocali, diaframma, nn intercostali, muscoli prossimali**
CMT2D (7p15; *GARS*): ***> interessamento AASS***

dHMN VII (AD; *DCTN1): esordio giovani adulti,* ***paralisi bilaterale ccvv ("respiratory difficulty"),*** **ipostenia e affaticamento progressivo faciale e AA**

Charcot-Marie-Tooth

Alcuni sintomi molto utili nel guidare l'approfondimento diagnostico (molecolare)

Recurrent focal neuropathies (autosomal dominant)			
HNPP	162500	17p11·2–12	*PMP22* deletion or nonsense mutations
HNA	162100	17q25	*SEPT9*

Frequent; transient painless recurrent focal mononeuropathies and brachial plexopathies caused by compression or without apparent precipitating cause; can have CMT-like phenotype; conduction slowing or blocks at entrapment sites in nerve-conduction studies, and generalised neuropathy; nerve biopsy: tomacula

Episodes of pain followed by weakness and atrophy, usually involving the brachial plexuses

Charcot-Marie-Tooth

NFS

•Studi conduzione nervosa: presenza, grado, pattern rallentamento VC

Demielinizzante (CMT1 e 4) se VCM (mediano/ulnare) < 38 m/s;
Assonale se VCM >38 m/se riduzione CMAP e SAP (CMT2);
Forme intermedie con VCM 25 - 45 m/s (DI-CMTB, DI-CMTC, DI-CMTA);
spesso in CMT1X, CMT2E, late onset CMT1B, CMT4A.

•VCM con rallentamento uniforme (asimmetrico a "patchy" nelle CIDP)

CMTX1

- **Rallentamento conduzione M<F (ampio range ,18-60 m/s);**

Se VCN normale o quasi e SAP preservati: > probabile dHMN

Charcot-Marie-Tooth

NFS

Fondamentale per la diagnosi: valutazione nervi motori e sensitivi e eventuale danno muscolare secondario

Rallentamento lungo nn sensitivi e motori, segmenti prossimali e distali: segno di anomalie nella mielinizzazione, dei canali ionici, di nodi e paranodi, delle interazioni cellula di Schwann – assone.

Danno assonale e perdita fibre: riduzione CMAP e SAP; sia le CMT assonali che demielinizzanti possono presentare perdita assonale.

Charcot-Marie-Tooth

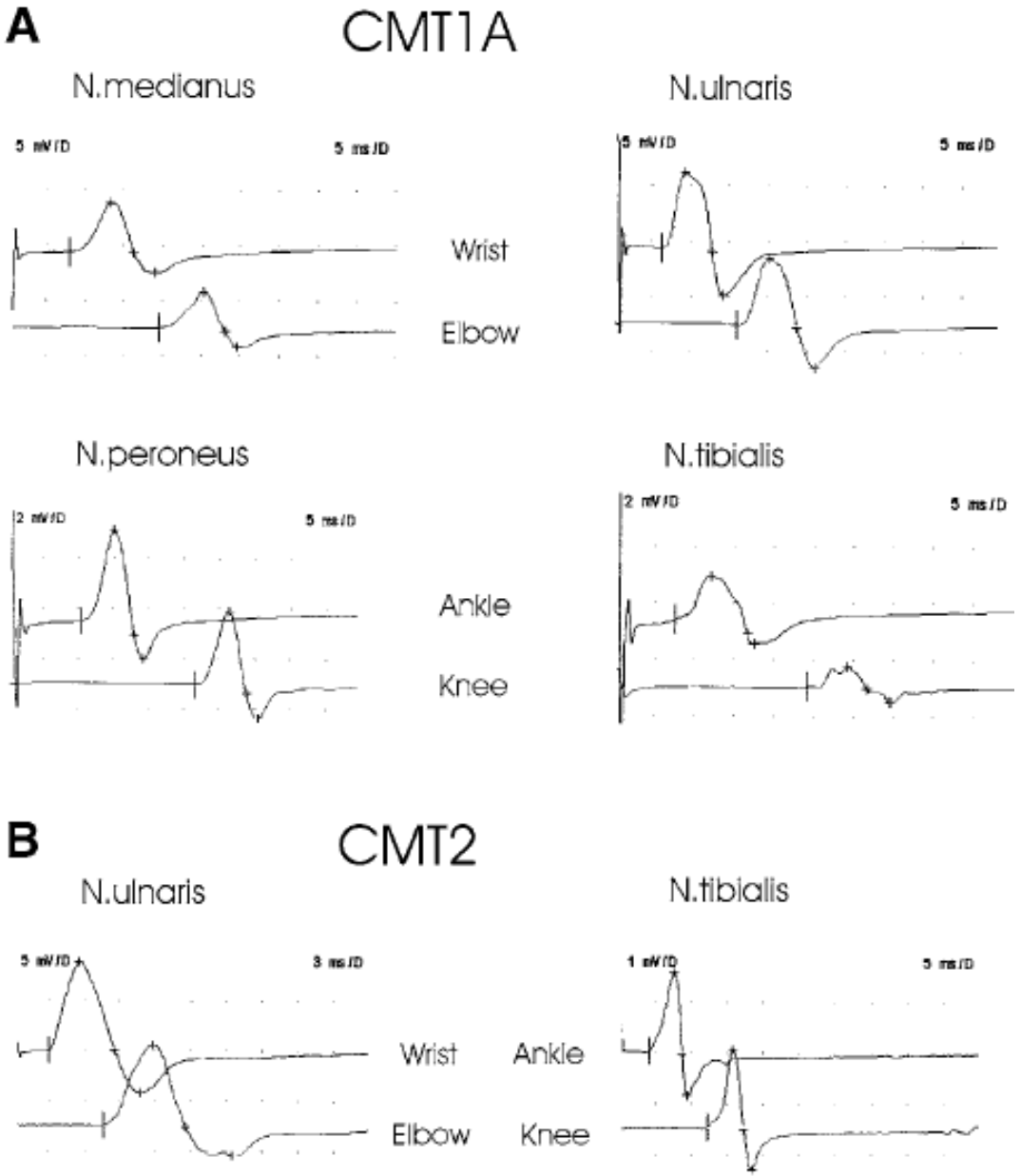
NFS

Fin da anni'80: rallentamento VC in forme ipertrofiche ereditarie (CMT1 e DS) diffuso e uniforme

- In CMT1 e DS disfunzione generalizzata CS e mielina (vero per CMT1A – PMP22 dup., diffuso, omogeneo, simile AASS e AAII, prox e dist, senza BC)
- In CIDP infiammazione e disarrangiamento mielina focale e sparso

- Eccezioni:
  - in CMTX (anomalie VC non uniformi tra differenti tronchi nervosi e per lo stesso nervo, aumento dispersione temporale, +/- BC)
  - CMT: anche se VC<, alla biopsia spesso predomina danno assonale cronico
  - Raramente BC in CMT – MPZ mut.
  - HNPP: rallentamento FOCALE siti di compressione

Charcot-Marie-Tooth



*(A) **CMT1A**: 24-yr-old female. The MCV are markedly reduced, ranging from 18.5 to 20 m/s in all tested nerves. **The distal motor latency is increased**, from 6.2 ms (ulnar nerve) to 10.4 ms (peroneal nerve). The CMAP shapes are simple, without temporal dispersion but very mild at the tibial nerve by proximal stimulation. These findings are in keeping with a homogeneous and diffuse demyelinating involvement of the peripheral nervous system.*

*(B) **CMT2**. MCV and distal motor latencies normal; ulnar nerve CMAP is of normal amplitude (10 mV), while **tibial nerve CMAP is reduced in amplitude**. The CMAP shape is simple and there is no temporal dispersion. The findings demonstrate a length-dependent axonal sensory-motor neuropathy*

Charcot-Marie-Tooth

- **CMT2**:
  - riduzione amp. cMAP e SAP, decorso lento progressivo = degenerazione assonale e perdita fibre.
  - VC normale o lievemente ridotta (perdita fibre grosso calibro)

- **Late-onset CMT2:** non noto come disfunzione di una proteina della mielina compatta risulti in neuropatia assonale.
- In dHMNs: risparmio nervi sensitivi, diminuzione cMAPs, VC preservata; difficile DD con CMT2, anche per geni comuni
  - glycil-tRNA synthetase, HSPB1, HSPB8

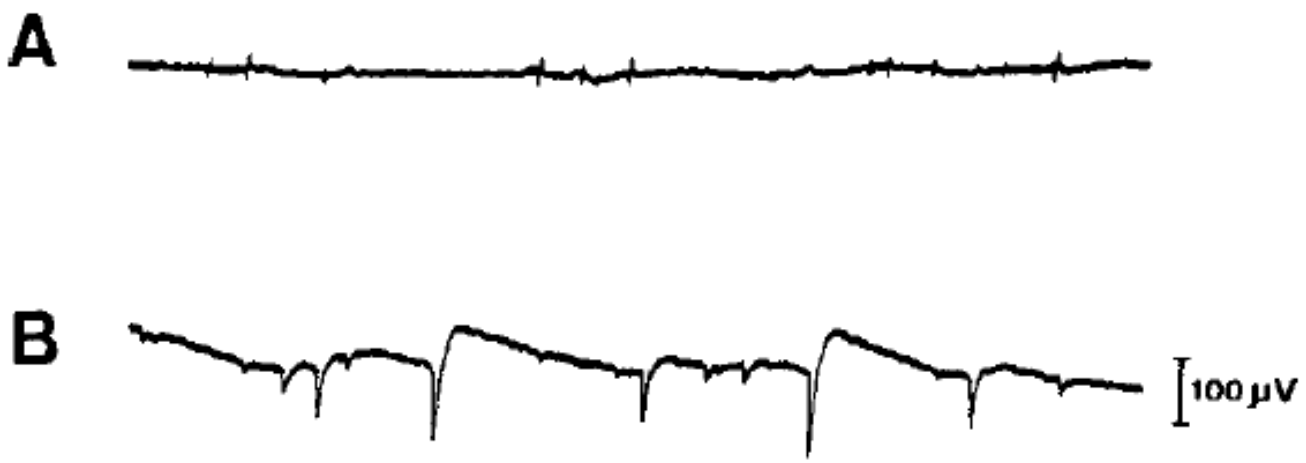
Sempre più arbitraria distinzione demielinizzante/assonale

Charcot-Marie-Tooth

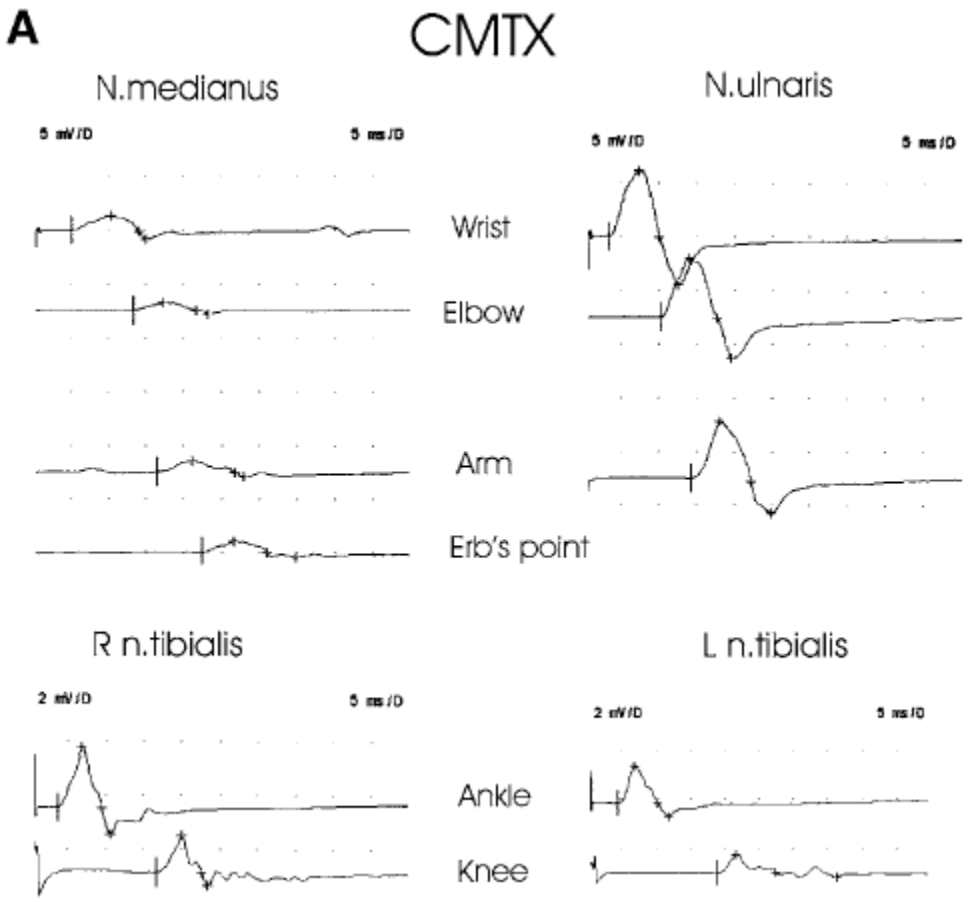
NFS

- EMG: spesso segni da denervazione cronica
  - PUM > durata e ampiezza
  - Distale>prossimale

- Segni da denervazione in atto: forme più aggressive
  - Potenziali di fibrillazione
  - Potenziali positivi

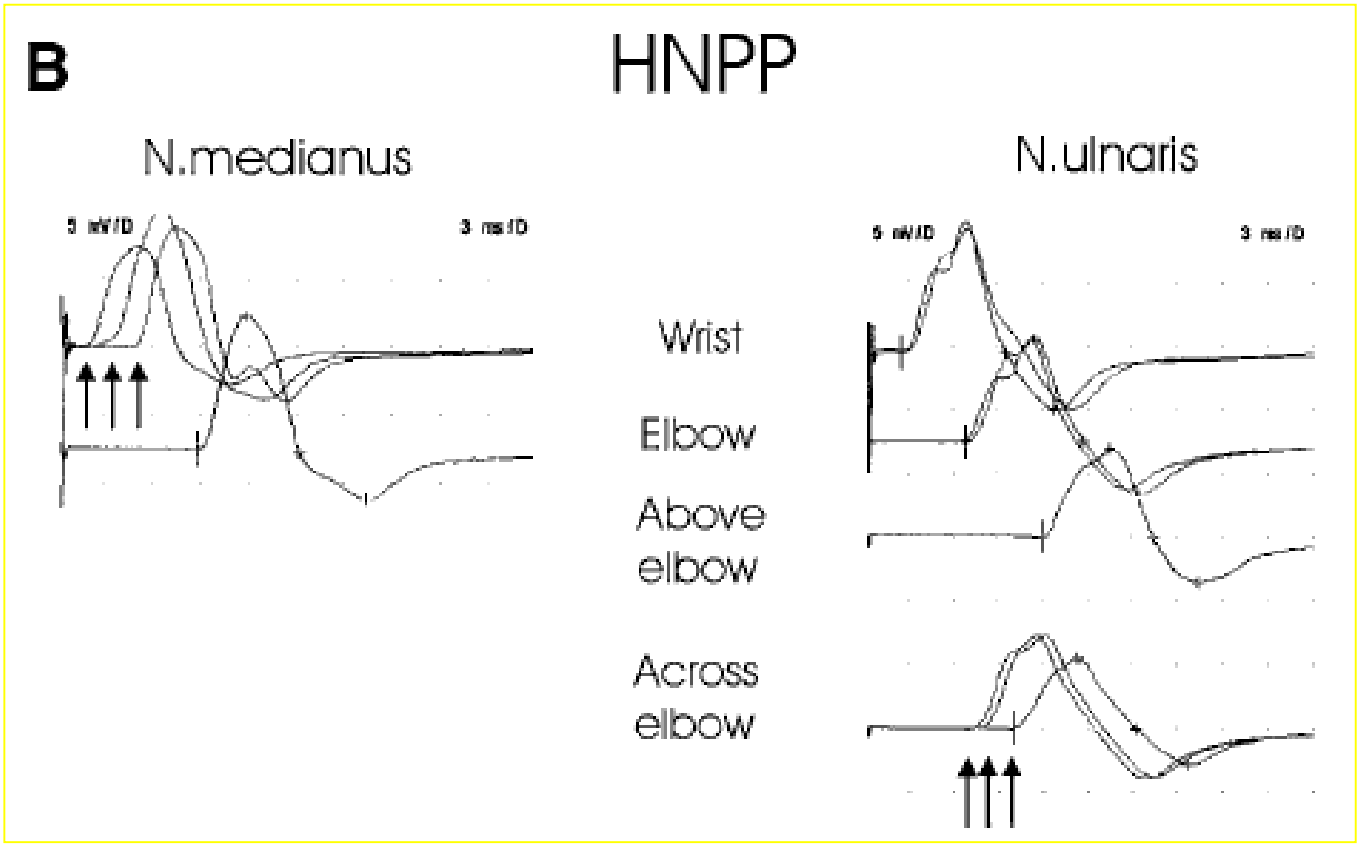


Charcot-Marie-Tooth



Median, ulnar and tibial nerve (a 31-yr-old male). In LL, MCV is clearly reduced (27.6 m/s), distal motor latency is within the norm, and the distal CMAP is reduced in amplitude and slightly dispersed. CMAP obtained by proximal stimulation (popliteal region) is further reduced in amplitude and shows an increased temporal dispersion. In the UULL: median MCV is reduced (29 m/s), with increased distal latency, severe reduction of CMAP amplitude. On the other hand, **the ulnar nerve motor conduction velocity is in the intermediate range (35 m/s**), the CMAP is normal, and there is no increased temporal dispersion.

VC intermedia agli AASS, più grave al mediano versus ulnare, aumento dispersione temporale: elementi NFS suggestivi di CMTX.



Charcot-Marie-Tooth

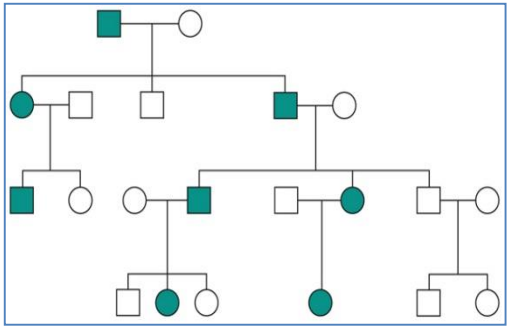
HNPP: **Median nerve**: distal motor latency is increased (4.8 ms), although MCV is normal (55 m/s). The CMAP is normal in amplitude and there is no temporal dispersion. The typical focal conduction slowing across the wrist is demonstrated by the inching stimulation technique; in the panel the arrows indicate the sites of stimulation, each 1 in. apart, across the wrist. **Ulnar nerve**: the distal motor latency (2.6 ms), and the conduction velocity elbow-to-wrist (53 m/s) are normal. However, the stimulation above the elbow shows a significant reduction in CV (38 m/s); the site of conduction slowing is shown to be localized to the elbow by stimulation 1 in. above and below elbow (arrows).

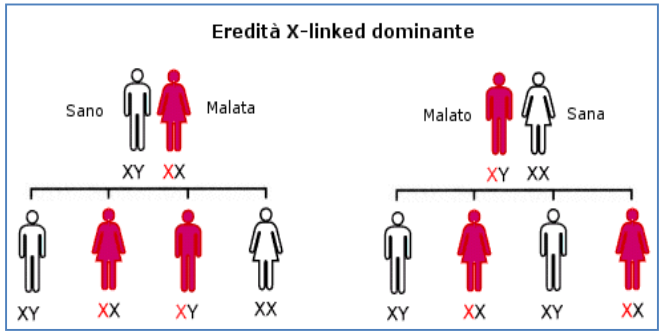
Charcot-Marie-Tooth

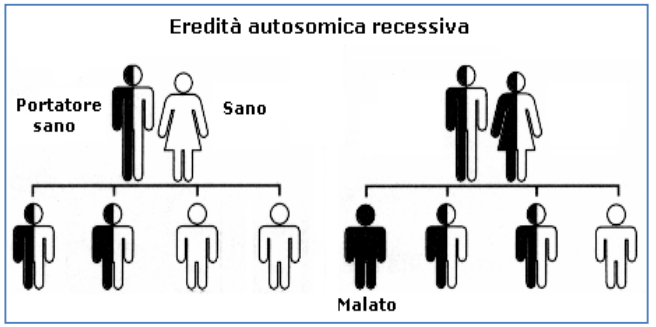
inheritance pattern

AD > comune (CMT1, most CMT2 and dHMN)
CMTX1: **dX-linked → no male-to-male**; più grave in emizigoti (M)

AR: CMT4 (dem), AR-CMT2 (ax), and AR-dHMN (pure motor)
Sporadic cases not uncommon: de novo mutations (> CMT1A duplication, *MFN2 mutations*)







Storia familaire non riconoscibile : espressione variabile, oligosintomatici

Esame clinico e NFS anche nei congiunti prossimi ("sani") di pazienti affetti

Charcot-Marie-Tooth

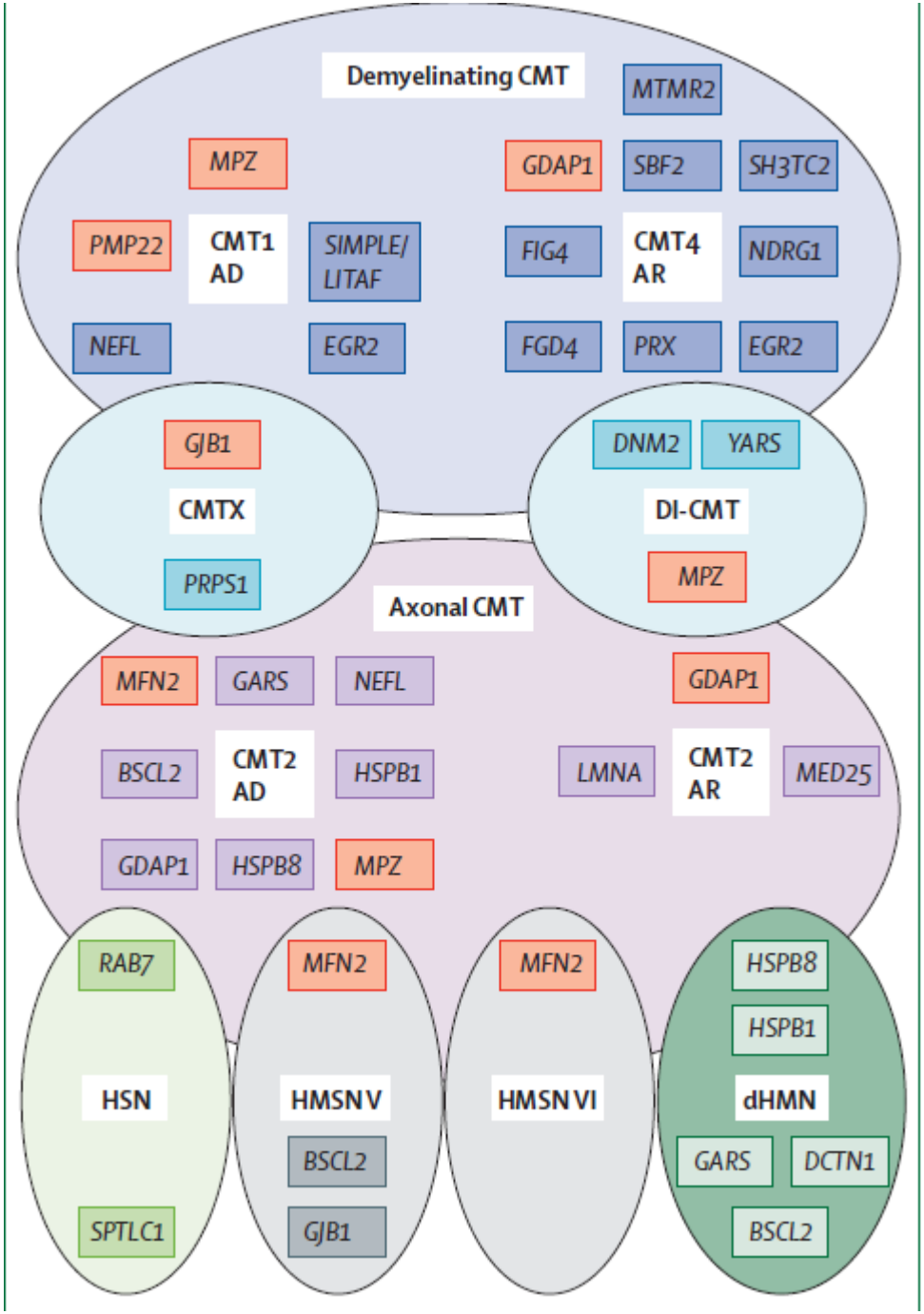
inheritance pattern

Aspetti importanti su CMT AR (CMT4)

Pochi casi
Polimorfosmi frequenti
Mutazioni eterozigoti patogenetiche
Screening su molti familiari per verifica patogeneticità mutazioni
Spesso necessario VCM muscoli prossimali

- CMT4 – LMNA: II decade, severa (coinvolgimento prossimale)

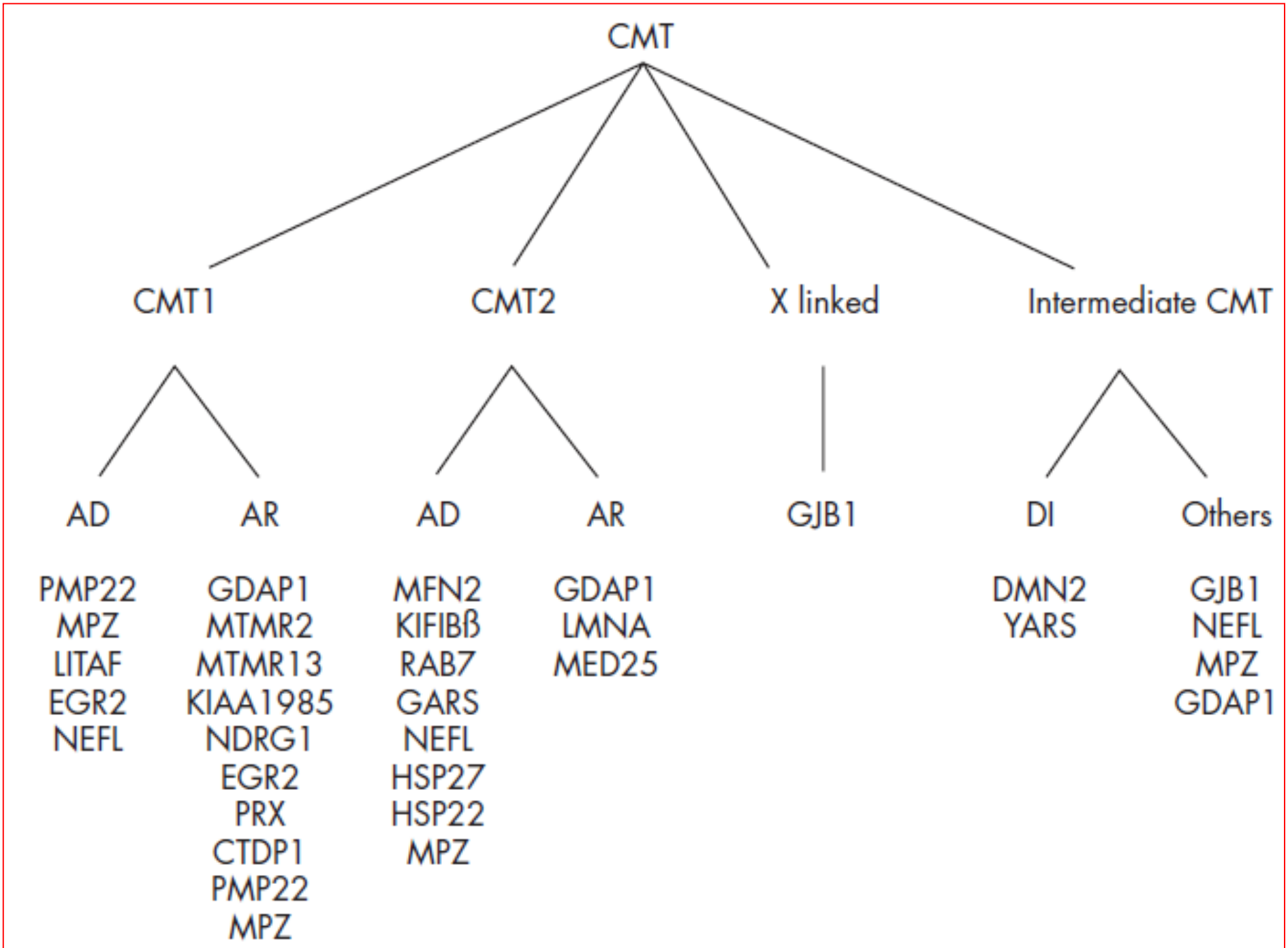
lamin A/C mutations associated with a wide spectrum of other phenotypes (Emery-Dreifuss muscular dystrophy, cardiomyopathy, and Dunnigan-type familial partial lipodystrophy)



CMT

Mutazioni genetiche in proteine con diversa localizzazione: mielina compatta e non, cell di Schwann, assoni; e con diverse funzioni (compattamento, mantenimento; mielina, formazione citoscheletro, trasporto ax, metabolismo mitocondri)

"the final common pathway is represented by an axonal degenerative process that, in most cases, mainly involves the largest and longest fibres"


CMT
CMT1
CMT2
X linked
Intermediate CMT
AD
AR
AD
AR
GJB1
DI
Others
PMP22
MPZ
LITAF
EGR2
NEFL
GDAP1
MTMR2
MTMR13
KIAA1985
NDRG1
EGR2
PRX
CTDP1
PMP22
MPZ
MFN2
KIFIBß
RAB7
GARS
NEFL
HSP27
HSP22
MPZ
GDAP1
LMNA
MED25
DMN2
YARS
GJB1
NEFL
MPZ
GDAP1

CMT

In European populations this duplication accounts for 70% of all CMT1 cases.

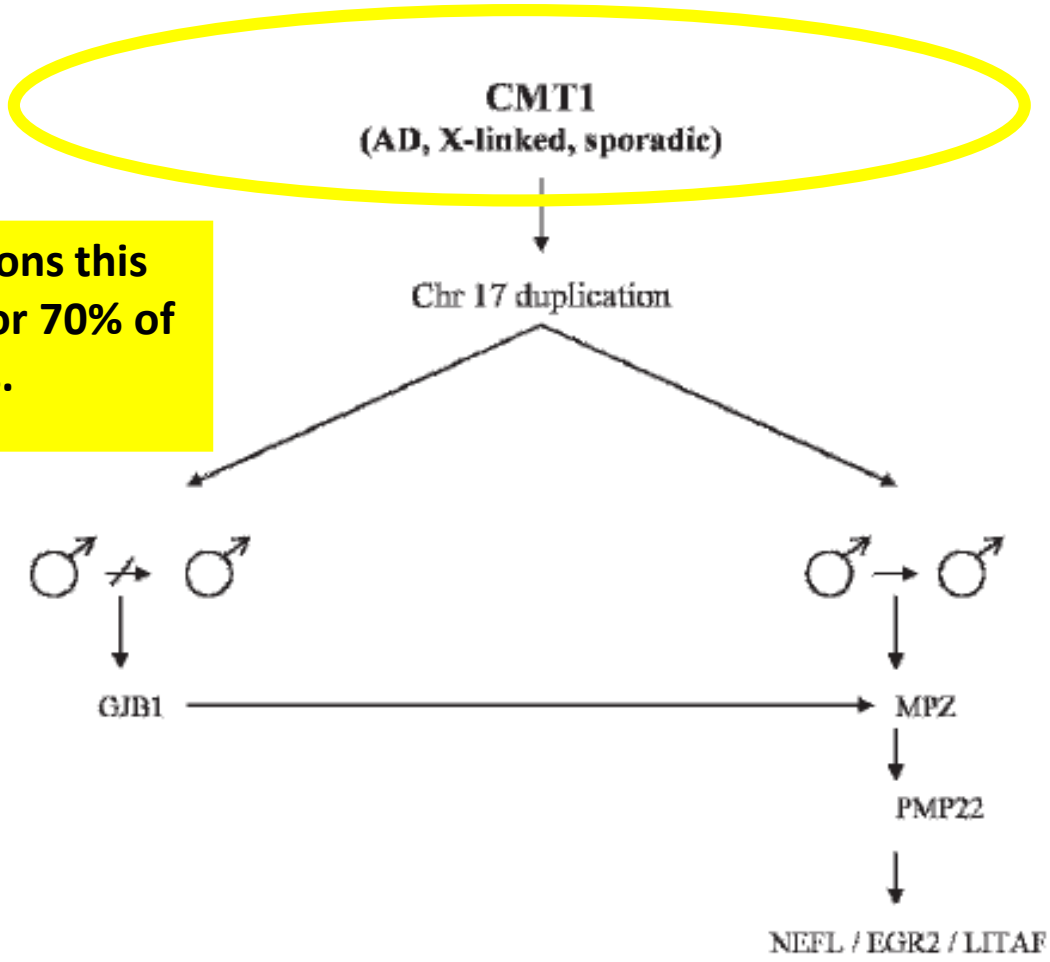


Figure 1 Algorithm for molecular diagnosis of autosomal dominant (AD) and X linked demyelinating Charcot–Marie–Tooth disease (CMT1). EGR2, early growth response 2; GJB, gap junction protein beta 1; LITAF, lipopolysaccharide induced tumour necrosis factor; MPZ, myelin protein zero; NEFL, neurofilament, light polypeptide 68 kDa; PMP22, peripheral myelin protein 22.

CMT

Maggioranza **CMT1** con 1.4 Mb dup. 17p11.2–p12, regione con gene *peripheral myelin protein 22 (PMP22)*. Meno comune, ***PMP22* point mutations** (CMT1A; 1% of CMT1 cases) o **point mutations in *P0*** *(MPZ; CMT1B;* 3–5% of cases)

In CMT AD o sporadiche con NFS demielinizzante (CMT1):

1. CMT1A dup. (PMP22);
2. CMTX1 - GJB1;
3. Gene per small integral membrane protein of lysosome/late endosome (*SIMPLE*; anche lipopolysaccharide-induced tumour necrosis factor [*LITAF*]);
4. early growth response 2 (*EGR2*);
5. NEFL

CMT

Maggioranza **HNPP** con delezione 1.4 Mb cr 17p11.2–p12, con gene ***peripheral myelin protein 22 (PMP22)*** gene.

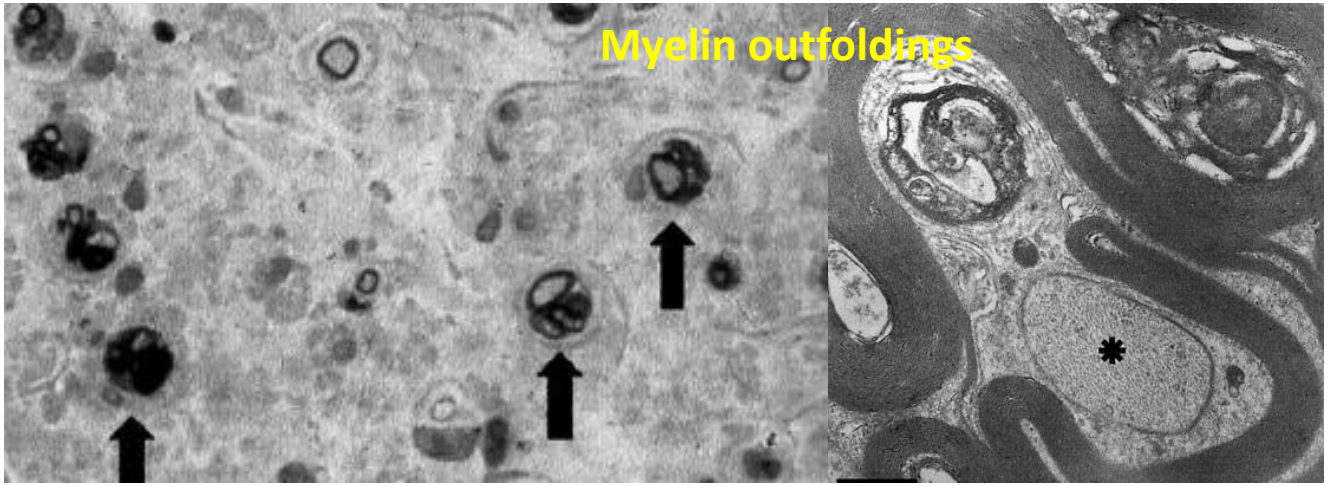
1. Un solo tronco nervoso alla volta clinicamente
2. NFS: neuropatia generalizzata demielinizzante
3. EpIsodiche e ricorrenti paralisi da compressione
4. Rara, sindrome deficitaria scapolo-peroneale o ricorrenti e transitori sintomi sensitivi

CMT

No un solo gene più frequente per AR-CMT1 ; alcune classificate geneticamente come CMT4…

Per AR CMT non algoritmi: regole cliniche

1. AR?: consanguineità, molti fratelli affetti, esordio precoce e fenotipo grave (> rapido e grave interessamento prossimale → perdita deambulazione)
2. CMT4A (GDAP): precoce progressiva, **diaframma** e **CCVV**
3. CMT4B1 e B2 biopsia: mielina con **riavvolgimenti focali**
4. CMT4C: scoliosi precoce e grave
5. CMT4D: atrofia lingua



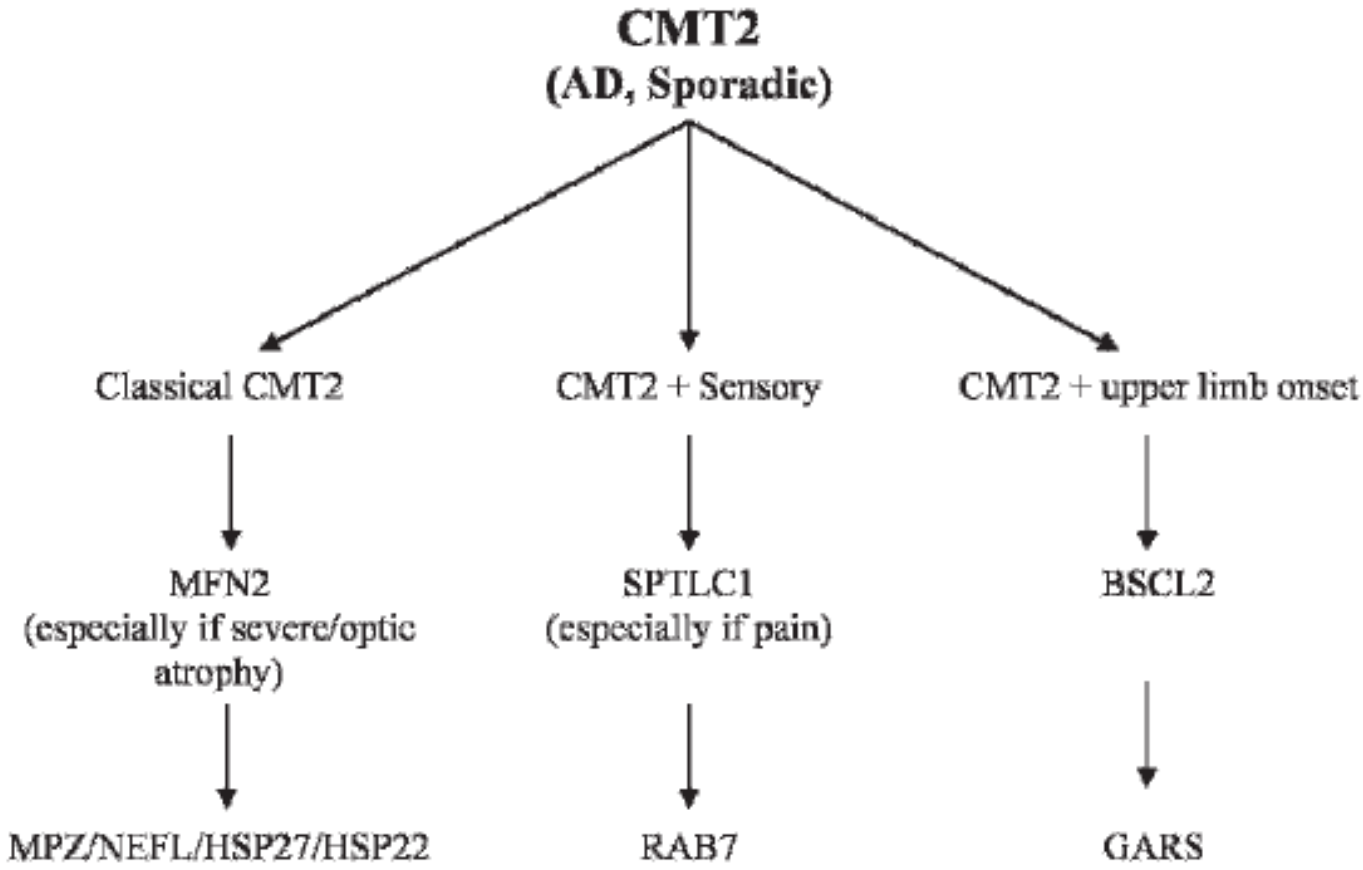


Figure 2 Algorithm for molecular diagnosis of autosomal dominant (AD) axonal Charcot–Marie–Tooth disease (CMT2). BSCL2, Berardinelli-Seip congenital lipodystrophy 2 (Seipin); GARS, glycyl tRNA synthetase; HSP22, heat shock 22 kDa protein 1; HSP27, heat shock 27 kDa protein 1; MFN2, mitofusin 2; MPZ, myelin protein zero; NEFL, neurofilament, light polypeptide 68 kDa; RAB7, RAB7, member RAS oncogene family; SPLTC1, serine palmitoyltransferase, long chain base subunit-1.

CMT

Se diagnosi clinica CMT2:

1. MFN2 e *MPZ*
2. Sempre in mente CMTX1, soprattutto nelle donne
3. Altri geni CMT2 – associati: NEFL

CMTX (X-linked dominant)				
CMTX1	302800	Xq13·1	*GJB1/Cx32*	7–12% of all CMT; moderate to severe in men, usually mild in women; subclinical CNS involvement (mild clinical signs, abnormalities of central components of multimodal-evoked potentials; cerebral white-matter abnormalities on MRI); rarely, there is severe transient CNS dysfunction

CMT2E	607684	8p21	*NEFL*
<2% of CMT; variable severity; occasionally intermittent ataxia			

CMT

- Difficile sospettare **CMT2** in adulto con neuropatia assonale (molte forme acquisite, lievi senza familiarità)
- A volte riflessi profondi vivaci (DD vasculiti o altre multineuropatie)
- Mutazioni MFN2: esordio precoce, rapida progressione, coinvolgimento prossimale, perdita deambulazione
- Mutazioni SPTCL1: dolore neuropatico lancinante

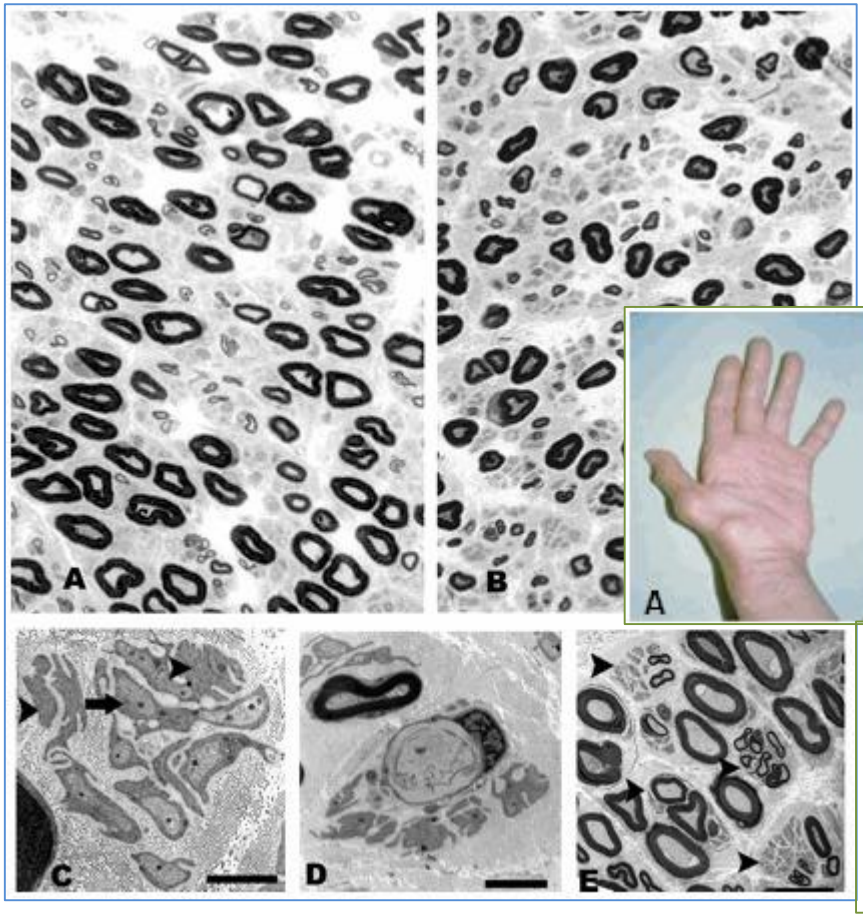
Se predominano sintomi sensitivi, in neuropatia assonale a ereditarietà AD, ricerca RAB7 e SPTLC1

- CMT2D (*GARS*-associated axonal neuropathy): interessamento > AASS, anche unilaterale (***DD sd egresso toracico***)

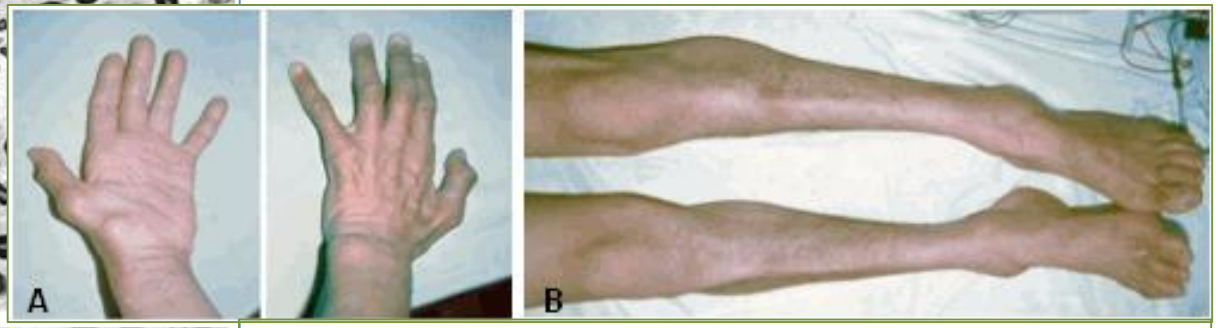
GARS-Associated Axonal Neuropathy: Included Disorders
•Charcot-Marie-Tooth neuropathy type 2D (CMT2D) •Distal spinal muscular atrophy V (dSMA-V)

CMT

GARS-Associated Axonal Neuropathy: Included Disorders
•Charcot-Marie-Tooth neuropathy type 2D (CMT2D) •Distal spinal muscular atrophy V (dSMA-V)



A. dSMA-V. Pathologic changes are minimal with a near-normal myelinated nerve fiber density. B. CMT2D. Myelinated nerve fiber density is moderately reduced. C. CMT2D. Unmyelinated fiber cluster . D. CMT2D. Active axonal degeneration of myelinated nerve fiber. E. CMT2D. Multiple regenerative clusters (arrowheads)



A. Thenar and first dorsal interosseus muscle wasting with relatively preserved hypothenar in an individual with dSMA-V phenotype. B. Peroneal atrophy, pes cavus, and hammerhead toes in an individual with the CMT2D clinical variant; this individual also has a reduction of pinprick, temperature, touch, and vibration sense in stocking distribution.

CMT

Se **predominano SS sensitivi con ulcere acrali**:

1. Geni RAS-associated GTP-binding protein (*RAB7*), serine palmitoyltransferase long chain subunit 1 (*SPTLC1*)

Nei pt con **velocità conduzione intermedie**:

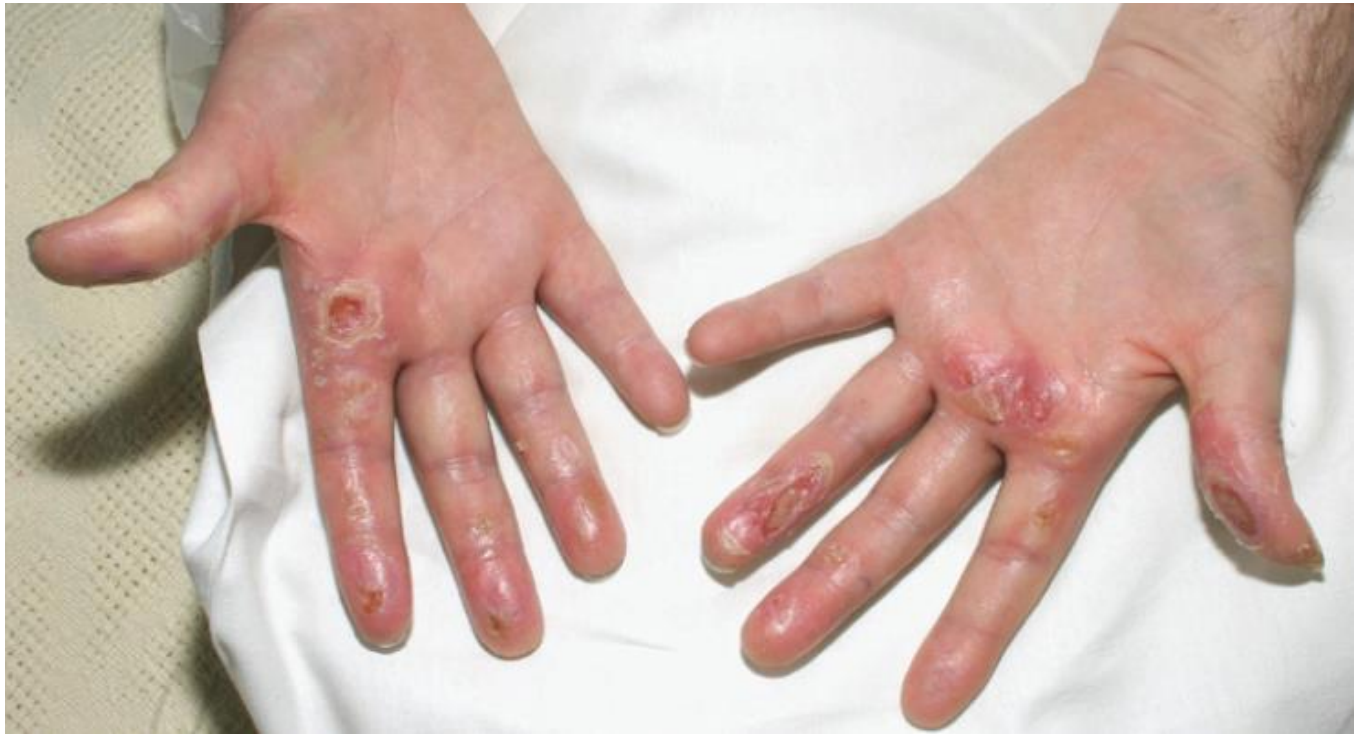
1. *GJB1* (CMTX1)
2. *MPZ*, *NEFL*, dynamin 2 (*DNM2*), and tyrosyl-tRNA synthetase (*YARS)*.

In casi AR :

1. GDAP1, sia per forme assonali che demielinizzanti;
2. Indagini successive in base:
    1. **background etnico (mutazioni *NDRG1* solo in Gypsy**)
    2. Biopsia di nervo
    3. Presentazione clinica generale

CMT

Difficult to differentiate from CMT2B secondary to RAB7 mutations:
lancinating pain in patients with SPTLC1 mutations is a useful guide to this diagnosis.



Ulcerated hands in a patient with HSAN1 secondary to a SPTLC1 mutation

HSAN IV and V are both autosomal recessive neuropathies characterised by congenital insensitivity to pain.

CMT

Forme AR più gravi di AD: precoci, sia assonali (AR-CMT2) che demielinizzanti (CMT4).

*ganglioside-induced diff erentiation-associated protein-1 (**GDAP1**) più frequentemente mutato in **ARCMT2 e CMT4**.*

dHMNs: molto eterogenee; classificate in base a ereditarietà e gene mutato.

N.B. In heterozygous disorders, the gain of function abnormalities often cause more severe disease than heterozygous loss of function.

PMP22, MPZ, GJB1, MFN2, e GDAP1 geni più importanti sul piano diagnostico: diverse forme di CMT e dHMN.

CMT

Presenza di **coinvolgimento piramidale: HMSN V/CMT5**

1. Mutazioni GJB1, MFN2 e BSCL2.

Atrofia ottica in HMSNVI (CMT6) molto suggestiva per mutazioni MFN2

Geni testabili per **dHMN** :

1. Bernardinelli-Seip congenital lipodystrophy 2 (BSCL2),
2. glycyl tRNA synthetase (GARS)
3. small heat shock 22 KDa protein (HSPB1) and small heat shock 27 kDA protein (HSPB8);

N.B. tutti questo geni possono dare anche CMT2

CMT: Pareyson et al, Lancet Neurol 2009

CMT4	AR	Earlier onset and more severe course than CMT1 Vocal cord paresis, sensorineural deafness, and facial and diaphragmatic weakness can occur Slowed NCV (<38 m/s)	GDAP1 MTMR2 SBF2/MTMR13 KIAA1985/SH3TC2 NDRG1 EGR2 PRX FGD4 FIG4
dHMN	AD or AR X-linked	Pure motor involvement on clinical, electrophysiological, and morphological basis Preserved or mildly slowed NCVs; >38 m/s in upper-limb motor nerves; normal sensory action potential Sural nerve biopsy normal or near-nor	HSBP1 HSBP8 GARS BSCL2 DCTN1 (ACHMBP2)
CMT1	AD	Usually typical clinical phenotype Uniform and diffuse motor and sensory NCV slowing (<38 m/s in upper-limb motor nerves) Nerve biopsy: onion bulbs or other myelin abnormalities; secondary axonal degeneration	*PMP22* duplication *MPZ* *PMP22* point mutations *EGR2* *SIMPLE/LITAF* *NEFL*
CMT2	AD or AR	Usually typical phenotype Normal or slightly reduced NCV (>38 m/s in upper-limb motor nerves) and decreased amplitudes Nerve biopsy: chronic axonal neuropathy usually without any specific diagnostic features	*MFN2* *MPZ* *NEFL* *HSPB1 (HSP27)* *HSPB8 (HSP22)* *RAB7* *GARS* *GDAP1* (AD/AR) *LMNA* (AD/AR) *MED25* (AR)
CMTX	X-linked	CMTX1: men more affected than women; motor NCV commonly intermediate in men (30–45 m/s) and in the lower range of CMT2 in women; NCV slowing can be non-uniform and asymmetrical; nerve biopsy: axonal loss and some demyelination, few onion bulbs; occasional CNS involvement Other CMTX types: only males affected	*GJB1/Cx32* *PRPS1*
Intermediate CMT	AD	Mild to moderate severity NCVs intermediate between CMT1 and CMT2 (25–45 m/s) Pathological features of both CMT1 and CMT2	*MPZ* *DNM2* *YARS* *(NEFL)*
CMT3 (HMSN III; DSN-CHN)	AD or AR	Early onset; more severe than CMT1 Very slow NCVs Nerve biopsy: dysmyelination, onion bulbs CHN: congenital onset, extreme severity, hypomyelination	*PMP22* *MPZ* *EGR2* *PRX*
CMT5 with pyramidal features (HMSN V)	AD	Pyramidal involvement ranges from increased deep-tendon reflexes with Babinski sign to spastic paraplegia Electrophysiology: usually axonal loss; reduced sensory action potential amplitudes	*MFN2* *BSCL2* *GJB1*
CMT6 with optic atrophy (HMSN VI)	AD	Early onset Severe visual loss with optic atrophy NCVs preserved or mildly slowed	*MFN2*

CMT

PRACTICE POINTS

- Charcot-Marie-Tooth (CMT) and related disorders are a relatively common cause of peripheral neuropathy and should be included in the differential diagnosis of any patient with peripheral neuropathy without an obvious cause.
- Clinical clues which raise the possibility of an inherited neuropathy in a patient without a family history include a long slowly progressive history, pes cavus and no positive sensory symptoms.
- A genetic diagnosis is important for prognosis and genetic counselling, and to prevent unnecessary invasive tests and trials of immunosuppressive therapy.
- X linked CMT due to connexin 32 mutations should be in the differential when a diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy is being considered, especially in a patient who has failed to respond to immunosuppressive therapy.
- Most patients in the UK with CMT1 (70%) have the chromosome 17 duplication.
- All patients with genetically proven hereditary neuropathy with liability to pressure palsies have diffusely abnormal nerve conduction studies.
- A specialist opinion is appropriate for complex cases.

CMT - Diagnosi differenziale

Other genetic disorders with CNS involvement

CMT5	Spastic paraplegias	Clinical picture DNA tests
Demyelinating CMT, CMT2, CMT5	Krabbe's leucodystrophy, metachromatic leucodystrophy	Brain MRI, enzyme assays
CMT2, CMT5	Hereditary ataxias	Brain and cervical cord MRI DNA tests Haematological assessment
Demyelinating CMT, CMT2, CMT5, CMT6	Mitochondrial encephalomyopathies (*MNGIE*, *POLG1* mutations)	Other clinical features Lactate and pyruvate levels Muscle biopsy DNA tests
CMT2, dHMN	Spinal dysraphism	Lumbar spine MRI

CMT=Charcot–Marie–Tooth disease. dHMN=distal hereditary motor neuronopathy. DSN=Déjèrine-Sottas neuropathy. EMG=electromyography. HNPP=hereditary neuropathy with liability to pressure palsies. NCS=nerve-conduction study. *MNGIE*=mitochondrial neurogastrointestinal encephalopathy syndrome. *POLG1*=polymerase gamma subunit 1.

Table 4: **Differential diagnoses of CMT**

CMT - Diagnosi differenziale

Altre neuropatie non ereditarie

- Neuropatie acquisite
- Miopatie distali
- MND
- Atassie ereditarie
- Malattie mitocondriali
- Paraparesi spastiche ereditarie
- leucodistrofie

	Differential diagnoses	Useful examinations and criteria
Dysimmune and other acquired neuropathies		
Dysmyelinating or demyelinating CMT (CMT1, CMTX, CMT4, DSN, intermediate forms)	Chronic inflammatory demyelinating polyradiculoneuropathy Anti-MAG neuropathy Paraproteinemic neuropathy	Clinical distribution and course NCS Examination of the cerebrospinal fluid Anti-ganglioside antibodies Anti-MAG antibodies Search for monoclonal gammopathy
dHMN (HNPP)	Motor neuropathy with multifocal conduction blocks	Clinical course, response to therapy EMG, NCS Anti-GM1 antibodies
CMT2	Toxic, metabolic, and nutritional neuropathies	Clinical data Haematological assessment
Other hereditary neuropathies		
Demyelinating CMT and CMT2	HNPP	NCS (entrapments) DNA test (*PMP22* deletion or nonsense mutations) Nerve biopsy
CMT2	Hereditary amyloidosis	Course, sensory and autonomic involvement DNA test: transthyretin gene (*TTR*) Biopsy (amyloid deposition in different tissues)
CMT2, CMT5	Giant axonal neuropathy	Curly hair, CNS involvement DNA test: gigaxonin gene (*GAN*) Nerve biopsy
CMT1, CMT4	Refsum's disease	Phytanic acid levels DNA tests: phytanoyl-CoA hydroxylase (PHYH), peroxisome biogenesis factor 7 (PEX7)

CMT - Diagnosi differenziale

Altre neuropatie non ereditarie

- acquired neuropathies
- distal myopathies
- motor neuron diseases
- hereditary ataxias
- mitochondrial disorders
- hereditary spastic paraplegias
- leucodystrophies

Other neuromuscular disorders		
dHMN	Distal myopathies	Creatine kinase concentrations, EMG, muscle biopsy, DNA tests
dHMN	Lower motor neuron disorders (spinal muscle atrophy and so on)	EMG

CMT - Diagnosi differenziale

CMTX coinvolgimento non omogeneo clinico e NFS: DD con CIPD

PDF

GJB1 gene mutations in suspected inflammatory demyelinating neuropathies not responding to treatment

J Neurol Neurosurg Psychiatry 2009;**80**:6 699-700

Box 4 Potential genetic and acquired chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) mimics

Alternative diagnoses to consider in treatment failure CIDP Genetic Mimics

- GJB1 mutations (CMT1X)
- Transthyretin familial amyloid polyneuropathy (TTR-FAP)
- CMT 4C (SH3TC2 mutations)
- CMT4J (FIG 4)
- HSAN1 (SPTLC1)
- CMT1A (homogenous slowing)
- CMT1b
- HNPP
- GDAP1
- MNGIE and rare mitochondrial disorders

Red flags for the diagnosis of typical chronic inflammatory demyelinating polyradiculoneuropathy (CIDP):

Symptoms in the history

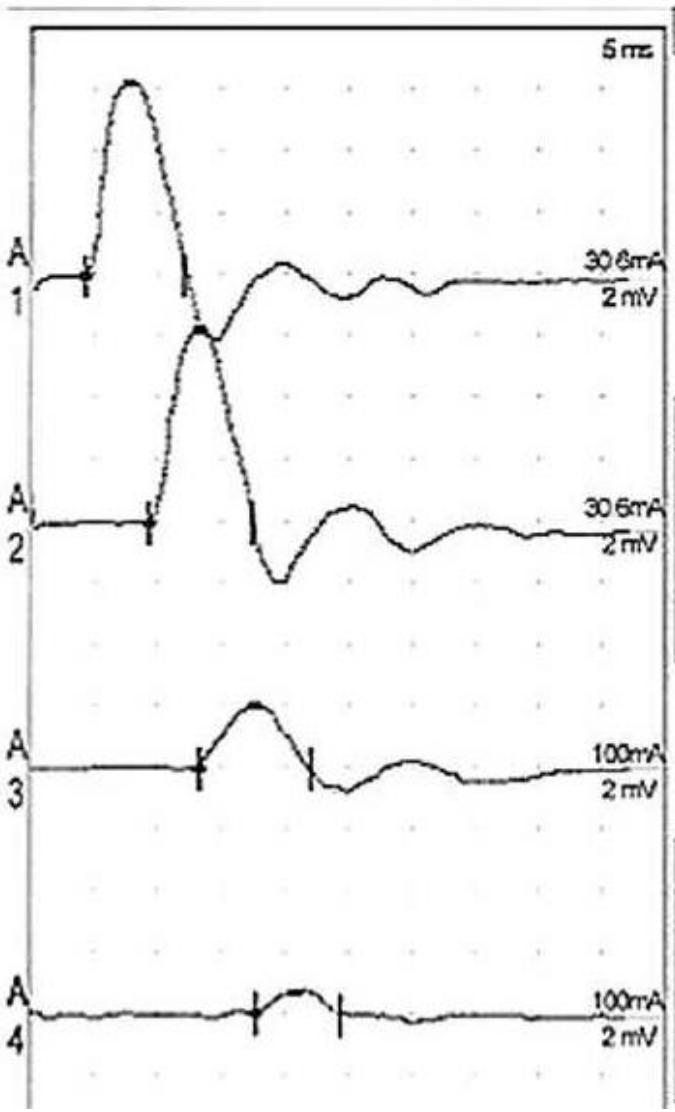
Signs in the examination

- Cranial nerve invol
- ...ally in early disease
- Significant relative dominant hand weakness with median/ulnar separation*

*Relative weakness of the dominant hand with median/ulnar separation suggests an alternative diagnosis, such as CMT1X[9] but is not of itself diagnostic of any single condition.

CMT - Diagnosi differenziale

Spesso per CMTX coinvolgimento non omogeneo clinico e NFS: difficoltà DD con CIPD



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Recording Site: Abductor pollicis brevis

Stimulus Site	Lat1 ms	Dur ms	Amp mV	Area mVms
A1: Wrist	4.2	7.8	6.2	29.1
A2: Elbow	9.2	8.1	6.3	29.8
A3: Axilla	13.2	8.7	2.1	10.1
A4: Supraclavicular	17.6	6.7	0.7	2.6

Segment	Dist mm	Diff ms	CV m/s
Abductor pollicis brevis-Wrist		4.2	
Wrist-Elbow	201	5.0	
Elbow-Axilla	185	4.0	
Axilla-Supraclavicular	160	4.4	36

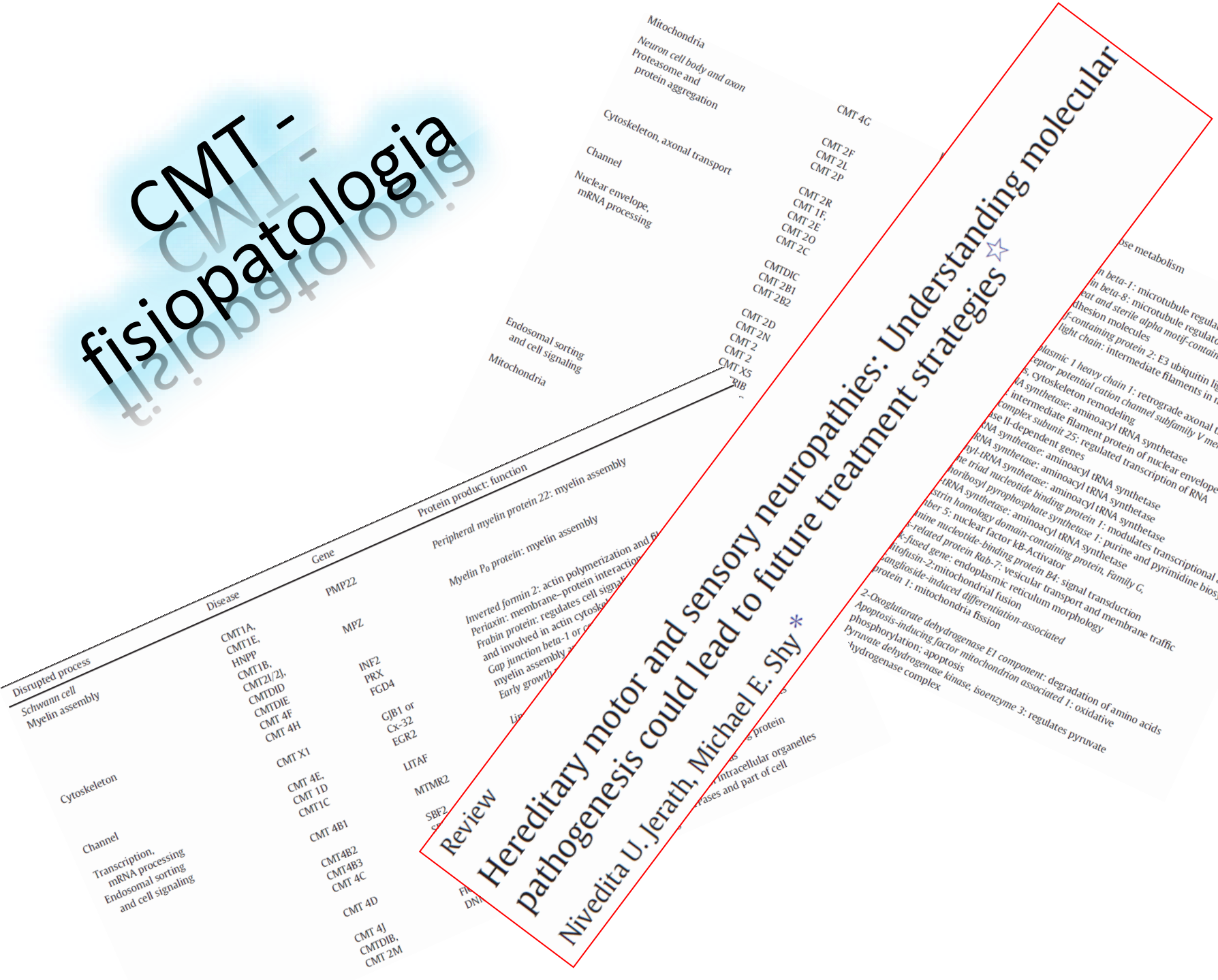
NFS con DT disomogenea o BC nell'ambito di una polineuropatia demielinizzante motoria e/o sensitiva aiuta di solito a distinguere CIDP vs HSMN, tranne che per CMT-X

CMT – diagnosi differenziale

GARS-Associated Axonal Neuropathy: Included Disorders
•Charcot-Marie-Tooth neuropathy type 2D (CMT2D) •Distal spinal muscular atrophy V (dSMA-V)

- Senza storia familiare, parestesie e dolore e disfunzione clinica mediano al polso in pt con sd tunnel **carpale** simile primi stadi GARS-associated axonal neuropathy (spesso asimmetrica e limitata al mediano).
- Compressione radici cervicali basse e T1 da costa cervicale porta **sd egresso toracico neurogeno**. Ipostenia **tenar, ipotenar e interossei con ipostesia antebrachiale mediale** (ridotte amp SAP in nervi ulnare e cutaneo mediale avambraccio).
- **Neuropatia motoria multifocale:** disturbi motori progressivi con distribuzione "periferica", soprattutto distali AASS, asimmetrici e muscoli mani innervati da due nervi (BC e GM1+).

CMT - fisiopatologia



CMT - fisiopatologia

Assemblaggio mielina: PMP22, MPZ	Curcumina, geldanamicina, deprivazione nutritiva, rapamicina, onapristone, acido ascorbico, oligonucleotidi antisenso e siRNA
Citoscheletro CS: INF2, PRX, FGD4, FBLN5; Citoscheletro neuroni: NEFL2, DYNC1H1	Celastrolo, inibitori HDAC-6
Proteosomi e aggregazione proteica: HSP, LRSAM1, TRIM2	arimoclomolo
Traffico lisosomiale e vie del segnale intracellulare	

CMT - fisiopatologia

Mitocondri

Aumento MFN1

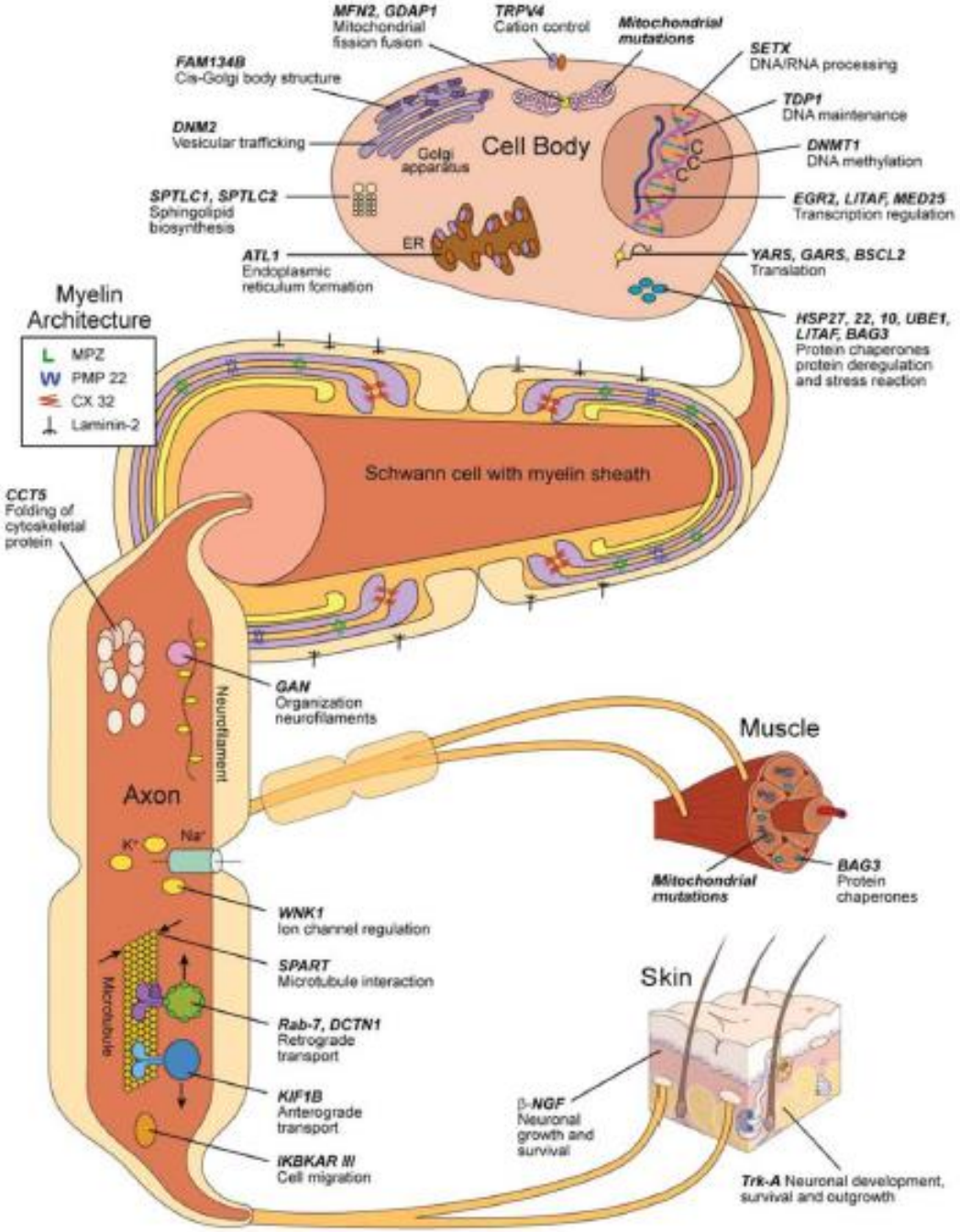
Processing mRNA

Canali

Altri approcci terapeutici su fisiopatologia:

- Fattori trofici
- Interazione CS – assoni
- Cellule staminali
- Terapia genica
- Riprogrammazione cellulare

CMT - fisiopatologia

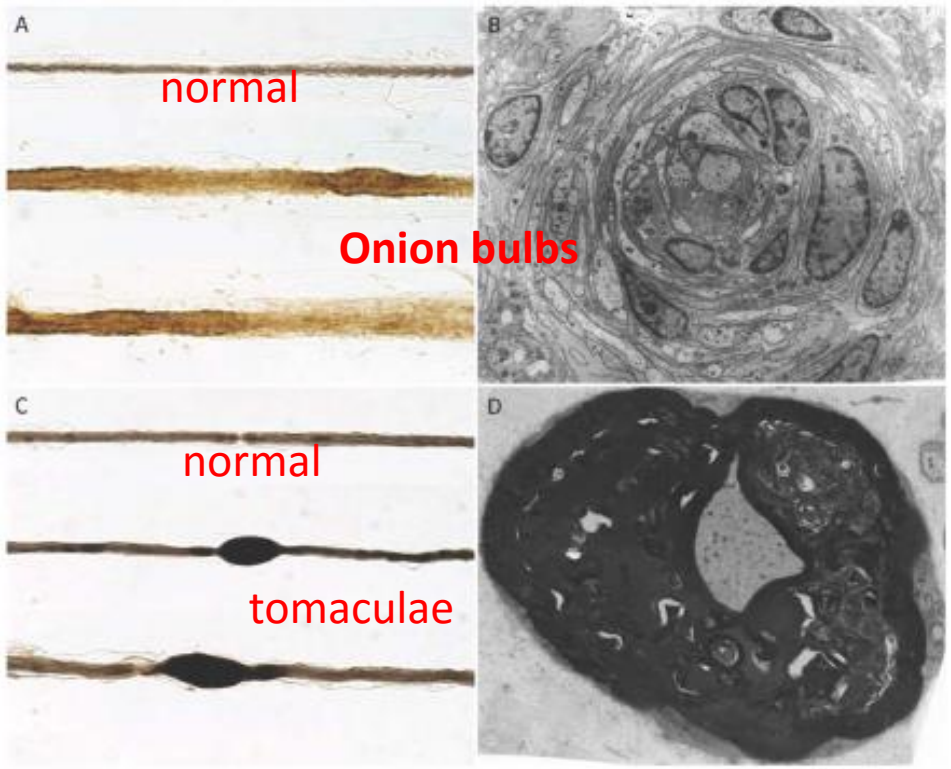


- *GJB1* codifica per **connexina-32**: gap-junctions nella mielina non compatta nelle regioni paranodali nelle incisure di Schmidt-Lantermann: anomalie anatomiche giunzione → alterata **interazione CS e assone → assonopatia**

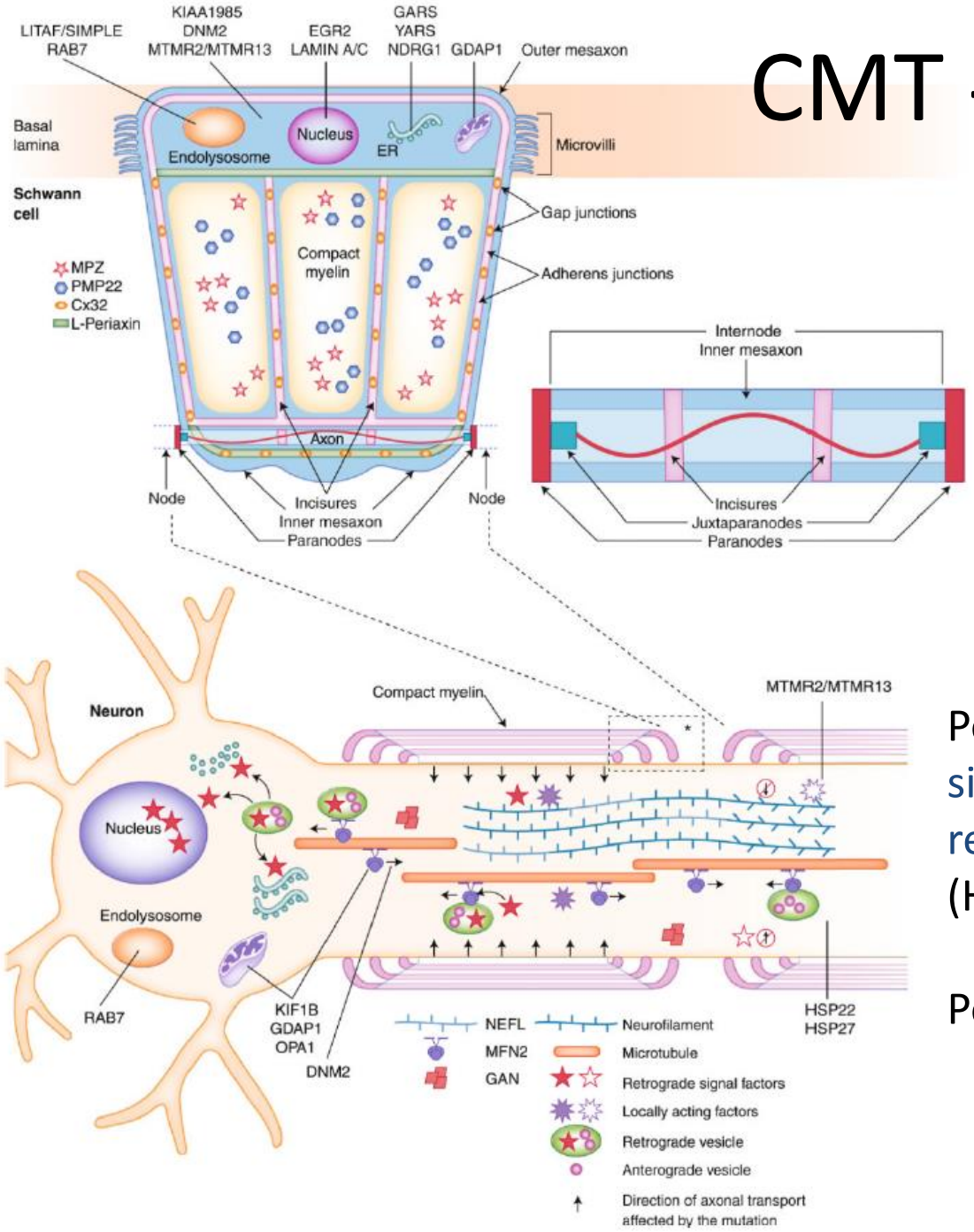
CMT - fisiopatologia

Anomalie mielina

1. Pt con **HMSN 1A da PMP22 dup**. Onion bulbs: ispessimento generalizzato da lamelle di collagene esuberante con perdita della definizione dei nodi.
2. **HNPP** da **PMP22 del**. Al contrario, tomaculae: ispessimento focale mielina da loops ridondanti di mielina



CMT - fisiopatologia



Alcune mut causali in **proteine SNP–specifiche (PMP22,MPZ,periaxin),** altre in **proteine con ruolo non specifico/definito (GARS,HSP27,Cx32).**

Per forme **CMT > motorie**: alterata sintesi prot (GARS,YARS), stress response (HSP22,HSP27), apoptosi (HSP27), trasporto ax (HSP27).

Per **CMT > sensitive**: SPTLC1,RAB7.

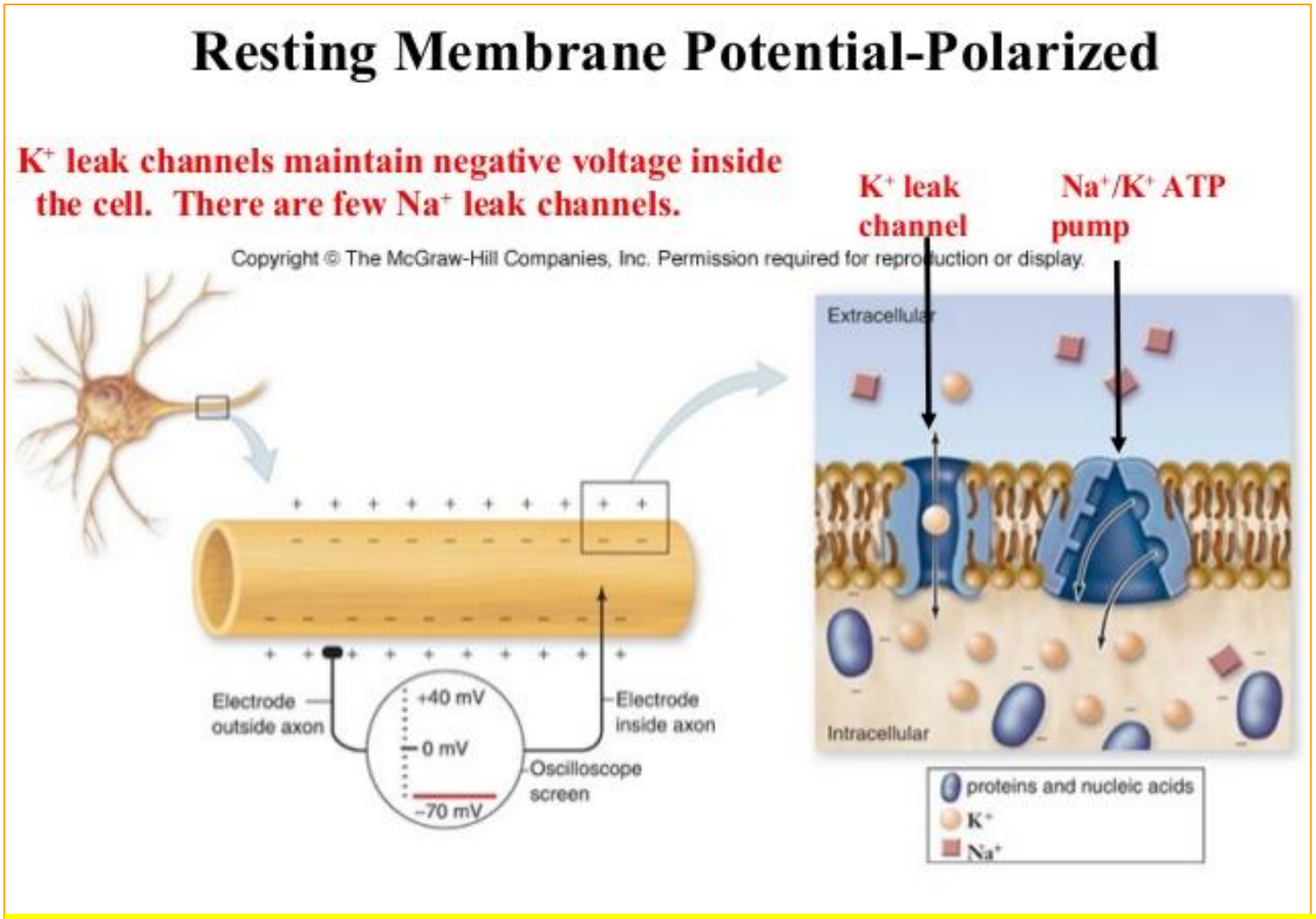
CMT - fisiopatologia

Progesterone e acido ascorbico **alterano i livelli di PMP22 mRNA nei roditori**.

•Ratti PMP22 complementary DNA overexpressor, con caratteristiche cliniche, NFS, patologiche di CMT1A si aggravano se ricevono quotidianamente progesterone → **in sviluppo antagonisti recettoriali non tossici**

•L'acido ascorbico necessario per mielinizzazione SNP nelle cocolture di CS e GRD; ruolo fondamentale per la formazione MB → trials clinici per pt CMT1A

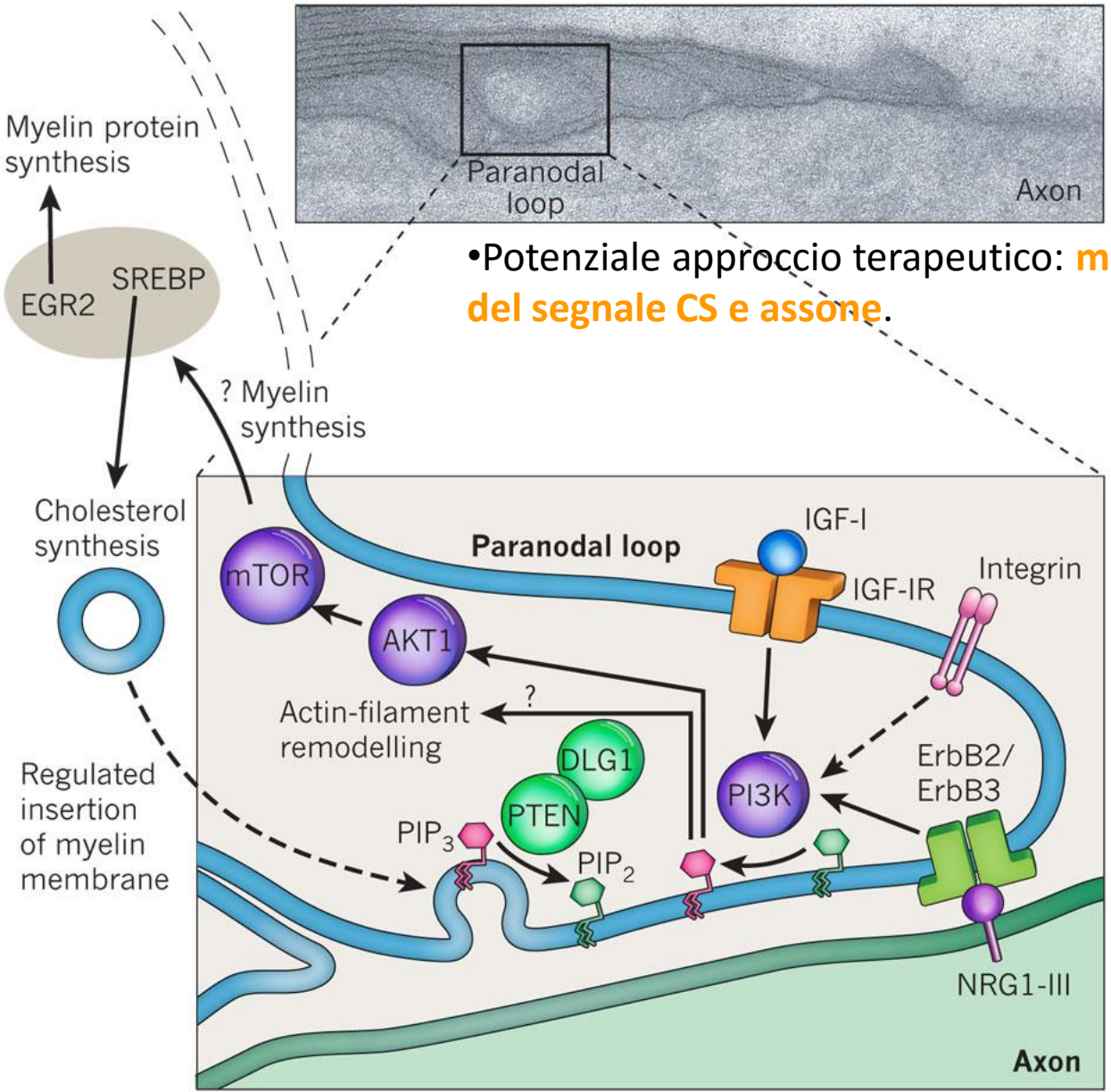
CMT - fisiopatologia



- La demielinizzazione aumenterebbe domanda energetica dei neuroni e ridurrebbe la capacità di mantenere separate le cariche

- Considerati bloccanti canali K+per migliorare neuropatie demielinizzanti: 3,4 dAP non miglioramento significativo in CMT; in sviluppo bloccanti più specifici

CMT - fisiopatologia



•Potenziale approccio terapeutico: **manipolazione trasduzione del segnale CS e assone**.

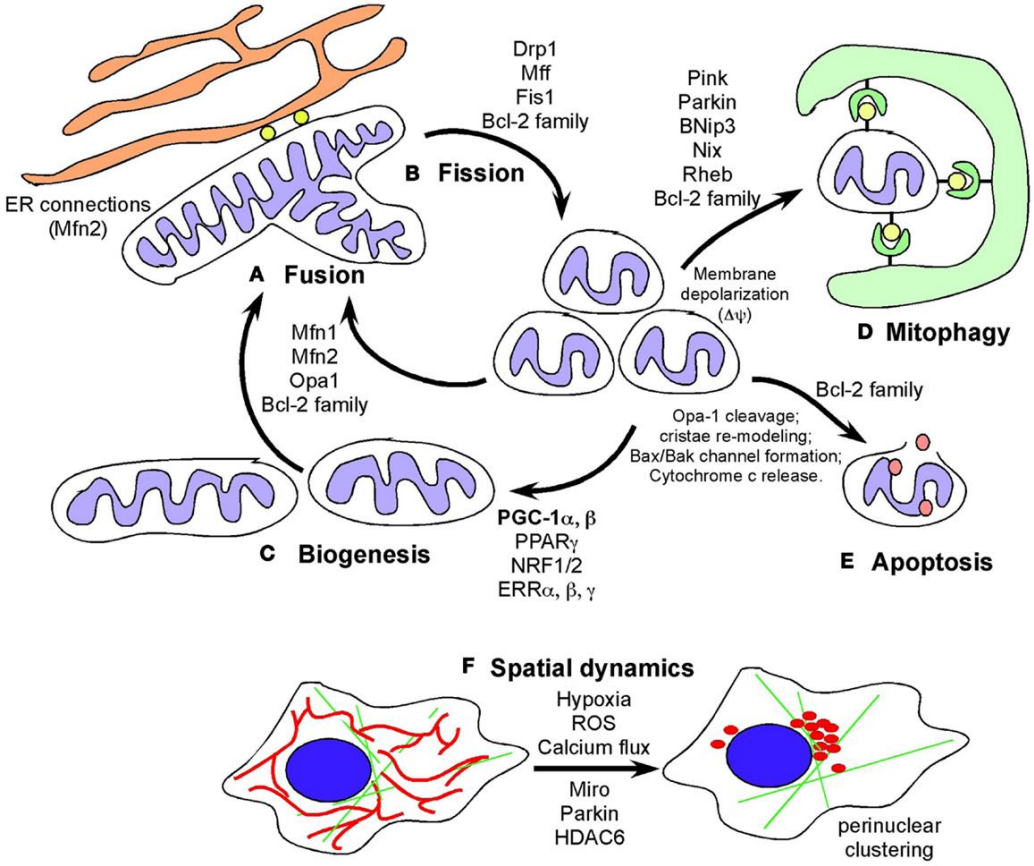
Gli assoni esprimono neuroregulina 1 tipo III in superficie, che lega I recettori ErbB sulle CS come tappa iniziale della mielinizzazione. L'overespressione transgenica di NRG1-III induce un'ipermielinizzazione nelle CS

CMT - fisiopatologia

•Il **trasporto mitocondriale** da un supporto energetico per le parti distali degli assoni lontane dal corpo cellulare.

•Mitocondri hanno **ciclo dinamico di dififfione e fusione** regolati in parte dalle **mitofusine** (MFN1 e MFN2): mitocondri mancanti di MFN non si fondono

•**MFN2 si accumula** nei siti di concatenamento ER-mitocondri favorendone la comunicazione

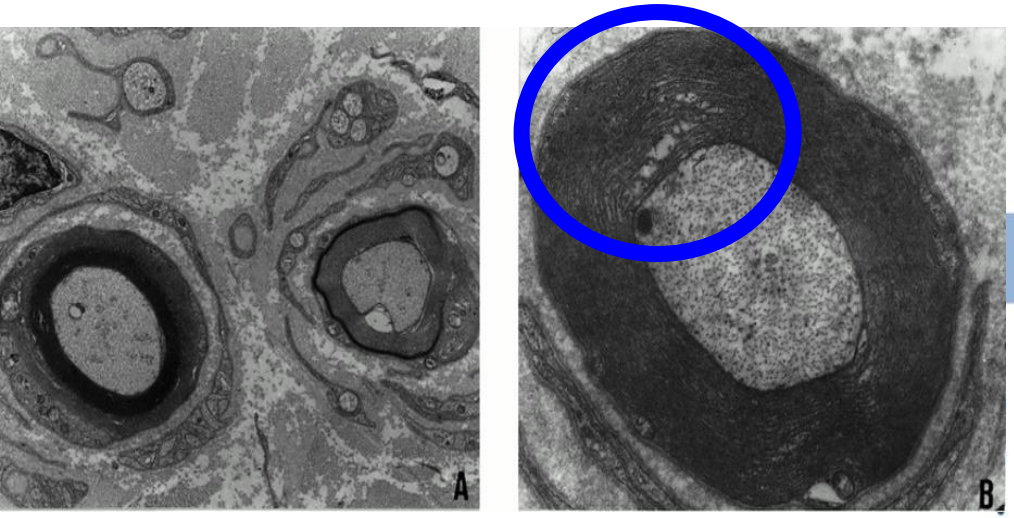


•E' una via che coinvolge l'uptake del Ca++ e quindi la regolazione dell'apoptosi.
•La neurodegenerazione in CMT2A può essere conseguenza di una ridotta attività della MFN2

CMT - neuropatologia

Per anomalie peculiari della mielina:
Myelin uncompaction…

… and small tomacula with MPZ mut



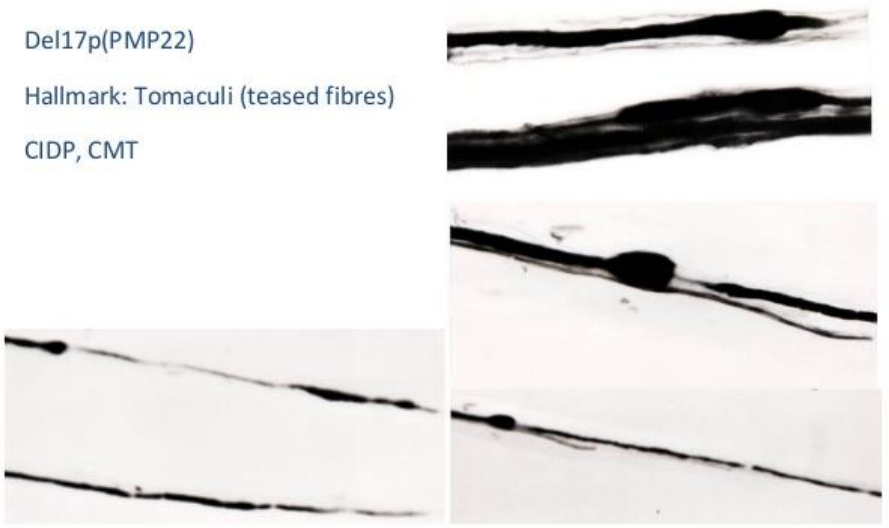
(A) Patient III-3. Two fibers with uncompacted lamellae in the inner or outer portions of the myelin sheath. Both fibers are surrounded by Schwann cell processes arranged concentrically in an “onion bulb” fashion. (B) Patient III-3. Uncompaction of the entire myelin sheath. The major dense line is particularly dilated and contains islands of Schwann cell cytoplasm.

Hereditary neuropathy with liability to pressure palsies (HNPP)
“Tomaculous neuropathy”

Del17p(PMP22)

Hallmark: Tomaculi (teased fibres)

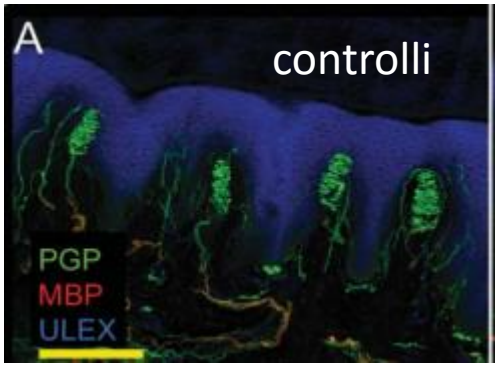
CIDP, CMT

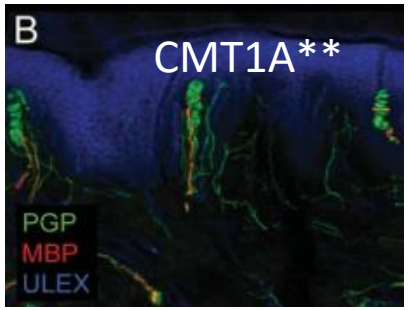


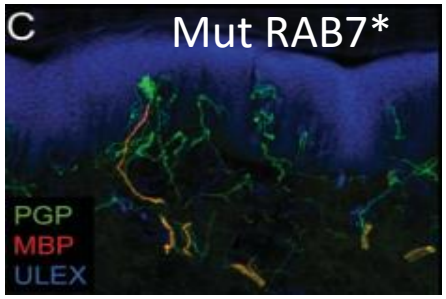
CMT – biopsia cute

Biopsia di cute: esame morfologico, relativamente poco invasivo

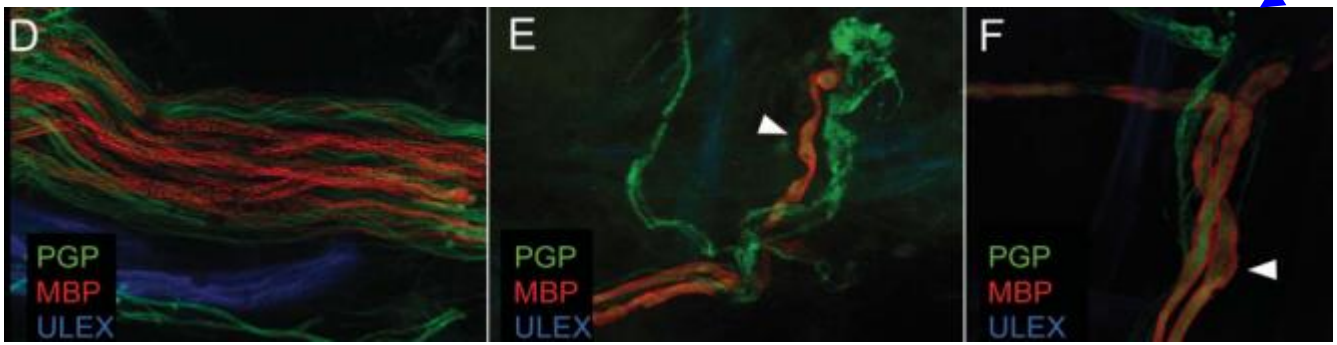
Da primi studi su CMT1A: meno corp Meissner, <dL internodale, anomalie architettura paranodale-iuxtanodale



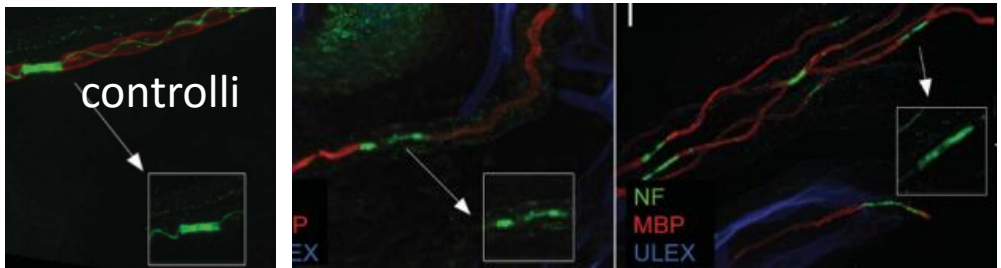




Anomalie ff mieliniche: rigonfiamento e frammentazione



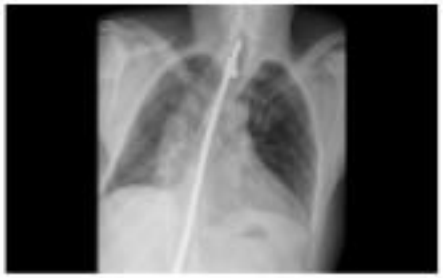
Anomalie architettura nodale - paranodale

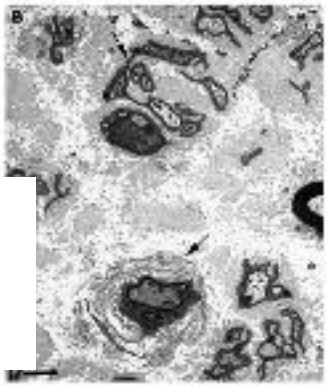


CMT - neuropatologia

Meno necessaria rispetto al passato la biopsia di nervo

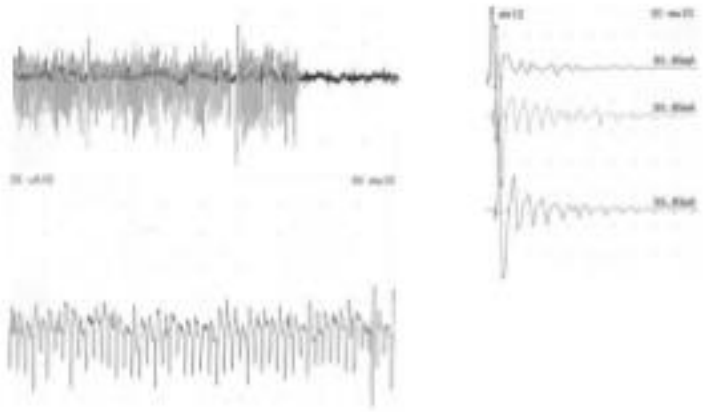
•Assoni giganti in casi con mut NEFL.
•Onion bulbs di membrana basale di CS (con +/- citoplasma) tipici della **CMT4C con SH3TC2 mut** (SH3 domain and tetratricopeptide repeat domain 2).





-cranial nerve involvement

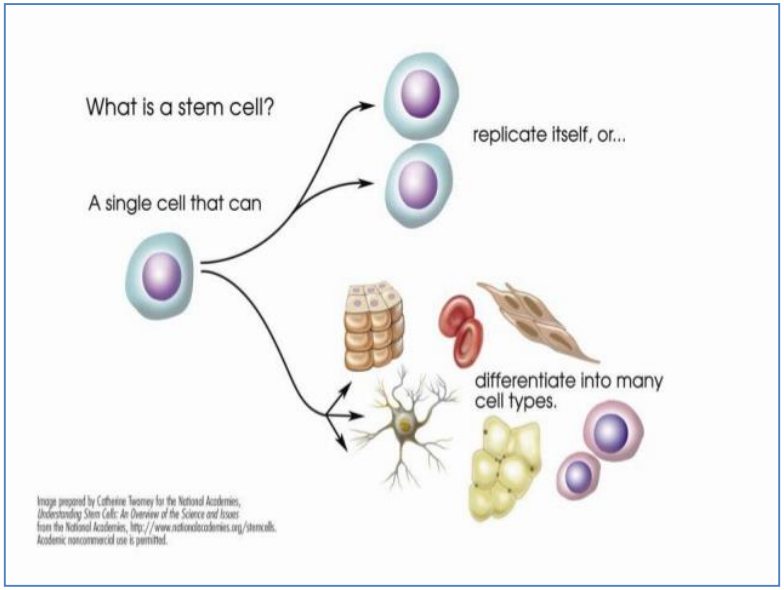
•**Abbondanti ripiegamenti mielina** tipici di CMT4 da MTMR2 e MTMR13 mut. (myotubularin-related protein 2 and 13; *SBF2*) e frabina (FGD1-related F-actin binding protein; FGD4)



HINT1 – AR CMT2

CMT - terapie

•**Terapia genica**: strategia per trasferire materiale biologico (geni o proteine) in cellule malate
•**Vettori** virali o plasmidi DNA più usati sistemi di veicolo
•**Rimpiazzo genico e silenziamento** sono altre tecniche per modulare l'espressione genica (mut con perdita di singola funzione, es. del di uno degli alleli PMP22 in HNPP; silenziamento in CMT1A per ridurre quantità di PMP22 o in mut missenso con guadagno di funzione)



•Uso **cellule staminali** per **differenziazione** in CS che prendano contatti con e avvolgano assoni demielinizzati; perchè **secernano fattori trofici** per assoni danneggiati.

CMT – terapie “sintomatiche”

Riabilitazione

- esercizio lieve-moderato per forza AAII e deambulazione
- Esercizio aerobico
- Esercizio ad alta intensità dovrebbe essere evitato
- Esercizi posturali e per equilibrio

Protesi, scarpe, plantari, assistive devices

- Plantari per posizione piedi, evitare ulcere da pressione e callosità
- Ortosi caviglia-piede per compensare al piede cadente e migliorare deambulazione
- Ortosi meglio se disegnate sul paziente

Ventilazione assistita e laser aritenoidectomia per forme da coinvolgimento CCVV e diaframma (CMT1A, CMT2C)

CMT – terapie “sintomatiche”

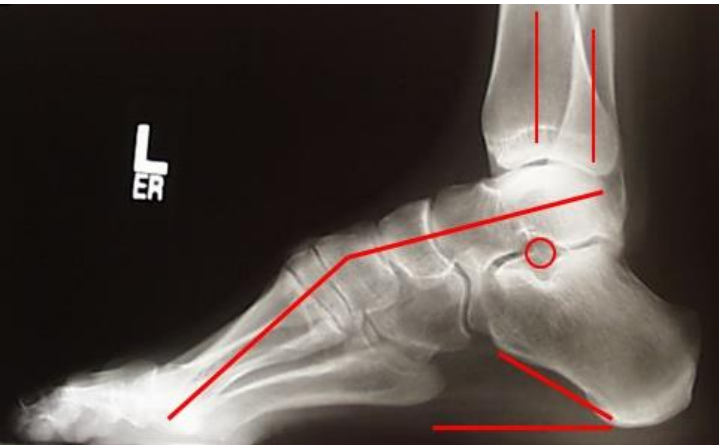
Chirurgia per correzione deformità scheletriche:

•Chirurgia tessuti molli: fasciotomia (per ridurre deformità in cavus), trasposizioni tendinee (peroneus longus al peroneus brevis, tibialis anterior al laterale cuneiforme, tibiale posteriore al compartimento anteriore, …), e rilascio tendini

•Osteotomie

•Fusioni articolari

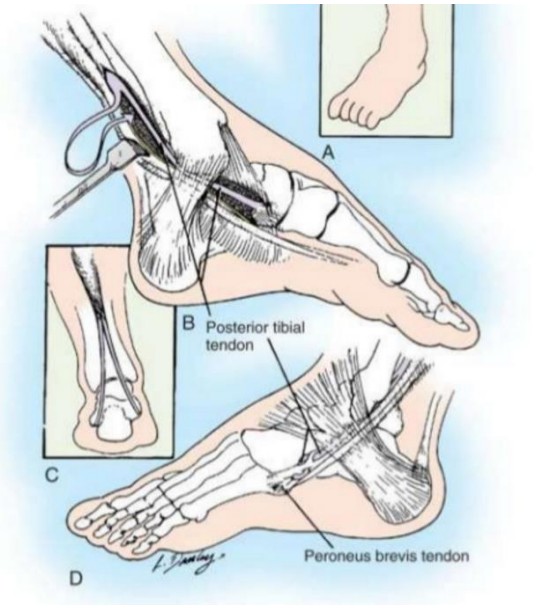
… da soli o in combinazione



- **Split Tendon Transfers**
  - Split posterior tibial tendon transfer

It is one of the most common procedures for equinovarus deformity treatment.

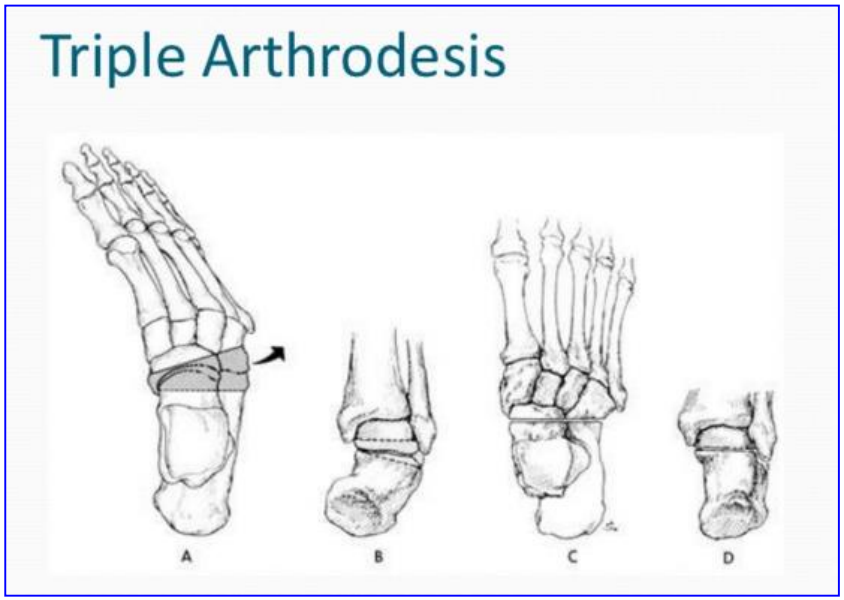
The posterior one-half of the posterior tibialis tendon is rerouted posterior to tibia and woven into the peroneus brevis tendon.

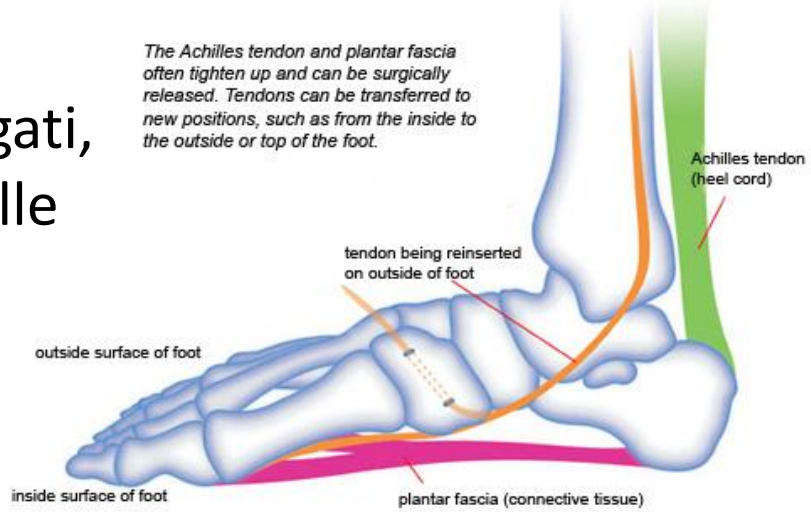


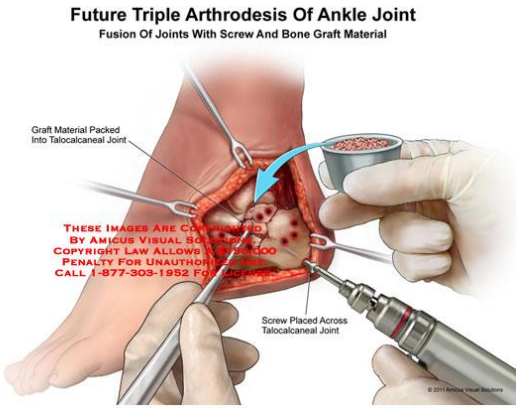
CMT – terapie “sintomatiche”

- Atrodesi tripla: fusione chirurgica di talocalcaneale, talonavicolare, calcaneocuboide, usata molto per defomità pedidee gravi;

MA risultati a lungo termine poco indagati, con documentata elevata frequenza delle altre articolazioni del piedi.







CMT – terapie “sintomatiche”

Terapie sintomatiche farmacologiche

- Per dolore, neuropatico e non-neuropatico

- Antifatica: modafinil (trial in CMT1A: qualche beneficio ma troppi effetti collaterali)

Evitare farmaci che causano tossicità al SNP, soprattutto chemioiterapici come alcaloidi vinka, cisplatino, oxaliplatino, taxoli.

Neuropatia acuta tipo GBS precipitata da alcaloidi vinka in pt con CMT non nota/riconosciuta

Neuropatie ereditarie associate («plus»)

Neuropathies in which the neuropathy is part of a more widespread neurological or multisystem disorder

- Familial amyloid polyneuropathy
- Disturbances of lipid metabolism
- Porphyrias
- Disorders with defective DNA
- Neuropathies associated with mitochondrial diseases
- Neuropathies associated with hereditary ataxias
- Miscellaneous

Familial Amyloid Polyneuropathy (FAP)

Gruppo di amiloidosi ereditarie con prominente coinvolgimento SNP e SNA

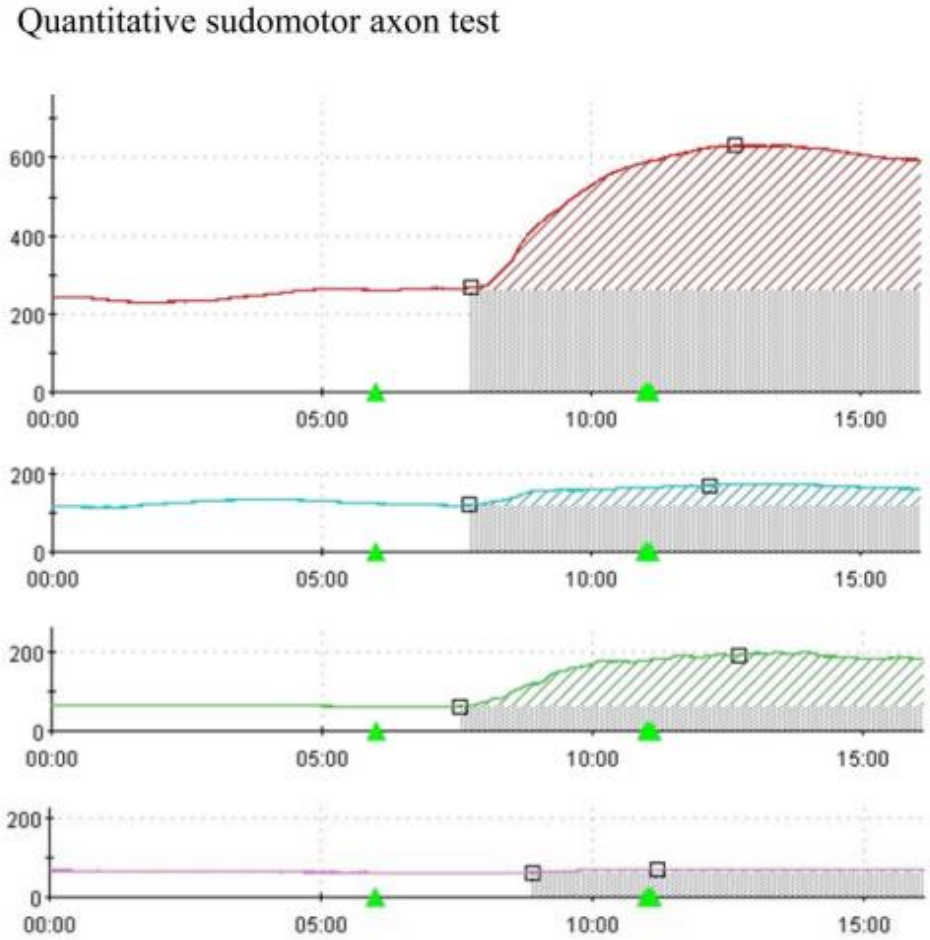


Figure 3.
Quantitative sudomotor axon test demonstrating normal sweat volume in the forearm (top trace), diminished sweating in the proximal and distal leg (middle traces), and near absent sweating in the foot. This is consistent with a length dependent neuropathic process.

Neuropatie ereditarie associate («plus»)

FAP

- Classificazione dalla proteina che si accumula: transtiretina (> comune), apoproteina A1, gelsolina
- Prima descrizione nel 1952 da Andrade: nord Portogallo. Poi in Svezia e Giappone.
- Sost. gene TTR, Val30Met (mut > comune; descritte altre)

Neuropatie focali, PN sensorimotorie, neuropatia autonomica. Nervo mediano al polso: interessamento comune e precoce in FAP.

Type of Amyloidosis	Transmission	Clinical Features	Age of Onset	Treatment
TTR related-FAP	Autosomal Dominant	Sensorimotor PN, autonomic neuropathy, CTS, cardiomyopathy, vitreous deposits	3rd to 4th decade for early onset 6th to 8th decade for late onset	Liver transplant Tafamidis Diflunisal
ApoA1 related-FAP	Autosomal Dominant	Sensorimotor PN, kidneys, liver, gastrointestinal tract affected	4th to 5th decade	Transplantation of affected organs
Gelsolin related-FAP	Autosomal Dominant	Cranial neuropathies, CTS, cutis laxa, corneal lattice dystrophy	3rd to 4th decade	Plastic surgery for facial deformities

Neuropatie ereditarie associate («plus»)

FAP

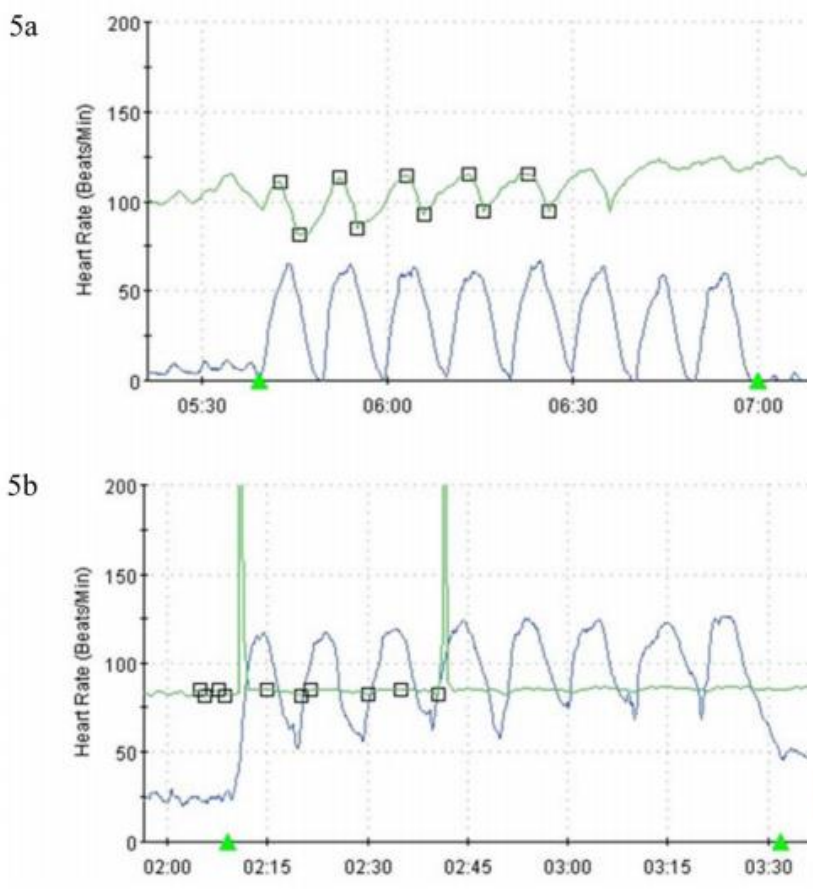


Figure 5.
(a) Normal heart rate variability (green trace) in response to paced deep breathing (blue trace). This reflex is mediated by the vagus nerve. (b) This figure demonstrates near absent heart rate variability in a patient with autonomic neuropathy.

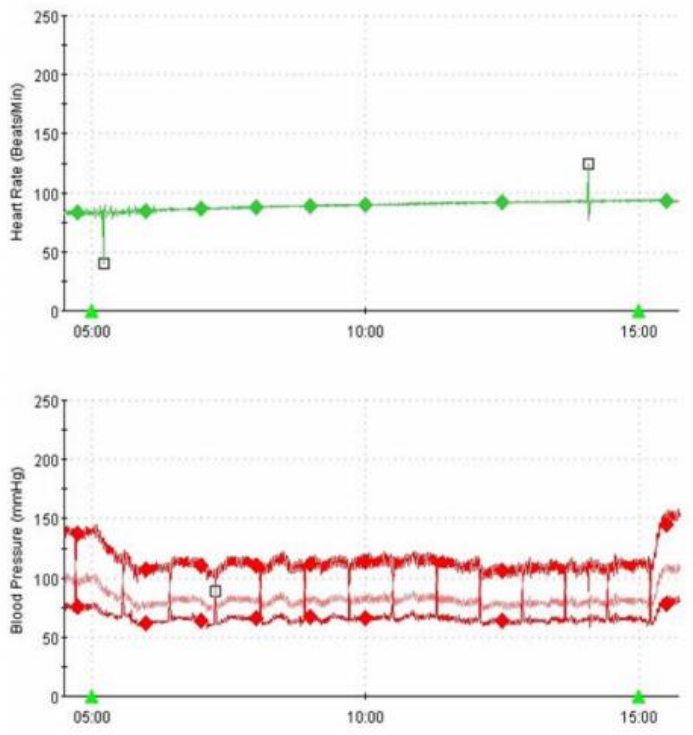


Figure 6.
Hemodynamic responses to upright tilt in a patient with autonomic neuropathy demonstrate orthostatic hypotension and lack of compensatory tachycardia.

Cranial nerves

- ***Neuropathy with facial nerve damage***
- GBS
- C/C inflammatory polyradiculonuropathy
- Lyme diasease
- Sarcoidosis
- HIV-1infection
- Gelsolin familial amyloid neuropathy
- Tangier's disease

Neuropatie ereditarie associate («plus»)

Neuropathies in which the neuropathy is part of a more widespread neurological or multisystem disorder

- Familial amyloid polyneuropathy
- Disturbances of lipid metabolism
- Porphyrias
- Disorders with defective DNA
- Neuropathies associated with mitochondrial diseases
- Neuropathies associated with hereditary ataxias
- Miscellaneous

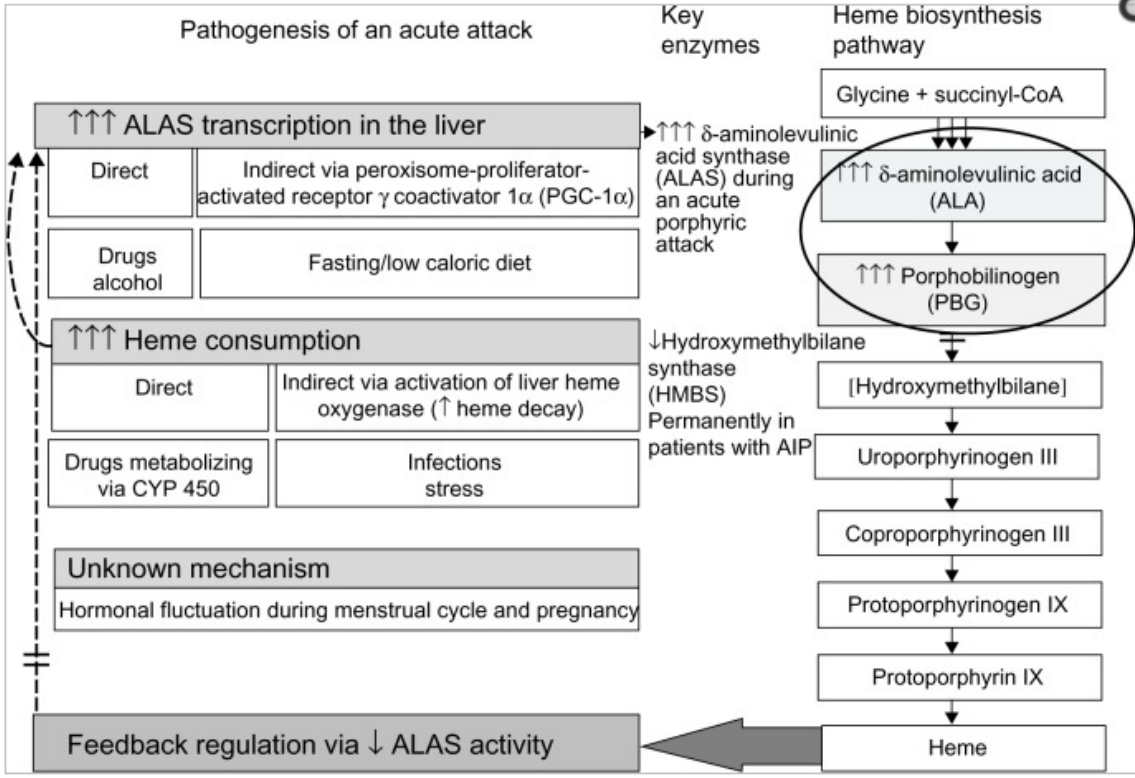
Metabolismo lipidi

•Sd di Bassen- Kornzweig: abeta-/ipobetalipoproteinemia fam omozigote (ABL/HoFHBL), livelli bassi apolipoprot. B e col-LDL,ritardo crescita,malassorbimento, epatomegalia e SS neuromuscolari

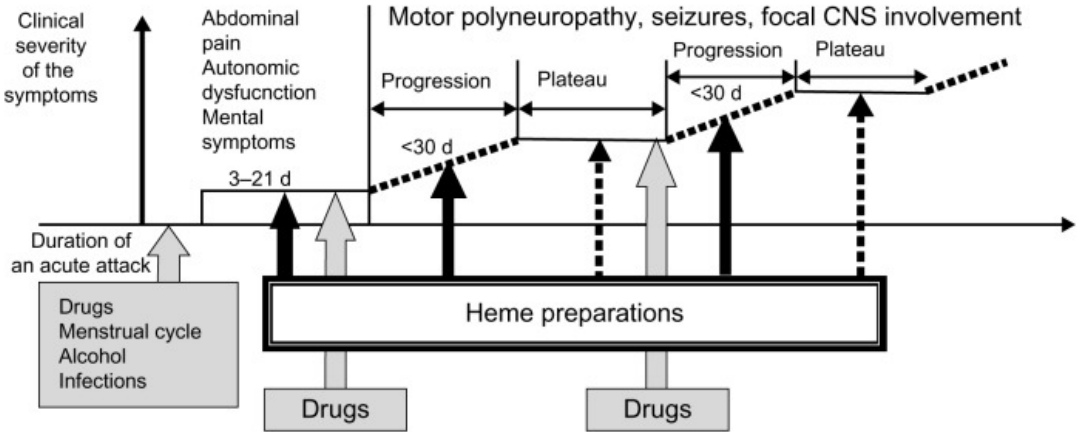
•Malattia di Tangier: AR, alterato efflusso COL (mut ABCA1). Neurop. per. nel 50%: 2 presentazioni: **(1) RR mono/poli, (2) pseudosiringomielico**. Altri SS: tonsille gialle, epatosplenomegalia, LN-patia, xantomi, distrofia corneale, CAD precoce.

Neuropatie ereditarie associate («plus»)

Fig. 4 Urine sample obtained from patient #20 during the por-
phyric attack, with dark port wine colour evident after the samp
was left standing in sunlight, in comparison to a control sample.



Precipitating factors and pathogenesis of an acute attack in AIP.



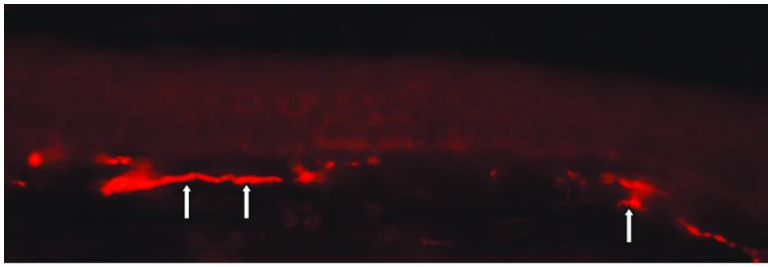
Staging of an acute attack in connection with precipitating factors and recommendations of heme therapy.

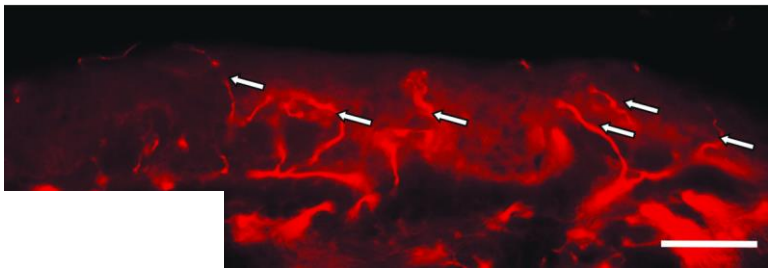
Porfirie

- Deficit enzimi biosintesi EME
- AIP (PBGD), AD, > comune neuroporfirina.
- **In AIP: >% neuropatia motoria ax** (da deficit energetico neurale + effetti tox precursori porfirina)

Neuropatie ereditarie associate («plus»)

Malattia di Fabry

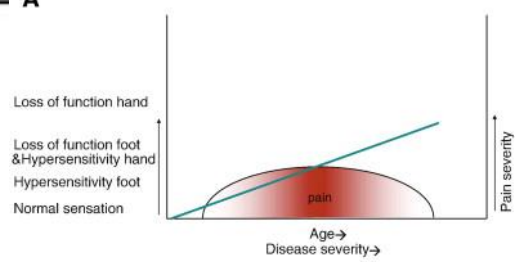


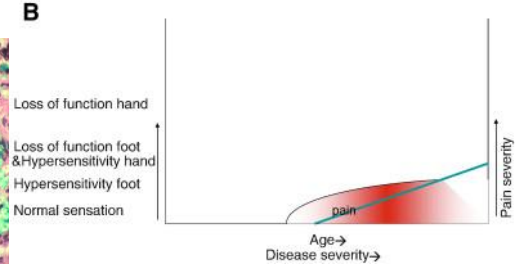


X-linked, da accumulo lisosomiale di Gb3, deficit attività α-gal-A

Dolore neuropatico e attacchi di dolore dai 9 aa nei M e dai 16 aa nelle F

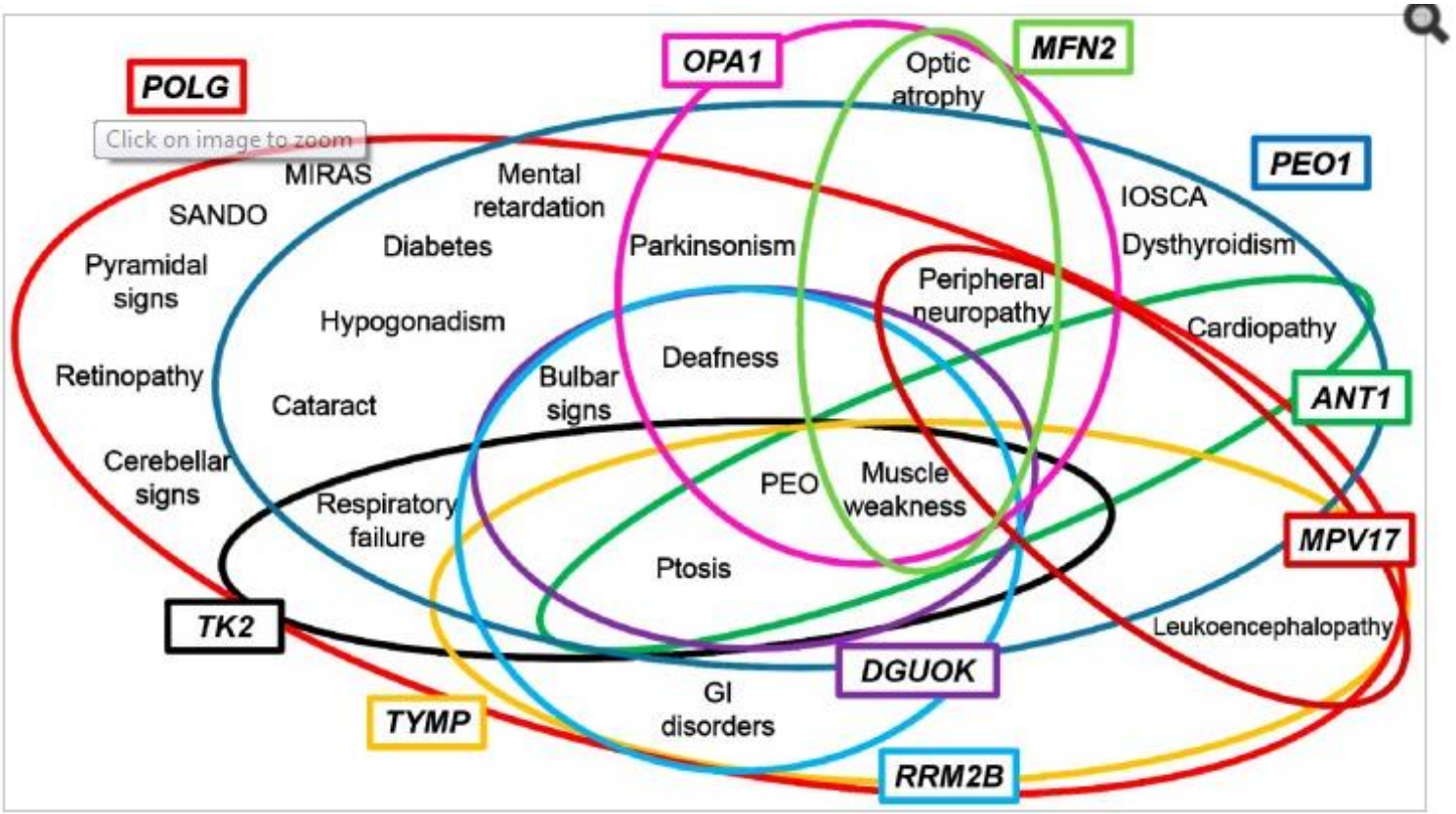
Fisiopatologia: SFN da accumulo glicolipidi GRD





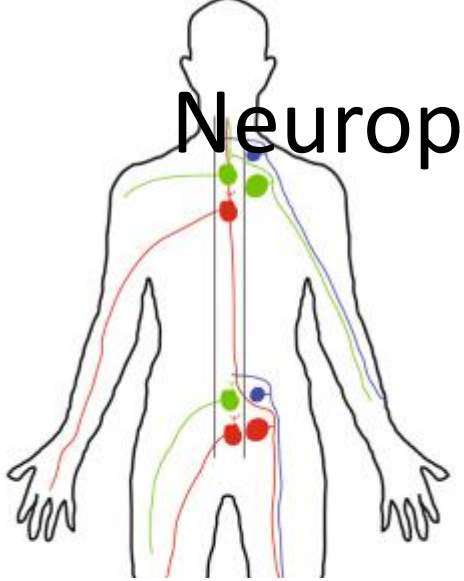
Neuropatie ereditarie associate («plus»)

Neuropatie e malattie mitocondriali



Representation of clinical phenotypes related to nuclear genes involved in mtDNA maintenance. Abbreviations: progressive external ophthalmoplegia (PEO), mitochondrial recessive ataxia syndrome (MIRAS), infantile-onset spinocerebellar ataxia (IOSCA), sensory ataxic neuropathy, dysarthria, and ophthalmoparesis (SANDO).

Neuropatie ereditarie associate («plus»)



Difetti riparazione DNA

Neuroni più vulnerabili sono quelli con corpi cellulari e fibre di grande diametro, per il senso di vibrazione e posizione

Table 1 Summary of neurological symptom and neuropathological correlate if known

	A-T (*ATM*)	ATLD (*MRE11A*)	EAOH (a.k.a. AOA1) *APTX*	SCAR1 (a.k.a. AOA2) *SETX*	SCAN1 *TDP1*
Ataxia	Prominent, 2° to Purkinje cell loss	Prominent, 2° to Purkinje cell loss	Prominent, 2° to Purkinje cell loss	Prominent, 2° to Purkinje cell loss	Prominent, cerebellar degeneration
Length-dependent neuropathy (motor)	Yes, distal weakness, 2° to axonal loss	Yes, distal weakness, 2° to axonal loss	Yes, distal weakness, 2° to axonal loss	Yes, distal weakness, 2° to axonal loss	Yes, distal weakness, 2° to axonal loss
Length-dependent neuropathy (sensory)	Yes, distal vibration and position, 2° to axonal loss	Yes, distal vibration and position, 2° to axonal loss	Yes, distal vibration and position, 2° to axonal loss	Yes, distal vibration and position, 2° to axonal loss	Yes, distal weakness, 2° to axonal loss
Extrapyramidal symptoms	Yes, neuronal localization unknown	Yes, neuronal localization unknown	Yes, neuronal localization unknown	Yes, neuronal localization unknown	No
Oculomotor apraxia	Yes, neuronal localization unknown	Yes, neuronal localization unknown	Yes, neuronal localization unknown	Yes, neuronal localization unknown	No
Spasticity	Rare	Occasional	No	Occasional	No

Neuropatie ereditarie associate («plus»)

Neuropatie e atassie ereditarie

SCA1	Ataxin-1	Ataxia, pyramidal signs, neuropathy, dysphagia, restless legs syndrome
SCA2	Ataxin-2	Ataxia, slow saccades, neuropathy, restless legs syndrome
SCA3	Ataxin-3	Ataxia, pyramidal signs, ophthalmoplegia, neuropathy, dystonia, restless legs syndrome
SCA4	Unknown	Ataxia, sensory neuropathy
SCA8	Ataxin-8	Ataxia, sensory neuropathy, spasticity
SCA18	Unknown	Ataxia, sensory neuropathy, neurogenic muscle atrophy
SCA23	Unknown	Ataxia, sensory neuropathy, pyramidal signs
SCA25	Unknown	Ataxia, sensory neuropathy

Neuropatie ereditarie associate («plus»)

Neuropatie e atassie ereditarie

Da: The Autosomal Recessive Cerebellar Ataxias, NEJM 2012

EMG

Axonal sensorimotor neuropathy
Ataxia with oculomotor apraxia type 1, ataxia with oculomotor apraxia type 2, ataxia telangiectasia, cerebrotendinous xanthomatosis,* Refsum's disease,* ARSACS*

Pure sensory neuronopathy
Friedreich's ataxia, AVED, abetalipoproteinemia, SANDO

No neuropathy
ARCA1, ARCA2, NPC

Friedreich's ataxia	Mean, 16; 7–25 in most cases; reported range, 2–60	Most frequent recessive ataxia, bilateral extensor plantar reflexes, scoliosis, square-wave jerks	GAA triplet repeat expansion in intron 1 of the FXN gene	No cerebellar atrophy, spinal cord atrophy	*FXN*, frataxin
Sensory axonal neuropathy with dysarthria and ophthalmoplegia	Range, 20–60	Ophthalmoparesis, dysarthria, ptosis, myoclonus	Variable elevation of serum lactic acid level	Variable cerebellar atrophy, cerebellar white-matter changes, strokelike lesions	*POLG*, polymerase gamma
Autosomal recessive spastic ataxia of Charlevoix–Saguenay	Mean, 2; up to 12	Spastic paraparesis followed by spastic ataxia, demyelinating component of the neuropathy, hypertrophy of the myelinated fibers (of the fundus)		Anterior superior cerebellar atrophy, variable T_2-weighted linear hypointensities in pons	*SACS*, sacsin
Refsum's disease	Range, 10–20	Retinitis pigmentosa, sensorineural deafness, demyelinating neuropathy	Elevated serum phytanic acid level††	No cerebellar atrophy	*PhyH*, phytanoyl-CoA hydroxylase and *PEX7*, PEX7

Neuropatie ereditarie associate («plus»)

Altre neuropatie ereditarie…in corso di malattie metaboliche

- in corso di leucodistrofia metacromatica;
- in corso di leucodistrofia a cellule globoidi;
- la adrenomieloneuropatia;
- in corso di CDG;
- da deficit di cobalamina;
- in corso di NARP.

ADRENOMYELONEUROPATHY

- X linked recessive disorder.
- Mutation in ABCD1 gene on chromosome Xq28 – harmful accumulation of Very long chain fatty acids in affected cells – interfere with membrane components of both neurons and axons.

Accumulo di VLCFA effetti dannosi su membrane (struttura e funzione), ma grande variabilità nelle fam ALD + non correlazione Qt VLCFA e disabilità: altri fattori, forse di tipo immune.

“The rapid neurological progression in the childhood cerebral form is associated with demyelination and an intense perivascular inflammatory response”.

Neuropatie ereditarie associate («plus»)

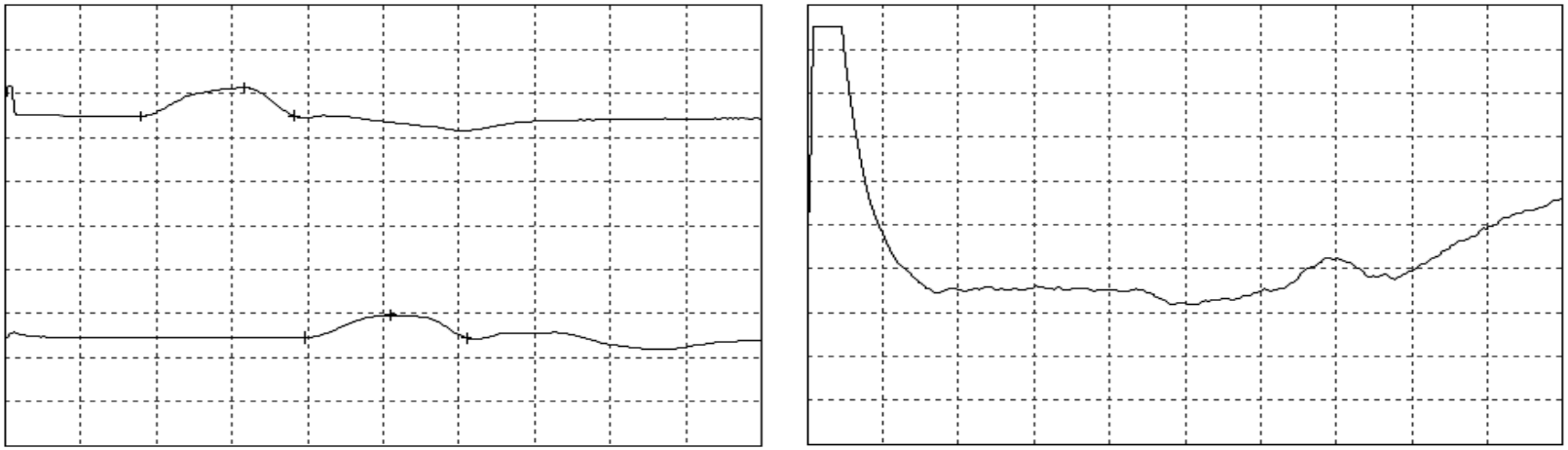
ALS – spectrum & Kennedy's disease

ALS: Hereditary & Familial

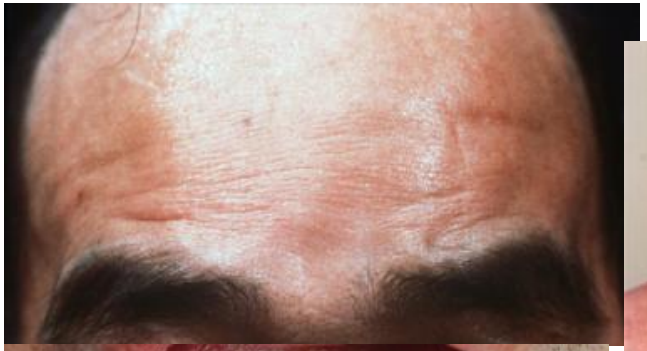
Recessive SMA (es. SMA1: SMN 5q)
Dominant, Proximal
X-linked SMA (Recessive) (es. Bulbospinal (Kennedy): AR; Xq12)

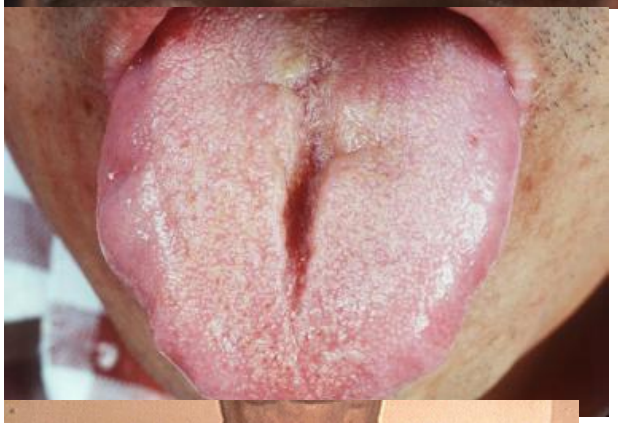
Malattia di Kennedy o SBMA: M, multisistemica, ipostenia AA e faciobulbare, da perdita LMN. Oltre ovvia **neuronopatia motoria, neuropatia sensitiva**, segni da deficit androgeni (impotenza, ridotta fertilità, ginecomastia).
Da espansione di CAG tandem-repeat in esone 1 del recettore degli androgeni (AR) su cr. Xq11-12

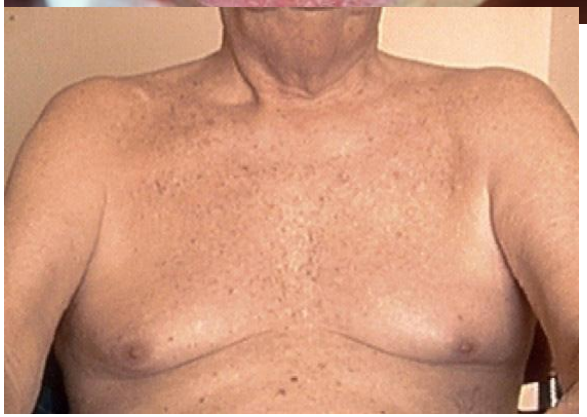
Figure 3. (a) Reduced Median CMAP amplitude, (b) Absent Ulnar



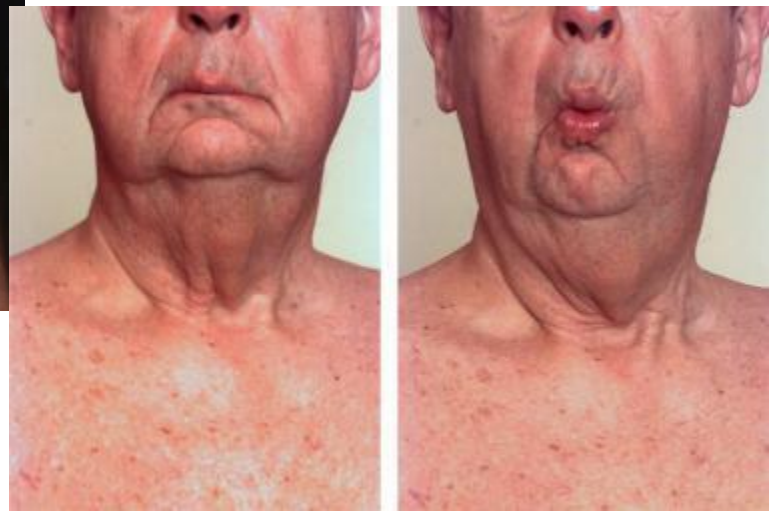
Neuropatie ereditarie associate («plus»)



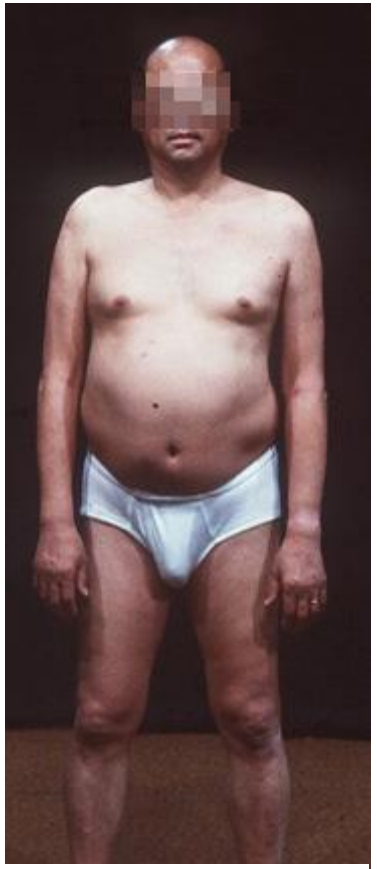




Kennedy's disease



Di solito l'interessamento bulbare segue quello agli AA.



Sospetto diagnostico: maschio con MND, con ipostenia prossimale e bulbare, familiarità, fascicolazioni faciali, ginecomastia, assenza segni piramidali (spasticità) e anomalie NFS sensitive e pattern neuropatico all'EMG ad ago.

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