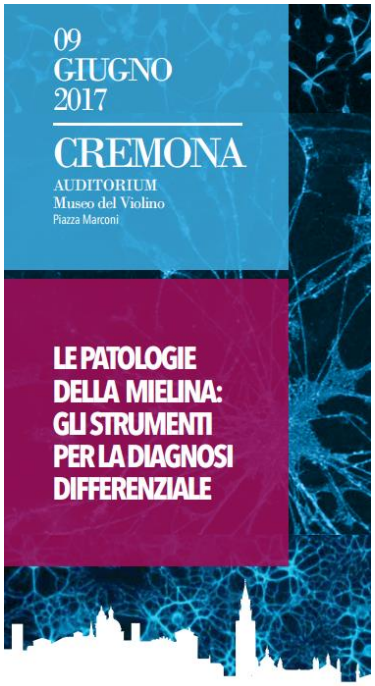

Il ruolo dell'anamnesi e dell'esame obiettivo neurologico

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European Reference Networks

EURO-NMD

European network of reference centers for rare neuromuscular diseases

Associazione Italiana Sistema Nervoso Periferico

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DOES THE HISTORY AND EXAMINATION SUGGEST THAT THE PATHOLOGICAL PROCESS IS LOCALISED TO THE PERIPHERAL NERVE?

Box 1: Diagnostic pitfalls in establishing a neuropathy

- Transverse myelitis
- Hypokalaemia
- Spinal arteriovenous malformation
- Conus tumour

Certain neuropathies co-exist with CNS disease, such as vitamin B12 deficiency, adrenomyeloneuropathy, neuroacanthocytosis, spinocerebellar syndromes, to name but a few of many.

A common co-occurrence, particularly in the elderly, is the combined presence of cervical spondylotic myelopathy and late onset predominantly sensory axonal neuropathy.

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CAUSES OF PERIPHERAL NEUROPATHIES - 1

Table 1. Causes of Peripheral Neuropathy

Cause	*Type of neuropathy*	*Comments*	*Laboratory tests*
Diseases			
Acquired immunodeficiency syndrome	A	Mainly sensory	Human immunodeficiency virus test
Carcinoma (paraneoplastic syndrome)	A	Usually sensory	Paraneoplastic panel (anti-Hu, anti-Yo, anti-Ri, anti-Tr, anti-Ma, and anti-CV2 antibodies)
Chronic liver disease	M	Mainly demyelinating, especially in viral hepatitis	Hepatic transaminase, bilirubin, albumin, and alkaline phosphatase levels
Critical illness neuropathy	A	Usually acute or subacute	No specific laboratory test
Diabetes mellitus	M	Chronic; axonal may predominate	Fasting blood glucose level, glucose tolerance test, A1C level
End-stage renal disease	A	—	Serum creatinine and blood urea nitrogen levels
Hypothyroidism	A	Usually acute or subacute, but can be chronic	Thyroid-stimulating hormone level
Leprosy	A	Usually sensory	Phenolic glycolipid-1 antibody, skin biopsy
Lyme disease	A	—	Lyme titers
Lymphoma	M	Mainly axonal	CBC, imaging
Monoclonal gammopathy		Usually chronic	Urine and serum protein electrophoresis with immunofixation
Amyloidosis	A	Usually sensory	
Multiple myeloma	M	Axonal damage predominates after treatment	
Plasmacytoma (osteosclerotic myeloma)	D	May have some axonal damage	
Monoclonal gammopathy of undetermined significance			
IgM	D	Most common; may have some axonal damage	
IgG or IgA	M	Demyelinating features often predominate	
Porphyria	A	Acute	Porphyrin titers
Syphilis	A	—	Rapid plasma reagin, VDRL, cerebrospinal fluid analysis
Vitamin B_6 deficiency	A	Sensory more than motor	Vitamin B_6 level
Vitamin B_{12} deficiency	A	Peripheral neuropathy is intermixed with upper motor neuron signs	CBC; vitamin B_{12} and homocysteine levels; methylmalonic acid test

continued

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CAUSES OF PERIPHERAL NEUROPATHIES - 2

Table 1. Causes of Peripheral Neuropathy *(continued)*

Cause	*Type of neuropathy*	*Comments*	*Laboratory tests*
Drugs*			
Amiodarone (Cordarone)	M	Mainly axonal with sensorimotor	No specific tests
Chloroquine (Aralen)	D	May have some axonal damage	
Digoxin	A	Mainly sensory	
Heroin	A	Sensorimotor	
Hydralazine	A	Mainly sensory	
Isoniazid	A	Mainly sensory	
Lithium	A	Sensorimotor	
Metronidazole (Flagyl)	A	Mainly sensory	
Misoprostol (Cytotec)	A	Motor	
Nitrofurantoin (Furadantin)	A	Sensorimotor	
Phenytoin (Dilantin)	A	Mainly sensory	
Procainamide (Pronestyl)	D	May have some axonal damage	
Statins	A	Mainly sensory	
Vincristine (Oncovin)	A	Sensorimotor	
Vitamin B_6 excess	A	Mainly sensory	
Genetic disorders†			
Charcot-Marie-Tooth disease			Genetic testing
Type 1	D	Also called HMSN-I	
Type 2	A	Also called HMSN-II	
Metachromatic leukodystrophy	D	—	
Neuropathy with liability to pressure palsies	D	—	
Refsum disease	D	Also called HMSN-IV	
Toxins*			
Diphtheria toxin	D	Acute presentation	Histopathology
Ethanol (alcohol)	A	Sensorimotor	No specific or practical laboratory test
Heavy metals (e.g., arsenic, lead, mercury, gold)	A	Lead and mercury mainly cause motor neuropathy Arsenic causes sensorimotor neuropathy Gold may cause some demyelination	24-hour urine collection for heavy metal titers
Organophosphates	A	Sensorimotor	No specific or practical laboratory test
Tetanus	A	Motor; acute presentation	No specific or practical laboratory test
Tic paralysis	A	Motor; acute presentation	No specific or practical laboratory test
Other causes			
Idiopathic polyneuropathy	A	Diagnosis of exclusion; usually chronic	No laboratory test

A = axonal; CBC = complete blood count; D = demyelinating; HMSN = hereditary motor-sensory neuropathy; Ig = immunoglobulin; M = mixed; VDRL = Venereal Disease Research Laboratory.

**—Usually acute or subacute, but can be chronic.*

†*—Usually chronic.*

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HAVE I OBTAINED ADEQUATE PAST, FAMILY, OCCUPATIONAL, AND DRUG HISTORIES?

- To establish whether the neuropathy is an **isolated illness** of peripheral nerve, or whether it is occurring in the context of disease elsewhere.
  - Concurrent systemic diseases, particularly organ failure, endocrine disorders, connective tissue disease, diabetes and latent diabetes, celiac disease, infectious diseases

- Toxic exposure

- Medications resulting in neuropathy i.e. amiodarone, phenytoin, statins, many antibiotics and chemotherapies

- Abused drugs [tobacco (paraneoplastic), alcohol (toxic), cocaine (vasculitic)]and the behaviour related consequences, including HIV or hepatitis C infection and nutritional deficiency

- Certain types of neuropathy may be more prominent in particular groups. There is no point suspecting a Scottish highlander of having leprosy, but he may have acquired **neuroborreliosis** locally, or have returned with it from a walking tour of the Black Forest. The contrary applies to an immigrant from India, **leprosy** being one of the most common causes of neuropathy worldwide. Vegans are vulnerable to **nutritional deficiency**

- Detailed family history; intrafamilial marriages throw up recessive neuropathies

WHAT FEATURES OF DIAGNOSTIC HELP MIGHT I PICK UP FROM THE NEUROLOGICAL EXAMINATION?

- Acute, subacute or chronic
- Distribution: focal, multifocal, generalized
- Sensory, motor or sensory-motor
- Autonomic involvement; painful neuropathy
- Axonal or myelin involvement
- Foot deformity
- Cranial nerve involvement

Example:

A chronic, generalized, sensory-motor, demyelinating neuropathy with no autonomic involvement

IS THE NEUROPATHY ACUTE, SUBACUTE OR CHRONIC?

- **Acute**

- demyelinating or axonal Guillain Barre syndrome (GBS)

- porphyria

- **Chronic**

– chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

– paraproteinemia related

– amiodarone toxicity

– Refsum's disease

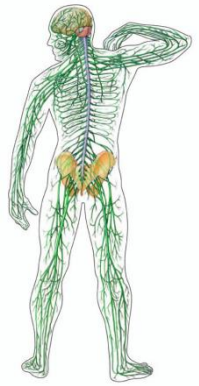
– Charcot-Marie-Tooth (CMT) types 1, X and AR CMT 1

– metachromatic leucodystrophy

– statins

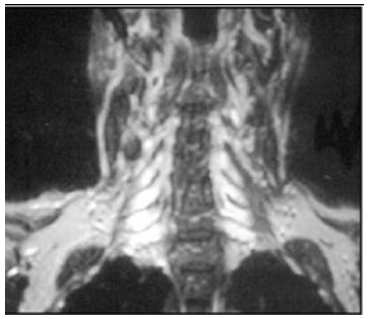
IS THE NEUROPATHY FOCAL, MULTIFOCAL OR GENERALISED?

- **Mononeuropathies**: single nerve involvement



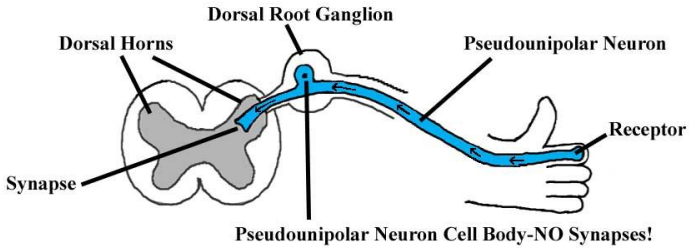
- **Multineuropathies**: asymmetrical involvement of two or more nerves

- **Polyneuropathies**: symmetrical and diffuse nerve involvement



- **Polyradiculoneuropathies:** root involvement

- **Ganglionopathies:** primary degeneration of sensory neurons in dorsal root ganglia



IS THE NEUROPATHY FOCAL, MULTIFOCAL OR GENERALISED?

Box 3: Focal and multifocal neuropathies

- Entrapment neuropathy—for example, carpel tunnel syndrome (CTS), ulnar nerve at elbow, common peroneal nerve over fibular head
- Myxoedema, acromegaly
- Amyloid
- Diabetes
- Hereditary neuropathy with liability to pressure palsies (HNPP A)
- Vasculitis
- Multifocal motor neuropathy

Conditions causing mononeuropathy

Acute (trauma-related)

Chronic (nerve entrapment)

Disorders causing mononeuropathy multiplex

Acute

- Diabetes mellitus*
- Multifocal motor neuropathy
- Vasculitic syndromes

Chronic

- Acquired immunodeficiency syndrome
- Leprosy*
- Sarcoidosis

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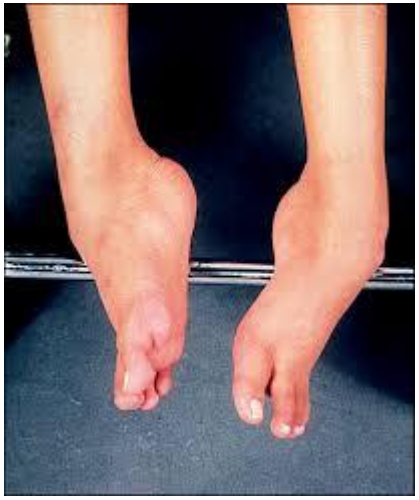
WHAT IS THE RELATIVE EXTENT OF MOTOR AND SENSORY NERVE INVOLVEMENT?

Sensory involvement

- **NEGATIVE**: sensory reduction
- **POSITIVE**: sensory abnormalities (paresthesia; dysesthesia; neuropathic pain; hyperesthesia; allodynia)

Motor involvement

- **DISTAL**
- **DISTAL AND PROXIMAL**



WHAT IS THE RELATIVE EXTENT OF MOTOR AND SENSORY NERVE INVOLVEMENT?

Motor multifocal neuropathy

Dorsal root Ganglionopathy

Box 4

- Predominantly sensory neuropathies
  - diabetes
  - thiamine deficiency
  - malignancy
  - leprosy
  - hereditary sensory neuropathies
  - amyloid
  - uraemia
  - sarcoid
- Predominantly motor neuropathies
  - Guillain-Barre syndrome and CIDP
  - porphyria
  - diphtheria
  - botulism
  - lead
  - Charcot-Marie-Tooth

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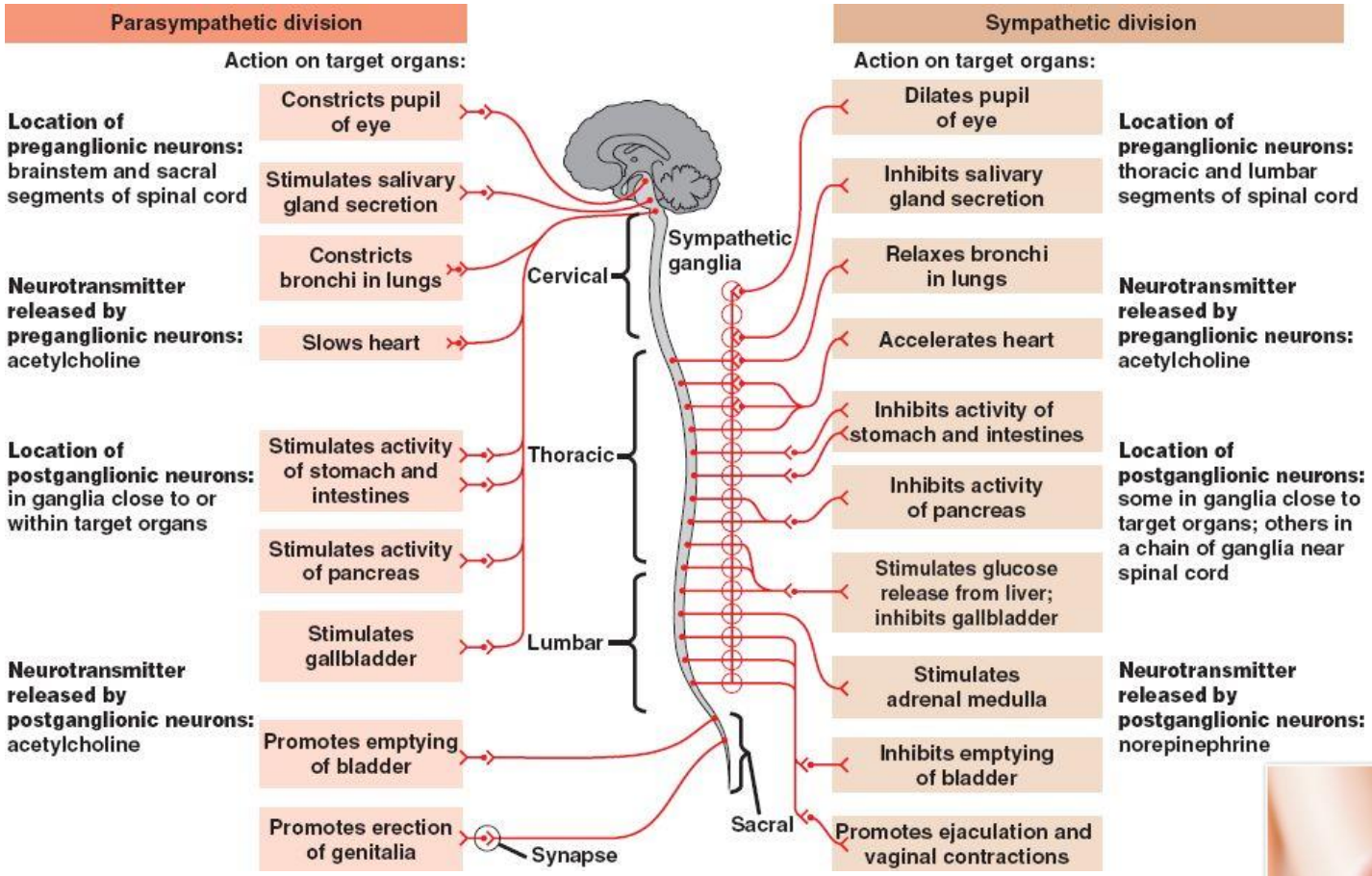
IS THERE PROMINENT SMALL FIBRE AND AUTONOMIC INVOLVEMENT?



IS THERE PROMINENT SMALL FIBRE AND AUTONOMIC INVOLVEMENT?

Conditions causing neuropathy with autonomic features

Alcoholism
Amyloidosis
Chemotherapy-related neuropathy
Diabetes
Heavy metal toxicity
Paraneoplastic syndrome
Porphyria
Primary dysautonomia
Vitamin B_{12} deficiency

Conditions causing painful neuropathy

Alcoholism
Amyloidosis
Chemotherapy (heavy metal toxicity)
Diabetes
Idiopathic polyneuropathy
Porphyria

Box 5: Small fibre and autonomic neuropathies

- Diabetes
- Amyloidosis
- Fabry's disease
- Tangier disease
- Hereditary sensory and autonomic neuropathies
- Chronic idiopathic small fibre sensory neuropathy
- Sjogren's syndrome

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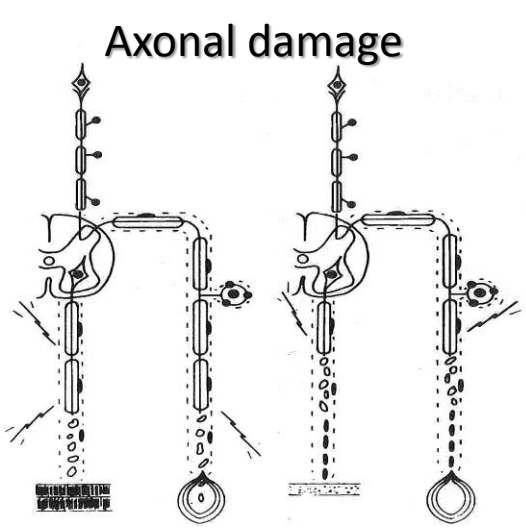
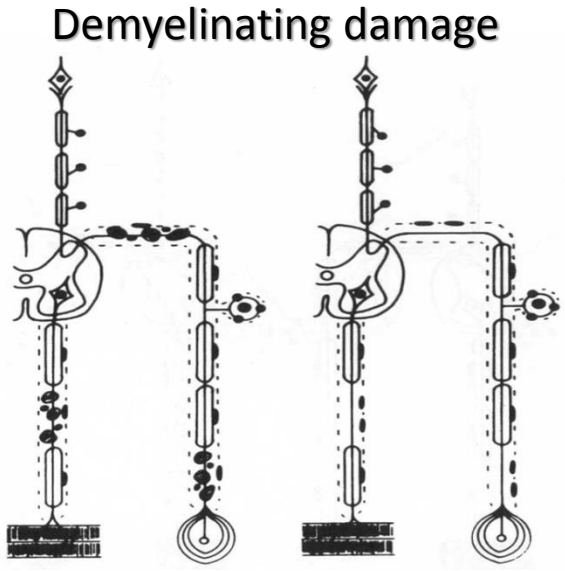
IS THE NEUROPATHY AXONAL OR DEMYELINATING ON CLINICAL GROUNDS?

The medical student view that weakness in polyneuropathy is invariably distal also rarely proves true in modern practice

In **length dependent axonopathies**, such as Charcot-Marie-Tooth 2 (CMT 2) or metabolic neuropathies, this may be the case.

Demyelinating neuropathy, such as GBS and CIDP, is often characterized by proximal dominant weakness, since multiple roots are often affected by conduction block





Widespread reflex loss, including in muscle groups that are not particularly weak or wasted, is more a feature of **demyelination**.

In contrast, selective loss of the ankle jerks in the presence of **distal wasting and weakness** is more typical of an axonopathy, especially if accompanied by a stocking distribution of sensory loss

IS THE NEUROPATHY AXONAL OR DEMYELINATING ON CLINICAL GROUNDS?

Box 2: Demyelinating neuropathies

- Acute
  - Guillain Barre syndrome (GBS)
- Chronic
  - chronic inflammatory demyelinating polyradiculo-neuropathy (CIDP)
  - paraproteinemia related
  - amiodarone toxicity
  - Refsum's disease
  - Charcot-Marie-Tooth (CMT) types 1, X and AR CMT 1
  - metachromatic leucodystrophy
  - statins

Box 6: Chronic axonal neuropathies

- Drugs or toxins
  - alcohol
  - chemotherapeutic agents—for example, vincristine, cisplatinum
  - organophosphate
  - phenytoin
  - antibiotics—for example, metronidazole, dapsone
  - statins
- Infections
  - leprosy
  - Borrelia
  - HIV, HTLV1
- Connective tissue diseases
  - Sjogren's syndrome
  - systemic lupus erythematosus
  - rheumatoid arthritis
- Metabolic
  - diabetes
- Paraneoplastic
  - lung, ovarian carcinoma
- Inherited
  - CMT 2 and X
  - familial amyloid neuropathies
- Vitamins
  - vitamin B12
  - vitamin E
  - pyridoxine toxicity
- Endocrine
  - hypothyroidism
- Paraprotein
  - myeloma
  - Waldenstrom's disease
  - benign monoclonal gammopathies

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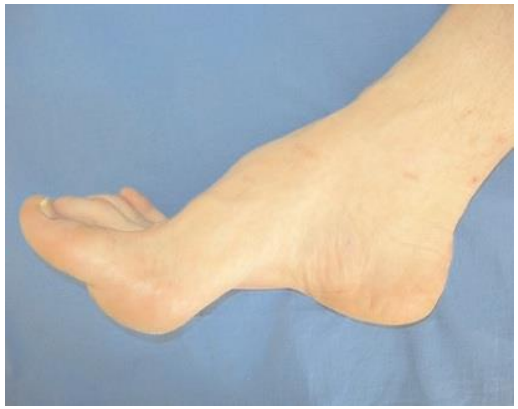
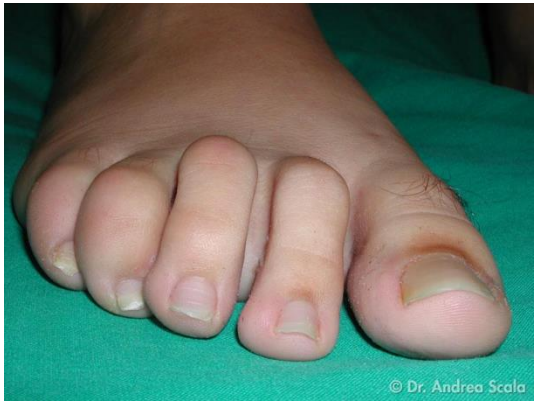
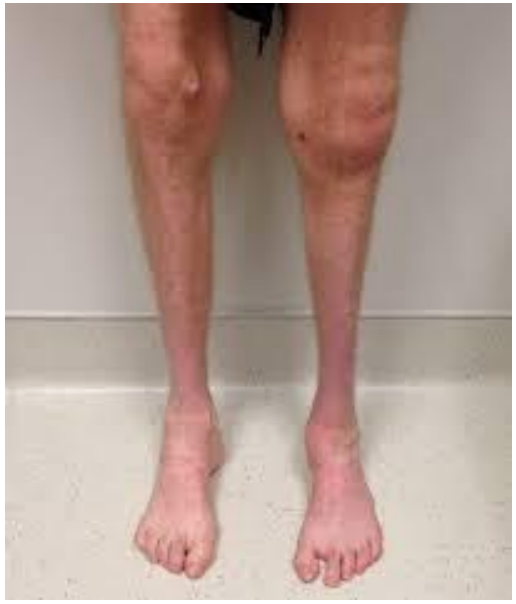
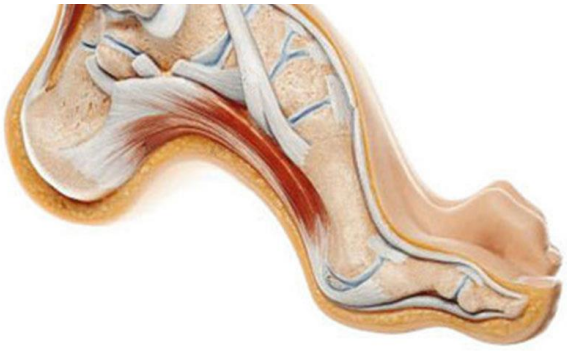
FOOT DEFORMITY







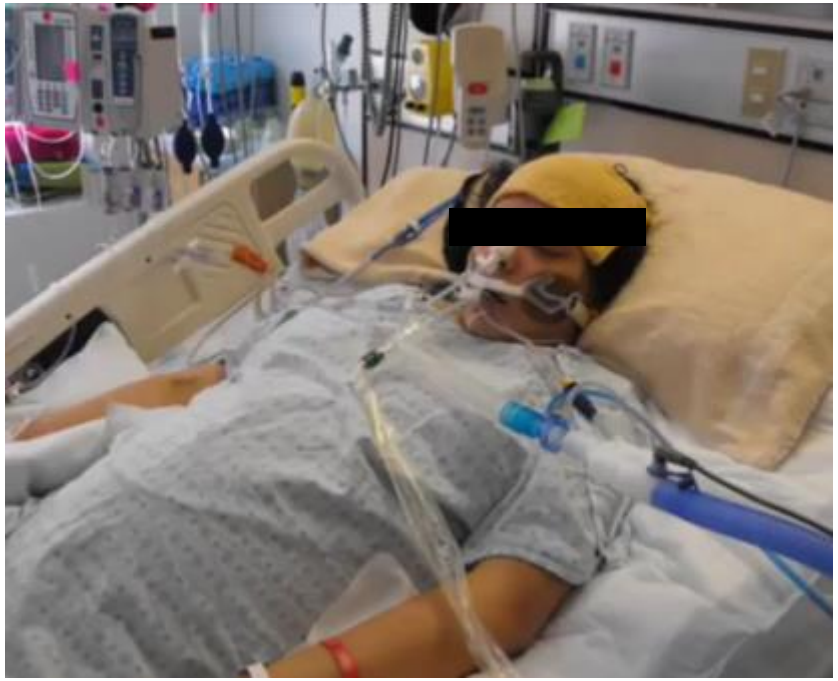


CRANIAL NERVE INVOLVEMENT

Guillain-Barre syndrome and its variants
Diabetes
Diphtheria
Human immunodeficiency virus/acquired immunodeficiency syndrome
Lyme disease
Sarcoidosis
Idiopathic cranial polyneuropathy
Chemotherapy-related neuropathies (vincristine/vinblastine/cisplatinum)
Neuromuscular junction disease
Myasthenia gravis
Botulism
Myopathies with bulbar involvement
Mitochondrial (chronic progressive external ophthalmoplegia)
Fascioscapular humeral dystrophy (FSHD)
Oculopharyngeal dystrophy

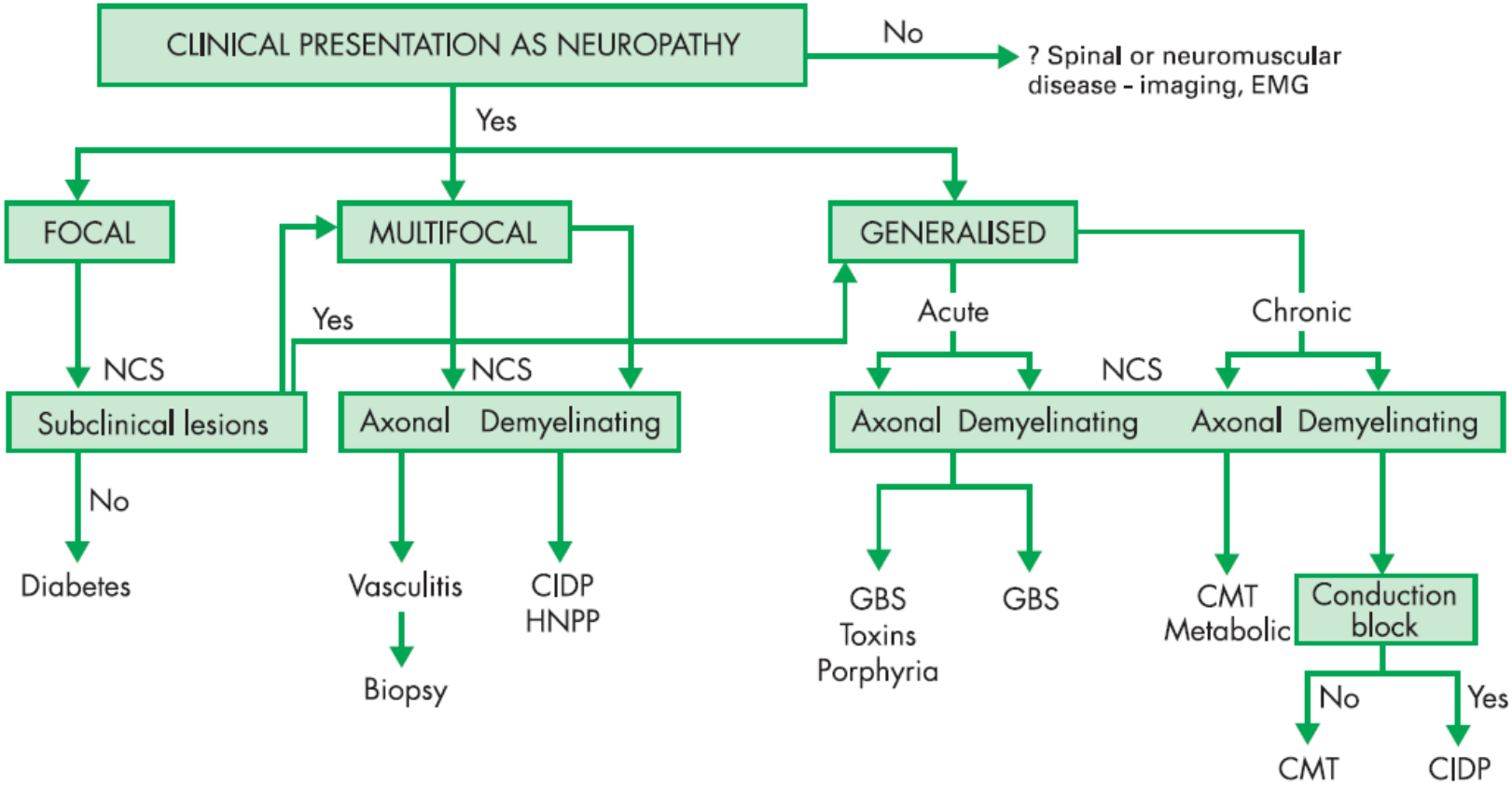
BACK TO THE CLINICAL CASE

PNS disorder with progressive involvement of upper limbs, cranial region and lower limbs



BACK TO THE CLINICAL CASE

- **History**: Gastroenteric and respiratory infectious disease
- **Course**: acute-subacute
- **Distribution**: generalized
- **Predominant system involvement**: motor system
- **No autonomic** involvement
- **Axonal** versus **demyelinating**


CLINICAL PRESENTATION AS NEUROPATHY
No
? Spinal or neuromuscular disease - imaging, EMG
Yes
FOCAL
MULTIFOCAL
GENERALISED
Yes
Acute
Chronic
NCS
NCS
NCS
Subclinical lesions
Axonal Demyelinating
Axonal Demyelinating
Axonal Demyelinating
No
Diabetes
Vasculitis
Biopsy
CIDP
HNPP
GBS
Toxins
Porphyria
GBS
CMT
Metabolic
Conduction block
No
Yes
CMT
CIDP

Aknowledgment

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