A diagnostic approach to chronic polyneuropathy

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Division of neurology

TBH / SU

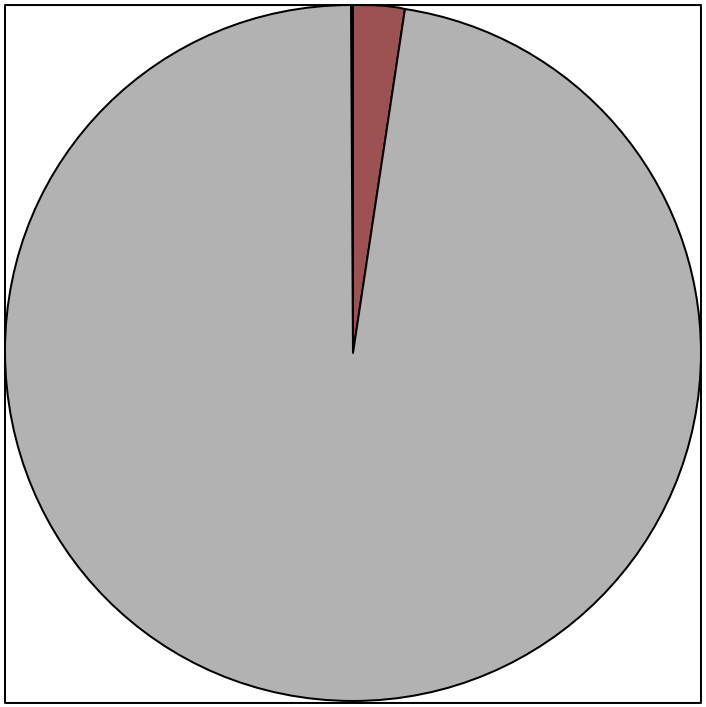
Outline

1. Introduction and definition of entities.
2. Diagnostic workup of patients with chronic polyneuropathy (PN)
    - Which patients do not need an extensive diagnostic workup?
    - How to investigate patients who do need further investigation.
3. Discussion of a few relevant causes of chronic polyneuropathy.

Prevalence of peripheral neuropathy

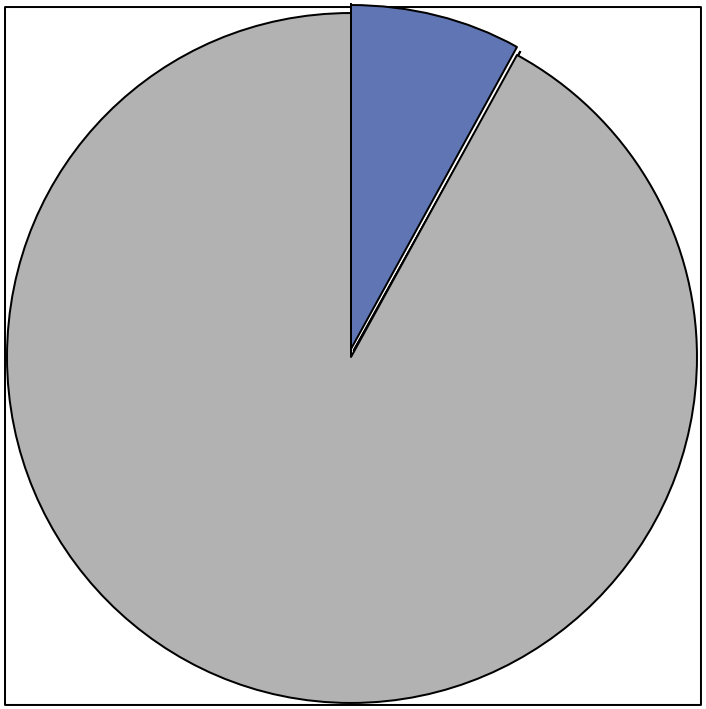
OVERALL

2400/100 000



> 55 YRS

8000/100 000



Definitions

Peripheral neuropathies

Mononeuropathy	Mononeuropathy multiplex	Polyneuropathy
Focal lesion of a single peripheral nerve	Involvement of multiple peripheral nerves simultaneously or serially	± symmetric involvement of peripheral nerves
e.g. carpal tunnel syndrome	e.g. vasculitic neuropathy	e.g. diabetic polyneuropathy

Note

1. Acute / subacute polyneuropathies and mononeuropathy multiplex will not be discussed
2. Basic knowledge of the clinical features / presentation of polyneuropathy is assumed
3. Aim: to provide an evidence-based diagnostic framework for polyneuropathies in a limited resource environment.

Diagnostic workup of patients with chronic axonal polyneuropathies

History and examination suggestive of polyneuropathy

1st CONSULTATION

History and examination suggestive of polyneuropathy

1. Clinical features of a demyelinating PN?

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Axonal PN	Demyelinating PN
• Sensory predominant • Painful • Most = small fibre sensory loss • Exclusively distal weakness (early in course) if present • Tendon reflexes decreased / absent distally • Generally slower progression	• Motor predominant • Usually not painful (but there are exceptions) • Large fibre sensory loss • Global weakness, but usually distal > proximal • Globally decreased / absent reflexes • Generally faster progression

History and examination suggestive of polyneuropathy

1. Clinical features of a demyelinating PN? yes → Electrophysiology

1st CONSULTATION

History and examination suggestive of polyneuropathy

1. Clinical features of a demyelinating PN?

no

2. Known cause present and typical phenotype?

- Diabetes
- Alcohol abuse
- Chronic renal failure
- Toxic (chemotherapy)
- HIV

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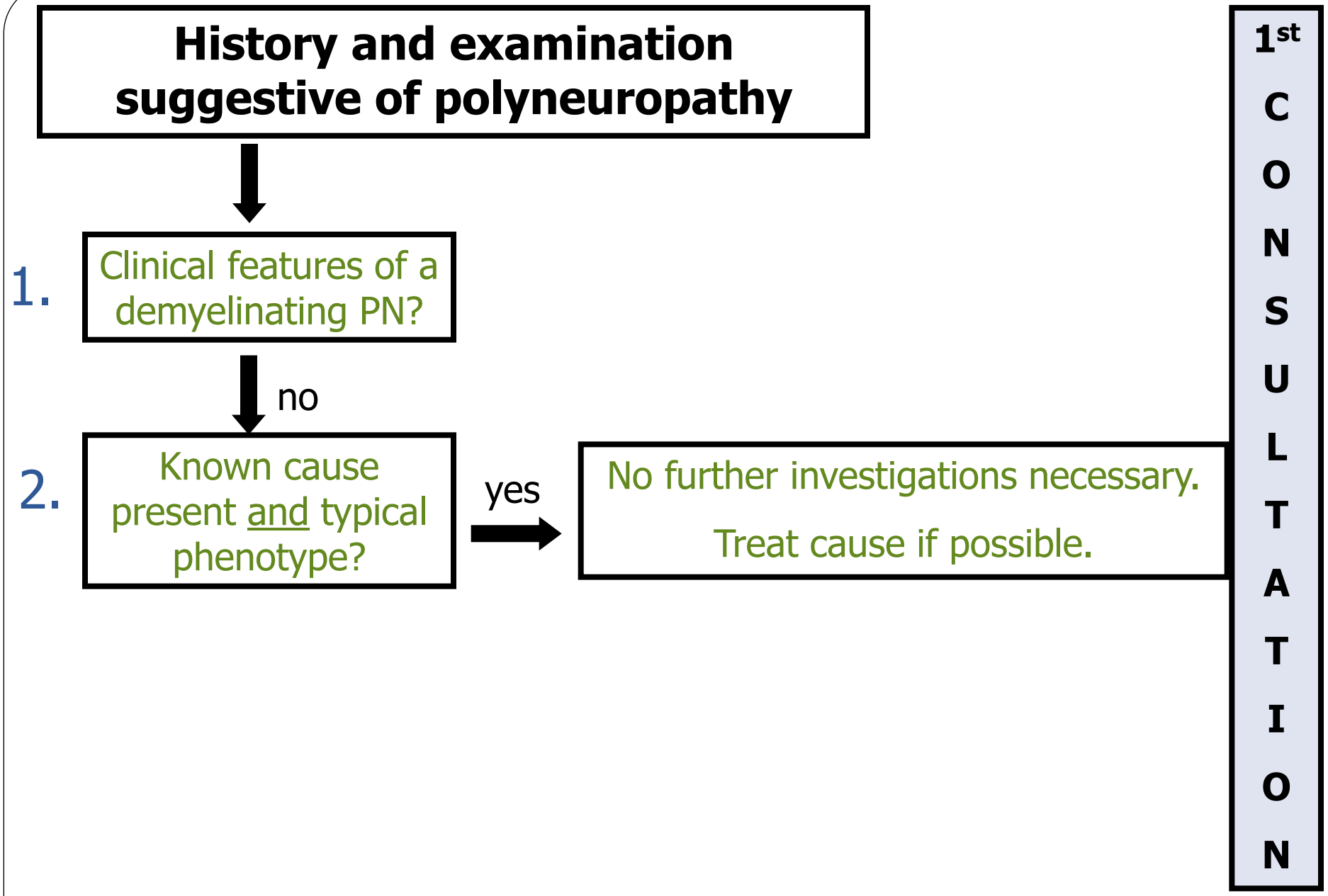

History and examination suggestive of polyneuropathy
1.
Clinical features of a demyelinating PN?
no
2.
Known cause present and typical phenotype?
yes
No further investigations necessary.
Treat cause if possible.
1st CONSULTATION

Diabetic polyneuropathy

TABLE 1. Classification of Diabetic Neuropathy Based on Clinical Patterns

Symmetry	Type of Neuropathy	Subtype
Symmetrical	Diabetic polyneuropathy (DPN)	
	Diabetic autonomic neuropathy (DAN)	
	Painful distal neuropathy with weight loss, "diabetic cachexia"	
	Insulin neuritis	
	Hypoglycemic neuropathy	
	Polyneuropathy after ketoacidosis	
	Polyneuropathy with glucose impairment*	
	CIDP in diabetes*	
Asymmetrical	Diabetic radiculoplexus neuropathies	Lumbosacral (DLRPN)
		Thoracic (DTRN)
		Cervical (DCRPN)
	Mononeuropathies	Median neuropathy at the wrist (MNW)
		Ulnar neuropathy at the elbow (UNE)
		Peroneal neuropathy at the fibular head*
	Cranial neuropathies	Oculomotor palsy
		Abducens palsy

Diabetic polyneuropathy

- Slowly progressive, symmetric, often painful, sensory>motor neuropathy affecting distal lower limbs ± autonomic features
- Distal upper limbs affected late
  - DD: co-existing mononeuropathy (e.g. carpal tunnel syndrome)

Diabetic polyneuropathy

- Usually only develops if hyperglycemia has been present for several years
  - Implication: PN in newly diagnosed Type I diabetic require diagnostic work-up
- Highly significant association with retinopathy or nephropathy Dyck; Neurology; 1993
  - Implication: PN without retinopathy or nephropathy: reconsider

Alcoholic polyneuropathy

- How much alcohol is necessary?
- And for how long?
- Occurs in 12.5-48.6% of chronic alcoholics
  - Depends on patient population (e.g. age) and diagnostic criteria (clinical vs electrophysiological)

Koike, Ann Neurol, 2003

	Alcoholic PN without thiamine deficiency (n=36)	Alcoholic PN with thiamine deficiency (n=28)	Non-alcoholic thiamine deficiency PN (n=32)
Progression	Months to years	Rapid or slow	Most <1 month, some slow
Associated disorders	-	Wernicke's & CCF	Wernicke's & CCF
Clinical	Sensory-dominant with impaired superficial sensation and pain (all sensory mod. involved in ≈ 33%). 25% unable to walk.	Motor- or sensory-dominant with impaired superficial and deep sensation in majority. Pain in ≈ 50%. About 50% unable to walk.	Motor-dominant with impaired superficial and deep sensation in majority. Pain uncommon. 85% unable to walk.
NCS	Axonal sensorimotor	Axonal sensorimotor	Axonal sensorimotor, often severe.
Histopathology	Small-fibre predominant axonal loss.	Mixed	Large-fibre predominant axonal loss.

Neuropathy of CRF ("Uremic neuropathy")

- Insidious onset, progresses over months
- Paresthesias, ↓ reflexes, ↓ vibration sense, weakness, atrophy (large fiber neuropathy)
- "Restless legs" frequent
- NCS: generalized axonal sensorimotor polyneuropathy
- Develops at GFR < 12ml/min
- Symptoms present in 80-95% patients with ESKD (end stage kidney disease)

Neuropathy of CRF ("Uremic neuropathy")

- Treatment
  - Dialysis: improvement unlikely
  - Transplantation: extent of improvement inversely related to severity of neuropathy
  - EPO (erythropoietin):
    - May be beneficial
    - Improved motor NCS, no effect on sensory NCS

Chemotherapy-induced PN

- Commonly:
  - Vinca alcaloids (vincristine)
  - Taxanes (paclitaxel)
  - Platinum compounds (cisplatin, oxaliplatin)
  - Bortezomib
  - Thalidomide
- Most chemotherapeutic drugs poorly penetrate blood-brain barrier, but readily penetrate blood-nerve barrier

Chemotherapy-induced PN

- Length-dependent, distal symmetrical, sensory predominant sensory PN ± autonomic involvement
- Sometimes sensory neuronopathy (e.g. cisplatin)
- May develop early (within weeks of starting chemotherapy)
- Dose dependent and progressive
- Partially reversible when chemotherapy stopped

Distal symmetric polyneuropathy (DSP)

- Most frequent neurologic complication of HIV
  - Clinical findings in ±50% of patients (CD4 < 300)
  - ± 2/3 of these are symptomatic
  - Not consistent correlation with ↓CD4+, ↑viral load
    - Manhattan HIV brain bank study: median CD4 count = 228 in pts with DSP, 128 in those without neuropathy
- Note: DSP is a phenotypic description, not an etiological diagnosis

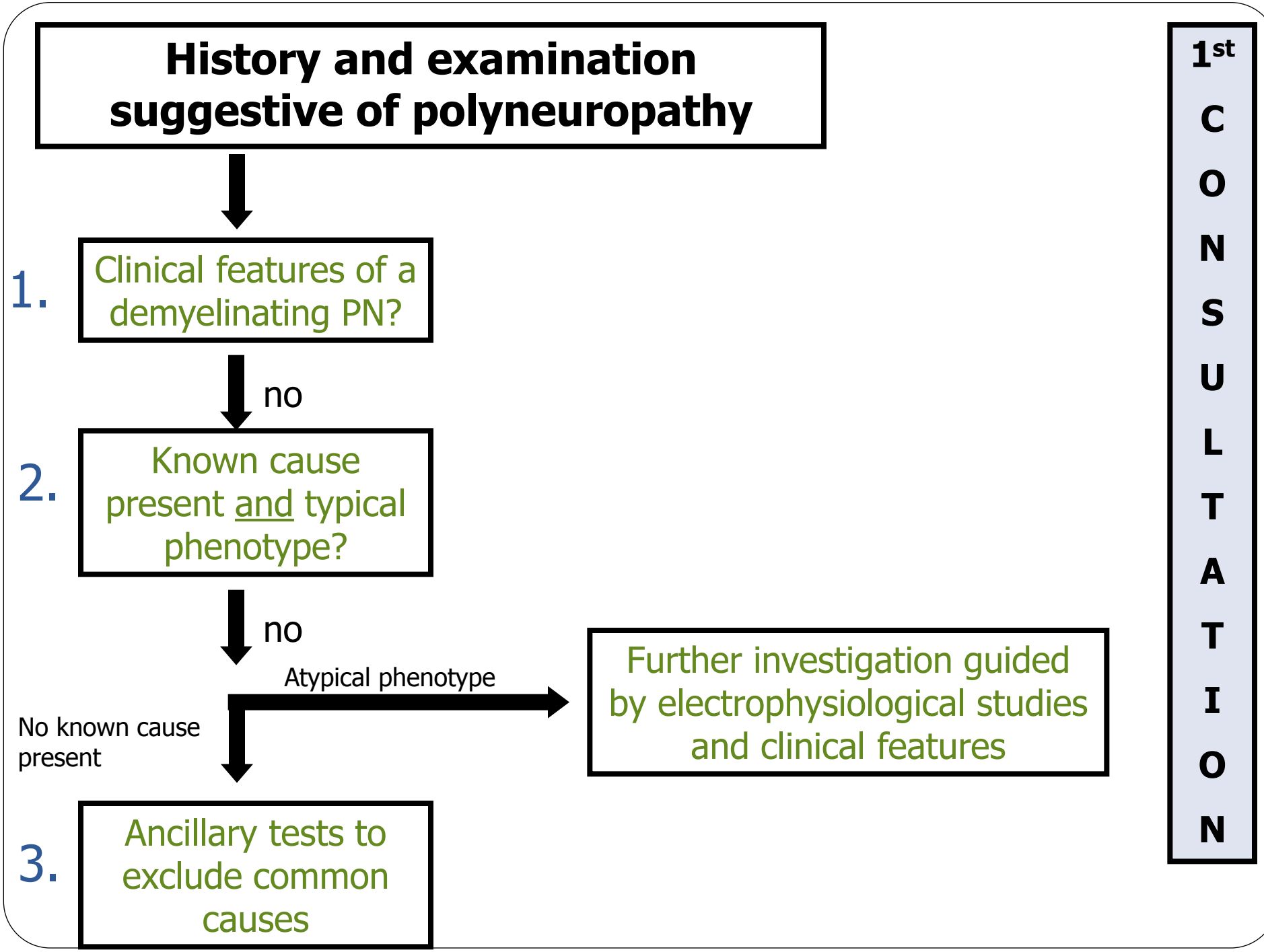
Distal symmetric polyneuropathy (DSP)

- Diagnosis
  - Abnormalities in 2 of:
    - Pinprick sensation
    - Vibration sense
    - Ankle reflexes
- Classified as:
  - Due to HIV itself (HIV-DSP)
  - After initiation of Antiretroviral treatment (ART) – d4T, ddI, ddC (ATN)

	Correlation with lower CD4 count	Correlation with ART (d-drugs)
Dana cohort (Schifitto et al, 2002)	No	No
Manhattan HIV Brain Bank (Morgello et al, 2004)	No	No
Crossroads, WC (Maritz et al, 2010)	Yes	Yes

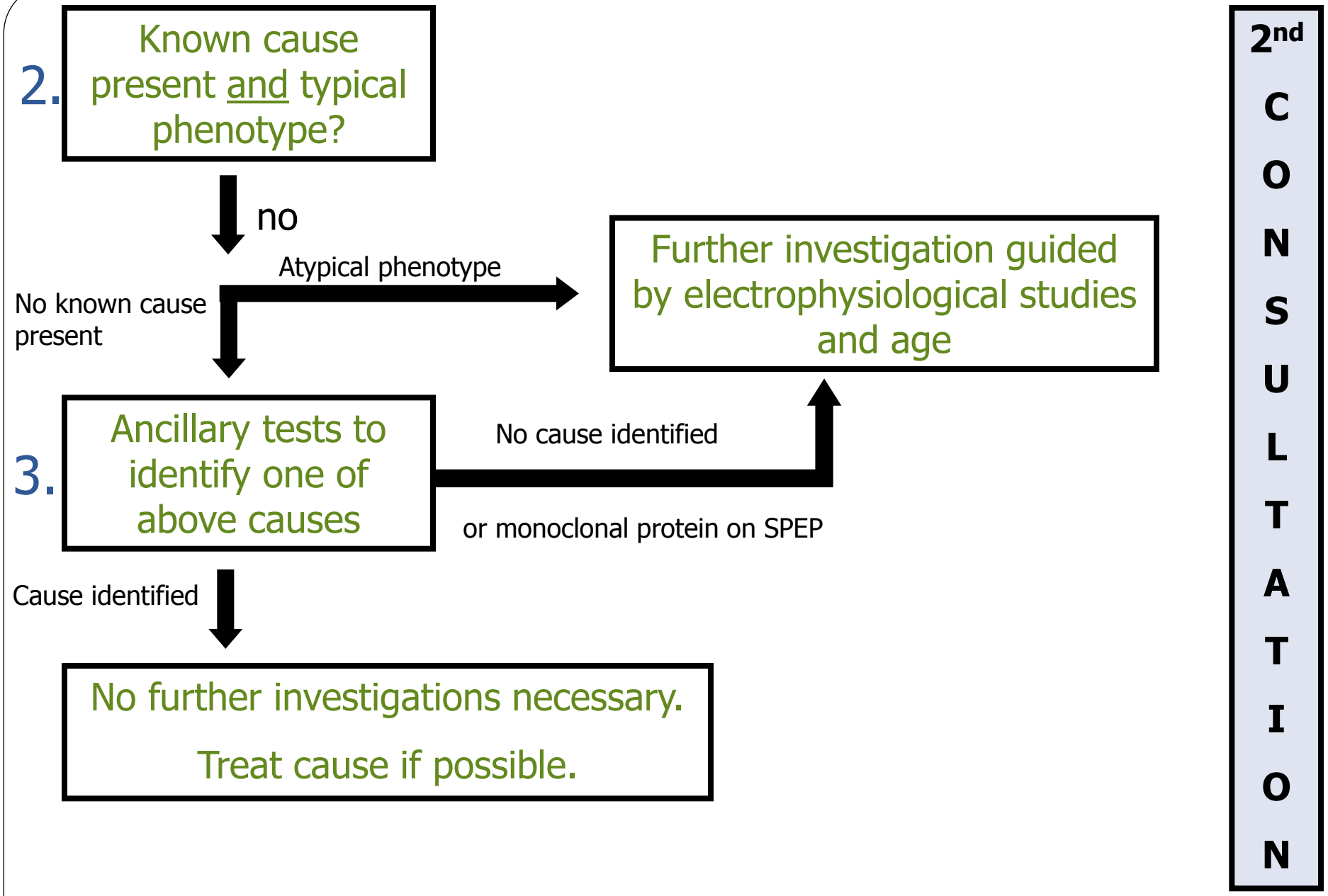
- Diabetes
- Alcohol abuse
- Chronic renal failure
- Toxic (chemotherapy)
- HIV

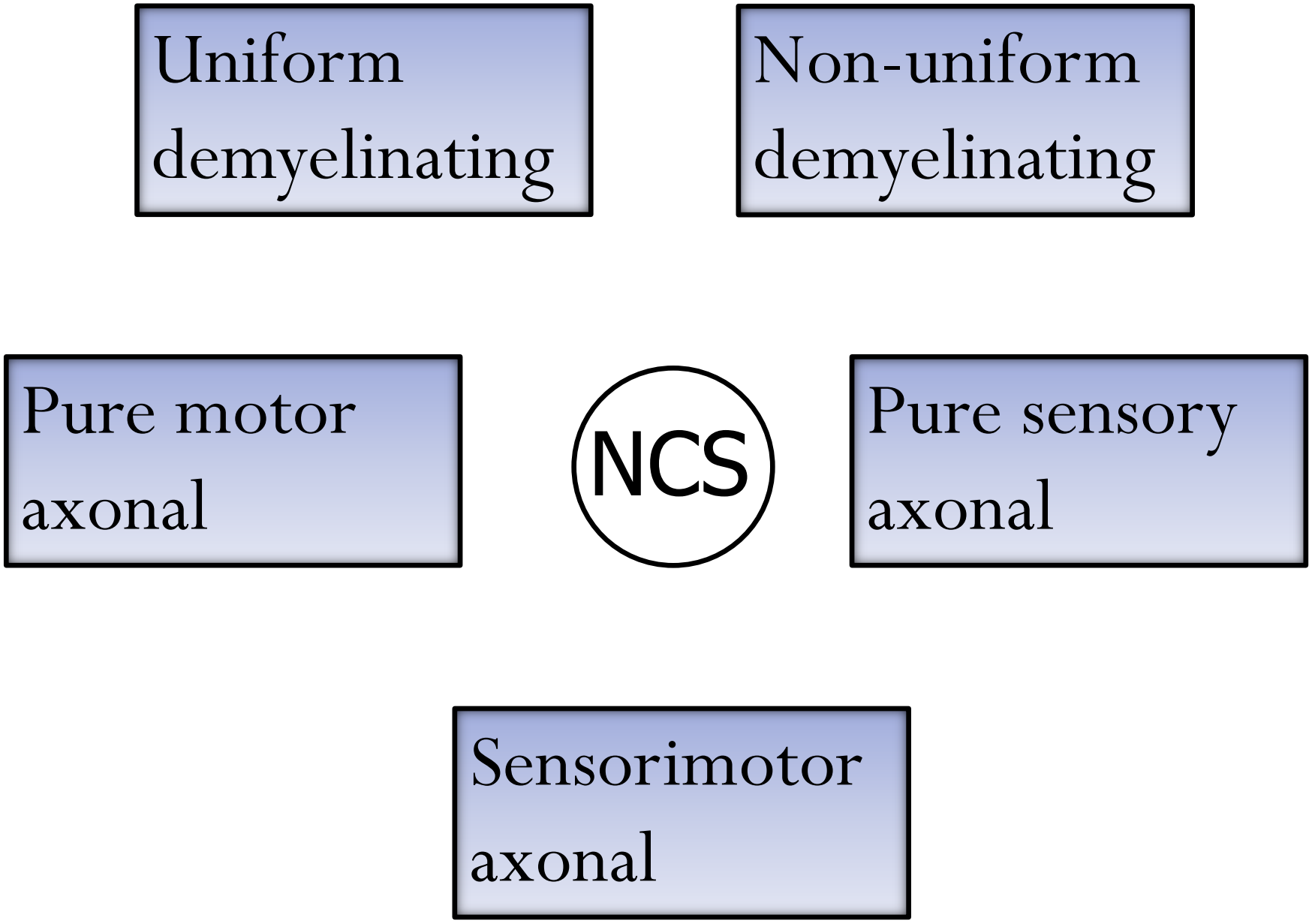
- One of these known causes and typical phenotype: ADDITIONAL BLOOD TESTS AND ELECTROHYSIOLOGY NOT INFORMATIVE
- Reasons for further investigation in these conditions
  - Clinical features other than those described above
  - Atypical course


History and examination suggestive of polyneuropathy
1.
Clinical features of a demyelinating PN?
no
2.
Known cause present and typical phenotype?
no
Atypical phenotype
Further investigation guided by electrophysiological studies and clinical features
No known cause present
3.
Ancillary tests to exclude common causes
1st CONSULTATION

Step 1: Ancillary investigations

- Identify above common causes:
  - Fasting blood glucose ± glucose tolerance test (GTT)
  - MCV, gamma GT, AST:ALT ratio
  - HIV serology
- Additional:
  - Vit B12, if low N: homocystein, methylmalonic acid (if available)
  - Serum protein electrophoresis & immunofixation


2.
Known cause present and typical phenotype?
no
Atypical phenotype
No known cause present
Further investigation guided by electrophysiological studies and age
3.
Ancillary tests to identify one of above causes
No cause identified
or monoclonal protein on SPEP
Cause identified
No further investigations necessary.
Treat cause if possible.
2nd CONSULTATION


Uniform demyelinating
Non-uniform demyelinating
Pure motor axonal
NCS
Pure sensory axonal
Sensorimotor axonal

Uniform demyelinating

- Charcot-Marie-Tooth disease

- Strategy:
  - If NCV ≤ 35 m/s and no delayed walking or adult onset:
    - CMT1A
  - If NCV ≤ 35 m/s and delayed walking:
    - CMT1A or 1B
  - If intermediate NCV:
    - CMT1B or CMTX1
- SA: Molecular diagnosis available only for CMT1A (PMP22 mutation – 70% of CT)

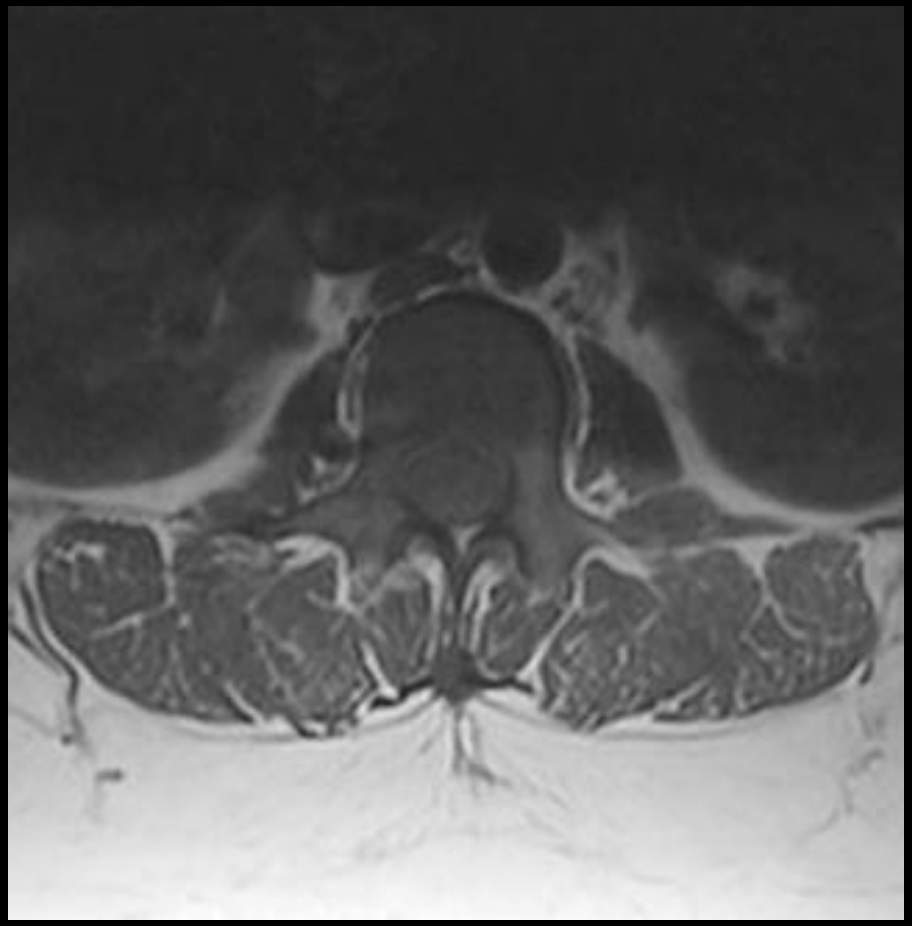
- Strategy:
  - Exclude diabetes mellitus
  - Serum M-protein determination in all patients

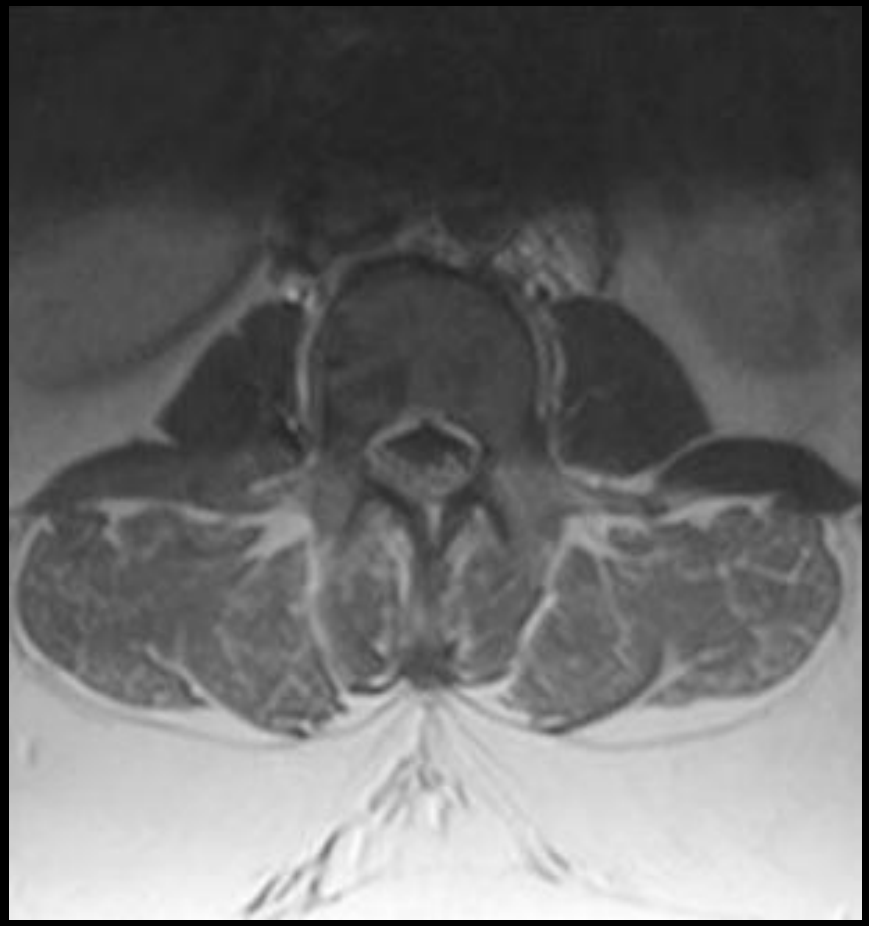
Non-uniform demyelinating

- CIDP
- Paraproteinemic neuropathy
  - Malignant, e.g. myeloma
  - MGUS
- Sequellae of GBS

CIDP and diabetes

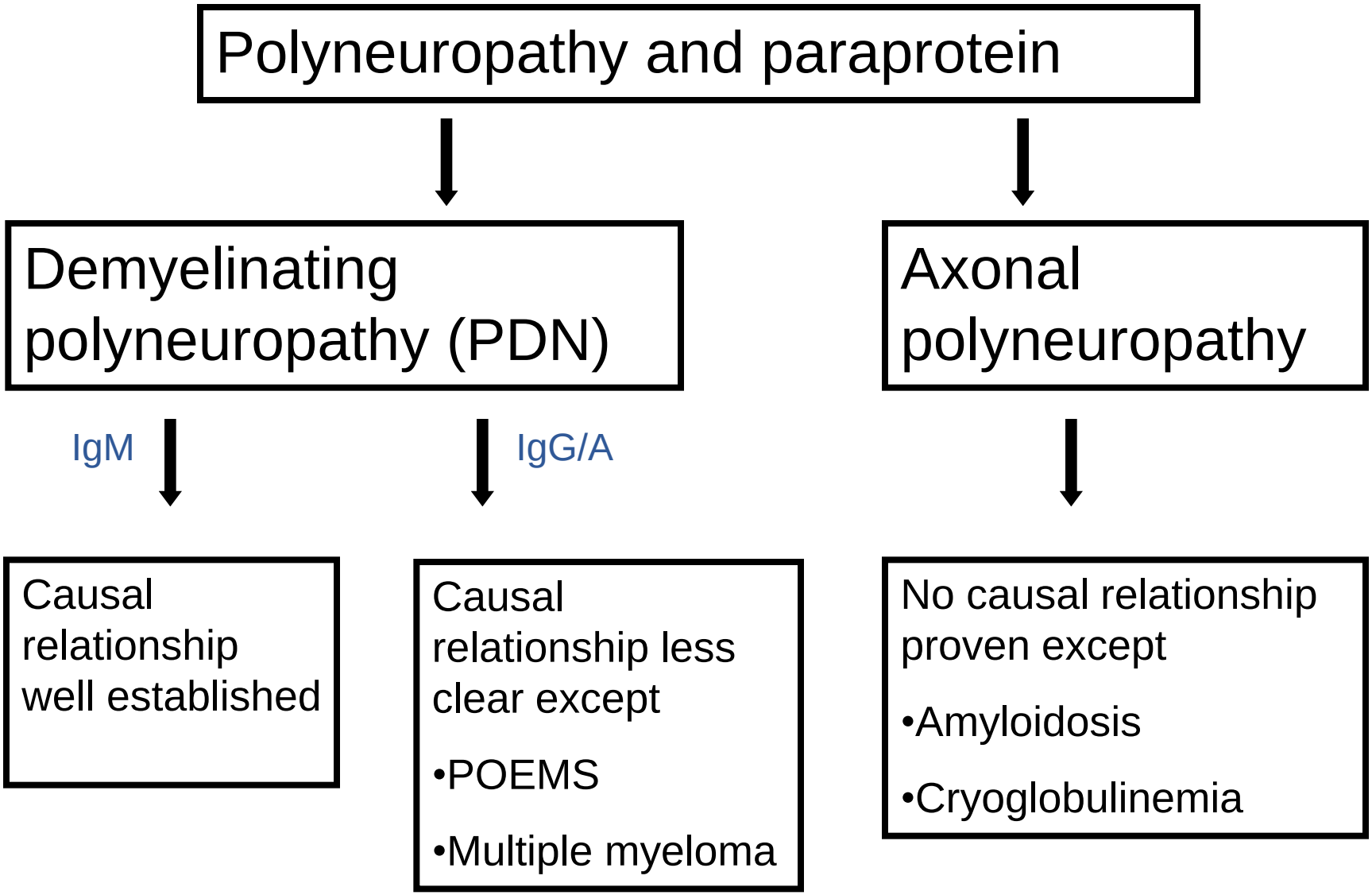
- Hospital-based observational studies:
  - ± 11X higher incidence in diabetics compared to non-diabetics
- Requires high index of suspicion
  - Recent (few weeks to months) subacute worsening in neuropathy symptoms
  - Motor > sensory symptoms
  - Proximal & distal weakness
  - Globally depressed / absent reflexes
  - NCS: demyelinating neuropathy
- Diagnosis may be difficult
  - CSF protein may be elevated due to diabetes (although not as high as in CIDP)
  - Consider MRI of roots / plexi

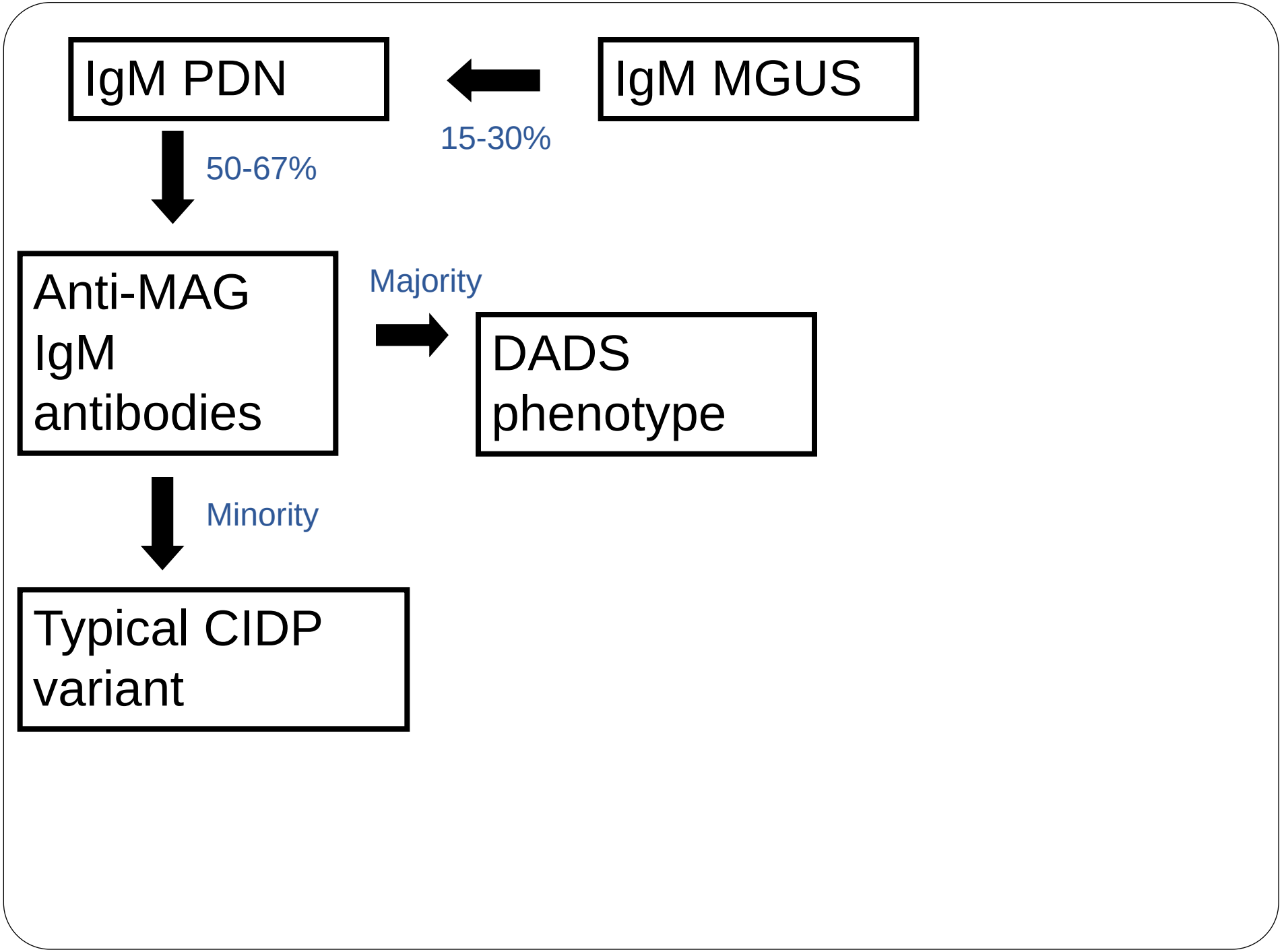




Paraproteinemic neuropathies

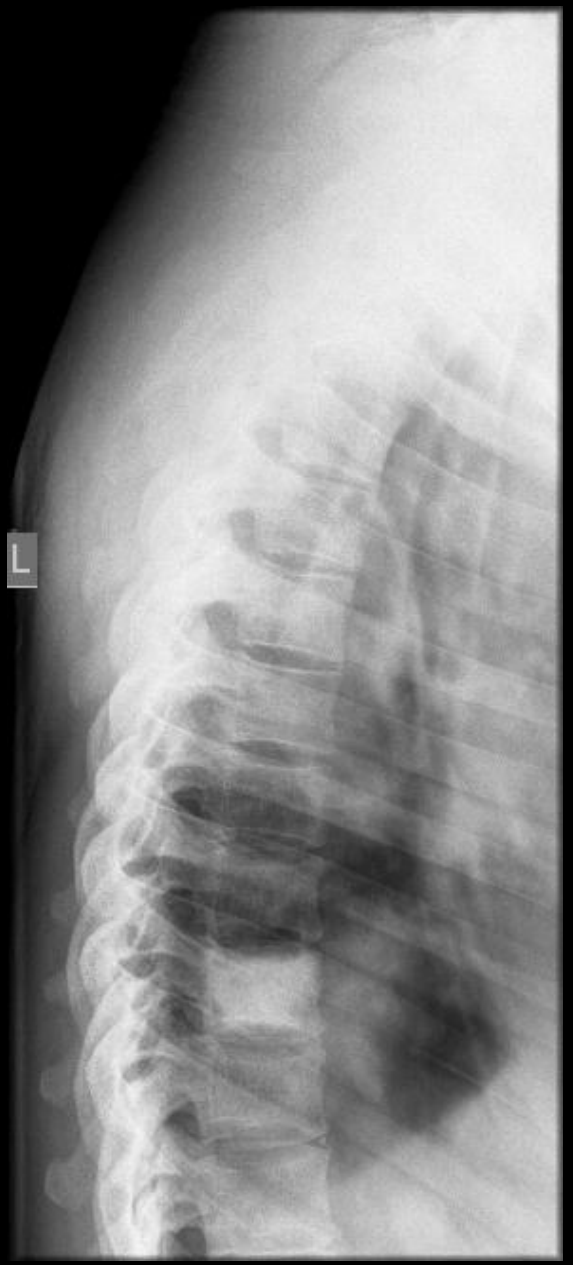
- 8% of people over 55 yrs of age have a peripheral neuropathy
- Monoclonal gammopathy occurs in
  - 1% of those over 25 yrs of age
  - 3% of those over 70 yrs of age
  - Majority are IgG


Polyneuropathy and paraprotein
Demyelinating polyneuropathy (PDN)
Axonal polyneuropathy
IgM
IgG/A
Causal relationship well established
Causal relationship less clear except
•POEMS
•Multiple myeloma
No causal relationship proven except
•Amyloidosis
•Cryoglobulinemia


IgM PDN
IgM MGUS
15-30%
50-67%
Anti-MAG IgM antibodies
Majority
DADS phenotype
Minority
Typical CIDP variant

POEMS

- A.k.a. osteosclerotic myeloma, Crow-Fukase syndrome
- Multisystem disorder
  - **P**olyradiculoneuropathy, **O**rganomegaly, **E**ndocrinopathy, **M**onoclonal plasma cell disorder, **S**kin changes
- NB
  - Not all features of acronym are required
  - Other important features not included in acronym
    - Papilloedema, peripheral oedema, osteosclerotic bone lesions
  - Features may develop over months to years
- Small IgG λ M-protein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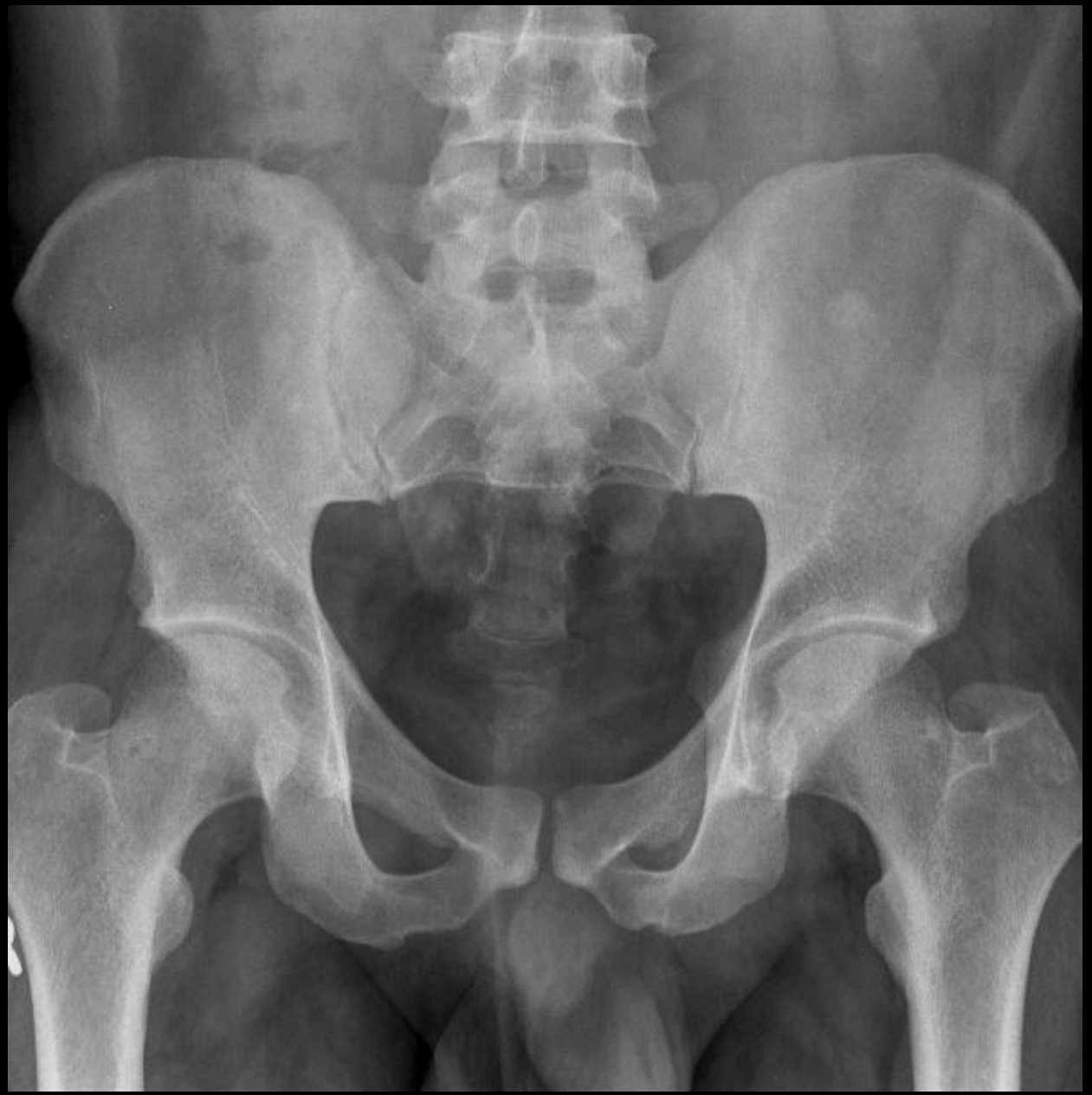


Pure motor axonal

UNCOMMON

- Multifocal motor neuropathy (MMN)
- Pure motor CIDP
- Lead toxicity
- Porphyria (rarely)

- Strategy:
  - Differentiate sensory neuropathy from sensory neuronopathy (SNN)

Pure sensory axonal

In a patient with clinically pure sensory neuropathy:

	Yes	Points
a. Ataxia in the UL or LL	□	+3.1
b. Asymmetrical distribution of sensory loss	□	+1.7
c. Sensory loss not restricted to the lower limbs	□	+2.0
d. At least 1 SNAP absent or 3 SNAP amplitudes < 30% of LLN in UL	□	+2.8
e. Less than 2 nerves with abN motor NCS in the LL	□	+3.1
If >6.5, a diagnosis of SNN is **possible**	Total	
A diagnosis of SNN is **probable** if score is >6.5 and:		
a. The patient has • Onconeural antibodies or a cancer within 5 years • Cisplatin treatment • Sjögren syndrome **OR** b. MRI shows high signal in the posterior column of the spinal cord		

Note: a diagnosis of definite SNN requires DRG biopsy – not recommended!

Camdessanché, Brain, 2009

- Sensory neuronopathy:
  - Paraneoplastic
  - Toxic (e.g. cisplatin, alcohol)
  - Dysimmune
    - Sjögren syndrome, MGUS, SLE
  - Inherited
    - Friedreich's ataxia, mitochondrial disease
  - Idiopathic
- Sensory neuropathy
  - Paraproteinemic
  - Paraneoplastic
  - Sjögren syndrome
  - Vit B12 deficiency
  - HIV
  - CIAP

Pure sensory axonal

CIAP

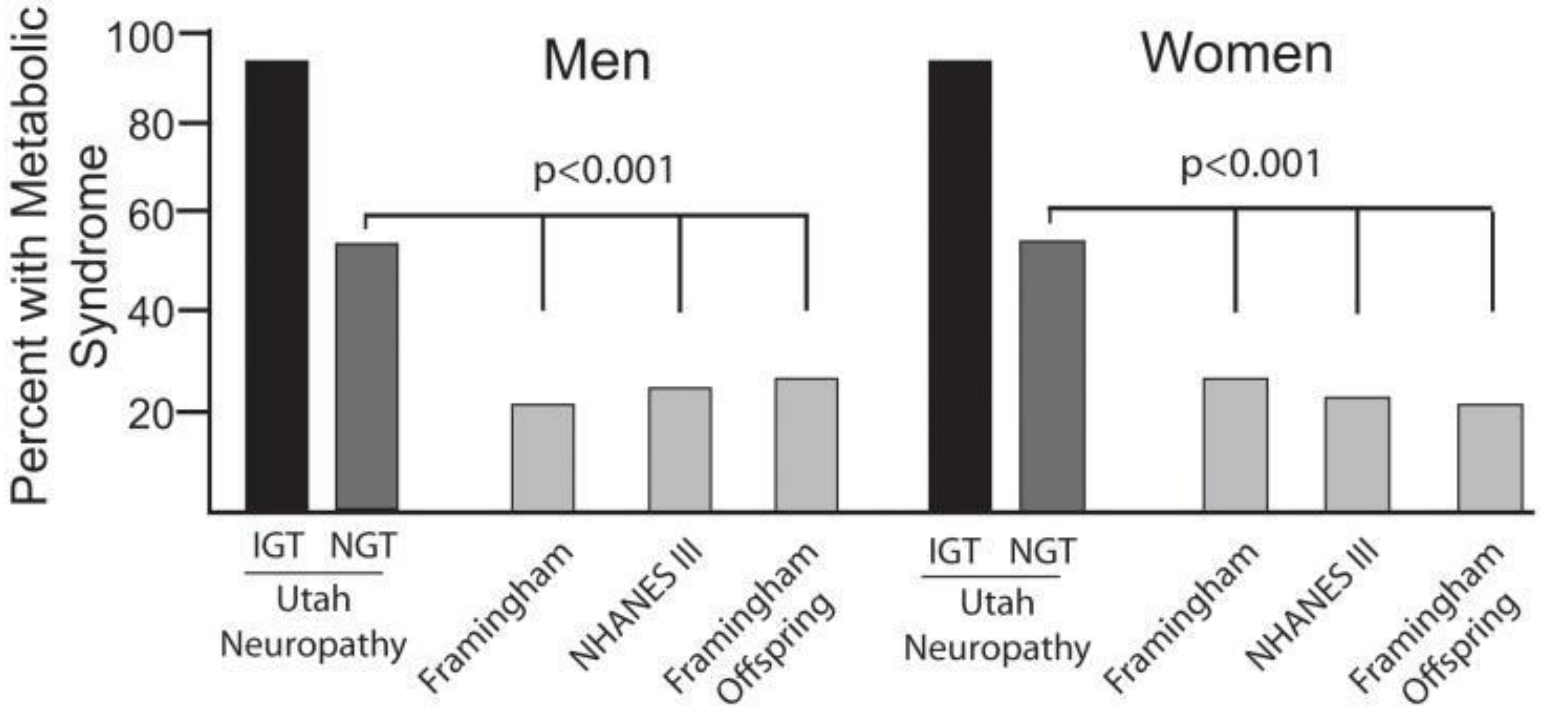
(Chronic idiopathic axonal polyneuropathy))

- Age of onset = 6th decade
- Most patients present with foot discomfort
- Predominantly sensory neuropathy with minimal motor features (usually later in course)
- Progresses slowly
- Diagnosis
  - Above features
  - Length-dependent, axonal sensory or sensorimotor polyneuropathy on NCS
  - Common causes excluded
    - Diabetes, renal failure, alcohol, HIV, Vit B12 deficiency, monoclonal gammopathy
- Common neuropathy in the elderly

Strategy

- Routine (in addition to tests already done)
  - FBC & ESR
  - Renal panel
  - CXR
  - ANA, ANCA
  - Thyroid function
    - Yield 0-3%
  - BP, lipid profile, waist circumference [Smith, J Neurol Sci, 2008]

Sensorimotor axonal



- BP, lipid profile, waist circumference [Smith, J Neurol Sci, 2008]

Sensorimotor axonal

Strategy

- Routine (in addition to tests already done)
  - FBC & ESR
  - Renal panel
  - CXR
  - ANA, ANCA
  - Thyroid function
    - Yield 0-3%
  - BP, lipid profile, waist circumference [Smith, J Neurol Sci, 2008]
- Based on clinical/other clues
  - Onconeural Ab's
  - CT chest (Ca, Sarcoidosis)
  - FDG-PET
  - Anti-Ro &-La Ab's, salivary flow rate, lip biopsy

Sensorimotor axonal

Summary

- Diabetes, alcoholism and HIV causative in 50-80% of cases
- A stepwise approach is preferable to a "shotgun" approach
- If one of the "Big 5" is present, no further investigations (incl NCS) are indicated, provided that the phenotype is typical

Summary

- Diabetes, alcoholism and HIV causative in 50-80% of cases
- A stepwise approach is preferable to a "shotgun" approach
- If one of the "Big 5" is present, no further investigations (incl NCS) are indicated, provided that the phenotype is typical
- In patients with a pure sensory neuropathy, sensory neuronopathy should be considered.
- In patients older than 55 who present with a slowly progressive sensory/sensory predominant axonal PN, limited investigations are indicated.

A few additional comments…

1. Neuropathies in HIV

- Common neuropathies
  - Distal symmetric polyneuropathy (DSP)
  - Inflammatory demyelinating polyneuropathies
- Less common neuropathies
- Rare neuropathies

Inflammatory demyelinating polyneuropathies

- CIDP & AIDP (GBS)

- Both occur with ↑ frequency in HIV-infected
- Clinical features and treatment similar to CIDP and AIDP in HIV-negative

Diffuse infiltrative lymphocytosis syndrome (DILS)

- Any stage of HIV
- Usually diagnosed in presence of:
  - HIV +
  - CD8+ count > 1000
  - Abundant CD8+ cell infiltration in ≥ 3 organs / tissues
- However:
  - Most studies used parotid gland enlargement or sicca symptoms as entry criteria
  - Limited form exists – symmetric or asymmetric painful sensorimotor polyneuropathy or mononeuropathy multiplex

Nutritional neuropathies

- Pyridoxine
  - Frequency of INH-related polyneuropathy 4x higher in TB+HIV+ TB+HIV-ve on standard doses of INH [Marks, Int J STD AIDS, 2009]
  - Many patients prescribed sub-therapeutic Pyridoxine doses (4mg), only ± 10% therapeutic doses (25mg/day) [Maritz, Muscle Nerve, 2010]

Nutritional neuropathies

- Thiamine deficiency
  - More common in HIV infection [Müri, Clin Nutr, 1999;
  - Suspect if:
    - Sensorimotor polyneuropathy, especially sub-acute onset (see earlier slides)
    - Concomitant alcohol abuse
    - Chronic diarrhoea
  - Treat with high-dose intravenous thiamine

Other neuropathies in HIV

- Neuropathy associated with cryoglobulinemia
- Mononeuropathy multiplex
  - Any stage: DILS
  - Early: immune-mediated, self-limiting
  - Late: CMV infection, rapidly progressive

2. Vasculitic neuropathy

Vasculitic neuropathy

- Classification
  - Systemic vasculitides
    - Primary: Wegener's, Churg-Strauss, PAN, MPA
    - Secondary: Rheumatoid vasculitis, SLE, Sjögren syndrome, drug-related, viral infection
  - Non-systemic vasculitic neuropathy
- Diagnosis by means of nerve biopsy
  - Not sufficient to only do serologic markers etc. – will miss non-systemic vasculitis
  - Sensitivity 60-70%

3. Nerve biopsy

Nerve biopsy

- Indications
  - Suspected vasculitic neuropathy
  - Suspected DILS
  - Suspected amyloid neuropathy
- Usually superficial peroneal or sural nerves

Treatment of DSP

- Focused on treatment of neuropathic pain

- Recommendations based on
  - Studies performed specifically in HIV-DSP
  - Inference from diabetic PN data

- Modalities can be classified as:
  1. Proven inefficacy (i.e. not better than placebo)
  2. Proven efficacy
  3. Uncertain
  4. No data

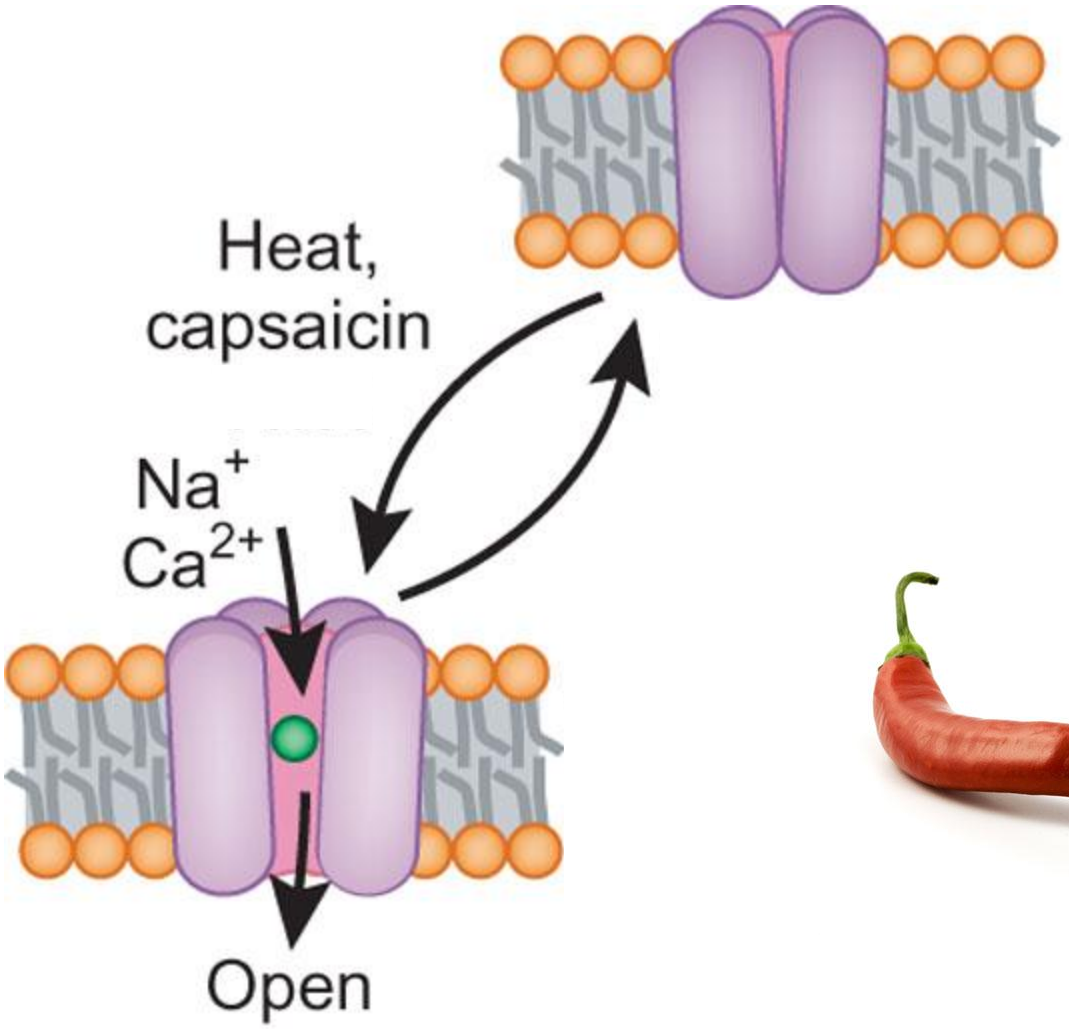
1. Proven inefficacy in HIV-DSP

- **Amitriptyline**
  - 2 RCTs (100mg/day, n=97 and 75mg/day, n=136)
- **Lamotrigine**
  - 2 RCTs (300mg/day, n=42 and 600mg/day, n=227)
  - No difference in primary outcome measures (Gracely pain score)
  - However, subgroup analysis in larger study:
    - Superiority over placebo in ART-DSP stratum for secondary outcome (VAS)
- **Pregabalin**
  - 2 RCTs (300-600mg /day)
- **Acetyl-L-carnitine**
  - 1 RCT (n=90)
- **Mexilitine**
  - 1 RCT (600mg/day, n=98)

2. Proven efficacy in HIV-DSP

- Capsaicin 8% patch on feet
  - 1 RCT , n=307
    - % change NPRS at 12 weeks: Capsaicin -22.8; placebo -10.7 (p=0.0026)

Transient receptor potential vanilloid 1 (TRPV1) channel



2. Proven efficacy in HIV-DSP

- Capsaicin 8% patch on feet
  - 1 RCT , n=307
    - % change NPRS at 12 weeks: Capsaicin -22.8; placebo -10.7 (p=0.0026)
- Smoked cannabis
  - 2 "double blind" RCTs (n=55 and n=56)
  - Both trials of fair quality, but:
    - Study 1: high proportion of unblinding – 92% correctly guessed treatment arm
    - Study 2: lack of measurement of unblinding, **but** all participants had previous experience of smoking cannabis
- Recombinant human NGF
  - 1 RCT
  - Experimental

3. Uncertain

- Gabapantin
  - 1 RCT (n=26; 2400 mg/day)
  - VAS: Gabapentin: -44.1 vs placebo: -29.8; p=not significant
  - Problems:
    - Small number of patients – not sufficiently powered