A diagnostic approach to chronic polyneuropathy

Franclo Henning
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
Focal lesion of a single peripheral nerve
  e.g. carpal tunnel syndrome

Mononeuropathy multiplex
Involvement of multiple peripheral nerves simultaneously or serially
  e.g. vasculitic neuropathy

Polyneuropathy
± symmetric involvement of peripheral nerves
  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
History and examination suggestive of polyneuropathy

1. Clinical features of a demyelinating PN?
<table>
<thead>
<tr>
<th>Axonal PN</th>
<th>Demyelinating PN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory predominant</td>
<td>Motor predominant</td>
</tr>
<tr>
<td>Painful</td>
<td>Usually not painful (but there are exceptions)</td>
</tr>
<tr>
<td>Most = small fibre sensory loss</td>
<td>Large fibre sensory loss</td>
</tr>
<tr>
<td>Exclusively distal weakness (early</td>
<td>Global weakness, but usually distal &gt; proximal</td>
</tr>
<tr>
<td>in course) if present</td>
<td></td>
</tr>
<tr>
<td>Tendon reflexes decreased / absent</td>
<td>Globally decreased / absent reflexes</td>
</tr>
<tr>
<td>distally</td>
<td></td>
</tr>
<tr>
<td>Generally slower progression</td>
<td>Generally faster progression</td>
</tr>
</tbody>
</table>
History and examination suggestive of polyneuropathy

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

## Table 1: Classification of Diabetic Neuropathy Based on Clinical Patterns

<table>
<thead>
<tr>
<th>Symmetry</th>
<th>Type of Neuropathy</th>
<th>Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symmetrical</td>
<td>Diabetic polyneuropathy (DPN)</td>
<td>Lumbosacral (DLRPN)</td>
</tr>
<tr>
<td></td>
<td>Diabetic autonomic neuropathy (DAN)</td>
<td>Thoracic (DTRN)</td>
</tr>
<tr>
<td></td>
<td>Painful distal neuropathy with weight loss, “diabetic cachexia”</td>
<td>Cervical (DCRPN)</td>
</tr>
<tr>
<td></td>
<td>Insulin neuritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypoglycemic neuropathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Polyneuropathy after ketoacidosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Polyneuropathy with glucose impairment*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CIDP in diabetes*</td>
<td></td>
</tr>
<tr>
<td>Asymmetrical</td>
<td>Diabetic radiculoplexus neuropathies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mononeuropathies</td>
<td>Median neuropathy at the wrist (MNW)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ulnar neuropathy at the elbow (UNE)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peroneal neuropathy at the fibular head*</td>
</tr>
<tr>
<td></td>
<td>Cranial neuropathies</td>
<td>Oculomotor palsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abducens palsy</td>
</tr>
</tbody>
</table>
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
  - 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)
<table>
<thead>
<tr>
<th></th>
<th>Alcoholic PN without thiamine deficiency (n=36)</th>
<th>Alcoholic PN with thiamine deficiency (n=28)</th>
<th>Non-alcoholic thiamine deficiency PN (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression</td>
<td>Months to years</td>
<td>Rapid or slow</td>
<td>Most &lt;1 month, some slow</td>
</tr>
<tr>
<td>Associated disorders</td>
<td>-</td>
<td>Wernicke’s &amp; CCF</td>
<td>Wernicke’s &amp; CCF</td>
</tr>
<tr>
<td>Clinical</td>
<td>Sensory-dominant with impaired superficial sensation and pain (all sensory mod. involved in ≈ 33%). 25% unable to walk.</td>
<td>Motor- or sensory-dominant with impaired superficial and deep sensation in majority. Pain in ≈ 50%. About 50% unable to walk.</td>
<td>Motor-dominant with impaired superficial and deep sensation in majority. Pain uncommon. 85% unable to walk.</td>
</tr>
<tr>
<td>NCS</td>
<td>Axonal sensorimotor</td>
<td>Axonal sensorimotor</td>
<td>Axonal sensorimotor, often severe.</td>
</tr>
<tr>
<td>Histopathology</td>
<td>Small-fibre predominant axonal loss.</td>
<td>Mixed</td>
<td>Large-fibre predominant axonal loss.</td>
</tr>
</tbody>
</table>
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)
<table>
<thead>
<tr>
<th></th>
<th>Correlation with lower CD4 count</th>
<th>Correlation with ART (d-drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dana cohort (Schifitto et al, 2002)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Manhattan HIV Brain Bank (Morgello et al, 2004)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Crossroads, WC (Maritz et al, 2010)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
• Diabetes
• Alcohol abuse
• Chronic renal failure
• Toxic (chemotherapy)
• HIV

• One of these known causes and typical phenotype: ADDITIONAL BLOOD TESTS AND ELECTROPHYSIOLOGY 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
       - No known cause present

3. Ancillary tests to exclude common causes

Further investigation guided by electrophysiological studies and clinical features
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: homocysteine, methylmalonic acid (if available)
  • Serum protein electrophoresis & immunofixation
2. Known cause present and typical phenotype?
   - no
     - Atypical phenotype
       - Further investigation guided by electrophysiological studies and age
     - No known cause present
       - 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.
   - Cause identified
     - No further investigations necessary. Treat cause if possible.
Uniform demyelinating

Non-uniform demyelinating

Pure motor axonal

Pure sensory axonal

Sensorimotor axonal

NCS
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)
Non-uniform demyelinating

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

Strategy:
- Exclude diabetes mellitus
- Serum M-protein determination in all patients
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)
- IgM
  - Causal relationship well established

Axonal polyneuropathy
- IgG/A
  - No causal relationship proven except
    - Amyloidosis
    - Cryoglobulinemia
  - Causal relationship less clear except
    - POEMS
    - Multiple myeloma
IgM PDN

50-67%

Anti-MAG IgM antibodies

Minority

Typical CIDP variant

IgM MGUS

15-30%

Majority

DADS phenotype

Typical CIDP variant
POEMS

• A.k.a. osteosclerotic myeloma, Crow-Fukase syndrome
• Multisystem disorder
  • Polyradiculoneuropathy, Organomegaly, Endocrinopathy, Monoclonal plasma cell disorder, Skin 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
Pure motor axonal

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

UNCOMMON
Strategy:
- Differentiate sensory neuropathy from sensory neuronopathy (SNN)
In a patient with clinically pure sensory neuropathy:

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Ataxia in the UL or LL</td>
<td>✅</td>
<td>+3.1</td>
</tr>
<tr>
<td>b. Asymmetrical distribution of sensory loss</td>
<td>✅</td>
<td>+1.7</td>
</tr>
<tr>
<td>c. Sensory loss not restricted to the lower limbs</td>
<td>✅</td>
<td>+2.0</td>
</tr>
<tr>
<td>d. At least 1 SNAP absent or 3 SNAP amplitudes &lt; 30% of LLN in UL</td>
<td>✅</td>
<td>+2.8</td>
</tr>
<tr>
<td>e. Less than 2 nerves with abN motor NCS in the LL</td>
<td>✅</td>
<td>+3.1</td>
</tr>
</tbody>
</table>

If >6.5, a diagnosis of SNN is **possible**

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
Pure sensory axonal

- 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
CIAP
(Chronic idiopathic axonal polyneuropathy))

- Age of onset = 6\textsuperscript{th} 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
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 ineffectiveness (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)

- **Mexilidine**
  - 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