DIAGNOSTIC WORK UP AND THERAPEUTIC MANAGEMENT OF PERIPHERAL NEUROPATHIES

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ASSESSMENT OF A POLYNEUROPATHY

INTRODUCTION

⇒ The diagnosis of peripheral neuropathy is essentially based on the 
   clinical data

⇒ The electrophysiological findings are useful but not indispensable

⇒ Etiologies are numerous: acquired and genetic (the whole medicine…)

⇒ A general clinical exam and a few biological tests are mandatory
TEASING: NORMAL HUMAN NERVE

RANVIER NODE
MULTIFOCAL RANDOMLY DISTRIBUTED DEMYELINATING LESIONS: ACQUIRED
DIFFUSE ACUTE AXONAL LESIONS
To obtain an history

An accurate physical examination

Electrophysiologic tests

Laboratory evaluation
DIAGNOSIS OF A NEUROPATHY

HISTORY

- Past medical history (underlying disease, treatments...?)
- Social history (occupations, behaviour...)
- Origin: country?
- Family history: family tree (consanguinity?)
- Course of the disease:
  acute, subacute, chronic, long standing
  monophasic, progressive, relapsing
ASSESSMENT OF A POLYNEUROPATHY

CLINICAL PRESENTATION

Main symptoms:

- weakness
- sensory disturbances
- walking difficulties

Others:

- cramps, fasciculations, myotonia, tremor
- autonomic symptoms
DIAGNOSIS OF A NEUROPATHY

CLINICAL SYMPTOMS AND SIGNS

(2)

- Sensory-motor

- Pure motor
  - ganglionopathy or neuronopathy

- Pure sensory:
  - « small fiber neuropathy »

- Predominant involvement of the autonomic nervous system
DIAGNOSIS OF A NEUROPATHY

PATTERN OF DISTRIBUTION OF NERVE INVOLVEMENT (3)

- Mononeuropathy
- Multiple mononeuropathy
  (or mutiplex mononeuropathy, mononeuritic multiplex)
- Polyneuropathy (distal, proximal, diffuse)
- Polyradiculopathy, polyradiculoneuropathy
- Plexopathy
  (Radiculopathy)
CLINICAL CLASSIFICATION OF NEUROPATHIES
(traumatic and entrapment N excluded)

- **Sensori-motor or motor**:
  - acute: GBS, AMAN, AMSAN
  - subacute:
    - symmetrical: nutritional, dysimmune (subacute GBS)
    - asymmetrical:
      - multiplex mononeuritis: polyarteritis nodosa, leprosy
  - chronic:
    - symmetrical: proximal and/or distal: toxic, diabetes, hemopathies, CIDP, nutritional
      - distal: CMT, DADS
    - asymmetrical (mono, multiplex neuritis): leprosy, diabetes

- **Sensory**:
  - ataxic and/or sensory (large fibers): ganglionopathy, neuropathy
    - symmetrical: toxic, dysimmune, HSAN
    - asymmetrical: diabetes, paraneo
  - small fibers neuropathies: diabetes, Sjögren...??

- **Autonomic system involvement**:
  - latent
  - severe (or pure):
    - rarely acute: GBS
    - chronic: diabetes, amyloidosis (small fibers)
STEPS TO DIAGNOSE A NEUROPATHY

- To obtain an history
- An accurate physical examination
- Electrophysiologic tests
- Laboratory evaluation
ASSESSMENT OF A POLYNEUROPATHY

ENMG

- Not mandatory
- Helpful

Motor nerve: velocities, distal latencies, F waves, action potentials
Sensory nerve: velocities, action potentials
Electromyogram

AXONAL LOSS-DEMYELINATION
EFNS/PNS CIDP GUIDELINES

European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating CIDP polyradiculoneuropathy: Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society – First Revision

Joint Task Force of the EFNS and the PNS†

Abstract  Background: Consensus guidelines on the definition, investigation, and treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) have been published (J Peripher Nerv Syst 2005; 10:220–228, Eur J Neurol 2006; 13: 326–332). Objectives: To revise these guidelines. Methods: Disease experts, including a representative of patients, considered references retrieved from MEDLINE and Cochrane Systematic Reviews published between August 2004 and July 2009 and prepared statements that were agreed in an iterative fashion.

Recommendations: The Task Force agreed on Good Practice Points to define clinical and electrophysiological diagnostic criteria for CIDP with or without concomitant diseases and investigations to be considered. The principal treatment recommendations were: (i) intravenous immunoglobulin (IVig) (Recommendation Level A) or corticosteroids (Recommendation Level C) should be considered in sensory and motor CIDP; (ii) IVig should be considered as the initial treatment in pure motor CIDP (Good Practice Point); (iii) if IVig and corticosteroids are ineffective, plasma exchange (PE) should be considered (Recommendation Level A); (iv) if the response is inadequate or the maintenance doses of the initial treatment are high, combination treatments or adding an immunosuppressant or immunomodulatory drug should be considered (Good Practice Point); (v) symptomatic treatment and multidisciplinary management should be considered (Good Practice Point).

Key words: chronic inflammatory demyelinating polyradiculoneuropathy, definition, diagnosis, guidelines, treatment
Suggestions for pathophysiological classification of polyneuropathy

1. Demyelinating PNP: two nerves fulfilling definite demyelinating criteria\textsuperscript{a} or one nerve fulfilling definite demyelinating criteria and two nerves fulfilling probable demyelinating criteria\textsuperscript{b} or four nerves fulfilling probable demyelinating criteria

   Criteria for definite demyelination
   (a) $\geq 5.5$ SD$\downarrow$ in sensory/motor CV
   (b) $\geq 8$ SD$\uparrow$ in DML
   (c) $\geq 8$ SD$\uparrow$ in F-wave latency
   (d) Definite conduction block: CMAP amplitude decay of $\geq 50\%$ in UE or $\geq 60\%$ in LE
   (e) Increased temporal dispersion: $\geq 30\%$ $\uparrow$ in negative-peak CMAP duration

   Criteria for probable demyelination
   (a) $\geq 4.5$ SD$\downarrow$ $\leq 5.5$ SD$\downarrow$ in sensory/motor CV
   (b) $\geq 6.0$ SD$\downarrow$ $\leq 8$ SD$\uparrow$ in DML
   (c) $\geq 7.0$ SD$\downarrow$ $\leq 8$ SD$\uparrow$ in F-wave latency
   (d) Probable conduction block: CMAP amplitude decay of $\geq 40\%$ $\leq 50\%$ in UE and $\geq 50\%$ $\leq 60\%$ in LE

2. Axonal PNP: two nerves fulfilling criteria for axonal loss
   Sensory nerves: $\geq 2.5$ SD$\downarrow$ in SNAP amplitude and $\leq 2.5$ SD$\downarrow$ in sensory CV
   Motor nerves: $\geq 2.5$ SD$\downarrow$ in CMAP amplitude and $\leq 2.5$ SD$\downarrow$ in motor CV or $\leq 2.5$ SD$\uparrow$ in DML and consistent EMG findings

3. Mixed PNP: fulfilled criteria for demyelinating PNP and fulfilled criteria for axonal PNP in different nerves

PNP, polyneuropathy; CV, conduction velocity; DML, distal motor latency; CMAP, compound muscle action potential; SNAP, sensory nerve action potential; UE, upper extremity; LE, lower extremity; $\uparrow$, increase; $\downarrow$, decrease.

\textsuperscript{a} At least one of the definite demyelinating criteria a–e fulfilled in each nerve.

\textsuperscript{b} At least one of the probable demyelinating criteria a–d fulfilled in each nerve.
<table>
<thead>
<tr>
<th></th>
<th>LD (ms)</th>
<th>Amp (mV)</th>
<th>VC (m/s)</th>
<th>F (ms)</th>
</tr>
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<tbody>
<tr>
<td>PERONIER P D</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
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<tr>
<td>TIBIAL D</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>MEDIAN D</td>
<td>4.0</td>
<td>2</td>
<td>44</td>
<td>NO</td>
</tr>
<tr>
<td>ULNAIRE D</td>
<td>2.8</td>
<td>5.7</td>
<td>16</td>
<td>35.9</td>
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### CONDUCTION SENSITIVE

<table>
<thead>
<tr>
<th></th>
<th>Amp (µV)</th>
<th>VC (m/s)</th>
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<tbody>
<tr>
<td>SURAL D</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>MEDIAN D</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>RADIAL D</td>
<td>1.5</td>
<td>42.5</td>
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### EMG

<table>
<thead>
<tr>
<th></th>
<th>Fasciculations</th>
<th>Fibrillations</th>
<th>Tracé effort</th>
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<tr>
<td>1er IOD D</td>
<td>0</td>
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NO: not obtained
DIAGNOSIS OF A NEUROPATHY

Fibers:
- motor
- sensory: large and small, large, small ("small fiber neuropathies")

Lesions:
- demyelinating
  - axonal (wallerian degeneration, dying back)
  - mixed
  - nodo-, para-nodopathy
1. Demyelination

2. Wallerian degeneration (axonal process)

3. Dying back axonopathy
ACUTE INFLAMMATORY **DEMYELINATING** POLYRADICULONEUROPATHY

CIDP: most of cases

**NODOPATHIES**

AMAN: acute motor **axonal** neuropathy

AMSAN

CIDP: a few cases
NODO-, PARANODOPATHIES (Uncini)

- May induce: « AXONAL CONDUCTION BLOCK » (CB) (in conditions which affect the excitable axolemma at the nodal region)
- Arrest of nerve conduction
- No dispersion
- May promptly reverse: « reversible conduction failure »
- NC may be slow and improve in parallel with the resolution of CB

necessity of several recordings
STEPS TO DIAGNOSE A NEUROPATHY

- To obtain an history
- An accurate physical examination
- Electrophysiologic tests
- Laboratory evaluation
DIAGNOSIS OF A NEUROPATHY

SCREENING LABORATORY TESTS

- Complete blood count
- Erythrocyte sedimentation rate
- Blood glucose test (impaired glucose tolerance tests)
- (Vitamins?)
- Liver, renal, thyroid function tests
- Serum protein electrophoresis (immunofixation?)
- Genetic testing: DNA

STORE SERUM IN A FREEZER
CSF STUDY IS NOT MANDATORY
(Sjogren’s disease, systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, polyarteritis nodosa, Churg–Strauss disease, Wegener’s granulomatosis, ANCA syndrome) — antinuclear antigen profile, rheumatoid factor, ant-Ro/SSA, anti-La/SSB, antineutrophil cytoplasmic antigen antibody (ANCA) profile, cryoglobulins

**Infectious agents** — Campylobacter jejuni, cytomegalovirus (CMV), hepatitis panel (B and C), HIV tests, Lyme disease tests, herpes viruses tests, West Nile virus tests, cerebrospinal fluid analysis

**Diseases of gut** — antibodies for celiac disease (gliadin, transglutaminase, endomysial), vitamin E level, B vitamin levels; most require endoscopic confirmation with biopsy

**Sarcoidosis** — serum angiotensin converting enzyme (ACE), cerebrospinal fluid analysis including ACE

**Heavy metal toxicity** — blood, urine, hair and nail analysis for heavy metals (arsenic, lead, mercury, thallium)

**Porphyria** — blood, urine, and stool for porphyrins
<table>
<thead>
<tr>
<th>Subtypes and variants</th>
<th>IgG autoantibodies to</th>
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<tbody>
<tr>
<td><strong>Guillain–Barré syndrome</strong></td>
<td></td>
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<tr>
<td>Acute inflammatory demyelinating polyneuropathy (AIDP)</td>
<td>None</td>
</tr>
<tr>
<td>Facial variant: Facial diplegia and paresthesia</td>
<td>None</td>
</tr>
<tr>
<td><strong>Acute motor axonal neuropathy</strong> (AMAN)</td>
<td>GM1, GD1a</td>
</tr>
<tr>
<td>More and less extensive forms</td>
<td></td>
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<tr>
<td>Acute motor–sensory axonal neuropathy (AMSAN)</td>
<td>GM1, GD1a</td>
</tr>
<tr>
<td>Acute motor-conduction-block neuropathy</td>
<td>GM1, GD1a</td>
</tr>
<tr>
<td>Pharyngeal–cervical–brachial weakness</td>
<td>GT1a &gt; GQ1b &gt;&gt; GD1a</td>
</tr>
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</table>

| **Miller Fisher syndrome**                                |                       |
| Incomplete forms                                          |                       |
| Acute ophthalmoparesis (without ataxia)                   | GQ1b, GT1a            |
| Acute ataxic neuropathy (without ophthalmoplegia)         | GQ1b, GT1a            |
| CNS variant: Bickerstaff’s brain-stem encephalitis         | GQ1b, GT1a            |

*Yuki N and Hartung HP  NEJM 2012*
ANTIBODIES IN PERIPHERAL NEUROPATHY

- **MAG** (myelin associated glycoprotein): Monoclonal IgM MGUS Waldenström

- **GANGLIOSIDES**:
  - **GM1**: multifocal motor neuropathy (MMN) AMAN AMSAN GBS
  - **GQ1b**: Miller Fisher syndrome (MFS) CANOMAD (Chronic Ataxic Neuropathy, Ophthalmoplegia, M protein, cold Agglutinins, Disialosys)
  - **Multi**: GD1b, GT1b, GT1a, GD2, GD3 CANOMAD

- **PARANEOPLASIC**: Hu; CV2/CRMP5

- **ANTI PARANODAL – NODAL proteins**: CNT1, Caspr1, NF155, NF186 CIDP (nodoparanodopathy)
DIAGNOSIS OF A NEUROPATHY

Salivary accessory glands (*amyloidosis; Sjogren?)

Skin :
- classical techniques (*amyloidosis?)
- to count intra-epidermous nerve fibers (*small fiber neurop*)

Sensory nerve

Muscle
Salivary gland biopsy
Sjogren
Skin biopsy

*Congo red*

Amyloid deposits

epidermis
dermis

50 μm
Normal skin: intra-epidermic nerve fibers (IENF)

IENF have completely disappeared
POLYNEUROPATHIES

MANAGEMENT

- CAUSES

- SYMPTOMS
According to the causes

- Some patients do not need to be treated immediately → follow up:
  - non malignant dysglobulinemia
  - CIDP
Symptomatic management

- Neuropathic pain
- Rehabilitation
- Outcome measures
Figure 1 : Évolution des nouveaux cas de lèpre de 2000 à 2015 au Burkina Faso.

(Moneuropathies and multiplex mononeuropathies)

The diagnosis of peripheral neuropathy is essentially based on the clinical data.

The electrophysiological findings are useful but not indispensable.

Think of CIDP.

The understanding of lesion mechanisms may be mandatory to decide a specific treatment.