DIAGNOSTIC WORK UP AND THERAPEUTIC MANAGEMENT OF PERIPHERAL NEUROPATHIES

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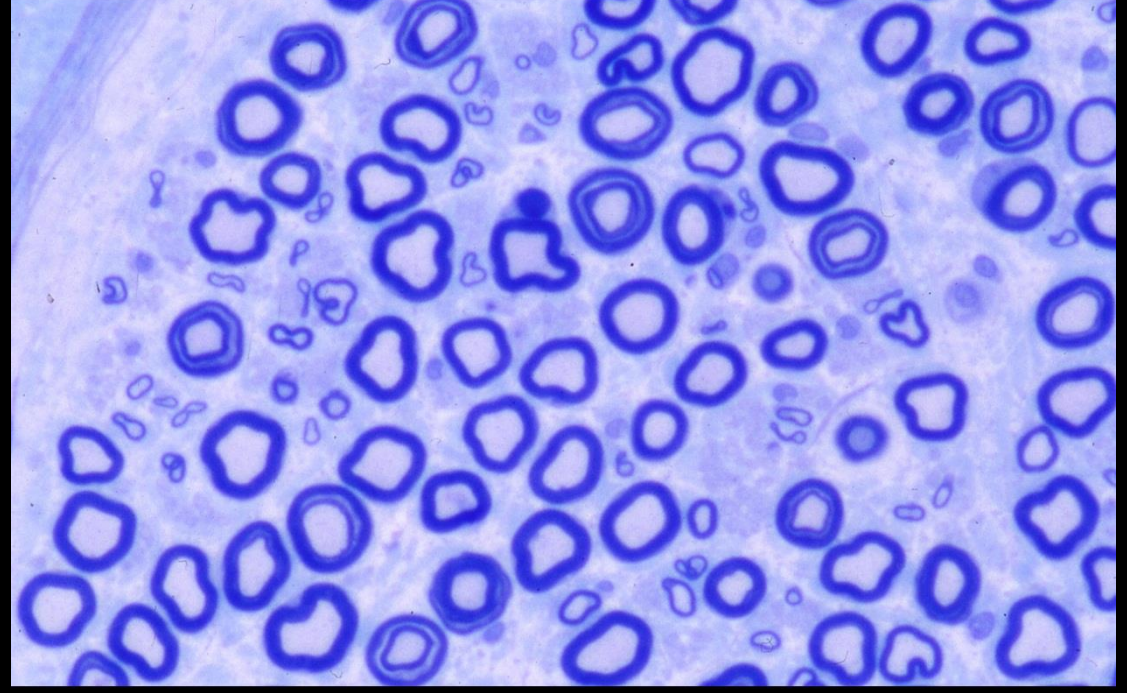
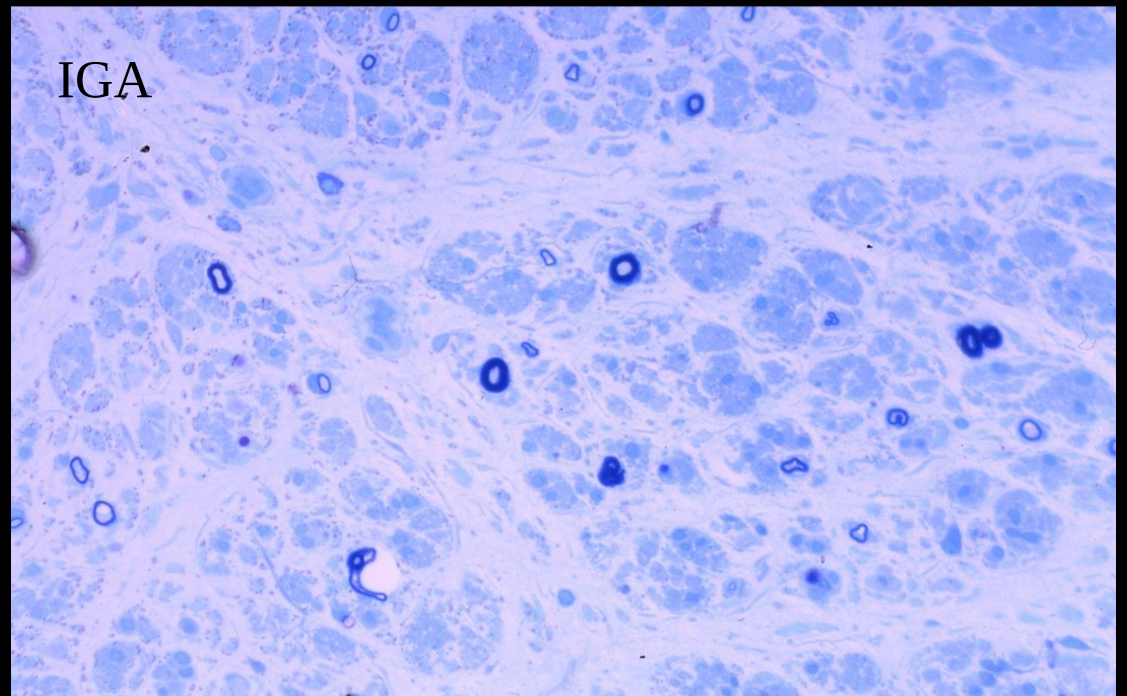
ASSESSMENT OF A POLYNEUROPATHY

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***

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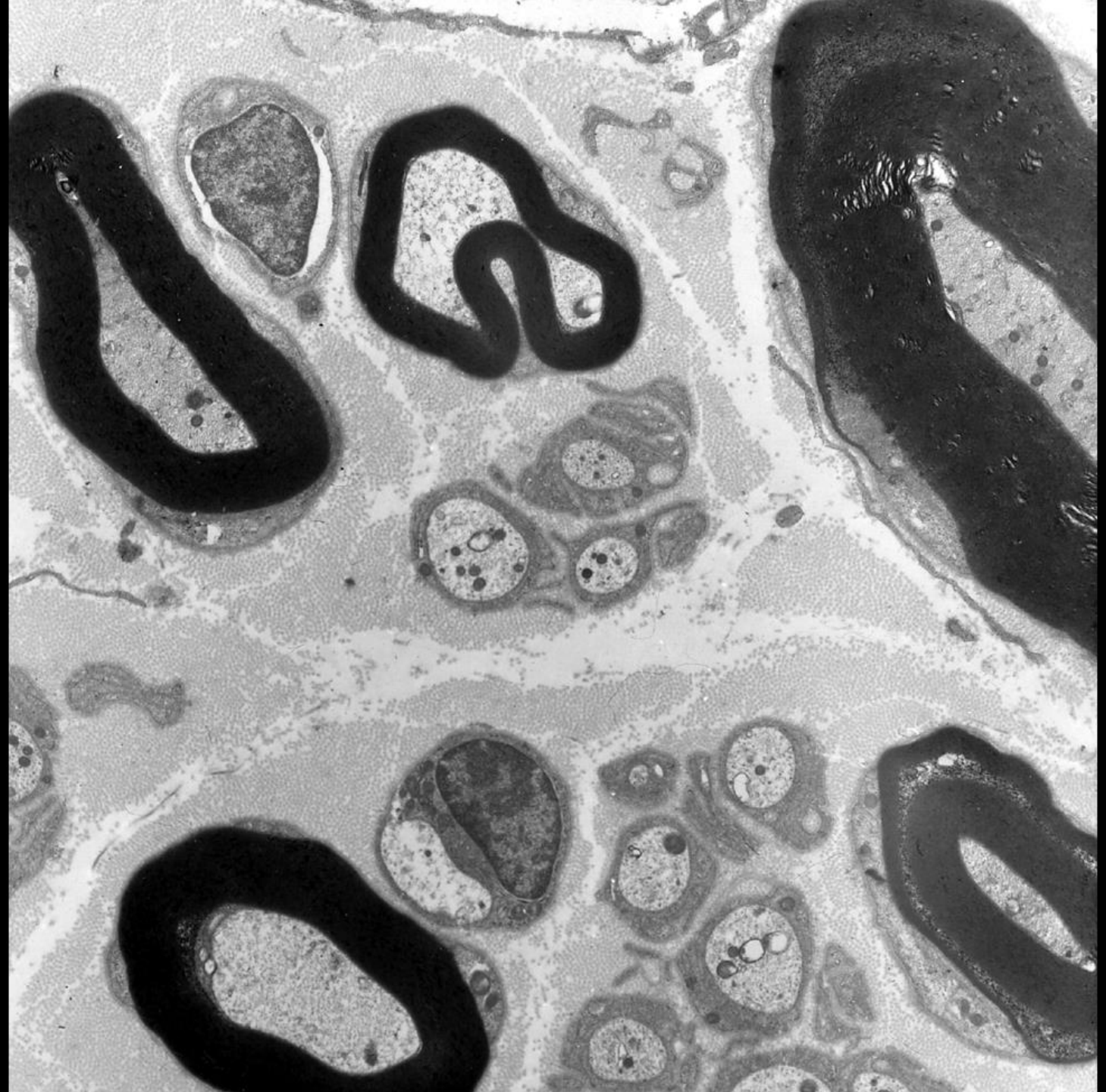
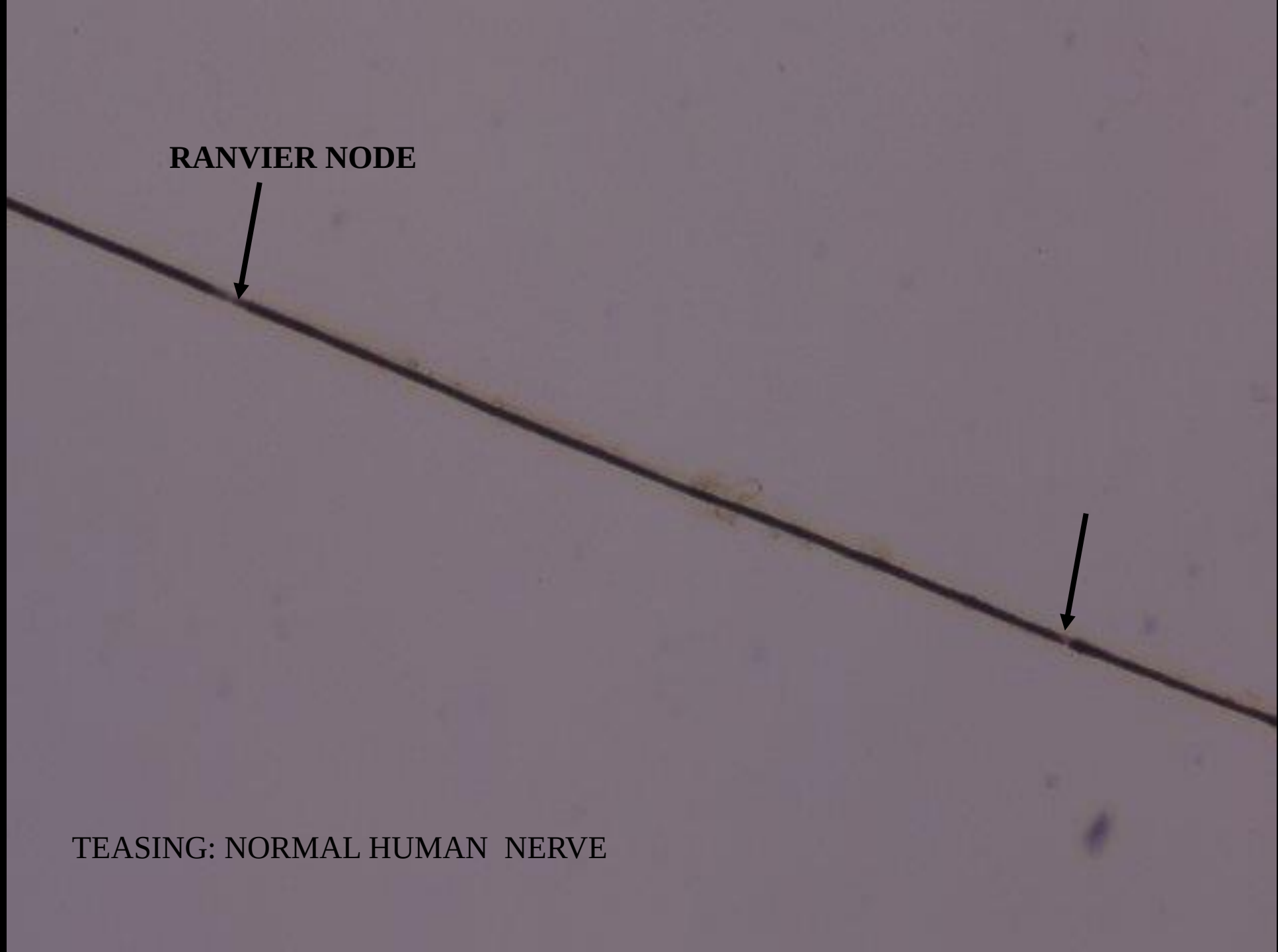
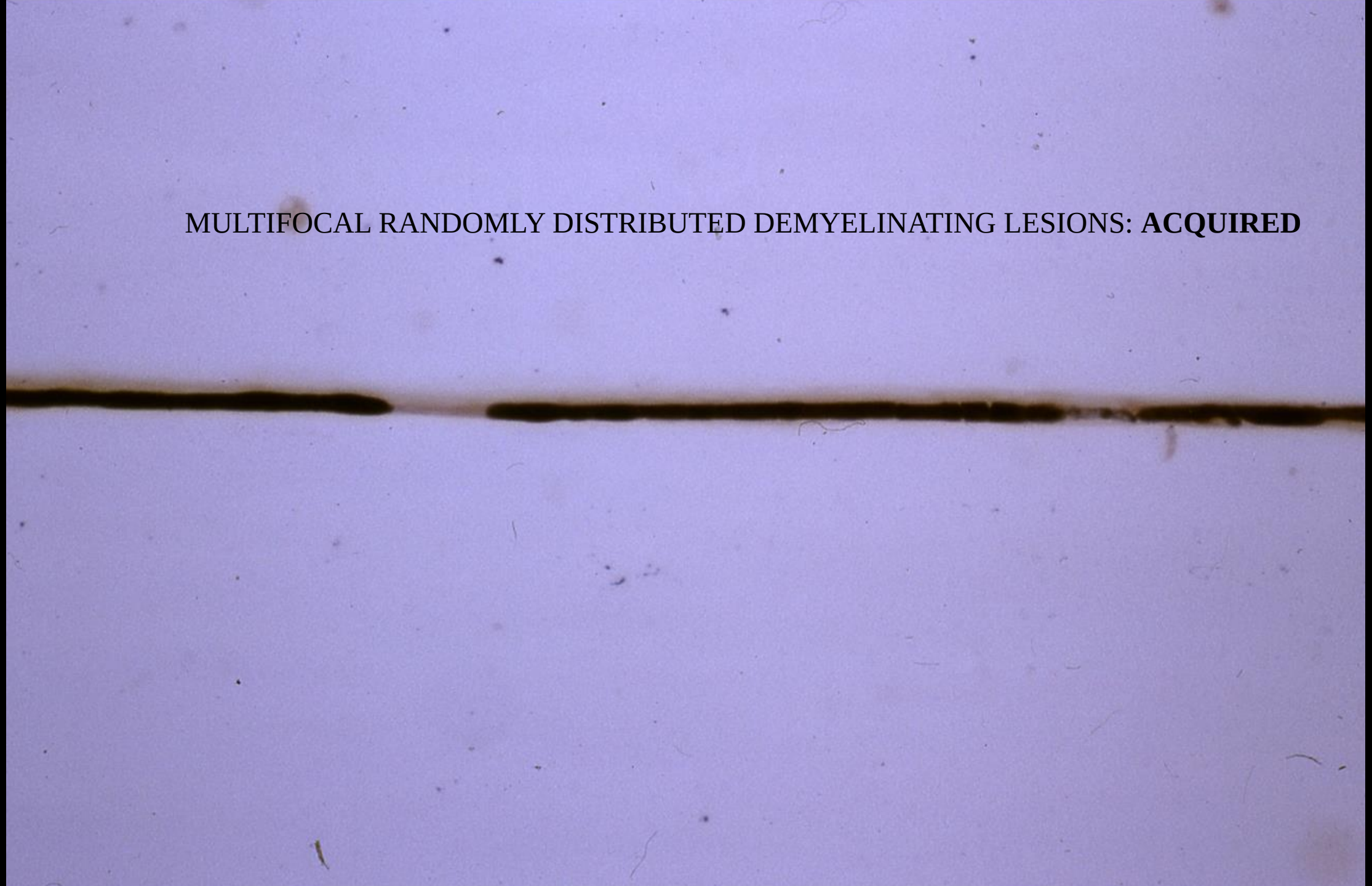




TEASING: NORMAL HUMAN NERVE

MULTIFOCAL RANDOMLY DISTRIBUTED DEMYELINATING LESIONS: **ACQUIRED**



DIFFUSE ACUTE AXONAL LESIONS

STEPS TO DIAGNOSE A NEUROPATHY

- 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, neuornopathy
    - *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

Journal of the Peripheral Nervous System 15:1–9 (2010)

EFNS/PNS CIDP GUIDELINES

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

CIDP

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

TANKISI Clinical neurophysio 2005

Suggestions for pathophysiological classification of polyneuropathy

1. Demyelinating PNP: two nerves fulfilling definite demyelinating criteria[a] or one nerve fulfilling definite demyelinating criteria and two nerves fulfilling probable demyelinating criteria[b] or four nerves fulfilling probable demyelinating criteria
   - Criteria for *definite* demyelination
     - (a) >5.5 SD↓ in sensory/motor CV
     - (b) >8 SD↑ in DML
     - (c) >8 SD↑ in F-wave latency
     - (d) Definite conduction block: CMAP amplitude decay of ≥50% in UE or ≥60% in LE
     - (e) Increased temporal dispersion: ≥30% ↑ in negative-peak CMAP duration
   - Criteria for *probable* demyelination
     - (a) >4.5 SD–<5.5 SD↓ in sensory/motor CV
     - (b) >6.0 SD–<8 SD↑ in DML
     - (c) >7.0 SD–<8 SD↑ in F-wave latency
     - (d) Probable conduction block: CMAP amplitude decay of ≥40–<50% in UE and ≥50–<60% in LE
2. Axonal PNP: two nerves fulfilling criteria for axonal loss
   - Sensory nerves: ≥2.5 SD↓ in SNAP amplitude and ≤2.5 SD↓ in sensory CV
   - Motor nerves: ≥2.5 SD↓ in CMAP amplitude and ≤2.5 SD↓ in motor CV or <2.5 SD↑ 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; ↑, increase; ↓, decrease.

[a] At least one of the definite demyelinating criteria a–e fulfilled in each nerve.

[b] At least one of the probable demyelinating criteria a–d fulfilled in each nerve.

NO: not obtained

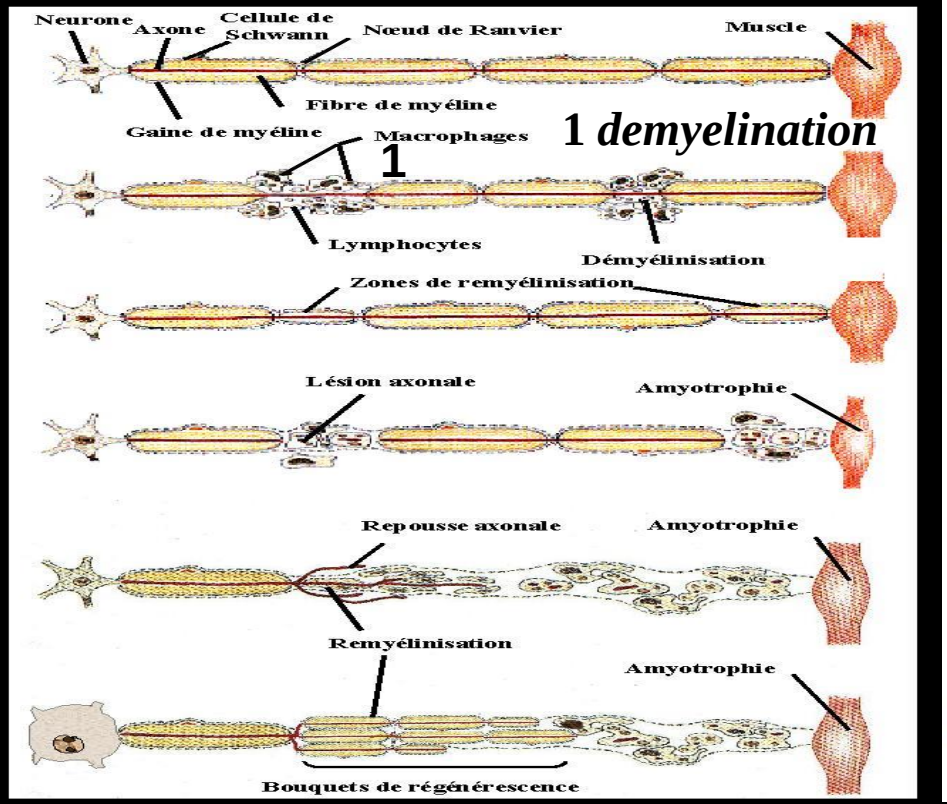
CONDUCTION MOTRICE				
	LD (ms)	Amp (mV)	VC (m/s)	F (ms)
PERONIER P D	NO	NO	NO	NO
TIBIAL D	NO	NO	NO	NO
MEDIAN D	4.0	2	44	NO
ULNAIRE D	2.8	5.7	16	35.9
CONDUCTION SENSITIVE				
		Amp (µV)	VC (m/s)	
SURAL D		NO	NO	
MEDIAN D		NO	NO	
RADIAL D		1.5	42.5	
EMG				
	Fasciculations	Fibrillations	Tracé effort	
1er IOD D	0	0	Neurogène	
Jambier ant D	0	0	Neurogène	
Jambier ant G	0	0	Neurogène	

DIAGNOSIS OF A NEUROPATHY

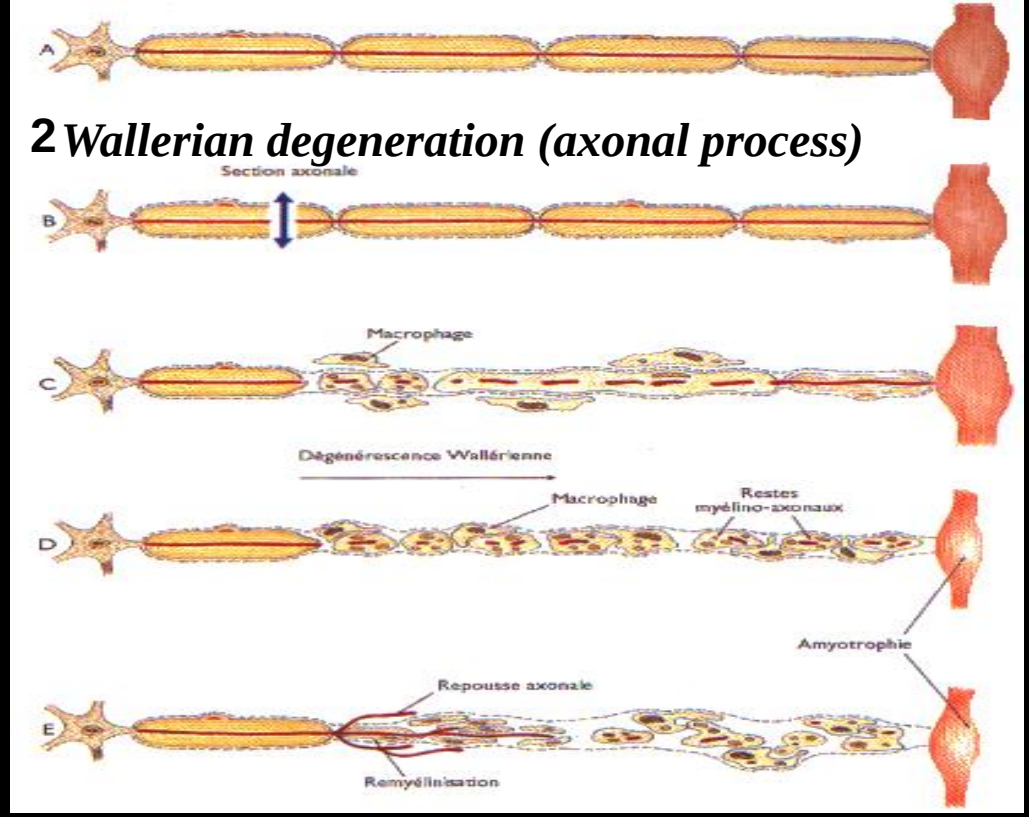
LESIONS

- **Fibers:**
  motor
  sensory: ***large and small, large, small (« small fiber neuropathies »)***

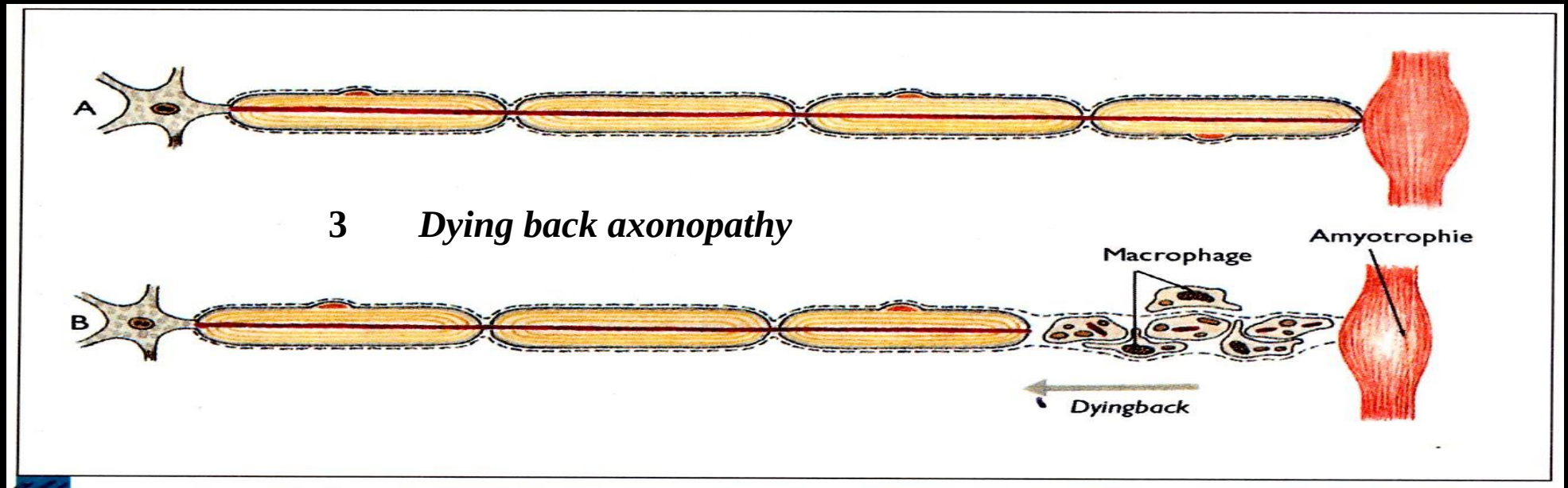
- **Lesions**: ***demyelinating***
  axonal (wallerian degeneration, dying back)
  mixed
  nodo-, para-nodopathy



1 ***demyelination***



2 ***Wallerian degeneration (axonal process)***



ACUTE INFLAMMATORY **DEMYELINATING** POLYRADICULONEUROPATHY

CIDP: most of cases

NODOPATHIES

AM**A**N: acute motor **axonal** neuropathy
AMSAN

CIDP: a few cases

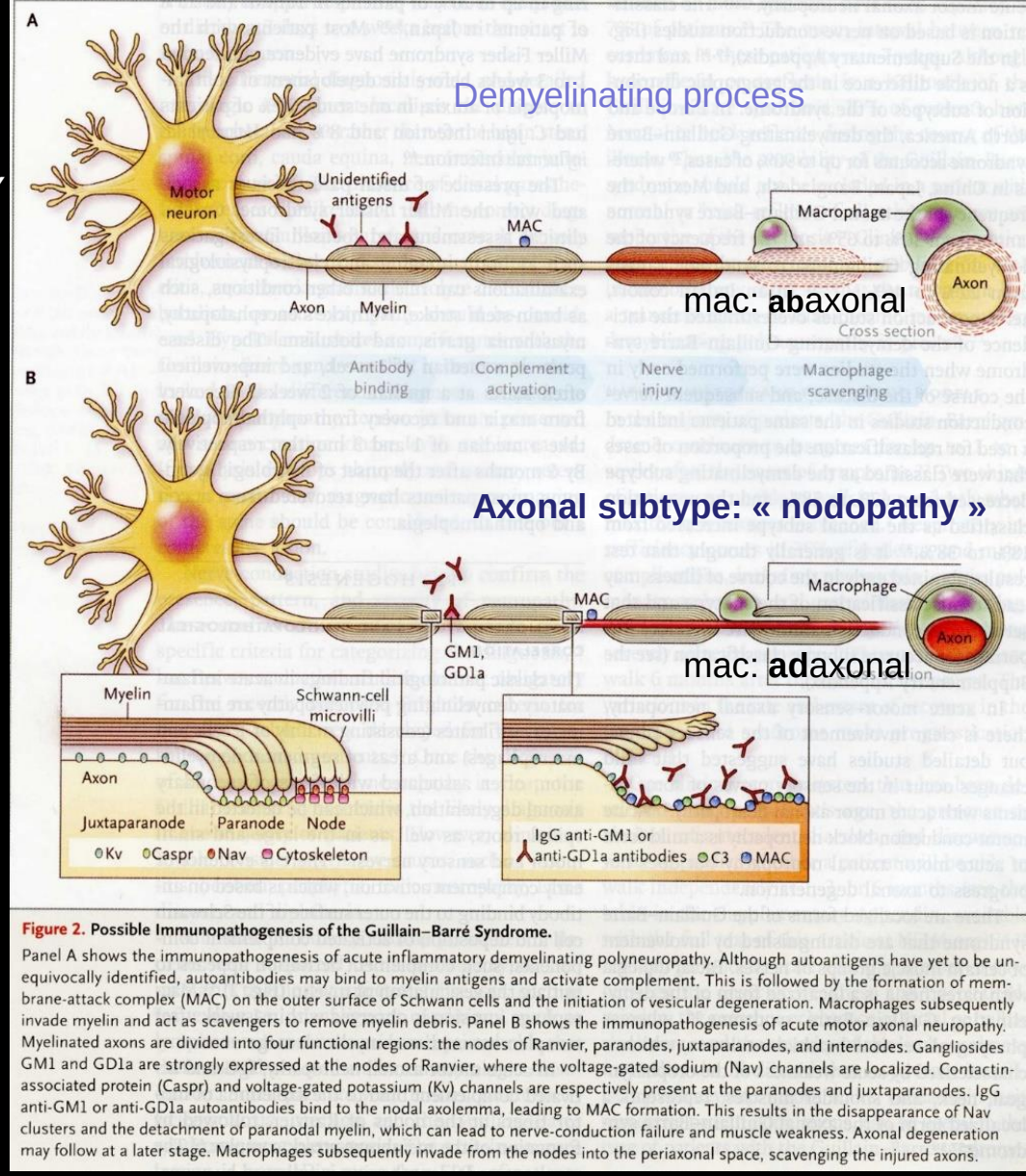


Figure 2. Possible Immunopathogenesis of the Guillain–Barré Syndrome.

Panel A shows the immunopathogenesis of acute inflammatory demyelinating polyneuropathy. Although autoantigens have yet to be unequivocally identified, autoantibodies may bind to myelin antigens and activate complement. This is followed by the formation of membrane-attack complex (MAC) on the outer surface of Schwann cells and the initiation of vesicular degeneration. Macrophages subsequently invade myelin and act as scavengers to remove myelin debris. Panel B shows the immunopathogenesis of acute motor axonal neuropathy. Myelinated axons are divided into four functional regions: the nodes of Ranvier, paranodes, juxtaparanodes, and internodes. Gangliosides GM1 and GD1a are strongly expressed at the nodes of Ranvier, where the voltage-gated sodium (Nav) channels are localized. Contactin-associated protein (Caspr) and voltage-gated potassium (Kv) channels are respectively present at the paranodes and juxtaparanodes. IgG anti-GM1 or anti-GD1a autoantibodies bind to the nodal axolemma, leading to MAC formation. This results in the disappearance of Nav clusters and the detachment of paranodal myelin, which can lead to nerve-conduction failure and muscle weakness. Axonal degeneration may follow at a later stage. Macrophages subsequently invade from the nodes into the periaxonal space, scavenging the injured axons.

Modifié, d'après Yuki N et Hartung HP, N Engl J Med, 2012, 366(24):2294-304

NODO-, PARANODOPATHIES (Uncini)

- May induce : « AXONAL CONDUCTION BLOCK » (CB) (in conditions which affect the excitable axolemma at the nodal region)
- Arrest ot 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 **<u>several</u>** 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

Specialized Laboratory Investigation of Acute and Chronic Polyneuropathy

England JD 2009 AAN, AANEM, AAPMR

(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

ACUTE « PRIMITIVE » DYSIMMUNE NEUROPATHIES

Subtypes and variants		IgG autoantibodies to
Guillain–Barré syndrome		
Acute inflammatory demyelinating polyneuropathy	*(AIDP)*	None
Facial variant: Facial diplegia and paresthesia		None
Acute motor axonal neuropathy	*(AMAN)*	GM1, GD1a
More and less extensive forms		
Acute motor–sensory axonal neuropathy	*(AMSAN)*	GM1, GD1a
Acute motor-conduction-block neuropathy		GM1, GD1a
Pharyngeal–cervical–brachial weakness		GT1a > GQ1b >> GD1a
Miller Fisher syndrome		GQ1b, GT1a
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** : mutifocal 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**

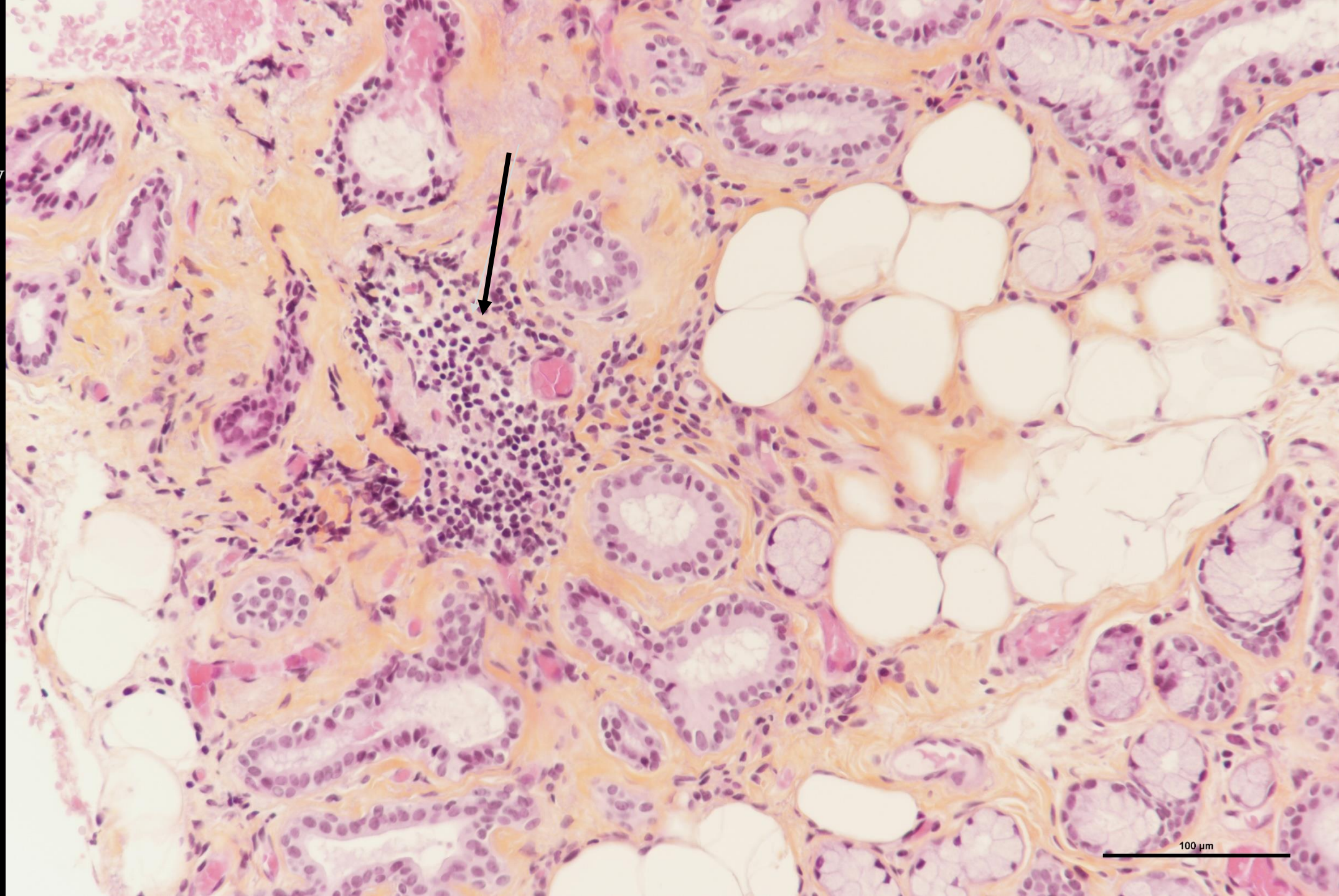
- ANTI PARANODAL – NODAL proteins : **CNT1, Caspr1, NF155, NF186**
  CIDP (nodoparanodopathy)

DIAGNOSIS OF A NEUROPATHY

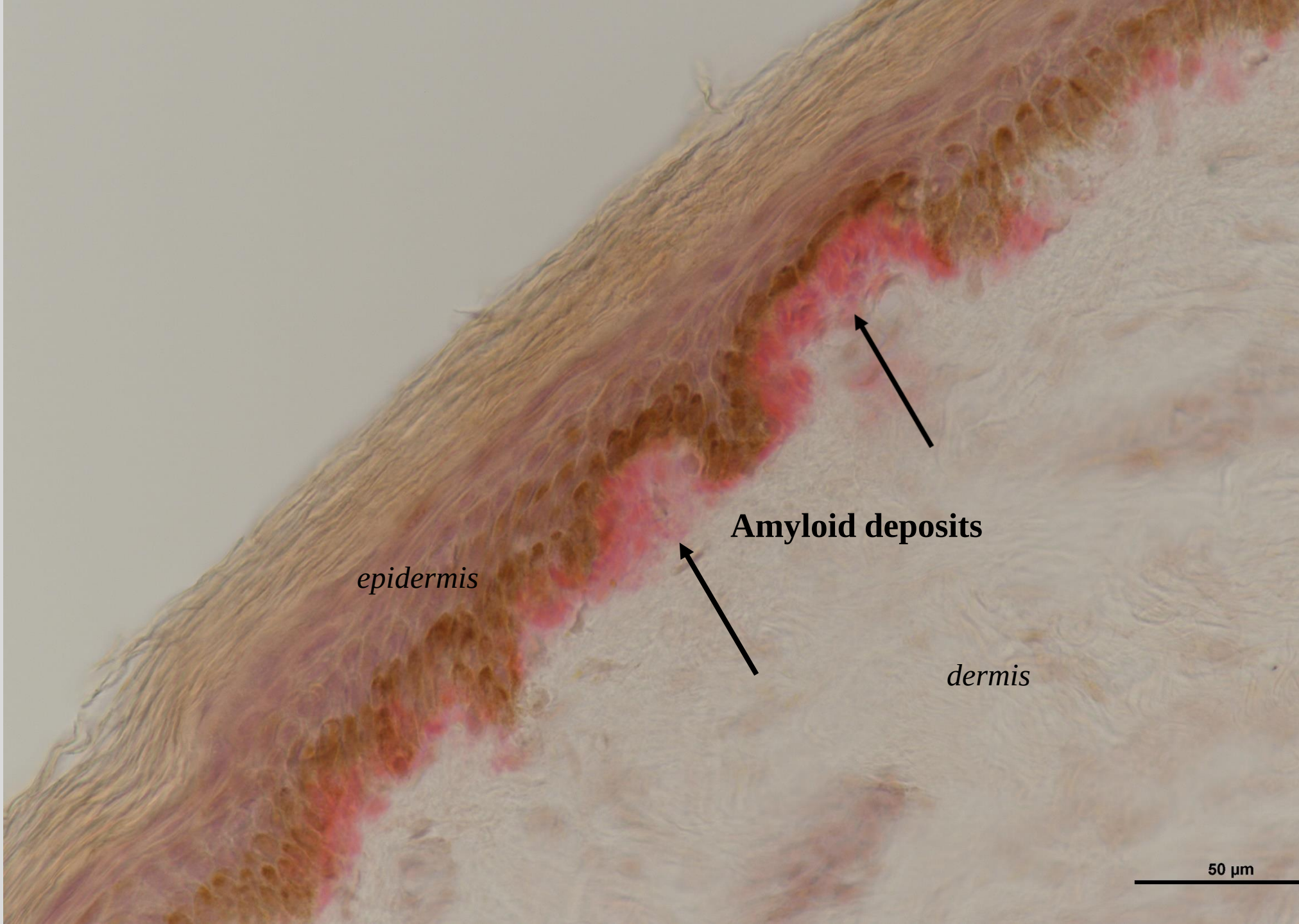
BIOPSIES

- **Salivary accessory glands** *(amyloidosis; Sjogren?)*
- **Skin :**
  - classical techniques *(amyloidosis?)*
  - to count intra-epidermous nerve fibers *(small fiber neurop)*
- **Sensory nerve**
- **Muscle**

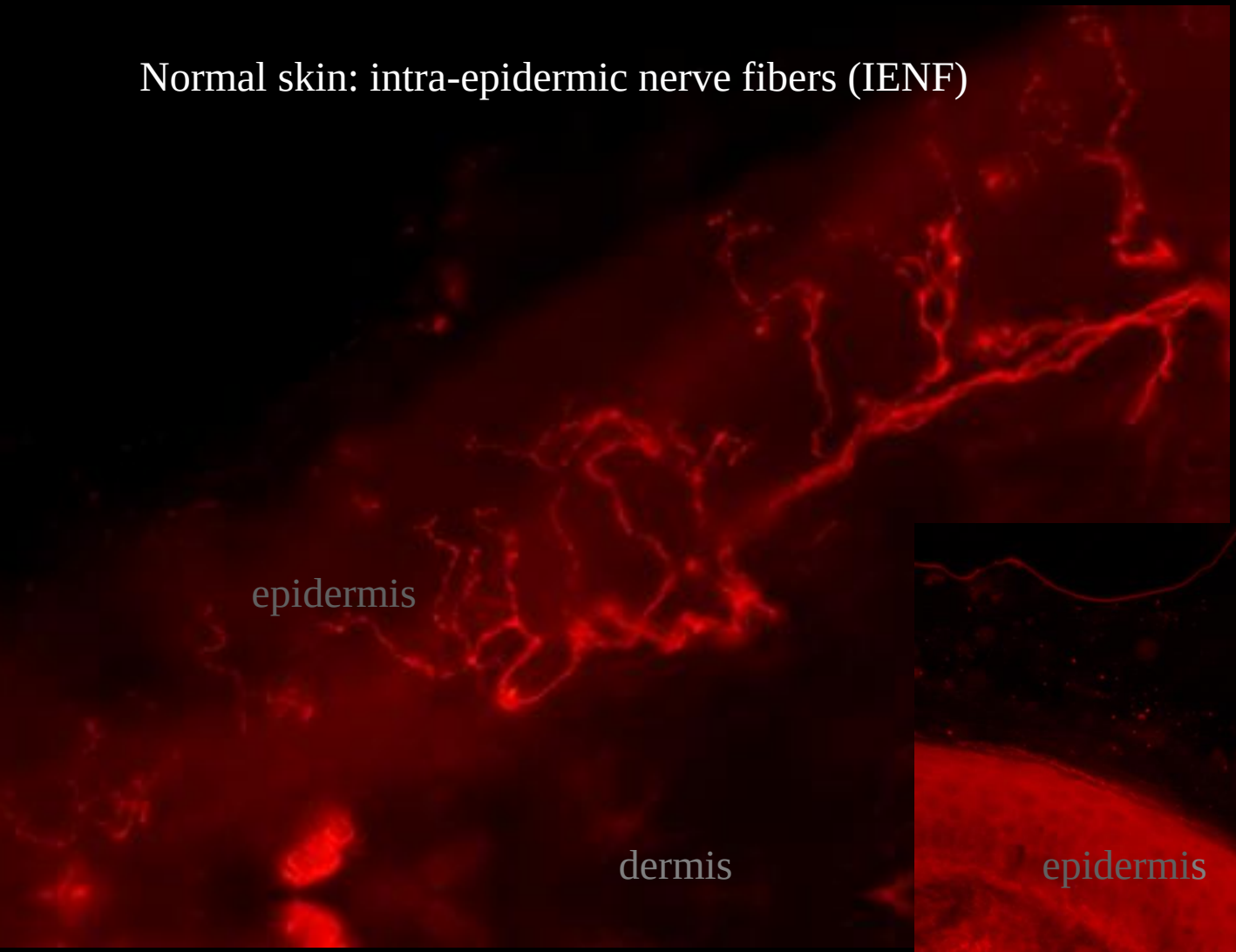
Salivary gland biopsy
Sjogren



Skin biopsy
Congo red



Normal skin: intra-epidermic nerve fibers (IENF)



POLYNEUROPATHIES

MANAGEMENT

- CAUSES
- SYMPTOMS

POLYNEUROPATHIES

MANAGEMENT

- According to the causes

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

POLYNEUROPATHIES

Symptomatic management

- Neuropathic pain
- Rehabilitation
- Outcome measures

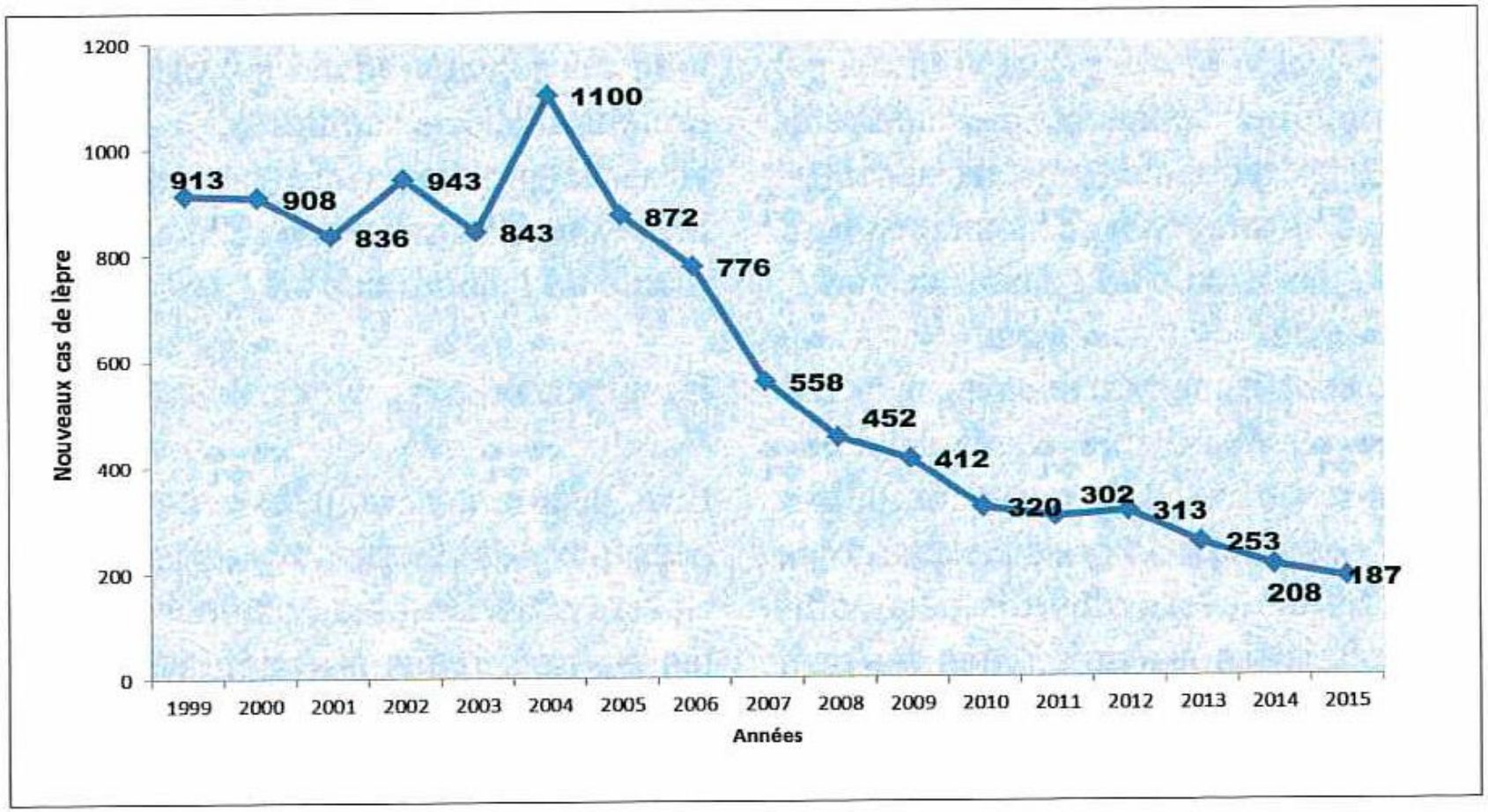


Figure 1 : *Évolution des nouveaux cas de lèpre de 2000 à 2015 au Burkina Faso.*

(Moneuropathies and multiplex mononeuropathies)

Ouedraogo et coll. Bull. de l'ALLF n° 32, Juin 2017, 11-14

ASSESSMENT OF A POLYNEUROPATHY

CONCLUSION

- **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**