CHRU
HÔPITAUX DE TOURS

UNIVERSITÉ
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TOURS

Instituts thématiques

Inserm
Institut national
de la santé et de la recherche médicale

Polyneuropathies Inflammatoires Démyélinisantes Chroniques

NANTES
13 JUIN 2014

PIDC

- Groupe hétérogène de neuropathies:
  - Plutôt Symétriques
  - Sensitives et motrices
  - Acquises
  - Démyélinisantes
- Evolution imprévisible
- Etiologie:
  - dysimmunitaire
  - Médiation inflammatoire

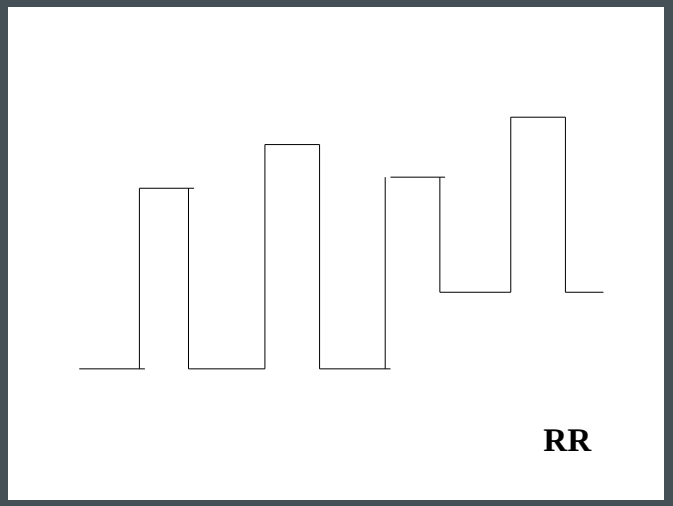
Epidémiologie

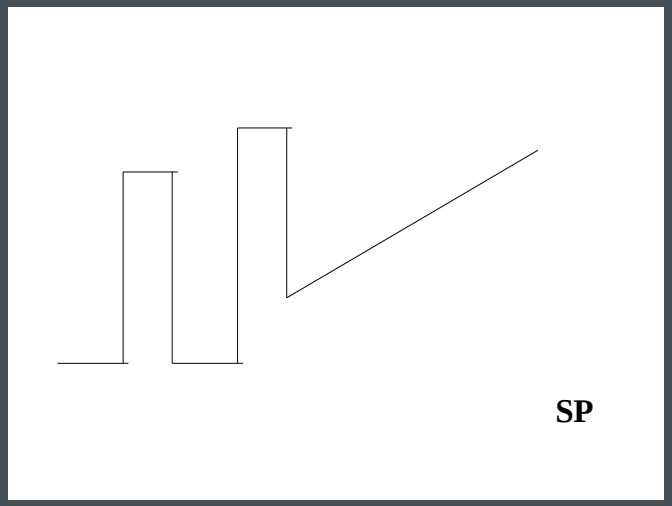
- Neuropathie rare:
  - Prévalence 6-7/100.000 entre 70-80 ans
  - 5% des neuropathies
  - 10-20% des neuropathies chroniques
- Prédominance masculine: 2.3/1
- France:
  - Environ 200 nouveaux cas/an
  - Environ 1500 patients atteints

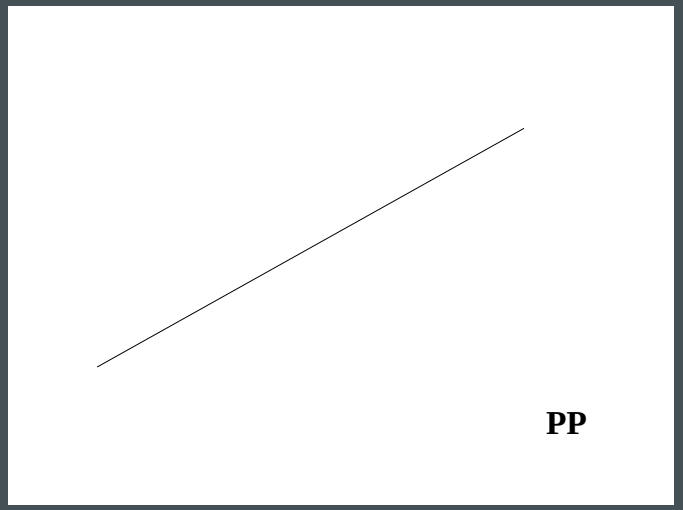
Epidémiologie PIDC

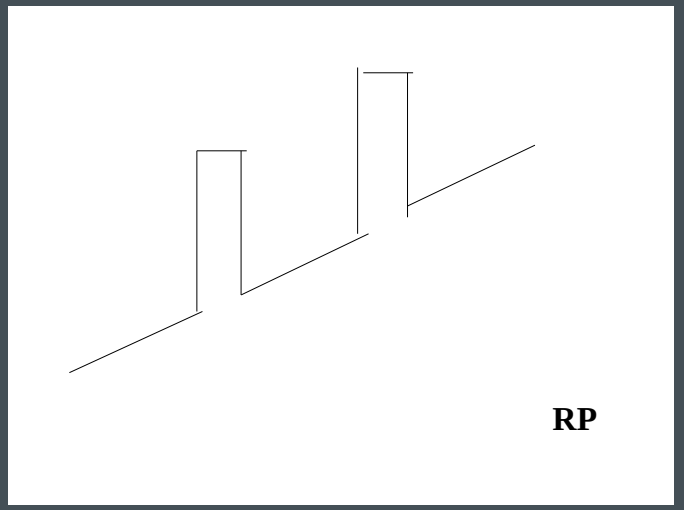
Study region	Diagnostic criteria	Population (year of prevalence)	Prevalence per 100 000 population	Male prevalence per 100 000 population	Female prevalence per 100 000 population	Incidence per 100 000 population	Mean age at onset (years)
Tottori, Japan [2]	AAN [15]	614 725 (1992)	0.8 (0.3–1.9)	1.4 (0.4–3.6)	0.3 (0.01–1.7)	Not reported	Not reported
South-east England [3]	AAN	3 717 638 (1995)	1.2 (0.9–1.7)	Not reported	Not reported	Not reported	54.4
New South Wales, Australia [4]	AAN	5 999 544 (1996)	1.9 (1.5–2.2)	2.2 (1.7–2.8)	1.6 (1.2–2.1)	0.2 (CI not given)	53.5
Vest-Agder, Norway [5]	Albers and Kelly [29]	155 464 (1999)	7.7 (3.2–12.2)	14.7 (7.3–26.4)	5.0 (1.4–12.8)	Not reported	48
Olmsted county, United States of America [8]	Dyck *et al.* and Mayo EMG laboratory[a]	Not available (2000)	8.9 (CI not given)	Not available	Not available	1.6 (CI not given)	Not available
Piemonte, Italy [1]	AAN	4 334 225 (2001)	3.6 (3.0–4.2)	5.0 (4.1–6.1)	2.2 (1.7–2.9)	0.4 (0.2–0.5)	59.6
Japan [6]	AAN INCAT [30] Saperstein [31]	127 655 000 (2005)	1.6 (CI not given)	2.0 (CI not given)	1.2 (CI not given)	0.6 (CI not given)	Not reported
Leicestershire and Rutland, UK [7]	EFNS/PNS AAN	963 600 (2008)	4.8 (3.5–6.3)[b] 2.0 (1.2–3.1)[c]	6.7 (4.6–9.5)[b] 2.9 (1.6–4.9)[c]	2.9 (1.6–4.8)[b] 1.0 (0.3–2.4)[c]	0.7 (0.4 –1.1)[b] 0.4 (0.2–0.6)[c]	52.9
This study	EFNS/PNS [11,12]	3 557 352 (2008)	2.8 (2.3–3.5)	3.8 (3.0–4.9)	1.9 (1.3–2.7)	–	57.7

PIDC: Profil Evolutif

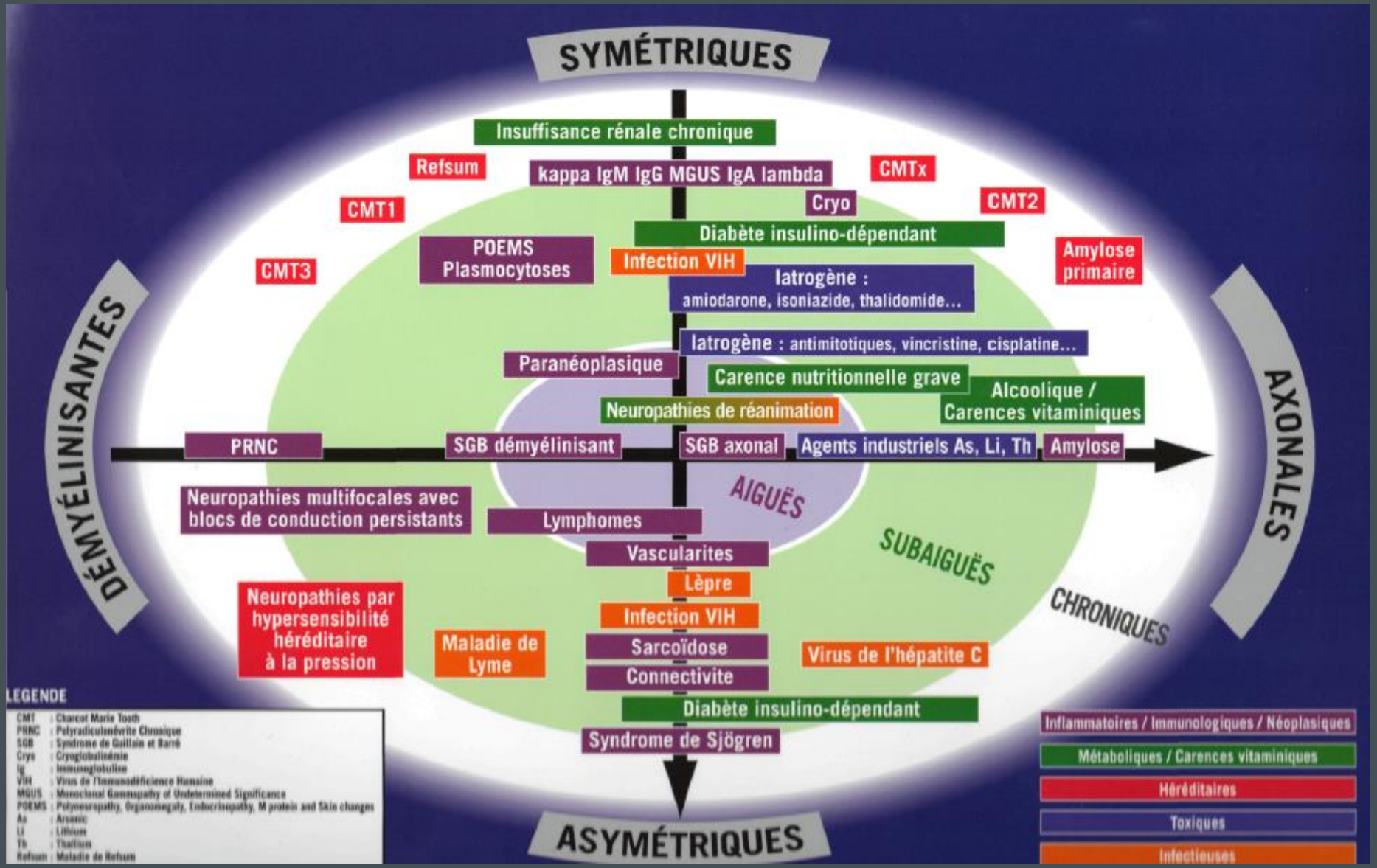








Diagnostics différentiels

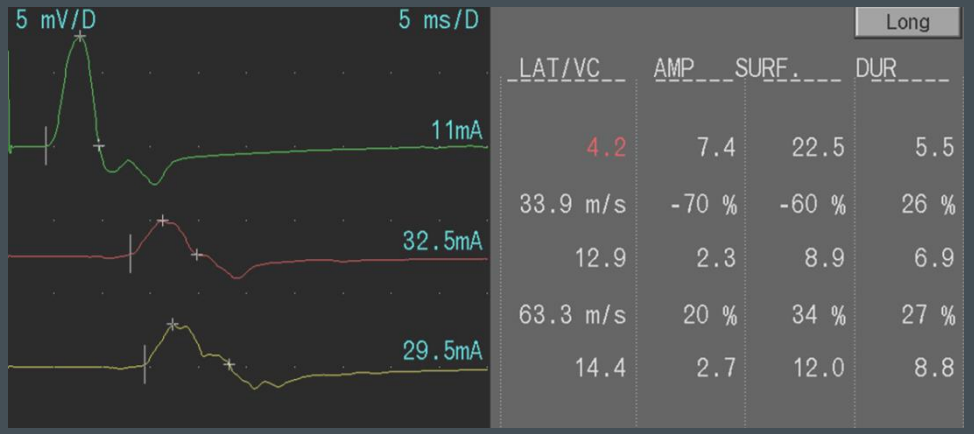


Forme classique de PIDC.

- Déficit moteur prédominant dans 80%:
  - Des 4 membres
  - Symétrique
  - Proximal>Distal
  - Installation progressive sur plus de 2 mois.
- Aréflexie
- Troubles sensitifs:
  - Atteinte profonde> superficielle
- Atteinte possible des nerfs crâniens
- Tremblement postural et d'action possible

PIDC: Examens Complémentaires

- ENMG
- Ponction Lombaire
- Potentiels Evoqués
- Imagerie
- Biopsie nerveuse

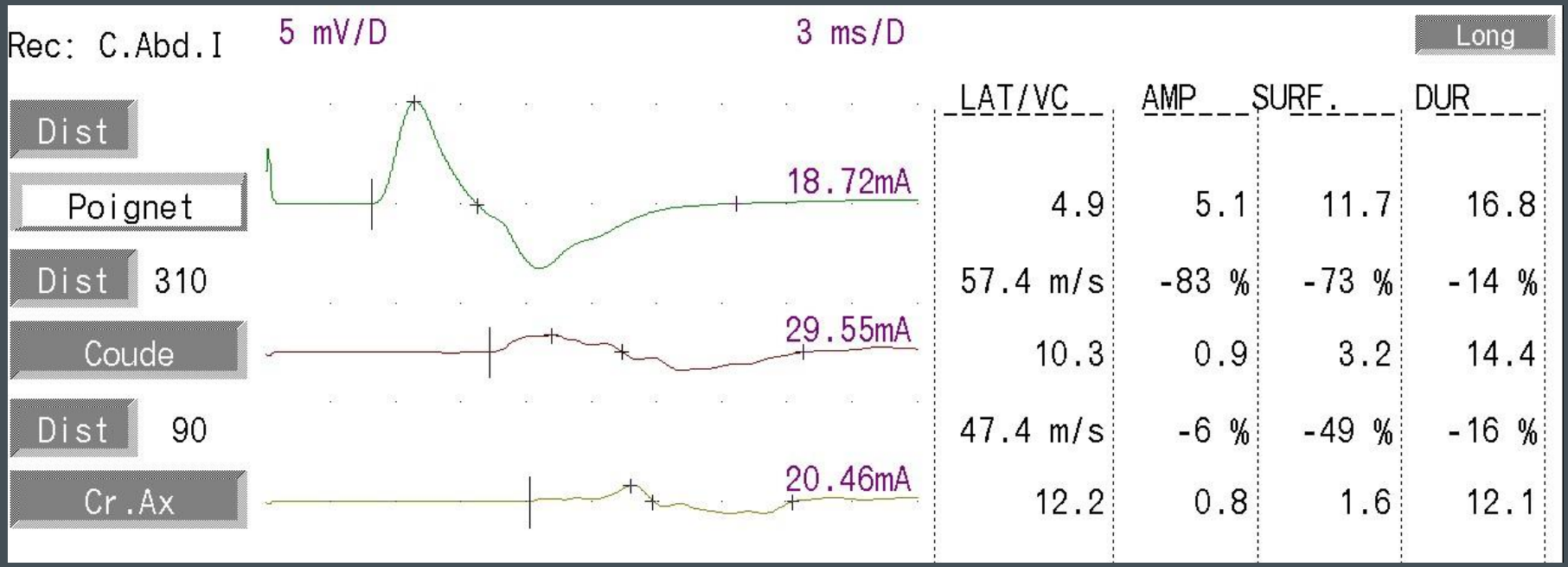


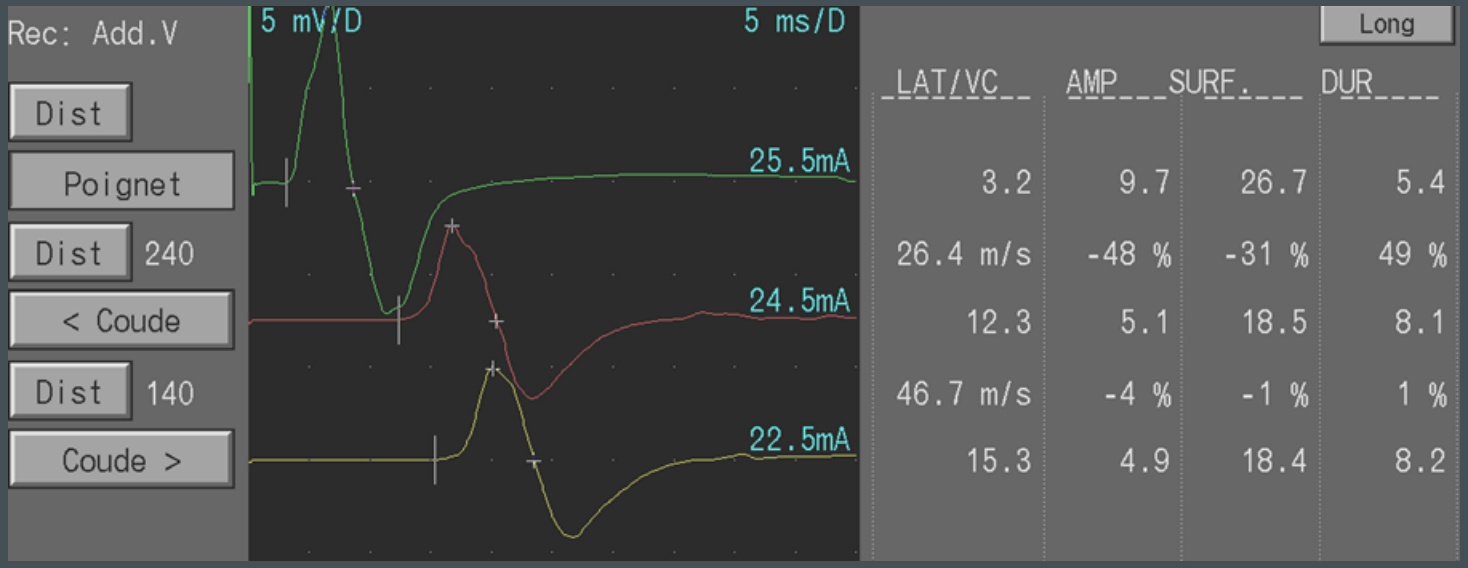
PIDC: Critères ENMG

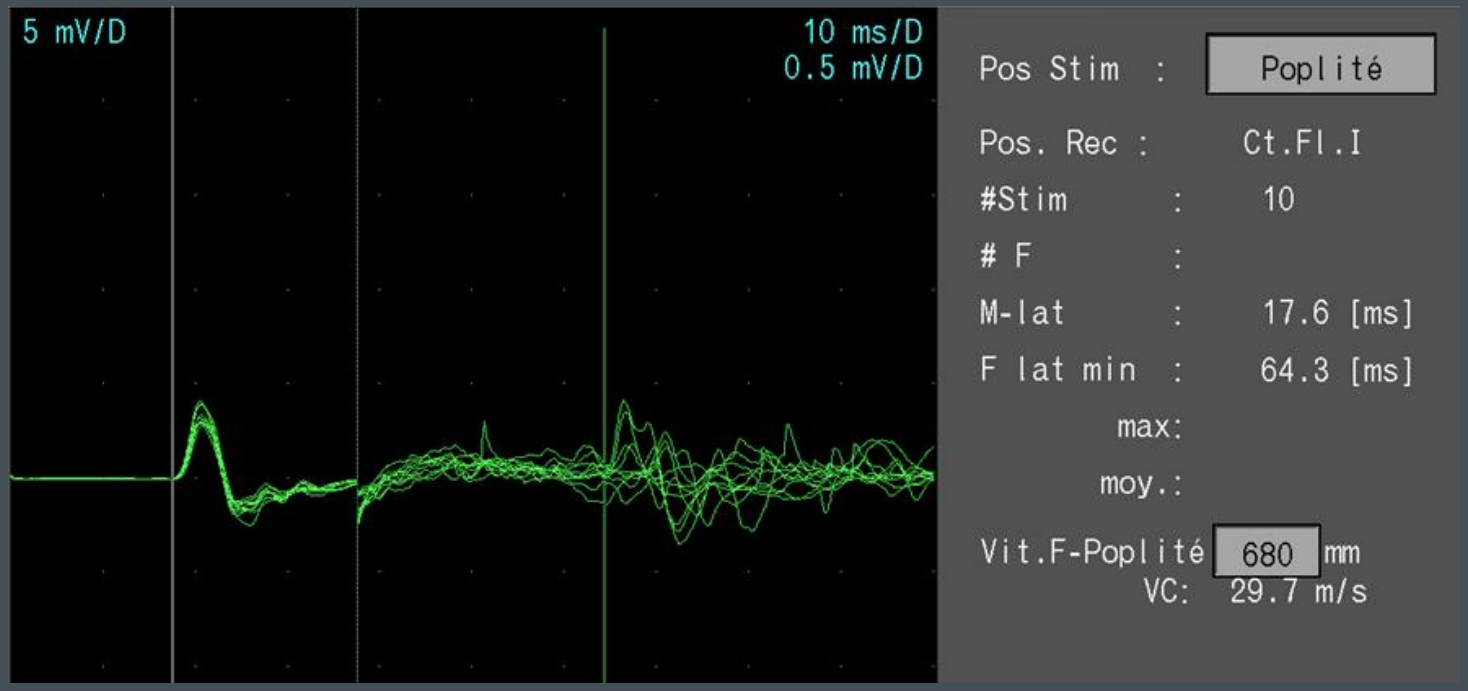
- Présence d'un bloc de conduction
- Diminution des VCM
- Augmentation des latences distales motrices
- Abolition ou Augmentation de la latence des ondes F

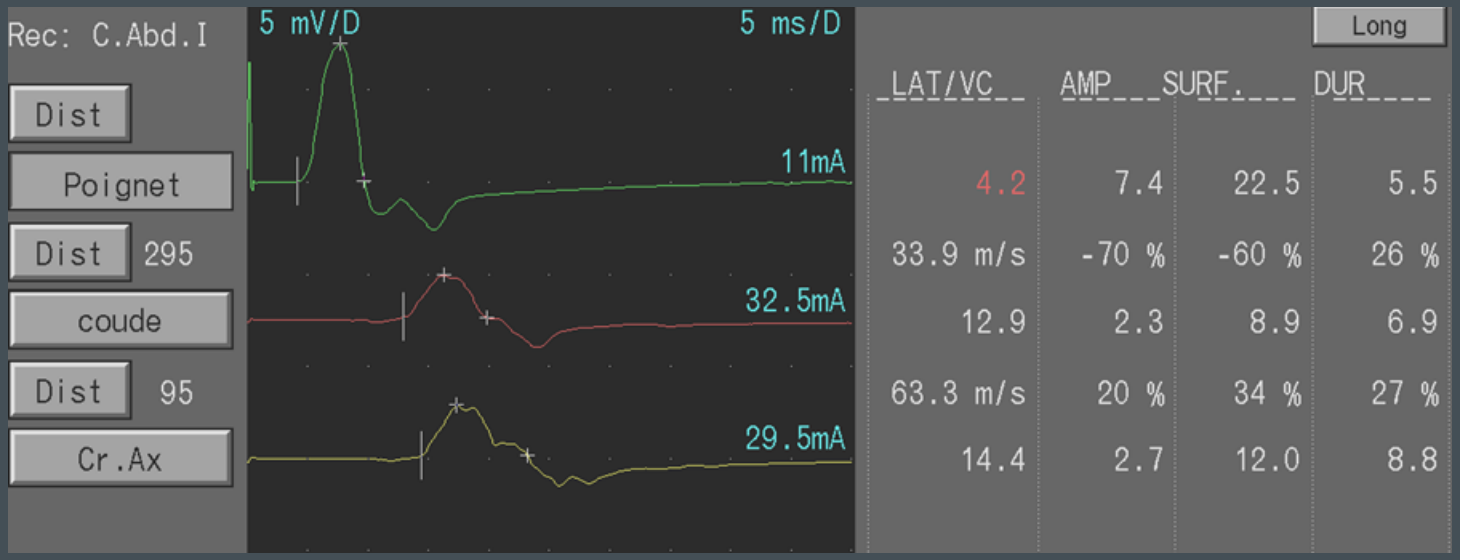
- Pour simplifier:
  - Présence de 4 anomalies avec 2 critères

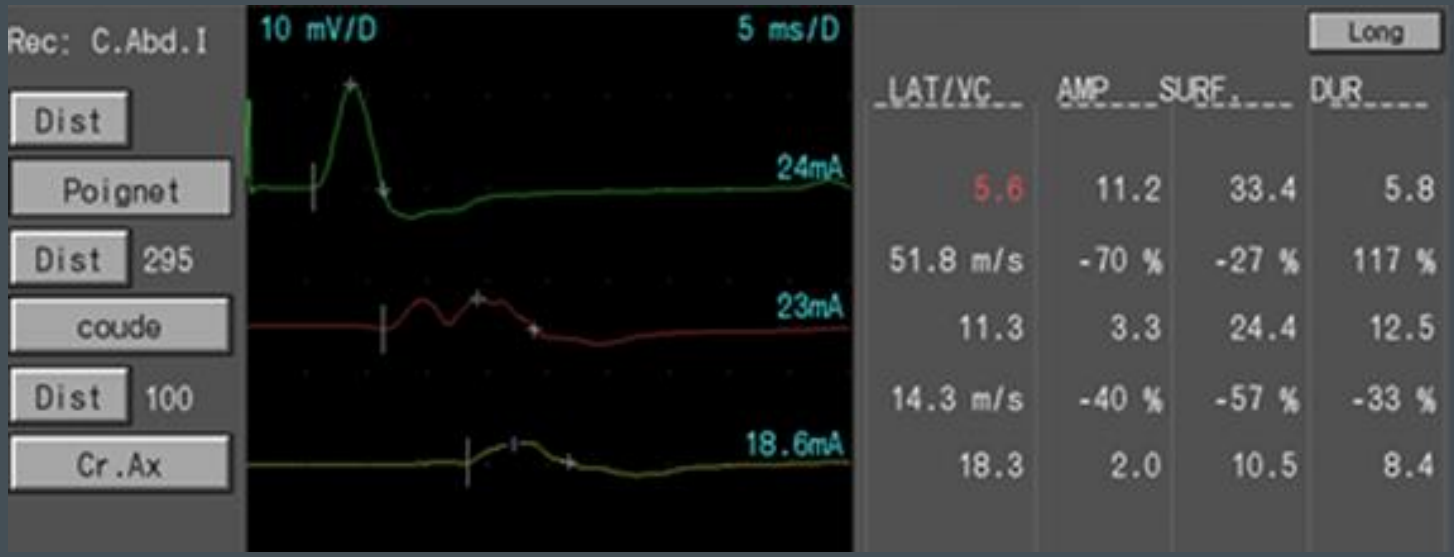
Bloc de conduction




Rec: Add.V
Dist
Poignet
Dist 240
< Coude
Dist 140
Coude >
5 mV/D
5 ms/D
25.5mA
24.5mA
22.5mA
Long
LAT/VC AMP SURF. DUR
3.2 9.7 26.7 5.4
26.4 m/s -48 % -31 % 49 %
12.3 5.1 18.5 8.1
46.7 m/s -4 % -1 % 1 %
15.3 4.9 18.4 8.2


5 mV/D
10 ms/D
0.5 mV/D
Pos Stim : Poplité
Pos. Rec : Ct.Fl.I
#Stim : 10
F :
M-lat : 17.6 [ms]
F lat min : 64.3 [ms]
max:
moy.:
Vit.F-Poplité 680 mm
VC: 29.7 m/s


Rec: C.Abd.I
Dist
Poignet
Dist 295
coude
Dist 95
Cr.Ax
5 mV/D
5 ms/D
11mA
32.5mA
29.5mA
Long
LAT/VC AMP SURF. DUR
4.2 7.4 22.5 5.5
33.9 m/s -70 % -60 % 26 %
12.9 2.3 8.9 6.9
63.3 m/s 20 % 34 % 27 %
14.4 2.7 12.0 8.8


Rec: C.Abd.I
Dist
Poignet
Dist 295
coude
Dist 100
Cr.Ax
10 mV/D
5 ms/D
24mA
23mA
18.6mA
Long
LAT/VC AMP SURF. DUR
5.6 11.2 33.4 5.8
51.8 m/s -70 % -27 % 117 %
11.3 3.3 24.4 12.5
14.3 m/s -40 % -57 % -33 %
18.3 2.0 10.5 8.4

PIDC: Critères ENMG

Table 1 Electrodiagnostic criteria

(1) Definite: at least one of the following
- (a) Motor distal latency prolongation ≥50% above ULN in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome), or
- (b) Reduction of motor conduction velocity ≥30% below LLN in two nerves, or
- (c) Prolongation of F-wave latency ≥30% above ULN in two nerves (≥50% if amplitude of distal negative peak CMAP < 80% of LLN values), or
- (d) Absence of F-waves in two nerves if these nerves have distal negative peak CMAP amplitudes ≥20% of LLN + ≥1 other demyelinating parameter[a] in ≥1 other nerve, or
- (e) Partial motor conduction block: ≥50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parameter[a] in ≥1 other nerve, or
- (f) Abnormal temporal dispersion (> 30% duration increase between the proximal and distal negative peak CMAP) in ≥2 nerves, or
- (g) Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in ≥1 nerve (median ≥ 6.6 ms, ulnar ≥ 6.7 ms, peroneal ≥ 7.6 ms, tibial ≥ 8.8 ms)[b] + ≥1 other demyelinating parameter[a] in ≥1 other nerve

(2) Probable
- ≥30% amplitude reduction of the proximal negative peak CMAP relative to distal, excluding the posterior tibial nerve, if distal negative peak CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parameter[a] in ≥1 other nerve

(3) Possible
- As in (1) but in only one nerve

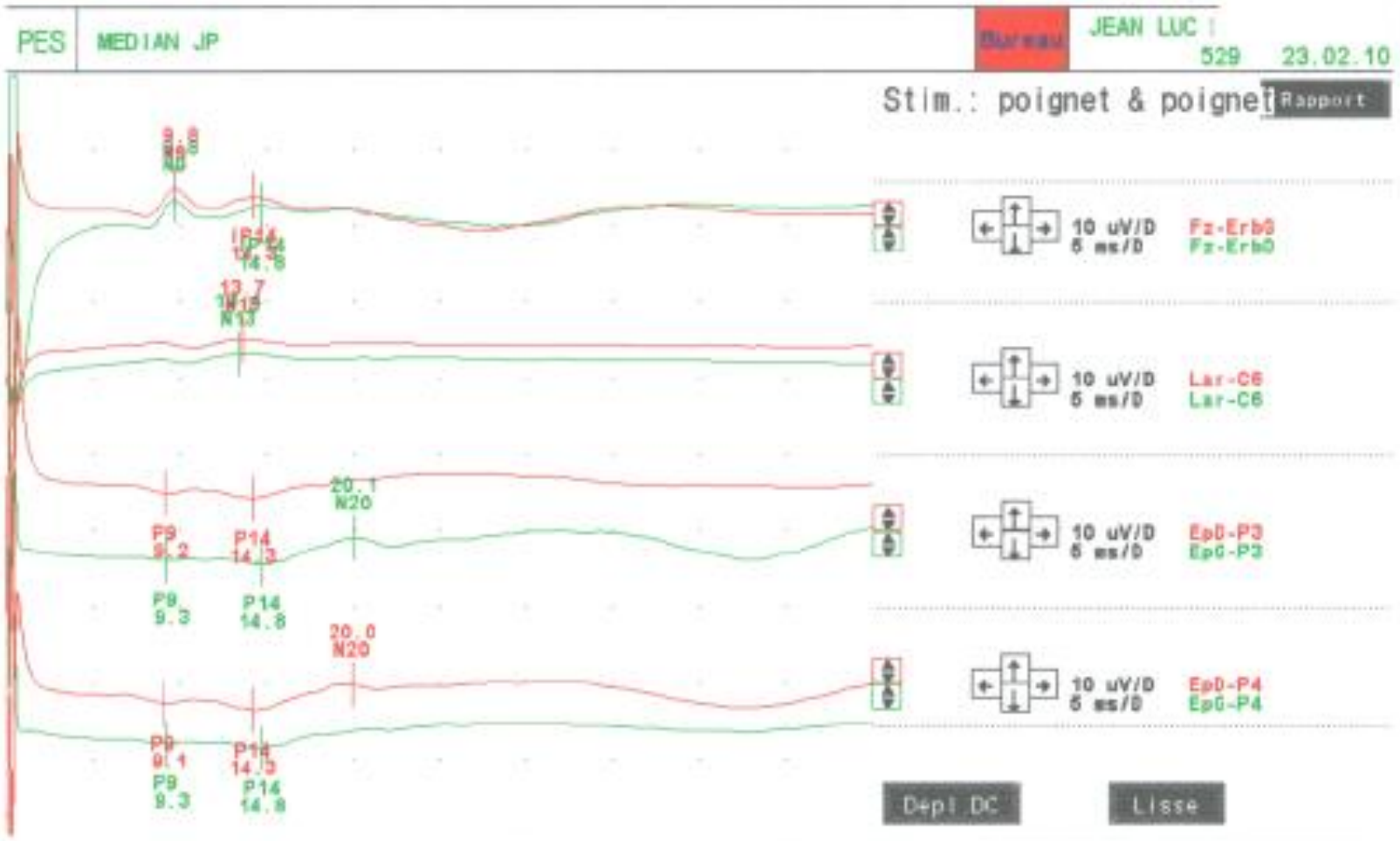
To apply these criteria, the median, ulnar (stimulated below the elbow), peroneal (stimulated below the fibular head), and tibial nerves on one side are tested. If criteria are not fulfilled, the same nerves are tested at the other side, and/or the ulnar and median nerves are stimulated bilaterally at the axilla and at Erb's point. Motor conduction block is not considered in the ulnar nerve across the elbow and at least 50% amplitude reduction between Erb's point and the wrist is required for probable conduction block. Temperatures should be maintained to at least 33°C at the palm and 30°C at the external malleolus (good practice points).

CMAP, compound muscle action potential; ULN, upper limit of normal values; LLN, lower limit of normal values.

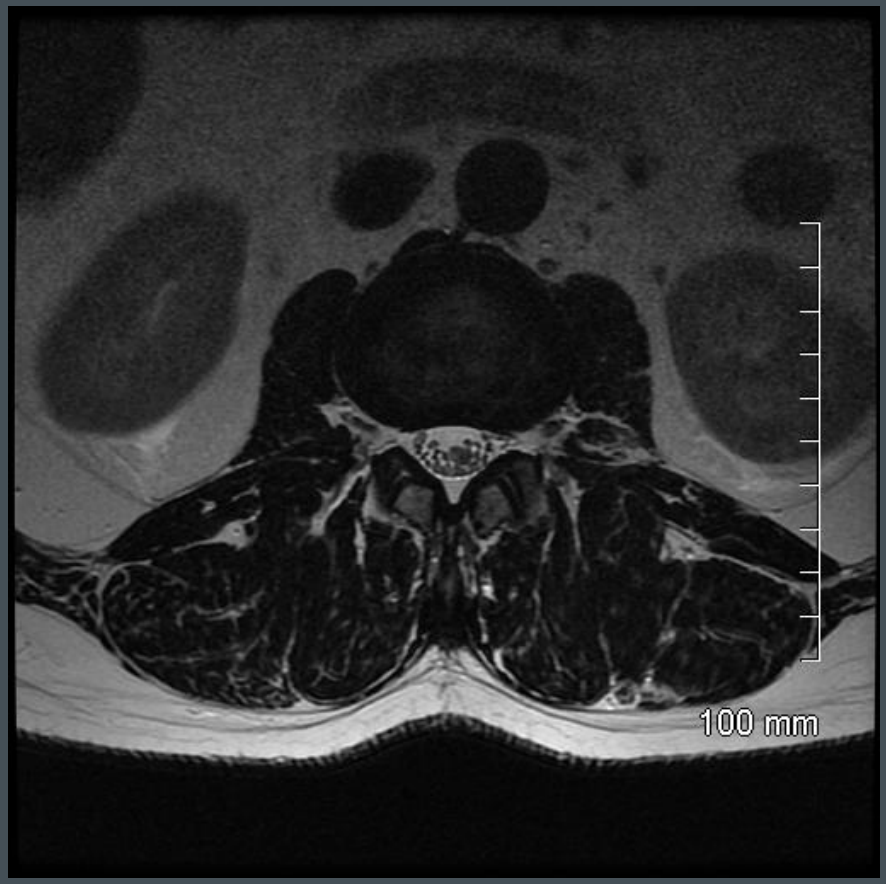
[a]Any nerve meeting any of the criteria (a–g).

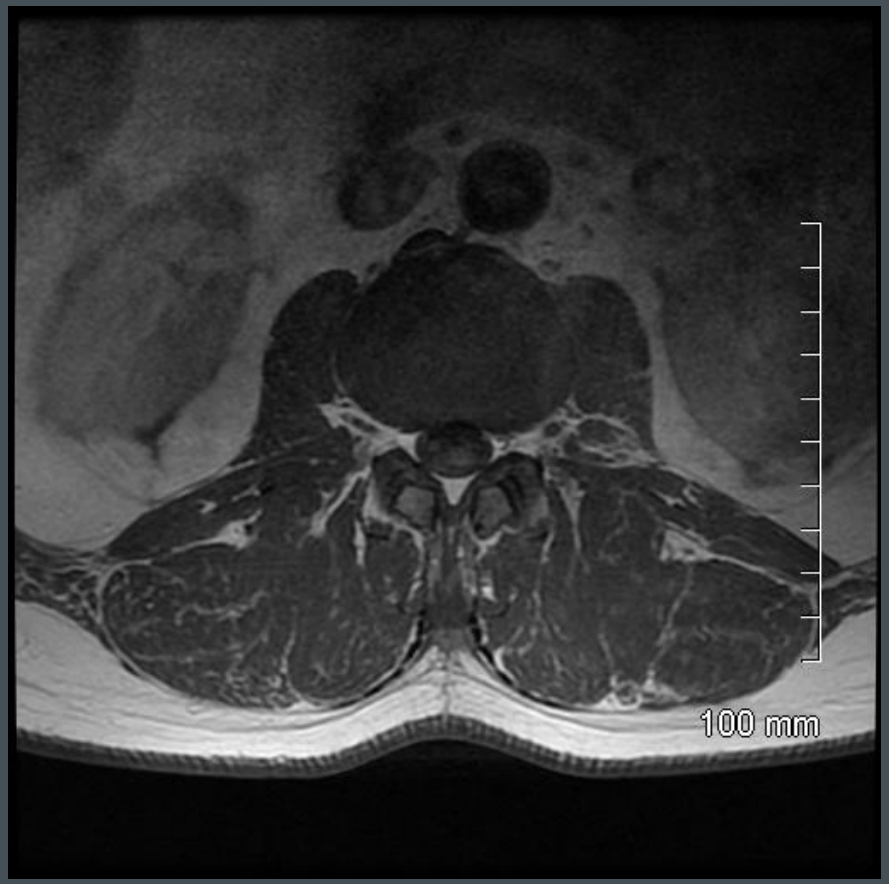
[b]Isose S. *et al.*, in press [16].

Potentiels Evoqués Somesthésiques



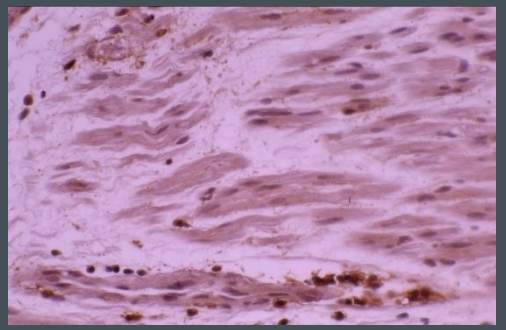
IRM: Epaississement des racines.

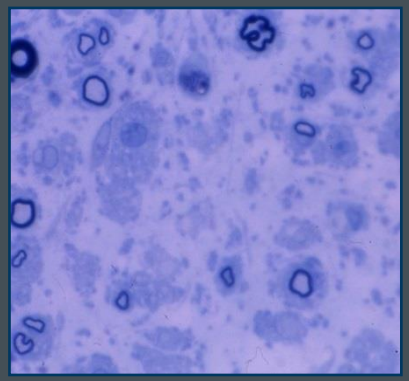




Biopsie nerveuse

- Démyélinisation segmentaire
- Bulbe d'oignon
- Œdème endoneural
- Infiltrats inflammatoires perivasculaires
- Perte axonale





Phénotypes des PIDC

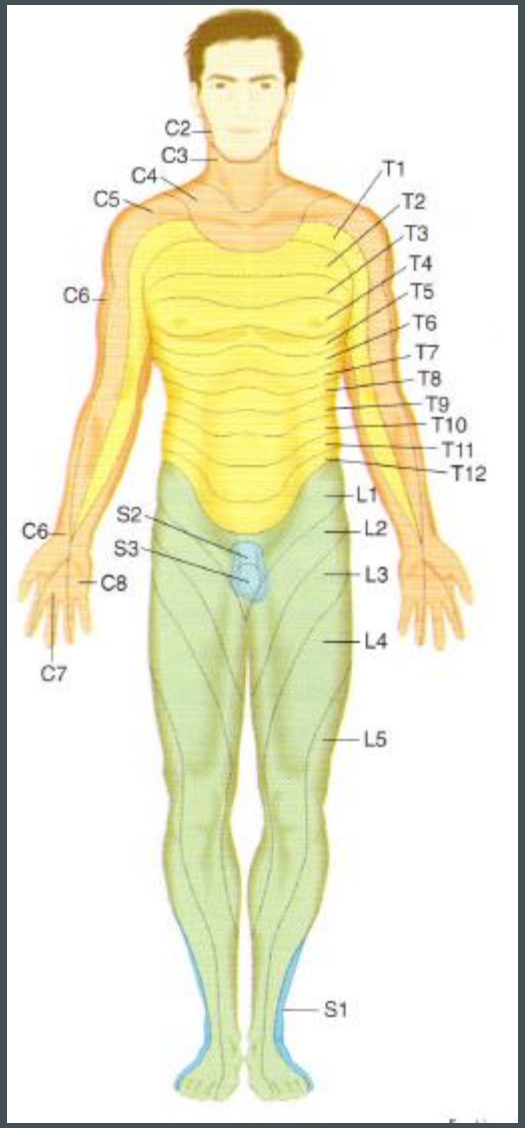
	Comments
Pure motor form[49,50]	Symmetrical and selective involvement of motor fibres; nerve conduction studies show frequent conduction blocks; the condition seems to be more responsive to IVIg than it is to steroids
Sensory CIDP or chronic sensory demyelinating neuropathy[51,52]	Numbness in the extremities is a frequent presenting symptom; ataxia can be prominent; despite pure sensory symptoms, nerve conduction studies show motor abnormalities typical of CIDP; significant weakness can appear at follow-up
Minimal forms[53,54]	Strength is usually normal; symptoms consist of distal numbness or tingling or fatigue; worsening can occur in the long term
Multifocal form;[55] Lewis-Sumner syndrome;[56] multifocal acquired demyelinating sensory and motor neuropathy[57,58]	Clinical presentation is that of a multifocal neuropathy; conduction block is found in affected nerves; by contrast with multifocal motor neuropathy, sensory involvement is manifest and response to steroids is usually good
Distal form; distal acquired demyelinating symmetric neuropathy[59,60]	Proximal weakness is absent; when no monoclonal protein is found, response to therapy seems similar to that of typical CIDP
Chronic immune sensory polyradiculopathy[61]	Clinical picture consists of sensory ataxia and large fibre sensory loss; nerve conduction studies are normal, although somatosensory evoked potentials suggest sensory root involvement; histological pattern of rootlet biopsy is similar to that of CIDP

IVIg=intravenous immunoglobulin. CIDP=chronic inflammatory demyelinating polyradiculoneuropathy.

Table: **Main clinical variants of CIDP based on pattern of symptoms and signs**

Formes topographiques de PIDC

- Formes distales pures
- Formes motrices pures
- Formes sensitives pures
- Formes sensitives proximales
- Formes multifocales
- Formes subaiguës
- Formes à début brutal



Formes sensitives de PIDC

- Formes purement sensitives clinique et ENMG.
- PISC:
  - Utilité des PES, de la PL, de l'IRM

Distal acquired demyelinating symmetric neuropathy

J.S. Katz, MD; D.S. Saperstein, MD; G. Gronseth, MD; A.A. Amato, MD; and R.J. Barohn, MD

- Déficit distal
  - Sensitif
  - Sensitivo-moteur.
- Démyélinisation à prédominance distale:
  - TLI<0.2

Distal Acquired Demyelinating Symmetric Neuropathy: DADS.

Table 1 *Comparison of clinical and laboratory characteristics*

Characteristics	DADS-M	DADS-I	CIDP*	*p* Value
No.	20	10	23	—
Gender	19 M, 1 F	6 M, 4 F	8 M, 15 F	0.001†‡
Mean age at onset, y (range)	62 (35–81)	47 (27–67)	51 (22–81)	0.006†‡
Mean duration of symptoms, mo (range)	60 (3–180)	44 (1–144)	16 (2–120)	0.004‡¶
Sensory symptoms, n (%)	20 (100)	10 (100)	22 (96)	NS
Mean CSF protein, mg/dL (range)	95 (40–177)	78 (26–223)	124 (23–385)	NS

* Includes patients with and without a monoclonal protein.
† The comparison between DADS-M and DADS-I is significant.
‡ The comparison between DADS-M and CIDP is significant.
¶ The comparison between DADS-I and CIDP is significant.

DADSn = distal acquired demyelinating symmetric neuropathy; DADS-M = DADS neuropathy associated with a monoclonal protein; DADS-I = idiopathic DADS neuropathy (not associated with a monoclonal protein); CIDP = chronic inflammatory demyelinating polyneuropathy; NS = not significant.

Katz, Neurology 2000;54:615-620

ENMG:

- Démyélinisation à prédominance distale
- TLI<0.2

Absence de Gammapathie et de sécrétion Anti-MAG

Formes motrices de PIDC

- <5% des cas.
- Aggravation sous corticothérapie
- Overlap avec NMMBC?

Formes sensitives de PIDC

- 10% des cas.
- Clinique:
  - Paresthésies distales
  - Ataxie proprioceptive
- Diagnostic: ENMG
  - Signes de démyélinisation sur les troncs moteurs
  - Diminution de l'amplitudes des potentiels sensitifs

PIDC Multifocale

- Syndrome de Lewis Sumner
- MADSAM:
  - Multifocal Acquired Demyelinating Sensory And Motor Neuropathy

DOI: 10.1093/brain/awh222 *Brain* (2004), **127**, 2010–2017

Follow-up study and response to treatment in 23 patients with Lewis–Sumner syndrome

K. Viala,[1] L. Renié,[1] T. Maisonobe,[1] A. Béhin,[2] J. Neil,[3] J. M. Léger[2] and P. Bouche[1]

Summary

Lewis–Sumner syndrome (LSS) is a dysimmune peripheral nerve disorder, characterized by a predominantly distal, asymmetric weakness mostly affecting the upper limbs with sensory impairment, and by the presence of multifocal persistent conduction blocks. The nosological position of this neuropathy in relation to multifocal motor neuropathy (MMN) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is still debated. We report the clinical, biological and electrophysiological features, the course and the response to treatment in 23 LSS patients. The initial symptoms started in the distal part of an upper limb in 70% of patients. They were sensorimotor in 65% and purely sensory in 35% of patients. A cranial nerve involvement was observed in 26% of patients and a distal limb amyotrophy in 52%. The CSF protein level was normal in 67% of patients and mildly elevated in the remainder. None had serum anti-GM1 antibodies. There were multiple motor conduction blocks (average of 2.87/patient), predominantly located in the forearm, whereas demyelinating features outside the blocked nerves were rare. Abnormal distal sensory potentials were found in 87% of patients. The electrophysiological pattern suggests a very focal motor fibre demyelination sparing the nerve endings, whereas sensory fibre involvement was widespread. The course was chronic progressive in 71% of patients and relapsing–remitting in the others. During the follow-up study (median duration of 4 years), half of the patients progressed with a multifocal pattern and the distribution of the motor deficit remained similar to the initial presentation. The other patients showed a progression to the other limbs, suggesting a more diffuse process. Fifty-four percent of the patients treated with intravenous immunoglobulin showed an improvement, compared with 33% of the patients treated with oral steroids. Overall, 73% of patients had a positive response to immune-mediated therapy. LSS may be distinguished from MMN by the presence of sensory involvement, the absence of serum anti-GM1 antibodies and, in some cases, a positive response to steroids. In some of the patients in our study, LSS evolved into a more diffuse neuropathy sharing similarities with CIDP. Others had a clinical course characterized by a striking multifocal neuropathy, which suggests underlying mechanisms different from CIDP. Overall, whatever the clinical course, LSS responded to immune-mediated treatment in a manner similar to CIDP.

Syndrome de Lewis et Sumner:

- Déficit moteur:
  - Asymétrique
  - Distal > Proximal
  - MS > MI (78%)
  - Atteinte proximale occasionnelle:
    - Nerf phrénique, supra-scapulaire
- Déficit sensitif:
  - Distal
  - Toutes les modalités
  - Second plan/moteur
- ROT:
  - Abolition focale
- Evolution: Rémittente ou progressive

Syndrome de Lewis Sumner

- ENMG:
  - Blocs de conduction multifocaux
  - VCN: Ralentissement hétérogène
    - Atteinte VCM et VCS
  - LDM: Allongement
- Ponction lombaire:
  - Protéinorachie <100 mg/dL
- Immunologie:
  - IgM anti-GM1 toujours Négatifs
- IRM:
  - Hypersignal T2 en proximal du plexus brachial

Syndrome de Lewis Sumner

- Corticothérapie:
  - JAMAIS CAR AGGRAVATION
- Immunoglobulines IV:
  - Cures de 2 g/kg

Distinguishing acute-onset CIDP from fluctuating Guillain-Barré syndrome

- Rechute après 8 semaines
- Formes moins sévère sur le plan moteur
- Pas d'atteinte des nerfs crâniens
- Pas de signes dysautonomiques
- Pas de nécessité de ventilation
- ENMG:
  - VCN plus altérées

PIDC avec Ac anti-NF155

- Déficit moteur distal.
- Ataxie proprioceptive.
- Tremblement postural et d'intention invalidant.
- Résistance aux IgIV.

Neurofascin IgG4 antibodies in CIDP associate with disabling tremor and poor response to IVIg

Table 1 Epidemiologic, clinical, and electrophysiologic features of patients with CIDP positive for anti-NF155 antibodies

Patient	Age at onset (sex)	Symptoms	mRS score	CSF	Brain MRI	Treatments (responses)	Tremor frequency (amplitude)	NF155 titers
1	46 (M)	Rapidly progressive onset; severe weakness, predominantly distal; sensory disturbances; ataxia; severe intention tremor	4	1.5 g/L; 2 cells	Normal	IVIg (no); prednisone (no); PEx (yes)	3 Hz (9/10)	1:70,000
2	22 (M)	Chronic progressive; severe weakness, predominantly distal; sensory disturbances; ataxia; moderate intention tremor	4	4.6 g/L; 6 cells	Normal	IVIg (no); prednisone (partial); PEx (yes, partial)	6.6 Hz (2/10)	1:70,000
3	29 (M)	Chronic progressive; severe weakness, proximal and distal; sensory disturbances; ataxia; severe intention tremor	4	1.4 g/L; 7 cells	Normal	IVIg (no); prednisone (no); methotrexate (no)	4 Hz (8/10)	1:25,000
4	67 (F)	Chronic progressive; severe weakness, predominantly distal; sensory disturbances; no tremor	4	0.41 g/L; 0 cells	ND	IVIg (no); prednisone (no); cyclophosphamide (no); rituximab (no)	Not present	1:8,000

Abbreviations: CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; IVIg = IV immunoglobulin; mRS = modified Rankin Scale; ND = not determined; NF155 = neurofascin 155; PEx = plasma exchange.

Neurofascin IgG4 antibodies in CIDP associate with disabling tremor and poor response to IVIg

Anticorps anti-NF155

PIDC: Maladies associées

- Dyscrasies lymphoplasmcytaires:
  - Lymphomes:
  - Waldenström
  - POEMS syndrome
- Néoplasies solides:
  - Mélanome malin
  - Syndromes paranéoplasiques avec Ac anti-Hu
- Diabète:
  - Association fortuite (Neurology 2009;73:39-45)
- Infections:
  - HIV, HVC.
- Greffe:
- Maladies inflammatoires systémiques:
  - LEAD, Sarcoïdose, Sjögren, PR..

PIDC et Diabète.

- Risque x 11 chez les patients diabétiques.
- Clinique:
  - Plutôt des formes motrices.
- ENMG:
  - Perte axonale compliquant la démyélinisation.
- Traitement:
  - Efficacité de la corticothérapie
  - Moindre efficacité des IG IV.

Said, Nature Clin Pract 2007

PIDC: Pronostic

- Tout est possible
  - Sans retentissement
  - Handicap sévère
- Mortalité: 3% (Barohn, 1989)
- Effet bénéfique du traitement:
  - 2/3 améliorés ou en rémission

PIDC: Traitement

- Corticothérapie.
- Immunoglobulines intra veineuses (IgIV).
- Echanges plasmatiques.
- Immunosuppresseurs.

Corticothérapie

- Niveau de preuve: B vs A pour Ig IV
- Per os:
  - 1 mg/kg/j pendant 4-8 semaines
  - 60 mg/j (Vallat et Magy, 2012)
  - Décroissance progressive si efficacité
    - 5mg/2 semaines
  - Arrêt si échec
- Forme IV:
  - Solumedrol: 500 mg 4j/mois pendant 6 mois
  - Dès efficacité, 60 mj/J CS + AZT

Immunoglobulines:

- Immunoglobulines IV:
  - Pas de consensus mais des habitudes de prescription
  - 2 cures IG IV (2 g/kg) à 4 semaines d'intervalle
  - Cures successives en fonction de la clinique.

- Immunoglobulines en Sous-cutané:
  - Moindre coût
  - Efficacité comparable
  - Même posologie sur l'intervalle mais fractionné en 3/semaine

Echanges plasmatiques:

- 10 EP sur 4 semaines.
- Puis en fonction de l'état clinique.

Immunosuppresseurs

- Objectif:
  - ***Réduire la posologie ou la dépendance aux traitements de 1e ligne***

- Possibilités thérapeutiques:
  - IMUREL
  - ENDOXAN
  - CYCLOSPORINE A
  - CELLCEPT

PIDC et Rituximab.

- PIDC Réfractaires.
- Protocole:
  - 375 mg/m^2/semaine QSP: 4 semaines.
- Effet:
  - Dès le 2e mois
  - Pendant 1 an
  - Plus important si CIDP associée à Hémopathie

Table 2 Results of published studies on rituximab therapy in patients with CIDP

Author(s)	No. of patients	Neuropathy duration (months)	Pre-rituximab therapy	Comorbidity	Clinical response	Months before improvement	Duration of improvement (years)*
Gorson *et al*[11]	2	60 (mean)	IVIg, AZA, MM, Ster, PE, Cyclopho	No	No	—	—
Kilidireas *et al*[5]	1	10	No	Gastric lymphoma	Yes	2	>5
Knecht *et al*[6]	1	17	Ster, PE, AZA, Cyclopho	Evans Syndrome	Yes	6	1.5
Kasamon *et al*[8]	1	<12	Ster	Non-Hodgkin's lymphoma	Yes	2	NA
Műnch *et al*[7]	1	20	IVIg	DM	Yes	1	1

*Which corresponded to duration of follow-up.
AZA, azathioprine; Cyclopho, Cyclophosphamide; DM, diabetes mellitus; IVIg, intravenous immunoglobulin; MM, mycophenolate mofetil; NA, not available; PE, plasma exchange; Ster, steroids.

Benedetti et al. J Neurol Neurosurg Psychiatry 2011;82:306-308

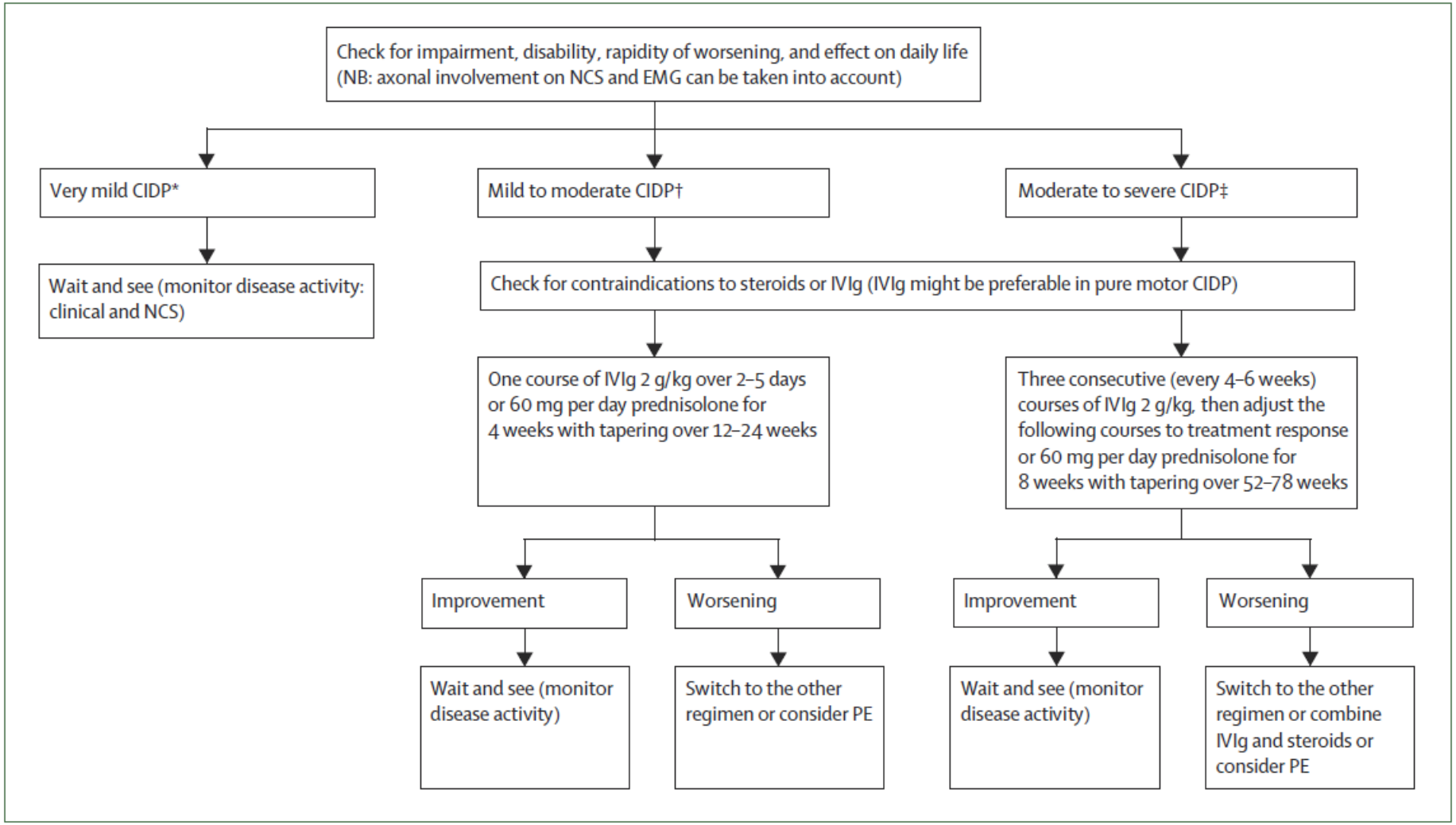


Figure 4: **Proposed algorithm for CIDP treatment**

At any step, if treatment fails, consider the following diagnoses: POEMS syndrome, lymphoma, amyloidosis, or sarcoidosis. If the patient still worsens under treatment or needs constant treatment maintenance, consider adding an immunosuppressant. CIDP=chronic inflammatory demyelinating polyradiculoneuropathy. EMG=electromyography. IVIg=intravenous immunoglobulin. NCS=nerve conduction studies. PE=plasma exchange. POEMS=polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes. *Almost no impairment and disability, and no effect on daily life, no axon loss. †Mild to moderate impairment and disability, no serious effect on daily life (the patient can work or has near normal social life). ‡Moderate to severe impairment or disability, clear effect on daily life, active axon loss.

PIDC: Conclusions

- Plus fréquente qu'attendue.
- Attention aux PIDC avec atteinte axonale à l'ENMG.
- Importance des examens complémentaires pour le diagnostic.
- Importance des données neuropathologiques.
- Traitement de 1^{e} intention:
  - Corticothérapie ou Ig IV.