Patient male 45 years-old

Gilbert's disease

Since 6 months :

- Painful and distal paresthesiae of hind limbs and hands
- Progressive weakness, noticeably for steps
- Loss of weight (7 kgs)

Clinical exam :

- Tactile loss feet
- Reduction in vibration sense on hindlimbs
- Slight ataxia with Romberg
- Proximal motor weakness (4/5)
- Areflexia : achilles and patellar

First line exams

- MNCV studies :

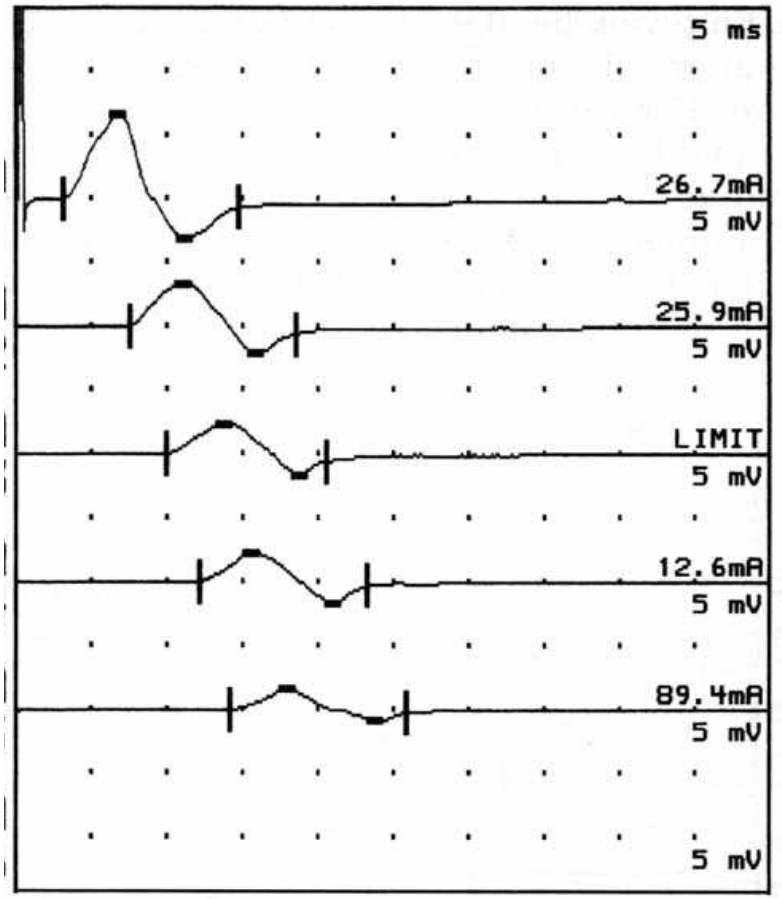
Conduction blocks

Reduced Motor Nerve Velocities

Prolonged Distal Motor Latencies

Absent/Prolonged Late Responses

- Sensory potentials more affected in upper limbs



First line exams

CSF

- Cytologie normale
- Proteines 1.21 g/l, glucose normal

Biology :

- ERC : normal. Plaquettes : 493.000/mm3
- Ionogramme sanguin normal. Pas diabetes. CRP<1
- Serologies (hepatitis B, C, HIV, syphilis, Lyme) : négatives
- Antinuclear Ac, anti ENA, ECA : normal
- Cryoglobuline negative
- TSH normale : 4.1 (N : 0.270-4.2)
- Vit B12 normal

Clinical diagnosis of CIDP

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

Joint Task Force of the EFNS and the PNS†

J Peripheral Nervous System 15:1–9 (2010)

Typical CIDP

- Chronically progressive, stepwise, or reccurent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected, and
- Absent or reduced tendon reflexes in all extremities

Clinical diagnosis of CIDP

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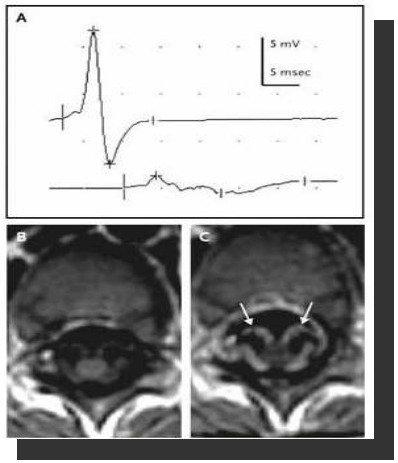
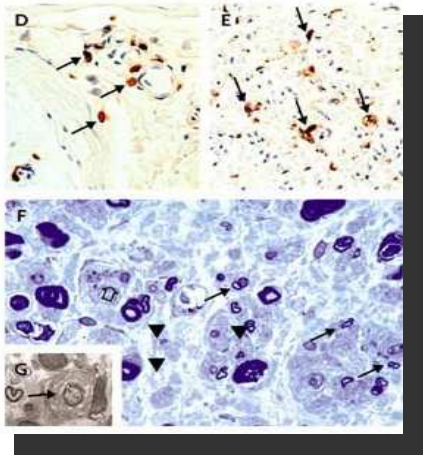
J Peripheral Nervous System 15:1–9 (2010)

Atypical CIDP

- One of the following, but otherwise as in A
- Predominantly distal weakness (DADS)
- Pure motor or sensory presentations
- Asymetric presentations (LSS)
- Focal presentations (ie involvement of the brachial plexus or 1 or more peripheral nerves in 1 upper limb)
- CNS involvement (may occur with otherwise typical or other forms of atypical CIDP)

CIDP diagnosis





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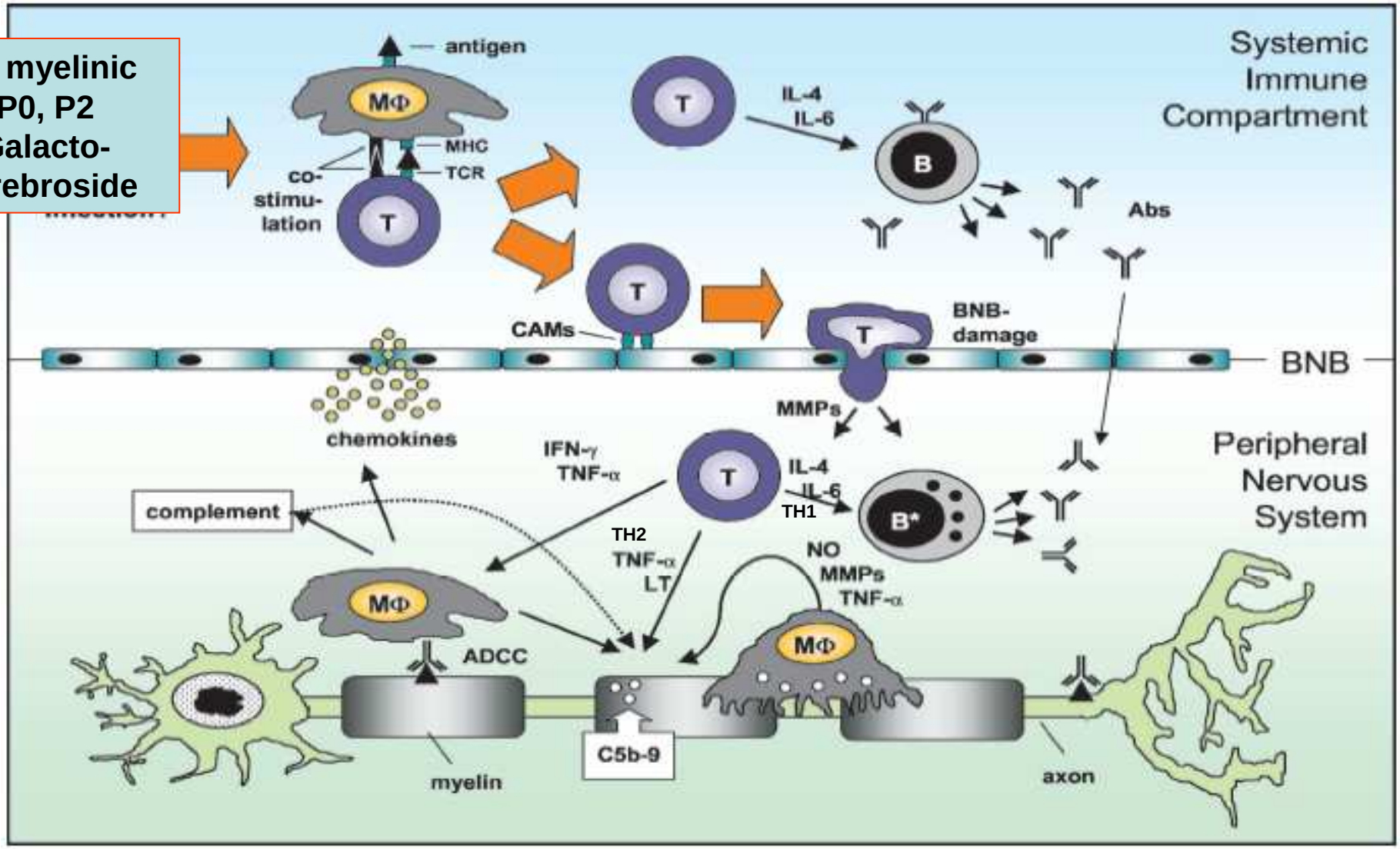
J Peripheral Nervous System 15:1–9 (2010)

1. Elevated CSF protein with leukocyte count <10/mm^3 (level A recommendation)
2. MRI showing gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses (level C recommendation)
3. Abnormal sensory electrophysiology in at least one nerve (Good Practice Points):
   a. Normal sural with abnormal median (excluding median neuropathy at the wrist from carpal tunnel syndrome) or radial sensory nerve action potential (SNAP) amplitudes; or
   b. Conduction velocity <80% of lower limit of normal (<70% if SNAP amplitude <80% of lower limit of normal); or
   c. Delayed somatosensory evoked potentials without central nervous system disease
4. Objective clinical improvement following immunomodulatory treatment (level A recommendation)
5. Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy or teased fibre analysis (Good Practice Points)

The model of EAN

Ab myelinic
P0, P2
Galacto-
cerebroside



Kieseier et al., 2002

Rationale of the treatment of CIDP

Similarities with that of multiple sclerosis

- CIDP is a demyelinating disease affecting the peripheral nerve, clinically and electrophysiologically heterogeneous
- CIDP course is relapsing (1/3 of cases) or progressive (2/3 of cases)
- The natural history is unpredictable
- The prognosis is linked to the severity of secondary axonal degeneration

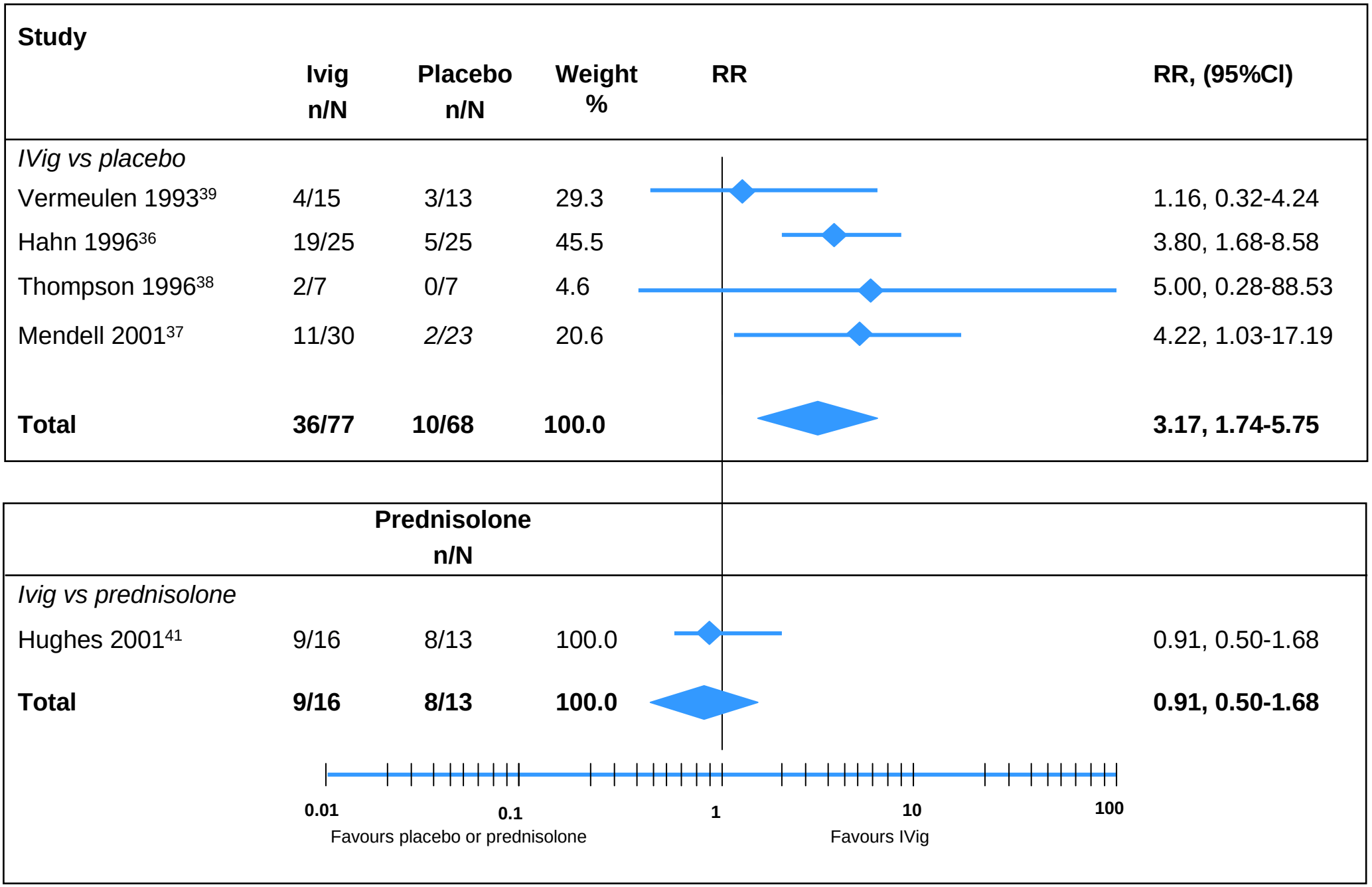
CIDP: first-line therapy (* RCT)

Corticosteroids: 1982*, 1997

Plasma exchanges: 1986*, 1996*

IVIg: 1991, 1996*, 2001*, 2008*

Reference	Year	Therapy	No. of Patients	Duration	Design	Result
Dyck et al	1994	Plasma exchange vs. Iv. immune globulin	15	42 days	Randomized, observer blinded, crossover	NS
Hahn et al	1996	Plasma exchange	15	28 days	Double-blind, sham controlled, crossover	Improvement in 80% of patients
Hahn et al	1996	Iv. immune globulin	30	28 days	Double-blind, placebo controlled, crossover	Improvement in 63% of patients
Mendell et al.	2001	Iv. immune globulin	53	42 days	Double-blind, randomized, placebo-controlled	Improvement in 76% of patients
Hughes et al.	2001	Iv. immune globulin vs. oral prednisone	32	14 days	Double-blind, randomized, crossover	NS
Dyck et al.	1985	Azathioprine in combination with prednisone vs. prednisone alone	30	9 mo	Open, parallel-group, randomized	NS


Study
Ivig n/N
Placebo n/N
Weight %
RR
RR, (95%CI)
IVig vs placebo
Vermeulen 1993[39] 4/15 3/13 29.3 1.16, 0.32-4.24
Hahn 1996[36] 19/25 5/25 45.5 3.80, 1.68-8.58
Thompson 1996[38] 2/7 0/7 4.6 5.00, 0.28-88.53
Mendell 2001[37] 11/30 2/23 20.6 4.22, 1.03-17.19
Total 36/77 10/68 100.0 3.17, 1.74-5.75
Prednisolone n/N
Ivig vs prednisolone
Hughes 2001[41] 9/16 8/13 100.0 0.91, 0.50-1.68
Total 9/16 8/13 100.0 0.91, 0.50-1.68
0.01
0.1
1
10
100
Favours placebo or prednisolone
Favours IVig

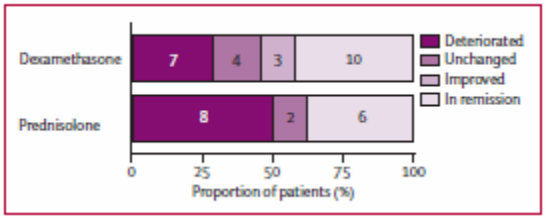
Corticosteroids

Six weeks of oral prednisolone starting at 60 mg daily produced benefit that was not significantly different from that of IVIg 2g/kg (Hughes et al. 2001)

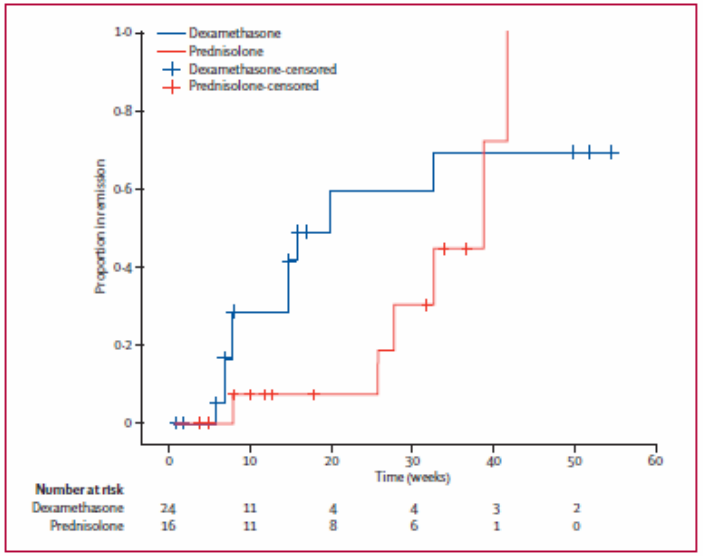
Pulsed high-dose dexamethasone versus standard prednisolone treatment for chronic inflammatory demyelinating polyradiculoneuropathy (PREDICT study): a double-blind, randomised, controlled trial

Lancet Neurol 2010; 9: 245–5

Ivo N van Schaik, Filip Eftimov, Pieter A van Doorn, Esther Brusse, Leonard H van den Berg, W Ludo van der Pol, Catharina G Faber, Joost C H van Oostrom, Oscar J M Vogels, Rob D M Hadden, Bert U Kleine, Anouk G W van Norden, Jan J G M Verschuuren, Marcel G W Dijkgr Marinus Vermeulen



Dexamethasone
(40 mg/d for 4 days x 6 weeks)
has the same efficacy that oral prednisolone



Plasma exchanges (PE)

- PE might be considered as an initial treatment as neurological disability may improve rapidly
- For stabilization of CIDP, PE needs to be combined with other treatments
- Because adverse events (difficulty with venous access, use of citrate and haemodynamic changes) are not uncommon, either corticosteroids or IVIg should be considered first

EFNS/PNS Guidelines 2010

Intravenous immunoglobulin versus intravenous methylprednisolone for chronic inflammatory demyelinating polyradiculoneuropathy: a randomised controlled trial

*Eduardo Nobile-Orazio, Dario Cocito, Stefano Jann, Antonino Uncini, Ettore Beghi, Paolo Messina, Giovanni Antonini, Raffaella Fazio, Francesca Gallia, Angelo Schenone, Ada Francia, Davide Pareyson, Lucio Santoro, Stefano Tamburin, Roberta Macchia, Guido Cavaletti, Fabio Giannini, Mario Sabatelli, for the IMC Trial Group**

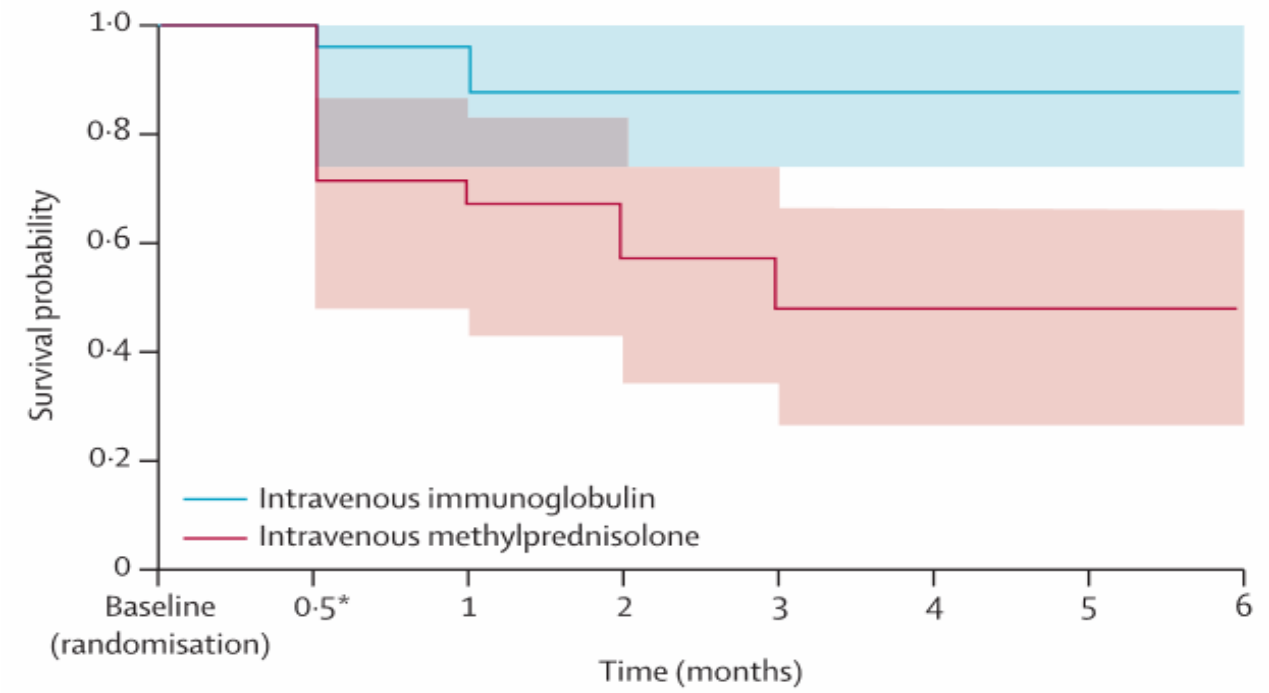
Lancet Neurol 2012; 11: 493-502

- Essai multicentrique, randomisé, double insu, contre placebo, 2 groupes parallèles,
- Efficacité et tolérance,
- Efficacité : variation 1 point ONLS ou Rankin,
- IgIV 0,5g/kg/j → 4j /methylprednisolone 0,5g/j → 4j,
- Suivi 6 mois,
- Critère primaire : nombre de patients en échec pour inefficacité ou intolérance,
- Critère secondaire : nombre de patients avec EI ou aggravation à l'arrêt du traitement.

	Intravenous methylprednisolone (n=21)	Intravenous immunoglobulin (n=24)	Risk difference (95% CI)	Relative risk (95% CI)	p value
15 days	6 (29%)	1 (4%)	0·24 (0·03–0·45)	0·75 (0·56–0·99)	0·0389
2 months	9 (43%)	3 (13%)	0·30 (0·05–0·55)	0·65 (0·44–0·97)	0·0406
6 months*	11 (52%)	3 (13%)	0·40 (0·15–0·65)	0·54 (0·34–0·87)	0·0085

Data are number (%) unless otherwise stated, risk difference, or relative risk (95% CI). *Primary outcome.

***Table 2*: Cumulative treatment failures**



Suivi 6 mois :

- 10 patients améliorés par methylprednisolone → pas de rechute,
- 21 patients améliorés par IgIV → 8 (38%) rechutes entre 1 et 5 mois (médiane 4),
- p=0,0317.

***A* 12 mois :**

48% des patients initialement traités par methylprednisolone et 54% des patients traités par IgIV sont améliorés et stables sans traitement (p=0,763).

Intérêt de l'identification de biomarqueurs de réponse thérapeutique dans la PIDC !

Serum IgG levels in IV immunoglobulin treated chronic inflammatory demyelinating polyneuropathy

Krista Kuitwaard,[1] Pieter A van Doorn,[1] Marinus Vermeulen,[2] Leonard H van den Berg,[3] Esther Brusse,[1] Anneke J van der Kooi,[2] W-Ludo van der Pol,[3] Ivo N van Schaik,[2] Nicolette Notermans,[3] Anne P Tio-Gillen,[1,4] Wouter van Rijs,[1,4] Teun van Gelder,[5] Bart C Jacobs[1,4]

On line, JNNP 2013

J Neurol
DOI 10.1007/s00415-013-6938-7

ORIGINAL COMMUNICATION

Immunoglobulin G level variations in treated chronic inflammatory demyelinating polyneuropathy: clues for future treatment regimens?

Yusuf A. Rajabally · Siew L. Wong · David A. Kearney

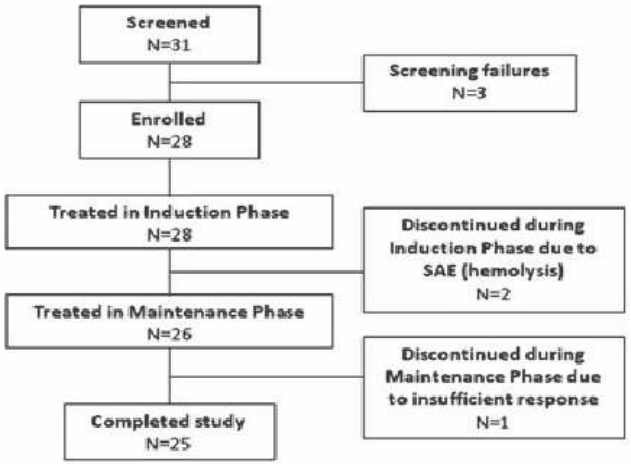
2013

- **Taux plasmatique IgIV : un biomarqueur incontournable,**
- **Stabilité intra-patient versus variabilité inter-patient à prendre en compte.**

RESEARCH REPORT

Efficacy and safety of Privigen® in patients with chronic inflammatory demyelinating polyneuropathy: results of a prospective, single-arm, open-label Phase III study (the PRIMA study)

Jean-Marc Léger[1], Jan L. De Bleecker[2], Claudia Sommer[3], Wim Robberecht[4], Mika Saarela[5], Jerzy Kamienowski[6], Zbigniew Stelmasiak[7], Orell Mielke[8], Björn Tackenberg[9], Amgad Shebl[8], Artur Bauhofer[8], Othmar Zenker[8], and Ingemar S. J. Merkies[10]; on behalf of the PRIMA study investigators[†]



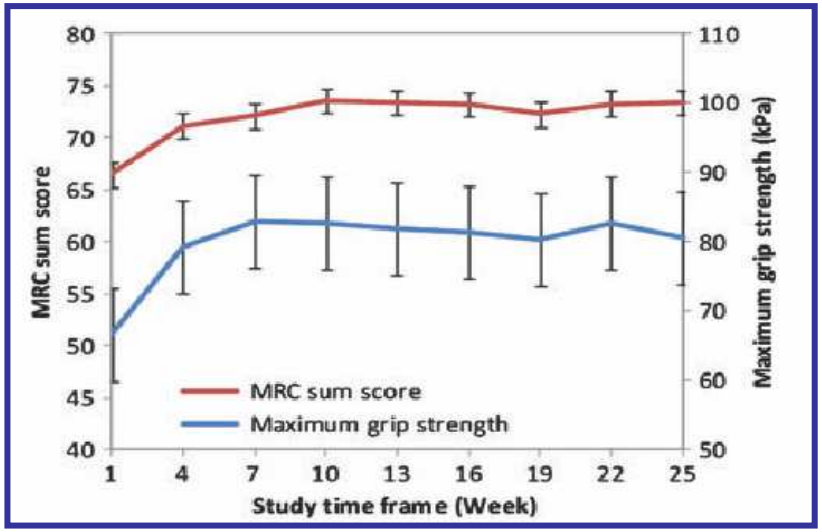
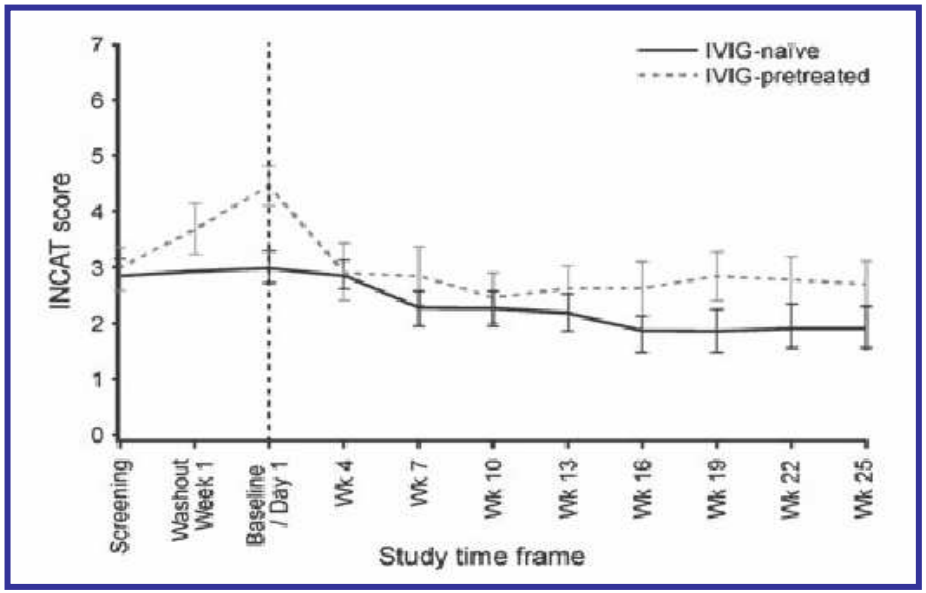


Table 2. Number of responders by the adjusted INCAT score at completion (ITT).

	All patients	IVIG-pretreated patients	IVIG-naïve patients
Total number of patients	28	13	15
Number of responders, n	17	10	7
Responder rate (%)	60.7	76.9	46.7
Wilson-Score 95% CI of the responder rate (%)	42.4–76.4	49.7–91.8	24.8–69.9



Échelle de l 'INCAT

Bras

0 : Pas de problèmes aux membres supérieurs

1 : Symptômes dans l'un ou les deux bras ne gênant pas la capacité à réaliser l'une quelconque des taches suivantes : utiliser l'ensemble des fermetures éclair et des boutons, laver ou coiffer ses cheveux, utiliser un couteau et une fourchette ensemble, manipuler de petites pièces de monnaie.

2 : Symptômes dans l'un ou les deux bras affectant sans l'interdire l'une quelconque des taches sus-citées.

3 : Symptômes dans l'un ou les deux bras empêchant une ou deux des taches sus-citées.

4 : Symptômes dans l'un ou les deux bras empêchant trois ou toutes les taches sus-citées, quelques mouvements intentionnels restant possibles.

5 : Incapacité à utiliser l'un ou l'autre des deux bras pour quelque mouvement intentionnel que ce soit.

Jambes

0 : Marche non affectée.

1 : Marche affectée mais marche indépendante en extérieur possible.

2 : Utilisation habituelle d'une aide unilatérale pour marcher en extérieur (une canne, une béquille, un bras).

3 : Utilisation habituelle d'une aide bilatérale pour marcher en extérieur (deux cannes, deux béquilles, cadre de marche, deux bras).

4 : Utilisation habituelle d'un fauteuil roulant pour les déplacements en extérieur mais possibilité de se tenir debout et de marcher quelques pas avec aide.

5 : Confiné au fauteuil roulant, incapable de se tenir debout et de marcher quelques pas avec aide.

Handicap Total = somme du handicap des bras et des jambes.

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Table 4. Pre- and post-infusion serum IgG levels (ITT).

	All patients	Responders	Non-responders
Total number of patients	28	17	11
Serum IgG levels (mg/dl)			
Pre-infusion, mean (SD)	1828.4 (547.7)	1881.3 (583.6)	1757.8 (490.9)
Post-infusion, mean (SD)	3363.5 (880.0)	3592.4 (939.7)	3081.8 (711.7)
Change from pre-infusion to post-infusion (mg/dl)			
Mean (SD)	1574.0 (725.4)	1759.0 (758.8)	1342.7 (612.2)
Range	−867 to 3,392	−867 to 3,392	84 to 2,685

The mean and standard deviation (SD) of the pre- and post-infusion serum IgG levels are shown for all patients in the intention-to-treat (ITT) analysis, and for responders and non-responders at completion.

- IgIV efficace dans la PIDC……!
- Différence taux IgIV pré/post < non répondeurs
- Savoir attendre un bénéfice non immédiat

Journal of the Peripheral Nervous System 18:130–140 (2013)

Recommendations for treatment, EFNS 2010

For induction of treatment

- IVIg or corticosteroids should be considered in sensory and motor CIDP in the presence of disabling symptoms
- PE is similarly effective but may be less tolerated
- The presence of relative contraindications to any of these treatments should influence the choice

For maintenance treatment

- If the first-line treatment is effective, continuation should be considered until the maximum benefit has been achieved and then the dose reduced to find the lowest effective maintenance dose
- If the response is inadequate or the maintenance doses of the initial treatment (IVIg, steroids, or PE) result in adverse effects, the other first-line treatment alternatives should be tried before considering combination treatments or adding an immunosuppressor or immunomodulatory drug may be considered, but there is no sufficient evidence to recommend any particular drug

EFNS/PNS Guidelines 2010

Long-term prognosis of CIDP: a 5 year follow-up of 38 cases

- Retrospective study of 38 patients with CIDP
- 89% treated with steroids, 45% with IVIg and 34% with PE: 58% with association
- After 5 years, 10 (26%) had prolonged remission (> 2 years), 23 (61%) partial remision with (26%) or without (34%) other immunomodulator, 5 (13%) had severe disability (unable to walk)
- An overall good response to treatment was associated with symmetric forms, subacute onset, predominantly distal BC and good response to steroids.

Kuwabara et al. JNNP 2006; 77: 66-70

Immunosuppressant and immunomodulatory drugs that have been reported to be beneficial in CIDP (class IV evidence)

	Mechanism	Cost	Evidence		Safety
			CIDP	MMN	
Cyclophosphamide	broad	+	+	+	---
Azathioprine	broad	+	+	?	--
Methotrexate	broad	+	0	0	-
Ciclosporin	broad	++	+	0	--
Mycophenolate	lymphocyte	++	+	?	-
Rituximab	B cell	+++	?	+	-
Beta interferon 1a	broad	+++	+	+	-
Alpha interferon	broad	+++	+	0	-
Etanercept	T cell	+++	?	0	-

Mahdi, Cochrane, 2009

Interferon beta-1a as an investigational treatment for CIDP

Neurology 2003; 60 : S23-S28

J.-M. Vallat, MD; A.F. Hahn, MD; J.-M. Léger, MD; D.P. Cros, MD; L. Magy, MD; F. Tabaraud, MD; P. Bouche, MD; P.-M. Preux, MD, PhD

- Phase II multicentric trial with Avonex, 30 µg/week, 6 months
- Good tolerability (as in MS)
- 7 patients (35%) improved (NDS, clinical grading scale and grip strength), 10 patients (50%) were stable and 3 (15%) worsened

R.A.C. Hughes, MD
K.C. Gorson, MD
D. Cros, MD

Intramuscular interferon beta-1a in chronic inflammatory demyelinating polyradiculoneuropathy

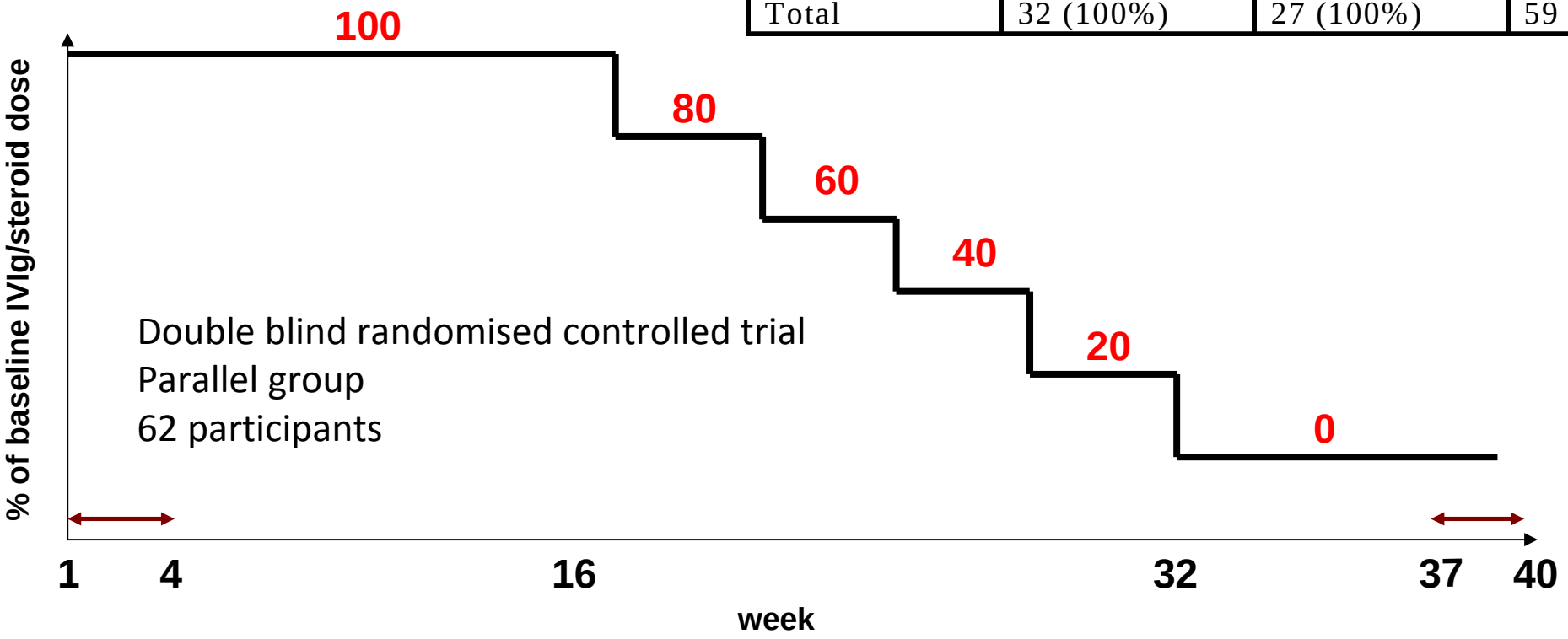
Neurology 2010;74:651-657

Bêta-1a interferon has no efficacy as adjuntive therapy during 6 months

Randomised controlled trial of methotrexate for chronic inflammatory demyelinating polyradiculoneuropathy (RMC trial): a pilot, multicentre study

RMC Trial Group*

Responder	Placebo	Methotrexate	Total
No	18 (56%)	13 (48%)	31(53%)
Yes	**14 (44%)**	**14 (52%)**	**28 (47%)**
Total	32 (100%)	27 (100%)	59 (100%)



7.5 → 10 → 15 Methotrexate mg/week

60 patients enrolled from 26 European centres

Lancet Neurol 2009; 8: 158–64

Clinical diagnosis Of CIDP

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

Joint Task Force of the EFNS and the PNS†

(1) Inclusion criteria
  (a) Typical CIDP
  Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected; and
  Absent or reduced tendon reflexes in all extremities
  (b) Atypical CIDP (still considered CIDP but with different features) One of the following, but otherwise as in (a) (tendon reflexes may be normal in unaffected limbs):
  Predominantly distal (distal acquired demyelinating symmetric, DADS) or
  Asymmetric [multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), Lewis-Sumner syndrome] or
  Focal (e.g., involvement of the brachial or lumbosacral plexus or of one or more peripheral nerves in one upper or lower limb)
  Pure motor or
  Pure sensory (including chronic immune sensory polyradiculopathy affecting the central process of the primary sensory neuron)

(2) Exclusion criteria
  Borrelia burgdorferi infection (Lyme disease), diphtheria, drug or toxin exposure probably to have caused the neuropathy
  Hereditary demyelinating neuropathy
  Prominent sphincter disturbance
  Diagnosis of multifocal motor neuropathy
  IgM monoclonal gammopathy with high titre antibodies to myelin-associated glycoprotein
  Other causes for a demyelinating neuropathy including POEMS syndrome, osteosclerotic myeloma, diabetic and non-diabetic lumbosacral radiculoplexus neuropathy. PNS lymphoma and amyloidosis may occasionally have demyelinating features

Köller H et al. N Engl J Med 2005

Table 2. Differential Diagnosis.

Neuropathy	Examples	Remarks
Guillain–Barré syndrome	—	Muscular weakness progressing over a period of ≤1 mo
Inherited neuropathy	Hereditary motor and sensory neuropathy; hereditary neuropathy with susceptibility to pressure palsies	Family history and DNA analysis needed
	Recessively inherited neuropathies	Family history often negative
Metabolic neuropathy	Diabetic neuropathy and neuropathy associated with impaired glucose tolerance; uremic, hepatic, and acromegalic neuropathy; neuropathy associated with hypothyroidism	Appropriate laboratory testing needed
Paraneoplastic neuropathy	Neuropathy associated with lymphoma or carcinoma	Workup for underlying cancer needed
Neuropathy associated with monoclonal gammopathy	Neuropathy associated with osteosclerotic myeloma, with monoclonal gammopathies of undetermined significance, and with Waldenström's macroglobulinemia	Workup for underlying cancer needed
Neuropathy associated with infectious diseases	Infection with the human immunodeficiency virus	Appropriate laboratory testing needed
	Leprosy	Typically starts with sensory loss; minor weakness in later stages
	Borreliosis (including Lyme disease)	Appropriate laboratory testing needed
	Diphtheria	Microbiologic culture of isolates
Neuropathy associated with systemic inflammatory or immune-mediated diseases	Sarcoidosis; neuropathy associated with acquired amyloidosis; vasculitis, including polyarteritis nodosa, Churg–Strauss syndrome, rheumatoid arthritis, Sjögren's syndrome, Wegener's granulomatosis, systemic lupus erythematosus, systemic sclerosis, giant-cell arteritis, Behçet's syndrome, cryoglobulinemia, Castleman's disease	Appropriate laboratory testing needed and sural-nerve or muscle biopsy if condition is suspected
	Nonsystemic vasculitic neuropathy	Sural-nerve or muscle biopsy needed if condition is suspected
Toxic neuropathies	Alcohol, industrial agents (e.g., acrylamide), metals (e.g., lead), drugs (e.g., platinum-based agents, amiodarone, perhexiline, tacrolimus, chloroquine, and suramin)	Axonal more than demyelinating
Neuropathy due to nutritional deficiency	Deficiency of vitamin B_1, B_6, B_{12}, or E	Appropriate laboratory testing needed
Porphyria-associated neuropathy	—	Appropriate laboratory testing needed
Polyneuropathy associated with critical illness	Polyneuropathy associated with sepsis, multiple-organ failure, or long-term ventilation	—

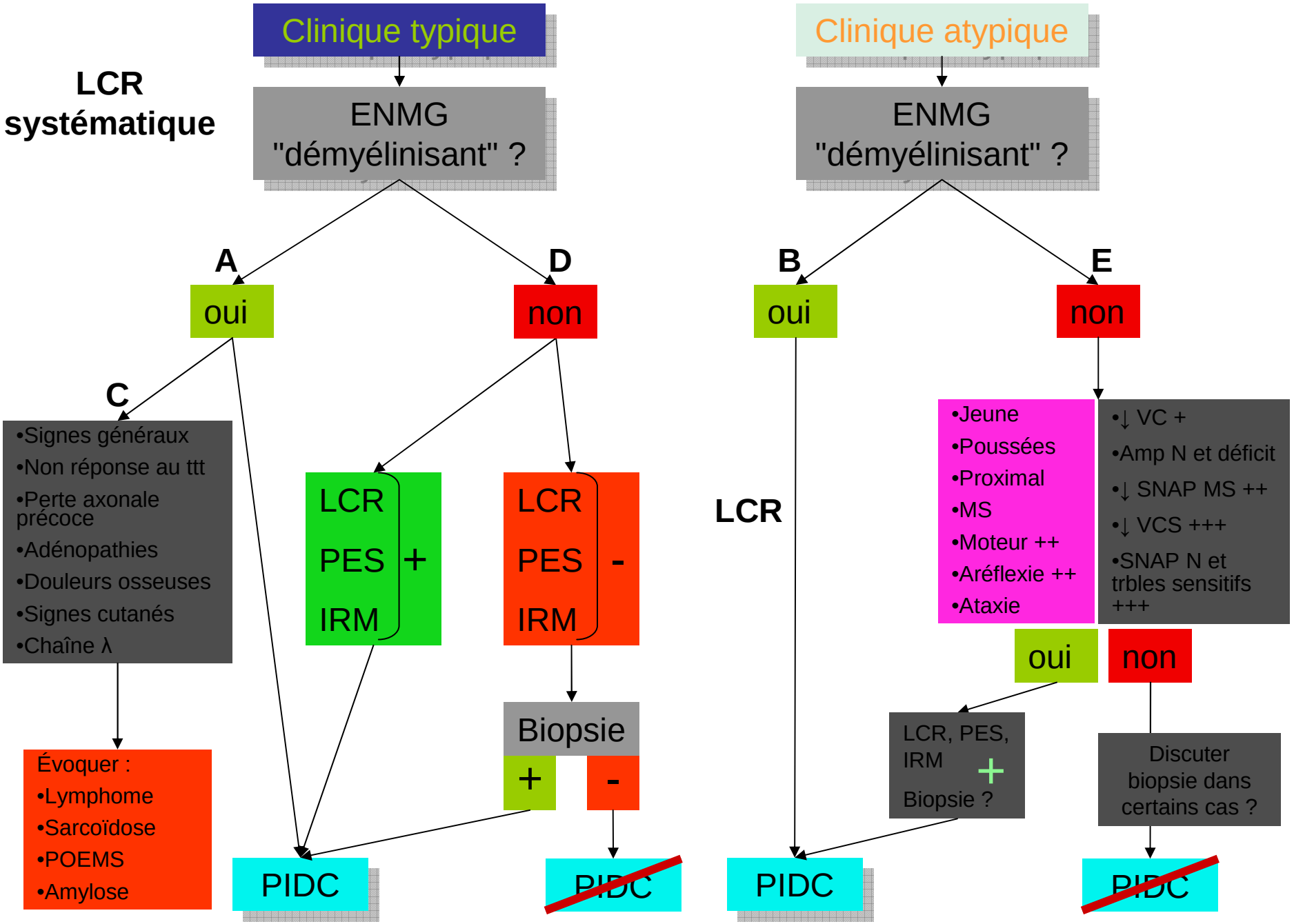
Glycemia, renal, hepatic & thyroid functions

Total body CT scan/PET scan

Electrophoresis & immunoelectrophoresis

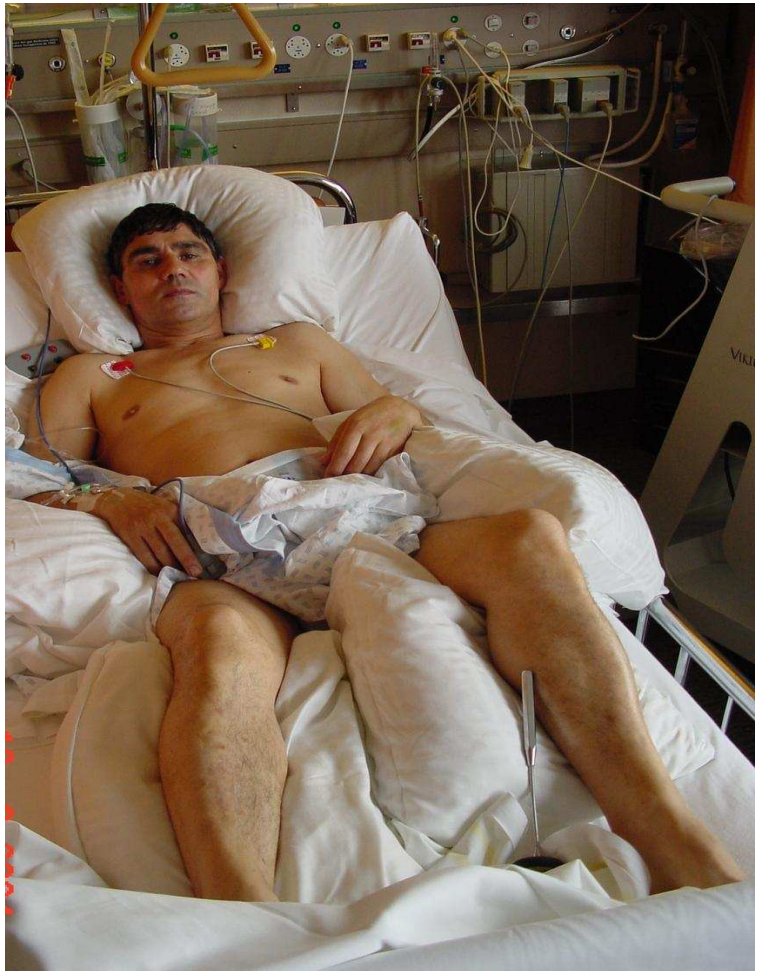
HIV serology

Erythrocyte sedimentation rate , C-reactive protein , anemia, white blood cell count and eosinophilia, antineutrophil cytoplasmic antibody levels and hematuria


LCR systématique
Clinique typique
ENMG "démyélinisant" ?
A
oui
D
non
C
•Signes généraux
•Non réponse au ttt
•Perte axonale précoce
•Adénopathies
•Douleurs osseuses
•Signes cutanés
•Chaîne λ
Évoquer :
•Lymphome
•Sarcoïdose
•POEMS
•Amylose
LCR
PES
IRM
+
LCR
PES
IRM
-
Biopsie
+
-
PIDC
PIDC
Clinique atypique
ENMG "démyélinisant" ?
B
oui
E
non
LCR
•Jeune
•Poussées
•Proximal
•MS
•Moteur ++
•Aréflexie ++
•Ataxie
•↓ VC +
•Amp N et déficit
•↓ SNAP MS ++
•↓ VCS +++
•SNAP N et trbles sensitifs +++
oui
non
LCR, PES, IRM
+
Biopsie ?
Discuter biopsie dans certains cas ?
PIDC
PIDC

Diagnosis of typical GBS

Case report. – 45 yo – Day 3 after his admission to the ICU. Weakness in the 4 limbs (MRC 1 to 2); areflexia; no sensory loss; nocturnal pain in the back.



Features required for diagnosis

- Progressive weakness in both arms and legs (might start with weakness only in the legs)
- Areflexia (or decreased tendon reflexes)

Features that strongly support diagnosis

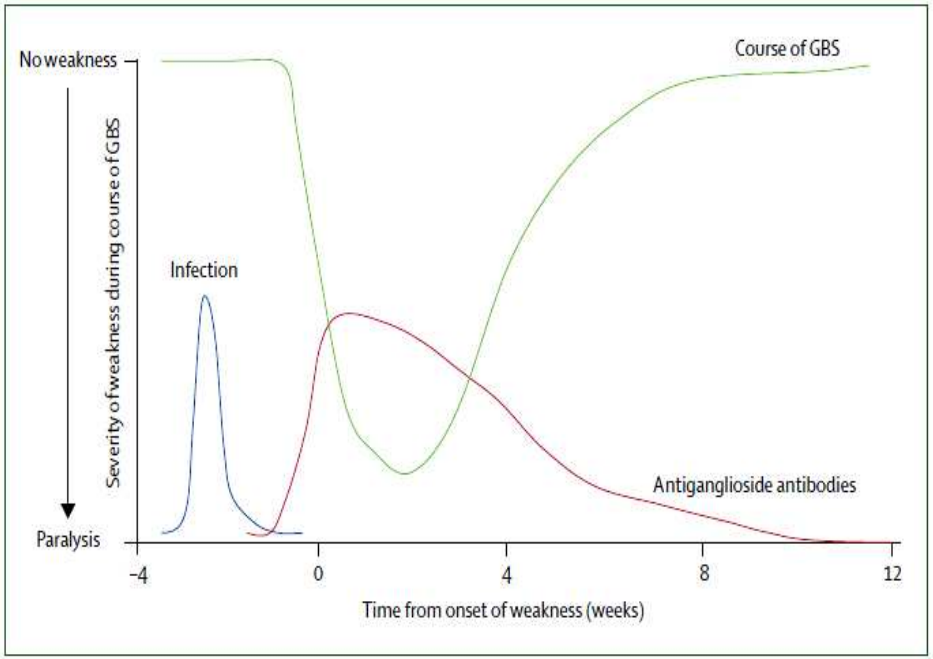
- Progression of symptoms over days to 4 weeks
- Relative symmetry of symptoms
- Mild sensory symptoms or signs
- Cranial nerve involvement, especially bilateral weakness of facial muscles
- Autonomic dysfunction
- Pain (often present)
- High concentration of protein in CSF
- Typical electrodiagnostic features

Features that should raise doubts

- Severe pulmonary dysfunction with limited limb weakness at onset
- Severe sensory signs with limited weakness at onset
- Bladder or bowel dysfunction at onset
- Fever at onset
- Sharp sensory level
- Slow progression (consider CIDP)
- Marked persistent asymmetry of weakness
- Persistent bladder or bowel dysfunction
- Increased number of mononuclear cells in CSF (>50×10^6/L) or polymorphonuclear cells in CSF

van Doorn et al, Lancet Neurology 2008

Investigations for GBS



	Antibodies
Acute inflammatory demyelinating Polyradiculoneuropathy	Unknown
Acute motor (and sensory) axonal neuropathy (AMAN or AMSAN)	GM1, GM1b, GD1a, GalNAc-GD1a
MFS and GBS overlapping syndrome	GQ1b

Table: Spectrum of GBS subtypes and serum antiganglioside antibodies

Studies related to establishing the diagnosis

Electrodiagnostic studies : a minimum study could include 3 sensory nerves (conduction velocity and amplitude), 3 motor nerves (distal latency, amplitude, and conduction velocity) with F waves and bilateral tibial H-reflexes

CSF examination: a minimum study could include glucose, protein, cell count, and bacterial culture

Studies to be done in special circumstances

Urine porphobilinogen and delta-aminolaevulinic acid concentrations

Antinuclear factor

HIV testing in at risk subjects

Drug and toxin screen

Studies related to general medical care

Urine analysis

Complete blood count

Erythrocyte sedimentation rate

Biochemical screening

Coagulation studies

ECG & Chest radiograph, Pulmonary function tests

Studies related to understanding causation

Stool culture and serology for C jejuni

Stool culture for poliovirus in pure motor syndromes

Acute and convalescent serology for cytomegalovirus, Epstein-Barr virus and M. pneumoniae as a minimum

Antibodies to gangliosides GM1, GD1a, and GQ1b

van Doorn PA et al, Lancet Neurology 2008

Hughes RAC et al, Lancet 2005

Quelle(s) donnée(s) clinique(s) peuvent vous aider à faire la différence entre un Guillain-Barré et une PIDC subaigüe ?

1. **Une infection précessive ?**
2. **L'existence de douleurs ?**
3. **L'âge ?**
4. **Une atteinte de paire crânienne ?**
5. **La vitesse d'installation des troubles ?**

Distinguishing acute-onset CIDP from fluctuating Guillain-Barré syndrome

A prospective study

Neurology, 2010; 74: 1680-1686.

L. Ruts, MD
J. Drenthen, MD
B.C. Jacobs, MD, PhD
P.A. van Doorn, MD, PhD
On behalf of the Dutch GBS Study Group

	GBS-TRF (n = 16)	A-CIDP (n = 8)	*p* Value
Male, n (%)	12 (75)	6 (75)	1.0
Age at onset, y, mean ± SD	54 ± 17	47 ± 18	0.37
Previous GBS-like episode in medical history, n (%)	1 (6)	1 (13)	1.0
Paresthetic/hypesthetic sensations, n (%)	14 (88)	8 (100)	0.54
Pure motor, n (%)	1 (6)	2 (25)	0.25
Pain before onset of weakness, n (%)	6 (38)	4 (50)	0.67
Pain in acute phase, n (%)	13 (81)	5 (71)[a]	0.62
Cranial nerve dysfunction, n (%)	11 (69)	1 (13)	0.03
III, IV, or VI	6 (38)	0	
VII	10 (63)	1 (13)	
IX, X, or XII	4 (25)	0	
Clinical preceding infections			
Respiratory tract/influenza(-like), n (%)	5 (31)	2 (25)	1.0
Gastroenteritis/diarrhea, n (%)	4 (25)	2 (25)	1.0

	GBS-TRF (n = 16)	A-CIDP (n = 8)	*p* Value
Course			
Days to reach nadir, median (95% CI)[a]	8.5 (6–11)	16.5 (5–22)	0.03
Days to reach first TRF/exacerbation, median (95% CI)[a]	18 (15–27)	51 (31–63)	0.00
Days to reach second TRF/exacerbation, median (95% CI)[a]	38 (31–46)[b]	105 (52–116)[b]	0.01
Days from onset of weakness to inclusion	5 (2–10)	14.5 (5–26)	0.01
Days from onset of paresthesia to inclusion	8 (5–17)[c]	12.5 (7–24)	0.04
Days from onset of hypesthesia to inclusion	6.5 (3–12)[d]	10 (7–21)[e]	0.12

Quelle(s) donnée(s) biologique(s) peuvent vous aider à faire la différence entre un Guillain-Barré et une PIDC ?

1. La protéinorachie ?
2. La cellularité du LCR ?
3. La VS ?
4. Les données de l'EMG (vitesses – blocs) ?
5. Une dénervation à l'aiguille ?

	GBS-TRF (n = 16)	A-CIDP (n = 8)	*p* Value
CSF			
Cells, 10^6/L, median (95% CI)	2 (2-4)[b]	2 (0-5)[c]	0.30
Protein, g/L, median (95% CI)	0.9 (0.4-1.8)	0.7 (0.5-1.6)[a]	0.68
Increased protein, >0.55 g/L, n (%)	10 (63)	4 (57)[a]	1.0
Antiganglioside antibodies			
IgM reactivity against GM1, GM2, GD1a, GD1b, or GQ1b	2 (13)	1 (13)	1.0
IgG reactivity against GM1, GM2, GD1a, GD1b, or GQ1b	3 (19)	0	0.53

PIDC « aiguë » :

Nerfs crâniens respectés
Moins aigu / PRNA
Moins sévère
VCM plus altérées

Neurology, 2010; 74: 1680-1686.

	GBS-TRF (n = 14)	A-CIDP (n = 8)	*p* Value[a]	A-CIDP second EMG (n = 6)
Demyelinating features, n (%)				
Prolonged DML	9 (64)	6 (75)	0.86	6 (100)
Decreased mNCV	4 (29)	6 (75)	0.04	4 (67)
Conduction block and/or temporal dispersion	4 (29)	3 (38)	0.67	2 (33)
Increased latency F-wave	5 (50)[b]	5 (83)[c]	0.18	5 (100)[d]
Axonal features, n (%)				
Denervation potentials	7 (54)[e]	6 (75)	0.06	1 (20)[d]
Sensory abnormality arms, n (%)	7 (50)	0 (0)	0.08	5 (83)
Classification, n (%)			0.53	
Demyelinating	9 (64)	6 (75)		5 (83)
Axonal	2 (14)	0		0
Equivocal	3 (21)	2 (25)		1 (17)
Normal	0	0		0
CIDP criteria fulfilled	2 (14)	2 (25)	0.90	2 (33)

Two questions

Is there an indication for admission to an intensive care unit ?

- Rapid progressive severe weakness often with impaired respiration (vital capacity <20 mL/kg)
- Need for artificial ventilation
- Insufficient swallowing with high chance of pulmonary infection
- Severe autonomic dysfunction

Consider treatment with IVIg or PE

- Severely affected patients (inability to walk unaided)
- Start IVIg preferably within first 2 weeks from onset: 0.4 g/kg for 5 days; or 4× PE with total exchange volume of five plasma volumes in 2 weeks

Unknown whether IVIg is effective:

- Mildly affected patients

Indications for re-treatment with IVIg:

- No proven effect of re-treatment with IVIg in patients who continue to worsen

Others immunomodulating drugs??

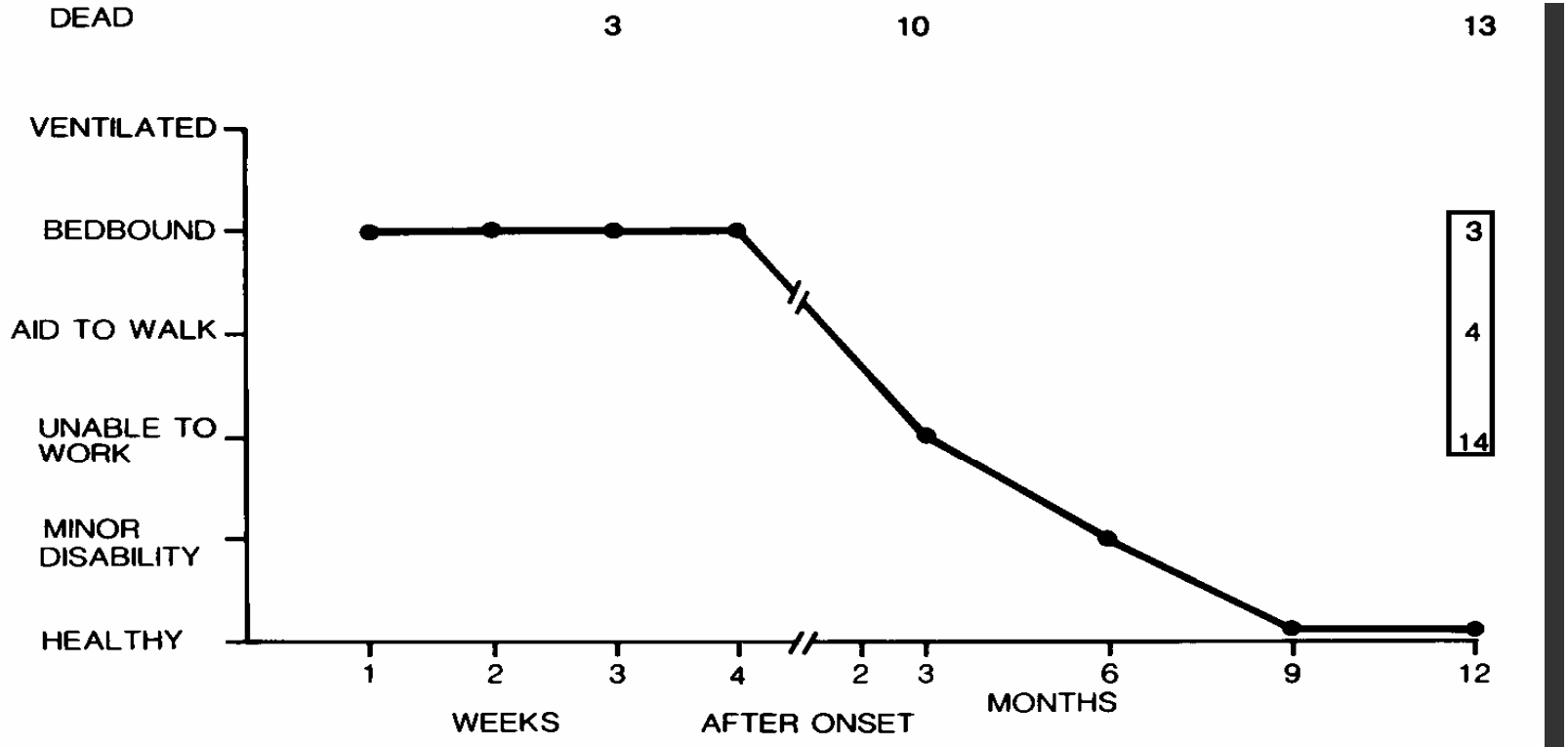


Fig. 6.1. Recovery from Guillain–Barré syndrome. The points on this diagram represent median disability grades of 100 patients. The figures on the top line represent the cumulative numbers of dead patients at those times. The figures in the box on the right represent the number of disabled survivors after one year. (Data from Winer et al. (1988), with permission.)

Despite IVIg treatment, many patients only partially recover and have residual weakness, pain, and fatigue

Management of GBS during the course of disease diagnosis

Give good general care, monitor progression and prevent and manage potentially fatal complications, especially:

- Regularly monitor pulmonary function (vital capacity, respiration frequency), initially every 2–4 h, in stable phase every 6–12 h
- Regularly check for autonomic dysfunction (blood pressure, heart rate, pupils, ileus), initially continuous monitor heart rate , pulse and blood pressure. If logistically impossible, check every 2–4 h, in stable phase every 6–12 h
- Check for swallowing dysfunction
- Recognise and treat pain: acute nociceptive pain, according to WHO guidelines (try to avoid opioids); amitriptyline or antiepileptic drugs
- Prevent and treat infections and pulmonary embolism
- Prevent cornea ulceration due to facial weakness
- Prevent decubitus and contractures

Rehabilitation and fatigue

- Start physiotherapy early during course of disease, as soon as improvement starts
- Consider a physical training programme for severe fatigue
- Consider contacting patients' organisation for additional information and help

	Categories	Score
Age at onset (years)	>60	1
	41–60	0·5
	≤40	0
Diarrhoea (≤4 weeks)	Absence	0
	Presence	1
GBS disability score (at 2 weeks after entry)	0 or 1	1
	2	2
	3	3
	4	4
	5	5
Erasmus GBS outcome score		1–7

Table 3: **The Erasmus GBS outcome score**

van Koningsveld R et al. Lancet Neurol 2007

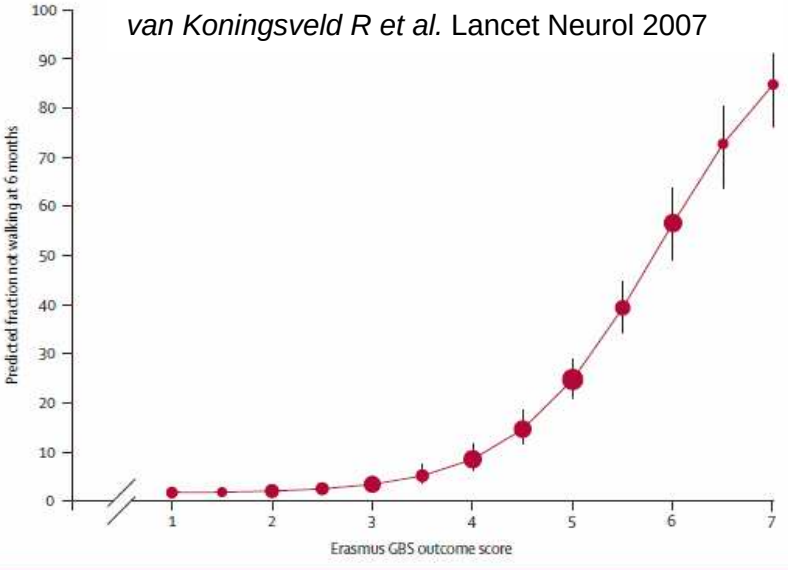


Figure: **Predicted fraction of patients unable to walk independently at 6 months after randomisation on the basis of the Erasmus GBS outcome score (n=762)**
Vertical bars indicate 95% CI. Point sizes proportionate to the number of patients with a specific score. The probability of not walking independently at 6 months is given by the equation 1/(1+exp[8·2–1·4×EGOS]).

Practical points for Guillain-Barré syndrome:

- The most frequently encountered acute neuropathy
- Patients are in particular need of excellent multidisciplinary care to prevent and manage potentially fatal complications (previous panel), so hospitalize each patient
- After the acute phase, plan to review periodically each patient to prevent and manage chronic complications, such as cramps (quinine), pain (gabapentine & others), weakness and fatigue (physical training programme)

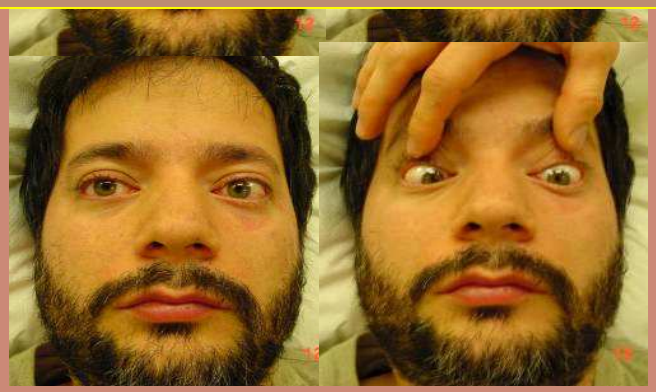
Miller-Fisher Syndrome

Triad: Ophthalmoplegia – Ataxia – Areflexia

Case report: A 31 year old man referred with the chief complaint of diplopia and mild ataxia

Over the next few days he developed ophtalmoplegia, facial palsy , dysesthesia in hands, areflexia and marked unsteadiness of gait. A MRI of the head was normal; CSF was normal

Anti- GQ1b antibody on admission
> 15,000 in serum



- Initial symptoms; n=267

  Ito et al. Rinsho Shinkeigaku 2005
  - Diplopia 63%
  - Gait disturbance 33%
  - Dysesthesia 17%
  - Blepharoptosis 5%
  - Photophobia 3%
- Incidence

  Mori et al. Neurology 2005
  - 5% of GBS in Western countries
  - 0.09 / 100,000 population in Italy
  - 19% of GBS in Taiwan
  - 25% of GBS in Japan
- Anti-GQ1b antibodies in 85 %

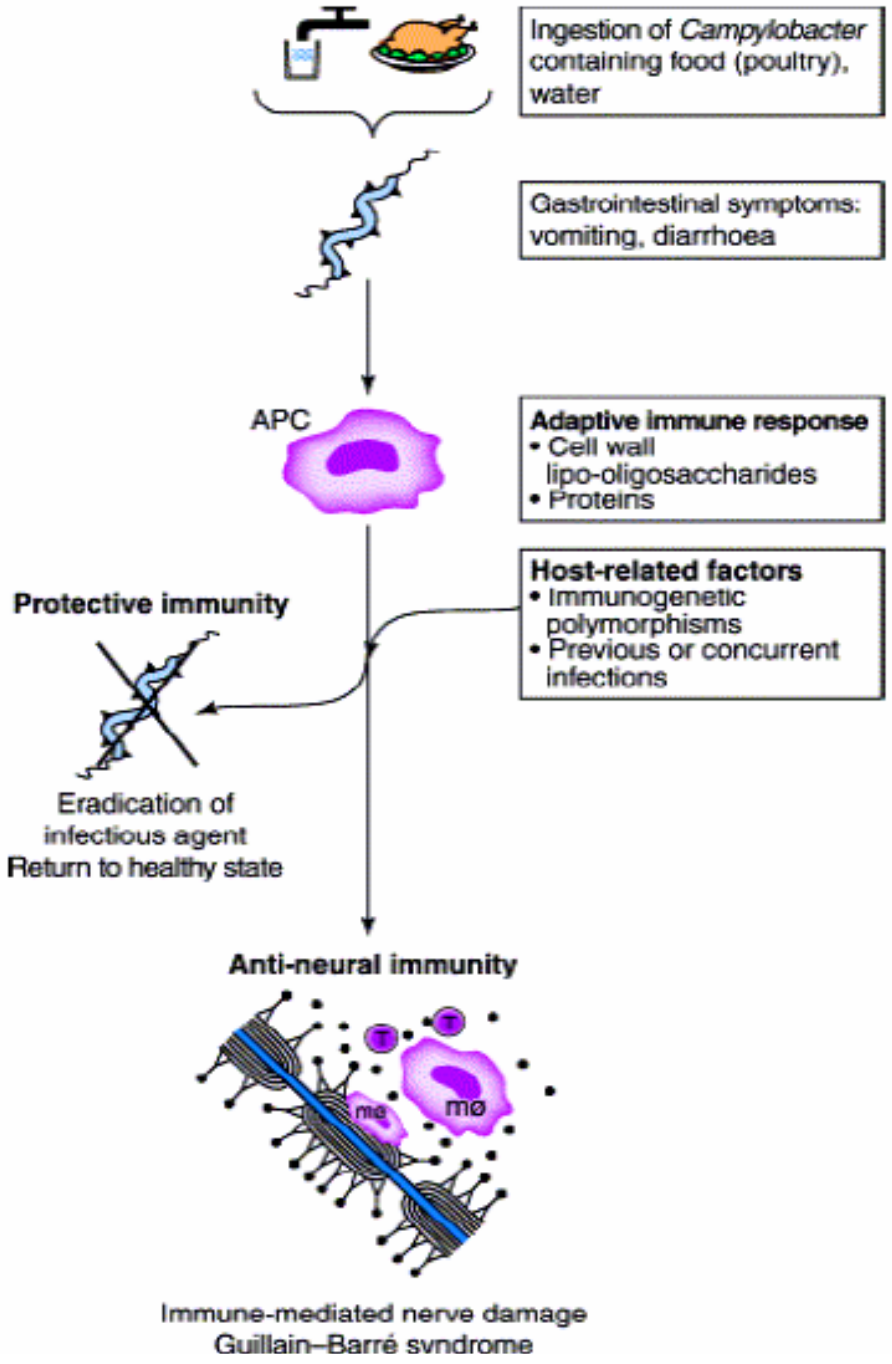
Mimétisme moléculaire

1/ Association épidémiologique agent infectieux et désordre auto-immun

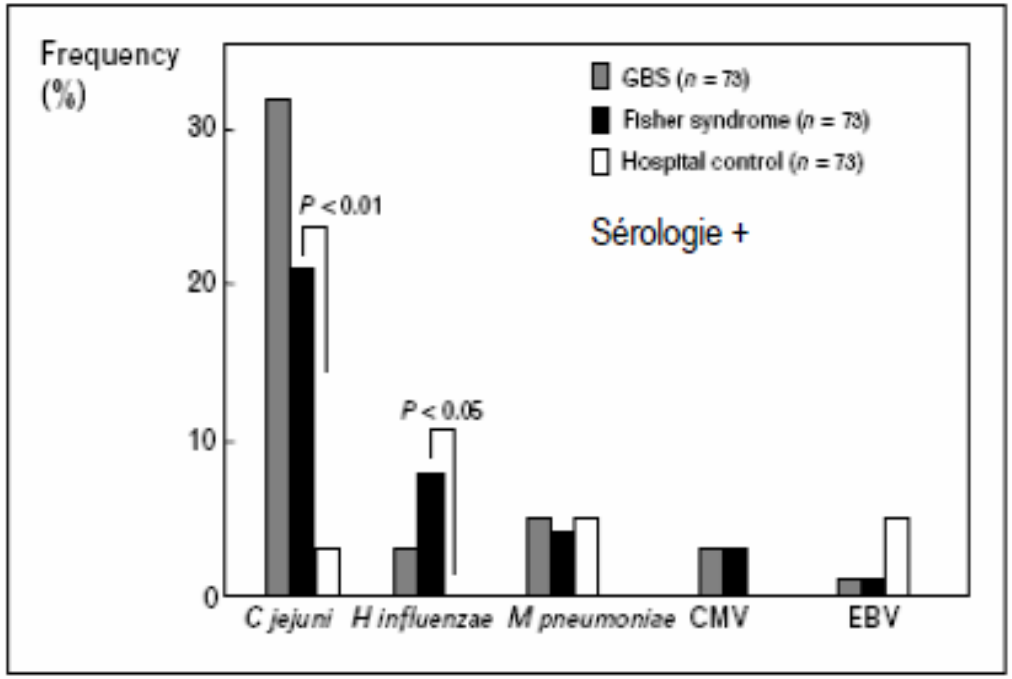
2/ Identification AC dirigés contre cibles antigéniques de l'hôte

3/ Identification mimétisme moléculaire avec Ag de la cible

4/ Reproduction de l'affection sur un modèle animal



Les preuves épidémiologiques



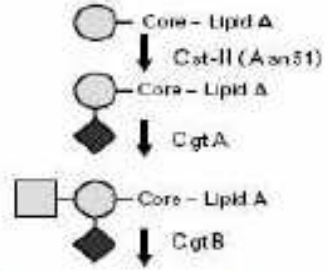
Yuki et al 2006. étude cas/témoin

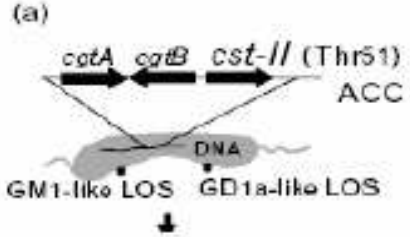
Syndrome de Guillain-Barré
Lié à l'infection par *C jejuni* (20 à 30%)
- Atteinte motrice prédominante
- Évolution axonale fréquente
- Lésions histologiques particulières

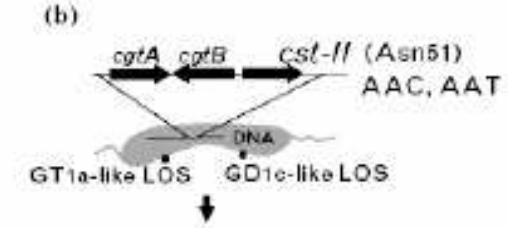
Syndrome de Miller-Fisher
Association à des IgG anti-QG1b : 90%
20% d'infection à *C. jejuni*

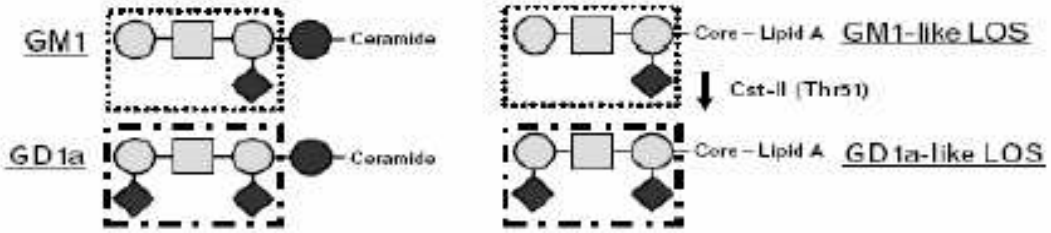
D'après Yuki et Koga 2006
Wilison et Yuki 2002

C jejuni et polymorphisme de la sialiltransférase Cst-II

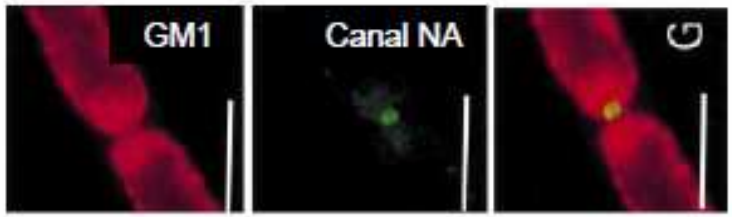








AC IgG anti-GM1 et GD1a complexe GM1/GD1a
GBS moteur



Modèle animal d'immunisation avec GM1

Risque 1/3000

AC IgG anti-GQ1b
Syndrome de Fisher

Modèle in vivo

Activation du complément C5B9

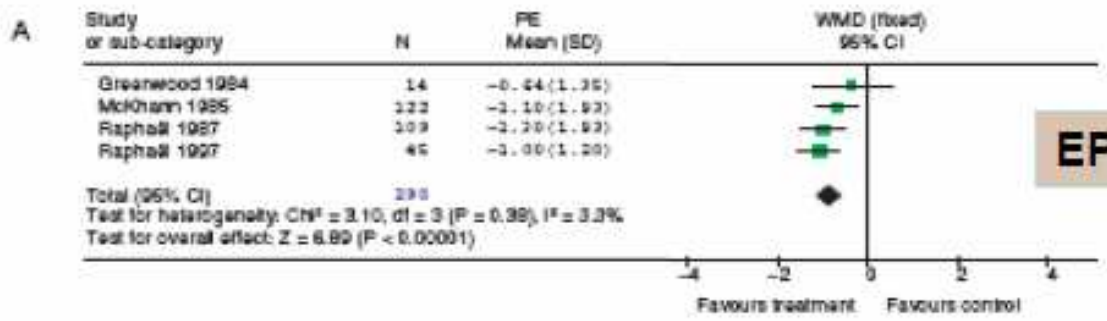
4/ Reproduction de l'affection sur un modèle animal

Infection CJ et Immunisation LOS purifiées induit une réaction croisée anti-ganglioside Spécificité des AC proche de ceux retrouvés chez l'homme

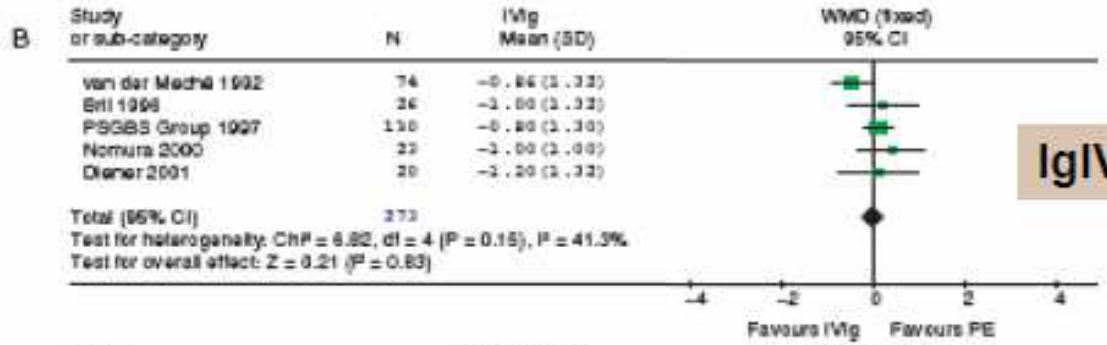
(Ang, Infect Immun, 2001)

Immunisation lapins avec Ac anti-gangliosides induit neuropathie type GBS
Reproduction tableau avec CJ-LOS

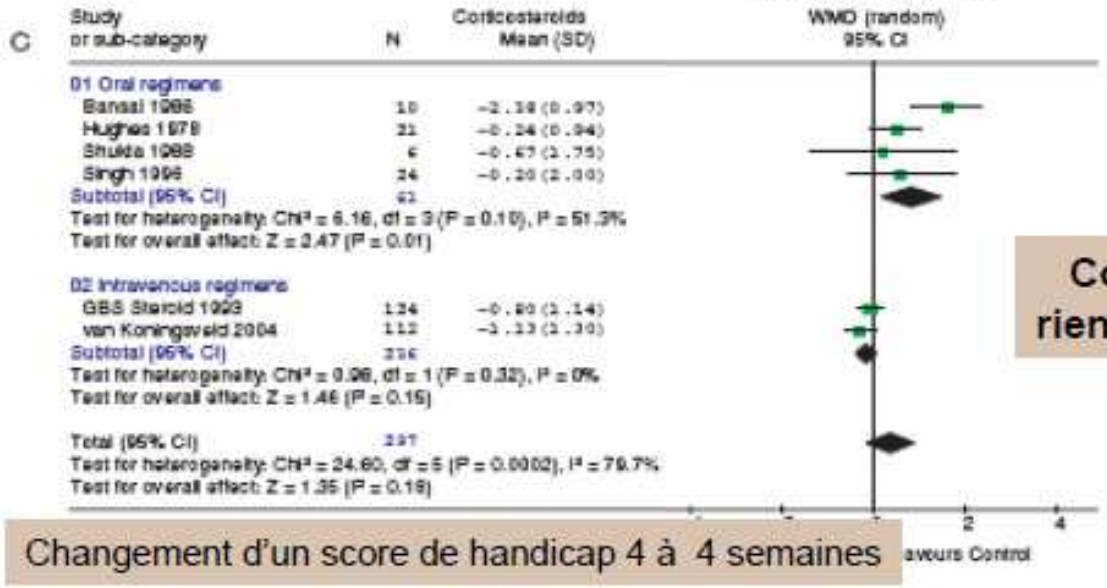
(Yuki, J Periph Nerv Syst, 2003)



EP/placebo



IgIV/EP



Corticoïdes/ rien ou placebo

20% de mortalité ou séquelles par atteinte axonale

Changement d'un score de handicap 4 à 4 semaines

Brain (2007), 130: 2245–2257

REVIEW ARTICLE

Immunotherapy for Guillain-Barré syndrome: a systematic review

Richard A. C. Hughes,[1] Anthony V. Swan,[1] Jean-Claude Raphaël,[2] Djillali Annane,[3] Rinske van Koningsveld[3] and Pieter A. van Doorn[3]

Echanges Plasmatiques

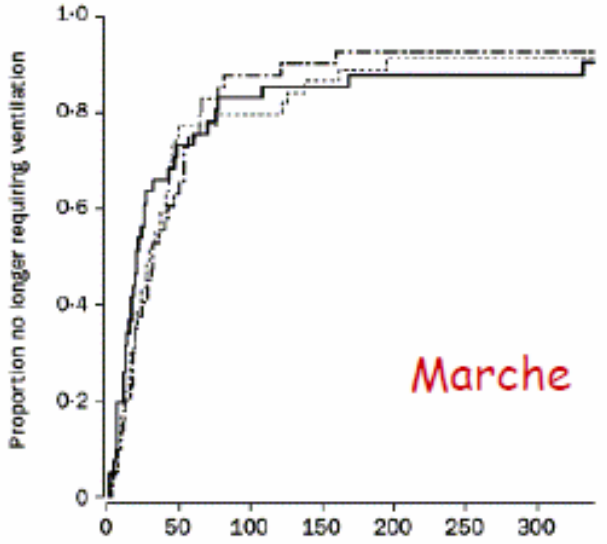
French Cooperative Group, Ann Neurol 1997

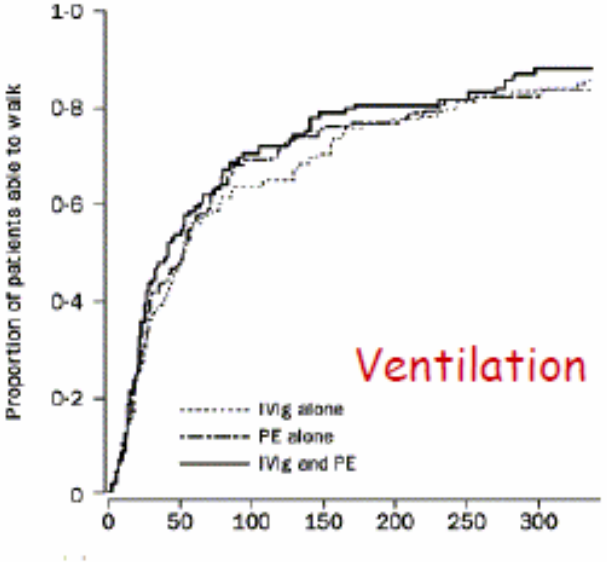
	Symptômes légers			Symptômes modérés			Symptômes sévères		
	0 PE n =46	2 PE n=45	*p*	2 PE n=149	4 PE n=155	*p*	4 PE n=81	6 PE n=80	*p*
Temps de récupération motrice	8	4	0.0002	6	5	0.1	8	8	0.11
Marche avec assistance	14	14	0.8	24	20	0.04	56	60	0.89
Marche sans assistance	28	15	0.4	64	52	0.13	113	103	0.64
Détérioration clinique	18	2	0.0001	-	-	-	-	-	
Ventilation	6	1	0.11	42	41	1.0	81	80	
Durée de la ventilation	30	7	-	37	15	0.005	43	34	0.96
Durée du décubitus	18	13	0.02	26	21	0.04	50	44	0.57
A 1 an									
Patients avec une récupération totale	20	28	0.1	45	67	0.006	29	31	0.63
Patient sans séquelle motrice sévère	5	5	-	22	26	-	16	8	
Patients avec séquelles motrices sévères	2	0	0.24	24	12	0.05	15	14	1.0

IgIV vs EP vs Combinaison

379 patients
EP (5 ; 50 ml/kg) : 121
Ig IV (400 ml/kg/j pdt 5 jours) : 130
EP puis IgIV : 128

	EP	IgIV	EP+IgIV
H/F	61%	61%	56%
Délai	6.9	6.4	6.7
Score	3.9	4.0	3.9
Ventil.	9.9%	11.5%	15.6%
PGAM bas	13.9%	16.1%	11.7%
Entérite	24%	18.5%	19.5%





Plasma Exchange/Sandoglubulin Guillain-Barré Syndrome Trial Group The Lancet 1997

Corticostéroïdes

Guillain-Barré Syndrome Steroid Trial Group
Lancet 1993 ; 341 : 586-590 (242 Patients MP vs Placebo)

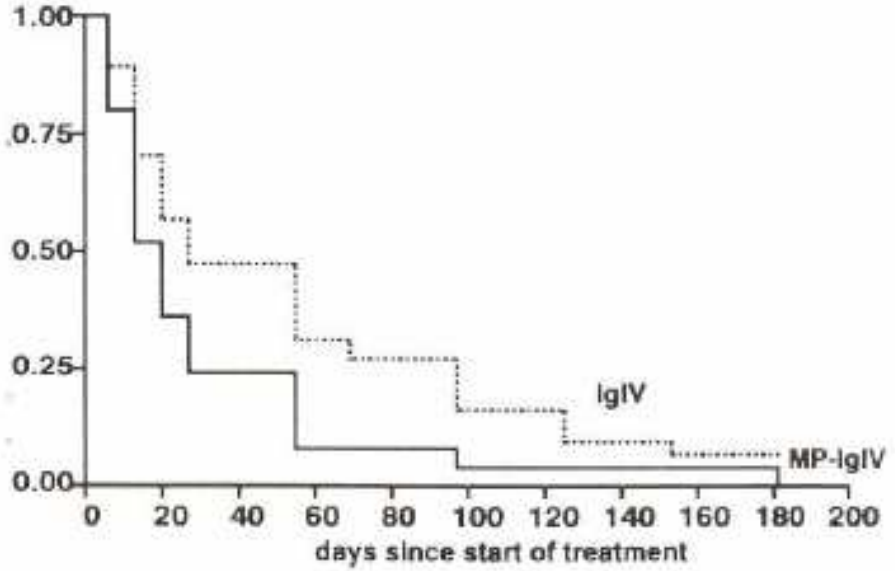
Pas d'efficacité

Ventilation : 18j vs 27 j / Marche sans aide : 38j vs 50 j

The Dutch Guillain-Barré Study Group.
Ann Neurol 1994 ; 35 : 749-752 (25 patients MP+IgIV ouvert)

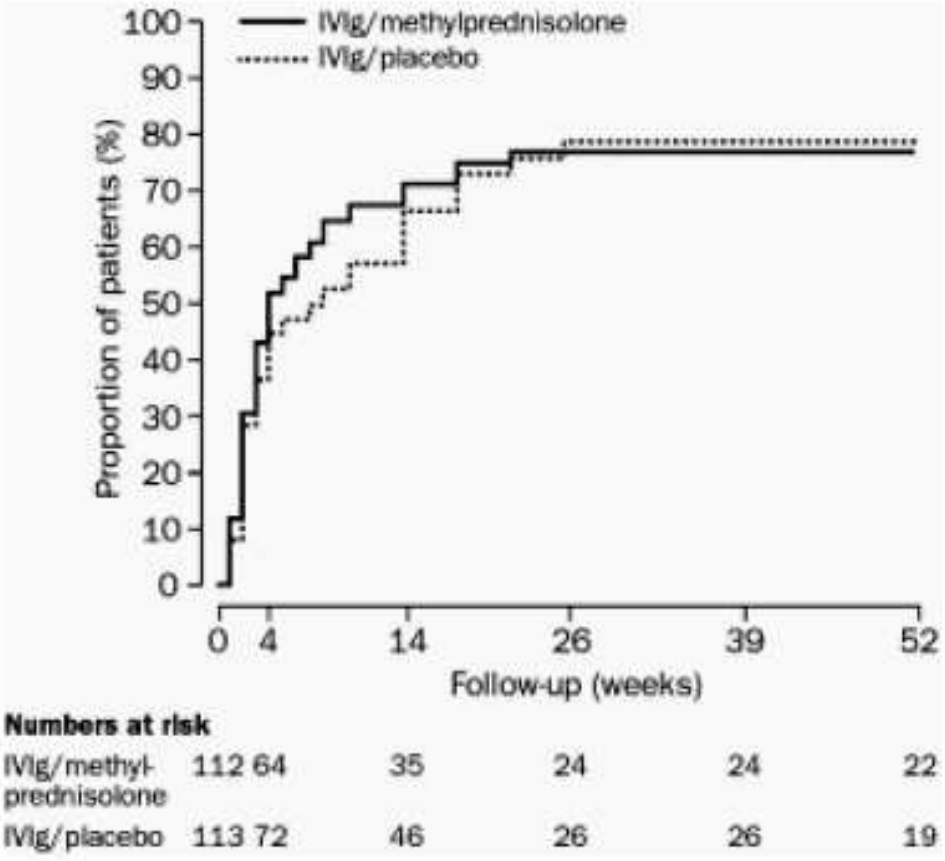
Amélioration : 76% vs 53%

	IgIV	MP+IgIV
Amélior.	27%	52%
Stable	50%	32%
Aggrav.	23%	16%



Corticostéroïdes

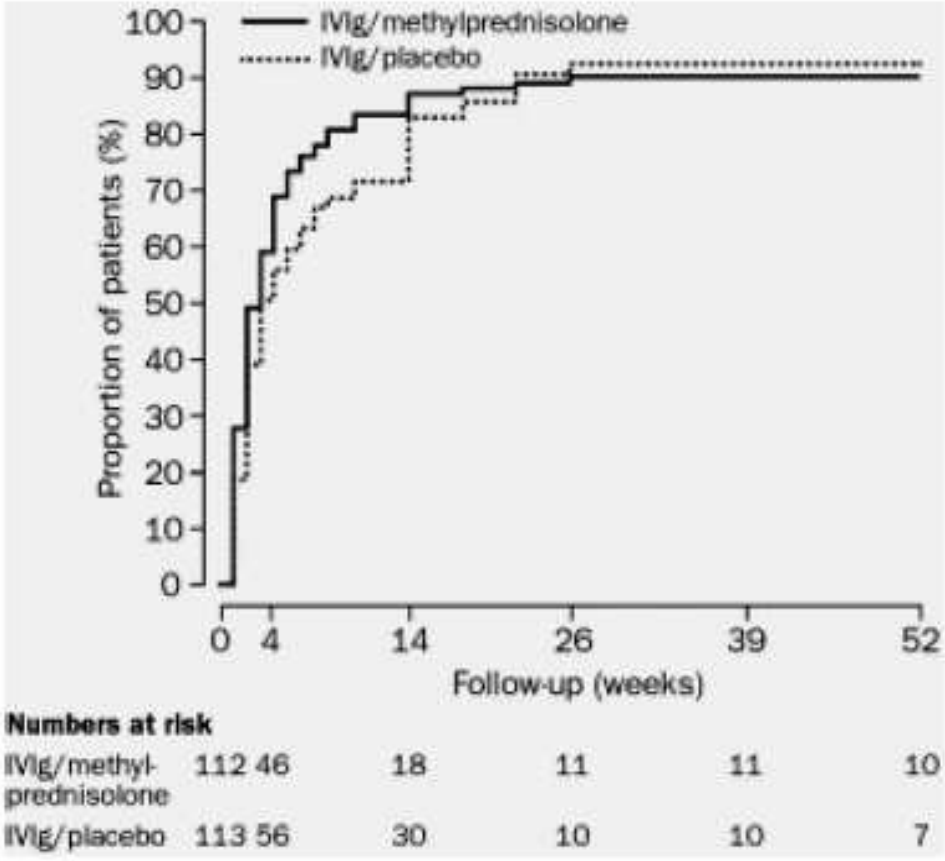
Marche sans aide



Numbers at risk

IVIg/methyl-prednisolone	112	64	35	24	24	22
IVIg/placebo	113	72	46	26	26	19

Amélioration score fonctionnel



Numbers at risk

IVIg/methyl-prednisolone	112	46	18	11	11	10
IVIg/placebo	113	56	30	10	10	7

Van Koningsveld R. The Lancet 2004 ; 363 : 192-196

Marche sans aide

- Echanges Plasmatiques
  - 85 jours North American Trial (18% incapables)
  - 70 jours French Trial
- Ig IV
  - 51 jours Dutch Trial (19% incapables)
  - 55 jours Sandobuline GBS Trial
- Corticostéroides
  - 38 jours GBS Steroid Trial
  - 28 jours Ig IV et MP (8% incapables)

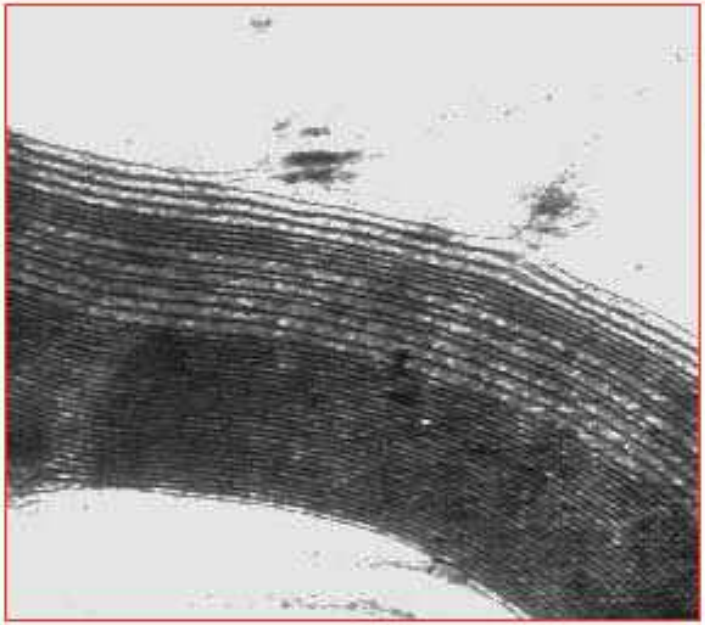
Characteristics of anti-MAG neuropathy:

•A slowly progressive length dependent demyelinating neuropathy with distal symmetric sensory-motor symptoms

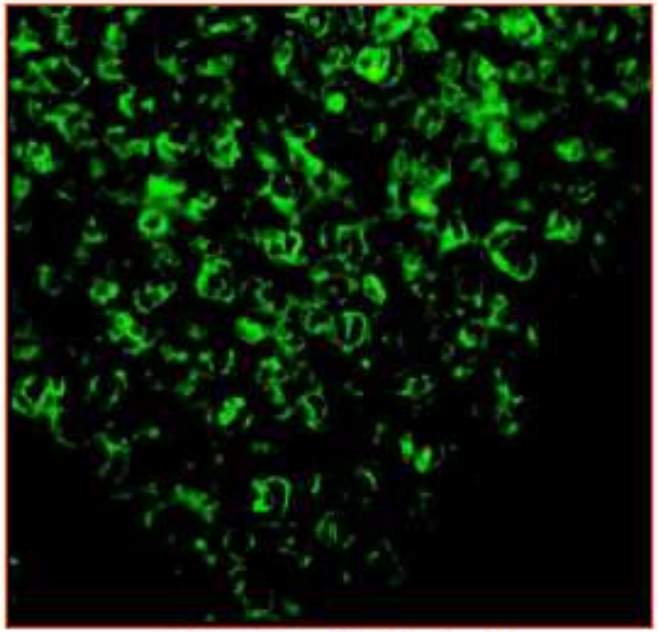
•Tremor and ataxia

•Peripheral neuropathy with IgM gammopathy, & elevated anti-MAG antibodies

Neuropathie avec IgM monoclonale anti-MAG



Élargissement de
la ligne dense interne



Dépôts d'IgM dans
le nerf du patient

+

Activation
du
Complément

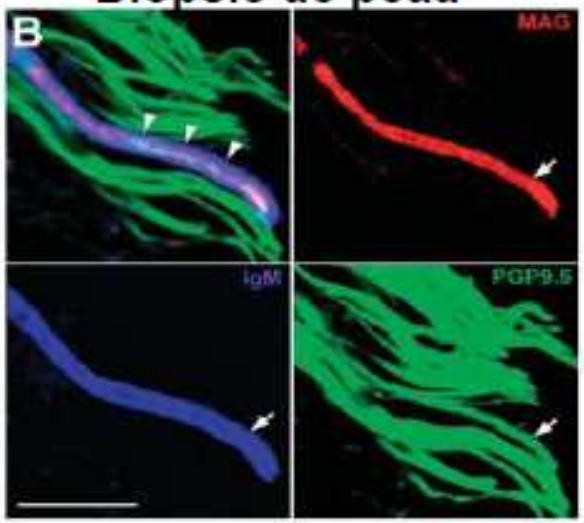
L'atteinte myélinique à prédominance distale

Clinique

EMG: index de latence terminale

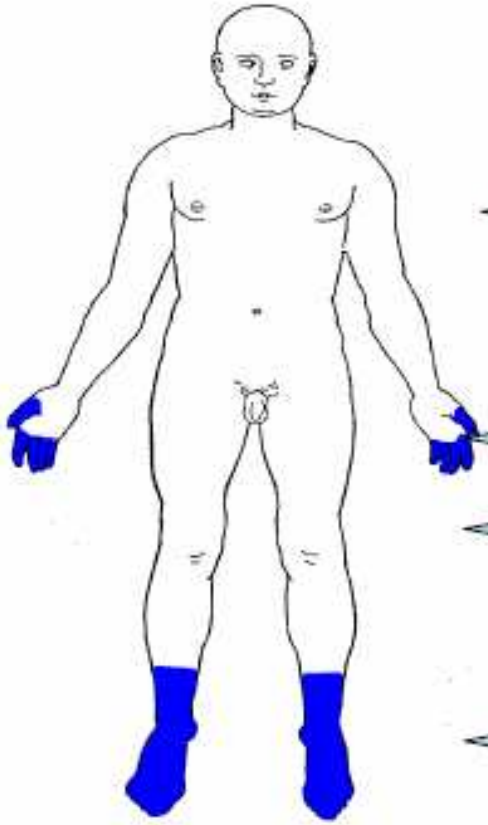
Dépots d'IgM

Biopsie de peau



+ dépôts de complément

Lombardi et al., 2005



Proportion de fibres Co-exprimant MAG et IgM

18,8%

30,6%

11,9%

38,2%

Neuropathies avec IgM anti-MAG: traitement

- Sur 22 études dont deux contrôlées
  - IgIV
  - EP
  - cyclophosphamide
  - chlorambucil
  - fludarabine, adriamicine...
  - interféron alpha
  - Immuno-adsorption
- 50% de répondeurs à court ou moyen terme

Brain (2000), 123, 710–717

Long-term prognosis of neuropathy associated with anti-MAG IgM M-proteins and its relationship to immune therapies

E. Nobile-Orazio,[1,2] N. Meucci,[1,2] L. Baldini,[1] A. Di Troia[1,2] and G. Scarlato[2]

Years	Mortality	Disability
5	8%	16%
15	33%	50%

19/25 traités

9 améliorés

1 de façon durable

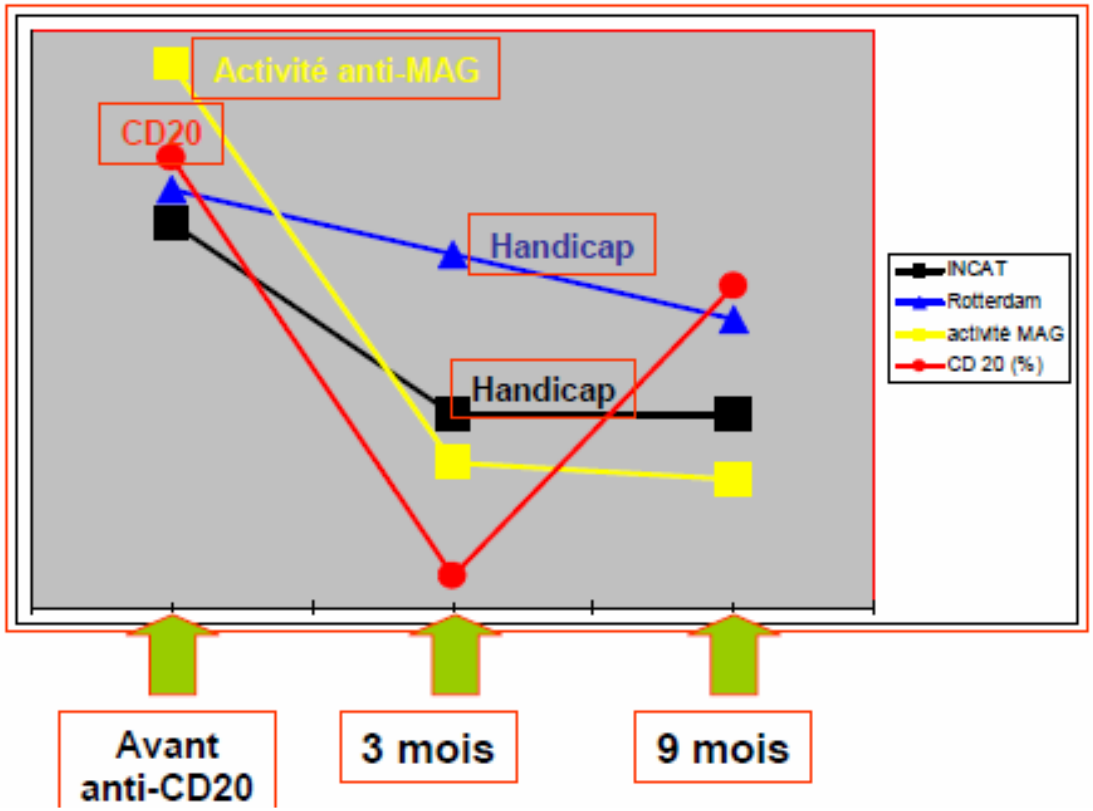
10 effets secondaires graves liés au traitement dont 3 DC

- **New Treatment**: B-cell depletion with anti-CD 20, Rituximab®, a mouse-human chimeric antibody
- Specific depletion of CD 20+ cells via antibody-dependent cell + complement mediated cytotoxicity
- Intravenous once weekly for 4 weeks, and retreatment is usually necessary
- Effective in the treatment of B cell lymphoma; rheumatoid arthritis;
- Rituximab is the first drug that improves some patients with A-MAG-DP in a controlled study (Ann Neurol 2009 ;65:286-93)

CD20 : molécule de différentiation spécifique des lympho B

- pré B
- B matures
- plasmocytes IgM circulants (20%)

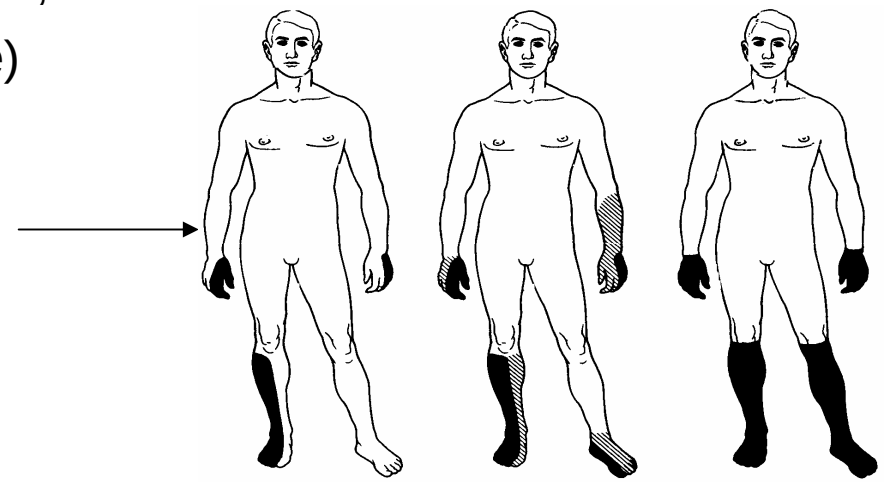
AC anti-CD20
(Rituximab® 375 mg/m²)



- Etudes ouvertes
  - Renaud et al., 2003. 9 cas. 375 mg/m2
    - Baisse de l'activité anti-MAG > 52% chez 8/9.
    - 6 améliorés, 2 stables, 1 aggravé
  - Nobile Orazio et al., 2007: 13 cas. 375 mg/m2
    - 60% améliorés surtout si taux d'IgM bas et diminue avec le ttt
  - **Steck et al. 2006 : 8 cas. 750 mg/m2**
    - 4/8 non ou partiellement répondeurs à 375 mg/m2 s'améliorent
- Etude contre un groupe contrôle non randomisée
  - Pestronk et al., 2003. 20 IgM M (12 gangliosides-8 MAG). 375 mg/m2 et 13 contrôle
    - Force améliorée de 23%
    - taux d'IgM abaissé de 55%
- Etudes contrôlées randomisée contre placebo
  - Dalakas AAN 2007: 28 patients 375 mg/m2
    - nb de patients améliorés >= 1 pt INCAT à 8 mois $p<0.05$
    - baisse du titre des AC de 50%
  - JM Leger : en cours

Peripheral neuropathies with IgM or IgG Gammopathy without anti-MAG activity are heterogeneous…

- Waldenström macroglobulinemia
  - Hyperviscosity
  - Amyloid deposit
  - IgM/G
- Myeloma
- POEMS (peripheral neuropathy, organomegaly, endocrine disorder, monoclonal protein, skin disease)
- Cryoglobulinemia with monoclonal IgM
- Amyloidosis
- Lymphoma
- Neurolymphomatosis



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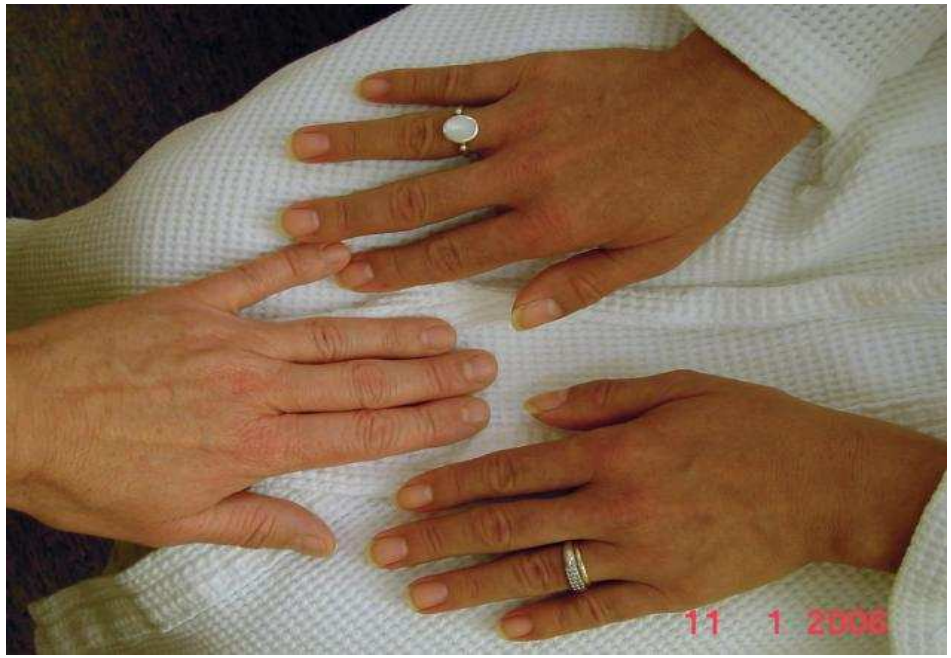
- ↑ CSF protein
- Demyelinating NP (efficacy of bevacizumab)
- Oseteosclerosis-lysis



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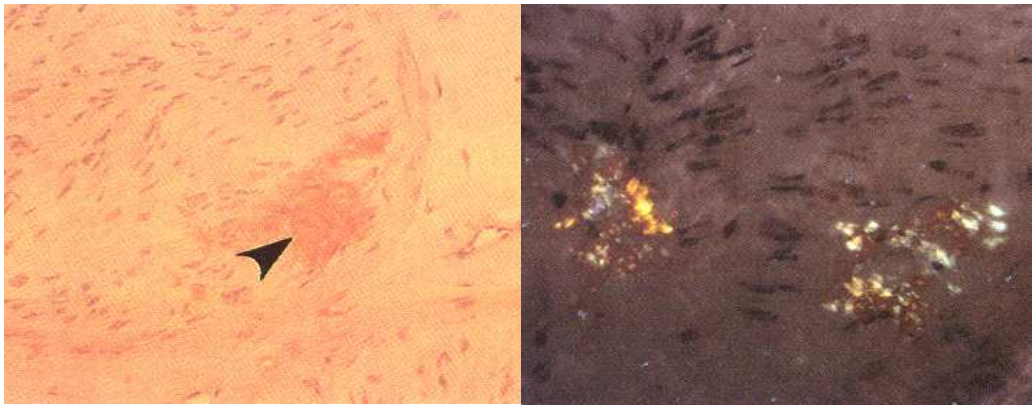

- Carpal tunnel (1/3)
- Distal axonal asymetric neuropathy
- Dysautonomia (2/3)
- Amyloid deposit

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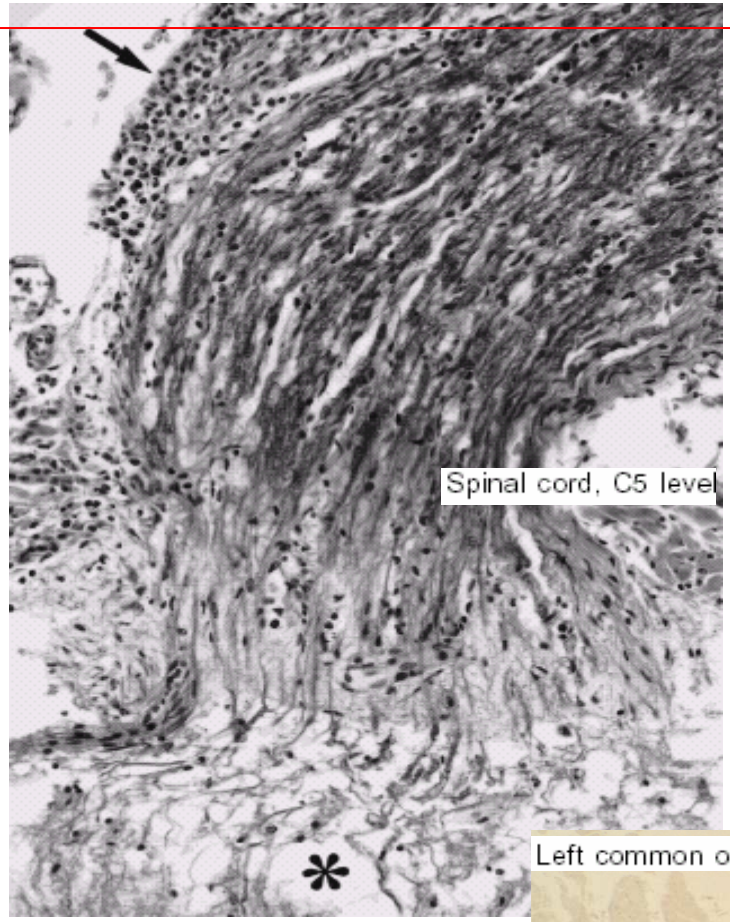
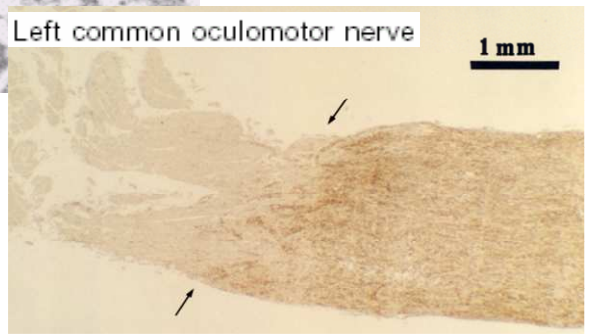


- Local infiltration
- Castleman's disease
- In association with HIV



Investigation and classification of the paraprotein, EFNS TASK FORCE, 2006 :

Classification of haematological conditions with a paraprotein :

(1) Malignant monoclonal gammopathies

(a) Multiple myeloma

(b) Plasmacytoma (solitary, extramedullary, multiple solitary)

(c) Malignant lymphoproliferative disease:

(i) Waldenström's macroglobulinaemia

(ii) Malignant lymphoma

(iii) Chronic lymphocytic leukaemia

(d) Heavy chain disease

(e) Primary amyloidosis (AL) (with or without myeloma)

(2) MGUS

Definition of monoclonal gammopathy of undetermined significance (MGUS):

(1) IgM–MGUS is defined by all of the following:

(a) No lymphoplasmacytic infiltration on bone marrow biopsy

(b) No symptoms or signs suggesting tumour infiltration (e.g. constitutional symptoms, hyperviscosity syndrome and organomegaly)

(c) No evolution to malignant lymphoproliferative disease requiring treatment within 12 months from first detection of paraprotein

(2) IgG or IgA–MGUS is defined by the presence of all of the following:

(a) Monoclonal component <30 g/l

(b) Bence-Jones proteinuria <1 g/24 h

(c) No lytic lesions in bone

(d) No anaemia, hypercalcaemia, or chronic renal insufficiency

(e) Bone marrow plasma cell infiltration <10%

(f) No evolution to myeloma or 1c

Brain (2001), **124**, 1968–1977

The clinical and laboratory features of chronic sensory ataxic neuropathy with anti-disialosyl IgM antibodies

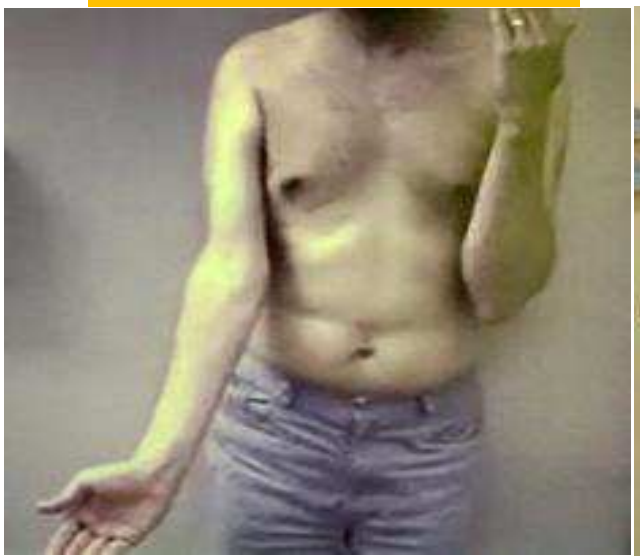
H. J. Willison,[1] C. P. O'Leary [1], J. Veitch,[1] L. D. Blumhardt,[2] M. Busby,[3] M. Donaghy,[3] P. Fuhr,[10] H. Ford,[4] A. Hahn,[11] S. Renaud,[10] H. A. Katifi,[5] S. Ponsford,[8] M. Reuber,[4] A. Steck,[10] I. Sutton,[6] W. Schady,[7] P. K. Thomas,[9] A. J. Thompson,[9] J.-M. Vallat[12] and J. Winer[6]

CANOMAD **Chronic Ataxic Neuropathy with Ophthalmoplegia, M protein, Agglutination and Disialosyl antibodies**

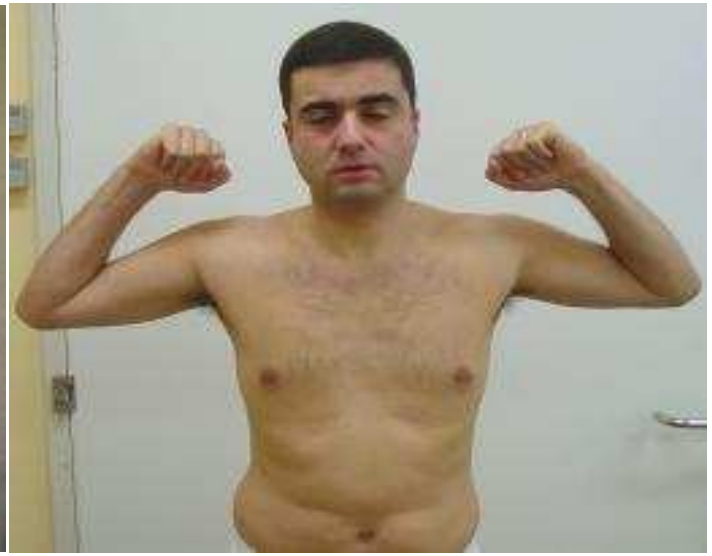
Think about it when there is evidence of « **Chronic Miller Fisher syndrome** » + anti-ganglioside IgM (kappa) antibodies against the NeuNac(α2-8)NeuNac(α2-3)Gal epitope of gangliosides GD2 ,GD3, GD1b, GT1b, GT1a et GQ1b

IvIg and Rituximab are the drugs that can improve patients …

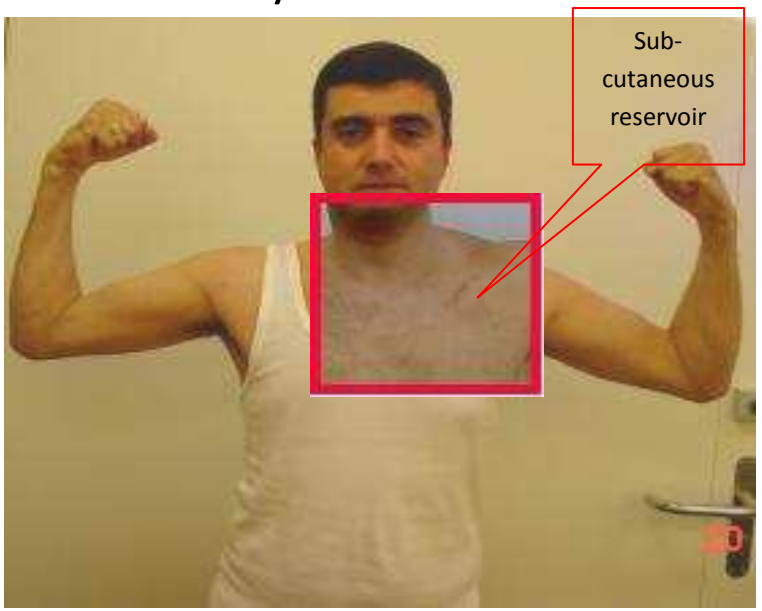
At diagnosis onset

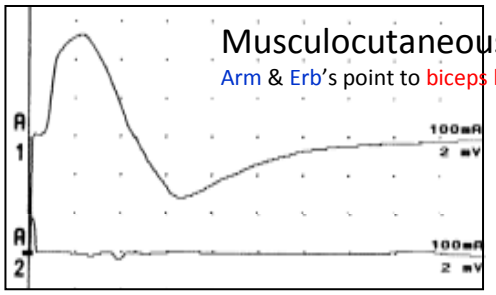


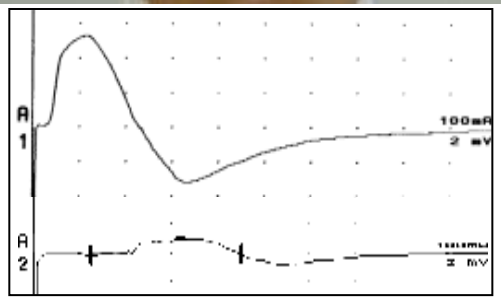
4 days after IvIg infusion 2g/kg

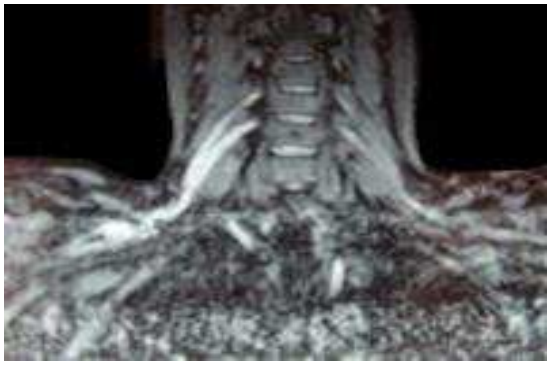


8 years later

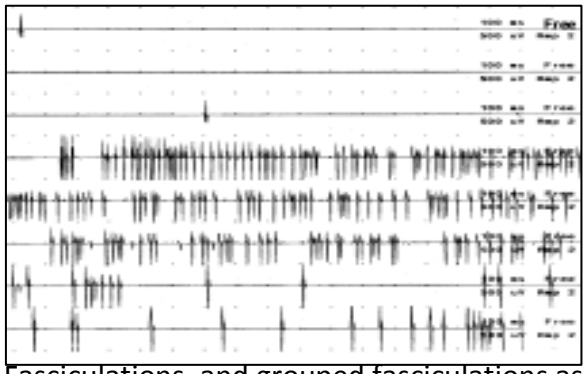




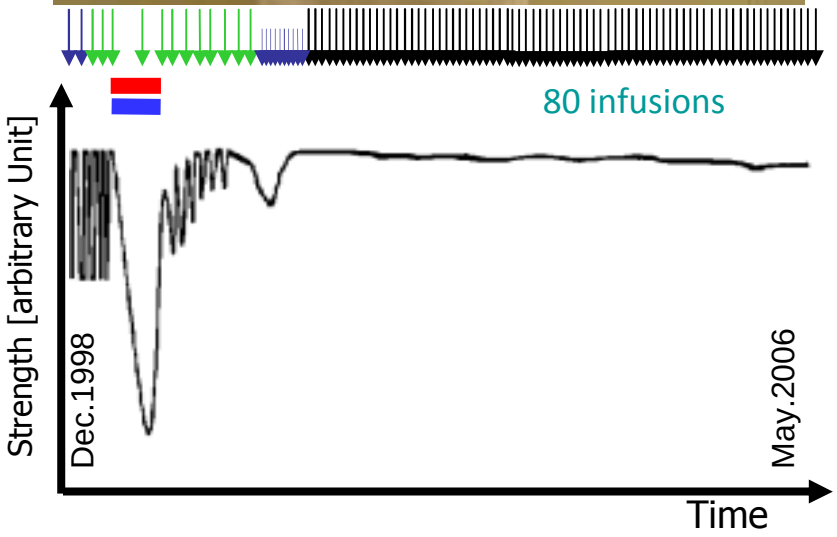




Fat-suppressed, T2-weighted, fast spin-echo image of the brachial plexus : swelling and increased intensity.



Fasciculations, and grouped fasciculations as recorded from surface lectrode from the Bb muscle



European Journal of Neurology 2006, **13:** 802–808

EFNS TASK FORCE ARTICLE

Multifocal Motor Neuropathy, diagnostic criteria

Table 1 Clinical criteria for MMN

Core criteria (both must be present)
1. Slowly progressive or stepwise progressive, asymmetric limb weakness, or motor involvement having a motor nerve distribution in at least two nerves, for more than 1 month[a]
2. No objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs

Supportive clinical criteria
3. Predominant upper limb involvement[b]
4. Decreased or absent tendon reflexes in the affected limb[c]
5. Absence of cranial nerve involvement[d]
6. Cramps and fasciculations in the affected limb

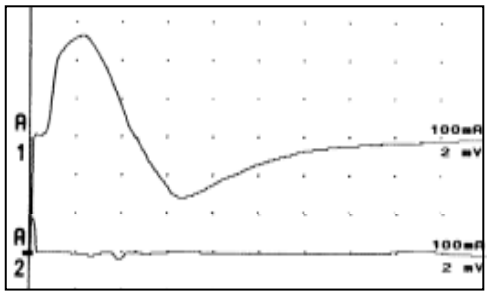
Exclusion criteria
7. Upper motor neuron signs
8. Marked bulbar involvement
9. Sensory impairment more marked than minor vibration loss in the lower limbs
10. Diffuse symmetric weakness during the initial weeks
11. Laboratory: CSF protein >1 g/l

The diagnosis of MMN is based on clinical, laboratory, and electrophysiological characteristics, the **CBs are the hallmark of the disease**

Supportive criteria
1. Elevated IgM anti-ganglioside GM1 antibodies
2. Magnetic resonance imaging showing gadolinium enhancement or hypertrophy of the brachial plexuses
3. Clinical improvement following IVIg treatment

100% CB of the musculocutaneous nerve

Arm & Erb's point to biceps brachii m.

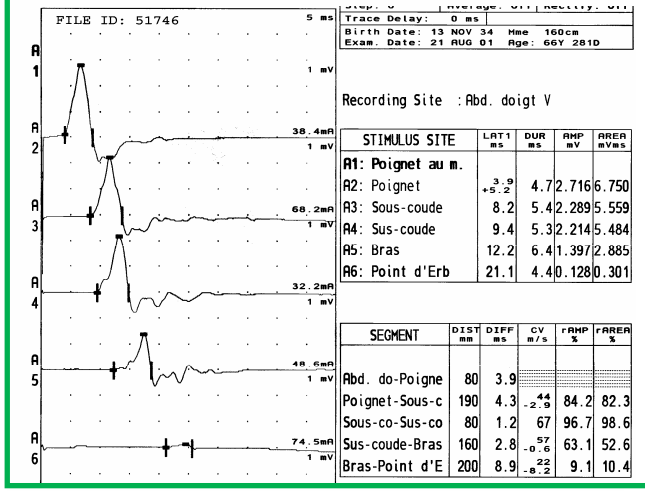


Arm

Erb's point

90% CB of the ulnar nerve

Wrist toErb's point to ADM m.



Wrist

Below

Above

Arm

Erb's point

Multifocal Motor Neuropathy, treatment

1. IVIg (2 g/kg given over 2-5 days) should be considered as the first line treatment when disability is sufficiently severe to warrant treatment
2. Prednisone and other corticosteroides are not recommended
3. If an initial treatment with IVIg is effective, repeated IVIg treatment should be considered in selected patients. The frequency of IVIg maintenance therapy should be guided by the response. Typical treatment regimens are 1 g/kg every 2–4 weeks, or 2 g/kg every 1–2 months
4. If IVIg is not or not sufficiently effective then immunosuppressive treatment may be considered. Cyclophosphamide, ciclosporin, azathioprine, interferon beta1a, or rituximab are possible agents (good practice point)
5. Toxicity makes cyclophosphamide a less desirable option

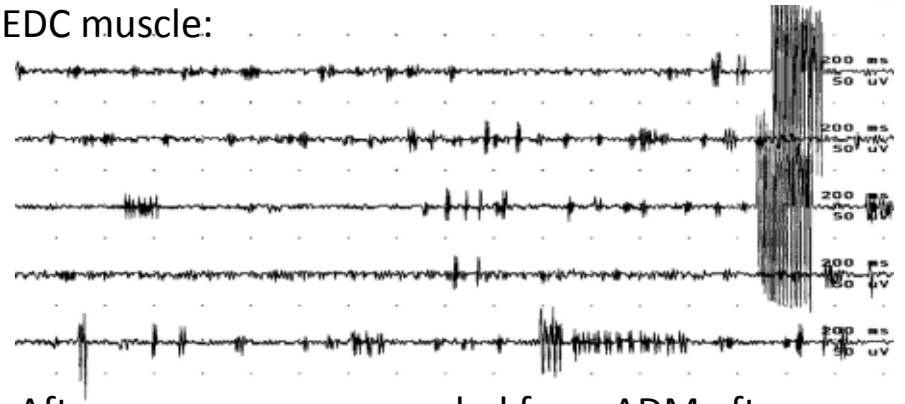
Peripheral nerve hyperexcitability

- Shoulder pain / muscle stiffness
- Cramps, discrete fasciculations at rest that increase clearly by motion
- Briskness of the direct percussion of the muscles whereas deep reflexes are weak
- Excessive sweating and weight loss, and insomnia
- Anti –VGKC antibodies negative (can be detected in about 50% of the cases)

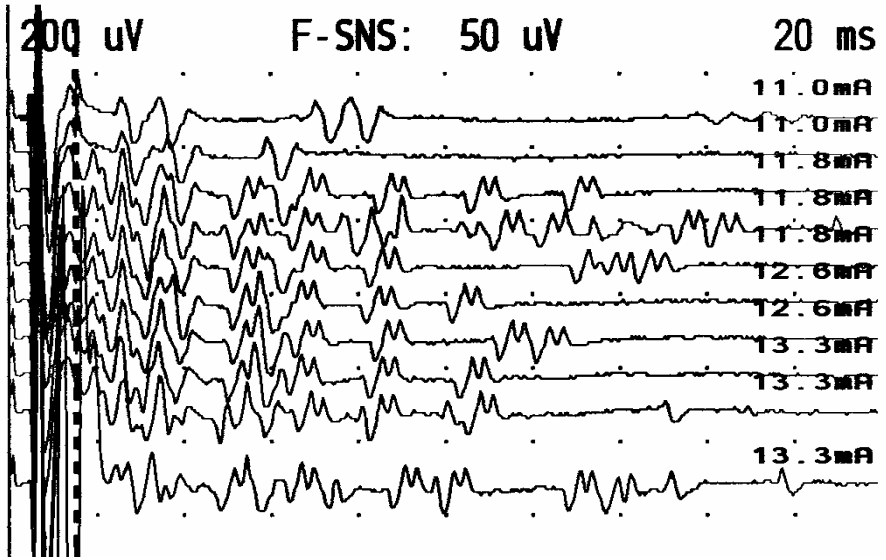
Morvan's syndrome

Treatment = plasma exchanges (phenytoin-carbamazepin may help)

Fasciculations, myokymias, grouped fasciculations and neuromyotonias recorded from surface lectrodes over the EDC muscle:



After-responses as recorded form ADM after stimulation of the R ulnar nerve:



Conclusions

1. *Dysimmune neuropathies include diverse neuropathies whose diagnosis and classification are based on the clinical presentations and results of ancillary tests*
2. *In some, controlled therapeutic trials demonstrated efficacy for Iv g-globulins, corticosteroids and plasmapheresis*
3. *In the other immune-mediated neuropathies, there are no reported controlled therapeutic trials, but efficacy has been reported for some treatments in non-controlled trials on case studies*

1. Usefulness of repeated examinations, extensive nerve conduction studies, blood testings and nerve biopsies
2. Treat asp and strong
3. Usefulness of new drugs (monoclonal AB rituximab, alemtuzumab & bevacizumab; TNF alpha blockers etanercept; & newly used immunosupressors, Fingolimod; cladribine; fumarate; teriflunomide; laquinimod…)

Clinical spectrum of chronic immune-mediated neuropathies