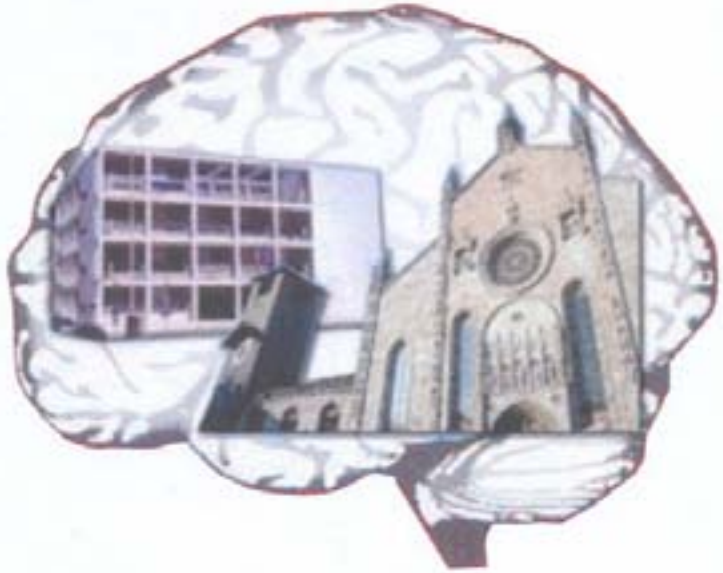

Comobrain 2009

3ª Edizione

12 - 13 ottobre 2009

Como, Villa Olmo

Neuropatie croniche immunomediate

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IMMUNE MEDIATED NEUROPATHIES

I. Idiopathic neuropathies

1 Guillain Barré Syndrome (GBS):

- Acute inflammatory demyelinating polyneuropathy (AIDP)
- Acute motor (-sensory) axonal neuropathy (AMAN & AMSAN)
- (Miller) Fisher Syndrome and other regional or functional variants

2 Subacute inflammatory demyelinating polyneuropathy

3 Chronic inflammatory demyelinating polyneuropathy (CIDP)

- (?) chronic relapsing axonal form

4 Multifocal demyelinating (motorsensory) neuropathy (Lewis-Sumner)

5 Multifocal motor neuropathy (MMN)

II. Neuropathies associated with other disorders

6 Neuropathies associated with monoclonal gammopathies:

- IgG & IgA (?)
- IgM: anti-MAG; anti-sulfatides, -GM1, -GD1a, -GD1b, -ChSC,; antigen unknown

7 Paraneoplastic neuropathies:

- subacute sensory neuronopathy: anti-Hu (mostly in lung carcinoma);- not anti-Hu
- subacute motor neuronopathy in lymphoma (?)

8 Vasculitic neuropathies (?)

ANTI-NERVE ABS IN CHRONIC DYSIMMUNE PN

Antigens	Antibody Isotype	Clinical syndrome	Fre-quency	Clinical impairm	Nerve Pathology	Authors
MAG/SGPG/P0	IgM	PN+IgM	50%	S>>M	Dem.	Latov et al 1980
Chondr. sulf C	IgM	PN+IgM	1%	SM	Axonal	Sherman et al 1983
Sulfatide	IgM	PN axonal	?	S,S>M,	Axonal	Pestronk et al 1991
		PN+IgM	5%	SM	Dem.	Nobile-Orazio al 1994
β-tubulin	IgM	CIDP	57%	M>>S	Dem.	Connolly et al 1993
GM1	IgM	MMN+IgM	20-80%	M	Dem	Pestronk et al. 1991
		LMND+IgM	? 5%	M	MND	Freddo et al 1986
GM2	IgM	PN+IgM	?	M>S	Dem.	Ilyas et al 1988
GD1a	IgM	PN+IgM	2%	M	Dem.	Bollensen et al 1989
GQ1b/Disialog.	IgM	PN+IgM	2%	S>>M	Dem.	Ilyas et al 1986
Hu	IgG	SSN-PLE	?	S>>M	Axonal	Graus et al 1985

CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULO-NEUROPATHY (CIDP)

- **Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of two or more extremities**, developing over at least 2 months; cranial nerves may be affected
- **Absent or reduced tendon reflexes** in all extremities
- **Elevated cerebrospinal fluid protein** with leukocyte count < 10/mm^3
- Electrophysiological and/or morphological features of a **demyelinating neuropathy**

Diagnostic criteria for CIDP

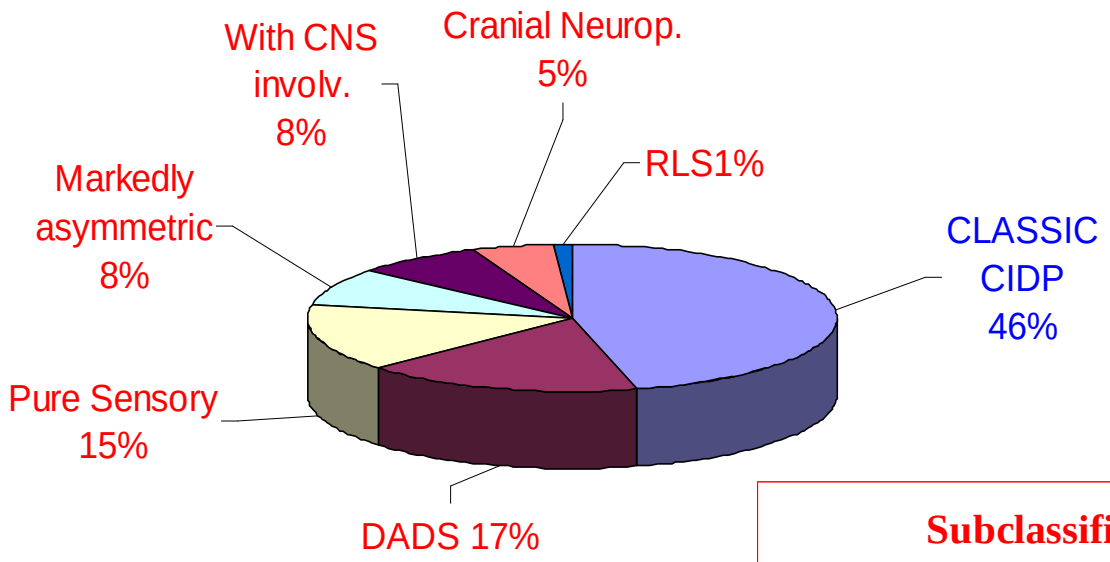
Table 1. Diagnostic Criteria.*

Feature	AAN Criteria	Saperstein Criteria	INCAT Criteria
Clinical involvement	Motor dysfunction, sensory dysfunction of >1 limb, or both	Major: symmetric proximal and distal weakness; minor: exclusively distal weakness or sensory loss	Progressive or relapsing motor and sensory dysfunction of more than 1 limb
Time course (mo)	≥2	≥2	>2
Reflexes	Reduced or absent	Reduced or absent	Reduced or absent
Electrodiagnostic test results	Any 3 of the following 4 criteria: partial conduction block of ≥1 motor nerve, reduced conduction velocity of ≥2 motor nerves, prolonged distal latency of ≥2 motor nerves, or prolonged F-wave latencies of ≥2 motor nerves or the absence of F waves†	2 of the 4 AAN electrodiagnostic criteria	Partial conduction block of ≥2 motor nerves and abnormal conduction velocity or distal latency or F-wave latency in 1 other nerve; or, in the absence of partial conduction block, abnormal conduction velocity, distal latency, or F-wave latency in 3 motor nerves; or electrodiagnostic abnormalities indicating demyelination in 2 nerves and histologic evidence of demyelination
Cerebrospinal fluid	White-cell count <10/mm³, negative VDRL test; elevated protein level (supportive)	Protein >45 mg/dl; white-cell count <10/mm³ (supportive)	Cerebrospinal fluid analysis recommended but not mandatory
Biopsy findings	Evidence of demyelination and remyelination	Predominant features of demyelination; inflammation (not required)	Not mandatory (except in cases with electrodiagnostic abnormalities in only 2 motor nerves)

From: Koller, Kieseier, Jander& Hartung (NEJM 2005)

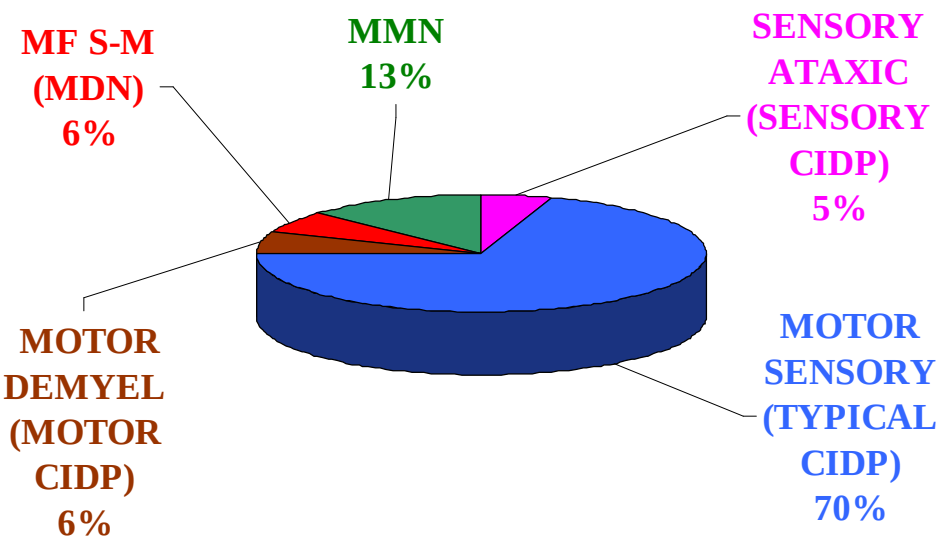
CIDP AND CLINICAL VARIANTS

Rotta et al.
J Neurol Sci 2000



87 pts. with AAN dem features in ≥ 1 motor or ≥ 2 sensory nerves

Subclassification of chronic dysimmune neuropathies in 102 patients



Bushby & Donaghy J Neurol 2003

List of presumed CIDP variants

Clinical

- DADS (Distal Acquired Demyelinating Symmetric)
- Pure sensory (ataxic) neuropathy
- Pure motor neuropathy
- Focal or multifocal neuropathy
- Lewis-Sumner syndrome (MDN; MADSAM)
- *MMN (Multifocal Motor Neuropathy)*

Pathological

- Axonal CIDP

Adapted from: Hahn et al (Dyck & Thomas, Peripheral Neuropathy 2005; Said (Neuromusc Dis 2006) & Koller et al (NEJM 2005)

Journal of the Peripheral Nervous System 10:220–228 (2005)

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

Joint Task Force of the EFNS and the PNS†

†Membership of Task Force: Richard A. C. Hughes (Chair), UK; Pierre Bouche, France; David R. Cornblath, USA; Eileen Evers, UK; Robert D. Hadden, UK; Angelika F. Hahn, Canada; Isabel Illa, Spain; Carol L. Koski, USA; Jean-Marc Léger, France; Eduardo Nobile-Orazio, Italy; John D. Pollard, Australia; Claudia Sommer, Germany; Peter Van den Bergh, Belgium; Pieter A. van Doorn, Netherlands; Ivo N. van Schaik, Netherlands.

Revised EFNS/PNS Criteria for CIDP

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

- Pure motor *or*
- Pure sensory, including chronic sensory immune polyradiculo-neuropathy affecting the central process of the primary sensory neuron, *or*
- DADS: Predominantly distal (distal acquired demyelinating symmetric) *or*
- Lewis-Sumner syndrome: Asymmetric (multifocal acquired demyelinating sensory and motor, MADSAM) *or*
- Focal presentations (e.g., involvement of the brachial plexus or of one or more peripheral nerves in one upper limb),

and Absent or reduced tendon reflexes in the affected limbs

Supportive criteria for CIDP

A. **Elevated cerebrospinal fluid protein with leukocyte count < 10/mm^3** (Level A recommendation)

B. **Magnetic Resonance Imaging showing gadolinium enhancement** and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses (Level C recommendation)

C. **Nerve biopsy* showing unequivocal evidence of demyelination and/or remyelination** in >= 5 fibres by electron microscopy or in > 6 of 50 teased fibres

D. **Clinical improvement after immunomodulatory treatment** (Level A recommendation)

EVIDENCES FOR IMMUNE PATHOGENESIS IN CIDP

- Pathological evidence of demyelination with macrophage and T cell infiltrates and Ig deposits in nerve;
- Association with HLA-B8 (HLA-CW7 & HLA-DR2);
- Increased circulating (Th1) cytokine levels;
- Similarity with chronic EAN in Lewis rat (P0, P2; T cell mediated) & rabbit (myelin, GalC; ab. mediated);
- Passive transfer studies with serum (α-P0) of CIDP;
- Serum antineural reactivity in patients' sera;
- Response to immune therapy (Steroids, PE, IVIg);

Prevalence and Severity of CIDP

- *Prevalence of CIDP*
  - SE England: **1.32/100.000** on 1/1/95 (Lunn et al, 1999)
  - Piemonte: **3.5/100,000** on 31/12/2001 (Chiò et al, 2007)
  - Olmstead County: **8.9/100,000** (Laughlin et al, 2009)
- *On the prevalence date:*
  - Mean age: 54.4 years (range 10-95)
  - Mean age of onset: 45.6 years (41.8 RR, 50 for CP) *(59.6)*
  - Mean duration of CIDP: 8.9 yrs (2-490 months) *(7.3)*
  - **13% of patients required aid to walk *(11.6%)***
  - **54% were still on treatment**
  - The average Rankin score at the worse relapse was 3.5

54% (8.5%, Chiò) severely disabled during the illness at some time (Rankin score 4 or 5)

CORTICOSTEROIDS FOR CIDP

Mehndiratta MM & Hughes RAC

Cochrane Database of Systematic Reviews 2002

PLASMAEXCHANGE FOR CIDP

Mehndiratta MM, Hughes RAC, Agarwal P

Cochrane Database of Systematic Reviews 2004

IVIg FOR CIDP

Eftimov F, Winer JB, Vermeulen M,, de Haan R, van Schaik IN

Cochrane Database of Systematic Reviews 2009

OPEN ISSUES IN CIDP TREATMENT

What therapy should we first use in CIDP (IVIg, steroids or PE)?

- Which is the most effective therapy?
- Which is the best tolerated therapy?
- Which is the most convenient therapy?

Comparison of effective therapies in CIDP

A Plasma Exchange Versus Immune Globulin Infusion Trial in Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Peter James Dyck, MD,* William J. Litchy, MD,* Kay M. Kratz,* Guillermo A. Suarez, MD,* Phillip A. Low, MD,* Alvaro A. Pineda, MD,† Anthony J. Windebank, MD,* Jeannine L. Karnes, MSc,* and Peter C. O'Brien, PhD‡

20 patients; cross-over;
IVIg (0,4->0,2g/kg/wk x 6wks)
vs. PE (2->1/wk x **6 wks**

IVIg = PE

Ann Neurol 1994

24 patients; cross-over;
IVIg (2g/kg) vs Prednisolone
(60->10 mg x **6 wks**)

IVIg =Prednisolone

Ann Neurol 2001

Randomized Controlled Trial of Intravenous Immunoglobulin Versus Oral Prednisolone in Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Richard Hughes, MD, FMedSci,[1] Siân Bensa, BSc,[1] Hugh Willison, PhD,[2] Peter Van den Bergh, MD, PhD,[3] Giancarlo Comi, PhD,[4] Isabel Illa, MD, PhD,[5] Eduardo Nobile-Orazio, PhD,[6] Pieter van Doorn, PhD,[7] Marinos Dalakas, MD,[8] Martin Bojar, CSc,[9] Anthony Swan, PhD,[10] and the Inflammatory Neuropathy Cause and Treatment (INCAT) Group*

Steroids, PE & IVIg are similarly effective (~60%) as initial therapy in CIDP

Response to initial therapy in CIDP

Therapy	Responder	Non Respond.	Side Effect
Steroids *136 (51%)*	**87 (64%)**	**49 (36%)**	**18 (13%)***
IVIg *115 (43%)*	**90 (78%)**	**25 (22%)**	**5 (4%)***
PE *16 (6%)*	**9 (56%)**	**7 (44%)**	**4 (25%)**
TOTAL *267*	**186 (69%)**	**81 (31%)**	

* *Steroids vs IVIg: p= 0.02*

Cocito et al., 2009

Advantage & Disadvantage of Steroids and IVIg in CIDP

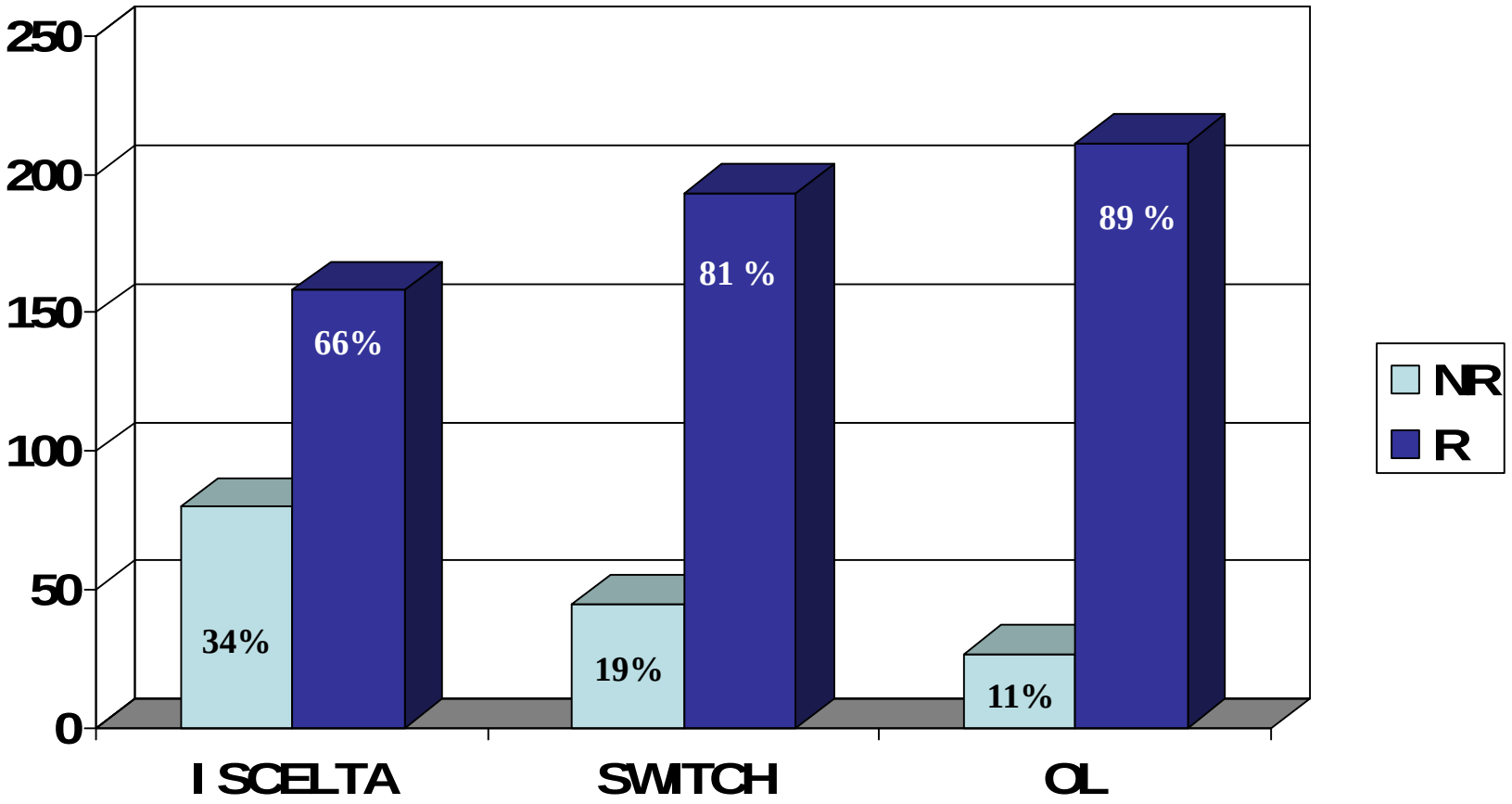
- Steroids
  - Pros:
    - Low cost
    - Easy oral assumption
    - No need for hospital stay
  - Cons:
    - Major side effects especially on the long term
    - More contraindications

- IVIg
  - Pros:
    - Well tolerated
    - Few side effects
    - Less contraindications
  - Cons
    - High cost
    - Repeated periodic hospital access (1-2d/month)

Response to second therapy in CIDP patients NR to initial treatment

1st Treat.	*2nd Treat.*	*No. Treated*	*Responsive*	*Intolerant*
Steroids -> (N=43)	**–> IVIg**	38	**21 (56%)**	0
	–> PE	5	1 (20%)	0
IVIg -> (N=14)	**–> STE**	14	**6 (43%)**	1 (7%)
PE - > (5 pt)	**–> STE**	5	**2 (40%)**	0

Risultati: pazienti NR



Recommendations for Treatment

2) Maintenance Treatment

1. If the first line treatment is effective continuation should considered until maximum benefit, then dose reduced to the lowest effective maintenance dose (Good Practice Point).
2. If response is inadequate or maintenance doses are high, alternative or combination treatments or adding immuno-suppressant/ modulatory drug may be considered (GPP).
3. Advice about foot care, exercise, diet, driving and life style management should be considered. Neuropathic pain should be treated with drugs according to EFNS guideline (Attal et al 2005, in preparation). Depending on patients' needs, orthoses, physiotherapy, occupational therapy, psychological support and referral to a rehabilitation specialist should be considered (Good Practice Points)
4. Information about patient support groups should be offered to those who would like it (Good Practice Point)

Efficacy in open-trial of Immunosuppressant and immunomodulatory drugs in CIDP

1.	Cyclosporin	*82%*
2.	Azathioprine	*64%*
3.	Cyclophosphamide	*75%*
4.	Methotrexate	70%
5.	Interferon α	64%
6.	Mycophenolate mofetil	39%
7.	Interferon β 1a	35%
8.	Rituximab (anti-CD20)	?%
9.	Etanercept	30%
10.	Autologous hematopoietic stem cell transplantation	

RCT OF AZATHIOPRINE IN CIDP

Dyck et al, Neurology 1985; 35: 1173-6

- 27 CIDP patients
- Randomized open controlled trial (not blind)
- Azatioprine (2mg/kg) + Prednisone (120mg/alt day $\rightarrow$ 0) versus Prednisone alone for 9 months
- No significant difference in any of the 16 parameters examined between the two groups

BUT

1. *Azathioprine Dose & duration insufficient*
2. *Only analyzed the adjunctive effect and not the steroid-sparing effect of Azathioprine*

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

RMC Trial Group*

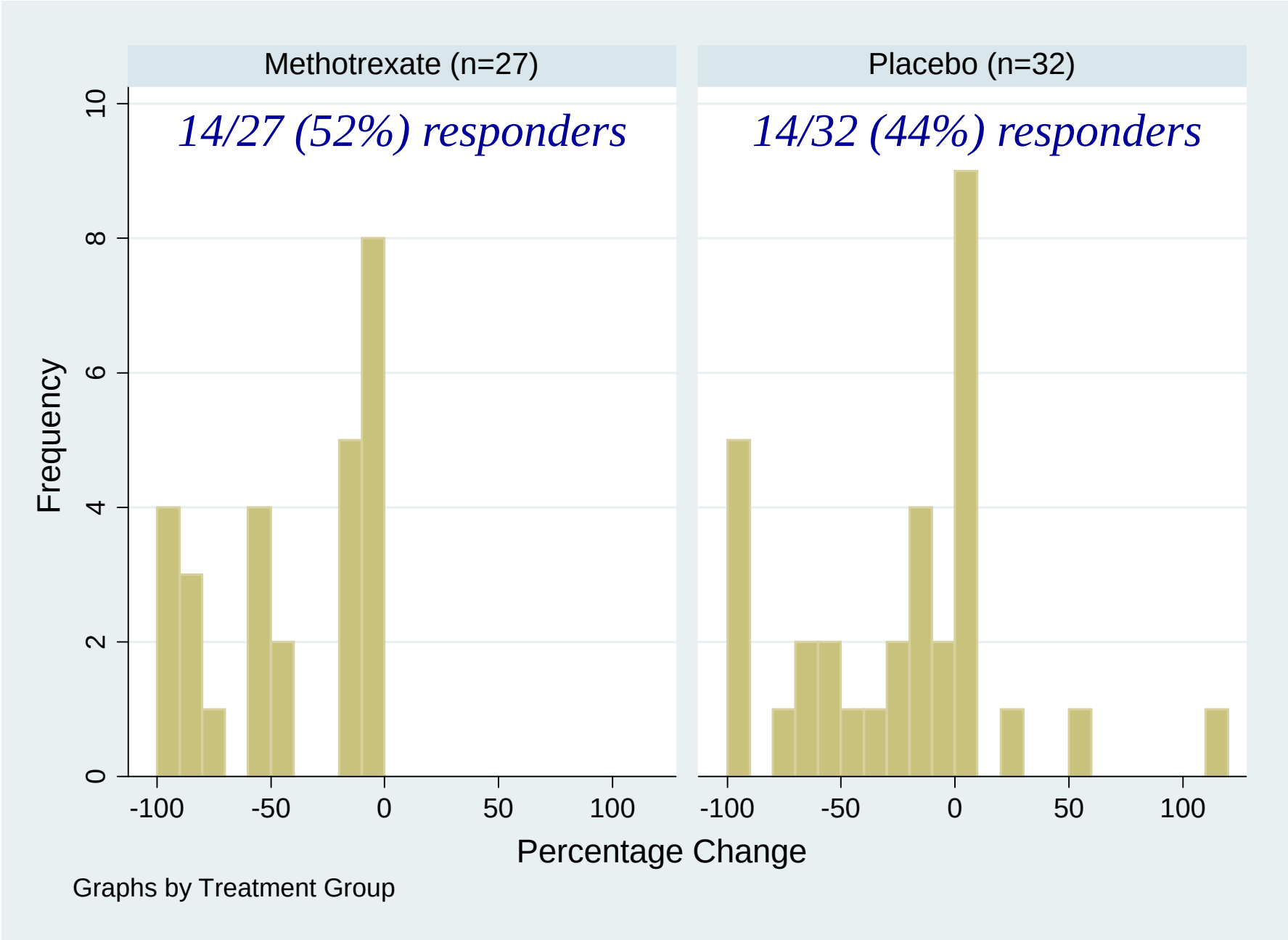
Lancet Neurology 2009; 8: 158-64

Patients: 60 pts. randomised 26 centres in 5 European countries

Trial design: oral methotrexate (up to15 mg weekly) or placebo &folic acid 5 mg twice weekly for 40 weeks in addition to standard IVIg or steroid dose. After 16 weeks corticosteroids or IVIg were reduced, subject to satisfactory progress, at a rate of 20% of the baseline dose every 4 weeks.

Primary outcome: At least 20% reduction in mean weekly dose of steroids or IVIg from week 37-40 compared with week 1– 4.
Secondary outcome: change in disability and impairment from baseline to week 16 and to week 40.

Results: Oral methotrexate 15 mg weekly showed no significant benefit, but limitations in trial design and the high response in the placebo group meant thata tretament effect could not be excluded



Adjusted odds ratio 1.21 (95% CI 0.40 to 3.70).

INTERFERON β–1a ADJUNCTIVE TO IVIg IN CIDP

Gorson et al (AAN 2008, in preparation)

- 67 IVIg dependent CIDP patients.
- Multicenter RCT, IFNβ-1a, 30 or 60 ug (45 pts) vs placebo (22 pts) once or twice weekly
- After 16 wks IVIg discontinued and restarted upon worsening by 2 or more MRC points (0-60).
- The mean IVIg dose in week 16-32 (1g/kg) in IFNβ-1a treated did not differ from placebo (1.9g/kg)
- In both groups 47% of patients did not relapse by 32 weeks
- Patients more severe (MRC <51) or more intensely treated with IVIg (>0.95g/kg/mo) treated with IFNβ-1a required less IVIg than placebo treated patients.

Cytotoxic and Interferons for CIDP

Hughes RAC, Swan AV, van Doorn PA
Cochrane Database of Systematic Reviews 2004 (4)

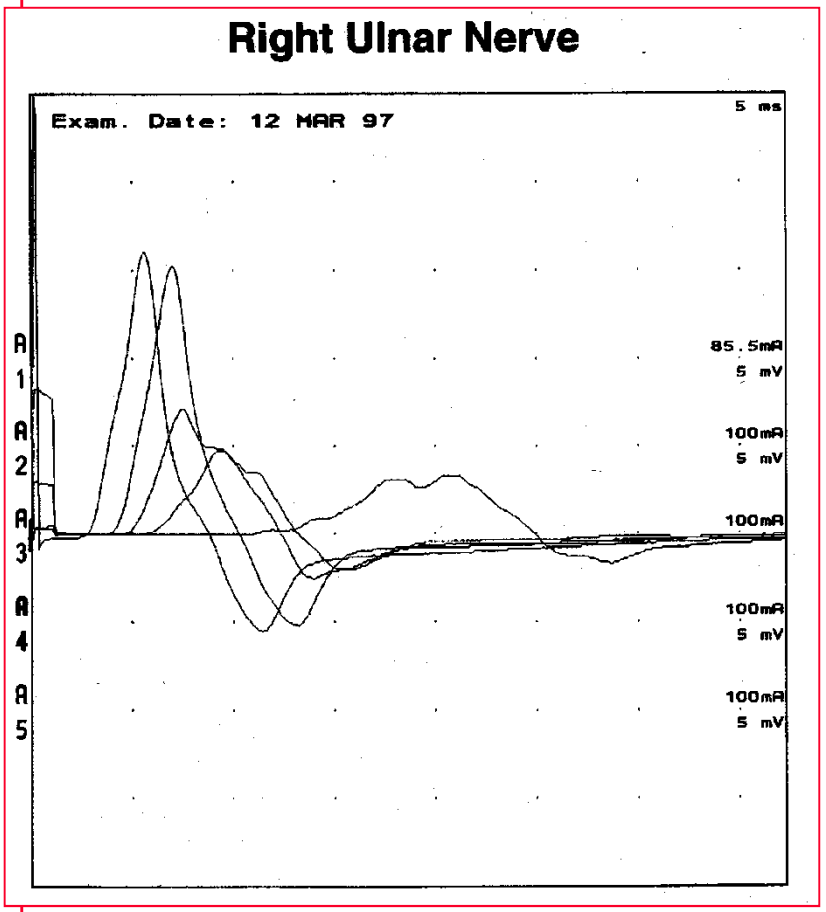
- Reviewers' conclusion:

- Only two RCT assessing the effect of azathioprine or interferon beta have been performed in CIDP.
- The evidence is inadequate to decide whether azathioprine, interferon beta or any other immuno-suppressive drug or interferon is beneficial in CIDP.
- More research is needed to determine whether immunosuppressive drugs or interferon are beneficial for CIDP.

Multifocal Motor Neuropathy

Rare disorder characterized by:

- progressive, predominantly distal, multineuropathic limb weakness, usually more pronounced in the arms;
- minimal or no sensory loss;
- multifocal persistent partial motor conduction block.
- Frequent (30-50%) association with anti-GM1 IgM antibodies
- Frequent (80%) response to IVIg



Distinguishing features in CIDP, MMN & MND

Features	CIDP	MMN	LMND
Distribution	**Symmetric**	**Multineuropathic**	**Asymm or Symm**
Arms >legs	**no**	**Yes (80%)**	**sometimes**
Distal>prox.	**no**	**Yes**	**often**
Sensory loss	**yes**	**NO**	**NO**
Gen. Areflexia	**yes**	**NO**	**NO**
Cranial/bulbar	**yes**	**NO**	**yes**
Motor CB	yes	Yes	NO
Reduced CV	yes	NO	no
Reduced SNAP	yes	NO	no
↑CSF proteins	yes	Rare (1/3)	no
↑ GM1 IgM	no	YES (30-40%)	Sometimes (5-10%)
S. Nerve biopsy	demyelin.	NORMAL	Normal
Steroid effective	yes (2/3)	No (1/10)	No
IVIg effective	yes (2/3)	yes (4/5)	No

Journal of the Peripheral Nervous System 11:1–8 (2006)

EFNS/PNS MMN GUIDELINES

European Federation of Neurological Societies/Peripheral Nerve Society Guideline* on management of multifocal motor neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society

Joint Task Force of the EFNS and the PNS†

†Membership of Task Force: Richard A. C. Hughes (Chair), UK; Pierre Bouche, France; David R. Cornblath, USA; Eileen Evers, UK; Robert D. Hadden, UK; Angelika F. Hahn, Canada; Isabel Illa, Spain; Carol L. Koski, USA; Jean-Marc Léger, France; Eduardo Nobile-Orazio, Italy; John D. Pollard, Australia; Claudia Sommer, Germany; Peter Van den Bergh, Belgium; Pieter A. van Doorn, Netherlands; Ivo N. van Schaik, Netherlands.

1) Clinical Criteria for MMN

A) 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 one month[#]
2. **No objective sensory abnormalities** except for minor vibration sense abnormalities in the lower limbs.

B) Supportive clinical criteria

3. Predominant upper limb involvement
4. Decreased or absent tendon reflexes in the affected limb
5. Absence of cranial nerve involvement
6. Cramps and fasciculations in the affected limb

C) Exclusion criteria

7. Upper motor neuron signs
8. Marked bulbar involvement
9. Sensory impairment beside for minor vibration loss in the legs
10. Diffuse symmetric weakness during the initial weeks

Electrodiagnostic Criteria in MMN

1. **Definite motor CB:**

   proximal vs distal neg. CMAP area reduction ≥ 50% whatever the nerve segment length. Negative distal CMAP amp. must be >20% of lower NL & > 1 mV & increase of proximal CMAP duration (temporal dispersion: **TD) ≤ 30%.**

2. **Probable motor CB:**

   negative CMAP area reduction of ≥ 30% over a long segment of an UL nerve with **TD ≤ 30%;**

   OR

   negative CMAP area reduction of ≥ 50% with **TD ≥ 30%.**

3. **Normal sensory nerve conduction** in upper limb segments with CB and normal SNAP amplitudes.

Distinguishing features in CIDP, MMN & MND

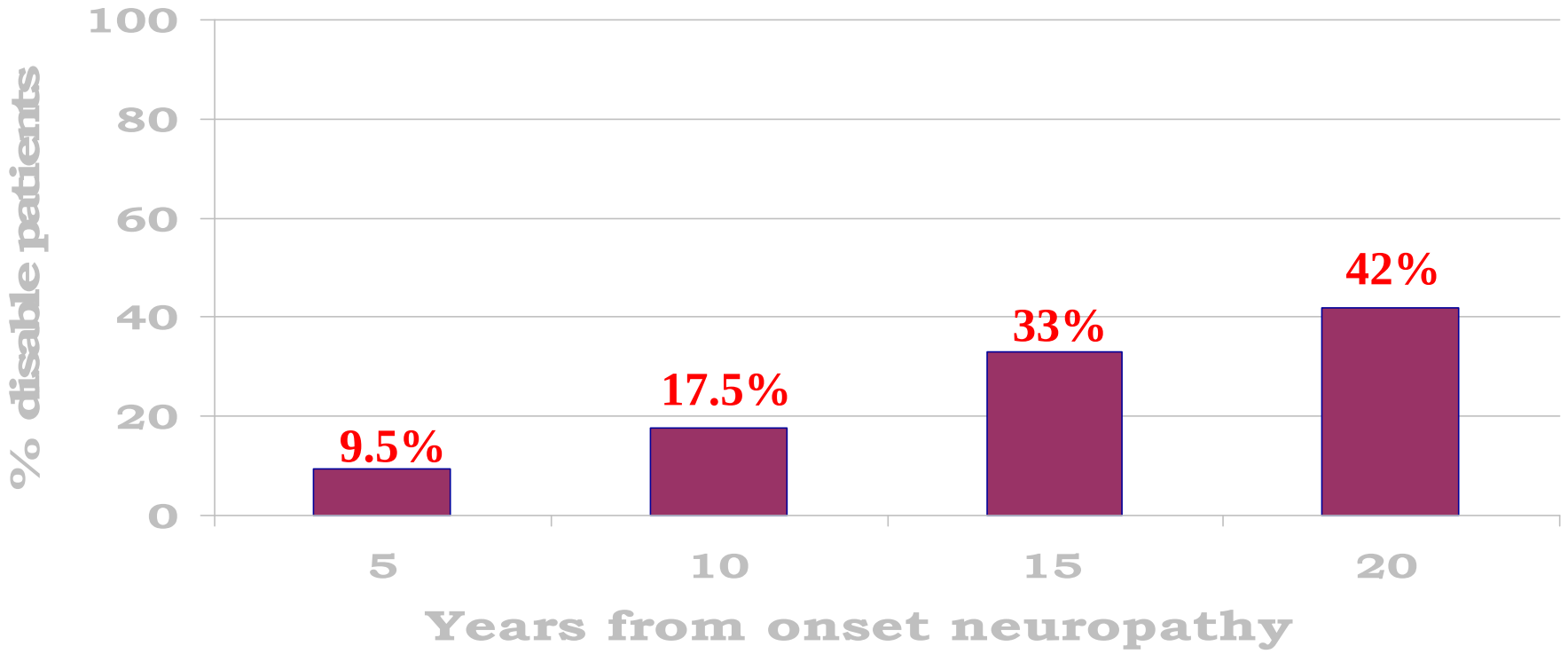
Features	CIDP	MMN	LMND
Distribution	Symmetric	Multineuropathic	Asymm or Symm
Arms >legs	no	Yes (80%)	sometimes
Distal>prox.	no	Yes	often
Sensory loss	yes	NO	NO
Gen. Areflexia	yes	NO	NO
Cranial/bulbar	yes	NO	yes
Motor CB	yes	**Yes**	NO
Reduced CV	yes	**NO**	NO
ReducedSNAP	yes	**NO**	NO
↑CSF proteins	yes	**Rare (1/3)**	no
↑ GM1 IgM	no	**YES (30-40%)**	Sometimes(5-10%)
S.Nerve biopsy	demyelin.	**NORMAL**	Normal
Steroid effective	yes (2/3)	No (1/10)	No
IVIg effective	yes (2/3)	yes (4/5)	No

EVIDENCES FOR IMMUNE PATHOGENESIS IN MMN

- IgM antibodies to GM1 or other gangliosides are present in 30-50% of MMN patients (*but may be also found in other PN and MND*) and often *though not always* decrease during clinical improvement;
- Deposits of IgM were found at the nodes of Ranvier of sural nerves in a patient with CB (*and MND*);
- CB can be induced *in vitro & vivo* by serum from MMN patients with and without anti-GM1 IgM;
- Most patients with MMN respond to immune therapies (IVIg and CTX).

Disability progression in MMN

Years of neuropathy	5	10	15	20
• N° pts	21	17	12	7
• N° pts Rankin score ≥ 3	2	3	4	3



IMMUNE THERAPIES IN MMN

Therapy	No. treated	No. (%) improved	No. (%) worsened
Steroids *(alone)*	64 (62)	7 (11%)	14(22%)
Plasmaexch.*(alone)*	21 (20)	4 (20%)	2 (10%)
IVIg:	383		
↓↓ impairment:		303/373	(81%)
↓↓ disability:		91/123	(74%)

IVIg for Multifocal Motor Neuropathy

Van Schaik I, van den Berg L, de Haan R, Vermeulen M
Cochrane Database of Systematic Review, 2005, April 18

- Reviewers' summary and conclusion:

- Four RCT assessing the effect of IVIg in MMN have been performed including a total of 34 patients.
- Strength improved in 78% pts treated with IVIg vs 4% with placebo; disability improved in 39% treated and 11% untreated patients
- IVIg has beneficial effect on strength in MMN and provide a non-significant trends toward improvement in disability
- More research is needed to discover whether IVIg improves disability and is cost-effective.

LONG-TERM IVIg THERAPY IN MMN

- *Azulay et al., J Neurol Neurosurg Psychiatry 1997*
  - 8/12 (66%) responding pts required repeated Ig x 9-48 mos, uneffective in 3 after 3 mos; 2 (11%) in remission after 1 yr.
- *Van den Berg et al., Brain 1998*
  - 6/7 (86%) responding pts required weekly Ig (0.4g/kg/wk) x 2-4 yrs (follow-up); 3 (43%) had some deterioration.

Periodic IVIg are necessary in most MMN patients

Editorial

Neurology 2000;55:1246–1247

IVIg treatment improves multifocal motor neuropathy

Easy to start but difficult to stop

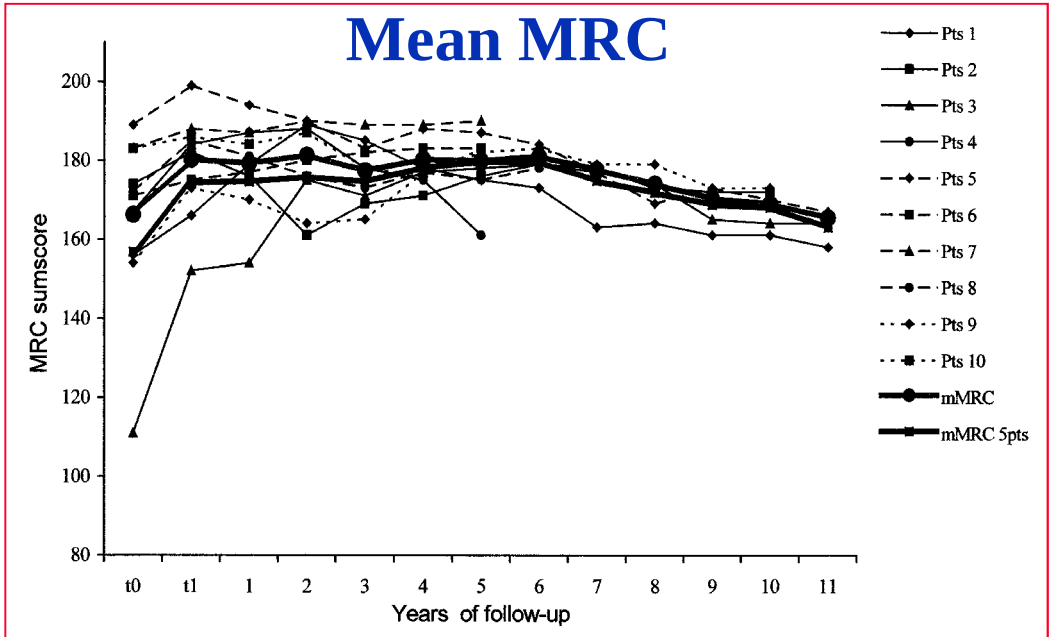
P.A. van Doorn, MD, PhD; and F.G.A. van der Meché, MD, PhD

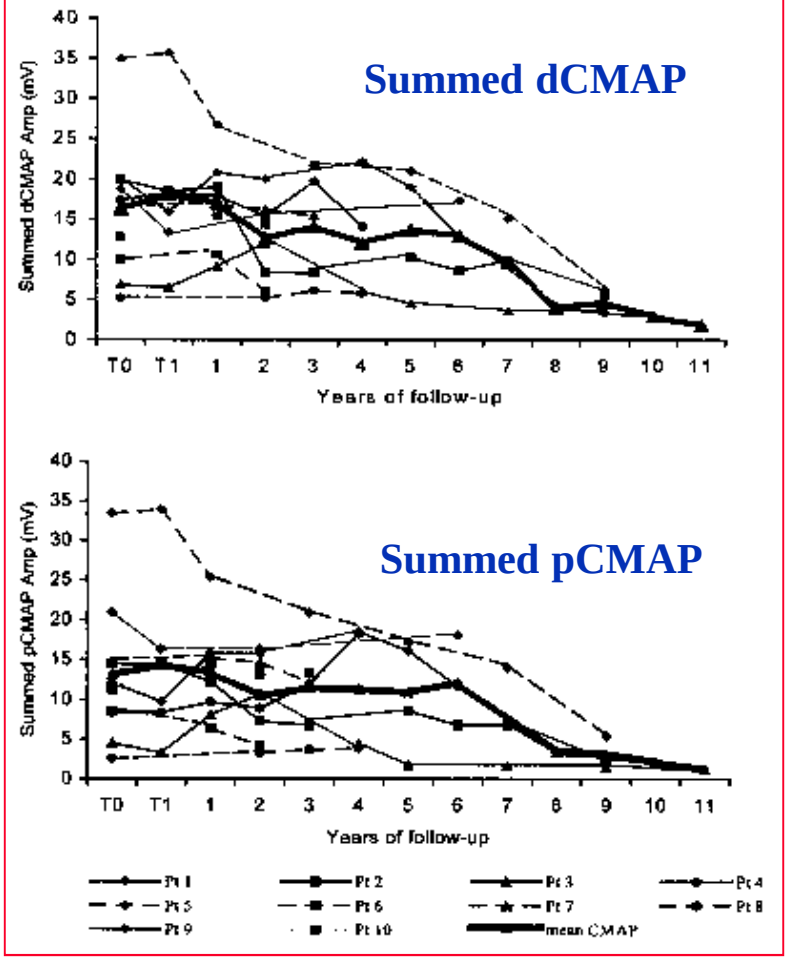
How long is IVIg effective in multifocal motor neuropathy?

F. Terenghi, MD; A. Cappellari, MD; A. Bersano, MD; M. Carpo, MD, PhD; S. Barbieri, MD, PhD; and E. Nobile-Orazio, MD, PhD

Neurology 2004

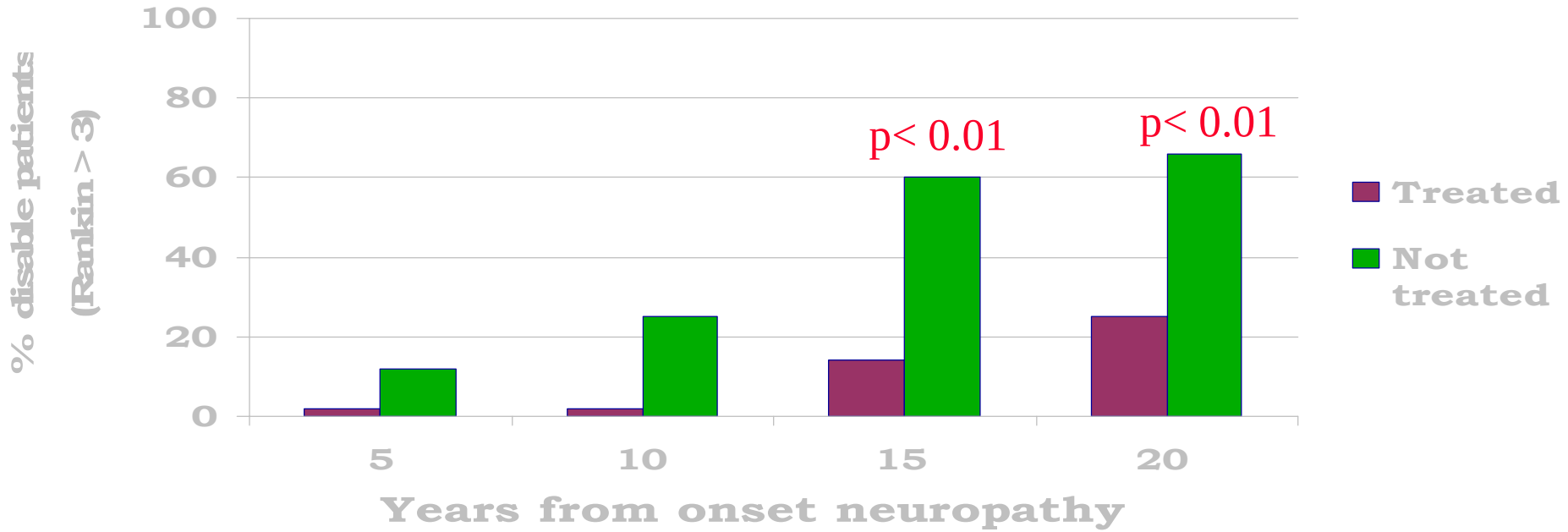
10 MMN patients responding to IVIg treated with periodic IVIg infusions for 5-12 yrs (mean 8.2)





Disability progression in MMN

Years of neuropathy	5	10	15	20
Treated patients	6	5	7	4
Rankin ≥ 3	0	0	1 (14%)	1 (25%)
Untreated patients	**15**	**12**	**5**	**3**
Rankin ≥ 3	**2 (12%)**	**3 (25%)**	**3 (60%)**	**2 (66%)**



OTHER IMMUNE THERAPIES IN MMN

- To treat patients not responsive to IVIg
- To treat patients progressively less responsive or unresponsive to IVIg
- To reduce the cost of IVIg use
- To reduce patients' dependency from IVIg and Hospital admission

OTHER IMMUNE THERAPIES IN MMN

Therapy	No. treated	No. (%) improved
Cyclophoshamide i.v.	40	30 (75%)
" " oral	6	3 (50%)
Interferon-β1a	12	6 (50%)
Azathioprine, *(alone)*	10 *(4)*	5 *(2)* (50%)
Mycophenolate	1	0
Cyclosporine	2	2
Rituximab	14	11 (?) (81% of 21, incl. 7 MAG+)

Long term effect of intravenous immunoglobulins and oral cyclophosphamide in multifocal motor neuropathy

Nicoletta Meucci, Alberto Cappellari, Sergio Barbieri, Guglielmo Scarlato, Eduardo Nobile-Orazio

JNNP 1997

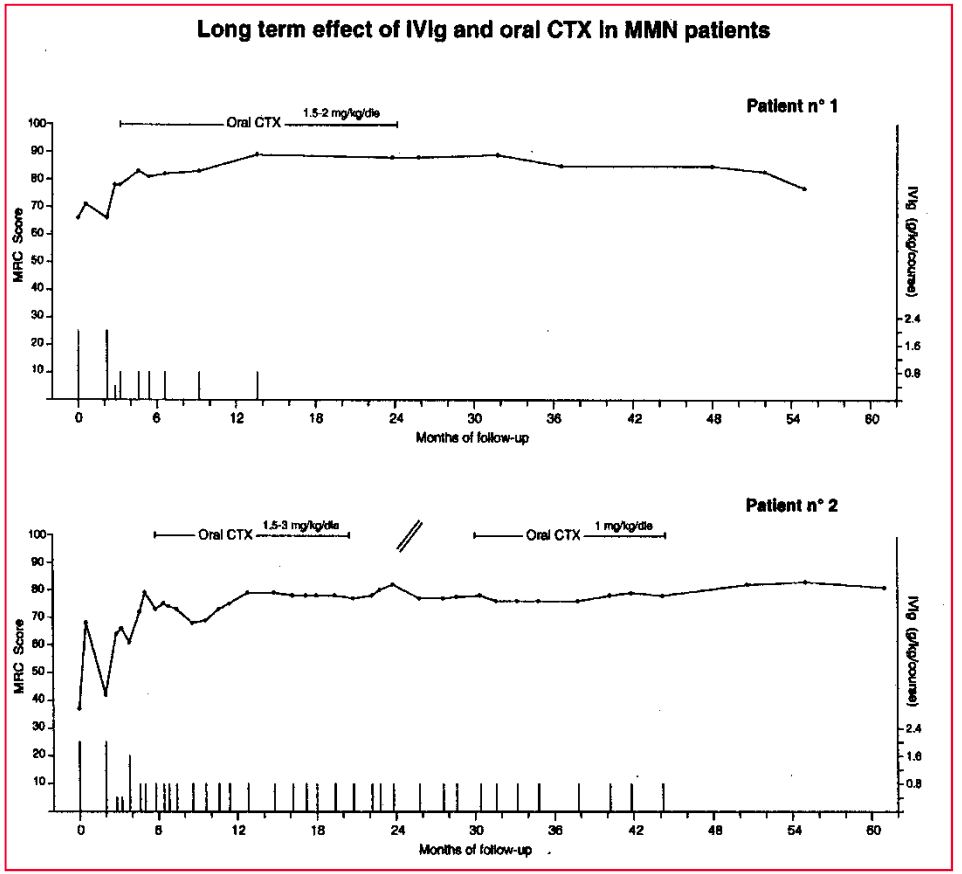
Pts. treated: 6

Follow-up: 47 mos (37-61)

Remission after 1-4 yrs of IVIg+CTX: 3 (50%)

Requiring reduced doses of IVIg: 3 (50%)

Pts. with severe side effects: 2 (33%)



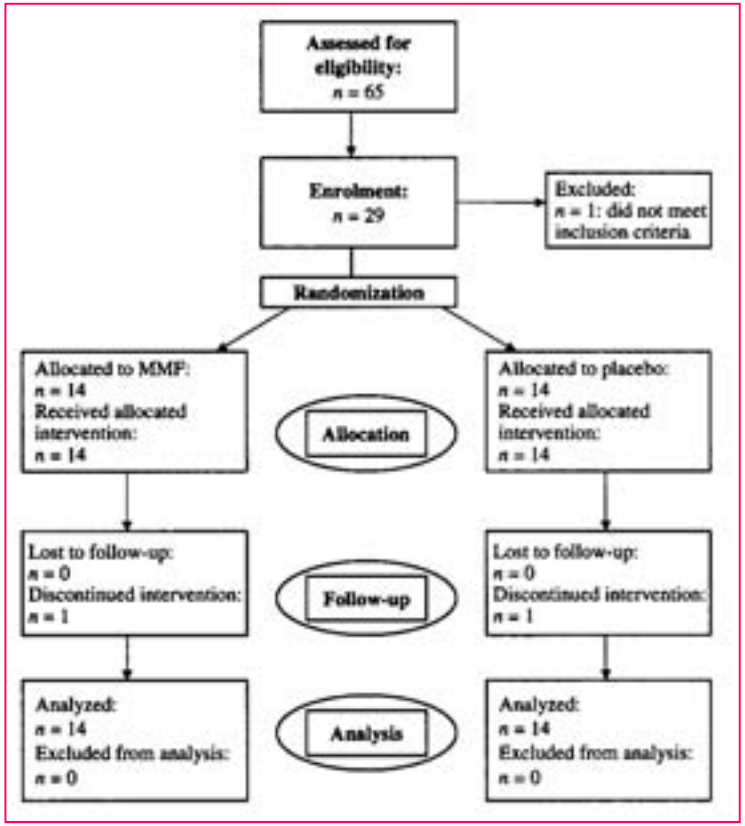
doi:10.1093/brain/awm144 Brain (2007), 130, 2004–2010

Mycophenolate mofetil as adjunctive therapy for MMN patients: a randomized, controlled trial

Sanne Piepers, Renske Van den Berg-Vos, W-Ludo Van der Pol, Hessel Franssen, John Wokke and Leonard Van den Berg

Department of Neurology, Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, the Netherlands

- *28 pts randomized*
- *1 pt with **MMF** ↓↓ IVIg by 50%.*
- *No signif. ↓↓ of IVIg after 12 mo.*
- *Pts did not have drug toxicity.*
- *No signif. progression after 12 mo*
- *Muscle strength, FS unchanged after 3 months & GMI-IgM after 12 months.*



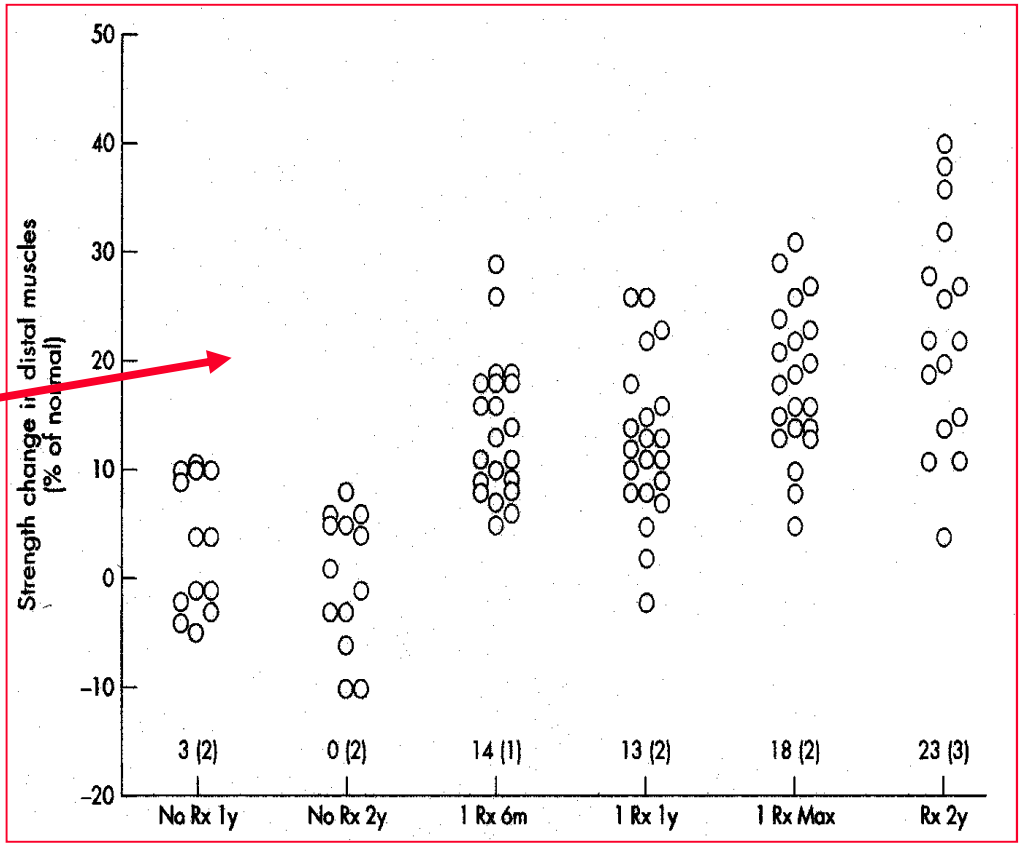
Adjunctive MMF was safe but did not alter MMN course or allow IVIg reduction

Treatment of IgM antibody associated polyneuropathies using rituximab

A Pestronk, J Florence, T Miller, R Choksi, M T Al-Lozi, T D Levine

J Neurol Neurosurg Psychiatry 2003;**74**:485–489

- **14 MN (11+CB) & α-GM1 IgM; 7 with PN & α-MAG IgM; 13 untreated**
- **Rituximab: 375mg/ m2/ wk x 4 -> (16) 1/wk x 2-> 1/10 wks- > 2yrs**
- **Strength ↑ 23% after 2 years (81% pts ↑ 12%)**
- **IgM ↓ to 55%; Abs ↓ to 43%**
- **No major side effects**



An open-label trial of Rituximab in MMN

Chaudhry & Cornblath, INC , Paris 2008

- **6 patients with MMN** under chronic IVIg therapy treated with 2 doses of Rituximab 1g iv, 2 weeks apart.
- Primary outcome total amount of IVIg used during 12-month study compared to 12 months prior.
- Secondary outcomes: changes in MRC sumscores, grip strength, disability & handicap scores, & safety.
- **No significant change in IVIg use** in the group over the 12-month study. 2 able to reduce their IVIg use by 11%.
- **No significant change in any score** (MRC, grip strength, overall disability, Rotterdam handicap scale), although some improved on these measures.
- Rituximab can be safely given to people with MMN but in this pilot study was unable to reduce the amount of IVIg

LETTER TO THE EDITOR

Oral methotrexate as adjunctive therapy in patients with multifocal motor neuropathy on chronic IVIg therapy

- In 7/8 patients the association of MTX to IVIg was followed by mild to moderate (1-15 MRC) improvement and in 1by loss of muscle strength (4 MRC) (*mean: + 5.5; p: 0.0543*).
- In 5/7 pts IVIg were reduced by 10% to 30% without worsening while higher Ig reduction (50%) or suspension could be achieved in only 2 pts (*mean Ig reduction 32%; p: 0,0253)*
- After 12.6 mos (range 4-18) of MTX, 2/8 pts had improved and 5/8 had side effects

Oral MTX was well tolerated or effective in 2/8 patients with MMN

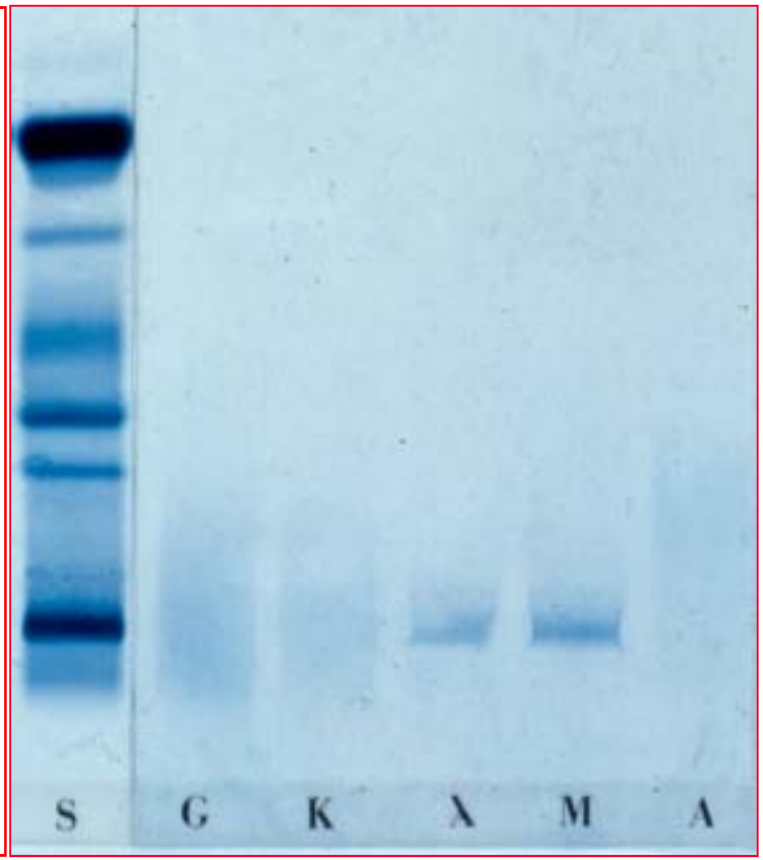
Nobile-Orazio et al, J Periph Nerv Sys, 2009

EFNS/PNS TREATMENT RECOMMENDATIONS

1. IVIg (2 g/kg over 2 to 5 days) should be considered as first line treatment (Level A recommendation) when disability is sufficiently severe to warrant treatment.
2. Steroids are not recommended (Good Practice Point).
3. If IVIg is initially effective, repeated IVIg should be considered (Level C) and its frequency guided by the response (Good Practice Point). Typical treatment regimens are 1 g/kg every 2 to 4 weeks, or 2 g/kg every 1 to 2 months (Good Practice Point).
4. *Only* if IVIg is not sufficiently effective immunosuppression may be considered. Cyclophosphamide, interferon β1a, cyclosporin, azathioprine are possible agents (GPP).
5. Toxicity makes cyclophosphamide less desirable (GPP)

Neuropathy in Monoclonal Gammopathy

Osteosclerotic Myeloma (POEMS)	50-85%
WM	30-50%
MGUS	**5-37%**
Amyloidosis	10-20%
Cryoglobulinemia	7-15%
Multiple Myeloma	3-14%
Lymphoma	2-8%



Prevalence of PN in MGUS in relation to isotype

	No. of patients	**Clinical PN**	Subclinical PN	Total PN
Total MGUS	74	**8%**	8%	16%
IgG	34	**3%**	3%	6%
IgA	14	**7%**	7%	14%
IgM	26	**15%**	15%	31%

IgM vs IgG+IgA: $p < 0.025$ *Nobile-Orazio et al. 1991*

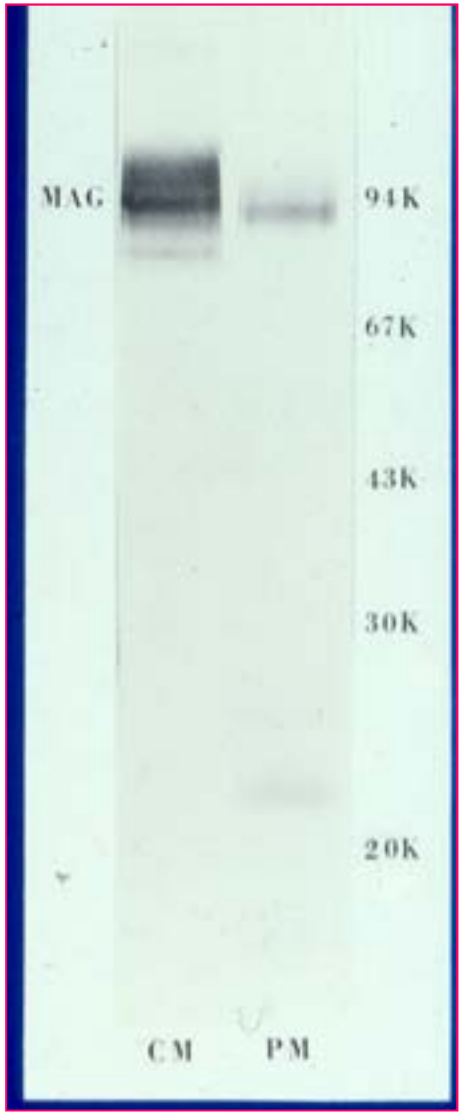
	PN+MG at our Institute (1984-2000)
PN+IgM	95 (83%)
PN+IgG	15 (13%)
PN+IgA	5 (5%)

Anti-neural reactivities of IgM M-proteins in PN

Antigens	%	PN type	Pathology	Authors
MAG/SGPG/P0	50%	S>>M (DADS-M)	Dem	Latov et al 1980 (Katz et al 2000)
Sulfatide	6%	S; S>M; SM	Ax or Dem	Pestronk et al 1991
GQ1b+Disyalo	2%	S>M (CANOMAD)	Dem	Ilyas et al 1986 (Willison et al 2000)
GD1a	3%	M; M>S	Dem	Bollensen et al 1989
GM2	2%	M; M>S	Dem	Ilyas 1988
GM1	<2%	M; LMNS (MMN)	Focal Dem	Latov et al 1988 (Pestronk et al 1988)
ChS-C	<2%	SM	Axonal	Sherman et al 1983

NEUROPATHY ASSOCIATED WITH ANTI-MAG IgM MONOCLONAL GAMMOPATHY

- **Slowly progressive Distal, Acquired, Demyelinating Symmetric (DADS) predominantly sensory, ataxic, PN** often associated with arm tremor;
- Estimated **prevalence of 20/100,000**, mostly affecting men aged 50-70 yo;
- **Electrophysiologically** characterized by signs of a **demyelinating PN** with disproportionately increased DL compared to CV (reduced TLI); CB rare
- **Pathologically** characterized by **demyelination,** abnormally spaced myelin lamellae by EM and **IgM & complement deposits in nerve** by IF



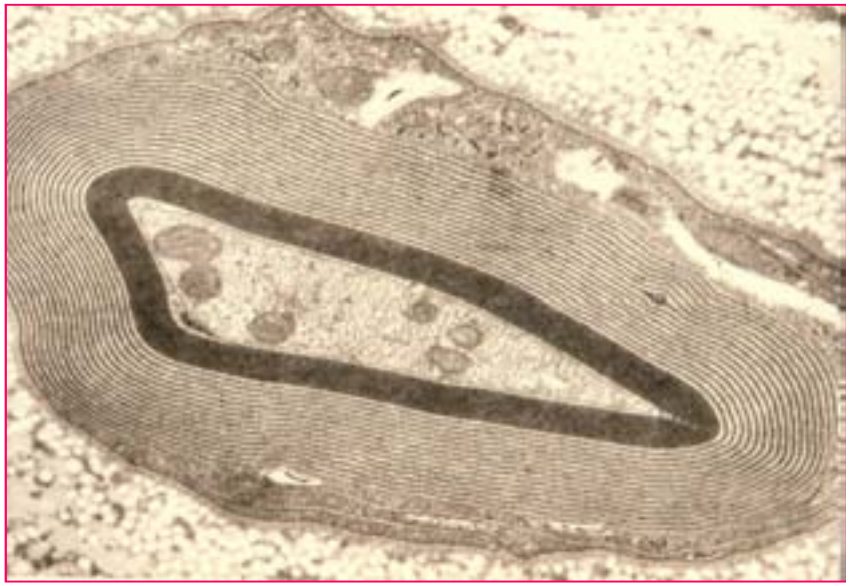
LONG-TERM PROGNOSIS OF PN & ANTI-MAG IgM

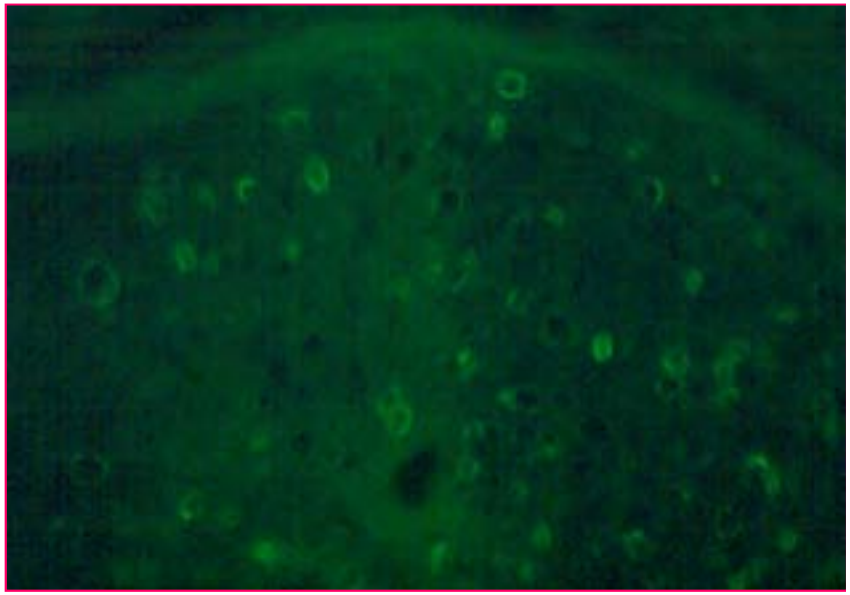
(Nobile-Orazio et al, Brain 2000)

	At entry	At last follow-up
No. of patients (M/F):	26 (22/4)	25 (96%)
Mean age at PN onset:	61.2 (42-78)	73.3 (58-84)
Years of follow-up:		8.5 (2-13)
Mean years from PN onset :	3.4 (0-10)	11.8 (3-18)
Median Rankin score	1 (0-3)	2 (1-5)
Walk+support/or unable/tremor	2/0/0	6/1/5
Total disabled (Rankin>2):	2 (8%)	11 (44%) (24%at 10 yrs; 50%at 15 yrs)
Patients deceased:		8*(32%)* *6% at 10,33% at 15 yr*)

Pathogenetic role of anti-MAG IgM

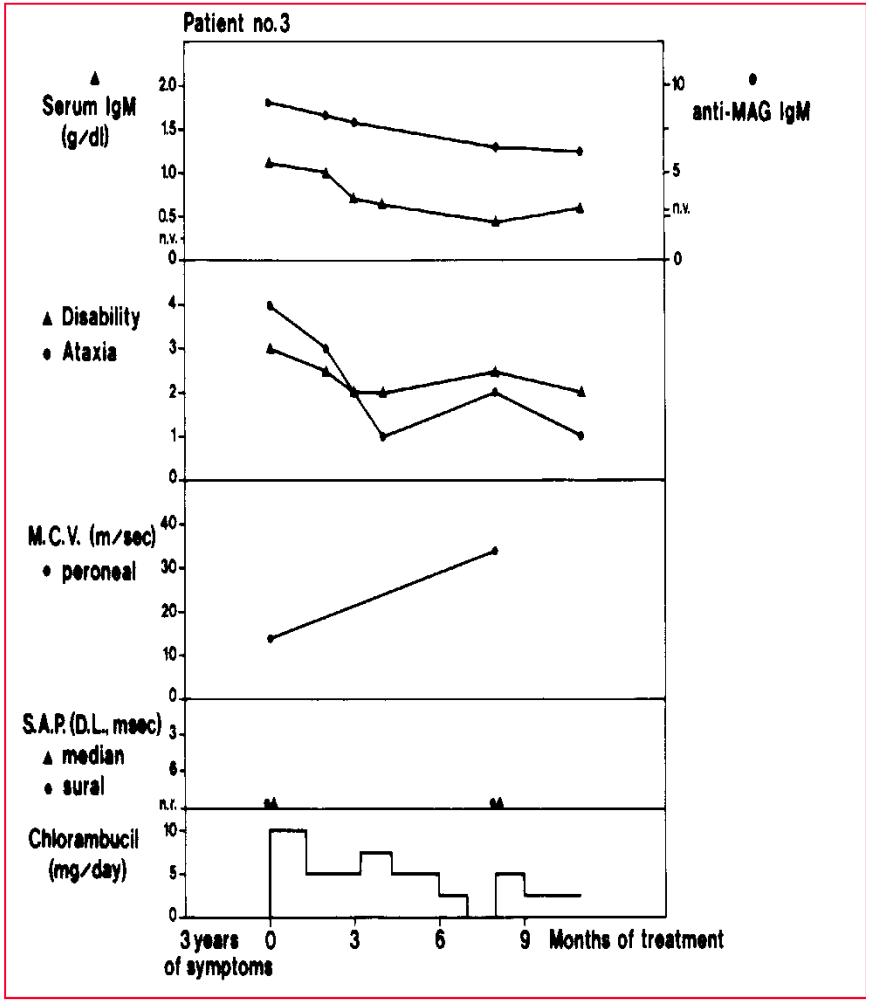
1. Anti-MAG IgM are almost invariably associated with PN or predict its onset
2. Clinical & electrophysiological homogeneous features of the neuropathy;
3. Pathological evidence of demyelination and IgM & complement deposits in nerve;
4. Complement mediated nerve demyelination induced in animals by anti MAG IgM;
5. Improvement correlates with reduction of anti-MAG IgM





THERAPY OF NEUROPATHY AND ANTI-MAG IgM

Therapy	No. treated	No (%) improved
Plasmaexchange	**80**	**36 (45%)**
Chlorambucil	78	31 (40%)
Steroids	46	18 (39%)
Cyclophosphamide	**38**	**18 (47%)**
IVIg	45	8 (18%)
Interferon α	32	9 (27%)
Fludarabine	**27**	**14 (52%)**
5/16 (31%) in one trial		
Rituximab	**16**	**10 (62%)**
double dose	***8***	***4 (50%)***
Cladribine	1	1
Other therapies	7	1 (14%)
Total patients	***378***	***150 (40%)***



RCT in PN & anti-MAG IgM

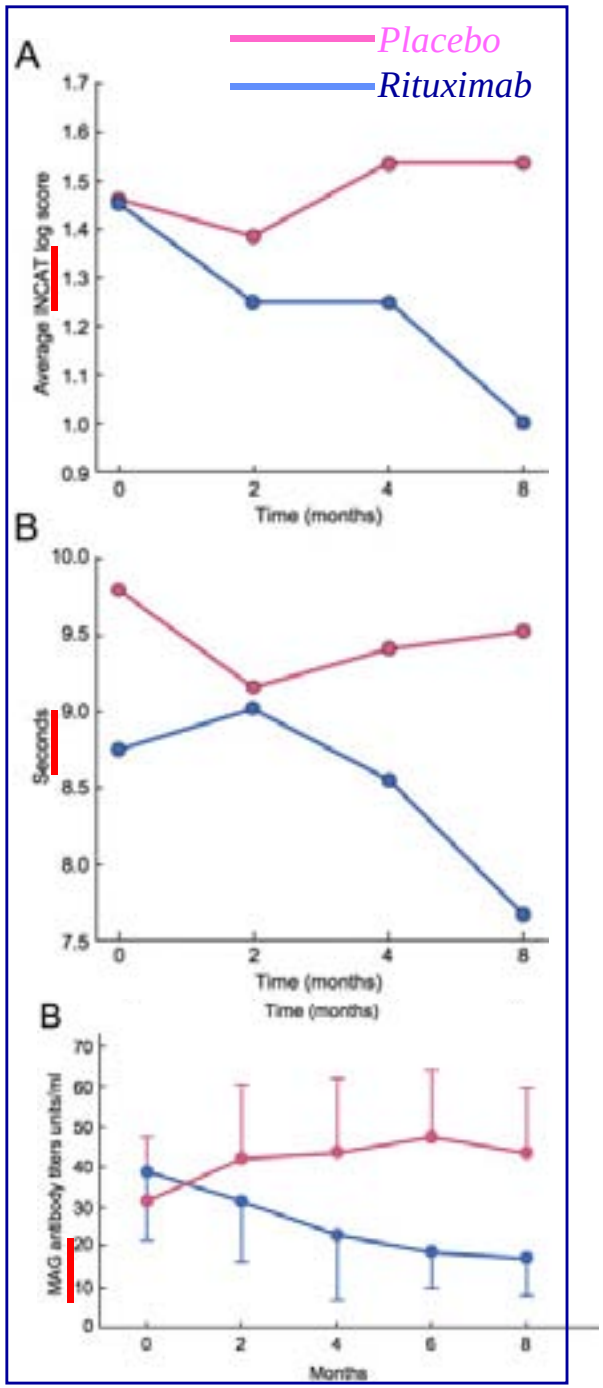
- Dyck et al. 1991: **PE (2/wk x 3 wks)** vs sham exchange; double-blind
  39 PN+MGUS (21 IgM); PE **effective in IgG/IgA, not IgM MGUS**
- Oksenhendler et al.1995: Chloranbucil (Ch) **+/- PE (15 in 4 mos);** open
  44 PN+IgM (33 MAG); **No difference** between Ch and Ch+PE
- Dalakas et al 1996: **IVIg** vs placebo x 3 mos; double-blind, cross-over
  11 PN+IgM (9 MAG); IVIg **effective in 2 IgM (18%)** (1 MAG, 11%)
- Comi et al 2002: **IVIg** vs placebo x 1 mos; double-blind, cross-over
  22 PN+IgM (11/19 MAG); **IVIg slightly better (p=0.05)** than placebo
- Mariette et al 1997: **IFN-a vs IVIg** x 12 mos; open
  20 PN+MAG; **Sensory improvement in 8/10 IFN-a** and 1/10 IVIg
- Mariette et al 2000: **IFN-a** vs placebo x 6 mos; double blind
  24 PN+MAG; **No difference** between IFN-a and placebo.
- Niermejier et al 2007: **Oral CTX+ Prednisone** (16) vs Placebo (19) x 6 mos
  double-blind; 35 PN+IgM (17 MAG); **No difference in functional scales (33% better vs 21%); MRC, sensory & DL better** at 6 mos.

Placebo-Controlled Trial of Rituximab in IgM Anti–Myelin-Associated Glycoprotein Antibody Demyelinating Neuropathy

Marinos C. Dalakas, MD, Goran Rakocevic, MD, Mohammad Salajegheh, MD, James M. Dambrosia, PhD, Angelika F. Hahn, MD, Raghavan Raju, PhD, and Beverly McElroy, CNRN

Ann Neurol 2009; 65: 286-293

- RCT on 26 patients with 4 weekly infusions of Rituximab, 375 mg/m2, versus placebo.
- After 8 months, 4/13 (31%) patients on Rituximab improved by 1 point in INCAT score compared to 0/13 controls (p = 0.096; p = 0.036 without 1 pat. with 0 score at entry)
- Time to 10 m walk reduced in the Rituximab group (p = 0.042);
- IgM reduced at 8 month by 34% and anti-MAG by 50% in the Rituximab group
- Rituximab was the first drug shown to be effective in some anti-MAG patients..



Blood. 2009 Mar 5. [Epub ahead of print]

Progressive multifocal leukoencephalopathy following rituximab therapy in HIV negative patients: a report of 57 cases from the Research on Adverse Drug Event and Reports (RADAR) project.

Carson KR, Evens AM, Richey EA, et al Siteman Comprehensive Cancer Center, Washington University School ofMedicine, Sto Louis, MO, United States.

… We reviewed PML case descriptions among patients treated with rituximab from the FDA, the manufacturer, physicians, and a literature review from 1997 to 2008. **Overall, 52 patients with lymphoproliferative disorders, two patients with systemic lupus erythematosus, one patient with rheumatoid arthritis, one patient with an idiopathic auto immune pancytopenia, and one patient with immune thrombocytopenia developed PML following treatment with rituximab and other agents.** Other treatments included hematopoietic stem cell transplantation (7 patients), purine analogues (26 patients), or alkylating agents (39 patients). One patient with an auto immune hemolytic anemia developed PML following treatment with corticosteroids and rituximab and one patient with autoimmune pancytopenia developed PML following with corticosteroids, azathioprine and rituximab. Median time from last rituximab dose to PML was 5.5 months.Median time to death was 2.0 months. The case-fatality ratio was 90%. **Awareness is needed of the potential for PML among Rituximab-treated individuals.**

Journal of the Peripheral Nervous System 11:9–19 (2006)

EFNS/PNS PDN GUIDELINES

European Federation of Neurological Societies/Peripheral Nerve Society Guideline* on management of paraproteinemic demyelinating neuropathies. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society

Joint Task Force of the EFNS and the PNS†

†Membership of Task Force: Robert D. Hadden, UK; Eduardo Nobile-Orazio, Italy; Claudia Sommer, Germany; Angelika Hahn, Canada; Isabel Illa, Spain; Enrica Morra, Italy; John D. Pollard, Australia; Richard A.C. Hughes (Chair), UK; Pierre Bouche, France; David R. Cornblath, USA; Eileen Evers, UK; Carol L. Koski, USA; Jean-Marc Léger, France; Peter Van den Bergh, Belgium; Pieter A. van Doorn, Netherlands; Ivo N. van Schaik, Netherlands.

EFNS/PNS PDN GUIDELINES

Good practice points for treatment of IgM PDN

1. In patients without significant disability, consideration should be given to withholding immunosuppressive or immunomodulatory treatment, providing symptomatic treatment for tremor and paraesthesiae, and giving reassurance that symptoms are unlikely to worsen significantly for several years.

2. In patients with significant disability or rapid worsening, IVIg or PE should be considered as initial treatment, although their efficacy is unproven.

3. In patients with moderate or severe disability, immunosuppressive treatment should be considered, although its long term efficacy remains unproven. Preliminary reports suggest that Rituximab may be a promising therapy.

2° Neurology, Department of Translational Medicine, IRCCS Humanitas Clinical Institute Milan University, Rozzano, Milan

Fabrizia Terenghi
Francesca Girolami
Francesca Gallia
Barbara Bossi
Francesco Tuccillo
Claudia Giannotta

Rituximab in patients with CIDP: A report of 13 cases and review of the literature

Benedetti et al J Neurol Neurosurg Psychiatry 2009, In press

- 13 CIDP patients (8 with haematological diseases) poorly responsive to conventional therapies were treated with Rituximab.
- 9 patients (7 with haematological diseases) improved or reduced or suspended therapy after Rituximab: 6 improved, and 3 maintained the improvements achieved with IVIg or plasma exchange.
- Rituximab was often effective in patients with CIDP and co-occurring haematological diseases.

Immunosuppressant and immunomodulatory drugs reported to be beneficial in CIDP

Class IV evidence (see Hughes et al. 2004)

1. Azathioprine
2. Cyclophosphamide
3. Ciclosporin
4. Etanercept
5. Interferon alpha
6. Interferon beta1a
7. Mycophenolate mofetil
8. Rituximab (anti-CD20)

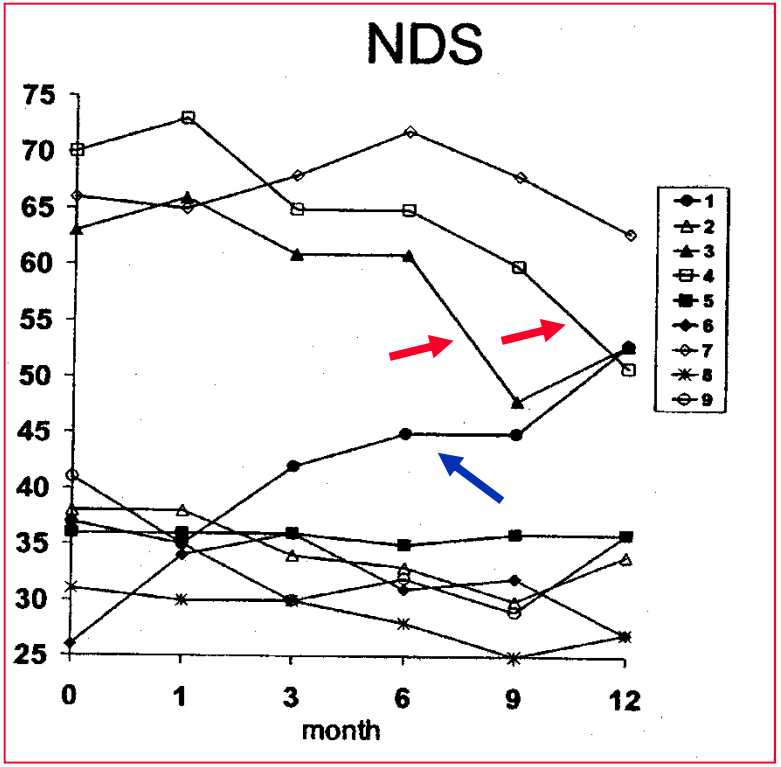
Worsening of neuropathy under Rituximab

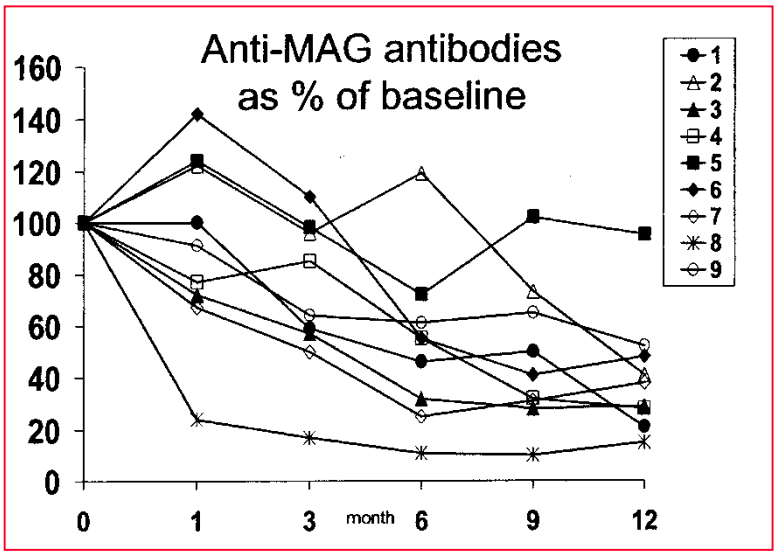
- **1 patient** with WM had acute worsening of pre-existing neuropathy consistent with ***GBS*** during therapy with **Rituximab and fludarabine** *(Noronha et al 2006)*
- **1 patient** with NHL in complete remission developed ***GBS*** during **Rituximab** maintenance therapy*(Carmona et al 2006)*
- **1 patient** with NHL **developed *GBS*** soon after combined CHOP and **Rituximab** therapy *(Terenghi et al 2007)*
- **3 patients** with neuropathy with anti-MAG *(Broglio et al 2005; Renaud et al 2003)* or -ganglioside *(Rojas-García et al 2003)* IgM M-protein had ***severe worsening of neuropathy*** **within one month after treatment with Rituximab**.
- **1 patient** with WM & mild sensory PN evolved into severe ***vasculitic mononeuritis multiplex*** with conversion of type I to II cryoglobulin during **Rituximab** *(Mauermann et al 2007)*

RITUXIMAB (α-CD20 MAB) IN PN AND ANTI-MAG IgM

Renaud et al 2003 Muscle Nerve

- 9 pts with PN & anti–MAG
- Rituximab 375mg/m2/wk x 4
- B cells decreased in all
- IgM ↓ in all by 35% to 82 %
- Anti-MAG ↓ by ≥ 50% in 8/9
- NDS ↑ in 6 (≤5 in 4, ≥10 in 2) . 1 ↓ (16) , 2 =
- Ulnar MCV ↑ by ≥10% in 7





Predictors of response to rituximab in patients with neuropathy and anti–myelin associated glycoprotein immunoglobulin M

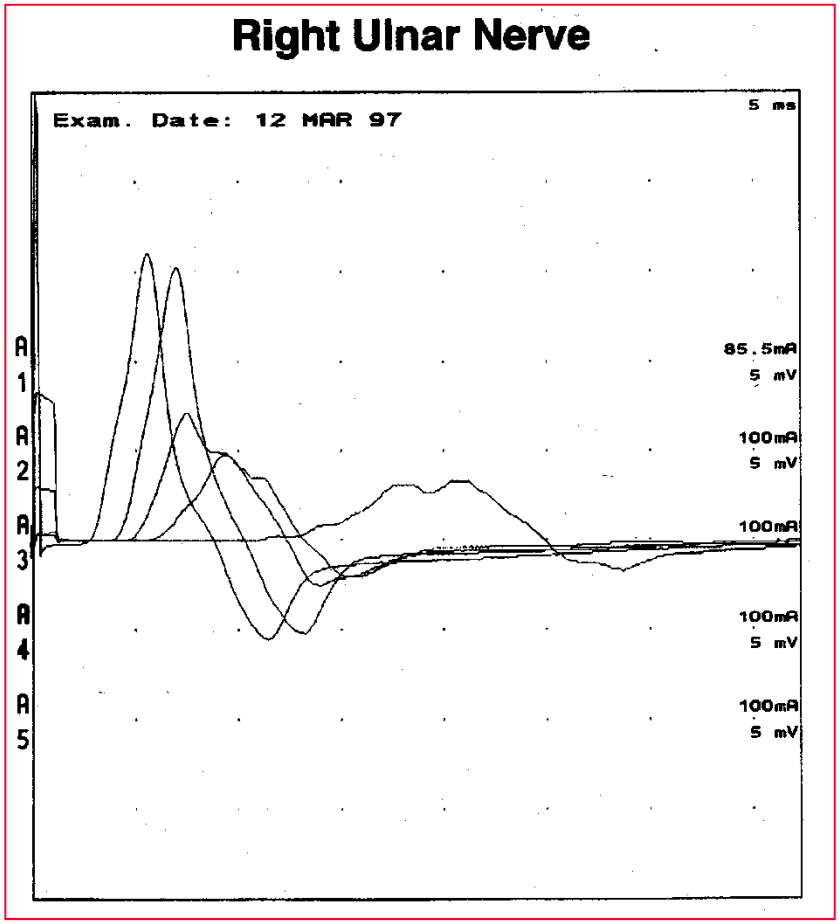
Luana Benedetti[1], Chiara Briani[2], Marina Grandis[1], Tiziana Vigo[1], Marco Gobbi[3], Elisabetta Ghiglione[1], Marinella Carpo[4], Dario Cocito[5], Christina M. Caporale[6], Maria P. Sormani[7], Giovanni L. Mancardi[1], Eduardo Nobile-Orazio[8], and Angelo Schenone[1]

JPNS 2007, 12:102-7

- **13 patients** with PN & anti-MAG IgM-M-protein.
- **Anti-MAG IgM** significantly **reduced after 1 year**.
- **8 patients (62%) improved** in INCAT sensory & MRC score and **7 (54%) in disability** too.
- **Improvement** in INCAT sensory sumscore **correlated with lower anti-MAG** titres at entry and at follow-up.

Antibody reduction below a critical level may be necessary to achieve clinical improvement

VARIABILITY IN THE DEFINITION OF CONDUCTION BLOCK (CB) IN MMN



Reduction in the ratio of proximal/ distal CMAP amplitude and/or area ranging from:

> 20%, without abnormal temporal dispersion *(Roth et al al 1986; Pestronk et al 1988)*

to:

> 50%, ± *focal* abnormal temporal dispersion *(Lewis et al 1982; Rhee et al 1990; Kaji et al 1992)*

EFNS/PNS Electrodiagnostic criteria

I Definite: at least one of the following

A. At least 50% prolongation of motor distal latency in 2 nerves, or

B. At least 30% reduction of motor conduction velocity in 2 nerves, or

C. At least 20% prolongation of F-wave latency in 2 nerves (> 50% if amplitude of distal negative peak CMAP < 80% of lower limit of normal values), or

D. Absent F-waves in 2 nerves if distal CMAP amp ≥ 20% of lower normal limit + at least 1 other demyelinating parameter[1] in at least one other nerve, or

E. Partial motor conduction block: at least 50% amplitude reduction, if distal CMAP at least 20% of lower normal limit, in 2 nerves, or in 1 nerve + at least one other demyelinating parameter[1] in at least one other nerve, or

F. Abnormal temporal dispersion (> 30% increased duration) in ≥ 2 nerves, or

G. Distal CMAP duration of at least 9 msecs in ≥ 1 nerve + ≥ 1 other demyelinating parameter[1] in at least one other nerve

II Probable

At least 30% proximal-to-distal CMAP amplitude reduction, excluding posterior tibial nerve, if distal CMAP ≥ 20% of lower normal limit, in 2 nerves, or in 1 nerve + ≥1 other demyelinating parameter[1] in > 1 one other nerve

III Possible

As in Definite but in only one nerve

CIDP: EFNS/PNS Diagnostic Categories

Definite CIDP

1) Clinical Criteria I A or B & II with Electrodiagn. criteria Def.
2) or Probable CIDP + at least 1 Supportive Criterion
3) or Possible CIDP + at least 2 Supportive Criteria

Probable CIDP

1) Clinical criteria I A or B & II with Electrodiagn. criteria Prob.
2) or Possible CIDP + at least 1 Supportive Criterion

Possible CIDP

1) Clinical criteria I A or B & II with Electrodiagn. criteria Poss.

CIDP (definite, probable, possible) with concomitant dis.

I: Inclusion A: Typical CIDP; B: Atypical CIDP; II: Exclusion

ANTI-NERVE ABS IN CHRONIC DYSIMMUNE PN

Antigens	Antibody Isotype	Clinical syndrome	Fre-quency	Clinical impairm	Nerve Pathology	Authors
MAG/SGPG/P0	IgM	PN+IgM	50%	S>>M	Dem.	Latov et al 1980
Chondr. sulf C	IgM	PN+IgM	1%	SM	Axonal	Sherman et al 1983
Sulfatide	IgM	PN axonal	?	S,S>M,	Axonal	Pestronk et al 1991
		PN+IgM	5%	SM	Dem.	Nobile-Orazio al 1994
β-tubulin	IgM	CIDP	57%	M>>S	Dem.	Connolly et al 1993
GM1	IgM	MMN+IgM	20-80%	M	Dem	Pestronk et al. 1991
		LMND+IgM	? 5%	M	MND	Freddo et al 1986
GM2	IgM	PN+IgM	?	M>S	Dem.	Ilyas et al 1988
GD1a	IgM	PN+IgM	2%	M	Dem.	Bollensen et al 1989
GQ1b/Disialog.	IgM	PN+IgM	2%	S>>M	Dem.	Ilyas et al 1986
Hu	IgG	SSN-PLE	?	S>>M	Axonal	Graus et al 1985

EFNS/PNS Recommendations

1) Initial Treatment

1. Patients with very mild symptoms not or slightly interfering with daily activities may be monitored without treatment.
2. IVIg or corticosteroids should be considered in sensory and motor CIDP in presence of troublesome symptoms (Level B recommend.). The presence of contraindications to either treatment should influence the choice (Good Practice Point)
3. The advantages and disadvantages should be explained to the patient who should be involved in the decision making (Good Practice Point).
4. In pure motor CIDP IVIg should be considered as the initial treatment (Good Practice Point)
5. If IVIg and corticosteroids are ineffective PE should be considered (Level A recommendation)

Dosage, Regimen & Duration of Treatment: Steroids

1. Common initial doses of corticosteroids are prednisone or predniso(lo)ne 1 mg/kg or 60 mg daily but there is a wide variation in practice. There is no evidence and no consensus about whether to use daily or alternate day prednisone or prednisolone or intermittent high dose monthly intravenous or oral regimens.
2. For patients starting on corticosteroids a course of up to 12 weeks on their starting dose should be considered before deciding whether there is no treatment response. If there is a response, tapering the dose to a low maintenance level over one or two years and eventual withdrawal should be considered.