Diagnosis and treatment of chronic immune-mediated neuropathies

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Conflict of Interest:
Eduardo Nobile-Orazio

- *Steering/Advisory Board: Baxter, USA; CSL Behring, Switzerland; Novartis, Switzerland;*
- *Honorarium for Lectures: Baxter, USA & Italy; CSL Behring, Italy; Grifols, Spain; Kedrion, Italy*
- *Travel grants for Scientific Meetings: Baxter, Grifols, Kedrion, and Novartis, Italy*

Learning objectives

1. What is the spectrum of immune-mediated neuropathies?
2. How to diagnose CIDP and MMN?
3. What is the pathogenesis of CIDP and MMN?
4. What is the best therapy for CIDP and MMN?

CHRONIC IMMUNE NEUROPATHIES

1. Chronic inflammatory demyelinating polyneuropathy (CIDP)
    1. Purely motor CIDP
    2. Sensory CIDP (including chronic immune sensory polyradiculoneuropathy)
    3. Multifocal demyelinating neuropathy (Lewis-Sumner syndr.)
    4. Focal CIDP
    5. Distal acquired demyelinating symmetric (DADS) neuropath.
2. Multifocal motor neuropathy (MMN)
    1. Multifocal motor neuropathy without conduction block
3. Neuropathy associated with IgM monoclonal gammopathy:
    1. Anti-MAG
    2. Anti-glycolipid (sulfatide, GM1, GD1a, GD1b, ChSC, …)
    3. Unknown reactivity
4. Neuropathy associated with IgG/A monoclonal gammopathy
    1. CIDP?

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

Prevalence and Severity of CIDP

- *Prevalence of CIDP*
  - SE England: 1.24/100.000 *(AAN)*, 1/1/95 (Lunn et al 1999)
  - SE England: 2.84/100.000 *(EFNS-PNS)*, 1/1/08 (Mahdi-Rogers et al 2013)
  - Piemonte: 3.5/100,000 *(AAN)*, 31/12/01 (Chiò et al, 2007)
  - Olmstead County: 8.9/100,000 *(Mayo)* (Laughlin et al, 2009)
- *On the prevalence date* (Lunn et al 1999) *:*
  - Mean age: 54.4 years (range 10-95)
  - Mean age of onset: 45.6 years (41.8 RR, 50 for CP)
  - Mean duration of CIDP: 8.9 yrs (2-490 months)
  - 13% of patients required aid to walk
  - 54% were still on treatment
  - *54% severely disabled at some time*

Causes of chronic polineuropathy

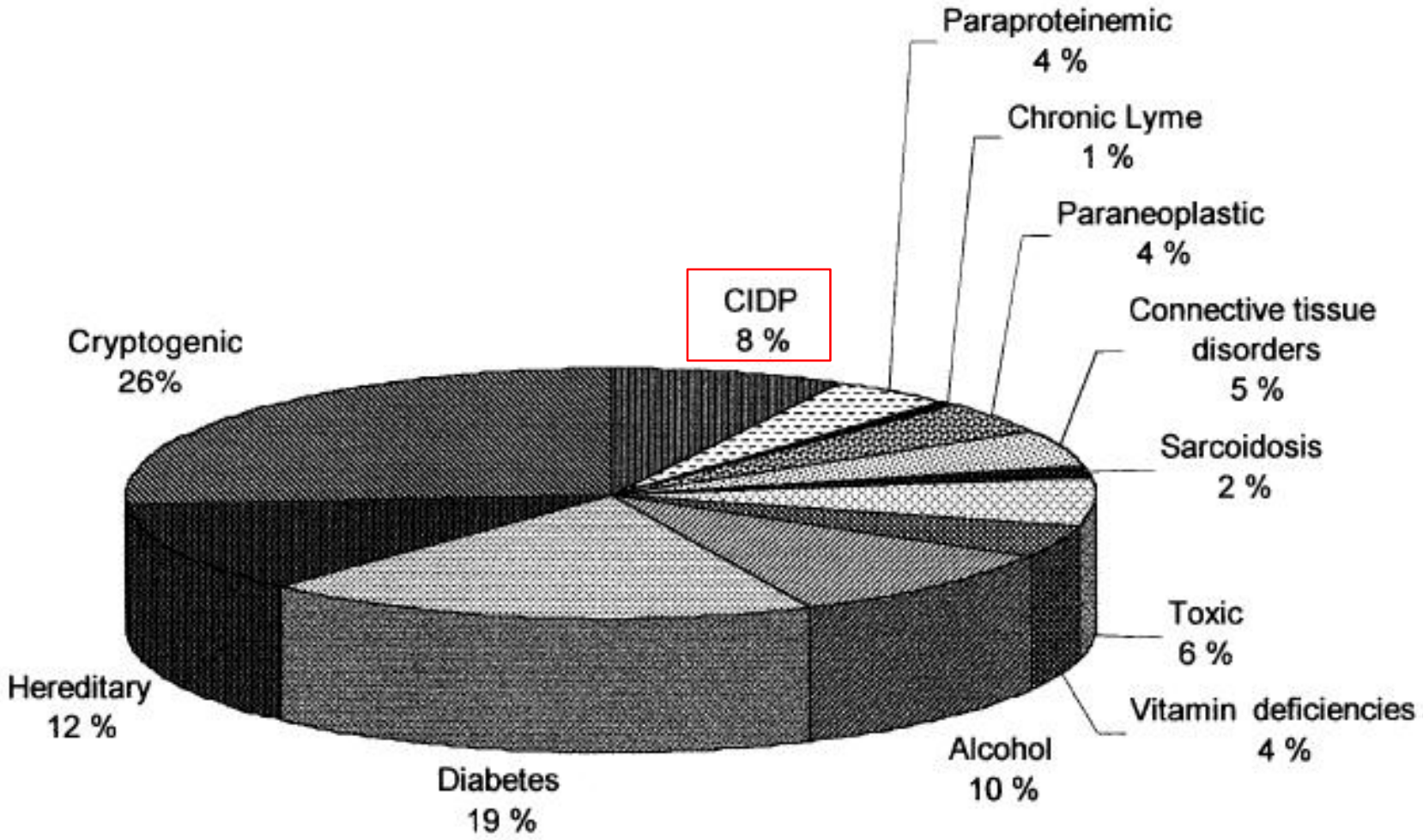
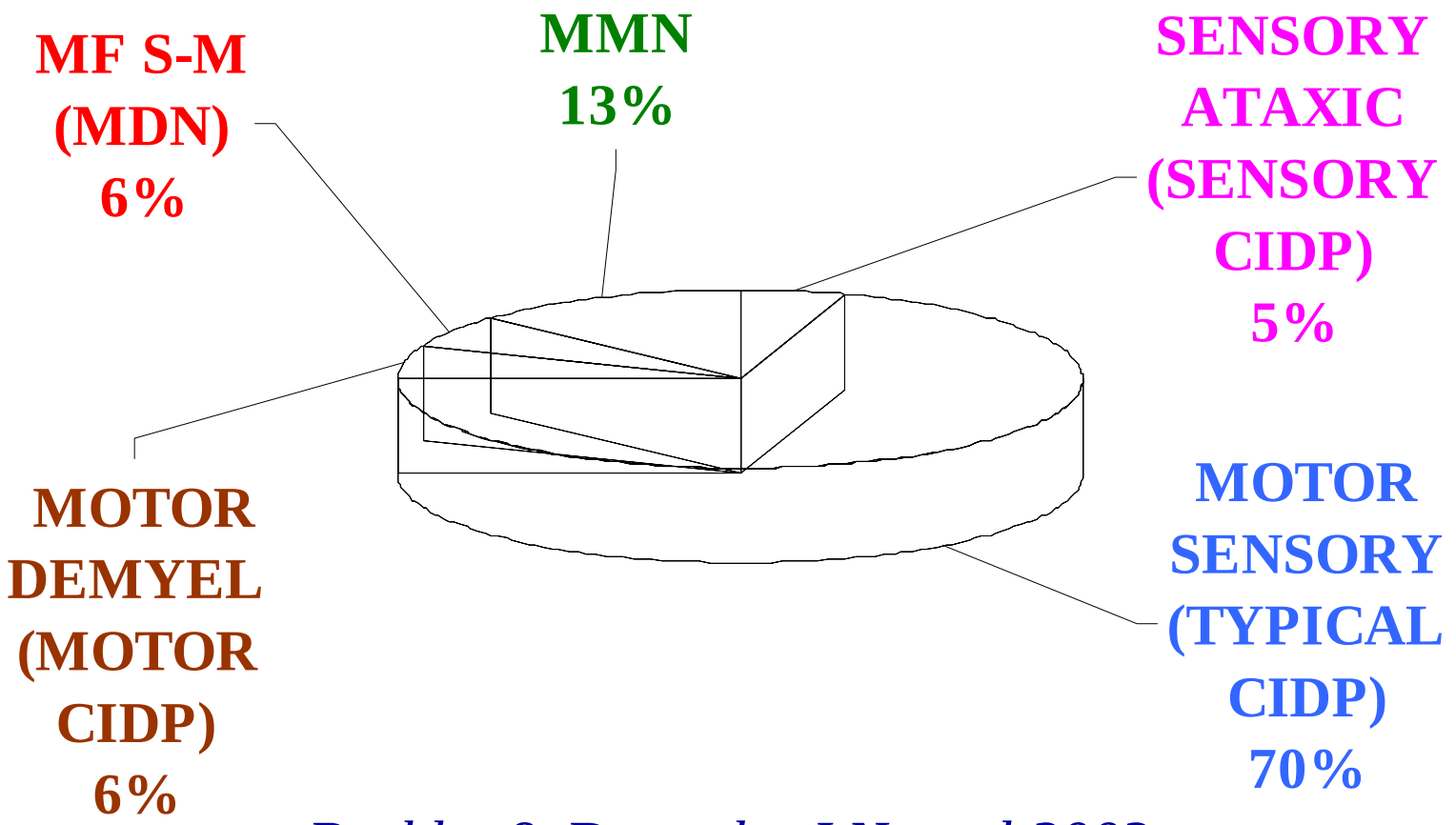


Figure 2 Causes of chronic polyneuropathy in Vest-Agder ($n = 192$).

Mygland & Monstad, Eur J Neurol 2001

CIDP AND CLINICAL VARIANTS

Subclassification of chronic immune mediated demyelinating neuropathies in 102 patients



Bushby & Donaghy J Neurol 2003

2010 EFNS/PNS Revised 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

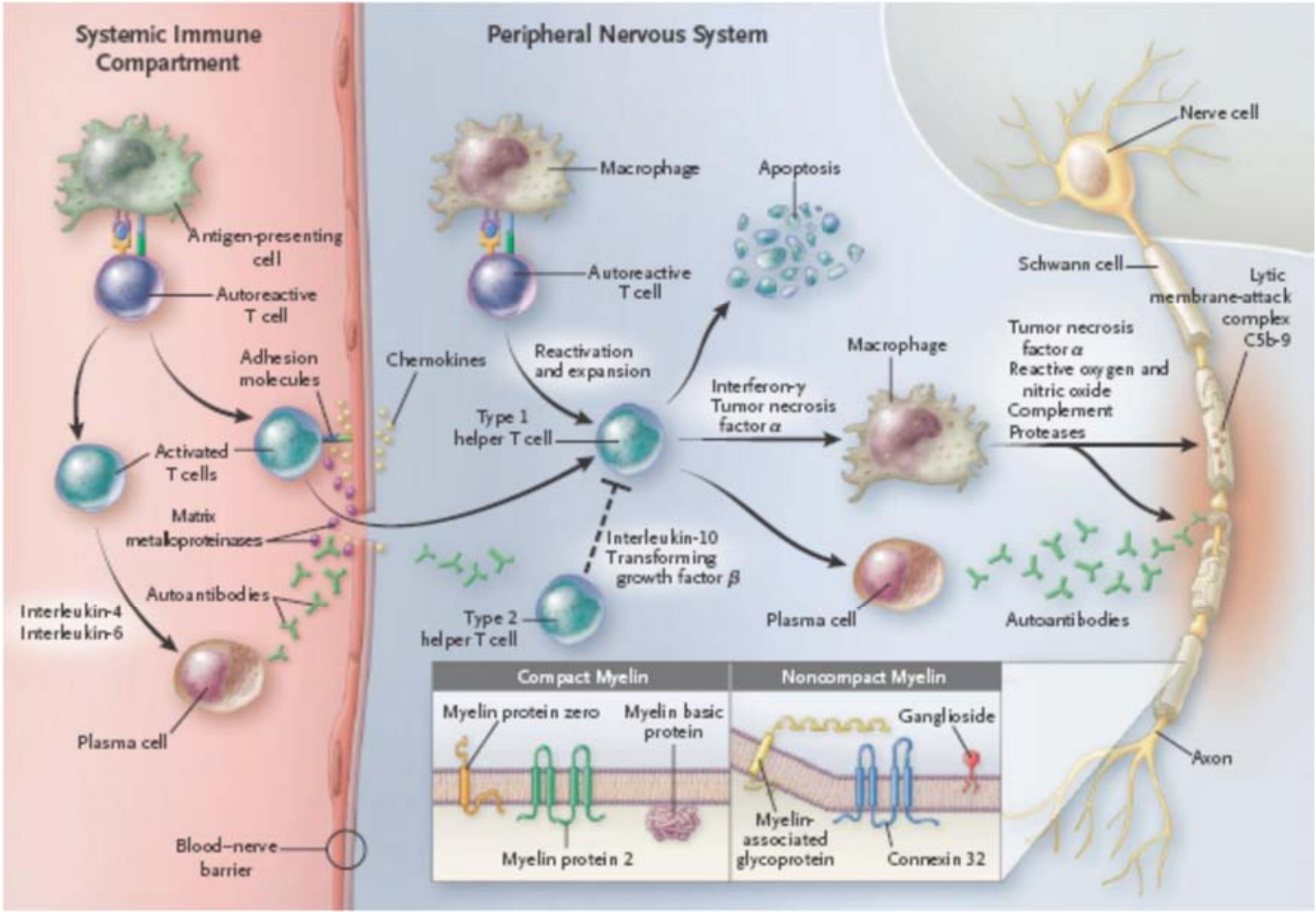
- **Pure motor** *or*
- **Pure sensory**, including chronic sensory immune polyradiculo- neuropathy *or*
- **DADS,** predominantly distal *or*
- **Lewis-Sumner syndrome**: asymmetric *or*
- **Focal presentations** (brachial plexus or single nerves)

and Absent or reduced tendon reflexes in the affected limbs

CIDP: variants or different diseases?

- Lewis- Sumner syndrome: why almost 50% of patients do not evolve into CIDP after several years?
- Sensory CIDP: why it maintains for several years a selective sensory impairment? Why it is reported to respond less well to immune therapy?
- Motor CIDP: why it maintains for several years a selective motor impairment? Why it often worsen with steroid therapy? Can it be a diffuse variant of MMN?
- DADS: is it only a clinical phenotype observed either in patients with otherwise typical CIDP or, more often, in those with anti-MAG IgM associated neuropathy?

PATHOGENESIS OF CIDP



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

Anti-neural antibodies in CIDP

Glycolipids	% positive	Proteins	% positive
GalC	0-9%	Connexin 32	4%
GM1	12-25%	35/6 kD P0 like	5-20%
a-GM1	25%	PMP22	0-50%
LM1	12-67%	MBP	1 pt.
SGPG	0-20%	Bovine P2	0-34%
Sulfatide	0-10%	Human P0	16-29%
All*+ChS	32%	Beta tubulin	7-57%

% of CIDP patients with IgM antibodies to neural antigens (1994-1995-2008-2009-2013)

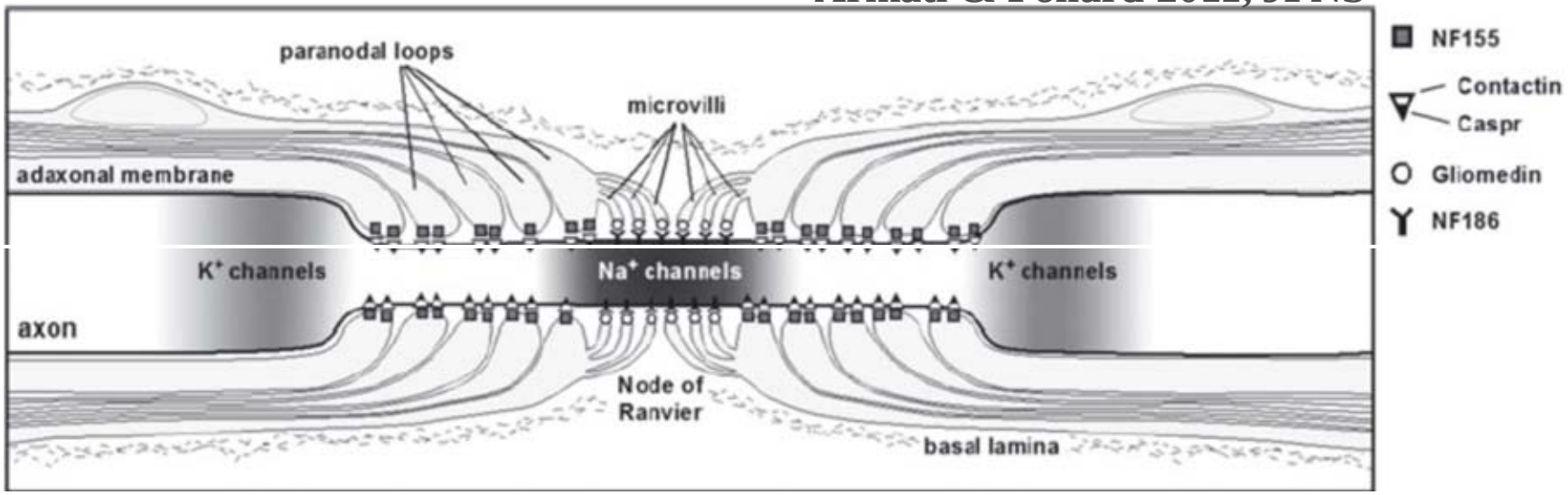
Antigens	**% positive**	**Antigens**	**% positive**
GM1	10%	Gang compl. GM1-2	3%
GM2	5%	Galactocerebroside	29%
GD1a	3%	GM1-Galactocerebr.	17%
GD1b	3%	Heparin Disac N6H6	21%
GQ1b	8%	α & tubulin	10 %
Sulfatide	0%	35 kD P0 like	20 %

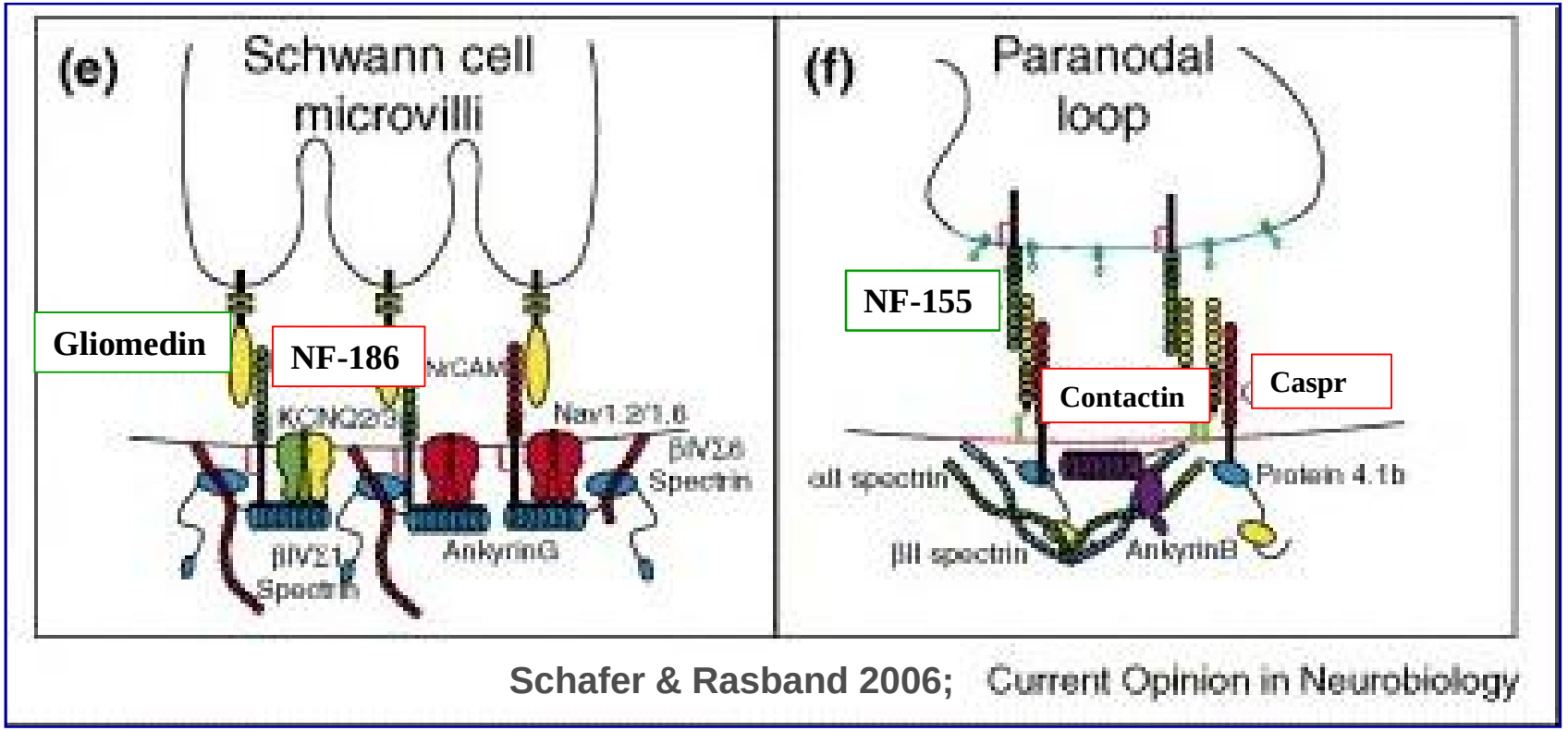
No significant difference compared to non-immune neuropathies

No. of CIDP patients tested in our laboratory ranged from 38 to 62

Overall 20/38 (53%) CIDP patients have one or more antibodies

Armati & Pollard 2011, JPNS

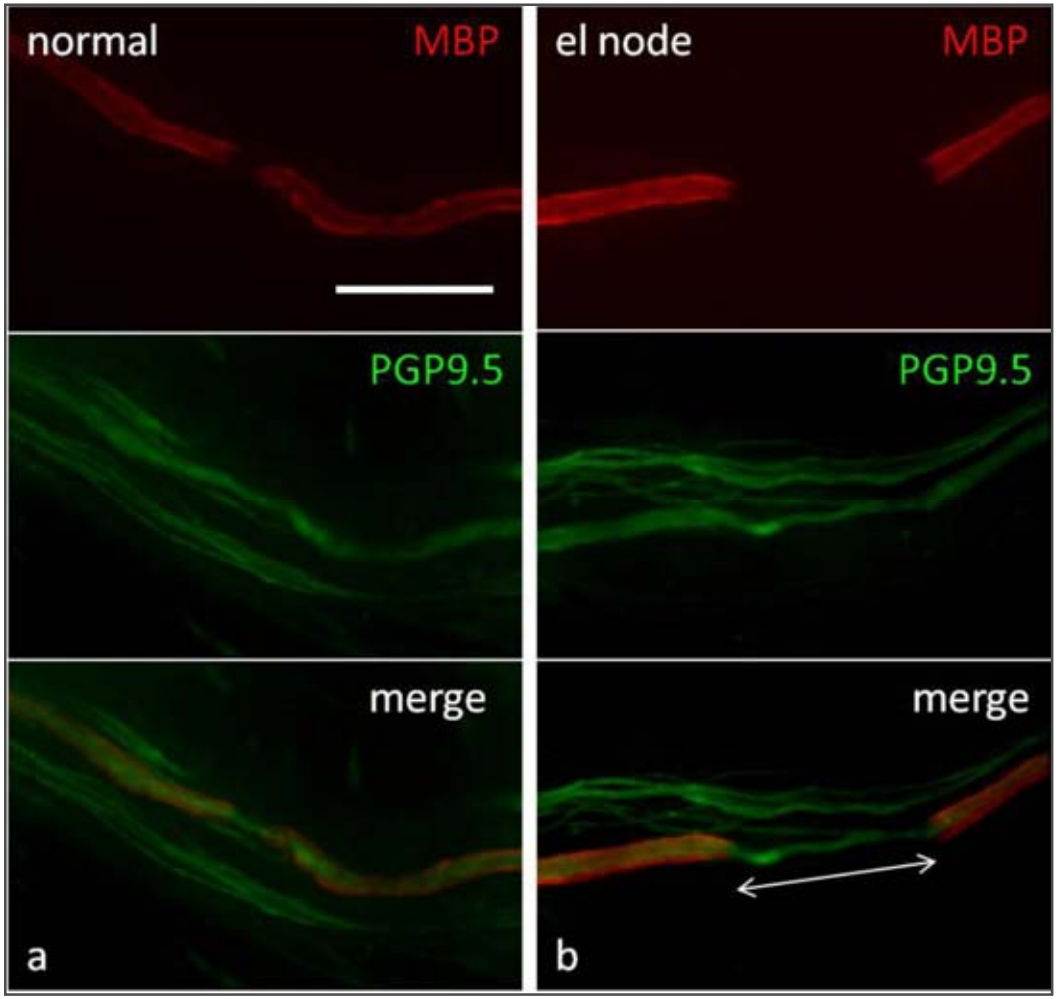




Schafer & Rasband 2006; Current Opinion in Neurobiology

Disruption of nodal architecture in skin biopsies of patients with demyelinating neuropathies

Kathrin Doppler, Christian Werner, and Claudia Sommer

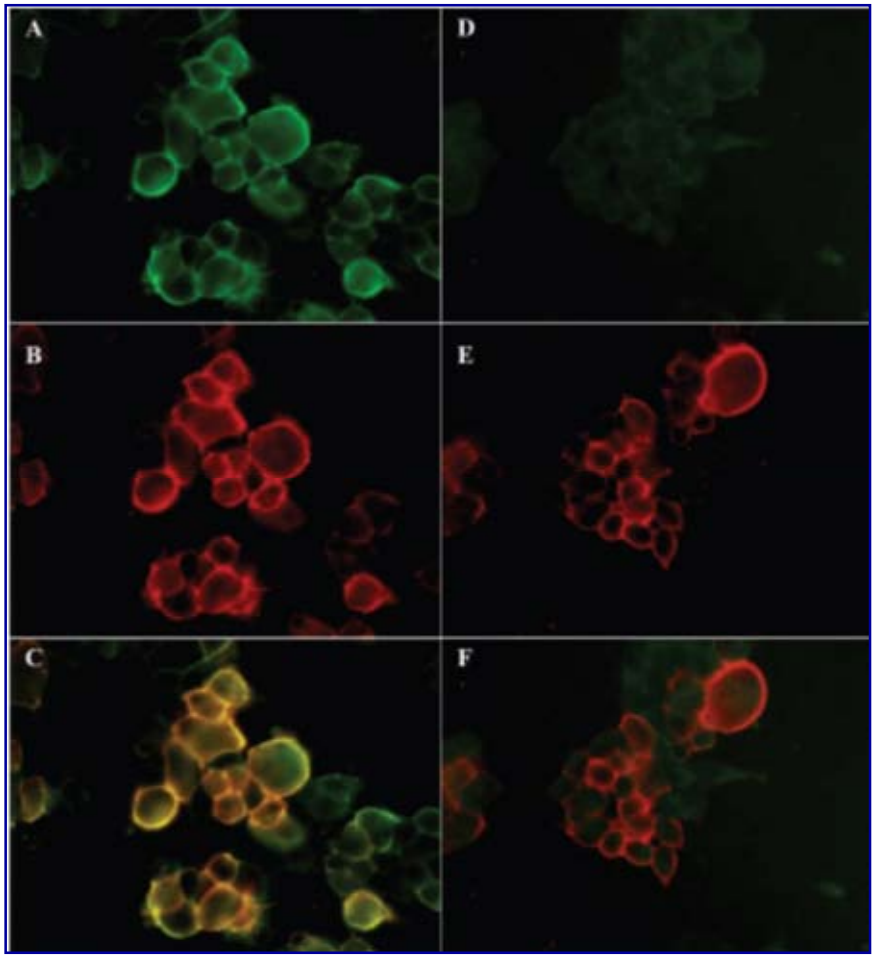


	Elongated nodes	Dispersion of caspr	Dispersion of neurofascin
CIDP-def (5)	4/5	5/5	4/5
CIDP-clin (9)	4/9	4/9	2/9
Other demyelinating NP (5)	1/5	1/5	2/5
AMN (1)	1/1	1/1	0/1
CMT (1)	1/1	0/1	1/1

JPNS 2013

Antibodies to Contactin-1 in Chronic Inflammatory Demyelinating Polyneuropathy

- 4/46 (8.6%) CIDP sera reacted with hippocampal neurons & paranodal structures on nerve.
- Reactivity with CNTN1 in 2, & CNTN1 & CASPR1 in 1.
- Common features: aged patients, severe, mostly motor, early axonal loss & poor response to IVIg.



Querol et al. Ann Neurol 2013

Therapy for CIDP

CORTICOSTEROIDS FOR CIDP

Mehndiratta MM & Hughes RAC

Cochrane Database of Systematic Reviews 2012

PLASMAEXCHANGE FOR CIDP

Mehndiratta MM, Hughes RAC, Agarwal P

Cochrane Database of Systematic Reviews 2012

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 has the longer effect?
- Which is the best tolerated therapy?
- Which is the most convenient therapy?

Comparison of effective therapies in CIDP

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

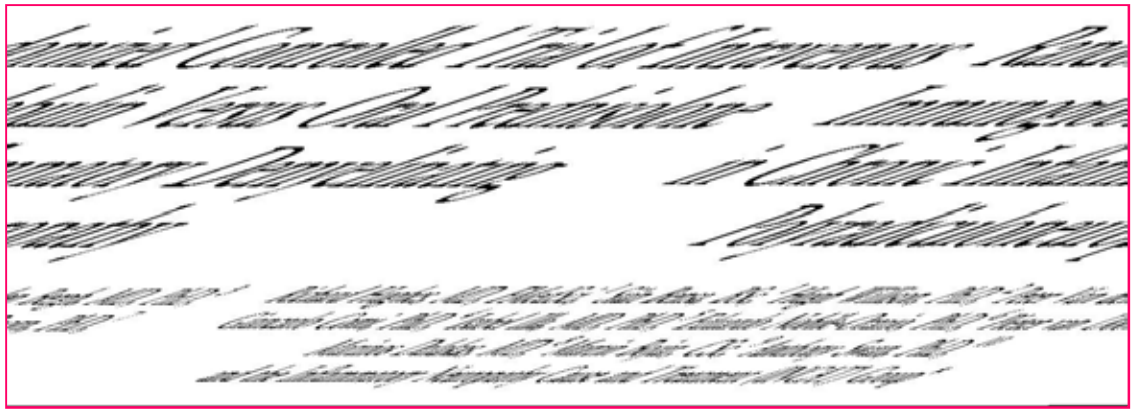
IVIg = PE

Ann Neurol 1994

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

IVIg =Prednisolone

Ann Neurol 2001



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

Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial

Richard A C Hughes, Peter Donofrio, Vera Bril, Marinos C Dalakas, Chungin Deng, Kim Hanna, Hans-Peter Hartung, Norman Latov, Ingemar S J Merkies, Pieter A van Doorn, on behalf of the ICE Study Group*

Lancet Neurol 2008; 7: 136-44

117 CIDP Patients

At 24 weeks,
- 32/59 (54%) improved on Ig vs
- 12/58 (21%) on placebo (p<0.0002)

Extension Phase:
time to relapse

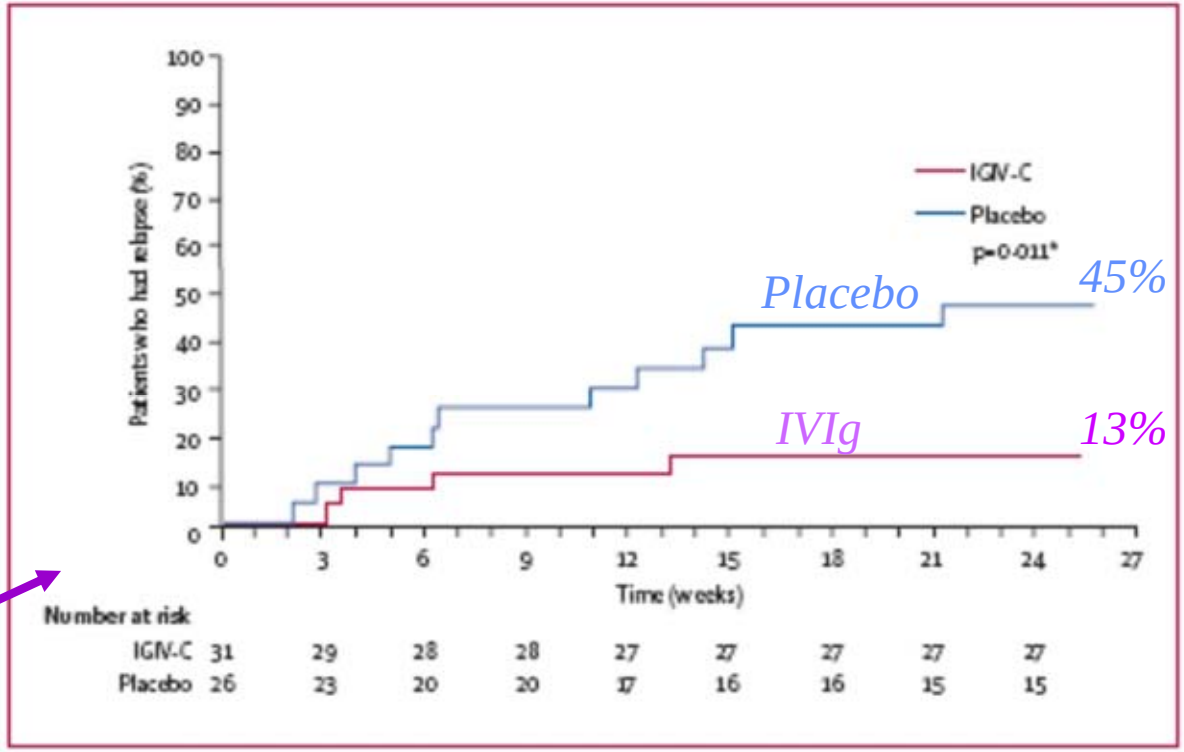


Figure 3: Time to relapse

- IVIg-C, 2g/kg, then 1g/kg every 3 wks for 24 wks; crossover if failure
- Patients improved at 24 wks assigned to 24 wks random extension

Long-term remission of CIDP after pulsed dexamethasone or short-term prednisolone treatment

Eftimov et al, Neurology 2012

- 39/40 patients included (median follow-up 4.5 yrs).
- Cure (5 yrs off therapy) or remission in 10/39 patients (26%) after 1-2 courses of dexamethasone or daily prednisolone
- *50% of patients in remission after treatment relapsed after 17.5 months for dexamethasone, and 11 months for prednisolone.*
- *Alternative diagnosis in 7/12 (58%) not responders*

- *10/24 (42%) in remission with oral dex. 40mg/dx4d every 28d x 6 cycles*
- *6/16 (37.5%) in remission with oral pred. 60mg/dx5 wks, tapered in 27wk*

Lancet Neurol 2010; 9: 245-53

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**

- To compare the efficacy & tolerability of therapy with IVIg (IgVena, Kedrion SpA) or i.v. methylprednisolone (IVMP) for six-months in patients with CIDP
- To compare the rate of relapse in the six-months following therapy suspension

Lancet Neurol 2012; May 9 online

Results II:
Per-group number of failures within 6 mos

	IVMP (n=21)	**IVIg (n=24)**	p-value
	n (%)	*n (%)*	
Success	**10 (47,6)**	**21 (87.5)**	**0.0085**
Failure	**11 (52,4)**	**3 (12.5)**	

Results X: Patients worsening during the 6 month following therapy discontinuation (completers only, 31 patients)

	IVMP (n=10)	**IVIg (n=21)**	p-value
	n (%)	*n (%)*	
Relapse	**0 (0)**	**8 (38.1)**	**0.0317**

IMC-Follow-up Study:

Patients worsening after therapy discontinuation

(Including 11 patients shifted after treatment failure)

	IVIg (n=32)	**IVMP (n=24)**	**p-value**
	n (%)	*n (%)*	
Improved	**28 (87.5)**	**13 (54.2)**	**0.0072**
Median follow-up, months (*range*)	42 *(1-57)*	43 *(7-60)*	0.765
Worsening at follow-up*	24/28 *(85.7)*	10/13 *(76.9)*	0.659
Median months to relapse, *(range)*	**4.5** *(1-24)*	**14** *(1-31)*	**0.0126**

** Including two patients who retired 1 & 7 months after the trial and two who died 1 & 3 months after the trial (3 after IVIg,1 after IVMP)*

What to do in CIDP patients not responsive to conventional therapy?

1. Review the therapy regimen:

1. *Steroids dosage and duration of therapy*
2. *IVIg dosage and frequency*

2. Reconsider the diagnosis:

1. *POEMS*
2. *Osteosclerotic myeloma*
3. *Neural B-cell lymphoma*
4. *Amyloidosis*
5. *PN+ IgM anti-MAGCMT1*

Response to second therapy in CIDP patients not responsive 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

Cocito et al., 2010

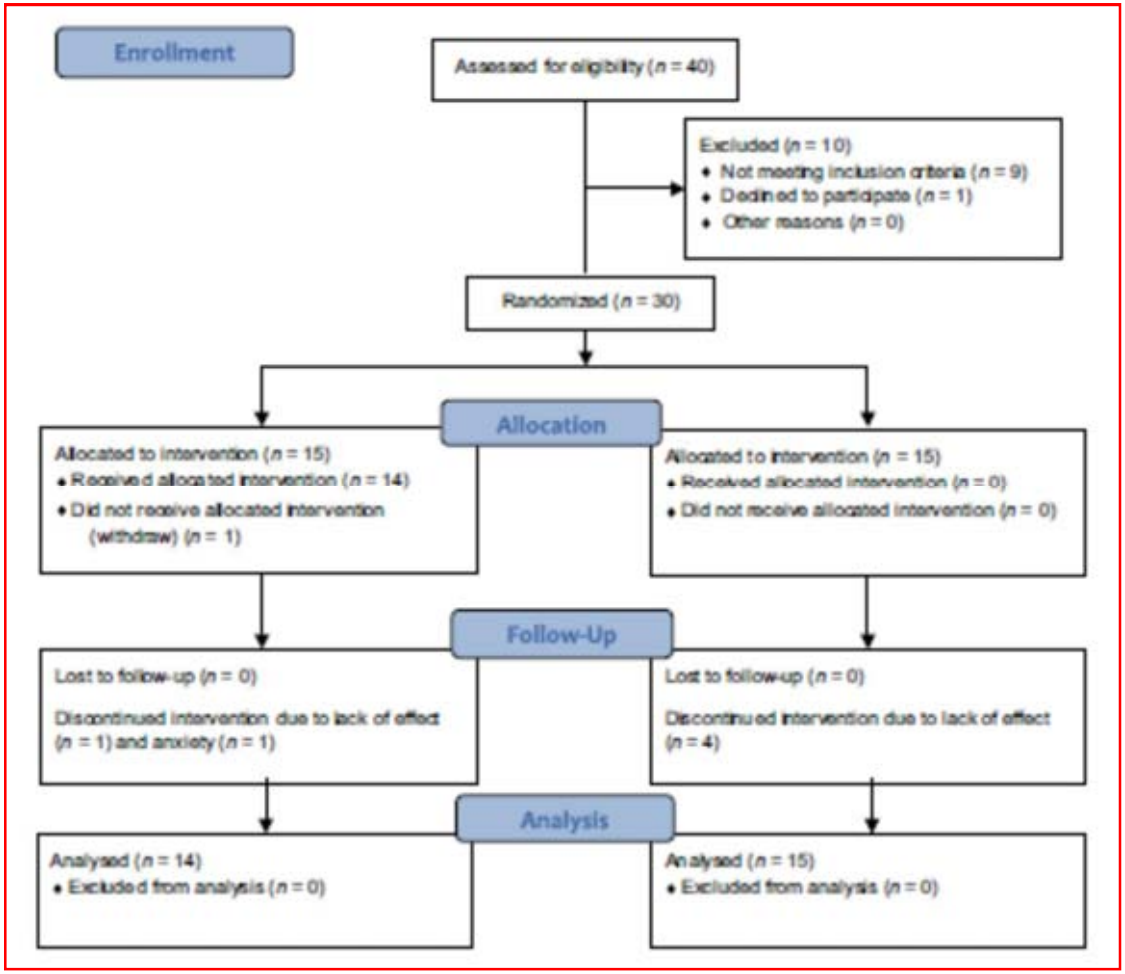
IMMUNESUPPRESSANT IN CIDP

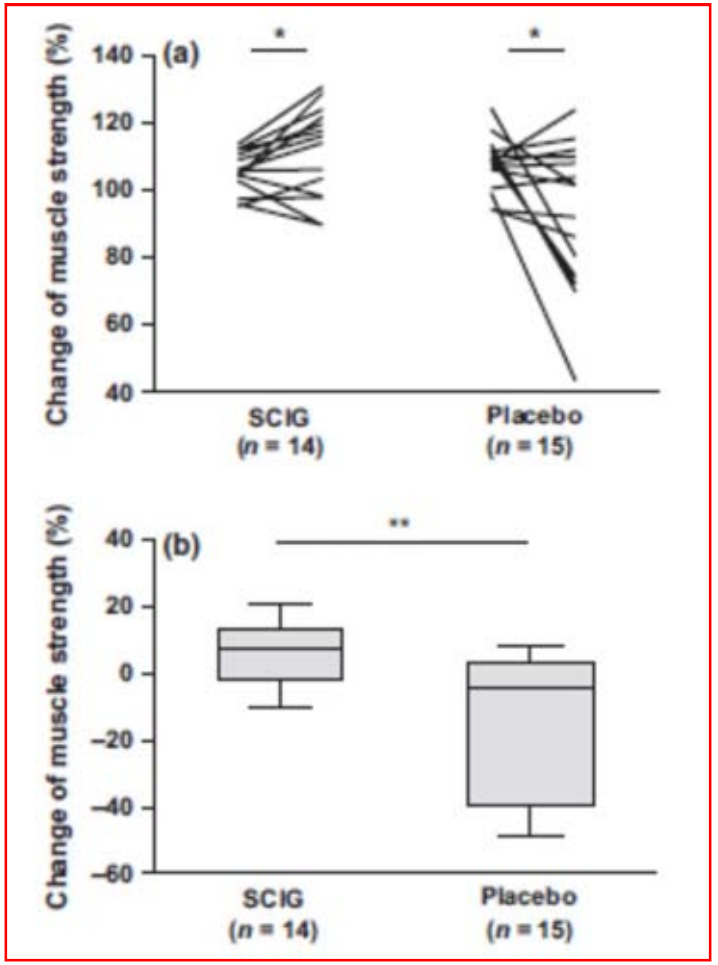
- To treat the 20-30% of patients not responsive to IVIg, steroids or PE
- To treat patients becoming progressively less responsive to IVIg or steroids
- To reduce side effects of chronic steroids
- To reduce the cost of IVIg use
- To reduce patients' dependency from IVIg and Hospital admission

Subcutaneous immunoglobulin in responders to intravenous therapy with chronic inflammatory demyelinating polyradiculoneuropathy

L. H. Markvardsen[a], J.-C. Debost[a], T. Harbo[a], S. H. Sindrup[b], H. Andersen[a], I. Christiansen[c], M. Otto[d], N. K. Olsen[e], L. L. Lassen[f], J. Jakobsen[a,c] and The Danish CIDP and MMN Study Group

European Journal of Neurology 2013, **20**: 836–842





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

1.	Cyclosporin	82%
2.	Cyclophosphamide	75%
3.	Rituximab (anti-CD20)	75%
4.	Methotrexate	70%
5.	Azathioprine	64%
6.	Interferon α	%
7.	Alentuzumab	57%
8.	Mycophenolate mofetil	46%
9.	Interferon 1a	35%
10.	Etanercept	30%
11.	Autologous hematopoietic stem cell transplantation	

Response to immune suppressive/modulatory agents in 110 CIDP patients (158 procedures)

	Treated	Responders	%	% with SE
AZA	77	21	**27**	**21** *(13% stop)*
RTX	18	4	**22**	**11**
CsA	12	3	**25**	**50** *(41% stop)*
CYP	13	5	**38**	**15** *(8% stop)*
MTX	12	2	**17**	**8**
MFM	12	3	**25**	**17**
IFN?B	3	0	**0**	
IFN?Û	11	4	**36**	**9**

Cocito et al, 2011

Immunomodulatory treatment other than steroids, IVIg & PE for CIDP

Mahdi-Rogers M, Swan AV, van Doorn P A, Hughes RA
Cochrane Database of Systematic Reviews 2010 (11)

- Reviewers' conclusion:

- Four RCT assessing the effect of azathioprine (*27 pts*), interferon -1a (2 trials, *77 pts*) and methotrexate (*60 pts*) have been performed in CIDP.
- The evidence from these trials does not show significant benefit from any of these therapies but none of the trials was large enough to rule out small or moderate benefit.
- The evidence from observational studies is insufficient to avoid the need for randomized controlled trials to discover whether these drugs are beneficial.

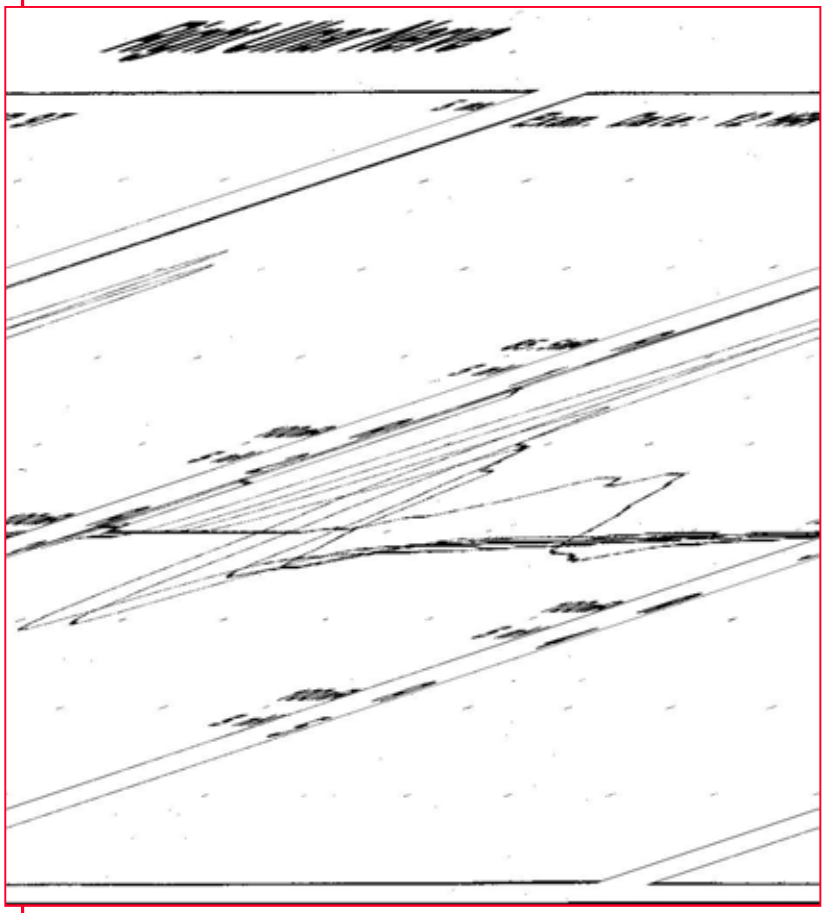
IMMUNE THERAPY FOR CIDP

- IVIg, PE & steroids are effective in CIDP;
- PE is less suitable for the long term treatment of CIDP;
- Steroids have more contraindications than IVIg especially in aged people (diabetes, cardiac disease, hypertension,)
- IVIg is better tolerated but more expensive than steroids; subcutaneous Ig may improve its home feasibility
- IVIg are more frequently effective than steroids in CIDP but steroids, when effective, have a more prolonged efficacy that, together with their lower cost may favor their choice as initial treatment in CIDP
- Despite the number of open studies no RCT supports the efficacy of immune suppressant in CIDP and should be limited to non responding/intolerant patients

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



Prevalence of MMN

- Prevalence was estimated to be 1-2 per 100,000 inhabitants (*Nobile-Orazio et al, 2005*) and was 0.6 per 100,000 inhabitants in the Dutch study (*Cats et al. 2010*)
- MMN is more frequent in men than women (*Nobile-Orazio et al, 2.6:1; Cats et al, 2010: 2.7:1*)
- Age at onset is 41 y.o. with 80% of reported patients between 20 and 50 y.o. (*Nobile-Orazio et al, 2005*). MMN affects men earlier than women (38 vs 45 y.o.) (*Cats et al, 2010*).

CLINICAL FEATURES OF MMM

Total reported patients until 2001	294
Men/women (ratio)	200/76 (2.6:1)
Mean age of onset (range)	41.0 (15-72)
Progression: chronic progressive	82%
step-wise/rel.-rem.	14%/4%
Limb weakness:	100%
Asymmetric	94%
Distal > proximal	87%
Upper > lower limbs	79%
Muscle atrophy (often mild)	86%
Fasciculations	58%
Cramps	55%
Deep tendon reflexes: Reduced or absent	72%
Normal or Brisk	28%
Sensory impairment (minor)	20%

Initial diagnosis in MMN	
MMN	31 (35)
Motor neuron disease	28 (32)
Mononeuropathy	11 (13)
Polyneuropathy	13 (15)
Radiculopathy	2 (2)
Chronic inflammatory demyelinating neuropathy	1 (1)
Hereditary neuropathy	1 (1)
Minor stroke	1 (1)

Cats et al. Neurology 2010

2010 EFNS/PNS Criteria for MMN

A) Core criteria (both must be present)

1. **Asymmetric limb weakness, or motor involvement having a nerve distribution in > 2 nerves,** slowly progressive or stepwise progressive, for > 1 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*
7. *Response to immune therapy*

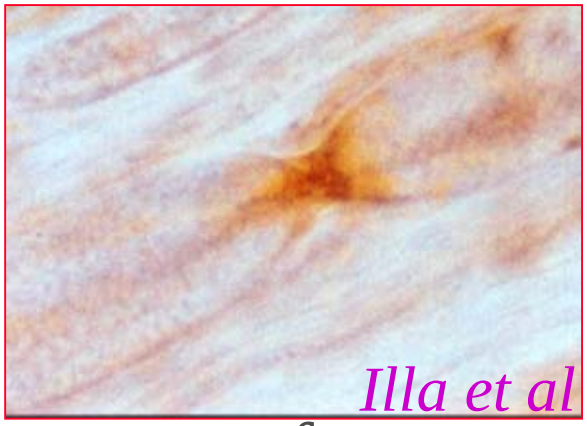
C) Exclusion criteria

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

JPNS 2010

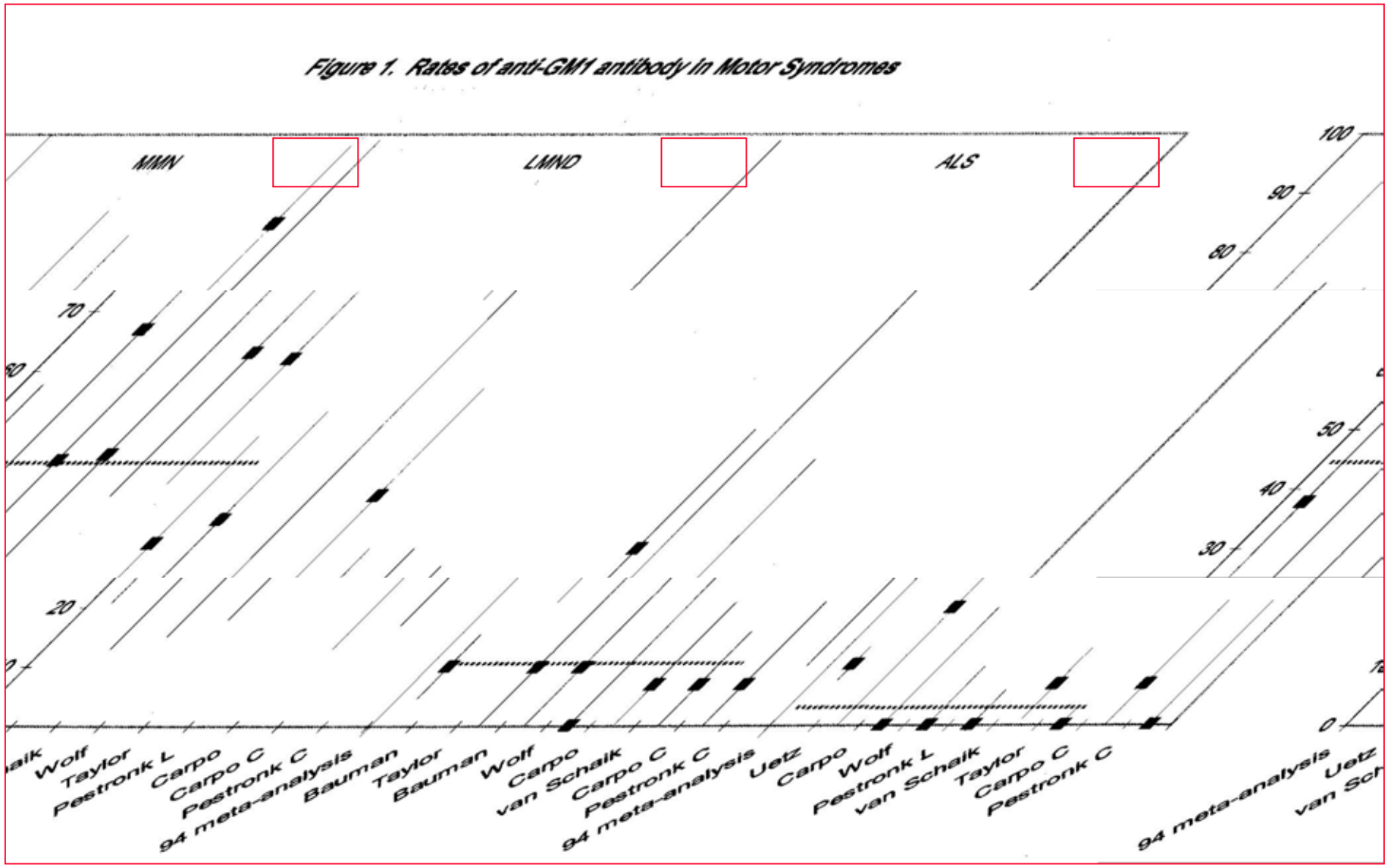
EVIDENCES FOR IMMUNE PATHOGENESIS IN MMN

- 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 decrease during clinical improvement;
- Deposits of IgM were found at the nodes of Ranvier of sural nerve 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).

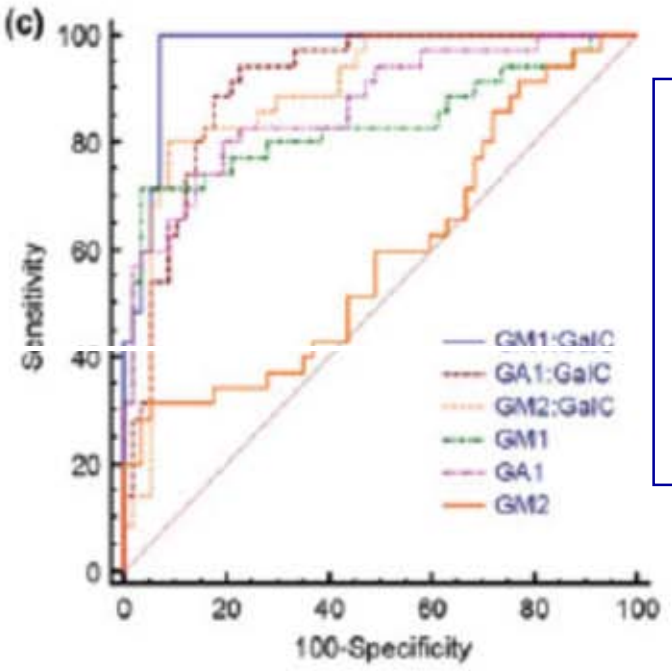
ANTI-GM1 IgM ANTIBODIES BY ELISA IN MOTOR NEURON SYNDROMES



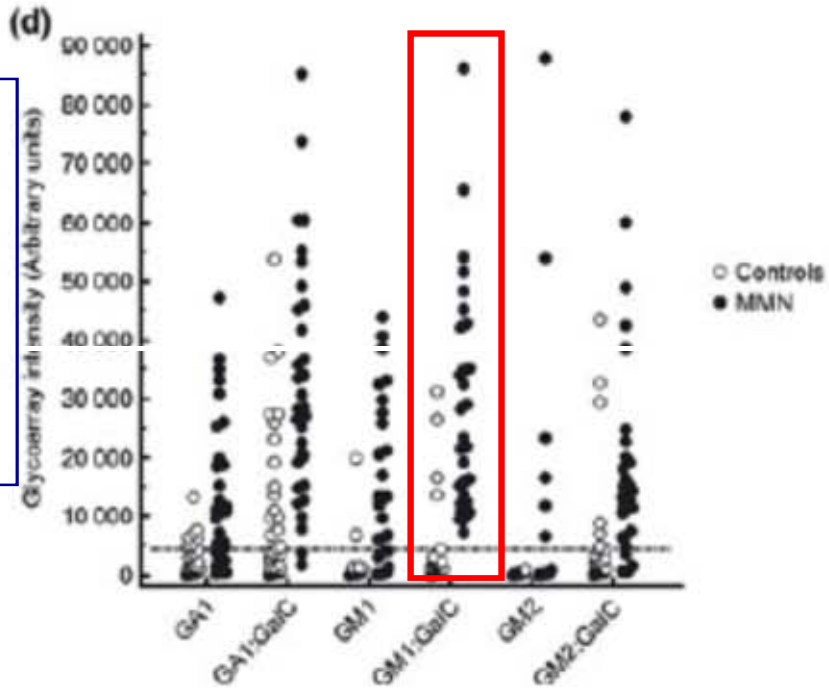
Eur J Neurol 2013, 20; 62-70

Antibodies to heteromeric glycolipid complexes in multifocal motor neuropathy

F. Galban-Horcajo[a], A. M. Fitzpatrick[a], A. J. Hutton[a], S. M. Dunn[a], G. Kalna[b], K. M. Brennan[a], S. Rinaldi[a], R. K. Yu[c], C. S Goodyear[a] and H. J. Willison[a]



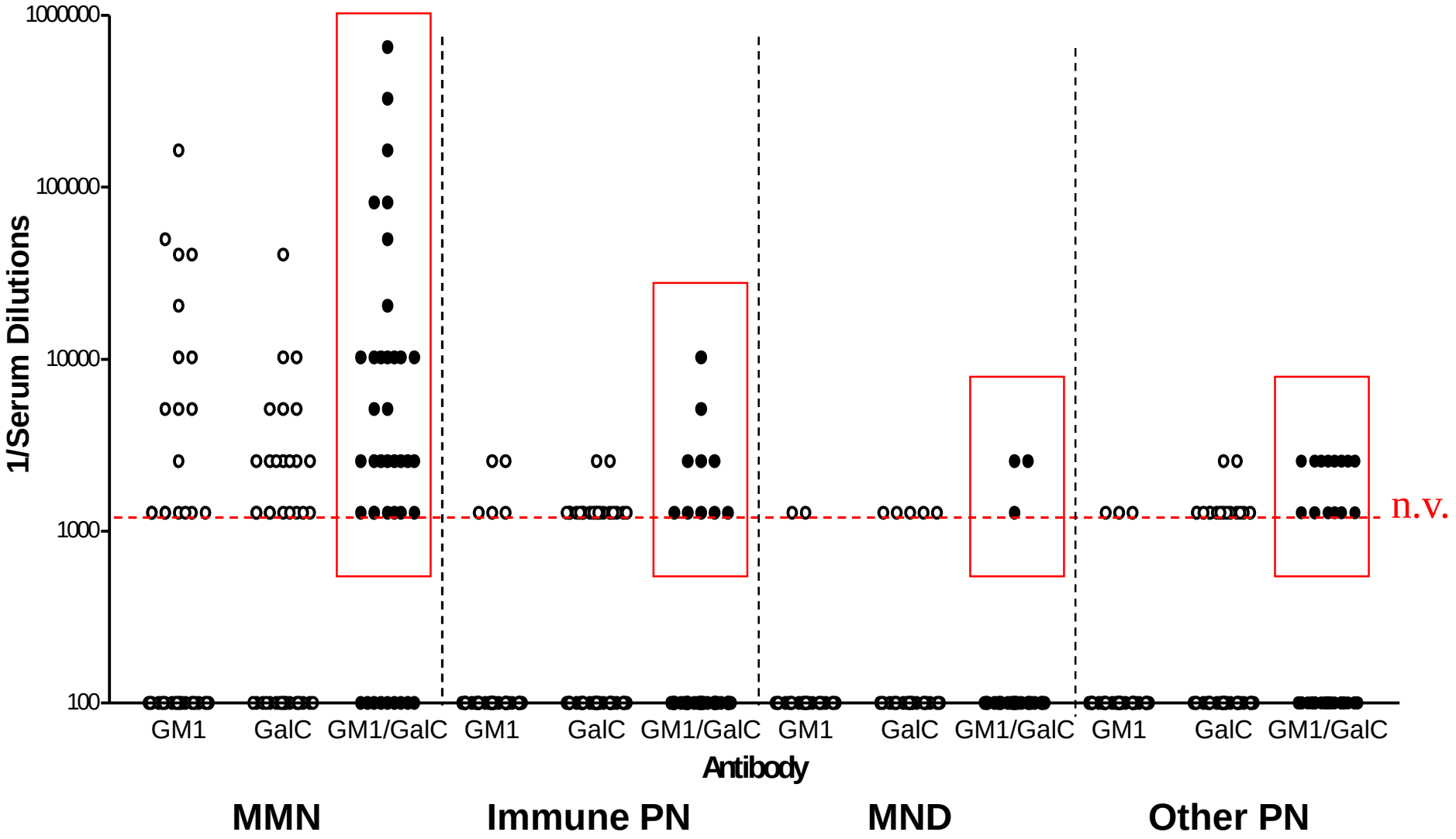
- Ø 33 MMN
- Ø 30 OND
  - 6 PN
  - 3 MND
  - 4 MS
- Ø 27 NS



Anti GM1 IgM in 22/33 (66.6%) MMN patients by ELISA

Anti-GM1-Gal IgM in 29/33 (87.9%) MMN patients by ELISA

Anti-GM1, -Gal & -GM1-Gal IgM in patients' groups



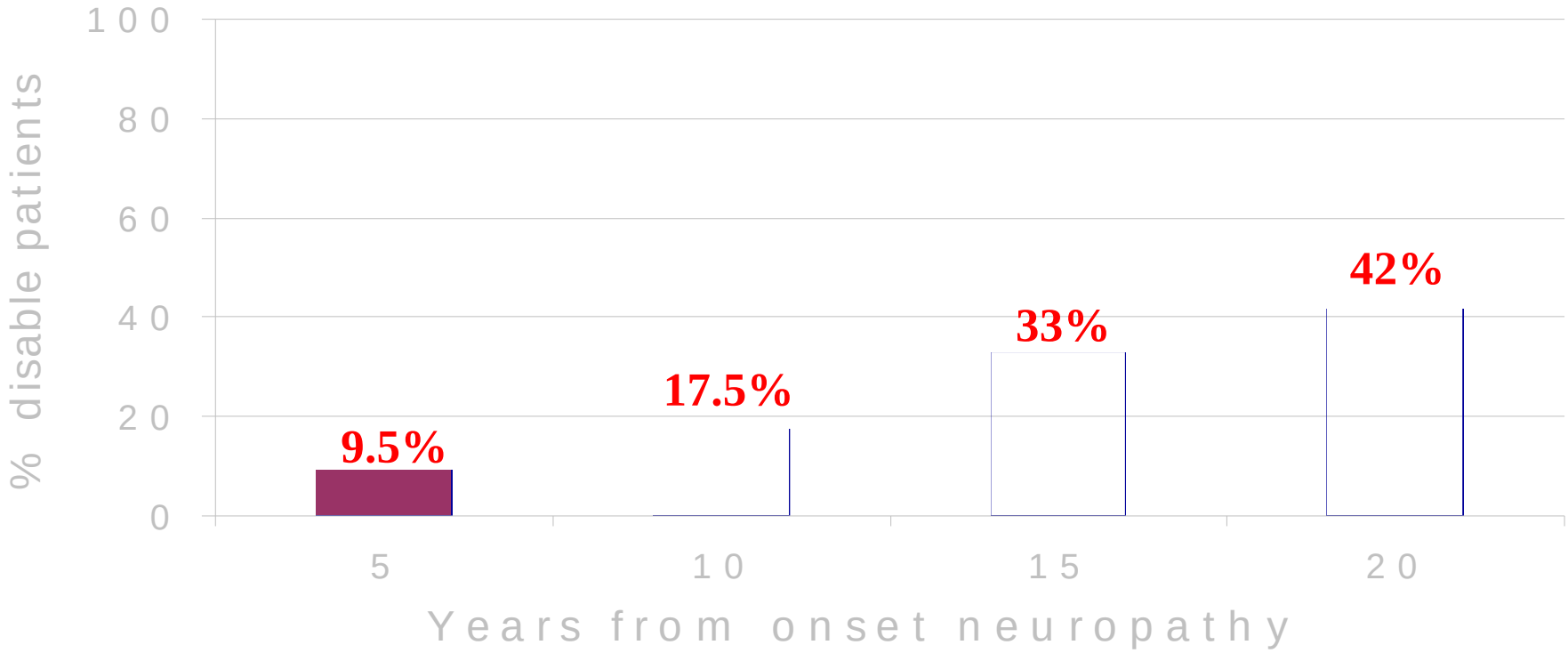
Antibody testing in MMN

IgM antibody	Frequency versus controls	Sensitivity	Specificity	Positive Predictive value
GM1	**p< 0.0001**	**47.5%**	**93%**	**65.5%**
GM1 ≥1/2560	***p<0.0001***	***27.5%***	***99.3%***	***91.2%***
GM2	n.s.	7.5%	98.1%	50%
NS6S	n.s.	22.5%	91.4%	39.1%
Galactocerebroside	p< 0.0003	60.0%	70.4%	37.5%
GM1-Gal	**p< 0.00001**	**75%**	**85.2%**	**58.8%**
GM1-Gal ≥1/2560	***p<0.0001***	***60%***	***92.2%***	***66.6%***
GM1-Gal ≥1/5120	***p<0.0001***	***40%***	***98.6%***	***88.9%***

Nobile-Orazio et al., JNNP 2013

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

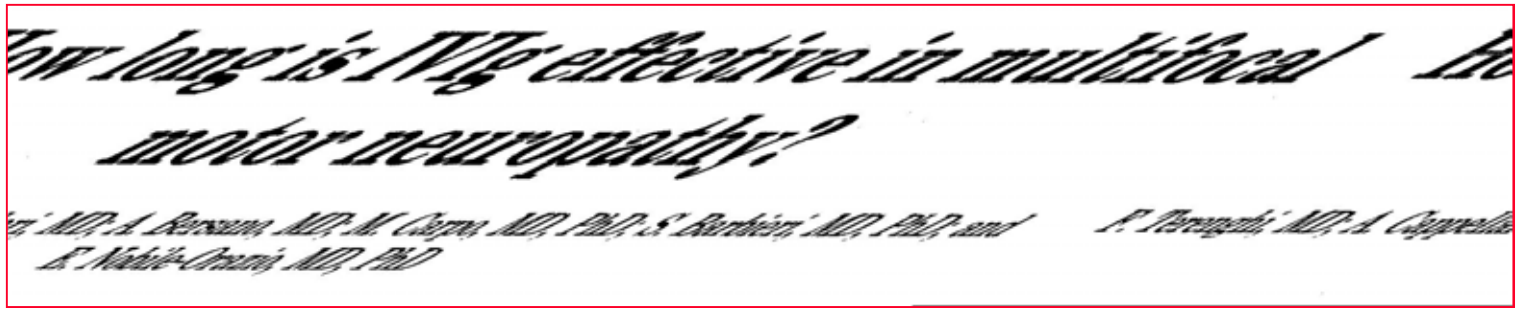
- Reviewers' summary and conclusion:

- 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

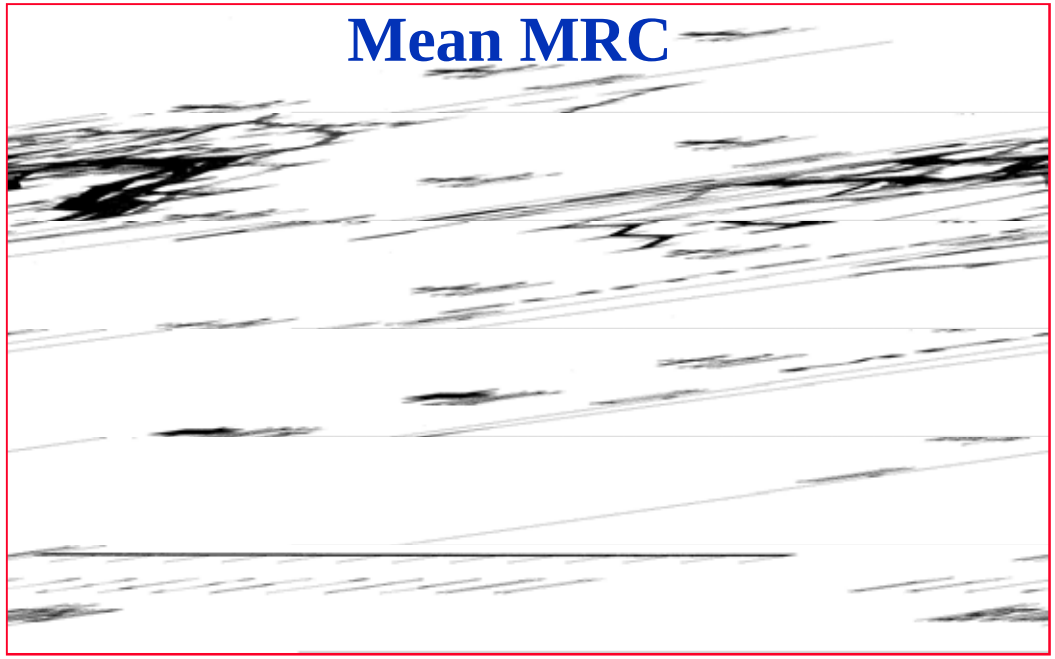
- *Azulay et al., J Neurol Neurosurg Psychiatry 1997*
  - **8/12 (66%) responding pts required repeated Ig x 9-48 mos, uneffective in 3 after 3 mos; 2 (11%) in remission after 1 yr.**
- *Van den Berg et al., Brain 1998*
  - **6/7 (86%) responding pts required weekly Ig (0.4g/kg/wk) x 2-4 yrs (follow-up);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

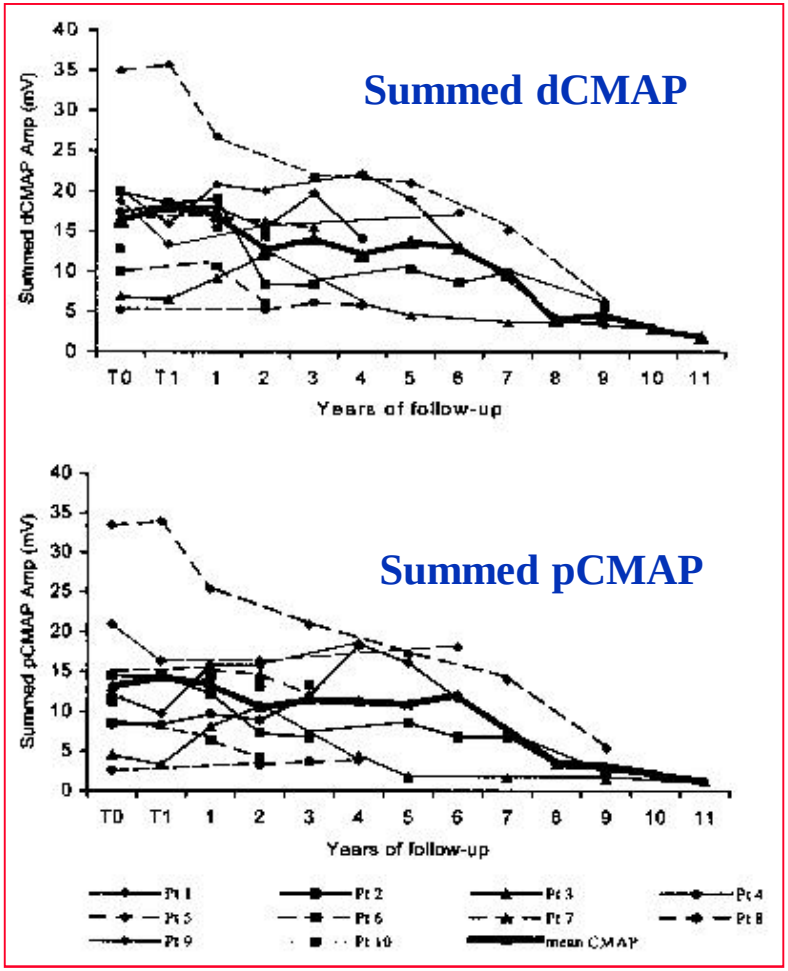
Periodic IVIg are necessary in most MMN patients


How long is IVIg effective in multifocal motor neuropathy?

Neurology 2004

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





SHOULD WE CONSIDER 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

Subcutaneous versus intravenous immunoglobulin in multifocal motor neuropathy: a randomized, single-blinded cross-over trial

T. Harbo[a], H. Andersen[a], A. Hess[b], K. Hansen[c], S. H. Sindrup[d] and J. Jakobsen[a]

[a]*Department of Neurology, Aarhus University Hospital, Aarhus, Denmark;* [b]*Department of Clinical Neurophysiology, Aarhus University Hospital, Aarhus, Denmark;* [c]*Department of Neurology, Rigshospitalet, Copenhagen, Denmark; and* [d]*Department of Neurology, Odense University Hospital, Odense, Denmark*

Eur J Neurol 2009; 16: 631-8

a) 9 patients in a single blinded cross-over study of IVIg vs SCIg
b) IVIg (+4.3%) & SCIg (+3.6%) were equally effective for 3 courses

Subcutaneous immunoglobulin therapy for multifocal motor neuropathy

Filip Eftimov[1], Marinus Vermeulen[1], Rob J. de Haan[2], Leonard H. van den Berg[3], and Ivo N. van Schaik[1]

[1] *Departments of Neurology and;* [2] *Clinical Epidemiology and Biostatistics, Academic Medical Centre, Amsterdam; and* [3] *Department of Neurology, Rudolf Magnus Institute of Neuroscience University Medical Centre Utrecht, Utrecht, The Netherlands*

J Periph Nerv Syst 2009; 14: 93-100

a) 5/5 deteriorated or did not tolerate 50% reduced SCIg
b) 4/5 maintained for 6 mos improvement with equal dose of SCIg

OTHER IMMUNE THERAPIES IN MMN

Therapy	No. treated	No. (%) improved
Cyclophoshamide i.v.	40	30 (75%)
" " oral	6	3 (50%)
Interferon- 1a	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+)

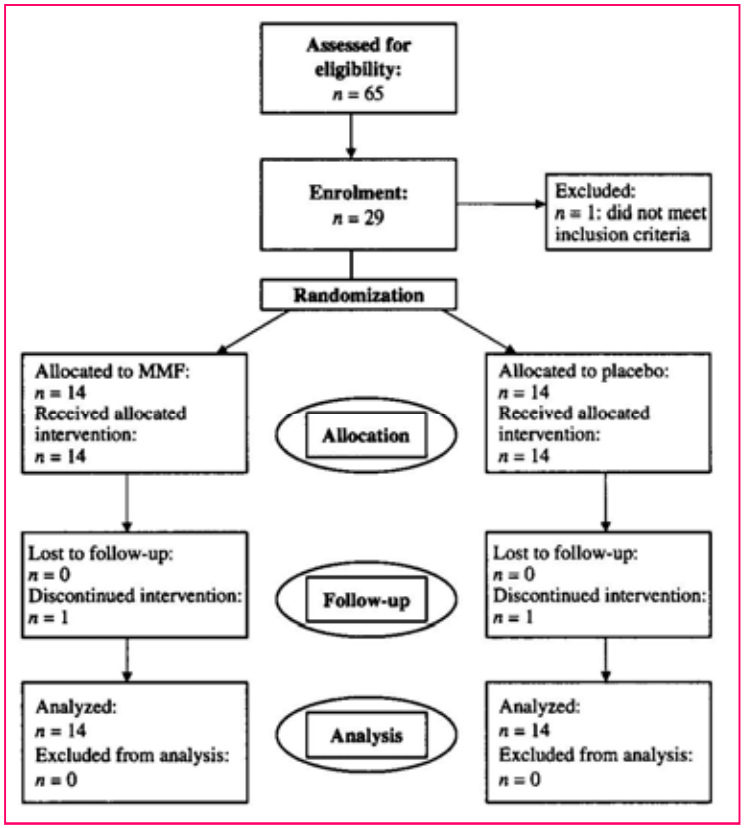
doi:10.1093/brain/awm144 Brain (2007), 130, 2004–2010

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 MMN
2010 EFNS/PNS 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 1a, cyclosporin, azathioprine are possible agents (GPP).
5. Toxicity makes cyclophosphamide less desirable (GPP)

PNS
PERIPHERAL NERVE SOCIETY

ASNP

2° Neurology, Dept. Medical Biotechnology & Translational Medicine,
IRCCS Humanitas Clinical Institute
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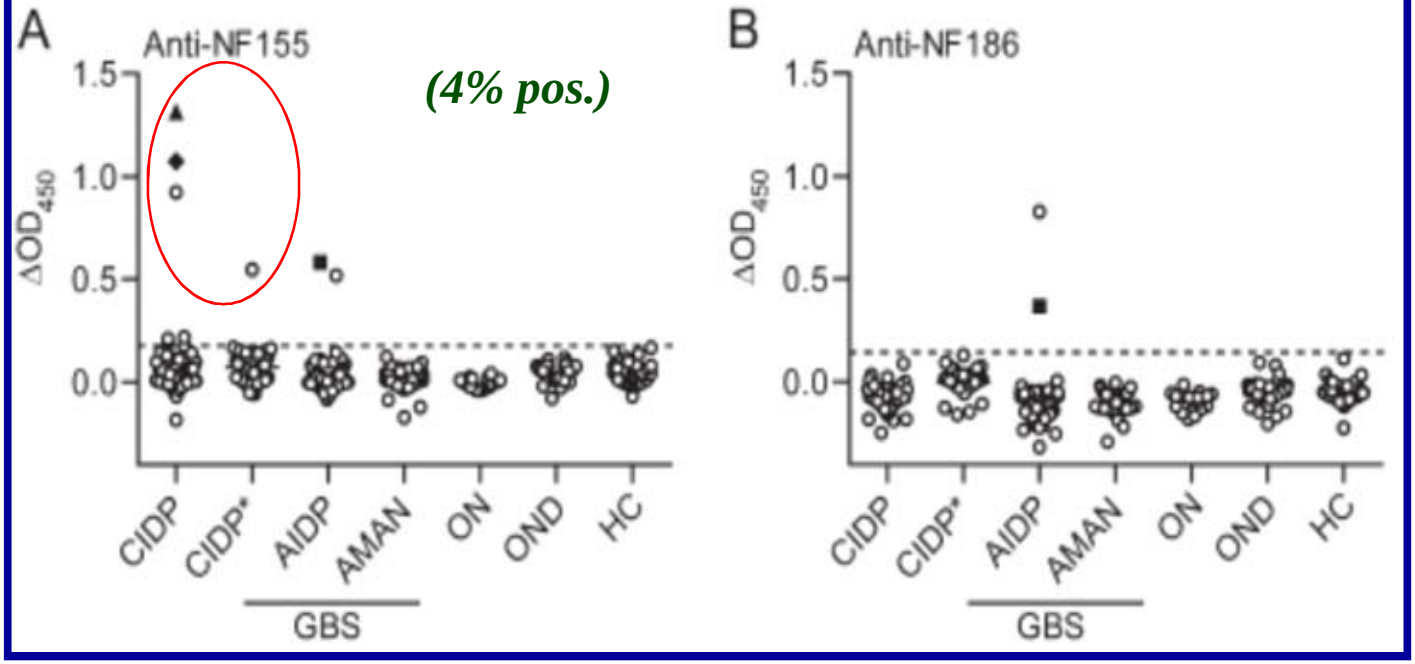
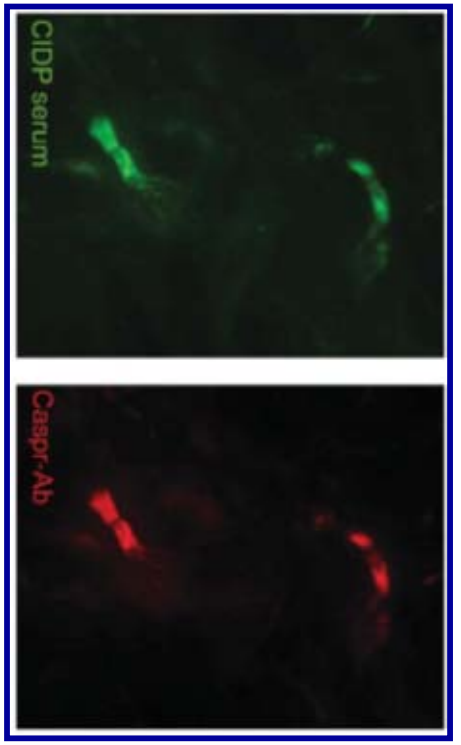
Francesca Gallia
Fabrizia Terenghi
Mariangela Bianco
Davide Di Pietro
Claudia Giannotta
Antonella Scarale

Neurofascin as a target for autoantibodies in peripheral neuropathies

Judy King Man Ng, Joachim Malotka, Naoto Kawakami, et al.

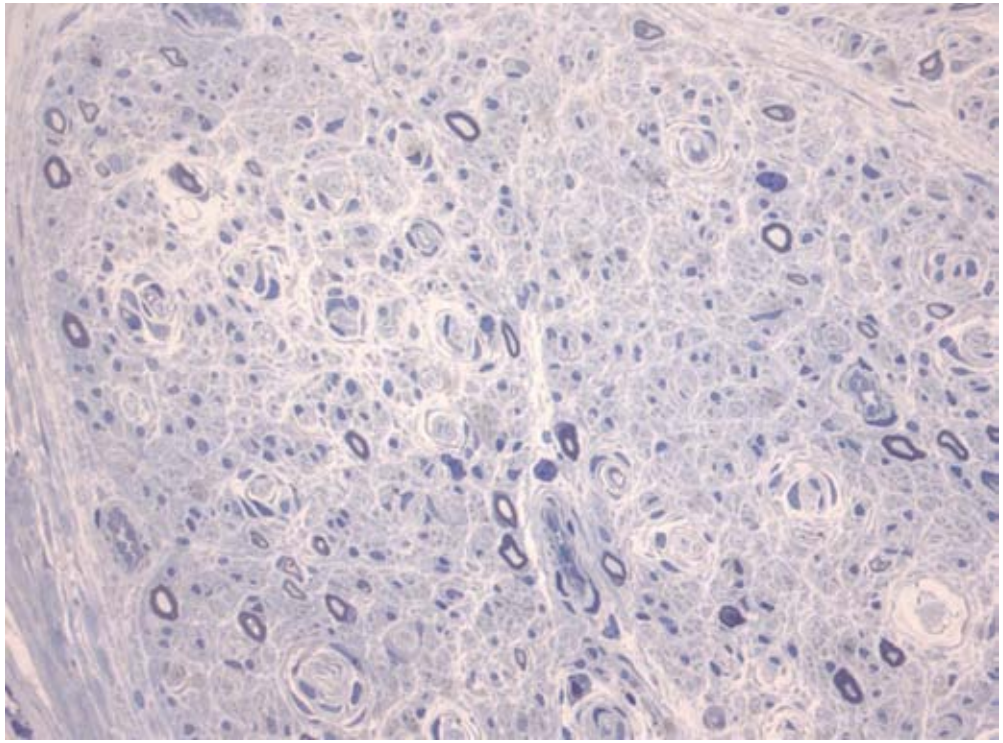
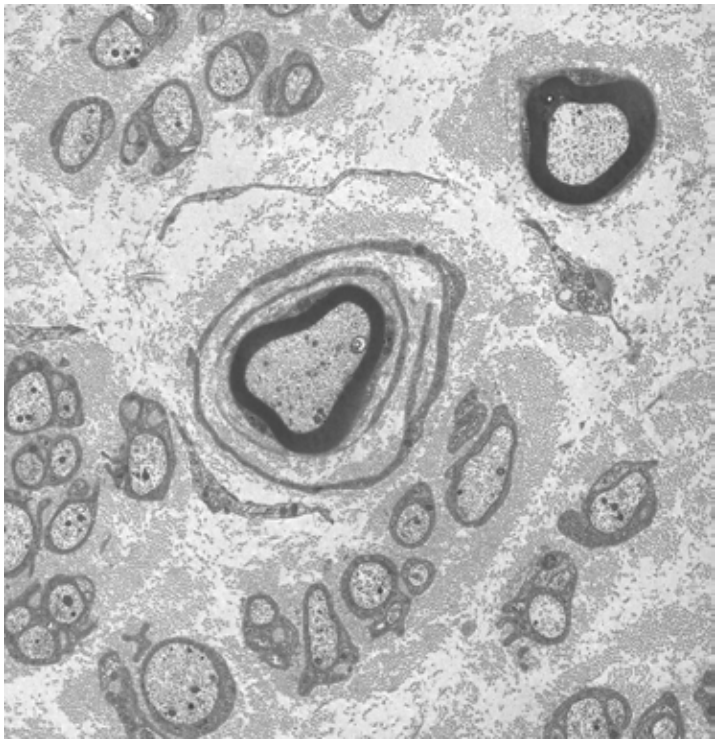
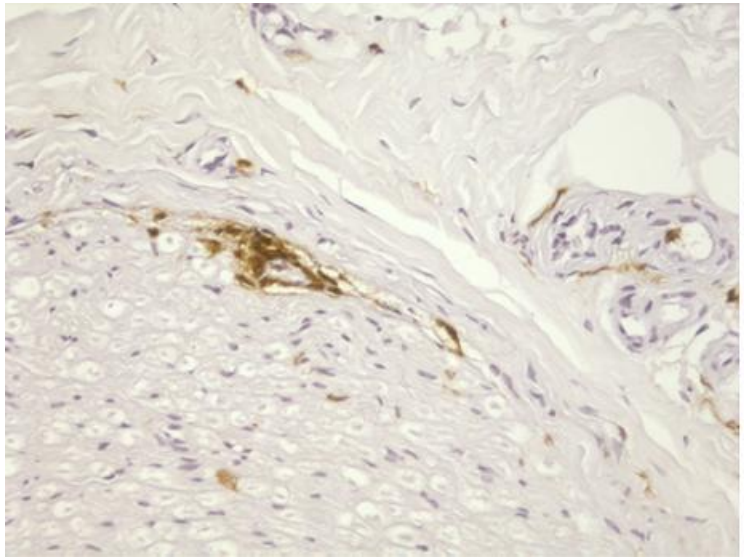
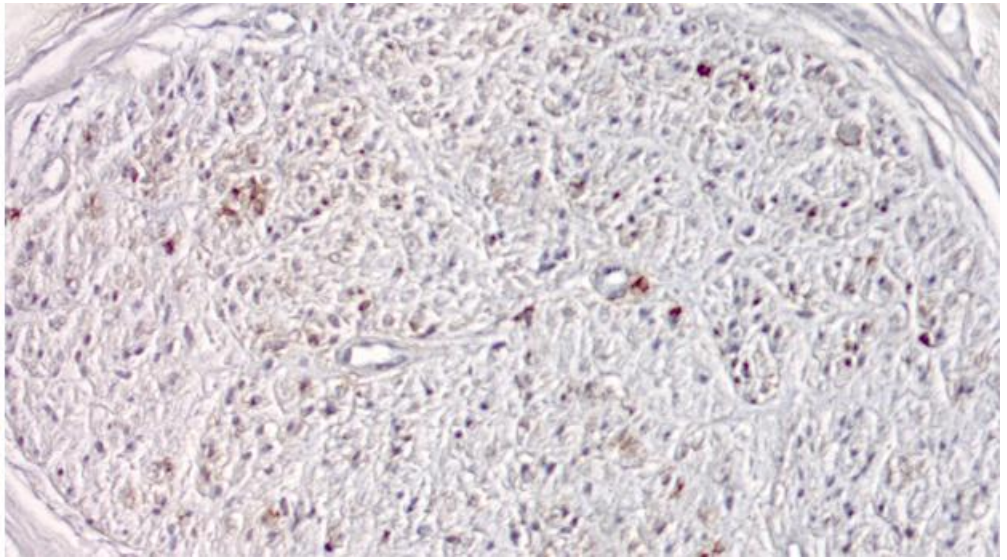
Figure 1 Autoantibodies to NF155 and NF186 in a very small proportion of patients with neuropathy





Clinical association in positive CIDP not mentioned. 3/4 improved with PE

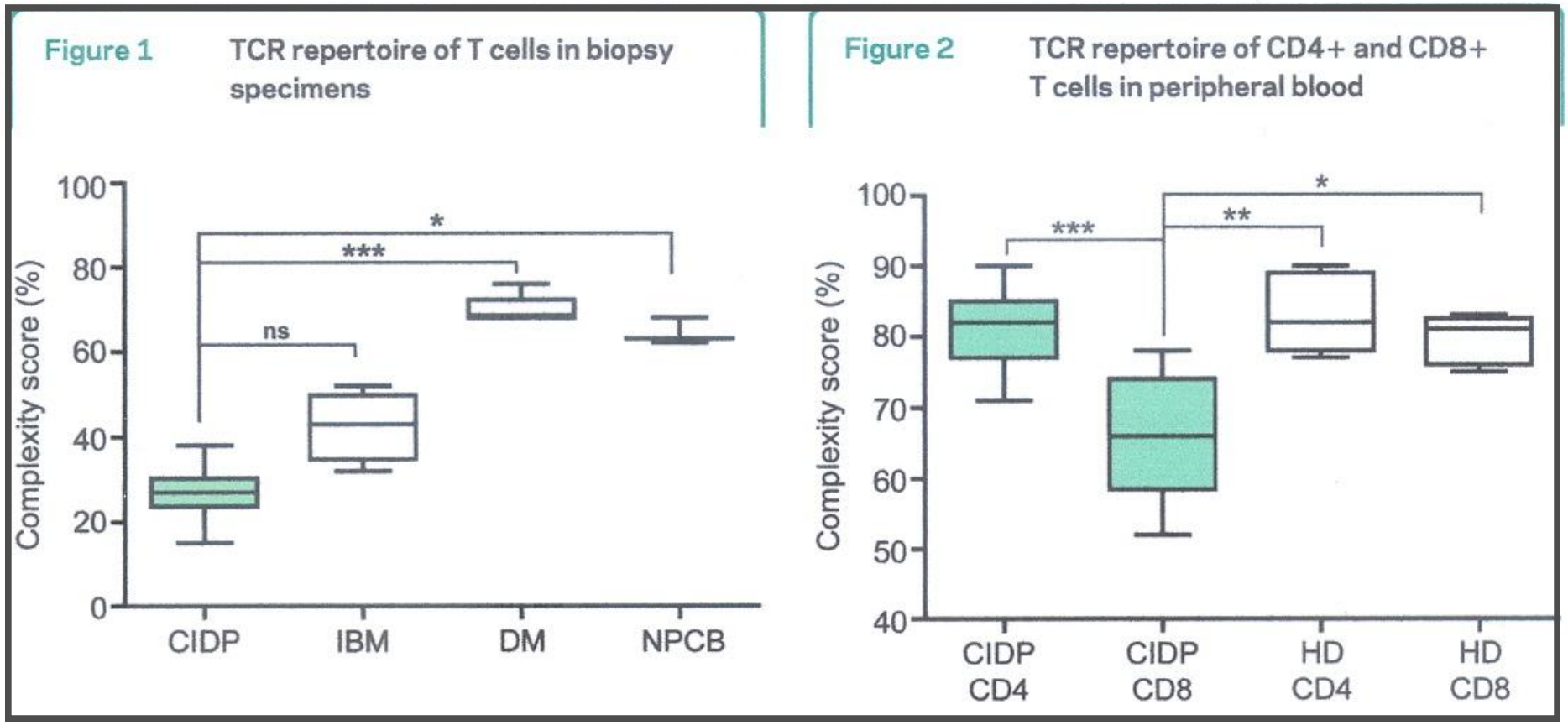
Neurology® 2012;79:2241-

From Dr. Angelo Quattrini, San Raffaele Hosp., Milan

CD8+ T-cell immunity in chronic inflammatory demyelinating polyradiculoneuropathy

Schneider-Hohendorf et al., Neurology 2012



Response to initial therapy in CIDP

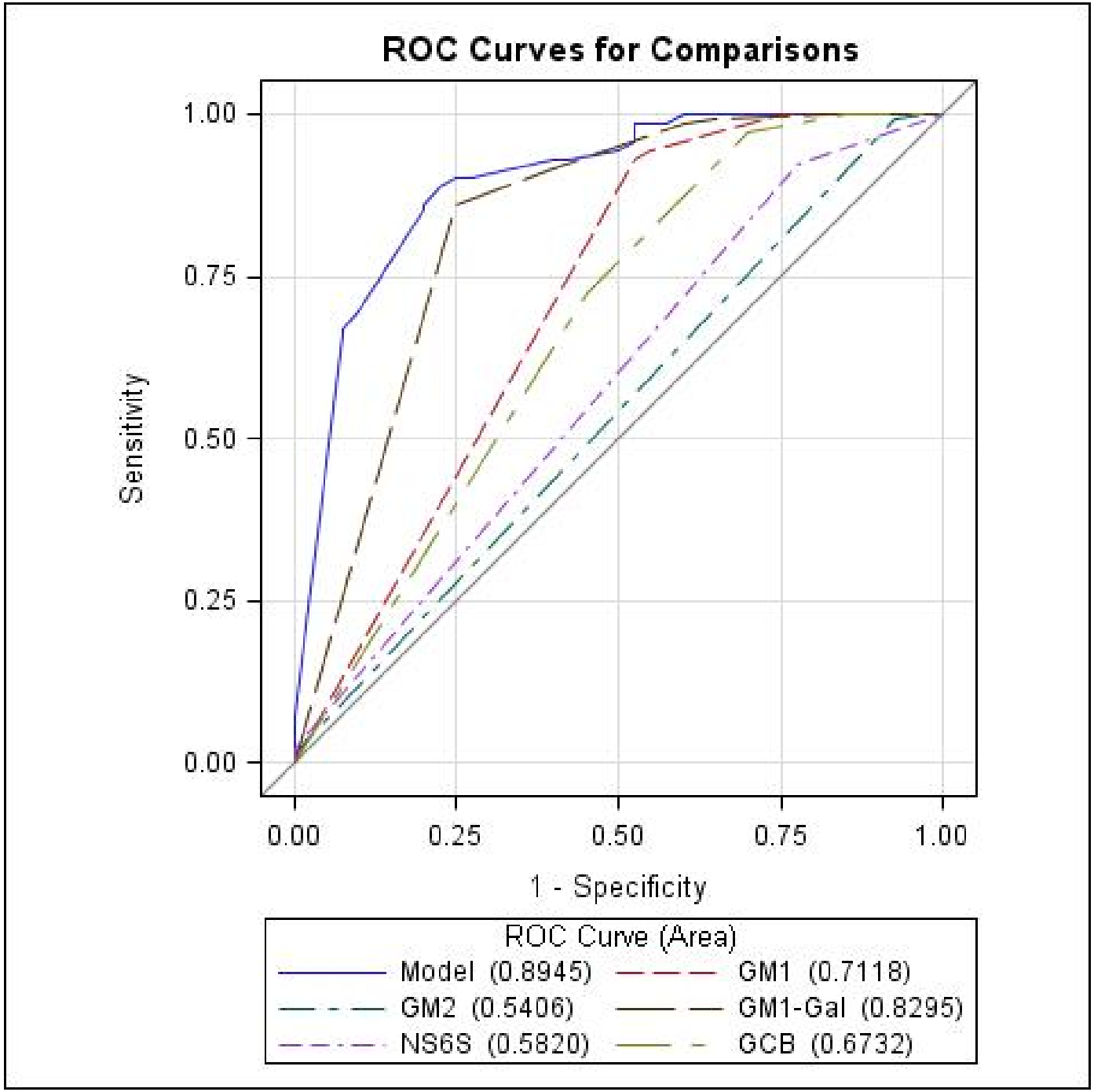
Therapy	Responder	Non Respond.	Side Effect
Steroids *136 (51%)*	**87 (64%)**	**49 (36%)**	**18 (13%)***
IVIg *115 (43%)*	**90 (78%)**	**25 (22%)**	**5 (4%)***
PE *16 (6%)*	**9 (56%)**	**7 (44%)**	**4 (25%)**
TOTAL *267*	**186 (69%)**	**81 (31%)**	

** Steroids vs IVIg: p= 0.02*

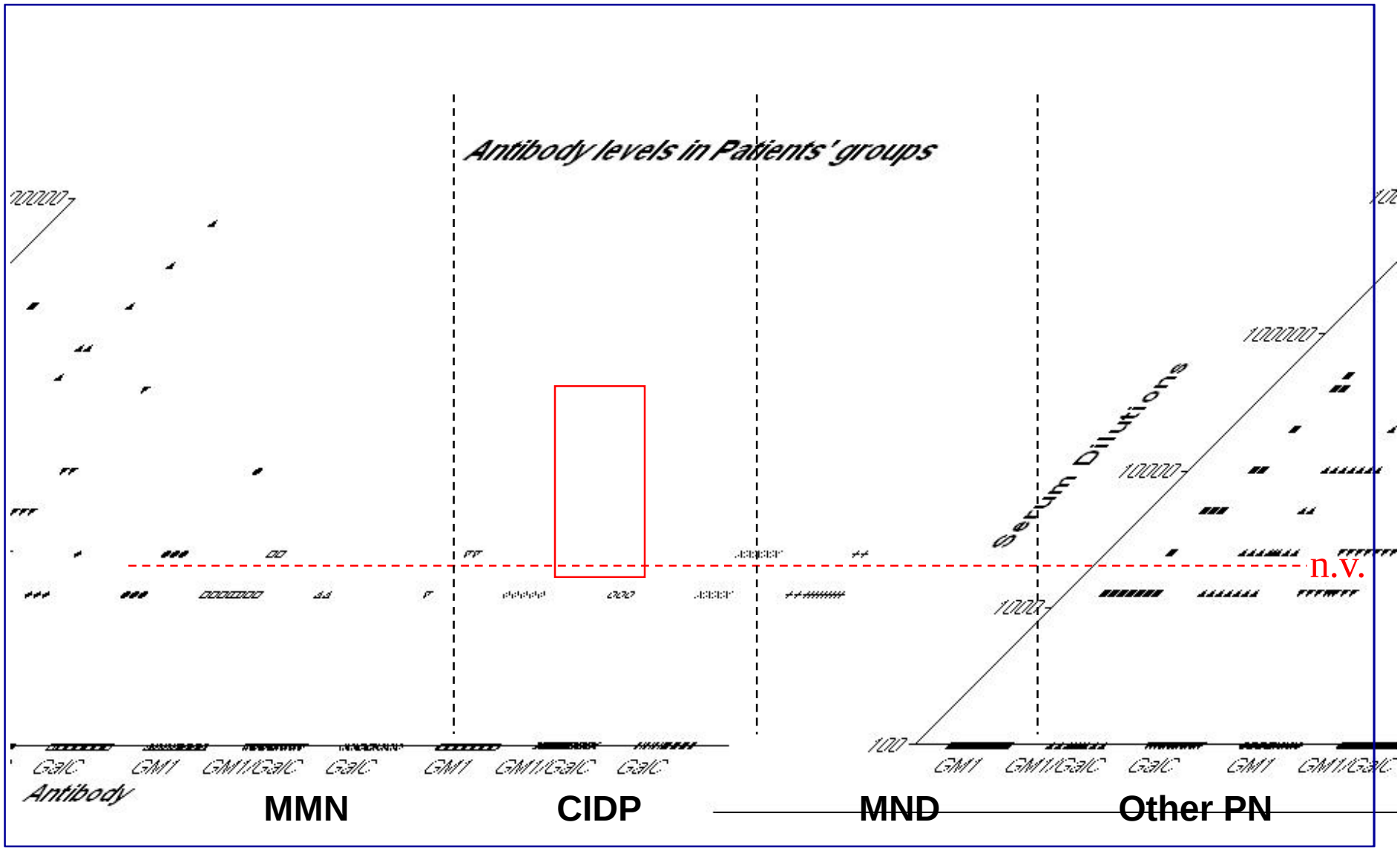
Cocito et al., 2010

Distinguishing features in CIDP, MDN, MMN, MND

Features	CIDP	MDN	MMN	LMND
Distribution	Symmetric	Multineuro-pathic	Multineuro-pathic	Asymm or Symm
Arms >legs	no	yes (40-70%)	yes (80%)	sometimes
Distal>prox.	no	yes	yes	often
Sensory loss	yes	yes	no	no
Gen.Areflexia	yes	no	no	no
Cranial/bulbar	yes	no	no	yes
Motor CB	yes	yes	yes	no
Reduced CV	yes	no	no	no
ReducedSNAP	yes	yes	no	no
↑CSF proteins	yes	rare (1/3)	rare (1/3)	no
↑ GM1 IgM	no	no	yes (30-40%)	rare (5-10%)
Sural biopsy	demyelin.	demyelin.	normal	normal
Steroid response	yes (2/3)	yes (2/3)	no (1/10)	no
IVIg effective	yes (2/3)	yes (1/2)	yes (4/5)	no


ROC Curves for Comparisons
Sensitivity
1.00
0.75
0.50
0.25
0.00
0.00
0.25
0.50
0.75
1.00
1 - Specificity
ROC Curve (Area)
Model (0.8945)
GM1 (0.7118)
GM2 (0.5406)
GM1-Gal (0.8295)
NS6S (0.5820)
GCB (0.6732)

Anti-GM1, -GalC & -GM1/GalC IgM



PAPER

Axon loss is an important determinant of weakness in multifocal motor neuropathy

J T H Van Asseldonk, L H Van den Berg, S Kalmijn, R M Van den Berg-Vos, C H Polman, J H J Wokke, H Franssen

J Neurol Neurosurg Psychiatry 2006;**77**:743–747. doi: 10.1136/jnnp.2005.064816

Table 4 Logistic regression analysis for the determinants of weakness

Determinant	Univariate	p Value	Multivariate	p Value
Axon loss	5.7 (2.9 to 11.1)	<0.001	4.4 (2.0 to 9.7)	<0.001
Conduction block	7.1 (2.6 to 19.4)	<0.001	2.1 (0.7 to 6.6)	NS
Demyelinative slowing	6.6 (3.1 to 14.0)	<0.001	2.0 (0.8 to 4.8)	NS
Years untreated	1.1 (1.1 to 1.2)	<0.001	1.1 (1.0 to 1.2)	<0.01
Years treated	1.0 (0.9 to 1.2)	NS	1.1 (0.9 to 1.3)	NS
Nerve length	2.1 (1.4 to 3.1)	<0.001	1.9 (1.1 to 3.2)	<0.05

Table 3 Relation between disease duration and the percentage of nerves with weakness, axon loss, conduction block, and demyelinative slowing

Disease duration (years)	No of patients	Percentage of nerves with*			
		Weakness	Axon loss	Conduction block	Demyelinative slowing
0–5	4	24	54	5	3
5–10	7	44	55	12	27
10–15	6	60	65	27	42
15–20	3	86	73	27	55

*For each disease duration category, the total number of nerves with abnormalities was assessed and expressed as a percentage of the total number of nerves within that category.