Neuropathy in monoclonal gammopathy

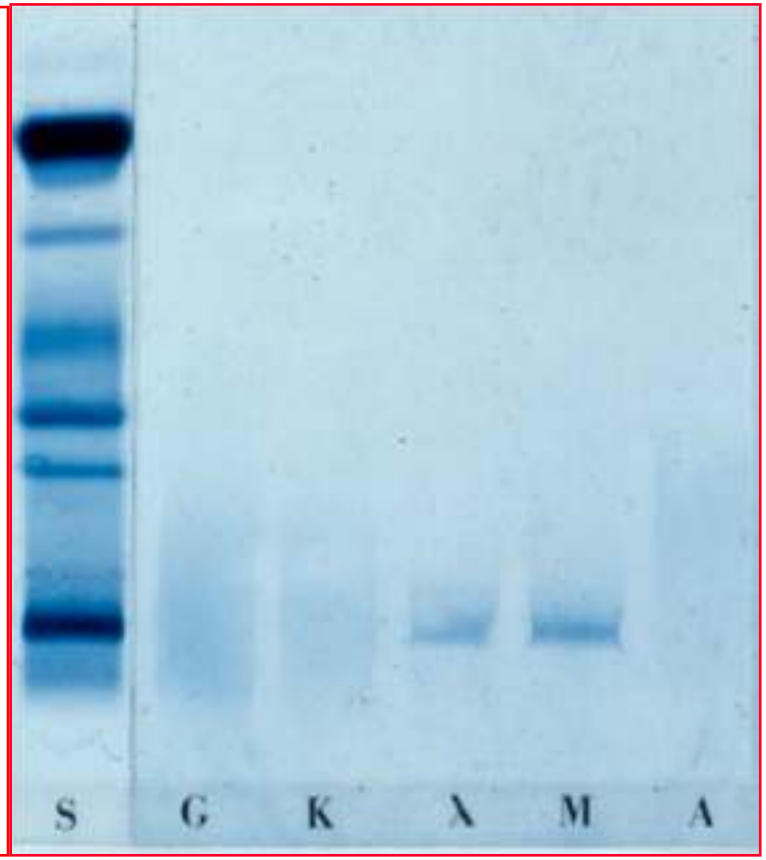
Eduardo Nobile-Orazio

Dept. Translational Medicine, Milan University.
2nd Neurology, IRCCS Humanitas Clinical Institute,
Rozzano, Milan, ITALY

The author reports no Conflict of Interest

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%



Monoclonal Gammopathy and Neuropathy

Kelly et al 1981

Causes of PN in 692 patients at Mayo Clinic:

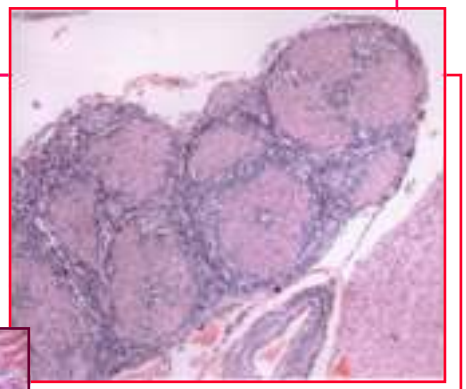
- Idiopathic 48%
- Secondary 52%
  - Diabetes 31%
  - Inherited 7%
  - Alcohol 4%
  - Vitamin def. 3%
  - Malignancy 2%
  - Other diseases 5%

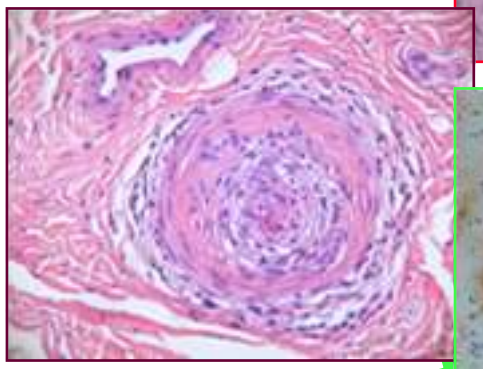
28 patients (8%) with idiopathic PN (4% of total PN) had monoclonal gammopathy including:

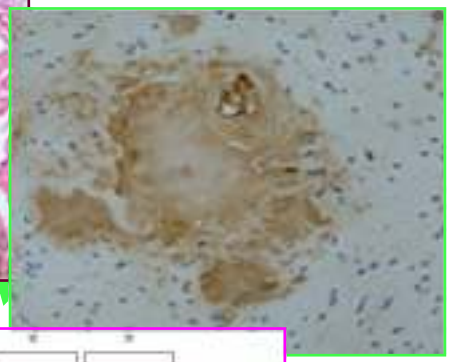
- MGUS 16
- Amyloidosis 7
- Multiple myeloma 3
- WM 1
- Heavy Chain Disease 1

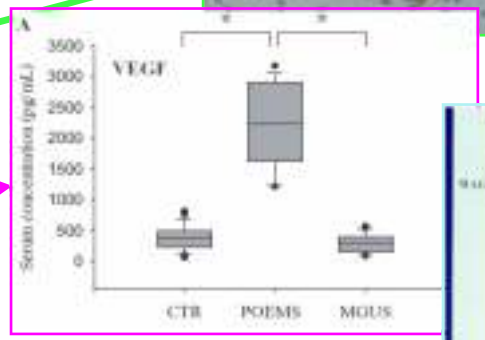
Type and mechanisms of neuropathy in plasma cell dyscrasias

- Mono-, multi-, cranial neuropathy & radiculopathy *(MM, **WM**, LL, **lymphoma**)*
  - direct infiltration
  - nerve/root compression
  - hyperviscosity
  - bleeding diathesis
  - cryoglobulinemia (also)
- Symmetric polyneuropathy
  - Amyloidosis (AL) *(±MM)*
  - Activation of VEGF *(POEMS)*
  - Drug related toxicity (often painful)
  - **M-protein reactivity with nerve *(MGUS, IgM)***
  - Unknown *(MGUS, mostly IgG & IgA)*









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

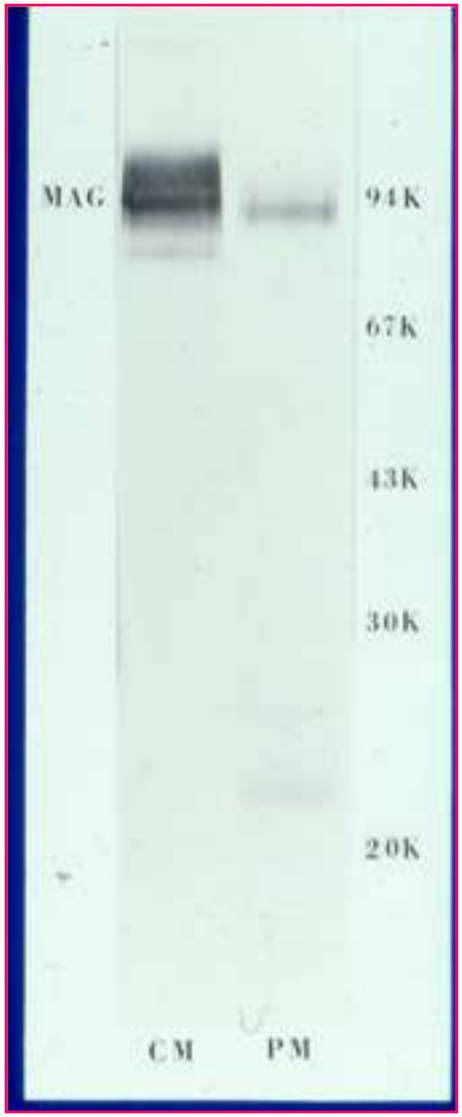
Antigens	%	PN type	Pathology	Authors
MAG/SGPG/P0	50%	S>>M (DADS-M)	Dem	Latov et al 1980 (Katz et al 2000)
Sulfatide	6%	S; S>M; SM	Ax or Dem	Pestronk et al 1991
GQ1b+Disyalo	2%	S>M (CANOMAD)	Dem	Ilyas et al 1986 (Willison et al 2000)
GD1a	3%	M; M>S	Dem	Bollensen et al 1989
GM2	2%	M; M>S	Dem	Ilyas 1988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

Open issues in anti-nerve antibody testing in IgM related neuropathies

1. *How useful are anti-nerve antibodies in identifying different forms of IgM related neuropathies?*
2. *Are different antibodies associated with different response to treatment?*
3. *What is the role of these antibodies in the pathogenesis of these neuropathies?*

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



PN ASSOCIATED WITH ANTI-MAG IgM

Homogeneous clinical and electrophysiological features consistent with a chronic, slowly progressive, predominantly sensory, demyelinating neuropathy

	MAG + (42)	MAG - (26)	p
Type of PN			
S or S>M	*62%*	31%	< 0.025
SM	31%	38%	n.s.
M>S	7%	*31%*	< 0.01
NCS Peroneal			
Mean MCV	22.9 m/s	39.6 m/s	< 0.000001
< 35 m/s	90%	23%	< 0.0001
MGUS/WM-NHL	*81%*/19%	27%/*73%*	< 0.0005

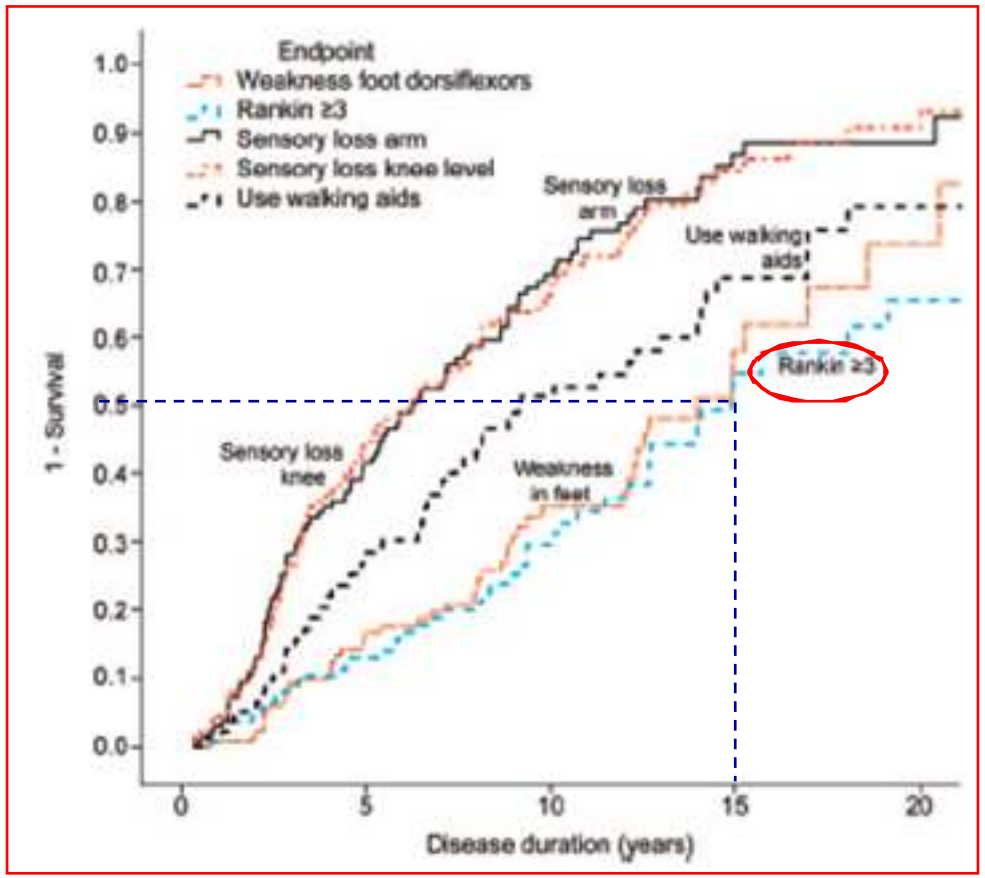
Nobile-Orazio et al 1994

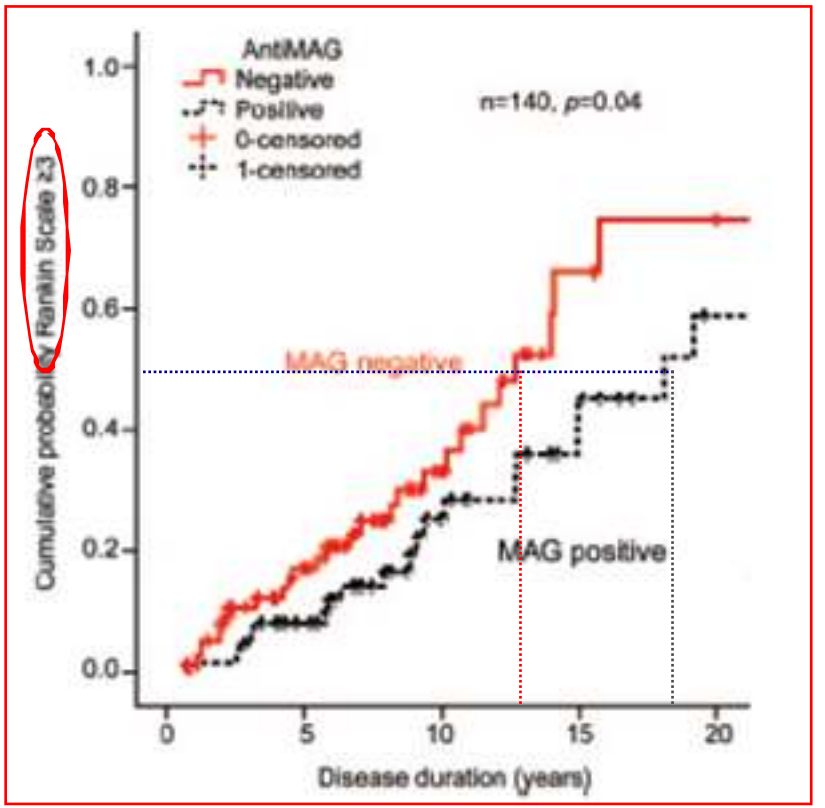
Prognosis of polyneuropathy due to IgM monoclonal gammopathy

A prospective cohort study

J.M.F. Niermeijer, MD, PhD
K. Fischer, MD, PhD
M. Eurelings, MD, PhD
H. Franssen, MD, PhD
J.H.J. Wolde, MD, PhD
N.C. Notermans, MD, PhD

Neurology® 2010;74:406-412





- *140 pts. (72% Dem, 28% Ax, 44% MAG+) followed for 23 yrs:*
- *Demyelination & higher onset age ↑↑ risk of disabiliy, MAG+ ↓↓*

Anti-MAG IgM (>1/3,200) in PN+IgM

Abs / Disease (No.)	MAG	GM1	GM2	GD1a	GD1b	Sulfatide
	75	47	9	7	10	6
MMN (41)		12 (29%)	4 (10%)	1	1	
CIDP (57)		6 (10%)	1	1	2 (3%)	
Lewis Sumner (5)				1		
PN+IgA (2)						
PN+IgG (23)		2 (10%)				
PN+IgM(166)	**75 (45%)**	10 (6%)	1	3 (2%)	4 (2%)	6 (4%)
POEMS (8)		2 (25%)	1	1	1	
Other PN (89)		2 (3%)				
Unknown PN(64)		3 (3%)				
Monon. mul. (9)		1				
Radic-plexop.(21)		3 (14%)				
MND (63)		6 (9%)	2 (3%)		2 (3%)	

Total 539

Nobile-Orazio et al. 2008

. High titers of anti-MAG IgM predict the development of PN in asymptomatic IgM patients

CLINICAL NEUROPATHY AFTER 3-12 YEARS (Mean 6) IN 24 ASYMPTOMATIC PATIENTS WITH IgM M-PROTEIN IN RELATION TO ANTI-MAG TITERS

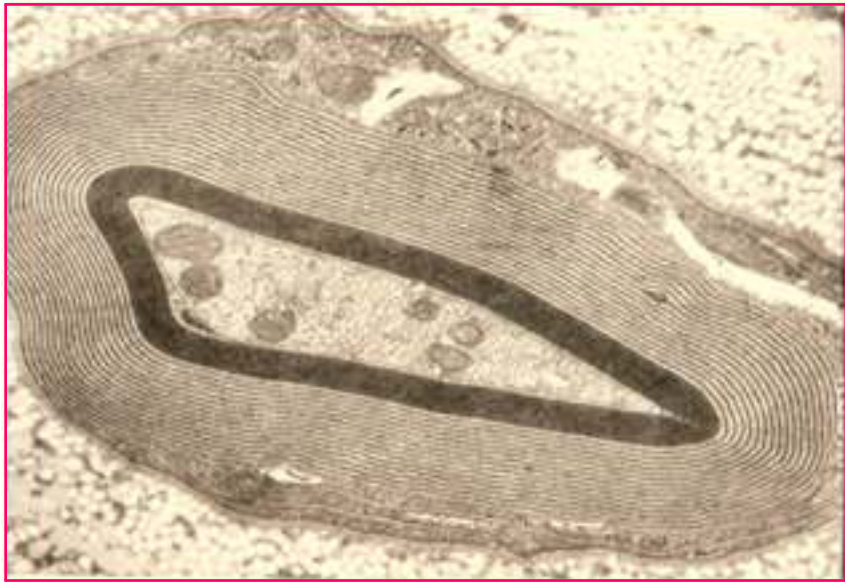
Anti-MAG titers	No. Pats.	CLINICAL NEUROPATHY First visit	Last visit
High titers	4	0	3 (75.0%)
Low titers	7	0	1 (14.3%)
Negative	13	0	2 (15.4%)
Total	24	0	6 (25.0%)

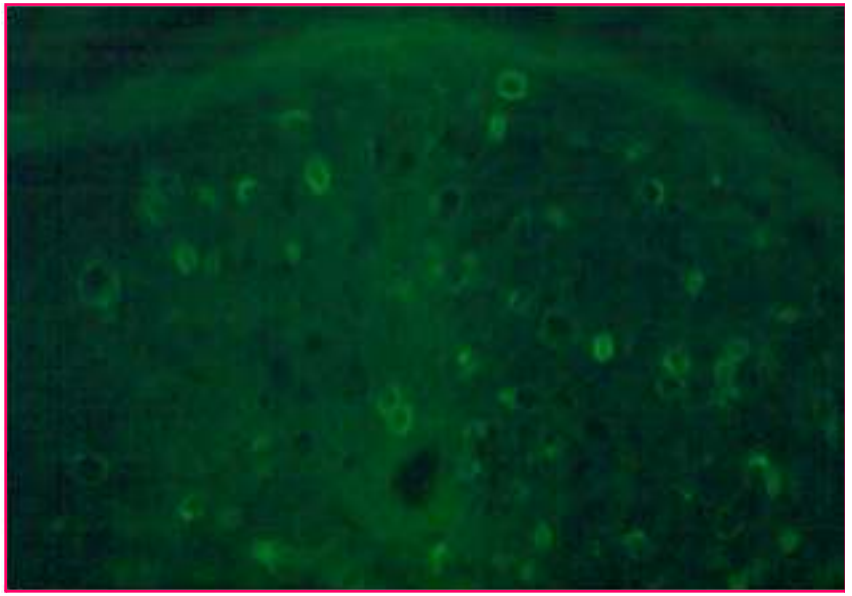
Fisher exact test: **High vs. Low titers + Negative: p = 0.03529**

Meucci et al 1999

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





RCT in PN & anti-MAG IgM

Plasma exchange (PE)

- Dyck et al 1991: **effective in IgG/IgA, not IgM MGUS**
- Oksenhendler 1995: **No difference if associated with Chlorambucil**

High dose Intravenous Immunoglobulina (IVIg)

- Dalakas et al 1996:: **effective in 2/11 IgM (18%)** (1/9 MAG, 11%)
- Comi et al 2002: **IVIg slightly better (p=0.05) than placebo**

Interferon Alfa (IFN-α)

- Mariette et al 1997: **Sensory improvement in 8/10 IFN-a**
- Mariette et al 2000: **No difference between IFN-a and placebo**.

Oral CTX+ Prednisone

- Niermejier et al 2007: **No difference in functional scales with placebo; sensory & DL better at 6 mos**.

Rituximab

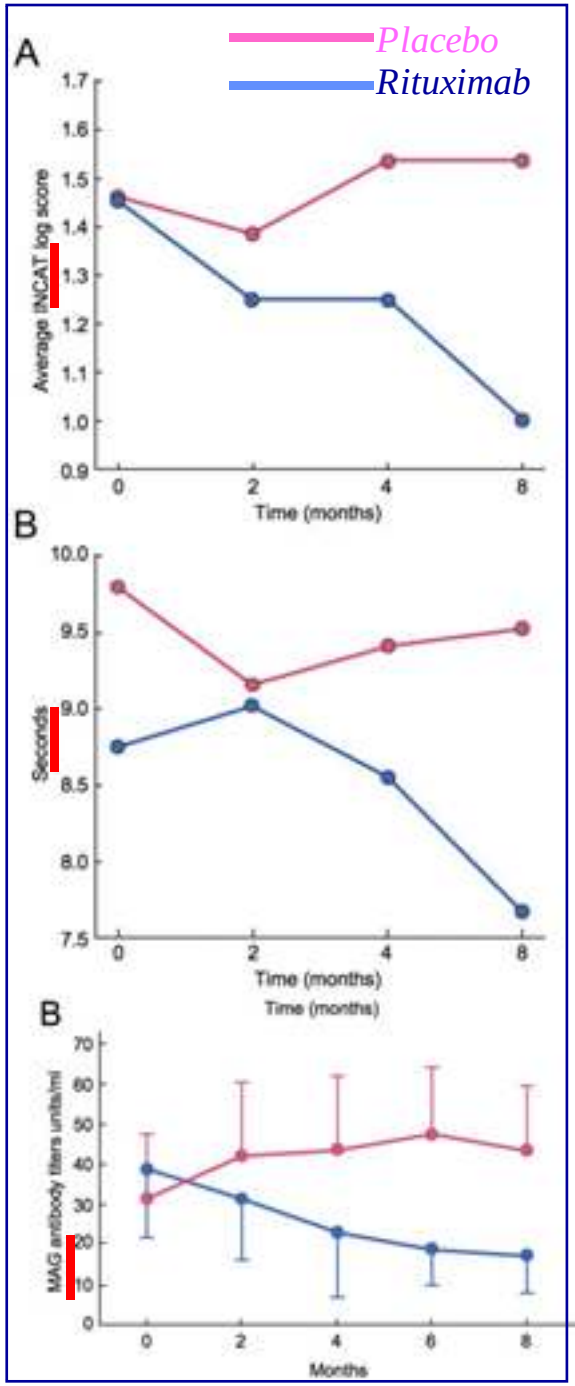
- Dalakas et al 2009: **4/13 (31%) patients on Rituximab improved by 1 point in INCAT score compared to 0/13 controls (p = 0.096);**

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..



A RANDOMIZED CONTROLLED TRIAL OF RITUXIMAB IN DEMYELINATING NEUROPATHY ASSOCIATED WITH ANTI-MAG IGM GAMMOPATHY (RIMAG STUDY)

Léger J-M1, Viala K1, Bombelli F1, Nicolas G2, Créange A3, Vallat J-M4, Pouget J5, Preux P-M6; for the RIMAG Trial Group (France and Switzerland).

- Randomized double-blind controlled study with Rituximab (4 weekly infusions of 375 mg/m2) (26 patients) vs Placebo (28 patients);
- 54 pts with PN & anti-MAG IgM in 9 centres in France & 1 in Switzerland. INCAT sens. score (ISS) ≥4, VAS score >4, ataxia score ≥2.
- Primary outcome: Change of ISS between baseline & 12 mos.
- Secondary outcome: disability Hughes score, MRC, self-evaluation sc.
- 7 patients did not complete the trial (6 with Rituximab and 1 placebo). 47 patients (20 rituximab, 27 placebo) eligible for final analysis.
- After 12 months, no difference in mean ISS variation between Rituximab (1.3± 3.0) & placebo (1.0 ± 2.8). More pts under Rituximab improved in Hughes scale (20 vs 0%) and self ev. scale (26.3 vs 4%)

Rituximab was not effective on primary outcome

Rituximab for polyneuropathy with IgM monoclonal gammopathy

J M F Niermeijer,[1] M Eurelings,[1] H L Lokhorst,[2] W-L van der Pol,[1] H Franssen,[1]
J H J Wokke,[1] N C Notermans[1]

J Neurol Neurosurg Psychiatry 2009 80: 1036-1039

- **Prospective open label trial**
- **17 pts with PN & IgM MGUS (6 anti-MAG +)**
- **Rituximab 375 mg/sq/week x 4 weeks**
- **Follow-up 12 months (12-30 mos)**
- **Outcome:**
  - **ODSS: 2/17 (12%) improved, 1 (6%) deteriorated**
  - **MRS: 5/17 (30%) improved**
  - **MRC: 4/17 (25%) improved ≥5%**
  - **SSS: 9/17 (53%) improved ≥5%, 4 (25%) worse**
  - ***ODSS or MRC: 6 (35%) improved***

Rituximab appeared to be as effective and better tolerated that CTX +Prednisone or Fludarabine

Long-term effect of Rituximab in anti-MAG polyneuropathy

Benedetti et al Neurology 2008, 71:1742-37

- **10 patients with PN & anti-MAG IgM improved at month 12 after Rituximab (375 mg/sq/week x 4 weeks), by ≥ 1 point in 2 of MRC, INCAT or ISS.**
- **36 month follow-up**
- **8/10 maintained or further improved at month 24**
- **6/10 maintained the improvement at month 36**
- **Anti-MAG IgM reduced by 93% at month 12, 80% at month 24, 60% at month 36.**
- **All patients deteriorating during follow-up but none of those stable had baseline titers >1/100,000**
- **CD19+ B cell undetectable at 1 month & in 8 at 1 year**

The benefit of rituximab lasted 24 months in 80% & 36 months in 60% of responding patients

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
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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

RESULTS: Sulfatide >1/16,000 (ELISA)

Abs	MAG	GM1	GM2	GD1a	GD1b	Sulfatide
Diseases	**75**	**47**	**9**	**7**	**10**	**6**
MMN (41)		12 (29%)	4 (10%)	1	1	
CIDP (57)		6 (10%)	1	1	2 (3%)	
Lewis Sumner (5)				1		
PN+IgA (2)						
PN+IgG (23)		2 (10%)				
PN+IgM(166)	75(100%)	10 (6%)	1	3 (2%)	4 (2%)	**6 (100%)**
POEMS (8)		2 (25%)	1	1	1	
Other PN (89)		2 (3%)				
Unknown PN(64)		3 (3%)				
Monon. mul. (9)		1				
Radic-plexop.(21)		3 (14%)				
MND (63)		6 (9%)	2 (3%)		2 (3%)	

Total: 539

Nobile-Orazio et al 2008

RESULTS: SULFATIDE *

PN+IgM (4%+) vs other PN (0%+): p <0.0005

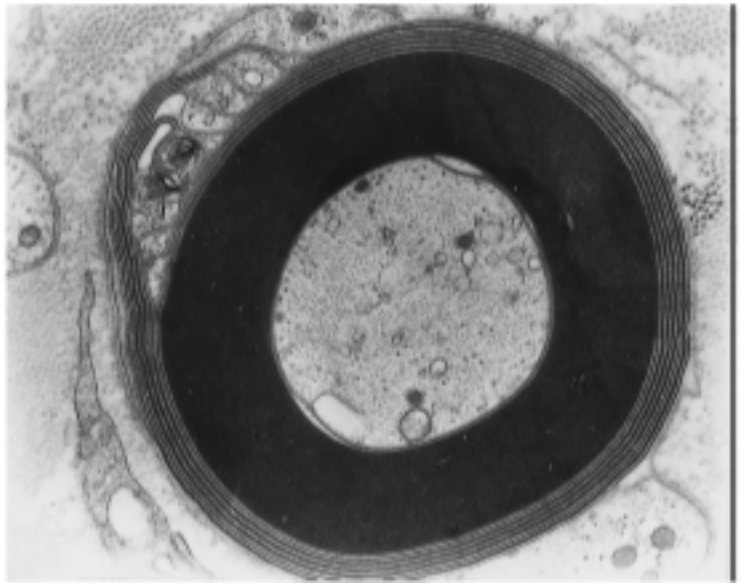
PN+IgM vs 103 pts with IgM no PN (0%+): p <0.025

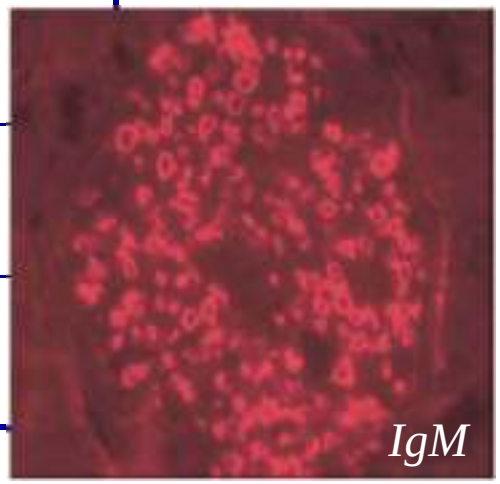
	Sensitivity	Specificity	PPV	IG
Diagnostic values for PN+IgM among total PN pts				
>1/16,000	4%	100%	100%	+69%
> 1/8,000	*4%*	*98%*	*43%*	*+12%*
Diagnostic values for PN among total IgM M-protein pts				
	4%	100%	100%	+38%

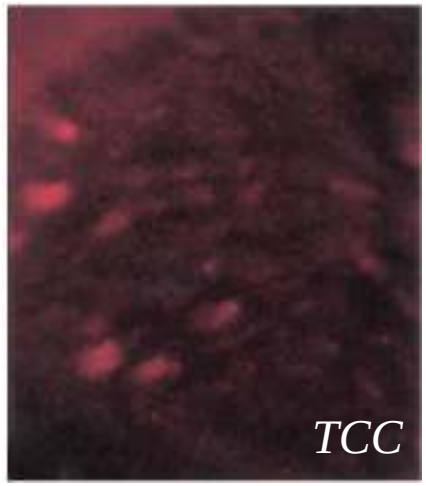
** 6 patients with titer >1/16,000 (including 4 also MAG+)*

Clinical and electrophysiological features of patients with high anti-sulfatide IgM

P.	Hem. Dis	Ab Titer	Clinical	Median CV
1.	IgMl, MGUS	512000	SM, ataxia	NR
2.	IgMl, NHL	512000	M	10
3.	IgMk, MGUS	512000	SM, ataxia	35
4.	IgMl, MGUS	32000	SM, ataxia	20
5.	IgMk, MGUS	32000	SM, ataxia	34







Carpo et al , J Neurol Sci 2000

Anti-Disyalo Gangliosides (GD1b, GQ1b) IgM

Abs	MAG	GM1	GM2	GD1a	GD1b	GQ1b*
Diseases	**75**	**47**	**9**	**7**	**10**	**4**
MMN		12 (29%)	4 (10%)	1	1	
CIDP		6 (10%)	1	1	2 (3%)	2 (8%)
Lewis Sumner				1		
PN+IgA						
PN+IgG		2 (10%)				
PN+IgM	75(100%)	10 (6%)	1	3 (2%)	4 (2%)	1
POEMS		2 (25%)	1	1	1	1
Other PN		2 (3%)				
Unknown PN		3 (3%)				
Mononeur. mul.		1				
Radicoloplexop.		3 (14%)				
MND		6 (9%)	2 (3%)		2 (3%)	

Brain (2001), **124**, 1968–1977

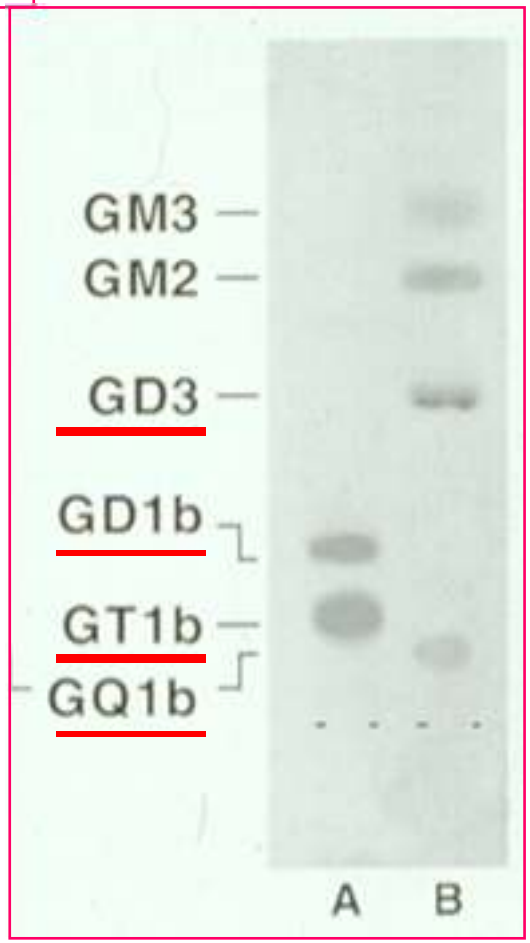
The clinical and laboratory features of chronic sensory ataxic neuropathy with anti-disialosyl IgM antibodies

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]

18 patients
14 M, 4 F
Age at onset:
28-72 (M: 53)

Chronic
Ataxic — *10 substantial*
Neuropathy (S>>M):
Motor impairment: *14 none or mild*
Ophtalmoplegia: *6*
Demyel. EMG *11*
M-protein (IgM MGUS) 17
Agglutinins (cold):: 9
Dysialosil antibodies: all *(by def.)*

Therapy: ***9/13 responded to IVIg***
(Attarian et al JNNP 2010)



Anti-nerve antibody in IgM related neuropathies

1. *Testing for anti-nerve antibodies in IgM related neuropathies help identifying specific clinical forms of the neuropathy, characterizing their prognosis and defining their most effective therapy.*
2. *Even if the specific pathogenetic role of these antibodies in the neuropathy is not always defined, their finding support the hypothesis that the neuropathy is immune mediated and help explaining the higher prevalence of neuropathy in IgM than IgG or IgA monoclonal gammopathies.*

Neuropathy and IgG MGUS

	Pats. No.	Clinical PN	Subclinical PN	Total PN
IgM	26	15%	15%	31%
IgG	**34**	**3%**	**3%**	**6%**
IgA	14	7%	7%	14%

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

Clinical and electrophysiological features of PN+IgG MGUS

Reported	Type of progression		ENG classification		
patients	relaps/remitt	progressive	Dem	Ax	Mixed
205	54	127	94	65	13

Pats No. *(Authors)*	CIDP-like (M>S/S>M/SM)	Axonal PN (SM or S)
17 (*Di Troia 1999*)	10 (7/2/1)	7 (5/2)
14 (*Hermosilla 1996*)	5 (0/0/5)	9 (4/5)

Response to immune therapies in PN+IgG MGUS

	Responders	Therapy
CIDP-like	54/67 *(81%)*	Steroids, IVIg, PE *(Immunosuppr.)*
Axonal PN	7/34 *(21%)*	Steroids, IVIg, PE *(Immunosuppr.)*

Immunological findings in 91 patients with PN+IgG MGUS

	No. of patients	Site/Reactivity
IgG deposits in nerve	**6**	Myelin (2), endoneurium/ vasa (1), light chains in small vessels(3)
Anti-neural IgG reactivity	**9**	Nerve myelin (2), vessels (1), Schwann cells (1), MAG (3), 68kD NF (1), GQ1b (1)

Time relationship between IgG MGUS and PN

	CIDP like (10)	Sensory axonal (7)
MGUS bef. PN *(time interval)*	0	2 *(6 mos, 9 yrs)*
PN bef. MGUS *(time interval)*	8 (6.8 yrs,1-18 yrs)	2 (1 & 8 yrs)
PN = MGUS	2	3
Other causes for PN	0	3

Neuropathy and IgA MGUS

	Pats. No.	Clinical PN	Subclinical PN	Total PN
IgM	26	15%	15%	31
IgG	34	3%	3%	6%
IgA	**14**	**7%**	**7%**	**14%**

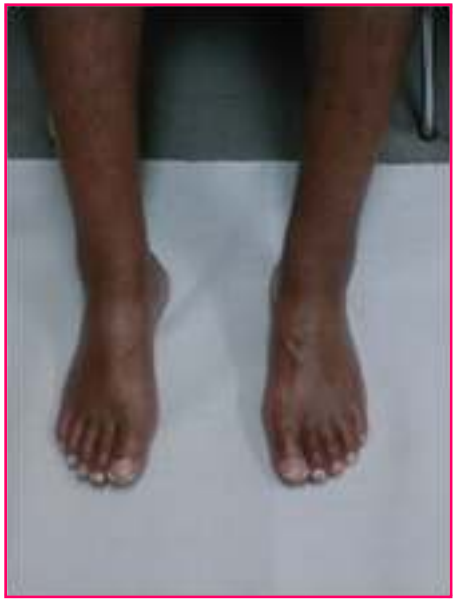
	Patients with PN+MG observed at our Institute in 1984-2000
PN+IgM	95 (83%)
PN+IgG	15 (13%)
PN+IgA	**5 (5%)**

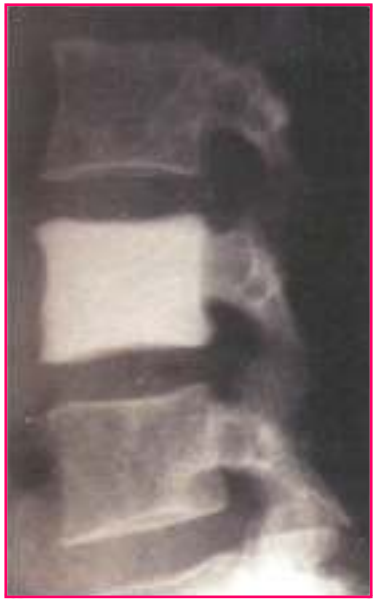
Clinical and electrophysiological features of PN+IgA MGUS

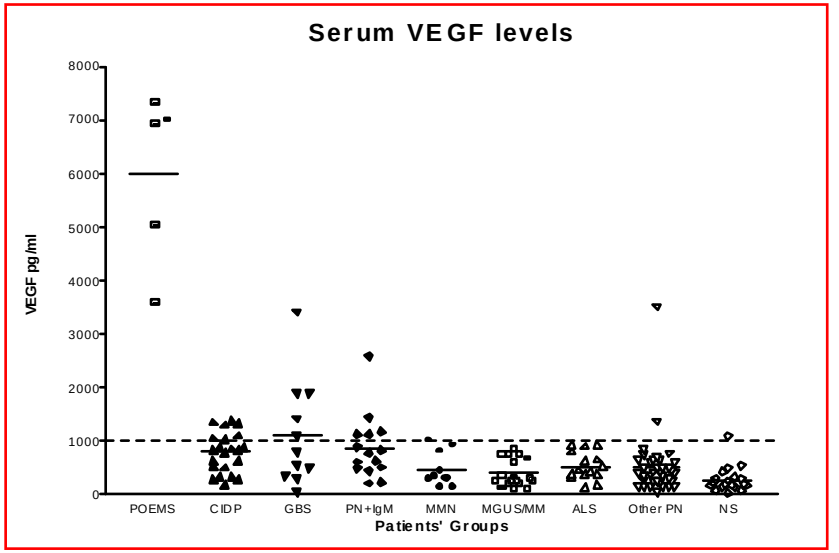
		Clinical impairment			ENG classification		
Patients	No	S or S>M	**SM**	M or M>S	Dem	Ax	**Mixed**
Reported	**28**	5	**18**	3	4	7	**17**
Our	**6**	1	**3**	2	2	2	**2**

POEMS syndrome

- **P**olyneuropathy (100%)
  - SM, D>A, CIDP-like, severe
- **O**rganomegaly (80%)
- **E**ndocrinopathy (70%)
- **M**-protein (75%)
  - *(50% IgG-50%IgA;mostly λ)*
- **S**kin changes (90%)
- osteosclerotic myel. (80%)
- lymphadenopathy (40%)
- peripheral edema (30%)
- ascites (10%)
- high CSF proteins (100%)





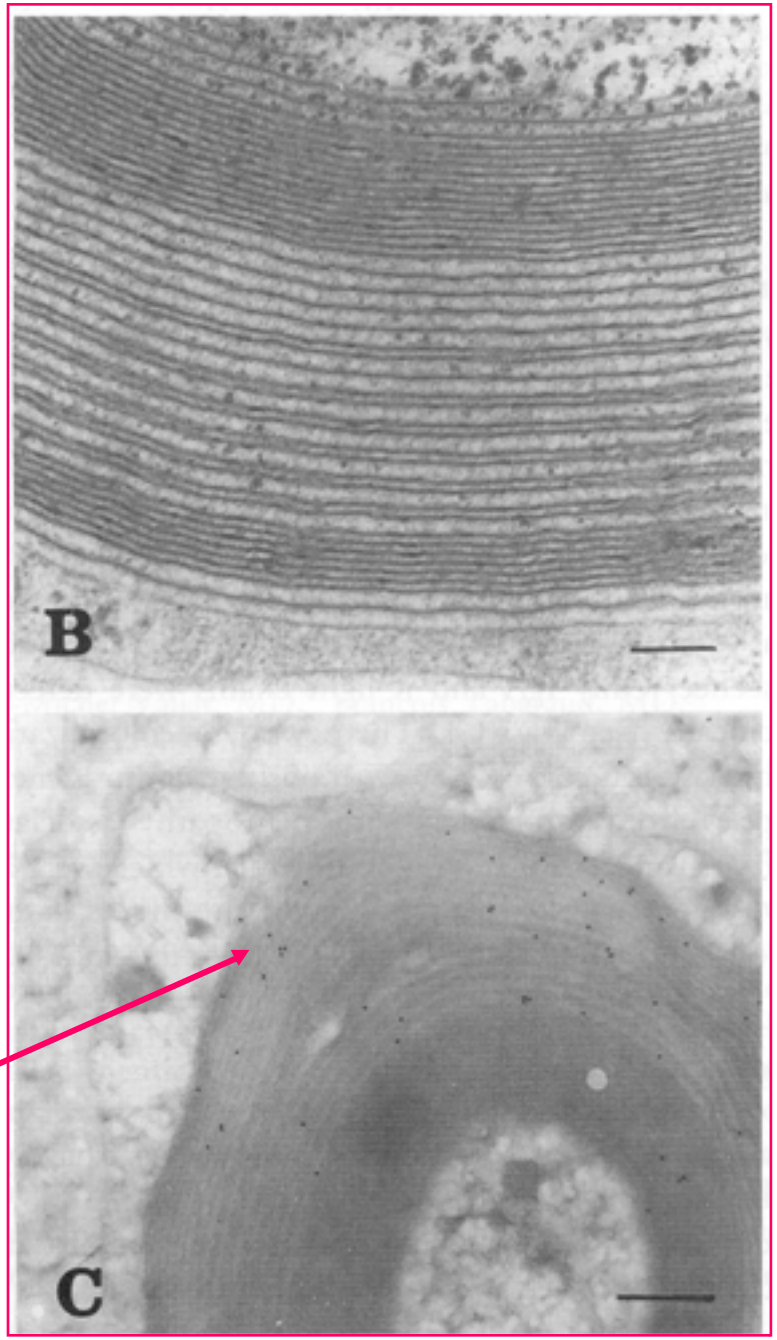


Myelin Widenings and MGUS-IgA: An Immunoelectron Microscopic Study

Jean-Michel Vallat, MD,* François Tabaraud, MD,* Philippe Sindou, PhD,* Pierre-Marie Preux, MD,* Antoon Vandenberghe, PhD,† and Andreas Steck, MD‡

Ann Neurol 2000; 47:808-11

- 72 y.o man;
- 1 year progressive paresthesias, ↓ sensation & ataxia;
- IgAλ MGUS (1,240 mg/dl);
- SCV (m/sec): LL 10-21, UL 21-42
- Deposits of IgAλ & C3d in nerve



NEUROPATHY AND MGUS

SUMMARY

In patients with **IgM MGUS** there is consistent evidence for a pathogenetic role of the M-protein in the neuropathy, particularly when directed against MAG, sulfatide or gangliosides. Despite these evidences, the efficacy of immune/cytostatic therapies in these patients still remains to be adequately confirmed.

In patients with **IgG MGUS** there is little evidence to support a primary pathogenetic role of the M-protein in PN. Immune therapies are however often effective in patients with a CIDP-like presentation

The few reports on PN and **IgA MGUS** and the heterogeneous findings do not allow conclusions on the pathogenicity of this association and on the efficacy of immune therapies. These should be considered only in patients with some evidence of anti-nerve reactivity

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

Fabrizia Terenghi
Francesca Gallia
Elda Judica
Davide Di Pietro
Claudia Giannotta
Antonella Scarale

Treatment for IgG/IgA paraproteinaemic PN

Allen D, Lunn MPT, Niermeijer J, Nobile-Orazio E

The Cochrane Library 2007, Issue 1

Reviewers' conclusion:

- One RCT with 18 participants revealed a modest short-term benefit of plasma exchange in IgG or IgA paraproteinaemic PN, over a short follow-up, when compared to sham exchange. Four other trials were identied but these were not RCT. The evidence from randomised controlled trials for the treatment of IgG or IgA paraproteinaemic PN is currently inadequate.
- Observational or open trial data provide limited support for the use of treatments such as plasma exchange, cyclophosphamide combined with prednisolone, IVIg and corticosteroids. These show potential therapeutic promise but the potential benefits must be weighed against adverse effects.

RESULTS: MAG *

PN+IgM (45%+) vs other PN (0%+): p <0.000001

PN+IgM vs 103 pts with IgM no PN (7%+): p <0.00001

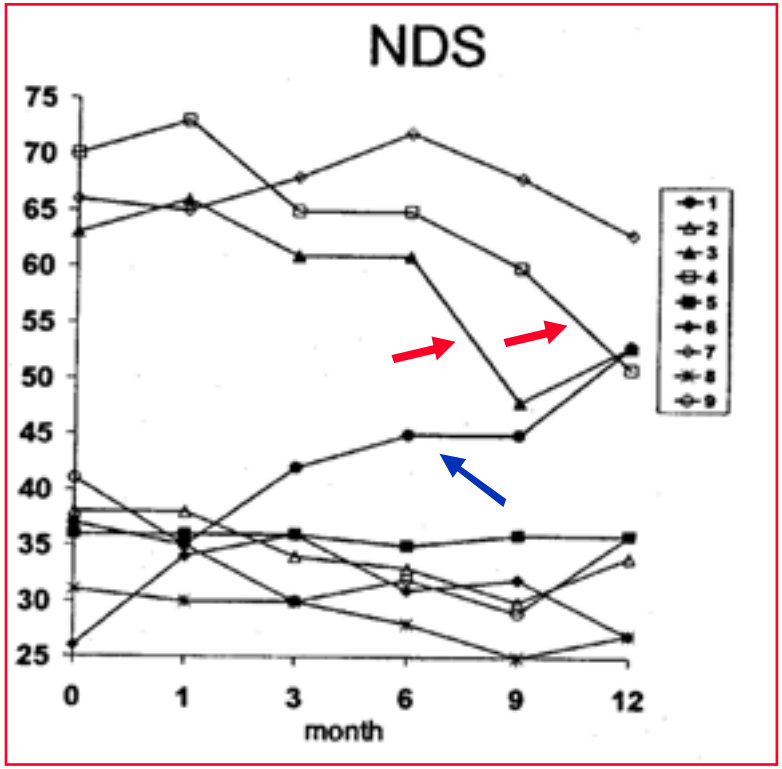
	Sensitivity	Specificity	PPV	IG
Diagnostic values for PN+IgM among total PN pts	45%	100%	100%	+69%
Diagnostic values for PN among total IgM M-protein pts	45%	93%	91%	+29%

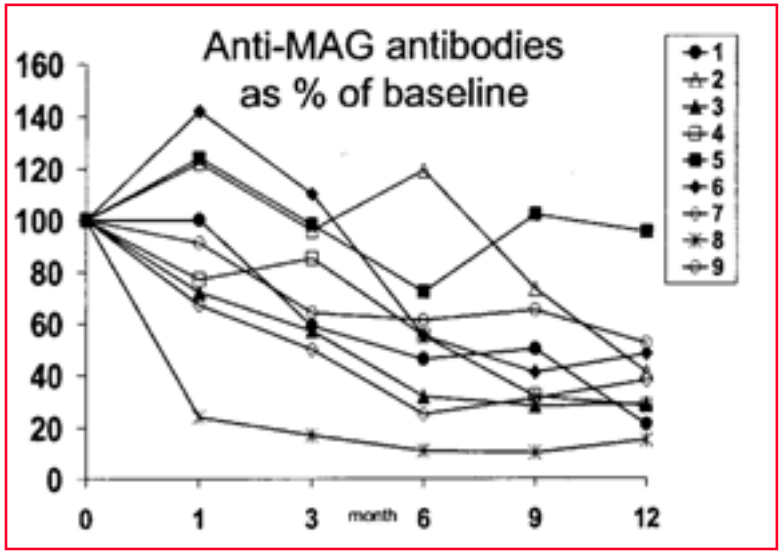
* *75 patients with titer >1/3,200*

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

Renaud et al 2003 Muscle Nerve

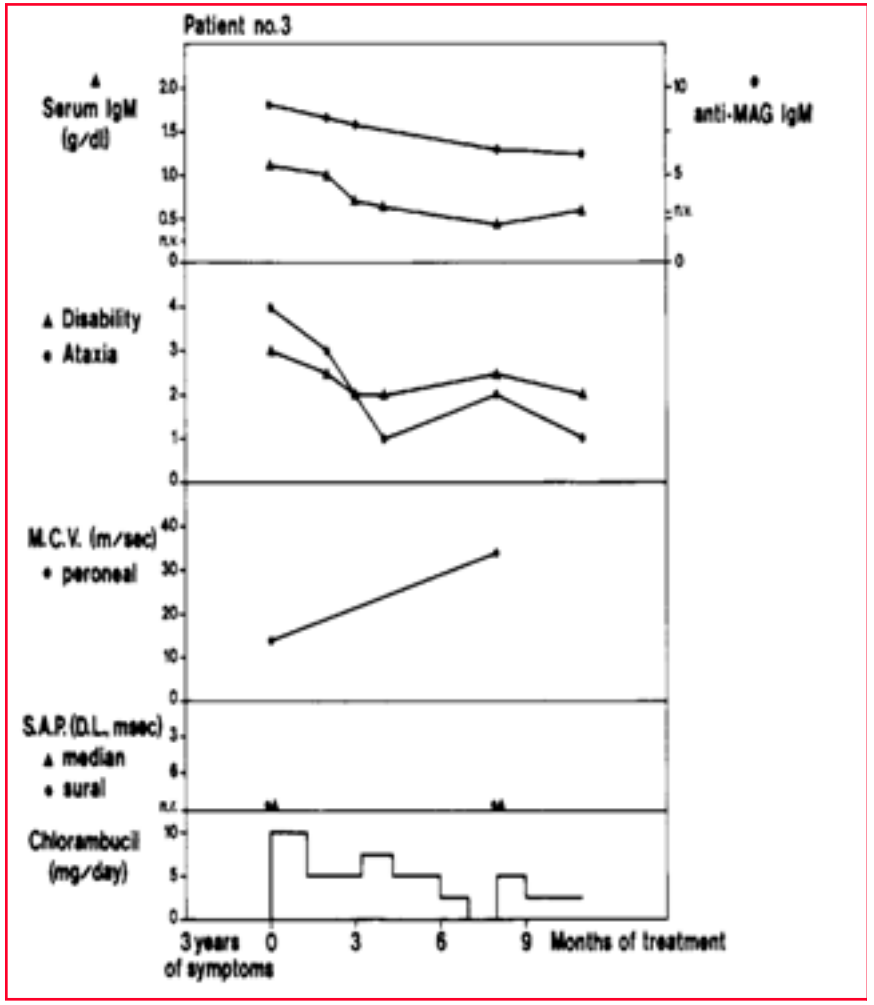
- 9 pts with PN & anti–MAG
- Rituximab 375mg/m2/wk x 4
- B cells decreased in all
- IgM ↓ in all by 35% to 82 %
- Anti-MAG ↓ by ≥ 50% in 8/9
- NDS ↑ in 6 (≤5 in 4, **≥10 in 2**)
. 1 ↓ (16) , 2 =
- Ulnar MCV ↑ by ≥10% in 7





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%)***



Anti-neural IgM antibodies in PN+IgM

Abs / Disease (No.)	MAG	GM1	GM2	GD1a	GD1b	Sulfatide
	75	47	9	7	10	6
MMN (41)		12 (29%)	4 (10%)	1	1	
CIDP (57)		6 (10%)	1	1	2 (3%)	
Lewis Sumner (5)				1		
PN+IgA (2)						
PN+IgG (23)		2 (10%)				
PN+IgM(166)	75 (45%)	**10 (6%)**	**1**	**3 (2%)**	**4 (2%)**	6 (4%)
POEMS (8)		2 (25%)	1	1	1	
Other PN (89)		2 (3%)				
Unknown PN(64)		3 (3%)				
Monon. mul. (9)		1				
Radic-plexop.(21)		3 (14%)				
MND (63)		6 (9%)	2 (3%)		2 (3%)	

Total 539

Nobile-Orazio et al. 2008

Response to immune therapies in patients with PN + IgA MGUS

Authors	Responding/ treated	Therapy
Bosch et al. 1982	0/1	Steroids, PE, Azathioprine
Hemachudha et al 1989	1/1	PE
Yeung et al. 1991	3/3	Steroids (1+IS)
Simmons et al. 1993	3/3	Steroids (1 +IVIg)
Farrer et al. 1996	1/1	Steroids (PE uneffective)
Ponsford et al. 2000	0/1	nk
Mehndiratta et al 2004	1/1	Steroids
Our series	0/4	Steroids
Total	9/15	

Response to immune therapies in PN+IgG MGUS

Authors	No. of Pats.	No. responding Demyel.	Axonal	Therapy
Contamin 1976	1	1/1		Steroids
Read 1978	3	2/3		Steroids (1+IS)
Noring 1980	2	1/1		Steroids
Dalakas 1981	7	4/4		IS (3 +steroids)
Bosch 1982	1	1/1		Steroids+IS+PE
Fineman 1990	1	1/1		PE
Yeung 1991	11	4/5		Steroids (1 + IS, 1+ IS & PE)
Waterston 1992	1	1/1		IS
Moorhouse 1992	1	0/1		Steroids
Bleasel 1993	5	5/5		Steroids+IS, PE
Notermans 1996a	11		0/3	Steroids +IS
Notermans 1996b	5	4/5		Steroids +IS
Hermosilla 1996	14	4/4	0/3	IVIg(1+1PE,2+IS)/Steroids(1+IS)
Gorson 1997	16	15/20§	3/12§	Steroids, PE, IVIg,
Di Troia 1999	17	6/8	1/3	Steroids,PE,IS,IVIg/Steroids
Ponsford 2000	8	6		Steroids (5)
Gorson 2002	20	5/7	3/13	IVIg
Total	**124**	**54/67 (81%)**	**7/34 (21%)**	

Immunological findings in PN + IgG MGUS

Authors	*No.* pats.		IgG deposits in nerve/ IgG anti-neural reactivity
Dalakas et al 1981	7		Light chain deposits on blood vessels in 3
Sewell et al 1981	1		IgG deposits/reactivity with nerve myelin
Bosch et al 1982	1		IgG deposits on myelin sheaths
Fazio et al 1992	3		IgG reactivity with 68kD neurofilaments
Moorhouse et al 1992	1		IgG deposits on endoneurium/vasanervorum
Bromberg et al 1992	17		Ig reactivity with MAG in 2
Bleasel et al 1993	5		IgG reactivity with myelin/Schwann/vasa in 3
Vrethem et al 1993	3		IgA reactivity with MAG in 1
Di Troia et al 1999	17		Ig reactivity with various neural antigens in 7*
Ponsford et al 2000	11		No anti-neural reactivity in any
Eurelings et al 2001	25		Anti-GQ1b Ig in 1
Total	91		IgG deposits in 3 IgG reactivity in 5

* A similar reactivity found in 13/35 patients with IgG MGUS without neuropathy

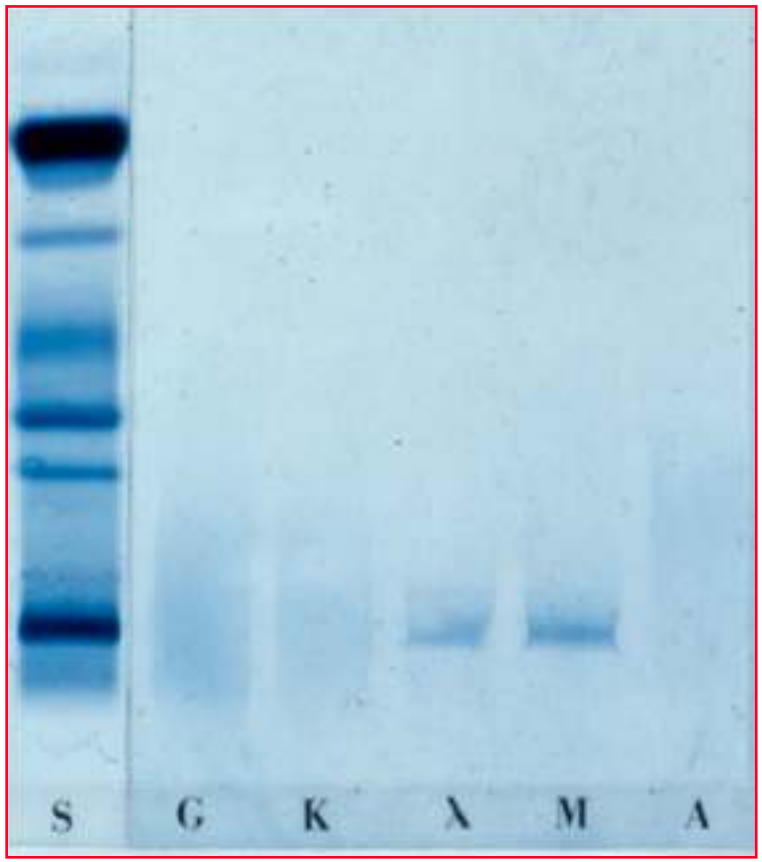
POEMS syndrome: diagnostic criteria

- Major criteria:
  - **P**olyneuropathy
  - **M**onoclonal plasma cell cell proliferative dis.
  - Sclerotic bone lesions
  - Castelman disease
  - VEGF elevation
- Minor criteria:
  - **O**rganomegaly (hepatosplenomegaly or lymphadenopathy)
  - Edema (edema, ascites, pleural effusion)
  - **E**ndocrinopathy (adrenal, thyroid, pituitary, gonadal, paratiroid pancreatic)
  - **S**kin changes (Hyperpigmentation, hypertrichosis, plethora, hemangiomata, white nails)
  - Papilledema
  - Thrombocytosis/polycythemia,

Dispenzieri et al. Blood 2006

Neuropathy and Monoclonal Gammopathy

- Malignant monoclonal gammopathies
  - Multiple myeloma (*overt, smoldering, etc)*
    Plasmocitoma (*solitary, extramedullary*)
  - Malignant lymphoproliferative diseases:
    - Waldenström's macroglobulinemia
    - Malignant lymphoma
    - Chronic lymphocytic leukemia
  - Heavy chain diseases
  - Amyloidosis (AL) (*Primary, +myeloma*)
- Monoclonal gammopathy of undetermined significance (MGUS)



Prevalence of neuropathy in patients with IgM monoclonal gammopathy

Diagnosis	No. studied	No. with PN	% with PN
IgM MGUS	**31**	14	**45%**
IWM	**24**	8	**33%**
WM	**10**	4	**40%**
Total IgM	**65**	**26** ***19 clinical PN***	**43%** ***29% clinical PN***

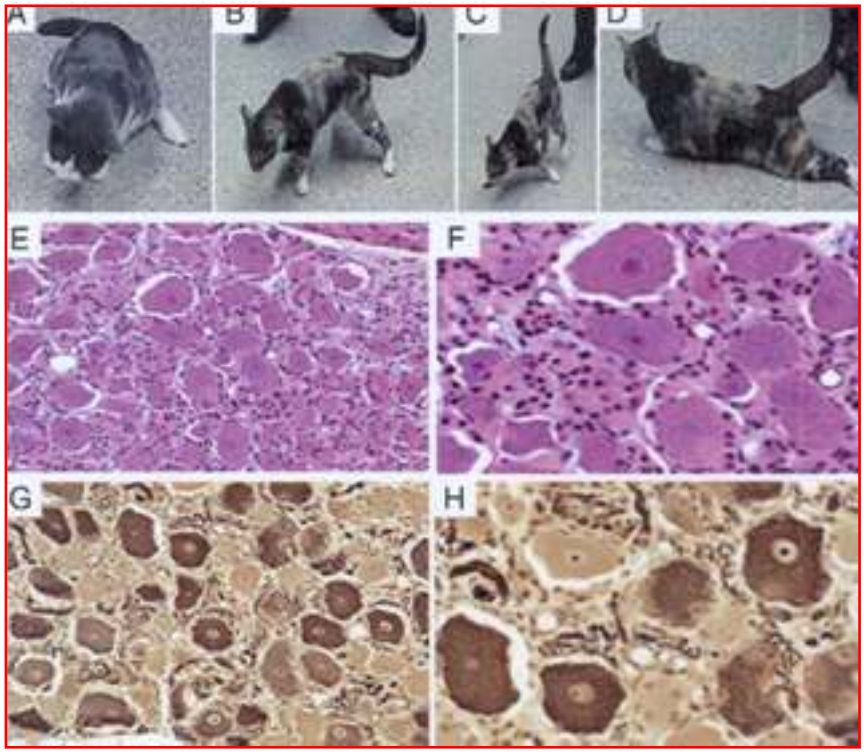
Baldini et al 1994

Induction of experimental ataxic sensory neuronopathy in cats by immunization with purified SGPG

A.A. Ilyas [a,*], Y. Gu [a], M.C. Dalakas [b], R.H. Quarles [b], S. Bhatt [a]

J Neuroimmunol 2008, 193:87-93

1. Four cats immunized with SGPG developed high titers of anti-MAG/SGPG IgM antibodies.
2. All four cats developed clinical signs of sensory and motor neuropathy within 11 months from immunization.
3. Pathology revealed sensory ganglionitis with inflammatory infiltrates in DRG. No nerve or root pathology.



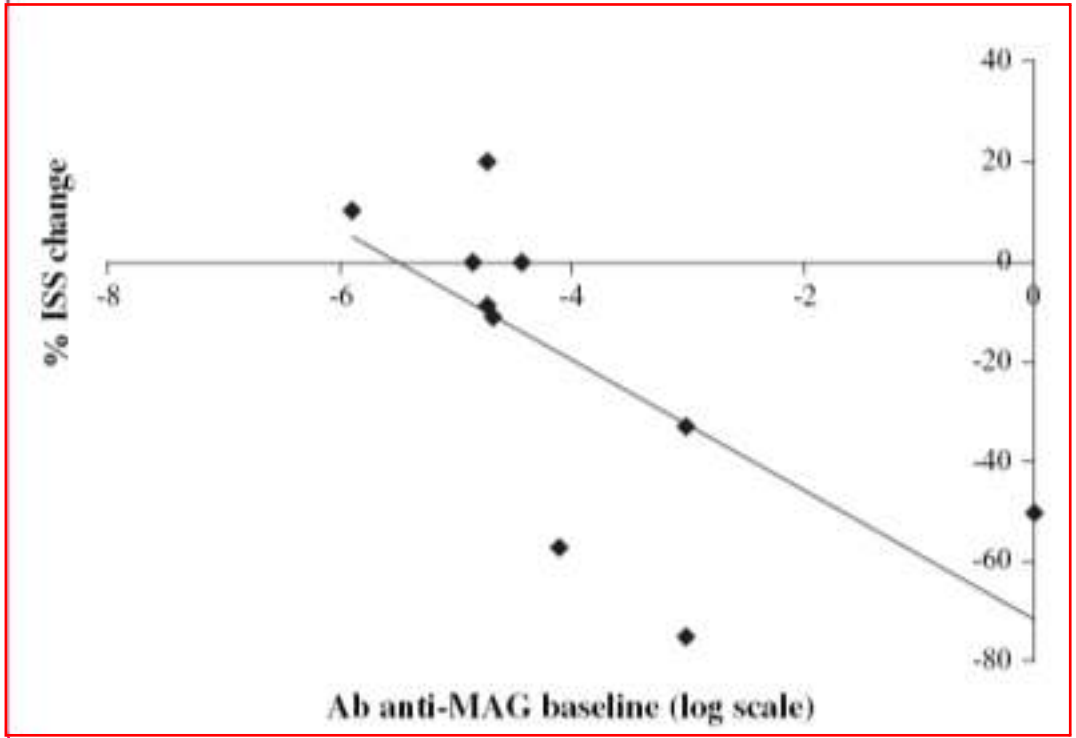
Predictors of response to rituximab in patients with neuropathy and anti–myelin associated glycoprotein immunoglobulin M

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 pts** with PN+anti-MAG
- **8 pts (62%) improved** in INCAT sens.& MRC score & 7 (54%) in disability.
- **Improvement correlated with lower anti-MAG** at entry and follow-up.

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



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)*

2010 EFNS/PNS PDN GUIDELINES
Good practice points for treatment of IgM PDN

1. In patients without significant disability there is no evidence that immunosuppressive/modulatory treatment is beneficial. Patients may be offered treatment for tremor and paresthesia, and reassurance that symptoms are unlikely to worsen significantly for years.

2. In patients with significant chronic or progressive disability, immunosuppressive/modulatory treatment may be considered, although none are of proven efficacy. IVIg or PE may be considered, but benefit may be short term and repeated treatments may be required. To achieve longer-term benefit, clinicians have used rituximab, cyclophospha-mide with prednisolone, fludarabine, and chlorambucil. All remain unproven and all have risks which must be balanced against any possible benefits.

JNNP 2010; 15: 185-195

PN associated with anti-Sulfatide IgM

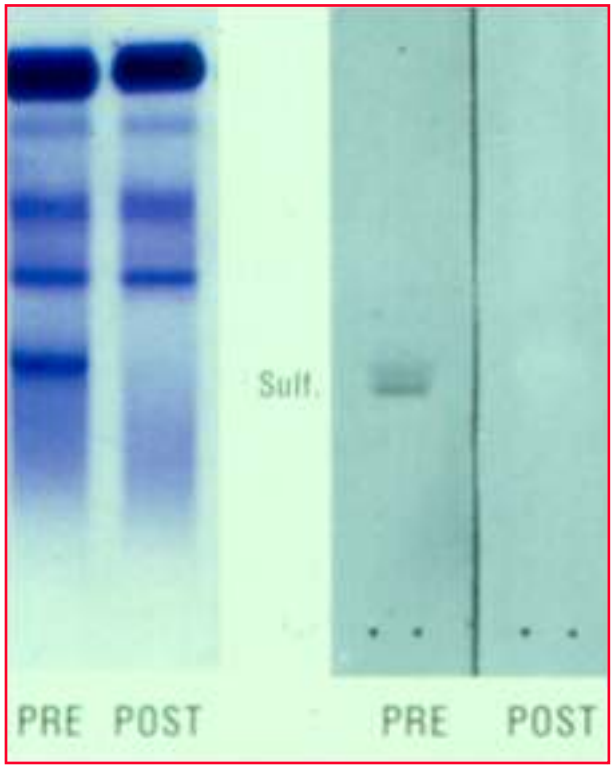
Authors, years	*Clinical presentation of PN*		*Pathology*	
Pestronk et al, 1991 Lopate et al, 1997	S (Pan or SF), S>M, SM	+/- IgM-M	Axonal Normal	Demyelinating
Ilyas et al, 1992	NK (PN)	+ anti-MAG IgM		Demyelinating
Quattrini et al, 1992	S, SM		Axonal	Demyelinating
Nemni et al, 1993	S		Axonal	
van den Berg et al, 1993 Eurelings et al, 2001	S, SM	+/- anti-MAG/SGPG IgM	Axonal	Demyelinating
Nobile-Orazio et al, 1994 Carpo et al, 2000	SM	+/- IgM-M		Demyelinating
Petratos et al, 2000	SM			Demyelinating
Erb et al, 2000	S, SM		Axonal	
Dabby et al, 2000	S (Pan or SF), SM	+/- IgM-M	Axonal Normal	Demyelinating

Polyneuropathy syndromes associated with serum antibodies to sulfatide and myelin-associated glycoprotein

A. Pestronk, MD; F. Li, MD; J. Griffin, MD; E.L. Feldman, MD; D. Cornblath, MD; J. Trotter, MD; S. Zhu, MD; W.C. Yee, MD; D. Phillips, MD; D.M. Peeples, MD; and B. Winslow, BS

8 patients (2 with IgM-MGUS) with chronic S or S>M, mostly axonal PN

Neurology 1991

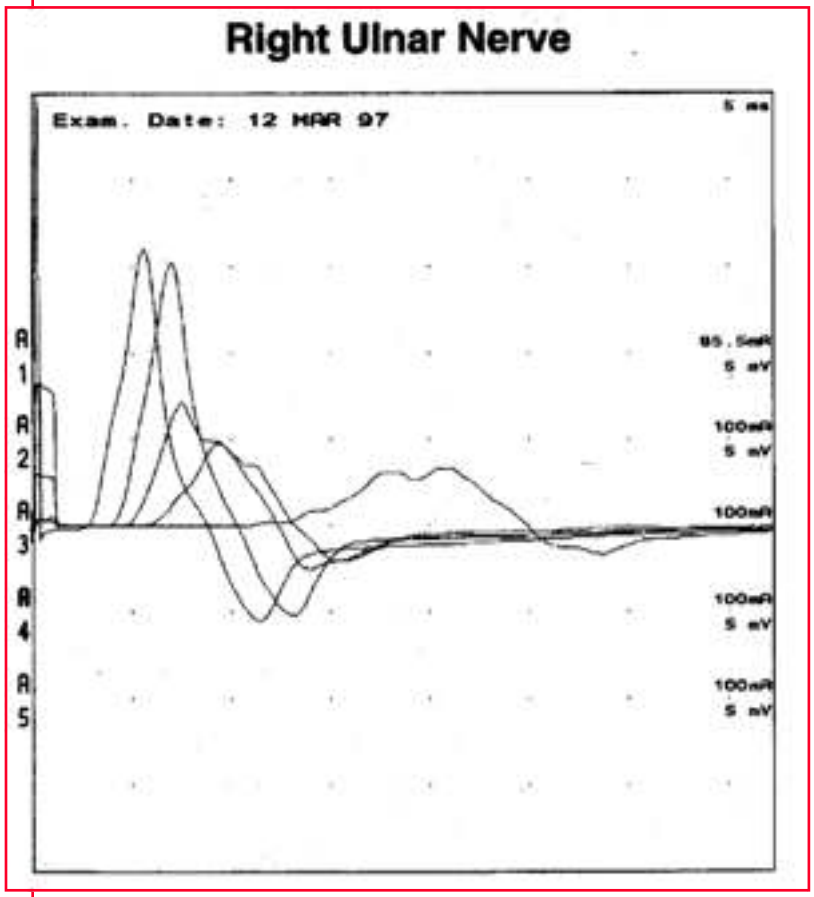


AGE HPTLC

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
- ***80% of patients respond to Ig***



NEUROPATHY ASSOCIATED WITH IgG-MGUS

SUMMARY

- In patients with a CIDP-like neuropathy the detection of IgG MGUS does not justify a different clinical classification or a different therapeutical approach from CIDP-I.

- The old age and frequent presence of other possible causes for the neuropathy in patients with sensory or sensorimotor axonal neuropathy and IgG MGUS may be consistent with a coincidental association, and is probably not sufficient per se to warrant the use of immune therapies.

Immunological findings in PN+IgA MGUS

Authors	No.	Ig neural reactivity/deposits in nerve
Dhib-Jalbut 1986	1 myeloma	IgA anti-endoneurium by IIF and to several protein bands by immunoblot
Bailey 1986	1	Myelin and endo-perineurial deposits of IgA
Nemni 1991	3	IgG to 68kD NF/axonal deposits of IgG
Farrer 1996	1	Polyclonal IgA anti-LM1 & IgM anti-MAG
Vallat 2000	1	WML with myelin deposits of IgA and C3d
Mehndiratta 2004	1	Myelin deposits of IgA
Ponsford 2000	1	No anti-neural reactivity
Eurelings 2001	2	No anti-neural reactivity
Our series	14	No IgA reactivity in 14/no IgA deposits in 1
Total	25	IgA deposits in 3 anti-neural Ig in 6 (1 IgA-M)

NEUROPATHY ASSOCIATED WITH IgA-MGUS

SUMMARY

The very small number of reported patients with PN and IgA MGUS and their etherogeneous clinical presentation **do not permit to establish a clinical phenotype for this PN**.

Even if anti-neural reactivity or endoneurial deposits of IgA M-proteins and response to immune therapy have been occasionally reported suggesting, at least in some patients a possible immune pathogenesis for the PN, in our opinion **the mere finding of IgA MGUS in a patient with PN is not sufficient to support the immune pathogenesis and therapy for the PN**.

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*)