Paraproteinemic neuropathies

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European Reference Networks

EURO-NMD
European network of reference centers for rare neuromuscular diseases

Associazione Italiana Sistema Nervoso Periferico

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Alnylam						x	
Ionis						x	
Takeda						x	Travel grant
Kedrion							Travel grant
CSL Behring							Travel grant
Astra Zeneca						x	

CLASSICAL LANDSCAPE OF MONOCLONAL GAMMOPATHIES

Type of Gammopathy | Pre-neoplastic conditions | Neoplastic diseases

asymptomatic | symptomatic

IgM

MGUS → Waldenstrom Macroglobulinemia

Chronic lymphocytic leukemia / Marginal zone Lymphoma

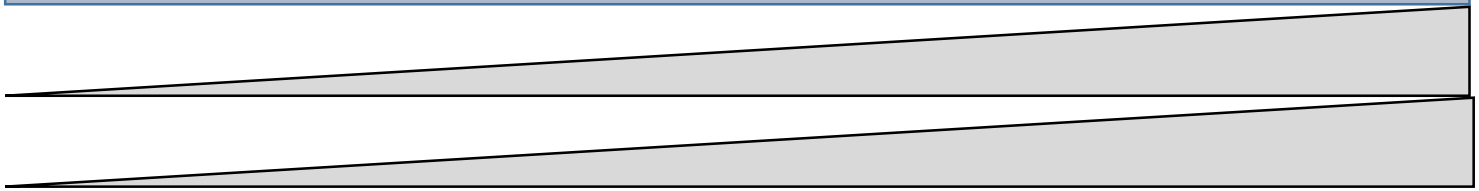
	MGUS	MM	WM	CLL	MZL
lymphocytosis	-	-	+/-	++	+
Splenomegaly	-	-	+	+	++
Lymph nodes	-	-	+	++	+
Lytic lesions	-	+	-	-	-
MYD88 L265P	+ (IgM)	-	++	rare	+/-

Non-IgM
IgG>IgA>>IgD> IgE

MGUS → Multiple myeloma

M-protein levels

Neoplastic cells



CONTEMPORARY LANDSCAPE OF MONOCLONAL GAMMOPATHIES

Type of Gammopathy | pre-neoplastic conditions | neoplastic diseases

asymptomatic | symptomatic

IgM

MGUS

Waldenstrom Macroglobulinemia

Chronic lymphocytic leukemia / Marginal zone Lymph.

MGCS^A

MONOCLONAL GAMMOPATHY OF CLINICAL SIGNIFICANCE

- **Monoclonal gammopathy of clinical significance**
- Monoclonal gammopathy of skin significance
- Monoclonal gammopathy of kidney significance
- **Monoclonal gammopathy of neurological significance**

MG can cause damage via mechanisms independent of tumor growth

non-IgM
IgG>IgA>>IgD> IgE

MGUS

Multiple myeloma

M-protein levels

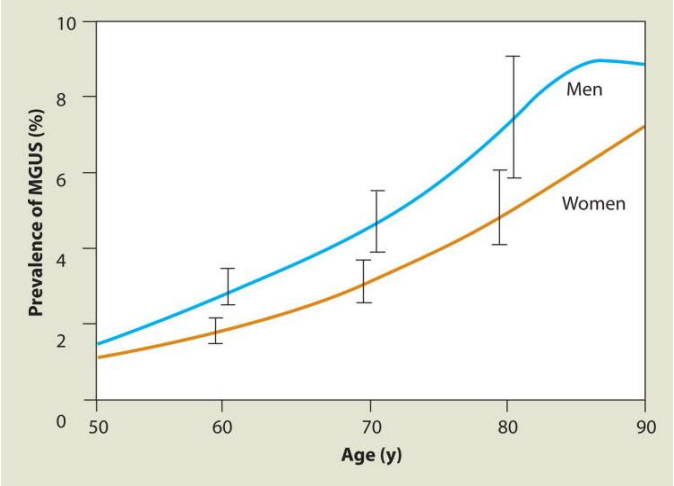
Neoplastic cells

Neoplastic cells

Prevalence of Monoclonal Gammopathy of Undetermined Significance

Robert A. Kyle, M.D., Terry M. Therneau, Ph.D., S. Vincent Rajkumar, M.D., Dirk R. Larson, M.S., Matthew F. Plevak, B.S., Janice R. Offord, B.S., Angela Dispenzieri, M.D., Jerry A. Katzmann, Ph.D., and L. Joseph Melton III, M.D.

N Engl J Med 2006;354:1362-9.



- 3% persons >50 yrs
- 5.3% persons >70 yrs
- 7.5% persons > 85 yrs

10% patients with otherwise idiopathic neuropathy has a MGUS (prevalence 6-10 times higher than the general population) *(Kelly JJ 1981)*

1-36% patients with MGUS has symptomatic neuropathy: 5% IgG, 15% IgA, 30-50% IgM

(Gosselin 1991, Nobile-Orazio 2002,Vrethem 1993, Yeung 1991)

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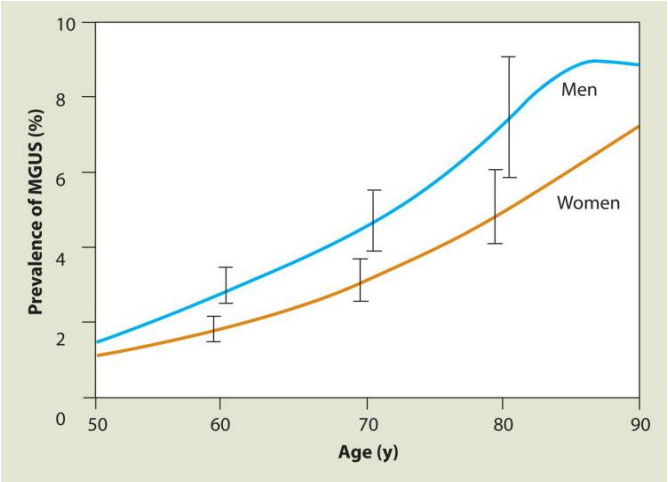

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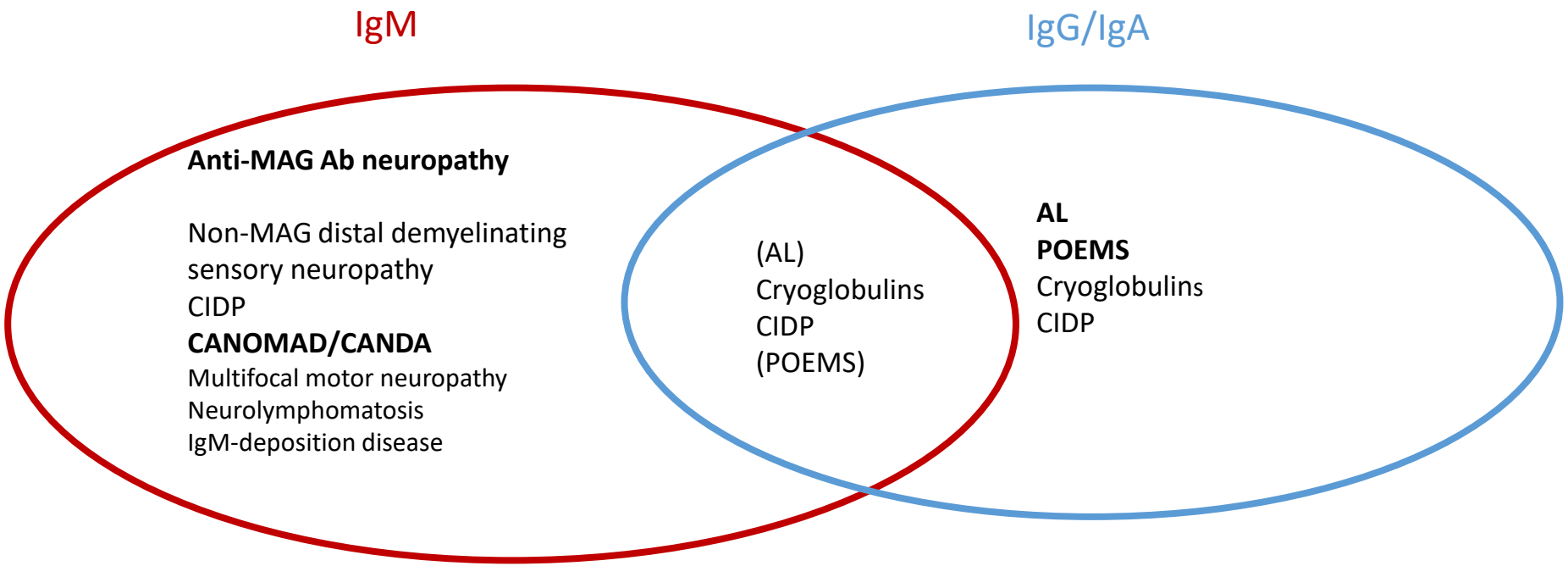
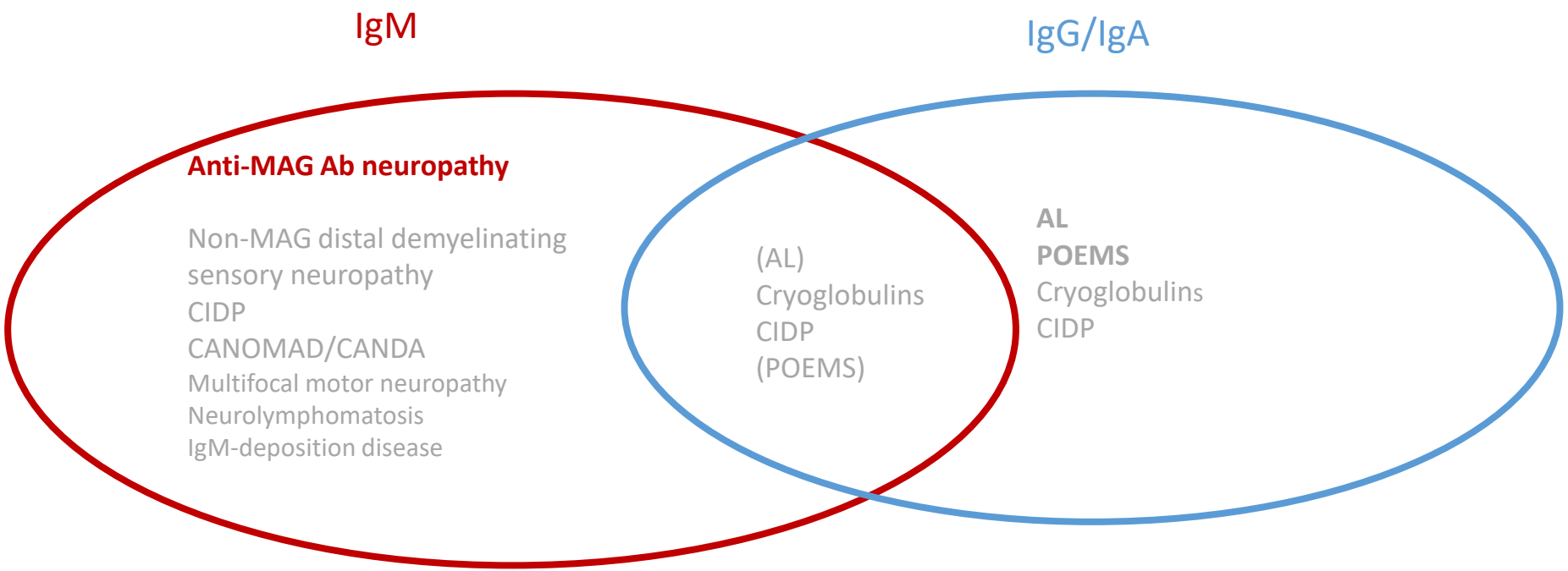
Paraproteinemic neuropathies



Paraproteinemic neuropathies



The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 1980; 303:618-621
DOI: 10.1056/NEJM198009113031105

Plasma-Cell Dyscrasia and Peripheral Neuropathy with a Monoclonal Antibody to Peripheral-Nerve Myelin

Norman Latov, M.D., Ph.D., William H. Sherman, M.D., Raffaello Nemni, M.D., Giuliana Galassi, M.D., Joanna S. Shyong, M.S., Audrey S. Penn, M.D., Leonard Chess, M.D., Marcelo R. Olarte, M.D., Lewis P. Rowland, M.D., and Elliott F. Osserman, M.D.

- The most common IgM paraproteinemic neuropathy
  Prevalence 1 in 100.000, male/female ratio 1.9 to 1

- Clinical features
  Length-dependent symmetric mostly sensory polyneuropathy, with secondary sensory ataxia and gait imbalance
  Motor involvement generally occurs in late stages of the disease
  Upper limb tremor is common and often interferes with patients' activities

- The IgM monoclonal gammopathy that may underlie a MGUS or a lymphoproliferative disorder, commonly Waldenstrom's macroglobulinemia (WM), and also marginal zone lymphoma (MZL) or chronic lymphocytic leukemia (CLL)

- Neurophysiological studies: demyelinating neuropathy with symmetric impairment of conduction velocities and sensory nerves action potentials, disproportionately prolonged distal motor latencies, no conduction blocks.
  In long disease duration, axonal features may be reported in association with demyelinating findings

Functioning and quality of life in patients with neuropathy associated with anti-MAG antibodies

Yuri M. Falzone[1] · Marta Campagnolo[2] · Mariangela Bianco[3] · Patrizia Dacci[4] · Daniele Martinelli[1] · Marta Ruiz[2] · Silvia Bocci[8] · Federica Cerri[1] · Angelo Quattrini[1] · Giancarlo Comi[1,6] · Luana Benedetti[7] · Fabio Giannini[8] · Giuseppe Lauria[4,5] · Eduardo Nobile-Orazio[3] · Chiara Briani[2] · Raffaella Fazio[1] · Nilo Riva[1]

Journal of Neurology (2018) 265:2927–2933

- 67 patients (24 F, 43 M)
- mean age at onset 69.2 yrs (SD 8.0), mean duration 7.2 years (SD 4.8)

- Balance was the main determinant of walking ability, highlighting the relevance of gait ataxia

- Sensory impairment was the main determinant of participation. Sensory disturbances markedly interfere with patient's autonomy

- QoL, measured with SF36 questionnaire, was lower in patients with anti-MAG antibody neuropathy compared with the Italian general population

Long-term disability and prognostic factors in polyneuropathy associated with anti-myelin-associated glycoprotein (MAG) antibodies

Giuliana Galassi [1], Manuela Tondelli [1], Alessandra Ariatti [1], Francesca Benuzzi [1], Paolo Nichelli [1], Franco Valzania [1]

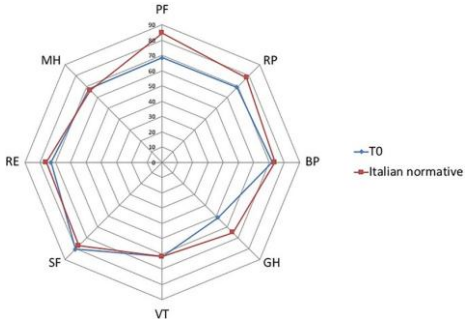
Int J Neurosci. 2017 May;127(5):439-447.

44 pts, median follow-up 93 months
Demyelinating pattern, older age and absence of treatment were significant risk factors for disability worsening

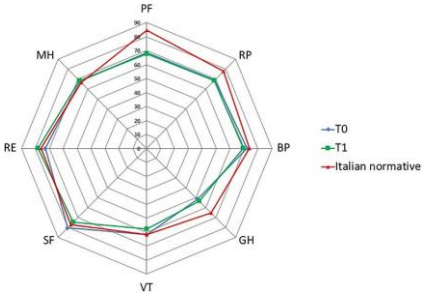
Limitations in daily activities and general perception of quality of life: Long term follow-up in patients with anti-myelin-glycoprotein antibody polyneuropathy

Marta Campagnolo[1] | Marta Ruiz[1] | Yuri M. Falzone[2] | Mario Ermani[1] | Mariangela Bianco[3] | Daniele Martinelli[2] | Federica Cerri[2] | Angelo Quattrini[2] | Alessandro Salvalaggio[1] | Francesca Castellani[1] | Giancarlo Comi[2,4] | Fabio Giannini[5] | Eduardo Nobile-Orazio[3] | Raffaella Fazio[2] | Nilo Riva[2] | Chiara Briani[1]

J Peripher Nerv Syst. 2019;1-7.



Comparison between SF-36 subscales in normative Italian sample (red line) and anti-MAG neuropathy patients (blue line)



SF-36 subscales at baseline (blue line) and follow-up evaluation (green line)

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

Placebo-controlled trial of rituximab in IgM anti-myelin–associated glycoprotein neuropathy

Neurology 80 June 11, 2013

Jean-Marc Léger, MD
Karine Viala, MD
Guillaume Nicolas, MD, PhD
Alain Créange, MD, PhD
Jean-Michel Vallat, MD
Jean Pouget, MD
Pierre Clavelou, MD
Christophe Vial, MD
Andreas Steck, MD
Lucile Musset, MD, PhD
Benoit Marin, MD, PhD
For the RIMAG Study Group (France and Switzerland)

Cochrane Library

Cochrane Database of Systematic Reviews

Immunotherapy for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies (Review)

Lunn MPT, Nobile-Orazio E

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Immunotherapy for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies (Review)

Lunn MPT, Nobile-Orazio E

- A careful meta-analysis of the two trials showed that rituximab seems to be beneficial in improving disability scales, especially INCAT, and in the response to questionnaires in the global impression of the disease

- We would encourage the authors of future trials to collect consistent, comparable and clinically-meaningful endpoint data. The inclusion of a disability measure in future trials would be appropriate, being relevant both to patients and to healthcare providers

IgM anti-MAG$^{\pm}$ peripheral neuropathy (IMAGiNe) study protocol: An international, observational, prospective registry of patients with IgM M-protein peripheral neuropathies

Tatiana Hamadeh[1] | Perry T. C. van Doormaal[2,3] | Mariëlle H. J. Pruppers[1] | Johannes P. M. van de Mortel[2] | Janneke G. J. Hoeijmakers[1] | David R. Cornblath[4] | Alexander F. J. E. Vrancken[2] | Catharina G. Faber[1] | Nicolette C. Notermans[2] | Ingemar S. J. Merkies[1,5] | on behalf of the IMAGiNe Consortium[†]

J Peripher Nerv Syst. 2023;1–7.

Università degli Studi di Padova

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

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Milano, Best Western Hotel Madiso

Placebo-controlled trial of rituximab in IgM anti-myelin–associated glycoprotein neuropathy

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Benoit Marin, MD, PhD
For the RIMAG Study Group (France and Switzerland)

Neurology 80 June 11, 2013

Rituximab has been assessed in 2 randomized controlled trials,
both of them accounting only for MGUS patients,
WM being an exclusion criteria

IgM MGUS and Waldenstrom-associated anti-MAG neuropathies display similar response to rituximab therapy

Marta Campagnolo,[1] Renato Zambello,[2] Eduardo Nobile-Orazio,[3] Luana Benedetti,[4] Girolama Alessandra Marfia,[5] Nilo Riva,[6] Francesca Castellani,[1] Mariangela Bianco,[3] Alessandro Salvalaggio,[1] Martina Garnero,[4]

Marta Ruiz,[1] Giorgia Mataluni,[5] Raffaella Fazio,[6] Mario Ermani,[1] Chiara Briani[1]

J Neurol Neurosurg Psychiatry December 2017 Vol 88 No 12

8/33 WM

Rituximab benefits less than 50% of the patients

Efficacy of rituximab in anti-myelin-associated glycoprotein demyelinating polyneuropathy: Clinical, hematological and neurophysiological correlations during 2 years of follow-up

Mattia Parisi[1] | Irene Dogliotti[2] | Michele Clerico[3,4] | Davide Bertuzzo[5] | Giulia Benevolo[4] | Lorella Orsucci[6] | Irene Schiavetti[7] | Roberto Cavallo[8] | Federica Cavallo[3,4] | Simone Ragaini[3,4] | Alessandra Di Liberto[8] | Martina Ferrante[3] | Giulia Bondielli[3] | Carlo Alberto Artusi[1] | Daniela Drandi[3] | Leonardo Lopiano[1] | Bruno Ferrero[1] | Simone Ferrero[3,4]

Eur J Neurol. 2022;29:3611–3622.

17/23 WM

MYD88 L265P Somatic Mutation in Waldenström's Macroglobulinemia

N Engl J Med 2012;367:826-33.

♦ The discovery of the mutational profile of the *MYD88* and *CXCR4* genes have radically changed the diagnosis and prognostic evaluation of IgM monoclonal gammopathies

♦ Whole-genome sequencing has revealed a single activating somatic mutation in myeloid differentiation factor 88 (*MYD88*) gene (resulting in a predicted protein change from leucine to proline at amino acid position 265) and multiple activating mutations in the C-terminal domain of *CXCR4* in patients with WM

♦ **MYD88^{L265P} is a gain of function mutation resulting in increased cellular proliferation and survival mediated by the Bruton's tyrosine kinase (BTK). BTK can be inhibited by ibrutinib, a drug used in the treatment of WM**

♦ Somatic mutations of CXCR4 are associated with more aggressive disease

♦ MYD88 mutated and CXCR4 WT: better and longer response to ibrutinib

Ibrutinib in Previously Treated Waldenström's Macroglobulinemia

N ENGL J MED 372;15 NEJM.ORG APRIL 9, 2015

- 63 WM patients, who had received at least one previous treatment
- Aim: to investigate the effect of *MYD88* and *CXCR4* mutations on outcomes

- Ibrutinib (daily dose 420 mg) orally until disease progression
- $MYD88^{L265P}$ $CXCR4^{WT}$: 100% overall response rate and 91.2% major response rate

- 9 (3 with anti–MAG antibodies) had received ibrutinib for progressive neuropathy

- All 9 patients had a response:
-subjective improvements in neuropathy in 5 patients
-neuropathy stable in 4 patients during the treatment course

Ibrutinib for patients with rituximab-refractory Waldenström's macroglobulinaemia (iNNOVATE): an open-label substudy of an international, multicentre, phase 3 trial

www.thelancet.com/oncology Vol 18 February 2017

- 4/31 patients had neuropathy: 2 remained stable and 2 had subjective improvement from week 9 with continued amelioration of symptoms over time and complete resolution of the neuropathy in one patient

- Despite the hematological evaluation might have lacked of specific (clinical or neurophysiological) neurological scales to properly grade the response of neuropathy to ibrutinib, still these preliminary data are promising and show that ibrutinib does not worsen neuropathy and rather can improve it

- Since the response to ibrutinib strictly depend on the IgM paraprotein mutation profile, and given the lack of efficacious therapy in at least half of anti-MAG antibody neuropathy, may ibrutinib be a possibility?

- Assess the mutational profile of the *MYD88* and *CXCR4* genes in patients with anti-MAG neuropathy

The Bruton tyrosine kinase inhibitor ibrutinib improves anti-MAG antibody polyneuropathy

Francesca Castellani, MD,* Andrea Visentin, MD, PhD,* Marta Campagnolo, MD, Alessandro Salvalaggio, MD, Mario Cacciavillani, MD, PhD, Cinzia Candiotto, PhD, Roberta Bertorelle, MD, Livio Trentin, MD, and Chiara Briani, MD

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Neurol Neuroimmunol Neuroinflamm 2020;7:e720. doi:10.1212/NXI.0000000000000720

Neurology® Neuroimmunology & Neuroinflammation | American Academy of Neurology®

Methods

All 3 patients underwent bone marrow biopsy showing WM, with MYD88^{L265P} mutated and CXCR4^{S338X} wild type, and were started on ibrutinib 420 mg/die. Patients were assessed at baseline, at 3-6-9 months, and at 12 months in 2 patients with a longer follow-up, using Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Score, INCAT sensory sum score, and Medical Research Council sum score. The modified International Cooperative Ataxia Rating Scale was performed in 2 patients, whereas it was not used in the patient with Parkinson disease as a major comorbidity. Responders were considered the patients improving by at least one point in 2 clinical scales.

Results

All the patients reported an early and subjective benefit, consistent with the objective improvement, especially of the sensory symptoms as shown by clinical scales. Treatment was well tolerated.

Conclusion

These preliminary data point to a possible efficacy of ibrutinib in anti-MAG antibody neuropathy, which is the most common disabling paraproteinemic neuropathy, where active treatment is eagerly needed.

Table 2 Clinical scales at the baseline and the follow-up of ibrutinib-treated patients

	INCAT disability score (upper limbs + lower limbs)	ISS	MRC sum score	mICARS
1				
Baseline	2 + 2	8	53	27
3 mo	2 + 2	6	55	27
6 mo	2 + 1	5	55	25
9 mo	2 + 1	5	55	25
12 mo	2 + 1	5	55	23
2				
Baseline	4 + 4	9	51	—
3 mo	3 + 3	6	53	—
6 mo	3 + 3	6	53	—
9 mo	3 + 3	6	53	—
12 mo	3 + 3	6	53	—
3				
Baseline	0 + 1	5	60	15
3 mo	0 + 1	4	60	15
6 mo	0 + 1	3	60	13
9 mo	0 + 0	3	60	10

Abbreviations: INCAT = Inflammatory Neuropathy Cause and Treatment Disability Score; ISS = INCAT sensory sum score; MRC = Medical Research Council sum score; mICARS = modified International Cooperative Ataxia Rating Scale.

RESEARCH ARTICLE OPEN ACCESS

Mutational Profile in 75 Patients With Anti–Myelin-Associated Glycoprotein Neuropathy

Clinical and Hematologic Therapy Response and Hints on New Therapeutic Targets

Francesca Castellani, MD,* Andrea Visentin, MD, PhD,* Erika Schirinzi, MD, Alessandro Salvalaggio, MD, PhD, Mario Cacciavillani, MD, PhD, Cinzia Candiotto, PhD, Claudia Baratè, MD, Alessandro Cellini, MD, Roberta Bertorelle, PhD, Gabriele Siciliano, MD, Livio Trentin, MD, and Chiara Briani, MD

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Neurol Neuroimmunol Neuroinflamm 2023;10:e200122. doi:10.1212/NXI.0000000000200122

- **Objective:** to assess the mutational profile of MYD88 and CXCR4 genes in anti-MAG Ab neuropathy and possible correlations with neuropathy severity and therapy response
- 75 patients with anti-MAG antibody neuropathy:
  - 47 men, mean age 70.8±10 years
  - Associated hematological disease:
    - 38 (50.7%) IgM-MGUS
    - 29 (38.7%) WM
    - 8 (10.6%) CLL/MZL/HCL
- Molecular analysis: allele specific–PCR, from bone marrow mononuclear cells in 57/75 patients and from circulating mononuclear cells in 18/75
- Clinical evaluation: at baseline and every 6 months, for a mean follow-up of 48.8±52 months:
  - INCAT (Inflammatory Neuropathy Cause and Treatment) Disability Score
  - INCAT Sensory Sum Score (ISS)
  - MRC sum score
- Responders: patients who improve of at least 1 point in 2 clinical scales

Results

- **55/75 (66.7%) patients carried the *MYD88^{L265P}* mutation**:
  - 26/29 (89.7%) WM patients
  - 21/38 (55.3%) MGUS IgM patients
  - 3/8 (37.5%) CLL/MZL patients
  - The mutation was significantly more frequent in WM patients (p=0.0107)
- All the patients were *CXCR4* wild-type

Of the 75 enrolled patients, 44/57 (77%) of those therapy naive carried the MYD88^{L265P} mutation, versus 6/18 (33.3%) of the previously treated patients (p= 0.0012)
MYD88^{L265P} mutation was significantly more common in therapy-naïve patients (p=0.0002)

Why? *MYD88* wild-type patients might have a higher relapse rate despite a similar response rate
Rituximab might eradicate MYD88-altered cells favoring the occurrence of a *MYD88* wild-type B-cell clone

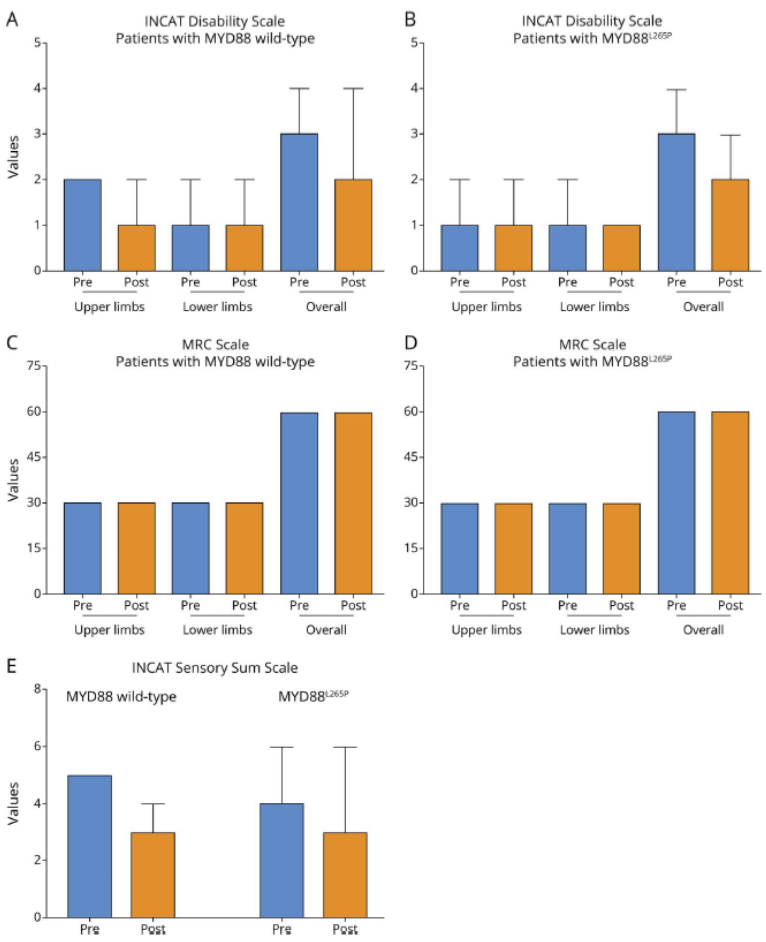
No significant difference in neuropathy severity in *MYD88^{L265P}* mutated *vs* wild-type patients

No significant difference in hematological parameters in *MYD88^{L265P}* mutated *vs* wild-type patients:
(M protein levels, IgM levels, Anti-MAG antibody titers)

Neurol Neuroimmunol Neuroinflamm 2023;10:e200122. doi:10.1212/NXI.0000000000200122

- 40 patients treated with rituximab, with clinical benefit in 26 (65%), including 14/23 (61%) MYD88 mutated and 12/17 (70.6%) wild type (p=0.7385)

- **No significant difference in therapy response** between mutated and unmutated patients (p=0.16), nor in necessity of additional cycles for relapse (16.6% in mutated patients *vs* 40% in wild-type; p= 0.14)



Neurol Neuroimmunol Neuroinflamm 2023;10:e200122. doi:10.1212/NXI.0000000000200122

- **Ibrutinib**
- 6 patients, all WM, *MYD88*^{L265P} mutated and *CXCR4* wild-type
- previously treated with rituximab with lack of benefit
- Ibrutinib 420 mg/d orally
- Treatment was well tolerated (no atrial fibrillation or major bleeding; occasional cramps and petechiae)

		INCAT Disability Score (U.E.+L.E.)	ISS	MRC Sum Score
Patient 1	Baseline	2 + 2	8	53
	6 months	2 + 1	5	55
	12 months	2 + 1	5	55
	24 months	2 + 1	4	55
	36 months	2 + 1	4	55
Patient 2	Baseline	4 + 4	9	51
	6 months	3 + 3	6	53
	12 months	3 + 3	6	54
	24 months	3 + 3	6	55
Patient 3	Baseline	0 + 1	5	60
	6 months	0 + 1	3	60
	12 months	0 + 0	3	60
	24 months	0 + 0	3	60
Patient 4	Baseline	1+1	5	59
	6 months	0+0	4	60
Patient 5	Baseline	3+2	6	54
	6 months	3+2	6	54
	12 months	3+2	6	55
Patient 6	Baseline	1+1	4	58
	6 months	1+1	4	58
	12 months	0+1	2	58

		Paraprotein (gL)	IgM (g/L)	Anti-MAG (BTU/L)
Patient 1	Baseline	6.50	7.2	52.9
	6 months	5.40	4.3	67.9
	12 months	4.30	4.0	60.4
	24 months	3.25	3.5	>70.0
	36 months	3.40	3.6	>70.0
Patient 2	Baseline	7.20	13.7	>70.0
	6 months	3.30	6.6	50.6
	12 months	2.80	6.4	68.0
	24 months	1.73	6.1	>70.0
Patient 3	Baseline	10.60	15.9	51.5
	6 months	5.60	8.8	37.8
	12 months	3.70	7.7	>70.0
	24 months	2.80	7.2	>70.0
Patient 4	Baseline	1.90	1.88	49.1
	6 months	0.94	1.27	47.3
Patient 5	Baseline	24.80	31.8	>70.0
	6 months	12.40	19.7	>70.0
	12 months	8.00	13.4	>70.0
Patient 6	Baseline	6.01	10.6	>70.0
	6 months	5.73	9.78	>70.0
	12 months	5.61	9.54	48.6

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	6 months	0 + 1	3	60
	12 months	0 + 0	3	60
	24 months	0 + 0	3	60
Patient 4	Baseline	1+1	5	59
	6 months	0+0	4	60
Patient 5	Baseline	3+2	6	54
	6 months	3+2	6	54
	12 months	3+2	6	55
Patient 6	Baseline	1+1	4	58
	6 months	1+1	4	58
	12 months	0+1	2	58

		Paraprotein (gL)	IgM (g/L)	Anti-MAG (BTU/L)
Patient 1	Baseline	6.50	7.2	52.9
	6 months	5.40	4.3	67.9
	12 months	4.30	4.0	60.4
	24 months	3.25	3.5	>70.0
	36 months	3.40	3.6	>70.0
Patient 2	Baseline	7.20	13.7	>70.0
	6 months	3.30	6.6	50.6
	12 months	2.80	6.4	68.0
	24 months	1.73	6.1	>70.0
Patient 3	Baseline	10.60	15.9	51.5
	6 months	5.60	8.8	37.8
	12 months	3.70	7.7	>70.0
	24 months	2.80	7.2	>70.0
Patient 4	Baseline	1.90	1.88	49.1
	6 months	0.94	1.27	47.3
Patient 5	Baseline	24.80	31.8	>70.0
	6 months	12.40	19.7	>70.0
	12 months	8.00	13.4	>70.0
Patient 6	Baseline	6.01	10.6	>70.0
	6 months	5.73	9.78	>70.0
	12 months	5.61	9.54	48.6

Neurol Neuroimmunol Neuroinflamm 2023;10:e200122. doi:10.1212/NXI.0000000000200122

- Ibrutinib
- 6 patients, all WM, *MYD88*^{L265P} mutated and *CXCR4* wild-type
- previously treated with rituximab with lack of benefit
- Ibrutinib 420 mg/d orally
- Treatment was well tolerated (no atrial fibrillation or major bleeding; occasional cramps and petechiae)

		INCAT Disability Score (U.E.+L.E.)	ISS	MRC Sum Score
Patient 1	Baseline	2 + 2	8	53
	6 months	2 + 1	5	55
	12 months	2 + 1	5	55
	24 months	2 + 1	4	55
	36 months	2 + 1	4	55
Patient 2	Baseline	4 + 4	9	51
	6 months	3 + 3	6	53
	12 months	3 + 3	6	54
	24 months	3 + 3	6	55
Patient 3	Baseline	0 + 1	5	60
	6 months	0 + 1	3	60
	12 months	0 + 0	3	60
	24 months	0 + 0	3	60
Patient 4	Baseline	1+1	5	59
	6 months	0+0	4	60
Patient 5	Baseline	3+2	6	54
	6 months	3+2	6	54
	12 months	3+2	6	55
Patient 6	Baseline	1+1	4	58
	6 months	1+1	4	58
	12 months	0+1	2	58

		Paraprotein (gL)	IgM (g/L)	Anti-MAG (BTU/L)
Patient 1	Baseline	6.50	7.2	52.9
	6 months	5.40	4.3	67.9
	12 months	4.30	4.0	60.4
	24 months	3.25	3.5	>70.0
	36 months	3.40	3.6	>70.0
Patient 2	Baseline	7.20	13.7	>70.0
	6 months	3.30	6.6	50.6
	12 months	2.80	6.4	68.0
	24 months	1.73	6.1	>70.0
Patient 3	Baseline	10.60	15.9	51.5
	6 months	5.60	8.8	37.8
	12 months	3.70	7.7	>70.0
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Neurol Neuroimmunol Neuroinflamm 2023;10:e200122. doi:10.1212/NXI.0000000000200122

Why these antibody fluctuations?

- If despite the halving of the monoclonal paraprotein, the antibody titer persists elevating, it is likely that the quantity of the antibody-producing cells is low compared with the whole paraprotein

- Another possibility is that ibrutinib may succeed in eliminating the WM malignant cells, but it is less active in the lymphoplasmocytes producing anti-MAG antibodies

- Finally, the lymphoplasmocytes that produce the anti-MAG antibodies may have a survival advantage, explaining why only less than 50% of anti-MAG neuropathy patients respond to rituximab or eventually relapse

- The possibility of serum factors that influence the *in vitro* antibody binding or the assays' variability because of the differences in the ELISA plates or their handling, or standard curves generated by positive controls, should also be considered

Why these antibody fluctuations?

♦ If despite the halving of the monoclonal paraprotein, the antibody titer persists elevating, it is likely that the quantity of the antibody-producing cells is low compared with the whole paraprotein

♦ Another possibility is that ibrutinib may succeed in eliminating the WM malignant cells, but it is less active in the lymphoplasmocytes producing anti-MAG antibodies

♦ Finally, the lymphoplasmocytes that produce the anti-MAG antibodies may have a survival advantage, explaining why only less than 50% of anti-MAG neuropathy patients respond to rituximab or eventually relapse

A recent meta-analysis of 50 retrospective studies with 410 patients: a relative 50% reduction in anti-MAG antibody titre is associated with a clinical response to immunotherapies

Decrease in Serum Anti-MAG Autoantibodies Is Associated With Therapy Response in Patients With Anti-MAG Neuropathy

Neurol Neuroimmunol Neuroinflamm 2022;9:e1109. doi:10.1212/NXI.0000000000001109

Clinical, biological, electrophysiological and therapeutic profile of patients with anti-MAG neuropathy according to MYD88^{L265P} and CXCR4 mutations and underlying haemopathy

Alexandre Guérémy[1] · José Boucraut[2,3] · John Boudjarane[4] · Aude-Marie Grapperon[1] · Etienne Fortanier[1] · Laure Farnault[5,6] · Jean Gabert[7,8] · Frédéric Vely[2,8] · Romaric Lacroix[9,10] · Ludivine Kouton[1] · Shahram Attarian[1] · Emilien Delmont[1]

Journal of Neurology (2024) 271:1320–1330

- Retrospective cohort of 79 patients, a subgroup of whom had undergone genetic analysis for *MYD88* and *CXCR4* genes mutations.

62 (78.5%) IgM-MGUS, 13 (16.6%) WM, 3 (3.8%) marginal zone lymphoma and 1 (1.3%) a mantle cell lymphoma.

- MYD88^{L256P} mutation was searched for in 60 patients using allele specific polymerase chain reaction (AS-PCR) **on peripheral blood mononuclear cells**. CXCR4 mutation was searched for in 51 patients with targeted next-generation sequencing (NGS) on peripheral blood mononuclear cells.

- **The MYD88^{L265P} mutation was detected in 29/60 patients (48.3%): 7/14 (50%) lymphoma, 21/52 (40%) IgM-MGUS.**

The CXCR4 mutation was only found in 1 patient (2%) with a diagnosis of IgM-MGUS.

- 41 patients received an RTX-based therapy: 32 RTX alone, 9 received RTX combined with an alkylating-based chemotherapy (6 including cyclophosphamide, 2 bendamustine and 1 fludarabine).

- **No significant differences** in hematological data, neuropathy severity nor response to RTX between MYD88^{L265} and MYD88$^{wild-type}$ patients

- **High prevalence of the *MYD88*^{L265P} mutation in anti-MAG antibody neuropathy**
- The *MYD88*^{L265P} mutation does not seem to be a prognostic factor of neuropathy severity or response to rituximab
- In relapsed patients, treatment should be tailored based on the mutational profile favoring BTK inhibitors in *MYD88*^{L265P} mutated patients

Hematological Oncology. 2022;40:332–340.

Use of BTK inhibitors with special focus on ibrutinib in Waldenström macroglobulinemia: An expert panel opinion statement

S. Ferrero[1,2] | Massimo Gentile[3] | Luca Laurenti[4] | Francesca Romana Mauro[5]
Maurizio Martelli[5] | Paolo Sportoletti[6] | Carlo Visco[7] | Pier Luigi Zinzani[8]
Alessandra Tedeschi[9] | M. Varettoni[10]

Is ibrutinib (+/-R) appropriate for WM patients with polyneuropathy?

- Anti-MAG polyneuropathy is often an indication for treatment of otherwise asymptomatic WM patients
- Little evidence exists to recommend specific therapies; however, rituximab might be beneficial
- Single agent ibrutinib might be a reasonable choice in selected patients - those who no longer respond to rituximab or when rituximab has not improved polyneuropathy

- We confirmed the high prevalence of the *MYD88*^{L265P} mutation in anti-MAG antibody neuropathy
- The *MYD88*^{L265P} mutation does not seem to be a prognostic factor of neuropathy severity or response to rituximab
- In relapsed patients, treatment should be tailored based on the mutational profile favoring BTK inhibitors (e.g. ibrutinib) in *MYD88*^{L265P} mutated patients

Use of BTK inhibitors with special focus on ibrutinib in Waldenström macroglobulinemia: An expert panel opinion statement

S. Ferrero[1,2] | *Hematological Oncology*. 2022;40:332–340. Francesca Romana Mauro[5] Maurizio Martelli[5] | Paolo Sportoletti[6] | Carlo Visco[7] | Pier Luigi Zinzani[8] Alessandra Tedeschi[9] | M. Varettoni[10]

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- Little evidence exists to recommend specific therapies; however, rituximab might be beneficial
- Single agent ibrutinib might be a reasonable choice in selected patients - those who no longer respond to rituximab or when rituximab has not improved polyneuropathy

Second generation BTK inhibitors: zanubrutinib, acalabrutinib

AMSTERDAM
Zanubrutinib + rituximab (MAGNAZ)

BOSTON
Acalabrutinib+ rituximab

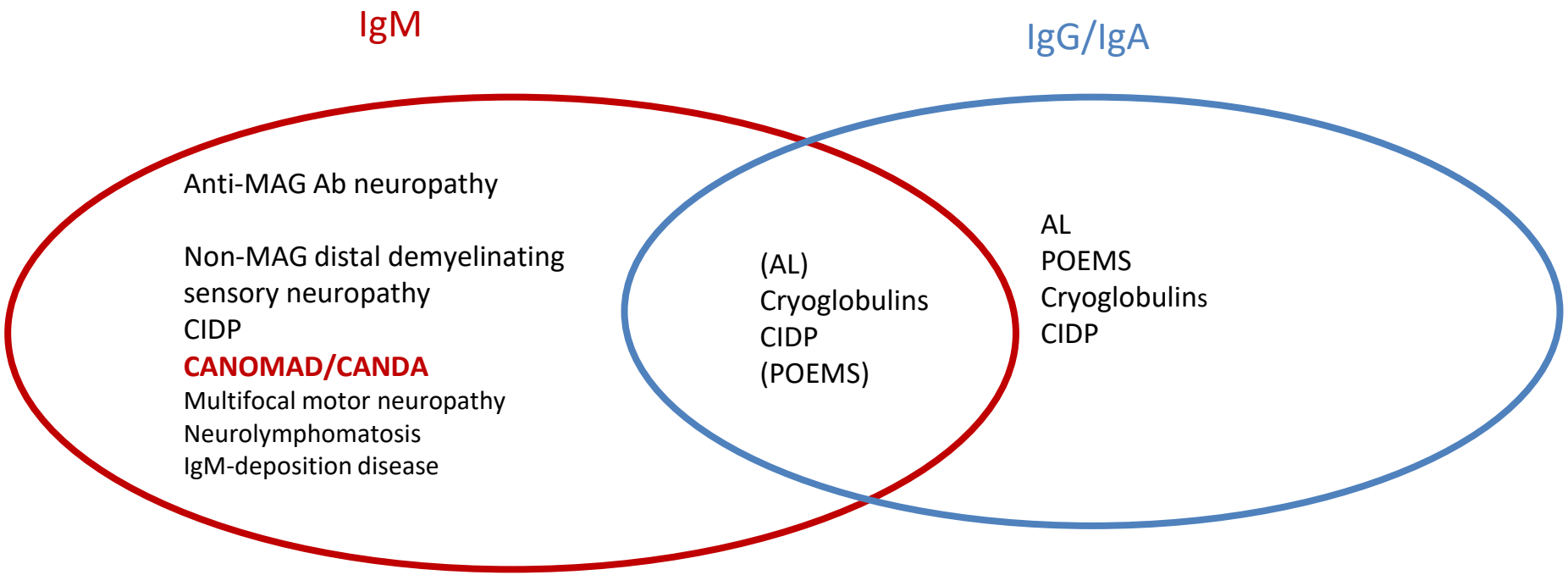
PADOVA
zanubrutinib (MAZINGA)

- Azienda Ospedale – Università Padova
- Città della Salute e della Scienza, Torino
- Policlinico Gemelli, Roma
- Ca’Granda Niguarda Hospital, Milano
- Ospedale Universitario di Trieste
- Ospedale Tor Vergata, Roma
- Ospedale San Martino, Genova
- Humanitas, Rozzano
- IRCCS San Matteo, Pavia

AIFA AUTHORIZED!

ZANUBRUTINIB, A SECOND GENERATION BTK INHIBITOR, IN ANTI-MAG ANTIBODY NEUROPATHY: A PHASE II ITALIAN MULTICENTER CLINICAL TRIAL (MAZINGA)

Paraproteinemic neuropathies



Brain (2001), **124**, 1968–1977

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

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

- CANOMAD: chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins and disialosyl antibodies

- In 17/18 cases, benign IgM paraproteins, and in four of these cases at least two IgM paraproteins were present. The IgM antibodies were also cold agglutinins in 50% of cases

- Electrophysiology /CSF: demyelinating and axonal features; CSF protein <0.5 g/L in 5, >0.5<1g/L in 9, >1 g/L in 2

- Serum IgM antibodies which react principally withdisialosyl epitopes common to many gangliosides including GDlb, GD3, GTlb and GQlb

CANOMAD: a neurological monoclonal gammopathy of clinical significance that benefits from B-cell–targeted therapies

Blood. 2020;136(21):2428-2436

Marie Le Cann,[1,*] Françoise Bouhour,[2,*] Karine Viala,[3] Laurence Simon,[1] Céline Tard,[4] Cédric Rossi,[5] Guillaume Morel,[6] Emmeline Lagrange,[7] Laurent Magy,[8] Alain Créange,[9,10] Maud Michaud,[11] Jérôme Franques,[12] Andoni Echaniz-Laguna,[13-15] Jean-Christophe Antoine,[16] Marine Baron,[1] Bertrand Arnulf,[17] Angela Puma,[18] Emilien Delmont,[19] Thierry Maisonobe,[3] Véronique Leblond,[1,†] and Damien Roos-Weil,[1,†] on behalf of the French CIDP and FILO Groups

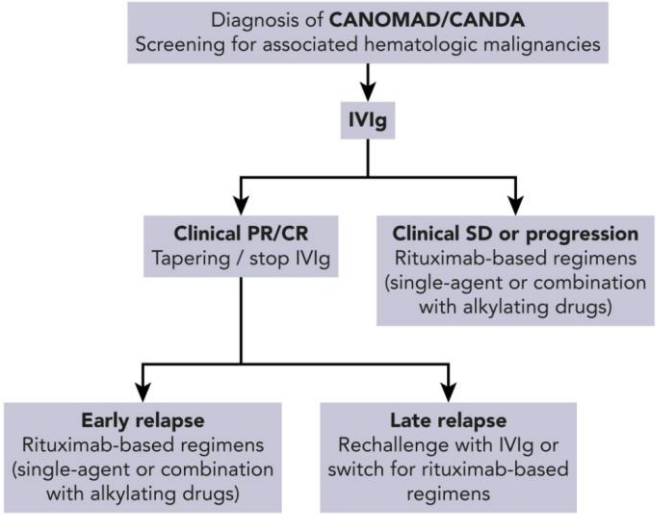
- French multicenter retrospective study: 45 patients with serum IgM antibodies reacting against disialosyl epitopes in the context of evocating neurologic symptoms

- Main clinical features: sensitive symptoms (ataxia, paresthesia, hypoesthesia; n = 45, 100%), motor weakness (n = 18, 40%), ophthalmoplegia (n = 20, 45%), and bulbar symptoms (n = 6, 13%)

- Electrophysiology: demyelinating (60%) or axonal (27%) pattern

- All patients had serum monoclonal IgM gammopathy.

Overt hematologic malignancies were diagnosed in 16 patients (36%), with the most frequent being Waldenström macroglobulinemia (n = 9, 20%)



Early relapse: relapse during IVIg tapering or < 2 years after IVIg treatment
Late relapse: > 2 years after IVIg treatment

european journal of neurology
the official journal of the european academy of neurology

Chronic ataxic neuropathy with disialosyl antibodies responsive to zanubrutinib. *(in press)*

62-year-old-man with chronic ataxic neuropathy with disialosyl antibodies (CANDA) with **clinical and neurophysiological improvement after zanubrutinib therapy.**

Clinical picture and tests

Sensory symptoms in his hands and feet extending over time to the knees and elbows.
Nerve conduction studies: sensory axonal ganglionopathy.
Blood tests revealed an IgM λ paraprotein expression of a WM. Anti-MAG and anti-neuronal antibodies were negative.
Anti-ganglioside IgM antibodies (GD1b; GD2, GD3, GT1a, GT1b, GQ1b) were positive.
Neurological examination disclosed pinprick, and tactile hypoesthesia with stocking-glove distribution.

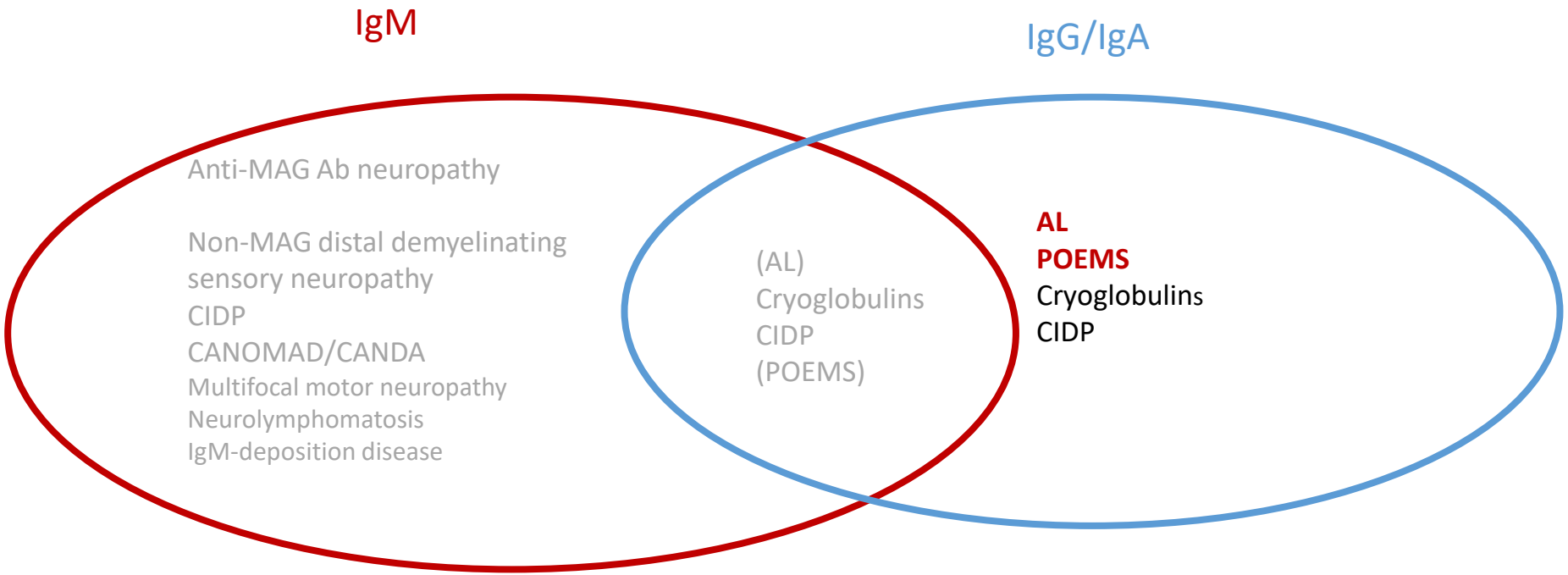
Therapy

The patient was responsive to intravenous immunoglobulin (IVIg) but reported end-dose fluctuations.
Rituximab was started but soon discontinued for clinical worsening so IVIg therapy was resumed.
The patient was started on zanubrutinib (80 mg 2 cp x2) while continuing IVIg with global improvement and absence of end of dose efficacy.
After 15 months, besides a clinical and hematological amelioration, a dramatic neurophysiological improvement also occurred.
Antibodies to IgM GM1 and GM2 were not detectable, whereas anti-disialosyl antibodies GD1a and GD1b persisted unchanged.

Discussion

To the best of our knowledge, this **is the first patient with WM-associated CANDA with clinical, hematological and neurophysiological benefit after zanubrutinib therapy**.

Paraproteinemic neuropathies



Prevalence and Spectrum of Neuropathies in a Cohort of 585 Patients With Immunoglobulin A Monoclonal Gammopathy

Valentine Perrain[1] | Valérie Molinier-Frenkel[2] | Jehan Dupuis[3] | Alain Créange[1,4,5] | Jean-Pascal Lefaucheur[5,6] | Thierry Gendre[1,4]

European Journal of Neurology, 2025; 32:e70087
https://doi.org/10.1111/ene.70087

Methods

Patients newly diagnosed with IgA gammopathy by immunofixation (Jan 2016 to Dec 2020) were retrospectively analyzed. The etiology was reviewed by two neurologists and classified into three groups:
(i) IgA-related neuropathies, (ii) IgA-unrelated neuropathies with an identified alternative etiology, and (iii) neuropathies of uncertain relationship with IgA (NURIA) based on a negative extensive work-up.

Results

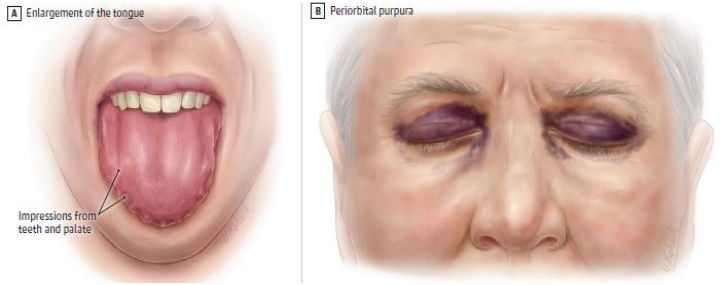
Among 585 patients with IgA gammopathy, 79 had neuropathy (14%).
Neuropathy was IgA-related in 10 patients (13%): 8 AL amyloidosis and 2 POEMS.
Core features: neuropathic pain, autonomic dysfunction, fatigue or weight loss, and a lambda light chain.
IgA-unrelated neuropathies were more frequent (*N* = 64, 81%), encompassing mainly chemotherapy-induced (*N* = 34) and diabetic (*N* = 15) neuropathies.

Conclusions

In IgA gammopathy, neuropathies have a low prevalence and a wide etiological spectrum.
AL amyloidosis and POEMS syndrome are rare but crucial to identify, as disease-modifying treatments are available.

AL amyloidosis:

highly specific **but not sensitive** signs **(15%)**



Macroglossia, periorbital purpura

When to suspect AL amyloidosis in a patient with neuropathy?

- Symmetric axonal sensory neuropathy especially when associated with:
  - bilateral carpal tunnel syndrome
  - **pain**
  - **autonomic nervous system** disorders (gastroparesis, weight loss, early satiety, diarrhea, impotence, urination urgency, retention; sweating abnormal, orthostatic hypotension)
- **Proteinuria** (with no history of diabetes or hypertension)
- **Hypertrophic cardiomyopathy** with preserved ejection fraction

→ **heart and kidney (>95%)**

- Hepatomegaly, increased ALP
- Smoldering myeloma or monoclonal gammopathy of uncertain significance, especially if **lambda** light chains

Diagnostic Challenges of Amyloidosis in Waldenström Macroglobulinemia

Giovanni Palladini, Giampaolo Merlini

Clinical Lymphoma, Myeloma & Leukemia, Vol. 13, No. 2, 244-6

IgM amyloidosis

A retrospective analysis of clinical features and treatment outcome in 21 patients with immunoglobulin M-related light-chain amyloidosis in Japan: a study from the Amyloidosis Research Committee

Shin-ichi Fuchida[1] · Mizuki Ogura[2] · Tadao Ishida[2] · Hiroyuki Hata[3] · Hiroshi Handa[4] · Nagaaki Katoh[5] · Chiaki Nakaseko[6] · Kazutaka Sunami[7] · Yuta Katayama[8] · Hironobu Nobata[9] · Kazuiku Oshiro[10] · Shinsuke Iida[11] · Yoshiki Sekijima[5] · Hironobu Naiki[12] · Chihiro Shimazaki[1]

AL amyloidosis associated with IgM paraproteinemia: clinical profile and treatment outcome

BLOOD, 15 NOVEMBER 2008 • VOLUME 112, NUMBER 10

Ashutosh D. Wechalekar,[1] Helen J. Lachmann,[1] Hugh J. B. Goodman,[1] Arthur Bradwell,[2] Philip N. Hawkins,[1] and Julian D. Gillmore[1]

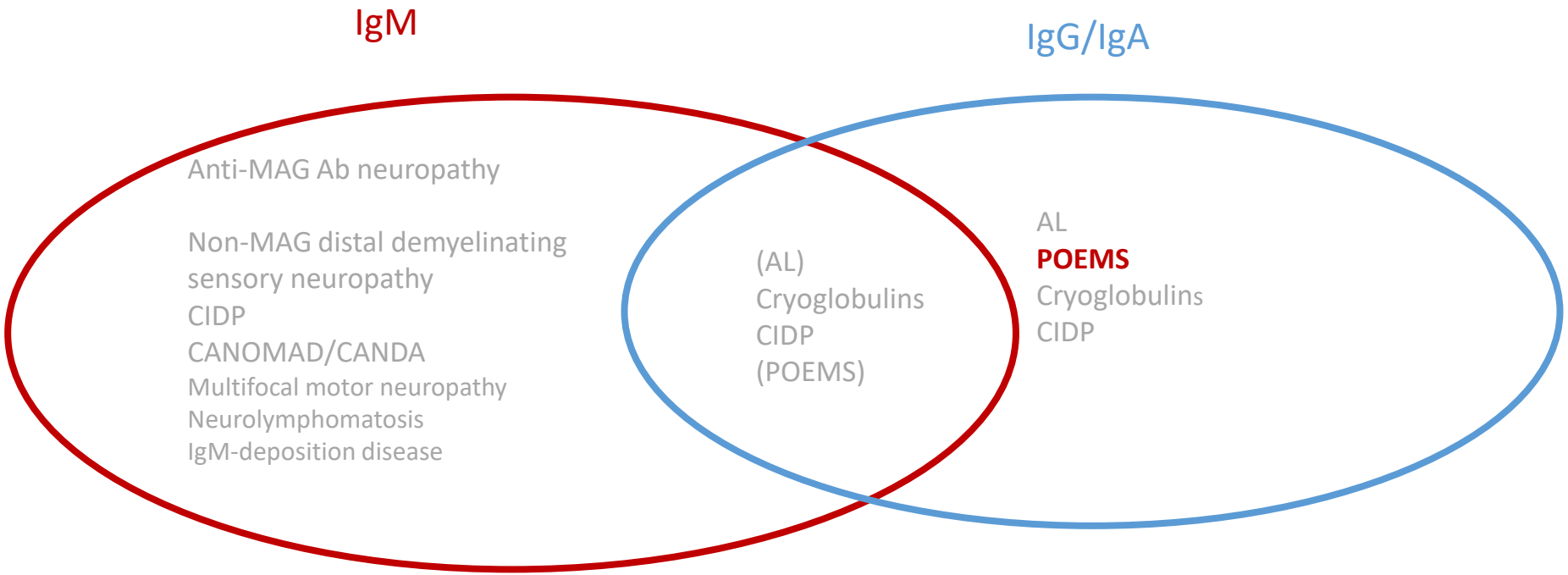
International Journal of Hematology (2023) 118:443–449

- An IgM clone is responsible for amyloidosis in approximately 4% to 7% of cases

- Patients with IgM–AL amyloidosis share many of the major characteristics of other patients with this disease. However, they are **more likely** to have amyloid deposits in lungs (3%-22), lymph nodes (21%-31%) **peripheral or autonomic neuropathy** (10%-38%).

- **Lambda light chain is less common (60% versus 80%)**
- Less than 1% of IgM-related amyloidosis have isolated peripheral nervous system involvement *(Palladini G, personal communication)*

Paraproteinemic neuropathies



POEMS syndrome: diagnostic criteria

TABLE 1 Criteria for the diagnosis of POEMS syndrome.[a]

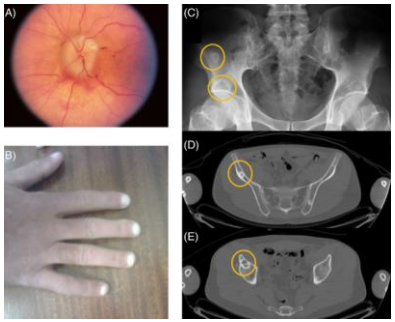
Mandatory major criteria	1. Polyneuropathy (typically demyelinating)
	2. Monoclonal plasma cell-proliferative disorder (almost always λ)
Other major criteria (one required)	3. Castleman disease[a]
	4. Sclerotic bone lesions
	5. Vascular endothelial growth factor elevation
Minor criteria	6. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)
	7. Extravascular volume overload (edema, pleural effusion, or ascites)
	8. Endocrinopathy (adrenal, thyroid,[b] pituitary, gonadal, parathyroid, pancreatic[b])
	9. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails)
	10. Papilledema
	11. Thrombocytosis/polycythemia[c]
Other symptoms and signs	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin B_{12} values

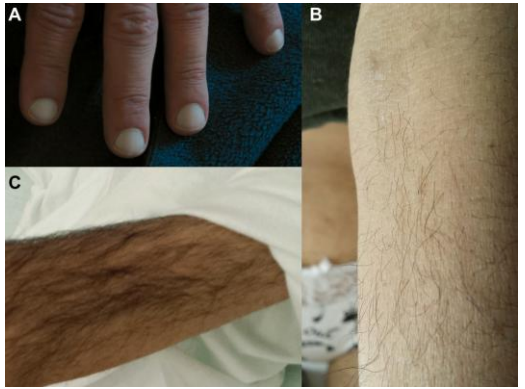
Am J Hematol. 2023;98:1934–1950.

Misdiagnosed with CIDP!

Both mandatory criteria as well as 1 major criterion and 1 minor criterion are required for diagnosis

Prevalence 0.3 per 100 000 population in Japanese nationwide survey
(Suichi T 2019)





THROMBOCYTOSIS DISTINGUISHES POEMS SYNDROME FROM CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

ELIE NADDAF, MD,[1] ANGELA DISPENZIERI, MD,[2] JAY MANDREKAR, MD,[3] and MICHELLE L. MAUERMANN, MD[1]

Muscle Nerve **52**: 658–659, 2015

- 136 POEMS patients and 67 CIDP patients

- There was a highly significant difference in platelet count between the 2 groups with a mean of 504,162/µl and a median of 467,000/µl in patients with POEMS, as compared with a mean of 280,627 and a median of 275,000 in patients with CIDP ($P < 0.0001$)

- The presence of thrombocytosis in a patient with progressive sensorimotor neuropathy is highly suggestive of POEMS syndrome since **only 1.5% of CIDP patients have thrombocytosis compared with more than 50% of POEMS patients**

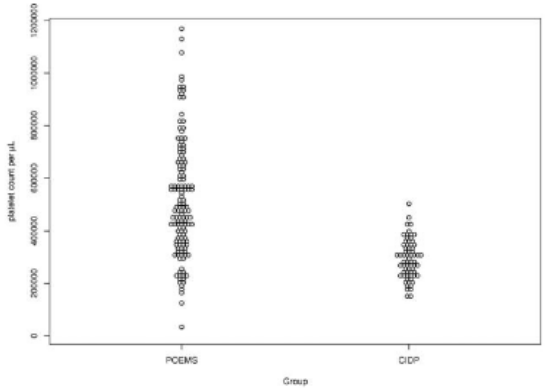


FIGURE 1. Dot plot shows platelet counts of patients with POEMS syndrome vs. patients with CIDP.

Clinical characteristics, risk factors, and outcomes of POEMS syndrome

A longitudinal cohort study

Stephen Keddie, MRCP, David Foldes, MRCP, Francisca Caimari, PhD, Stephanie E. Baldeweg, PhD, Joshua Bomsztyk, MRCP, Oliver J. Ziff, MRCP, Janev Fehmi, MRCP, Aviva Cerner, Zane Jaunmuktane, FRCPath, Sebastian Brandner, FRCPath, Kwee Yong, PhD, Hadi Manji, PhD, Aisling Carr, PhD, Simon Rinaldi, PhD, Mary M. Reilly, PhD, Shirley D'Sa, PhD, and Michael P. Lunn, PhD

Neurology® 2020;95:e268-e279. doi:10.1212/WNL.0000000000009940

- 100 patients, median follow-up of 59 months (range, 1-252)
- **Polyneuropathy:** was length-dependent in 93% and painful in 75%.
  54% of patients initially misdiagnosed with CIDP!
  At diagnosis, 35% of patients were wheelchair or bedbound
- **Organomegaly** (63%): 42% lymphadenopathy, 31% splenomegaly, 23% hepatomegaly
- **Endocrinopathy** (68%): **hypogonadism (72%),** hypothyroidism (45%), adrenal insufficiency (15%)
- **M protein**: IgG or IgA, 98% carrying lambda light chain (only 1 kappa). 55 found on serum protein electrophoresis, **immunofixation** positive in additional 23 patients. 21% had both negative SPE and immunofixation a monoclonal plasma cell disorder was confirmed in 11 of these cases through bone marrow biopsy and 10 targeted plasmacytoma biopsy.
- **Skin** (69%): acrocyanosis (46%), hypertrichosis (25%) and glomerular hemangiomata (23%). Scleroderma-like skin thickening

- **CNS**: 9 patients had a stroke, 7 ischemic and 2 subarachnoid hemorrhages; in 3 patients the stroke was the presenting feature
- **Extravascular volume overload (70%):** peripheral edema, pleural effusion, and ascites
- **Median** pretreatment **VEGF** was 3,594 pg/mL (200-30,101 pg/mL):

Increased VEGF: anemia with low serum iron, chronic obstructive pulmonary disease or sleep apnea, connective tissue disease, pulmonary infection and low-grade non-Hodgkin lymphoma*(Pihan et al. Neurol Neuroimmunol Neuroinflamm. 2018)*
Suppressed VEGF: in patients recently treated with steroids for incorrectly diagnosed CIDP.

Pachymeningeal involvement in POEMS syndrome: MRI and histopathological study

Chiara Briani,[1] Marny Fedrigo,[2] Renzo Manara,[3] Chiara Castellani,[2] Renato Zambello,[4] Valentina Citton,[3] Marta Campagnolo,[1] Chiara Dalla Torre,[1] Marta Lucchetta,[1] Enrico Orvieto,[5] Antonino Rotilio,[6] Sabrina Marangoni,[7] Stefania Magi,[8] Davide Pareyson,[9] Igor Florio,[10] Elena Pegoraro,[1] Gaetano Thiene,[2] Leontino Battistin,[1,11] Fausto Adami,[4] Annalisa Angelini[2]

J Neurol Neurosurg Psychiatry 2012;**83**:33–37

- 11 patients (7 men, 4 women; mean age at diagnosis 54.45 years)
  9 controls (multiple myeloma)
  Brain and spine 1.5 T MRI
- 9/11 pachymeningeal involvement; none had spinal involvement

- Histopathological study (2 POEMS, 2 rheumatological pachymeningitis, 2 meningioma, 3 healthy specimens). In POEMS:
  - hyperplasia of meningothelial cells
  - neovascularisation
  - obstructive vessel remodelling, without inflammation

- VEGF and VEGF receptor were strongly coexpressed on endothelium, smooth-muscle cells of arterioles and meningothelial cells

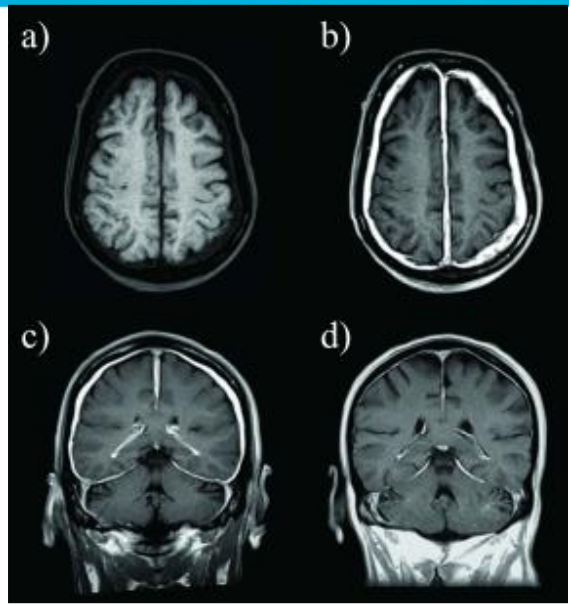
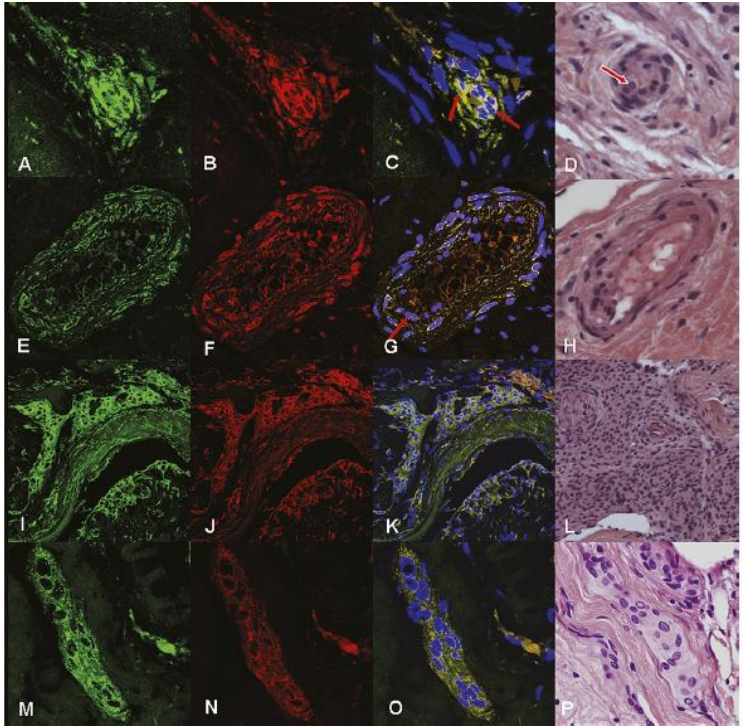


Figure 1 Axial T1 weighted images of patient 1 above the lateral ventricles (A) before and (B) after contrast medium administration showing marked pachymeningeal thickening with intense contrast enhancement. Coronal contrast-enhanced T1 weighted images of (C) patient 1 and (D) patient 3 revealing severe and moderate pachymeningeal involvement, respectively.

VEGFR-2 and
VEGF endothelial cells



luminar obstruction owing
to endothelial proliferation

thickening of the tunica media

meningothelial cells
proliferation without inflammatory infiltrate

VEGFR-2 and
VEGF meningothelial cells

Figure 2 Vascular endothelial growth factor receptor (VEGFR)-2 and vascular endothelial growth factor (VEGF) expression in pachymeningitis and meningothelial cells: confocal photomicrograph depicting expression of (A, E) VEGFR2 and (B, F) VEGF. VEGF and VEGFR2 (C, G) figures have been merged; expression of colocalisation was evidenced by the yellow colour on the endothelial cells (C) (arrows) and completed with TO-PRO3 fluorocrome (blue) for cell nuclei, and on smooth muscle cells in the pachymeningeal artery (G) (arrow) (zoom from original magnification of 40×). H&E on the contiguous sections shows the luminar obstruction owing to endothelial proliferation (arrow) (d) (original magnification 40×) and thickening of the tunica media (H). (I, M) Expression of VEGFR2 and (J, N) VEGF on meningothelial cells. (L, P) H&E on the same slides showing meningothelial cells proliferation without inflammatory infiltrate (original magnification 20× and 40× respectively). The merged image shows that both markers are coexpressed on the cytoplasm and the cytoplasmatic membrane (K, O) (original magnification of 40×). Zoom from original magnificatioin (M, N, O).

Frequent central nervous system, pachymeningeal and plexus MRI changes in POEMS syndrome

Journal of Neurology (2019) 266:1067–1072

Oliver J. Ziff[1,2] · Chandrashekar Hoskote[3] · Stephen Keddie[1] · Shirley D'Sa[4] · Indran Davangnanam[3] · Michael P. T. Lunn[1,2,5]

- Retrospective study of 77 POEMS syndrome

- 41 had MRI brain and 29 had MRI spine
- 33 CIDP patients (control group): 12 both brain and spine MRI, 7 had solely MRI brain and 14 had MRI spine

- **29/41 (71%) POEMS had diffuse meningeal thickening of the cerebral convexities and falx**
  17/41 (41%) had vascular abnormalities including white-matter disease, of which 4 had established infarcts
  17/29 (58.6%) had thickening of the brachial and lumbosacral plexus at MRI

- **CIDP (controls): none of the 19 CIDP patients had meningeal thickening at MRI brain ($p < 0.0001$ vs. POEMS)**
  9/26 (34.6%) CIDP patients had thickening and enhancement of nerve roots ($p = 0.06$ vs. POEMS), involving the brachial plexus in 7, lumbosacral plexus in 1 and both the brachial and lumbosacral plexi in the remaining 1 patient

- **Current diagnostic criteria for POEMS syndrome do not include neuroimaging features**

⇩

To improve diagnostic speed, the POEMS diagnostic criteria may benefit from the addition of pachymeningeal thickening as a minor criterion

May pachymeningeal thickness changes be a marker of therapy response?

Pachymeningeal Involvement in POEMS Syndrome: Longitudinal Follow-Up Study and Correlation With Therapeutic Response

Journal of the Peripheral Nervous System, 2026; 31:e70098
https://doi.org/10.1111/jns.70098

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Aims

- To assess pachymeningeal changes in POEMS patients in response to therapy
- To analyze possible correlation with sVEGF, neurological and hematological findings

Longitudinal prospective study

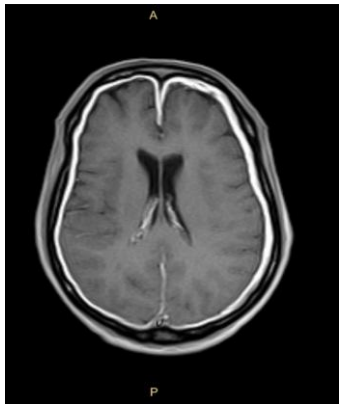
Patients: 18 (9 M/9 F), mean age 54.5 yrs (±9.5)
Monoclonal gammopathy: IgG/lambda or IgA/lambda: 17, IgM lambda 1 patient
Follow-up: mean 4.3 yrs, range 0.75-14.9
Median disease duration at first MRI: 10.7 months (±13.9)
Hematological response: according to Dispenzieri A. *Am J Hematol. 2017;92(8):814-829.*

Brain MRI

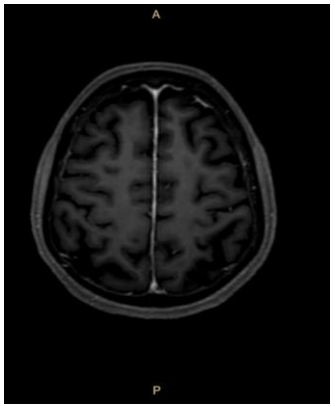
Median disease duration at first MRI (months): 10.7 months median 2.0, range 0-42 months)
Median time between baseline MRI and last follow-up MRI: 64.4±55.5 months (median 44)
Four patients, referred from other centers, underwent the first MRI after therapy initiation.

Qualitative brain MRI analysis was seen independently by 2 experienced neuroradiologists and jointly reviewed

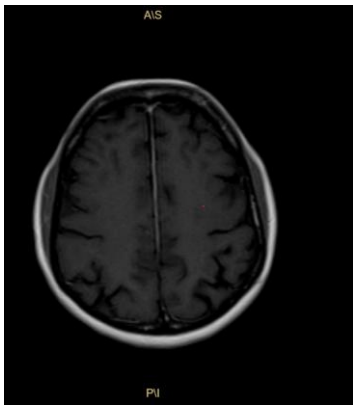
Based on pachymeningeal involvement:
3: diffuse thickening
2: moderate thickening
1: mild thickening



DIFFUSE THICKENING



MODERATE THICKENING



MILD THICKENING

Results

- At baseline, 17/18 patients had pachymeningeal thickening (PT)

- At follow-up, PT decreased in 7 (39%) (2 complete normalization), remained stable in 10 (56%), and increased in one

Neurological response

- Among the 7 patients with decreased PT, 5 (83%) showed neurological improvement
  Of the 10 patients with stable MRI findings, 6 remained stable, 3 showed clinical improvement, and one progressed

- The degree of PT at baseline was unrelated to neurological outcome

Hematological response

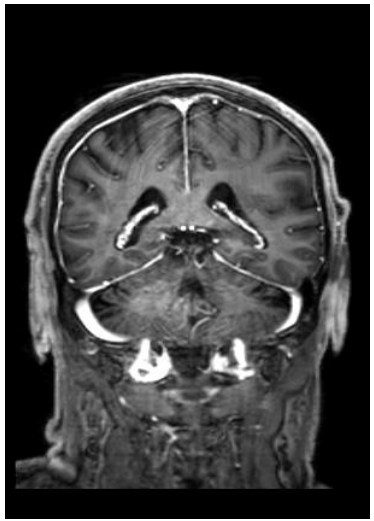
- Among the 12 patients with hematologic improvement, 50% showed PT reduction, 5 (42%) stability and one (8%) an increase. All the 5 unresponsive patients (100%) showed PT stability

- The degree of PT at baseline was unrelated to hematologic response

- VEGF reduction was independent of pachymeningeal changes (no significant differences between patients with PT reduction and those with stable or increased PT)

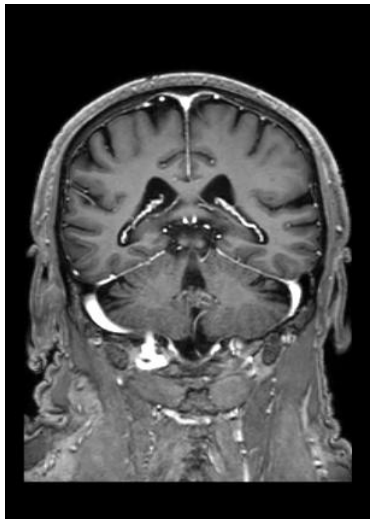
70 yr-old, Onset at January 2019 sensory motor neuropathy
IgGk and IgG lambda, thrombocytosis, impotence, gynecomastia, distal edema, redness in the lower limbs
Therapy: velcade-dexamethasone plus radiotherapy for an isolated rib lesion

S-VEGF: 98.200 ng/L (v.n. 62 - 707)



September 2019

Patient in complete response



September 2023

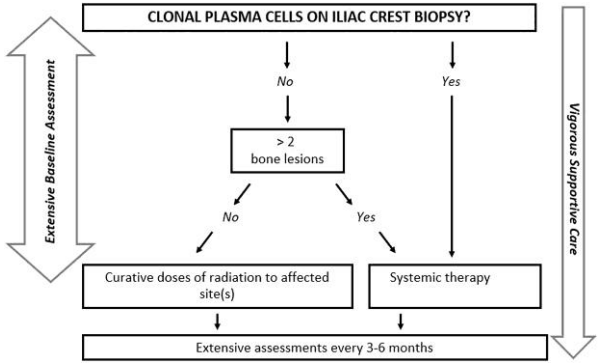
Discussion

- PT is common at diagnosis
- Pachymeningeal **changes seem slower to occur than biochemical hematological changes**
- Specifically, patients with hematologic improvement had a higher rate of PT reduction (50%) compared to non-responders (0%). Indeed, those with neurologic improvement also had a higher frequency of radiologic improvement (62.5%) than those with clinical stability or progression
- **Unlike VEGF, a marker of treatment response, PT changes do not seem to offer reliable monitoring utility**
- Pachymeningeal involvement in POEMS: possible diagnostic marker, less useful as marker of therapy response

POEMS syndrome: Update on diagnosis, risk-stratification, and management

Am J Hematol. 2023;98:1934–1950.

Regimen	Outcome
Radiation	50%–70% of patients have significant clinical improvement
Melphalan-dexamethasone	81% hematologic response rate; 100% with some neurologic improvement
Corticosteroids	50% of patients have significant clinical improvement
Cyclophosphamide-dexamethasone	At least 50% of patients have significant improvement
ASCT	100% of surviving patients have significant clinical improvement
Thalidomide-dexamethasone	Reported responses, but not recommended as first line due to risk of neuropathy
Lenalidomide-dexamethasone	75%–95% patients have significant clinical improvement and VEGF improvement
Bortezomib	Nearly 100% in combination with cyclophosphamide and dexamethasone. Caution regarding risk of worsening neuropathy. Usually used after first line.
Bevacizumab	No consistent benefit



*Take home message

♦ Paraproteinemic Neuropathies: widespread range of manifestations, ranging from slowly progressive polyneuropathy with anti-MAG antibody to subacute rapidly progressive forms as in POEMS syndrome

♦ The monoclonal gammopathy **isotype**, the accompanying **light chain**, the **neurophysiological** study, the presence of systemic symptoms or biochemical markers, help guide the correct diagnosis

♦ **Rapid** progression, a mixed axonal and demyelinating neuropathy: possibility of amyloidosis, especially if neuropathic pain or autonomic dysfunction are present, or cryoglobulinemia

♦ IgG and IgA neuropathies are more heterogeneous, sometimes casual association

♦ If the clinical picture is CIDP-like, POEMS must be excluded (IgG and IgA lambda)! IgM rare, but possible

♦ Where neurotoxic therapy has been used, chemotherapy-induced neuropathy, which is almost always axonal, needs to be considered, based on the temporal pattern, characteristics and electrophysiology

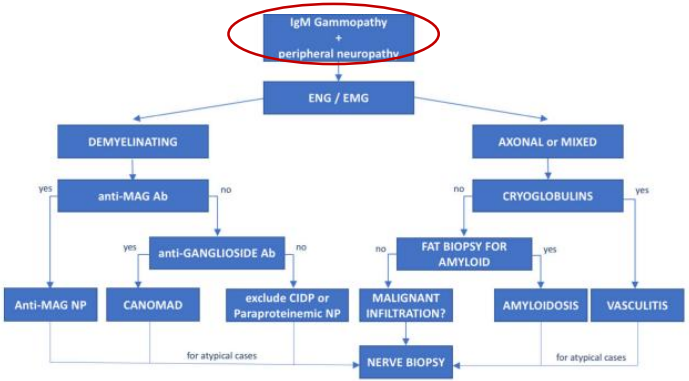
Review

From Biology to Treatment of Monoclonal Gammopathies of Neurological Significance

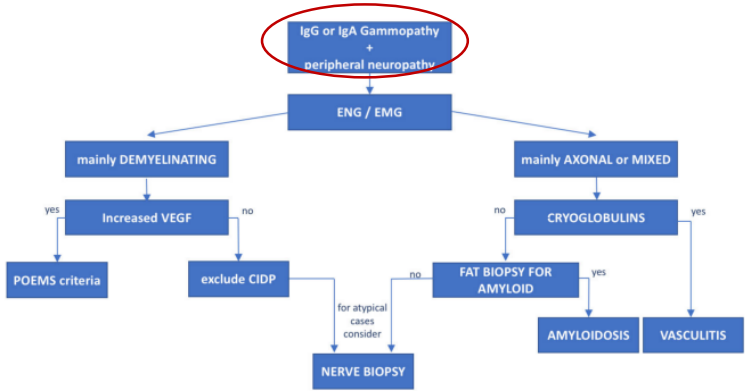
Andrea Visentin [1,*], Stefano Pravato [1], Francesca Castellani [2], Marta Campagnolo [2], Francesco Angotzi [1], Chiara Adele Cavarretta [1], Alessandro Cellini [1], Valeria Ruocco [1], Alessandro Salvalaggio [2], Alessandra Tedeschi [3], Livio Trentin [1] and Chiara Briani [2]

Cancers **2022**, *14*, 1562. https://doi.org/10.3390/cancers14061562

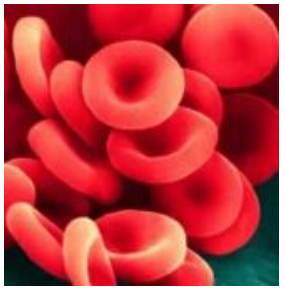
Diagnostic flowchart IgM neuropathy

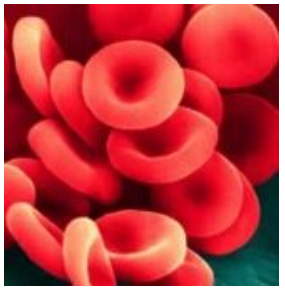


Diagnostic flowchart IgG/IgA neuropathy




Thank You





PROPOSTA di studio collaborativo:
Raccolta retrospettiva italiana di pazienti con Neuropatia con Ab ANTI-MAG trattati con inibitori del BTK?

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