

## ORIGINAL ARTICLE

# A diagnostic score for anti-myelin-associated-glycoprotein neuropathy or chronic inflammatory demyelinating polyradiculoneuropathy in patients with anti-myelin-associated-glycoprotein antibody

Pietro E. Doneddu<sup>1</sup>  | Marta Ruiz<sup>1</sup> | Elisa Bianchi<sup>2</sup> | Giuseppe Liberatore<sup>1</sup>  |  
Fiore Manganelli<sup>3</sup>  | Dario Cocito<sup>4</sup> | Giuseppe Cosentino<sup>5</sup> | Luana Benedetti<sup>6</sup>  |  
Girola A. Marfia<sup>7</sup> | Massimiliano Filosto<sup>8</sup>  | Chiara Briani<sup>9</sup>  | Claudia Giannotta<sup>1</sup> |  
Eduardo Nobile-Orazio<sup>1,10</sup> 

<sup>1</sup>Neuromuscular and Neuroimmunology Service, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy

<sup>2</sup>Laboratorio di Malattie Neurologiche, IRCCS-Istituto Mario Negri, Milan, Italy

<sup>3</sup>Department of Neuroscience, Reproductive Sciences and Odontostomatology, University of Naples 'Federico II', Naples, Italy

<sup>4</sup>Presidio Sanitario Major, Istituti Clinici Scientifici Maugeri, Turin, Italy

<sup>5</sup>IRCCS Foundation C. Mondino National Neurological Institute, Pavia, Italy

<sup>6</sup>Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa and IRCCS AOU San Martino-IST, Genoa, Italy

<sup>7</sup>Dysimmune Neuropathies Unit, Department of Systems Medicine, Tor Vergata University of Rome, Rome, Italy

<sup>8</sup>Department of Clinical and Experimental Sciences, NeMO-Brescia Clinical Center for Neuromuscular Diseases, University of Brescia, Brescia, Italy

<sup>9</sup>Neurology Unit, Department of Neuroscience, University of Padova, Padova, Italy

<sup>10</sup>Department of Medical Biotechnology and Translational Medicine, Milan University, Milan, Italy

## Correspondence

Eduardo Nobile-Orazio, Department of Medical Biotechnology and Translational Medicine (BIOMETRA), Milan University, 2nd Neurology, IRCCS Humanitas Research Hospital, Via Manzoni 56, Rozzano, Milan 20089, Italy.  
Email: [eduardo.nobile@unimi.it](mailto:eduardo.nobile@unimi.it)

## Funding information

The study was supported by a grant from Ministero della Salute, Ricerca Finalizzata (Progetto RF-2016-02361887). The study derives from a project initially supported by Regione Lombardia, Italy (Rare Disease Project 2013 "A Database from Lombardia on CIDP"), and by the GBS-CIDP Foundation International (USA). The study was also supported by unrestricted grants from Kedrion Biopharma (Italy).

## Abstract

**Background and purpose:** A diagnostic score was developed to discriminate anti-myelin-associated-glycoprotein (MAG) neuropathy from chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and applied it to patients with atypical anti-MAG neuropathy.

**Methods:** The clinical and electrophysiological features of patients with a diagnosis of typical anti-MAG neuropathy were compared to those of patients with a diagnosis of CIDP. The association of each feature with the diagnosis was assessed in the two groups. Features showing a significant association with the diagnosis were included in a multivariable logistic regression model and adjusted odds ratios were estimated for each feature. A score ranging from 1 to 3 was applied to each feature based on the magnitude of the estimated odds ratios. The score was then applied to patients with a clinical diagnosis of CIDP who also had high anti-MAG antibody titers (CIDP-MAG).

Pietro E. Doneddu and Marta Ruiz contributed equally to the study.

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CSL Behring (Italy) and Humanitas Clinical and Research Institute (Milan, Italy). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Results:** Thirty-one anti-MAG neuropathy patients, 45 typical CIDP patients and 16 CIDP-MAG patients were included. Scores in anti-MAG antibody patients ranged from 1 to 5 and in CIDP patients from -7 to -1. Using the score, 4/16 CIDP-MAG patients were diagnosed to have anti-MAG neuropathy and 12/16 patients to have CIDP. Response to intravenous immunoglobulin in the CIDP-MAG patients classified as CIDP was similar to that of definite CIDP patients and higher than that of anti-MAG neuropathy patients.

**Conclusions:** Our score allowed an accurate discrimination to be made, amongst patients with anti-MAG antibodies, of those affected by CIDP and the patients with anti-MAG neuropathy. This score may help proper treatment to be chosen for patients with anti-MAG antibodies with a CIDP-like presentation.

#### KEYWORDS

chronic inflammatory demyelinating polyradiculoneuropathy, antibody, diagnostic criteria, CIDP, MAG, neuropathy

## INTRODUCTION

Neuropathy associated with anti-myelin-associated-glycoprotein (MAG) antibodies is a chronic demyelinating neuropathy typically characterized by a slowly progressive, predominantly sensory, distal impairment, associated with sensory ataxia and tremor [1]. Nerve conduction studies reveal sensory abnormalities compatible with demyelination and abnormally increased distal latencies in motor nerves, whilst motor nerve conduction blocks are uncommon [2]. Diagnosis rests upon this typical clinical and electrophysiological spectrum, the presence of immunoglobulin M (IgM) monoclonal gammopathy and an increased titer of serum anti-MAG antibodies [3,4]. Specific diagnostic criteria for anti-MAG neuropathy, beside the presence of high titers of anti-MAG antibodies, have not been established, however.

A quite variable, although small, proportion of patients with anti-MAG antibodies present with an atypical phenotype [5–8] that is often similar to the typical presentation of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) [5,6]. It is still unclear whether these atypical phenotypes are part of the spectrum of anti-MAG neuropathy or represent false-positive patients with different neuropathies. Several studies failed to find an anti-MAG antibody titer cut-off able to distinguish the two groups of patients [5–8]. Understanding whether these patients have an anti-MAG antibody neuropathy or a different neuropathy may have relevant therapeutic implications. Moreover, the European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) consider the presence of anti-MAG antibodies as an exclusion criterion for the diagnosis of CIDP [9].

Sera from 80 patients with anti-MAG neuropathy and 383 subjects with other neuropathies or healthy subjects were recently analyzed to assess the best anti-MAG antibody titer cut-off with enzyme-linked immunosorbent assay (ELISA) for the diagnosis of anti-MAG neuropathy [10]. It was found that, using the Bühlmann assay, the best combination of sensitivity/specificity was reached at a threshold of 7000 BTU (Bühlmann titer units) [10]. A similar

discriminative threshold was not reported in a large French study, however, where 17% of the patients with a titer of anti-MAG antibodies  $\geq 10,000$  BTU had an atypical presentation [5].

Identifying the proper diagnostic boundaries of anti-MAG neuropathy is necessary to avoid an incorrect diagnosis in the few patients with other neuropathies in whom anti-MAG antibodies may be detected and who might be excluded from appropriate therapy. It is also important to assess whether response to therapies in atypical anti-MAG neuropathy is similar to that of the typical form or, instead, more similar to that of CIDP.

## Aim of the study

The aim of this study was to develop a specific diagnostic score (CIDP-MAG score), based on clinical and electrophysiological features, to distinguish anti-MAG neuropathy from CIDP in patients with demyelinating neuropathy and anti-MAG antibodies. In order to evaluate its diagnostic validity, this score was applied in three patient populations: (i) patients with a typical anti-MAG neuropathy, (ii) patients with typical CIDP and (iii) patients with atypical anti-MAG neuropathy with a CIDP-like presentation (CIDP-MAG). The response to intravenous immunoglobulin (IVIg) in patients with CIDP-MAG was also compared with that in patients with typical CIDP or typical anti-MAG neuropathy.

## METHODS

### Identification of disease cohorts

Three patient groups were retrospectively identified and included in our study: (i) 31 non-selected patients diagnosed with a typical anti-MAG neuropathy followed at our center (Humanitas Research Hospital), (ii) 45 non-selected patients with a definite diagnosis of typical CIDP followed at our center and (iii) 16 non-selected patients

with a clinical diagnosis of CIDP included in the Italian CIDP database in whom a monoclonal IgM paraprotein and high titers of anti-MAG antibodies (BTU > 7000) were found. The first two groups were studied to establish the various weights for each feature. The third group of patients served as the validation cohort.

The 31 patients with anti-MAG neuropathy were diagnosed at our center between 1995 and 2019 on the basis of the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) guidelines for IgM paraproteinemic demyelinating neuropathy together with the presence of anti-MAG IgM antibodies (BTU > 7000) [4]. All these patients underwent routine follow-up visits every 6 months. The 45 patients with definite CIDP were diagnosed at our center between 1998 and 2019. All these patients had a definite diagnosis of typical CIDP according to the EAN/PNS criteria [9] were negative for the presence of IgM monoclonal gammopathy and anti-MAG antibodies, and underwent routine follow-up visits at least every 6 months. The third group consisted of 16 of the 267 patients enrolled in the Italian CIDP database who had been tested in our laboratory and found to have anti-MAG antibodies (at titers over 7000 BTU). The latter group of patients (CIDP-MAG) was excluded from the CIDP database since the diagnosis of CIDP is not allowed by the EAN/PNS criteria in the presence of anti-MAG antibodies [9]. The study was approved by the Ethical Committee of each participating center and the study conforms with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from all participants at enrollment.

## Clinical features

Clinical assessment consisted in a complete neurological examination including the presence of ataxia, tremor, cranial nerve involvement, presence and distribution of weakness and sensory symptoms. Type of clinical onset and progression was assessed. Relapsing–remitting course was defined in the presence of a clinical worsening after an initial improvement that was not related to reduction or discontinuation of therapy. Clinical, laboratory and electrophysiological data of the patients with CIDP were retrieved from the Italian CIDP database, whilst data of patients with anti-MAG neuropathy were retrieved from medical charts.

## Electrophysiology

Electrophysiological studies included motor and sensory nerve conduction studies of the four limbs. For demyelination the EAN/PNS criteria were considered [9]. Terminal latency index (TLI) was calculated using the formula distal conduction distance (mm)/(conduction velocity [m/s] × distal motor latency [ms]) [2,11,12]. Distal conduction distances, between the recording electrode over the motor point and the site of distal nerve stimulation, were 60 mm for median and ulnar nerves, 80 mm for peroneal nerves and 85 mm for tibial nerves.

## Laboratory findings

Immunoglobulin M monoclonal gammopathy was detected by serum electrophoresis and immunofixation at the time of diagnosis. A commercially available ELISA method (Bühlmann Laboratories AG) was used for the measurement of anti-MAG antibody. Results were expressed in arbitrary units (BTU). Serum dilutions were used to measure antibody titers above the maximal value considered by the assay (70,000 BTU). Most of the patients with typical CIDP and CIDP-MAG had been tested for anti-MAG antibodies after neuropathy treatment, whilst all the patients with typical anti-MAG neuropathy were tested at diagnosis.

## Selection of features used to define the diagnostic score

To establish a score that might help in distinguishing anti-MAG neuropathy from CIDP, lists of clinical and electrophysiological features that are more likely to be present in anti-MAG neuropathy (see below) [4–8,13] and features that are more often encountered in CIDP and that are not part of the anti-MAG neuropathy typical phenotype were arbitrarily selected from the literature [9,13]. There is agreement in the literature on the clinical definition of typical anti-MAG neuropathy, which is described as a distal, chronic, slowly progressive, symmetric, predominantly sensory polyneuropathy, with ataxia, relatively mild or no weakness, and often upper limb tremor [1,4–8,11–13]. Nerve conduction studies in patients with typical anti-MAG neuropathy may reveal specific electrophysiological features which can help to distinguish it from CIDP, typically uniform symmetrical and predominantly distal reduced conduction velocity (TLI < 0.25) without conduction block [1,4–8,11–13]. Four features (three clinical and one electrophysiological) supportive of the diagnosis of anti-MAG neuropathy were therefore arbitrarily chosen (Table 1). The definition of CIDP is more complex given the existence of a typical CIDP form and several variants. Based on the published literature and our own clinical expertise, three features (two clinical and one electrophysiological) supportive of the diagnosis of CIDP and instead unsupportive of anti-MAG neuropathy diagnosis were selected (Table 1). A diagnostic score (CIDP-MAG score) based on seven supportive and unsupportive features was developed. For this analysis the clinical and electrophysiological data of the patients at the time of diagnosis were used. The score was then applied to patients with CIDP-MAG.

## Response to intravenous immunoglobulin in atypical anti-MAG neuropathy

Response to IVIg in patients with CIDP-MAG was assessed. Given the reported different frequency in the response to IVIg in patients with CIDP (>50%) [14] and anti-MAG neuropathy (<20%) [15,16] the frequency of response to IVIg was used as a possible supportive

**TABLE 1** Supportive features for the diagnosis of anti-MAG neuropathy or CIDP in patients with demyelinating neuropathy and anti-MAG antibodies

Supportive features for anti-MAG neuropathy
Clinical
a. Length-dependent <sup>a</sup> , symmetric, predominantly <sup>b</sup> or purely sensory polyneuropathy
b. Ataxia
c. Tremor
Electrophysiology
a. TLI $\leq 0.25$ in at least two different motor nerves
Supportive features for CIDP
Clinical
a. Relapsing–remitting <sup>c</sup> course or acute <sup>d</sup> –subacute <sup>e</sup> clinical onset
b. Proximal muscle weakness
Electrophysiology
a. Motor conduction blocks

Abbreviations: CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; MAG, myelin-associated-glycoprotein; TLI, terminal latency index.

<sup>a</sup>Length-dependent pattern was defined as symptoms and signs starting distally in the four limbs, without proximal limb–trunk–face involvement.

<sup>b</sup>Predominantly sensory polyneuropathy was defined in the presence of a clinical picture dominated by sensory symptoms and signs with only mild motor deficits.

<sup>c</sup>Relapsing–remitting course was defined in the presence of a clinical worsening after an initial improvement that was not related to a suspension or reduction of the dose of therapy.

<sup>d</sup>Acute onset was defined in the presence of signs and symptoms appearing abruptly and progressing rapidly with nadir within 1 month.

<sup>e</sup>Subacute onset was defined in the presence of signs and symptoms of definite duration that appeared progressively with nadir beyond 1 month.

diagnostic criterion in patients with CIDP-MAG. Response to other therapies, such as rituximab or plasma exchange, was not analysed as both anti-MAG neuropathy and CIDP may respond to these therapies [1,4,5,9,17,18]. Response to treatment was defined as a subjective improvement that was objectively confirmed by a sustained (at least 6 months) increase of at least 2 points in the Medical Research Council (MRC) sum score (range 0–60) or at least 1 point in the Inflammatory Neuropathy Cause and Treatment (INCAT) score (range 0–10) [9,19].

## Statistical methods

Descriptive statistics were used in patients with anti-MAG neuropathy, typical CIDP and CIDP-MAG. Categorical variables were described by using percentages, whilst continuous variables were described by using mean, median and range. Differences amongst the three groups of patients were assessed with the chi-squared test for categorical variables and the Kruskal–Wallis test for continuous

variables. In order to define a score to discriminate patients with typical anti-MAG neuropathy from patients with typical CIDP, the presence of each of the seven identified features was compared between the two groups using the chi-squared test (univariate analysis). Features showing a significant difference between the two groups were then included as independent variables in a multivariate logistic regression model, with the diagnosis (typical anti-MAG neuropathy vs. typical CIDP) as the dependent variable. Adjusted odds ratios (ORs) were estimated for each feature. For features associated with a higher probability of being diagnosed as anti-MAG neuropathy (supportive features) the OR was estimated modeling the probability of being diagnosed as anti-MAG neuropathy. The *p* value for the global Wald test and the Tjur R2 were also reported: a *p* value  $< 0.05$  for the global Wald test indicates that at least one variable of the model is statistically significant, whilst a *p* value  $\geq 0.05$  indicates that all variables of the model are not statistically significant; the Tjur R2 is a measure of the predictive ability of the model (the ability to make predictions that are close to the real value), with a score ranging from 0 (no predictive ability) to 1 (perfect predictive ability). For features associated with a higher probability of being diagnosed as typical CIDP (unsupportive features) the OR was estimated modeling the probability of being diagnosed as typical CIDP. A score ranging from 1 to 3 was then applied to each feature using the following categorization for the estimated OR: features with OR ranging from 1 to below 5 received a score of 1; features with OR ranging from 5 to below 10 received a score of 2; features with OR of 10 or above received a score of 3. Positive values were assigned to supportive features, whilst negative values were assigned to unsupportive features. For each patient, the total score was defined as the sum of scores of each feature that was detected in the patient. The best cut-off score was then selected as the score leading to the maximum level of diagnostic accuracy (maximum percentage of correctly classified observations). The score value that best discriminated typical anti-MAG neuropathy from typical CIDP was then applied to the group of patients with CIDP-MAG, in order to classify them as CIDP or anti-MAG neuropathy. Statistical analysis was performed using SAS version 9.4 (SAS Institute). The significance level was set to 0.05.

## RESULTS

The main demographic, clinical and laboratory characteristics of the three groups are illustrated in Table 2. The mean titer of anti-MAG antibodies in typical anti-MAG neuropathy patients was 60.398 BTU (range 8135–265.585) whilst in CIDP-MAG patients it was 53.320 BTU (range 8137–125.000; *p* = 0.3974). All the patients with definite typical CIDP were negative for anti-MAG antibodies. Although patients with typical CIDP had a younger age at onset, shorter disease duration and were more balanced in gender than patients with typical anti-MAG neuropathy and CIDP-MAG, none of the differences was statistically significant. Compared to the patients with anti-MAG neuropathy, at symptom onset patients with CIDP-MAG had a

**TABLE 2** Main demographic, clinical and laboratory characteristics of the patients with anti-MAG neuropathy, definite typical CIDP and CIDP-MAG

	Anti-MAG neuropathy (n = 31)	Definite typical CIDP (n = 45)	CIDP-MAG (n = 16)	p value
Gender (M:F)	25:6	27:18	13:3	NS
Age at onset, years, mean (range)	62 (40–69)	49.5 (35–72)	60.3 (44–75)	NS
Disease duration, years, mean (range)	9.3 (3–16)	7.5 (1.5–18)	8.8 (2–13)	NS
Anti-MAG antibodies titer (BTU)	68,337 (8135–274,908)	ND	53,320 (8137–125,000)	NS
MRC sum score at symptom onset, mean (range)	57.2 (50–60)	52.1 (40–60)	54.6 (42–60)	0.0031 <sup>a</sup>
I-RODS score at symptom onset, mean (range)	38 (26–48) <sup>b</sup>	34.4 (6–48) <sup>c</sup>	35.3 (9–48) <sup>d</sup>	0.0002 <sup>a</sup>
INCAT disability score at symptom onset, mean (range)	5.2 (2–6)	7 (5–10)	6.8 (3–10)	0.0012 <sup>a</sup>

Abbreviations: BTU, Bühlmann titer unit; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; F, female; INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory Rasch-built Overall Disability Scale; M, male; MAG, myelin-associated-glycoprotein; MRC, Medical Research Council; ND, not detected; NS, not significant.

<sup>a</sup>Anti-MAG neuropathy vs. CIDP-MAG.

<sup>b</sup>I-RODS obtained from nine patients.

<sup>c</sup>I-RODS obtained from 12 patients.

<sup>d</sup>I-RODS obtained from six patients.

**TABLE 3** Frequency of supportive/unsupportive features and total CIDP-MAG diagnostic score in patients with anti-MAG neuropathy, definite CIDP and CIDP-MAG

Supportive and unsupportive features	Anti-MAG neuropathy (n = 31)		Definite CIDP (n = 45)		CIDP-MAG (n = 16)	
	n	%	n	%	n	%
Length-dependent symmetric predominant or purely sensory polyneuropathy	30	96.7	4	8.8	5	31.2
Ataxia	27	87	17	37.7	7	43.7
Tremor	23	74.1	6	13.3	2	12.5
TLI ≤ 0.25 in at least two different motor nerves	20	64.5	9	20	8	50
Relapsing–remitting or acute–subacute course	2	6.4	34	75.5	9	56.2
Proximal muscle weakness	0	0	45	100	11	68.7
Motor conduction blocks	0	0	30	66.6	4	25
	<b>Median</b>	<b>Range</b>	<b>Median</b>	<b>Range</b>	<b>Median</b>	<b>Range</b>
CIDP-MAG score	4	1; 5	–4	–7; –1	–2	–6; 3

Abbreviations: CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; MAG, myelin-associated-glycoprotein; TLI, terminal latency index.

more severe motor impairment (MRC 54.6 vs. 57.2;  $p = 0.0031$ ) and more severe disability measured with the Inflammatory Rasch-built Overall Disability Scale (35.3 vs. 38;  $p = 0.0002$ ) and INCAT (6.8 vs. 5.2;  $p = 0.0012$ ). No difference in terms of motor impairment and disability at symptom onset was instead found between patients with typical CIDP and CIDP-MAG.

Table 3 summarizes the frequency of each supportive and unsupportive feature in the three groups. Four patients with definite typical CIDP were found to have a length-dependent, predominantly sensory neuropathy at the time of diagnosis (Table 3). Both had acute or subacute onset of symptoms with involvement of cranial

nerves and all of them developed a sensory-motor polyneuropathy involving proximal and distal segments at the four limbs within 1 year of disease onset. When comparing typical anti-MAG neuropathy patients with typical CIDP patients in univariate analysis, a highly significant difference between the proportion of patients with and without supportive and unsupportive features was confirmed ( $p < 0.0001$  for each of the seven features). All seven features were therefore included in the multivariate logistic regression model used to define the diagnostic score. In the multivariate model none of the selected features was found to be significantly associated with the diagnosis (global Wald test,  $p$  value 0.9953), but this may perhaps

be explained by the small sample size. However, point estimates confirmed the expected direction of the association for supportive and unsupportive features with, respectively, positive and negative model parameters (Table 4). The Tjur R2 *p* value was 0.97 indicating a good predictive ability.

In the group of typical anti-MAG neuropathy patients, the diagnostic score ranged from 1 to 5, with a median value of 4. In patients with definite typical CIDP, the diagnostic score ranged from -7 to -1, with a median value of -4. There was no overlap of the scores between the two groups of patients indicating that this tool was able to discriminate typical anti-MAG neuropathy from typical CIDP (Figure 1; Table 3). In the group of patients with CIDP-MAG the diagnostic score ranged from -6 to 3 (median value of -2; Figure 1). The cut-off score leading to the maximum level of diagnostic accuracy was 0. When this cut-off was applied to patients with CIDP-MAG, patients with a score >0 were classified as anti-MAG neuropathy, whilst those with a score ≤0 were classified as typical CIDP. Using these criteria, 4/16 (25%) CIDP-MAG patients were classified as anti-MAG neuropathy, whilst 12/16 (75%) were classified as CIDP. Patients with CIDP-MAG classified as CIDP according to the score had a more frequent response to IVIg compared to the patients with anti-MAG neuropathy (71.4% vs. 22.2%), but the difference was not statistically significant probably for the small sample size. There was no difference in the response to IVIg between the CIDP-MAG patients classified as CIDP by the score and the patients with definite typical CIDP (71.4% vs. 74.3%) (Table 5). At the time of diagnosis, 11 of the 12 patients with CIDP-MAG classified as CIDP by the score had a symmetric sensorimotor polyneuropathy involving proximal and distal segments of the four limbs with a subacute onset or a relapsing–remitting course, whilst one had a subacute

length-dependent symmetric predominant sensory polyneuropathy with distal weakness and motor nerve conduction blocks. All the four patients with CIDP-MAG classified as anti-MAG neuropathy by the score had a sensory or sensorimotor distal acquired demyelinating symmetric neuropathy phenotype with a relapsing–remitting course. Three of them were treated with IVIg without improvement.

## DISCUSSION

A few studies have recently shown that some patients with anti-MAG antibodies have a clinical presentation different from the typical phenotype of anti-MAG neuropathy [5–8]. Most of these patients have a clinical picture and electrodiagnostic testing consistent with CIDP [5,6]. So far these patients have been considered under the spectrum of anti-MAG neuropathy as “atypical phenotype” possibly reflecting a different pathogenic mechanism [5–8]. It is not possible, however, to exclude that some atypical phenotypes may be false-positive cases. Luigetti et al. [8] showed that patients with an atypical phenotype had different demographic, clinical, pathological and immunohistochemical characteristics compared to patients with a typical phenotype. Magy et al. showed that, in patients with atypical anti-MAG neuropathy with a CIDP-like phenotype, widening of myelin lamellae, positive immunofluorescence and high titers of anti-MAG antibodies were less frequently found than in patients with the typical phenotype, even if none of these findings was able to distinguish the two groups [6]. Svahn et al. [5] reported that 17% of 202 patients with anti-MAG antibodies had an atypical clinical presentation, including 22 patients with a sensorimotor polyradiculoneuropathy, six with an asymmetric or multifocal neuropathy, four with

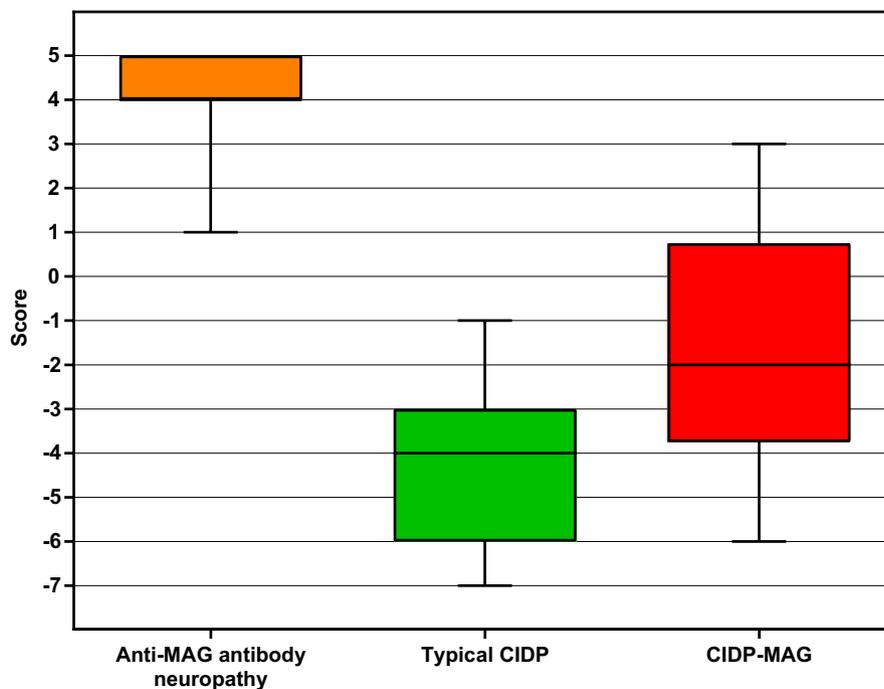
**TABLE 4** Odds ratios and assigned scores for supportive and unsupportive features from multivariable logistic regression model

Features	OR <sup>a</sup>	<i>p</i> value	Assigned score
Supportive features for anti-MAG neuropathy			
Clinical			
(a) Length-dependent, symmetric, predominantly or purely sensory polyneuropathy	6.27	0.9335	+2
(b) Ataxia	1.45	0.9833	+1
(c) Tremor	2.26	0.9673	+1
Electrophysiology			
(a) TLI ≤ 0.25 in at least two different motor nerves	2.13	0.9701	+1
Unsupportive features for anti-MAG neuropathy			
Clinical			
(a) Relapsing–remitting course or acute–subacute clinical onset	4.90	0.9452	-1
(b) Proximal muscle weakness	>999.99	0.6973	-3
Electrophysiology			
(a) Motor conduction blocks	>999.99	0.5687	-3

Abbreviations: MAG, myelin-associated-glycoprotein; OR, odds ratio; TLI, terminal latency index.

<sup>a</sup>For supportive parameters the OR was obtained from a logistic regression model, modeling the probability of being diagnosed as anti-MAG neuropathy; for unsupportive parameters the OR was obtained from a logistic regression model, modeling the probability of being diagnosed as typical CIDP.

**FIGURE 1** Mean score amongst patients with typical CIDP, anti-MAG neuropathy and CIDP-MAG. CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; MAG, myelin-associated-glycoprotein



**TABLE 5** Comparison of intravenous immunoglobulin response in CIDP-MAG patients classified as CIDP or anti-MAG neuropathy by the score, definite typical CIDP patients and anti-MAG neuropathy patients

Patients	CIDP-MAG classified as CIDP by the score	CIDP-MAG classified as anti-MAG neuropathy by the score	Definite typical CIDP	Anti-MAG neuropathy	<i>p</i> value
Response to IVIg	5/7 (71.4%)	0/3 (0%)	29/39 (74.3%)	2/9 (22.2%)	NS

Abbreviations: CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; IVIg, intravenous immunoglobulin; MAG, myelin-associated-glycoprotein.

a sensory polyradiculoneuropathy, one with small-fiber neuropathy and one with amyotrophic lateral sclerosis. The issue of anti-MAG antibody specificity has become more evident after the widespread use of the commercially available Bühlmann ELISA, where the specificity varies depending on the cut-off used. The commercially proposed cut-off titer of >1000 BTU was reported to include some patients without anti-MAG neuropathy [20]. Kuijff et al. [21] reported that a cut-off value of 1500 BTU had a 95% specificity for anti-MAG neuropathy. A cut-off of 10,000 BTU did not improve specificity, with only 83% of the positive patients having a typical anti-MAG neuropathy phenotype [5]. Additional testing for reactivity against sulfate-3-glucuronyl paragloboside or Human Natural Killer 1 did not increase specificity [21,22]. False-positive anti-MAG antibody assays were reported also with Western blot [21,23,24] including a small proportion of patients with IgM monoclonal gammopathy without clinical and electrophysiological evidence of neuropathy even after several years [23,24]. The reason for the incomplete specificity of anti-MAG antibodies remains unclear. It is possible that the currently available tests do not discriminate pathogenic from not pathogenic antibodies, being unable to assess different antibody affinity or accessibility to the target antigen *in vivo*. The possibility that in some patients a release of antigenic myelin proteins leads to an increased reactivity to MAG does not explain, however, the monoclonal nature of the response. Screening of large unselected populations for

anti-MAG antibodies might decrease their positive predictive value with a consistent number of false-positive results, as recently shown for anti-MOG antibodies in patients without the clinical features of typical anti-MOG encephalomyelitis [25]. False-positive antibody testing has also been reported in other immune-mediated diseases, such as myasthenia gravis [26]. Specifically, in any test of a disease with a low frequency of occurrence, the more persons with low pre-test probability of having the disease are tested, the more false positives will be seen [27].

Although our study does not help clarify whether patients with atypical anti-MAG neuropathy are part of the anti-MAG neuropathy spectrum or have a different disease, it confirms that some of these patients are clinically indistinguishable from CIDP [5,6] and have a more frequent response to IVIg than patients with typical anti-MAG neuropathy. These results are in line with previous reports on anti-MAG neuropathies with a motor phenotype responsive to IVIg [28] supporting the advice of the EFNS/PNS to consider IVIg in patients with anti-MAG neuropathy clinically similar to typical CIDP [4].

The distinction between anti-MAG neuropathy and CIDP has relevant prognostic and therapeutic implications. According to the EAN/PNS guidelines, these patients would not receive a diagnosis of CIDP and might be denied the common CIDP therapies, including IVIg [9]. In addition, they are excluded from clinical trials on CIDP. The heterogeneity of anti-MAG neuropathy might explain the failure

of the two previous controlled trials with rituximab [29,30] or the different response to therapy [1,4]. Our study does not allow the nosological status of atypical anti-MAG neuropathy to be better defined. It supports, however, the need for further studies aimed at clarifying the underlying pathogenic mechanisms in patients with atypical anti-MAG neuropathy including the search for IgM or complement deposit or widening of myelin lamellae in the nerve biopsy of anti-MAG neuropathy patients with a CIDP-like phenotype. It would also be worth evaluating the clinical features and response to treatment of patients with other forms of atypical anti-MAG neuropathy. An international collaborative study to apply the score to a larger validation cohort will help confirm these data.

Our study has several limitations, including the small sample size which leads to poor accuracy for model parameter estimates and did not allow the external validity of the score to be tested by splitting the total cohort into derivation and validation cohorts. Other limitations include the exclusion of patients with atypical CIDP, the retrospective design, and the arbitrary choice of the criteria included in the score. Since most of the patients with definite typical CIDP have been tested for anti-MAG antibodies after treatment, it cannot be excluded that some of them might have antibodies at the time of diagnosis, although the absence of IgM monoclonal gammopathy in each of them makes this possibility very unlikely. In addition, serum anti-MAG antibody levels do not always decrease after treatment, from literature data. A recent retrospective analysis reports that a reduction in serum anti-MAG antibodies seems to be associated with a clinical response to immunotherapies but this reduction was reported to be only relative [31]. In addition, since there is no gold standard for the detection of anti-MAG antibodies as these have been measured with different methods, it is not possible to exclude that these results are limited to the technique used in the study [20]. This technique is widely used, however, in the majority of centers so that the possible limit of its specificity might justify the need of diagnostic criteria to support the diagnosis, as was the case for other diseases [25].

In conclusion, our score may serve in the diagnostic evaluation of patients presenting with atypical anti-MAG antibody neuropathy and may help in the choice of treatment. If confirmed on a larger cohort of patients, our results may pave the way for studies aimed at investigating the underlying pathogenic mechanism in patients with atypical presentation and support the revision of the current diagnostic criteria of CIDP that preclude the diagnosis in patients with anti-MAG antibodies.

## ACKNOWLEDGEMENT

Open Access Funding provided by Università degli Studi di Milano within the CRUI-CARE Agreement.

## CONFLICT OF INTEREST

PED, MR, GL, GC report travel grants to attend scientific meetings from CSL Behring and Kedrion. EB, LB, GAM, CG report no disclosures relevant to the paper. FM reports personal fees for scientific events from CSL Behring and travel grants to attend scientific meetings from CSL Behring and Kedrion. DC reports honoraria for lecturing from

Shire, CSL Behring and Kedrion and travel grants to attend scientific meetings from Shire, Kedrion and CSL Behring. MF has served on scientific advisory boards for CSL Behring and has received travel grants from Kedrion, Baxter and CSL Behring to attend scientific meetings. CB has served on scientific advisory boards for Pfizer, Alnylam and Akcea, and has received travel grants from Kedrion and CSL Behring to attend scientific meetings. ENO reports personal fees for Advisory or Scientific Boards from Argenx, Belgium, Baxter/Takeda, Italy and Japan, CSL Behring, Italy, Janssen, USA, Kedrion, Italy, LFB, France, Novartis, Switzerland, Roche, Switzerland, Sanofi, USA, outside the submitted work and travel grants to attend scientific meetings from Baxter, Grifols, Kedrion and Novartis, Italy.

## AUTHOR CONTRIBUTIONS

Pietro E. Doneddu: Conceptualization (lead); data curation (equal); formal analysis (lead); investigation (lead); methodology (equal); project administration (equal); resources (equal); software (equal); supervision (equal); validation (lead); visualization (lead); writing—original draft (lead); writing—review and editing (lead). Marta Ruiz: Conceptualization (lead); data curation (equal); formal analysis (lead); investigation (lead); methodology (lead); resources (equal); software (equal); supervision (equal); validation (lead); visualization (lead); writing—original draft (lead); writing—review and editing (lead). Elisa Bianchi: Conceptualization (equal); data curation (equal); formal analysis (lead); investigation (equal); methodology (equal); resources (equal); software (equal); validation (equal); visualization (equal); writing—review and editing (equal). Giuseppe Liberatore: Data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); resources (equal); software (equal); validation (equal); visualization (equal); writing—review and editing (equal). Fiore Manganelli: Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); resources (equal); software (equal); supervision (equal); visualization (equal); writing—review and editing (equal). Dario Cocito: Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); resources (equal); software (equal); supervision (equal); validation (equal); visualization (equal); writing—review and editing (equal). Giuseppe Cosentino: Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); resources (equal); software (equal); validation (equal); visualization (equal); writing—review and editing (equal). Luana Benedetti: Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); resources (equal); software (equal); validation (equal); visualization (equal); writing—review and editing (equal). Girolama A. Marfia: Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); resources (equal); software (equal); validation (equal); visualization (equal); writing—review and editing (equal). Massimiliano Filosto: Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); resources (equal); software (equal); validation (equal); visualization (equal); writing—review and editing (equal). Chiara Briani: Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); resources

(equal); software (equal); validation (equal); visualization (equal); writing—review and editing (equal). Claudia Giannotta: Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); resources (equal); software (equal); validation (equal); visualization (equal); writing—review and editing (equal). Eduardo Nobile-Orazio: Conceptualization (lead); data curation (lead); formal analysis (lead); funding acquisition (lead); investigation (lead); methodology (lead); project administration (lead); resources (equal); software (equal); supervision (lead); validation (lead); visualization (lead); writing—review and editing (lead).

#### DATA AVAILABILITY STATEMENT

Anonymized data used for this study are available upon reasonable request from the corresponding author.

#### ORCID

Pietro E. Doneddu  <https://orcid.org/0000-0003-4203-6792>

Giuseppe Liberatore  <https://orcid.org/0000-0003-2666-1678>

Fiore Manganeli  <https://orcid.org/0000-0001-9478-3744>

Luana Benedetti  <https://orcid.org/0000-0002-9540-9727>

Massimiliano Filosto  <https://orcid.org/0000-0002-2852-7512>

Chiara Briani  <https://orcid.org/0000-0001-8035-0200>

Eduardo Nobile-Orazio  <https://orcid.org/0000-0003-2624-8138>

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**How to cite this article:** Doneddu PE, Ruiz M, Bianchi E, et al. A diagnostic score for anti-myelin-associated-glycoprotein neuropathy or chronic inflammatory demyelinating polyradiculoneuropathy in patients with anti-myelin-associated-glycoprotein antibody. *Eur J Neurol*. 2022;00:1–10. doi:[10.1111/ene.15296](https://doi.org/10.1111/ene.15296)

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