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# Nerve Conduction Abnormalities Beyond Conduction Block in Multifocal Motor Neuropathy. Impact on Diagnostic Criteria Accuracy

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**Keywords:** conduction block | diagnosis | diagnostic criteria | MMN | multifocal motor neuropathy

## ABSTRACT

**Background:** Multifocal motor neuropathy (MMN) is a rare motor neuropathy diagnosed by identifying motor conduction block (CB), which may be absent or transient. This study aimed to evaluate nerve conduction abnormalities beyond CB and their diagnostic value.

**Methods:** A retrospective analysis included patients fulfilling the 2010 EFNS/PNS clinical criteria for MMN and controls with axonal polyneuropathy, lower motor neuron disease, or chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

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Electrophysiological studies evaluated motor distal latency prolongation, reduced motor conduction velocity, prolonged F-wave latency, absence of F-waves, abnormal temporal dispersion, and distal CMAP duration prolongation. The 2010 EFNS/PNS criteria for MMN were compared to an 'extended' set incorporating additional electrophysiological parameters.

**Results:** A total of 70 MMN patients and 359 controls were included. At least one nerve conduction abnormality, excluding motor CB, was detected in one or more nerve segments unaffected by CB in 71% of MMN patients, significantly more frequently than in axonal polyneuropathy or lower motor neuron disease patients. These parameters included abnormal temporal dispersion (47%), distal CMAP duration prolongation (31%), reduced motor conduction velocity (26%), absence of F-waves (9%), prolonged F-wave latency (6%), and motor distal latency prolongation (3%). Incorporating these parameters increased sensitivity for diagnosing probable/definite MMN by 26% ( $p < 0.001$ ; compared to EFNS/PNS criteria), with minimal impact on specificity, even when compared to CIDP patients.

**Conclusion:** Including additional electrophysiological parameters into the diagnostic criteria for MMN may enhance diagnostic sensitivity while maintaining comparable specificity. The observation of nerve conduction abnormalities beyond CB indicates a broader electrophysiological profile for MMN.

## 1 | Introduction

Multifocal motor neuropathy (MMN) is a rare autoimmune motor neuropathy causing significant disability and showing a favorable response to intravenous immunoglobulin (IVIg) therapy [1–3]. Its diagnosis relies on detecting motor conduction blocks (CBs) in noncompressible sites during nerve conduction studies [4–11]. Supportive criteria, while acknowledged in some guidelines [10, 11], are not universally accepted [9], and remain supplementary to the core criterion of motor CB.

Despite available diagnostic tools, underdiagnosis and diagnostic delay in MMN are common [12–15]. This may result in delayed treatment potentially causing increased neurologic impairment and disability [14, 16]. The diagnostic challenges in MMN are partly due to the reduced sensitivity (53%–64%) of the current criteria for MMN [17]. This low sensitivity may be explained by the potential failure to detect CBs due to concomitant axonal degeneration or their localization in proximal nerve segments, less accessible to standard nerve conduction studies [1–3, 10, 11]. Another complicating factor is the phenomenon of temporal dispersion, which can cause a spurious reduction in the amplitude and area of the proximal compound motor action potential (CMAP) through phase cancellation [3, 10, 11]. Current CB definitions in MMN require the absence of temporal dispersion or impose stringent criteria in its presence, potentially further reducing diagnostic sensitivity [4–11]. Some studies, however, suggest temporal dispersion is common in MMN and could serve as a marker for therapeutic response [18, 19]. Its exclusion from MMN diagnostic criteria contrasts with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), where motor CB is also a key diagnostic parameter [20]. Other nerve conduction abnormalities typically seen in demyelinating neuropathies, such as reduced conduction velocities and prolonged distal latencies, have been noted in MMN but are not included in the criteria and need further validation [7, 18, 19, 21–24]. Demonstrating the presence of additional nerve conduction abnormalities beyond CB could aid in redefining diagnostic criteria for MMN and may contribute to a greater understanding of the primary site of nerve injury.

The study assessed the frequency of nerve conduction abnormalities, beyond CB, in a large MMN cohort and their impact on

diagnostic accuracy by analyzing the sensitivity and specificity of criteria incorporating these parameters.

## 2 | Methods

### 2.1 | Study Population

#### 2.1.1 | MMN Patients

We implemented a web-based database on Italian MMN patients [17, 25], which includes data from 85 patients fulfilling the 2010 European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria for possible, probable, or definite MMN, and 11 patients with a clinical MMN diagnosis who do not meet the same criteria. These 11 patients had a medical history, clinical signs, and supportive exams consistent with MMN [11]. In nine of them, however, the response to IVIg was unclear, precluding a diagnosis of possible MMN. Two newly diagnosed patients were included prior to initiating IVIg treatment.

The treating neurologist entered data into a database prepared by CINECA, Bologna, Italy. The MMN diagnosis was originally made by the treating neurologist and subsequently reviewed by the coordinating center based on the 2010 EFNS/PNS diagnostic criteria. Data monitoring included diagnosis reassessment, identification of potential duplicate entries, verification of missing data, and plausibility checks. Patients with an alternative diagnosis for the neuropathy, or with symptoms and signs inconsistent with MMN, or without available nerve conduction studies, were excluded from the study. The reasons for suspecting MMN when nerve conduction studies were not diagnostic were also reported by the treating neurologist and included, besides a clinical history and presentation consistent with MMN, abnormality of the supportive tests (cerebrospinal fluid [CSF] analysis, MRI of the brachial plexus, anti-GM1 IgM antibody positivity, and objective clinical improvement following IVIg treatment). All patients underwent a comprehensive clinical assessment, supplemented by medical records [17, 25]. Clinical findings from previous examinations and nerve conduction studies performed throughout the disease course were included. Treatment response was defined as a subjective improvement objectively confirmed by

$\geq 2$  points in the Medical Research Council (MRC) sum score (range 0–60) or  $\geq 1$  point in the Inflammatory Neuropathy Cause and Treatment (INCAT) disability score (range 0–10) [17, 20, 25, 26].

## 2.2 | Controls

To evaluate the specificity of diagnostic criteria that incorporated additional nerve conduction abnormalities, we analyzed electrophysiological data from 359 controls with sensory, sensorimotor, or motor axonal peripheral neuropathy, CIDP, and lower motor neuron disease. Controls were consecutively selected from patients regularly monitored at Humanitas Research Institute and included typical CIDP ( $n=100$ ) or multifocal CIDP ( $n=16$ ), diabetic peripheral neuropathy ( $n=74$ ), amyotrophic lateral sclerosis (ALS) with lower motor neuron involvement ( $n=63$ ), chemotherapy-induced neuropathy ( $n=38$ ), chronic idiopathic axonal polyneuropathy ( $n=38$ ), vasculitic neuropathy ( $n=7$ ), vitamin B12 deficiency neuropathy ( $n=6$ ), rheumatoid arthritis-associated neuropathy ( $n=5$ ), IgG monoclonal gammopathy of undetermined significance ( $n=5$ ), HCV-related neuropathy ( $n=3$ ), toxic neuropathy ( $n=2$ ), amyloid neuropathy ( $n=1$ ), and paraneoplastic neuropathy associated with anti-CV2 (CRMP5) antibodies ( $n=1$ ).

## 2.3 | Study Design

Given the retrospective design of the study, electrophysiological studies were performed in a non-standardized manner but consistently included clinically affected nerves. The number of motor nerves studied varied from 4 to 10.

Pretreatment electrophysiological studies were prioritized; when unavailable, post-treatment studies were used. The extensiveness of the study of arm nerves varied from the distal forearm segment to full-length study up to Erb's point. Patients were also managed in a non-standardized fashion, with ancillary exams and treatments at the discretion of the treating physician. While this variability may be seen as a limitation in research, it reflects real-world practice and is particularly relevant in the context of rare diseases such as MMN. Furthermore, previous studies evaluating the sensitivity and specificity of electrodiagnostic criteria for MMN and other inflammatory neuropathies have employed a retrospective methodology [17, 27–29].

Compound muscle action potentials (CMAPs) were evoked from the median (stimulating at wrist, elbow and, in some cases, axilla, and Erb's point; recording at the abductor pollicis brevis muscle), ulnar (stimulating at wrist, below elbow and, in some patients, above elbow, axilla, Erb's point; recording at the abductor digiti minimi), common peroneal (stimulating at ankle and fibular neck; recording at the extensor digitorum brevis), tibial (stimulating at ankle and popliteal fossa; recording at the abductor hallucis) and in some patients from the radial nerve (stimulating at forearm, elbow and above elbow, and Erb's point; recording at the extensor indicis proprius). Sensory nerve conduction studies were performed on the median, ulnar, and sural nerves, and in some cases, the radial nerve. Measurements

included distal latency, sensory nerve action potential (SNAP) amplitude, and conduction velocity. Studies were performed at a minimum temperature of 33°C at the palm and 30°C at the external malleolus. Sensory conduction studies were performed using the antidromic technique. Age-dependent sural SNAP reference values were used, and results were analyzed according to each laboratory's range of normal values.

To assess the frequency of nerve conduction abnormalities beyond CB, the following variables were analyzed in patients with MMN and control subjects: (1) motor distal latency prolongation  $\geq 50\%$  above the upper limit of normal values (ULN), (2) motor conduction velocity reduction  $\geq 30\%$  below the lower limit of normal values (LLN), (3) F-wave latency prolongation  $\geq 20\%$  above ULN ( $\geq 50\%$  if the amplitude of the distal negative peak CMAP is  $< 80\%$  of LLN), (4) absence of F-waves (if the distal negative peak CMAP amplitude is  $\geq 20\%$  of LLN), (5) abnormal temporal dispersion defined as  $> 30\%$  increase in duration between the proximal and distal negative peak CMAP (with a threshold of 100% for the tibial nerve), and (6) distal CMAP duration prolongation (interval between the onset of the first negative peak and return to baseline of the last negative peak), using separate criteria for low-frequency filters of 2, 5, 10, and 20 Hz.

These parameters were selected based on previous studies demonstrating their occurrence in a subset of MMN patients [7, 18, 19, 21–24]. Cutoff values and definitions were derived from the 2021 European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) criteria for CIDP [20]. Their presence in MMN patients was evaluated in nerve segments not affected by CB. For this analysis, CB was defined according to the 2010 EFNS/PNS criteria for MMN [11], as this definition provides a clearer distinction between CB and temporal dispersion compared to the 2021 EAN/PNS criteria for CIDP [20].

In the second part of the study, the sensitivity and specificity of the 2010 EFNS/PNS criteria for MMN were compared with those of an 'extended' set of criteria that incorporated additional electrophysiological abnormalities identified in MMN patients from the previous analysis. Both sets of criteria were applied to MMN patients and controls to assess their diagnostic performance. Sensitivity and specificity analyses were initially conducted for all patients, irrespective of the number of nerves examined, to test both criteria sets with real-world data. Subsequently, they were repeated in MMN patients and controls with at least five motor nerves examined (extensive nerve conduction study protocol). Specificity was assessed both across all control subjects and specifically in CIDP patients.

To precisely evaluate CMAP amplitude, area and duration, and distal CMAP duration prolongation, nerve conduction studies waveforms of the MMN and control patients were reviewed. For each patient, the waveforms were sent to the coordinating center. Patients whose nerve conduction study waveforms were not available for review were excluded from the study analyses. CMAP area was measured from the onset of the negative peak to its return to baseline [11]. Subjects who did not have sensory conduction velocities examined in the affected nerves were excluded from the study. The analysis was repeated for the groups of patients with 1–3, 4–7 nerves and at least 8 nerves.

In this study, only MMN patients who demonstrated an objective response to IVIg were included in the analyses. This selection ensured the inclusion of a population in which the diagnosis was corroborated by a therapeutic gold standard. By standardizing the response-to-therapy criterion, this approach facilitated the evaluation of electrophysiological criteria in confirming the diagnosis of MMN and determining the level of diagnostic certainty (definite, probable, or possible). Notably, response to therapy is a requirement for accessing the diagnosis of possible MMN in patients without CB, as defined by the 2010 EFNS/PNS criteria [11]. This method also provided a clearer comparison between the 2010 EFNS/PNS and 'extended' criteria, simulating a pre-treatment setting.

The study was approved by the Ethical Committee of IRCCS Humanitas Clinical Institute (D.M. 8/2/2013; 413/17) and of each participating center. Written informed consent was obtained from all participants in the study.

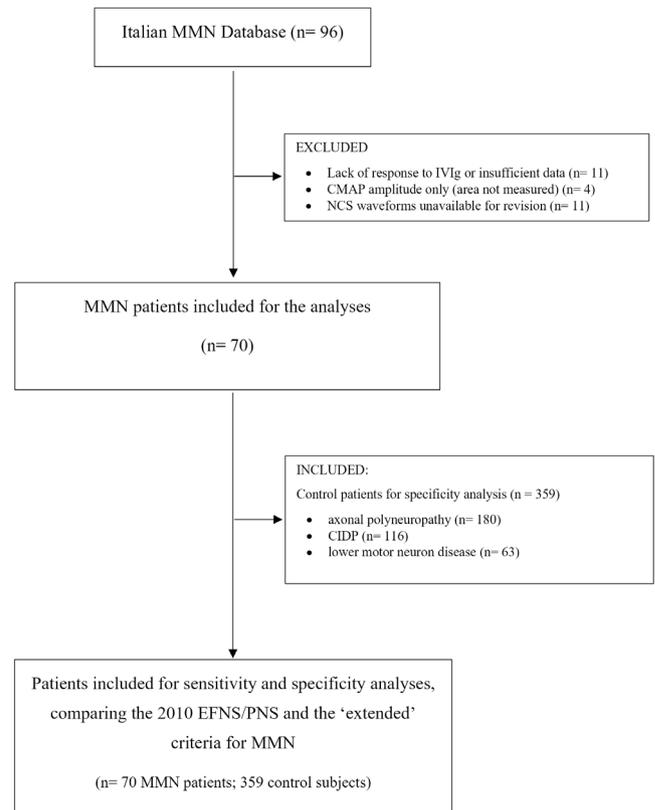
### 3 | Statistical Analysis

Descriptive statistics were reported for the entire sample of MMN patients and controls. Categorical variables were described using frequencies and percentages, while continuous variables were described using mean, median, and ranges. The comparative diagnostic gain in sensitivity and specificity achieved with the more sensitive or specific criteria was calculated using a McNemar test. Diagnostic accuracy was defined as the proportion of correctly classified subjects (TP + TN) among all subjects (TP + TN + FP + FN). All tests were two-tailed, with a significance level of 0.05. Analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA). Sensitivity and specificity were assessed considering the number of nerves examined, consistent with previous studies.

### 4 | Results

Among the 96 MMN patients included in the database, 11 patients were excluded due to an unclear IVIg response or because they were entered into the database prior to treatment. Additionally, four were excluded because only CMAP amplitude, not area, was measured and recorded by the treating physician. A further 11 were excluded due to unavailable nerve conduction study waveforms. The final study population consisted of 70 MMN patients, 41 of whom had undergone an extensive nerve conduction study (Figure 1). Of the 359 controls, 200 had undergone an extensive nerve conduction study. Demographic and clinical characteristics, along with the number of nerves examined in MMN patients and controls, are summarized in Table 1. All MMN patients fulfilled the 2010 EFNS/PNS clinical criteria for diagnosis (Table 1) [11]. A median of 7 (range 4–10) motor nerves and 5 (range 3–8) sensory nerves were evaluated in MMN patients, compared to 5 (range 3–8) motor nerves and 4 (range 2–7) sensory nerves in controls. A total of 484 motor nerves from MMN patients and 1604 from controls were analyzed.

Table 2 shows the frequency and distribution of nerve conduction abnormalities in MMN patients and controls. At least one nerve conduction abnormality, excluding motor CB, was



**FIGURE 1** | Flowchart of patients' selection for sensitivity and specificity analyses comparing the 2010 EFNS/PNS and 'extended' criteria for MMN. CIDP = chronic inflammatory demyelinating polyradiculoneuropathy, CMAP = compound muscle action potential, EFNS/PNS = European Federation of Neurological Societies/Peripheral Nerve Society, MMN = multifocal motor neuropathy, *n* = number, NCS = nerve conduction study.

present in at least one nerve segment unaffected by CB in 71% of MMN patients, and in at least two unaffected segments in 34% (Figure 2). Definite and probable motor CB were observed in 39% and 47% of MMN patients, respectively, with a total of 64% having CB. Compared to lower motor neuron disease patients, MMN patients more frequently exhibited reduced motor conduction velocity (26% vs. 0%,  $p=0.0001$ ), abnormal temporal dispersion (47% vs. 6%,  $p=0.0001$ ), distal CMAP duration prolongation (31% vs. 5%,  $p=0.0001$ ), definite motor CB (39% vs. 2%,  $p=0.0001$ ), probable CB (47% vs. 0%,  $p=0.0001$ ), and the presence of at least one nerve conduction abnormality, excluding CB, in at least one or two nerve segments unaffected by CB (71% vs. 8% and 34% vs. 3%, respectively,  $p=0.0001$ ). Compared to axonal polyneuropathy patients, MMN patients were more likely to display reduced motor conduction velocity (26% vs. 2%,  $p=0.0001$ ), absent F-waves (9% vs. 0%,  $p=0.0004$ ), abnormal temporal dispersion (47% vs. 1%,  $p=0.0001$ ), distal CMAP duration prolongation (31% vs. 1%,  $p=0.0001$ ), definite and probable motor CB (39% vs. 0% and 47% vs. 0.5%,  $p=0.0001$ , respectively), and the presence of at least one nerve conduction abnormality, excluding CB, in at least one or two nerve segments unaffected by CB (71% vs. 4% and 34% vs. 1%, respectively,  $p=0.0001$ ). When compared to CIDP patients, MMN patients less frequently had motor distal latency prolongation (3% vs. 30%,  $p=0.0001$ ), reduced motor conduction velocity (26% vs. 57%,  $p=0.0001$ ), prolongation of F-wave latency (6% vs. 53%,  $p=0.0001$ ), absent F-waves (9%

**TABLE 1** | Demographic and clinical characteristics, and number of nerves examined with nerve conduction study in MMN patients and controls.

	MMN patients ( <i>n</i> = 70)	Control subjects ( <i>n</i> = 359)
Gender, male, <i>n</i> (%)	45 (64%)	232 (65%)
Age at onset, years, mean (SD)	42 (12)	70 (11)
Disease duration, years, mean (SD)	15 (8)	16 (10)
Time from symptom onset to nerve conduction study, months, mean (SD)	29 (11)	92 (45)
No. of motor nerves examined at nerve conduction study, median (range)	7 (4–10)	5 (3–8)
No. of sensory nerves examined at nerve conduction study, median (range)	5 (3–8)	4 (2–7)
Slowly progressive or stepwise progressive, focal, asymmetric <sup>a</sup> limb weakness in the motor nerve distribution of at least two nerves, for more than 1 month <sup>b</sup>	70 (100%)	
No objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs	70 (100%)	
Predominant upper limb involvement	53 (76%)	
Decreased or absent tendon reflexes in the affected limb	53 (76%)	
Absence of cranial nerve involvement	69 (99%) <sup>c</sup>	
Cramps and fasciculations in the affected limb	42 (60%)	
Response to IVIg treatment, <i>n</i> (%)	70 (100%)	
Elevated IgM anti-ganglioside GM1 antibodies/tested, <i>n</i> (%)	26/63 (41%)	
Increased CSF proteins/tested, <i>n</i> (%)	14/30 (47%)	
Brachial plexus MRI; positive/tested, <i>n</i> (%)	6/15 (40%)	
Nerve Ultrasound; positive/tested, <i>n</i> (%)	12/16 (75%)	
MRC sumscore (0–60) at enrolment, mean (range)	54 (27–60)	

Abbreviations: CSF = cerebrospinal fluid, IgM = immunoglobulin M, IVIg = intravenous immunoglobulin, MMN = multifocal motor neuropathy, MRC = Medical Research Council, MRI = magnetic resonance imaging, *n* = number, SD = standard deviation.

<sup>a</sup>Asymmetric = a difference of 1 MRC grade if strength is MRC > 3 and 2 MRC grades if strength is MRC ≤ 3.

<sup>b</sup>Usually more than 6 months.

<sup>c</sup>One patient had an 8-year history of MMN with dysphagia, which showed a positive response to intravenous immunoglobulin treatment.

vs. 28%,  $p=0.0018$ ), and distal CMAP duration prolongation (31% vs. 65%,  $p=0.0001$ ). However, MMN patients more frequently exhibited abnormal temporal dispersion (47% vs. 28%,  $p=0.0108$ ), definite motor CB (39% vs. 7%,  $p=0.0001$ ), and probable motor CB (47% vs. 7%,  $p=0.0001$ ).

Given the frequent observation of nerve conduction abnormalities beyond CB in patients with MMN, an ‘extended’ set of diagnostic criteria incorporating these parameters was developed (Table 3).

Table 4 presents the comparison of the sensitivity of the two sets of criteria. Sensitivity of the EFNS/PNS criteria was 39% (95% CI, 27%–50%) for definite MMN, 54% (95% CI, 43%–66%) for definite/probable MMN, 60% (95% CI, 49%–61%) for definite/probable MMN using supportive criteria, and 40% (95% CI, 29%–51%) for possible MMN. In contrast, the sensitivity of the ‘extended’ criteria, including additional nerve conduction abnormalities, was 39% (95% CI, 27%–50%) for definite MMN, 80% (95% CI, 71%–89%) for definite/probable MMN, 81% (95% CI, 72%–91%) for definite/probable MMN using supportive criteria, and 19% (95% CI, 9%–28%) for possible MMN. Using the extensive nerve conduction study protocol, the sensitivity of both diagnostic criteria remained similar. Compared to the EFNS/PNS criteria, the ‘extended’ criteria demonstrated significantly higher sensitivity for definite/probable MMN ( $p < 0.001$ ).

Eighteen patients were missed by the EFNS/PNS electrodiagnostic criteria; of these, eight had nerve conduction abnormalities, excluding CB, in one nerve, and 10 in two nerves. Specifically, two patients demonstrated distal CMAP duration prolongation in one nerve, four showed increased temporal dispersion in one nerve, and two exhibited reduced motor conduction velocity in one nerve. Additionally, two patients had distal CMAP duration prolongation in two nerves, and another two showed increased temporal dispersion in two nerves. One patient had increased temporal dispersion in two nerves and absence of F-wave in two different nerves. Another patient exhibited distal CMAP duration prolongation in two nerves, reduced conduction velocity in two nerves, increased temporal dispersion in one nerve, and F-wave prolongation in another. One patient had increased temporal dispersion in two nerves, distal CMAP duration prolongation in one, and reduced conduction velocity in another. Another displayed distal CMAP duration prolongation and increased temporal dispersion in two nerves, while two patients showed distal CMAP duration prolongation in two nerves, respectively associated with reduced conduction velocity and increased temporal dispersion in one nerve. These 18 patients had a median of 7 (range 4–10) motor nerves tested, with normal sensory conduction velocities in all tested nerves. Among these patients, seven tested positive for IgM anti-GM1 antibodies, and three exhibited albuminocytologic dissociation in CSF.

Table 5 shows the specificity of the two sets of electrodiagnostic criteria. When all control subjects were analyzed, the EFNS/PNS criteria demonstrated a specificity of 99% for both definite MMN (95% CI, 99%–100%) and definite/probable MMN (95% CI, 98%–100%). In comparison, the specificity of the ‘extended’ criteria for definite/probable MMN was 96% (95% CI, 94%–98%). Using the extensive nerve conduction study protocol, the specificity of both criteria remained comparable (Table 5). Among

**TABLE 2** | Frequency and distribution of electrophysiological abnormalities in MMN patients and control groups.

<b>Electrophysiological parameters<sup>a</sup>, n (%)</b>	<b>MMN (n = 70)</b>	<b>Lower motor neuron disease (n = 63)</b>	<b>Axonal polyneuropathy (n = 180)</b>	<b>CIDP (n = 116)</b>	<b>p</b>
1. Motor distal latency prolongation $\geq 50\%$ above ULN (excluding median neuropathy at the wrist from carpal tunnel syndrome)	2 (3%)	1 (2%)	0	35 (30%)	0.0001*
2. Reduction of motor conduction velocity $\geq 30\%$ below LLN	18 (26%)	0	3 (2%)	66 (57%)	0.0001*; 0.0001**; 0.0001***
3. Prolongation of F-wave latency $\geq 20\%$ above ULN in two nerves ( $\geq 50\%$ if amplitude of distal negative peak CMAP $< 80\%$ of LLN)/tested	4 (6%)	0	2 (1%)	54/102 (53%)	0.0001*
4. Absence of F-waves (if these nerves have distal negative peak CMAP amplitudes $\geq 20\%$ of LLN)/tested	6 (9%)	2 (3%)	0	29/102 (28%)	0.0018*; 0.0004***
5. Abnormal temporal dispersion: $> 30\%$ duration increase between the proximal and distal negative peak CMAP (at least 100% in the tibial nerve)	33 (47%)	4 (6%)	2 (1%)	32 (28%)	0.0108*; 0.0001**; 0.0001***
6. Distal CMAP duration prolongation (interval between onset of the first negative peak and return to baseline of the last negative peak) <sup>b</sup>	22 (31%)	3 (5%)	2 (1%)	75 (65%)	0.0001*; 0.0001**; 0.0001***
7. Definite motor CB: negative peak CMAP area reduction on proximal vs. distal stimulation of $\geq 50\%$ whatever the nerve segment length (median, ulnar, and peroneal) <sup>c</sup>	27 (39%)	1 (2%)	0	8 (7%)	0.0001*; 0.0001**; 0.0001***
8. Probable motor CB: negative peak CMAP area reduction of $\geq 30\%$ over a long segment of an upper limb nerve with increase of proximal to distal negative peak CMAP duration $\leq 30\%$ , OR $\geq 50\%$ (same as definite) with an increase of proximal to distal negative peak CMAP duration $> 30\%$	33 (47%)	0	1 (0.5%)	8 (7%)	0.0001*; 0.0001**; 0.0001***
Presence of probable or definite motor CB (7,8) in $\geq 1$ nerve	45 (64%)	1 (2%)	1 (0.5%)	14 (12%)	0.0001*; 0.0001**; 0.0001***
Presence of $\geq 1$ electrophysiological parameter, excluding CB, (1–6) in $\geq 1$ nerve	50 (71%)	5 (8%)	8 (4%)	96 (83%)	0.0001**; 0.0001***
Presence of $\geq 1$ electrophysiological parameter, excluding CB, (1–6) in $\geq 2$ nerves	24 (34%)	2 (3%)	2 (1%)	69 (59%)	0.0014*; 0.0001**; 0.0001***

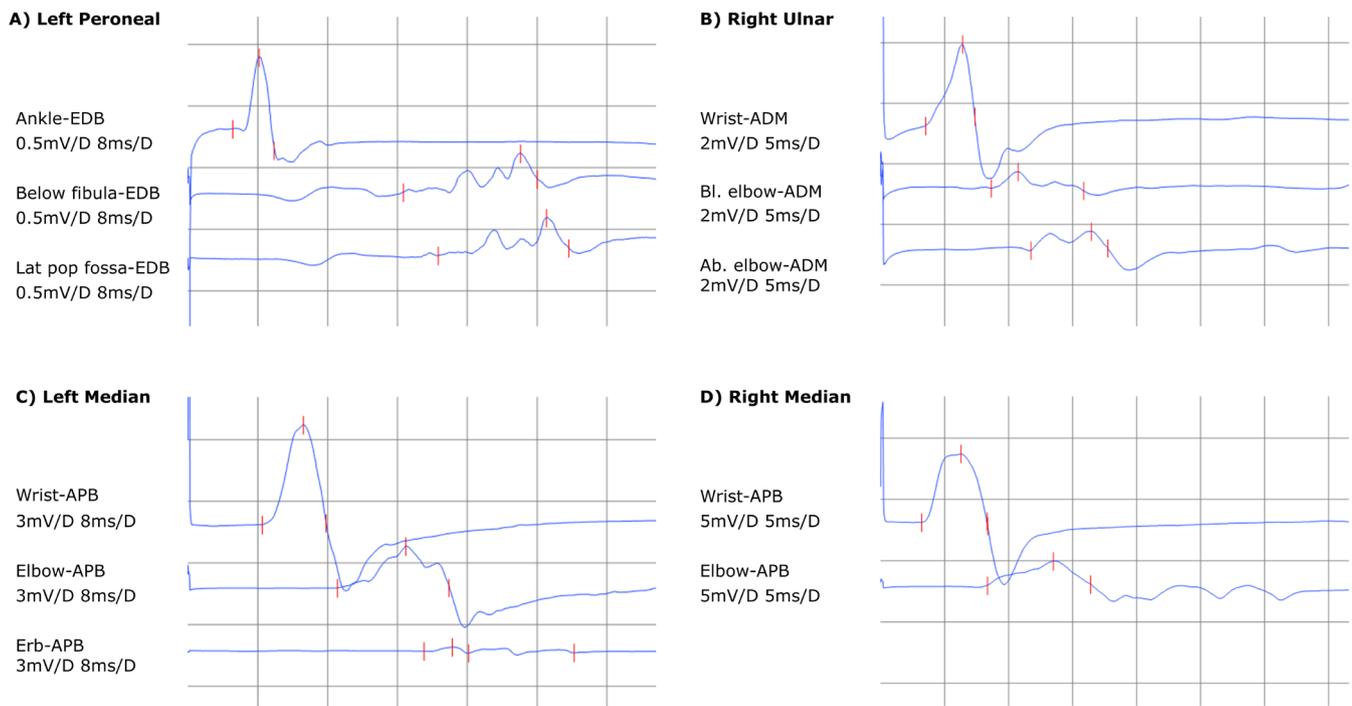
Note. \* MMN vs. CIDP; \*\* MMN vs. lower motor neuron disease; \*\*\* MMN vs. axonal polyneuropathy.

Abbreviations: CB = conduction block, CIDP = chronic inflammatory demyelinating polyradiculoneuropathy, CMAP = compound muscle action potential, LLN = lower limit of normal values, MMN = multifocal motor neuropathy, ULN = upper limit of normal values.

<sup>a</sup>For parameters 1–6, the values represent their presence in nerve segments that are not affected by conduction block.

<sup>b</sup>(LFF 2 Hz) median  $> 8.4$  ms, ulnar  $> 9.6$  ms, peroneal  $> 8.8$  ms, tibial  $> 9.2$  ms; (LFF 5 Hz) median  $> 8.0$  ms, ulnar  $> 8.6$  ms, peroneal  $> 8.5$  ms, tibial  $> 8.3$  ms; (LFF 10 Hz) median  $> 7.8$  ms, ulnar  $> 8.5$  ms, peroneal  $> 8.3$  ms, tibial  $> 8.2$  ms; (LFF 20 Hz) median  $> 7.4$  ms, ulnar  $> 7.8$  ms, peroneal  $> 8.1$  ms, tibial  $> 8.0$  ms.

<sup>c</sup>Negative peak CMAP amplitude on stimulation of the distal part of the segment with motor CB must be  $> 20\%$  of the lower limit of normal and  $> 1$  mV and increase of proximal to distal negative peak CMAP duration must be  $\leq 30\%$ .



**FIGURE 2** | Representative examples of temporal dispersion in patients with MMN. Panels A, B, C, and D demonstrate temporal dispersion in the motor nerves of four patients who meet the 2010 European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) clinical criteria for multifocal motor neuropathy (MMN). These patients had a mean disease duration of 6 years (range 4–10 years), with normal sensory nerve conduction studies, and all responded to intravenous immunoglobulin therapy. All four patients are regularly followed by the authors (PED, ENO) at the Humanitas Research Institute.

controls with CIDP, the specificity of both criteria was also maintained (Table 5). Notably, none of the controls with multifocal CIDP met the ‘extended’ criteria for definite/probable MMN. The ‘extended’ criteria demonstrated lower specificity than the EFNS/PNS criteria for definite/probable MMN ( $p=0.008$ ).

The higher specificity of the 2010 EFNS/PNS criteria led to 10 additional controls being correctly identified as not having MMN. Among them, seven ALS patients showed nerve conduction abnormalities: three with temporal dispersion in one nerve, one with distal CMAP duration prolongation in one nerve, one absent F-wave in three nerves, one with distal CMAP duration prolongation in two nerves plus increased motor distal latency in another, and one with distal CMAP duration prolongation in one nerve, temporal dispersion in another, and an absent F-wave in a third nerve. Three sensorimotor CIDP patients had prolonged or absent F-waves in at least two nerves, with normal sensory conduction studies (tested with four sensory nerves). Three patients were misclassified as having MMN by both criteria: one with diabetic polyneuropathy and probable CB in two nerves, one with ALS and definite CB in one nerve, and one with sensorimotor CIDP showing definite CB in one nerve and abnormal sensory conduction studies limited to the lower limbs.

When the analyses were repeated, requiring the presence of additional nerve conduction abnormalities, excluding CB, in at least two motor nerves instead of one for a probable MMN diagnosis with the ‘extended’ criteria, there was a substantial reduction in sensitivity (65%; 95% CI, 55%–77% compared to EFNS/PNS,  $p=0.016$ ) with only a marginal improvement in specificity (97%; 95% CI, 95%–99%) compared to EFNS/PNS,  $p=0.250$ .

Overall, the ‘extended’ criteria demonstrated slightly greater diagnostic accuracy compared to the EFNS/PNS criteria (94%; 95% CI, 89%–94% vs. 92%; 95% CI, 91%–96%).

## 5 | Discussion

Diagnosing MMN is challenging due to its reliance on detecting CB, which may be absent, transient, or located in proximal nerve segments difficult to assess. Although the 2010 EFNS/PNS criteria include supportive tests, they do not allow for a diagnosis of definite or probable MMN without evidence of CB [11]. Under these criteria, IVIg response can support a possible MMN diagnosis [11], but in some countries including Italy, reimbursement issues arise as treatment before diagnosis is restricted. These challenges contribute to misdiagnosis and diagnostic delays, leading to greater disability in MMN patients [12–16].

This study demonstrates that 71% of MMN patients exhibit nerve conduction abnormalities beyond CB, significantly more frequent than in lower motor neuron disease or axonal polyneuropathies. These findings align with previous studies [18, 19, 21–24] and suggest that electrophysiological abnormalities seen in demyelinating [20] and paranodal [30, 31] neuropathies are part of the electrophysiological profile of MMN.

Compared to CIDP, MMN patients more frequently presented with CB and temporal dispersion but less often with F-wave alterations, distal latency prolongation, and reduced conduction velocity. This suggests that MMN primarily affects the nerve trunk, reflecting patchy involvement observed in biopsy studies

**TABLE 3** | Comparison of the 2010 EFNS/PNS electrodiagnostic and supportive criteria for MMN and an 'extended' set of criteria incorporating additional electrophysiological parameters.

	2010 EFNS/PNS	'Extended' criteria
<b>Definite MMN</b>		
Motor NCS criteria	Clinical criteria <sup>a</sup> and CB in one nerve under the following criteria: Negative peak CMAP area reduction on proximal vs. distal stimulation of at least 50% whatever the nerve segment length (median, ulnar, and peroneal). Negative peak CMAP amplitude on stimulation of the distal part of the segment with motor CB must be > 20% of the LLN and > 1 mV and increase of proximal to distal negative peak CMAP duration must be ≤ 30%	
Sensory NCS criteria	Normal sensory NCS in UL segments with CB	
<b>Probable MMN</b>		
Motor NCS criteria	Clinical criteria <sup>a</sup> and CB in two nerves (or in just one nerve plus at least two supportive criteria <sup>b</sup> ) under the following criteria: a. Negative peak CMAP area reduction of at least 30% over a long segment of an UL nerve with increase of proximal to distal negative peak CMAP duration ≤ 30%, or b. Negative peak CMAP area reduction of at least 50% (same as definite) with an increase of proximal to distal negative peak CMAP duration > 30%	
		or, Clinical criteria <sup>a</sup> and at least one of the following electrophysiological parameters in at least one nerve: c. Motor distal latency prolongation ≥ 50% above ULN (excluding median neuropathy at the wrist from carpal tunnel syndrome) d. Reduction of motor conduction velocity ≥ 30% below LLN e. Prolongation of F-wave latency ≥ 20% above ULN in two nerves (≥ 50% if amplitude of distal negative peak CMAP < 80% of LLN) f. Absence of F-waves (if these nerves have distal negative peak CMAP amplitudes ≥ 20% of LLN) g. Abnormal temporal dispersion: > 30% duration increase between the proximal and distal negative peak CMAP (at least 100% in the tibial nerve) h. Distal CMAP duration prolongation (interval between onset of the first negative peak and return to baseline of the last negative peak) <sup>c</sup> , i. and objective clinical improvement following IVIg treatment
Sensory NCS criteria	Normal sensory NCS in UL segments with CB	Normal sensory NCS on all tested nerves <sup>d</sup>
<b>Possible MMN</b>		
	Clinical criteria <sup>a</sup> and normal sensory NCS and objective clinical improvement following IVIg or Clinical criteria <sup>a</sup> with clinical signs and electrophysiological criteria present in only one nerve	Clinical criteria <sup>a</sup> and normal sensory NCS and objective clinical improvement following IVIg or Clinical criteria <sup>a</sup> and normal sensory NCS on all tested nerves <sup>d</sup> and at least one electrophysiological parameter (a–h) at motor NCS in at least one nerve or Clinical criteria <sup>a</sup> with clinical signs and electrophysiological criteria present in only one nerve

Abbreviations: CB = conduction block, CMAP = compound muscle action potential, EFNS/PNS = European Federation of Neurological Societies (EFNS)/Peripheral Nerve Society, EP = Erb's point, IVIg = intravenous immunoglobulin, LLN = lower limit of normal values, MMN = multifocal motor neuropathy, NCS = nerve conduction studies, SN = sciatic notch, TD = temporal dispersion, UL = upper limbs, ULN = upper limit of normal values.

<sup>a</sup>As in 2010 EFNS/PNS [11].

<sup>b</sup>(1) elevated IgM anti-ganglioside GM1 antibodies; (2) laboratory: increased CSF protein (< 1 g/L); (3) magnetic resonance imaging showing increased signal intensity on T2-weighted imaging associated with a diffuse nerve swelling of the brachial plexus; (4) objective clinical improvement following IVIg treatment [11].

<sup>c</sup>Low-frequency filter (LFF) settings: (LFF 2 Hz) median > 8.4 ms, ulnar > 9.6 ms, peroneal > 8.8 ms, tibial > 9.2 ms; (LFF 5 Hz) median > 8.0 ms, ulnar > 8.6 ms, peroneal > 8.5 ms, tibial > 8.3 ms; (LFF 10 Hz) median > 7.8 ms, ulnar > 8.5 ms, peroneal > 8.3 ms, tibial > 8.2 ms; (LFF 20 Hz) median > 7.4 ms, ulnar > 7.8 ms, peroneal > 8.1 ms, tibial > 8.0 ms.

<sup>d</sup>Age-dependent reference values for sural SNAP amplitude should be used.

**TABLE 4** | Sensitivity of the 2010 EFNS/PNS and the 'extended' criteria for MMN.

Criteria	Total, <i>n</i> (%)	95% CI	Extensive NCS protocol <sup>a</sup> , <i>n</i> (%)	95% CI
2010 EFNS/PNS criteria				
Definite MMN	27/70 (39%)	27%–50%	17/41 (41%)	26%–57%
Definite or Probable MMN	38/70 (54%)	43%–66%	22/41 (54%)	38%–69%
Definite or Probable MMN using supportive criteria	42/70 (60%)	49%–71%	25/41 (61%)	46%–76%
Possible MMN	28/70 (40%)	29%–51%	16/41 (39%)	24%–54%
'Extended' criteria				
Definite MMN	27/70 (39%)	27%–50%	17/41 (41%)	26%–57%
Definite or Probable MMN	56/70 (80%)	71%–89%	33/41 (80%)	68%–93%
Definite or Probable MMN using supportive criteria	57/70 (81%)	72%–91%	34/41 (83%)	71%–94%
Possible MMN	13/70 (19%)	9%–28%	7/41 (17%)	6%–29%

Abbreviations: EDX = electrophysiological, EFNS/PNS = European Federation of Neurological Societies/Peripheral Nerve Society, MMN = multifocal motor neuropathy, *n* = number; NCS = nerve conduction study.

<sup>a</sup>At least five motor nerves examined in MMN patients and controls.

**TABLE 5** | Specificity of the 2010 EFNS/PNS and the 'extended' electrodiagnostic criteria for MMN.

Criteria	Total, <i>n</i> (%)	95% CI	Extensive NCS protocol <sup>a</sup> , <i>n</i> (%)	95% CI
Considering all control subjects ( <i>n</i> = 359)				
2010 EFNS/PNS criteria				
Definite MMN	357/359 (99%)	99%–100%	198/200 (99%)	98%–100%
Definite or Probable MMN	356/359 (99%)	98%–100%	197/200 (98.5%)	97%–100%
'Extended' criteria				
Definite MMN	357/359 (99%)	99%–100%	198/200 (99%)	98%–100%
Definite or Probable MMN	346/359 (96%)	94%–98%	196/200 (98%)	96%–100%
Considering CIDP patients as controls only ( <i>n</i> = 116)				
2010 EFNS/PNS criteria				
Definite MMN	115/116 (99%)	97%–100%	88/89 (99%)	97%–100%
Definite or Probable MMN	115/116 (99%)	97%–100%	88/89 (99%)	97%–100%
'Extended' criteria				
Definite MMN	115/116 (99%)	97%–100%	88/89 (99%)	97%–100%
Definite or Probable MMN	112/116 (96.5%)	93%–100%	85/89 (95.5%)	91%–100%

Abbreviations: CIDP = chronic inflammatory demyelinating polyradiculoneuropathy, EFNS/PNS = European Federation of Neurological Societies/Peripheral Nerve Society, MMN = multifocal motor, *n* = number, NCS = nerve conduction study/neuropathy.

<sup>a</sup>At least five motor nerves examined in MMN patients and controls.

[32] and distinguishing it from CIDP, where nerve terminals and spinal roots are more involved [33].

Temporal dispersion was more frequent in MMN than CIDP, consistent with prior studies [18, 19, 21–24] and animal models [34, 35] showing IgM anti-GM1 antibodies induce CB and temporal dispersion. These characteristics differentiate MMN from another disorder mediated by anti-GM1 antibodies, acute

motor axonal neuropathy (AMAN), where temporal dispersion is rare or absent [36] and, instead, align it more closely with paranopathies mediated by anti-contactin-1 (CNTN1) and neurofascin-155 (NF155) antibodies [30, 31]. Despite a shared pathophysiological mechanism, it remains unclear why temporal dispersion is common in MMN and paranopathies but not in AMAN. The limited pathological studies on MMN yield conflicting results [32, 37, 38].

Incorporating additional electrophysiological parameters in the diagnostic criteria increased definite/probable diagnoses by 26%, with minimal specificity loss (3%). The high specificity is attributable to the normality of sensory nerve conduction parameters—pathognomonic for MMN—but rare in axonal polyneuropathy or CIDP. In our cohort, the modest reduction in specificity was primarily attributable to overlap with ALS patients—who, like those with MMN, typically present with a pure motor phenotype and normal sensory conduction studies—rather than with CIDP patients, who usually show sensorimotor involvement. In a condition like MMN, where effective therapy exists to significantly improve symptoms and reduce disability, greater diagnostic sensitivity is preferable to minimizing false positives. However, even a small reduction in specificity may lead to misclassification and unnecessary treatment in a limited number of patients. This underscores the importance of interpreting these additional findings in the broader clinical context, supported by characteristic clinical features and complementary diagnostic investigations. Furthermore, including these electrophysiological criteria in the ‘possible MMN’ category may enable diagnosis in patients who do not exhibit CB, without requiring prior treatment with IVIg.

In this study, the sensitivity of the extended criteria was unchanged by the inclusion of supportive criteria, suggesting that the additional electrophysiological parameters may capture diagnostic features otherwise provided by supportive investigations. This finding may reflect characteristics of our cohort and the retrospective design. Further studies in larger, independent cohorts are needed to determine whether the extended criteria consistently complement or partially substitute supportive criteria in clinical practice.

This study has several limitations. First, its retrospective design and non-standardized nature of nerve conduction studies could introduce variability in the data collection process. While efforts were made to include pretreatment studies and standardize evaluations, variations in the number and types of nerves studied, as well as the techniques used across different centers, may have affected the consistency of the findings. Additionally, the higher number of control subjects compared to MMN patients could bias the specificity results, favoring false-negative findings. The absence of a definitive diagnostic biomarker for MMN means that our study, like others, relies on the expert opinion of treating physicians. Despite our efforts to minimize diagnostic errors through rigorous review, the possibility of misdiagnosis cannot be entirely excluded. Further studies, ideally involving treatment-naïve patients and standardized electrophysiological protocols, are needed to validate these findings and support the refinement of diagnostic criteria.

In conclusion, our study highlights the possible advantage of expanding the diagnostic criteria of MMN to include additional nerve conduction parameters beyond CB, significantly improving the diagnostic sensitivity and only marginally reducing the specificity. The frequent occurrence of temporal dispersion and other electrophysiological abnormalities observed in demyelinating or paranodal neuropathies suggests a broader electrophysiological profile in MMN than is currently recognized. Adopting a more inclusive diagnostic framework may facilitate earlier and more accurate diagnoses, reducing the delay in initiating

effective IVIg therapy, improving patient outcomes, and facilitating patient inclusion in clinical trials.

### Author Contributions

**Pietro Emiliano Doneddu:** conceptualization, investigation, writing – original draft, methodology, writing – review and editing, project administration, data curation, supervision, resources. **Chiara Gallo:** investigation, methodology, writing – review and editing, project administration, data curation, formal analysis. **Yuri Falzone:** investigation, methodology, writing – review and editing, data curation, resources. **Sabrina Matà:** investigation, methodology, writing – review and editing, data curation, resources. **Giuseppe Cosentino:** investigation, methodology, writing – review and editing, data curation, resources. **Vincenzo Di Stefano:** investigation, methodology, writing – review and editing, data curation, resources. **Massimiliano Filosto:** investigation, methodology, writing – review and editing, data curation, resources. **Luca Leonardi:** investigation, methodology, writing – review and editing, data curation, resources. **Dario Ricciardi:** investigation, methodology, writing – review and editing, data curation, resources. **Anna Mazzeo:** investigation, methodology, writing – review and editing, data curation, resources. **Luana Benedetti:** investigation, methodology, writing – review and editing, data curation, resources. **Marco Luigetti:** investigation, methodology, writing – review and editing, data curation, resources. **Paolo Solla:** investigation, methodology, writing – review and editing, data curation, resources. **Maurizio Inghilleri:** investigation, methodology, writing – review and editing, data curation, resources. **Dario Cocito:** investigation, methodology, writing – review and editing, data curation, resources. **Francesco Habetswallner:** investigation, methodology, writing – review and editing, data curation, resources. **Alberto De Lorenzo:** investigation, methodology, writing – review and editing, data curation, resources. **Benedetta Sorrenti:** investigation, methodology, writing – review and editing, data curation, resources. **Maddalena Spalletti:** investigation, methodology, writing – review and editing, data curation, resources. **Elisa Vegezzi:** investigation, methodology, writing – review and editing, data curation, resources. **Christian Messina:** investigation, methodology, writing – review and editing, data curation, resources. **Barbara Risi:** investigation, methodology, writing – review and editing, data curation, resources. **Francesca Forcina:** investigation, methodology, writing – review and editing, data curation, resources. **Alessandra Fasolino:** investigation, methodology, writing – review and editing, data curation, resources. **Luca Gentile:** investigation, methodology, writing – review and editing, data curation, resources. **Alessandro Beronio:** investigation, methodology, writing – review and editing, data curation, resources. **Francesca Vitali:** investigation, methodology, writing – review and editing, data curation, resources. **Federica Moret:** investigation, methodology, writing – review and editing, data curation, resources. **Giacomo Iabichella:** investigation, methodology, writing – review and editing, data curation, resources. **Stefano Gazzina:** investigation, methodology, writing – review and editing, data curation, resources. **Corrado Cabona:** investigation, methodology, writing – review and editing, data curation, resources. **Claudia Cutellè:** investigation, methodology, writing – review and editing, data curation, resources. **Elisa Bianchi:** methodology, validation, writing – review and editing, formal analysis. **Eduardo Nobile-Orazio:** investigation, funding acquisition, methodology, validation, writing – review and editing, project administration, resources, supervision.

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### Ethics Statement

The study was approved by the Ethical Committee of IRCCS Humanitas Clinical Institute (D.M. 8/2/2013; 413/17) and of each participating center.

## Consent

Patient Consent: Obtained.

## Conflicts of Interest

Pietro Emiliano Doneddu reports personal fees for Advisory from ArgenX, and received travel grants to attend scientific meetings from CSL Behring and Kedrion. Giuseppe Cosentino has received travel grants to attend scientific meetings from CSL Behring and Kedrion. Massimiliano Filosto has served on scientific advisory boards for CSL Behring, Sanofi, and Amicus, and has received travel grants from Sanofi, Biogen, Kedrion, and CSL Behring to attend scientific meeting. Anna Mazzeo has received travel grants from Kedrion and CSL Behring to attend scientific meeting. Maurizio Inghilleri has received travel grants to attend scientific meetings from CSL Behring, ArgenX, and Alexion. Federica Moret has received travel grants to attend scientific meetings from CSL Behring, ArgenX, and Alexion. Eduardo Nobile-Orazio reports personal fees for Advisory or Scientific Board from ArgenX—Belgium, Takeda—Italy and USA, CSL Behring—Italy and USA, Janssen—USA, Kedrion—Italy, LFB—France, Roche—Switzerland, Sanofi—USA. The other authors declare no conflicts of interest.

## Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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