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Received: 15 May 2024 | Accepted: 31 July 2024

DOI: 10.1111/ene.16444

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

ORIGINAL ARTICLE

Comparison of the diagnostic accuracy of the 2010 European Federation of Neurological Societies/Peripheral Nerve Society and American Association of Electrodiagnostic Medicine diagnostic criteria for multifocal motor neuropathy

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Funding information
Takeda Italia SPA, Grant/Award Number: IIR-ITA-BXLT-001955/ IISR-2017-104226; Fondazione Humanitas per la Ricerca

Abstract

Background and Purpose: This study was undertaken to compare the sensitivity and specificity of the 2010 European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) diagnostic criteria for multifocal motor neuropathy (MMN) with those of the American Association of Electrodiagnostic Medicine (AAEM).

Methods: Sensitivity and specificity of the two sets of criteria were retrospectively evaluated in 53 patients with MMN and 280 controls with axonal peripheral neuropathy,

Pietro Emiliano Doneddu and Chiara Gallo contributed equally to the study.

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inflammatory demyelinating polyneuropathy, or amyotrophic lateral sclerosis. Comparison of the utility of nerve conduction studies with different numbers of nerves examined was also assessed.

Results: The 2010 EFNS/PNS criteria had a sensitivity of 47% for definite MMN and 57% for probable/definite MMN, whereas the AAEM criteria had a sensitivity of 28% for definite MMN and 53% for probable/definite MMN. The sensitivity of the AAEM criteria was higher when utilizing area compared to amplitude reduction to define conduction block. Using supportive criteria, the sensitivity of the 2010 EFNS/PNS criteria for probable/definite MMN increased to 64%, and an additional 36% patients fulfilled the criteria (possible MMN). Specificity values for definite and probable/definite MMN were slightly higher with the AAEM criteria (100%) compared to the EFNS/PNS criteria (98.5% and 97%). Extended nerve conduction studies yielded slightly increased diagnostic sensitivity for both sets of criteria without significantly affecting specificity.

Conclusions: In our patient populations, the 2010 EFNS/PNS criteria demonstrated higher sensitivity but slightly lower specificity compared to the AAEM criteria. Extended nerve conduction studies are advised to achieve slightly higher sensitivity while maintaining very high specificity.

KEYWORDS
diagnosis, diagnostic criteria, guidelines, MMN, multifocal motor neuropathy

INTRODUCTION

Multifocal motor neuropathy (MMN) is a rare acquired motor neuropathy characterized by progressive multifocal or asymmetric weakness without sensory symptoms and signs [1–3]. It typically affects the upper limbs more than the lower limbs [1–3]. Electrodiagnostic studies reveal an asymmetric motor neuropathy with characteristic conduction block (CB) [1–3]. Serum immunoglobulin M (IgM) anti-ganglioside (anti-GM1) antibodies are present in approximately 50% of patients [1–3]. Its nosological characterization is relatively recent, dating back to 1988 [4].

Unlike some motor neuropathies, MMN is treatable with intravenous immunoglobulin (IVIg), and untreated patients are likely to experience progressive muscle weakness that may result in serious functional impairment and reduced quality of life, making early diagnosis crucial. Since its nosological characterization, numerous sets of diagnostic criteria have been proposed for MMN [5–12]. In the absence of a pathognomonic diagnostic biomarker, diagnosis still relies on clinical manifestations and nerve conduction studies, possibly supported by some additional diagnostic examinations. Multifocal CB in motor nerves, occurring outside typical sites of nerve compression, remain the key instrumental and pathological hallmark of MMN. CB can be defined as the focal failure of a nerve impulse to propagate along a structurally intact axon. The CB observed in MMN is distinctive in that it exclusively affects motor fibers, whereas sensory conduction remains normal through the same nerve segment. There remains a debate regarding whether the decrease in the area or amplitude of the compound muscle action potential (CMAP) should be the preferred parameter for defining CB, as well as the extent of reduction of CMAP amplitude/area necessary to classify a reduction as a true CB [10–12]. Consequently, over the years, different criteria have been employed to define CB and thus for the electrophysiological diagnosis of MMN [5–12]. Presently, two main sets of diagnostic criteria are commonly utilized for MMN diagnosis: those of the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS), which defines CB based on CMAP area decline, and those of the American Association of Electrodiagnostic Medicine (AAEM), which considers CB as a decline in either amplitude or area (Table 1) [10–12].

The objective of this study was to evaluate the sensitivity and specificity of the 2010 EFNS/PNS criteria in comparison with the AAEM criteria in a large population of patients with MMN and controls. Comparison of nerve conduction studies with different numbers of nerves examined was also made.

METHODS

Study population

MMN patients

We implemented a web-based database of Italian MMN patients, which currently includes data from 73 patients fulfilling the 2010 EFNS/PNS criteria for possible, probable, or definite MMN, and 11 patients with a clinical diagnosis of MMN who do not meet the same criteria. These 11 patients had a medical history, clinical signs, and supportive examinations compatible with the diagnosis of MMN

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TABLE 1 2010 EFNS/PNS and AAEM electrophysiological criteria for conduction block.

	EFNS/PNS	AAEM
Definite MMN	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 lower limit of normal and >1 mV, and increase of proximal to distal negative peak CMAP duration must be ≤30%	CB in two or more nerves under the following criteria: >50% CMAP amplitude reduction with minimal[a] TD in the median,[c] ulnar,[c] or peroneal nerve across fibular head, or >60% CMAP amplitude reduction with minimal[a] TD in the peroneal (below fibular/ankle) or tibial nerve (knee/ankle) OR >40% CMAP area reduction with minimal[a] TD in the median,[c] ulnar,[c] or peroneal nerve across fibular head, or >50% CMAP area reduction with minimal[a] TD in the peroneal (below fibular/ankle) or tibial nerve (knee/ankle)
Probable MMN	CB in two nerves (or in just one nerve plus supportive criteria) under the following criteria: Negative peak CMAP area reduction of at least 30% over a long segment of an upper limb nerve with increase of proximal to distal negative peak CMAP duration ≤ 30% OR Negative peak CMAP area reduction of at least 50% (same as definite) with an increase of proximal to distal negative peak CMAP duration > 30%	CB in two or more motor nerve segments (or in just one plus definite CB in a different motor nerve) under the following criteria: Minimal temporal dispersion[a]: 40%–49% CMAP amplitude reduction in the median,[d] ulnar,[d] or peroneal nerve across fibular head, or >50% CMAP amplitude reduction in the radial nerve, or 50%–59% CMAP amplitude reduction in the peroneal (below fibular/ankle) or tibial nerve (knee/ankle), or >50% in the peroneal (SN/above fibular) and tibial nerve (SN/knee) OR 30%–39% CMAP area reduction in the median,[d] ulnar,[d] or peroneal nerve across fibular head, or >40% CMAP area reduction in the radial nerve, or 40%–49% CMAP area reduction in the peroneal (below fibular/ankle) or tibial nerve (knee/ankle), or >40% in the peroneal (SN/above fibular) or tibial nerve (SN/knee) Moderate temporal dispersion[b]: >50% CMAP amplitude reduction in the median, ulnar, radial, or peroneal nerve across fibular head, or >60% CMAP amplitude reduction in the peroneal (below fibular/ankle and SN/above fibular) or tibial nerve OR >40% CMAP area reduction in the median, ulnar, radial, or peroneal nerve across fibular head, or >50% CMAP area reduction in the peroneal (below fibular/ankle and SN/above fibular) or tibial nerve
Sensory nerve conduction criteria	Normal sensory nerve conduction in upper limb segments with CB	Normal results for sensory nerve conduction studies on all tested nerves, with a minimum of three nerves tested

Abbreviations: AAEM, American Association of Electrodiagnostic Medicine; CB, conduction block; CMAP, compound muscle action potential; EFNS/PNS, European Federation of Neurological Societies/Peripheral Nerve Society; MMN, multifocal motor neuropathy; SN, sciatic notch; TD, temporal dispersion.

[a]Duration increased by 30% or less.

[b]Proximal (Erb's point/axilla) nerve segment not accepted.

[c]>40% amplitude or >30% area reduction in proximal (Erb's point/axilla) nerve segment.

[d]Duration increased by 31%–60%.

[13]. In nine of these 11 cases, the response to IVIg was unclear, precluding a diagnosis of possible MMN. Furthermore, two newly diagnosed patients were included in the database before initiating IVIg treatment.

The treating neurologist included all the data in a web-based electronic database expressly prepared by Cineca (Bologna, Italy). The treating neurologist initially made the diagnosis of MMN, which was reviewed and classified by the coordinating center (P.E.D. and E.N.-O.) according to 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, magnetic resonance imaging [MRI] of the brachial plexus, anti-GM1 IgM antibody positivity, and objective clinical improvement following IVIg treatment). Upon enrollment, all patients underwent a comprehensive clinical history assessment, supplemented by information extracted from medical records [13]. Clinical findings from previous examinations were included when available, along with results from nerve conduction studies performed throughout the disease

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course. Treatment response was defined as a subjective improvement that was objectively confirmed by an increase of at least 2 points in the Medical Research Council sum score (range = 0–60) or at least 1 point in the Inflammatory Neuropathy Cause and Treatment disability score (range = 0–10) [14, 15]. Informed consent was obtained from all participants upon enrollment, and the study was approved by the ethical committee of each participating center.

Controls

To ascertain the specificity of the two sets of criteria, we analyzed electrophysiological data from 280 control patients diagnosed with sensory, sensorimotor, or motor axonal peripheral neuropathy, inflammatory demyelinating polyneuropathy, or lower motor neuron disease, who were regularly monitored at our outpatient peripheral neuropathy clinic at the Humanitas Research Institute. The control patients were chosen consecutively, including all those followed regularly in our clinic. The control population comprised individuals with various conditions, including diabetic peripheral neuropathy ($n = 74$), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP; $n = 45$), amyotrophic lateral sclerosis with lower motor neuron involvement ($n = 44$), chemotherapy-induced neuropathy ($n = 38$), chronic idiopathic axonal polyneuropathy ($n = 38$), Guillain–Barré syndrome ($n = 10$), vasculitic neuropathy ($n = 7$), vitamin B12 deficiency neuropathy ($n = 6$), rheumatoid neuropathy ($n = 6$), IgG paraproteinemic neuropathy ($n = 5$), hepatitis C virus-related neuropathy ($n = 3$), toxic neuropathy ($n = 2$), amyloid neuropathy ($n = 1$), and paraneoplastic neuropathy ($n = 1$).

Study design

In view of the retrospective design, electrophysiological studies were performed in a nonstandardized manner but consistently included the clinically affected nerves. The number of motor nerves studied varied from four to 10.

Pretreatment electrophysiological studies were preferentially included; if these were not available, a later or posttreatment study was selected. The extensiveness of the study of arm nerves varied from the distal forearm segment only to a full-length study up to Erb's point. Patients were also managed in a nonstandardized fashion, with ancillary examinations and treatments selected according to the clinical judgment of the treating physician. Although this variability may be suboptimal for research purposes, it likely reflects real-life clinical practice. 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, and 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 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 along the median, ulnar, sural, and in some patients, radial nerves; distal latency, sensory nerve action potential (SNAP) amplitude, or conduction velocity was evaluated. All nerve conductions were performed at a temperature of at least 33°C at the palm and 30°C at the external malleolus. Age-dependent reference values for sural SNAP amplitude were considered. Results were analyzed according to each laboratory's range of normal values. To precisely evaluate CMAP amplitude, area, and duration, nerve conduction study waveforms of the MMN and control patients were reviewed, and measurements were redone following the indications of the two sets of criteria. For each patient, the waveforms were sent to the coordinating center via email. Patients whose nerve conduction study waveforms were not available for review were excluded from the study analyses. CMAP amplitude was measured from baseline to negative peak. CMAP area was measured from the onset of the negative peak to its return to baseline. Sensory conduction studies were performed in all patients using the antidromic technique. Both sets of criteria require normal results for sensory nerve conduction studies in the same segment affected by motor CB. Therefore, subjects who did not have sensory conduction velocities examined in the affected nerves were excluded from the study. For each patient, the clinical and electrophysiological data were reviewed to determine fulfillment of the two sets of criteria. Sensitivity and specificity analyses were first ascertained in all included patients regardless of the number of nerves examined, to test the two sets of criteria using real-life data, and then repeated in the patients and controls with at least seven motor nerves examined ("extended nerve conduction study protocol").

Statistical analysis

The comparative diagnostic gain in sensitivity and specificity, achieved with the use of the more sensitive or specific set of criteria, was calculated using a McNemar test. Diagnostic accuracy was calculated as the proportion of correctly classified subjects (true positive [TP] + true negative [TN]) among all subjects (TP + TN + false positive + false negative). All tests were two-tailed, and the significance level was set at 0.05. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Sensitivity and specificity were assessed taking into account the number of nerves examined, in line with previous studies.

RESULTS

Among the 84 MMN patients included in the database, 14 patients were excluded because only CMAP amplitude, but not area, was measured and subsequently recorded in the database by the treating physician, and 17 were excluded due to the unavailability of nerve

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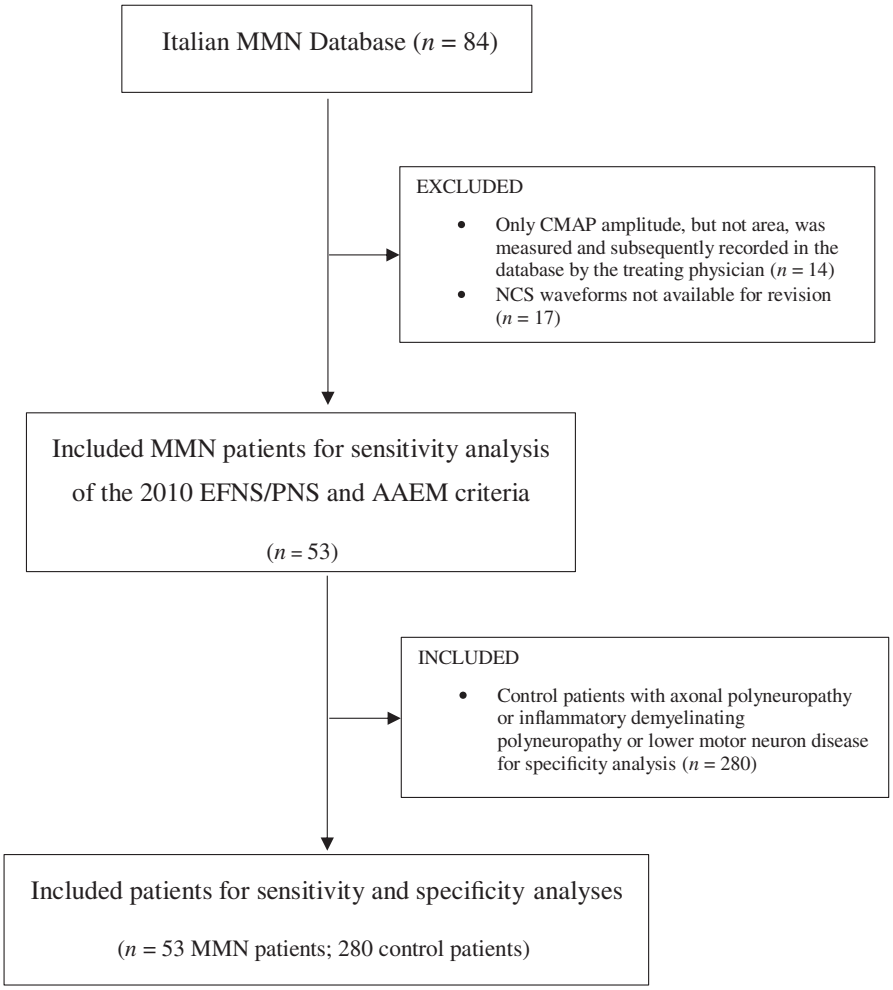

FIGURE 1 Flowchart of patients' selection for sensitivity analyses of the 2010 European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) and American Association of Electrodiagnostic Medicine (AAEM) criteria for multifocal motor neuropathy (MMN). CMAP, compound muscle action potential; NCS, nerve conduction study.

conduction study waveforms for review (Figure 1). The final study population included 53 patients with MMN, 30 of whom had undergone an extended nerve conduction study. Of the 280 controls, 219 had undergone an extended nerve conduction study. Demographic and clinical characteristics and number of nerves examined with nerve conduction studies in MMN patients and controls are summarized in Table 2. A median of 7 (range = 4–10) motor nerves and 5 (range = 3–8) sensory nerves were evaluated in MMN patients, and a median of 4 (range = 3–8) motor nerves and 4 (range = 3–6) sensory nerves in control patients. A total of 320 and 1226 motor nerves of MMN patients and controls, respectively, were included in the analyses.

Table 3 shows sensitivity of the two sets of criteria. Sensitivity of the EFNS/PNS criteria was 47% for definite MMN and 57% for probable/definite MMN, whereas sensitivity of the AAEM criteria was 28% for definite MMN and 53% for probable/definite MMN. Using extended nerve conduction study protocol, sensitivity of the EFNS/PNS criteria slightly increased, being 50% for definite MMN and 60% for probable/definite MMN, whereas sensitivity of the AAEM criteria rose to 33% for definite MMN and 57% for probable/definite MMN. When we also considered supportive criteria, sensitivity of the EFNS/PNS criteria for possible MMN was 36% and for probable/definite MMN was 64%, resulting in 19 additional diagnoses (possible MMN) and in four additional patients fulfilling the criteria for probable/definite MMN. Of the 19 patients who had a diagnostic upgrading to possible MMN, all of whom demonstrated a response to IVIg treatment, 12 did not exhibit CB, and seven showed probable CB in only one nerve, without any other supportive criteria apart from a response to IVIg. In the four patients who underwent diagnostic upgrading to probable MMN, the supportive criterion most frequently contributing to the diagnostic improvement was response to IVIg treatment in all four patients, elevated IgM GM1 antibodies in three of four tested patients (75%), increased CSF proteins in one of two tested patients (50%), and positive MRI findings in one of two patients (50%). Compared to the AAEM criteria, the EFNS/PNS electrodiagnostic criteria exhibited greater sensitivity for the diagnosis of definite MMN ($p = 0.0094$), whereas the sensitivity of both criteria for the diagnosis of probable/definite MMN was found to be similar ($p = 0.4497$).

Four patients were missed by the AAEM electrodiagnostic criteria; each had definite or probable CB in only one nerve. Conversely, two patients who did not meet the EFNS/PNS criteria for probable MMN were identified by the AAEM criteria: one patient with probable CB (area and amplitude) in both the tibial and ulnar nerves, and another with definite CB (area and amplitude) in the tibial nerve and probable CB in the ulnar nerve. Neither

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TABLE 2 Demographic and clinical characteristics and number of nerves examined with NCS in MMN patients and controls.

	MMN patients, $n=53$	Control patients, $n=280$
Gender, male, *n* (%)	35/53 (67%)	171/109 (61%)
Age at onset, years, mean (SD)	59 (12)	72 (12)
Motor nerves examined at NCS, *n*, median (range)	7 (4–10)	4 (3–8)
Sensory nerves examined at NCS, *n*, median (range)	5 (3–8)	4 (3–6)
Response to IVIg treatment, *n* (%)	52/53 (98%)	
Elevated IgM anti-GM1 antibodies/tested, *n* (%)	14/27 (52%)	
Increased CSF proteins/tested, *n* (%)	9/20 (45%)	
Nerve imaging, positive/tested, *n* (%)	8/13 (61.5%)	
MRC sum score (0–60) at enrolment, mean (range)	42.5 (30–55)	

Abbreviations: anti-GM1, antiganglioside; CSF, cerebrospinal fluid; IgM, immunoglobulin M; IVIg, intravenous immunoglobulin; MMN, multifocal motor neuropathy; MRC, Medical Research Council; NCS, nerve conduction studies.

TABLE 3 Sensitivity of the 2010 EFNS/PNS and AAEM criteria.

	EFNS/PNS electrodiagnostic criteria for definite MMN	EFNS/PNS electrodiagnostic criteria for probable/definite MMN	EFNS/PNS criteria for probable/definite MMN using supportive criteria	EFNS/PNS criteria for possible MMN
Total, *n* (%)	25/53 (47%)	30/53 (57%)	34/53 (64%)	19/53 (36%)
Extended NCS protocol, *n* (%)	15/30 (50%)	18/30 (60%)	20/30 (67%)	10/30 (33%)
	AAEM electrodiagnostic criteria for definite MMN	AAEM electrodiagnostic criteria for probable/definite MMN	AAEM electrodiagnostic criteria for probable/definite MMN with CB defined as amplitude reduction only	AAEM electrodiagnostic criteria for probable/definite MMN with CB defined as area reduction only
Total, *n* (%)	15/53 (28%)	28/53 (53%)	24/53 (45%)	28/53 (53%)
Extended NCS protocol, *n* (%)	10/30 (33%)	17/30 (57%)	18/30 (60%)	18/30 (60%)

Abbreviations: AAEM, American Association of Electrodiagnostic Medicine; CB, conduction block; EFNS/PNS, European Federation of Neurological Societies/Peripheral Nerve Society; MMN, multifocal motor neuropathy; NCS, nerve conduction studies.

of these patients had positive supportive criteria as required by the EFNS/PNS. The median number of motor nerves examined in the four patients who missed the diagnosis using the AAEM criteria was 6 (range = 4–8). Six patients with one definite CB and one probable CB, who fulfilled the EFNS/PNS diagnostic criteria for definite MMN, were reclassified as probable MMN using the AAEM diagnostic criteria. When the analysis of the sensitivity of the AAEM criteria was repeated taking into account only CB defined as amplitude reduction versus those defined as area reduction, the latter parameter showed greater sensitivity (53% vs. 45%) for probable/definite MMN.

Table 4 shows the specificity of the two sets of electrodiagnostic criteria. Specificity of the EFNS/PNS criteria was 98.5% for definite MMN and 97% for probable/definite MMN, whereas specificity of the AAEM criteria was 100% for definite and probable/definite MMN. Using the extended nerve conduction study protocol, specificity of the two sets of criteria remained similar (Table 4). Compared to the AAEM criteria, the EFNS/PNS criteria had similar specificity for definite MMN ($p=0.125$) but lower specificity for probable/definite MMN ($p=0.0039$).

The higher specificity of the AAEM criteria resulted in nine additional control patients correctly identified as not having MMN. Among them, seven diagnosed with CIDP exhibited either probable or definite CB (area and amplitude) in one nerve ($n=4$) or in two nerves ($n=3$), with normal sensory nerve conduction studies in these nerves, despite abnormalities in others. Furthermore, of the two remaining control patients, one with diabetic neuropathy exhibited a probable CB (area and amplitude) in one ulnar nerve, whereas another diagnosed with amyotrophic lateral sclerosis presented a definite CB (area and amplitude) in a median nerve. These two

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TABLE 4 Specificity of the 2010 EFNS/PNS and AAEM electrodiagnostic criteria.

	EFNS/PNS electrodiagnostic criteria for definite MMN	EFNS/PNS electrodiagnostic criteria for probable/definite MMN	AAEM electrodiagnostic criteria for definite MMN	AAEM electrodiagnostic criteria for probable/definite MMN
Total, *n* (%)	276/280 (98.5%)	271/280 (97%)	280/280 (100%)	280/280 (100%)
Extended NCS protocol, *n* (%)	218/219 (99.5%)	217/219 (99%)	219/219 (100%)	219/219 (100%)

Abbreviations: AAEM, American Association of Electrodiagnostic Medicine; EFNS/PNS, European Federation of Neurological Societies/Peripheral Nerve Society; MMN, multifocal motor neuropathy; NCS, nerve conduction studies.

control patients also had normal sensory nerve conduction studies in the affected nerves, despite abnormalities in others.

We investigated the diagnostic utility of including CB in the tibial nerve as specified by AAEM criteria. In our cohort, 69 tibial nerves were examined across 35 MMN patients, among whom 10 exhibited probable or definite CB (area and amplitude) in one ($n=6$) or both ($n=4$) tibial nerves. Although all of these patients also had CB in another nerve, two were incorrectly classified as not having MMN by the EFNS/PNS criteria due to the absence of positive supportive criteria. In the control group, where 457 tibial nerves were examined across 252 patients, 19 individuals (13 with CIDP) showed CB in one ($n=12$) or both ($n=7$) tibial nerves. None of these control subjects was misidentified as having MMN by the AAEM criteria, as all had at least one abnormal sensory nerve conduction result. We also assessed the diagnostic relevance of considering CB in other upper limb motor nerves. Specifically, the radial nerve was tested in our cohort in 13 MMN patients and three control subjects, with 26 and five radial nerves examined, respectively. Five MMN patients had CB (area and amplitude) in one radial nerve; however, only one patient, lacking CB in other nerves, failed to meet the AAEM criteria. In the control group, one CIDP patient exhibited CB (area and amplitude) in one radial nerve but was accurately identified as not having MMN by the EFNS/PNS criteria due to an abnormal sensory nerve conduction study in the same nerve. The musculocutaneous and axillary nerves were not tested in any of the patients or control subjects.

Compared with the AAEM criteria, the EFNS/PNS electrodiagnostic criteria had a greater diagnostic accuracy for definite MMN (90% vs. 88.5%) and a lower accuracy for probable/definite MMN (90% vs. 92.5%).

DISCUSSION

The diagnosis of MMN relies on the identification of a characteristic pattern of clinical symptoms and signs, the exclusion of alternative causes that could mimic MMN, and the combination of nerve conduction studies with ancillary tests [1–3, 11, 12]. Similar to CIDP, a pathognomonic disease biomarker for MMN remains elusive. Consequently, diagnosis primarily hinges on electrophysiological tests, particularly the detection of CB in motor nerves. Numerous studies have proposed varying definitions of CB [5–12, 16–20], with some indicating that defining CB based on area rather than amplitude reduction provides greater specificity [11, 12, 19, 20]. Computer modeling of CB and temporal dispersion in an animal model have demonstrated that up to 50% area reduction of the proximal to distal CMAP may result entirely from interphase cancellation [20]. Based on these studies, the 2010 EFNS/PNS diagnostic criteria for MMN define CB as area reduction, albeit acknowledging the limited evidence supporting this choice [12]. In contrast, the AAEM criteria define CB as a decrease in either amplitude or area [10]. Unlike the 2010 EFNS/PNS criteria, the AAEM criteria mandate the presence of at least two CB in two different motor nerves, consider CB in the tibial nerve valid, do not recognize CB resulting from proximal stimulations for the definite MMN category, and establish diverse diagnostic cutoffs of CB in individual nerves [10]. Both criteria sets, developed based on expert consensus, are widely utilized for MMN diagnosis, although our analysis of data from the Italian MMN registry revealed varying preferences among centers regarding criteria usage [13].

The accuracy of these criteria sets has not been directly compared to date, despite evidence indicating the possibility of MMN misdiagnosis and frequent diagnostic delays associated with disability accumulation [2, 21, 22]. Misdiagnosis of MMN can lead to inappropriate treatments and delayed initiation of disability-modifying IVIg treatment, and negatively impact patients' quality of life [2, 21–23]. Our study demonstrates higher sensitivity of the 2010 EFNS/PNS criteria, particularly for definite MMN, compared to the AAEM criteria. This increased sensitivity persisted even when an extended nerve conduction study protocol was employed. The primary reason for the lower sensitivity of the AAEM criteria in our population was the requirement for the mandatory presence of two CB in two different nerves, as opposed to only one CB as required by the 2010 EFNS/PNS criteria. Considering the supportive criteria, recognized by the 2010 EFNS/PNS but not considered by the AAEM, further increased the difference in sensitivity of the two criteria, highlighting the utility of the supportive criteria in MMN diagnosis. Applying the 2010 EFNS/PNS criteria also resulted in an additional 36% of patients without CB being diagnosed with MMN due to their positive response to IVIg therapy. Our recent study showed that patients with possible MMN exhibit similar clinical characteristics and positivity on supporting tests compared to patients with probable and definite MMN. Therefore,

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the inclusion of this diagnostic category should be considered an advantage of the EFNS/PNS criteria compared to the AAEM criteria [13]. Overall, the greater sensitivity of the 2010 EFNS/PNS criteria in clinical practice translates into greater access to IVIg therapy. Additionally, it allows for the inclusion of a greater number of patients in clinical trials, both of which are highly relevant for a rare disease that causes significant disability.

Conversely, the AAEM criteria showed slightly higher specificity compared to the EFNS/PNS criteria, particularly for probable/definite MMN (100% vs. 97%). Specificity values of the two sets of criteria remained high even in patients who underwent an extended nerve conduction study protocol. The high specificity of the two sets of criteria reinforces the recommendation of the 2010 EFNS/PNS criteria to base the diagnosis of definite MMN entirely on the electrophysiological criterion [12]. Even for the probable MMN category, the 2010 EFNS/PNS electrodiagnostic criteria exhibited high specificity. These findings do not support the common clinical practice, as reported in our recent study, of utilizing supportive criteria in patients already diagnosed with definite or probable MMN based on electrophysiological criteria [13]. Our study implies that the supporting criteria mainly increase the diagnostic sensitivity of the electrophysiological criteria, whereas their value in increasing specificity appears limited considering the already high specificity of the electrophysiological examination. The primary reason for the lower specificity of the EFNS/PNS criteria in our population was the requirement for the mandatory presence of normal sensory nerve conduction in upper limb segments with CB only, as opposed to the AAEM criteria requirement of normal results for sensory nerve conduction studies on all tested nerves. This criterion should be considered for revision in the next update of the EFNS/PNS criteria. Including CB in the tibial nerve as valid under the AAEM criteria did not enhance sensitivity significantly and could have reduced specificity if not for frequent sensory conduction alterations in control patients. Our study lacks sufficient data to assess the value of including evaluations of the radial nerve and other upper limb motor nerves in the diagnostic criteria.

Overall, the EFNS/PNS electrodiagnostic criteria had greater diagnostic accuracy for definite MMN (90% vs. 88.5%) and lower accuracy for probable/definite MMN (90% vs. 92.5%) compared to the AAEM criteria. However, the inclusion of the supporting criteria and the possible MMN category makes the EFNS/PNS criteria as a whole significantly more sensitive.

In conclusion, our study demonstrates that the 2010 EFNS/PNS criteria are more sensitive but slightly less specific than the AAEM criteria for diagnosing MMN. Implementing more extended nerve conduction studies improved the diagnostic sensitivity while maintaining very high specificity. Given these findings, the use of 2010 EFNS/PNS criteria should be preferred in both clinical practice and research setting. This preference will facilitate greater access to therapy and increase patient inclusion in clinical trials, both of which are crucial in a rare and disabling disease like MMN. Further large-scale studies are warranted to confirm our results and to refine the criteria for better balance between sensitivity and specificity.

Limitations of our study include a relatively limited patient series for comparison analysis, a retrospective design, and the inclusion of patients from tertiary centers, which may introduce selection bias. However, the rarity of MMN necessitates collaboration across multiple centers to assemble a substantial patient cohort for meaningful analysis. 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.

AUTHOR CONTRIBUTIONS

Pietro Emiliano Doneddu: Conceptualization; writing – original draft; writing – review and editing; project administration; data curation; methodology. **Chiara Gallo:** Writing – original draft; conceptualization; methodology; writing – review and editing; data curation. **Luca Gentile:** Validation; visualization; writing – review and editing; data curation. **Dario Cocito:** Validation; visualization; writing – review and editing; data curation. **Yuri Falzone:** Validation; visualization; writing – review and editing; data curation. **Vincenzo Di Stefano:** Validation; visualization; writing – review and editing; data curation. **Maurizio Inghilleri:** Validation; visualization; writing – review and editing; data curation. **Giuseppe Cosentino:** Validation; visualization; writing – review and editing; data curation. **Sabrina Matà:** Validation; visualization; writing – review and editing; data curation. **Anna Mazzeo:** Validation; visualization; writing – review and editing; data curation. **Massimiliano Filosto:** Validation; visualization; writing – review and editing; data curation. **Erdita Peci:** Validation; visualization; writing – review and editing; data curation. **Benedetta Sorrenti:** Validation; visualization; writing – review and editing; data curation. **Filippo Brighina:** Validation; visualization; writing – review and editing; data curation. **Federica Moret:** Validation; visualization; writing – review and editing; data curation. **Elisa Vegezzi:** Validation; visualization; writing – review and editing; data curation. **Martina Sperti:** Validation; visualization; writing – review and editing; data curation. **Barbara Risi:** Validation; visualization; writing – review and editing; data curation. **Eduardo Nobile-Orazio:** Validation; visualization; writing – review and editing; data curation; supervision; resources; project administration; conceptualization; funding acquisition.

FUNDING INFORMATION

The study was supported by Baxalta, now part of Takeda, with investigator-initiated grant no. IIR-ITA-BXLT-001955/IISR-2017-104226, Italy. The study was also supported by IRCCS, Humanitas Research Hospital (Rozzano, Milan, Italy). The funders and supporters had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

CONFLICT OF INTEREST STATEMENT

P.E.D. has received travel grants to attend scientific meetings from CSL Behring and Kedrion. D.C. has received honoraria for lecturing from Shire, CSL Behring, and Kedrion and travel grants to attend scientific meetings from Shire, Kedrion, and CSL Behring. A.M. has

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received travel grants from Kedrion and CSL Behring to attend scientific meetings. M.F. 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 meetings. G.C. has received travel grants to attend scientific meetings from CSL Behring and Kedrion. M.I. has received travel grants to attend scientific meetings from CSL Behring and Alexion. E.P. has received travel grants to attend scientific meetings from CSL Behring. E.N.-O. reports personal fees for advisory or scientific boards from ArgenX (Belgium), Takeda (Italy and USA), CSL-Behring (Italy and USA), Janssen (USA), Kedrion (Italy), LFB (France), Roche (Switzerland), and Sanofi (USA). The other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The study was approved by the ethical committee of IRCCS Humanitas Clinical and Research Center (No. 413/17, 19/09/2017) and of each participating center.

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How to cite this article: Doneddu PE, Gallo C, Gentile L, et al. Comparison of the diagnostic accuracy of the 2010 European Federation of Neurological Societies/Peripheral Nerve Society and American Association of Electrodiagnostic Medicine diagnostic criteria for multifocal motor neuropathy. *Eur J Neurol*. 2024;00:e16444. doi:10.1111/ene.16444

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