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Variably Defined Conduction Block, Temporal Dispersion and Other Electrophysiological Abnormalities in Multifocal Motor Neuropathy: A Multicentre Study

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ABSTRACT

Background: The definition of conduction block (CB) is variable in multifocal motor neuropathy (MMN). In current criteria, excessive temporal dispersion (TD) may preclude the recognition of CB and the diagnosis of MMN.

Methods: We retrospectively studied the electrophysiological data of 47 consecutive subjects with MMN and of 69 consecutive controls with upper limb-onset motor neuron disease, from three neuromuscular centres in the United Kingdom and Korea.

Results: Compared to CB defined by compound muscle action potential (CMAP) area reduction (CB-Area) > 30%, CB defined by CMAP amplitude reduction (CB-amp) > 30% was more sensitive (78.7% vs. 63.8%; McNemar's Test: $p = 0.008$), but less specific versus controls (90.1% vs. 96.7%; McNemar's Test: $p = 0.001$). CB-amp > 30% offered greater diagnostic accuracy than CB-Area > 30% (Youden's Index: 0.688 vs. 0.606). TD showed a sensitivity of 59.6% and specificity of 94.3%. F-wave prolongation or absence showed a sensitivity of 42.6% and specificity of 96.9%. Considering CB-amp > 30% or TD or F-wave prolongation or absence, as independent electrodiagnostic markers of MMN, improved diagnostic sensitivity from 78.7% to 91.5% compared to CB-amp > 30% alone (McNemar's Test: $p = 0.031$), also offering optimal accuracy (Youden's Index: 0.816). Within this three-parameter combination, CB defined by CMAP amplitude reduction > 30% offered similar sensitivity, specificity and accuracy to when defined by CMAP amplitude reduction > 50%.

Conclusions: CB-amp has higher sensitivity and accuracy than CB-Area for the electrodiagnosis of MMN. Consideration of TD or F-wave prolongation or absence, as independently diagnostic of MMN, in addition to CB-amp > 30% alone, may improve electrophysiological sensitivity as well as accuracy.

Yusuf A. Rajabally and Young Gi Min contributed equally to this article and are co-first authors.

1 | Introduction

Multifocal motor neuropathy (MMN) is a treatable autoimmune neuropathy causing multifocal motor deficits affecting predominantly the muscles of the distal upper limbs [1, 2]. Electrophysiologically, the hallmark of MMN is the presence of persistent motor conduction block (CB). Although supportive investigations are recommended, such as IgM anti-ganglioside antibodies to GM1, magnetic resonance (MR) neurography and ultrasonography (US) [1], these may be unhelpful in practice [3]. To date, MMN remains a clinical and electrophysiological diagnosis.

The European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) MMN Guidelines were initially published in 2006 [4] and updated in 2010 [5]. The electrophysiological requirements for diagnosis are similar in both versions. They define 'definite' CB as a > 50% reduction of the compound muscle action potential (CMAP) area, with the mandatory condition of temporal dispersion (TD) being of ≤ 30% within the studied nerve segment. 'Probable' CB is defined as a > 30% reduction of CMAP area, also with TD of ≤ 30%, or > 50% reduction of CMAP area, if TD is > 30%. The American Association of Electrodiagnostic Medicine (AAEM) criteria, for their part, allow consideration of both CMAP amplitude or area reduction [6]. 'Definite' CB as per AAEM criteria requires, in ≥ 2 nerves and in absence of TD > 30% in all cases, either (i) > 50% CMAP amplitude reduction for median/ulnar/radial nerves, > 60% for fibular and tibial nerves, or (ii) > 40% CMAP area reduction for median/ulnar/radial nerves, > 50% for fibular and tibial nerves. 'Probable' CB is defined as the presence, in two or more nerve segments of amplitude or area reductions 10% lower than the above-mentioned values for 'definite' CB, again in absence of TD > 30%. Alternatively, electrodiagnosis of 'probable' CB may be achieved through identical amplitude and area percentage reductions to those of the 'definite' category, in presence of TD > 30%.

Existing MMN criteria are, in practice, variably applied [3, 7]. A multicentre Italian study found that EFNS/PNS 2010 criteria were more sensitive (47% vs. 28%) but slightly less specific (97% vs. 100%), compared to the AAEM criteria [8]. These results for sensitivity contrasted with the findings of a recent UK multicentre study [3], which defined CB through CMAP amplitude reductions of > 50% ('definite CB') or > 30% ('probable CB'), irrespective of TD, as performed routinely in local practice, and as supported by previous data from a study in chronic inflammatory demyelinating polyneuropathy (CIDP) [9]. The UK MMN study reported, through these methods, definite or probable CB in at least one nerve in 90% of subjects from a large cohort of 95 subjects [3]. Otherwise, few studies have previously reported that TD as well as other electrophysiological parameters may be affected in MMN and may therefore have diagnostic value [10, 11].

The main objectives of our current study were to analyse the motor electrophysiological data of a cohort of subjects meeting clinical criteria for MMN and those of a control group with motor neuron disease (MND) (i) to evaluate effects of variably defined CB on sensitivity and specificity of MMN electrodiagnosis, (ii) to assess the sensitivity and specificity of TD in MMN, its occurrence independent of CB and its impact on CB diagnosis, and (iii) to determine the sensitivity and specificity of demyelinating range abnormalities of other nerve conduction study parameters in the electrodiagnosis of MMN.

2 | Materials and Methods

We included consecutive subjects with a clinical diagnosis of MMN attending University Hospitals Birmingham, UK; University Hospital Southampton, UK; and Seoul National University Hospital, Republic of Korea, between 2014 and 2025. Inclusion criteria were (i) meeting core clinical criteria for a diagnosis of MMN and all exclusion criteria, as per EFNS/PNS 2010 Guidelines [5], and (ii) having normal sensory nerve conduction studies in the upper limbs [5]. We recruited consecutive controls with upper limb-onset MND, whom we considered the clinically most relevant mimic of MMN. Patients with (i) definite or probable amyotrophic lateral sclerosis (ALS) as per the revised El Escorial criteria [12], or (ii) progressive muscular atrophy (PMA) diagnosed on the basis of the presence of both clinical and electrophysiological signs of lower motor neuron involvement in ≥ 2 segments without clinical upper motor neuron signs during > 1 year of follow-up [13].

Electrophysiological records were retrospectively analysed to determine CMAP amplitude, area and duration for each assessed motor nerve for each point of stimulation. Waveforms were reviewed in the absence of the required detailed data in the tabulated reports. Presence of 'definite' CB or 'probable' CB was ascertained, defined by (i) CMAP amplitude reduction, or (ii) CMAP area reduction, from the most distal to the proximal stimulation site, by > 50% and > 30%, respectively. TD was defined as prolongation of the proximal CMAP duration compared to the most distal CMAP duration by > 30%. Cut-off values for distal CMAP duration (DCMAPD) prolongation were defined for each motor nerve by local EMG low-cut filter settings used at each participating centre (2 Hz in Seoul; 3 Hz in Birmingham and Southampton) [14]. Distal motor latency (DML) and motor conduction velocity (MCV) results were classified as within 'demyelinating' or 'non-demyelinating' range through current diagnostic criteria for chronic inflammatory demyelinating polyneuropathy (CIDP) [15], using our normative values. F-wave abnormalities were similarly defined, with in addition, consideration of F-wave absence if the distal CMAP amplitude was ≥ 20% of the lower limit of normal [15].

We included available records for median, ulnar, fibular, radial, musculocutaneous and axillary nerves for CB and TD. The tibial nerve was excluded from CB/TD evaluation in view of low reliability of supramaximal popliteal fossa stimulation. Assessment for DCMAPD, DML and F-waves included median, ulnar, fibular and tibial nerves only, in absence of availability of normative data for radial, musculocutaneous and axillary nerves. MCV evaluation was performed for median, ulnar and fibular nerves, excluding tibial and radial nerves as rarely routinely measured in UK practice. Evaluation for presence of CB through both amplitude and area decrement, and for TD were done for (i) the median nerve at elbow, axilla and Erb's point; (ii) the ulnar nerve, below the elbow, at axilla and Erb's point; (iii) fibular nerve, below the fibular neck; (iii)

the radial nerve, at the elbow, axilla and Erb's point; (iv) for the musculocutaneous and axillary nerves, at the axilla and Erb's point. When multiple proximal sites were studied, the stimulation point producing the most severe CB and/or TD was selected as the proximal site for the studied nerve for the purposes of the current analysis.

Sensitivity for MMN of any parameter evaluated in the current analysis was defined as the proportion of subjects with an abnormality of that parameter in at least one motor nerve. We evaluated the sensitivity, specificity and accuracy of definite (> 50%) or probable CB (> 30%) through CMAP amplitude as well as area reduction. The sensitivity of TD was determined, as was the frequency of TD occurring in association with CB, and that of TD observed independently of CB. Sensitivities of demyelinating-range DML, DCMAPD, MCV and of minimum F-wave demyelinating range delay or absence were ascertained. Specificity was evaluated for each parameter versus the control population with upper limb-onset MND. We defined specificity as the proportion of control nerves without abnormality for the parameter under consideration. We arbitrarily selected parameters as diagnostically potentially helpful on the basis of a specificity > 80% and accuracy level corresponding to a Youden's Index > 0.300 [16].

Statistical analyses were performed with SPSS 28.0 (Armonk, USA). Comparison of proportions was performed by Fisher Exact tests, and sensitivity/specificity gains were established through McNemar's Tests. Youden's Index was used to determine test accuracy. Significance was set at $p < 0.05$ for all tests.

This study was reviewed and approved at our respective institutional review boards. In Korea, this study received approval as part of a wider study of electrophysiology in inflammatory neuropathies (2504-172-1635). For the two UK centres, this analysis was conducted as part of registered and approved retrospective clinical audits of the diagnosis and management of MMN at University Hospitals Birmingham and University Hospital Southampton (Reg. no.: CARMS-20703 and SEV-0890, respectively). Audit does not require Ethics Committee approval in the UK.

3 | Results

3.1 | Baseline Characteristics

Main characteristics of the included subjects with MMN are summarised in Table 1. The MMN cohort consisted of 18 females and 29 males (ratio 1:1.61). We included 18 subjects from Birmingham, UK; 14 from Southampton, UK; and 15 from Seoul, Korea. The clinical phenotype was pure upper limb and asymmetric in 34/47 (72.3%), pure upper limb and symmetric in 1/47 (2.1%), mixed upper and lower limb in 9/47 (19.1%), and pure lower limb in 3/47 (6.4%). Mean age at the time of the electrophysiological study was 49.4 years (SD: 12.8). Electrophysiological studies had been performed pre-immunoglobulin treatment initiation in 37/47 subjects (78.7%) and post-treatment initiation in 10/47 (21.3%). Mean disease duration from symptom onset to time of electrophysiological study was 42.9 months (SD: 53.4). Mean number of tested motor nerves was 7.8 (SD: 3.0) per subject. Three of 47 subjects (6.4%) (1 from each of the 3 participating centres), all of whom had electrophysiology pre-treatment and all of whom were later confirmed to be immunoglobulin-responsive, had motor nerve conduction studies which did not meet requirements for definite or probable CB, TD or demyelination in any nerve.

TABLE 1 | Characteristics of 47 subjects with a clinical diagnosis of MMN from Birmingham, UK; Southampton, UK; and Seoul, Korea.

Mean age at time of electrophysiological study—years (SD)	50.2 (13.8)
Gender F:M (ratio)	18:29 (1:1.61)
MMN clinical phenotype	34/47 (72.3%): upper limb asymmetric 1/47 (2.1%): upper limb symmetric 9/47 (19.1%): upper and lower limb 3/47 (6.4%): pure lower limb
Mean disease duration at time of electrophysiological study—months (SD)	42.9 (53.4)
Mean number of tested motor nerves (SD)	7.8 (3.0)

Sixty-nine control subjects (mean age: 59 years [SD: 10.3], consisting of 27 females and 42 males [ratio 1:1:1.56]) with a diagnosis of upper limb-onset ALS or PMA were recruited from Seoul, Korea. Their age at initial symptom onset was 59.0 (SD: 10.3), with a mean disease duration prior to electrophysiological study of 22.6 months (SD: 17.6). The mean revised ALS Functional Rating Scale of the control subjects was 39.0 (SD: 6.8) [17].

3.2 | Electrodiagnosis of Definite or Probable CB

The main findings in relation to definite or probable CB (i.e., defined by > 30% CMAP amplitude or area reduction) are summarised in Table 2.

CB defined by CMAP amplitude reduction (CB-amp > 30%) was found for at least one motor nerve in 37/47 subjects (78.7%). The mean number of CB-amp > 30% identified per patient was 1.6 (SD: 1.42), and the mean number of CB-amp > 30% per tested motor nerve was 0.21 (SD: 0.20). CB-amp > 30% was detected in 7/47 subjects (14.9%) without CB defined by CMAP area reduction (CB-Area > 30%). CB-Area > 30% was found for at least one motor nerve in 30/47 (63.8%) subjects. The mean number of CB-Area > 30% identified per patient was 1.17 (SD: 1.37) and the mean number of CB-Area > 30% per tested motor nerve was 0.18 (SD: 0.19). All subjects with CB-Area > 30% also had CB-amp > 30%. CB-amp > 30% in any one nerve was diagnostically more sensitive than CB-Area > 30% in any one nerve (37/47 [78.7%] vs. 30/47 [63.9%]; McNemar's Test $p = 0.008$). The specificity of CB-amp > 30% was significantly lower than that of CB-Area > 30% (90.1% vs. 96.7%;

TABLE 2 | Comparison of CB-amp ≥ 30% and CB-Area ≥ 30% in 47 subjects with a clinical diagnosis of MMN from Birmingham, UK; Southampton, UK; and Seoul, Korea.

	CB-amp > 30%	CB-Area > 30%	CB-amp > 30% vs. CB-Area > 30%
Sensitivity: (Defined as number of subjects with at least 1 CB-amp or CB-Area > 30%)	37/47 (78.7%)	30/47 (63.8%)	+14.9% (McNemar's Test: $p = 0.008$)
Specificity: (vs. controls with MND)	90.1%	96.7%	−6.6% (McNemar's Test $p = 0.001$)
Diagnostic accuracy (Youden's Index)	0.688	0.606	+0.080

McNemar's Test: $p = 0.001$). The diagnostic accuracy of CB-amp > 30% was greater than that of CB-Area > 30% (Youden's Index: 0.688 vs. 0.606).

3.3 | Electrodiagnosis of TD

TD was detected in 28/47 subjects (59.6%). TD occurred independently of concurrent CB-amp > 30% or CB-Area > 30% in the same nerve, in 13/28 subjects (46.4%) and was observed with concurrent CB-amp > 30%/CB-Area > 30% in the same nerve, in the remaining 15/28 (53.6%). Through EFNS/PNS criteria of 2010 [5], TD precluded diagnosis of CB-Area in 4/47 subjects (8.5%). With AAEM criteria [6], TD had no impact on CB-Area diagnosis and precluded diagnosis of CB-amp in 1/47 subjects (2.1%). The specificity of TD was 94.3%. Youden's Index was 0.539.

3.4 | Abnormalities of Other Electrophysiological Parameters

F-wave demyelinating range prolongation or absence was detected in 20/47 subjects (42.6%). F-wave abnormalities were observed in upper limb nerves in the majority of cases (16/20; 80%). F-wave prolongation was observed in 15/20 subjects (75%), amongst whom 4 (20%) had another nerve presenting with F-wave absence. F-wave prolongation or absence was not found in any upper limb nerve without concurrent CB-amp > 30% or TD. However, F-wave prolongation or absence was found in lower limb nerves in 9/47 subjects (19.1%), without concurrent CB-amp > 30% or TD in the corresponding nerve. The specificity of F-wave prolongation or absence was 96.9% versus controls with MND. Youden's Index was 0.395.

DML was prolonged in one subject (2.1%), affecting a median nerve, without any other electrophysiological abnormality. MCV was slowed in 5/47 subjects (10.6%), in all cases with concurrent CB-amp > 30% or TD in the same nerve. DCMAPD was prolonged in 2/47 subjects (4.3%), in both cases without concurrent CB-amp > 30% or TD. Although with specificities > 80% for all, Youden's Index was < 0.15 for DML, MCV and DCMAPD.

3.5 | Diagnostic Value of the Combination of Electrophysiological Parameters

The potential contribution of parameters, other than CB-amp > 30%/CB-Area > 30%, of specificity > 80% and accuracy > 0.300 is summarised in Table 3. Considering as an alternative to CB-amp > 30% in any one nerve, either TD in any one nerve or F-wave prolongation or absence in any one nerve, as diagnostic of MMN, increased sensitivity from 78.1% to 91.5% (McNemar's Test: $p = 0.031$). Specificity was equivalent to that of the least specific of the three parameters (CB-amp > 30%), that is, 90.1%. Considering any one of these three parameters as electrodiagnostic of MMN also provided optimal diagnostic accuracy (Youden's Index: 0.816).

3.6 | Comparison of the Value of CB-Amp > 30% and CB-Area > 30% vs. CB-Amp > 50% and CB-Area > 50% in the Electrodiagnosis of MMN

Results of the comparative analyses are detailed in Table 4 and in Figure 1.

CB-amp > 50% had greater sensitivity than CB-Area > 50% (66% vs. 48.9%; McNemar's Test: $p = 0.008$). Specificity versus controls was 99.1% for both CB-amp > 50% and CB-Area > 50%. Youden's Index was greater for CB-amp > 50% than for CB-Area > 50% (0.651 vs. 0.480).

In comparison to CB-amp > 30%, CB-amp > 50% had lower sensitivity (66% vs. 78.7%; McNemar's Test: $p = 0.031$). CB-amp > 50% was more specific than CB-amp > 30% (99.1% vs. 90.1%; McNemar's Test: $p < 0.001$). Youden's Index was lower for CB-amp > 50% than for CB-amp > 30% (0.651 vs. 0.686).

Compared to CB-amp > 50% in any one nerve alone, consideration of CB-amp > 50% or TD or F-wave prolongation or absence in any one nerve as diagnostic of MMN increased sensitivity from 66% to 87.2% (McNemar's Test: $p = 0.002$).

The sensitivity of the combination of CB-amp > 50% or TD or F-wave prolongation or absence was comparable to that of the combination of CB-amp > 30% or TD or F-wave prolongation or absence (87.2% vs. 91.5%; McNemar's Test: $p = 0.500$). Specificity of the combination of CB-amp > 50% or TD or F-wave prolongation or absence was that of the least specific of the three parameters (TD), and therefore equivalent to that of the combination of CB-amp > 30% or TD or F-wave prolongation or absence (94.3% vs. 90.1%; McNemar's Test: $p = 0.383$). Within the triad of parameters, accuracy was equivalent with CB-amp > 50% and CB-amp > 30% (Youden's Index: 0.815 vs. 0.816).

TABLE 3 | Value of CB-amp ≥ 30% and electrophysiological parameters other than CB, identified with specificity ≥ 80% and diagnostic accuracy ≥ 0.300 (TD and F-wave prolongation or absence), alone and in combination, for the electrodiagnosis of 47 subjects with a clinical diagnosis of MMN from Birmingham, UK; Southampton, UK; and Seoul, Korea.

	CB-amp > 30%	TD	F-wave prolongation or absence
Sensitivity (%)	37/47 (78.7%)	28/47 (59.6%)	20/47 (42.6%)
Specificity (%)	192/213 (90.1%)	214/227 (94.3%)	251/259 (96.9%)
Diagnostic accuracy (Youden's Index)	0.688	0.539	0.395
	CB-amp > 30% in any one nerve or TD in any one nerve or F-wave prolongation or absence in any one nerve		
Sensitivity (%)	43/47 (91.5%)		
Specificity (%)	192/213 (90.1%)		
Gain in sensitivity vs. CB-amp > 30% only (significance)	+12.8% (McNemar's Test: $p = 0.031$)		
Diagnostic accuracy (Youden's Index)	0.816		
Gain in diagnostic accuracy vs. CB-amp > 30% only	+0.128		

3.7 | Sub-Analysis of Subgroup of Subjects Having Undergone Electrophysiology Pre-Treatment

In order to determine eventual treatment effects on our findings, we performed additional sub-analyses, considering the optimal definitions for CB and optimal parameter combination, excluding the 10 subjects who had received immunoglobulin therapy prior to the electrophysiological evaluation.

Parameter sensitivity in the untreated subgroup was similar to that of the full cohort for all parameters (CB-amp > 30%: 29/37 vs. 37/47 [$p = 1$]; CB-Area > 30%: 22/37 vs. 30/47 [$p = 0.82$]; TD: 21/37 vs. 28/47 [$p = 0.83$]; F-wave prolongation or absence: 16/37 vs. 20/47 [$p = 1$]). As in the full cohort, CB-amp > 30% in any one nerve in the untreated cohort was more sensitive than CB-Area > 30% in any one nerve (78.4% vs. 59.5%; McNemar's Test $p = 0.031$). Consideration of CB-amp > 30% or TD or F-wave prolongation or absence in any one nerve as diagnostic of MMN in the untreated cohort offered comparable sensitivity to that achieved in the full cohort (33/37 vs. 43/47; $p = 0.73$). The improvement in diagnostic sensitivity compared to that of CB-amp > 30% alone did however not reach significance in the subgroup of the 37 immunoglobulin-naïve subjects (89.2% vs. 78.4%; McNemar's Test: $p = 0.063$).

4 | Discussion

Existing electrodiagnostic criteria for MMN provide a strict set of definitions for CB evaluation [5, 6]. These definitions are, however, not always rigorously applied in routine clinical practice [3, 7], although the appropriateness and equivalence of other methods are unproven. TD represents, in MMN, a restrictive factor for CB diagnosis in current criteria, and its intrinsic diagnostic value, although suggested by previous small studies [11], has remained unknown. The value of TD in CIDP is otherwise well demonstrated [9, 18], whereas, as opposed to MMN, it is consistent with the demyelinating pathophysiology. Although reported as common in one previous single-centre study [10], demyelinating range abnormalities of other parameters are otherwise not included in current MMN diagnostic criteria.

We found higher sensitivity with moderate compromise on specificity and with overall better accuracy for CB-amp versus CB-Area. This was the case with cut-offs of both > 30% and > 50%. CB-amp was not considered adequate by EFNS/PNS criteria due to the possibility of overdiagnosis through coexisting excessive TD caused by inter-phase cancellation [5]. Although CB-amp was, on the other hand, included in the AAEM criteria, this was with higher cut-offs [6]. Our current results challenge these recommendations, both through the higher sensitivity achieved in this MMN cohort with CB-amp > 30% and by its demonstrated high specificity versus a relevant control group with an MMN clinical mimic.

Our results showed that TD may commonly occur outside the context of concurrent CB, while representing a sensitive and specific electrophysiological feature of MMN. Similarly, F-wave abnormalities were also found to be sensitive and specific. The combination of CB-amp > 30% or TD or F-wave abnormalities as independent electrodiagnostic markers of MMN significantly improved sensitivity compared to CB-amp > 30% alone and offered optimal accuracy. Of note, we also found that although CB-amp > 50% independently offered greater specificity than CB-amp > 30%, no such benefit was observed in the combination of the three parameters, with CB-amp > 30% offering better sensitivity and marginally higher accuracy within the triad.

It is noteworthy that in other disorders such as Guillain-Barré syndrome or nodo-paranodopathies, the strict separation of nodal versus demyelinating pathophysiological disease mechanisms is not deemed possible on electrophysiological grounds [19, 20]. This limitation of electrophysiology appears also applicable to MMN where, as demonstrated in our current analysis, non-uniform demyelinating slowing may frequently be detected. Although

TABLE 4 | Comparison of variable CB definitions ≥ 30% and ≥ 50% for CMAP amplitude and Area, independently and in combination with TD and F-wave prolongation or absence, for the electrodiagnosis of 47 subjects with a clinical diagnosis of MMN from Birmingham, UK; Southampton, UK; and Seoul, Korea.

	CB-amp > 30%	CB-amp > 50%	CB-Area > 30%	CB-Area > 50%	With CB-amp > 30% vs. with CB-amp > 50% (McNemar's Test, *p*)
Sensitivity (%)	37/47 (78.7%)	31/47 (66%)	30/47 (63.8%)	23/47 (48.9%)	$p = 0.031$
Specificity (%)	192/213 (90.1%)	211/213 (99.1%)	206/213 (96.7%)	211/213 (99.1%)	$p < 0.001$
Diagnostic accuracy (Youden's Index)	0.688	0.651	0.605	0.480	NA
	CB-amp > 30% in any one nerve or TD in any one nerve or F-wave prolongation or absence in any one nerve		**CB-amp > 50% in any one nerve or TD in any one nerve or F-wave prolongation or absence in any one nerve**		
Sensitivity %	91.5% (43/47)		87.2% (41/47)		$p = 0.500$
Specificity %	90.1%		94.3%		$p = 0.383$
Gain in sensitivity vs. CB-amp only (significance)	+12.8% (McNemar's Test: $p = 0.031$)		+23.4% (McNemar's Test: $p = 0.002$)		NA
Diagnostic accuracy (Youden's Index)	0.816		0.815		NA
Gain in diagnostic accuracy vs. CB-amp only	+0.128		+0.210		NA

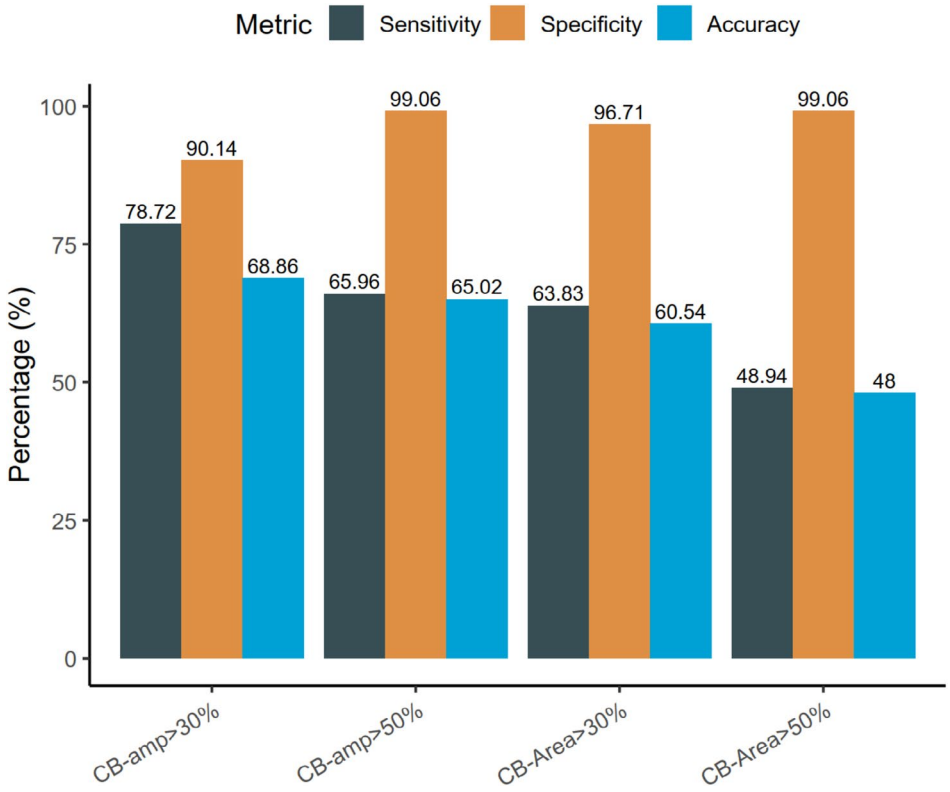

FIGURE 1 | Bar chart illustrating comparative sensitivity, specificity and accuracy of variably defined CB, (i) through CMAP amplitude versus area reduction (ii) through ≥30% CMAP amplitude or area reduction versus >50% CMAP amplitude or area reduction, for the electrodiagnosis of 47 subjects with a clinical diagnosis of MMN from Birmingham, UK; Southampton, UK; and Seoul, Korea.

different excitability patterns have been suggested in MMN compared to CIDP, with reduction in sodium and potassium conductance in the former, as opposed to increased nodal to inter-nodal and fast potassium conductance in the latter [21], strict separation of underlying pathophysiology and resulting electrophysiological presentation of the two disorders remains highly uncertain. This is well illustrated from the detailed conventional nerve conduction studies from that study, in which lower mean MCVs were unexpectedly observed in subjects with MMN compared to subjects with CIDP, except in a CIDP subgroup with forearm CB [21].

Although we found CB-amp > 30% and CB-Area > 30% in similar proportions to those previously reported [7, 10, 22], the frequency of TD in our cohort was significantly lower than that reported by Van Asseldonk et al. [10] (28/47 vs. 33/39; $p = 0.0016$). In addition, in comparison to the Dutch study, we found significantly less DML prolongation (1/47 vs. 15/39; $p < 0.001$), less MCV reduction (5/47 vs. 25/39; $p < 0.001$) and less F-wave prolongation (15/47 vs. 24/39; $p = 0.009$). This may in part be explained by the more stringent cut-offs for demyelination in our study. Also, whereas all electrophysiological studies had been performed pre-immunoglobulin treatment in the Dutch study, > 20% of our subjects had undergone post-treatment evaluations. Whether immunoglobulin treatment exposure may partly account for these discrepant findings is possible, CB reversal in some nerves having been reported with immunoglobulin treatment through previous therapeutic studies of MMN [23]. Finally, it is possible that the explanation for the differences observed partly also resides in the lesser study extensiveness in our patients who had a mean of 7.8 tested nerves, compared to systematic testing of 12 nerves in all subjects of the Dutch study.

Our study has several limitations, which include its retrospective design, lack of homogeneously conducted electrophysiological studies, suboptimal number of tested nerves and inclusion of tests done after treatment initiation in a minority of subjects, although we could not ascertain effects of immunoglobulin exposure through sub-analyses of untreated subjects only. The number of subjects included was otherwise relatively small; this illustrates mainly the low prevalence of MMN [24]. Finally, the low-cut filter settings used were different in-between centres (2 and 3 Hz) and may have impacted the findings for DCMAPD and TD, although the consistency of results we found for DCMAPD in a previous analysis with similarly close multiple filter settings [25] makes this, in our opinion, unlikely.

Despite these drawbacks, we believe that our results, which included subjects with MMN from three centres and a clinically relevant control population with upper limb-onset MND, are important in demonstrating the greater diagnostic accuracy of CB-amp in comparison to CB-Area. The results also show the appropriateness of defining CB by > 30%, instead of > 50% CMAP amplitude reduction, as well as the potential value of the combined use of CB-amp > 30%, TD and F-wave abnormalities in the electrodiagnosis of MMN. These findings require confirmation in other large cohorts and may allow in future to optimise the value of electrophysiology in cases of suspected MMN.

Conflicts of Interest

Y.A.R. has received consultancy honoraria from Sanofi, Argenx, Janssen, LFB, Polyneuron, Grifols, Takeda, Dianthus, Vitaccess, has received educational sponsorships from LFB and CSL Behring and has obtained research grants from LFB. Y.G.M., A.A.-A., W.J., R.A. and J.-J.S. have no disclosures. C.O. has received speaker/consultancy honoraria from Takeda, Grifols and Terumo BCT.

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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