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Clinical Utility of Repetitive Nerve Stimulation Test in Differentiating Multifocal Motor Neuropathy From Progressive Muscular Atrophy

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Abstract

Objectives:
To evaluate the utility of repetitive nerve stimulation test (RNS) for differentiating multifocal motor neuropathy (MMN) and progressive muscular atrophy (PMA).

Methods:
We retrospectively enrolled 20 patients with MMN or PMA. We extracted the results of the initial 3-Hz RNS in the ulnar and accessory nerves and compared the percentage and frequency of abnormal decremental responses between both groups.

Results:
RNS was performed in 8 ulnar and 9 accessory nerves in patients with MMN, and in 8 ulnar and 10 accessory nerves in patients with PMA. Patients with MMN had a significantly lower decrement percentage (0.6 ± 4.0% in MMN vs. 10.3 ± 6.5% in PMA, $P < 0.01$) and frequency of abnormal decremental response (0 of 9 in MMN vs. 6 of 10 in PMA, $P = 0.01$) than patients with PMA in the accessory nerve.

Conclusions:
The RNS has clinical utility for differentiating MMN from PMA.

Key Words: repetitive nerve stimulation test, multifocal motor neuropathy, progressive muscular atrophy, neuromuscular junction

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INTRODUCTION

Multifocal motor neuropathy (MMN) is characterized by asymmetric, upper-limb dominant muscle weakness and sometimes a conduction block (CB), but without sensory symptoms.[1,2] Progressive muscular atrophy (PMA) is considered a variant of amyotrophic lateral sclerosis (ALS) and is characterized by lower motor neuron signs. It accounts for 2.5% of adult-onset motor neuron disease (MND).[3] Detection of CB can differentiate MMN from PMA, but approximately 40% of MMN cases do not show CB, which complicates the diagnosis.[4,5]

MMN patients respond well to intravenous immunoglobulin (IVIg) therapy, whereas IVIg is ineffective in PMA treatment.[1,2,6,7] In a study by Kim et al,[3] 22% of 91 patients with PMA developed upper motor neuron signs and were diagnosed with ALS within 61 months. In another study, Carvalho et al[8] reported that 7 of 17 patients with PMA developed upper motor neuron signs within 1 year, leading to the diagnosis of ALS. Ince et al[9] reported that up to 50% of patients with PMA showed corticospinal tract degeneration at autopsy. PMA is the lowest categorization of ALS by the conventional criteria, because it is classified as suspected ALS by the revised El Escorial criteria and is not classified as ALS according to the Awaji criteria.[10,11] However, PMA is currently classified as ALS according to the Gold Coast criteria.[12] Therefore, respiratory management, nutritional management such as percutaneous endoscopic gastrostomy, and administration of disease-modifying drugs should be considered for patients with PMA. Early differentiation of MMN from PMA is crucial to select the appropriate treatment.

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Since the first report of a decremental response to repetitive nerve stimulation test (RNS) in ALS by Mulder et al[13] in 1959, RNS has been applied to the diagnosis of MND and neuromuscular junction disease. Patients with these conditions have a high frequency of abnormal decremental responses, especially in the proximal muscles, which has been reported to be useful for differentiating ALS from cervical spondylotic amyotrophy and Hirayama disease.[14–16] Although to our knowledge, a decremental response in PMA alone has not been studied, Iwanami et al[17] reported that patients with PMA within the ALS cohort showed abnormal decremental responses. Moreover, it remains unclear whether patients with MMN present decremental responses in RNS. We aimed to evaluate the characteristics of decremental responses in both diseases and the utility of RNS in differentiating MMN from PMA.

MATERIALS AND METHODS

Patient Selection

We retrospectively enrolled patients with MMN or PMA who underwent RNS. All the included patients were hospitalized in our department between 2013 and 2021. The present study is approved by the Medical Ethics Committee of the Kobe University Graduate School of Medicine (approval number: B210163).

Patients with MMN were diagnosed as definite, probable, or possible according to current EFNS/PNS criteria.[6] The diagnosis of PMA was made using the criteria reported by Vlam et al, where the patients' age at onset is more than 18 years and clinical or needle electromyographic evidence of lower motor neuron signs is detected. Patients were excluded if they had a family history of MND; PMA mimics such as acute poliomyelitis, spinal radiculopathy, diabetic amyotrophy, thyrotoxicosis, or hyperparathyroidism; sensory deficits or upper motor neuron signs; structural abnormalities in the brain or spinal cord on imaging studies; or demyelination findings on nerve conduction studies.[18]

RNS Procedures

We extracted the results of the initial RNS on patients with MMN and PMA performed routinely in our hospital. Board-certified neurologists performed RNS on these patients using an electromyography machine (MEB-2300 Nihon Kohden, Tokyo). Supramaximal stimulation was administered at a 3-Hz frequency. The percentage decrease of base-to-peak amplitude was measured between the first and the fourth or fifth response. A decremental response of >10% was defined as abnormal based on the conventional criterion recommended by the AAEM Quality Assurance Committee.[19] RNS was performed multiple times with sufficient time intervals to ensure reproducibility of the decremental response. We extracted the results of the ulnar nerve [abductor digiti minimi muscle (ADM)] and accessory nerve (trapezius muscle) on the more impaired side. The median nerve was excluded because of the influence of carpal tunnel syndrome. Hence, the ulnar nerve was chosen as a distal function representative and the accessory nerve as a proximal function representative.

Statistical Analysis of RNS Parameters

We determined the degree of amplitude decrease (ie, decrement percentage) and frequency of abnormal decremental responses (>10%). We used the Mann–Whitney *U* test for between-group comparisons of the decrement percentage in the ulnar and accessory nerves. We used Fisher exact test to compare the frequency of the abnormal decremental response in each nerve between patients with MMN and PMA.

Additional analysis was performed to determine whether decremental responses were prominent in the atrophic muscle in ALS by calculating the correlation between the decremental response and compound muscle action potential (CMAP) amplitude of each nerve using Spearman correlation analysis.[17,20]

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All the analyses were performed using GraphPad Prism 8.0 software (GraphPad Software Inc, CA). For all statistical tests, significance was set at $P < 0.05$.

RESULTS

Subjects

We enrolled a total of 20 patients: 10 with MMN (sex, male: female = 5: 5; age, 50.7 ± 11.4 years) and 10 with PMA (sex, male: female = 5: 5; age, 64.2 ± 15.1 years). The patients with MMN had a longer duration from onset to examination than patients with PMA (MMN, 115.9 ± 110.4 months; PMA, 26.1 ± 31.3 months, $P < 0.01$). IVIg treatment was administered to all 10 patients with MMN and 9 of 10 patients with PMA. All patients with MMN showed improvement; 9 patients are still on maintenance therapy, and 1 patient is in remission. However, IVIg treatment was ineffective in all patients with PMA, and they had a progressive course. Of the 10 patients with PMA, 3 died, 4 were transferred, and 3 are in follow-up. Among the patients with MMN, 9 of 10 had undergone IVIg treatment several times before the initial RNS. Antiganglioside antibodies were measured in all MMN patients and anti-GM1 IgM antibodies were detected in 7 patients. In contrast, antiganglioside antibodies were not detected in any of the 4 evaluated patients with PMA. Table 1 presents the patients' characteristics.

RNS Results

In the patients with MMN, RNS was performed on the ulnar nerve in 8 patients and on the accessory nerve in 9 patients. In patients with PMA, RNS was performed on the ulnar nerve in 8 patients and on the accessory nerve in 10 patients.

For the ulnar nerve, there was no significant difference in distal CMAP amplitude (MMN, 5.2 ± 2.7 mV; PMA, 4.6 ± 0.9 mV, $P = 0.56$) or decrement percentage (MMN, 1.4 ± 2.5%; PMA, 3.5 ± 1.7%, $P = 0.08$). No abnormal decremental response (>10%) was seen in both groups (Table 2, Fig. 1). In the patients with MMN, CB of the ulnar nerve was observed in 5 of 8 patients. The comparison between MMN with CB and MMN without CB in the ulnar nerve is shown in Table 3. Although there was no significant difference, patients with CB tended to have a lower CMAP amplitude and a larger decrement percentage. The CMAP amplitude, decrement percentage, and presence of CB in each patient are described in Figure 2.

In the accessory nerve, the CMAP amplitude was significantly lower in patients with PMA than in patients with MMN (MMN, 6.1 ± 2.3 mV; PMA, 3.4 ± 0.7 mV, $P = 0.03$), and the decrement percentage was significantly higher (MMN, 0.6 ± 4.0%; PMA, 10.3 ± 6.5%, $P < 0.01$). None of the patients with MMN showed an abnormal decremental response (>10%), whereas 6 patients with

TABLE 1. Characteristics of the Patients

	MMN (n = 10)	PMA (n = 10)	*P*
Age, y	50.7 ± 11.4	64.2 ± 15.1	0.02*
Sex (male %)	50.0 (5/10)	50.0 (5/10)	>0.99
Disease duration at evaluation, mo	115.9 ± 110.4	26.1 ± 31.3	<0.01†
Onset (upper limb %)	80.0 (8/10)	40.0 (4/10)	0.17
CB in at least 1 nerve (%)	100 (10/10)	0 (0/10)	<0.01†
ALSFRS-R		43.1 ± 3.1	
Anti-GM1 IgM antibody	7/10	0/4	0.07
Clinical involvement following IVIg (%)	100 (10/10)	0 (0/9)	<0.01†

*$P < 0.05$.
†$P < 0.01$.
ALSFRS-R, amyotrophic lateral sclerosis functional rating scale-revised.

TABLE 2. Results of RNS

	MMN	PMA	
Ulnar Nerve (ADM Muscle)	**N = 8**	**N = 8**	***P***
CMAP amplitude, mV	5.2 ± 2.7	4.6 ± 0.9	0.56
Decrement percentage (%)	1.4 ± 2.5	3.5 ± 1.7	0.08
Frequency of >10% decrement (%)	0 (0/8)	0 (0/8)	>0.99
Conduction block (%)	62.5 (5/8)	0 (0/8)	0.03*
	MMN	**PMA**	
Accessory Nerve (Trapezius Muscle)	**N = 9**	**N = 10**	***P***
CMAP amplitude, mV	6.1 ± 2.3	3.4 ± 0.7	0.03*
Decrement percentage (%)	0.6 ± 4.0	10.3 ± 6.5	<0.01†
Frequency of >10% decrement (%)	0 (0/9)	60.0 (6/10)	0.01*

*$P < 0.05$.
†$P < 0.01$.

PMA showed an abnormal decremental response ($P = 0.01$) (Table 2, Fig. 1). Of the 6 patients with abnormal decremental responses, 2 displayed a U-shape with maximal decrement at the 4th or 5th stimulus, and for 4 patients, the nadir was between the 6th and 10th stimulus.

Decrement percentage and CMAP amplitude showed a significantly negative correlation only in the accessory nerve of patients with PMA ($r = -0.74$, $P = 0.02$, Fig. 3).

DISCUSSION

Since Mulder et al[13] reported the decremental response of RNS in patients with ALS, detection of the decremental response in MND is now widely recognized. Several studies have investigated the role of RNS in differentiating ALS from other diseases. Hatanaka et al compared ALS with cervical spondylotic amyotrophy and reported that an abnormal decremental response in the trapezius muscle was strongly suggestive of ALS. Moreover, they suggest that a lack of decremental response in the deltoid muscle could exclude ALS with upper-limb onset.[14] Although there are no reports of RNS in PMA alone, Iwanami et al[17] reported that among the ALS cohort, patients with PMA showed the highest rate of abnormal decremental responses. To our knowledge, the present study is the first to investigate the RNS decremental response in MMN and use it to distinguish between MMN and PMA.

We found that, compared with patients with MMN, patients with PMA had a significantly larger decrement percentage in the accessory nerve. Abnormal decremental response (>10%) was not found in patients with MMN, but it was found in 60.0% (6/10) of accessory nerve recordings in patients with PMA, and the frequency of abnormal decremental response was also significantly higher. Thus, the detection of an abnormal decremental response in the accessory nerve may be strongly suggestive of PMA. However, we did not find RNS in the ulnar nerve to be useful in differentiating MMN from PMA because the decrement percentage in the ulnar nerve was similar in the 2 conditions, and no patient showed an abnormal decremental response.

The mechanism of a decremental response in ALS remains unclear, but several theories have been proposed. One theory is that it is because of an instability of acetylcholine release caused by presynaptic failure, caused by immature nerve terminals during early terminals of reinnervation.[21] In relation

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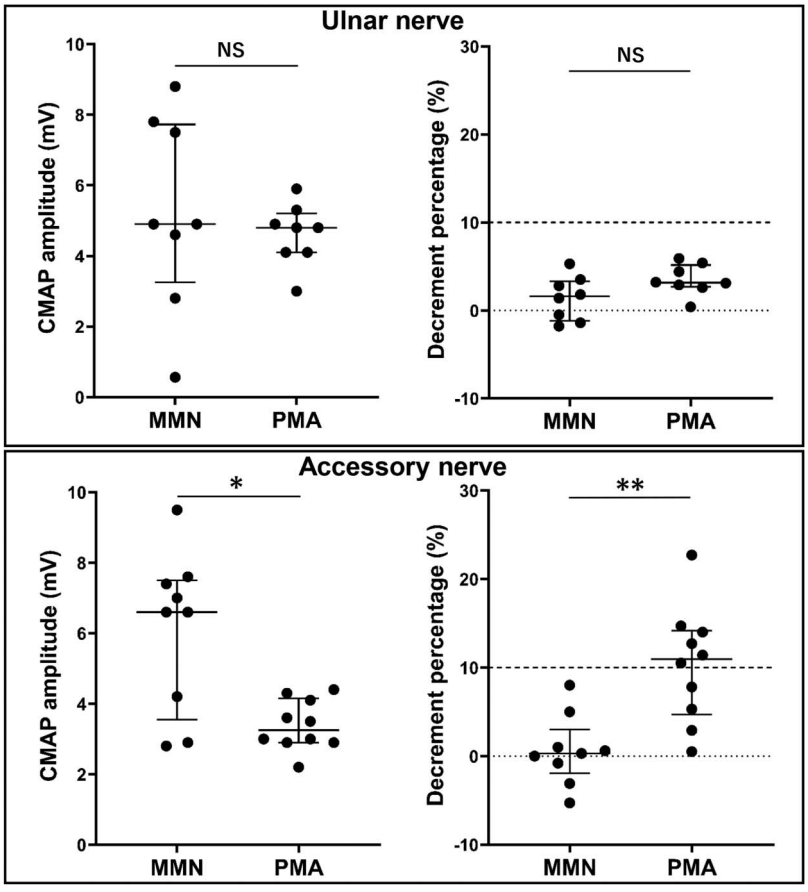

FIGURE 1. CMAP amplitude and decrement percentage of the ulnar nerve and accessory nerve in patients with MMN and PMA. *$P < 0.05$; **$P < 0.01$.

to this, a decremental response is more likely to occur in atrophic or severely affected muscles in patients with ALS, as shown by a similar trend in the accessory nerve in PMA observed in the present study (Fig. 3).[17,20] In addition, the distribution of the decremental response in patients with PMA in the present study corroborates with that in previous studies. Killian et al reported a higher detection rate in proximal muscles, such as the trapezius and deltoid muscles, than in the distal muscles in patients with ALS, even though the distal muscles are more severely affected.[14,15,17,20,22] The precise mechanism

TABLE 3. Comparison Between MMN With Conduction Block or Without CB in the Ulnar Nerve

	MMN With CB in the Ulnar Nerve (n = 5)	MMN Without CB in the Ulnar Nerve (n = 3)	*P*
Age, y	52.0 ± 14.2	44.3 ± 8.5	0.57
Disease duration at evaluation, mo	149 ± 152.8	59.0 ± 21.9	0.14
Distal CMAP amplitude, mV	4.1 ± 2.6	7.2 ± 2.0	0.11
Decrement percentage (%)	2.5 ± 2.2	−0.5 ± 2.0	0.14

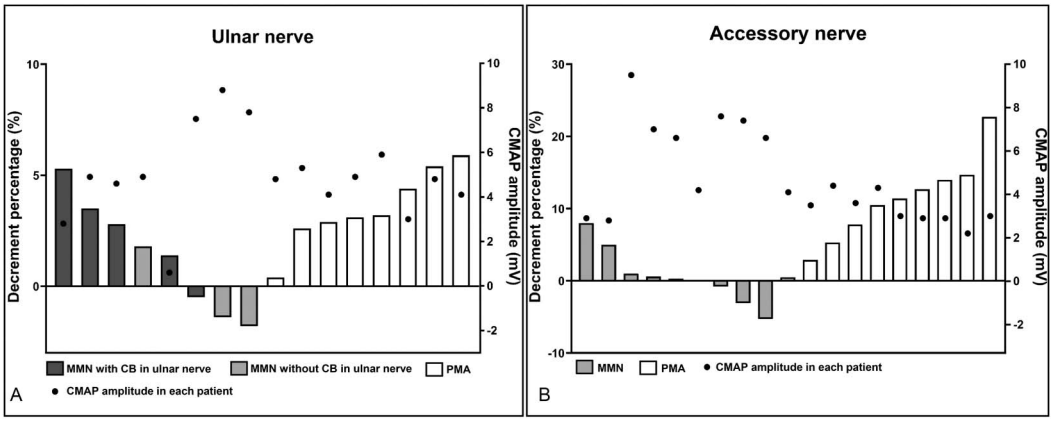

FIGURE 2. Graphical representation of CMAP amplitude and decrement percentage with and without CB. A, In the ulnar nerve and (B) In the accessory nerve. The left and right vertical axes show the decrement percentage and CMAP amplitude, respectively. The bars and black circles represent the decrement percentage and CMAP amplitude for each patient.

for this paradoxical finding has not been clarified. Conversely, proximal muscles are less likely to be affected in patients with MMN. MMN develops greater CB in the distal muscles than in the proximal muscles [median nerve (77%), ulnar nerve (80%), and musculoskeletal nerve (9%)].[1] The frequency of CB in the accessory nerve remains unclear; however, it is unlikely that proximal muscles are affected in patients with MMN. These reasons may have led to a significant difference in decremental response in the accessory nerve.

On the contrary, the decremental response is small in distal muscles in patients

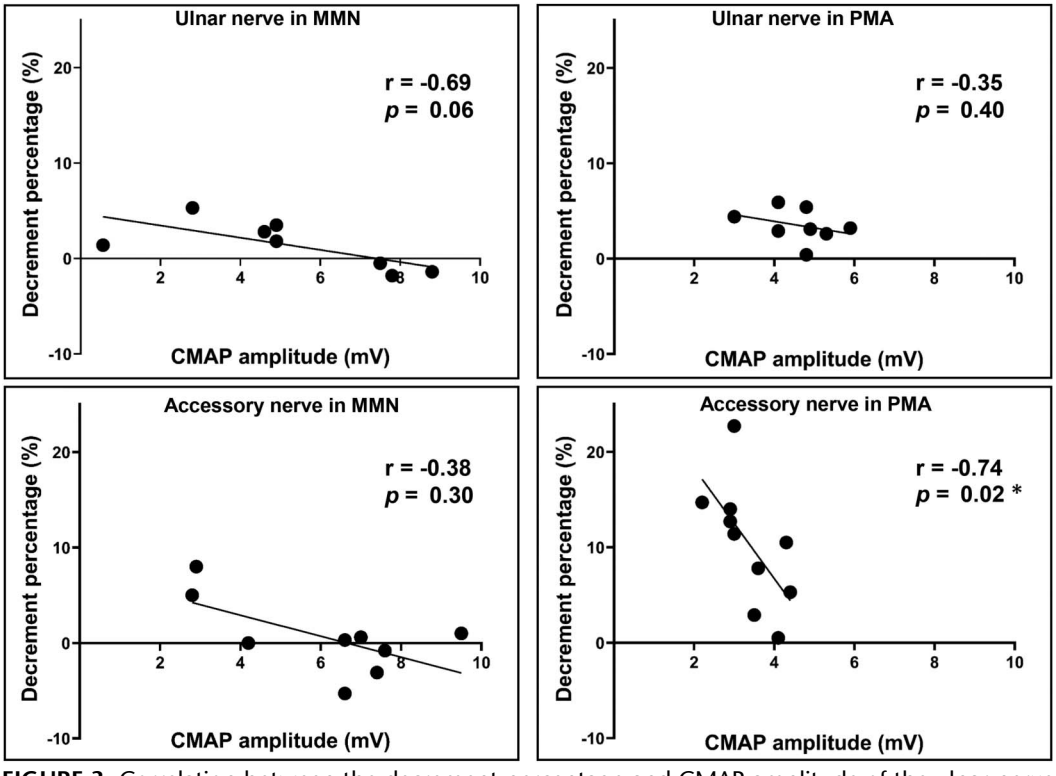

FIGURE 3. Correlation between the decrement percentage and CMAP amplitude of the ulnar nerve and accessory nerve in patients with MMN and PMA. *$P < 0.05$.

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with ALS. In particular, it has been reported that the decremental response is small in ADM muscles because of split hand,[23] which may have prevented the difference from MMN in the ulnar nerve. Comparison with APB muscles and first dorsal interossei muscles, which are considered to have a larger decremental response than ADM muscles,[23] may be more useful for differentiating the 2 diseases. In addition, 5 patients with CB in the ulnar nerve in MMN had a low CMAP amplitude and relatively higher decrement percentage than 3 patients without CB. MMN without CB, which is more difficult to differentiate from PMA, may have a lower frequency of decremental response. Therefore, RNS in distal muscles may also be useful for differentiation, if the muscle and subject of RNS are appropriately selected.

The present study has some limitations. First, a small number of patients were included in this study. Second, in most of the patients with MMN, RNS was performed during maintenance treatment with IVIg and therefore pretreatment data were insufficient. Further accumulation of pretreatment data is required.

In conclusion, our findings indicate that decremental responses are less prominent in patients with MMN than in patients with PMA, and thus RNS can be used clinically in distinguishing between MMN and PMA. Lack of prominent decremental responses in MMN could be because of degeneration of nerve axons and not because of neuromuscular junction pathology.

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