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Research paper

Compound muscle action potential of whole-forearm flexors: A clinical biomarker for inclusion body myositis

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ABSTRACT

Objective: This study aimed to investigate the potential of whole-forearm flexor muscle (WFFM) compound muscle action potential (CMAP) as a quantitative biomarker for inclusion body myositis (IBM) pathology.
Methods: We prospectively enrolled 14 consecutive patients (10 men and 4 women) diagnosed with IBM based on muscle biopsies. We evaluated the baseline-to-peak amplitude of the WFFM CMAP and other quantitative parameters, including grip and pinch strength, Inclusion Body Myositis Functional Rating Scale (IBMFRS) score, and other routine muscle CMAP amplitudes.
Results: The WFFM CMAP was strongly correlated with disease duration and the IBMFRS score. The WFFM CMAP on the more affected side was lower than that on the less affected side. Furthermore, grip power was strongly correlated with the WFFM CMAP, whereas lateral pinch strength was strongly correlated with the WFFM and first dorsal interosseous CMAPs. The 3-point pinch strength was also correlated with the WFFM CMAP.
Conclusions: This study demonstrates that the WFFM CMAP may serve as a biomarker of severity in IBM.
Significance: Identification of this biomarker can support drug development, diagnosis, prognosis, and treatment options for patients with IBM.

1. Introduction

Sporadic inclusion body myositis (IBM) is a chronic, progressive muscle disease that primarily affects individuals aged > 50 years. It is characterized by asymmetric weakness and muscle atrophy in the quadriceps and finger/wrist flexors. Typical patterns of involvement include a preference for the anterior muscle groups, with selective involvement of the flexors in the entire forearm and thigh muscles, such as the flexor digitorum profundus (FDP),vastus lateralis, and vastus medialis muscles (Nodera et al., 2016; Cox et al., 2011; Tasca et al., 2015). Skeletal muscle involvement is characterized by the presence of marginal vacuolar tissue changes with inflammatory cell infiltration, which may not respond to immunotherapy and may worsen. Furthermore, the involvement of cytosolic 5′-nucleotidase 1A antibodies in IBM has been investigated (Tawara et al., 2017).

The exact cause of IBM is unknown; however, several treatments are currently under development, including clinical trials of new drugs and rehabilitation treatments such as robotic suits (Hanna et al., 2019; Amato et al., 2021). Despite these advancements, quantitative clinical biomarkers reflecting the pathology of IBM are unavailable, making disease evaluation difficult (Fig. 1). The compound muscle action potential (CMAP) consists of hundreds of motor unit action potentials that are summed in a complex manner. Due to differences in conduction velocity between axons, motor unit potentials become more desynchronized over longer conduction distances, leading to lower complete summation, altered phase cancellation, and changes in CMAP morphology. In this study, we did not aim to evaluate pathological changes such as partial conduction block or abnormal temporal dispersion but rather focused on the evaluation of the pathological condition. We investigated the use of the CMAP amplitude, which

List of Abbreviations: ADM, abductor digiti minimi; AIN, anterior interosseous nerve; APB, abductor pollicis brevis; CCI, Charlson comorbidity index; CMAP, compound muscle action potential; FDI, first dorsal interosseous; FDP, flexor digitorum profundus; IBM, inclusion body myositis; IBMFRS, Inclusion Body Myositis Functional Rating Scale; MUP, motor unit potentiation; NCS, nerve-conduction studies; WFFM, whole-forearm flexor muscle; WFFMm, whole-forearm flexor muscle-median nerve stimulation; WFFMu, whole-forearm flexor muscle-ulnar nerve stimulation.

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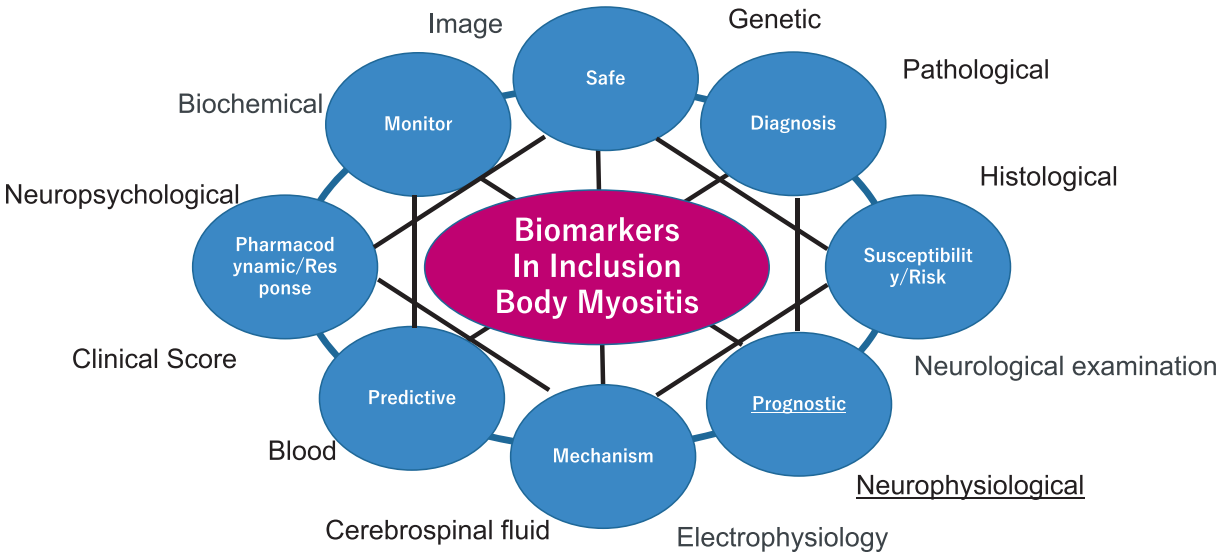

Fig. 1. Biomarker candidates in IBM. Abbreviations: IBM, inclusion body myositis.

reflects the number of nerve fibers of the whole-forearm flexor muscle (WFFM), as a clinical biomarker for IBM (Rhee et al., 1990; Olney et al., 1987).

2. Methods

2.1. Participants

We prospectively analyzed the muscle biopsy findings of 14 consecutive patients (10 men and 4 women) diagnosed with IBM (Aoki et al., 2014; Griggs et al., 1995; Needham and Mastaglia, 2007). The clinical characteristics of the study population are summarized in Table 1. All the participants were Japanese nationals. Three of the fourteen patients required a cane for ambulation, and two were either bedridden or required a wheelchair for mobility. The symptoms at onset included gait disturbances and difficulty in standing up, upper-limb weakness, difficulties in opening the cap of a plastic bottle, or dysphagia. Disease onset was defined as the time when muscle weakness or dysphagia began rather than when the creatine kinase level was evaluated.

This study was approved by the Ethics Committee of the Nara Medical University (approval no. 2688). All the participants provided written and verbal informed consent. All study procedures were conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan.

2.2. WFFM CMAP recordings under median and ulnar nerve stimulation

All nerve-conduction studies (NCS) were performed using an electromyography machine (Nicolet Synergy EDX system; Natus, Middleton, WI, USA) with bandpass filter settings of 3 Hz and 10,000 Hz for low and high frequencies, respectively. The stimulus consisted of a rectangular electrical pulse of 0.2 ms duration. The skin temperature was measured at the participants' forearm surface and maintained at $\geq$ 31.0 °C.

WFFM CMAP measurements were obtained at a point immediately lateral to the posterior margin of the ulna, approximately 8 cm from the elbow, and the reference electrode was placed distally (Felsenthal et al., 1986; Mano et al., 2023). The site with the highest surface electromyography amplitude when the whole finger was flexed was determined to be the entire forearm flexor and was selected as the site immediately above the constructed entire forearm flexor. The standard technique involved motor conduction by stimulating the antecubital fossa proximal to the medial brachial artery of the elbow joint for the median nerve or 2–3 cm distal to the medial epicondyle near the ulnar notch for the ulnar nerve (Fig. 2A). CMAP was measured at supramaximal stimuli: the stimulus intensity was continuously increased by 30 %–

Table 1
Clinical features of patients with IBM.

	N = 14	
Sex (male: female)	10:4	
	Median (95%CI:95 % Confidence Interval)	
Age at examination (years)	73.5 (66.9–79.3)	
Disease duration (years)	8.5 (5.1–10.2)	
CCI	2.0 (1.1–2.9)	
Muscle Strength	Right	Left
Grip Power	14.7 (10.8–18.4)	10.0 (8.8–13.8)
Lateral pinch	4.1 (3.6–6.0)	3.5 (2.8–4.8)
3-point pinch	3.78 (2.5–4.6)	3.1 (2.0–3.7)
CMAP of Nerve conduction study	Right	Left
WFFMsum	6.4 (4.3–7.5)	5.2 (3.8–6.5)
WFFMm	3.3 (2.4–4.8)	2.8 (1.8–4.1)
WFFMu	2.4 (1.6–3.1)	2.1 (1.7–2.7)
APB	8.2 (7.5–10.9)	7.5 (7.4–11.1)
ADM	9.9 (8.6–12.3)	9.5 (7.8–11.2)
FDI	14.0 (11.9–16.2)	11.4 (10.3–15.4)
forearm temperature	32.1 (31.8–32.7)	

Abbreviations: IBM, inclusion body myositis; CMAP, compound muscle action potential; CCI, Charlson Comorbidity Index; WFFM, whole-forearm flexor muscle; FDI, first intervertebral muscle; ADM, abductor digiti minimi; APB, abductor pollicis brevis.

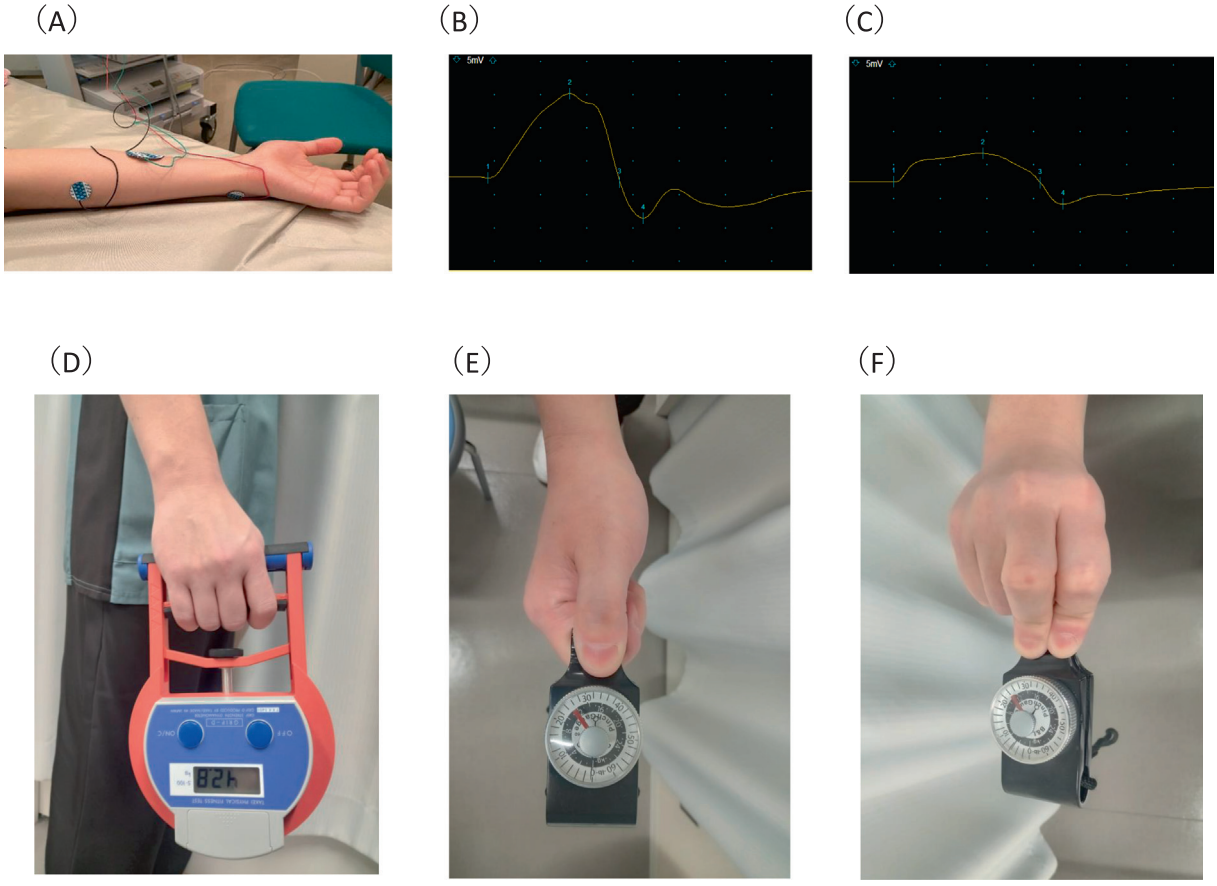

Fig. 2. Photos of WFFM's nerve conduction studies and muscle strength evaluation. A: Registration electrodes and reference electrode; B: CMAP of WFFM with median nerve stimulation; C: CMAP of WFFM with ulnar nerve stimulation; D: grip strength evaluation; E: lateral pinch test; F: 3-point pinch test. Abbreviations: CMAP, compound muscle action potential; WFFM, whole-forearm flexor muscle.

40 % until the CMAP reached the maximal value, and the baseline-to-peak amplitude of CMAP was assessed. Recordings were obtained with median nerve stimulation (WFFMm) (Fig. 2B) and ulnar nerve stimulation (WFFMu) (Fig. 2C). WFFMsum is calculated by algebraically summing WFFMm and WFFMu. The location of the registration electrode was kept constant for both median and ulnar nerve stimulation. In addition, NCS of the first dorsal interosseous (FDI) and abductor digiti minimi (ADM) were performed using ulnar nerve stimulation, and those of the abductor pollicis brevis (APB) were performed using median nerve stimulation. All electromyography studies were conducted and evaluated by physicians with over 10 years of training and experience.

2.3. Evaluations

The Inclusion Body Myositis Functional Rating Scale (IBMFRS), which is based on the Amyotrophic Lateral Sclerosis Functional Rating Scale, is a disease-specific 10-point functional rating (Jackson et al., 2008; Kasarskis et al., 2005) that has been validated previously (Goyal et al., 2022; Ramdharry et al., 2019; Charlson et al., 1987). The comorbidities in IBM were evaluated using the Charlson Comorbidity Index (CCI) (Lindberg and Oldfors, 2012). Grip strength, which reflects muscular strength or the maximum force generated by the forearm muscles, has been used to evaluate IBM pathology (Dimachkie and Barohn, 2013) (Fig. 2D). The side with the lowest grip strength was defined as the more affected side. We also obtained two pinch-strength measurements three times at 1-min intervals and recorded the maximum strength each time. In the lateral pinch test, a pinch meter was placed between the index finger and the radial side of the thumb, and the patient was instructed to pinch as hard as possible (Fig. 2E). Despite individual differences, this technique may reflect the early stages of symptoms, such as difficulty in opening the lid of a plastic bottle. In the 3-point pinch test, a pinch meter was placed between the pads of the thumb, index finger, and middle finger (Fig. 2F). Tip-pinch measurements could not be obtained in all patients with IBM in this study; they were not included.

2.4. Statistical analyses

All data are presented as mean ± standard deviation. Differences in categorical variables were assessed using the χ^2 test. The Shapiro–Wilk test was used to assess the distribution of the data, and Spearman's correlation coefficients ® were calculated to evaluate the association between the CMAP background and muscle strength. A correlation coefficient (r) > 0.4 was considered to indicate a strong correlation. Differences in categorical variables were assessed using the χ^2 test. Multiple regression analysis was used for multiple classification analysis. Statistical significance was set at $p < 0.05$. The analysis was performed using the statistical software package SPSS 21.0 J (SPSS Japan, Tokyo, Japan).

3. Results

3.1. Clinical characteristics and WFFM CMAP in IBM

The clinical characteristics of the participants are summarized in Table 1. Fourteen IBM patients confirmed by pathological exam-

ination were included, with a median age of 73.5 years (66.9–79.3) and a median disease duration of 8.5 years (5.1–10.2). The comparison of WFFM CMAP between median and ulnar stimulation is presented in Fig. 3A. The CMAP WFFMm was significantly larger than WFFMu.

3.2. Comparison between the more and less affected sides

The right side was more affected in five patients, whereas the left side was more affected in nine patients. We classified by limb and compared the WFFM CMAP between the more and less affected sides (n = 28). The WFFM CMAP of the more affected side was significantly lower than that of the less affected side (Fig. 3B).

3.3. Relationships of variables with WFFM CMAP

3.3.1. Background characteristics

The IBMFRS score, disease duration, and age were strongly correlated with the WFFMsum, but the CCI was not correlated (Fig. 3-C-F).

3.3.2. Grip and pinch strengths

Grip strength showed significant correlations with WFFMm and WFFMsum but showed no correlation with the WFFMu. Lateral pinch strength was significantly correlated with WFFMm and FDI, and the 3-point pinch strength was significantly correlated with WFFMm and WFFMsum (Table 2). Grip and pinch strengths were not correlated with the CMAP of ADM and APB.

4. Discussion

This study investigated whether WFFM CMAP measurements could be used as biomarkers for IBM pathology. WFFM CMAPs were strongly correlated with grip strength and IBMFRS scores, which have already been used to assess IBM pathology. Although many reports described little correlation between disease duration and IBM pathology, disease duration was correlated with WFFM CMAP. IBM has an inflammatory and degenerative disease component, and serum CK levels and other indicators may initially respond to immunotherapy such as steroids; however, these therapeutic effects do not last long. Therefore, it is considered to be a degenerative disease. The diagnosis of IBM is often delayed by an average of five years from symptom onset and is usually made by a combination of clinical, electrodiagnostic, and pathological assessments (Dimachkie and Barohn, 2013). In clinical experience, electromyography in IBM shows mixed myopathic and neurogenic patterns. Therefore, the findings are considered nonspecific, and electromyographic examinations were excluded from the latest criteria for sporadic IBM (Rose and ENMC IBM Working Group, 2013). It has been previously speculated that Motor unit potentiation (MUP) takes on a neurogenic-like pattern in the late stage, as IBM progresses slowly and reinnervation occurs. We experience MUP instability due to positional recruitment failure. Neurogenic-like MUP in IBM has sufficient density to mask myogenic changes (Mano et al., 2024). The previous study suggested that MUP in IBM is often complex in morphology and mimics subacute neuropathic processes (Lotz et al., 1989; Noda et al., 2022). In contrast, Several studies have reported peripheral neuropathy in IBM (Lindberg and Oldfors, 2012). Axonal loss reduced CMAP drop, which is suggestive of Wallerian degeneration and atrophy of axon terminals, and delayed F-wave latency suggests peripheral nerve involvement in IBM (Lee et al., 2020). Abnormalities may be seen on sensory nerve conduction tests and may indicate damage to nerve fibers within the muscle that may not be detected on neurological tests.

However, there is low pathological specificity, with scattered cases in which signs of axonal damage were predominant, along with numerous changes observed in Schwann cells and myelin sheaths (Hermanns et al., 2000). We believe that the characteristics of MUP do not necessarily negate neurogenic changes but rather reflect the complexity of the underlying disease mechanism. Since mixed myogenic and neurogenic electromyograms may represent

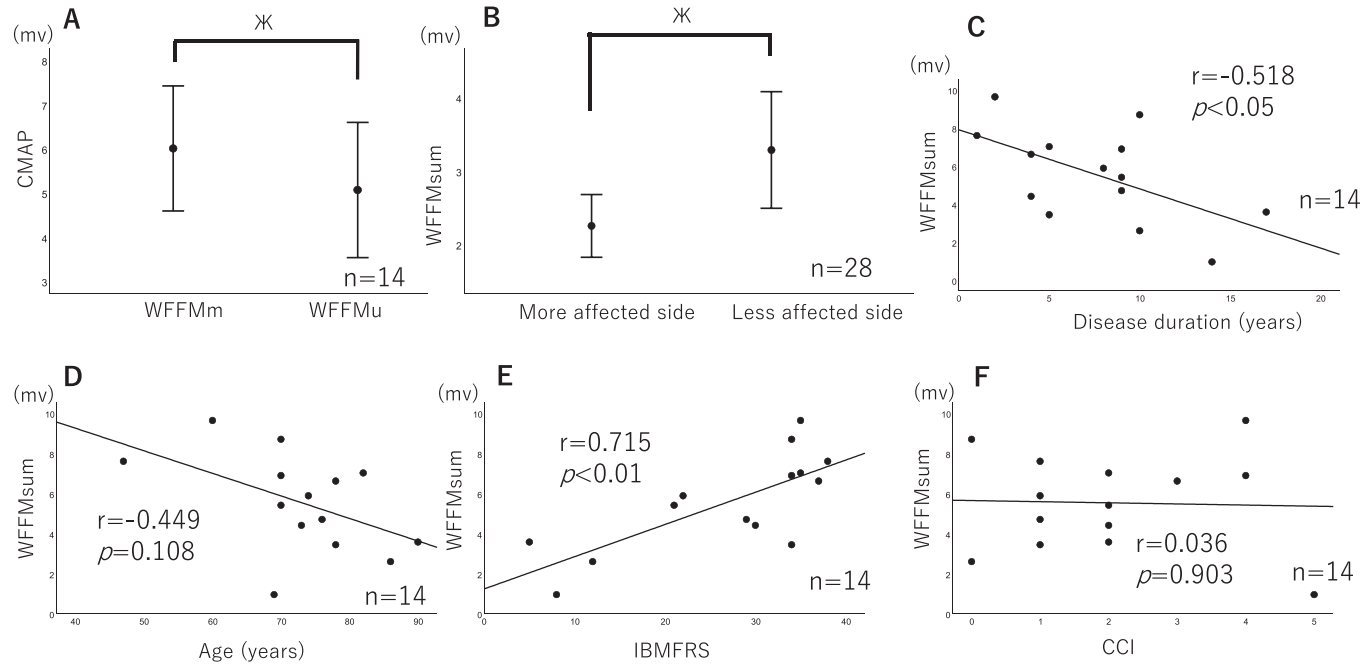

Fig. 3. CMAP of whole-forearm flexor muscle in IBM. A: Comparison between median and ulnar stimulation; B: comparison between the more and less affected sides; C: relationship with disease duration; D: relationship with age; E: relationship with IBMFRS; F: relationship with CCI. Abbreviations: IBM, inclusion body myositis; CMAP, compound muscle action potential; CCI, Charlson Comorbidity Index; IBMFRS, Inclusion Body Myositis Functional Rating Scale; WFFM, whole-forearm flexor muscle.

Table 2
Correlations between muscle strength and CMAP.

	WFFMsum	WFFMm	WFFMu	APB	ADM	FDI
Grip strength	***r* = 0.626**	***r* = 0.625**	*r* = 0.248	*r* = -0.048	*r* = 0.323	*r* = 0.277
	***p* < 0.001**	***p* < 0.001**	*p* = 0.204	*p* = 0.808	*p* = 0.093	*p* = 0.153
Lateral pinch	*r* = 0.356	***r* = 0.409**	*r* = 0.016	*r* = 0.027	*r* = 0.284	***r* = 0.430**
	p = 0.063	***p* < 0.05**	*p* = 0.935	*p* = 0.890	*p* = 0.143	***p* < 0.05**
3-point pinch	***r* = 0.742**	***r* = 0.740**	*r* = 0.332	*r* = -0.160	*r* = 0.149	*r* = 0.243
	***p* < 0.001**	***p* < 0.001**	*p* = 0.084	*p* = 0.416	*p* = 0.450	*p* = 0.213

Abbreviations: CMAP, compound muscle action potential; WFFM, whole-forearm flexor muscle; FDI, first intervertebral muscle; ADM, abductor digiti minimi; APB, abductor pollicis brevis.

the possibility of neurogenic pathologies other than myogenic, we examined whether NCS findings could be used as a surrogate biomarker for IBM pathology.

Our results show that grip impairment was more strongly associated with WFFMm than with WFFMu, potentially indicating that the anterior interosseous nerve (AIN) region was more affected than the ulnar region in IBM. Moreover, the association between pinch measurements and WFFM may quantitatively reflect the difficulties in opening plastic bottle lids in the early stages of IBM. Previous anatomical studies have shown that WFFM innervation varies among individuals: the AIN innervates the lateral half of the FDP, whereas the UN innervates the medial half (Segal et al., 2002; Hwang et al., 2018). AIN disorder may be involved in the pathology of IBM's flexor-dominant disorder.

This study had some limitations. The small sample size reduces the generalizability of the results. Furthermore, the study population showed a heterogeneous distribution of disease duration, and the association with disease duration was inconclusive. Moreover, overlapping longitudinal assessments may show greater reliability for slowly progressive neuromuscular diseases such as IBM. Another limitation is that all patients were Japanese, among whom there were more patients with distal myopathy than among other foreigners (Suzuki et al., 2019). Genetic testing was not conducted in this study, and the possibility that genetic factors are involved in the results cannot be ruled out. This biomarker could be easily performed using standard EMG equipment and could potentially be used for longitudinal studies (follow-up) of patients. Additionally, comparisons with other biomarker candidates and longitudinal analysis were not conducted in this study. Normative controls, inter- and intra-rater variability, and ICC data in IBM patients were also lacking. These aspects should be addressed in future studies.

WFFM CMAP may have been influenced by several other factors, including muscle mass, tissue fat, forearm flexors (such as the flexor digitorum superficialis and flexor carpi radialis other than FDP), and the positioning of the extremities when CMAP was obtained, or strength measurements were taken. Stimulating currents to adjacent nerves and unwanted volumetric conduction recordings from adjacent muscles can also affect the CMAP size. However, WFFM CMAP may be a potential surrogate marker for clinical severity. Biomarker endpoints in clinical trials can be proof-of-mechanism, proof-of-concept, or potential surrogate endpoints (known markers or markers that are likely to be reasonably predictive of clinical efficacy). The identification of some intermediate surrogate markers could support drug development, diagnosis, prognosis, and treatment options. Clinical trial results of disease-modifying therapies for neurodegenerative diseases have underscored the need for testing and assessment before the onset of neurological symptoms.

We believe that using WFFM CMAP in combination with other anatomical factors can improve the understanding of focal myopathy in IBM (Greenberg et al., 2022). This was a pilot study; future studies should aim to validate the accuracy of this method.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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CRediT authorship contribution statement

Tomoo Mano: Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing. **Naohiko Iguchi:** Data curation, Writing – original draft, Writing – review & editing. **Naoki Iwasa:** Conceptualization, Methodology. **Nanami Yamada:** Data curation. **Kazuma Sugie:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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