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Clinical features of Japanese patients with inclusion body myositis

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ABSTRACT

Background: The incidence of sporadic inclusion body myositis (sIBM) has been much lower in Japanese than in Western populations. Because of a few reports on Asian populations, it is unclear whether the clinical characteristics of sIBM are identical in Caucasian and Japanese patients.
Methods: We compared 18 patients with sIBM, divided into 3 groups by age-of-onset, with previous cohort studies. We calculated the ΔIBM functional rating scale/time duration (ΔIBMFRS/Δtime) as an index of functional disability progression. Patients' electrophysiology was analyzed in relation to their clinical characteristics.
Results: The cohort was 83.3% male and showed uniform initial muscle weakness in the lower and/or upper limbs. An older age-at-onset was associated with a more rapid progression, and patients with a longer duration frequently showed F-wave abnormalities and findings of chronic denervation.
Conclusions: The clinical characteristics of sIBM were relatively homogeneous beyond the ethnic differences. Aging might be a synergistic factor for the progression of sIBM pathology.

1. Introduction

Sporadic inclusion body myositis (sIBM) is a progressive myopathy characterized by proximal and distal muscle weakness and atrophy as well as an age of onset of symptoms over 50 years of age, especially in Western countries. The incidence of sIBM in the Japanese population is increasing, but there are only a few reports on the clinical, electrophysiological, and histopathological findings of sIBM in Japanese populations [1,2].

sIBM is known to mimic the clinical and electrophysiological features of motor neuron disease: some patients with a pathologic diagnosis of sIBM could initially be misdiagnosed as having motor neuron disease (MND) or amyotrophic lateral sclerosis (ALS) [3]. Early electrophysiological studies showed that IBM demonstrates a heterogeneous electromyography (EMG) profile: abundant short-small motor unit potentials (MUPs) with fibrillations and positive sharp waves, a mixed pattern of large and small MUPs, and only neurogenic features [4]. Moreover, morphological and electrophysiological studies demonstrated peripheral nerve involvement such as the loss of axons, Wallerian degeneration, and axon terminal atrophy in many cases of sIBM [5]. However, the possible relationship between the disease stages and the involvement of peripheral nerves and/or motor neurons remains unknown.

The aim of this study is to clarify the clinical characteristics and electrophysiological findings of sIBM in Japanese patients, to illustrate the ethnical and regional variability in clinical phenotypes between Japanese and other ethnic groups, and to examine electrophysiologically whether peripheral nerves and/or lower motor neurons are affected in the patients.

2. Materials and methods

2.1. Patients

The study was approved by the Ethics Committee of Kumamoto University Hospital. We retrospectively analyzed the medical records of 18 consecutive patients admitted to the Department of Neurology, Kumamoto University Hospital, from 1991 to 2013. All patients were diagnosed with sIBM through muscle biopsy. The diagnosis of sIBM was based on the diagnostic criteria established by Hilton-Jones et al. [6]. In brief, they were classified into three groups: pathologically defined IBM, clinically defined IBM, and possible IBM. Pathologically defined IBM is supported by the following items: invasion of non-necrotic fibers by mononuclear cells and rimmed vacuoles (RVs), and either intracellular amyloid deposits or 15–18 nm filaments. Clinically defined IBM meets the following standards: duration weakness >12 months, age > 35 years, weakness of finger flexion > shoulder abduction AND of knee extension > hip flexion, invasion of non-necrotic fibers by mononuclear cells or RVs or increased MHC-I, but no intracellular amyloid deposits or 15–18 nm filaments. Possible IBM is diagnosed by the above-mentioned "AND" is set to "OR". The percentage of RV-positive fibers was calculated by counting in randomly selected areas for a total of 200 myofibers per muscle sample.

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2.2. Clinical evaluation

For the patients who were admitted after 2009, several neurologists tested their muscle strength and scored the IBM functional rating scale (IBMFRS) [7], which is a widely used scoring system for the functional status of patients with IBM. We evaluated each patient who was admitted before 2008 with IBMFRS scores according to the description in their medical records. In each group, we calculated the ΔIBMFRS/Δtime for an index of progression in functional disabilities, which are the differences in IBMFRS scores between the 2 time points divided by the duration between the 2 time points (years).

2.3. Electrophysiological assessment

In 8 patients with sIBM, the shortest F-wave latency after distal stimulation was recorded in the median, ulnar, tibial, and peroneal nerves. Needle EMG was performed in 12 patients to detect the presence of acute or chronic denervation, or myogenic changes in the deltoid, biceps brachii, or quadriceps femoris muscles. The recordings were obtained using a Neuropack (Nihon Kohden, Tokyo, Japan). Abnormalities in F-wave measurements were defined as a prolongation of the shortest F-wave latency or a lower F-wave frequency. Acute denervation was judged by the presence of a positive sharp wave (PSW), fibrillation potentials (Fib), or fasciculation potentials (Fas). Chronic denervation was determined by an MUP amplitude higher than 1000 μV and its duration longer than 10 ms during weak contraction or by poor recruitment during maximum contraction. Myogenic change was evaluated by an MUP amplitude of less than 200 μV and its duration shorter than 5 ms. All clinicopathological information of each patient were summarized in sTable 1.

2.4. Statistics

We performed statistical evaluations between groups with Mann–Whitney U tests.

3. Results

3.1. Clinical characteristics

Table 1 and sTable 1 illustrate the clinical features of all the patients we evaluated as well as patients in previous reports, which include gender, age at onset, age at diagnosis, pretreatment serum creatine kinase level, treatment, and outcome. The clinical demographics of our 18 patients who met either the defined or possible diagnostic criteria for sIBM established by Hilton-Jones et al., revealed male predominance (83.3%), a mean age of 62.4 years at onset, and a uniform initial symptom of muscle weakness in the upper and/or lower limbs (Table 1).

We categorized the 18 patients into 3 groups based on their age at onset: 2 in the <50 group, 11 in the 50–69 group, and 5 in the ≥ 70 group (Table 2). In the latter 2 groups, which were typical with regard to age at onset, more than 80% of the patients were male (Table 2). The group with the youngest age at onset had a longer duration between onset and definite diagnosis (biopsy). We next assessed whether progression rates in functional disabilities were different among the 3 groups. We compared ΔIBMFRS/Δtime for an index of the progression of functional disabilities. The ≥ 70 group had a significantly higher ΔIBMFRS/Δtime ($P = 0.01947$, Mann–Whitney U test), suggesting that progression in functional disabilities of the group with age 70 or more was more rapid (Fig. 1). We also categorized them into 2 groups based on the diagnostic criteria for sIBM established by Hilton-Jones et al.: pathologically defined IBM and clinically defined IBM, or possible IBM. We performed the same consideration with the former 2 groups and the possible IBM group. These 2 groups had no significant differences in their ΔIBMFRS/Δtime (Mann–Whitney U test, data not shown).

3.2. Electrophysiological characteristics

Of our 18 patients with sIBM, 8 and 12 patients were examined by nerve conduction (NC) and needle EMG studies, respectively. We divided those patients into 2 groups: a group with disease duration of less than 12 years, and a group with disease duration of more than 12 years from onset to examination. In the NC study, 4 and 4 patients belonged to the groups with disease duration of less and more than 12 years, respectively. In the needle EMG study, 8 and 4 patients were categorized into the former and latter groups, respectively (sTable 1). Abnormalities in F-waves were frequently detected in the group (75%) with a duration of more than 12 years, whereas no patients in the group with a duration of less than 12 years showed an abnormal F-wave finding (Fig. 2A). All patients showed acute denervation findings, including PSW/Fib in the group with shorter duration, although no patients presented those findings in the group with the longer duration (Fig. 2B). Fas were observed in 12.5% of patients in the group with shorter disease duration, but were not detected in the group with the longer duration (Fig. 2B). Myogenic changes were observed in 62.5% and 50% of patients in the group with the shorter and longer duration, respectively (Fig. 2C). Chronic denervation findings were observed in 75% and 100% of patients in the group with the shorter and longer duration, respectively (Fig. 2D).

Table 1
Clinical summary of our 18 patients diagnosed with sIBM between 1991 and 2013, and comparison between our cases and the cases described in previous reports.Modified from a report by Benveniste et al.

	n	Male dominancy (%)	Age at onset (years)	Age at diagnosis (years)	Creatine kinase level (IU/l)	Patients receiving immunosuppressant (%)	Progression despite therapy (%)
This study	18	83.3	62.4	70.2	646.2	61.1	100
Ringel et al.(1987)	19	79	57.8	62.9			
Lotz et al.(1989)	40	72.5	56.1	62.4	197	72.5	80.2
Sayers et al.(1992)	32	62.5	58	61	1145	87.5	46.4
Beyenburg et al.(1993)	36	58.3	47	53.1	279	44.4	93.75
Lindberg et al.(1994)	18	55.5	60.4	62.7		88.8	75
Amato et al.(1996)	15	86.6	58	64	698	73.3	100
Peng et al.(2000)	78	78.2	56.5				
Felice and North(2001)	35	65.7	64.3	70	444	49	100
Badrising et al.(2005)	64	67.2	57.6		417	35.9	82.6
Benveniste et al. (2011)	136	57.3	61	66	267	52.2	100

IU, international unit.

Table 2
Clinical characteristics in each group categorized by age at onset.

Age at onset (year)	<50	50–69	≥70	Overall
Number of patients	2	11	5	18
Age at onset	43	60.4	74.8	62.4
Gender, male (%)	50.00%	90.90%	80%	83.30%
Patients receiving immunosuppressants (%)	1 (50%)	7	3	11 (61.1%)
Duration between first symptoms and diagnosis, years	17	7.54	4.6	7.8
Pretreatment CK level (IU/l)	254	317.7	1525.8	646.2
Number of patients with inflammatory cellular infiltration into non-necrotic fibers (%)	1 (50%)	9 (81.8%)	3 (60%)	13 (72.2%)
Number of patients with rimmed vacuoles (%)	2 (100%)	11 (100%)	5 (100%)	18 (100%)

CK, creatine kinase; IU, international unit.

4. Discussion

Comparison with the previous cohort studies regarding sIBM cases revealed that the natural histories of our patients with sIBM was similar to those of Western people, as well as those of other Japanese cohorts [2, 8–17]. These observations suggest that the clinical characteristics of sIBM were relatively homogeneous beyond the ethnic differences although people in the United States or Europe with an African origin seem to be less affected with sIBM. In our cohort, the initial diagnoses in more than half of the total patients with sIBM were PM, and the duration to the definite diagnoses was longer than that in the previous reports. Thus, we should keep in mind the possibility of sIBM for aged people with muscle weakness.

In this study, the patients with sIBM with a longer duration frequently showed abnormalities in their F-wave measurements as well as chronic denervation findings. Hokkoku et al. reported that high-amplitude of MUPs can be seen in muscle diseases, especially in the advanced stage of chronic myopathies with hypertrophic fibers such as sIBM [18]. Our observation of F wave abnormalities in the long duration group may suggest conduction impairment at the proximal region including the spinal anterior horns. We assume that aging would be one of the factors that induce chronic denervation as well as F wave abnormalities in long duration groups. In addition, we hypothesized that the pathology of sIBM could affect the lower motor neurons, including the neuromuscular junctions and the spinal anterior roots although we do not have a direct evidence that indicates the involvement of peripheral neuropathy or radiculopathy. Growing evidence suggests that some inherited types of inclusion body myopathy affects not only the skeletal muscles, but also the motor neurons as well as the frontotemporal cortices [19,20]. Thus, a further study would be useful to realize that sIBM pathology involves the motor neurons and/or peripheral neurons, as suggested in literature [4,5].

Fig. 1. ΔIBMFRS/Δtime in each group categorized by age at onset: less than 69 years, and aged 70 or more. In the box and whisker plots, the bottom and top of the box are the first and third quartiles, and the band inside the box is the median. The ends of the whiskers represent the minimum and maximum of all of the data. The asterisk indicates a significance of less than 0.05.

In this study, the oldest group showed a significantly more rapid progression of functional disabilities regarding sIBM. Interestingly, one patient who showed an extremely high value in the ΔIBMFRS/Δtime score had more frequent Fas, compared with other patients in the oldest group. The reason why the patient showed a rapidly progressive course might be the presence of Fas, which strongly suggests on-going denervation. Because the patient had no special reasons that deteriorated the disease course, we should include the patient into the analysis as far as the patient fulfilled the diagnostic criteria for clinically possible IBM.

It is still enigmatic whether inflammation is a primary trigger or a secondary event following muscle degeneration in sIBM pathology. The accumulation of misfolded proteins such as amyloid-like substances and TDP-43 emphasizes the degenerative aspect of the pathophysiological mechanisms of sIBM [21,22]. Moreover, poor responsiveness to immunosuppressants in most cases of sIBM strongly suggests that inflammation does not play a central role in sIBM pathology [23]. In our study, none of our patients showed a substantial recovery of muscle strength, although a few patients showed a transient improvement of serum creatine kinase levels. The patients of case 4 who underwent muscle biopsies twice definitely increased the numbers of RVs (sFig. 1). Thus, the presence of RVs might be related with aging whether the trigger of sIBM is inflammatory cellular infiltration or muscle degeneration.

The principal methodological limitation was the retrospective use of medical records on limited number of patients. Thus, a prospective multicenter study of a large number of patients should be valuable. For understanding of the involvement of motor neurons in sIBM, it would be helpful to analyze the postmortem spinal cord tissues derived from autopsied patients. However, we assume that the clinical characteristics of sIBM are relatively homogeneous beyond the ethnic differences. The group with a younger age at onset had a longer duration between onset and definite diagnosis. The progression of functional disabilities in the group with the older age at onset was more rapid as previously reported [16]. These suggest that aging might be a synergistic factor for the progression of pathology in sIBM, and such age-dependent progression might emphasize the degenerative aspect of pathophysiological mechanisms of sIBM. Further evaluation of how gender-differences and aging could affect clinical findings would be useful for a better understanding of the pathophysiology of sIBM.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jns.2014.08.009.

Conflict of interest

None.

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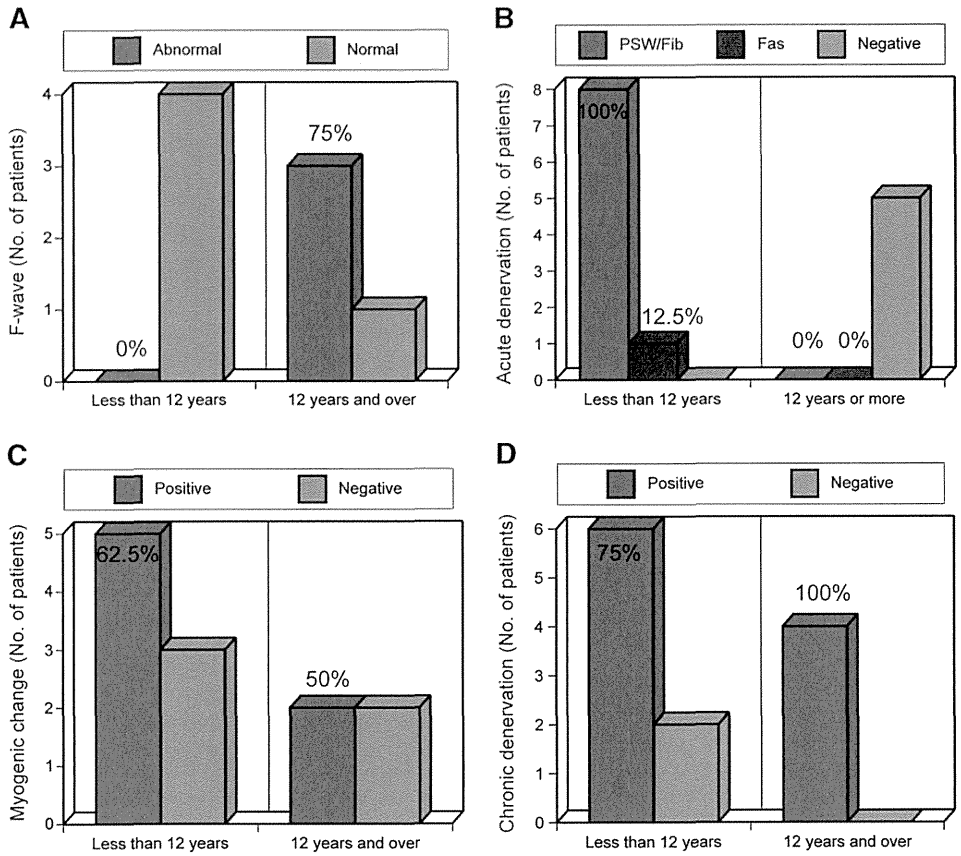

Fig. 2. (A) The number of patients with sIBM who showed abnormal findings in F-wave evaluation in the groups with the disease duration of less than 12 years (left) and 12 or more (right). (B) The number of patients with sIBM who showed acute denervation findings [positive sharp waves (PSW)/fibrillation potentials (Fib) in red, fasciculation potentials (Fas) in blue] in groups with duration of less than 12 years (left) and 12 years or more (right). (C) The number of patients with sIBM who showed myogenic changes in the groups with disease duration of less than 12 years (left) and 12 years or more (right). (D) The number of sIBM patients who showed chronic denervation findings in the groups with duration less than 12 years (left) and 12 years or more (right).

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