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Abstract

A patient with chronic sarcoid myopathy without other organ involvement

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We herein report the patient of a 69-year-old woman who presented with the chronic myopathic form of sarcoid myopathy. She had experienced slowly progressive limb muscle weakness for three years. She was found to be thin, but otherwise normal, on a physical examination. Neurologically, proximal muscles are predominantly involved without any sensory or other focal deficits. Electromyography revealed myopathic motor unit potentials exhibiting spontaneous discharge. Muscle biopsy demonstrated extensive connective tissue and few residual muscle fibers with a hint of granuloma formation. Repeated sectioning of the muscle biopsy revealed noncaseatious granuloma with a multinucleated giant cell, confirming the diagnosis. The findings of all imaging studies, including a systemic PET (positron emission tomography) scan, were unremarkable. Without careful pathological observation with repeated sectioning, this patient would have been misdiagnosed with limb-girdle muscular dystrophy.

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Key words: sarcoid myopathy, chronic myopathic form, muscular dystrophy

OPEN

Statins and Myotoxic Effects Associated With Anti-3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase Autoantibodies

An Observational Study in Japan

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Abstract: Statins have a variety of myotoxic effects and can trigger the development of inflammatory myopathies or myasthenia gravis (MG) mediated by immunomodulatory properties. Autoantibodies to 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) have been identified in patients with statin-associated myopathy. The purpose of the present study is to develop an enzyme-linked immunosorbent assay (ELISA) of anti-HMGCR antibodies and to elucidate the clinical significance of anti-HMGCR antibodies in Japanese patients with inflammatory myopathies or MG.

We enrolled 75 patients with inflammatory myopathies, who were all negative for anti-signal recognition particle and anti-aminoacyl transfer RNA synthetase antibodies. They were referred to Keio University and National Center of Neurology and Psychiatry between October 2010 and September 2012. We also studied 251 patients with MG who were followed at the MG Clinic at Keio University Hospital. Anti-HMGCR antibodies were detected by ELISA. We investigated demographic, clinical, radiological, and histological findings associated with anti-HMGCR antibodies.

We established the anti-HMGCR ELISA with the recombinant protein. Protein immunoprecipitation detected autoantigens corresponding to HMGCR. Immunohistochemistry using muscle biopsy specimens revealed regenerating muscle fibers clearly stained by polyclonal anti-HMGCR antibodies and patients' serum. Anti-HMGCR autoantibodies were specifically detected in 8 patients with necrotizing myopathy. The seropositivity rate in the necrotizing myopathy patients was significantly higher than those in the patients with other histological diagnoses of inflammatory myopathies (31% vs 2%, $P = 0.001$). Statins were administered in only 3 of the 8 anti-HMGCR-positive patients. Myopathy associated with anti-HMGCR antibodies showed mild limb weakness and favorable response to immunotherapy. All 8 patients exhibited increased signal intensities on short T1 inversion recovery of muscle MRI. Of the 251 patients with MG, 23 were administered statins at the onset of MG. One late-onset MG patient experienced MG worsening after 4-wk treatment with atorvastatin. However, anti-HMGCR antibodies were not detected in the 251 MG patients except for one early-onset MG patient with no history of statin therapy.

Anti-HMGCR antibodies are a relevant clinical marker of necrotizing myopathy with or without statin exposure, but they are not associated with the onset or deterioration of MG.

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Abbreviations: ELISA = enzyme-linked immunosorbent assay, HMGCR = 3-hydroxyl-3-methylglutatyl-coenzyme A reductase, MG = myasthenia gravis, MHC = major histocompatibility complex, MRI = magnetic resonance image, NCAM = neural cell adhesion molecules, OD450 = optical density at 450 nm, SRP = signal recognition particle.

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INTRODUCTION

Statins lower cholesterol levels by specifically inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), a key enzyme in the cholesterol biosynthesis pathway. Statins are associated with ≥1 myotoxic effects including myalgia,

elevation of creatine kinase and transaminases, and weakness. Muscle problems occurred in 10% to 25% of patients treated with statins in clinical practice and in approximately 13% of participants of published clinical trials.[1] Statins have immunomodulatory properties, and they may unmask or worsen certain neuromuscular disorders including myasthenia gravis (MG), myotonic dystrophy, McArdle disease, and mitochondrial myopathy.[2] The most severe problem is the development of inflammatory myopathy requiring immunosuppressive therapy; this is now known to be mediated by anti-HMGCR antibodies.[3,4]

Anti-HMGCR antibodies were first found as 200- and 100-kDa proteins using protein immunoprecipitation.[5] In 2011, the 100-kDa autoantigen was identified as HMGCR by Mammen et al.[4] Anti-HMGCR antibodies were detectable using different methods, including enzyme-linked immunosorbent assay (ELISA), addressable laser beam assay, and chemiluminscent immunoassay.[4,6–8] These assays showed qualitative agreement and level of anti-HMGCR antibodies showed significant correlation.[8] Clinical features associated with anti-HMGCR antibodies detected by these methods in United States and Europe; however, there were no detection methods in Japan.

MG is the most common autoimmune neuromuscular disorder mediated by autoantibodies to acetylcholine receptor (AChR) or muscle-specific tyrosine kinase.[9] MG can be exacerbated by a variety of medications, which increase weakness by interrupting neuromuscular junction transmission. Some drugs potentially induce a new onset of MG. In 2002, Parmer et al[10] first reported the case of a 67-year-old woman who suffered from the aggregation of generalized MG 12 weeks after being treated with atorvastatin. Special attention has been paid to the association between MG and statins. Some investigators suggested that MG occurs after therapy with statins, and others suggested that statins worsen previously diagnosed MG.[10–15] The myotoxic effects of statins on MG symptoms were speculated to be immune-mediated, but the pathogenesis has not been investigated.

The purpose of the present study was to develop an ELISA of anti-HMGCR antibodies and to elucidate the clinical significance of anti-HMGCR antibodies in Japanese patients with inflammatory myopathies and MG.

METHODS

Patients

We examined 75 adult patients with inflammatory myopathies, who were referred to Keio University or National Center of Neurology and Psychiatry between October 2010 and September 2012. We included patients with the definite diagnosis of idiopathic inflammatory myopathies by a comprehensive histological examination.[16] In addition, the patients were all negative for anti-signal recognition particle (SRP) and anti-aminoacyl transfer RNA synthetase antibodies using RNA immunoprecipitation assay. The 75 patients' mean age at the examination was 61 ± 15 years (range 20–82), and the sex breakdown (M:F) was 30:45.

Histological diagnoses were based on the established criteria.[17,18] Briefly, sporadic inclusion body myositis was diagnosed by the identification of rimmed vacuoles with non-necrotic fibers invaded by mononuclear cells or increased major histocompatibility complex (MHC) class I expression. Polymyositis was diagnosed based on exclusively endomysial inflammation cell infiltrate surrounding or invading non-necrotic muscle fibers, accompanied by ubiquitous MHC class I expression. Dermatomyositis was diagnosed by clinical criteria including a rash typical of dermatomyositis and the identification of perifascicular atrophy. Necrotizing myopathy was diagnosed based on the observation of necrotic fibers with diffuse distribution without or with minimal inflammatory cell infiltration.

We also studied 251 patients with MG, who were followed at the MG Clinic at Keio University Hospital. The diagnosis of MG was based on clinical, electrophysiologic, and immunologic criteria.[9] The clinical classification and quantitative MG score were graded based on the recommendation issued by the Task Force of the Medical Advisory Board of the Myasthenia Gravis Foundation of America.[19] Disease subtypes were divided into early-onset, late-onset, and thymoma-associated MG. As disease controls and normal controls, we used serum samples from 25 patients with Duchenne muscular dystrophy and 30 healthy volunteers.

Clinical information was retrospectively obtained for all patients by reviewing their clinical charts. All clinical samples and information were collected after the patients and controls gave their written informed consent as approved by the Institutional Review Boards of both the National Center of Neurology and Psychiatry and Keio University. All analyses were performed using statistical analysis software (IBM/SPSS version 20).

Anti-HMGCR ELISA

Our anti-HMGCR ELISA was developed based on the original method with some modifications.[4] First, 96-well polyvinyl plates (Smilon multiwell plate H type; Sumitomo Bakelite) were coated with C-terminal recombinant HMGCR protein (Sigma, St. Louis, MO) at 0.1 μg/mL diluted in phosphate buffered. The remaining blocking sites were blocked with 3% bovine serum albumin. The wells were incubated with serum samples diluted at 1:400 and subsequently with peroxidase-conjugated anti-human IgG (Jackson Immuno Research, Westgrove, PA) diluted 1:100000. The antibody binding was visualized by incubation with tetramethylbenzidine (1 mg/mL) in phosphate-citrate buffer. The reaction was stopped by 1 mol/L sulfuric acid. The optical density at 450 nm (OD450) was read with an automatic plate reader (Biorad, Hercules, CA). Samples were tested in duplicate. The antibody index was calculated from the OD450 of the samples divided by the OD450 of the referential serum (patient 1 in Table 1). The cut-off value was set as the mean + 5SD of 30 healthy control sera.[20]

Protein Immunoprecipitation Assay

Autoantigens were analyzed by protein immunoprecipitation assay using ^{35}S-labeled RD cellular extracts.[21] RD cells (5×10^6 per sample) were cultured in methionine-free DMEM (Sigma) containing 3% heat-inactivated fetal bovine serum in the presence of 20 μCi/mL ^{35}S-methionine for 14 h. The ^{35}S-labeled cells were suspended in an ice-cold buffer containing 500 mmol/L NaCl, 0.1% Nonidet P-40, 10 mmol/L Tris-HCl, and a cocktail of protease inhibitors (Complete; Roche, Indianapolis, IN), and sonicated intermittently on ice for a total of 90 s. The supernatant (containing ^{35}S-labeled soluble proteins originating from the nuclei, cytoplasm, and cellular membrane) was recovered by centrifugation (13,000*g* for 15 min) and used as the antigen source. Two milligrams of protein A-Sepharose CL-4B (Pharmacia Biotech, Little Chalfont) was incubated with 10 μL of a human serum sample. The immunoglobulins that were bound to protein A-Sepharose beads were then incubated with the ^{35}S-labeled cellular extracts for 2 h. The immunoprecipitated

TABLE 1. Characteristics of the 8 Patients With anti-HMGCR Antibodies

	Patients no.							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Age/sex	75/M	75/F	70/M	79/F	64/M	57/M	55/F	49/M
Statin exposure	(+)	(+)	(+)	(-)	(-)	(-)	(-)	(-)
Disease duration (mo)	3	2	1	1	2	4	15	3
Neurological examination								
Upper/lower limbs (MRC grade)	4–5/5	3–4/4	5/4	3/3–4	4/4–5	3/4	4/5	5/4
Neck weakness	(-)	(-)	(-)	(+)	(-)	(+)	(-)	(-)
Dysphagia	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Muscle atrophy	(-)	(-)	(-)	(+)	(+)	(+)	(-)	(-)
Myalgia	(-)	(+)	(+)	(-)	(-)	(-)	(+)	(-)
Deep tendon reflex	D	D	D	D	N	D	D	N
Laboratory data								
Creatine kinase (IU/L, nl: 60–250)	9695	9680	10452	3028	6603	7238	8510	6694
Aspartate aminotransferase (IU/L, nl: 10–35)	196	235	317	110	244	154	262	146
Alanine aminotransferase (IU/L, nl: 5–40)	357	353	246	209	325	248	454	199
Lactate dehydrogenase (IU/L,nl: 120–220)	1248	762	788	898	772	925	1436	683
C-reactive protein (mg/dL, nl: 0–0.35)	0.1	8.1	0.1	0.1	0.6	0.5	0.1	0.1
Electromyography								
Spontaneous activity	(+)	(+)	(+)	(-)	(+)	(+)	(+)	n/a
Low-amplitude, short-duration MUPs	(+)	(+)	(+)	(+)	(+)	(+)	(+)	n/a
Histology								
Variation in fiber size	Marked	Moderate	Mild	Moderate	Marked	Marked	Moderate	Moderate
Necrosis fiber	Some	Scattered	Some	Many	Many	Scattered	Some	Scattered
Regeneration fiber	Some	Many	Some	Many	Many	Scattered	Several	Scattered
Cell infiltration	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Endomysial fibrosis	Minimal	Minimal	Minimal	Minimal	Minimal	Mild	Minimal	Minimal
MHC class I expression	(-)	(+)	(-)	(+)	(+)	(+)	(-)	(-)
MHC class II expression	(-)	(-)	(-)	(-)	(+)	(+)	(-)	(-)
Treatment	mPSL, PSL	PSL, IVIg	mPSL	PSL	mPSL, PSL, IVIg	mPSL, PSL, IVIg	PSL, IVIg	n/a
Modified Rankin scale								
Pre-treatment	3	3	2	4	2	3	2	2
2-year follow-up	0	2	0	2	0	0	0	n/a

D = decreased, IVIg = intravenous immunoglobulin, MHC = major histocompatibility complex, mPSL = high-dose methylprednisolone plus therapy, MRC = Medical Research Council, MUPs = motor unit potentials, n/a = not available, N = normal, nl = normal values, PSL = prednisolone.

material was resolved by electrophoresis on SDS-7.5% polyacrylamide gels, which were subsequently treated with 0.5 mol/L sodium salicylate to enhance the radioactivity, and evaluated by autoradiography using a BAS-5000 system (Fuji Film, Tokyo).

Immunohistochemistry

Six micrometer sections of frozen muscle tissue from biopsies were prepared. The sections were incubated with monoclonal mouse anti-neural cell adhesion molecule (NCAM) antibodies (Leica, Wetzlar) diluted 1:25, polyclonal rabbit anti-HMGCR antibodies (Sigma) diluted 1:125 and serum samples diluted 1:40. After incubation with the primary antibodies for 16 h, the sections were incubated for 2 h with a fluorescein isothiocyanate-conjugated anti-mouse, anti-rabbit or anti-human IgG antibody (Jackson Immuno-Research), and the sections were examined with a fluorescence microscope (Eclipse E-800, Nikon, Tokyo).

RESULTS

Anti-HMGCR ELISA

Since the cut-off value was set as the mean + 5 × SD of 30 healthy control sera, the cut-off of anti-HMGCR index was 0.48. Positivity for the anti-HMGCR antibody was observed in 8 of 26 the patients with necrotizing myopathy (Figure 1). However, only one of the 24 patients with sporadic inclusion body myositis had a slight elevation of anti-HMGCR index. There was no positivity of anti-HMGCR antibodies in the 25 patients with polymyositis or dermatomyositis, or in the 25 patients with Duchenne muscular dystrophy. The

seropositivity rate in the 26 necrotizing myopathy patients was significantly higher compared with those of the 49 patients with other inflammatory myopathies (31% vs 2%, $P = 0.001$).

Protein Immunoprecipitation Assay

We analyzed autoantigens immunoprecipitated by anti-HMGCR-positive sera using the protein immunoprecipitation assay. Representative results obtained from 6 patients with anti-HMGCR antibodies detected by anti-HMGCR ELISA are shown in Figure 2A. Anti-HMGCR-positive sera immunoprecipitated the doublet autoantigens located around 50 kDa (lanes 1–6). However, no immunoprecipitates were found in sera without anti-HMGCR antibodies (lanes 7 and 8). Moreover, we added an excess of the recombinant HMGCR protein (50 ng) to the patient 1' serum at the incubation with protein A-Sepharose. The 50-kDa doublet autoantigens were clearly absorbed (lane 2 in Figure 2B).

We determine the sensitivity and specificity of the ELISA using this cutoff relative to the protein immunoprecipitation.[4,5] Among 75 patients with inflammatory myopathies, 8 sera immunoprecipitated HMGCR protein and all of them were positive by anti-HMGCR ELISA. Conversely, among 9 sera positivity by anti-HMGCR ELISA, 8 were positive by protein immunoprecipitation. Therefore, the sensitivity and specificity of the anti-HMGCR ELISA are 100% and 98.5%, respectively."

Immunohistochemistry

We next performed immunohistochemistry using the muscle tissues obtained from patient 3 (Figure 2C). Regenerated muscle fibers were clearly detected by anti-NCAM antibody. In addition, HMGCR was expressed in the regenerated fibers. Anti-HMGCR-positive sera produced similar staining on the regenerated muscle fibers. Thus, the immunoreactivity was clearly co-localized with staining by the polyclonal anti-HMGCR antibody and patient's sera (left panels, Fig. 2C). In contrast, the anti-HMGCR antibody and patient's sera did not show any staining on the muscle fibers of control muscle.

Clinical Features of Patients with Anti-HMGCR Antibodies

The clinical features of eight patients (five men and three women) with anti-HMGCR-positive necrotizing myopathy are summarized in Table 1. Their mean age was 66 years, ranging from 49 to 79 years. All but patient 7 deteriorated within two months with a markedly increase level of creatine kinase. The clinical course suggested the initial diagnosis of rhabdomyolysis. Atrovastatins were administered in 3 patients who were over 70 years' old. The diseases did not recover after the cessation of the statin treatment. Neurological examinations showed symmetrical and proximal limb weakness. Arms and legs were equally affected. The severe limb weakness with the grade $\leq$2/5 assessed by manual muscle strength (Medical Research Council scale grade) was not observed. No patients had dysphagia. Electromyography also indicated myopathic motor unit potentials (MUPs) in all patients.

With regard to the histology, all patients showed necrotic and regenerating muscle fibers without inflammatory cell infiltration. Endomysial fibrosis was minimal. MHC class I and class II expression were detected in 50% and 25% of the 8 anti-HMGCR-positive patients, respectively. The 2-year follow-up was available in 7 patients. All patients required immunotherapy and responded well. The recovery of muscle weakness was observed several weeks after the therapy. Since the creatine kinase persisted in higher levels, intravenous immunoglobulin therapy was added in 4 patients. None of the 7 patients experienced disease relapse. Neurological outcome evaluated using the modified Rankin scale showed that 5 of the 7 patients were able to return to their normal daily lives.

Muscle magnetic resonance images (MRIs) were useful for evaluating the distribution of inflammation. Short T1 inversion recovery images in particular showed high signal intensities in all 8 patients. Focal or diffuse abnormal signals were seen in trunk and limb muscles (Figure 3). In contrast to the neurological examination, asymmetry was found on muscle MRI.

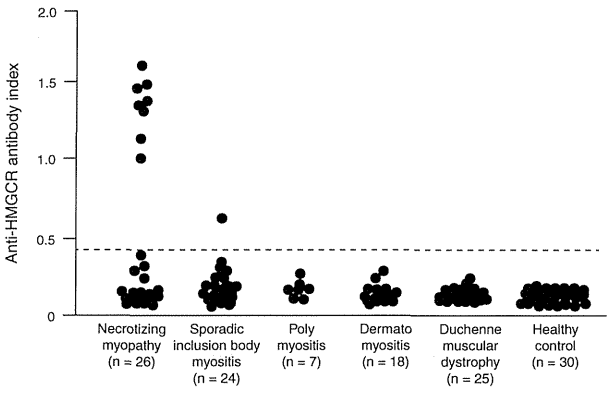

FIGURE 1. Anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) ELISA. Antibodies reactive with recombinant HMGCR protein by ELISA in sera from inflammatory myopathy patients, Duchenne muscular dystrophy patients, and healthy controls. The cut-off level for positivity is indicated by the broken line (anti-HMGCR index: 0.48).

Statin Exposure and Anti-HMGCR Antibodies in MG Patients

The profiles of 251 patients with MG are indicated in Table 2. Of the 251 patients with MG, 23 (9%) including the 5 early-onset, 10 late-onset, and 8 thymoma-associated MG received statins at the disease onset. Statin brands were atorvastatin in 9 patients, pravastatin in 4, fluvastatin in 4, simvastatin in 3, pivastatin in 2, and rosuvastatin in 1 patient. In contrast, only 1 late-onset MG patient experienced MG worsening after statin exposure (Figure 4). Briefly, this 68-year-old woman had a diagnosis of ocular myasthenia at the age of 62 years. Her diplopia and ptosis were well controlled by pyridostigmine and achieved 18-month remission. However, she developed diplopia and ptosis after a 4-week treatment with atorvastatin at the age of 66 years. Her quantitative MG score was increased to 8 with an elevation titer of anti-AChR antibody. Since pyridostigmine was not fully effective, she required prednisolone at a daily dose of 10 mg.

We examined the presence of anti-HMGCR antibodies by conducting our ELISA, using 251 serum samples from the patients with MG. Only 1 (0.4%) early-onset female patient was found to be seropositive for anti-HMGCR antibodies (anti-HMGCR index: 0.6). She had mild generalized MG (MG Foundation of America class 2A) with no history of statin treatment. She achieved pharmacological remission after treatment with prednisolone and extended thymectomy. In contrast, anti-HMGCR antibodies were not found in the 23 MG patients who had received statins at disease onset. Moreover, the patient with statin-associated MG exacerbation was also negative for anti-HMGCR antibodies at both the onset and the worsening of MG.

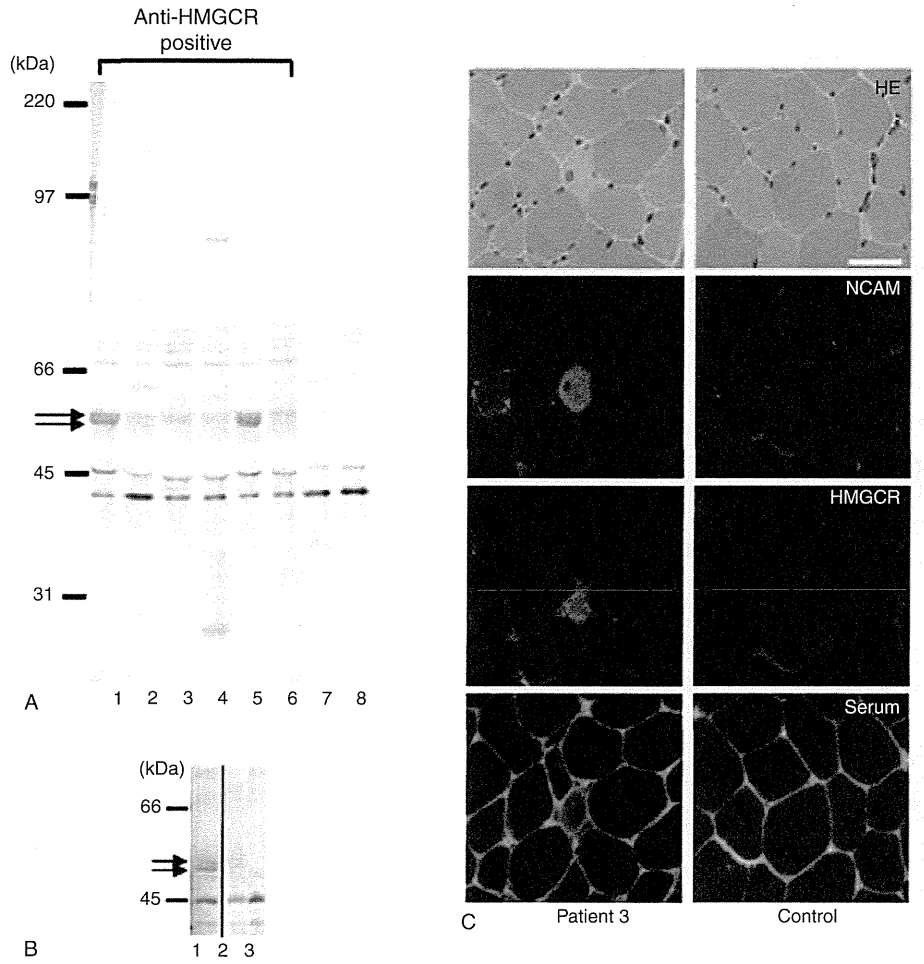

FIGURE 2. Confirmation of the HMGCR immunoreactivity. (A) Autoradiograms of immunoprecipitated ^{35}S-labeled RD extracts from serum samples are shown. Immunoprecipitated materials were analyzed on SDS-7.5% polyacrylamide gels. The positions of the molecular weight standards are at the left. Arrows indicate the 50-kDa doublet precipitates detected in the serum sample containing anti-HMGCR antibodies (lanes 1–6). (B) Arrows indicate the 50-kDa doublet precipitates detected in the patient 1 sera (lane 1), but not in a healthy control (lane 3). The autoantigens were absorbed in the presence of recombinant HMGCR protein (lane 2). The panel has been cropped between lanes 2 and 3 to exclude immunoprecipitations that are irrelevant to the current study. (C) Muscle sections were obtained from patient 3 (left panels) and control (right panels). Sections were stained with hematoxylin-eosin (HE), polyclonal anti-neural cell adhesion molecules (NCAM) antibody, polyclonal anti-HMGCR antibody, and anti-HMGCR-positive sera. Scale bar = 50 μm.

DISCUSSION

We established an anti-HMGCR ELISA and showed the following clinical relevance of its use:

(i) anti-HMGCR autoantibodies were specifically detected in necrotizing myopathy,
(ii) myopathy associated with anti-HMGCR antibodies was characterized by mild limb weakness and favorable response to immunotherapy with or without statin exposure;
(iii) of 251 MG patients, 1 woman (0.4%) with no history of statin therapy had anti-HMGCR antibody.

The molecular weight of HMGCR is 97-kDa. Original reports indicated that a 100-kDa autoantigen in protein immunoprecipitation was successfully identified as HMGCR.[4,5] In contrast, our studies showed the doublet autoantigens at around 50-kDa. It is likely that we detected 2 different cleaved forms of the HMGCR molecule. The discrepancy between the previous and present studies may be due to differences in the experimental protocols such as the culture cell lines used as the antigen source. Moreover, the HMGCR expression was upregulated predominantly in the regenerated muscle fibers of anti-HGMCR-positive patients.[4] Our findings demonstrated that the HMGCR expression in the muscle fibers was clearly co-localized with patients' serum. Taken together, the reactivity of our anti-HMGCR ELISA was successfully supported by other, different methods.

The most important pathogenesis of necrotizing myopathy is believed to be autoantibody-mediated. It is necessary to identify autoantibodies in sera of patients with necrotizing myopathy, since there is little or no evidence suggesting autoimmune mechanisms in muscle histology. Anti-SRP antibodies were found in 34 (53%) of 64 patients with necrotizing myopathy.[16] In the present study, we demonstrated that 31% of the 26 anti-SRP-negative necrotizing myopathy patients had anti-HMGCR antibodies. Our results showed that only 3 (38%) of the 8 anti-HMGCR-positive patients had undergone statin

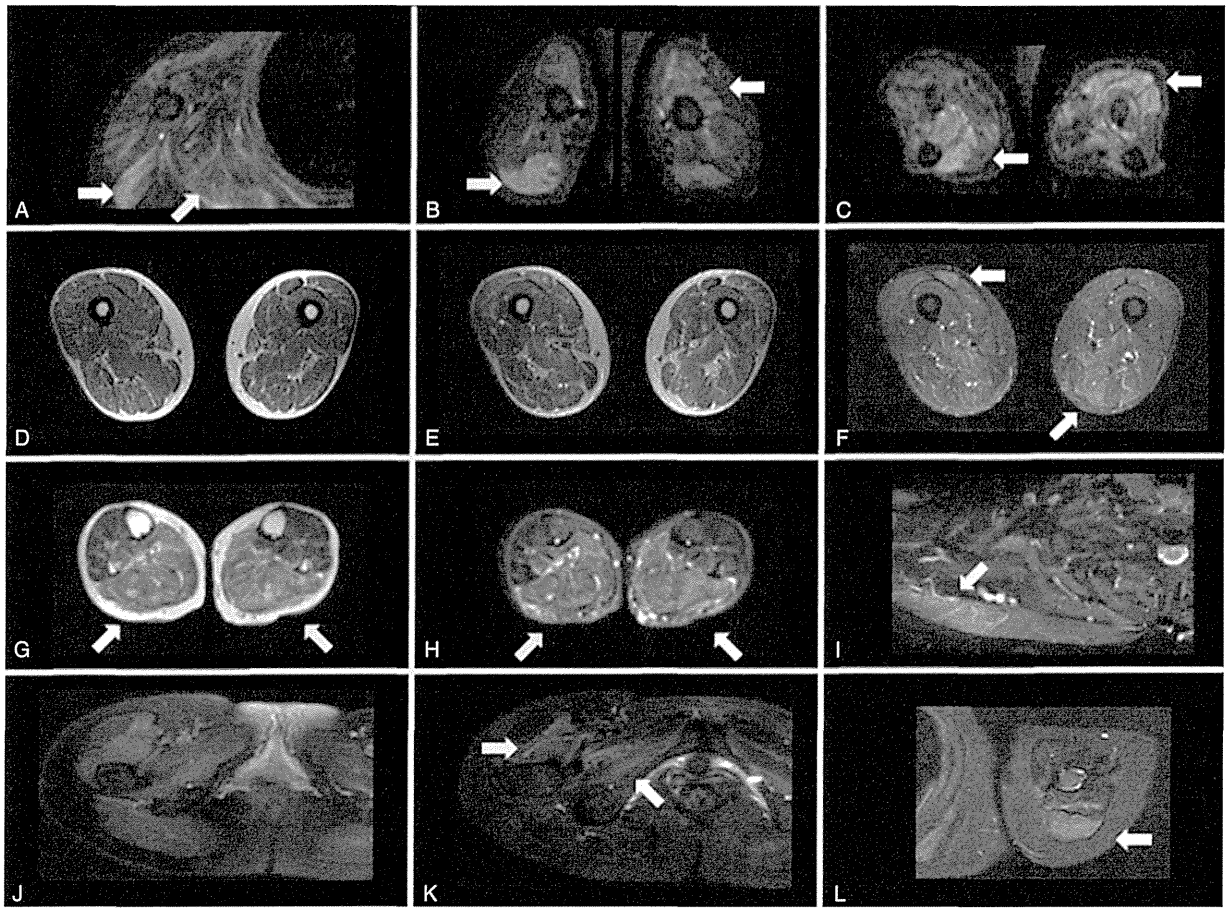

FIGURE 3. Muscle MRI of patients with anti-HMGCR antibodies. (A–C) Patient 2. Increased short T1 inversion recovery (STIR) signal abnormalities involving deltoid, infraspinatus muscles (A), biceps brachii and triceps brachii (B), and forearm muscles (C). (D–F) Patient 3. Images of thighs on T1 images (D), T2 images (E), and STIR images (F). High intensity in biceps femoris and semitendinousus muscles on STIR images. (G, H) Patient 4. Increased T2/STIR signal abnormalities in posterior calves. (I) Patient 6. Increased STIR signal in trapezius muscle. (J–L) Patient 7. STIR images of pelvis (J) and enhancement in vastus lateralis and obturator internus muscles (K). Increased signal with enhancement of triceps brachii on STIR images (L).

TABLE 2. Profiles of 251 Patients with Myasthenia Gravis

Age	
mean ± SD (range)	50 ± 17 (16–88)
Disease subtypes	
Early-onset	121 (48%)
Late-onset	70 (28%)
Thymoma-associated	60 (24%)
Classification of Myasthenia gravis Foundation of America	
Class I	73 (29%)
Class II	89 (35%)
Class III	54 (22%)
Class IV	11 (4%)
Class V	24 (10%)
Autoantibody status	
Acetylcholine receptor positive	198 (79%)
Muscle-specific tyrosine kinase positive	6 (2%)
Seronegative	47 (19%)

SD = standard deviation.

exposure. This prevalence was consistent with that in a European cohort (44%).[7] Taken these findings together, we emphasize that anti-HMGCR antibodies can be regarded as the second serological marker of necrotizing myopathy as well as a marker of statin-induced myopathy.

Importantly, there were clear differences in the clinical characteristics associated with autoantibodies to SRP and HMGCR in our investugation.[22] The neurological manifestations of the anti-HMGCR-positive patients were mild limb weakness with good response to immunotherapy. Older patients tended to have anti-HMGCR antibodies.[3] In contrast, anti-SRP myopathy was characterized by severe limbs weakness and atrophy as well as bulbar and trunk muscle involvement. Younger patients showed severe clinical deficits.[22]

Previous reports revealed the clinical features of 15 patients with statin-associated MG.[10–15] The ages were ranged as 41 to 71 years (average 58 years) and the sex ratio was 11:4 (M:F). Newly-onset MG was observed in 8 patients and worsening of MG in 7 patients. The patients experienced MG symptoms after 1 to 16 weeks after the statin exposure (average, 4 weeks and within 2 weeks in 8 patients). Ocular MG was observed in 3 patients and generalized MG in 12 patients. The

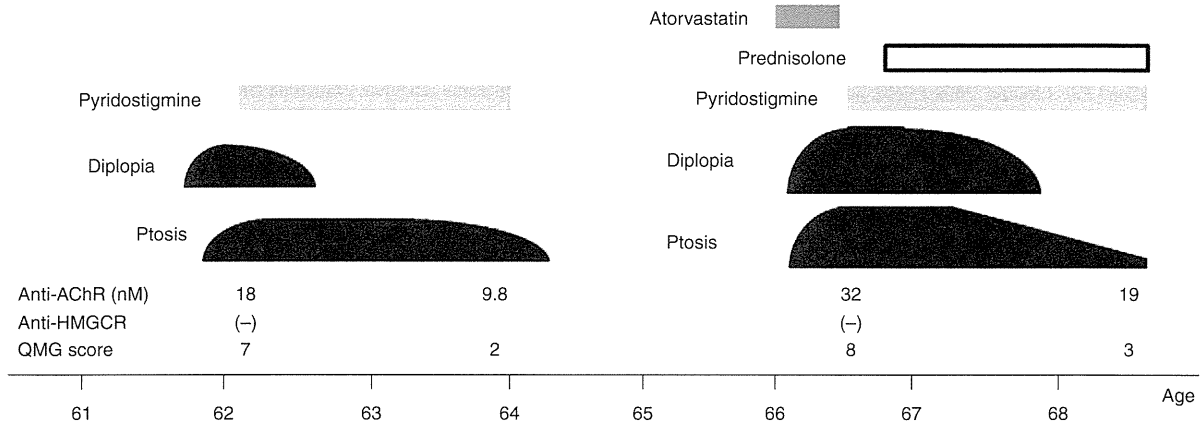

FIGURE 4. Clinical course of a 68-year-old woman with MG worsening after statin treatment. Anti-AChR = anti-acetylcholine receptor antibody, QMG = quantitative myasthenia gravis.

antibodies status was AChR-positive in 10 patients, muscle-specific tyrosine kinase-positive in 4, and seronegative in 1 patient. Discontinuance of statins and initiation of pyridostigmine were effective, but immunotherapy was necessary in 8 patients.

In our case series, it is likely that statins were less involved in the new onset of MG in 23 patients because myasthenic symptoms did not develop within several weeks after the start of the statin therapy. However, 1 patient's MG worsened after 4 weeks of statin use, after an 18-month MG remission. Her symptoms were limited to ocular myasthenia, but prednisolone was necessary to control her disease.

Oh et al[13] reported that MG worsening occurred in 6 (11%) of their 54 MG patients with statin treatment. However, the actual incidence of statin-associated MG exacerbation seems to be lower. In clinical practice, we also feel that statins should be used in patients with MG for the same indications as in individuals without MG.[23] Statins should be withdrawn if exacerbation of MG occurs, or if the anti-AChR antibody concentration increases markedly.

A limitation of the present study is that anti-HMGCR antibodies were evaluated in only 1 statin-associated MG patient, although the cases of 251 MG patients were examined. However, we think that anti-HMGCR antibodies do not affect the function of neuromuscular transmission. We regard seropositivity with a low titer of anti-HMGCR antibodies in 1 MG patient as a non-specific phenomenon. In a previous report, although organ-specific autoantibodies targeted to thyroid, gastric parietal cells, adrenal cortex, and islet cells were found in up to 30% of 283 MG patients, they had no clinical or pathogenic relevance.[24]

Our anti-HMGCR ELISA showed an extremely low frequency (0.4%) of seropositivity in MG patients. In this regard, a community-based study also showed that statin users without myopathy were all negative for anti-HMGCR antibodies.[25] Based on its high specificity of antibody detection, we contend that the anti-HMGCR ELISA is a useful tool for the diagnosis of necrotizing myopathy, discriminating from other various muscle problems linked to statin exposure.

In conclusion, anti-HMGCR antibodies are a relevant clinical marker of necrotizing myopathy with or without statin-exposure, but they are not associated with the onset or deterioration of MG.

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総説

封入体筋炎の病態と原因

村田顕也* 伊東秀文

封入体筋炎は，高齢者に好発する後天性筋疾患である。臨床的には，上肢遠位部と大腿四頭筋の筋萎縮・筋力低下が著明である。封入体筋炎は，多発筋炎や皮膚筋炎などの炎症性筋疾患の要素と，筋線維内への各種蛋白の沈着や空胞形成といった変性疾患の要素を併せ持つユニークな疾患であり，通常の免疫療法には治療抵抗性である。

封入体筋炎，炎症性筋疾患，縁取り空胞，筋変性

はじめに

封入体筋炎（sporadic inclusion body myositis：sIBM）は，多発筋炎（polymyositis：PM），皮膚筋炎（dermatomyositis：DM），壊死性筋炎とともに炎症性筋疾患に分類されている[1]。欧米では，50歳以上で発症する炎症性筋疾患の中では最も多く，すべての炎症性筋疾患の30%を占める。わが国でのsIBMの有病率は，1991年では100万人あたり1.28と少なかったが，2003年時点では9.83となり，欧米諸国と同水準にまで増加した[2]。2010年に施行された難治性疾患克服事業のIBM研究班による神経内科専門医へのアンケート調査では，国内の新規患者数は2005年から5年間で1,074名と推定されており，現在日本には1,000～1,500人前後のsIBM患者がいると考えられている。

Ⅰ．臨床症状

sIBMは，緩徐進行性の特発性の筋疾患である。初発症状としては，大腿四頭筋・深指屈筋の筋力低下と筋萎縮が特徴的である。足首での背屈困難も初発症状として重要である[1]。オーストラリアでのsIBM 53例の検討では，障害部位は大腿四頭筋（79%），指の屈曲障害（12%），垂れ足（7%），嚥下障害（1.8%）であった[3]。また，皮膚筋炎や多発筋炎と異なり，男性患者のほうが多い。このようにsIBMの臨床特徴は他の炎症性筋疾患とは異なるため，診断に時間を要し発症後5～8年経てから診断されることも多い。

患者は，上述のように歩行障害で初発することが多く，大腿四頭筋の筋力低下のため膝くずれや階段昇降が困難となり転倒回数が増加する。病初期は，上肢は近位部に比べ遠位部の筋力低下が顕著で，特に指先の使いにくさを自覚する。具体的には，鍵が回しにくい，ネクタイが結びにくい，ペットボトルのふたを開けにくい，ボタンがかけにくいなどの症状を訴える。患者は深指屈筋や長母指屈筋の筋力低下を補うため，虫様筋を使ってものを握るようになるので，握力低下を自覚していないことが多い。特に高齢発症の筋疾患患者では，sIBMを念頭においた問診や，2～5指関節の屈曲力や手関節の掌屈力を評価する必要がある。長母指屈筋の筋力低下のため，母指が背屈位を呈していることもあり，整形外科疾患と混同しないように留意すべきである（Fig. 1）。上肢の筋力低下は，左右非対称であり，多くの症例では非優位側の障害が高度である。sIBMは，手内筋の筋力低下や萎縮を呈する筋萎縮性側索硬化症（amyotrophic lateral sclerosis：ALS）と誤診されやすい。sIBMの上肢の筋障害は，手外筋の深指屈筋と長母指屈筋が主であ

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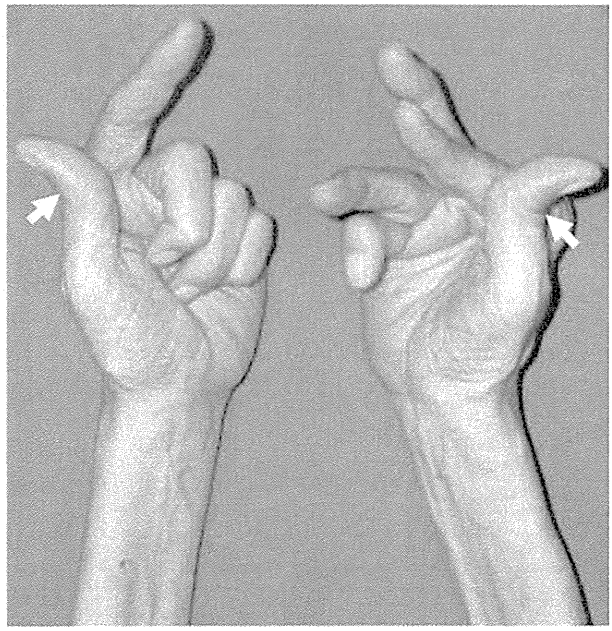

Fig. 1　手指屈曲を指示時の封入体筋炎症例の手
長母指屈筋の筋力低下のため，母指が中手指節関節で背屈している（矢印）。深指屈筋の筋力低下のため，遠位指節間関節での屈曲が行いにくい。

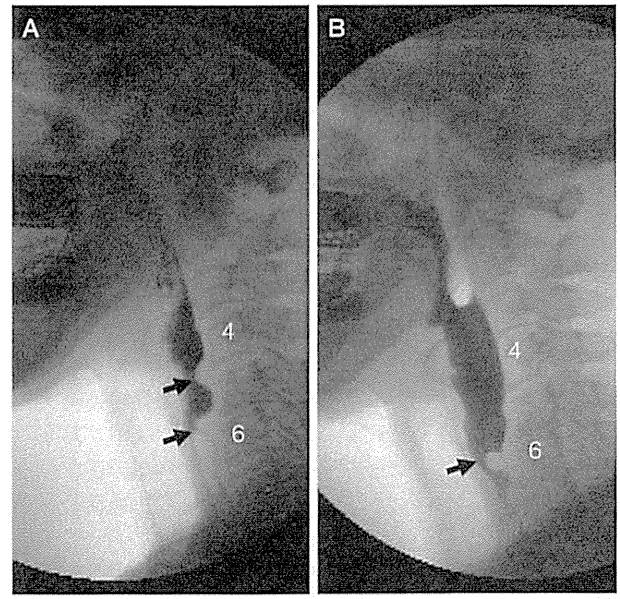

Fig. 2　Cricopharyngeal bar
A：ゼリー嚥下時，B：水分嚥下時。嚥下造影でC5-6に隆起病変を認める。この隆起病変は，ゼリー（A）と水分が多い嚥下剤（B）の使用により形態が異なるため，器質性変化でないと推測される。

り，DIP関節での指の屈曲力が低下している。一方，骨間筋や虫様筋や長母指外転筋は保たれ[1]，ALSに特徴的とされるsplit handも認められない点が重要な鑑別点である。

sIBMでは，嚥下障害が初発症状となることは比較的稀である。しかし，全経過では，約40%の症例で嚥下障害が存在する。患者は，嚥下障害を自覚していないことが多く，体重減少や誤嚥性肺炎で来院することが多い。嚥下障害の病変の主座は輪状咽頭筋の開大障害で，嚥下造影検査ではcricopharyngeal barが確認される。これは，食道入口部の開大障害により狭窄している部分（sIBMでは輪状咽頭筋部の筋は萎縮し結合織が増生している[5]）を造影剤が押し広げながら流れる際に出現する見かけ上の隆起様病変で，器質的な変化ではない。このbarは，検査に使用する造影剤の性状（例えば水分が多いもの，ゼリー状のもの）により，その形態が変わるのが特徴的である（Fig. 2）。同様のbarは，顔咽頭筋型筋ジストロフィーでも確認され慢性の嚥下障害を示唆する所見であり[6]，sIBMに特異的ではない。

そのほか軽度の顔面筋罹患が1/3で確認されている[7]。通常感覚障害は出現しないが，30%の症例では，電気生理学的検査や臨床所見で感覚性末梢神経障害を呈する[8]。15%の症例で，進行性エリテマトーデス，シェーグレン症候群，全身性強皮症，サルコイドーシスといった自己免疫疾患を併発する[9]。多発筋炎，皮膚筋炎と異なり心筋炎や肺疾患を併発することは少なく，悪性腫瘍の合併も少ない。血清CK値は正常か正常値の10倍以内の値を呈する。sIBMの約20%の症例で抗核抗体陽性となるが，筋炎特異抗体は通常陰性である。

針筋電図検査では，自発電位と刺入時電位が亢進し，多相性の低振幅運動単位電位と早期漸増を認める。一般に，筋線維直径が大きいほど，神経筋接合部から筋線維の方向に沿って流れる活動電位の伝播速度（神経筋伝導速度）が速くなる[10]。また，再生筋線維では神経筋伝導速度は低下する[11]。つまり，筋線維に大小不同がみられると，各筋線維の同期性が不良となり，神経筋伝導速度の時間的なばらつきも大きくなり多相性を呈する。このような多相性の持続の長い運動単位は，慢性進行性の炎症性筋疾患（多発筋炎，皮膚筋炎）でも高頻度に認められるが，sIBMではさらに高振幅の多相性電位が目立ち，中には線維束電位を呈するため神経原性変化と判断され，ALSと誤診されることもあり注意を要する[12]。

II. 臨床評価

sIBMの臨床評価の指標としてIBM-functional rating scale（IBM-FRS）が使用されている[1]。これは，ALS functional rating scaleをもとに作成されたもの

で，10項目［①嚥下，②書字，③食物を切る・食事の際に補助具を使う，④ドアを開ける，鍵を使うなどの細かい運動課題，⑤着衣，⑥衛生（入浴・用便），⑦寝返りをうつ・ベッドカバーを整える，⑧座位から起立，⑨歩行，⑩階段を昇る］につき，0～4のポイントで評価する。最高は40点で，点数が高いものほど症状が軽い。

IBM-FRSは下肢機能や上肢の指先の機能に注目して作成されているので，等尺性の筋力や徒手筋力テストの結果と相関しており臨床評価に有益である。しかし，IBM-FRSは，欧米の生活をもとに作成されているので，そのまま日本人に当てはめられるかについては検討を要する。

Ⅲ．画像診断

近年，MRIが筋炎やその他の神経筋疾患の診断に利用されている。筋疾患では，障害パターンの検討により診断に役立つことが多く，また治療介入時の効果判定や生検部位の決定にも有用である。T_1強調画像，T_2強調画像，脂肪抑制T_2画像（FST_2）を組み合わせて判断する。T_1強調画像，T_2強調画像で高信号を呈しFST_2で等信号になる部位が脂肪組織に相当し，T_1強調画像低～等信号，T_2強調画像で高信号を呈する部位が，FST_2でも高信号を呈していれば，炎症性（浮腫性）病変と判断する。ただし，脂肪組織の混在が多いとT_1，T_2高信号部位が，FST_2でも抑制されず高信号を呈することもあり，炎症混在との鑑別が困難な場合がある。

撮影部位はIBMの臨床特徴に合わせて大腿部および前腕で，横断像を作成する。前腕部は深指屈筋と浅指屈筋の障害が高度であり，しかも同一の筋群でも障害の程度がバラバラであるが，各指の深指屈筋の筋力低下の程度と脂肪混在の程度とは一致する（Fig. 3）。一方，下肢は大腿四頭筋の病変が高度で，その後内転筋群，大腿屈筋群へ病変が進行する。筆者らのsIBM 9例の検討では，大腿四頭筋は発症3年頃から中間・外側・内側広筋に脂肪混在が始まり，7年目頃から大腿直筋に及んでいく。大・短内転筋は発症5年目頃から，長内転筋は7年目頃から脂肪混在が始まる。大腿四頭筋の中でも大腿直筋が他の筋に比べて障害が起こりにくいのは，興味ある所見である（Fig. 4）[13,14]。

Ⅳ．症状の進行

sIBMは進行性の筋疾患であり，初診時と1年後の徒手筋力テスト（23筋）の評価では5.2%，IBM-FRSでは13.8%低下していた[15]。症状出現後，車椅子使用までの期間は，平均14年とされ，中でも，歩行に杖を使用するまでの期間は平均10年であり，女性患者や発症年齢が60歳以上の患者のほうが歩行に補助具を使用するまでの期間が短いと報告されている[16,17]。

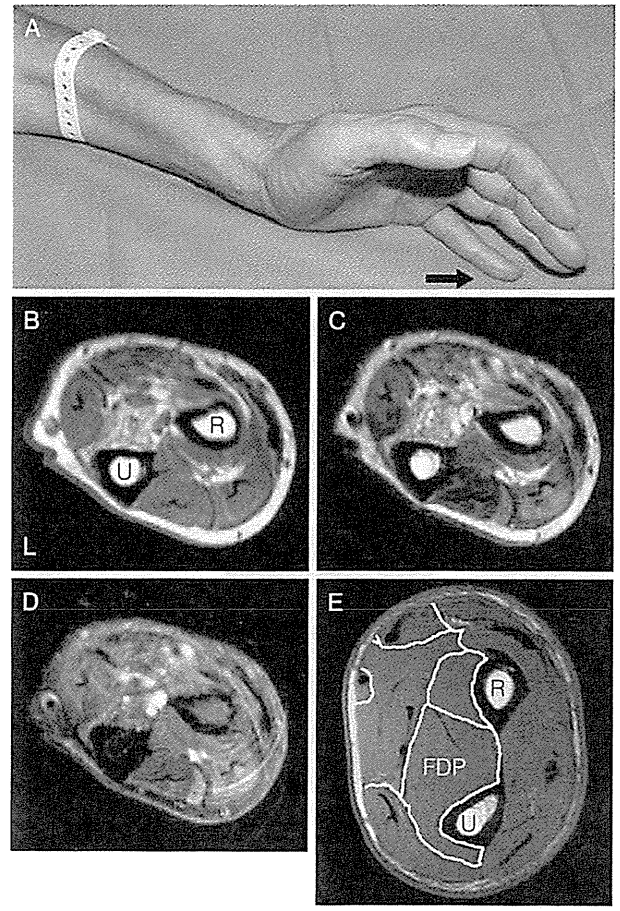

Fig. 3　封入体筋炎（sIBM）症例の左深指屈筋の脂肪性変化
A：左前腕部外形，B～E：左前腕部MRI。B，E：T_1強調画像，C：T_2強調画像，D：脂肪抑制画像。B～D：sIBM症例，E：正常対照（R：橈骨，U：尺骨，FDP：深指屈筋）。sIBMでは，深指屈筋の障害のため，2～5指のDIP関節での指の屈曲が困難となる（A矢印）。FDPは，橈骨（R）と尺骨（U）の間の前骨間膜に接して存在する（E）。sIBMではFDPが萎縮し，脂肪混在が著明となる。

Ⅴ．わが国での検討

わが国では厚生労働科学研究費補助金難治性疾患克服研究事業「封入体筋炎（IBM）の臨床病理学的調査および診断基準の精度向上に関する研究班」（研究代表者東北大学　青木正志教授　平成22～23年度）が，臨床的・病理学的にsIBMと確定された121例の臨床特徴

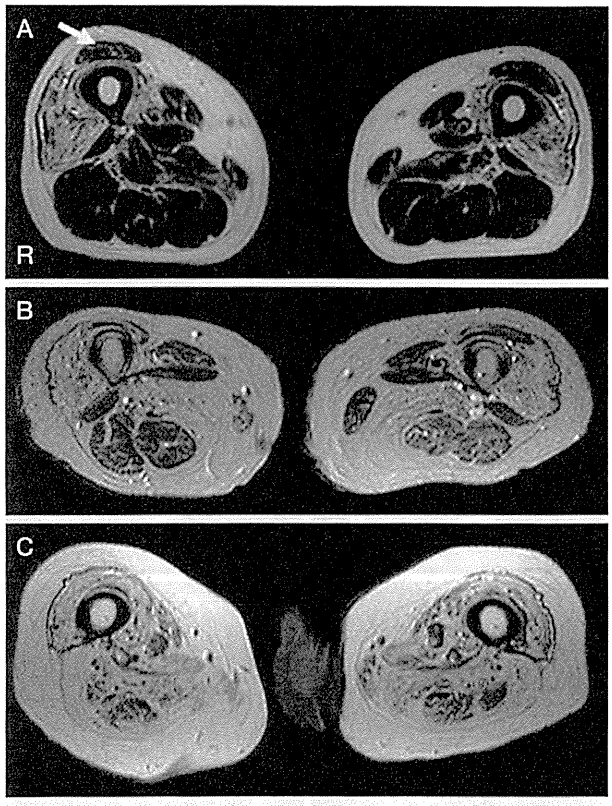

Fig. 4　封入体筋炎症例の大腿部 T_1 強調 MRI 画像
A：発症後3年，B：発症後12年，C：発症後20年。脂肪混在は，大腿四頭筋（A）から始まり，内転筋群（B）に広がり，大腿屈筋に波及する（C）。初期には，大腿四頭筋のうち大腿直筋は障害が軽度である（A矢印）。

を検討している。それによると，男女比は1.23：1で男性にやや多く，初発年齢は64.4±8.6歳（40～81歳），初発症状は74%が大腿四頭筋の脱力による階段昇り困難であった。嚥下障害は23%にみられ生命予後を左右する要因であった。CK値は511.2±361.8（30～2,401）IU/Lであった。初発症状が出てから診断確定までに52.7±47.6カ月（4～288カ月）要していた。またHTLV-1（human T-lymphotrophic virus-type 1）やC型肝炎ウイルス抗体陽性患者が20%，家族歴があるものが5例いた。

また，sIBM患者67名（男49名，女18名，平均年齢73歳，平均罹病期間8.7年）に対する患者アンケートでは，症状出現後，しゃがみ立ち不能になるまでの平均期間は4.6年，車椅子使用までが7.3年，電動車椅子使用までが13.7年，ペットボトルの開栓不能が6.6年と，欧米の報告に比べて進行が速かったが，これらは，患者背景（性別，発症年齢，罹病期間）の差によるものと考える。

Ⅵ. 診断基準

sIBMは，Chou[18]らが，慢性の多発筋炎のうち核内や細胞質内にミクソウイルス様の封入体を発見した症例の検討から始まったため，診断には筋細胞内の縁取り空胞（rimmed-vacuole：RV）や管状フィラメントの存在といった病理所見の解析が重要であった[7,19]。1995年にGriggsら[20]が提唱した診断基準でも，sIBMと確定診断するには，管状フィラメントやアミロイドの沈着を病理学的に診断することが必要であった。2007年のEuropean Neuromuscular Centre（ENMC）の診断基準では，sIBMの確定診断には前腕の筋力低下といった臨床徴候が加味され，電子顕微鏡を用いた16～21 nmの管状フィラメントの確認が不要となった。さらに2011年のENMCの診断基準では，clinically defined IBMという概念が導入され，臨床症状（①罹病期間が12カ月を超える，②発症年齢が45歳を超える，③膝を伸ばす力が股関節屈曲力より弱くかつ指の屈筋力が肩の外転力より弱い，④血清CK値が正常の15倍を超えない）の条件を満たせば，①間質内への炎症細胞浸潤，②主要組織適合抗原（MHC）クラスⅠの発現の亢進，③RV，④蛋白（アミロイドやp62，SMI31など）もしくは15～18 nmのフィラメントの沈着，の4条件のうち1つ以上の病理所見が確認できれば，診断可能となった[21]。

わが国でも診断基準が策定され，IBMに特徴的な臨床徴候を有しており，筋内鞘への単核球浸潤に加え，RVや非壊死性細胞を取り囲む細胞浸潤があれば，光学顕微鏡レベルでの確定診断が可能となった。電子顕微鏡で観察する核や細胞質におけるフィラメント状封入体の存在は参考所見となった（Table）[22]。

Ⅶ. 筋病理

sIBM患者の筋生検所見は，炎症と筋変性の要素が混在する。筋線維は円形で大小不同を呈し，筋細胞壊死・再生像と細胞浸潤を認める。炎症細胞の主体はCD8陽性のT細胞で，これらが筋内鞘に浸潤し，MHCクラスⅠを発現している非壊死筋線維を取り囲んでいる。これらの所見は，多発筋炎でも認められる。このような多発筋炎の病理像に加え，sIBMではRVが確認される。RVは，ゴモリトリクローム変法で赤く染まる顆粒で縁取られた筋細胞内の空胞である。通常，RVを有する筋線維への炎症細胞浸潤は認められない（Fig. 5）。RVは，通常の多発筋炎でも認めることがあるが，少数であ

Table　暫定版：封入体筋炎の診断基準

●診断に有用な特徴
A．臨床的特徴
　a．他の部位に比して大腿四頭筋または手指屈筋（特に深指屈筋）が侵される進行性の筋力低下および筋萎縮
　b．筋力低下は数カ月以上の経過で緩徐に進行する
　　*多くは発症後5年前後で日常生活に支障をきたす。数週間で歩行不能などの急性の経過はとらない。
　c．発症年齢は40歳以上
　d．安静時の血清CK値は2,000 IU/Lを越えない
　(以下は参考所見)
　　・嚥下障害が見られる
　　・針筋電図では早期動員，PSW/Fibrillation/CRDの存在
B．筋生検所見
　筋内鞘への単核球浸潤を伴っており，かつ以下の所見を認める
　a．縁取り空胞を伴う筋線維
　b．非壊死線維への単核球の侵入や単核球による包囲
　(以下は参考所見)
　　・筋線維の壊死・再生
　　・免疫染色が可能なら非壊死線維への単核細胞浸潤は主にCD8陽性T細胞
　　・形態学的に正常な筋線維におけるMHC class I発現
　　・筋線維内のユビキチン陽性封入体とアミロイド沈着
　　・COX染色陰性の筋線維：年齢に比して高頻度
　　・(電子顕微鏡にて) 核や細胞質における16-20 nmのフィラメント状封入体の存在
●合併しうる病態
　HIV，HTLV-I，C型肝炎ウイルス感染症
●除外すべき疾患
　・縁取り空胞を伴う筋疾患*（眼咽頭型筋ジストロフィー・縁取り空胞を伴う遠位型ミオパチー・多発筋炎を含む）
　・他の炎症性筋疾患（多発筋炎・皮膚筋炎）
　・筋萎縮性側索硬化症などの運動ニューロン病
　　*Myofibrillar myopathy（FHL1，Desmin，Filamin-C，Myotilin，BAG3，ZASP，Plectin変異例）やBecker型筋ジストロフィーも縁取り空胞が出現しうるので鑑別として念頭に入れる。特に家族性の場合は検討を要する。
●診断カテゴリー：診断には筋生検の施行が必須である
　Definite　AのａｰｄおよびBのａ，ｂの全てを満たすもの
　Probable　AのａｰｄおよびBのａ，ｂのうち，いずれか5項目を満たすもの
　Possible　Aのａｰｄのみ満たすもの（筋生検でBのａ，ｂのいずれもみられないもの）

●文献
・Griggs RC, Askanas V, DiMauro S, et al. Ann Neurol 1995; 38: 705-713.
・Needham M, Mastaglia FL. Lancet Neurol 2007; 6: 620-631.
厚生労働科学研究費補助金難治性疾患克服研究事業　封入体筋炎（IBM）の臨床病理学的調査および診断基準の精度向上に関する研究班（H 22-難治-一般-117）より転載

る。筋細胞内にユビキチンやアミロイドβ蛋白，リン酸化タウ蛋白が凝集している。アミロイドβの凝集体はRVの中や近傍で確認されることが多く，コンゴーレッドでも陽性である。また，赤色ぼろ線維（ragged red fiber：RRF）やチトクロームc酸化酵素（CCO）染色にて染色性が低下した筋線維がみられ，ミトコンドリア異常が想定される。

診断のためには，当初は，電子顕微鏡を用いて核や細胞質内における15～18 nmのフィラメント状封入体の存在を明らかにすることが必要であったが，近年では，ユビキチン陽性封入体やアミロイドβの沈着が重要となってきている。

Ⅷ．発症機序

sIBMの明確な発症機序は不明で，ウイルス感染，有毒蛋白の集積，自己免疫，筋核変性，小胞体ストレス，オートファジーやプロテアソーム機能低下などさまざまな説が提唱されている。

1．炎症の関与

sIBMの生検所見は，通常の多発筋炎の病理像と類似している。多発筋炎，sIBMとも，MHCクラスⅠを発現した非壊死線維をCD8陽性のリンパ球が取り囲んで

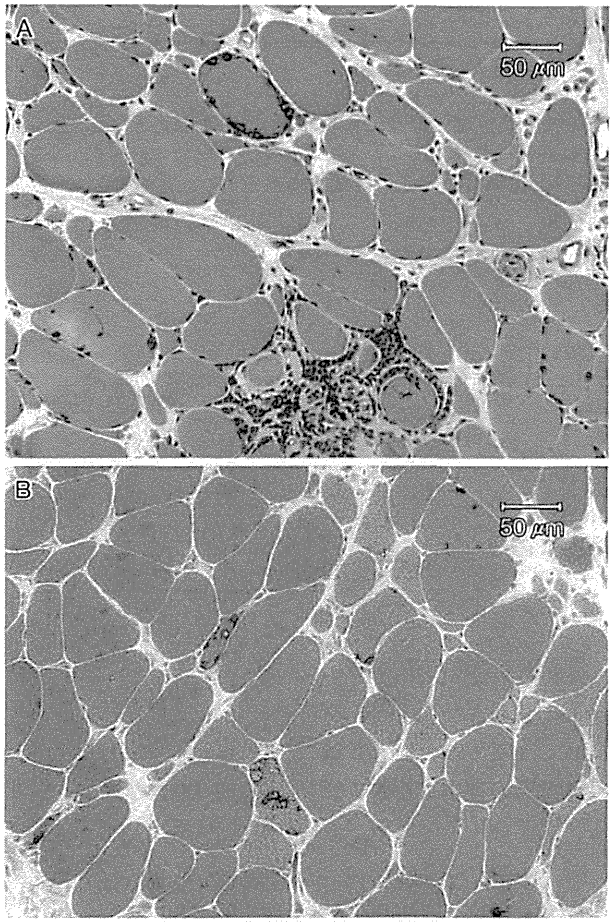

Fig. 5　封入体筋炎の筋生検病理像
A：ヘマトキシリン・エオジン（HE）染色，B：ゴモリトリクローム変法（mGT）。単核球の炎症細胞が非壊死性筋線維を取り囲んでいる。HE 染色で紫色，mGT 染色で赤紫色顆粒に縁取られた縁取り空胞（rimmed-vacuole）陽性の筋線維の周辺には炎症細胞浸潤は認めない。

いる。CD8 はパーフォリンを放出し，筋細胞膜を破壊して筋細胞内に浸潤する。CD8 陽性細胞は，グランザイムを放出し筋細胞を壊死させる。パーフォリンを介したこのシステムは，抗原特異性が高いとされている[23]。MHC は，T細胞に抗原提示しT細胞の活性化を誘発するが，その際に costimulatory molecule が関与する。筋細胞膜には B7 ファミリーの CD80，CD86 が発現し，Tリンパ球には，そのリガンドとして CD28，CTLA-4 が発現している。CD28 と B7 ファミリーが結合すると正のシグナルとなり，リンパ球増生が進み，CTLA-4 と結合すると負のシグナルとなり，リンパ球の増生が抑制される[24]。MHC クラス I や B7 ファミリーは，インターフェロン γ や TNF（tumor necrosis factor）α などのサイトカインやケモカインで誘導されるが[25]，これらのサイトカインやケモカインは IBM 患者の生検筋で発現が増強している[26]。

sIBM では，筋内鞘に浸潤するTリンパ球のT細胞受容体のタイプはある程度限られている。また，HIV（human immunodeficiency virus）[27] や HTLV-1[28] 感染患者が IBM を併発することがあり，その際に筋内鞘に浸潤して非壊死線維を取り囲む CD8 リンパ球のT細胞受容体のサブタイプも限られている。以上のことから，未だ抗原は見つかっていないが，sIBM にみられるT細胞の反応は抗原特異的と考えられる[29]。

2．βアミロイド仮説

sIBM 患者の生検筋の免疫染色では，アミロイド β 蛋白（Aβ）やアミロイド β 前駆蛋白（AβPP），リン酸化タウ，プリオン蛋白，アポリポ蛋白E，α-1アンチキモトリプシンなどが，RV 内に存在することから，Askanas らがアミロイド β 仮説を提唱した[30,31]。sIBM 患者骨格筋では AβPP の転写が促進されており[32]，さらに BACE1（beta-cite APP cleaving enzyme 1）や γ セクレターゼといった AβPP から Aβ を産生させる酵素の発現も増加している[33,34]。Aβ がどのようにして骨格筋を障害するかははっきりしないが，AβPP を筋特異的に発現させたマウスでは筋変性や封入体が形成されたとの報告や[35]，炎症細胞からの各種サイトカインが骨格筋内の AβPP の産生を増強すると報告されている[36]。一方で，sIBM での骨格筋内での AβPP の mRNA の発現量は，多発筋炎と比べて差異がないとの報告もある[37]。ジスフェルリンは，筋細胞膜の修復因子であり，LGMD2B では免疫染色にて筋細胞膜での発現が低下している。sIBM の生検筋を使った免疫染色にて，ジスフェルリンとアミロイド β42 の局在が類似しており，sIBM での両者の関係が注目されている[38]。

3．筋核異常

sIBM では，①核膜の内膜に存在するエメリンやラミニン A/C や②核内に存在するヒストン H1 が RV 内に存在することが報告されている[39,40]。

TDP-43（TAR DNA-binding protein of 43kDa）は，多くの組織や細胞で恒常的に発現している RNA 結合蛋白である。細胞内では主として核内に存在するが，核外や核内移行シグナルを有しているため，核と細胞質を行き来している。近年，TDP-43 は ALS や前頭側頭葉変性症に異常蓄積していることが判明した。sIBM において筋核内の TDP-43 が減少した筋線維では，逆に TDP-43 が筋細胞質内に集積している[41,42]。sIBM では種々の蛋白が細胞質内に沈着するが，TDP-43 は最も高頻度に

沈着し，筋線維内の23%に及ぶとの報告もある。筋核からTDP-43が消失すると，核の形態変化が出現しアポトーシスに陥る[43]。TDP-43の筋細胞質内分布がsIBMの病態に関与すると考えられている[41]。しかし，細胞質内へのTDP-43の沈着はsIBMに特異的ではなく[44,45]，筋細胞質への沈着は少数であるという報告もあり検討を要する[46,47]。

4．蛋白質分解の異常

細胞内には，蛋白質の合成ミスや，折りたたみ異常（ミスフォールディングやアンフォールディング）が生じ異常蛋白が形成されると，それらを除去するシステムが存在する。この蛋白質の恒常性に関与するのが，ユビキチン-プロテアソーム系やオートファジーである。

5．ユビキチン-プロテアソーム系

ユビキチンは，まず標的蛋白に結合し，その不要蛋白をプロテアソームが分解する。ユビキチンは，ATPのエネルギーを使用して活性化される。ユビキチンリガーゼE3は，この活性化したユビキチンと標的蛋白との仲介作用を有している。sIBMでは，ユビキチンリガーゼE3の1つであるRNF5（ring finger protein 5）の発現が増加しているが，RNF5を過剰発現させたマウスでは，筋萎縮・筋線維の壊死・再生と封入体形成が確認されたと報告されている[48]。一方，sIBMではプロテアソームの機能低下も報告されており[49,50]，ユビキチン-プロテアソーム系の異常が推定されている。

6．オートファジー

オートファジーは蛋白質分解システムの1つで，細胞質にある蛋白質やオルガネラを非選択的にオートファゴソームといわれる脂質膜で取り囲みライソゾームで分解することで細胞の恒常性維持を行っている。当初，オートファジーは，プロテアソーム系とは異なり，対象とする基質蛋白に選択性がないものと考えられていた。しかし，プロテアソームで分解できなかったユビキチン化した蛋白がオートファジーによって分解されることがわかり，さらにp62蛋白（別名sequestosome 1：SQSTM1）がオートファジーの基質選択性を与える主要なアダプター蛋白であることが明らかになった[51]。つまり，蛋白質を取り囲むオートファゴソームは，LC3蛋白が脂質膜とともに隔離膜と融合し，伸長して形成される。このときオートファゴソームと基質蛋白をつなぐのがp62である。このp62やLC3は，sIBMでは高度に発現している[46,47,52,53]。選択的オートファジーのその他のアダプター蛋白にはNBR1（neighbor of BRCA 1 gene 1）やオプチニューリンがあり，いずれもsIBMでは発現が確認されている[54,55]。

これらの蛋白増加が，sIBMでの筋障害の原因であるのか，単にオートファジーが亢進しているのかは不明であるが，LC3とAβPP/Aβがの生検筋内の空胞内に共存していることから，オートファジーを介し，ライソゾームを分解する際のターゲットにAβが関与している可能性がある。さらに，これらの筋線維は，MHCクラスⅠやⅡを発現しており，その前周りをCD4またはCD8陽性リンパ球が取り囲んでいる。以上のことは，筋変性としてのAβ，自己貪食のLC3が炎症機転と関連している可能性を示唆している[56]。

一方，sIBMでは，骨格筋内のライソゾーム機能が抑制され，オートファジー機能が低下しているとの報告もあり議論を要する[57]。さらに，培養筋を用いた検討で，INF-1β，IL-6，TNF-αといったサイトカインにより活性化されたグリコーゲン合成酵素キナーゼ3β（GSK-3β）により，筋線維内のリン酸化タウ産生が増加することが判明した。sIBMではGSK-3βとリン酸化タウが共存しており，炎症過程とAβとの関連性が示唆された[25,58]。

Ⅸ．封入体筋炎のバイオマーカー

生検筋の病理学的検討の際のバイオマーカーとしては，RV，非壊死線維への細胞浸潤，筋細胞内へのAβ，TDP-43，SMI-31，p62の沈着が挙げられる。近年，sIBM患者血清中に分子量43 kDaの自己抗体が見出された。ウエスタンブロットを用いた検討では，当初anti-IBM43といわれたこの自己抗体はsIBMの診断に関して感度50%，特異度100%であった。その後の検討で，この43 kDaは，cytoplasmic 5′-nucleotidase 1A（cN1A；NT5C1A）であることが判明し，抗cN1A抗体を用いたsIBMの病理学的検討では，cN1Aは筋核の周囲およびRVの周囲に局在し，TDP-43とは共局在しなかった。抗cN1A抗体は，IBMの診断に有益であるのみならず，IBMの自己免疫性疾患の要素と変性疾患の要素を介在するものとして注目されている[59]。

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Title　**The Etiology and Pathogenesis of Sporadic Inclusion Body Myositis**

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Abstract　Sporadic inclusion body myositis (sIBM) is the most common acquired muscle disease in older individuals. Muscle weakness and atrophy in the quadriceps, wrist flexor, and finger flexors are the typical clinical findings in sIBM. The etiology and pathogenesis of sIBM are still poorly understood; however, genetic factors, aging, and environmental factors might possibly play a role. The pathological characteristics of sIBM include two unique features: inflammatory changes in muscle fibers, and cytoplasmic and intranuclear inclusions containing several Alzheimer-type proteins. Based on these pathological findings, there is a continuing debate on whether sIBM is primarily a T cell-mediated inflammatory myositis or a myodegenerative disorder characterized by abnormal protein aggregation, presence of inclusions bodies, and secondary inflammation. Unfortunately, sIBM is also generally refractory to immune therapy.

Key words　**sporadic inclusion body myositis (sIBM), inflammatory myopathy, rimmed-vacuole, myodegenerative disorder**

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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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