

## Original article

**Pediatric necrotizing myopathy associated with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies**

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**Abstract**

**Objective.** Antibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) have recently been associated with immune-mediated necrotizing myopathy, especially in patients with statin exposure. As the data are very limited concerning phenotypes and treatment in paediatric patients, we aimed to identify the paediatric patients positive for anti-HMGCR antibodies and clarify their features and therapeutic strategies.

**Methods.** We screened 62 paediatric patients who were clinically and/or pathologically suspected to have inflammatory myopathy for anti-HMGCR antibodies. We further re-assessed the clinical and histological findings and the treatment of the patients positive for anti-HMGCR antibodies.

**Results.** We identified nine paediatric patients with anti-HMGCR antibodies (15%). This was more frequent than anti-signal recognition particle antibodies (four patients, 6%) in our cohort. The onset age ranged from infancy to 13 years. Five patients were initially diagnosed with muscular dystrophy, including congenital muscular dystrophy. Most patients responded to high-dose corticosteroid therapy first but often needed adjuvant immunosuppressants to become stably controlled.

**Conclusion.** Paediatric necrotizing myopathy associated with anti-HMGCR antibodies may not be very rare. Phenotypes are similar to those of adult patients, but a chronic slowly progressive course may be more frequent. Some patients share the clinicopathological features of muscular dystrophy indicating that recognizing inflammatory aetiology would be challenging without autoantibody information. On the other hand, most patients responded to treatment, especially those who were diagnosed early. Our results

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suggest the importance of early autoantibody testing in paediatric patients who have manifestations apparently compatible with muscular dystrophy in addition to those who have typical features of inflammatory myopathy.

**Key words:** 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), immune-mediated necrotizing myopathy, muscular dystrophy, paediatrics, major histocompatibility complex (MHC), membrane attack complex (MAC)

### Rheumatology key messages

- Paediatric necrotizing myopathy with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies may not be rare.
- Autoantibody testing should be considered for paediatric patients suspected to have undiagnosed muscular dystrophy.
- Early diagnosis of paediatric necrotizing myopathy with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies is crucial for outcome.

## Introduction

Idiopathic inflammatory myopathy (IIM) is currently categorized into PM, DM, anti-synthetase syndrome, inclusion body myositis, immune-mediated necrotizing myopathy (iNM) and non-specific myositis [1, 2]. iNM is a recently emerging subtype of IIM and often associated with specific autoantibodies such as anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) and anti-signal recognition particle (SRP) [3–5].

HMGCR is a key enzyme in the cholesterol biosynthesis pathway, whose inhibitors, statins, have been widely used as a lipid-lowering therapy and are known to cause variable muscle symptoms ranging from asymptomatic elevation of creatine kinase (CK) and myalgia to severe necrotizing myopathy and fatal rhabdomyolysis. Anti-HMGCR antibody was initially detected mainly in myopathic patients with statin exposure, directing attention to adult patients preferentially. So far most reported patients with anti-HMGCR antibody-associated iNM (anti-HMGCR iNM) were adult, usually older than 40–50 years [4–12]. Three previous studies identified some paediatric patients, although the information provided was limited [5, 6, 12]. In a cohort of iNM, eight paediatric patients ranging from 4 to 16 years of age were observed. However, detailed information is unavailable except that four of the eight patients were initially diagnosed as having limb-girdle muscular dystrophy due to slowly progressive muscle deficit [6].

We herein present nine paediatric patients with anti-HMGCR iNM. The phenotypes and management of these patients were investigated in detail.

## Methods

### Patients

We received 728 serum samples for autoantibody evaluation from October 2010 to September 2015, based upon the suspicion of inflammatory myopathy from clinical and

or pathological findings. Among them, 62 were from paediatric patients (defined as < 16 years of age at onset). All patients, except for three Egyptians, were East Asian. Biopsied frozen skeletal muscles of 60 patients were available. To exclude a range of muscular dystrophies, we performed immunohistochemistry using antibodies toward dystrophin,  $\alpha$ - to  $\delta$ -sarcoglycans,  $\alpha$ - and  $\beta$ -dystroglycans, dysferlin, caveolin-3, emerin, laminin  $\alpha$ 2 and collagen VI. In addition to the histological studies, we performed mini multiplex western blotting using antibodies toward dystrophin, dysferlin, calpain 3,  $\alpha$ -sarcoglycan and telethonin. Pathological classification by the first screening of the muscle samples consisted of necrotizing myopathy or muscular dystrophy without molecular diagnosis (n=24), DM (n=22), PM (n=1), neuropathic change (n=1) and non-specific change (n=12).

### Collection of clinical and pathological data

For the patients determined to have anti-HMGCR antibodies, the latest clinical information was additionally obtained from their medical records. Muscle pathology of the patients was reassessed by conventional histochemical methods including haematoxylin and eosin and modified Gomori Trichrome stain and on immunohistochemistry including MHC-1 and -2 and membrane attack complex (MAC; C5b-9). The scale bar shown in the pathology images is 20  $\mu$ m.

### Detection of autoantibodies

We measured anti-HMGCR antibodies in the frozen sera by enzyme-linked immunosorbent assay according to previously described methods [10]. Details of the assay are provided as Supplementary data, Methods section and Supplementary Fig. S1, available at *Rheumatology* Online. For comparison of the frequency, we screened anti-SRP antibodies and anti-aminoacyl-tRNA synthetase antibodies by means of RNA immunoprecipitation assay [13].

TABLE 1 Clinical and laboratory findings

Patient	Age of onset	Initial presentation	Initial diagnosis	Disease course	Other involvement	CK (IU/l) (first visit)
P1	10 m	Motor delay	CMD	Chronic	Nil	352-918
P2	3 y	Difficulty in climbing stairs, muscle pain	IM	Chronic	Nil	6175
P3	5 y	High CK with motor clumsiness	IM	Subacute	Nil	5453
P4	6 y	Asymptomatic high CK	MD	Chronic	Nil	6391
P5	7 y	Slow runner	IM	Chronic	Nil	5460
P6	10 y	Fatigue, skin rash	IM	Subacute	Fatigue, skin rash	10 891
P7	11 y	Fatigue, skin rash	DM	Subacute	Fatigue, skin rash	7508
P8	13 y	Difficulty in pedalling and climbing stairs	MD	Chronic	Nil	7183
P9	9 y	Difficulty in climbing stairs	MD	Subacute	Nil	9570

CK: creatine kinase; CMD: congenital muscular dystrophy; F: female; IM: inflammatory myopathy; M: male; MD: muscular dystrophy; m: months; y: years.

#### Targeted next generation sequencing of muscular dystrophy-related genes

In order to exclude the possibility of muscular dystrophy in patients with anti-HMGCR antibodies, targeted next generation sequencing was performed covering 61 reported muscular dystrophy related genes. Details of the method are given in Supplementary data, Methods Section, available at *Rheumatology* Online.

#### Standard protocol approvals, registrations and patient consents

All the clinical information and materials used in this study were obtained for diagnostic purposes and permitted for scientific use with written informed consent. All of the experiments were approved by the ethical committees of the National Center of Neurology and Psychiatry and Keio University.

## Results

### Clinical features

Anti-HMGCR antibodies were positive in 9 of 62 paediatric patients (15%). Clinical data are presented in Tables 1 and 2. Four patients were male and five were female. CK levels were markedly elevated in all. There was no medication history of statins in any of the nine patients. Anti-SRP antibodies and anti-aminoacyl-tRNA synthetase antibodies were detected in four (6%) and two (3%; PL-7 and KS) of the patients, respectively. All of the patients with anti-HMGCR antibodies were negative for the other antibodies.

The onset age of the patients with anti-HMGCR iNM ranged from 10 months to 13 years. The median duration from disease onset to diagnosis of inflammatory myopathy was 1 year (0.5-4 years). While four patients showed subacute onset of the disease (<6 months), the remaining five had a chronic onset. Five patients, of whom four presented with chronic onset of the disease, were initially diagnosed to have muscular dystrophy, including congenital muscular dystrophy (patient 1). All but patient 6, who did not show apparent muscle weakness, developed proximal muscle weakness. Scapular winging

was seen in patients 1 and 4. Two patients presented with myalgia (patients 2 and 3). No evidence of malignancy was detected in any patient.

Two patients developed skin rash together with fatigability at the initial or early stage of the disease: patient 6 showed facial papules, and patient 7 had generalized pruritic erythematous papules with photosensitivity, a butterfly-shaped rash on the face. Patients 4 and 6 had a fever at the beginning although we could not distinguish whether it was associated with the disease or coincidental. None showed cardiac or pulmonary involvement.

The CK levels of all patients at the first visit were elevated, ranging from 5000 to 10 000 IU/l, except for P1 whose CK level was 918 IU/l. On skeletal muscle MRI, oedematous changes were found in all four patients who received this examination before the beginning of treatment (Table 2; Supplementary Fig. S2, available at *Rheumatology* Online).

### Histological features

On muscle pathology, all nine patients who had muscle biopsy showed necrosis and regeneration of muscle fibres (Supplementary Fig. S3A, available at *Rheumatology* Online). In addition, we observed moderate to marked endomysial fibrosis with adipose tissue infiltration in four patients (Supplementary Fig. S3B, available at *Rheumatology* Online), mimicking muscular dystrophy. There was no definite mononuclear cellular infiltration surrounding or invading non-necrotic fibres, though there was mild to moderate perivascular mononuclear cellular infiltration seen in four patients. Perifascicular atrophy, perimysial necrosis or perimysial connective tissue fragmentation with elevated perimysial alkaline phosphatase activity was not observed. Small vacuoles in muscle fibres were found in two patients. On immunohistochemistry, eight of nine patients showed positive cytoplasmic MHC-1 expression in non-necrotic or regenerating fibres, although fainter than those seen in other IIM (Supplementary Fig. S3C, available at *Rheumatology* Online). MHC-2 was negative in all. We also observed sarcolemmal MAC deposition in scattered non-necrotic fibres in five out of seven patients (Supplementary Fig.

TABLE 2 Radiological and pathological findings

Patient	Muscle imaging	Muscle pathology						
		Duration from onset to biopsy	Necrosis and regeneration	Endomysial fibrosis	Mononuclear cellular infiltration	MHC-1/-2	Sarcolemmal MAC deposition	Others
P1	Atrophy in posterior thighs (CT)	2.7 y	+	Moderate	–	+/-	–	Muscle atrophy, variable among fascicles
P2	Unremarkable (CT)	1 y	+	Mild	Perivascular	+/-	NR	NR
P3	Unremarkable (CT)	<1 y	+	Minimal	–	+/-	NR	NR
P4	Oedematous change in posterior thighs (MRI at 9 yo)	3 y	+	Moderate	–	+/-	+	Degenerating fibres with small vacuoles
P5	Atrophic change in limb-girdle muscles without oedematous change (MRI at 14 yo)	4 y	+	Moderate	Perivascular	+/-	+	Degenerating fibres with small vacuoles
P6	Patchy oedematous change in thigh muscles (MRI at 10 yo)	< 1 y	+	–	Perivascular	+/-	+	NR
P7	Oedematous change in triceps brachii (MRI at 11 yo)	< 1 y	+	Mild	–	+/-	+	Cluster of atrophic fibres
P8	Oedematous change in posterior thighs (MRI at 16 yo)	3 y	+	Marked	Perivascular	+/-	+	NR
P9	Atrophy of gluteus and thigh muscles; fatty infiltration (MRI at 26 yo)	17 y	+	Mild	–	-/-	–	NR

MAC: membrane attack complex; NR: not reported; y: years; yo: years old.

S3D, available at *Rheumatology* Online). The detailed pathological findings of each patient are summarized in Table 2.

#### Gene screening for muscular dystrophy

Since the major feature of the patients on muscle pathology was a necrotic and regenerating process, which is also commonly seen in muscular dystrophies, we further performed targeted next generation sequencing for reported causative genes of muscular dystrophies to exclude the possibility of muscular dystrophies in all of the patients except for patient 7 whose DNA samples were not available. Only in patient 1, a *de novo* heterozygous mutation in LMNA, previously reported in a patient with Emery-Dreifuss muscular dystrophy (EDMD) was detected: c.1158-A>G (ENST00000368300) [14]. No known mutations were found in the other patients.

#### Treatments

Four patients (patients 1, 2, 3 and 5) received and responded to corticosteroid (CS) therapy to a variable extent by showing an increase of muscle strength, but the CK levels were not completely normalized except for patient 1, whose initial CK level was only mildly elevated. Two patients (patients 4 and 6) were treated with CS together with MTX and intermittent IVIg, showing excellent improvement of muscle power. CK level returned to normal in patient 6, although it remained around 2000 IU/l in Patient 4. Patient 4 showed clinical regression and CK elevation to 8240 IU/l after influenza

infection 2 years after the initial treatment. Further increase in the dose of CS reduced the CK level to 1735 IU/l but did not improve the clinical symptoms. Patient 7 initially received the combined therapy of CS, mycophenolate and MTX for 6 months, but her muscle power was only mildly improved. Therefore add-in IVIg was started, which resulted in fully recovered muscle power and CK levels in 1.5 months. Patient 8 showed only mild improvement with the treatment of CS and MTX in the first 3 years. Intermittent IVIg was thus added and MTX was switched to tacrolimus. This combination led to a further decrease of CK level (150–500 IU/l) and stabilization of the clinical symptoms, although she still requires support to stand up and walk. Patient 9 made an almost full recovery with the treatment of CS and *Tripterygium wilfordii* (a Chinese traditional herb) in the first 4 years. However, AZA or CYC was then added due to a relapse of the symptoms and continued for the next 10 years. The patient had only limited response and CK has never returned to the baseline. In the past 2–3 years, MTX, mycophenolate or ciclosporin A was tried together with intermittent IVIg, but she did not show significant improvement although the CK level was reduced to 200–500 IU/l.

#### Discussion

In this series, five of the nine patients were initially diagnosed with muscular dystrophy. Previous reports showed that most patients with anti-HMGCR iNM, of whom the

majority were adult, deteriorated with a subacute, or occasionally acute, onset [5, 10]. However, in this study, five of nine paediatric patients showed a chronic disease course. Although our cohort is still too small to draw any conclusion, younger patients may tend to show a relatively slow progression that would partially lead to clinical diagnosis of muscular dystrophy. In addition, iNM is pathologically characterized by active myofibre necrosis and regeneration with no or little endomysial inflammatory cellular infiltration. In our series, the longer the duration from onset to the time of biopsy, the more remarkable was the endomysial fibrosis we observed. The patients with these pathological features might often be given a tentative diagnosis of unspecified muscular dystrophy. Among these five patients, we would like to draw more attention to patient 1. This patient, initially suspected to have congenital muscular dystrophy, was enrolled for autoantibody testing because of cytoplasmic MHC-1 expression. The patient is so far the one with the youngest onset age (10 months) among all reported patients positive for anti-HMGCR antibodies. A *de novo* heterozygous mutation in *LMNA* was detected in this patient. This mutation was reported in an adult patient whose clinical manifestations were consistent with EDMD, including contractures of his elbow (severe) and neck and cardiac conduction block, although information on his childhood was not provided [14]. As the relationship between the mutation and EDMD was reported only in the single case and functional testing was not performed, the pathogenicity would still be inconclusive; it might be a mere single nucleotide polymorphism. Actually patient 1 did not show characteristic features of EDMD such as joint contracture and cardiac conduction defect, although these clinical features may possibly occur later. In addition, we confirmed that none of the sample from our cohort of definite muscular dystrophy patients was positive for the antibodies measured by our assay (Supplementary Fig. S3, available at *Rheumatology* Online). However, on the other hand, it should be noted that *LMNA*-associated congenital muscular dystrophy occasionally mimics infantile myositis [15]. Half of such patients were reported to show a favourable response to steroid therapy. It is therefore speculated that *LMNA* mutations may be related to some immunological changes including production of myositis-associated autoantibodies, although further studies to clarify this point are necessary.

Immunohistochemistry for MHC-1 and -2 has been known to be a useful pathological marker for IIM [16]. Especially MHC-1 is highly sensitive, albeit of low specificity. In this series, all patients showed negative MHC-2 staining but increased sarcoplasmic MHC-1 expression, although the pattern tended to be fainter compared with that of other IIM. However, the frequency of the patients with positive staining of MHC-1 differed among reports [6, 9, 10]. This could be due to the difference of staining methodology and judging criteria among institutes. Sarcolemmal deposition of MAC in non-necrotic fibres has also been described in previous papers [4, 6]. This

picture was frequently observed also in our study. The classification criteria proposed in 2004 deal with the sarcolemmal MAC deposition as an exclusion criterion for iNM [17]. However, this study together with the other reports suggests that the criteria should be reconsidered.

As for treatment, none of the patients got clinical and biochemical remission with only CS. CS together with MTX and intermittent IVIg seemed to be the most effective therapy in our cohort although the number of patients is limited. Notably, patients 6 and 7 with the earliest start of treatment showed the best response to the therapy, raising a possibility that early diagnosis and treatment may be the key to a favourable outcome.

We demonstrated the prevalence of anti-HMGCR iNM is higher than anti-SRP iNM, known to occur in children [18–21], indicating that paediatric anti-HMGCR iNM should not be extremely rare. However, we are aware of a few limitations concerning this point. First, most patients in our cohort had undergone muscle biopsy, raising the possibility of selection bias that could lead to a difference in the prevalence calculation. For example, patients with typical skin lesions of DM could be diagnosed without biopsy. Second, it has been known that the prevalence of autoantibodies can be affected by ethnic factors; for example, anti-MDA5 antibodies are more commonly detected in Japanese patients than European and American [22–24]. Therefore there remains a possibility that the high prevalence is unique to the Asian or Japanese population. Validation should be performed in other ethnic populations. Our recent study showed that the patients with anti-SRP iNM presented with more severe weakness, dysphagia and respiratory insufficiency than anti-HMGCR iNM, but no specific or exclusive features for each iNM could be concluded [25]. This cohort included only adults; the findings may therefore not be applicable to paediatric patients. Our results suggest that autoantibody testing, including that for HMGCR, should be considered early for paediatric patients clinically and pathologically suspected to have not only necrotizing myopathy but also undiagnosed muscular dystrophy.

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## Supplementary data

Supplementary data are available at *Rheumatology* Online.

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