Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 29 (2019) 543–548

www.elsevier.com/locate/nmd

Case report

Concurrent positive anti-3-hydroxy-3-methylglutaryl-coenzyme a reductase antibody with reducing body myopathy: Possible double trouble

Jantima Tanboon[a,h,*], Oranee Sanmaneechai[b], Sirirat Charuvanij[c], Tumtip Sangruchi[a], Angeles S. Galindo-Feria[d], Ingrid E. Lundberg[d], Yuko Ohnuki[e], Takashi Shiina[f], Shigeaki Suzuki[g], Ichizo Nishino[h,i]

[a] *Department of Pathology, Faculty of Medicine, Siriraj Hospital, Mahidol University, 2 Wanglang Road, Siriraj, Bangkok Noi, Bangkok 10700, Thailand*
[b] *Division of Neurology, Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand*
[c] *Division of Rheumatology, Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand*
[d] *Division of Rheumatology, Department of Medicine, Solna, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden*
[e] *Department of Medical Ethics, Tokai University School of Medicine, Kanagawa, Japan*
[f] *Department of Molecular Life Science, Tokai University School of Medicine, Kanagawa, Japan*
[g] *Department of Neurology, Keio University School of Medicine, Tokyo, Japan*
[h] *Department of Neuromuscular Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry (NCNP), Tokyo, Japan*
[i] *Departments of Genome Medicine Development and Clinical Genome Analysis, Medical Genome Center (MGC), National Center of Neurology and Psychiatry (NCNP), Tokyo, Japan*

Received 25 April 2019; accepted 20 May 2019

Abstract

Anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase myopathy is less common in children but has been associated with more favorable prognosis than adult patients after immunotherapies. We report anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibody positivity in a 6-year-old boy with progressive muscle weakness, scoliosis, spinal rigidity, multiple joint contractures, mild left ventricular hypertrophy, and elevated serum creatine kinase. In contrast to most of previously reported pediatric anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase myopathy, he showed little response to immunotherapies. Muscle biopsy contained changes suggestive of myofiber necrosis and regeneration and reducing bodies. The diagnosis of reducing body myopathy was later confirmed by reported c.368A>*G* (p.His123Arg) mutation in the *FHL1* gene. Although the level of association between these two conditions is still inconclusive, this is the first report of concurrent positive anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibody with reducing body myopathy emphasizing the possibility of co-occurrence of immune mediated necrotizing myopathy and muscular dystrophy and importance of comprehensive diagnostic investigations in unusual cases.

Keywords: Reducing body myopathy; FHL1; HMGCR; 3-hydroxy-3-methylglutaryl-coenzyme A reductase; Immune mediated necrotizing myopathy; IMNM.

1. Introduction

Immune mediated necrotizing myopathy (IMNM), a recently recognized but a common entity among the heterogenous group of inflammatory myopathies, has been classified by the ENMC Immune-Mediated Necrotizing Myopathies Working Group into (1) anti-signal recognition particle (anti-SRP) positive IMNM or anti-SRP myopathy, (2) anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) positive IMNM or anti-HMGCR myopathy, and (3) antibody negative IMNM using integrated clinical, serological, and pathological criteria [1]. Patients with proximal muscle weakness and elevated serum creatine kinase (CK) level can be classified into anti-SRP myopathy or anti-HMGCR myopathy if they are found to have anti-

* Corresponding author at: Department of Pathology, Faculty of Medicine, Siriraj Hospital, Mahidol University, 2 Wanglang Road, Siriraj, Bangkok Noi, Bangkok 10700, Thailand.
E-mail address: jantima.tan@mahidol.ac.th (J. Tanboon).

https://doi.org/10.1016/j.nmd.2019.05.007
0960-8966/

SRP or anti-HMGCR antibody, respectively [1]. Further workup such as muscle biopsy, electromyography (EMG), and muscle magnetic resonance imaging (MRI) is not required for subtyping these seropositive patients [1]. In contrast, compatible muscle pathology is essential to define antibody negative IMNM in patients with similar clinical features after excluding possibility of drug/toxin-induced myopathy [1]. Although most IMNM patients are adults, pediatric IMNM exists and is probably underrecognized. It is noteworthy that IMNM can be masquerading as muscular dystrophy and vice versa especially in pediatric individuals [1–11]. Instead of acute or subacute clinical presentation and necrotic and regenerating process on pathology, some IMNM patients show indolent clinical course and chronic or advance muscle pathology mimicking muscular dystrophy [3,4,6,12]. On the other hand, certain types of muscular dystrophies including anoctaminopathy, laminopathy, dysferlinopathy, sarcoglycanopathies, *FKRP*-related muscular dystrophy and fascioscapulohumeral muscular dystrophy (FSHD) can be pathologically deceptive as IMNM by showing prominent necrotic and regenerating process with lymphohistiocytic inflammation [1,3]. Interestingly, some of muscular dystrophy patients may show favorable response to immunotherapies [3]. Thorough clinical, laboratory, and genetic investigations are required to distinguish potentially treatable conditions, IMNM, from other non-treatable conditions.

Here, we report a case of a 6-year-old boy who has concurrent positive anti-HMGCR antibody and reducing body myopathy (RBM) emphasizing the possibility of co-occurrence of IMNM and muscular dystrophy and importance of comprehensive workup in cases with unusual presentations.

2. Case report

The patient was a 6-year-old Thai boy from a non-consanguineous family, who had presented with proximal muscle weakness for 18 months. His parents first noticed the symptoms after the patient recovered from chickenpox when he was 4 years and 6 months old. At 5 years of age, he had difficulties getting upstairs, rising from the floor, frequent falling, and walking tiptoe. At the age of 6, the patient could not walk up and down stairs and had difficulties raising his arms. The patient had uneventful prenatal and perinatal history and normal psychomotor development. None of his family members had history of muscle weakness or neuromuscular disorder. At physical examination, the patient was wheelchair-bound. He had scoliosis, spinal rigidity, and multiple joint contractures including elbows, proximal and distal interphalangeal joints, hips, knees, and ankles. Muscle atrophy was noted in both quadriceps and deltoid. Motor power of proximal muscles in the upper and lower extremities was grade III and II out of V by medical research council (MRC) scale, respectively while motor power of distal muscles in the upper and lower extremities was grade IV and III out of V by MRC scale, respectively. Serum CK level was 8452 U/L. Electromyography revealed myopathic changes. Nerve conduction velocity was within normal limits. Chest radiography revealed mild thoracic scoliosis, convex to the right. Electrocardiogram revealed mild concentric left ventricular (LV) hypertrophy with normal LV function. Muscle biopsy was performed on left quadriceps. On Hematoxylin and Eosin (HE) stain, there was moderate to marked fiber size variation with scattered necrotic and regenerating fibers (Fig. 1A). Endomysial mononuclear cell infiltration was focally observed. Most of the mononuclear cells were macrophages (Fig. 1B). Smaller number of CD4 and CD8 positive cells were noted (Supplementary Figure S1). There was mild endomysial fibrosis and perimysial adipose tissue infiltration. Many muscle fibers contained amorphous eosinophilic inclusions (Fig. 1C). On modified Gomori Trichrome (mGT) deep red to purple amorphous aggregates were present and usually associated with cytoplasmic bodies in the areas corresponding to eosinophilic inclusions seen in HE (Fig. 1D). Rimmed vacuoles were also present in many fibers (not shown). The deep red to purple aggregates on mGT corresponded to voids observed in oxidative enzyme stains (Fig. 1E). The above findings raised the possibility for the diagnosis of IMNM although staining for major histocompatibility complex class I (MHC1) and membrane attack complex (MAC) was positive only in 2C, possibly regenerating fibers (Supplementary Figure S2 and S3). Myofibrillar myopathy (MFM) and related disorders were also included in differential diagnosis because the clinical history of early contractures, scoliosis, spinal rigidity, and LV hypertrophy together with presence of cytoplasmic bodies, rimmed vacuoles and amorphous materials noted in muscle biopsy despite unusually high CK level for this disease category. While awaiting for further histochemical and genetic workups, the patient was treated as IMNM. The following autoantibody test showed anti-HMGCR antibody positivity by enzyme-linked immunosorbent assay (ELISA) [13], with the titer of 1.2 IU/mL while anti-SRP antibody and anti-FHL1 antibody were negative by RNA immunoprecipitation and ELISA, respectively [14,15]. Despite the combination of high dose prednisolone (2 mg/kg/day), monthly intravenous immunoglobulin (IVIG) and methotrexate, the degree of muscle weakness and serum CK level was persistent. The patient also developed severe headache and hypertension as well as elevated levels of transaminases following IVIG infusions and methotrexate treatment, respectively. Additional menadione-linked α-glycerophosphate dehydrogenase staining (MAG, Fig. 1F) without presence of substrate revealed reducing bodies in the areas corresponding to amorphous aggregates on mGT and voids observed in oxidative stain. Reducing bodies were confirmed by ultrastructural study (Fig. 1G and H). Fibers containing amyloid material highlighted by Congo red and fluorescent microscopy (not shown). Next generation sequencing using genomic DNA revealed previously reported hemizygous mutation, c.368A>*G* (p.His123Arg), in four and a half LIM domain 1 *(FHL1)* gene in the patient but not in other family members confirming the diagnosis of RBM. The patient was later identified as having homozygous HLA-DRB1*15:01

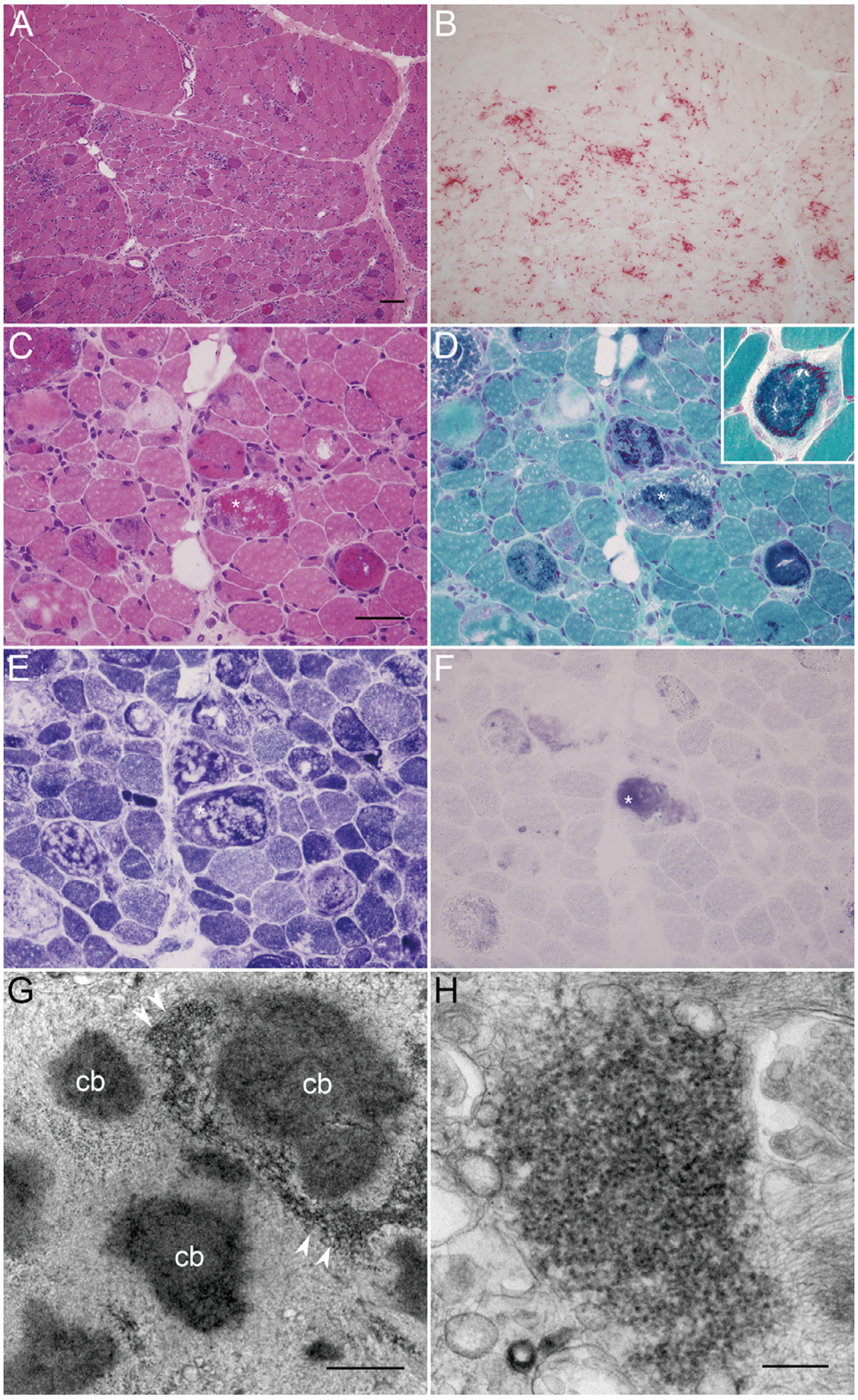

Fig. 1. Without MAG, RBM can be masquerading as IMNM. (A) Hematoxylin and Eosin (HE) stain shows moderate to marked fiber size variation and mild endomysial fibrosis. Scattered necrotic and regenerating fibers and mononuclear cell infiltration are noted. (B) Most of mononuclear cells are macrophages highlighted by acid phosphatase (ACP). (C) At higher magnification, amorphous eosinophilic inclusions are observed in many fibers. (D) On mGT, cytoplasmic bodies are often associated with deep red to purple aggregates in the areas corresponding to eosinophilic inclusions present in HE and voids present in nicotinamide adenine trinucleotide tetrazolium reductase (NADH-TR) stain (E). (F) The aggregates are positive for MAG stain without substrate (*) compatible with reducing body. It is difficult to distinguish reducing body from cytoplasmic body with mGT as both structures can appear deep red. "Necklace cytoplasmic bodies" as present in HMERF are occasionally seen in mGT (D, inset). (G) Ultrastructural study shows reducing body (double arrow) present associated with cytoplasmic body (cb) (bar = 1 μm). (H) At higher magnification, reducing body appears as dense osmiophilic tubulofilaments. (bar = 200 nm). (A-B 10 x magnification, bar 100 μm, C-F 40x magnification, bar = 50 μm).

Table 1
Concurrent positive anti-myositis specific autoantibody and presence of variants/mutations associated with muscular dystrophy/myopathy reported in the literature.

No.	Age of Onset (yrs)	Sex	Clinical features	CK (U/L)	Autoantibody	Gene	Outcome after immunotherapy	Ref.
1	40	M	Myalgia, dysphagia, slowly progressive proximal muscle weakness of lower limbs, abdominal muscle weakness, atrophy of quadriceps and hamstring, mild decreased VC	5000–7500	anti-HMGCR	*ANO5* c.191dupA[a]; c.1627dupA[a] (compound heterozygous)	Improved	[16]
2	10m	NA	Motor delay	352–918	anti-HMGCR	*LMNA* c.1158-*A*>*G*[a] (heterozygous)	Improved	[3]
3[b]	4.5	M	Weakness of all muscle in upper and lower limbs, proximally predominant, muscle atrophy, multiple joint contractures, scoliosis, spine rigidity, LVH	8452	anti-HMGCR	*FHL1* c.368A>*G*[a] (hemizygous)	No response, deteriorate, death	–
4	3.5	F	Progressive mild proximal muscle weakness of upper limbs and all muscle weakness of lower limbs, neck muscle weakness, myalgia	4020	anti-SRP	*COL6A3* c.1267G>*A*	Improved	[5]
5	NA	F	Biopsy-confirmed lupus nephritis, sicca symptoms	NA	anti-Jo1, anti-Ro52, ANA	NA LGMD2A[c]	NA	[11]
6	NA	F	Proximal muscle weakness, Skin rash typical for DM	NA	anti-Mi2	NA FSHD[c]	Improved	[11]
7	NA	F	Chronic external ophthalmoplegia	NA	anti-Mi2	NA Mitochondrial myopathy[d]	NA	[17]

Note: No. = Number; yrs = years; m = months; F = female; M = Male; CK = creatine kinase; Ref = reference; NA = not available; LVH = left ventricular hypertrophy; ANA = antinuclear antibody; LGMD = limb girdle muscular dystrophy; FSHD = fascioscapulohumeral dystrophy; DM = dermatomyositis.
[a] Variant previously reported in literature.
[b] Case in this report.
[c] Genetically confirmed but the associated information is not mentioned.
[d] Genetic information is not mentioned in the reference.

and heterozygous HLA-DQB1*03:01 and HLA-DQB1*06:02. Unfortunately, the patient was lost to follow up and passed away due to respiratory failure at another hospital at the age of 9 years. Autopsy was not performed.

3. Discussion

Several cases of concurrent myositis specific autoantibody (MSA) positivity with different types of muscular dystrophy/myopathy have been reported in the literature including positive anti-HMGCR antibody with reported *ANO5* [16] and *LMNA* [3] mutations, positive anti-SRP antibody with *COL6A3* variant [5], positive anti-Jo-1 antibody with genetically confirmed, muscular dystrophy (LGMD) 2A [11], positive anti-Mi2 antibody with mitochondrial myopathy [17] and genetically confirmed FSHD [11] (Table 1). Interestingly, except for our patient, most of these cases show clinical improvement at least partially after immunotherapy [3,5,11,16]. Without gene functional studies, responsiveness to immunotherapy may raise possibilities that MSA positivity may coincide with single nucleotide polymorphisms (SNP) instead of pathogenic mutations. Nevertheless, there are plausible evidences supporting the existence of "possibility of double trouble" cases for example muscle imaging suggestive of a specific type of myopathy [16], unusually high CK level in some type of muscular dystrophy/myopathy, unusual clinical findings for inflammatory myopathy, typical pathological features for specific types of muscular dystrophy/myopathy and unusual MHC class I and MAC positivity [16].

We report the first case of concurrent positive anti-HMGCR antibody with pathologically and genetically confirmed RBM. Both conditions are rare in pediatric population. Had our patient undergone serology test alone, he could have been classified as pediatric anti-HMGCR myopathy despite presence of unusual clinical features including scoliosis, spinal rigidity and concentric LV hypertrophy. In fact, typical anti-HMGCR myopathy patients do not show axial weakness and cardiac affection is rare. Notably, while most pediatric patients with positive anti-HMGCR antibody shows favorable response at least partially to immunotherapies [3,4,6,9,10,18], our patient continued to deteriorate. Without MAG stain, high CK levels and muscle pathology containing necrotic and regenerating fibers, mononuclear cell infiltration and cytoplasmic bodies could be compatible with the diagnosis of anti-HMGCR myopathy

although the immunohistochemical study for MHC 1 and MAC is not supportive. Nonetheless, the clinical features described above and presence of reducing bodies highlighted by MAG stain highly suggests *FHL1*-related myopathy especially RBM and X-linked scapuloperoneal myopathy (X-SM) [1,19]. The diagnosis of RBM in this case was confirmed by genetic analysis with de novo reported hemizygous mutation, c.368A>*G* (p.His123Arg), in the second LIM (LIM2) domain of *FHL1* gene [20].

RBM is one of *FHL1*-related disease spectrum which includes RBM, X-linked dominant scapuloperoneal myopathy (XSPM), X-linked myopathy with postural muscle atrophy and generalized muscle hypertrophy (XMPMA), Emery-Dreifuss muscular dystrophy (EDMD), and hypertrophic cardiomyopathy (HCM) with no or minimal musculo-skeletal involvement [19]. It is characterized by mutation confined in LIM2 domain of *FHL1* gene on Xq26.3 and presence of reducing bodies [19]. The latter are intrasarcoplasmic inclusions strongly stained by MAG with or without the presence of alpha-glycerophosphate as substrate [19,21]. Presence of cytoplasmic bodies are common; sometimes forming "necklace" pattern similar to those described in hereditary myopathy with early respiratory failure (HMERF) [19,22]. Membrane bound autophagic vacuoles as present in Danon disease and X-linked myopathy with excess autophagy are also reported in RBM [19]. RBM is inherited in X-link dominant pattern that male patients usually become symptomatic at younger age and associated with severe or fatal disease. On the other hand, there are variations of disease severity among female patients as skewed X-inactivation may play a role as disease modifier [19,23]. RBM patients tend to present with diffuse muscle weakness with asymmetric scapuloperoneal distribution. Spinal rigidity, contractures, cardiac and respiratory involvement are also reported [19,24]. Serum CK level is usually mild to moderately elevated; normal CK levels are noted in some cases [20,24,25]. Only rarely cases have CK level more than 10 times of the upper normal limit [24,26].

The unusual clinical and pathological features in our patient could be explained by the co-occurrence of anti HMGCR antibody and RBM. The level of association between anti-HMGCR positivity and RBM is still inconclusive as the patient bear homozygous HLA-DRB1*15:01 and heterozygous HLA-DQB1*03:01 and HLA-DQB1*06:02 which reported to have high allele frequency among normal Thai population. While HLA-DRB1*11:01 and HLA-DRB1*07:01 are reported to be associated with adult and juvenile anti-HMGCR myopathy, respectively, none of the alleles present in our patient is reported to have any association [1, 27]. We assessed serum anti-FHL1 antibody as we hypothesized that FHL1 protein breakdown may directly prompt antigen-antibody response. Interestingly, anti-FHL1 antibody which was reported to be associated with a subset of inflammatory myopathy was negative [14]. We further speculate that the mutated FHL1 protein may not give rise to autoantibodies targeting the FHL1 protein as the patient was born with this mutation and is likely to have been tolerized to this protein modification. Whereas the necrotic and regenerating fibers as a consequence to the mutation in RBM may be a possible reason that could unmask autoantigens and lead to antibody recognition such as anti-HMGCR antibody.

In conclusion we report a patient with concurrent anti-HMGCR antibody positive and RBM. The co-occurrence of these conditions raises awareness of possible underlying genetic alterations in IMNM patients who show unfavorable response to immunotherapy. Consideration of alternative possibilities and comprehensive investigations are essential to elucidate definite diagnosis and proper management in cases with diagnostic challenge.

Acknowledgments

This study was supported partly by Intramural Research Grant (29–4) for Neurological and Psychiatric Disorders of NCNP, and AMED under Grant Numbers JP19ek0109285h0003 and JP18kk0205001s0203.

Conflict of interest

Dr. Lundberg has filed a patent for anti-FHL1 antibody test. The other authors do not have conflict of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2019.05.007.

References

[1] Allenbach Y, Mammen AL, Benveniste O, Stenzel WImmune-Mediated Necrotizing Myopathies Working Group. 224th ENMC International Workshop: clinico-sero-pathological classification of immune-mediated necrotizing myopathies Zandvoort, The Netherlands, 14-16 October 2016. Neuromuscul Disord 2018;28(1):87–99.

[2] Watanabe Y, Uruha A, Suzuki S, Nakahara J, Hamanaka K, Takayama K, et al. Clinical features and prognosis in anti-SRP and anti-HMGCR necrotising myopathy. J Neurol Neurosurg Psychiatry 2016;87(10):1038–44.

[3] Liang WC, Uruha A, Suzuki S, Murakami N, Takeshita E, Chen WZ, et al. Pediatric necrotizing myopathy associated with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies. Rheumatol (Oxf) 2017;56(2):287–93.

[4] Mohassel P, Foley AR, Donkervoort S, Fequiere PR, Pak K, Bonnemann CG, et al. Anti-3-hydroxy-3-methylglutaryl-coenzyme a reductase necrotizing myopathy masquerading as a muscular dystrophy in a child. Muscle Nerve 2017;56(6):1177–81.

[5] Zhao Y, Liu X, Zhang W, Yuan Y. Childhood autoimmune necrotizing myopathy with anti-signal recognition particle antibodies. Muscle Nerve 2017;56(6):1181–7.

[6] Hama Y, Mori-Yoshimura M, Komaki H, Suzuki S, Kohsaka H, Nishino I, et al. Childhood-onset anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) necrotizing myopathy needs to be distinguished from muscular dystrophy: a case study. Rinsho Shinkeigaku 2017;57(10):567–72.

[7] Suzuki S, Ohta M, Shimizu Y, Hayashi YK, Nishino I. Anti-signal recognition particle myopathy in the first decade of life. Pediatr Neurol 2011;45(2):114–16.
[8] Binns EL, Moraitis E, Maillard S, Tansley S, McHugh N, Jacques TS, et al. Effective induction therapy for anti-SRP associated myositis in childhood: a small case series and review of the literature. Pediatr Rheumatol Online J 2017;15(1):77.
[9] Tansley SL, Betteridge ZE, Simou S, Jacques TS, Pilkington C, Wood M, et al. Anti-HMGCR autoantibodies in juvenile idiopathic inflammatory myopathies identify a rare but clinically important subset of patients. J Rheumatol 2017;44(4):488–92.
[10] Kishi T, Rider LG, Pak K, Barillas-Arias L, Henrickson M, McCarthy PL, et al. Association of anti-3-hydroxy-3-methylglutaryl-coenzyme a reductase autoantibodies with drb1*07:01 and severe myositis in juvenile myositis patients. Arthritis Care Res (Hoboken) 2017;69(7):1088–94.
[11] Mammen AL, Casciola-Rosen L, Christopher-Stine L, Lloyd TE, Wagner KR. Myositis-specific autoantibodies are specific for myositis compared to genetic muscle disease. Neurol Neuroimmunol Neuroinflamm 2015;2(6):e172.
[12] Ikeda K, Mori-Yoshimura M, Yamamoto T, Sonoo M, Suzuki S, Kondo Y, et al. Chronic myopathy associated with anti-signal recognition particle antibodies can be misdiagnosed as facioscapulohumeral muscular dystrophy. J Clin Neuromuscul Dis 2016;17(4):197–206.
[13] Watanabe Y, Suzuki S, Nishimura H, Murata KY, Kurashige T, Ikawa M, et al. Statins and myotoxic effects associated with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase autoantibodies: an observational study in Japan. Medicine (Baltimore) 2015;94(4):e416.
[14] Albrecht I, Wick C, Hallgren A, Tjarnlund A, Nagaraju K, Andrade F, et al. Development of autoantibodies against muscle-specific FHL1 in severe inflammatory myopathies. J Clin Invest 2015;125(12):4612–24.
[15] Suzuki S, Satoh T, Sato S, Otomo M, Hirayama Y, Sato H, et al. Clinical utility of anti-signal recognition particle antibody in the differential diagnosis of myopathies. Rheumatol (Oxf) 2008;47(10):1539–42.
[16] Claeys KG, Gorodinskaya O, Handt S, Reimann J, Kress W, Kornblum C, et al. Diagnostic challenge and therapeutic dilemma in necrotizing myopathy. Neurology 2013;81(10):932–5.
[17] Hengstman GJ, van Brenk L, Vree Egberts WT, van der Kooi EL, Borm GF, Padberg GW, et al. High specificity of myositis specific autoantibodies for myositis compared with other neuromuscular disorders. J Neurol 2005;252(5):534–7.
[18] Mohassel P, Mammen AL. Anti-HMGCR Myopathy. J Neuromuscul Dis 2018;5(1):11–20.
[19] Bertrand AT, Bonnemann CG, Bonne Gconsortium FHLm. 199th ENMC international workshop: FHL1 related myopathies, June 7-9, 2013, Naarden, The Netherlands. Neuromuscul Disord. 2014;24(5):453–62.
[20] Selcen D, Bromberg MB, Chin SS, Engel AG. Reducing bodies and myofibrillar myopathy features in FHL1 muscular dystrophy. Neurology 2011;77(22):1951–9.
[21] Brooke MH, Neville HE. Reducing body myopathy. Neurology 1972;22(8):829–40.
[22] Uruha A, Hayashi YK, Oya Y, Mori-Yoshimura M, Kanai M, Murata M, et al. Necklace cytoplasmic bodies in hereditary myopathy with early respiratory failure. J Neurol Neurosurg Psychiatry 2015;86(5):483–9.
[23] Schessl J, Zou Y, McGrath MJ, Cowling BS, Maiti B, Chin SS, et al. Proteomic identification of FHL1 as the protein mutated in human reducing body myopathy. J Clin Invest 2008;118(3):904–12.
[24] Schessl J, Taratuto AL, Sewry C, Battini R, Chin SS, Maiti B, et al. Clinical, histological and genetic characterization of reducing body myopathy caused by mutations in FHL1. Brain 2009;132(Pt 2):452–64.
[25] Schreckenbach T, Henn W, Kress W, Roos A, Maschke M, Feiden W, et al. Novel FHL1 mutation in a family with reducing body myopathy. Muscle Nerve 2013;47(1):127–34.
[26] Malfatti E, Olive M, Taratuto AL, Richard P, Brochier G, Bitoun M, et al. Skeletal muscle biopsy analysis in reducing body myopathy and other FHL1-related disorders. J Neuropathol Exp Neurol 2013;72(9):833–45.
[27] González-Galarza FF, Takeshita LY, Santos EJ, Kempson F, Maia MH, da Silva AL, et al. Allele frequency net 2015 update: new features for HLA epitopes, KIR and disease and HLA adverse drug reaction associations. Nucleic Acids Res 2015;43(Database issue):D784–8.