Anti-HMGCR myopathy: barriers to prompt recognition.

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ABSTRACT

Anti-HMGCR (3-hydroxy-3-methylglutaryl coenzyme A reductase) myopathy is an immune-mediated necrotizing myopathy. Atypical presentations hinder recognition and prompt treatment. We present two cases with either atypical clinical or pathological features. First patient was found with asymptomatic high CK (~10,000 IU/L) at age of 45. Muscle biopsy showed minimal changes. She then developed slowly progressive proximal weakness and diagnosed as limb-girdle muscular dystrophy (LGMD). Genetic investigations resulted negative. Twelve years later, she developed severe proximal weakness. Muscle MRI showed diffuse fatty degeneration with notable asymmetry, as well as conspicuous hyperintense STIR signal abnormalities. HMGCR antibodies resulted positive. Immunosuppressive therapy stopped progression with a partial improvement of symptoms. Second patient developed slowly progressive upper and lower proximal weakness with high CK (~4,000 IU/L); muscle biopsy revealed a lymphocyte infiltrate with angiocentric distribution suggestive for vasculitis. Clinical reassessment prompted testing of HMGCR antibodies that resulted positive. Anti-HMGCR myopathy can present as slowly progressive myopathy and atypical pathology. HMCR antibodies screening is recommended in suspected LGMDs and in atypical muscle inflammatory conditions.

Keywords

[myopathy]; [polymyositis]; [vasculitis]; [muscular dystrophy]

INTRODUCTION

Anti 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) myopathy is an immune-mediated necrotizing myopathy (IMNM) associated, in the majority of cases, to statin use, with a variable onset (from few months to few years after starting therapy).[1, 2] Most of patients present with an acute (within few weeks) or subacute (<6 months) progressive, proximal muscle weakness, and highly elevated CK levels (~1000–20000 IU/L). Although the association of such clinical picture along with the detection of anti-HMGCR antibodies make the diagnosis straightforward in most of cases, some of them could remain misdiagnosed or show a diagnostic delay due to i) lack of clear exposition to statins, ii) slow progressive disease resembling a limb-girdle muscular dystrophy (LGMD) [3,4] or iii) atypical findings at muscle biopsy.[3,4] Here we present two cases of anti-HMGCR myopathy in which the occurrence of these "hurdles" has led to a delay in the diagnostic pathway.

CASE 1. The first patient is a 57-year-old (yo) woman who was diagnosed with high CK at age 45 yo (ranging from 1096 to 11592 IU/L). At that point she complained generalised fatigue and very minor difficulties in getting up from the floor. She had an electromyography (EMG) test that revealed brief myotonic discharges, and a muscle biopsy that showed minimal changes (mildly increased variation in fibre size and occasional regenerating fibres). Five years later (at age 50) she developed more overt proximal muscle weakness with difficulty climbing stairs and lifting her arms over her head. She also reported muscle pain and occasional dysphagia with tablets or dry food. Her past medical history was remarkable for asthma, multiple lipomas in her arms and thighs and uterine fibroids. There was no positive family history for neuromuscular diseases. Whole genome sequencing did not identify any pathogenic variants in genes associated with LGMDs and myotonic dystrophy type 1 and type 2 screening was negative. At the time of revaluation at our Institute (55 yo) neurological examination showed scapular winging with limited abduction of both arms (<45 degree). Manual muscle testing (MMT) revealed a predominant proximal muscle weakness (Table 1). She could not stand from a chair and she needed support during walking. She had a skin rash over her neck and livedo reticularis over her legs. A muscle MRI of the LLs showed extensive fatty degeneration and loss of bulk of the thigh muscles, predominantly involving the posterior compartment but with significant asymmetry, as well

as abnormal intramuscular fatty changes within gastrocnemius medialis and soleus in the calves. STIR sequences also revealed patchy hyperintense signal abnormalities, particularly in the anterior compartment of both thighs and the anterior and posterior muscles of both calves (**Figure 1**). CK were 1002 IU/L. Pompe blood spot test resulted negative. Facioscapulohumeral dystrophy type 1 (FSHD1) genetic testing and methylation analysis for FSHD type 2 resulted within normal limits. Autoimmune screening revealed positive HMGCR antibodies with high titer (>200 CU). She started prednisolone (age 56 yo) 1 mg/kg once a day (OD). CK decreased to 426 IU/L but there was no improvement in MMT and she felt more unsteady during walking. Furthermore, she could not tolerate high dose of corticosteroids. Therefore, after few months she started intravenous immunoglobulin (IVIg) (2 mg/kg) and prednisolone was slowly tapered down to 0.25 mg/kg OD. When re-assessed after few months, she reported a better stability and there was an improvement in patient reported outcome (Health Assessment Questionnaire (HAQ) from 3 to 2.75 and MMT including knee extensor (L) from 3 to 4 and hip extension (R) from 2 to 3.

CASE 2. The second patient is a 67 yo man who started to complain weakness in his ULs. He first noticed this when trying to lift a suitcase above his head. Few months later he developed weakness in his LLs with difficulty walking and getting up from a chair. He did not report any myalgia, problem with speech or swallowing, or episode of myoglobinuria. He had no cardiac o respiratory symptoms. His past medical history was remarkable for a treated schistosomiasis when he was in Brazil. There was no positive family history for neuromuscular diseases. His first assessments included CK level which resulted elevated (4500 IU/L), an extensive infectious disease screening including HIV, HTLV, leptospirosis and hepatitis B and C that were all negative. He had an EMG test that showed some myopathic changes. Neurological examination showed mild proximal weakness in the ULs and moderate/severe in the LLs (Table 1). The remaining of neurological examination was unremarkable. There were no skin abnormalities. The patient underwent a muscle biopsy which revealed a lymphocyte infiltrate with angiocentric distribution without fibrinoid necrosis of the arterial wall and few necrotic fibres with inflammatory infiltrates, which was interpreted as possible vasculitis (**Figure 2**). In the suspicion of a vasculitis the patient underwent steroid and immunosuppressive therapy with three days of IVIg pulse methylprednisolone (then switched to prednisolone 40 mg od) and azathioprine 150 mg

od respectively, with a good clinical response and a complete recovery within three years from the onset of symptoms. Just before starting immunosuppressive therapy patient underwent a positron emission tomography (PET) that ruled out the occurrence of an associated neoplasm. After five years of therapy, azathioprine was stopped due to a persistent recovery of muscle strength and to a normalization of CK level. Given the atypical clinical presentation and the absence of other signs of vasculitis, the case was revaluated with further assessment including serological tests that revealed the presence of anti-HMGCR antibodies (186 CU). He has never been exposed to statin treatment.

DISCUSSION

IMNMs are a subgroup of inflammatory myopathies (IIMs) and they account for up to 19% of all IIMs; IMNMs are characterized by proximal muscle weakness of acute or subacute onset and high CK, and most patients have antibodies against signal recognition particle (SRP) or against HMGCR. Recognition of atypical manifestations is important to start appropriate treatment. In this paper we discuss two cases with either atypical clinical or pathological presentations. The first case, presented with a ten-year history of high CK followed by slowly progressive proximal weakness and scapular winging mimicking an inherited myopathy. She also had myotonic discharges reported in an EMG done externally. The clinical picture prompted initially to label the case as genetic and to perform several tests including genetic screening for LGMD, FSHD, DM1 and DM2. Of note, cases of anti-HMCR myopathy have been identified in a cohort of LGMD with negative genetic testing, with 35% of positive HMCR cases having scapular winging. [3] Brief myotonic discharges also are not specific for myotonic disorders and can be seen in other genetic and inflammatory myopathies. Our case further highlights the importance to reevaluate genetic myopathies not diagnosed by genetic testing. Clinical and radiological hints of an alternative diagnosis were the presence of skin rash and livedo reticularis, and a muscle MRI showing hyperintense STIR signal abnormalities, that could suggest an inflammatory process within the muscle. Extramuscular manifestations are considered rare in anti-HMGCR myopathy but skin involvement has been increasingly reported in several studies. [9] The absence of statin treatment prior to the symptoms should not refrain to test for HMGCR antibodies as a variable prevalence of statin exposure has been reported [5] with lower percentage in people with Asian background. There are speculations in

whether mushroom supplements, that are natural HMGCR inhibitors,[6] can trigger the autoimmune reaction and, of note, Case 1 was taking Reishi Mushrooms supplements. Despite the late treatment, disease progression was stopped with partial improvements.

The second case presented with slowly progressive weakness and atypical pathology that resembled the one you can find in vasculitis: necrotizing, non granulomatous inflammation of the perymisial vessels, associated with muscle atrophy, more common in medium and small vessels vasculitis.[7] The symmetric proximal involvement (instead of focal/multi-focal), the lack of systemic involvement, and the negative results at autoimmune serological screening have questioned the previous diagnosis of vasculitis, imposing a revaluation of the clinical case.

Typical pathology in IMNM is characterised by frequent necrotic fibres, usually with associated macrophage infiltrate (myophagocytosis), and endomysial capillary deposition of complement C5b-9 (or membrane attack complex).[8] The chronic inflammatory cell or lymphocytic cell response in the endomysium and MHC class I (HLA-ABC) upregulation in fibres can be variable, but are both relatively less prominent in comparison to other idiopathic inflammatory myopathies (e.g. dermatomyositis). However atypical pathology, such as perivascular inflammatory infiltrates, has been reported in anti-HMGCR myopathy. [8,9] The second case highlights the importance of anti-HMGCR antibodies screening in all cases with a suggestive clinical picture regardless the pathological features.

HMCR antibodies are considered highly specific and seem to have a pathogenic role likely through an activation of the complement cascade [5, 10]. HMCR antibodies can be used in association with clinical features to confirm a diagnosis of anti-HMGCR myopathy as suggested by a recent workshop on IMNM. [5] Our two cases further support this position, as well as screening of anti-HMGCR antidobodies in all cases with proximal weakness and high CK.

In our cases there was no association with cancer within three years of myositis onset. Malignancies risk is increased significantly in seronegative IMNM (approximately 8 folds compared to the general population)

and to a lesser extent anti-HMGCR myopathy (about 2 folds compared to the general population), whereas no increased risk is reported in anti-SRP positive patients [5].

In conclusion HMGCR myopathy can present with atypical clinical and pathological manifestations. Clinical revaluation of gene negative LGMDs and of atypical muscle inflammatory condition is paramount for the important therapeutic implications.

TABLES

Table 1. Manual Muscle Testing (MMT)

*Muscle tested (right/left)	Case 1	Case 2
Neck flexion	2	2
Neck extension	4	4
Shoulder abduction	2 / 2	4+ / 4+
Elbow flexion	4 / 3	5 / 5
Elbow extension	3 / 4-	5 / 5
Hip flexion	2 / 2	3 / 3
Hip extension	2/ 2	5 / 5
Knee flexion	3/ 3	5 / 5
Knee extension	2/ 3	5 / 5

*Only abnormal muscle are reported in the table. Score is based on Medical Research Council (MRC) scale.

KEYPOINTS

- Anti 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) myopathy can be misdiagnosed due to its slow progressive presentation resembling a limb girdle muscular dystrophy.
- HMGCR antibody testing is recommended in all cases with proximal weakness and high CK and in gene negative LGMDs.
- Patients with anti-HMGCR myopathy do not necessarily have an exposure to statins.
- Atypical findings at muscle biopsy can be observed in Anti-HMCR myopathy.

Contributors AB complied case reports and drafted the manuscript. AM provided histopathology images, reviewed, and edited the manuscript. SS provided neuroradiology images, reviewed, and edited the manuscript. MD collected clinical data of one case, critically reviewed the manuscript. MGH contributed to study concept and critically reviewed the manuscript. EB conceived and designed the study, reviewed, and edited the manuscript.

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Competing interest None to declare.

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FIGURE LEGENDS

Figure 1. Muscle MRI of the lower limbs of Case 1.

There is extensive intramuscular fatty change and loss of bulk of the thigh muscles, with conspicuous asymmetry and severe involvement of the hamstring muscles on the left. Intramuscular fatty degeneration is also demonstrated in the medial head of gastrocnemius on the right as well as soleus bilaterally. Patchy areas of associated high STIR signal are evident, particularly within the quadriceps muscles bilaterally, the posteromedial thigh muscles on the left, tibialis anterior and extensor digitorum longus on the right and the posterior calf muscles bilaterally.

Figure 2. Triceps muscle biopsy pathology of Case 2

Low magnification (x20) of the fixed muscle biopsy histology showing increased variation of fibre size with several atrophic fibres (without perifascicular distribution), some internal nuclei, moderately increased endomysial connective tissue and scattered necrotic fibres infiltrated by macrophages and foci of chronic inflammation in the endomysium and perimysium (A). High magnification (x50) histology of one of the foci of chronic inflammation which is centred around the blood vessel, with infiltration of the vessel wall and partial destruction of vessel wall suggestive of vasculitis, although there was no obvious fibrinoid necrosis of

224 the vessel wall (B). The lymphocytic infiltrate showed relatively less CD3+ T-lymphocytes (C) in comparison
225 to more prominent CD20+ B-lymphocytes (D). The possibility of lymphoma was excluded by specialist review.
226 Abbreviations: H&E – haematoxylin and eosin, CD- cluster of differentiation (immunohistochemistry marker)
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