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# Anti-HMGCR Autoantibodies in Juvenile Idiopathic Inflammatory Myopathies Identify a Rare but Clinically Important Subset of Patients

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**ABSTRACT. Objective.** We aimed to establish the prevalence and clinical associations of anti-HMG-CoA-reductase (anti-HMGCR) in a large UK cohort with juvenile myositis.

**Methods.** There were 381 patients investigated for anti-HMGCR using ELISA.

**Results.** Anti-HMGCR autoantibodies were detected in 4 patients (1%). These children had no or minimal rash and significant muscle disease. Muscle biopsies were considered distinctive, with widespread variation in fiber size, necrotic fibers, and chronic inflammatory cell infiltrates; all had prolonged elevation of creatine kinase and all ultimately received biologic therapies.

**Conclusion.** Anti-HMGCR in UK children with myositis are associated with severe disease that is poorly responsive to standard treatment. (J Rheumatol First Release February 15 2017; doi:10.3899/jrheum.160871)

**Key Indexing Terms:**

PEDIATRIC DERMATOMYOSITIS/POLYMYOSITIS      PEDIATRIC RHEUMATIC DISEASES  
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Necrotizing autoimmune myopathy (NAM) is a subgroup of the idiopathic inflammatory myopathies that is defined by common clinical and histopathological features. Patients present with high creatinine kinase (CK) levels and often profound weakness. On muscle biopsy, characteristic features include myofiber necrosis, minimal endomysial, and perivascular inflammatory infiltrate, and in some cases focal endomysial fibrosis<sup>1</sup>. Despite little or no muscle inflammation, NAM usually responds to immunomodulatory therapy, highlighting that this is an immune-mediated phenotype. It has been associated with 2 myositis-specific autoantibodies: antisignal recognition peptide (anti-SRP) and more recently anti-HMG-CoA-reductase (HMGCR).

Patients with anti-HMGCR-associated disease make up about 6% of adult idiopathic inflammatory myopathy cohorts<sup>2</sup>. In addition to NAM, anti-HMGCR antibodies are associated with statins, an intriguing finding given that HMGCR is the pharmacologic target of statins and is upregulated by statin use<sup>2</sup>. While statins are typically prescribed to adult patients, anti-HMGCR has been reported in patients with juvenile-onset NAM, but data are extremely limited<sup>3</sup>. Further, 40%–70% of adults with anti-HMGCR-associated NAM have no history of statin exposure, suggesting the presence of alternative disease triggers<sup>2,3</sup>. We aimed to establish the prevalence and clinical associations of anti-HMGCR in a large UK juvenile idiopathic inflammatory myositis (JIIM) cohort.

## MATERIALS AND METHODS

**Patients.** Serum samples and matched clinical data were obtained from 381 patients with JIIM recruited to the UK Juvenile Dermatomyositis Cohort and Biomarker Study described previously<sup>4</sup>. Ethical approval has been obtained (Northeast-York Research Ethics Committee 01/3/022). Parental consent and consent or age-appropriate assent was obtained in accordance with the Declaration of Helsinki.

**Autoantibody detection.** Immunoprecipitation of all samples was performed to determine the presence of myositis-specific and -associated autoantibodies, as previously described<sup>5,6</sup>. The presence of anti-HMGCR was determined in all samples by ELISA using recombinant antigen, as previously described<sup>7</sup>. Positive samples were confirmed by Western blotting (insufficient serum for patient 3). A further 48 juvenile healthy controls, 21 patients with juvenile systemic lupus erythematosus, and 27 muscular dystrophy were found to be negative for anti-HMGCR.

**Immunofluorescence.** Human epithelial cell line 2 indirect immunofluorescence was performed at 1:40 serum dilution for all anti-HMGCR-positive samples according to the manufacturer's instructions (Inova).

**Muscle biopsy.** Where tissue was available for reassessment, muscle biopsies were processed, stained, and scored (using the International Juvenile Dermatomyositis score tool) by an expert pediatric neuropathologist (TSJ) blinded to clinical data<sup>8,9</sup>.

## RESULTS

Anti-HMGCR autoantibodies were detected in 4 of the 381 patients (1%). None had a history of statin exposure. Anti-HMGCR autoantibodies were not found in conjunction with any other myositis-specific or -associated autoantibody. All patients with anti-HMGCR had a cytoplasmic staining pattern on immunofluorescence, and 2 had additional coarse speckled nuclear staining.

While numbers were insufficient for statistical analysis, based on Childhood Myositis Assessment Scores (CMAS) and the physician's global assessment of disease activity visual analog scores (PGA), children with anti-HMGCR were weaker and had greater disease activity (Table 1). Consistent with previous reports in juvenile-onset disease, CK at presentation was elevated in just 55.4% of patients<sup>10,11</sup>. Of those patients with an elevated CK, the median value was 1039 IU/l

(415–4115.25), compared with 15,500 (12,000–25,250) for those with anti-HMGCR.

**Patient 1.** A 4-year-old girl developed a relatively slow-onset muscular weakness with a lowest-ever CMAS of 28 (0–53), corresponding to a moderate degree of weakness<sup>12</sup>. CK at presentation was 12,000. She had no rash. Muscle biopsy was reported to be consistent with dermatomyositis (DM). Her highest-ever PGA was 4.8 out of 10. She responded to initial treatment with oral methotrexate (MTX) and steroids, but CK remained elevated. Her disease flared (lowest CMAS of 33 with no rash and peak CK of 7000) when MTX was stopped after a lengthy period of remission, following which treatment was restarted with subcutaneous MTX alongside oral prednisolone (PRED). She subsequently responded to infliximab (IFX) and entered remission.

**Patient 2.** A 13.8-year-old girl presented with periorbital puffiness and hyperpigmentation with progressive weakness over 1–2 months. Her CK was found to be 44,000. She received pulsed intravenous (IV) methylprednisolone with some improvement. Muscle biopsy revealed a destructive myopathy with inflammation and necrosis. One month later, her CMAS score was 0, indicating very severe weakness. She required nasogastric feeding. She received further pulses of IV methylprednisolone, cyclophosphamide (CYC), and subcutaneous MTX. Improvement in muscle power was extremely slow, leading to concern that there may be an additional underlying muscle disease. Further investigations, including magnetic resonance imaging (MRI), electromyography, and nerve conduction studies were consistent with myositis. This patient was subsequently treated with azathioprine, rituximab (RTX), and further CYC before entering remission with IFX.

**Patient 3.** An 11.8-year-old boy presented with a 6-month history of evolving proximal muscle weakness. CK was 19,000. Lack of any rash prompted consideration of muscular

*Table 1.* Summary of the characteristics of the 4 patients with anti-HMGCR autoantibodies compared with the remainder of the JIIM cohort. Patients with anti-HMGCR were weaker, had more severe disease, and had dramatically higher CK levels throughout their disease course.

Patient	Skin Rash	Sex	Age at Disease Onset, Yrs	Lowest CMAS, 0–53	Highest PGA, 0–10	CK at Onset, IU/l	CK at 6 Mos Postdiagnosis, IU/l	CK at 12 Mos Postdiagnosis, IU/l	Lowest CK, IU/l
1	No	Female	4	28	4.8	12,180	1275	278	231
2	Minimal	Female	13	0	8.3	44,002	404	13,065	251
3	No	Male	11	36	3	19,000	4702	4038	1527
4	Minimal	Female	9	2	9.5	12,662	2004	4638	2241
Median (IQR) for patients with anti-HMGCR			10.6 (7.5–12.3)	15 (1.8–30)	6.6 (4.4–8.6)	15,500 (12,000–25,250)	1057 (1057–2679)	4338 (3098–6744)	889 (246–1705.5)
Median (IQR) for all 381 patients			6.8 (3.9–10.1)	40 (24–47.3)	4 (2.2–7)	225 (78–1191.5) <sup>a</sup>	65 (41–106) <sup>b</sup>	88 (60–114) <sup>c</sup>	53 (37–82.5)

<sup>a</sup> Median for those with a raised CK 1039 (415.4–115.25). <sup>b</sup> CK available between 4 and 8 months for 60 patients. <sup>c</sup> CK available between 10 and 14 months for 48 patients. Anti-HMGCR: anti-HMG-CoA-reductase; JIIM: juvenile idiopathic inflammatory myositis; CK: creatine kinase; CMAS: Childhood Myositis Assessment Score, 0–53; PGA: physician's global assessment visual analog score of disease activity, 0–10; IQR: interquartile range.

dystrophy in the differential diagnosis, but electromyography and muscle biopsy were most consistent with an inflammatory myositis. While clinically this patient's myositis was not severe (CMAS 30–36, consistent with mild to moderate weakness and highest ever PGA 3), his CK has been persistently elevated. The patient had a poor response to MTX and ultimately responded clinically to RTX. CK remains > 1000.

**Patient 4.** A 9.4-year-old girl presented with a 4-month history of progressive muscle weakness. An inflammatory rash was confined to her antecubital fossae. CMAS was 2, consistent with severe weakness. At presentation, alanine aminotransferase was 600 U/l, lactate dehydrogenase 4000 U/l, and CK 12,000. A liver biopsy was normal. MRI showed widespread muscle edema. Following treatment with IV methylprednisolone, PRED, and subcutaneous MTX, CMAS remained between 5 and 30 (moderate to severe weakness) and muscle enzymes were persistently elevated with CK > 3000. Subsequent treatment included IFX, IV immunoglobulin (IG), mycophenolate mofetil (MMF), and

IV CYC. Her highest PGA was 9.5. The poor treatment response ultimately prompted diagnostic reassessment with muscle biopsy, skin biopsy, and weaning of all immunosuppression. The patient deteriorated without immunosuppression and PRED was reintroduced. Muscle biopsy showed necrosis and inflammation, and while not typical was felt to be consistent with myositis. Skin biopsy revealed inflammation in the dermis favoring DM. Following confirmation of anti-HMGCR status, the patient has been retreated with IVIG and MMF with a slow, but clear improvement.

**Muscle biopsy.** Muscle biopsy material was available for reassessment in 3 patients and the written report of the fourth biopsy was also available. Biopsy score components are shown in Table 2. The biopsies had similar and distinctive features with widespread variation in fiber size, regenerating fibers, necrotic fibers, and degenerating fibers. There were frequent fibers expressing immature isoforms of myosin and deposition of the membrane attack complex (MAC; C5b-C9) on the sarcolemma of many fibers. There were patchy dense

**Table 2.** Muscle biopsy score breakdown for patients with anti-HMGCR. Biopsy appearances were consistent with a destructive myopathy with high scores in the muscle fiber domain. All biopsies had evidence of inflammation. Muscle biopsies were analyzed using the JDM muscle biopsy score tool as previously described by Wedderburn, *et al*<sup>8,9</sup>.

Variables	Patient 1	Patient 2	Patient 3	Patient 4
Any treatment prebiopsy?	No	Yes	No	Yes
<b>Inflammatory domain</b>				
CD3+ endomysial infiltration, 0–2	2	No tissue available for histological reassessment. <sup>a</sup>	2	1
CD3+ perimysial infiltration, 0–2	0		1	0
CD3+ perivascular infiltration, 0–2	2		2	0
CD68+ endomysial infiltration, 0–2	2		2	1
CD68+ perimysial infiltration, 0–2	1		2	1
CD68+ perivascular infiltration, 0–2	2		2	1
Domain total	<b>9</b>		<b>11</b>	<b>4</b>
<b>Vascular domain</b>				
Capillary dropout, 0–1	0		0	0
Arterial abnormality, 0–1	0		0	0
Infarction, 0–1	0		0	0
Domain total	<b>0</b>		<b>0</b>	<b>0</b>
<b>Muscle fiber domain</b>				
MHC I over-expression, 0–1	1		1	0
Perifascicular atrophy	2		2	1
Neonatal myosin, 0–1	1		1	1
Fiber atrophy, 0–1	1		1	0
Regeneration/degeneration/necrosis perifascicular	2		2	2
Regeneration/degeneration/necrosis nonperifascicular	2		2	2
Internal myonuclei in nonbasophilic otherwise normal fibers, 0–1	1		1	1
Domain total	<b>10</b>		<b>10</b>	<b>7</b>
<b>Connective tissue domain</b>				
Any endomysial fibrosis, 0–1	1		1	1
Any perimysial fibrosis, 0–1	0		1	0
Domain total	<b>1</b>		<b>2</b>	<b>1</b>
Total score, 0–27	<b>20</b>		<b>23</b>	<b>12</b>
VAS severity, 0–10	<b>7</b>		<b>9</b>	<b>7</b>
MAC (C5-9b) staining of necrotic fibers	Yes		Yes	Yes

Significant data are in bold face. <sup>a</sup> Original muscle biopsy report comments on muscle fiber necrosis and inflammation. Biopsy findings were considered supportive of a diagnosis of a myositis in the correct clinical context, but not diagnostic on their own. Anti-HMGCR: anti-HMG-CoA-reductase; JDM: juvenile dermatomyositis; VAS: visual analog scale; MAC: membrane attack complex.

infiltrates of chronic inflammatory cells within the fascicles (Figure 1).

## DISCUSSION

Consistent with previous reports, patients with anti-HMGCR presented with either profound or insidious onset muscle weakness<sup>3</sup>. Unlike affected adults, however, half of our patients had cutaneous disease<sup>2,3</sup>. Lack of skin involvement is unusual in JIIM and minimal/absent rash contributed to the need to actively exclude alternative diagnoses in those with anti-HMGCR. Remarkably, all children with anti-HMGCR underwent muscle biopsy and 2 electromyography; these invasive procedures are not routinely used diagnostically in the United Kingdom for suspected JIIM, the majority of patients being diagnosed on the basis of clinical features plus laboratory and MRI results.

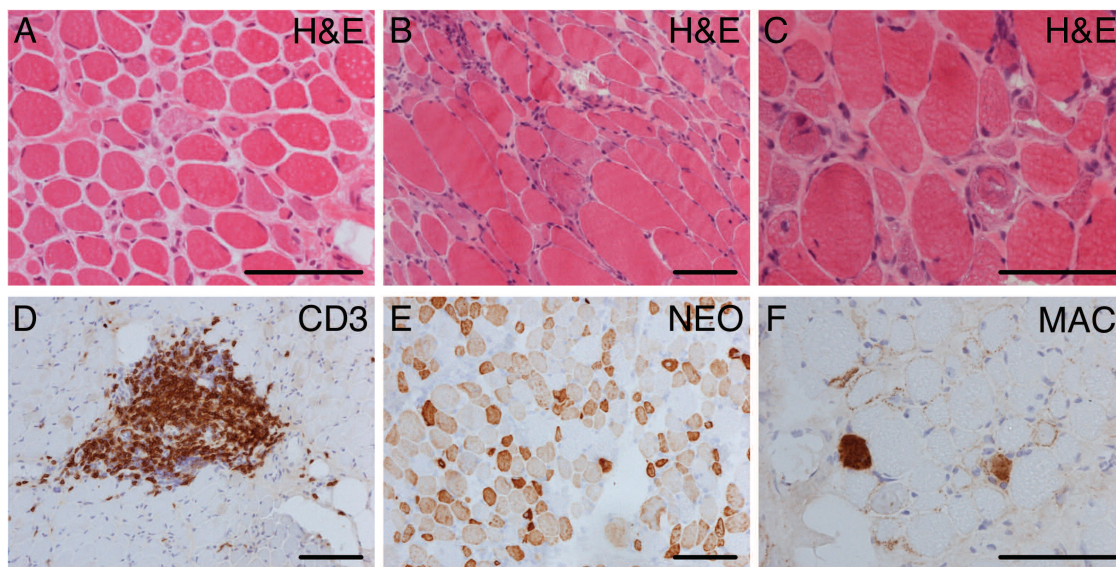
Muscle biopsies were distinctive and features included those previously reported by Allenbach, *et al*, with muscle fiber necrosis and degeneration/regeneration<sup>3</sup>. Contrary to previous reports of a pauciimmune necrotizing myopathy, however, there was evidence of inflammation in all 4 biopsies. JIIM muscle biopsies can display a wide range of changes that may not necessarily be considered “typical” of DM. All patients with anti-HMGCR had an abnormal muscle biopsy with a pattern of histological features that, while not classic for DM, was consistent and distinctive. Recognition of this phenotype is important to ensure that muscle biopsy can provide the maximum level of diagnostic accuracy. Earlier recognition of anti-HMGCR autoantibodies may aid

diagnosis, prevent potentially unnecessary investigations, and facilitate rapid treatment escalation in the absence of a good response to standard therapy. Mammen, *et al* confirmed the absence of anti-HMGCR in patients with genetic muscle diseases that often form the differential diagnosis<sup>13</sup>.

While rare, anti-HMGCR identify an important group of JIIM patients with severe disease necessitating aggressive treatment. In the United Kingdom, strict guidelines exist for funding biologic treatments, and it is remarkable that all 4 cases ultimately received this; in comparison with just 20.7% of the total cohort. We noted similarities in disease presentation to those patients with anti-SRP autoantibodies, in whom muscle weakness is also greater and cutaneous disease less common. Less than one-third of patients with anti-SRP, however, required treatment with a biologic drug and/or IV CYC. It is interesting to note that while statin-exposed adult patients with anti-HMGCR are reported to respond dramatically to treatment, statin-naïve patients have been noted to be younger, and may be refractory to immunosuppressive therapy<sup>2,14</sup>. Younger, statin-naïve patients with anti-HMGCR may represent a separate subgroup of patients who are less responsive to treatment. These data suggest that in those children with anti-HMGCR and severe weakness, there is an argument for the early use of aggressive immunosuppression.

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**Figure 1.** Muscle biopsy features of patients with anti-HMGCR autoantibodies. All 3 biopsies showed a similar distinctive pattern of pathology characterized by widespread variation in fiber size, regenerating fibers, necrotic fibers, and degenerating fibers with vacuoles and ill-defined eosinophilic granules (A–C). The abnormal fibers were present throughout all the fascicles with no perifascicular accentuation. There were patchy dense infiltrates of chronic inflammatory cells within the fascicles. The infiltrate showed a prominent component made up of T lymphocytes (D; CD3). There were fewer inflammatory cells in the perimysium. In all 3 cases, many of the fibers expressed a developmental isoform of myosin (E; NEO). Staining for the MAC (C5b-9) of the complement cascade highlighted necrotic fibers, but also outlined the sarcolemma of many of the non-necrotic fibers (F). Capillary deposition of MAC was not seen. Scale bars-100  $\mu$ m. Anti-HMGCR: anti-HMG-CoA-reductase; NEO: neonatal myosin; MAC: membrane attack complex.

## APPENDIX 1.

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