Anti-HMGCR autoantibodies in juvenile idiopathic inflammatory myopathies identify a rare but clinically important subset of patients.

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Abstract

Objectives: We aimed to establish the prevalence and clinical associations of anti-HMGCR in a large UK cohort with juvenile myositis.

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

Results: Anti-HMGCR autoantibodies were detected in four patients (1%). These children had no or minimal skin rash and significant muscle disease. Muscle biopsies were considered distinctive, with widespread variation in fibre size, necrotic fibres and chronic inflammatory cell infiltrates. All had prolonged elevation of CK 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.

Key words

Paediatric dermatomyositis/polymyositis

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Anti-HMGCR in Juvenile myositis

Introduction

Necrotising 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 levels and often profound weakness. On muscle biopsy, characteristic features include myofibre necrosis, minimal endomysial and perivascular inflammatory infiltrate, and in some cases focal endomysial fibrosis.(1) 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 two myositis specific autoantibodies; anti-SRP and more recently anti-HMG-CoA-reductase (HMGCR).

Patients with anti-HMGCR associated disease make up approximately 6% of adult idiopathic inflammatory myopathy cohorts.(2) 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.(2) Whilst statins are typically prescribed to adult patients, anti-HMGCR has been reported in patients with juvenile-onset NAM but data is extremely limited.(3) Furthermore, 40-70% of adults with anti-HMGCR associated NAM have no history of statin exposure suggesting the presence of alternative disease triggers. (2, 3) We aimed to establish the prevalence and clinical associations of anti-HMGCR in a large UK Juvenile Idiopathic Inflammatory Myositis (JIIM) cohort.

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.(4) 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. (5, 6) The presence of anti-HMGCR was determined in all samples by ELISA using recombinant antigen, as previously described. (7) Positive samples were confirmed by western blotting (insufficient serum for patient 3). A further 48 juvenile healthy controls, 21 juvenile SLE and 27 muscular dystrophy patients were found to be negative for anti-HMGCR.

Immunofluorescence

HEp2 Indirect immunofluorescence was performed at 1:40 serum dilution for all anti-HMGCR positive samples according to manufacturer's instructions (Inova).

Muscle biopsy

Where tissue was available for re-assessment, muscle biopsies were processed, stained and scored (using the International JDM score tool) by an expert paediatric neuropathologist (TSJ) blinded to clinical data.(8, 9)

Results

Anti-HMGCR autoantibodies were detected in four of the 381 patients (1%). None had a history of statin exposure. They 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, two had additional coarse speckled nuclear staining.

Whilst numbers were insufficient for statistical analysis, based on Childhood Myositis Assessment Scores (CMAS) and Physician Global assessment of disease activity visual analogue 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.(10, 11) Of those patients with an elevated CK the median value was 1039 IU/L (415-4115.25), compared to 15500 (12000-25,250) 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.(12) CK at presentation was 12000. She had no rash. Muscle biopsy was reported to be consistent with dermatomyositis. Her highest ever PGA was 4.8 out of 10. She responded to initial treatment with oral methotrexate and steroids but CK remained elevated. Her disease flared (lowest CMAS of 33 with no rash and peak CK of 7000) when methotrexate was stopped after a lengthy period of remission, following which treatment was restarted with subcutaneous methotrexate alongside oral prednisolone. She subsequently responded to infliximab 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 44000. She received pulsed 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 and subcutaneous methotrexate. Improvement in muscle power was extremely slow, leading to concern that there may be an additional underlying muscle disease. Further investigations, including MRI, electromyography and nerve conduction studies were consistent with

myositis. This patient was subsequently treated with azathioprine, rituximab and further cyclophosphamide before entering remission with infliximab.

Patient 3

An 11.8 year old boy presented with a six month history of evolving proximal muscle weakness. CK was 19000. Lack of any skin rash prompted consideration of muscular dystrophy in the differential diagnosis but electromyography and muscle biopsy were most consistent with an inflammatory myositis. Whilst clinically this patient's myositis was not severe, (CMAS 30-36 consistent with mild-moderate weakness and highest ever PGA 3) his CK has been persistently elevated. The patient had a poor response to methotrexate and ultimately responded clinically to rituximab. CK remains >1000.

Patient 4

A 9.4 year old girl presented with a four month history of progressive muscle weakness. An inflammatory rash was confined to her antecubital fossae. CMAS was 2, consistent with severe weakness. At presentation ALT was 600 U/L, LDH 4000 U/L and CK 12000. A liver biopsy was normal. MRI showed widespread muscle oedema. Following treatment with IV methylprednisolone, prednisolone and subcutaneous methotrexate, CMAS remained between 5 and 30 (moderate-severe weakness) and muscle enzymes were persistently elevated with CK >3000. Subsequent treatment included infliximab, IV immunoglobulin, mycophenolate mofetil and IV cyclophosphamide. 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 prednisolone was reintroduced. Muscle biopsy showed necrosis and inflammation and whilst not typical was felt to be consistent with myositis. Skin biopsy revealed inflammation in the dermis favouring dermatomyositis. Following

confirmation of anti-HMGCR status the patient has been re-treated with IV immunoglobulin and mycophenolate mofetil with a slow but clear improvement.

Muscle biopsy

Muscle biopsy material was available for reassessment in three patients and the written report of the fourth biopsy was also available. Biopsy score components are shown in Table 2. The biopsies were felt have similar and distinctive feature with widespread variation in fibre size, regenerating fibres, necrotic fibres and degenerating fibres. There were frequent fibres expressing immature isoforms of myosin and deposition of the membrane attack complex (MAC, C5b-C9) on the sarcolemma of many fibres. There were patchy dense 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.(3) Unlike affected adults however, half of our patients had cutaneous disease.(2, 3) 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 two electromyography; these invasive procedures are not routinely used diagnostically in the UK 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 fibre necrosis and degeneration/regeneration.(3) Contrary to previous reports of a pauci-immune necrotising myopathy, however, there was evidence of inflammation in all four biopsies. JIIM muscle biopsies can display a wide range of changes that may not necessarily be considered 'typical' of dermatomyositis. All patients with anti-HMGCR had an abnormal muscle

biopsy with a pattern of histological features that whilst not classical for dermatomyositis was consistent and distinctive. Recognition of this phenotype is important to ensure 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.* recently confirmed the absence of anti-HMGCR in patients with genetic muscle diseases that often form the differential diagnosis.(13)

Whilst rare anti-HMGCR identify an important group of JIIM patients with severe disease necessitating aggressive treatment. In the UK strict guidelines exist for funding biologic treatments and it is remarkable that all four cases ultimately received this; in comparison to 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 cyclophosphamide. 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.(2, 14) Younger, statin-naïve patients with anti-HMGCR may represent a separate subgroup of patients who are less treatment responsive. 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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Tables and Figure Legends

Table 1. Summary of the characteristics of the four patients with anti-HMGCR autoantibodies compared to the reminder of the JIIM cohort

Patients with anti-HMGCR were weaker, had more severe disease and had dramatically higher CK levels both at disease presentation and for the lowest ever recorded value.

Table 2. International JDM score tool assessment of muscle biopsies form patients with anti-HMGCR

Biopsy appearances were consistent with a destructive myopathy with high scores in the muscle fibre domain. All biopsies had evidence of inflammation.

Figure 1. Muscle Biopsy features of patients with anti-HMGCR autoantibodies

All three biopsies showed a similar distinctive pattern of pathology characterised by widespread variation in fibre size, regenerating fibres, necrotic fibres and degenerating fibres with vacuoles and ill-defined eosinophilic granules (A-C). The abnormal fibres were present throughout all the fascicles with no peri-fascicular 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 three cases, many of the fibres expressed a developmental isoform of myosin (E-Neonatal myosin). Staining for the membrane attack complex (MAC)(C5b-9) of the complement cascade highlighted necrotic fibres but also outlined the sarcolemma of many of the non-necrotic fibres (F). Capillary deposition of MAC was not seen. Scale bars-100μm

Tables

Anti-HMGCR autoantibodies in juvenile idiopathic inflammatory myopathies identify a rare but clinically important subset of patients.

Table 1. Summary of the characteristics of the four patients with anti-HMGCR autoantibodies compared to the reminder 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	Gender	Age at disease onset (years)	Lowest CMAS (0-53)	Highest PGA (0-10)	CK at onset (IU/L)	CK at 6 months post-diagnosis (IU/L)	CK at 12 months post-diagnosis (IU/L)	Lowest CK (IU/L)
1	No	Female	4	28	4.8	12,180	1,275	278	231
2	Minimal	Female	13	0	8.3	44,002	404	13,065	251
3	No	Male	11	36	3	19,000	4,702	4,038	1,527
4	Minimal	Female	9	2	9.5	12,662	2,004	4,638	2,241
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)	1,057 (1,057-2,679)	4,338 (3,098-6,744)	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 (78-1,191.5)[a]	65 (41-106)[b]	88 (60-114)[c]	56 (37-82.5)

a. Median for those with a raised CK 1,039 (415-4,115.25)
b. CK available between 4 and 8 months for 60 patients
c. CK available between 10 and 14 months for 48 patients

CMAS: Childhood myositis Assessment Score (0-53)
PGA: Physician Global Assessment visual analogue score of disease activity (0-10)

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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 fibre domain. All biopsies had evidence of inflammation. Muscle biopsies were analysed using the JDM muscle biopsy score tool as previously described by *Wedderburn et al.* (8,9)

		Patient 1	**Patient 2**	**Patient 3**	**Patient 4**
Any treatment pre-biopsy?		No	Yes	No	Yes
Inflammatory domain	CD3+ endomysial infiltration (0-2)	2	No tissue available for histological re-assessment. [a]	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	**9**		**11**	**4**
Vascular domain	Capillary dropout (0-1)	0		0	0
	Arterial abnormality (0-1)	0		0	0
	Infarction (0-1)	0		0	0
	Domain total	**0**		**0**	**0**
Muscl	MHC I over-expression (0-1)	1		1	0

	Perifascicular atrophy	2		2	1
	Neonatal myosin (0-1)	1		1	1
	Fibre atrophy (0-1)	1		1	0
	Regeneration/degeneration/necrosis perifascicular	2		2	2
	Regeneration/degeneration/necrosis non-perifascicular	2		2	2
	Internal myonuclei in non-basophilic otherwise normal fibres (0-1)	1		1	1
	Domain total	**10**		**10**	**7**
Connective tissue domain	Any endomysial fibrosis (0-1)	1		1	1
	Any perimysial fibrosis (0-1)	0		1	0
	Domain total	**1**		**2**	**1**
Total score (0-27)		**20**		**23**	**12**
VAS severity (0-10)		**7**		**9**	**7**
MAC (C5-9b) staining of necrotic fibres		Yes		Yes	Yes

a. Original muscle biopsy report comments on muscle fibre necrosis and inflammation. Biopsy findings were felt to be supportive of a diagnosis of a myositis in the correct clinical context but not diagnostic on their own.

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Figure 1. Muscle Biopsy features of patients with anti-HMGCR autoantibodies

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