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BRIEF REPORT

Association of Anti–3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase Autoantibodies With DRB1*07:01 and Severe Myositis in Juvenile Myositis Patients

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Objective. **Autoantibodies recognizing 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) are associated with statin exposure, the HLA allele DRB1*11:01, and necrotizing muscle biopsies in adult myositis patients. The aim of this study was to characterize the features of juvenile anti-HMGCR-positive myositis patients.**

Methods. **The sera of 440 juvenile myositis patients were screened for anti-HMGCR autoantibodies. Demographic and clinical features, responses to therapy, and HLA alleles were assessed. The features of anti-HMGCR-positive patients were compared to those of previously described adult patients with this autoantibody and to children with other myositis-specific autoantibodies (MSAs).**

Results. **Five of 440 patients (1.1%) were anti-HMGCR-positive; none had taken statin medications. Three patients had rashes characteristic of juvenile dermatomyositis and 2 patients had immune-mediated necrotizing myopathies. The median highest creatine kinase (CK) level of anti-HMGCR-positive subjects was 17,000 IU/liter. All patients had severe proximal muscle weakness, distal weakness, muscle atrophy, joint contractures, and arthralgias, which were all more prevalent in HMGCR-positive subjects compared to MSA-negative patients or those with other MSAs. Anti-HMGCR-positive patients had only partial responses to multiple immunosuppressive medications, and their disease often took a chronic course. The DRB1*07:01 allele was present in all 5 patients, compared to 26.25% of healthy controls (corrected $P = 0.01$); none of the 5 juvenile patients had DRB1*11:01.**

Conclusion. **Compared to children with other MSAs, muscle disease appears to be more severe in those with anti-HMGCR autoantibodies. Like adults, children with anti-HMGCR autoantibodies have severe weakness and high CK levels. In contrast to adults, in anti-HMGCR-positive children, there is a strong association with HLA–DRB1*07:01.**

Introduction

The autoimmune myopathies include adult and juvenile forms of dermatomyositis (DM), polymyositis (PM), and myositis overlapping with another connective tissue disease (CTM) (1). These patients typically present with proximal weakness, elevated serum muscle enzyme levels, and an abnormal muscle biopsy, and may have one of several different myositis-specific autoantibodies (MSAs). Each of the

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Significance & Innovations

- Autoantibodies to 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) are present in a rare but distinct subgroup of patients with juvenile myositis, and, as in adult myositis, they are associated with severe weakness and high creatine kinase levels.
- Children with anti-HMGCR autoantibodies have an associated allele, DRB1*07:01, which differs from the HLA–DRB1*11:01 allele associated with adult patients with anti-HMGCR autoantibodies.
- Unlike adults, these children do not have a documented prior exposure to statin medications.

MSAs is associated with distinct clinical features that may be useful for characterizing and classifying patients with myositis. The same autoantibody phenotypes are often present in juvenile and adult patients; however, a given autoantibody can be associated with different clinical features in adults compared to children. For example, autoantibodies recognizing p155/140 (transcription intermediary factor 1) are highly associated with malignancy in adults, but not in children (2).

It was recently reported by Mammen et al (3) that autoantibodies recognizing 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) are found in adult myositis patients with immune-mediated necrotizing myopathy (IMNM) and, in two-thirds of patients, a history of prior statin exposure (3). In a sera screening of 750 adult myositis patients (3), 45 (6%) were positive for anti-HMGCR autoantibodies. Of these, 80% had a predominantly necrotizing muscle biopsy consistent with IMNM, and the remaining 20% had significant inflammatory infiltrates consistent with a diagnosis of PM using the Bohan and Peter criteria (4). No patients had typical DM rashes (3). Interestingly, 2 of the 45 adult myositis patients (4%) first presented with weakness as children (3).

Since our initial description (3), 4 additional groups have systematically screened cohorts of adult myositis patients for anti-HMGCR autoantibodies (5–8). These 4 studies included a total of 1,289 myositis subjects, and 102 (8%) tested positive for anti-HMGCR autoantibodies. Of the anti-HMGCR-positive subjects, 85 (83%) had IMNM or PM, 9 (9%) had DM, and 8 (8%) had inclusion body myositis. Although none of these reports said that the onset of weakness was in childhood, one series of 45 adult myositis patients with anti-HMGCR autoantibodies included 8 patients who first experienced weakness in childhood (9).

To date, the prevalence of anti-HMGCR autoantibodies in juvenile myositis patients and the clinical characteristics of children with these autoantibodies have not been described. Therefore, we screened for anti-HMGCR autoantibodies in a large cohort of well-characterized juvenile myositis patients, and examined the clinical and immunogenetic associations, as well as responses to therapy and outcomes.

Dr. Mammen holds a patent on an anti–3-hydroxy-3-methylglutaryl-coenzyme A test that was licensed by Johns Hopkins University to Inova Diagnostics.

Drs. Kishi and Rider contributed equally to this work.

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Patients and methods

Patient populations. This study included 440 patients from the US and Canada who had probable or definite juvenile DM (n = 360), juvenile PM (n = 29), or juvenile CTM (n = 51) using the Bohan and Peter criteria (4) and had a serum sample available for HMGCR autoantibody testing; 55 patients were excluded due to the unavailability of serum. All patients were enrolled in investigational review board–approved studies of myositis from 1990 to 2016, as previously described (10), and all gave informed consent. A standardized physician questionnaire captured demographics, clinical features, laboratory features, environmental exposures at illness onset or diagnosis, as well as therapeutic usage and responses. The severity of illness at onset, up to the time of diagnosis, was graded on a 4-point Likert scale (ranging from mild to extremely severe disease activity) by the enrolling physician (10). The data for the majority of patients were verified via medical records review (10,11). HLA typing of DRB1 and DQA1 alleles was performed as previously described (12) and compared to 560 race-matched healthy control subjects. We also pooled data regarding autoantibody prevalence, statin exposure, and myositis subtype from published studies of adult myositis patients in which systematic screening for anti-HMGCR autoantibodies was performed in all myositis subjects in the cohort (3,5–8) (Table 1).

Myositis autoantibody assays. Patient sera obtained at the time of enrollment were tested for myositis autoantibodies by validated methods, including protein and RNA immunoprecipitation (IP) using radiolabeled HeLa or K562 cell extracts and double immunodiffusion (10). For anti-p155/140, anti-MJ, and anti–melanoma-differentiation-associated gene 5 autoantibodies, serum samples were screened by IP, with confirmation testing by IP-immunoblotting (10). Screening for anti-HMGCR autoantibodies was performed on all sera by enzyme-linked immunosorbent assay (ELISA) as previously described (3). ELISA-positive samples were confirmed by immunoprecipitation using ^{35}S-methionine-labeled HMGCR protein produced by in vitro transcription and translation (3).

Statistics. Analyses were performed using JMP (version 11.0.0, SAS Institute) and were considered exploratory. Median values and interquartile ranges or means and SDs were obtained for descriptive statistics and for nominal and ordinal variables. HLA data were corrected for multiple comparisons using the Bonferroni method (P_{corr}).

Table 1. Comparison of frequency of anti-HMGCR autoantibodies and statin exposure in adult myositis and juvenile myositis cohorts*

Myositis cohort (ref.)	No. patients	HMGCR Ab+	DM HMGCR Ab+/all HMGCR Ab+	DM HMGCR Ab+/all DM	PM*HMGCR Ab+/all HMGCR Ab+	PM*HMGCRAb+/ all PM	HMGCR+ taking statins/ all HMGCR Ab+
Mammen et al, 2011 (3)	750	45 (6.0)	0/45 (0.0)	0/228 (0.0)	45/45 (100.0)	45/204 (22.1)	30/45 (66.7)
Limaye et al, 2015 (6)	207	19 (9.2)	1/19 (5.3)	1/26 (3.8)	11/19 (53.1)	11/110 (10.0)	16/19 (84.2)
Ge et al, 2015 (8)	405	22 (5.4)	8/22 (36.4)	8/288 (2.8)	14/22 (28.9)	14/117 (12.0)	3/22 (13.6)
Klein et al, 2015 (7)	217	15 (6.9)	0/15(0.0)	0/90 (0.0)	15/15 (100.0)	15/92 (16.3)	15/15 (100.0)
Watanabe et al, 2016 (5)	460	46 (10.0)	0/46 (0.0)	0/56 (0.0)	46/46 (100.0)	46/280 (16.4)	8/46 (17.4)
Adult IIM total†	2,039	147 (7.2)‡	9/147 (6.1)§	9/688 (1.3)	131/147 (89.1)¶	131/803 (16.3)	72/147 (49.0)
Juvenile IIM (this study)#	440	5 (1.1)‡	3/5 (60.0)§	3/404 (0.7)	2/5 (40.0)¶	2/36 (5.6)	0/5 (0.0)

* Values are the number (%) unless otherwise indicated. HMGCR = 3-hydroxy-3-methylglutaryl-coenzyme A reductase; Ab = autoantibody; DM = dermatomyositis; PM = polymyositis; IIM = idiopathic inflammatory myopathy.
† Includes PM, immune-mediated necrotizing myopathy, and nonspecific myositis in adults. *P* values are comparing the adult IIM total to the juvenile IIM present study data.
‡ $P < 0.0001$.
§ $P = 0.004$.
¶ $P = 0.014$.
# Includes 7 with overlap myositis who have juvenile PM, whereas the juvenile DM patients also include 39 overlap myositis patients with juvenile DM. *P* values are comparing the adult IIM total to the juvenile IIM present study data.

Results

Comparing anti–HMGCR-associated myositis in children and adults. Of 440 screened juvenile myositis serum samples, 5 (1.1%) were positive for anti-HMGCR autoantibodies. In contrast, the prevalence of this autoantibody in 5 pooled adult myositis cohorts was significantly higher, at 7% ($P < 0.0001$) (Table 1) (3,5–8).

The demographic features of the juvenile myositis patients are included in Table 2. The median age at diagnosis was 8.1 years (range 6–15 years) with a median delay to diagnosis of 3.3 months. Three were female (60%), 3 were white, 1 was African American, and 1 was white and Hispanic. None had a common environmental exposure identified within 6 months of illness onset, including infections, medications, immunizations, stressful life events, or any other identified exposure. No patient had a history of receiving statins. In contrast, adult anti-HMGCR patients more frequently presented with a history of pharmacologic statin exposure (49% in adults versus 0% in children; $P = 0.06$) (Table 1).

The juvenile anti-HMGCR-positive cohort included 3 with juvenile DM (0.8% of juvenile DM cases), 1 with juvenile PM with no characteristic rashes of juvenile DM (3.4% of juvenile PM cases), and 1 with juvenile CTM (2.0% of juvenile CTM cases) who had myositis in association with linear scleroderma. The diagnosis of juvenile DM was based on the presence of Gottron's papules and heliotrope rash, proximal weakness, and elevated serum creatine kinase (CK) levels (ranging from 435 to 30,300 IU/liter); muscle biopsies were not performed. The other 2 patients showed clinical features of IMNM, 1 in association with linear scleroderma, based on the presence of proximal weakness, serum CK levels of ≥17,000 IU/liter, and muscle biopsies revealing prominent myofiber necrosis with minimal inflammation (additional details below), and no characteristic rashes. Although more children than adults with anti-HMGCR autoantibodies had characteristic DM rashes (60% versus 6%, respectively; $P = 0.004$) (Table 1), there was no difference in the prevalence of anti-HMGCR autoantibodies between the pooled adult DM and juvenile DM cohorts (1.3% versus 0.7%).

Laboratory investigations revealed that 2 anti-HGMCR-positive juvenile DM patients had positive antinuclear antibodies titers; one of these also had anti-p155/140 autoantibodies, and the other tested positive for anti-U1-ribonucleoprotein and anti-Ro autoantibodies. HLA typing showed no patient having DRB1*11:01, the class II HLA allele linked to anti-HMGCR in adult myositis (13). Instead, the DRB1*07:01–DQA1*02:01 haplotype was present in 4 pediatric patients with anti-HMGCR autoantibodies ($P = 0.0035$ versus controls), and the DRB1*07:01 allele was present alone in 1 patient ($P_{corr} = 0.01$ for the DRB1*07:01 allele in anti-HMGCR subjects versus controls).

Muscle biopsies were performed in the 2 patients without rashes. Myofiber necrosis, degeneration, and regeneration were the most prominent histologic features (see Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23113/abstract); focal perivascular inflammation was also present. Macrophages appeared to be the most common infiltrating cell type, present in perivascular regions and around degenerating myofibers. Although CD4+ and CD8+ lymphocytes were scattered within the endomysium, these did not surround and invade non-necrotic muscle fibers as classically described in PM. Perifascicular atrophy, the hallmark feature of DM, was not noted. Major histocompatibility complex class I antigen was strongly positive on myofibers. Three patients who underwent evaluation by magnetic resonance imaging had T2- or short T1 inversion recovery hyperintensity present diffusely and bilaterally in the thigh muscles.

Patients with anti-HMGCR versus other MSAs in juvenile myositis. Next, we compared the demographic and clinical features of children with anti-HMGCR autoantibodies to juvenile myositis patients with other myositis

Table 2. Demographic and clinical features and outcomes of juvenile myositis patients with anti-HMGCR autoantibodies compared to those with other myositis autoantibodies*

Feature	Anti-HMGCR (n = 5)	Anti-SRP (n = 8)	Anti-synthetase (n = 16)	Anti-p155/140 (n = 142)	Anti-MJ (n = 111)	MSA and MAA negative (n = 62)
Age at diagnosis, median (IQR) years	8.1 (7.1–12.0)	14.9 (10.7–16.0)	14.0 (8.2–16.6)	7.2 (4.4–11.0)	6.3 (4.5–10.3)	8.4 (5.4–11.5)
Delay in diagnosis, median (IQR) months	3.3 (2.8–4.6)	1.9 (1.1–5.4)	6.9 (1.5–13.0)	5.0 (2.0–10.0)	3.0 (1.0–7.0)	4.0 (2.0–12.0)
Female	3 (60.0)	5 (62.5)	13 (81.3)	115 (81.0)	76 (68.5)	37 (59.7)
Race						
White	3 (60.0)	1 (14.3)	9 (56.3)	115 (81.0)	79 (71.2)	41 (66.1)
African American	1 (20.0)	6 (85.7)	5 (31.3)	6 (4.2)	17 (15.3)	7 (11.3)
Other	1 (20.0)	0 (0)	2 (12.5)	21 (14.8)	15 (13.5)	14 (22.6)
Disease onset speed						
Insidious (>6 months)	0 (0)	2 (28.6)	10 (62.5)	60 (42.6)	33 (30.0)	24 (40.7)
Slow (3–6 months)	2 (40.0)	1 (14.3)	2 (12.5)	32 (22.7)	27 (24.6)	21 (35.6)
Subacute (1–3 months)	3 (60.0)	4 (57.1)	0 (0)	33 (23.4)	31 (28.2)	10 (17.0)
Onset severity						
Mild/moderate	0 (0)	0 (0)	8 (50.0)	114 (80.3)	73 (66.4)	42 (71.2)
Severe/very severe	5 (100)	7 (100)	8 (50.0)	28 (19.7)	37 (33.6)	18 (28.8)
Disease course						
Chronic	4 (80.0)	6 (75.0)	10 (62.5)	76 (53.5)	41 (36.9)	22 (35.5)
Polycyclic	1 (20.0)	0 (0)	2 (12.5)	22 (15.5)	26 (23.4)	14 (22.6)
Monocyclic	0 (0)	0 (0)	2 (12.5)	14 (9.9)	26 (23.4)	16 (25.8)
Undefined	0 (0)	2 (25.0)	2 (12.5)	30 (21.1)	18 (16.2)	10 (16.1)
Outcome						
Ever hospitalized	5 (100)	8 (100)	11 (68.8)	66 (48.9)	68 (64.2)	28 (50.0)
Calcinosis	1 (20.0)	0 (0)	1 (6.3)	41 (28.9)	40 (36.0)	24 (38.7)
Wheelchair use	2 (40.0)	6 (75.0)	3 (20.0)	16 (11.5)	27 (25.2)	4 (7.0)
Devices for mobility	0 (0)	5 (71.4)	2 (13.3)	12 (8.6)	12 (11.2)	1 (1.8)
Mortality	0 (0)	0 (0)	2 (12.5)	3 (2.1)	2 (1.8)	3 (4.8)

* Values are the number (%) unless otherwise indicated. HMGCR = 3-hydroxy-3-methylglutaryl-coenzyme A reductase; SRP = signal recognition particle; MSA = myositis-specific autoantibodies; MAA = myositis-associated autoantibodies; IQR = interquartile range.

autoantibodies, including 8 patients with anti–signal recognition particle (SRP), 16 with anti-synthetases, 142 with anti-p155/140, and 111 with anti-MJ autoantibodies (Table 2 and Table 3). An additional group of 62 myositis patients, who were negative for known MSAs and myositis-associated autoantibodies (MAAs), was also included.

Compared to anti-SRP-positive patients, anti-HMGCR subjects were younger at disease onset (8.1 versus 14.9 years) and were more frequently white (60% versus 14%), although these differences did not reach statistical significance (Table 2). Those with anti-synthetases, anti-p155/140, anti-MJ, and no MSAs/MAAs all had ages of onset and racial distributions similar to those of patients with anti-HMGCR. Patients with anti-synthetase autoantibodies had a more insidious illness presentation than those with HMGCR autoantibodies. While all anti-HMGCR patients had severe or very severe disease at onset, only 22–50% of those with anti-synthetases, anti-p155/140, anti-MJ, or no MSAs/MAAs presented as severely; anti-SRP patients had a similarly high prevalence of severe disease at onset.

All of the anti-HMGCR-positive patients had distal weakness in the wrist and ankle flexors and extensors, falling episodes, muscle atrophy, fatigue, and were hospitalized (Table 3). All were American College of Rheumatology functional class IV at diagnosis, and 2 required a wheelchair. All developed arthralgias and joint contractures. Three patients each developed dysphagia and gastroesophageal reflux, and 4 developed weight loss, which was more frequent than in anti-MJ and autoantibody-negative patients.

Both anti-HMGCR and anti-SRP patients had more frequent distal weakness (100%), falling episodes (100%), and muscle atrophy (86–100%) than patients with other MSAs or no autoantibodies (less than 50% for each of these features). Both groups had a similar frequency of myalgias (40–43%), and patients with anti-SRP were more likely to have Raynaud's phenomenon (57% versus 0%). Unlike those with anti-SRP autoantibodies, the anti-HMGCR-positive patients had low rates of electrocardiogram and/or echocardiogram abnormalities (20% versus 57%); similarly low rates of cardiac abnormalities were present in those with anti-synthetases, anti-p155/140, anti-MJ, or no MSAs/MAAs (10–22%). Interstitial lung disease was absent or uncommon in all of the autoantibody groups studied except the anti-synthetase group (69%).

The treatment and clinical course of children with anti-HMGCR-associated myositis. All juvenile anti-HMGCR-positive patients were treated with oral prednisone, along with an average of 7.2 (range 1–12) additional immunosuppressive medications during a mean followup period of 31.2 months (range 19.2–157 months). They received an average of 2.4 immunosuppressive medications

Table 3. Clinical features of juvenile myositis patients with anti-HMGCR autoantibodies compared to those with other myositis autoantibodies*

Feature	Anti-HMGCR (n = 5)	Anti-SRP (n = 8)	Anti-synthetase (n = 16)	Anti-p155/140 (n = 142)	Anti-MJ (n = 111)	MSA and MAA negative (n = 62)
Musculoskeletal						
Proximal weakness	5 (100)	7 (100)	16 (100)	141 (99.3)	110 (99.1)	62 (100)
Distal weakness	5 (100)	7 (100)	5 (31.3)	63 (45.7)	51 (47.7)	27 (43.6)
Falling episodes	5 (100)	7 (100)	4 (26.7)	52 (36.9)	54 (49.1)	26 (42.6)
Muscle atrophy	5 (100)	6 (85.7)	5 (33.3)	55 (39.0)	37 (33.6)	17 (28.3)
Myalgia	2 (40.0)	3 (42.9)	11 (73.3)	79 (57.7)	81 (74.3)	35 (58.3)
Asymmetric weakness	1 (20.0)	3 (42.9)	1 (6.3)	17 (12.1)	21 (19.1)	5 (8.5)
Muscle cramps	0 (0)	1 (14.3)	2 (12.5)	21 (15.3)	38 (34.9)	15 (25.9)
Arthralgia	5 (100)	2 (28.6)	13 (81.3)	80 (56.3)	74 (66.7)	33 (54.1)
Contractures	5 (100)	4 (57.1)	6 (40.0)	85 (59.9)	68 (61.8)	32 (51.6)
Arthritis	2 (40.0)	3 (42.9)	11 (68.8)	63 (44.4)	52 (47.3)	28 (45.2)
Cutaneous						
Gottron's papules	3 (60.0)	0 (0)	9 (56.3)	137 (96.5)	88 (79.3)	48 (78.7)
Heliotrope rash	3 (60.0)	0 (0)	12 (75.0)	128 (90.1)	90 (81.1)	43 (70.5)
Periungual capillary, abn.	3 (60.0)	4 (57.1)	11 (68.8)	123 (87.9)	82 (75.2)	35 (60.3)
Malar rash	3 (60.0)	0 (0)	5 (31.3)	131 (92.3)	75 (67.6)	34 (55.7)
Linear extensor erythema	3 (60.0)	0 (0)	3 (18.8)	72 (51.4)	24 (22.2)	18 (30.0)
V-sign or shawl rash	2 (40.0)	0 (0)	4 (25.0)	68 (48.2)	25 (22.5)	17 (27.9)
Raynaud's phenomenon	0 (0)	4 (57.1)	5 (31.3)	13 (9.2)	4 (3.6)	8 (13.1)
Mechanic's hands	0 (0)	1 (14.3)	5 (31.3)	7 (5.0)	2 (1.8)	3 (4.9)
Gastrointestinal						
Dysphagia	3 (60.0)	4 (57.1)	3 (18.8)	54 (38.0)	58 (52.3)	21 (34.4)
Regurgitation	3 (60.0)	1 (14.3)	3 (18.8)	29 (20.4)	29 (26.4)	8 (12.9)
Cardiopulmonary						
Abnormal PFT†	2 (40.0)	6 (85.7)	10 (76.9)	23 (23.5)	20 (24.1)	8 (16.7)
Interstitial lung disease	0 (0)	0 (0)	11 (68.8)	3 (2.1)	2 (1.8)	3 (4.9)
Abnormal EKG or ECHO†	1 (20.0)	4 (57.1)	3 (21.4)	12 (11.1)	11 (12.0)	11 (21.6)
Constitutional						
Weight loss	4 (80.0)	5 (71.4)	10 (62.5)	49 (34.5)	36 (32.7)	19 (31.7)
Fever	2 (40.0)	1 (14.3)	11 (68.8)	42 (29.6)	42 (37.8)	27 (44.3)
Adenopathy	2 (40.0)	0 (0)	3 (18.8)	30 (21.4)	22 (20.2)	10 (16.7)

* Values are the number (%) unless otherwise indicated. HMGCR = 3-hydroxy-3-methylglutaryl-coenzyme A reductase; SRP = signal recognition particle; MSA = myositis-specific autoantibodies; MAA = myositis-associated autoantibodies; abn. = abnormal; PFT = pulmonary function test; EKG = electrocardiogram; ECHO = echocardiogram.
† PFTs and EKG/ECHO were missing in 12–31% of patients.

in combination and had an average of 8 distinct medication trials. All patients received methotrexate; 4 received intravenous pulse methylprednisolone; 3 received intravenous gammaglobulin; 3 received other disease-modifying antirheumatic drugs (cyclosporine, azathioprine, mycophenolate mofetil, and cyclosphosphamide); and 2 received biologic therapies, including rituximab, abatacept, and anti–tumor necrosis factor therapies. Most responded partially (in myositis manifestations and laboratory tests) to these medications. None of the patients had a complete clinical response to therapy or entered remission as defined by the International Myositis Assessment and Clinical Studies Group (14), and none discontinued therapy. Four of the patients had a chronic continuous course and the fifth had a polycyclic course. On final evaluation, 3 patients had mild to moderate weakness and 2 had elevated CK levels, and only 1 had active DM rashes.

Discussion

In this study, we identified a rare but distinct subgroup of patients with juvenile myositis characterized by the presence of anti-HMGCR autoantibodies. We found that, when compared to children with other MSAs, those with anti-HMGCR autoantibodies were more likely to have severe proximal muscle weakness, distal weakness, muscle atrophy, joint contractures, and arthralgia compared to juvenile myositis subjects with anti-synthetases, anti-p155/140, anti-MJ, or no myositis autoantibodies. Of interest, anti-HMGCR patients were phenotypically similar to anti-SRP patients with the exceptions that the latter group were more likely to have cardiac involvement and less likely to have DM rashes. Those with anti-SRP also had more frequent Raynaud's phenomenon and were more often African American. Thus, HMGCR autoantibodies appear to define a distinct autoantibody group among juvenile myositis patients and are similar to anti-SRP, which has also been associated with necrotizing myopathy (15).

In our large cohort of juvenile myositis patients, we found a lower prevalence of anti-HMGCR-positive subjects compared to a pooled population of adults with this autoantibody (1% versus 7%). One explanation for this difference in frequency could be that children are rarely exposed to statin medications

and would thus be less likely to develop autoantibodies recognizing HMGCR. However, 75 of 2,039 pooled adult myositis patients (4%) were anti-HMGCR-positive without a known statin exposure, and the prevalence of this autoantibody is still significantly lower in our pediatric cohort compared to these adult patients (1% versus 4%; $P = 0.001$) (Table 1).

In a number of important respects, children and adults with anti-HMGCR-associated myositis have similar clinical features. As in adults, children with this autoantibody had very high CK levels, with a median value of 17,000 IU/liter. Furthermore, muscle biopsies from the 2 anti-HMGCR-positive cases showed the typical features of a necrotizing myopathy; these are also present in the majority of adult anti-HMGCR myositis cases. Finally, as in adult patients, all children had at least a partial response to immunosuppressive therapy, with strength returning to normal in 2 of 5 patients and CK levels normalizing in 3. One difference from adults was the frequent presence of distal weakness in the juvenile patients.

In adults, the class II HLA allele DRB1*11:01 is strongly associated with developing anti-HMGCR myositis, with an associated odds ratio of 24.5 in whites and 56.5 in African Americans (13). However, none of the children with anti-HMGCR autoantibodies in the present study had the DRB1*11:01 allele. Rather, the DRB1*07:01–DQA1*02:01 haplotype was present in 4 patients, and the DRB1*07:01 allele was present alone in 1 patient. Along with the absence of statin medication exposure, the different HLA association in juvenile myositis patients suggests differences in epitope reactivity between children and adults with anti-HMGCR autoantibodies, or that different mechanisms may underlie the development of these autoantibodies in children with myositis compared to adults. However, it should be noted that DRB1*11:01 is associated with the development of anti-HMGCR autoantibodies in adults with and without statin exposure (13). Thus, it may be that the mechanisms underlying HMGCR autoimmunity may even differ between children and adults without statin exposure.

The current study has several limitations. First, our ability to reliably define the phenotype of juvenile anti-HMGCR-associated myositis is limited because of the small number of autoantibody-positive cases identified. Second, our analysis of the muscle biopsy features in juvenile anti-HMGCR cases was limited since only 2 of the autoantibody-positive juvenile myositis patients underwent a muscle biopsy. It will certainly be interesting to see whether biopsies from anti-HMGCR-positive juvenile DM patients have perifascicular atrophy, as typically seen in juvenile DM, or predominant necrosis, as seen in the 2 IMNM cases with anti-HMGCR autoantibodies.

Despite these limitations, this study reveals that pediatric patients with anti-HMGCR autoantibodies have a number of features similar to their adult counterparts, including more severe weakness, and at least a partial response to treatment, but often requiring multiple immunosuppressive agents. However, unlike adults with anti-HMGCR autoantibodies, they are unlikely to have had statin exposure. Furthermore, they have a different immunogenetic risk factor for developing disease than their adult counterparts. In addition, this study shows that children with anti-HMGCR autoantibodies have more severe muscle disease compared to juvenile myositis patients with other autoantibodies except for anti-SRP. Given that the disease of some patients had a chronic progressive course, future studies will be required to define optimal treatment strategies in juvenile myositis patients with anti-HMGCR autoantibodies and to identify their etiology.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Mammen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design. Kishi, Rider, Miller, Mammen.
Acquisition of data. Rider, Pak, Barillas-Arias, Henrickson, McCarthy, Shaham, Weiss, Horkayne-Szakaly, Targoff, Miller, Mammen.
Analysis and interpretation of data. Kishi, Rider, Targoff, Miller, Mammen.

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APPENDIX A: PARTICIPATING MEMBERS OF THE CHILDHOOD MYOSITIS HETEROGENEITY STUDY GROUP

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