HHS Public Access

Author manuscript

Arthritis Care Res (Hoboken). Author manuscript; available in PMC 2018 July 01.

Published in final edited form as:

Arthritis Care Res (Hoboken). 2017 July ; 69(7): 1088–1094. doi:10.1002/acr.23113.

Anti-3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase Autoantibodies are Associated with DRB1*07:01 and Severe Myositis in Pediatric Myositis Patients

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Abstract

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Disclosures of conflict of interest: ALM holds a patent on an anti-HMGCR test that was licensed by Johns Hopkins to INOVA Diagnostics; however, he does not receive royalties or other compensation for this.

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 pediatric 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 (1.1%) of 440 patients were anti-HMGCR-positive; none had taken statin medications. Three patients had rashes characteristic of juvenile dermatomyositis and two patients had immune-mediated necrotizing myopathies. The median highest creatine kinase (CK) level of anti-HMGCR-positive subjects was 17,000 IU/L. 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 often a chronic course. The DRB1*07:01allele was present in all 5 patients compared to 26.25% of healthy controls (Pcorrected=0.01); none of the 5 pediatric patients had DRB1*11:01.

Conclusions—Compared to children with other MSAs, muscle disease appeared 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, anti-HMGCR-positive children have 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, an abnormal muscle biopsy, and may have one of several different myositis-specific autoantibodies (MSA). Each of the MSAs is associated with distinct clinical features that may be useful to characterize and classify patients with myositis. The same autoantibody phenotypes are often present in children and adult patients, however a particular autoantibody may be associated with different clinical features in adults compared to children. For example, autoantibodies recognizing p155/140 (transcriptional intermediary factor1; TIF-1) are highly associated with malignancy in adults, but not in children (2).

We (ALM) recently reported 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 screen of 750 adult myositis patients' sera (3), 45 (6%) were positive for anti-HMGCR autoantibodies. Among 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 by the criteria of Bohan and Peter

(4). No patients had typical DM rashes (3). Interestingly, two (4%) of the 45 adult myositis patients first presented with weakness as children (3).

Since our initial description, four additional groups have systematically screened cohorts of adult myositis patients for anti-HMGCR autoantibodies (5–8). In total, these four studies included 1289 myositis subjects and 102 (8%) of these tested positive for anti-HMGCR autoantibodies. Among the anti-HMGCR-positive subjects, 85 (83%) had IMNM or PM and nine (9%) had DM, and eight (8%) had IBM. Although none of these reports described the onset of weakness 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 pediatric myositis patients, and examined the clinical and immunogenetic associations, as well as responses to therapy and outcomes.

PATIENTS AND METHODS

Patient populations

This study included 440 patients from the United States and Canada who had probable or definite juvenile DM (JDM) (n=360), PM (JPM) (n=29), or CTM (JCTM) (n=51) by 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 provided 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. Severity of illness at onset, up to the time of diagnosis, was graded on a 4-point Likert scale as determined by the enrolling physician, and graded from mild to extremely severe disease activity (10). The majority had verification of the data via medical record 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 (MDA5) 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, Cary, NC) and were considered exploratory. Median values and interquartile ranges or mean and standard deviations were obtained for descriptive statistics and for nominal and ordinal variables. HLA data were corrected for multiple comparisons by the Bonferroni method (Pcorr).

RESULTS

Comparing anti-HMGCR-associated myositis in children and adults

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

The demographic features of the pediatric patients are included in Table 2. The median age at diagnoses was 8.1 years (range 6–15 years) with a median delay to diagnosis of 3.3 months. Three were female (60%), three were Caucasian, one was African American, and one was part Caucasian and part Hispanic. None had a common environmental exposure identified within 6 months of illness onset, including infections, medications, immunizations, stressful life events or 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% vs. 0%; p=0.06; Table 1).

The pediatric anti-HMGCR-positive cohort included 3 with JDM (0.8% of JDM cases), 1 with JPM with no characteristic rashes of JDM (3.4% of JPM cases) and 1 with JCTM (2.0% of JCTM cases) who had myositis in association with linear scleroderma. The diagnosis of JDM was based on the presence of Gottron’s papules and heliotrope rash, proximal weakness, and elevated serum creatine kinase (CK) levels in the range of 435 to 30,300 IU/L; muscle biopsies were not performed. The other 2 patients showed clinical features of IMNM, one in association with linear scleroderma, based on the presence of proximal weakness, serum CK levels of 17,000 IU/L or greater, 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% vs. 6%; p=0.004; Table 1), there was no difference in the prevalence of anti-HMGCR autoantibodies between the pooled adult DM and JDM cohorts (1.3% vs. 0.7%).

Laboratory investigations revealed that two anti-HGMCR-positive JDM 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 that no patient had 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 vs. controls) and the

DRB1*07:01 allele alone was present in 1 patient (Pcorr=0.01 for the DRB1*07:01 allele in anti-HMGCR subjects vs. controls).

Muscle biopsies were performed in the two patients without rashes. Myofiber necrosis, degeneration, and regeneration were the most prominent histological features (Supplemental Figure 1); 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. MHC Class I antigen was strongly positive on myofibers. Three patients who underwent evaluation by MRI had T2- or STIR-hyperintensity present diffusely and bilaterally in the thigh muscles.

Comparing patients with anti-HMGCR versus other MSAs in pediatric myositis

Next, we compared the demographic and clinical features of children with anti-HMGCR autoantibodies to juvenile myositis patients with other myositis 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 (Tables 2 and 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 vs. 14.9 years) and were more frequently Caucasian (60% vs. 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 similar ages of onset and racial distributions to 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 ACR functional class 4 at diagnosis, and two 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 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%) compared to 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 phenomenon (57% vs. 0%). Unlike those with anti-SRP autoantibodies, the anti-HMGCR positive patients had low rates of EKG and/or echocardiogram abnormalities (20% vs. 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 anti-HMGCR-positive pediatric patients were treated with oral prednisone along with an average of 7.2 (range 1–12) additional immunosuppressive medications during a mean follow-up period 31.2 months (range 19.2 – 157 months). They received an average of 2.4 immunosuppressive medications in combination and had an average of eight distinct medication trials. All patients received methotrexate, four received intravenous pulse methylprednisolone, three intravenous gammaglobulin, three other disease-modifying anti-rheumatic drugs including cyclosporine, azathioprine, mycophenolate mofetil and cyclosphosphamide, and two received biologic therapies, including rituximab, abatacept, and anti-TNF therapies. Most responded partially in myositis manifestations and laboratory tests to these medications. None patient 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, three patients had mild to moderate weakness and two had elevated CK levels, and only one 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. When compared to children with other MSAs, we found that 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 and were more often African American. Thus, HMGCR autoantibodies appear to define a distinct autoantibody group among pediatric myositis patients and are similar to anti-SRP, which has also been associated with necrotizing myopathy (15).

In our large cohort of pediatric myositis patients, we found a lower prevalence of anti-HMGCR-positive subjects compared to a pooled population of adults with this autoantibody (1% vs. 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 (4%) of 2039 pooled adult myositis patients 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% vs 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/L. Furthermore, muscle biopsies from the

two 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 two of five patients and CK levels normalizing in three. 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 allele is strongly associated with developing anti-HMGCR myositis with an associated odds ratio of 24.5 in Caucasians 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 four patients and the DRB1*07:01 allele alone was present in one patient. Along with the absence of statin medication exposure, the different HLA association in juvenile myositis patients suggest differences in the 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 pediatric 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 pediatric anti-HMGCR cases was limited since only two of the autoantibody-positive pediatric myositis patients underwent a muscle biopsy. It will certainly be of interest to see whether biopsies from anti-HMGCR-positive JDM patients have perifascicular atrophy, as typically seen in JDM, or predominant necrosis, as seen in the two IMNM cases with anti-HMGCR autoantibodies.

Despite these limitations, this study reveals that pediatric patients with anti-HMGCR have a number of features that are 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, they are unlikely to have had a statin exposure. Furthermore, they have a different immunogenetic risk factor for developing disease compared to their adult counterparts. In addition, this study shows that children with anti-HMGCR autoantibodies have more severe muscle disease compared to pediatric myositis patients with other autoantibodies except for anti-SRP. Given that some of them had a chronic progressive course, future studies will be required to define optimal treatment strategies in pediatric myositis patients with anti-HMGCR autoantibodies and to identify their etiology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Dr. James Katz for critical reading of the manuscript and Dr. Terrance O'Hanlon for assistance with sample preparation.

Funding: This work was supported in part by the National Institute of Environmental Health Sciences and the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health. Takayuki Kishi was supported by a research fellowship from The Myositis Association. Ira Targoff is a consultant to the Oklahoma Medical Research Foundation Clinical Immunology Laboratory regarding myositis antibody testing.

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Significance and 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 in adult patients with anti-HMGCR autoantibodies.
- Unlike adults, these children do not have a documented prior exposure to statin medications.

Table 1

Comparison of Frequency of Anti-HMGCR Autoantibodies and Statin Exposure in Adult Myositis Cohorts Compared to Juvenile Myositis.

Myositis Cohort (Reference)	Patients (N)	HMGCRAb+ N, (% of Total)	DM HMGCR Ab +/All HMGCR Ab+ N, (%)	DM HMGCR Ab +/All DM N, (%)	PM* HMGCR Ab+/All HMGCR Ab+ N, (%)	PM* HMGCRAb + /All PM N, (%)	HMGCR+ taking statins /All HMGCR Ab+ N, (%)
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	2039	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 data (present 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)

Abbreviations: HMGCR, hydroxy-3-methylglutaryl-coenzyme A reductase; DM, dermatomyositis; Ab, autoantibody; +, positive; PM, polymyositis; IIM, idiopathic inflammatory myopathies;

Adult IIM includes PM, immune-mediated necrotizing myopathy, and non-specific myositis in adults. Among juvenile IIM, includes 7 with overlap myositis who have juvenile PM, whereas the pediatric DM patients also include 39 overlap myositis patients with juvenile DM. The p values are comparing the adult IIM total to the juvenile IIM present study data.

* $P < 0.0001$

† $P = 0.004$

‡ $P = 0.014$

Arthritis Care Res (Hoboken). Author manuscript; available in PMC 2018 July 01.

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)
		Median [IQR]	Median [IQR]	Median [IQR]	Median [IQR]	Median [IQR]	Median [IQR]
Age at Diagnosis (yr.)		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 (mo.)		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]
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Gender	Female	3 (60.0)	5 (62.5)	13 (81.3)	115 (81.0)	76 (68.5)	37 (59.7)
Race	Caucasian	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 mo.)	0 (0)	2 (28.6)	10 (62.5)	60 (42.6)	33 (30.0)	24 (40.7)
	Slow (3–6 mo.)	2 (40.0)	1 (14.3)	2 (12.5)	32 (22.7)	27 (24.6)	21 (35.6)
	Subacute (1–3 mo.)	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)
Outcomes	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)

Abbreviations: hydroxy-3-methylglutaryl-coenzyme A reductase; SRP, signal recognition particle; ARS, anti-synthetase; p155/140, transforming inhibitory factor-1, TIF-1; MSA, myositis-specific autoantibodies; MAA, myositis-associated autoantibodies; Ab, autoantibodies;

Table 3

Clinical Features of Juvenile Myositis Patients with Anti-HMGCR Autoantibodies Compared to those with other Myositis Autoantibodies.

Feature		Anti-HMGCR (n=5), N (%)	Anti-SRP (n=8), N (%)	Anti-Synthetase (n=16), N (%)	Anti-p155/140 (n=142), N (%)	Anti-MJ (n=111), N (%)	MSA and MAA negative (n=62), N (%)
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 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)

Abbreviations: hydroxy-3-methylglutaryl-coenzyme A reductase; SRP, signal recognition particle; ARS, anti-synthetase; p155/140, transforming inhibitory factor-1, TIF-1; MSA, myositis-specific autoantibodies; MAA, myositis-associated autoantibodies; Ab, autoantibodies; PFT, pulmonary function testing; EKG, electrocardiogram; ECHO, echocardiogram. Note that PFTs and EKG/ECHO were missing in 12 – 31% of patients.