Anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies: incidence using different testing criteria and case series

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Abstract

Objective

To estimate the incidence of anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) antibodies utilising different testing criteria, and review the clinical details of a series of patients with associated autoimmune myopathy.

Methods

The incidence of anti-HMGCR antibodies in 2019 from 3 groups, South West London, Berkshire/Surrey and Southampton, were compared in the adult population. Anti-HMGCR antibodies were measured by commercial chemiluminescent and immunodot assays. The case notes of patients with anti-HMGCR antibodies were reviewed for the case series.

Results

The estimated incidence of anti-HMGCR antibodies in the first 2 groups was 1.94 per million adults per year, and in the third group 10.3 per million adults per year. In the first 2 groups the test criteria restricted analysis to specific clinician request for anti-HMGCR. In the third group test criteria included cases with less specific clinical features or a cytoplasmic indirect immunofluorescence anti-nuclear antibody pattern. The latter strategy had a positive predictive value of 66.1% for anti-HMGCR associated myopathy. A case series of 27 patients with anti-HMGCR antibodies revealed 19 with myopathy, oesophageal involvement in 26% and median peak CK 8000 IU/L. Response to treatment, including intravenous immunoglobulin, was good with CK normalising after median 5.5 months. In 8 cases there was no evidence of autoimmune muscle disease, 7 not statin exposed.

Conclusion

Varying criteria result in a 5-fold difference in estimated incidence of anti-HMGCR antibodies, revealing positive cases without evidence of myopathy. Patients with anti-HMGCR myopathy respond well to immune suppression, supporting wider testing for these antibodies amongst patients with myopathy.

Key words

myopathy, anti-HMGCR, intravenous immunoglobulin

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Introduction

A novel autoantibody in 16 patients with autoimmune necrotising myopathy (AINM) was first described in 2010 (1), with the antigenic target subsequently identified as the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) (2). HMGCR is up-regulated in regenerating skeletal muscle, and appears to be involved in muscle repair (3). It is unclear whether anti-HMGCR antibodies are pathogenic to muscle; either directly myopathic, indirectly via inhibition of HMGCR or an unrelated bio-marker of an immune mediated process which leads to muscle necrosis (3).

An association has also been established between anti-HMGCR antibodies, AINM and statin exposure (4, 5). HMGCR is inhibited by statins, and its expression on muscle is markedly increased on exposure to statins. Whilst this triad appears compelling, statin exposure is not a universal feature of anti-HMGCR AINM, varying from 18% - 75% (2, 4, 6-8) and is especially under-represented in those less than 50 years old (2, 8) in whom the prognosis is worse (6). Furthermore, statins have not been found to independently associate with the prognosis of anti-HMGCR AINM (6). It is possible that the association with statins is a chance phenomenon, considering that statin use is becoming increasingly prevalent, estimated at 12% of U.K. and 25% of U.S. adult populations (9, 10). Nonetheless, statins have not been associated with other types of AINM (*e.g.* anti-SRP), and so a specific interaction is plausible.

It is not known how likely it is that an individual with anti-HMGCR antibodies will develop a myopathy, nor whether, or how, statin exposure influences this. Epidemiologically, the association of anti-HMGCR antibodies with AINM is hard to assess, as both are very rare entities. Large epidemiologic studies of the prevalence and sequelae of anti-HMGCR in unselected adult populations have not been published. One study screened 1966 people (763 statin treated) from a community based prospective cohort, monitoring atherosclerosis risk, and failed to find any with anti-HMGCR antibodies (11). In contrast, of 1947 U.S. patients with suspected myopathy, 5.3% were positive for anti-HMGCR (6), whereas in a Japanese cohort of 657 cases with a tentative diagnosis of inflammatory myopathy, 7% were anti-HMGCR positive (8). From these, generalisability is not possible, as both prevalence figures relate to pre-selected populations with myopathic symptoms.

Ascertainment bias, linking a rare disease and antibody with a commonly used drug, is inadvertently documented in the reported literature if cases only fulfilling the triad of anti-HMGCR, AINM and statin use are published (5, 12, 13). Our understanding of the prevalence and full spectrum of sequelae of anti-HMGCR antibodies may be limited if clinicians only request a test for these antibodies in patients with AINM who have a history of statin exposure.

We report estimated incidence figures of anti-HMGCR in Southern England, from centres utilising different selection criteria to test samples for these antibodies. We have also reviewed 27 cases with anti-HMGCR antibodies, and compared the clinical and laboratory features and outcomes with other reports in the published literature.

Materials and methods

Data on positive anti-HMGCR antibody results over a 12-month period (January to December 2019) were obtained from three neighbouring laboratory groups, South West London Pathology, based at St George's London (StG), Berkshire and Surrey Pathology Services (BSPS) and Southampton. The StG and BSPS centres only test anti-HMGCR antibodies in patients when specifically requested by the referring clinician. All samples from StG and BSPS are assayed by chemiluminescent assay (QUANTA flash on Bio-Flash system; Werfen, Warrington, UK), processed by the Immunology laboratory, Oxford Radcliffe Hospital.

The Southampton immunology department test myositis antibodies, including HMGCR, using an algorithm based on patients' clinical details; where clinical information is consistent with myositis, interstitial lung disease or as part of a

Table I. Demographic features of 27 cases positive for anti-HMGCR antibodies.

	All anti-HMGCR positive cases	AINM	No AINM
Total number	27	19	8
Gender	19 females	12 females	7 females
Age at onset of muscle symptoms, or if amyopathic anti-HMGCR positivity, years	Mean 62.2 Median 63.5 Range 30-87	Mean 62.5 Median 63.5 Range 30-87	Mean 61.25 Median 61 Range 47-81
Ethnicity	21 White 1 Black British 4 South Asian 1 not specified	14 White 4 South Asian 1 not specified	7 White 1 Black British
Statin exposure	17	16	1

AINM: autoimmune necrotising myopathy.

connective tissue disease screen in the absence of myopathy based on a cytoplasmic indirect immunofluorescence anti-nuclear antibody (ANA) staining pattern. Samples are tested by myositis immunodot (MYO12D-24, D-tek, Cambridge Life Sciences, Ely, UK).

An estimate of the incidence of anti-HMGCR antibody positivity within the catchment areas of these laboratory groups was derived from population data. This was compared with published data on antibody prevalence and the clinical incidence of anti-HMGCR-mediated AINM. For this analysis, we adjusted the total population size for adults only, based on an estimate of 79% of UK population aged over 18 years, and prevalence of statin-use estimated as 12% of adults (9).

We reviewed the case notes of patients identified as having positive anti-HMGCR antibodies in these populations, not limited to cases first detected in 2019. The reasons for measuring anti-HMGCR, clinical features, statin exposure, specific myopathy investigations, disease course, treatment and outcomes were collected for all cases. HMGCR associated AINM was deemed present on the basis of muscle symptoms, elevated serum creatine kinase (CK) >320 IU/L, myopathic features on electromyography (EMG), magnetic resonance imaging (MRI) of thighs and muscle biopsy where available.

The epidemiologic work was defined as 'usual practice' and the case series review as 'service evaluation' according to the UK Health Research Authority definitions. As such no ethical approval or individual patient consent was required: http://hra-decisiontools.org.uk/ethics/

Results

Epidemiology

The StG/BSPS laboratories receive samples from a population of 3.25 million. In 2019, anti-HMGCR antibody tests were requested in 15 samples, with 5 positive results, 33% positivity rate. Adjusted for the adult population, this results in an estimated incidence of anti-HMGCR antibodies of 1 in 514,000 or 1.94 per million adults per year.

The Southampton immunology department receives samples from a population of 2.33 million. In the same period, a myositis screen was performed 768 times, with 19 positive cases, 2.5% positivity rate. Adjusted for the adult population, this results in an estimated incidence of anti-HMGCR antibodies of 1 in 97,000 or 10.3 per million adults per year. Of the 19 anti-HMGCR positive cases, 11 were true positive with AINM, 7 were false positive with no features of myopathy and the details of 1 remaining case were unknown. This testing strategy therefore has a specificity 99.1%, sensitivity 100% and a positive predictive value of anti-HMGCR AINM of 61.1%.

Case series analysis

The details of 27 patients positive for anti-HMGCR antibodies were reviewed. Demographic features are shown in Table I, for the whole series and those with and without AINM. Figure 1 shows the disposition of anti-HMGCR patients according to presence or absence of AINM.

Cases with autoimmune myopathy

19/27 cases were deemed to have AINM, based on muscle symptoms, an elevated CK and supportive findings from EMG, MRI of thighs and muscle biopsy.

A majority of patients reported subacute onset (up to 6 months) of predominantly proximal, symmetrical muscle weakness affecting both upper and lower limbs. The onset of muscle symptoms was more than 6 months in 4 patients, of which one reported onset of weakness over 9 years. The median peak CK was 8000 (mean 7388, range 900-27555) IU/L. EMG was recorded in 12/19 patients, all of which demonstrated myopathic changes. MRI of an affected muscle group was performed in 11/19, of which 9 demonstrated features of myositis including muscle oedema, loss of muscle bulk and fatty replacement of muscle, and the remaining 2 showed no features. Muscle biopsy was reported in 9/19 patients, all of which showed features consistent with necrotising myositis.

Mild dysphagia was reported by 5/19 (26%) patients, with none requiring protection of the airway or temporary gastrostomy. One patient had evidence of cardiac involvement with a raised cardiac troponin I, and one other had an asymptomatic small pericardial effusion. Extra-muscular disease was uncommon. Interstitial lung disease was

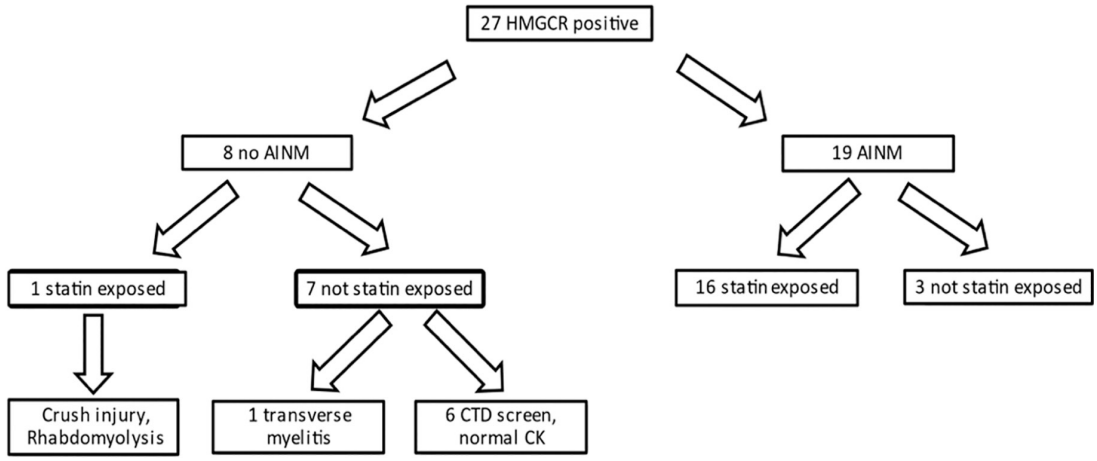

Fig. 1. Patient disposition according to presence of auto-immune necrotising myopathy (AINM).
CTD: connective tissue disease
CK: creatine kinase

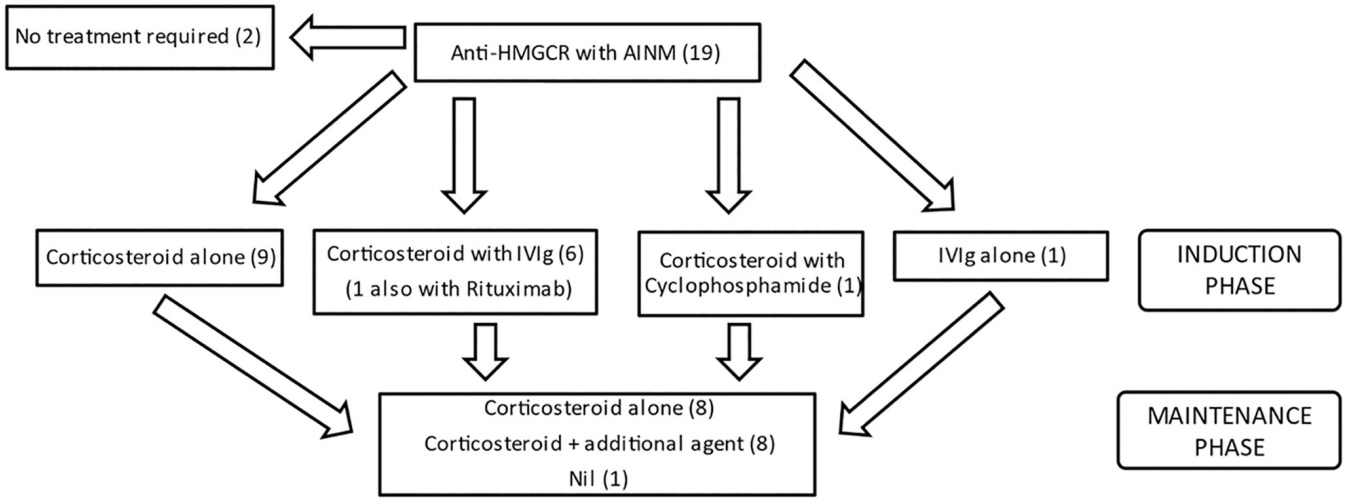

Fig. 2. Disposition of treatment protocols for 19 patients with anti-HMGCR AINM. IVIg: intravenous immunoglobulin.

not found, but 3 cases reported dyspnoea deemed secondary to respiratory muscle weakness. One patient had a rash on the eyelids and hands, consistent with dermatomyositis, however, all other myositis specific antibodies were negative. This patient had features of a necrotising myopathy on biopsy, diaphragmatic weakness on pulmonary function tests and normal appearances of lungs on CT scan.

Statin exposure was found in 16/19 (84%) cases (mean age 64.9 years, 10 female), atorvastatin in 14 and simvastatin in 2 at symptom onset. 2 patients on atorvastatin had previously been treated with simvastatin and 1 on simvastatin had previously been treated with atorvastatin. The median duration of statin exposure at onset of AINM was 48 (mean 63.8, range 9-192) months. In 3 cases the statin had been discontinued prior to onset of muscle symptoms (1 month in 1 case, 1 year in 2 cases) and was stopped soon after onset in the remaining cases, delayed by a year in 1. All 16 cases had proximal muscle weakness, both upper and lower limb in 14, and lower limb only in 2. The mean peak CK was 7898 (range 1245-27555) IU/L.

Treatment and clinical course

17/19 cases received immunomodulatory therapy, including 15/16 statin exposed, summarised in Figure 2. A range of corticosteroid-sparing immunosuppressive therapies were used in the maintenance phase; methotrexate (MTX) in 5, azathioprine (Aza) in 1, MTX and Aza in 1, MTX and rituximab (RTX) in 1. All treated cases responded, with partial or full functional recovery, and normalisation of CK at a median 5.5 (mean 5.5, range 2 – 11) months, after commencing treatment. Details of the 7 cases treated with IVIg induction therapy are shown in Table II.

In the 2 cases not treated, one was Atorvastatin exposed, with a peak CK of 1245 IU/L falling to 500 IU/L three months after stopping the statin. The other case was not statin exposed, with peak CK 900 IU/L. There was no long-term loss of function in either case.

Cases without autoimmune myopathy

8 anti-HMGCR cases had no evidence of AINM. The antibody had been measured as part of a connective tissue disease screen in 6 cases (4 white females aged 47-67, 1 Black-British female aged 55 years, 1 white male aged 71), presenting with non-specific symptoms including arthralgia, myalgia, facial rash, Raynaud's, and dyspnoea, with no elevation of CK nor statin exposure. No evidence of a connective tissue disease was found and as there was

Table II. Details of 7 cases with anti-HMGCR AINM treated with intravenous immunoglobulin (IVIg) induction therapy.

Age/gender	Statin years	Extra-muscular	Peak CK IU/L	resolution CK months	Maintenance	Functional outcome
30 / F	Nil	Skin	9717	6	Pred, Aza	Full strength
55 / F	S, 15	Nil	1395	8	Nil	Partial strength
55 / F	S, A 7.5	O, C – troponin	3911	5	Pred	Full strength
64 / F	S, A 6	Nil	10831	9	Pred, MTX	Full strength
72 / F	A, 1	O	8831	6	Pred, MTX	Still induction
48 / F	A, 4	C - pericardium	6253	3	Pred	Full strength
52 /F	A, 4.5	Nil	2634	3	Pred	Partial strength

CK: creatine kinase; S: simvastatin; A: atorvastatin; O: oesophagus; C: cardiac; Pred: prednisolone; Aza: azathioprine; MTX: methotrexate.

no weakness nor elevation of CK further muscle specific tests (EMG, MRI, biopsy) were not deemed necessary at the time. In another case, a 47-year-old Caucasian female, the antibody was measured as part of the investigation of acute unilateral leg weakness and back pain, found to be due to transverse myelitis. This patient was not statin exposed. The final case was an 81-year-old Caucasian female with acute crush injury induced rhabdomyolysis, following a fall and long lie, peak CK 5535 IU/L. She had been taking Pravastatin for 9 years and Simvastatin prior that for 3 years. She was also found to have weak positive anti-SAE antibodies. The CK fell to 1655 IU/L in 2 days and she made a full recovery.

Discussion

We report the estimated incidence of anti-HMGCR antibodies in southern England. The criteria for testing samples for these antibodies influences the results markedly. When testing is restricted to cases with specific clinician suspicion of HMGCR associated AINM, the estimated incidence from StG/BSPS of 1.94 per million adults is similar to a report from New Zealand of 1.7 per million per year, using similar testing criteria (14). In contrast, the broader testing criteria in Southampton results in a 5.3-fold higher estimated incidence of 10.3 per million adults. This strategy triggered more tests for anti-HMGCR, a lower yield but more cases overall. Whilst the different assay for measurement of anti-HMGCR in Southampton may have contributed to the variability in incidence, we believe the testing strategies were likely to have been the main factor. Furthermore, whilst testing in Southampton included cases without myopathy, all tested samples had a positive disease feature (*e.g.* cytoplasmic ANA pattern) and so it is likely that bias by indication means the higher estimated incidence from this strategy remains an underestimate of the true incidence of anti-HMGCR antibodies in the adult population.

If all positive anti-HMGCR antibodies were associated with statin use, and demographics and statin prescribing patterns are representative in the catchment regions of the national population, this would result in an estimated anti-HMGCR incidence of 1 in 61,620 statin users in the StG/BSPS regions and 1 in 11,625 statin users in the Southampton region. However, it is recognised that some patients with anti-HMGCR antibodies have no history of statin exposure, and this is reflected in our case series.

The finding of 8 anti-HMGCR cases without AINM reveals the wider existence of this antibody in the population. Thus, over and above the incomplete association of anti-HMGCR AINM with statin exposure, we demonstrate that anti-HMGCR antibodies can occur without myopathic sequelae. It is unclear whether the 8 cases we report would develop myopathy with time, though it is noteworthy that 7 of these were not statin exposed. The clinical relevance of these findings should be validated in other cohorts to confirm the utility of testing anti-HMGCR antibodies in 'atypical' clinical contexts. The time scale to progress from an autoreactive state to an autoimmune pathologic state may be very long, as demonstrated in rheumatoid arthritis where development of antibodies to cyclic citrullinated peptide (ACPA) may precede first joint symptoms by over 10 years (15). The statin exposed case without AINM presented with rhabdomyolysis following a crush injury, and was also found to have anti-SAE antibodies. Statin-associated rhabdomyolysis is well described (16) and in this case the addition of crush injury, and both anti-HMGCR and anti-SAE antibodies may have predisposed to muscle injury.

The case series we present shows many similarities with other descriptions in the literature, with the clinical phenotype dominated by proximal upper and lower limb striated muscle disease and few cases with peak CK <1000IU/L (8). Oesophageal involvement in 26% of our series is similar to 27% of 50 U.S. cases (6) and 44% of 45 Japanese cases (8). The rarity of cardiac muscle involvement is also consistent with others (4, 8, 14), though has been reported sporadically (17). The association of anti-HMGCR AINM with statin exposure, found in 84% of our cases, is high compared with 18% - 75% in other series (2, 4, 6-8). This may be due to ascertainment bias, as some of our centres limit testing for anti-HMGCR to cases specifically requested by the clinician. The long duration of statin exposure prior to onset of myopathy, ranging from 9 months to 16 years is also consistent with other reports (5). Of those not statin exposed, 3/10 (30%) had AINM, though we cannot rule out unintentional dietary statin exposure from certain foods such as red-yeast rice, fenugreek, oyster mushrooms and some fish oils.

Patients with immune mediated inflammatory myositis often have extra-muscular manifestations, such as interstitial lung disease, various connective tissue disease features such as Raynaud's, arthralgia or arthritis, a variety of cutaneous features including the characteristic rash of dermatomyositis or mechanics hands of the anti-synthetase syndrome, and cancer (18, 19). The absence of such features in anti-HMGCR AINM in our series and documented by others (2, 4, 6, 8) is striking, and an important diagnostic clue. In particular

there were no cases with cancer, following standard screening of all newly presenting cases of myositis.

We recommend that patients newly presenting with idiopathic inflammatory muscle disease and CK >1000 IU/L, not accompanied by systemic and extra-muscular features, should be routinely tested for anti-HMGCR antibodies. In a series of 387 cases with biopsy proven idiopathic inflammatory myositis the prevalence of anti-HMGCR was as high as anti-synthetase antibodies (8), yet in many laboratories a 'myositis panel' does not include anti-HMGCR. One benefit of securing the diagnosis of anti-HMGCR AINM is to enable commencement of immunomodulatory therapy. Whilst there are reports of treatment resistance and refractory disease in 23-30% of cases (6, 8), in our series and others (5) outcomes were generally favourable. Two cases required no treatment and recovered spontaneously, and the others demonstrated at least partial recovery of function and normalisation of CK within a short time scale of immunomodulatory therapy. The efficacy of IVIg is of particular note in our series and also observed by others (12, 20). In 6/7 cases reported here, a dramatic functional response was seen, and CK normalised within a year, mean 5.6 months from a mean peak CK of 5790 IU/L. IVIg is an increasingly scarce and expensive treatment, however, like others (21), we argue is justified in anti-HMGCR AINM.

In conclusion we have estimated the incidence of anti-HMGCR in southern England from laboratory groups using different test criteria. This has revealed similar results to others (14) from those laboratories that limit testing to cases with high pre-test probability determined by the clinician, whereas the incidence is 5.3-fold higher when broader testing criteria are applied. The latter strategy has demonstrated that anti-HMGCR can occur not only in the absence of statin exposure, but also in the absence of AINM. Our case series confirms the association with long-term statin exposure, and the characteristic low prevalence of cardiac and non-muscular manifestations of autoimmune disease, which contrasts to other immune mediated myopathies. Functional and biochemical outcomes to immunomodulatory therapies were generally good, and we highlight the particular efficacy of IVIg. Treatment responsiveness justifies wider testing for anti-HMGCR amongst patients with myopathy, irrespective of statin exposure.

Take home messages

- Anti-HMGCR antibodies may be found without myopathy or statin exposure.
- Anti-HMGCR should be tested in patients with myopathy, especially with few extra-muscular features of autoimmune disease.
- Severe anti-HMGCR myopathy responds well to IVIg treatment.

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