Statin-associated necrotizing autoimmune myopathy with concurrent myasthenia gravis

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Key Clinical Message: A patient developed necrotizing autoimmune myopathy and myasthenia gravis after statin exposure. Clinicians should be alerted to possible concurrent autoimmune neuromuscular disorders to discontinue the drug and promptly begin appropriate treatment.

INTRODUCTION

Statins are commonly prescribed for atherosclerotic disease, and although generally safe, their use has been associated with serious muscular involvement.[1] The spectrum of statin-associated neuromuscular involvement ranges from myalgia with increase of creatine kinase (CK), to severe conditions including necrotizing autoimmune myopathy (NAM), and less commonly, myasthenia gravis (MG).[1-2]

Serum myositis-specific autoantibodies associated with NAM include anti-3-hydroxy-3-methylglutarylcoenzyme-A reductase (HMGCR) and anti-signal recognition particle (SRP).[3] Anti-HMGCR myopathy is characterized by severe, rapidly progressive muscle weakness along with dysphagia in 16-30% of the patients, and elevated serum CK levels[4,5]. Muscle biopsy shows necrosis with scarce or no inflammation. In most patients with a history of statin exposure, symptoms do not resolve after withdrawing the drug, and only a prompt immunosuppressive treatment leads to clinical improvement.[6] Statin-associated MG is limited to few case reports, with ocular or, less frequently, generalized presentation.[7]

We report on a patient treated with statin and ezetimibe who developed NAM and generalized MG which responded favourably to immunosuppressive therapy.

CASE REPORT

A 65-year-old male complained of progressive lower limb weakness and calf muscle pain. No autoimmune or hereditary neuromuscular diseases was referred. His medical history was remarkable for arterial hypertension, mild carotid atherosclerosis, myocardial infarction, subclinical hypothyroidism, and hyperlipidemia. During the previous six months the patient had been taking atorvastatin (80 mg daily) replaced with rosuvastatin-ezetimibe 20/10 mg over the following eight weeks. The treatment was discontinued two weeks prior

to admission because of weakness and increased serum CK level (12,309 IU/L; reference range <223 IU/L).

On admission, three months after the onset of symptoms, the patient complained of easy fatigability, difficulties in getting up from a chair and walking, and his muscle strength was reduced at proximal (3/5 by MRC) and distal (4/5 by MRC) segments of all limbs; arm and thigh muscles were hypotrophic. The patient had mild facial and palatal weakness, severe dysphonia and dysphagia. Sensation and deep tendon reflexes were normal. Severity of weakness fluctuated during the day being worse at evening. During hospitalization the patient developed dyspnea at rest with decreased oxygen saturation values of 90% in room air.

Serum CK was 32000 IU/L, AST 950 IU/L (Reference range: 5–38 IU/L), ALT 655 IU/L (Reference range 5–41 IU/L), LDH 1100 (Reference: <248 IU/L). Anti-AchR turned out to be increased to 8.9 nmol/L (NV <0.5). Anti-HMGCR antibody titer was 255.2 IU/mL (reference range, < 19 IU/mL). ANA, anti-ds-DNA, anti-SSA and anti-SSB were negative. Among myositis-associated autoantibodies, a moderate positivity for anti-Ro-52 was detected by immunoblotting.

Needle electromyography (EMG) showed a myopathic pattern with abnormal spontaneous activity in proximal limb muscles; single-fibre EMG (SF-EMG) showed increased jitter. A lower limb MRI revealed asymmetric oedema and atrophy of proximal and distal thigh muscles (Figure 1a,b). A left vastus lateralis muscle biopsy showed fiber necrosis without inflammatory infiltrates. Echocardiogram and total body CT scan were normal.

The patient was treated with IVIg (0.4 g/kg die) for five days, prednisone 1 mg/kg, and azathioprine 100 mg/die, subsequently replaced by weekly intramuscular injections of methotrexate 10 mg/die. In addition piridostigmine 90 mg daily was started.

The patient gradually improved and after four months of treatment, he could walk and feed alone. CK was 241 IU/L, anti-HMGCR 25 IU/mL, and anti-AchR 9.3 nmol/L. A repeated

EMG recorded a myopathic pattern without denervation. Prednisone was tapered to 15 mg/die.

DISCUSSION

The most likely hypothesis to account for the coexistence of both NAM and MG in our patient is based on the immunomodulatory effects of statins,[4] which may trigger an increased immunogenicity to neuromuscular peptides in subjects with distinctive HLA haplotypes. These drugs are recognized to induce other autoimmune disorders such as a lupus-like syndrome, myositis, immune hepatitis.[2] The mechanisms underlying the production of antibodies to HMGCR and AchR, in addition to anti-Ro-52, are unknown, although autoimmunity could be driven by drug-induced loss of immune tolerance.

Timely immunosuppressive treatment in statin-exposed patients usually leads to muscle strength improvement and decrease in anti-HMGCR and CK levels, as we observed in our patient.[1] This is keeping with previous observations showing a strict correlation among anti-HMGCR titre, CK level, and muscle weakness.[4] Notably, in refractory cases or in patients receiving delayed treatment, accelerated muscle atrophy represents the major contributor to long-term disability.[5]

To our knowledge this is the first case of a patient with coexisting NAM and MG related to statin intake. In conclusion, clinicians should be alerted to the possible association between statin exposure and incident NAM/MG in order to discontinue the drug and promptly begin an immunosuppressive treatment.

REFERENCE

1. Mammen AL. Statin-Associated Autoimmune Myopathy *N Engl J Med* 2016;**374**:664-669.
2. Gras-Champel V, Batteux B, Masmoudi K, Liabeuf S. Statin-induced myasthenia: A disproportionality analysis of the WHO's VigiBase pharmacovigilance database. *Muscle Nerve*. 2019; **60**:382-386.
3. Mohassel P and Mammen AL. Anti-HMGCR Myopathy. *Journal of Neuromuscular Diseases*. 2018; **5**:11–20.
4. Yongchairat K, Tanboon J, Waisayarat J, et al. Clinical spectrums and outcomes of necrotizing autoimmune myopathy versus other idiopathic inflammatory myopathies: a multicenter case-control study. *Clin Rheumatol*. 2019; **38**:3459-3469.
5. Allenbach Y, Mammen AL, Benveniste O, Stenzel W; Immune-Mediated Necrotizing Myopathies Working Group.224th ENMC International Workshop: Clinico-sero-pathological classification of immune-mediated necrotizing myopathies Zandvoort, The Netherlands, 14-16 October 2016. *Neuromuscul Disord*. 2018; **28**:87-99.
6. Du Souich P, Roederer G, Dufour B. Myotoxicity of statins: Mechanism of action. *Pharmacology & Therapeutics* 2017; **175**:1–16.
7. Khalid R, Ibad A, Thompson PD. Statins and myasthenia gravis. *Muscle Nerve*. 2016; **54**:509-509.

Figure legend: From top to bottom: Examples of T1-weighted (T1W) hyperintensity reflecting connective tissue and fatty replacement; T2-weighted (T2W) and short tau inversion recovery (STIR) sequences showing asymmetrically signal increasing in the **1a)** proximal thigh (pectineus, adductor brevis and obturator externus) muscles and **1b)** distal thigh (semimembranosus) muscles.

ABBREVIATIONS

Myositis-specific autoantibodies (MSAs)

Creatinine kinase (CK)

Electromyography (EMG)

Single-fibre EMG (SF-EMG)

Azathioprine (AZT)

Methotrexate (MTX)