Antibody Miopathy Associated with Anti-Hydroximethylglutaryl Coenzyme: AReductase in a Simvastatin User

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Abstract

Autoimmune myopathies result from direct or indirect injury to muscle fibers mediated by the immune system. The term myositis is generally interchangeable with "Idiopathic Inflammatory Myopathy", which refers to primary autoimmune muscle diseases. These include dermatomyositis, inclusion body myositis, antisynthetase syndrome, and Immune Mediated Necrotizing Myopathy (IMNM). Other known causes of inflammatory myopathies include infections, drugs, mixed connective tissue diseases and cancer. In 2017, the European neuromuscular centre described two subtypes of IMNM, each mediated by a different antibody: Anti-SRP and Anti-3-Hydroxy-3-Methyl Glutaryl Coenzyme A reductase (Anti-HMG-CoA), each presents with a different clinical and histopathological course. The first is associated with a more aggressive disease and a low response to conventional immunotherapy. In this review, however, we will focus on the latter, MNIM related to anti-HMG-CoA.

Keywords

Immune necrotizing; Glutaryl coenzyme; Auto immune diseases; Electro myography; Intravenous immunoglobulin

Abbreviations

CK: Creatin Kinase; MRI: Magnetic Resonance Imaging; Anti- HMG- CoA: Anti Hydroxi methylglutaryl Coenzyme-A Reductase; IMNM: Immunomediated Necrotizing Myopathy; Anti-SRP: Anti-Signal Recognition Particle; ALT: A Lanineamino Transferase; ASt: A Spartateamino Transferase; LHD: Lactatede Hydrogenase; Anti- LKM-1: Anti Liver Kidney Microsome Type 1; Anti- DNA: Anti-Double Stranded DNA; Anti-SCL 70: Anti-Scleroderma-70; Anti- ENA SN RNP: Anti- Extractable Nuclear Antigens Small Nuclear Ribo Nucleo Protein; PAS: Periodic Acid Schiff ; SLCO1B1: Solute Carrier Organic AnionTransporter 1B1; CYP3A4: Cytochrome P450 3A4; MHC-1: Major Histocompatibility Complex 1; IVIg: Intravenous Immunoglobulin; PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9

Introduction

Anti-HMG-CoA related IMNM, whose pathogenesis is not fully understood, was first described in adults with a history of statin exposure [1]. Unlike patients with statin-induced toxic myopathies or intolerance to statin drugs, in whom symptoms improve upon discontinuation of drug, these patients persist with muscle weakness and elevated Creatine Kinase (CK) despite discontinuation of the drug [2].

The typical clinical presentation of statin-related IMNM occurs in adults and is characterized by the development of acute or sub-acute symmetrical proximal muscle weakness accompanied by significant elevation of CK [3]. Distal weakness, extra-muscular symptomatology or smooth muscle involvement is uncommon and occurs in less than 10% of cases [4]. Other rare manifestations include dysphagia,

arthralgias, myalgias and Raynaud's phenomenon. The classic presentation, so it is important to be aware of it and suspect this pathology even though it does not present in a common way [5]. In addition to elevated CK, reflecting cell membrane damage and muscle necrosis, other enzyme markers may be elevated, including aldolase, lactate dehydrogenase, transaminases, aspartate transaminase, alanine transaminase. Enzyme elevation has been linked to anti-HMG-CoA antibody titers [6].

Literature Review

A man with a relevant medical history of diabetes mellitus and dyslipidemia, under treatment with ezetimibe/simvastatin 10/20 mg for one year, presented to the Hospital [7]. He presented with a two month long ailment characterized by intermittent hand oedema and cervical pain exacerbated by movement, as well as proximal and distal muscle weakness in all four limbs, which made it difficult to walk [8]. Subsequently, dysarthria, dysphagia and cervical muscle weakness were added to his symptoms. The physical examination revelated preserved mental functions, unaltered cranial nerves, diminished gag reflex, 2/5 strength in shoulder and pelvic girdle muscles and lower limb distal muscles, meningeal signs were absent, proprioceptive and steroceptive sensitivity were preserved[9].

Initial blood tests revealed elevated transaminases: ALT 621 U/L, LDH 1448 U/L, ASt 506 U/L, and CK 62,334 U/L. There were no reports of elevated azoosides or electrolyte disturbances [10]. An MRI scan was requested, which showed a fatty infiltration of posterior muscle planes in both pelvic limbs and oedema in the right buttock. With a suspected myopathy, an electromyography of the four limbs was requested [11]. The results reported a polyneuromyopathic patter and revealed that the pelvic limbs were the most compromised. Therefore, the following myositis-specific antibodies laboratory tests were requested: anti- LKM-1, anti-smooth muscle, anti-DNA, anti-Jo, anti-La, anti-SCL 70, anti-ENA Sm RNP, all of which were negative.

A gastrocnemius muscle biopsy was also carried out, showing non-specific focal regenerative changes. Other typical markers of inflammatory myopathies such as macrophage infiltration or infiltration of other inflammatory cells, Pas, Gomori's trichrome and Masson's trichrome stainings were all negative. Fibrosis, collagen deposits, cytoplasmic bodies, inclusion bodies and tubular aggregates were also absent. Given the patient's clinical presentation and the results of paraclinical studies, we requested antibodies against HMG-CoA, which were found to be 9 times above the normal upper limit, therefore confirming the diagnosis of IMNM.

During hospitalization, he was managed with high-volume crystalloid solutions despite the fact that acute renal injury was never demonstrated. His statin was discontinued and immunosuppression with prednisone at 1 mg/kg/day was started as soon as the inflammatory myopathy was suspected. The patient showed partial clinical improvement and progressive decrease in CK and transaminases, until ASt 353 U/L, ALT 482 U/L, DHL 1079 U/L, CK 9115 U/L were obtained, which led to his hospital discharge, continuing with the same treatment scheme at home. Two weeks later, he presented again with difficulty walking and oedema in the pelvic limbs, as well as an increase in CK to 19,939 U/L. At this point it was decided to re-admit him for immunosuppressive adjustment with intravenous immunoglobulin 10 g/day for 5 days. The response to treatment was adequate, with a progressive decrease in CK to 10,500 U/L, as well as improvement in muscle strength and ability to walk.

Discussion

Like other autoimmune diseases, the interaction between immunological and environmental factors can predispose the patient to this condition. The presence of the HLA-DRB1 * 11:01 allele has been described as an immunogenic risk factor for developing anti-HMG-CoA myopathy. A polymorphism in the SLCO1B1 gene on chromosome has been identified as an important genetic risk factor. Other described risk factors are the use of drugs metabolized by CYP3A4 as these increase serum statin levels, alcoholism, hypothyroidism, renal failure, liver failure, and familial or personal history of statin intolerance. It has also been observed more frequently in women. Different drugs have been linked with the occurrence of muscular symptoms. Statins are commonly associated with manifestations ranging from mild asymptomatic CK elevation, myalgias, to life- threatening rhabdomyolysis.Less frequently;

autoimmune syndromes such as immune-mediated necrotizing myopathy with autoantibodies against hydroxymethylglutaryl coenzyme A reductase (anti-HMG-CoA) have been described. Several studies have reported a 37.5% to 94% association between these antibodies and statin exposure. There are antibodies were found in statin-naive patients who d been exposed to certain foods. The duration of statin exposure prior to the clinical presentation varies from 2 months to 10 years.

The electromyography pattern shows an irritative myopathy. Findings include low-amplitude, short-duration potentials, positive sharp ways, fibrillatory potentials and repetitive myotonic or pseudomyotonic discharges. The gold standard imaging study is a Magnetic Resonance Imaging (MRI). Common findings are oedema and muscle atrophy with fatty substitution mainly in the lateral rotators, glutes and the medial and posterior compartments of the pelvic limbs with preserved muscle architecture. The intensity of the signal is generally proportional to the swelling and the severity of said swelling. However, since these findings are non-specific, the main utility of MRI is in to select the areas for performing a biopsy and for disease monitoring.

Findings from the muscle biopsy in IMNM, unlike in other inflammatory myopathies, where cellular infiltrates composed mainly of CD8+ T lymphocytes and macrophages are usually observed, show muscle fibers in different stages of scattered necrosis with little or no lymphocytic infiltration. Diffusely distributed regenerating fibers and increased expression of Major Histocompatibility Complex 1 (MHC-1) in the sarcolemma are also characteristically observed. The histopathological findings described are variable and may not be universally present.

Corticosteroids are commonly the first line of treatment in inflammatory myopathies with doses equivalent to 0.5-1 mg/kg/day of prednisone. Most patients with statin-associated immune-mediated necrotizing myopathy require different lines of immunosuppressive therapy. Methotrexate, azathioprine, mycophenolate mofetil and plasmapheresis have been used with variable results. Recent evidence supports the use of IV immunoglobulin (IVIg) in IMNM, even as monotherapy, although the classic scheme combines methotrexate or azathioprine with corticosteroids. The intravenous immunoglobulin was started early in combination with steroids given the relapse in symptoms and severity of the disease. This was done with the patient responding adequately to treatment. Rituximab use has also been described in patients with anti-SRP-positive IMNM refractory to conventional immunotherapy. Withdrawal of immunosuppression is possible after showing improvement with the treatment for 6 months to 1 year 11. In patients at high cardiovascular risk, who require lipid-lowering management after statin withdrawal, PCSK9 inhibitors have been used safely.

Despite their low frequency, it is important to identify typical and atypical clinical manifestations related to statin use due to their variability and severity, with consequent repercussions on the initiation of timely and appropriate treatment, with rare symptomatology such as distal weakness, dysarthria and dysphagia; it also differs from most cases in that significant CK elevation often implies acute renal damage, which was never present in our patient.

Anti-HMG-CoA-related IMNM belongs to the group of idiopathic inflammatory myopathies, in which, although clinical symptomatology and serology support the identification of the specific type of myopathy, the gold standard for identification continues to be the muscle biopsy. This allows differentiation from other autoimmune myopathies such as polymyositis, dermatomyositis, and inclusion body myositis, non-specific and anti-synthetase syndrome. Magnetic resonance imaging should always precede the muscle biopsy in order to decide the site from which the biopsy will be taken.

Conclusion

In this clinical context, management includes, in addition to drug withdrawal, immunosuppression, which must be maintained for a long period of time to avoid relapses. Although corticosteroids are considered the first line of treatment, they are generally insufficient, so the following lines will be adapted on an individual basis. In this, the patient showed improvement with the administration of intravenous immunoglobulin, a drug that has been used as monotherapy. We used intravenous

immunoglobulin early in the relapse upon worsening of symptoms, with which we obtained excellent clinical and paraclinical response.

Author's Contributions

MACC compiled and interpreted the patient data, was a major contributor in writing the manuscript. BPA compiled patient data, collected data for use in academic research. SIM was in charge of clinical and paraclinical neurological review. RVL reviewed the proposed diagnostic pathways. DRH guided diagnostic path. All authors read and approved the final manuscript.

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None

Conflict of Interest

The authors declare that there was no conflict of interests.

References

1. Berth SH, lloyd TE. Secondary causes of myositis. Neurologic Manifestations of Systemic Disease 2020; 22: 01-15.
2. Karunaratne K, Amiras D, Pickering MC, Hofer M, Viegas S, et al. Autoimmune necrotising myopathy and HMGCR antibodies. Practical Neurology 2018; 18: 151-155.
3. Allenbach Y, Mammen AL, Benveniste O.224th ENMC International Workshop: Clinico-sero-pathological classification of immune-mediated necrotizing myopathies Zandvoort, The Netherlands 14–16 October 2016. Neuromuscular Disorder 2018; 28: 87-99.
4. Goyal NA. Immune-Mediated Myopathies. Continuum Lifelong Learning in Neurology 2019; 25: 1564-1585.
5. Mohassel P, Mammen AL. Statin-associated autoimmune myopathy and anti-HMGCR autoantibodies. Muscle and Nerve 2013; 48: 477-483.
6. Albayda J, Christopher-Stine L. Identifying statin-associated autoimmune necrotizing myopathy. Cleveland and Clinic Journal of Medicine 2014; 81: 736-741.
7. Mohassel P, Mammen AL. Anti-HMGCR Myopathy. Journal of Neuromuscular Diseases 2018; 5: 11-20.
8. Jones R. NIH Public Access. Bone 2014; 23: 1-7.
9. Guimaraes JB, Nico MA, Omond AG. Diagnostic imaging of inflammatory myopathies: new concepts and a radiological approach. Current Rheumatology Reports 2019; 21.
10. Chhibber S, Emg C, Amato AA. Clinical evaluation and management of inflammatory myopathies. Published online 2015.
11. Selva-Ocallaghan A, Alvarado-Cardenas M, Marin A, Pinal-Fernandez I. Statins and myositis: The role of anti-HMGCR antibodies. Expert Review of Clinical Immunology 2015; 11: 1277-1279.