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Treatment and outcomes in necrotising autoimmune myopathy: An Australian perspective

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Abstract

Necrotising Autoimmune Myopathy (NAM) presents as a subacute proximal myopathy with high creatine kinase levels. It is associated with statin exposure, 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) antibody, connective tissue diseases, signal recognition particle (SRP) antibody and malignancy. This case series presents our Western Australian NAM patient cohort: comparing the subgroup presentations, biopsy appearance and treatment outcomes. We retrospectively collected data on patients diagnosed with NAM at the Western Australian Neuroscience Research Institute between the years 2000 and 2015. We identified 20 patients with Necrotising Autoimmune Myopathy: 14 with anti-HMGCR antibodies; two with anti-SRP antibodies; three with connective tissue disease; two as yet unspecified. Median creatine kinase level was 6047units/L (range 1000–17000). The statin naïve patients with HMGCR antibodies and patients with SRP antibodies were the most severely affected subgroups, with higher creatine kinase levels, and were more resistant to immunotherapy. Two or more immunotherapy agents were required in 90%; eight patients required IVIG and rituximab. Steroid weaning commonly precipitated relapses. Four patients had complete remission, and the remaining patients still require immunotherapy. Necrotising Autoimmune Myopathy is a potentially treatable myopathy, which can be precipitated by statin therapy and requires early, aggressive immunotherapy, usually requiring multiple steroid sparing agents for successful steroid weaning.

Keywords: Necrotising autoimmune myopathy; HMGCR antibodies; Statin myopathy; Immune mediated necrotising myopathy

1. Introduction

Necrotising Autoimmune Myopathy (NAM), otherwise known as immune-mediated necrotising myopathy (IMNM), is an increasingly recognised condition that presents as a subacute symmetrical proximal myopathy accompanied by high creatine kinase (CK) levels [1–4]. It can be associated with myalgia, dysphagia, dyspnoea, fatigue and weight loss [1,5]. It has been linked to statin medication exposure, 3-hydroxy-3-methylglutaryl-CoA reductase antibody (anti-HMGCR) [6–8], connective tissue diseases, signal recognition particle antibody (anti-SRP) [9], malignancy and viral infections including the Human Immunodeficiency Virus (HIV) [1,2].

Muscle biopsy findings in NAM generally show necrotic and regenerating fibres with minimal inflammatory infiltrate, and no evidence of vasculitis [10,11].

There is still limited data on treatment options, with no prospective trials, but some case series have explored various immunosuppressive agents, with NAM symptoms generally being less receptive to immunotherapy than the inflammatory myopathies and requiring at least a 12-month trial of high dose prednisolone, usually with at least one steroid sparing agent [5,9,12]. A recent case series by Kassardjian et al. [5], exploring the clinical response of 63 patients to various immunomodulating therapies across the subtypes of NAM, showed that >50% of patients relapse during the taper of immunotherapy, and the

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majority of patients needed two or more immunosuppressive agents.

This study aims to add to the current literature with our Western Australian NAM patient cohort, documenting the clinical, biochemical, serological and biopsy findings along with the treatment and subsequent outcomes.

2. Methods

We identified patients that had presented to the Western Australian Neuroscience Research Institute (WANRI) between the years 2000 and 2015 and received the diagnosis of NAM by the treating neuromuscular specialist neurologist and immunologist. Other causes of a necrotising myopathy, such as hypothyroidism, muscular dystrophy and other toxic myopathies, were routinely excluded.

We retrospectively collected data on presentation, investigation, treatment and clinical course. All patients underwent serial CK levels and muscle power examinations, which were recorded using the Medical Research Council scale and used as a measure of patient response. These were performed at each clinic visit, which was initially monthly, then every three months during treatment for the majority of patients. Serological results were recorded, including myositis autoantibodies, anti-SRP and anti-HMGCR antibodies. These were performed using the Euroimmun Myositis Immunoblot and the PathWest HMGCR ELISA [13]. All muscle biopsies were sent to the Neuropathology Department of PathWest at Royal Perth Hospital and reviewed by a neuropathologist. All biopsies underwent the same standard muscle biopsy protocol, including H&E, modified Gomori trichrome, PAS and PASD, Oil red O, acid phosphatase, alkaline phosphatase, adenylate deaminase, myophosphorylase, NADH, SDH, COX, COX/SDH, ATPase 4.3/4.6/9.4, slow and fast myosin, PFK A, PFK B, developmental myosin, NCAM and utrophin, as well as CD31, MHC-I (Dako, Monoclonal antibody, clone W6/32), MHC-II (BD, Monoclonal antibody, clone L243), MAC (Dako, Monoclonal antibody, clone aE11), and negative control. Muscle biopsies were reviewed by three authors, and the intensity and distribution of necrotic and regenerating fibres and immunostaining were recorded.

This study was approved by the ethics committee of Sir Charles Gairdner Hospital as part of the Myositis project (approval number 2006-073).

3. Results

We identified 20 patients with NAM: 14 with anti-HMGCR antibodies (70%), two with anti-SRP antibodies (10%), three associated with connective tissue disease (15%), and two as yet unspecified. Patient age at presentation varied from 28 to 78 years (mean 58.3); 12 patients (60%) were women. All 20 presented with a history of proximal weakness; almost one third had dysphagia; six complained of myalgia (30%). Four patients had symptoms of dyspnoea, with pulmonary function tests consistent with respiratory muscle weakness in three patients, while the remaining patient had evidence of pulmonary fibrosis on imaging. The majority of patients had a symmetrical proximal limb-girdle weakness, with only four patients presenting with a pattern of more severe lower limb weakness than upper limb weakness (see Table 1). Neck flexor weakness was found in five patients (25%), while seven patients exhibited some weakness affecting movements of the elbows or knees. Only one patient, with connective tissue disease associated NAM, was found to have distal weakness. The tempo of symptom evolution prior to presentation ranged from two weeks to 6 months, with the median duration of symptoms at presentation being four months. One patient, from the statin associated anti-HMGCR group, presented with a more chronic history of myalgia and generalised subjective weakness over a period of three years, and had no objective weakness on examination.

Muscle biopsy was performed in 19 cases, processed at a single centre, and reviewed by a specialised neuropathologist. All biopsies had regenerating fibres; necrotic fibres were seen in seventeen cases, these were single fibres and polyphasic. Major Histocompatibility Complex-I (MHC-I) positive staining was seen in 16 cases: seven with diffuse sarcolemmal staining, two with sarcoplasmic staining, with the rest having patchy sarcolemmal staining of varying intensities. Three had patchy MHC-II positive staining, all of which were biopsies with very strong MHC-I staining. Six biopsies showed a mild inflammatory cell infiltrate consisting of sparse lymphocytes in the endomysium and perivascular region. Only three of the biopsies were positive for Membrane Attack Complex, all with only patchy weak sarcolemmal staining and no microvascular staining. Internal nucleation of muscle fibres was a prominent feature in four cases, with 15–20% muscle fibre involvement, a histological marker of chronicity (see Fig. 1 for biopsy examples). Although this did not correlate with symptom duration, there was a suggestion that this correlated with severity of muscle weakness. One patient did not have a biopsy performed, instead diagnosis was made based on clinical presentation and positive HMGCR serology in the context of statin exposure, and they improved with prednisolone and azathioprine immunotherapy, weaned over two years.

3.1. Anti-HMGCR antibody positive cases

There were 14 patients (67%) found to be positive for the anti-HMGCR antibody, with 12 having previous statin exposure. The mean initial CK level was 7189 units/L (range 1000–17,000); with power on examination at initial presentation varying from two to five on the Medical Research Council (MRC) scale for muscle strength.

There were two statin-naïve patients with positive antibodies. The first patient was of African descent with an initial CK of 13,000 U/L and muscle power with an MRC grading of 2, the other was Caucasian with a CK of 7000 and MRC power grading of 3+. They were younger than their statin-exposed counterparts, 51 and 37 years old respectively, compared with an average of 65 years old in the statin subgroup (see Table 1). Patient 1 had moderate numbers of necrotic fibres on biopsy with numerous regenerating fibres and moderate but patchy MHC-I positivity, and no inflammation. Patient 2 had only mild necrosis, but again with numerous regenerating fibres, moderate and diffuse MHC-I positivity and mild patchy sarcolemmal MAC staining. Both patients required high dose prednisolone, methotrexate