
Title: Treatment and outcomes in necrotising autoimmune myopathy: an australian perspective

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Treatment and Outcomes in Necrotising Autoimmune Myopathy:

An Australian Perspective

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Highlights

- NAM is related to SRP and HMGCR antibodies, connective tissue disease and cancer
- NAM is responsive to immunotherapy, but often requires three or more agents
- IVIG and Rituximab are often effective, and can be used as steroid-sparing agents
- MHC-II and MAC staining on muscle biopsy may be markers of more refractory disease

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 6047 units/L (range 1000 - 17000). The statin naïve patients with HMGCR antibodies and patients with SRP antibodies were 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, 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
Necrotizing Autoimmune Myopathy; HMGCR antibodies; statin myopathy; Immune mediated necrotizing 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 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.

1. **Methods:**

We identified patients that had presented to the Western Australian Neuroscience Research Institute (WANRI) between the years 2000 to 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, with intensity and distribution of necrotic and regenerating fibres and immunostaining recorded.

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

2. **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 – 78 years (mean 58.3); 12 patients (60%) were women. All 20 presented with 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 Figure 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 – 17000); 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 13000U/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 and azathioprine, as well as fortnightly IVIG infusions and eventually rituximab infusions to control their disease, and are still receiving immunotherapy for ongoing symptoms. Both relapsed on tapering of prednisolone therapy (see Figure 2.1 for illustrative case of patient 2).

Of the remaining 12 patients, all with previous stain exposure, eleven had muscle biopsies performed, all showing either necrotic or regenerating fibres. Two patients did not have necrotic fibres seen on biopsy, but these biopsies were performed after immunosuppression had already been commenced. Myonecrosis was mostly mild, with moderate numbers of regenerating fibres. Three biopsies also showed a mild perivascular inflammatory cell infiltrate and another, mild endomysial inflammation. Eight biopsies were mildly positive for MHC-I, with one of these also positive for MAC with mild patchy sarcolemmal staining. None of the biopsies stained positive for MHC-II.
One patient was managed conservatively without immunosuppression and one patient was only recently diagnosed and had not yet commenced immunotherapy. All other patients required high dose prednisolone weaned over at least 12 months; five patients required only one steroid-sparing agent (three had methotrexate, one mycophenolate, and one azathioprine). Three patients required regular intravenous immunoglobulin (IVIG) therapy (either fortnightly or monthly) and of those three, two received rituximab therapy due to difficulty weaning off the prednisolone or relapses. Three patients in total received rituximab. Of this subgroup, only four patients achieved a complete clinical and biochemical remission and no longer required therapy, with courses of immunotherapy ranging from 12 to 120 months (see Figure 2.2 for illustrative case). The remaining seven patients are still requiring immunotherapy. Of these, four patients have ongoing symptoms and proximal weakness, despite immunotherapy treatment ranging from 12 to 42 months total duration and multiple steroid sparing agents.

### 3.2 Anti-SRP Antibody positive

Only two patients were found to be positive for the anti-SRP antibody. Initial CK levels were 5762 and 10 000U/L and initial MRC power grade of 3 and 3- respectively. Both patient biopsies showed mild necrosis and regenerating fibres, and no inflammation. Patient B also had moderate diffuse MHC-I positivity.

Patient A is still experiencing ongoing symptoms, despite an immunotherapy regime that has included prednisolone, methotrexate, azathioprine, IVIG, rituximab and tacrolimus over a 14 year period. This particular patient responded very well to rituximab initially but then relapsed with prednisolone weaning (see Figure 2.3).
Patient B initially received prednisolone, methotrexate and IVIG, which induced a clinical recovery of power to baseline, but the patient continues to have persistently elevated CK over the 3.5 years of prednisolone and methotrexate tapering.

**3.3 Connective Tissue Disease Associated**

Three patients were found to have NAM associated with connective tissue disease, specifically Sjogren’s Disease, Systemic Lupus Erythematosus and Scleroderma, as diagnosed on clinical picture and positive autoimmune antibodies; anti-R052, anti-Sm, and anti-RNP respectively. Mean initial CK levels were 4490 U/L (range from 2609 to 6332) and MRC power ranged from 3+ to 4.

All three patients had mild-moderate necrosis and moderate numbers of regenerating fibres on biopsy with strong MHC-I positivity. One biopsy also had moderate MHC-II and patchy sarcolemmal MAC positivity. Two out of three biopsies also had a mild perivascular inflammatory cell infiltrate.

Of the three patients, one has not yet commenced therapy due to recent diagnosis. This patient was also found to have a low but positive titre for the anti-HMGCR antibody (15.1 RU, reference <11 RU), but it was thought that her NAM was likely due to her Sjogren’s Disease. The other two patients have had a clinical recovery of strength from immunotherapy: one with methotrexate and prednisolone, the other with methotrexate, prednisolone and azathioprine (see Figure 2.4). Both patients are still receiving immunotherapy due to climbing creatine kinase levels during prednisolone tapering.
3.4 Unspecified NAM

The cause for two patients’ NAM could not be found, with all antibody and viral serology results negative, as well as negative malignancy screens including CT imaging of chest, abdomen and pelvis.

Patient A had an initial CK of 2000 with an initial muscle power grading of 4. Biopsy showed necrosis and regenerating fibres, with MHC 1 positivity. This patient’s disease was biochemically and clinically responsive to rituximab, in conjunction with methotrexate, azathioprine and prednisolone, but consistently relapsed multiple times with prednisolone weaning.

Patient B had an initial CK of 9820, and an initial power grading of 3 in both proximal limb girdles. Biopsy showed moderate numbers of both necrotic and regenerating fibres, with strong diffuse MHC-I and patchy MHC-II positivity. This patient had a return to full power with a combination of high dose prednisolone, fortnightly IVIG and mycophenolate 500mg twice daily but relapsed following prednisolone taper, and eventually required rituximab infusions to aid in steroid weaning (see Figure 2.5).

3. Discussion:

We present a retrospective cohort of 20 Australian patients with Necrotising Autoimmune Myopathy, detailing our experience in diagnosing and treating this heterogeneous disease with comparisons across the aetiological subgroups: anti-HMGCR positive, anti-SRP positive and connective tissue disease associated.
All patients were initially referred to our clinic with a symmetrical proximal muscle weakness and a significantly elevated CK level, in keeping with the presentation findings of previous studies [1–5,10,12,14]. In our anecdotal experience, these patients also often have muscle atrophy at presentation, in comparison to the other inflammatory myopathy patients, where this is not commonly seen. In agreement with the 119th ENMC International Workshop on idiopathic inflammatory myopathies [15], none of our patients exhibited extra-ocular or neck extensor weakness. The majority of patients had equally weak upper and lower limb girdles, with only four patients exhibiting isolated weakness of the pelvic girdle. Five patients also had weakness of neck flexion on examination. Consistent with other recent studies, almost one third of our cohort had dysphagia and 30% complained of myalgia[1,5,16], with the majority of these patients being anti-HMGCR antibody positive with statin exposure (see Table 1). Creatine kinase levels were very high across the series (average 6858U/L), with the highest levels found in the anti-HMGCR positive group. Respiratory muscle weakness was not routinely investigated, nor was cardiac dysfunction, although both have been reported in the literature, particularly in association with anti-SRP (1,5,17).

Our study classified patients into subtypes according to serology and associated conditions. In all except two patients, we were able to identify potential precipitants to the development of NAM, the most common being statin exposure with positive anti-HMGCR antibodies (n=12, 60%). As expected, this group tended to be older than their statin-naïve counterparts, with on average less severe weakness. The anti-HMGCR positive patients without previous statin exposure were much younger with very high average CK levels of 10000 and more severe weakness (see Table 1). One of these patients was of African descent, the other Caucasian. Both these patients required Rituximab and IVIG therapy to gain symptomatic
improvement and are both requiring ongoing immunotherapy. This correlates with the findings of Mohassel et al [8]: that statin-naïve patients with positive anti-HMGCR antibodies are more resistant to therapy, and furthers the hypothesis that these patients could represent a clinically distinct subgroup of NAM. Both the anti-SRP positive and connective tissue disease related patients were also comparatively young, with the anti-SRP patients having similarly high CK levels and weakness severity. In contrast, the connective-tissue disease associated patients had relatively preserved power and lower CK levels. These findings are all consistent with previous studies, with the anti-SRP subgroup tending to have the most severe weakness and statin-naïve anti-HMGCR positive patients having CK levels disproportionately high for the weakness severity (1,16,18). Our entire cohort received serological testing and all but one patient had a muscle biopsy performed, with only four patients without either positive anti-SRP or anti-HMGCR serology. The one patient without muscle biopsy results was diagnosed with anti-HMGCR antibody associated NAM by clinical presentation and serology alone and improved with immunotherapy. This supports the recently published diagnostic algorithm by Mammen et al., [14] which recommends serological testing for anti-HMGCR antibodies prior to muscle biopsy. Given the specificity of positive anti-HMGCR antibodies for NAM in the context of patients over 50 years with previous stain exposure [6,18,19], perhaps future diagnoses could be based on clinical picture and serology alone, without the need for invasive muscle biopsies. All patients were screened clinically for malignancy and 40% of our cohort received formal malignancy screening including either PET or CT imaging of chest, abdomen, pelvis, although no patients were found to have malignancy. We recommend extensive investigation for malignancy if serology, autoimmune testing and viral studies do not highlight an alternative underlying aetiology, or if there is any clinical suspicion based upon individual patient presentation. It should be noted that there have been anti-HMGCR and anti-SRP antibodies reported in a
minority of cases of paraneoplastic NAM (2,17). In our centre, if antibody titres are strongly positive and there is no clinical indication of an underlying malignancy, such as weight loss, night sweats, systemic symptoms or history of smoking, then extensive malignancy screening is not performed. However, if no cause is readily identified for the NAM, antibody results are equivocal or clinical symptoms are suggestive, then full malignancy screen, including tumour markers and full body scanning (CT chest, abdomen, pelvis) and/or PET scanning is performed. Although HIV is a known cause for NAM [1,2], none of our patients were found to have the virus, with formal testing being available in 13 patients.

There was a large variation across patient biopsy results, and the number of necrotic and regenerating fibres did not necessarily correlate with weakness severity or creatine kinase levels. Patients in the statin naïve and connective tissue disorder groups tended to have the most florid necrotic and regenerating biopsies, all with moderate MHC-I positivity. These two subgroups were also more likely to have MHC-II and MAC positivity, with these markers only being present in biopsies with moderate-high levels of regenerating fibres. The majority of the statin-associated anti-HMGCR positive biopsies showed comparatively fewer necrotic and regenerating fibres. Of the four patients from the entire cohort with either MHC-II or MAC positivity, three required four or more immunosuppressive agents including prednisolone to gain symptom control. Further studies are needed to elucidate whether these could be markers of treatment resistance, used for prognostic purposes. We recommend that a panel of diagnostic stains for NAM, including H&E, MHC-I, MHC-II and MAC, be performed on all cases where the diagnosis is suspected by the treating clinician or where positive autoantibodies have been found. In our experience, the biopsy findings are variable, with some cases only showing a single necrotic fibre on histology, therefore correlation with patient presentation and serology is necessary for accurate diagnosis.
Treatment of NAM is notoriously difficult, with most cases being refractory to conventional immunotherapy with a high relapse rate when steroid weaning is attempted [1,4,5,7,8,12,14]. Our study results again confirm this, with only four patients able to discontinue immunotherapy and achieve complete remission, all from the statin exposed anti-HMGCR positive subgroup, with one patient requiring ten years of slowly weaning methotrexate and prednisolone. Of our cohort, 80% of patients (n = 16) are still requiring immunotherapy, with 40% of these still experiencing some residual weakness, although improved from initial presentation. The average duration of immunotherapy is 40 months thus far, with the majority of patients requiring two or more steroid sparing agents in addition to prednisolone, and 45% requiring three or more agents. As shown in the individual case graphs (see charts 1-5), NAM is clinically and biochemically responsive to steroids and liable to relapse with steroid weaning. Recent studies have focused on the role of IVIG and Rituximab in treating refractory NAM patients [20,21]. In our experience, IVIG plays an important role in enabling steroid tapering and improving clinical function, and is useful for treating acute and severe relapses. Of the eight patients who required IVIG and/or Rituximab therapy (see Table 1), three of the patients receiving IVIG achieved complete resolution of symptoms, but all are still requiring some additional form of immunotherapy. Rituximab use enabled prednisolone weaning and cessation of IVIG in two patients.

4. Conclusion:
Necrotising Autoimmune Myopathy is a potentially treatable immune-mediated myopathy, which needs to be differentiated from other causes of myocyte necrosis, such as hypothyroidism, muscular dystrophies and other toxic myopathies. It clinically presents with a subacute proximal limb girdle weakness that develops over weeks to months. Biopsy
findings include single and polyphasic necrotic and regenerating fibres with minimal inflammatory cell infiltrate. From our series, it appears that patients with MAC and MHC-II positive immunostaining on biopsy are more refractory to immunotherapy. Once a diagnosis of NAM is made, early, aggressive immunosuppressive treatment should be initiated, often requiring multiple steroid sparing agents. In our experience, Rituximab and IVIG are useful in symptom control and reducing steroid use, although disease may relapse with rapid steroid weaning.

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5. References:


Figure 1: NAM Muscle Biopsies

1) Connective tissue disease associated: Frozen section H&E staining showing internalized nucleation of muscle fibres, scattered necrotic and regenerating fibres and mild inflammatory infiltrate

2) Statin-naive anti-HMGCR antibody positive: a necrotic fibre (black arrow) and regenerating fibres (white arrow)

3) Statin-naive anti-HMGCR antibody positive: Regenerating fibres staining with developmental myosin

4) Connective tissue disease associated: with widespread sarcolemmal MHC-1 staining
Figure 2.1-5: Case examples showing Muscle Power and Creatine Kinase over time with associated immunotherapy

1. BRM/GE: Postecellular necrosis. The patient was successfully treated with muscle biopsy and muscle biopsy showed improved levels of muscle enzyme activity. Treatment included muscle enzyme replacement therapy and immunotherapy to improve muscle function.

2. BRM/GE: Postecellular necrosis. The patient showed improvements in muscle function after treatment with muscle biopsy and muscle biopsy showed improved levels of muscle enzyme activity. Treatment included muscle enzyme replacement therapy and immunotherapy to improve muscle function.

3. IgG and IgM: Elevated levels of muscle enzyme activity were observed in the patient's muscle biopsy. Treatment included muscle enzyme replacement therapy and immunotherapy to improve muscle function.

4. IgG and IgM: Elevated levels of muscle enzyme activity were observed in the patient's muscle biopsy. Treatment included muscle enzyme replacement therapy and immunotherapy to improve muscle function.

5. IgG and IgM: Elevated levels of muscle enzyme activity were observed in the patient's muscle biopsy. Treatment included muscle enzyme replacement therapy and immunotherapy to improve muscle function.

Note: The case examples show improvements in muscle function and reduced muscle enzyme activity after treatment with muscle biopsy and muscle biopsy showed improved levels of muscle enzyme activity. Treatment included muscle enzyme replacement therapy and immunotherapy to improve muscle function.
Table 1. Summary of Cohort Data

<table>
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<th>Feature</th>
<th>HMGCR Positive</th>
<th>HMGCR Positive</th>
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<td>Average months of therapy (range)</td>
<td>7 (2-12)</td>
<td>32 (12-120)</td>
<td>105 (40-170)</td>
<td>45 (1-117)</td>
<td>47.5 (35-60)</td>
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