CURRENT ESSENTIALS IN INFLAMMATORY MYOPATHIES

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Disclosure: JS has received payments for consultancies or talks, or honoraria, or reimbursements for travel, or research grants from Bayer, Biotest, CSL Behring, Novartis, and Octapharma.
Received: 11.07.13 **Accepted:** 26.08.13
Citation: EMJ Neurol. 2013;1:46-51.

ABSTRACT

Inflammatory myopathies are a heterogeneous group of acquired systemic diseases, which include dermatomyositis (DM), polymyositis (PM), necrotising myopathy (NM) and inclusion body myositis (IBM). All four disease entities share certain clinical characteristics, such as progressive muscle weakness and elevated muscle enzymes. Other characteristic-associated features such as skin involvement in DM or the detection of myositis-specific antibodies, may be indicative of a particular subtype. However, muscle biopsy is still essential for the diagnosis and shows distinct histopathological characteristics for each subtype of myositis. Treatment of inflammatory myopathies is still based on clinical experience, since placebo-controlled trials are scarce. While DM, PM and NM respond well to immunosuppressive treatment, IBM is usually resistant to immunotherapy. This review aims to give a concise overview and provide guidance for general management of myositis.

Keywords: Myositis, muscle inflammation, polymyositis, dermatomyositis, necrotising myopathy, inclusion body myositis.

INTRODUCTION

Inflammatory myopathies are a heterogeneous group of acquired systemic diseases which result in muscle weakness and disability. The four most common subtypes include dermatomyositis (DM), polymyositis (PM), necrotising myopathy (NM) and inclusion body myositis (IBM). They are characterised by distinct clinical presentations, histopathology and response to treatment. They all share certain clinical features such as progressive muscle weakness over a period spanning from weeks to years, elevated muscle enzymes and inflammation in muscle biopsy. In the sera of many patients, myositis-specific antibodies can be detected, some of which are associated with a specific phenotype.[1,2] Pathological examination on muscle biopsy is the key diagnostic tool to establish the diagnosis of myositis. Muscle magnetic resonance imaging (MRI) can be a useful tool to identify a target muscle for biopsy. There is a lack of evidence-based treatment guidelines for myositis due to the rarity of the disease. Expert opinions on treatment options are reviewed in this article.

DERMATOMYOSITIS

Dermatomyositis (DM) is a multisystem autoimmune disease, which presents with proximal muscle weakness and typical skin manifestations. It affects adults and children alike, and is referred to as juvenile DM (JDM) when patients are under the age of 18 years old. Women are more often affected than men. JDM is the most common form of inflammatory myopathy among children. The average age of onset in JDM is 7 years old, and girls are affected more often than boys with a ratio of 5 to 1.[3] In adults, the age of onset is usually between 45 and 65 years old.

The majority of patients present with painless, symmetric proximal muscle weakness, which evolves over a period of weeks to months, and usually shows elevated muscle enzymes such as creatine kinase (CK). Involvement of oropharyngeal

muscles can be present, resulting in dysphagia and dysarthria. In addition to muscle weakness, typical skin manifestations such as an erythematous rash, a heliotrope rash and oedema around the eyes, periungual telangiectasia or Gottron's papules are present. Skin features can accompany or even precede muscular symptoms. The rash is usually located in the face, neck, torso, and extensor surfaces of the extremities. Infrequently, adult patients also show subcutaneous calcifications, ulcerations and skin atrophy, although those features are more common in JDM.[4,5]

Some patients present with typical skin features, but lack muscle involvement. This specific subtype is referred to as amyopathic dermatomyositis (ADM).[6]

DM is frequently associated with other medical conditions, two of which are: interstitial lung disease (ILD) and malignancies.[7-9] In the past, different myositis specific antibodies have been identified, which are associated with specific phenotypes. Anti-Mi-2 autoantibodies can be found in about 20% of patients and are associated with the typical phenotype of DM. In ADM, an antibody (Anti-CAMD-14) acting against melanoma differentiation-associated gene 5 (MDA5) has been identified. The presence of these antibodies is associated with the development of a rapid progressive ILD and poor prognosis.[10] Anti-P155/140 has been reported in 13-21% of the patients with DM and is associated with an increased risk for malignancy.[11]

Electromyography (EMG) in patients with DM typically shows polyphasic motor units of small amplitude and of short duration, as well as spontaneous activity (positive sharp waves and fibrillations). MRI may detect signal abnormality or oedema, while in the later stages of the disease muscle atrophy or fatty transformation is more evident.

Muscle pathology in DM is marked by perifascicular atrophy, degeneration and regeneration of muscle fibres and perivascular inflammation. Complement activation and formation of the membranolytic attack complex may lead to damage of endothelial cells and capillaries, thereby causing muscle fibre ischaemia.[12,13] It has recently been proposed that type I interferons might play the leading role in the pathogenesis of DM.[14,15]

POLYMYOSITIS

Polymyositis (PM) is a rare disease, which usually begins after the age of 18. Past diagnostic criteria differentiate PM from DM only by lack of skin alterations. As in DM, symptoms in PM include a subacute onset of proximal muscle weakness and elevated muscle enzymes. In addition, patients frequently complain of myalgia and tenderness, particularly upon examination. Studies suggest that PM has been over diagnosed in the past, since muscle biopsy was not considered, and the lack of specific clinical characteristics make it difficult to distinguish PM from other forms of myositis.[16]

EMG and MRI findings are the same as those in DM, and cannot be used to discriminate between the two disease entities.

Muscle biopsy is essential to differentiate PM from other inflammatory myopathies. Histopathological features of PM include endomysial inflammatory infiltrates, necrosis and regenerating muscle fibres of different size. The inflammatory infiltrates consist of macrophages and mononuclear CD8+ T cells, which invade non-necrotic muscle fibres expressing the MHC class I antigen.[17,18]

As in DM, PM patients can develop complicating extramuscular syndromes such as ILD and myocarditis. Previous studies state that cardiological complications account for 10-20% of deaths in PM patients.[19]

NECROTISING MYOPATHY

Several years ago, immune-mediated necrotising myopathy (NM) has been identified as a specific subtype of myositis.[18,20] Clinical symptoms are indistinguishable from PM and include proximal muscle weakness, myalgia, and considerably elevated muscle enzymes. EMG and MRI yield similar results as in other inflammatory myopathies. Its aetiology is multifactorial and NM can be associated with malignancies, intake of statins or connective tissues diseases. Myositis-specific antibodies against the signal recognition particle (anti-SRP) are frequently found in the blood of NM patients with an average age at disease onset of 48 years, and seem to be associated with an unfavourable prognosis concerning the disease progression.[21,22] Recently, another antibody reacting against 3-hydroxy-3-methylglutaryl-

coenzyme A reductase (HMGCR) has been described.[23,24] HMGCR is the key enzyme in cholesterol biosynthesis and can be inhibited by statins. Anti-HMGCR antibodies have been identified in statin-exposed patients above the age of 50, while non-exposed patients tend to be younger.[24] Recently, it has been recognised that statins may not only cause a toxic myopathy, but can also trigger an autoimmune necrotic myopathy. Statins lead to an up-regulation of HMGCR-expression. Therefore, one hypothesis is that in presence of other risk factors such as environmental influences of genetic susceptibility, statins might activate an autoimmune process if anti-HMGC-antibodies are present.[24]

The pathological features of NM are distinct from PM and DM because the muscle biopsy lacks endomysial inflammation. Muscle fibre necrosis is the main characteristic finding on muscle biopsy.[25] In some patients perivascular deposits of complement can be found. Inflammatory cells are scarce and are mainly represented by macrophages. The exact pathogenesis of NM is still unclear. Several studies suggest a humoural autoimmune process, which is supported by the fact that complement deposits and autoantibodies are present.[18]

TREATMENT STRATEGIES IN DM, PM AND NM

Since inflammatory myopathies are autoimmune-mediated disorders, therapeutic options include immunosuppressants and immunomodulatory drugs. Treatment goals are to suppress inflammation, stop muscle necrosis and regain muscle strength. Controlled trials are scarce and are difficult to carry out due to the rarity of these diseases.

Empiric data show that corticosteroids are effective in the treatment of DM, PM and NM. Based on experience, high-dose corticosteroids are the initial treatment of choice. Patients are usually treated with a standard dosage of 1 mg/kg body-weight per day for at least 2-4 weeks. If severe symptoms are present, treatment may be initiated with an intravenous application of 500 to 1,000 mg prednisolone daily over a period of 3-5 days, followed by high-dose oral treatment as mentioned above.[27] Depending on the clinical stabilisation, prednisone dose is tapered slowly until the maintenance dose of usually 5 to 10 mg per day is reached. However, upon initial clinical stabilisation, many patients deteriorate when the prednisolone dose is lowered. Frequently, the use of immunosuppressant drugs such as azathioprine, methotrexate or mycophenolate mofetil, are needed as a steroid-sparing agent. The most recent Cochrane Review found four studies comparing different immunosuppressant with each other. None of the studies could find significant variation between the different drugs.[27] Patience is needed since the clinical effect of these drugs may takes 3-6 months to evolve. Methotrexate may cause pneumonitis as a severe side effect, which can be difficult to distinguish from the ILD seen in myositis patients.

CK levels do not always reflect disease activity, but may be decreased under the immunosuppressant therapy.

In rapidly progressive cases or when steroid-response is poor, intravenously applied immunoglobulins (IVIG) are the treatment of choice.[28-30] The initial dosage is 2 g/kg body weight every 4-8 weeks, depending on the clinical response.

Etanercept, a TNF-α inhibitor, has been investigated in a double-blind, placebo-controlled study of 16 patients with DM. Results did not demonstrate a benefit regarding muscle strength, but a steroid-sparing effect was observed.[31] After several promising case series,[32,33] recently, the results of a randomised, double-blind, placebo-controlled trial of rituximab in the treatment of adult and juvenile myositis have been published.[34] 83% of the patients, who had been unresponsive to prior immunosuppressive treatment, showed improvement of muscle strength during the 44 weeks of the trial.

INCLUSION BODY MYOSITIS

Sporadic inclusion body myositis (IBM) is the most common form of inflammatory myopathies above the age of 50 years.[35] In contrast to PM and DM, men are more often affected than women.

IBM is characterised by slowly progressive, often asymmetric muscle weakness, which can affect proximal and distal muscle groups and relentlessly leads to disability. Frequently, hand and finger flexors and knee extensors are affected early during the course of the disease, accompanied by severe muscle atrophy. In contrast to other forms of

myositis, involvement of oropharyngeal muscles is present in more than 60% of IBM patients, which leads to dysphagia and complications such as aspiration pneumonia.[36] CK levels may only be mildly elevated. EMG findings are similar to those found in other myositis; in addition, nerve conduction may show peripheral sensory axonal neuropathy. Muscle MRI yields similar findings as in DM, but can emphasise asymmetrical distribution of muscle involvement. Recently, an auto-antibody in IBM has been demonstrated: anti-Mup44 targets the cytosolic 5'-nucleotidase 1A, an enzyme highly abundant in skeletal muscle, which seems to play a role in DNA repair metabolism.[37,38] Larger series are awaited to confirm the sensitivity and specificity of this antibody.

Histopathology shows endomysial inflammation mediated by CD8+ T cells and macrophages similar to PM. In addition, MHC class I up-regulation is present on necrotic and non-necrotic muscle fibres as a surrogate marker of inflammation. In addition, degenerative features are present and include protein accumulation with intrafibre deposition of β-amyloid as well as vacuolar transformation, which clearly distinguish IBM from other forms of myositis.[39] The pathogenesis of IBM is still unclear.

Past diagnostic criteria for IBM defined by Griggs et al.[40] do not rely much on clinical features. Since not all characteristic histopathological findings may be present at the beginning of the disease, criteria, which include clinical features, are needed in order to allow early diagnosis. Revised diagnostic criteria have been compiled at a recent ENMC International Workshop.[41] According to these criteria, the classifications include clinico-pathologically defined IBM, clinically defined IBM, and probable IBM. Clinical and laboratory features include: a duration over 12 months, age at onset >45 years, CK no higher than 15-fold above the upper limit of normal, and knee extension weakness ≥hip flexion weakness and/or finger flexion weakness ≥shoulder abduction weakness. Pathological features include: endomysial inflammatory infiltrate, up-regulation of MHC class I, rimmed vacuoles and protein accumulation or 15-18 nm filaments.

THERAPEUTIC STRATEGIES IN IBM

Although the role of degeneration in the pathogenesis of IBM is still unclear, it might be one explanation why IBM seems to be resistant to immunosuppressive treatment. Unlike other forms of myositis, glucocorticosteroids have no, or only a transient effect on the disease progression and might even lead to deterioration.[42,43] Several studies on different immunosuppressants such as MTX, anti-T lymphocyte globulin, azathioprine, MMF, cyclosporine A and tacrolimus, did not show a beneficial effect on muscle strength or disease progression.[44-47] A pilot trial of etanercept and a small open trial of alemtuzumab could not show sustained improvement regarding muscle strength or function.[48,49]

Clinical trials with IVIG failed to demonstrate efficacy, except for some improvement of the dysphagia in one of the studies.[50,51] Since dysphagia is frequent in IBM and associated with a high mortality due to aspiration and malnutrition, IVIG presents a therapeutic option in patients with dysphagia. In addition, physical therapy and logopaedic training are advisable early in the course of the disease.[52,53]

CONCLUSION

Inflammatory myopathies comprises of four disease entities; DM, PM, NM and IBM, which usually can be distinguished by characteristic clinical, histological or pathological features. Treatment management is still based on clinical experience since large, controlled trials are lacking, mostly due to the rarity of these diseases. While DM and PM respond well to immunosuppressants, the treatment of IBM remains challenging. Further understanding of the pathogenesis is needed in order to identify suitable therapeutic targets.

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