Polymyositis and dermatomyositis: classification, risk factors and outcome
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Long-term outcome in idiopathic inflammatory myopathies: worse than expected

In this thesis we showed that the prognosis of the idiopathic inflammatory myopathies (IIMs) is not as favourable as was expected in diseases that generally are amenable to (immunosuppressive) treatment. In many reviews concerning IIMs the prognosis of PM and DM is described as favourable because of their response to immunosuppressive and immunomodulating therapy.

In our study concerning outcome, described in chapter 7, patients with an IIM (sporadic inclusion body myositis (s-IBM) excluded) were found to have a mortality risk of at least 10% due to disease-related causes (mostly malignancy) during the first years after the onset of myositis. This high mortality is impressive, especially when it is compared with the 5-year mortality risk of 1-2% in a general healthy age-matched Dutch population (Statistics Netherlands; www.cbs.nl).

In addition, most of the survivors in our study had a chronic continuous or polycyclic disease course, and many of them needed drugs for a long period of time with significant adverse effects. This notion place IIMs in the category of chronic autoimmune diseases, including chronic inflammatory demyelinating polyneuropathy or myasthenia gravis, in which a low maintenance dose of immunosuppressants is almost always needed. Although two-thirds of our patients had regained normal muscle strength, only one third had no or only slight disability, and even less were found to have normal scores on a quality-of-life scale. This discrepancy between outcome measures has been found in three other recent studies in myositis and also in other diseases.1-4 For example, in Guillain-Barré syndrome, patients may suffer from disabling persistent fatigue after regaining normal muscle strength.4

We would like to emphasize that physicians treating patients with myositis should be aware of the major impact of PM and DM on perceived disability and quality of life. One may conclude that present therapies are not good enough and give rise to serious side effects. Promising results were shown for oral pulsed dexamethasone versus oral continuous prednisone in a small open-label, non-randomised trial.5 However, a recently completed randomized controlled trial with oral pulsed dexamethasone did not show a better outcome for dexamethasone-treated patients, apart from significantly fewer side effects.6

Several drugs are currently being investigated in clinical trials in patients with inflammatory myopathies including tumour necrosis factor alpha (TNFα) inhibitors and rituximab, a monoclonal antibody against CD20 expressed on B cells.7
Pathogenesis-based classification is needed

Because of the treatment failure of generic immunosuppressive agents (steroids) in IIMs, new treatment trials should be more specific and focus on the immunopathogenetic pathways of the different subtypes of myositis. Subtypes of IIMs are traditionally classified on the basis of signs and symptoms but more recently an attempt was made to design a classification based on differences in pathogenesis. This is a prerequisite for better-targeted new therapies.

However, the pathogenesis of the IIMs is still ill-understood. In PM, as in s-IBM, there seems to be a muscle fibre-antigen directed and MHC I restricted cytotoxicity, mediated by cytotoxic CD8+ T cells. DM is thought to be a humorally mediated autoimmune disease in which the immune process is primarily directed against the intramuscular microvasculature. The presence of dendritic cells (the immune system’s professional producer of the type 1 interferons alpha and beta) and processes in IIMs suggests revisions in models of the pathogenesis of the inflammatory myopathies and provides rationales for future therapeutic approaches.

Genetic factors may modulate these pathogenetic processes and may contribute to susceptibility for the different IIMs. Candidate gene studies in non-familial IIM have mainly concentrated on the HLA class II region. HLA DRB1*0301 and DQA1*0501 have now been determined to be risk factors for all the major clinical forms of sporadic and familial IIM in both white adults and children in the US and Europe. In addition to the HLA locus, other genes may contribute to the genetic risk for IIM.

We found a possible genetic risk factor for the IIMs, i.e. a genetically-determined functional polymorphism for one of the receptors for the constant part of antibodies (FcγR; FcγRIIIa-V-158) (chapter 6). These receptors are assumed to be crucial links between the cellular and humoral parts of the immune system. Interaction with these receptors confers potent effector functions to antibody and their efficiency is determined in part by functional polymorphisms which may contribute to susceptibility of various auto-immune diseases.

Revision of diagnoses by histopathology I

A subtype questioned: polymyositis

Following the Bohan and Peter classification, which were based on clinical criteria only, histopathological signs became major criteria to differentiate PM from DM in the Dalakas classification. In DM there is a B-cell infiltrate located around blood vessels in the perimysium. In PM there is T-cell infiltration invading non-necrotic muscle fibres. In chapter 3, we reviewed the diagnoses in a large group of clinically well-defined patients.
with IIM (IBM excluded) and found PM to be very rare as that diagnosis could be made in only nine out of 165 patients (5%). On average six years after presentation, five out of these nine patients fulfilled the criteria for the diagnosis s-IBM. None of the remaining four PM patients complied with the classical clinical picture of limb-girdle distribution of weakness in young adults. On the basis of these findings one can doubt about the separate entity of polymyositis. The implication of this notion goes beyond semantics: s-IBM is resistant to corticosteroids, while long term corticosteroid- treatment is often harmful, particularly in elderly patients.¹⁹

Our results are in line with the findings of others.¹⁷-¹⁹ In 1997, Blume et al.¹⁷ described ten patients with late onset, slowly progressive weakness of predominantly quadriceps muscles, with only mildly elevated serum creatine kinase activity. The muscle biopsy showed endomysial mononuclear cell infiltrates invading non-necrotic muscle fibres, no vacuoles or amyloid, and an excess of cytochrome-negative fibres. The response to prednisone treatment was poor. These investigators proposed to identify patients with too many COX-negative fibres as a separate subgroup of PM, with poor prognosis, but it is now known that an excess of COX negative fibres (and other subclinical signs of mitochondrial dysfunction) is a prominent sign of s-IBM, and we are of the opinion that these ten patients should have been diagnosed as s-IBM. Likewise, in a more recent larger study, Chahn and Engel found that one-third of patients with muscle biopsy features indicating PM (no signs of degenerative disease) had the clinical features of s-IBM (“PM/IBM”).¹⁸ They also found patients with both the clinical and the histopathological signs of PM. However, it is unclear how the clinical data were obtained, how clinical improvement was defined, and auto-aggressive invasion was present in only part of the patients diagnosed as PM. Some of these patients may well have had DM or nonspecific myositis (see below), and others may have had s-IBM. Trayanov et al. found that PM is rare (9%), was always chronic and was associated with the highest rate (50%) of refractoriness to initial corticosteroid treatment.¹⁹

This report and many other reflect the current discussion regarding PM as a separate entity and the criteria that should be used to diagnose PM and s-IBM.²⁰-²³ The recent international European Neuromuscular Centre (ENMC) consensus criteria include PM as a separate entity.⁸ Future studies will have to show whether this is justified, or whether, alternatively, s-IBM can present in various forms. Currently, a study entitled “Development of Classification Criteria for the Idiopathic Inflammatory Myopathies and their Major Subgroups” is ongoing to which a significant number of specialists involved in the diagnosis and treatment of patients with IIMs are engaged (https://dir-apps.niehs.nih.gov/imacs/index.cfm?action=security.login).
Revision of diagnoses by histopathology II

A new subtype emerges: nonspecific myositis

In chapter 3 we described the distinction of two types of myositis in addition to the existing forms, i.e. nonspecific myositis (or unspecified) and immune-mediated necrotising myopathy (see below). As a consequence of our results these types are now inserted in the ENMC consensus on adult IIM in 2003 as separate entities. The distinction of these types is important not only for clinical reasons but it also may have implications for the hypothesis about pathogenesis.

Nonspecific myositis is now defined as a disorder with subacute or insidious onset of symmetrical proximal muscle weakness without skin abnormalities, associated with an elevated serum creatine kinase activity and the following histopathological features in the muscle biopsy specimen: perivascular mononuclear cell infiltrate at perimysial sites, no endomysial cell infiltrates apart from reaction to muscle fibre necrosis and scattered endomysial CD8+ T-cells which do not surround or invade muscle fibres, and no perifascicular atrophy. It is noted that patients with these features are being diagnosed as PM when applying the Bohan and Peter criteria. In our study, nonspecific myositis was diagnosed in almost 40% of all patients that were diagnosed with an IIM, (s-IBM excluded). These patients clinically differed from PM patients by shorter disease duration and a younger age, by the presence of myositis-specific auto-antibodies, and by the co-occurrence of connective tissue disorder (CTD) and malignancies. In these respects, patients with nonspecific myositis did not differ from DM. Our findings are corroborated by those of Trayanov et al. who found nonspecific myositis in 60% of their patients previously considered to have PM. The clinical implications of these findings are important: physicians engaged in diagnosis and treatment of patients with IIMs should be cautioned about the development of a CTD or a malignancy in the course of the disease in a patient with nonspecific myositis. Future studies are warranted to determine whether screening on malignancies should also be performed in this subtype of myositis.

Since nonspecific myositis and DM share histopathological features (by definition), and histopathological features to some extent reflect pathogenetic processes, it is conceivable that these entities share underlying pathogenetic mechanisms. Several histopathological abnormalities in DM (e.g. perivascular inflammation, endothelial hyperplasia with tubuloreticular structures, reduction of capillary density) point to a primary microvasculopathy. Microtubular inclusions in muscle capillaries are a conspicuous early sign. We found this feature in 20% of patients with nonspecific myositis, in 40% of patients with DM (and in none of the patients with IBM) (chapter 5). Remarkably, all of the nonspecific myositis patients with microtubular inclusions also had signs and symptoms of another CTD. This can suggest that there are differences in pathogenesis between nonspecific myositis with and without a CTD. However, in large groups of patients we did
not found differences between nonspecific myositis patients with and without CTD with respect to serum creatine kinase activity, erythrocyte sedimentation rate, the presence of auto-antibodies, and clinical outcome. Future studies should include analyses of the mononuclear cell accumulation in both disorders and the quantification of the different subsets at these sites (i.e. B-cells, T-helper cells, cytotoxic T-cells, dendritic cells and macrophages).

Of much interest in this respect are the recent studies in muscle biopsy specimens of DM patients done by Greenberg. Micro-array studies showed overexpression of genes induced by interferon-α/β. This suggested that plasmacytoid dendritic cells (pDCs) may be present in DM. Immunohistochemical studies subsequently identified pDCs in DM. pDCs also express CD4, and likely account for most of the CD4+ cells present in DM, previously interpreted as T-helper cells. This leads to the hypothesis that auto-antibodies bound to DNA or RNA in DM muscle may stimulate pDCs to secrete interferon-α/β, as occurs in SLE. So DM and SLE seem to share not only clinical features but may also share pathogenetic mechanisms. It would be interesting to investigate whether pDC are present in nonspecific myositis too.

Revision of diagnoses by histopathology III

A second subtype emerges: immune-mediated necrotising myopathy

Immune-mediated necrotising myopathy is now defined as subacute or insidious onset of symmetrical proximal muscle weakness associated with elevated serum creatine kinase activity and many necrotic muscle fibres in the muscle biopsy specimen, with no or only sparse perivascular cells, in which a toxic myopathy and acute rhabdomyolysis are excluded. In our retrospective study, necrotising myopathy was diagnosed in one fifth of patients with an IIM, s-IBM excluded. Patients with a necrotising myopathy had higher sCK activity than the other patients. There were no differences in age, sex, MSAs, nonspecific auto-antibodies, or ESR compared to the other patients. Seven percent of the patients with a necrotising myopathy developed a malignancy.

Necrosis of skeletal muscle without significant inflammation in association with carcinoma is also described in some small, non-randomised clinical studies. The Dutch guideline on the diagnosis and management of the IIM’s remarks this subtype only indirectly. We recommend that future editions of this guideline include this subtype of myositis and pay attention to the risk of cancer in this form of myositis.

Necrotising myopathy is now included in the ENMC consensus as an immune-mediated myopathy. Patients may be easily misdiagnosed as an muscular dystrophy, as illustrated by a recent case report by Sadeh. Differentiation between myositis and a muscular dystrophy is thus of paramount importance, but may be difficult on the basis of clinical features and
the increased serum creatine kinase activity. This distinction is further complicated by the occasional finding of mononuclear cell infiltrates in many muscular dystrophies.\textsuperscript{23} The pathogenetic mechanisms causing this type of myositis are unknown. We performed further immunohistochemical analyses on the muscle biopsy specimen of patients with a necrotising myopathy with good response to prednisone (chapter 4). Immunostaining of the muscle biopsy specimens showed T-lymphocytes (CD3) or macrophages (CD68) or both, in the vicinity of necrotic muscle fibres in all patients, but not around or invading non-necrotic muscle fibres. B-cell lymphocytes were sparse or absent in all specimens. In all muscle biopsy specimens there was overexpression of MHC-I on capillaries and necrotic or regenerating fibres, but no or only minimal MHC-I staining of non-necrotic muscle fibres was found.

One can argue that the muscle pathology in our patients was not mediated by cytotoxic lymphocytes since inflammatory cells were lacking with no or minimal MHC-I staining on non-necrotic muscle fibres and that instead a humoral mechanism might be involved. Future studies should reveal the pathogenetic basis of this disorder. RNA micro-array technology is a method for measuring large scale gene expression within tissue samples, providing relatively unbiased views of the disease mechanisms present. This technique could be helpful to unravel the pathogenesis of this immune-mediated necrotising myopathy.
References


