Polymyositis and dermatomyositis: classification, risk factors and outcome
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1 General introduction
The idiopathic inflammatory myopathies (IIMs) are diseases in which skeletal muscles become injured by the immune system. Subtypes of IIMs include polymyositis (PM), dermatomyositis (DM) and sporadic inclusion body myositis (s-IBM). The classification of these three diseases has been subject to many controversies over the past century. The classification of PM, DM and s-IBM is not only a semantic discussion, but the distinction between the different disorders is important for various clinical and therapeutic reasons. Firstly, clear information about the classification allows the clinician to inform a patient with PM, DM or s-IBM about the therapeutic possibilities, about the related chance of improvement and about the risk for the development of a malignancy or connective tissue disorder (CTD). Secondly, only clinically and histopathologically well defined disease entities provide more insight into the clinical aspects, pathogenesis, outcome and prognostic factors, and allow for future research into customized treatment regimes.

In this thesis we investigate: 1) the validity of the current classification of the distinct myositis groups; 2) possible genetic risk factors for the different IIMs; and 3) the long-term outcome of a large group of well-described adult patients with PM and DM.

History of the classification of the idiopathic inflammatory myopathies

In 1887 Wagner and Unverricht, independently of each other, described three patients with acute muscle weakness in combination with skin lesions. Both authors called the disease polymyositis. Because of the almost simultaneous occurrence of cutaneous abnormalities, Unverricht changed the name to dermatomyositis. From that time, these terms were used interchangeably for many years.

In 1975 separate diagnostic criteria for polymyositis and dermatomyositis were established by Bohan and Peter based on clinical, laboratory, neurophysiological, and histopathological features (table 1). According to these criteria, skin features were the only distinction between DM and PM. Bohan and Peter also suggested to subclassify the patients into five clinical subgroups, i.e. PM, DM, childhood PM or DM, PM or DM with an associated CTD, and myositis associated with malignancy. For many years these criteria have been of major importance for diagnosis and for clinical trials and other research items. Currently, the Bohan and Peter criteria are still in use, in particular by rheumatologists, although major criticisms about the sensitivity and specificity of the criteria have been voiced.

Pathological findings in skeletal muscles were already indicated in the first descriptions of PM. Nevertheless it took until the 1950s before muscle biopsies became a common diagnostic tool in differentiating myositis from other muscular disorders. An inflammatory infiltrate in muscle was the most striking pathological feature of PM and DM. It was the merit of Engel and Arahata in 1984 to stress the histological differences between PM
and DM. The characteristic histologic features of DM were perifascicular atrophy and inflammation that was found predominantly at perivascular sites, located in the perimysium. The inflammatory infiltrate was composed of macrophages, B-cells, and CD4+ (T-helper) cells. At the ultrastructural level abundant abnormalities were found in endothelial cells showing various stages of degeneration and regeneration. A characteristic finding early in the disease process, even before degeneration of muscle tissue, was the presence of microtubular inclusions in endothelial cells.10

The histopathological features reported by Arahata and Engel in their PM patients were remarkably distinct from those in DM. The prominent histologic features of PM were the presence of mononuclear cell infiltrates surrounding and invading non-necrotic muscle fibres, associated with muscle fibre necrosis and signs of regeneration.7,8 The endomysial inflammatory cells consisted primarily of CD8+, cytotoxic T-cells and macrophages.7,8 Notably, these findings in PM showed a great similarity with the type and localization of inflammatory cells in sporadic inclusion body myositis (s-IBM).8 This disease was first described by Yunis and Samaha in 1971.11 Until that time IBM was mainly characterized on pathological grounds by the presence of basophilic rimmed vacuoles.12 On electron microscopy intracellular amyloid deposits and 15-21 nm cytoplasmic and intranuclear tubulofilaments in the vicinity of myeloid bodies which are the ultrastructural equivalent of rimmed vacuoles were found in s-IBM.12,13 In later studies s-IBM appeared to have specific clinical features as well.14,15 s-IBM was characterized by the insidious onset of slowly progressive proximal as well as distal weakness, i.e. of quadriceps muscles and of wrist and finger flexors and ankle dorsiflexors. Men seemed to be more commonly affected than women, in contrast to the female predominance in DM and PM. Another clinical difference with PM and DM was the asymmetric distribution of muscle weakness without muscle soreness in s-IBM.12,14,15 Recognition of s-IBM as a clinical and histopathological entity has broadened the spectrum of the IIMs. These clinical and histopathological studies led to the refinement of the criteria of Bohan and Peter for IIMs by Dalakas in 1991 (table 2).9

**Table 1: Bohan & Peter’s diagnostic criteria**

- Progressive (over weeks to months), symmetrical limb-girdle and anterior neck flexor muscle weakness
- Muscle biopsy evidence of necrosis, phagocytosis, regeneration, perifascicular atrophy, and an inflammatory exudate
- Increased serum creatine kinase activity
- Electromyographic evidence of myopathic motor units, fibrillations, positive sharp waves, increased insertional irritability
- Dermatological features: lilac discoloration eyelids, Gottron’s sign, and erythematous dermatitis of knees, elbows, upper part torso, face, and neck.

Exclusion criteria: a slowly progressive course, a positive family history to rule out muscular dystrophies, and many other neuromuscular disorders. Definite PM requires the inclusion criterion 1-4, and a diagnosis of definite DM is made if the typical skin abnormalities are present in addition to at least 3 of the other criteria.
In chapter 2 we review the history and the discussion concerning the classification of PM in detail. In chapter 3 we describe the investigations on the applicability of the more recently developed clinical and histopathological criteria in the work-up of PM and DM. In addition, we investigate specific clinical and histopathological characteristics of patients in the different subgroups in chapter 3, 4 and 5.

Pathogenesis

There is convincing evidence for an immune-mediated pathogenesis in IIM. The evidence originates from the mononuclear cell infiltrates that are found in muscle biopsy specimens, from the frequently reported association with other autoimmune diseases in PM, DM and s-IBM and from the response to immunosuppressive treatment in PM and DM.9,16 Furthermore, myositis specific autoantibodies are found in about 25% of the patients with...
PM and DM. Due to the different histopathological abnormalities that are found in PM, DM, and s-IBM distinct pathogenetic processes are presumed. There is strong evidence that DM is a mainly humorally mediated autoimmune disease, wherein the microvasculature in muscle- and skin tissue appears to be the primary target for an immunological attack. Contrarily, PM is thought to result from cell-mediated immune-processes in which there is antigen-directed cytotoxicity against an unknown muscle fibre autoantigen. Despite these considerations, we observed in our studies that most of the patients with the clinical syndrome of PM show histopathological features that are similar to DM (as described in chapter 3). These findings suggest another pathogenesis, and therefore we introduced the term nonspecific myositis. The pathogenesis of this nonspecific myositis is further studied in chapter 5.

The histopathological features in s-IBM also suggest an immune-mediated pathogenesis, but later studies showed the presence of amyloid deposits and other abnormal accumulation of proteins in s-IBM pointing towards a myodegenerative process. The failure of clinical responsiveness to immunosuppressive or immunodulating therapy supports this hypothesis. Genetic factors may contribute to the development of immune-mediated disorders including IIMs. Prevalence of autoimmune diseases in first-degree relatives exceeds 20%. Several HLA haplotypes are reported to be associated with PM, DM and s-IBM, although these findings are not consistent and seem to differ between various ethno-geographic populations. In addition to the HLA locus, other genes may contribute to the genetic risk for IIM. Research of the genetic background may allow identification of immune-responses genes that predispose certain populations to IIMs. In chapter 6 we investigate possible genetic risk markers for PM, DM, and s-IBM.

**Outcome, associated disorders and prognostic factors in polymyositis and dermatomyositis**

In many patients with PM and DM there is an association with a well-defined CTD. Associated CTDs include systemic lupus erythematosus, scleroderma, mixed connective tissue disorder, Sjögren syndrome, and rheumatoid arthritis. For the diagnosis of two diseases, independent criteria should be met for each disorder. Some studies have reported that up to 20% of patients with PM and DM have an associated CTD, especially patients with DM. However, many more patients with DM and PM show symptoms and signs which may be indicative of a (developing) CTD, but do not entirely satisfy the established criteria (i.e., arthralgias, Raynaud’s phenomena and xerophthalmia). There is also an increased incidence for an underlying malignancy in adult DM, ranging from 6 to 45%. While detection of an underlying neoplasm can precede or follow the
diagnosis of DM, most malignancies are identified within three years of the presentation of myositis. All types of malignancy, including lymphomas and solid tumors, can be found in DM. In s-IBM and PM the risk of malignancies is not clear, but malignancies are described in some small, not-randomised clinical trials of patients with a necrotising myopathy.\textsuperscript{29-31} The occurrence and development of CTDs and malignancies is studied and described in \textbf{chapter 3, 4 and 7.}

While PM and DM are amenable to immunosuppressive and immunomodulating therapies, their prognosis is not well known since long-term outcome and prognostic factors vary widely.\textsuperscript{5,32-44} Mortality rates in PM and DM range from 4 - 45% of patients and favourable long-term outcome ranges from 18 - 90\%.\textsuperscript{32-44} Analyses of prognostic factors are done in many studies, but results are contradictory. Some investigators did and others didn’t find predictors of poor outcome such as old age, male sex, dysphagia, longstanding symptoms prior to the diagnosis or to the start of therapy, various types of myositis, pulmonary or cardiac involvement, and the presence of antisynthetase or anti-SRP auto-antibodies.\textsuperscript{32-44} Differences in the reported outcome and prognostic factors may be due to several methodological shortcomings, including a heterogeneous patient group, and variation in treatments, outcome measures, and follow-up time. The clinical prognosis and the long-term outcome parameters are described in a well-characterised large group of PM and DM patients in \textbf{chapter 7.}

In \textbf{chapter 8} we summarise the main findings of our study and discuss the results. We conclude with clinical implications and suggestions for future research that should add to the understanding of the etiology and underlying pathogenesis of the different IIMs.
References


