

Subgrouping of primary Sjögren's syndrome

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Introduction

Patients with a definite connective tissue disease may be divided into more homogenous subsets reflecting pathogenic, therapeutic, and prognostic significance. The age at onset of the disease, the sex, or the autoantibody pattern, among other factors, may be associated with particular disease expressions, and define some specific subsets of patients of therapeutic and prognostic significance. Subgrouping has thus proven to be relatively successful in systemic lupus erythematosus both when disease expression and prognosis (1,2) is considered, and subgrouping may therefore also be of interest in other connective tissue diseases.

Differences in the classification criteria for primary Sjögren's syndrome (pSS) are a form of subgrouping of pSS-patients already at the time of diagnosis. The preliminary classification criteria suggested by The European Classification Criteria Group (3) might include 6-10 times more patients than other more conservative criteria. The validity of the various classification criteria are debated, however, and in this review different suggestions for subgrouping based mainly on demographic data, disease manifestations, serological profile and immunogenetic markers will be discussed.

Subgrouping based on age at diagnosis

Subgroups of pSS-patients have been suggested based on the observation that the immunological expression differs in various age groups. The initial description undertaken by Whaley et al. (4) drew attention to the lack of immunological and serological abnormalities in the elderly group of pSS-patients. Our group has recently demonstrated that pSS-patients diagnosed before the age of 45 years have a significantly higher prevalence of the autoantibodies anti-SSA/SSB, rheumatoid factor and high IgG-level in serum (5), and Ramos-Casals et al. demonstrated that pSS-patients diagnosed before 35 years of age had higher frequency of autoantibodies and incidence of lymphomas than patients with a late disease onset, concluding that the age at onset has a prognostic significance (6). It has been reported that the presence of autoantibodies is associated with extraglandular manifestations in pSS (7), but we did not find any differences in disease expression in the various age groups (6).

Subgrouping based on disease manifestations

In contrast to SLE, there is presently no valid instrument to assess disease activity in pSS. Recently, however, a model for standardised assessment of disease status has been proposed (8). In this classification model, quantitative and qualitative assessment of disease manifestations has been suggested. The model infers a hierarchical classification of clinical disease manifestations into two main groups, exocrine and nonexocrine, and seven subgroups of disease manifestations with presumed similar pathomechanisms. The disease manifestations are graded, and finally summary scores are calculated. By evaluating this model, only few relations were found between clinical status indices and soluble immune activation products (8), but the authors conclude that this model may assist in elucidating important pathobiological aspects of pSS. Our group has evaluated the same model and demonstrated a correlation between scores for surface exocrine disease and the presence of anti-SSA/SSB, rheumatoid factor and high level of serum immunoglobulin G, thereby connecting a subgroup of disease manifestations to serological abnormalities (6). Subgrouping based on this model may be important in future studies of pathogenic markers in pSS.

Subgrouping based on immunological characteristics

Several studies have demonstrated that the presence of the autoantibodies anti-SSA/SSB is associated with severe systemic disease and extraglandular features in pSS (7,9-11). This may indicate that these autoantibodies play a role in disease pathogenesis of pSS, but no conclusive evidence regarding this question has yet been presented. In patients with SLE, however, anti-SSA antibodies have been reported to be associated with certain disease manifestations such as photosensitivity, as well as congenital heart block in infants with neonatal lupus (1), and may have an important pathogenic influence on these manifestations. These autoantibodies have been found to be produced by infiltrating glandular B-cells from patients with pSS, however, illustrating their potential involvement in the autoimmune exocrinopathy of this disease (12). Although the presence of anti-SSA/SSB autoantibodies is associated with extraglandular complications illustrating its prognostic significance, it has not been found to be a predictor of lymphoma development in pSS (13). Moutsopoulos and Manoussakis have suggested, on the basis of the immune response, that pSS patients can be subdivided into three major subgroups: those with anti-SSA and anti-SSB response; those without specific autoantibody response; and those with autoantibodies against certain autoantigens, such as thyroid peroxidase, mitochondria and centromere (14). They also suggest that the detailed analysis of the initial pathological lesions in the exocrine glands may be instructive for the subclassification of patients with SS (14).

Subgrouping based on immunogenetic markers

The association between the histocompatibility antigens (HLA) B8, DR3 and primary Sjögren's syndrome has been described for certain Caucasoid populations (10, 15-18). Our group has demonstrated that in a Norwegian population of pSS-patients the most frequent DRB3, DRB4 and DRB5 alleles were: DRB3*01011-*01013, DRB4*0103101 and DRB5*0101 (17). The presence of the autoantibodies anti-SSA or anti-SSB has been reported to correlate to HLA-DR3 in some populations of pSS-patients (19), and it has been suggested that anti-SSB production may be under control of genes linked to DR3 (20). Pease et al. have suggested that there are two clinical groups of patients with pSS (10). One group in which extraglandular disease is unusual and the prevalence of DR3 is slightly raised, and another in which the age of onset is younger, the prevalence of DR3 greater than normal, extraglandular disease and autoantibodies more common. Suthcliffe et al. (13) searched for an association between HLA status and lymphomas, and found that HLA B44 was slightly more common in the lymphoma group. Subgrouping based on immunogenetic markers may therefore give valuable information about pathogenic mechanisms in pSS, but it remains to be seen whether a distinct susceptibility gene can be found for the extraglandular manifestations in pSS.

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