
**SJÖGREN’S SYNDROME: A HUMAN MODEL OF AUTOIMMUNITY AND MALIGNANCY**

SJÖGREN’s syndrome (Ss) is a common, chronic autoimmune rheumatic disease with strong female preponderance [1, 2], possessing unique features that make it suitable for research of the pathogenesis of both autoimmunity and malignancy. These include:

1. The occurrence of the disease alone—primary SJÖGREN’s syndrome (pSs)—or in association with almost all other autoimmune diseases—secondary (sSs) [3].
2. A wide clinical spectrum, expanding from an exocrinopathy to a systemic process and which in 10% can evolve to B-cell neoplasia [2].
3. A slow progression, averaging 8–10 years from the initial complaints to the well recognized clinical picture of the syndrome [4].

The prevalence of pSs in the general population is unknown. A study from Great Britain reported a 3.3% frequency in a geriatric population, but without histological confirmation [5]. A recent study of 62 residents of a Greek nursing
The majority of pSS patients have symptoms related to decreased exocrine gland function, i.e. xerophthalmia, xerostomia, xerotrichia, dyspareunia, dry skin, atrophic gastritis, pancreatitis, etc., accompanied by a variety of local functional disorders and infectious complications.

Low grade fever and easy fatigue are common, as are Raynaud’s phenomenon, myalgias and arthralgias. Arthritis resembling RA but without erosions can occur [7]. Interstitial nephritis is a well recognized systemic manifestation. Diffuse interstitial lung disease, with minimal clinical implications, is also common in pSSs [8]. It may also occur uncommonly in sSS [9].

Systemic vasculitis and nervous system involvement deserve special attention, since they constitute recently recognized features of pSSs [10, 11]. Most with vasculitis have palpable purpura. In addition, ulcerative leg lesions and digital gangrene can arise. Acute abdomen with haematochesia are characteristic of mesenteric vasculitis, but in contrast to PAN it is not associated with angiographic changes. Gall bladder perforation has also been reported. Kidney involvement may be manifested as membranous or membranoproliferative glomerulonephritis [12]. Myositis and peripheral neuropathy, symmetric or of the mononeuritis multiplex type, may be other presentations of systemic vasculitis. Histologically, the patterns of vessel disease include leucocytoclastic and lymphocytic vasculitis affecting capillaries and venules, acute necrotizing vasculitis and endarteritis obliterans involving small and medium size muscular arteries [10].

Over the last 4 years, the literature has been overwhelmed by reports from Baltimore indicating that severe CNS abnormalities including seizure disorders, motor and/or sensory deficits, brain stem and cerebellar syndromes, aseptic meningitis, psychiatric disorders and transverse myelopathy, are common in pSSs [11]. This experience is not shared by other investigators. A retrospective study from the UK in this issue [13] reports transient CNS dysfunction in only three of 50 pSSs patients. In a prospective study [14] of 40 Greek pSSs patients mild peripheral neuropathy was the main neurological manifestation. CNS disease was not observed in these patients. Genetic differences between various ethnic groups and probably bias due to the recognized interest of the Baltimore group in the neurological manifestations of pSSs may account for these disparities.

The prevalence of sSS in RA is about 30% [15]. The majority of these patients do not volunteer sicca complaints. When they do, xerophthalmia is elicited much more frequently than xerostomia. Parotid gland enlargement is uncommon [3, 15], as are extraglandular manifestations. In RA, sSSs is benign, subclinical and obviously distinct from pSSs, even more so in view of the serological and genetic differences between the two syndromes [16]. Ss occurs in about 20% of scleroderma and is characterized by xerophthalmia, xerostomia, parotid gland enlargement and anti-Ro(SSA) positivity reminiscent of pSSs [17]. The same seems true for Ss accompanying SLE [18], although conclusive studies are not available.

Significant progress has been made recently in the understanding of the immunopathogenesis of Ss. Autoimmunity is expressed with a B-lymphocyte hyperreactivity and a focal lymphocytic infiltration of the affected organs.

The polyclonal B-cell hyperreactivity is responsible for the plethora of organ and non-organ specific autoantibodies, including anti-Ro(SSA), anti-La(SSB), etc. Immune complexes and cryoglobulins are very common [2, 19]. Using a high resolution agarose electrophoretic technique, combined with immunofixation, we have shown that systemic pSSs patients possess in their serum and excrete in the urine monoclonal light chains and immunoglobulins [20, 21], whereas in many of them, the circulating cryoglobulins consist of a monoclonal IgMk immunoglobulin with rheumatoid factor activity [19]. Other investigators, using immunoglobulin gene rearrangement, have come to the same conclusions [22]. These indicate that such patients present a monoclonal B-cell expansion, long before they develop an overt lymphoid malignancy. Furthermore, cross-reactive idiotypes are present in the kappa light chain of monoclonal rheumatoid factors of patients with Ss and those with Waldenström’s macroglobulinaemia and lymphoma [23].

The majority of lymphocytes infiltrating the salivary glands of pSSs patients consist of T-helper cells. T-suppressor cells are 3-5 times fewer, whereas B-cells make up approximately 20% of
the infiltrating population. Monocytes–macrophages and NK cells are very scanty (<5%) [24, 25]. The infiltrating T-helper cells express on their surface HLA-DR antigens, and lack interleukin-2 (IL-2) receptor. IL-2 is not present in the lesion, but interferon-γ (IFN-γ) is found in abundance [26, 27]. It appears that the B-cell hyperreactivity cannot be explained by aberrant T-cell function. CD5(+) B-cells, recently found increased in blood and salivary glands of Ss patients, may play a fundamental role [28, 29]. In autoimmune mice these cells develop clonal proliferation [30], produce growth factors and express helper activity [31]. If this is the case in humans, it may be that an unknown causative agent, infecting the exocrine glands of an individual genetically susceptible to Ss, can act on the CD5(+) subpopulation, resulting in its expansion. These cells in turn can activate other B-cell clones as well as T-cells, and through IFN-γ induce HLA-DR expression in the glandular cells [25]. This leads to further T-cell activation, tissue destruction and autoantibody formation. Finally, eventual exhaustion of the immune capability with defective IL-2 production and impaired NK cell function predispose to monoclonal B-cell proliferation and lymphoid malignancy.

As mentioned, susceptibility of Ss is under strong genetic control. It has been shown that pSs is strongly associated with the HLA-DR3 and HLA-DRw52 alloantigens and sSs in RA with the HLA-DR4 antigen [16]. Exceptions to the above have been reported in certain ethnic groups: HLA-DR5 in Greeks with pSs [32] and HLA-DRw53 in Japanese [33]. This may indicate that the Ss susceptibility gene(s) may be in linkage disequilibrium with various DR genes or belong to other than the DR locus.

Other non-HLA genetic markers like blood groups, serum proteins and immunoglobulin allotypes have been studied in pSs patients without conclusive results [34–36]. In the current issue of the Journal, Papiha et al. [37] present the study of a large number of genetic markers (blood groups, serum proteins and red cell enzymes) in well-defined subgroups of Ss patients and showed a rather clear genetic distinction between the Ss groups. This finding further substantiates the genetic differences observed in pSs and sSs RA patients described previously with the HLA-alloantigen studies [16]. A study of HLA and non-HLA genetic markers, however, is needed in these patient groups to examine whether an interaction between the above genetic markers operates.

In spite of the above progress, Ss basically remains an incurable disease. This should not discourage patients and physicians. Patients with Ss may feel miserable, mainly because of symptoms originating from dry mucous membranes. The physicians therefore should remember that there is nothing minor about these symptoms and that every attempt should be made to alleviate them. Cyclosporin-A [38] and nandrolone decanoate [39] have been tried in double blind studies, but unsuccessfully. It has been claimed that bromhexine given orally improves sicca complaints [40]. Substitution or stimulation of the missing secretions, however, remains the basis of symptomatic management. Finally, steroids and/or cyclophosphamide and plasmapheresis should be reserved for the treatment of life threatening major organ involvement [41].

ACKNOWLEDGEMENTS

We wish to thank Miss E. E. Papanikolaou for excellent secretarial assistance.

H. M. MOUTSOPoulos
A. P. ANDONOPOULOS

Department of Internal Medicine, School of Medicine, University of Ioannina, 451 10 Ioannina, Greece.

REFERENCES

31. Sherr DH, Braun J, Dorf ME. Idiotype-


