Sjögren's syndrome

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How does the physician confidently diagnose Sjögren's syndrome?

In individuals complaining of eye or mouth dryness, the physician should take a complete history and perform a physical examination. Patients with dry mouth (xerostomia) complain of difficulty in swallowing dry food, inability to speak continuously, a burning sensation, increase in dental caries and problems in wearing complete dentures. On physical examination, the oral mucosa appears erythematosus and sticky, the tongue can present atrophy of filiform papillae on the dorsum, and saliva from the major glands is either absent or cloudy. Enlargement of the parotid or other major salivary glands occurs in a third of patients with primary Sjögren's syndrome (SS). Xerostomia is documented by measuring salivary flow rate with stimulation (lemon) or without stimulation (sialometry). Sialography and scintigraphy [1,2], as well as newer imaging techniques, including ultrasound, MRI or magnetic resonance sialography of the major salivary glands, are also being used [3].

Ocular involvement is the other major manifestation of SS. Patients usually complain of a sandy or gritty feeling under the eyelids. Other symptoms include burning, accumulation of thick strands at the inner canthi, decreased tearing, redness, itching, eye fatigue and increased photosensitivity. These symptoms are attributed to the destruction of corneal and bulbar conjunctival epithelium, defined as keratoconjunctivitis sicca. Diagnostic evaluation of keratoconjunctivitis sicca includes measurement of tear flow by Schirmer's I test and tear composition as assessed by the tear breakup time or tear lysozyme content. Slit-lamp examination of the cornea and conjunctiva after rose bengal staining reveals punctuate corneal ulcerations and attached filaments of corneal epithelium [4].

The patient's serum should be also tested for autoantibodies (ANA, anti-Ro[SSA], anti-La[SSB] and rheumatoid factors). If the patient has keratoconjunctivitis sicca and/or xerostomia and posses anti-Ro(SSA) and/or anti-La(SSB) antibodies in the serum, the diagnosis of SS is definite. If diagnosis is uncertain, labial minor salivary gland biopsy should be performed to rule out conditions, such as sarcoidosis, amyloidosis, lipoproteinemias and lymphoma, which can cause dry mouth or eyes [2,5,6].

The syndrome is the second most common autoimmune condition, why does it remain underdiagnosed & undertreated?

In the majority of patients the syndrome runs a rather indolent course. Thus, physician awareness

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and improved ability to diagnose the syndrome is mandatory. This can be accomplished with lectures and symposia organized by medical centers, and national and international meetings. The lectures should focus on the presentation of the diverse clinical (exocrine gland and systemic manifestations), pathogenetic and therapeutic aspects of the syndrome.

What is the current therapeutic approach for SS?

Treatment of SS is aimed at symptomatic relief and limiting the damaging local effects of chronic xerostomia and keratoconjunctivitis sicca by substituting or simulating the missing secretions.

To replace deficient tears, there are several readily available ophthalmic preparations (Tearisol; Liquifilm; 0.5% methylcellulose; and Hypo Tears). If corneal ulcerations are present, eye patching and boric acid ointments are recommended. Certain drugs that may decrease lacrimal and salivary secretion, such as diuretics, antihypertensive drugs, anticholnergics and antidepressants should be avoided.

For the management of xerostomia, the best replacement is water administration. Propionic acid gels may be used to treat vaginal dryness. To stimulate secretions, pilocarpine (5 mg three-times daily) or cevimeline (30 mg three-times daily) administered orally appears to improve sicca manifestations, and both are relatively well tolerated. Hydroxychloroquine (200–400 mg daily) is helpful for arthralgias and mild arthritis.

Patients with renal tubular acidosis should receive daily disodium bicarbonate orally (0.5–2 mmol/kg in four divided doses). Glucocorticoids (1 mg/kg per day) and/or immunosuppressive agents (e.g., azathioprine, cyclophosphamide) are indicated only for the treatment of systemic vasculitis. Anitumor necrosis factor biologic agents are ineffective. Anti-CD20 monoclonal antibody therapy appears to be effective in patients with systemic disease and is particularly helpful for fatigability, arthritis and vasculitis. Combination of anti-CD20 with a classic cyclophosphamide, hydroxydaunorubicin, Oncovin® (vincristine) and prednisone regimen leads to increased survival in patients with high-grade lymphomas [7–9].

What is the current opinion on cause & where is research currently focusing to further understand it?

As with many autoimmune diseases, the primary etiopathogenetic events are still unknown. According to the current belief, the interplay between environmental contributors (such as viruses, stress or hormones) and the host's genetic background can lead to inappropriate immune responses against self, chronic inflammation and tissue injury. The epithelium of salivary glands or perenchymal organs (liver, kidneys and lungs) appears to be the principal initiator and perpetuator of the autoimmune SS lesion. Given the increased expression of several immunomodulatory molecules, by the epithelia of the affected organs, implicated in lymphocyte recruitment/homing/expansion/differentiation, apoptosis, antigen presentation and sensing of innate stimuli, the term autoimmune epithelitis has been proposed [10]. A current pathophysiological scenario would implicate inappropriate exposure of intracellular autoantigens, such as Ro(SSA) and La(SSB), resulting from enhanced epithelial apoptosis, followed by generation of disease-specific autoreactivities, immune complex formation and subsequent induction of type I interferon production by plasmacytoid dendritic cells and activated epithelial cells. Type I interferon, along with hormonal alterations (such as reduced estrogen/androgen levels), lead to overexpression of B-cell activating factor and autoantibody production [11–13]. The activated epithelial cell acting as an antigen presenting cell, through upregulation of chemotactic molecules can lead to further recruitment of inflammatory cells, activation of T and B cells, autoantibody production and tissue damage. Identification of the major immunoregulatory factors (interferon) that keep the inflammatory process active may provide excellent target(s) for an efficient therapeutic intervention of the syndrome [13,14].

Which patients with SS are at risk for lymphoma development?

Among all systemic or organ-specific autoimmune disorders, SS patients have the highest risk for non-Hodgkin's lymphoma. SS patients who present with palpable purpura, peripheral neuropathy, leucopenia, low C4 complement levels, IgMκ monoclonal type II cryoglobulin and ectopic germinal centers within the affected salivary glands are at high risk for lymphoma development. At a cellular and molecular level, the presence of macrophages and the expression of the cytokine IL-18 in salivary gland biopsies, respectively, are also associated with lymphoma development. The most common type of lymphoma encountered in SS patients is mucosa-associated lymphoid tissue lymphomas followed

by nodal marginal zone and diffuse large B-cell lymphomas. In the majority of cases, lymphoma is located in minor and/or major salivary glands with the stomach and lungs also being involved in some cases. Patients with adverse predictors for lymphoma development should be carefully monitored for lymphoma development. Cytotoxic drugs, such as cyclophosphamide, should be avoided [15–20].

Multicenter, randomized, controlled studies using B-cell depletion therapies in patients with SS and adverse predictors are long warranted in order to answer the question if this therapeutic approach can prevent lymphoma development.

■ Where is research focused in terms of treatment of SS & what advances can be expected in the next 10 years?

Despite the progress, fundamental questions with regard to disease pathogenesis and therapeutic strategies still remain unanswered. The main issues, in terms of basic and clinical research, need to be addressed in the next decade are as follows:

- Identification of main triggers (exogenous or endogenous) accounting for the epithelial activation and immunological injury;
- Detailed characterization and clustering of various SS clinical phenotypes based on their association with distinct pathogenetic pathways and/or cellular and molecular biomarkers. On the basis of this classification, designation of targeted effective therapies, can eventually be instituted;
- Classification and clinical evaluation of the underlying genetic, epigenetic and immunological mechanisms of SS related lymphomagenesis;
- Implementation of preventive therapeutic strategies against lymphoma development in SS patients with adverse predictors.

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