Sjögren's Diagnosis Requires a Team Approach

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SNOWMASS, COLO. — Arriving at a diagnosis Sjögren's syndrome requires a team effort, Dr. Alan N. Baer asserted at a symposium sponsored by the American College of Rheumatology.

A rheumatologist or primary care physician working alone cannot provide the sort of diagnostic accuracy Dr. Baer has in mind.

"We are very accustomed to making diagnoses ourselves and having the tools to do so in our offices, but here there is clearly the need for an ophthalmologist, you need a good oral pathologist, and ideally you should have an oral surgeon to do the biopsy," he said.

A Sjögren's-savvy neurologist can be a big help, too. Peripheral neuropathies occur in 20% of patients with Sjögren's syndrome. The neuropathic symptoms often precede diagnosis of the rheumatic disorder, according to Dr. Baer, a rheumatologist who directs the Jerome L. Greene Sjögren's Syndrome Center at Johns Hopkins University, Baltimore.

These peripheral neuropathies can take multiple, often overlapping forms. The most common is a painful small-fiber sensory neuropathy predominantly affecting unmyelinated nociceptive fibers. Symptoms include an electric shock sensation and burning or stabbing pain. On physical examination there is loss of pinprick and temperature sensations.

Importantly, electromyographic nerve conduction studies are often normal in this small-fiber neuropathy. The diagnosis is made by taking skin biopsies from the proximal, midportion, and distal part of an affected limb. Patients with the small-fiber sensory neuropathy of Sjögren's will not have small nerve fibers reaching from the dermis up into the epidermis, Dr. Baer explained.

Other neuropathies encountered in the setting of Sjögren's include mononeuritis multiplex, ataxic sensory neuropathy, autonomic neuropathies, and trigeminal neuropathy.

Among the difficulties in establishing a diagnosis of Sjögren's syndrome is that many pathologists are not skilled in interpreting labial gland biopsies.

"This is a big problem in the diagnosis of Sjögren's syndrome," Dr. Baer noted. "It's important for the pathologist to give you the focus score: the total number of foci seen in the total specimen divided by the total surface area of glandular tissue. It's a laborious process, and often they don't do it."

The Schirmer's test is still widely used for objective documentation of the ocular component of Sjögren's syndrome, but its poor specificity renders it inadequate for this purpose. Corneal and conjunctival staining or tear breakup time are better measures of the severity of dry eyes. While rose bengal stain has long been used for this purpose, it's quite painful for patients with Sjögren's syndrome; lissamine green stain is a much better option, he continued.

Major mimickers of Sjögren's syndrome that cause persistent symmetric enlargement of the salivary and lacrimal glands and thus figure in the differential diagnosis are HIV, sarcoid, prior head and neck surgery or radioiodine therapy, and hepatitis C, which can produce a salivary gland biopsy looking exactly like the classic picture in Sjögren's syndrome.

The lifetime risk of lymphoma in patients with Sjögren's syndrome is 5%-10%, roughly 16-fold greater than that of the general population.

A pooled analysis of nearly 30,000 patients with various autoimmune disorders in case-controlled studies demonstrated that Sjögren's syndrome stood out as having far and away the highest risk of non-Hodgkin's lymphoma.

In patients with primary Sjögren's syndrome, the risk was increased 4.8-fold over that in the general population, while in secondary Sjögren's—that is, Sjögren's occurring in association with rheumatoid arthritis or SLE—the risk was 9.6-fold. By comparison, patients with SLE, who had the second-highest risk of non-Hodgkin's lymphoma of all the autoimmune disorders, had a 2.7-fold increase.

Accurate diagnosis and careful delineation of distinct phenotypes will be essential to any future development of biologic agents or any other systemic immunomodulatory therapy for Sjögren's syndrome. To date, there is a dearth of convincing clinical-trial evidence supporting the efficacy of any immunomodulatory therapies, including hydroxychloroquine, even though it is widely considered the first-line drug, Dr. Baer said.

He indicated he had no relevant financial interests. ■

Major Project Aims to Improve Diagnosis of the Syndrome

An ambitious National Institutes of Health–funded international project is underway with the goal of developing simplified, standardized, reliable, and more clinically relevant classification criteria for Sjögren's syndrome.

The Sjögren's International Collaborative Clinical Alliance (SICCA) registry has already amassed detailed clinical data and biospecimens from more than 1,600 patients who range across the full spectrum from possible early Sjögren's syndrome to well-established advanced disease, Dr. Baer said.

The SICCA registry is headquartered at the University of California, San Francisco. Among the nine international participating centers is Johns Hopkins University, Baltimore.

NIH officials have committed to at least a decade of funding for the SICCA project because Sjögren's syndrome is a relatively common rheumatic condition with substantial morbidity, many unanswered questions regarding pathogenesis, a problematic diagnostic scheme that has not been accepted by the American College of Rheumatology or other key groups, and no proven disease-modifying therapies.

There is a strong feeling among experts that some of the biologic therapies that have already had major impact in other rheumatic diseases hold promise in Sjögren's syndrome, but their successful application will require early identification of affected patients and reliable markers of disease activity, which the SICCA registry aims to provide, according to Dr. Baer.

The prevalence of Sjögren's syndrome is roughly 1 in 200. It is a disorder mainly of peri- and postmenopausal women; the female-to-male ratio is 20:1. The risk of lymphoma is the highest of all the autoimmune diseases, for reasons unknown. It's also unclear why up to 50% of patients with Sjögren's syndrome are seronegative.

The last 35 years have brought a succession of at least nine classification schemes for Sjögren's syndrome. All were wanting in various ways. The most liberal are the 1993 European criteria, which are limited by low specificity. The most recent criteria—the 2002 U.S./European consensus criteria—are cumbersome and, many believe, too restrictive.

Dr. Baer noted that the SICCA registry has borne early fruit in the form of a recently published simplified quantitative means for diagnosing the ocular component of Sjögren's syndrome. The investigators identified a large group of patients with keratoconjunctivitis sicca but none of the nonocular components of Sjögren's syndrome, a novel finding suggesting the existence of two different forms of keratoconjunctivitis sicca the causes of which may differ (Am. J. Ophthalmol. 2010;149:405-15).

Dr. Baer indicated he has no relevant financial relationships.

Vaginal Tablets Useful for Oral Candidiasis in Sjögren's

SNOWMASS, COLO. — Optimal treatment of chronic erythematous candidiasis in patients with Sjögren's syndrome is complicated by the severe burden of dental caries associated with the rheumatic condition.

"The problem with the usual liquid nystatin preparations used for oral thrush is they contain a lot of sugar. They are not good for patients with Sjögren's syndrome," Dr. Alan N. Baer said at a symposium sponsored by the American College of Rheumatology.

"We use the nystatin vaginal tablets, which don't contain the excess sugar. The patient places a nystatin vaginal tablet in the mouth twice a day, allowing it to dissolve slowly. It's not the greatest taste in the world, but patients get tremendous benefit from clearing this infection," explained Dr. Baer, director of the Jerome L. Greene Sjögren's Syndrome Center at Johns Hopkins University in Baltimore.

Clotrimazole vaginal tablets can be employed as topical therapy in identical fashion, the rheumatologist added.

In patients with Sjögren's syndrome who have mild salivary hypofunction, oral fluconazole or another systemic antifungal agent is effective therapy. The vaginal tablets are reserved for patients with severe chronic hyposalivation that precludes the achievement of therapeutic levels of the systemic antifungal in the mouth.

Chronic erythematous candidiasis is distinct from pseudomembranous candidiasis, which is by far the most common form of oral candidiasis in settings other than Sjögren's syndrome. Pseudomembranous candidiasis features distinctive white plaques or specks that can be wiped off. Chronic erythematous candidiasis, in contrast, is marked by flat red patches. Symptoms include a mucosal burning sensation, metallic taste, and intolerance to spicy or acidic foods.

Sjögren's syndrome patients commonly have dry mouth. Saliva substitutes can bring relief, as can oral pilocarpine or cevimeline, but relatively few patients seem to stick with them. Instead, they often prefer simply to carry a water bottle and drink from it frequently. If they choose this option, it's important to tell them to take only small sips—large quantities will dilute the beneficial mucins in the oral cavity, according to Dr. Baer.

Dry eyes are the other troublesome sicca symptom that's extremely common in Sjögren's syndrome. A humidifier in the bedroom is beneficial. Artificial tears are important. Topical therapy with corticosteroid or cyclosporine eye drops is very helpful. Oral fish oil and flaxseed oil have also been shown to be beneficial, he said. ■

Disclosures: *Dr. Baer reported having no relevant financial involvements.*