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Addressing Diagnostic Challenges in Sjögren's Disease

Announcer:

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This episode of Living Rheum, titled "Addressing Diagnostic Challenges in Sjögren's Disease," is sponsored by Novartis US Clinical Development and Medical Affairs. The host and speaker have been compensated for their time. This program is intended for health care professionals.

Here's your host, Dr Ethan Craig.

Dr Craig:

Sjögren's disease can be challenging to diagnose, with its presentation ranging from typical sicca symptoms and absent significant systemic manifestations to patients with life-threatening, systemic disease without clinically apparent sicca symptoms. So, here we're going to review some of the most common diagnostic challenges that may come up in clinical practice.

This is ReachMD, and I'm Dr Ethan Craig. Joining me to discuss how we can address some of these obstacles to diagnosing Sjögren's disease is Dr Sara McCoy. Dr McCoy is an associate professor of rheumatology at the University of Wisconsin. She also runs the Sjögren's Clinic at the University of Wisconsin and serves on the board of directors for the Sjögren's Foundation. Dr McCoy, thanks for being here today.

Dr McCoy:

Hey, thanks for having me.

Dr Craig:

A pleasure. So, let's dive right in. Dr McCoy, in clinical practice, what's the most common presentation we're seeing of Sjögren's disease, and what manifestations typically bring a patient to a rheumatologist's office as opposed to elsewhere?

Dr McCoy:

So, a large proportion of the US population, and in general, populations experience dryness at some point in their life. At least a third do. And only a small number of those patients actually have Sjögren's disease. So how do we sort out when these patients who are dry, which is one of the very typical presenting features of Sjögren's disease, have Sjögren's disease? So, features that help sort out when a Sjögren's disease patient is at our doorstep, as opposed to somebody who has dryness from another cause, include the severity and chronicity of the dryness associated with disease. And it's also helpful to evaluate for other comorbidities and medications that can mimic Sjögren's disease, and that includes things like hepatitis C or medications that can cause dryness, such as some antidepressants or diuretics. So, other less specific symptoms that can bring Sjögren's patients to rheumatologists include things like fatigue and pain, including myalgias and arthralgias. Specific organ involvement tends to be less common as an initial presenting feature of a Sjögren's patient seeking rheumatology care for the first time.

Dr Craig:

So, just to help us get a little better scope of Sjögren's disease, how do primary and secondary Sjögren's disease differ? And do you see any ongoing use to this terminology in medical practice?

Dr McCoy:

This is an evolving topic and actually we just, at the International Sjögren's Symposium just a few weeks ago, this was a major point of discussion. So, I think it's pretty salient to discuss it.

So right now, the term secondary Sjögren's disease is falling out of favor, and it used to indicate Sjögren's disease in the presence of another autoimmune disease. And essentially, the Sjögren's community came together, and they said, "Well, why are we secondary? I have concomitant lupus, or concomitant RA, but it's really my pain, fatigue, dryness that's bothering me." And I don't think those symptoms should be secondary. And so right now, there's a movement to use the term either "associated Sjögren's disease" or "overlap Sjögren's disease," so you might say, for example, "lupus associated with Sjögren's disease" or "lupus overlap with Sjögren's disease."

Dr Craig:

Can you speak to the role in diagnosis of autoantibodies, including the ANA, SSA, SSB, and then any others in Sjögren's disease that you feel are helpful for diagnosis?

Dr McCoy:

Yeah, so I'll speak about some of the common and then the less common associations, and some of the newer things we've discovered. So, Ro/SSA are the prototypical, common Sjögren's disease diagnostic autoantibodies, but being that it is a B cell-associated disease, there are other autoantibodies that are implicated in both the pathogenesis and have interesting diagnostic implications.

So, one example is the anticentromere antibody. And when this is present, it's associated with lower rates of anti-SSA antibody, rheumatoid factor, and hypergammaglobulinemia. But folks who have an anticentromere antibody-positive tend to have higher lymphocytic infiltrate. They also have greater glandular dysfunction, and this includes things like lower tear and salivary flow, and this was actually described by Dr Baer, who happens to be a mentor of mine, and is an expert in Sjögren's disease as well.

Another really interesting phenomenon is what we do now with SSB, or La, in isolation, right? So, in our previous diagnostic criteria, either SSA or SSB could serve as the autoantibody to help you diagnose Sjögren's disease. So, SSB alone is uncommon. It occurs in about 2% of participants in the sicca registry, which is a large, international registry of Sjögren's patients based at UCSF. Participants with SSA, or SSA and SSB, had overall greater disease activity than those who lacked SSA and SSB, or had SSB alone. And ultimately, this led to the conclusion that SSB alone had no association with Sjögren's disease phenotypic features, compared with those who lacked both antibodies. And so that finding is what led to the SSB alone being dropped from the diagnostic criteria, and I really don't, when I find this alone, I don't use it for the diagnosis of Sjögren's disease clinically, whereas sometimes other combinations of clinical features and autoantibodies help me make a diagnosis in somebody who doesn't have any anti-SSA antibody.

Another autoantibody of interest are the aquaporin antibodies. Patients with aquaporin antibodies have more severe dry eye compared with those who are negative. And this suggests a potential pathogenic role of these autoantibodies, as well.

Dr Craig:

And what do you make of these early Sjögren's profiles?

Dr McCoy:

So, the early Sjögren's profile consists of several antibodies, and this includes the carbonic anhydrase antibody, salivary protein, and anti-parotid antibodies. These antibodies were initially discovered in mice, and it was found that they precede Sjögren's onset in mice and also it was found they occur earlier than SSA and SSB antibodies. But in humans, when we took a look at these antibodies—cross-sectionally, not longitudinally—we really found that they occur pretty similarly in, especially the IgG, pretty similarly in Sjögren's disease as controls. And because of these human studies, we've come to the conclusion that these antibodies should not be used for diagnosis

Dr Craig:

So, let's pivot to the other end of the spectrum, from the autoantibodies we've talked about. So, how often can we expect to see truly seronegative patients with Sjögren's? And how do you approach evaluating these patients?

Dr McCoy:

Yeah, so what is seronegative? I think that's a good question. I think that you'll find different definitions in the literature. Because when I started my research and I really started spending a lot of time with Sjögren's patients, it was at that time the 2016 ACR/EULAR criteria came out in which SSB was no longer part of the diagnostic criteria. And so, I really define seronegative Sjögren's disease as Sjögren's that's SSA-negative. And so, among all Sjögren's disease patients, about 70%, 70 to 75% are going to be anti-SSA antibody-positive,

and the remaining 25 to 30% of Sjögren's disease patients are anti-SSA antibody-negative. And these 2 groups differ, right? So, SSA-positive patients tend to have greater clinical and immunologic disease activity than SSA-negative patients. So, having an SSA antibody seems to correlate with a greater ESSDAI (remember that's a disease activity score we talked about), low white count, hypocomplementemia, and cryoglobulinemia. And SSA-positive patients tend to have higher frequency of germinal centers, whereas SSA-negative patients have higher frequency of dry eye, greater tooth loss, greater neurologic, and articular involvement.

It seems to be clinically relevant to know you have an SSA-negative or seronegative Sjögren's disease patient. So how do we sort that out? And so, in all of these cases, I recommend getting a salivary gland biopsy in a patient with features of Sjögren's disease but is seronegative.

In addition to lab testing, I want to emphasize that to help differentiate dryness from, like for example, seronegative Sjögren's, we can also fall back to longstanding validated questions. So, I actually start off a visit, before I even get to the question of maybe this patient has seronegative Sjögren's and needs a biopsy or blood testing, with some simple questions, and they're the following: 1, do you have a recurrent sensation of sand or gravel in your eyes? Two, have you had daily, persistent, troublesome dry eye for more than 3 months? Three, do you use tear substitutes more than 3 times a day? Four, have you had a daily feeling of dry mouth for more than 3 months? Five, do you frequently drink liquids to aid in swallowing dry food, like crackers? And 6, have you had recurrent or persistent swollen salivary glands as an adult? And these, taken individually, have usually around an 80% sensitivity or specificity for a diagnosis of Sjögren's, and the most specific one would probably intuitively be the fact that they have persistent or recurrent swollen salivary glands. And so, these are really nice screening tools, to even help you determine, if you're just starting to consider diagnosis of Sjögren's, if they're dry enough to proceed with the rest of your evaluation.

Dr Craig:

That's really helpful, thank you. And to follow up on one small point from the last discussion, I'm curious. We know, for example, in rheumatoid arthritis, we've got good data that rheumatoid factors, CCP, tend to precede the onset of disease by 10 years, 20 years, or so. Do we have any similar data in Sjögren's syndrome? Do we know at what timepoint we expect to see the SSA-positive compared to onset of disease?

Dr McCoy:

Yeah, so it's pretty similar. So, we know from large studies that SSA antibody tends to form years before diagnosis of Sjögren's. And so, that's one of the reasons why we suspect maybe hormones are at play, because you can get antibody status, if I recall, maybe 18 years prior to onset of disease, but it's really in that perimenopausal time period that you have disease onset.

Dr Craig:

Interesting. Well, thank you so much. You know, with those final thoughts in mind, I want to thank my guest for helping us address this issue of diagnosis in Sjögren's disease. Dr McCoy, it was a great pleasure to speak to you today, thank you.

Dr McCoy:

Thank you so much for having me.

Announcer:

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