Is it Multiple Sclerosis or Sjögren’s Syndrome?

The overlapping symptoms of these two conditions can create a confusing conundrum for clinicians.

Clinical Case
A 49-year-old woman presents with ataxia and two weeks of band-like paraesthesias around her waist. She describes an episode of right leg weakness associated with back pain two years ago. A lumbar MRI is normal and a nerve conduction study has absent sural nerve responses bilaterally. A review of symptoms reveals Reynaud’s phenomenon and a recent decrease in vision only partially corrected by new glasses. Past medical history is significant for high cholesterol, and she takes a lipid-lowering agent and non-prescription drops for dry eyes. The patient’s mother has rheumatoid arthritis and hypertension.

You suspect multiple sclerosis with transverse myelitis and begin a work-up. An MRI of the brain shows four subcortical white matter lesions with a normal corpus callosum. MRI of the spinal cord shows a T6/7 intramedullary lesion extending less than one segment with minimal cord swelling. The right P100 is prolonged on visual evoked potential testing, and a lumbar puncture shows three lymphocytes and two oligoclonal bands. Blood work reveals an elevated anti-myelin antibody of the IgG class in the CSF. Despite normal imaging, the patient’s history and symptoms strongly suggest a diagnosis of MS.

Expert Opinion
This patient meets clinical criteria for a diagnosis of MS, given the two episodes of neurologic symptoms affecting motor and sensory systems. The neuroimaging, CSF analysis and evoked potentials all seem supportive of this. However, the history raises several red flags. MS should affect only the central nervous system, so the absent sural potentials are a concern in this otherwise healthy woman. The white matter changes seen on brain imaging are non-specific and the CSF results equivocal. The history of Reynaud’s and the positive ANA should also give you cause for a second thought, as should the patient’s use of drops for dry eyes.

A salivary gland biopsy will confirm that the patient has Sjögren’s syndrome (SS). But making the distinction between the two entities before this procedure can be a challenge, as there is considerable overlap in their clinical symptoms and diagnostic testing. This article will discuss the similarities and differences between MS and Sjögren’s in an attempt to help with differential diagnosis and work-up.

Sorting Sjögren’s from MS
The exact frequency of central nervous system involvement in Sjögren’s is difficult to ascertain, as there is a huge variability in reported prevalence, but it is generally believed to be between 20 to 25 percent. Potential explanations for the discrepancy are disagreements about diagnostic criteria for SS, referral bias as patients in academic centers may be investigated more thoroughly and are included in studies, and the differential abilities among neurologists to seek and recognize neurological manifestations of Sjögren’s.

One case series1 found that when the neurologic manifestations were clinically significant they were the presenting symptoms of Sjögren’s in 57 percent of patients with a mean delay in diagnosis of six years. The neurologic symptoms preceded the onset of keratoconjunctivitis sicca symptoms in 38 percent, and were concurrent in 15 percent. The mean time to k. sicca symptoms was six years. Eighty-six percent of patients in this series went on to have other extraglandular features of Sjögren’s, but several had solely nervous system involvement. The extraglandular complications were more common in patients with PNS disease than CNS disease. Finally, while neuroimaging, electrophysiologic testing, CSF analysis and serology may suggest one diagnosis over the other, there remains overlap in the test results between Sjögren’s and MS.

Changes on MRI that resemble MS are frequently seen in Sjögren’s. Delalande et al. studied 82 consecutive SS patients with neurologic manifestations and found that brain MRIs showed white matter lesions in 70 percent of patients and were suggestive of MS in 40 percent. However, 17 percent had gray matter lesions in the basal ganglia, and only 14 percent had lesions involving the corpus callosum. Brain lesions were found significantly more frequently in patients with central nervous system involvement than peripheral nervous system involvement (80 percent vs. 25 percent, p=0.008). Spinal cord imaging was abnormal in 75 percent of patients imaged with clinical myelopathy. Similar to MS, most lesions were cervical (82 percent), but unlike what is common in MS, 12 percent had lumbar cord T2 abnormalities. Furthermore, while cord lesions were dorsal in approximately half of patients and extended less than one vertebral level in 65 percent, many did not follow that typical MS pattern.

As optic neuritis is a known feature of Sjögren’s, visual evoked potential (VEP) testing can be abnormal in both Sjögren’s and MS. Delalande’s group found clinical symptoms of ON in 15.9 percent of
patients and abnormal VEPs in 61 percent. VEP abnormalities are typically found in 75 to 97 percent of patients with MS. Electrodiagnostic studies such as nerve conduction may reveal clinically suspected peripheral neuropathy or sub-clinical sensory neuropathy in Sjögren’s. Neuropathy comprises nearly half of the nervous system involvement in Sjögren’s, and in one case series seven percent of general SS patients were found to have a peripheral neuropathy.2

CSF testing is a cornerstone of MS diagnosis, but is not specific to that disease. Sjögren’s patients can also have an increased cell count with lymphocytic predominance and oligoclonal bands. However, the number of bands is usually two or fewer in Sjögren’s versus more than two in MS and the IgG synthetic rate is also more frequently increased in MS.3 As in MS, spinal fluid analysis in Sjögren’s is performed to rule out infectious or malignant causes of neurologic symptoms.

**Truth Serum**

Clinicians frequently rely on serology to help distinguish rheumatologic and connective tissue causes of neurologic symptoms from multiple sclerosis. However, serum analyses of autoantibodies can be fraught with ambiguity. Many autoantibodies—including ANA, Anti-Ro (SSA) and Anti-La (SSB) antibodies, and rheumatoid factor (RF)—are commonly associated with Sjögren’s, but in a review of 400 Sjögren’s patients nearly a quarter tested negative for all four.2 In this review, the frequency was 74 percent with ANA, 40 percent with SSA, 38 percent with RF and 26 percent with SSB.

There are some studies suggesting a clinical correlation with the presence or absence of autoantibodies. Carrasco found that the immune negative patients had a lower incidence of Reynaud’s phenomenon and cutaneous vasculitis while patients who were ANA positive but SSA and SSB negative had a greater frequency of Reynaud’s phenomenon and pulmonary involvement but less peripheral neuropathy. Male patients generally demonstrated SSA antibodies less frequently than female patients. Early onset disease (defined as before 35 years) was associated with a higher rate of SSA antibodies, fever and lymphadenopathy. Late-onset disease, conversely, had no significant association with a particular antibody.

Delalande’s series of Sjögren’s patients with neurologic involvement had a somewhat lower rate of ANA antibodies (53.7 percent) but similar rates of SSA and SSB (43 percent). They also noted cryoglobulins in 36.6 percent, all of whom had PNS symptoms.
To make matters more complicated, MS patients have an increased frequency of autoantibodies, as high as 66 percent. De Andres studied 42 patients with Posner defined MS for the presence of ANA, SSA and antichondroitin antibodies (ACA). ANA was positive in 23.8 percent of patients at titers of 1:160 or less. One patient was ACA positive and three were SSA positive. Only the two patients who received a lip biopsy, neither had clinical or pathologic evidence of SS.

Interestingly, one relapsing-remitting MS patient fulfilled clinical criteria of SS with xerophthalmia, keratoconjunctivitis sicca, xerostomia and a positive salivary gland biopsy but had normal ANA, ACA and SSA titers. The authors concluded that the presence of autoantibodies in MS is an epiphenomenon of a generalized immune dysregulation rather than the coexistence of two diseases or an overlapping syndrome. While MRI activity seems to be correlated with the presence of autoantibodies, other researchers have not found clinical correlations.

De Seze studied 60 consecutive patients with primary progressive MS (PPMS) and found that 16.6 percent met four diagnostic criteria for SS and 23.3 percent met three criteria, including xerophthalmia (35 percent), an abnormal Shimer test (40 percent), xerostomia (35 percent), positive salivary scinigraph, a positive biopsy and systemic manifestations (inflammatory arthritis, Reynaud’s). These rates are higher than the general population. He asked if a novel autoantibody, alpha-fodrin, could help determine if MS and Sjögren’s are on a spectrum of the same disease or are two separate entities.

Twenty patients with Sjögren’s and neurological manifestations (10 with peripheral neuropathy, six with myelitis, and four with brain lesions) and 60 control MS patients were studied for the presence of SSA, SSB and alpha-fodrin antibodies. Ten of the Sjögren’s patients also met criteria for PPMS. The MS controls included even numbers of PPMS, SPMS and RRMS patients. Alpha-fodrin was found to have a sensitivity of 70 percent, specificity of 86.7 percent, positive predictive value of 63.6 percent and negative predictive value of 89.6 percent. The authors concluded that their data support a difference between the two diseases, and that testing for alpha-fodrin may help diagnose Sjögren’s in cases that are SSA and SSB negative.

Pathology Finder

More striking and reliable differences between MS and Sjögren’s emerge when the two diseases are studied histopathologically. In Sjögren’s, mononuclear cells infiltrate both glandular and extraglandular organs, leading to vasculitis and ischemic necrosis. Both B- and T-cells are involved and hypergammaglobulinemia, general autoantibodies and organ-specific autoantibodies are all present (e.g., to the thyroid, salivary and lacrimal glands, gastric mucosa, erythrocytes, pancreas, etc.). CD4+ helper cells are seen along with inflammatory cytokines including IL-2, IL-4, IL-6, IL-1β, and TNF alpha7.

Sural nerve biopsies in patients can show a lymphocytic infiltration in the perineurium and epineurium even in the absence of peripheral nerve symptoms. Vasculitis, demyelination, and myositis are seen on peripheral nerve and muscle biopsies.

The few pathological CNS specimens show a diffuse necrotizing vasculitis of small arteries and arterioles without demyelination. Despite the lack of histological evidence, some believe an immune-mediated inflammation with direct infiltration of chronic inflammatory cells into the CNS plays a role as a mechanism of injury. In contrast, MS is characterized by perivascular infiltration of T- and B-lymphocytes into the CNS, which causes local inflammation by macrophage activation and results in repeated bouts of demyelination, remyelination and axonal transaction.

Conclusion

Crucial to the diagnosis of MS, patients must have disease limited to the CNS and not have signs of a systemic illness involving the peripheral nerves or other organ systems. When symptoms and/or signs develop outside the CNS in MS patients, clinicians must reconsider the diagnosis. Given the high prevalence of SS in the general population and its extensive clinical and diagnostic overlap with MS, it should remain high on the differential diagnosis. Finally, it also goes without saying that the treatments of the two diseases differ significantly with a great cost in delayed or misdiagnosis.