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CASE REPORT

Primary Sjögren's Syndrome White Matter Changes and Cognitive Dysfunction

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This case report describes a 52-year-old, female applicant for long term-care insurance with a history of an autoimmune connective tissue disease initially diagnosed as systemic lupus erythematosus (SLE). Over several years, the signs and symptoms evolved into a clear diagnosis of primary Sjögren's syndrome (PSS). The specific criteria for this diagnosis are reviewed including the symptoms, antinuclear antibodies (ANA), extractable nuclear antigen antibodies (ENA), abnormal salivary scintigraphy and positive Schirmer test. Symptoms of neuropathy and the possibility of a cognitive dysfunction are discussed as part of PSS. The association of white matter lesions (WML) with PSS is significant for underwriting consideration.

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Primary Sjögren's syndrome (PSS) is a systemic chronic inflammatory disorder characterized by lymphocytic infiltrates in exocrine organs. Most individuals with (PSS) present with the sicca complex of xerophthalmia (dry eyes) and xerostomia (dry mouth) with parotid gland enlargement due to lymphocytic infiltrates.[1-3]

PSS is considered an autoimmune connective tissue disorder and can share features with other rheumatologic disorders along the course of the disease.[1-3] The citeria by which a diagnosis is made of a presumptive autoimmune connective tissue disease are not always recorded in medical records. Systemic treatments for rheumatologic disorders are similar between connective tissue disorders. All of this overlap makes assessment of long-term risk a challenge for both clinician and underwriter.

Some research series have shown a significant prevalence of signs of cognitive impairment with PSS. There have also been associated white matter lesions (WML) on

MRI of the brain. This case report describes PSS evolving over time with neurological symptoms likely correlating with findings of white matter lesions on brain MRI.

CASE REPORT

A 52-year-old female in self-reported good health applied for long-term care insurance. Per the application, her height was 5′6″ and her weight was 132# for a BMI of 21.3. Her family history was significant for a fatal stroke in her father at age 64 and hypertension in her mother. Two siblings were healthy. There was no other admitted medical history and no current medications. She was employed as an auditor and lived with her husband. She enjoys reading and knitting.

Medical records were obtained from her primary care physician (PCP). The records began 5 years prior to application with a history of anxiety, facial skin rash felt to be seborrheic dermatitis and joint swelling of the 2nd through 5th proximal interphalangeal joints (PIP) of both hands. Though her hand x-rays were normal, the PCP diagnosed the joint swelling as "osteoarthritis" and told her to take over the counter anti-inflammatory medications like ibuprofen or clinoril.

Over the next 2 years, she visited her PCP every couple of months with various symptoms of upper respiratory infection and cystitis, but also with complaints of fatigue, anxiety, and migratory joint pain. In 2012, 3 years prior to application, a worsening complaint of generalized arthralgia and myalgia led her PCP to order rheumatologic studies: erythrocyte sedimentation rate (ESR) was 46 (0-40 mm/hr) and the rheumatoid factor slightly elevated at 14 (0.0-13.9 I.U.) The ANA titer was (+) at 1:320 and the ENA panel noted positive anti-dsDNA antibodies at 14 IU/ml (0-9.0 IU/ml) and anti-RNP antibodies at 2.0 (0.0-0.9 AI). No other ENA were positive. Her PCP made the diagnosis of systemic lupus erythematosis (SLE) based on her symptoms and lab studies. He started her on hydroxychloroquine at 200 mg twice a day. Her arthralgia and myalgia markedly improved with this treatment.

After 2 years of being on hydroxychloroquine, she noted "blurred vision" in her right eye. Her ophthalmologist, following her for adverse visual effects of hydroxychloroquine, noted a bilateral premaculopathy along with dry eyes. The ophthalmologist recommended discontinuation of the hydroxychloroquine and reassured her that the premaculopathy was reversible and should resolve on its own. The ophthalmologist was concerned she had a "dry eye syndrome" (DES) that was related to her autoimmune disorder.

The hydroxychloroquine was stopped by her PCP who again recommended ibuprofen for mild arthralgias that were experienced intermittently. She was referred to a rheumatologist and seen just over 1 year prior to application.

The rheumatology medical records revealed the long reported history of generalized muscle and joint pains. Within the past year, she had noticed her mouth was frequently dry, and her eyes felt dry and scratchy. This had made it difficult for her to work at the computer as an auditor as well as read and knit, two things she loved to do. She also felt her fatigue getting worse and that she had a "brain fog." She related that there were days when her brain "just isn't working right." Overall, she felt in increasingly poorer health.

On physical exam, the rheumatologist noted dry red eyes, swollen parotid salivary glands along with dry buccal mucosa. There were swollen PIP joints in both hands. Her physical exam was otherwise normal. A mental status screen was not done.

Diagnostic studies were as follows:

- Complete blood count - normal
- ESR – elevated at 56 (0-40 mm/hr)
- Rheumatoid factor – positive at 20 (0.0-13.9 IU)
- ANA titer – positive at 1:320 (normal <1:40)
- Anti-dsDNA and anti-RNP were both normal

- Anti-SSA antibody elevated at > 8.0 (0.0-0.9 AI)
- Anti-SSB antibody elevated at 1.0. (0.0-0.9 AI)
- Immunoglobulins and complement levels – normal
- Parotid gland scintigraphy – mildly decreased uptake of Technetium 99 bilaterally in parotid glands consistent with inflammatory infiltrate
- Schirmer test for eye tearing – abnormal with wetting of 3-4 mm (normal $\geq$ 5 mm at 5 minutes)

The rheumatologist diagnosed primary Sjögren's syndrome (PSS) with sicca complex. He recommended doing a lip biopsy (functionally a salivary gland biopsy), which was refused. He replaced the ibuprofen with meloxicam, a prescription nonsteroidal anti-inflammatory drug (NSAID), for her increasing arthralgias. He recommended over-the-counter "artificial tears", 1 drop 4 times a day for her dry eyes. For her dry mouth, he recommended dental cleanings every 3 months, good hydration and frequent sugar-free lozenges.

Because of her neurological symptoms, an MRI was done which showed 4 left hemispheric and 6 right hemispheric subcortical white matter lesions, with 1 lesion questionable for a demyelinating lesion. She was referred to a neurologist.

Upon referral, the consulting neurologist concluded that she did not have multiple sclerosis. The MRI findings were not consistent with demyelinating disease, nor was the history. Her exam revealed subtle findings of stocking-glove neuropathy with diminished sensation to light touch. A Folstein Mini-Mental Status Exam was normal at 27. The neurologist was most concerned that the MRI findings were consistent with her diagnosis of PSS and felt she needed optimal treatment for the Sjögren's. After consulting with her rheumatologist, a trial of etanercept 25 mg SQ q week was started. The neurologist recommended neuropsychological testing to establish a baseline for future evaluations. The applicant refused this as she still felt she was alright being able to work as an auditor.

The last recorded visit with the rheumatologist was in late 2014, four months prior to her application for long-term care insurance. Since the initiation of etanercept, her neuropathy and arthralgias improved. Her fatigue was slightly improved, but she still had days where her brain felt like there were "cobwebs" in it. She noted that there are times when "my words just don't come out the way I want them to." Her sons teased her that it was "her old age creeping up." The plan was to continue the etanercept and use meloxicam as needed. A repeat brain MRI was planned for fall 2015. The applicant did not want to undergo neuropsychological testing.

CASE DISCUSSION

Autoimmune connective tissue disease can be complex due to evolving signs, symptoms and ever changing and often conflicting results of diagnostic studies. The initial signs and symptoms together with ANA and ENA antibodies may suggest one autoimmune connective tissue disorder only to evolve over months to years into a different clinical picture. This calls for continued reassessment of the patient and makes it easy to be behind in the diagnosis. For example, despite a prevalence of primary Sjögren's syndrome (PSS) that ranges between 1% and 3% of the general population, more than 50% of PSS patients do not receive a correct diagnosis and approximately 30% of patients presenting with other autoimmune diseases actually suffer from PSS.[4] This case study is an example of how evolving signs and symptoms might be misdiagnosed if not regularly reevaluated.

The initial presentation of this applicant's autoimmune connective tissue disease was non-specific with a skin rash felt to be seborrheic dermatitis and swollen PIPs in both hands. Her PCP at first felt her signs and symptoms were that of osteoarthritis, and the use of NSAIDs was recommended. The x-ray of her hands did not show degenerative joint changes. The use of NSAID was acceptably effective for several years.

Clinicians often use diagnostic labels to communicate with patients and as placeholders

for a problem. It is not unusual to see this in review of primary care records, and it represents a challenge to underwriters both in underestimating and in overevaluating the severity of a disorder. Depending on the point in time of review, this presents a significant challenge to an underwriter to evaluate. This was not a case of garden variety osteoarthritis with symmetrical inflammation of the PIPs.

The applicant had well-established regular care with this PCP and brought forward symptoms of generalized fatigue, increasing arthralgia and some myalgia, 2 years after the initial joint symptoms. The physician reevaluated with a general rheumatology workup. The initial elevated ANA and ENA antibodies, particularly the anti-dsDNA, as well as the signs and symptoms were consistent with the diagnosis of systemic lupus erythematosus. A middle-aged female with systemic complaints of fatigue, arthralgia with swollen joints, a positive ANA and specifically, a positive anti-dsDNA has a clinical picture consistent with SLE. The ANA is positive in 99% of diagnosed SLE, but only 60% will have a positive anti-dsDNA antibody. The anti-dsDNA is 95% specific for SLE so functionally approaching this patient as having SLE was effective.[3] Hydroxychloroquine is a first line medication for mild SLE and was effective in controlling her arthropathy for 2 years.

She received excellent care with a referral to an ophthalmologist to monitor for ocular toxicity caused by hydroxychlorquine. Discontinuation of the hydroxychloroquine was recommended after the development of a retinal premaculopathy, a complication of hydroxychloroquine. Besides retinal changes, one can also rarely see corneal and lense abnormalities. The most common presenting symptom is that of central or paracentral scotomas, which can be associated on exam with irregular pigmentary changes in the macula. Early changes can be referred to as premaculopathy or preretinopathy. The retinal changes can progress to a clinical picture similar to retinitis pigmentosa with increasing loss of central vision. Early changes have been reported to regress with prompt discontinuation of hydroxychloroquine.[5]

A golden rule of rheumatology is that a positive ANA does not equal systemic lupus.[4] Autoimmune connective tissue diseases can have numerous referrals to different consultants as the signs and symptoms, labs and diagnostic studies change over time. It was the ophthalmologist consulting with the PCP that helped to bring the rheumatologist on board.

The detailed workup done by the rheumatologist revealed a new picture. A diagnosis of primary Sjögren's syndrome was met by the symptoms of dry eyes and mouth, results of the ANA and autoantibodies (anti-SSA (Ro)/anti-SSB (La), the abnormal uptake on the parotid gland scintigraphy and the low result on the Schirmer test. According to the 2002 American-European Consensus Group criteria, this applicant met 5 out of the 6 items (only 4 needed) indicative of PSS (Table 1). The only test not performed was the recommended lip biopsy. This result would likely have showed histopathology of a focal lymphocytic sialoadentitis. This criteria has the highest sensitivity and specificity, but the applicant did not want this invasive test and the serology with the positive autoantibodies was enough to diagnose PSS.[1]

This still could be a secondary Sjögren's with systemic lupus being the primary. The negative anti-dsDNA antibody 2 years after the initial positive value does not rule out this diagnosis. It is only 60% sensitive and anti-dsDNA antibodies do wax and wane over time. A repeat study could be positive for anti-dsDNA antibody in the future. Sjögren's syndrome has protean manifestations that overlap with SLE including fatigue, non-erosive arthritis, and neuropsychiatric manifestations.[6]

As with many autoimmune connective tissue disease cases, this one did not present "typically" for PSS. Well over half of those with PSS present with sicca complex at time of diagnosis. Peripheral neuropathy occurs in 10% of PSS and neuropathic pain can

Table 1. 2002 American-European Consensus Criteria for Sjögren's Syndrome.[1]

I. Ocular Symptoms (at least one)	• Symptoms of dry eyes for at least 3 months • A foreign body sensation in the eyes • Use of artificial tears 3 or more times per day
II. Oral Symptoms (at least one)	• Symptoms of dry mouth for at least 3 months • Recurrent or persistently swollen salivary glands • Need for liquids to swallow dry foods
III. Ocular Signs (at least one)	• Abnormal Schirmer's test, (without anesthesia; ≤5 mm/5 minutes) • Positive vital dye staining of the eye surface
IV. Histopathology	• Lip biopsy showing focal lymphocytic sialoadenitis (focus score ≥1 per 4 mm^2)
V. Oral Signs (at least one)	• Unstimulated whole salivary flow (≤1.5 mL in 15 minutes) • Abnormal parotid sialography • Abnormal salivary scintigraphy
VI. Auto antibodies (at least one)	• Anti-SSA (Ro) or Anti-SSB (La), or both

For a primary Sjögren's syndrome diagnosis:

- Any 4 of the 6 criteria, must include either item IV (Histopathology) or VI (Auto antibodies)
- Any 3 of the 4 objective criteria (III, IV, V, VI)

precede the diagnosis of PSS. Twenty- eight percent of PSS present with joint symptoms.[5] In this case study, the symptoms of fatigue and arthralgia with myalgia persisted alone for several years before sicca complex was noted and a workup for Sjögren's was started.

Neurological involvement has been described in PSS since Sjögren first described the syndrome in 1935.[7] It has both peripheral and central nervous system manisfestations. The peripheral neuropathy is diverse including: sensory neuropathy, carpal tunnel syndrome, sensorimotor axonal polyneuropathy, chronic polyradiculoneuropathy and motor neuron syndrome.[8,9] However, it has just been in the last 2 decades that the central nervous system effects of PSS have been researched.

The reported prevalence of central nervous system disease in PSS individuals has been highly variable, ranging from 2.5% to 60% without specific syndromic definition.[4] In 2004, Delalande et al described central nervous system disease in 56 out of 82 persons with PSS (68%) referred to their clinic with neurological symptoms.[9] Soliotis et al identified in 2004 that a consensus on the definition of central nervous system (CNS) involvement with PSS was needed and that discrepancies of the reported prevalences of the CNS impairment with PSS may reflect the true differences of the coexistent CNS diseases in different populations due to different genetic and environmental factors.[10] The authors advocated for more well designed multicenter studies in the future.

In 2014 Morreale et al evaluated the prevalence of CNS signs and symptoms in PSS patients.[4] Of 120 persons diagnosed with PSS, 81 had central and peripheral nervous system involvement, a prevalence of 67.5%. The clinical-demographic characteristics of the group with neurological involvement reflect the epidemiologic features of Sjögren's with a female:male ratio of approximately 9:1, and mean age in the 50s. (Table 2). The prevalence of those with CNS involvement was 81 (84%) compared to 43 (53%) with peripheral neuropathy. Approximately 40%-45% of those with non-focal CNS manifestations had headaches (especially migraine without aura), cognitive disorders with subcortical frontal executive functions and verbal memory impairments, and mood disorders including apathy/alexythimia (difficulty in experiencing, expressing and describing emotional responses).

Table 2. Neurological Involvement in Primary Sjögren's Syndrome (PSS).[4]

Total number of patients with PSS	120
Total patients with neurological symptoms, number	81 (68%)
• Female sex, number, number	77 (95%)
• Average age (years) ± sd	54.5 ± 11.6
• Mean duration from immunologic diagnosis (years) ± sd	9.3 ± 6.8
• Neurological onset – first symptoms (years) ± sd	16.7 ± 6.2
Non-focal CNS symptoms, number	68 (84%)
• Headache (especially migraine without aura)	47%
• Cognitive disorders	44%
• Mood disorders	38%
Focal CNS symptoms, number	64 (79%)
Peripheral symptoms, number	43 (53%)

Cognitive dysfunction is well-described in PSS. Blanc et al found 15 of 25 PSS patients (60%) presented with cognitive disorders, 5 of whom had dementia.[11] Cognitive domains impacted were attention, immediate recall, long-term memory, and executive function. There was overall cognitive slowing. Segal et al also found decreased psychomotor processing speed and verbal reasoning in 20 of 29 tested.[12] Malinow et al found mild memory impairment with attention and concentration deficiencies 7 of 16 patients who had undergone cognitive function testing.[13] Lafitte et al found changes in attention and executive function in 8 of 10 patients tested.[7] Finally, frontal lobe function and memory deficits were described by Mataro et al in 7 of 15 patients with PSS.[14] These are not primarily amnestic features and the cognitive screening tools used in the industry may not be sensitive to mild features of these cognitive impairments.

Studies have suggested a relationship of cognitive impairment, especially psychomotor slowing, with white matter changes. On the other hand, Blanc et al found 50% of cognitive tested individuals with cognitive impairment did not have white matter lesions.[11] They postulated inflammatory changes not yet visable by MRI as a cause. Likewise, La Guern et al demonstrated a strong correlation between impaired executive function and visuospatial disorders with hypoperfusion of the frontal, temporal, and parietal cortices on Technetium-99m scan.[15] Eight of 10 of their cognitively impaired PSS patients had no white matter changes. A process of microvascular inflammation associated with positive anti-SSA has been proposed.

Clearly primary Sjögren's syndrome, as a systemic autoimmune disease which is associated with positive rheumatoid factor and positive anti-SSA and anti-SSB antibodies, can widely damage the neurological system. The applicant discussed here had clear white matter changes on MRI and a history suggestive of cognitive impairment. A "brain fog" could be consistent with decreased psychomotor processing speed and executive function. One might expect these findings to be currently subtle as the individual continued to be able to work as an auditor. Neuropsychologic testing would likely uncover early deficits.

Given an overall clinical picture of fatigue, arthralgia, myalgia, sensory peripheral neuropathy, cognitive complaints and a positive MRI with white matter lesions, this individual was started on biologic therapy. Aggressive treatment of progressive neurologic symptoms is warranted and pulse cyclophosphamide and steroids or other immunosuppressants (chlorambucil or azathioprine) are sometimes used. Anti-TNF agents (infliximab and etanercept) and B cell targeted therapies (rituximab and epratuzumab) are used in primary SS however their efficacy on CNS manifestation is still unclear.[16] This individual had a slow and insidious course and a trial of etanercept for evaluation of overall systemic relief was chosen for her.

SUMMARY

Dry eyes are a common symptom in older individuals as is osteoarthritis. Serologic testing shows that 22% of heallthy elderly individuals have a positive rheumatoid factor and 14% a positive ANA.[17] It may not be

rare for a clinician to be faced with this triad of dry eyes, arthritis, and positive serology and attach a diagnosis of Sjögren's on an elderly individual. These individuals will not necessarily appear ill or frail. On the other hand, primary Sjögren's syndrome, as a systemic autoimmune connective tissue disease of middle age, carries with it insidious debility associated with fatigue, arthralgia, and frequently neurologic signs and symptoms.

The range of neurologic symptoms include CNS manifestations, and frequently cognitive impairment. Studies have associated cognitive impairment with white matter lesions (WML) but a proposed vascular compromise due to autoimmune inflammation is needed to explain cognitive impairment without WML. The cognitive domains impacted include attention, executive function, processing speed, and to a lesser degree immediate recall and long term memory. Primary Sjögren's syndrome carries with it significant morbidity and cognitive screens may not be sensitive enough to pick up early changes in cognition. Along with the debility of chronic disease, progression of cognitive impairment is a risk for frailty and loss of independence. This disorder should be treated aggressively by clinicians and assessed carefully for long-term morbidity risk.

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