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Relation of Sensory Peripheral Neuropathy in Sjögren Syndrome to anti-Ro/SSA

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Abstract

Background—Sjögren syndrome is a common, chronic autoimmune disease that typically produces inflammation and poor function of the salivary and lacrimal glands. Other organs can be affected, including the nervous system. Sensory peripheral neuropathy is a common manifestation of the disease.

Methods—Eight-eight patients attending a dry eyes-dry mouth clinic were classified as primary Sjögren syndrome and underwent a neurological examination. Anti-Ro (or SSA) and anti-La (or SSB) were determined using immunodiffusion as well as Inno-Lia and BioPlex ANA screen. Serum vitamin B12 levels were determined using an enzyme-linked microtiter plate assay.

Results—Twenty-seven (31%) of the 88 patients had peripheral neuropathy as defined by loss of light touch, proprioception or vibratory sensation. Anti-Ro and anti-La were found by immunodiffusion in 12 patients, and 8 of these 12 had neuropathy (χ^2=8.46, p=0.0036, odds ratio = 6.0 compared to those without precipitating anti-Ro and anti-La). Of the 27 patients with only anti-Ro by immunodiffusion, 13 (48.1%) of these had neuropathy (χ^2 =5.587, p=0.018 compared to those without anti-Ro). There was no relationship of the other, more sensitive measures of anti-Ro and anti-La to neuropathy. In addition, we found no association of serum vitamin B12 levels to neuropathy among these patients with Sjögren syndrome.

Conclusion—Sensory peripheral neuropathy is common among patients with Sjögren syndrome, and is associated with the presence of anti-Ro and anti-La when determined by immunodiffusion.

Keywords

Sjögren syndrome; autoantibodies; peripheral neuropathy; vitamin B12

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Introduction

Sjögren syndrome is a common, chronic autoimmune disorder in which the salivary and lacrimal glands are the targets of immune injury (1). Criteria for classification for research purposes have been agreed upon (2), while disease activity and damage indices are less well established. This illness may be one of the most common of the rheumatic autoimmune diseases, and is found most commonly among women in the fifth and sixth decades of life (3).

Dry eyes and dry mouth are the common clinical symptoms that lead to the diagnosis, but there are several other manifestations of Sjögren syndrome including skin, lung and kidney disease as well as vasculitis and peripheral neuropathy (1). The last can take a variety of forms including mononeuritis multiplex, peripheral sensory neuropathy possibly with ataxia, multiple mononeuropathies, multiple cranial neuropathy, trigeminal neuropathy, autonomic neuropathy, and radiculoneuropathy (4). However, patients with Sjögren syndrome most commonly have a sensory neuropathy affecting the feet and lower legs in a `stocking' pattern, which affects light touch, proporioception and vibratory sensation (4).

Sjögren syndrome is considered autoimmune based on two findings. First, there is a characteristic infiltration of lymphocytes found in the salivary and lacrimal glands, as well as other affected organs. The salivary lymphocytes are found in clusters of greater than 50 cells and are graded according to a focus score, which counts the number of clusters per mm^3 of tissue (5). The second finding that defines the disease as autoimmune is the presence of antibodies binding self. Anti-Ro (or SSA) is found in the serum of up to 90% of patients with Sjögren syndrome, while anti-La (or SSB) is found in a smaller number (6). The function of the Ro protein is not completely known but it exists as a complex with short structural RNA molecules called the hY RNAs. The La protein is physically associated with the Ro-hY RNA particle at times. Some extra-glandular manifestations (that is, problems elsewhere besides the salivary and lacrimal glands) are found more commonly in patients with anti-Ro and/or anti-La. These include lymphoma (7).

Another common autoimmune disease that also predominately affects middle aged women is pernicious anemia, which was originally described by Thomas Addison in 1849 (8 and see 9). In this disease the ability to absorb vitamin B12 is impaired because of an autoimmune destruction of gastric parietal cells, which produce intrinsic factor. Only about half of patients with vitamin B12 deficiency develop anemia, while the remainder have a peripheral neuropathy that is similar to the peripheral neuropathy found in Sjögren syndrome (10,11). Diabetes and sarcoidosis can also produce peripheral neuropathy similar to what is found among patients with Sjögren syndrome.

This study was undertaken to determine the percentage of Sjögren syndrome patients with a sensory peripheral neuropathy, the association of this neuropathy with anti-Ro and anti-La, and whether or not peripheral neuropathy found among patients with Sjögren syndrome is related to Vitamin B12 deficiency.

Methods

Subjects

Patients were examined in the Sjögren Syndrome Research Clinic at Oklahoma Medical Research Foundation, where a detailed history and physical examination were conducted. This included general medical, neurologial and rheumatological examinations as well as examination by a dentist and an ophthalmologist. Peripheral neuropathy was assessed by semi-qualitative vibratory sensation (12), 10-gram monofilament (13), and proprioception.

All patients underwent a minor salivary gland biopsy unless a previous biopsy result was available. If patients gave a history of a past diagnosis of rheumatoid arthritis, mixed connective tissue disease, systemic sclerosis, primary biliary cirrhosis or systemic lupus erythematosus, classification criteria for these illnesses were specifically ascertained. Patients meeting the criteria for these illnesses; and, therefore has secondary Sjögren syndrome, were excluded from further consideration. Blood, saliva, and tears were collected as well. Sjögren syndrome was classified as present or absent according to the combined American-European Classification Criteria (2). Thus, all subjects classified as Sjögren syndrome had at least one of a positive minor salivary gland biopsy, or anti-Ro. All procedures were approved by the Oklahoma Medical Research Foundation Institutional Review Board. Each subject provided written informed consent prior to entering the study.

Biopsy

Minor salivary gland specimens were formalin-fixed and parafin-embedded. Sections were cut, and stained with hematoxylin and eosin. Two dental pathologists reviewed the specimens blinded to other results. Infiltration of the glands by lymphocytes was graded by focus score (5). If a consensus could not be reached, a third pathologist reviewed the pathology and provided a focus score.

Serology

Anti-Ro (or SSA) and anti-La (or SSB) were determined by multiple methods. These included double immunodiffusion using rabbit thymus extract as antigen, as previously described (14). This assay, the one used to describe the Ro/La antigen-antibody system measures anti-Ro60 and anti-La, but does not specifically determine anti-Ro52. We measured anti-Ro60, anti-Ro52 and anti-La by a commercial line immunoassay (Inno-Lia ANA Update, Innogenetics NV, Gent, Belgium), following the manufacturer's recommendations, and has been previously reported for anti-Ro/La (15). This assay utilizes miniaturized Western immunoblot techniques to determine antibody to various antigens. We also determined autoantibodies using the Bio-Rad BioPlex 2200 ANA (Bio-Rad, Hercules, CA). The BioPlex ANA Screen utilizes dyed magnetic beads to simultaneously perform automated measurements. We followed the recommendations of the manufacturer, loading undiluted sera samples onto the BioPlex 2200. This method was used to detect antibodies 60 kD Ro, 52kD Ro, and La (16).

Vitamin B12 ELISA

Serum vitamin B12 levels were determined by a microbiological enzyme-linked, microtiter plate assay (Alpico Immunoassays, Salem, New Hampshire, USA catalogue #30-KIF012), according to the manufacturer's instructions.

Statistics

Categorical data were assessed by Chi square analysis with 95% confidence intervals (95%CI), while continuous data were assessed by Student's t test (calculations performed at http://faculty.vassar.edu/lowry/VassarStats.html). A p value of 0.05 was considered statistically significant.

Results

Eighty-eight patients were classified as primary Sjögren syndrome and entered this study of peripheral neuropathy. There were 79 women and 9 men. Seventy-seven patients were white Americans, while six were black Americans, three were Asian Americans, and two were American Indians. The average age was 56.1 years (±13.7).

Of the 88 with primary Sjögren syndrome, 27 were found to have a peripheral neuropathy, manifested by one or more of: loss of 10 gram filament sensation, decrement of vibratory sensation, or loss of proprioception. There was no difference in demographics between those with and without neuropathy (not shown). Three patients presented had neurological symptoms that led to the consideration of Sjögren syndrome after consultation with a neurologist. The remainder generally presented with complaints of dry eyes and dry mouth, but on specific questioning were found to have numbness, tingling, and/or difficulty with balance. Balance problems were especially troublesome with walking down steps, in the dark or on uneven surfaces.

Given that many extra-glandular manifestations of Sjögren syndrome are related to the presence of anti-Ro and anti-La, we wished to determine whether or not there was an association between these autoantibodies and peripheral sensory neuropathy in our cohort of patients. First, anti-Ro and anti-La were determined by double immunodiffusion. This method is the traditional one used to determine the presence of anti-Ro and anti-La (14) so that most of the associations with clinical manifestations are based on this highly specific measurement. On the other hand, double immunodiffusion positivity requires high levels of antibody; and, therefore, may miss the presence of low-titer or low-affinity antibody. Thus, this method is not highly sensitive.

We found that 12 (13.6%) of the 88 primary Sjögren syndrome patients had both anti-Ro and anti-La by double immunodiffusion. Of these 12, 8 (66.7%) had neuropathy. Among the 76 patients without both anti-Ro and anti-La, only 19 (25%) had neuropathy. This difference was statistically significantly (Table 1). Thus, patients with both anti-Ro and anti-La were almost 3 times as likely to have neuropathy (χ^2=8.46, p=0.0036, odds ratio = 6.0, 95%CI=1.6–22.0); however, only 29.6% of the patients with neuropathy had anti-Ro and anti-La (Table 1). When considering those with only anti-Ro by immunodiffusion there were considerably more patients, but there was a much weaker association of anti-Ro alone with neuropathy. Of the 27 patients with only anti-Ro by immunodiffusion, 13 (48.1%) of these had neuropathy, while 14 (23.0%) of the 61 without anti-Ro had neuropathy (χ^2 =5.587, p=0.018, odds ratio=3.12, 95%CI=1.2–8.2). Finally, we considered all those with anti-Ro by immunodiffusion, regardless of anti-La status. Among the 27 patients with peripheral neuropathy, 21 (78%) had anti-Ro by this method, while 18 of 61 primary Sjögren syndrome patients without neuropathy had precipitin anti-Ro (χ2=15.7, p=0.00003, odds ratio=8.4, 95%CI=2.9–24.0). Thus, the presence of anti-Ro, when determined by immunodiffusion, was strongly associated with sensory peripheral neuropathy.

We also determined anti-Ro and anti-La by other methods, which are more sensitive than immunodiffusion (Table 2). These methods detect low levels of antibodies but the clinical significance of low level and/or low affinity antibodies is not known. We found that 32 patients had both anti-Ro and anti-La by the Inno-Lia assay, and 13 (40.6%) these had neuropathy. Meanwhile 14 (25.0%) of those patients without anti-Ro and anti-La had neuropathy (χ^2 =2.238, p=0.17, odds ratio=2.1, 95%CI=0.81–5.2). Thus, combined anti-Ro and anti-La as determined by these assays was somewhat increased among those with neuropathy, but did not reach the level of statistical significance. Further, when considering anti-Ro positivity by the bead assay (BioPlex ANA Screen), there was no relationship with neuropathy either (see Table 2).

We also considered the manner in which patients satisfied the classification criteria. Patients must have one of anti-Ro or salivary gland biopsy focus score greater than 1. Of course, patients might have both of these criteria present. Of interest, there were 11 patients who were classified as Sjögren syndrome on the basis of a positive anti-Ro while their biopsy was negative for focal lymphocytic infiltration. Thus, these patients met the classification

criteria by having anti-Ro, dry eyes, dry mouth and at least one abnormal objective test for dry eyes (Schirmer test or corneal staining with Lissamine Green) or dry mouth (whole unstimulated salivary flow). Only 2 of these 11 had neuropathy compared to 21 of the remaining 77 patients who had a positive biopsy.

We also determined the serum vitamin B12 levels in this cohort of Sjögren syndrome patients. While several of the subjects had levels consistent with insufficiency (that is, less than 300 pg/dl but above 200 pg/dl), there was no difference between those patients with (average = 410 ±86) and without (average = 390 ±55) neuropathy (Student's t test = 0.908, p=0.37). Thus, there was no association of low serum vitamin B12 with neuropathy as a manifestation of Sjögren syndrome.

Discussion

This study investigated peripheral neuropathy in Sjögren syndrome. The results indicate that peripheral neuropathy is related to anti-Ro and anti-La. Those patients with precipitin anti-Ro and anti-La were much more likely to have neuropathy than those without these antibodies. These results show that with determination of autoantibodies by immunodiffusion, a highly specific, but less sensitive assay, improves correlation to this manifestation. In a clinical setting, many commercial laboratories now use ELISA or other high throughput method to determine the presence of anti-Ro and anti-La. The methods used by commercial labs include the BioPlex ANA Screen, which is an assay similar to ELISA. Our data suggest that these more sensitive but less specific assays may not correlate well with neuropathy.

Sjögren syndrome can involve organs other than the salivary and lacrimal glands. These manifestations can include fibrotic lung disease and interstitial kidney disease resulting in renal tubular acidosis. In addition, patients may have vasculitis. Lymphoma, typically mucosa-associated, is found about 80 times more commonly among Sjögren patients than in the general population (7). Most of the extraglandular complications of Sjögren syndrome are more common among patients with anti-Ro and anti-La, including lymphoma (7), vasculitis (17), renal tubular acidosis (18), and interstitial lung disease (19). Our study shows that sensory peripheral neuropathy is found in those patients with anti-Ro and anti-La. Autoantibody testing has been recommended in patients with peripheral neuropathy of unknown origin (20), but the method of detection of anti-Ro and anti-La is likely critical. Alexander and colleagues found more neuropathy in Sjögren patients with anti-Ro in a study of 75 patients, of whom 25 had peripheral neuropathy, but the difference was not statistically significant and the study included both primary and secondary Sjögren syndrome (21).

A recent study examined 120 Sjögren syndrome in which peripheral neuropathy was found in 30 patients. Non-ataxic sensory neuropathy was not associated with anti-Ro or anti-La (22). This study determined these antibodies by Inno-Lia; and, thus, is in agreement with this aspect of our study. Another study in 2011 found 20 of 32 Sjögren syndrome patients had neurological involvement. Of these 20, 8 (25%), had a pure sensory neuropathy similar to that found in our patients (23). Anti-Ro and anti-La were found in 75% and 20% of patients, respectively, but were not different between those with and without neurological manifestations. Unfortunately, the method of detection is not given, but given that 75% of patients had anti-Ro, it is likely the method was a highly sensitive ELISA or commercial line assay such as Inno-Lia. Of six patients with a pure sensory neuropathy, all had normal or near normal nerve conduction velocities (23).

We found a pure sensory neuropathy in 27 of 88 (30%) patients, a percentage similar to the report of Gono, et al. (23). Others have found a much lower prevalence of neuropathy among patients with Sjögren syndrome (24). In a recent study from the Sjögren research group in Athens only 9 of 509 patients had clinical polyneuropathy and abnormal findings of elecrophysiological testing such as electomyleogram or nerve conduction studies (25). The difference between the incidence of neuropathy in this study and others is likely related to the requirement for abnormal elecrophysiological testing. As noted above, in patients with small fiber disease such testing is usually normal (23). The most useful definitively diagnostic testing is skin biopsy in which small nerve fibers are examined. However, determining the density of small nerve fibers in a skin biopsy is a highly specialized pathological procedure that is available from only a few anatomical pathology laboratory (25). We have not performed this test in our patients. We can conclude, however, that the definition of neuropathy is critical when comparing results between studies.

Similar to Sjögren syndrome, vitamin B12 deficiency is common among middle to older aged women. It results from an autoimmune attack against the parietal cells of the stomach, causing an inability to produce intrinsic factor. Thus, without intrinsic factor to bind B12 (originally known as the extrinsic factor), the vitamin cannot be absorbed out of the intestines, creating a deficiency. Pernicious anemia is a common result of this disease. Another result of this deficiency is peripheral neuropathy. Similar to the peripheral sensory neuropathy found in Sjögren syndrome, vitamin B12 deficiency produces a neuropathy with light touch and vibratory sensory deficits. Despite the fact that some autoimmune diseases, especially organ-specific ones, tend to occur together (26), this study found no relation between neuropathy in Sjögren syndrome and vitamin B12 deficiency.

Our study gives clinicians information that can be used in evaluating patients with Sjögren syndrome. Namely, one has to know the methods by which anti-Ro and anti-La are determined. The presence of anti-Ro and anti-La can be used for diagnostic purposes. In this setting highly sensitive assays such as ELISA, Inno-Lia ANA or BioPlex 2200 ANA may be most useful for case finding. These methods are used by large commercial laboratories. Because of the ability of these assays to detect low-titer, low-affinity antibodies, false-positives may be a problem. This is likely to be especially true in individuals with rheumatoid factor in the serum. Meanwhile, the presence of anti-Ro and anti-La may be used for prognostic information. Some patients have only sicca symptoms with involvement of the salivary and lacrimal glands. Meanwhile, others with the disease have manifestations such as vasculitis, neuropathy, interstitial pulmonary disease, renal tubular acidosis, and lymphoma. So-called extraglandular (that is, outside of the lacrimal and salivary gland) involvement is associated with the presence of anti-Ro and anti-La (27). Our data suggest that this association is most robust for highly specific antibody testing by immunodiffusion, or perhaps counter immunoelectrophoresis. To our knowledge, such testing as this is done only at highly-specialized, small clinical laboratories dedicated to only rheumatic disease. Thus, clinicians caring for Sjögren syndrome patients should know not only the reason for testing, but the method employed. In conclusion, neuropathy is common in Sjögren syndrome, especially if anti-Ro and anti-La are present. However, the association of anti-Ro and anti-La is most robust when these autoantibodies are determined by immunodiffusion. Vitamin B12 deficiency does not contribute to neuropathy found in Sjögren syndrome.

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Table 1

Relationship of peripheral sensory neuropathy with anti-Ro and anti-La determined by double immunodiffusion. Left - Both anti-Ro and anti-La present. Right - anti-Ro present.

	Peripheral Neuropathy			Peripheral Neuropathy	
Anti-Ro/La	**Present**	**Absent**	**Anti-Ro**	**Present**	**Absent**
Positive	8	4	Positive	21	18
Negative	19	57	Negative	6	49

χ^2 = 8.46, p=0.0036, odds ratio = 6.0

χ^2 = 15.7, p=0.00003, odds ratio = 8.4

Table 2

Relationship of peripheral sensory neuropathy with anti-Ro and anti-La determined by Inno-Lia and BioRad.

	Peripheral Neuropathy	
Anti-Ro/La	**Present**	**Absent**
Positive	13	19
Negative	14	42

χ^2 =2.338, p=0.126, odds ratio = 2.1