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## **Peripheral neuropathies in Sjögren's syndrome: a new reappraisal.**

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## **ABSTRACT**

### **Background**

The prevalence of peripheral neuropathy in patients with Sjögren's syndrome remains unclear due to conflicting results in the published series, with numbers ranging from 2 to over 60% of Sjögren's syndrome patients. Whether peripheral neuropathy is a feature of the systemic or glandular disease or if it is related to a circulating anti-neuronal antibody, remains also uncertain.

### **Methods**

We reviewed the records of patients with primary Sjögren's syndrome (pSS), fulfilling the Revised European - American Classification Criteria, seen in our department from 1992 to 2009. The patients with previously recorded neuropathic features were re-examined by us clinically and electrophysiologically. Other causes of polyneuropathy were excluded. We also searched for circulating anti-neural antibodies using immunofluorescence and Western Blot and for antibodies against muscarinic and nicotinic acetylcholine receptors as potential biomarkers.

### **Results**

509 cases met the diagnostic criteria for pSS. Among them, 44 patients were recorded as having neuropathic symptoms. After completing our evaluation however, only 9 (1,8%) of them had polyneuropathy with **objective clinical signs and abnormal electrophysiological findings**. The neuropathy was axonal in all; in 5 was pure sensory and in 4 sensorimotor. The patients with peripheral neuropathy had extraglandular manifestations such as palpable purpura and vasculitis. No evidence of anti-neural autoimmunity was found and no candidate biomarkers were identified.

## **Conclusion**

Polyneuropathy is a rare manifestation of pSS occurring in 1,8% of patients. In the majority of patients, it is a late event and frequently associated with systemic disease or risk factors for lymphoma development.

## **INTRODUCTION**

Sjögren's syndrome is a systemic autoimmune disease that affects 0,5 to 1% of the general population.[1, 2] It usually presents as an isolated glandular disease affecting exocrine glands, typically manifested with xerostomia and xerophthalmia.

Extraglandular manifestations are due to involvement of virtually every organ including the musculoskeletal system, skin, kidneys, lungs, liver and the central or peripheral nervous system (PNS).[1, 3] The most serious complication of Sjögren's syndrome is lymphoma, which affects 3 – 6% of patients and is 44 times more frequent than in the general population.[4, 5]

The clinical spectrum of peripheral neuropathies encountered in Sjögren's syndrome patients is wide [6-9], with sensory neuropathies being the most common.[8, 9] The sensory neuropathies are of three distinct sub-types: distal (length-dependent) affecting sensory fibers with electrodiagnostic features of axonal involvement; painful, due to small-fiber involvement [10-14]; and sensory ataxic, a disabling neuropathy involving the dorsal root ganglia (ganglionopathy)[15, 16] resulting in deafferentation[17]. Axonal sensorimotor polyneuropathy, cranial neuropathy, multiple mononeuropathy, demyelinating polyradiculoneuropathy and autonomic neuropathy are other less frequently encountered types.[8, 9]

Although several studies have focused on the peripheral nerve manifestations of Sjögren's syndrome, two issues remain contentious; the prevalence of peripheral neuropathy, with a reported range between 2-60%,[6, 13, 18-29], and the stage of the

disease in which peripheral neuropathy is most commonly manifested. Some studies claim that peripheral neuropathy is a late event, presenting in patients with manifestations of severe systemic disease such as palpable purpura, low C4 complement factor, mixed monoclonal cryoglobulinaemia, glomerulonephritis and increased risk of lymphoma development.[23] Other studies however, suggest that peripheral neuropathy is the presenting feature of an isolated glandular disease that has a benign course.[8, 9] The pathogenesis of these neuropathies is also poorly investigated. Because Sjögren's syndrome is a systemic autoimmune disease engulfing many autoimmune processes, correlating the temporal profile and clinical patterns of the neuropathy with the type of Sjögren's syndrome's manifestations will help us understand the pathogenesis for each neuropathy subtype. Our study was therefore designed to assess the frequency of neuropathy diagnosed by means of **objective clinical signs and abnormal electrophysiology**, in the various stages of the disease. We also sought to examine whether the neuropathy is immune-mediated by searching for antibodies against a variety of peripheral nerve tissue antigens and for antibodies against muscarinic and ganglionic acetylcholine receptors, which have been implicated in both, Sjögren's syndrome and in various peripheral neuropathies.[31, 32]

## **PATIENTS AND METHODS**

### **Patients**

Clinical information was retrospectively obtained from the records of patients who met the diagnostic criteria of primary Sjögren's syndrome, according to the Revised European-American diagnostic criteria.[33] These patients had been followed from 1992

to 2009 at the Pathophysiology Clinic of the University of Athens Medical School,, that serves as a national referral center for systemic autoimmune diseases. All patients with previously recorded manifestations indicative of peripheral neuropathy (after providing written informed consent) were invited to participate in the current study that took place from 2008 to 2010. These patients were re-examined by a certified neurologist (MLK). Sensory examination was based on assessing pinprick, light touch, position and vibratory sensation. Patients with objective clinical signs of neuropathy underwent electromyography and nerve conduction studies of the sural, peroneal, and median nerve (ES). Normal values, **defined as the mean plus or minus 2 standard deviations,** were determined from 100 normal individuals from different age groups. Skin temperature was measured to be greater than 32°C when all electrophysiologic studies were conducted. The cut-off was amplitude of the sural SNAP was 10µV for ages younger than 65 and 8µV for ages 65 to 75 ; for people older than 85 the sural nerve amplitude was considered abnormal only when it was not elicited. The mean normal sural conduction velocity was determined at 48m/s. Peroneal CMAP amplitude cut-off was 4mV and conduction velocity 46m/s. Median nerve SNAP was 20µV and sensory conduction velocity (from digit to wrist) was 47m/s. Median nerve CMAP was 5mv and conduction velocity 50m/s. MRI or CT of the brain and/or spine were performed on a case by case basis to exclude spinal or cranial abnormalities as a possible cause for the clinical manifestations. New patients diagnosed during the study period, were also included. Patients with other causes of peripheral neuropathy were excluded. Serum samples were obtained from all peripheral neuropathy patients and stored at -20°C for immunological



studies (see below). The study was approved by the University of Athens' Medical School Ethics Committee.

### **Anti-neural antibody screening**

We searched for anti-neural antibodies in eight patients with clinically and electrophysiologically confirmed neuropathy, from eight controls with Sjögren's syndrome without neurologic involvement and from eight healthy controls using indirect immunofluorescence and Western blot on a variety of nerve tissues. As positive controls we used sera with known reactivities to brain and nerve antigens, namely Aquaporin-4, and MAG. Primate cerebellum and sciatic nerve sections were obtained from Euroimmun (Nerve Mosaic, No 1111-1003-2 Euroimmun, Lübeck, Germany). Human dorsal root ganglia were obtained from the Netherlands Brain Bank (Netherlands Institute for Neuroscience, Amsterdam) and sectioned in a Leica cryostat. Briefly, sections were fixed in 4% paraformaldehyde and incubated with 1% CHAPS. After blocking with 10% goat serum, they were incubated with the patients' sera diluted 1:100 in 1% goat serum followed by AlexaFluor 488 goat anti-human IgG or IgM (Invitrogen, Carlsbad, CA) diluted 1:250 in 1% goat serum. Western blot experiments were carried out as previously described,[34] with the only modification being the use of the AEC peroxidase substrate kit (Vector laboratories, Burlingame, CA) for development.

### **Anti-M1 and M3 receptor antibodies**

Peptides corresponding to the second extracellular loop of M1 muscarinic acetylcholine receptor (165-185) and M3 muscarinic receptor in dimer form (213-237) were

synthesised (Biosynthesis, Lewisville, TX) and ELISA experiments were carried out as previously described,[35] with the only modification being that a control well corresponding to each sample was coated only with blocking solution. The optical density (OD) of the control well was subtracted from each sample's OD. Samples were deemed positive for anti-muscarinic antibodies when the final OD was greater than the mean plus three standard deviations of normal samples tested in the same manner.

Ganglionic acetylcholine receptor antibody radioimmunoprecipitation assay.

Solubilised membrane fractions from IMR32 cells[32] were labeled with <sup>125</sup>I-epibatidine and incubated with 5µl of patient's serum overnight at 4°C in duplicates. Following incubation for 2 hours with goat anti-human IgG (RSR Ltd, Cardiff, UK) and precipitation, the pellets were washed with 0,5% Triton-X 100 in phosphate buffer and radioactivity was measured. The value 10 arbitrary Units was defined as the mean counts per minute value of healthy controls and samples with values greater than 25 Units were deemed positive. mAb 198 which binds to muscle acetylcholine receptor alpha-1 subunit and cross-reacts with the ganglionic alpha-3 subunit was used as positive control.

## **RESULTS**

### **Patients**

The records of 509 patients with primary Sjögren's syndrome were reviewed.[33]. Fourty four patients were recorded as having neuropathic symptoms or signs including paraesthesias, pain, gait unsteadiness, Romberg sign, superficial or deep sensory deficits,

diminished deep tendon reflexes or muscle weakness. Two of the 44 patients were excluded from further analysis because they were found to have secondary Sjögren's syndrome or did not meet the criteria for Sjögren's syndrome. Of the remaining 42 patients, originally recorded as having neuropathic symptoms, 11 were excluded from further analysis because their symptoms were caused by various musculoskeletal problems; two others with a history of trigeminal neuralgia, were asymptomatic and were also excluded. Among the remaining 29 patients, three had clinical and electrodiagnostic findings of carpal tunnel syndrome; one other was diagnosed with motor neuron disease and another with spinal stenosis. Among the remaining 24 patients, 15 complained for neuropathic symptoms such as pain and paraesthesias but the clinical and electrophysiological evaluation were normal. These patients are suspected of having a small fiber neuropathy, but they did not undergo quantitative sensory testing or skin biopsy. Accordingly, only nine patients from the initial cohort of 509 patients (1,8%) fulfilled the clinical and electrophysiological criteria of polyneuropathy; five of them were diagnosed with sensory and four with sensorimotor polyneuropathy (Table 1).

These patients with *bona fide* neuropathy were female, with a mean age of 65 years (range 54-84 years) at the time of the last evaluation. All complained of distal paraesthesias and had distal (length-dependent) neurological findings in the lower limbs; the upper limbs were affected only in two. In the majority of patients (6/9) the neurological findings were symmetrical. Among the patients with sensory polyneuropathy, two had position and vibratory sensation deficits, two had pinprick and light touch sensory deficits and one had sensory deficits in all tested modalities; the

patients with sensorimotor polyneuropathy had mostly light touch and pinprick sensory deficits. Deep tendon reflexes were diminished or absent in eight of the nine patients. The neuropathy was mild and all patients were ambulatory; only one needed a cane for ambulation. All patients had the electrophysiological pattern of axonal dysfunction. One patient with sensory polyneuropathy developed an acute mononeuropathy, in the setting of generalised vasculitis, confirmed by intestinal biopsy. (see Table 1 for a detailed description of the patients).

In six of nine patients, the neuropathy was a late event in the course of the disease with a median of six years (range of 2 to 24) from the time of the initial diagnosis of Sjögren's syndrome; in one the neuropathy was the presenting manifestation of Sjögren's syndrome, confirmed soon thereafter; and in the rest two the neuropathy was present at the time of Sjögren's syndrome diagnosis, but the temporal relationship between the two could not be ascertained. One of the latter three patients had no extraglandular manifestations; this is in contrast to the other two who had prominent extraglandular manifestations as described below.

The majority of patients with neuropathy had active systemic disease. Extraglandular manifestations were present in seven of nine and included palpable purpura in five patients, Raynaud phenomenon in four, arthralgias in three, biopsy-documented vasculitis (in organs other than the nerves) in three, arthritis in two and lymphadenopathy in two. Glomerulonephritis and atrophic gastritis were present in two others. Six patients (three with sensory and three with sensorimotor polyneuropathy) were classified as type I Sjögren's syndrome, which confers higher risk for lymphoma development.[36] Type I

Sjögren's syndrome is defined based on the presence of at least two of the following manifestations: parotid enlargement, low C4 complement factor at the time of Sjögren's syndrome diagnosis, or palpable purpura.[36]

All patients with peripheral neuropathy had antinuclear antibodies; eight had anti-Ro antibodies and two had anti-La antibodies. Rheumatoid factor was found in five. Three patients had cryoglobulinaemia. Low C4 complement factor at the time of Sjögren's syndrome diagnosis was found in 5 patients.

Table 1

(see supplemental file)

### **Anti-neural antibody screening**

Immunofluorescence and Western blot

Eight of nine polyneuropathy patients were screened for the presence of anti-neural antibodies with immunofluorescence and Western Blot.

*Brain and dorsal root ganglion immunofluorescence.* No consistent IgG or IgM immunostaining pattern on neuronal structures was observed with the patient's sera, with the exception of occasional antinuclear staining, as expected.

*Peripheral nerve immunofluorescence.* Staining primate nerve using an IgG and IgM secondary antibodies, yielded no specific staining.

Western Blot experiments of mouse brain extracts probed with patients and healthy control sera, also revealed no specific bands.

Screening for putative peripheral neuropathy biomarkers

*Muscarinic receptor autoantibodies*

*ELISA for anti-M1 muscarinic receptor autoantibodies* We tested eight polyneuropathy patients, 33 Sjögren's syndrome patients without neurologic involvement and 20 healthy controls. Antibodies against M1 muscarinic acetylcholine receptor were not found in any of the polyneuropathy patients or healthy controls. Four of 33 Sjögren controls were positive for anti-M1 muscarinic receptor antibodies (Figure 1).

*ELISA for anti-M3 muscarinic receptor autoantibodies* . One of eight polyneuropathy patients was positive for antibodies against M3, as was one of 31 Sjögren's syndrome patients without neurological involvement. None of the 20 healthy controls was positive (Figure 2). This patient was diagnosed as having axonal sensorimotor polyneuropathy.

*Ganglionic ( $\alpha 3$ ) acetylcholine receptor autoantibodies*. None of the eight polyneuropathy patients and none of the four healthy controls was tested positive for ganglionic acetylcholine receptor antibodies (Figure 3).

## **DISCUSSION**

The study found a surprisingly low (1,8%) prevalence of polyneuropathy, diagnosed by means of **objective signs and abnormal electrophysiology**, among a large number of patients with *bona fide* Sjögren's syndrome This is in contrast to previous studies which have shown a much higher prevalence ranging from 2% to 60%. [6, 13, 18-29] Such a wide discrepancy can be explained on several factors. First, most of the other studies were published during the time when the diagnostic criteria for Sjögren's syndrome were

still evolving and the diagnosis was at times questionable. Second, many studies have been retrospective and included contemporaneous neurological or electrophysiological assessments in a relatively small number of patients. Third, the definition of neuropathic symptoms varied greatly between series and the electrophysiological parameters, especially among patients with sensory polyneuropathy, were quite variable. Fourth, the screen samples of pSS patients were generally small. Our study has attempted to address these issues by assessing peripheral neurological involvement in the largest ever cohort of primary Sjögren's syndrome patients, while applying the latest criteria for diagnosis. Although its retrospective design is a limitation, the study was strengthened by re-evaluating all the patients with previously recorded neuropathic symptoms clinically and electrophysiologically. Further, on account of objectivity, we relied more on electrodiagnostic techniques rather than patient history or neurologic examination alone. One notable finding was the absence of ataxic neuropathy from our study cohort. This may be linked to a referral bias as most of such cases are referred directly to neurologists or are misdiagnosed as ataxias related to other causes. Another interesting finding was the types of neuropathy; we noted an equal frequency of sensory (n=5) and sensorimotor (n=4) polyneuropathy patterns. Sensory polyneuropathy has, according to previous series, been considered a frequent manifestation compared to sensorimotor polyneuropathy.[8, 9] The highly subjective nature of sensory examination or the lack of consensus on the diagnosis may account for some of these discrepancies. Although we found a low frequency of polyneuropathy among Sjögren's syndrome patients, a much greater number of patients presented with painful neuropathic symptoms had normal clinical and electrophysiological evaluation. It is highly likely that these patients suffer

from small fiber sensory neuropathy, which has been also observed but never systematically studied in Sjögren's syndrome.[10-14] As this appears to be the commonest pattern, the prevalence of small fiber neuropathy among Sjögren's syndrome patients merits further investigation.

The timing of the manifestation of peripheral neuropathy during the course of Sjögren's syndrome has also been debated.[7-9, 23] In the majority of our patients (6/9), peripheral neuropathy was a late event. Studies suggesting the contrary may reflect the referral pattern, as such patients are referred first to neurologists. The majority of our patients with polyneuropathy, had active, systemic Sjögren's syndrome, especially Type I Sjögren's, a subset prone to developing lymphoma.[36] Although none of them had a lymphoproliferative disorder at the time of evaluation, the majority of them had risk factors, such as low C4 complement factor, parotid gland enlargement, and purpura. Whether those factors are responsible for the neuropathy remains unclear.

Because Sjögren's syndrome is a systemic autoimmune disease, we hypothesised that the neuropathy may have an autoimmune pathogenesis. Because ganglionic acetylcholine receptor autoantibodies have been recently found in a variety of peripheral neuropathies, [31, 32] and muscarinic acetylcholine receptor antibodies have been found in patients with primary Sjögren's syndrome,[30] we screened our neuropathy patients for these autoantibodies as candidate biomarkers. No immunoreactivity was however noted. Alas, no evidence of anti-neural tissue autoimmunity was observed based on our immunofluorescence and Western Blot screening. It is likely that examination of tissues



such as nerve biopsies might have been more informative to exclude or confirm the autoimmune pathogenesis. Such studies are in process in our ongoing prospective study.

Competing interests

The authors report no competing interests

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## Figure Legends

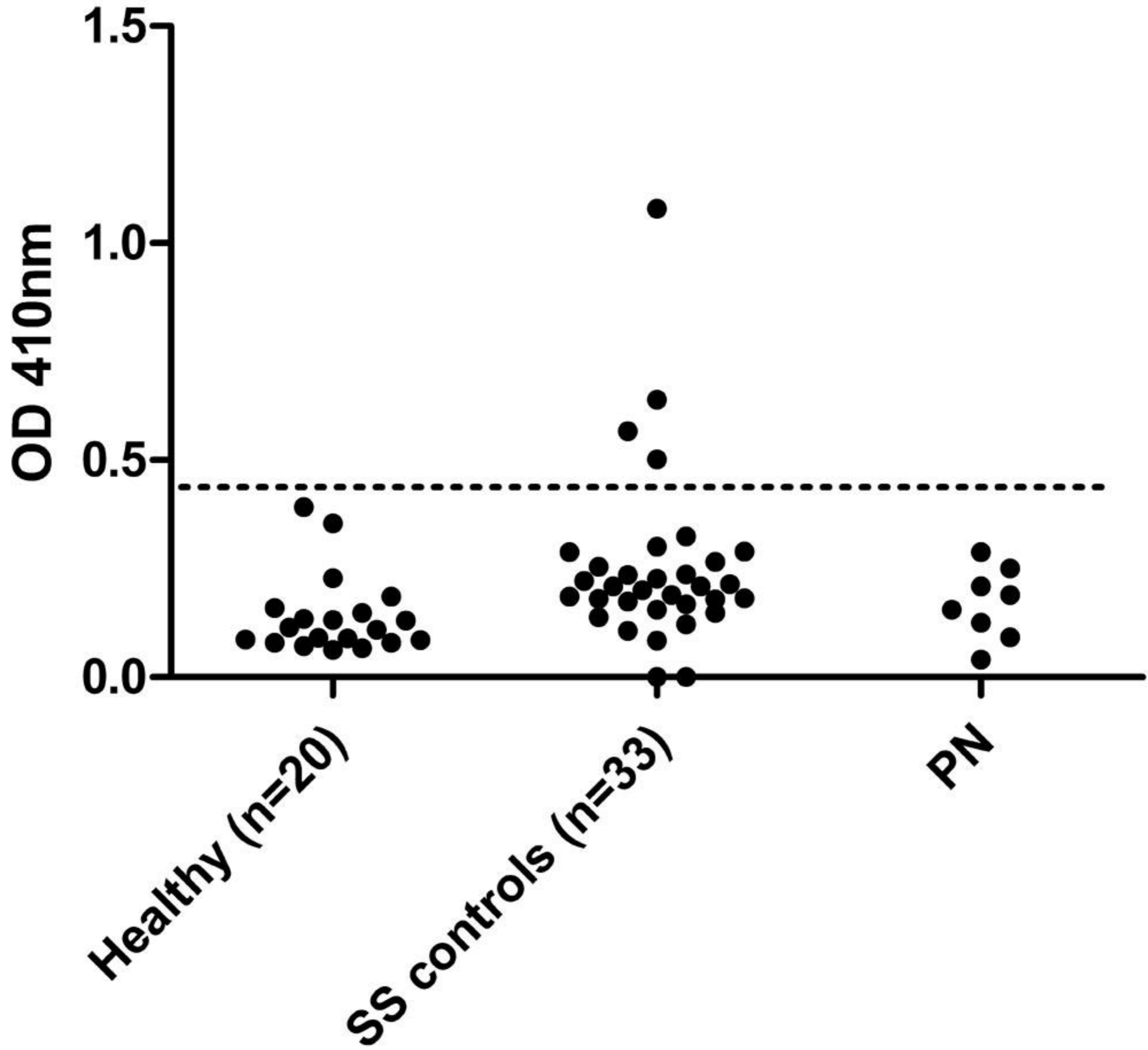
### Figure 1. Anti-M1 muscarinic antibodies ELISA

4 patients with Sjögren's syndrome (SS) were tested positive for anti-M1R antibodies, as opposed to peripheral neuropathy patients (PN) and healthy controls

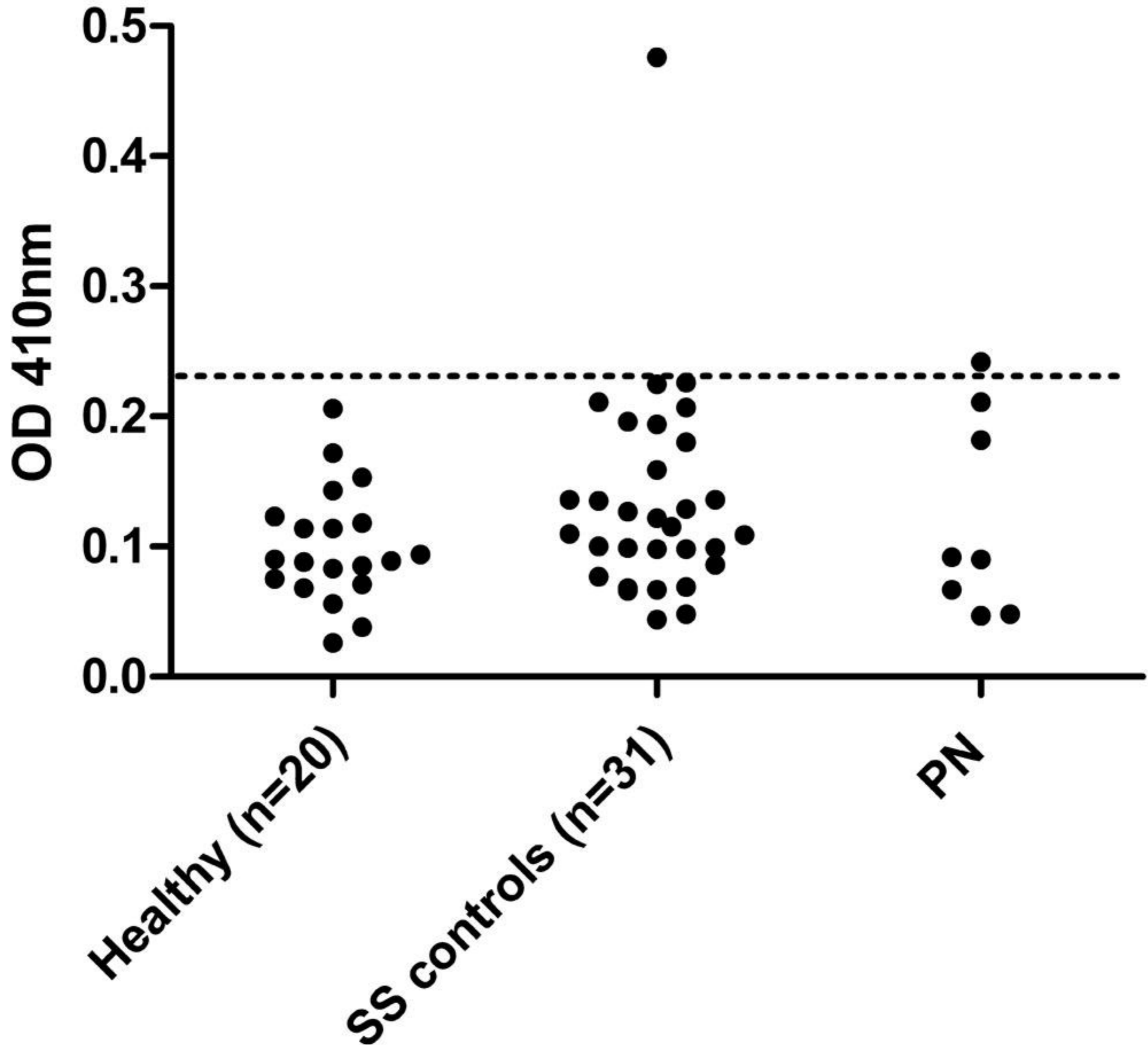
Figure 2. 1 patient with Sjögren's syndrome and peripheral neuropathy (PN) was tested positive for anti-M3R antibodies, as was 1 patient with Sjögren's syndrome (SS). None of the healthy controls was positive for these antibodies

Figure 3. Anti-ganglionic ( $\alpha 3$ ) Acetylcholine receptor antibodies radioimmunoassay  
None of the 8 peripheral neuropathy patients (SS), or healthy controls screened was positive for the tested antibodies.

# anti-M1R ELISA



# anti-M3R ELISA



# Ganglionic AchR antibodies RIA

