

# Accepted Article

## Neurophysiological features of peripheral nervous system involvement and immunological profile of patients with primary Sjögren syndrome

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## Abstract

**Objectives:** The aim of this study was to evaluate: the prevalence, type of neuropathy and the relationship between the presence of autoantibodies and neuropathy development in patients with primary Sjögren syndrome (pSS).

**Material and methods:** 61 pSS patients underwent a complete neurological and electrophysiological examination as well as immunological tests including rheumatoid factor (RF) and autoantibodies as antinuclear antibodies, (ANA), anti-Ro/SSa, anti-La/SSB antibodies.

**Results:** The axonal loss or demyelination were found in 39 patients (63.9%). 29 (47.5%) subjects fulfilled both clinical and electrophysiological criteria of peripheral neuropathy of predominantly axonal type. Seropositivity to both anti-Ro and anti-La antibodies was more frequently found in patients with normal nerve conduction study. Seropositivity to anti-Ro alone was present in the majority of patients with axonal neuropathy ( $p<0.05$ ). The presence of RF was associated with several electrodiagnostic signs of demyelination ( $p<0.01$ ). The ANA titer showed no independent association with neuropathy.

**Conclusions:** Peripheral neuropathy is a frequent complication in patients with primary Sjögren syndrome. Seropositivity limited to anti-Ro is associated with increased risk of axonal neuropathy in comparison to seropositivity to both anti-Ro and anti-La antibodies. Seropositivity to RF may contribute to demyelination.

**Keywords:** Sjögren's Syndrome, Neuropathy, Autoantibodies

**Introduction:** Primary Sjögren syndrome (pSS) is an autoimmune connective tissue disease affecting the exocrine glands, leading to the damage of their structure and impairment of their function. In the course of pSS the involvement of internal organs may also occur and symptoms associated with every system may occur. Neurological complications account for 8.5-70% of pSS cases (1). Peripheral neuropathy, especially the distal sensory or sensorimotor axonal neuropathy, is the most frequent neurological complication of pSS (2-

60%) (2; 3; 4; 5; 6; 7). Cranial neuropathy and central nervous system involvement (2-25%) were also reported in the course of pSS (8;9;10).

Although the clinical presentation of peripheral neurologic pathologies in pSS were extensively described but the clear underlying pathogenic mechanisms are still not well known. One of highligded causes of neuropathy in pSS is vasculitis, which is especially associated with development of mononeuropathy multiplex. The multifocal T-cell infiltration in the dorsal root ganglia, seems to be responsible for the development of sensory neuronopathy. B cells hyperactivity and the production of autoantibodies have been also considered as candidate contributors to the nerve damage due to their reactivity against nerve tissue antigens (11;12;13). Data concerning the immunological profiles of patients with pSS and concomitant neuropathy are sparse and controversial. One study showed that patients with pSS-associated sensory neuropathy had a higher prevalence of both anti-Ro and anti-La antibodies (5; 14;15;16). However, in other studies, neuropathies were associated with a negative immunological profile (17;18). Moreover, despite many epidemiological studies, there are inconsistencies of the prevalence of neuropathy associated with pSS in different centers. The cause of such discrepancies is linked with different definitions of peripheral neuropathy, and the fact that the definition is not always based on objective clinical and electrophysiological criteria. Some studies relied more on neurological and electrophysiological testing, others depended entirely on symptomatology as reported by patients themselves. Moreover, electrophysiological studies were sometimes limited and insufficient.

**Objectives:** The main aim of the study was to evaluate the prevalence and the type of peripheral neuropathy in patients with pSS. The secondary purpose was to assess the

relationship between specific immunologic profiles regarding the presence of serologic markers significant for patients with pSS, such as rheumatoid factor (RF), antinuclear antibodies (ANAs), anti-Ro, anti-La antibodies, and neuropathy development.

#### **Material and methods:**

**Patients:** Sixty one patients aged 21-80 (Mean (M)=50.82; SD=14.01), including 56 women aged 21-80 (M=51.05; SD=14.64) and five men aged 35-55 (M=48.20; SD=7.73) with pSS diagnosed between September 2014 and June 2016 in the National Institute of Geriatrics, Rheumatology and Rehabilitation (GRR) were enrolled. All patients fulfilled the diagnostic criteria for pSS proposed both by the American-European Consensus Group and by the American College of Rheumatology in 2012 (20). The study was approved by the Ethics Committee of National Institute of Geriatrics, Rheumatology and Rehabilitation (nr KBT - 1/1/15), and signed informed consent forms were obtained from all patients.

We excluded patients with secondary SS and with comorbidities potentially affecting peripheral nervous system such as: diabetes mellitus, glucose intolerance, renal failure, hyperthyroidism or hypothyroidism, proliferative diseases, amyloidosis, sarcoidosis, hepatitis C and Hepatitis B infections, alcohol abuse, vitamin B12 deficiency, and exposition to neurotoxic factors.

**Serology:** In the course of diagnostics basic laboratory tests were performed, including rheumatoid factor (RF), autoantibodies (ANA, anti-Ro/SSA, anti-La/SSB). Anti-nuclear antibodies were detected by indirect immunofluorescence (IIF) using a human epithelial cell line-2 (HEp-2) as an antigen. The anti-Ro/SSA and anti-La/SSB antibodies were evaluated using semiquantitative method (by Euroimmun with EUROblotOne analyser). The Rheumatoid Factor was measured using nephelometric assay (normal range <34 IU/ml).

**Neurological assessment:** All patients underwent a complete neurological examination. Muscle strength was assessed according to the Medical Research Council Scale (MRCs). Examination included the strength of distal and proximal muscles of upper and lower extremities. Patients performed following movements against resistance: shoulder abduction, elbow flexion and extension, finger flexion and extension, hand grip, hip flexion and extension, knee flexion and extension, as well as foot flexion and extension. Sensory examination was based on assessment of light touch, pinprick, temperature sensations, and deep sensation (joint position sense, presence of sensory ataxia and Romberg's sign, vibratory sensation). Vibration was quantified using a Rydel- Seiffer tuning fork bilaterally at the distal interphalangeal joints, medial malleolus and radial styloids. Cranial nerve function, deep tendon reflexes and pathological reflexes were also assessed. In patients reporting symptoms suggestive of the carpal tunnel syndrome we looked for Tinel's sign and we performed Phalen's test.

**Nerve conduction study:** All patients underwent nerve conduction studies, even if their neurological exam was normal. The electrodiagnostic examinations were done in the EMG Laboratory of National Institute of GRR using a Neuropack X1 MEB -2300 system (Nihon Kohden, Japan). Nerve conduction studies were performed bilaterally using surface electrodes. Standard sites of stimulation and recording response from individual nerves were used, based on commonly adopted methodology (20). Motor conduction studies involved the median, ulnar, peroneal and tibial nerves. Sensory conduction studies were performed in the median, ulnar, superficial peroneal and sural nerves. Stimulation in multiple sites was done in ulnar neuropathy at the elbow but not in other entrapment neuropathies. For motor NCS low frequency filter was set to 2Hz and high frequency filter to 10 kHz. The sweep speed

was set at 5ms, the gain (sensitivity) was set at 2mV per division for tibial and peroneal nerve and at 5mV for median and ulnar nerve. Distal latency, amplitude, conduction velocity and the F-wave latency were measured. For sensory conduction studies low frequency filter was set to 30Hz and high frequency filter to 2 kHz, the gain (sensitivity) was set at 10 uV per division, the sweep speed was set at 2ms. Amplitude of sensory nerve action potential (SNAP) and conduction velocity were measured. The amplitude of both CMAP and SNAP was measured from the baseline to the negative peak. If the amplitude was low, the sensitivity was increased. Demyelination or axonal loss were diagnosed according to the criteria of ESTEEM project (*European Standardized Telematic tool to Evaluate Electrodiagnostic Methods*) (21). The presence of conduction block was recognized using guidelines of the *American Association of Neuromuscular & Electrodiagnostic Medicine, AANEM* (22).

Basing on electrophysiologic findings, mononeuropathy, mononeuropathy multiplex or polyneuropathy were diagnosed. For mononeuropathy multiplex involvement of at least two nerves was required with concomitant pain and subacute onset. For diagnosis of the polyneuropathy, the respective electrodiagnostic criteria (*Oh SJ. Clinical Electromyography: Nerve Conduction Studies. 3rd ed. Philadelphia: Lippincott William & Wilkins; 2003*) needed to be fulfilled and additionally chronic, progressive pattern needed to be documented clinically or electrophysiologically. Electrodiagnostic criteria cited above required: prolongation of the distal motor latency and/or motor conduction velocity slowing in at least two separate nerves and/or decrease in the amplitude of the sensory nerve action potential or a decrease in sensory conduction velocity in at least two separate nerves.

Due to distinct pathogenic mechanism, entrapment neuropathies were analyzed separately. Symptomatic neuropathy was diagnosed on the basis of abnormalities in both, neurological

examination and electroneurography (ENG). The time-interval separating serologic workup and NCS did not exceed several days.

### Statistical analysis

IBM SPSS Statistics Software, version 24 (Armonk, NY: IBM Corp.USA) was used to perform the whole statistical analysis. In order to determine distribution of quantitative variables, the Kolmogorov–Smirnov test was used. Relation between particular parameters of nerve conduction to age, titer of particular antibodies as well as other numeric variables was analyzed with Pearson correlation coefficient or in case of non-normal data distribution with the Spearman's rank correlation coefficient. For parameters of nerve conduction significantly correlating with age, analysis with other variables was controlled for age using partial correlations. Logistic regression analysis, also controlled for age was used to investigate the influence of RF positivity and concentration, ANA titer, anti-La positivity, concurrent anti-La positivity in anti-Ro positive subgroup (independent variables), on clinical signs of neuropathy and parameters of nerve conduction (dependent variables). Data are presented as mean and standard deviation. Significance level was set at  $p < 0.05$ .

**Results:** Nerve conduction studies revealed axonal loss or demyelination in 39 out of 61 patients (63.9%). Twenty-nine (47.5%) subjects fulfilled both clinical and electrophysiological criteria of peripheral neuropathy. In the vast majority of patients, neurography showed axonal damage, which was present in 37 subjects (94.8% of all subjects with neuropathy). In two patients (5.1% of all subjects with neuropathy) axonal loss was accompanied by demyelination. Neuropathy affected predominantly nerves of lower extremities and sensory fibers in 28 subjects (71.8% of all subjects with neuropathy). In 15 cases (38.5% of all subjects with neuropathy) only sensory nerves were affected. Regarding

the number of affected fibers, the most frequent diagnosis was polyneuropathy, which was found in 16 patients (41% of all patients with neuropathy), in 10 patients (25.6% of all patients with neuropathy) it was sensorimotor polyneuropathy and in 6 patients (15.4% of patients with neuropathy) it was sensory polyneuropathy. Fourteen patients (35.9% of all patients with neuropathy) revealed mononeuropathy, most often of the peroneal nerve, and 9 patients (23% of all patients with neuropathy) revealed mononeuropathy multiplex, (table 1). Moreover, in 18 (29.5%) patients a compression neuropathy was found, usually concomitant to axonal peripheral neuropathy. In 12 (19.7%) patients, it was the carpal tunnel syndrome, in four of them (6.5%) as an isolated finding. In seven patients (11.5%) we found ulnar neuropathy at the elbow, which in one (1.6%) was as an isolated electrodiagnostic abnormality.

Seventeen patients reported symptoms typical for neuropathic pain. The most frequent form was burning feet, which was present in 14 patients, suggesting involvement of small fibers. In four of these patients the nerve conduction was normal, which indicates the pure small fiber neuropathy. All of these four were ANA-positive. In one of them no other seropositivity was found. The second one was also anti-Ro positive. The third anti-Ro and anti-La and the fourth was anti-Ro, anti-La and RF positive. The diagnosis small fiber neuropathy could however not be confirmed as the skin biopsy was not performed. Four patients complained about facial pain (one describing symptoms typical for trigeminal neuralgia), in five patients pain was located also in the trunk.

Involvement of the cranial nerves assessed by neurological examination was detected in seven patients (11,5%). The most frequent was a pure sensory trigeminal neuropathy (V nerve) – in five patients (one patient with numbness restricted to the trigeminal nerve region, four patient with



trigeminal neuralgia). The vestibulocochlear nerve (VIII nerve) impairment, revealed by unilateral hearing loss was found in two patients. Cranial neuropathies usually coexisted with other types of neuropathies (most frequently with sensory polyneuropathy). Only in one case trigeminal neuropathy was found as an isolated abnormality.

#### **Presence of antibodies:**

The RF was found in 27 patients (44.3%). The concentration of RF ranged from 20 to 1515 IU/ml (Me=29,15; IQR=139,75); (M=134.08; SD=251.11). ANA antibodies (in titer over 1:160) were detected in 57 patients (93,4%). In a titer of over 1:320, ANA antibodies were found in 51 patients (83,6%). The titer of ANA antibodies ranged from 1:80 to 1:40960 (Me=1280.00; IQR=2240.00); (M=1:2790.82; SD=1:6013.96).

Anti-Ro/SSA specific antibodies were found in 51 pSS patients (83.6%) and anti-La/SSB specific antibodies were found in 23 patients (37.7%). Among 51 patients, 29 (47.5%) had only anti-Ro antibodies (without anti-La antibodies), 22 (36.1%) had antibodies directed against both Ro and La. Only one patient was found to have anti-La antibodies in the absence of anti-Ro antibodies (figure 1 ).

#### **Antibodies and neuropathy:**

The Chi-square test revealed statistically significant relation between axonal nerve damage and the presence anti-Ro/SSA or both anti-Ro/SSA and anti-La/SSB antibodies,  $\chi^2(1)=4.56$ ,  $p<0.05$ . Seropositivity to both anti-Ro and anti-La in the same subject was more frequently found in patients with normal nerve conduction study (12/22 patients with both anti-Ro and anti-La comparing to 7/22 patients with anti-Ro). Seropositivity to anti-Ro alone was present

in the majority of patients with axonal neuropathy (21/37 patients with anti-Ro comparing to 10/37 patients with both anti-Ro and anti-La) (figure 2).

Mean ANA titer was higher in patients without neuropathy ( $p<0.05$ ), and correlated negatively with age. Using partial correlation analysis under age control we found that the age is the main risk factor of developing of neuropathy and ANA titer does not influence nerve conduction independently.

There were four patients with clinical signs of peripheral neuropathy and no detectable autoantibodies. One of them showed in NCS sensory axonal polyneuropathy and other three sensorimotor axonal polyneuropathy.

We found a significant correlation between age and the nerve conduction study. The age correlated with the prolongation of the distal motor and F-wave latencies of median and ulnar nerve and with the amplitude decrease of compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) of the median nerve and the peroneal nerve, reduced amplitude of the CMAP of the tibial nerve, reduced amplitude of the SNAP of the ulnar and sural nerve ( $p<0.01$ ). The age correlated negatively with the motor conduction velocity of the median, ulnar, peroneal nerve and sensory conduction velocity of the median, ulnar, sural and peroneal nerve ( $p<0.01$  or  $p<0.05$ ), (table 2).

Using partial correlation analysis under age control we found that the association of antibodies with the nerve conduction study was limited to only a few conduction parameters in some nerves. Statistically significant negative correlation between the presence of rheumatoid factor and ulnar motor conduction velocity at the forearm ( $r= -0.353$ ,  $p<0.01$ ), and statistically significant positive correlation between the presence of RF and F-wave latency in the tibial nerve ( $r= -0.349$ ,  $p<0.01$ ). The presence of anti-La antibodies correlated

positively with the amplitude of CMAP of the median nerve ( $r= 0.300$ ,  $p<0.05$ ). An inverse correlation was found between co-occurrence of anti-Ro and anti-La antibodies and distal motor latency of the peroneal nerve ( $r= -0.334$ ,  $p<0.05$ ).

**Discussion:** In presented cohort, nerve conduction studies revealed axonal loss or demyelination in large part of patients with pSS. The prospective character and vast electrophysiological diagnostics engaged in our investigations yielded the prevalence of neuropathy in pSS comparable to the upper limit of the range of the until now published results (2-60%) [2-7] and markedly higher than the data for general population, which varies between 2.4 to 8% (23).

In the vast majority of patients, neurography showed axonal damage and affected predominantly nerves of lower extremities and sensory fibers. Delalande et al (18), Pavlakis et al (24), Gono et al (25), Brito-Zeron et al (26), Mori et al (27) and Jamilloux et al (28) also emphasized the predominance of axonal type of neuropathy in patients with pSS.

Described results confirmed that the age was negatively associated with the sensory as well as the motor conduction. Previous studies also demonstrated age-related slowing of nerve conduction velocity (NCV) and reduction in nerve response amplitude in general population (29;30). On the other hand, this study underlines that the frequency of peripheral neuropathy is significantly higher in patients with pSS comparing to general population which indicate that have to be associated with this disease.

In presented study ANA antibodies in titer over 1:320, were found in 83% of patients with pSS. With regard to previous studies, it is known that presence of ANA is the most frequently detected in pSS (16). Using partial correlation analysis under age control we

found that ANA titer does not influence nerve conduction independently. This result is quite different from Sène et al (7) study, where patients with nonataxic sensory neuropathies were characterized by a lower prevalence of ANA compared to patients without neuropathy. They did not notice this relationships between prevalence of ANA and sensorimotor neuropathy. In the same study patients with nonataxic sensory neuropathy were older compared to the patients without neuropathy. It can be assumed , that relationship between ANA seronegativity and sensory neuropathy described by Sène et al (7) may become insignificant, if they had used partial correlation analysis under age control.

We found that the presence of RF correlated positively with F-wave latency in the tibial nerve and, inversely, with ulnar motor conduction velocity at the forearm. Seropositivity to RF is probably associated with demyelination but RF concentration does not influence the nerve conduction parameters. Indeed, we did not observed any relationship between clinical signs of neuropathy and the RF. Our results are consistent with those of Jamiloux et al (28), where the presence of RF did not influence on neurological manifestations in pSS patients. Ramos-Casals et al (16) also did not confirm the association between RF and neuropathy. Similarly, Bharadwaj and Haroon (31) reported no relationship between RF and extra-articular manifestations of rheumatoid arthritis. On the other hand, Biswas et al (32) noticed that RF- positive patients with rheumatoid arthritis had a higher frequency of neuropathy.

The subset of patients with fully normal nerve conduction study had the highest prevalence of both anti-Ro and anti-La antibodies. Whereas patients with axonal neuropathy were seropositive to only anti-Ro antibodies. This result is consistent with the previous studies about systemic lupus erythematosus (SLE), where patients with both anti-Ro and anti-La antibodies have been shown to have a lower risk of nephritis and seizures than those

with anti-Ro antibodies alone (33). The opposite results regarding to a prevalence of anti-Ro and anti-La antibodies in pSS patients reported Jamilloux et al (28), Sène et al (7) and Scofield et al (34). Jamilloux et al (28) found that patients with neuropathy, both sensorimotor and sensory, had lower prevalence of anti-Ro antibodies compared with those without neuropathy. Sène et al (7) found that patients with sensory neuropathies were characterized by a lower prevalence of anti-Ro and anti-La antibodies compared to patients without neuropathy. In the same study patients with sensory neuropathy were older than patients without neuropathy. They did not use partial correlation analysis under age control, which could show that the age was the highest risk of neuropathy. They did not compare patients positive to both anti-Ro and anti-La antibodies with those with only anti-Ro antibodies. Scofield et al (34) found that patients with both anti-Ro and anti-La antibodies were much more likely to have neuropathy than those with anti-Ro antibodies alone. The association of anti-Ro and anti-La antibodies was most robust when these antibodies were determined by double immunodiffusion. Their data suggest that the method of detection can be the reason for different results obtained from previous studies. Different results obtained by Scofield et al, could also be a result of limiting the diagnosis of neuropathy to clinical evaluation without electrophysiologic assessment.

**Limitations:**

The main limitation was the suboptimal EDX approach with lacking examination with needle electrode, which could detect coexistent myopathic or subtle neurogenic changes, not resulting in abnormalities in the nerve conduction study. The previous data did not show however a significant relation between pSS and myopathy. The neurogenic changes have low specificity, especially in older population and could be hardly pathophysiologically attributed to pSS when there was no healthy control. We therefore believe that additional

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electromyography would not change our results significantly. The second limitation is the lack of skin biopsy, which might reveal neuropathy of small fibers in the part of our patients with otherwise no objective signs of polyneuropathy.

**Conclusions:** Peripheral neuropathy is a frequent complication in pSS, especially in older patients. Most frequently, an axonal form of neuropathy affecting predominantly lower extremities and sensory fibers is observed. Seropositivity limited to only anti-Ro antibodies is associated with increased risk of axonal neuropathy, whereas seropositivity to both anti-Ro and anti-La antibodies may be associated with lower incidence of neuropathy. The ANA titer probably does not influence nerve conduction independently. Seropositivity to RF may contribute to demyelination however with a weak impact. Humoral immune response in pSS probably damages peripheral nerves, but this effect is mediated by still unrecognized mechanisms as the routinely tested antibodies cannot be used as a marker of neuropathy. A vast nerve conduction study is still the most reliable method of detecting early peripheral neuropathy in pSS. We recommend to perform electrophysiologic tests in all patients with pSS even those without clinical signs of neuropathy.

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Table 1. Types of neuropathy according to nerve conduction study

Type of neuropathy	n	%
No neuropathy (normal nerve conduction)	22	36,1
Mononeuropathy	14	23
Mononeuropathy multiplex	9	14,7
Sensory axonal polyneuropathy	6	9,8
Sensorimotor axonal polyneuropathy	8	13,1
Mixed axonal and demyelinating sensorimotor polyneuropathy	2	3,3
Total	61	100

Table 2. Significant correlation between age and nerve conduction

	r	p
DML of median nerve	0.399	<0.01
CMAP amplitude of median nerve	-0.506	<0.01
Motor CV of median nerve	-0.553	<0.01
F-wave latency of median nerve	0.458	<0.01
DML of ulnar nerve	0.351	<0.01
Motor CV of ulnar nerve	-0.321	<0.05
F-wave latency of ulnar nerve	0.311	<0.05
Amplitude of tibial nerve	-0.644	<0.01
CMAP amplitude of tibial nerve	-0.347	<0.01
CMAP amplitude of peroneal nerve	-0.299	<0.05
Motor CV of peroneal nerve	-0.389	<0.01
SNAP amplitude of median nerve	-0.554	<0.01
Sensory CV of median nerve	-0.462	<0.01
SNAP amplitude of ulnar nerve	-0.569	<0.01
Sensory CV of ulnar nerve	-0.374	<0.01
SNAP amplitude of sural nerve	-0.565	<0.01
Sensory CV of sural nerve	-0.362	<0.01
SNAP amplitude of peroneal nerve	-0.424	<0.01
Sensory CV of peroneal nerve	-0.418	<0.01

DML - distal motor latency, CMAP - compound motor action potential, CV - conduction velocity, SNAP - sensory nerve action potential

Figure 1. Percentage distribution of incidence of anti-Ro and anti-La antibodies in the studied group

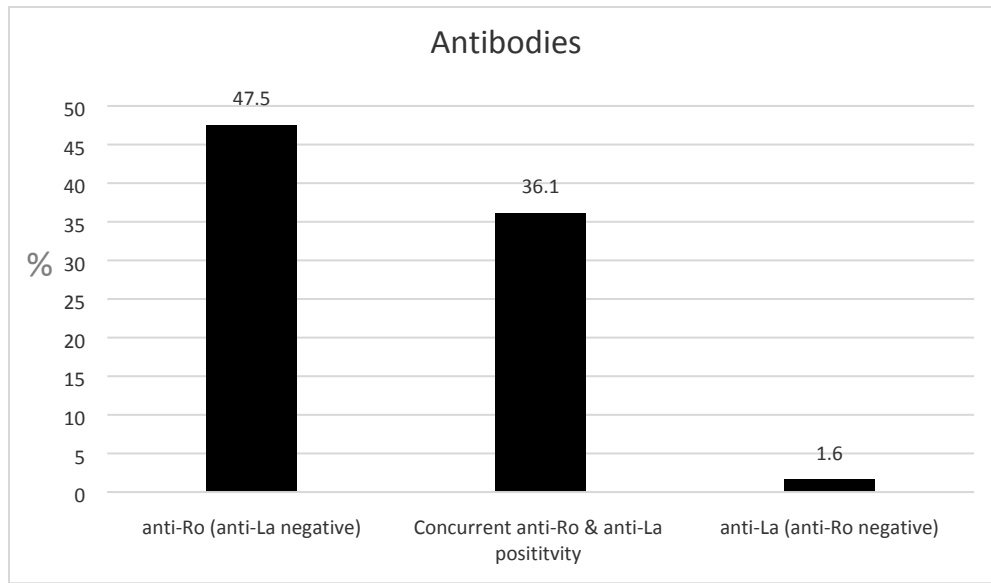


Figure 2. Percentage distribution of incidence - Presence of anti-Ro antibodies and coexistence of anti-Ro and anti-La antibodies in the group of patients without neuropathy and in the group with axonal neuropathy

