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Prevalence of various forms of peripheral neuropathy in patients with systemic connective tissue diseases: a clinical and electrophysiological study

Učestalost različitih formi neuropatija kod obolelih od sistemskih bolesti vezivnog tkiva: klinička i elektrofiziološka studija

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Abstract

Background/Aim. Peripheral neuropathy (PN) in systemic connective tissue diseases (SCTDs) represents the apparent disease complications or initial manifestations of clinically undiagnosed conditions. The aim of the study was to identify neuropathies (Ns) and their prevalence, point out the diagnostic significance of some electrophysiological (EP) parameters in patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc), and establish their association with disease activity (DA) and disease duration (DDu). **Methods.** A prospective study was conducted at the Rheumatology Clinic of the Institute for Treatment and Rehabilitation "Niška Banja" over a three-year period. The study included 157 patients in total, of whom 61 had RA, 40 had SLE, and 56 had SSc. The following parameters were analyzed: age, gender, DDu, course of the disease, and DA index. Moreover, clinical, rheumatological, and neurological examinations, as well as neurology tests, nerve conduction studies (NCS), and laboratory analyses, were also conducted. **Results.** In the studied population, we were able to identify various forms of Ns (in 28.7% of patients) by NCS. In all three groups, the most prevalent type of Ns was axonal (23.6%), sensorimotor (18.5%), and polyneuropathy (23.6%). There was a significant association between DA and the occurrence of Ns ($p < 0.001$) in the total population. The most important EP parameter was the sensory nerve action potential amplitude of *nervus peroneus superficialis* [in 70 (44.6%) patients] and *nervus suralis* [in 35 (22.3%) patients], and compound muscle action potential amplitude of *nervus peroneus* [in 32 (20.4%) patients]. DDu in all three groups was longer in the population of patients with Ns. **Conclusion.** Ns are most common in patients with longer DDu and higher DA. The EP method is important in detecting Ns, especially in the early detection of subclinical forms of Ns and the prevention of disease complications.

Key words:
arthritis, rheumatoid; autoimmune diseases; connective tissue; diagnosis; lupus erythematosus, systemic; peripheral nervous system diseases; scleroderma, systemic.

Apstrakt

Uvod/Cilj. Periferna neuropatija (PN) u sistemskim bolestima vezivnog tkiva (SBVT) predstavlja jasnu komplikaciju bolesti ili inicijalnu manifestaciju klinički nedijagnostikovane bolesti. Cilj rada bio je da se odrede tipovi i procenat zastupljenosti neuropatija (N), ukaže na dijagnostički značaj pojedinih elektrofizioloških (EF) parametara kod bolesnika sa reumatoidnim artritisom (RA), sistemskim eritemskim lupusom (SLE) i sistemskom sklerozom (SSc) i utvrdi njihova povezanost sa aktivnošću bolesti (AB) i dužinom trajanja bolesti (DTB). **Metode.** Istraživanje je obavljeno u formi prospektivne studije na Klinici za reumatologiju Instituta za lečenje i rehabilitaciju „Niška Banja" u trajanju od tri godine. U istraživanje je bilo uključeno ukupno 157 bolesnika, od kojh je 61 imalo RA, 40 je imalo SLE i 56 je bilo sa SSc. Analizirani su sledeći parametri: godine života, pol, DTB, tok bolesti i indeks AB. Obavljeni su i klinički, reumatološki i neurološki pregledi, neurološki testovi, ispitivanje sprovodljivosti nervnih vlakana (SNV) i laboratorijske analize. **Rezultati.** U ispitivanoj populaciji, ispitivanjem SNV registrovani su različiti oblici N (kod 28,7% bolesnika). U sve tri grupe, najčešći tipovi N bile su aksonska (23,6%), senzomotorna (18,5%) i polineuropatija (23,6%). Utvrđena je statistički značajna povezanost AB i pojave N ($p < 0,001$) u ukupnoj populaciji. Najznačajniji EF parametri bili su

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amplitude senzitivnih neurograma *nervus peroneus superficialis*-a [kod 70 (44,6%) bolesnika] i *nervus suralis*-a [kod 35 (22,3%) bolesnika] i motorna amplituda *nervus peroneus*-a [kod 32 (20,4%) bolesnika]. DTB u sve tri grupe bila je veća u grupi bolesnika sa N. **Zaključak.** Kod bolesnika sa većom DTB i većom AB, N su najčešće. Elektrofiziološka metoda važna je u detekciji N, naročito u ranom otkrivanju subkliničkih formi N i prevenciji komplikacija bolesti.

Ključne reči:
artritis, reumatoidni; autoimunske bolesti; vezivno tkivo; dijagnoza; lupus, eritematozni, sistemski; živci, periferni, bolesti; sklerodermija, sistemska.

Introduction

Systemic connective tissue diseases (SCTDs) represent a heterogeneous group of autoimmune diseases that can affect all body systems, including the central nervous system (CNS) and peripheral nervous system (PNS) [1–3]. Neurogenic inflammation, autoantibodies-mediated changes, ischemia of the vascular wall, and metabolic mechanisms are believed to contribute to peripheral neuropathy (PN) in connective tissue disease (CTD). Earlier investigations have confirmed the correlation between disease activity (DA) and the degree of neuropathy (N) in small groups of patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), while some other studies demonstrated low DA scores in patients with neurological damage [4–5].

Concerning the number of nerves whose roots are affected, we distinguish between small fiber N and large fiber N. The diagnosis of large fiber N is made based on clinical and nerve conduction study (NCS) criteria, which is not possible in the case of small fiber N diagnosed by quantitative sensory testing (QST) and skin biopsy [6–8]. PN is more common, but most studies are focused on CNS; therefore, PN has been less frequently identified, possibly because it represents the apparent disease complications or initial manifestations of clinically undiagnosed conditions [9–11].

PN can be divided into different categories. Based on the number of damaged nerves, PN is divided into mononeuropathy, mononeuritis multiplex (MNM), and polyneuropathy (PoN). Depending on the damage to the nerve structures, it is divided into axonopathy, myelinopathy, and ganglionopathy or neuronopathy. Based on the function of the damaged nerves, there is autonomic, motor, and sensory N. Based on the anatomical site of the lesion, there is radiculopathy and plexopathy [12–14]. Neuropathies (Ns) are divided into length-dependent and non-length-dependent. Length-dependent Ns occur in a distal "stocking and glove" distribution, and non-length-dependent patterns affect the face, torso, and proximal extremities [7].

Taking into account the fact that studies conducted so far investigated PNS disorder in SLE and RA but not in systemic sclerosis (SSc), as well as their connection with the activity and duration of the disease, the aim of our study was to identify N types and their prevalence using neurological examination and NCS in all three clinical groups of patients and establish their association with DA and disease duration (DDu). Furthermore, we tried to establish the diagnostic importance of certain electrophysiological (EP) parameters related to DA and DDu, which would be relevant in the early detection of Ns as the complications of SCTDs.

Methods

The investigation was performed as a prospective study from September 2017 to February 2020 at the Rheumatology Clinic of the Institute for Treatment and Rehabilitation "Niška Banja", Serbia. A total of 189 patients were asked to participate, and 157 were enrolled in the study. There were 61 patients with RA (54 females and 7 males), 40 patients with SLE (39 females and 1 male), and 56 patients with SSc (50 females and 6 males). All of these patients were diagnosed in the previously mentioned healthcare institution and were regularly followed up as outpatients by their rheumatologists. Informed consent was obtained from all the study participants. The approval of the Ethics Committee (No. 80921, from July 5, 2017) of the Institute for Treatment and Rehabilitation "Niška Banja" was also obtained. The enrolled patients fulfilled the classification criteria of the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) for SLE, RA, and SSc [15–17]. The patients with some other autoimmune rheumatic disease, non-differentiated or mixed systemic disease, acute or chronic disease of other organs, as well as those with Ns of another etiology (hypothyreosis, diabetic Ns, metabolic causes, infectious causes, uremia, traumatic Ns, iatrogenic Ns, alcohol abuse, paraneoplastic syndrome, hypovitaminosis B1, B12, and E) were excluded from our investigated group of patients. The following parameters were analyzed: age, gender, DDu, course of the disease, and DA; clinical, rheumatological, and neurological examinations were performed, as well as neurology tests and NCS assessment, and laboratory analyses. Neurological impairment was graded using the Neuropathy Impairment Score (NIS) = Neurologic Disability Score (NDS). Using this scoring system, 24 muscle groups were evaluated (cranial and muscles of the upper and lower limb), as well as muscle reflexes in five muscle groups and sensibility (touch-pressure, vibration, joint position, pinprick). Muscle strength scores were graded as follows: 0 = normal strength; 1 = 25% weak; 2 = 50% weak; 3 = 75% weak; 4 = paralysis. Reflexes and sensations are scored as follows: 0 = normal; 1 = decreased; 2 = absent [18–20]. NIS score was graded from 0 to 244, where a higher score denoted greater impairment [19, 21–23]. EP studies complemented the clinical assessment of the patients. N was assessed as the clinical form in patients with N on neurological examination, which was subsequently confirmed by NCS, and subclinical when it was not evidenced by neurological examination but was confirmed by NCS instead.

Nerve conduction study

The form and degree of Ns were determined by NCS of peripheral nerves using a 4-channel *Neurowerk* electromyoneurography (EMNG) system at the Institute for Treatment and Rehabilitation "Niška Banja". The compound muscle action potential (CMAP) was measured bilaterally in the median, ulnar, tibial, peroneal, medial plantar, and lateral plantar nerves, applying supramaximal percutaneous nerve stimulation. Sensory nerve action potential (SNAP) was measured in the median, ulnar, sural, and superficial peroneal nerves. Sensory nerve conduction was assessed antidromically. The median nerve CMAP was stimulated at the wrist, elbow, and axilla and registered above the *musculus* (*m.*) *abductor policis brevis*. The ulnar nerve CMAP was stimulated at the wrist, below and above the elbow and axilla, and registered above the *m. abductor digiti minimi.* The peroneal nerve CMAP was stimulated at the ankle, below and above the fibular head, and registered above the *m. extensor digitorum brevis*. The tibial nerve CMAP was stimulated posteriorly to the medial malleolus and proximally at the popliteal fossa and registered above the *m. flexor hallucis brevis*. Distal latency, amplitude, duration, velocity, F-wave latency, conduction blocks, and temporal dispersion were all measured. Skin temperature was measured at the dorsum of the foot using a digital surface thermometer, and the temperature ranged from 30 °C to 32 °C. A surface stimulating and recording electrode was used. Based on the clinical findings and NCS, all Ns were divided into the following groups: sensory, sensorimotor, axonal, axonal-demyelinating, demyelinating, MNM, distal symmetrical PoNs which did not fulfill the criteria for chronic inflammatory demyelinating PoN (CIDP) and MNM, and compressive Ns (syndromes of the carpal and tarsal tunnel). Electrodiagnostic examinations were performed using the standardized methodology according to the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) [24, 25]. The results were compared with the reference values used in our institution.

Laboratory analyses

The laboratory and serological markers included parameters that are part of the index of the DA. Within the Disease Activity Score (DAS) 28 scale (DAS-28), erythrocyte sedimentation rate (ESR) was performed; within the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scale, complement, anti-dsDNA antibodies, the presence of protein in the urine, urine sediment, and platelet and leukocyte levels were determined; within the European Scleroderma Trials and Research (EUSTAR) activity index, sedimentation, C-reactive protein, antinuclear antibodies (ANA), and Anti-Scl 70 antibodies were analyzed [26–28].

Disease activity index

In patients with RA, an appropriate DA index (DAS-28 ESR score) was used to monitor the DA. Based on this score, DA in RA patients was classified as follows: DAS-28 < 2.6, remission; DAS-28 2.6–3.1, low activity; DAS-28 3.2–5.1, moderate activity; DAS-28 ≥ 5.2, high activity [26]. In all SLE patients, the SLEDAI was used, i.e., the Modified SLEDAI – 2000. The score was calculated as follows: 0–5, low activity; 6–12, moderate activity; and 13–20, high activity [27]. In SSc patients, a revised EUSTAR activity index was used to assess DA. According to this index, SSc patients were classified into two groups: < 2.5 inactive/moderately active disease; ≥ 2.5 active/very active disease [28].

Statistical data processing

The data were presented as arithmetic mean plus standard deviation (SD), i.e., in the form of absolute and relative numbers. The comparison of continuous values between the two groups was made using the *t*-test or Mann-Whitney *U* test. The comparison of categorical variables was performed using the Chi-squared or Fisher's test of exact probability. The hypothesis was tested with the statistical significance cut-off value set at $p < 0.05$. Statistical data processing was performed using the SPSS 20.0 software package.

Results

Sixty-one patients with RA, 40 patients with SLE, and 56 patients with SSc were included in the study. The mean age of the population was 55.2 years (± 10.8 SD) [minimum (min) – maximum (max): 33–82 years]. The average DDu was 13.7 ± 9.1 years (min 4 months; max 43 years). Females comprised 88.5% of RA patients, 97.5% of SLE patients, and 89.3% of SSc patients. There were no differences in DDu ($p = 0.249$), gender ($p = 0.180$), or NIS total score ($p = 0.587$) between the studied groups (Table 1). There was no correlation between biochemical and serological markers performed within the scales of DA with N (data are not shown).

In the study population, acute N was registered in 1 (2.2%) patient, subacute in 3 (6.7%) patients, and chronic in 41 (91.1%) patients. In our study, the group of patients with RA, SLE, and SSc was mainly affected by length-dependent PoN and was registered in 38 (84.4%) patients. Non-length-dependent N was recorded in a smaller percentage and was registered in 7 (15.6%) patients. There were no patients in our group with clinical signs of cranial nerve damage.

NCS findings did not differ significantly between the studied groups. Pathological findings were observed in 23.3% of RA patients, 35.0% of SLE patients, and 30.4% of SSc patients. In the studied population, we were able to identify various forms of Ns in 28.7% of patients with NCS. The prevalence of N forms was non-significantly different among groups ($p > 0.05$). In the studied population, 14.6% of examinees had a clinical form of N, while 14.0% had a subclinical form of N. The prevalence of clinical and subclinical forms did not differ significantly between the investigated groups ($p = 0.538$, $p = 0.734$) (Table 2).

Increased age was registered in all three groups (RA, SLE, and SSc), in which N was present in relation to patients without N.

Table 1

Demographic and clinical characteristics of the studied groups of patients

Characteristics	Groups			*p*-value
	RA	SLE	SSc	
Age, years	60.7 ± 10.6[a]	49.9 ± 9.0	58.9 ± 10.4[a]	< 0.001[1]
Age at diagnosis, years	46.8 ± 11.9[a]	34.7 ± 10.5	47.7 ± 12.7[a]	< 0.001[1]
Disease duration, years	13.9 ± 9.4	15.2 ± 9.1	14.6 ± 22.7	0.249 [1]
Gender				
male	7 (11.7)	1 (2.5)	6 (10.7)	0.180[2]
female	54 (88.5)	39 (97.5)	50 (89.3)	
NIS total score	2.4 ± 6.5	4.2 ± 9.5	2.4 ± 6.9	0.587[3]

NIS – Neuropathy Impairment Score; SLE – systemic lupus erythematosus; RA – rheumatoid arthritis; SSc – systemic sclerosis. All results are shown as mean ± standard deviation, except gender which is shown as number (percentage).

[1] *t*-test; [2] Chi-squared test; [3] Mann-Whitney *U* test; [a] vs. SLE $p < 0.05$.

Table 2

Type of neuropathy based on nerve conduction study and clinical findings related to the studied groups

Type of neuropathy	Groups				p^1-value
	Total	RA	SLE	SSc	
Type 1					
normal finding	112 (71.3)	47 (77.0)	26 (65.0)	39 (69.6)	
sensory	16 (10.29)	6 (9.8)	4 (10.0)	6 (10.7)	0.651
sensorimotor	29 (18.5)	8 (13.3)	10 (25.0)	11 (19.6)	
Type 2					
normal finding	112 (71.3)	47 (77.0)	26 (65.0)	39 (69.6)	
axonal	37 (23.6)	12 (19.7)	10 (25.0)	15 (26.8)	0.122
axonal-demyelinating	5 (3.2)	2 (3.3)	1 (2.5)	2 (3.6)	
demyelinating	3 (1.9)	0 (0.0)	3 (7.5)	0 (0.0)	
Type 3					
normal finding	112 (71.3)	47 (77.0)	26 (65.0)	39 (69.6)	0.398
distal symmetrical polyneuropathy	37 (23.6)	11 (18.0)	10 (25.0)	16 (28.6)	0.394
mononeuritis multiplex	5 (3.2)	2 (3.3)	3 (7.5)	0 (0.0)	0.093
carpal tunnel syndrome	16 (10.2)	6 (9.8)	4 (10.0)	6 (10.7)	0.987
tarsal tunnel syndrome	1 (0.6)	0 (0.0)	1 (2.5)	0 (0.0)	0.255
CIDP	1 (0.6)	0 (0.0)	1 (2.5)	0 (0.0)	0.255
Neuropathy in the total population	45 (28.7)	14 (23.3)	14 (35. 0)	17 (30.4)	0.428
clinical form of neuropathy	23 (14.6)	8 (13.1)	8 (20.0)	7 (12.5)	0.538
subclinical form of neuropathy	22 (14.0)	6 (9.8)	6 (15.0)	10 (17.9)	0.734

CIDP – chronic inflammatory demyelinating polyneuropathy. For abbreviations of other terms, see Table 1. The results are expressed as numbers (percentages). [1] Chi-squared test.
Type 1 neuropathy – division of neuropathies based on the involvement of sensory or motor fibers; Type 2 neuropathy – pathophysiological division of neuropathies based on axonal or myelin damage; Type 3 neuropathy – patterns of peripheral neuropathy.

DDu in all three groups was longer in the population of patients with N, but the difference was insignificant. There was a statistically significant association between DA and the occurrence of N in all three groups of our patients ($p < 0.001$). The highest DA and association with N were encountered in the group of RA patients (64.3%) and the lowest in the group of SLE patients (35.7%) (Table 3). DDu was significantly higher with a reduced SNAP amplitude of nervus (*n.) peroneus superficialis* ($p = 0.029$), CMAP amplitude of *n. peroneus* ($p = 0.029$) and SNAP amplitude of *n. suralis* ($p = 0.011$) (Table 4). A reduced SNAP amplitude of *n. peroneus superficialis* was not significantly associated with DA ($p = 0.307$). In contrast to that, a reduced CMAP amplitude of *n. peroneus* and SNAP amplitude of *n. suralis* was significantly associated with DA ($p = 0.001$). DA was high in 51.7% of patients with a reduced CMAP amplitude of *n. peroneus* and in 41.4% of patients with a reduced SNAP amplitude of *n. suralis* (Table 5). A high DA associated with N was found in 18% of patients and in only 11% of those without N (Figure 1).

The most important diagnostic EP parameters were amplitude and latency (but predominantly amplitude) of SNAP of *n. peroneus superficialis* (70 patients – 44.6%), SNAP of *n. suralis* (35 patients – 22.3%), and CMAP of *n. peroneus* (32 patients – 20.4%).

Table 3

Association of neuropathy and SCTDs characteristics

Disease characteristics	With neuropathy	Without neuropathy	*p*-value
RA			
Age, years (mean ± SD)	67.4 ± 7.3	58.6 ± 10.7	0.006[1]
Disease duration, years (mean ± SD)	15.8 ± 11.8	13.3 ± 8.7	0.889[3]
DAS-28, n (%)			
remission	0 (0.0)	2 (4.3)	
low activity	0 (0.0)	10 (21.3)	< 0.001[2]
moderate activity	5 (35.7)	34 (72.3)	
high activity	9 (64.3)	1 (2.1)	
SLE			
Age, years (mean ± SD)	55.3 ± 6.5	47.0 ± 8.9	0.004[1]
Disease duration, years (mean ± SD)	16.6 ± 12.5	14.5 ± 6.8	0.726[3]
SLEDAI, n (%)			
low activity	0 (0.0)	9 (34.6)	
moderate activity	9 (64.3)	14 (53.8)	0.005[2]
high activity	5 (35.7)	3 (11.5)	
SSc			
Age, years (mean ± SD)	64.5 ± 5.4	56.5 ± 11.2	0.001[1]
Disease duration, years (mean ± SD)	15.1 ± 11.2	10.7 ± 9.1	0.141[3]
Revised EUSTAR activity index, n (%)			
low activity	0 (0.0)	20 (51.3)	
moderate activity	14 (82.4)	13 (33.3)	0.001[2]
active/very active	3 (17.6)	6 (15.4)	
Total population disease activity, n (%)			
remission	0 (0.0)	2 (1.8)	
low activity	0 (0.0)	39 (34.8)	< 0.001[2]
moderate activity	27 (60.0)	60 (53.6)	
high activity	18 (40.0)	11 (9.8)	

SCTDs – Systemic connective tissue diseases; DAS-28 – Disease Activity Score 28; SLEDAI – Systemic Lupus Erythematosus Disease Activity Index; EUSTAR – European Scleroderma Trials and Research. For abbreviations of other terms, see Table 1.
[1] *t*-test; [2] Chi-squared test; [3] Mann-Whitney *U* test.

Table 4

Disease duration related to the reduced CMAP and SNAP amplitude of *nervus peroneus, nervus suralis,* and *nervus peroneus superficialis*

Nerve	Disease duration (years)
Nervus peroneus superficialis	
reduced amplitude (SNAP)	15.0 ± 10.3
normal amplitude (SNAP)	11.4 ± 8.1
p[1]	0.029
Nervus peroneus	
reduced amplitude (CMAP)	16.4 ± 10.8
normal amplitude (CMAP)	12.5 ± 9.0
p[1]	0.029
Nervus suralis	
reduced amplitude (SNAP)	18.1 ± 11.5
normal amplitude(SNAP)	12.5 ± 8.8
p[1]	0.011

CMAP – compound muscle action potential; SNAP – sensory nerve action potential. Results are expressed as mean ± standard deviation.

[1] Mann-Whitney *U* test.

Table 5

Disease activity related to reduced CMAP and SNAP amplitude of *nervus peroneus*, *nervus suralis*, and *nervus peroneus superficialis*

Nerve	Disease activity, n (%)			*p*-value[1]
	Low	Moderate	High	
Nervus peroneus superficialis				
reduced amplitude (SNAP)	29 (70.7)	52 (59.8)	21 (72.4)	0.307
normal amplitude (SNAP)	12 (29.3)	35 (40.2)	8 (27.6)	
Nervus peroneus				
reduced amplitude (CMAP)	5 (12.2)	28 (32.2)	15 (51.7)	0.001
normal amplitude (CMAP)	36 (87.8)	59 (67.8)	14 (48.3)	
Nervus suralis				
reduced amplitude (SNAP)	2 (4.9)	20 (23.0)	12 (41.4)	0.001
normal amplitude (SNAP)	39 (95.1)	67 (77.0)	17 (58.6)	

For abbreviations, see Table 4. [1] Chi-squared test.

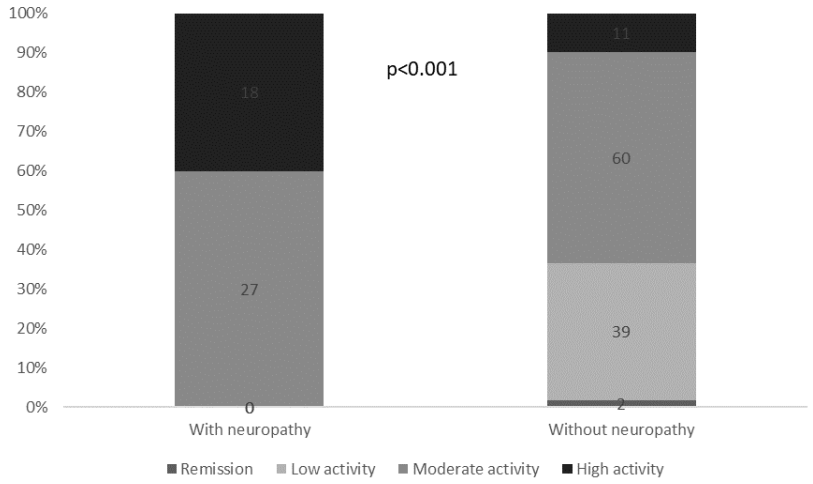

Fig. 1 – Disease activity related to neuropathy.

Discussion

PNS disorders in SCTDs are various forms of N with insufficiently elucidated pathogenesis. It has been proposed that not only antibody titer and DA are involved but also the infarctions of *vasa nervorum* of epineural arteries, which result in axonal degeneration [29–31]. The available literature data point to a large number of studies aimed to describe CNS disorders in SCTDs [1, 32]. In contrast, the studies aimed to examine the diagnostic significance of NCS parameters in these diseases are relatively scarce, and these have dealt mainly with SLE and RA. However, the prevalence of Ns, NCS findings, and DA scores were not examined simultaneously among all three disease groups (SLE, RA, and SSc). In a study of 4,924 SLE patients, the prevalence of PoN was 73 out of 4,924 (1.5%) patients and higher in patients with an active form of the disease. In a group of 1,827 SLE patients, different types of PNS damage were investigated, and the connection of peripheral Ns with the DA was determined. In a retrospective study of 1,224 patients with SLE, the prevalence of PNS damage was 6.9% and was correlated with a high SLEDAI score. PN is an underdiagnosed complication in CTD and a particular challenge for rheumatologists and neurologists [4, 10, 14, 33]. The same applies to the diagnostic relevance of particular EP parameters, which was the aim of our study.

Our results showed that in the total studied population, the prevalence of N differed among the groups – 30.4% in SSc, 23.3% in RA, and 35.0% in SLE, respectively. The most common type of PN in the total population was axonal distal symmetrical PoN in 23.6% of patients, followed by sensorimotor N in 18.5% of patients while demyelinating N was much less commonly identified in 1.9% of patients. MNM N type was detected in 3.2%, carpal tunnel syndrome in 10.2%, sensory N in 10.2%, and tarsal tunnel syndrome in 0.6% of patients, while there was 1 (0.6%) patient with CIDP in the SLE group. Concerning systemic diseases, axonal N was present in 19.7% of RA patients, 25.0% of patients in the SLE group, and 26.8% of patients in the SSc group. The distal symmetrical PoN, which was more of an axonal type and did not fulfill the criteria for MNM [34], was found in 23.6% of the total studied population. In the paper by Olney [31], distal axonal Ns were most prevalent in SLE and SSc. Our results are similar to those. Aneja et al. [35] investigated a group of 66 patients with RA, with and without clinical manifestations of N, in whom NCS confirmed N in 37.8% of patients and demonstrated a high prevalence of subclinical N. Similar results were obtained by Canesi et

al. [36], Biswas et al. [37], and Lanzillo et al. [38]. In our study, there were 14.6% clinical and 14% subclinical disease forms. Subclinical disease was more prevalent in SSc and SLE patients. Studies have confirmed that patients may have EP signs of N in the absence of any clinical signs of peripheral nerve involvement, which underlines the importance of this method in the early detection of subclinical disease.

In the study by Toledano et al. [39] conducted on 524 patients with SLE, it was shown that PN was found in 93 (17.7%) patients. This percentage is lower compared to our results. Nevertheless, our cohort of patients had a longer DDu compared to the above group. Sensorimotor axonal PoN was the most common form, which was shown in our study as well. Similar results were reported by Florica et al. [9] in their retrospective study of 1,533 patients with SLE, out of which 14% had PN. The patients with N also had a high DA score (SLEDAI). PN most commonly affected the lower extremities, predominantly *n. peroneus* and *n. suralis*. Our study showed that the most severe changes affected *n. suralis* and *n. peroneus*, but also *n. peroneus superficialis*. Saigal et al. [40] reported 50 patients with SLE, out of whom N was electrophysiologically found in 36%. These authors reported that only SLEDAI was increased in patients with N. The underlying mechanism by which high DA influences the development of N has not been sufficiently studied so far. According to our results, there was a statistically significant association between DA and the prevalence of N, as well as between DA and EP parameters (amplitude of motor *n. peroneus* and *n. suralis*). Similar results were published by Mohamed et al. [41].

Various forms of Ns are also encountered in RA as a result of PNS damage. In the study by El-Hewala et al. [42], a group of 50 patients with RA was studied. Regardless of the DA, EP findings demonstrated N in 78% of patients, out of which 48% had compressive (entrapment) Ns, while the remaining 30% had symmetrical PoN with axonal degeneration. Our results showed that entrapment Ns were much less prevalent compared to other forms of Ns (in 6 patients – 9.8%). Several interesting studies reported a higher percentage of subclinical N forms confirmed by NCS and demonstrated a correlation of DDu and DA with N in RA [43], as was established in our study as well. Several studies could not demonstrate any association of N with DDu [44, 45].

SSc is a relatively rare systemic disease compared to SLE and RA. The correlation between N, EP parameters, and DA in SSc has been investigated in the smallest subset of studies, and this was one of the objectives of our study. In the study by Paik et al. [46], in a group of 60 patients with SSc, the PN was registered in 17 (28%) patients based on the Total Neuropathy Score (TNS) and EP changes in five patients with neuropathic symptoms and five patients without neuropathic symptoms. Our study showed that in SSc patients as well, distal symmetrical axonal N was the most common form. Our NCS demonstrated N in 30.4% of patients. There were 39 patients with a limited disease form in our study, while diffuse disease was found in 17 patients. Raja et al. [47] determined the prevalence of large fiber PN in the group of 60 patients diagnosed with SSc, and their results showed that 22 (36.7%) patients had PN, which is in correlation with the results of our study.

Since axonal N was seen at a higher percentage in the studied population, for which low amplitudes were specific electrophysiologically, our aim was to investigate the measure of the impact of DA and DDu on the reduction of amplitude given that it was the most important parameter in the initial N stages in autoimmune diseases. Some papers in the available literature show that amplitude changes are usually seen with *n. suralis* and motor *n. peroneus*, which agrees with our results. Our study demonstrated that DDu was significantly prolonged in the presence of reduced amplitude of motor *n. peroneus*, *n. peroneus superficialis*, and *n. suralis*. Decreased CMAP amplitude of *n. peroneus* and reduced SNAP amplitude of *n. suralis* correlated with DA and were the most significant neurophysiological parameter. Some studies show that peripheral Ns and neuropathic pain are more common in the elderly healthy population. For instance, Hanewinckel et al. [48] examined the prevalence of N in the elderly and middle-aged in a group of 1,310 participants and registered it in 5.5% of subjects. Most PoN were idiopathic and more common in men. They concluded that age was a risk factor for N. Similar results are published by Mello et al. [49], who applied NCS in older healthy individuals and concluded that abnormal tests were present in the elderly population. Our research also included elderly patients with a longer duration of systemic disease in whom we proved N by NCS testing, using normative values of EP parameters of our laboratory for elderly patients.

In our group of patients with RA, SLE, and SSc, large fiber N was registered in 45 (28.7%) patients, while in 25 (15.9%) patients, symptoms of tingling and burning were registered predominantly in the distal segments of the extremities, which was not confirmed by neurological examination and NCS. Therefore, there is a possibility that these patients have small fiber Ns that cannot be confirmed by neurological tests and NCS but can be confirmed by QST and skin biopsy, which would be important to conduct in future research.

Conclusion

Ns are more commonly encountered in SLE, RA, and SSc patients with prolonged DDu and higher DA. The most common N type in these diseases is axonal sensorimotor PoN. As evidenced by NCS, subclinical disease forms are also common, which suggests that the method is important in the early detection of peripheral Ns. The most significant EP parameter is the CMAP amplitude of *n. peroneus*, SNAP amplitude of *n. suralis* and *n. peroneus superficialis*, which was significantly reduced in prolonged and highly active disease. The results of a small number of studies from the literature available to us show that there are patients with PoN without clinical signs (subclinical form) in the mentioned systemic diseases, so our future research will be focused on the application of NCS in the early phase of the underlying disease in correlation with SLEDAI with the aim of timely application of the adequate therapy for PoN.

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