Upper extremity subclinical autonomic and peripheral neuropathy in systemic lupus erythematosus
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Background

Systemic lupus erythematosus (SLE) is an autoimmune, multiorgan disease that affects connective tissues of many organs or systems, including the nervous system, where it affects the autonomic, the peripheral, and the central nervous system.

Objective

The aim of this study was to investigate the association of subclinical autonomic and peripheral neuropathy with SLE and to correlate neurophysiological parameters with clinical and laboratory data.

Patients and methods

Fifty-six SLE patients were included in this study. In addition, thirty age-matched and sex-matched healthy participants served as a control group. Exclusion criteria included patients having symptoms or signs indicating autonomic dysfunction or peripheral neuropathy. Also, endocrinal, toxic, compression, and traumatic neuropathies were excluded. Patients were assessed clinically and by laboratory investigations. Neurophysiological assessment included sympathetic skin response of the median nerve including latency and amplitude. In addition, nerve conduction study of both median and ulnar nerves was performed including motor distal latency, amplitude, nerve conduction velocity, and distal sensory latency.

Results

Pure sensory abnormality was detected in one patient, whereas pure motor neuropathy was found in 19 patients. Mixed sensory–motor abnormalities were detected in two patients. Sympathetic skin response was not elicited in 13 patients, whereas latency and amplitude abnormalities were detected in 11/43 and 9/43 patients, respectively. Sympathetic and axonal neuropathy was not correlated with the disease duration or the disease activity.

Conclusion

The pattern of neuropathy in SLE is mainly axonal. Also, the sympathetic nervous system is affected in lupus patients with a rate of up to 40% of the cases.

Keywords:

autonomic neuropathy, electrophysiological study, nerve conduction study, peripheral neuropathy, sympathetic skin response, systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is an inflammatory, autoimmune, multiorgan disease that affects connective tissues in any organ or system, including the nervous system, where it affects the autonomic, the peripheral, and the central nervous system (CNS) [1–3].

In 1999, the American College of Rheumatology established case definitions for 19 central and peripheral nervous system syndromes in SLE patients. Central neuropsychiatric lupus (NPSLE) range from diffuse CNS disorders (i.e. acute confusional state, psychosis, anxiety and depressive disorders, cognitive disorders) to CNS syndromes (i.e. seizures, cerebrovascular disease, chorea and myelopathy, transverse myelitis, demyelinating syndrome and aseptic meningitis, headaches). In contrast, peripheral NPSLE include cranial and autonomic neuropathy, peripheral polyneuropathies and mononeuropathies, and plexopathy in addition to myasthenia gravis [4,5].

Neurologic and psychiatric manifestations of unknown etiology are common in SLE and have been proposed to represent a more severe form of the disease, occurring in up to 75% of the patients. Approximately 40% of the NPSLE manifestations develop before the onset of SLE or at the time of diagnosis and about 60% within the first year after diagnosis [6–8].

As NPSLE manifestations can occur in the absence of either serologic activity or other systemic disease manifestations [9], this encourages the use of other diagnostic measures for the detection of peripheral and autonomic nervous system (ANS) affection in SLE patients.

Conventional electrophysiological methods including nerve conduction studies are used to study the state

of peripheral nerves in patients suspected of having a neuropathy. This includes nerve latency, compound motor action potential amplitude (CMAP amplitude), and nerve conduction velocity (NCV), which are simple and noninvasive neurophysiological tests used to assess motor and sensory fibers in the peripheral nerve [10].

In contrast, several tools have been used to evaluate the autonomic function, including cardiovascular reflex tests, the sweating test, the pupillary reflex test, and the skin test [11]. One of the simple tools used to assess the sympathetic activity is the sympathetic skin response (SSR), which is defined as the momentary change of the electrical potential of the skin. It may be evoked by a variety of stimuli including auditory, magnetic, and electrical stimuli. SSR is easy to apply and has been proposed as a noninvasive approach to investigate the function of the sympathetic system [12].

Consequently, the aim of this study was to investigate the association of subclinical autonomic and peripheral neuropathy with SLE and to correlate neurophysiological parameters with clinical and laboratory data.

Patients and methods
The methodology of this prospective study was approved by the ethics committee of the Ain Shams Faculty of Medicine. A written informed consent was obtained from all participating individuals before initiating any study-related activities.

Participant selection
Fifty-six SLE patients who were randomly recruited from the Internal Medicine Department of Ain Shams University Hospital were included in this study. The study included both sexes without restriction to age. Diagnosis was based on the criteria revised by the American College of Rheumatology for the classification of SLE [13]. In addition, 30 age-matched and sex-matched healthy individuals served as a control group.

Exclusion criteria included the following:

(1) Patients who had symptoms or signs indicating autonomic dysfunction, including orthostatic hypotension, palpitation, dry/running nose, gastrointestinal symptoms, burning feet, warm/cold extremities, sweating disturbances, bladder dysfunction, and impotence [14].
(2) Patients who had symptoms and signs indicating peripheral neuropathy.

(3) Other causes of peripheral neuropathy such as the following:
   (a) Endocrinal: for example, diabetes mellitus, hypothyroidism (blood sugar, HbA1C, T3, T4, thyroid-stimulating hormone).
   (b) Metabolic, such as renal and liver failure (liver and kidney function tests).
   (c) Drug toxicity (vincristine, metronidazole, phenytoin, isoniazid, fluoroquinolone).
   (d) Compression neuropathy (using musculoskeletal ultrasonography and neurophysiological tests).
   (e) Traumatic neuropathy.
   (f) Others (shingles, malignant disease, radiation, chemotherapy).
(4) Cervical radiculopathy was excluded by performing F-wave latency and a cervical radiography.

Laboratory investigations
Hematological, biochemical, and urine tests were performed, including antinuclear antibody, anti-DNA, C3, C4, and CH50. In addition, kidney and liver function tests, screening for diabetes, and thyroid dysfunction were performed.

Systemic lupus erythematosus activity assessment
The SLE activity was assessed using the systemic lupus erythematosus disease activity index (SLEDAI) [15].

Neurophysiological assessment
Using the Tonnies version 1.59 EMG apparatus, (produced by Toennies, Germany) the SSR of the median nerve was assessed, and nerve conduction study (NCS) of both the ulnar and the median nerves was performed. Electrophysiological tests were conducted in a semidarkened silent room. Participants were admitted to the procedure room at least 15 min before the test to maintain a skin temperature of 22–25°C.

Sympathetic skin response of the median nerve [16,17]
The test was performed according to a protocol recommended by the International Federation of Clinical Neurophysiology. An EMG equipment was used with filter settings, including a band-pass of 0.16–3200 Hz, a sensitivity of 0.5–2 mV/division, and a sweep speed of 500 ms/division. The SSR test was recorded with a standard EMG surface electrode placed in the center of the palm, with the reference electrode placed on the dorsal surfaces of the hand. After the application of SSR electrodes on the hands, the participants were instructed to close their eyes and relax for ~10 min before the start of any recordings. A single electrical stimulus to the median nerve surface at the wrist contralateral to the recording side

was used. Stimuli were delivered unexpectedly and at irregular intervals of more than 1 min to prevent habituation. Latency and amplitude of the response were recorded. The latency was measured from the onset of the stimulus artifact to the onset of the first negative deflection of the signal baseline, and the amplitude was measured from peak to peak. The response was considered absent if no consistent voltage change occurred using a sensitivity of 50 mV/division after three trials at maximum stimuli intensity. The amplitude was considered pathological when it was more than 2 SDs below the mean amplitude of the control group; latencies were considered pathological when they were more than 2 SDs above the mean latency of the control group.

Nerve conduction study of both median and ulnar nerves [18,19]

Using surface-stimulating and recording electrodes, the NCS was performed according to the American Association of Electrodiagnostic Medicine guidelines. The abnormal cutoff values for NCSs parameters were calculated as ± 2 SDs from the mean values of the control group.

(1) The motor nerve distal latency (MDL), the CMAP amplitude, and the NCV

Stimulation was performed at the wrist and then at the elbow, while the compound muscle action potential was recorded from abductor pollicis brevis and abductor digiti minimi for median and ulnar nerves, respectively. The MDL, the CMAP amplitude, and the NCV were calculated. When values of the distal motor latency of patients were more than 2 SD the mean values of the controls, they were considered as abnormal, whereas values of the CMAP amplitude and NCV lower than mean−2 SD of the control were considered as abnormal.

(2) Sensory nerve latency

Distal sensory latencies (to peak) of ulnar, median, and radial nerves (uSDL, mSDL, rSDL) were recorded from the thumb for median and radial nerves, whereas from the ring finger for the ulnar nerve.

(3) F-wave latency

It was performed to exclude cervical radiculopathy.

Statistical analysis

Before statistical analysis, the Kolmogorov–Smirnov test was performed to assess the normality of the continuous data. The two groups showed normal distribution; therefore, a parametric statistical analysis was performed to analyze the data, that is, a main comparative analysis between both groups was performed using Student's *t*-test. Results were presented as mean ± SD. *P* values less than 0.05 were regarded as statistically significant. Also, Pearson's correlation coefficient was used to interpret the relationship between different variables in the same group.

Results

Fifty-six SLE patients fulfilled the criteria for inclusion in this study. In addition, 30 healthy control individuals participated in this study. The patients consisted of four (7.1%) men and 52 (92.9%) women, with a mean age of 27.81 ± 7.1 years (range 18–47 years). The control group consisted of three (10%) men and 27 (90%) women, with a mean age of 26.9 ± 4.42 years (range 21–49 years). There was no significant difference in the age and sex distribution between the patient and the control groups (*P* > 0.05).

Clinical and laboratory data of the patients are presented in Tables 1–3.

Table 1 Frequencies of clinical data in systemic lupus erythematosus patients

Clinical data	Number of patients (%)
Skin rash	6 (10.7)
Oral ulcers	4 (7.1)
Arthritis	6 (10.7)
Serositis	4 (7.1)
Nephritis	30 (53.6)
CNS manifestations	2 (3.6)
Antiphospholipid	8 (14.3)
Steroids	56 (100)
Hydroquine	28 (50)
Imuran	30 (53.6)
Endoxan	22 (39.3)

CNS, central nervous system.

Table 2 Values and frequencies of laboratory data of systemic lupus erythematosus patients

Laboratory data	Range	Mean ± SD
Hb (g/dl)	4.1–14.5	8.55 ± 3.26
Total leukocytic count (TLC) (×10³/mm³)	1.3–20.4	7.5 ± 3.6
Lymphocytes (×10³/mm³)	0.4–4.2	1.95 ± 0.96
Monocytes (×10³/mm³)	0.04–0.8	0.36 ± 0.25
Platelets (×10³/mm³)	51–410	217.2 ± 82.6
ESR (mm; 1st hour)	5–115	40.7 ± 24.1
Proteinuria (g/24 h)	0.01–6.5	0.63 ± 1.22
Serum creatinine (mg/dl)	0.4–2.1	1.03 ± 0.39
Blood urea nitrogen (BUN) (mg/dl)	8–45	24.1 ± 8.7
Creatinine clearance	5.4–94	47.58 ± 29.3
Protein/creatinine ratio	0.04–9.2	0.78 ± 1.89

ESR, erythrocyte sedimentation rate; Hb, hemoglobin.

Systemic lupus erythematosus activity assessment

The SLEDAI ranged from 2 to 30, with a mean of 15.6 ± 4.38.

Neurophysiological study

The results of the control group are shown in Table 4. The cutoff value for each parameter was calculated as mean ± 2 SD of the control results. Hence, the cutoff values were as follows:

(1) *Motor ulnar nerve parameters*: the cutoff value of the ulnar motor nerve distal latency (uMDL), the amplitude, and the NCV were 3.08 ms, 6.44 mV, and 45.84 m/s, respectively.
(2) *Motor median nerve parameters*: the cutoff value of the median motor nerve distal latency (mMDL), the amplitude, and the NCV were 3.99 ms, 6 mV, and 49.5 m/s, respectively.
(3) *The sensory ulnar nerve*: the cutoff value of the uSDL was 2.9 ms (normal value).
(4) *The sensory median nerve*: the cutoff value of the mSDL was 2.9 ms (normal value).
(5) *The sensory radial nerve*: the cutoff value of the rSDL was 2.7 ms (normal value).
(6) *For the SSR*: the cutoff values for the latency and the amplitude were 1580 ms and 1813 μV, respectively.

The systemic lupus erythematosus group

(1) Pure sensory abnormality was detected in one patient in whom sensory latency was delayed in the three studied nerves.
(2) Pure motor abnormality was found in 19 patients (two patients with ulnar and one with median demyelenating neuropathy, two patients with combined ulnar and median axonal neuropathy, and five patients with ulnar and nine with median axonal neuropathy).
(3) Mixed sensory–motor abnormalities were detected in two patients (one showed abnormalities in all median sensory–motor parameters, whereas the other showed delayed uSDL and reduced ulnar and median CMAP amplitude).
(4) SSR was not elicited in 13 patients.
(5) SSR latency abnormality was present in 11/43 patients.
(6) SSR amplitude abnormality was present in 9/43 patients (Tables 5 and 6).

On comparing the mean values of the control and the patient groups, there was a nonsignificant difference between both groups (Table 7 and Figs. 1 and 2). The neurophysiological parameters were not correlated with the disease duration, the erythrocyte sedimentation rate, and the SLEDAI score.

Table 3 Frequencies of laboratory data among patients

Laboratory data	N (%)
Anemia	49 (87.5)
Hematuria	0 (0)
Pyria	5 (8.9)
Casts	19 (30.4)
Anti-ANA	56 (100)
Anti-DNA	51 (91.1)

ANA, antinuclear antibody.

Table 4 Nerve conduction studies in the control group

Tests	Range	Mean ± SD	Cutoff value
Motor			
Ulnar nerve latency (ms)	2.3–2.9	2.6 ± 0.24	3.08
Ulnar nerve amplitude (mV)	7–21.2	15.04 ± 4.3	6.44
Ulnar nerve conduction velocity (m/s)	54–74	60.7 ± 7.08	45.84
Median nerve latency (ms)	2.6–3.6	3.21 ± 0.39	3.99
Median nerve amplitude (mV)	11.2–23	15.8 ± 4.9	6
Median nerve conduction velocity (m/s)	55–69.2	60.4 ± 5.45	49.5
Sensory			
Ulnar latency (ms)	2–3.1	2.4 ± 0.254	2.9
Median latency (ms)	1.8–2.9	2.4 ± 0.256	2.9
Radial latency (ms)	1.8–2.8	2.2 ± 0.259	2.7
SSR			
SSR latency (ms)	780–1465	1196 ± 192	1580
SSR amplitude (μV)	1932–4354	2463 ± 325	1813

SSR, sympathetic skin response.

Table 5 Nerve conduction studies in the patient group

Tests	Range	Mean ± SD
Motor		
Ulnar nerve latency	1.7–3.2	2.4 ± 0.32
Ulnar nerve amplitude	4.3–17.1	11.45 ± 3.11
Ulnar nerve conduction velocity	52.3–72.7	63.1 ± 5.12
Median nerve latency	2.1–6	2.9 ± 0.72
Median nerve amplitude	3.8–19.9	11.5 ± 3.75
Median nerve conduction velocity	47.7–84	62.53 ± 7.22
Sensory		
Radial latency	1.8–3.2	2.2 ± 0.28
Ulnar latency	2–3.6	2.55 ± 0.31
Median latency	1.8–3.4	2.5 ± 0.55
SSR		
SSR latency	830–2820	1441 ± 340
SSR amplitude	700–4126	2136 ± 238

SSR, sympathetic skin response.

Discussion

Neurological manifestations are known to occur in patients with autoimmune rheumatic diseases, often in subclinical form. The range of neurological symptoms accompanying NPSLE is very wide, and their presence is associated with a poor prognosis. Neurological symptoms can be primary or secondary, and their differentiation may be difficult [20].

The electrodiagnostic NCS is an essential well-established objective method for the diagnosis and the classification of neuropathies. Many neuropathic syndromes can be suspected on clinical grounds, but the optimal use of NCS techniques allows diagnostic classification and is therefore crucial in understanding the pattern of neuropathy [21,22].

Table 6 Frequencies of neuropathies among patients according to cutoff values

Tests	N (%)
Pure motor	
Ulnar demyelinating neuropathy	3 (5.35)
Median demyelinating neuropathy	6 (10.71)
Ulnar axonal neuropathy	13 (23.2)
Median axonal neuropathy	17 (30.35)
Mixed ulnar–median axonal neuropathy	2 (3.5)
Pure sensory	1 (1.78)
Mixed sensory–motor (median)	2 (3.5)
SSR	
Not elicited	13/56 (23.2)
SSR latency	11/43 (19.64)
SSR amplitude	9/43 (20.9)

SSR, sympathetic skin response.

In this study, regarding neurophysiological motor assessment, median and ulnar axonal neuropathy was present in 17 (30.3%) and 13 (23.2%) patients, respectively, whereas mixed ulnar–median axonal neuropathy was present in two (3.5%) patients. In contrast, demyelinating median and ulnar neuropathy was present in six (10.7%) and three (5.3%) patients, respectively. However, mixed sensory–motor neuropathy was present in two (3.5%) patients. This means that the pattern of peripheral neuropathy in SLE patients is mainly motor axonal neuropathy (23–30% of cases) and rarely sensory neuropathy (only three patients).

The presence of peripheral neuropathy in association with SLE agrees with Shehata et al. [23], who reported motor peripheral neuropathy in 26% of the patients. Detection of motor neuropathy in SLE patients agrees with the study of Aslam et al. [24], who reported a case who was unable to neither fully adduct nor abduct the left eye in addition to inability to achieve upward gaze in both eyes. This was interpreted as partial right III and VI and almost complete left III and VI cranial neuropathies. Also, there was bilateral facial weakness

Table 7 Comparison between patients and controls regarding the motor nerve conduction parameters

| Neurophysiological tests	Mean ± SD		t	P	Significance
	Control group (n = 30)	SLE group (n = 56)			
Motor					
Ulnar nerve latency	2.6 ± 0.24	2.4 ± 0.32	0.33	>0.05	NS
Ulnar nerve amplitude	15.04 ± 4.3	11.45 ± 3.11	0.63	>0.05	NS
Ulnar nerve conduction velocity	60.7 ± 7.08	63.1 ± 5.12	0.39	>0.05	NS
Median nerve latency	3.21 ± 0.39	2.9 ± 0.72	0.35	>0.05	NS
Median nerve amplitude	15.8 ± 4.9	11.5 ± 3.75	0.76	>0.05	NS
Median nerve conduction velocity	60.4 ± 5.45	62.5 ± 7.22	0.364	>0.05	NS
Sensory					
Radial latency	2.2 ± 0.259	2.2 ± 0.28	0.013	>0.05	NS
Ulnar latency	2.4 ± 0.254	2.55 ± 0.31	0.381	>0.05	NS
Median latency	2.4 ± 0.256	2.5 ± 0.55	0.362	>0.05	NS
SSR					
SSR latency	1196 ± 192	1441 ± 340	1.42	>0.05	NS
SSR amplitude	2463 ± 325	2136 ± 238	1.36	>0.05	NS

SLE, systemic lupus erythematosus; SSR, sympathetic skin response.

Figure 1
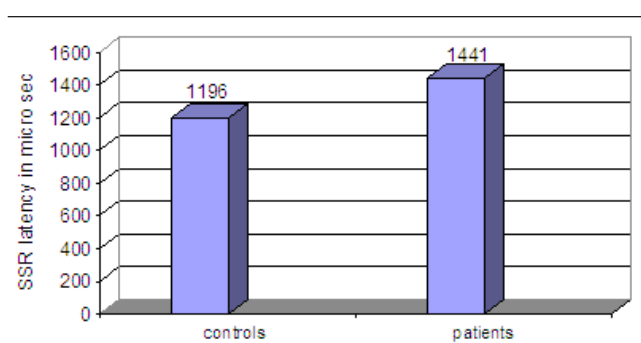
Comparison between patients and controls regarding the mean sympathetic skin response (SSR) latency.

Figure 2
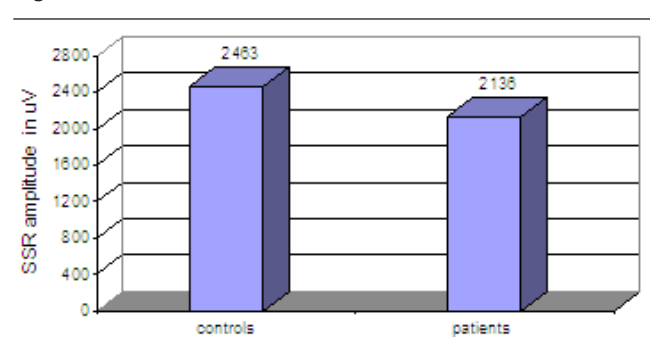
Comparison between patients and controls regarding the mean sympathetic skin response (SSR) amplitude.

indicating facial nerve palsy in addition to proximal muscular weakness and wasting of both upper and lower extremities. The distal strength was preserved, and reflexes were decreased to absent bilaterally denoting axonal affection of peripheral and cranial nerves [24].

The term ANS describes nerves that are concerned predominantly with the regulation of body functions. It is comprised of sympathetic and parasympathetic nerves, and their function is complementary. ANS involvement has rarely been studied in patients with autoimmune rheumatic disease. This may be because symptoms of autonomic dysfunction are nonspecific and extremely varied, and may pertain to several systems such as gastrointestinal, cardiovascular, and nervous systems. Moreover, tests to detect autonomic dysfunction are not used routinely in clinical rheumatological practice. Cardiovascular autonomic dysfunction is the most common type of autonomic dysfunction investigated in the majority of rheumatic patients, and cardiovascular reflex tests were used in the assessment of the ANS in such patients [25]. Also, automated standardized infrared pupillometry allows safe, noninvasive assessment of the pupillary innervation, and thus, pupillometry may be used in studying the ANS in rheumatic diseases [26]. In the present study, the SSR electrodiagnostic test was used to evaluate the sympathetic nervous system in the upper extremity in patients not complaining of autonomic dysfunction.

In our study, there was a nonsignificant difference between patients and controls regarding the latency and the amplitude of SSR. This agrees with the study of Tekatas et al. [27]. However, a limitation of such a study is that Tekatas and his colleagues did not calculate the cutoff values for SSR parameters (latency and amplitude), and so, the number of abnormal cases were not mentioned. In contrast, in our study, the cutoff value of SSR parameters were calculated (i.e. latency more than mean ±2 SD of the control and amplitude less than mean −2 SD of the controls). According to the cutoff values, 11 and nine patients showed delayed latency and reduced amplitude of SSR, respectively, whereas 13/56 patients showed nonelicited SSR. Hence, 24/56 (42%) and 22/56 (39.2%) patients showed abnormal latency and amplitude, respectively. Then, nearly 40% of our patients revealed sympathetic dysfunction in the form of delayed latency, reduced amplitude, or nonelicited SSR. Our results are supported by several studies that detected autonomic dysfunction in the cardiovascular system in SLE patients, although such studies did not perform SSR, but sympathetic dysfunction was evaluated by two cardiovascular reflex tests (blood pressure response to standing and blood pressure response to the handgrip test); their results prove autonomic dysfunction in SLE

patients, and sympathetic dysfunction was detected in ~24–44% of the SLE patients [28–30].

Sympathetic and axonal neuropathies were not correlated with the disease duration, the erythrocyte sedimentation rate, and the SLEDAI score; this agrees with the study conducted by Tekatas et al. [27].

Pathogenic etiologies of autonomic and peripheral neuropathies in SLE patients are likely to be multifactorial as the clinical manifestations of nervous system involvement in SLE are highly diverse, and their etiology is understood incompletely.

A large number of etiopathophysiologic processes are involved including autoantibodies in the cerebrospinal fluid and the serum of lupus patients, such as antineuronal antibodies and antibodies against ribosomal P-protein. Such autoantibodies have been proposed as an important factor in the etiology of CNS damage. This is suggested by the increased intrathecal synthesis of autoantibodies in the cerebrospinal fluid in SLE patients with CNS dysfunction [31–33]. Furthermore, many authors suggest that neuronal antibodies are involved in the pathogenesis of psychiatric disease, and parenchymal lesions associated with movement disorder have been documented in these patients, supporting the link between autoimmunity, neuronal death, and neurologic manifestation [34–36].

In addition, cytokines circulating in the systemic circulation and intrathecal production of proinflammatory cytokines may be implicated in the pathogenesis of neuropsychiatric symptoms [37–40].

Furthermore, focal neurological symptoms may be the consequence of vascular injury induced by the circulating immune complex, occlusive vasculopathy as a result of endothelial cell activation induced by cytokines and complement activation, or macrovascular and microvascular thrombosis induced by antiphospholipid antibodies. Also, immune complex deposition leading to complement activation will result in vasculitis of the vasa nervosa, ending in neuronal ischemia and peripheral neuropathy. In later stages of disease, cerebrovascular manifestations are often related to accelerated atherosclerosis, which is accompanied by increased intravascular complement turnover and antiphospholipid antibodies [8,41,42].

Such possible explanations for neurological manifestations in SLE patients are supported by the beneficial effects of intravenous Ig, which may be explained by acting through complement deactivation, receptor blockade, anti-idiotypes, and the modulation of cytokine production [41].

From the results of this study, it can be suggested that the pattern of neuropathy in SLE is most probably axonal. Also, it can be concluded that the sympathetic nervous system is affected at a rate of up to 40% of the cases. Sympathetic and axonal neuropathy was not correlated with disease duration or the disease activity.

References

1 Gøransson LG, Tjensvoll AB, Herigstad A, Mellgren SI, Omdal R. Small-diameter nerve fiber neuropathy in systemic lupus erythematosus. Arch Neurol 2006; **63**:401–404.

2 Fietta P, Fietta P, Delsante G. Psychiatric and neuropsychological manifestations of systemic lupus erythematosus. Acta Biomed 2011; **82**:97–114.

3 Florica B, Aghdassi E, Su J, Gladman DD, Urowitz MB, Fortin PR. Peripheral neuropathy in patients with systemic lupus erythematosus. Semin Arthritis Rheum 2011; **41**:203–211.

4 American College of Rheumatology. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999; **42**:599–608.

5 Meroni PL, Tincani A, Sepp N, Raschi E, Testoni C, Corsini E, et al. Endothelium and the brain in CNS lupus. Lupus 2003; **12**:919–928.

6 Scolding NJ, Joseph FG. The neuropathology and pathogenesis of systemic lupus erythematosus. Neuropathol Appl Neurobiol 2002; **28**:173–189.

7 Navarrete MG, Brey RL. Neuropsychiatric systemic lupus erythematosus. Curr Treat Options Neurol 2000; **2**:473–485.

8 Hanly JG. Neuropsychiatric lupus. Curr Rheumatol Rep 2001; **3**:205–212.

9 Hanly JG, Urowitz MB, Sanchez-Guerrero J, Bae SC, Gordon C, Wallace DJ, et al. Systemic Lupus International Collaborating Clinics Neuropsychiatric events at the time of diagnosis of systemic lupus erythematosus: an international inception cohort study. Arthritis Rheum 2007; **56**:265–273.

10 Crone C, Krarup C. Neurophysiological approach to disorders of peripheral nerve. Handb Clin Neurol 2013; **115**:81–114.

11 Louthrenoo W, Ruttanaumpawan P, Aramrattana A, Sukitawut W. Cardiovascular autonomic nervous system dysfunction in patients with rheumatoid arthritis and systemic lupus erythematosus. QJM 1999; **92**:97–102.

12 Vetrugno R, Liguori R, Cortelli P, Montagna P. Sympathetic skin response: basic mechanisms and clinical applications. Clin Auton Res 2003; **13**:256–270.

13 Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; **25**:1271–1277.

14 Syngle A, Verma I, Garg N, Krishan P. HYPERLINK "http://www.ncbi.nlm.nih.gov/pubmed/23549640" Autonomic dysfunction in psoriatic arthritis. Clin Rheumatol 2013 Jul; 32:1059-64. doi: 10.1007/s10067-013-2239-x. Epub 2013 Apr 3. PMID: 23549640.

15 Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum 1992; **35**:630–640.

16 Claus D, Schondorf R. Sympathetic skin response. In: Deuschl G, Eisen A, editors. Recommendation for the practice of clinical neurophysiology: guidelines of the International Federation of Clinical Neurophysiology. 2nd ed. Volume 52: Elsevier; 1999. 277–285.

17 Ellaway PH, Kuppuswamy A, Nicotra A, Mathias CJ. Sweat production and the sympathetic skin response: Improving the clinical assessment of autonomic function. Auton Neurosci 2010; **155**:109–114.

18 Jablecki CK, Andary MT, Floeter MK, Miller RG, Quartly CA, Vennix MJ, Wilson JR. Second American Association of Electrodiagnostic Medicine literature review of the usefulness of nerve conduction studies and needle electromyography for the evaluation of patients with carpal tunnel syndrome. Muscle Nerve 2002; **26**:S1–S53.

19 American Association of Electrodiagnostic Medicine, American Academy of Neurology, and American Academy of Physical Medicine and Rehabilitation. Practice parameter for electrodiagnostic studies in carpal tunnel syndrome: summary statement. Muscle Nerve 2002; **25**:918–922.

20 Leszczynski P, Pawlak-Bus K. Vocal cords palsy in systemic lupus erythematosus patient: diagnostic and therapeutic difficulties. Rheumatol Int 2013; **33**:1577–1580.

21 Franssen H, van den Bergh PY. Nerve conduction studies in polyneuropathy: practical physiology and patterns of abnormality. Acta Neurol Belg 2006; **106**:73–81.

22 Johnsen B, Fuglsang-Frederiksen A. Electrodiagnosis of polyneuropathy. Neurophysiol Clin 2000; **30**:339–351.

23 Shehata GA, Elserogy YM, Ahmad HE, Abdel-Kareem MI, Al-Kabeer AM, Rayan MM, El-Baky ME. Multimodal neurophysiological and psychometric evaluation among patients with systemic lupus erythematosus. Int J Gen Med 2011; **4**:325–332.

24 Aslam F, Bannout F, Russell EB. Cranial nerve palsies: sarcoidosis to systemic lupus erythematosus. Case Rep Rheumatol 2013; **2013**:175261.

25 Stojanovich L. Autonomic dysfunction in autoimmune rheumatic disease. Autoimmun Rev 2009; **8**:569–572.

26 Bertinotti L, Pietrini U, Del Rosso A, Casale R, Colangelo N, Zoppi M, Matucci-Cerinic M. The use of pupillometry in joint and connective tissue diseases. Ann N Y Acad Sci 2002; **966**:446–455.

27 Tekatas A, Koca SS, Tekatas DD, Aksu F, Dogru Y, Pamuk ON. R–R interval variation and sympathetic skin response in systemic lupus erythematosus. Clin Rheumatol 2014; **33**:65–70.

28 Stojanovich L, Milovanovich B, de Luka SR, Popovich-Kuzmanovich D, Bisenich V, Djukanovich B, et al. Cardiovascular autonomic dysfunction in systemic lupus, rheumatoid arthritis, primary Sjögren syndrome and other autoimmune diseases. Lupus 2007; **16**:181–185.

29 Aydemir M, Yazisiz V, Basarici I, Avci AB, Erbasan F, Belgi A, Terzioglu E. Cardiac autonomic profile in rheumatoid arthritis and systemic lupus erythematosus. Lupus 2010; **19**:255–261.

30 Milovanović B, Stojanović L, Milićevik N, Vasić K, Bjelaković B, Krotin M. Cardiac autonomic dysfunction in patients with systemic lupus, rheumatoid arthritis and sudden death risk. Srp Arh Celok Lek 2010; **138**:26–32.

31 Greenwood DL, Gitlits VM, Alderuccio F, Sentry JW, Toh BH. Autoantibodies in neuropsychiatric lupus. Autoimmunity 2002; **35**:79–86.

32 Yoshio T, Hirata D, Onda K, Nara H, Minota S. Antiribosomal P protein antibodies in cerebrospinal fluid are associated with neuropsychiatric systemic lupus erythematosus. J Rheumatol 2005; **32**:34–39.

33 Arinuma Y, Yanagida T, Hirohata S. Association of cerebrospinal fluid anti-NR2 glutamate receptor antibodies with diffuse neuropsychiatric systemic lupus erythematosus. Arthritis Rheum 2008; **58**:1130–1135.

34 Vincent A, Dalton P, Clover L, Palace J, Lang B. Antibodies to neuronal targets in neurological and psychiatric diseases. Ann N Y Acad Sci 2003; **992**:48–55.

35 Sakic B, Kirkham DL, Ballok DA, Mwanjewe J, Fearon IM, Macri J, et al. Proliferating brain cells are a target of neurotoxic CSF in systemic autoimmune disease. J Neuroimmunol 2005; **169**:68–85.

36 Rocca MA, Agosta F, Mezzapesa DM, Ciboddo G, Falini A, Comi G, Filippi M. An fMRI study of the motor system in patients with neuropsychiatric systemic lupus erythematosus. Neuroimage 2006; **30**:478–484.

37 Jennekens FG, Kater L. The central nervous system in systemic lupus erythematosus. Part 2. Pathogenetic mechanisms of clinical syndromes: a literature investigation. Rheumatology (Oxford) 2002; **41**:619–630.

38 Weiner SM, Peter HH. Neuropsychiatric involvement in systemic lupus erythematosus. Part 1: clinical presentation and pathogenesis. Med Klin (Munich) 2002; **97**:730–737.

39 Ballok DA. Neuroimmunopathology in a murine model of neuropsychiatric lupus. Brain Res Rev 2007; **54**:67–79.

40 Muscal E, Brey RL. Neurologic manifestations of systemic lupus erythematosus in children and adults. Neurol Clin 2010; **28**:61–73.

41 Levy Y, Uziel Y, Zandman GG, Amital H, Sherer Y, Langevitz P, et al. Intravenous immunoglobulins in peripheral neuropathy associated with vasculitis. Ann Rheum Dis 2003; **62**:1221–1223.

42 Luyendijk J, Steens SC, Ouwendijk WJ, Steup-Beekman GM, Bollen EL, van der Grond J, et al. Neuropsychiatric systemic lupus erythematosus: lessons learned from magnetic resonance imaging. Arthritis Rheum 2011; **63**:722–732.