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Research Article

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Brainstem Reflexes in Systemic Lupus Erythematosus Patients Without Clinical Neurological Manifestations

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ABSTRACT

Introduction: We aimed to assess central and peripheral nervous system involvement in systemic lupus erythematosus (SLE) patients without any neurological signs and symptoms by performing electrophysiological investigations.

Methods: Thirty-eight SLE patients and 35 healthy volunteers participated in this study. Peripheral nerve conduction and brainstem reflexes were evaluated by performing nerve conduction studies (NCSs) and blink reflex (BR) and masseter inhibitory reflex (MIR) recordings.

Results: Eleven patients (29%) had an abnormality in at least 1 NCS parameter, and 1 (2.6%) patient was diagnosed with polyneuropathy. The number of patients with abnormal BR and MIR was 23 (60.5%) and 14 (37%), respectively. The contralateral R2 latency of BR and the silent period 1 (SP1) latency of MIR were significantly prolonged in the patients compared with the controls ($p=0.015$ and $p<0.001$, respectively).

Conclusion: This study showed that irrespective of peripheral nervous system involvement, brainstem reflexes could be affected in SLE patients even without clinical neurological findings. Brainstem reflex abnormalities suggested that the functional integrity of the inhibitory or excitatory interneurons in the lateral caudal pons and lateral medulla is disturbed in SLE patients.

Keywords: Systemic lupus erythematosus, brainstem reflexes, electroneuromyography, peripheral nervous system

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that can affect multiple organ systems. One of the main clinical syndromes of SLE is nervous system involvement, both central and peripheral. The most common neuropsychiatric manifestations are cognitive dysfunction, headache, seizures, stroke, and peripheral neuropathy. These manifestations are seen in 37–95% of SLE patients (1-4). However, neuropsychiatric signs may be clinically silent. Therefore, investigations such as neuroimaging and electrophysiological recordings are warranted to delineate these clinically silent abnormalities.

Among the CNS syndromes of SLE, brainstem involvement is not rare (2,3,5,6,7,8). For assessing the brainstem functions, electrophysiological recordings of brainstem reflexes are still valuable tools. The best-studied brainstem reflexes are blink reflex (BR) and masseter inhibitory reflexes (MIRs). These electrophysiological recordings can help clinicians localize brainstem lesions. This information may be a guide for tailored neuroimaging of brainstem lesions in SLE patients. In addition, they may be used for follow up and prognosis prediction.
In this study, we aimed to perform electrophysiological investigations of the peripheral and central nervous systems in a group of SLE patients without clinical neurological abnormalities.

METHODS

Thirty-eight patients (36 women and 2 men) and 35 healthy volunteers (31 women and 4 men) participated in this study. All the patients fulfilled the American College of Rheumatology (ACR) classification criteria for SLE. Patients older than 65 years and patients with central and/or peripheral nervous system involvement related to any other systemic disease were excluded from the study. Normative electrophysiological data were obtained from the healthy volunteers who had no risk factors for any neurological disease with normal neurological examination. The study protocol conformed to the Helsinki Declaration of Human Rights and was approved by the local ethics committee. All the participants provided written informed consent to participate in the study.

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Electrophysiological Investigations

All electrophysiological investigations were performed using a Medelec Synergy electromyography (EMG) device (Medelec Synergy EMG, Oxford Instruments Medical, UK).

Nerve Conduction Studies (NCSs)

Surface bar recording and bipolar surface recording electrodes (Teca Corp. Pleasantville, New York) were used in NCSs. Sensory NCSs of the medial plantar, superficial peroneal, ulnar, and radial nerves were performed. Motor NCSs were performed on the posterior tibial, peroneal, and median motor nerves. Compound muscle action potential (CMAP) amplitude, distal latency, conduction velocity, and minimum F-response latency and F-wave persistence were calculated for motor NCSs. Minimum F-response latency was obtained using 20 stimulations. The onset and peak latency, onset and peak nerve conduction velocity (NCV), and amplitude were measured for sensory NCSs in the upper and lower extremities. The pattern was accepted as an "absent SNAP" if there was no recognizable SNAP or if SNAP was not repeatable and constant. A signal averaging of 8 responses was used for SNAP. In order to obtain the maximum SNAP, the stimulus intensity was supramaximal, i.e., at least 3 times the sensory threshold. The filter settings were 5 Hz–10 kHz for motor studies and 20 Hz–2 kHz for sensory studies. The skin temperature was maintained between 31°C and 34°C in all the subjects.

Brainstem Reflexes

BRs and MIRs were studied. BR studies were performed with the subject lying down. Electrical stimuli were applied to the supraorbital nerve at the supraorbital foramen and eyebrow. Bilateral active and reference surface electrodes were placed over the orbicularis oculi belly and 1 cm lateral to the rim of the eye, respectively. At least 10 signals were superimposed. The stimuli were randomly delivered with a minimum interval of 10 s to avoid habituation. The stimulation intensity was 2–3 times (8–14 mA) higher than the threshold, and the stimulation duration was 0.2 ms. Filters were set at 20 Hz to 10 kHz, the sweep speed was 100 ms, and the sensitivity was 100 μV.

MIR was recorded by applying electrical stimulation to the mentalis nerve while the patient was lying supine with a clenched jaw. Active electrodes were placed anterior to the zygomatic arch on the masseter belly. Reference electrodes were 2–3 cm caudal to the active ones. Stimuli were applied randomly, and the last 5 of the 10 responses obtained were superimposed. The filter settings were 20 Hz–5 kHz, the sweep speed was 20 ms, and the sensitivity was 100 μV.

Statistical Analysis

Statistical analyses were performed using GraphPad InStat, version 3.05 for Windows (GraphPad Software, San Diego, CA). Normal distribution of the data was determined using the Kolmogorov–Smirnov test. Depending on the normality of the distribution, either raw data or logarithmically transformed data were used. Student's *t* test and Mann–Whitney U test were used for comparison between groups. Categorical variables were compared using the chi-square test. A p value of less than 0.05 was accepted as significant.

RESULTS

The mean age of the patients was 38.6±10.1 years, and the age of the control group was 37.6±8.5 years (p=0.663). There was no significant difference between the 2 groups with regard to sex, height and body weight (Table 1). The mean number of the ACR SLE criteria fulfilled was 5.8±1.05.

Table 1. Demographics of patients and control subjects

	Patients (n=38)	Controls (n=35)	p
Female/Male	36/2	31/4	0.955
Age (years)*	38.6±10.1	37.6±8.5	0.663
Height (cm)*	163±0.05	161±0.07	0.309
Weight (kg)*	66.8±13.7	68.4±12.3	0.600
* Mean±standard deviation			

Electrophysiological Investigations

NCSs

Eleven patients (29%) had an abnormality in at least 1 NCS parameter, and 1 (2.6%) patient was diagnosed with polyneuropathy.

Brainstem Reflexes

The parameters of the control subjects for the brainstem reflexes were distributed normally. The upper and lower limits of these parameters were determined by calculating the mean±2 standard deviations. The data obtained from the patients were compared to this normative data. The brainstem reflex abnormalities were irrespective of the abnormalities in the peripheral nervous system.

BRs: The ipsilateral R1 (iR1), ipsilateral R2 (iR2), contralateral R2 (cR2), latency difference between ipsilateral R2 and contralateral R2 (iR2−cR2), latency difference between left R1 and right R1 (LR1−RR1), latency difference between ipsilateral R2s elicited by left and right stimulation (LiR2−RiR2), and latency difference between contralateral R2s elicited by left and right stimulation (LcR2−RcR2) were analyzed. The BR parameters were obtained in all patients. The comparisons of these parameters are shown in Table 2. Patients had a significantly prolonged cR2 latency (*P*=0.015) and iR2−cR2 (p=0.005). Figure 1 shows an abnormal cR2 latency response in a patient. The number of patients with an abnormal BR for any of these parameters was 23 (60.5%).

MIR: The onset latency of silent period 1 (SP1) was significantly prolonged in the patients compared to the controls (16.02±3 ms for the patients and 14.3±2.3 ms in the control subjects; p<0.001). MIR was not elicited in 2 patients bilaterally and in 2 patients unilaterally. The number of patients with a unilaterally abnormal or absent SP1 was 14 (37%). No significant difference was found between the 2 groups for the onset of the SP2 component of the MIR (p=0.5392).

DISCUSSION

The aim of this study was to evaluate the electrophysiological involvement of SLE patients without neurological findings. We found that more than half of the studied SLE patients had abnormal brainstem reflexes. On the other hand, the polyneuropathy rate was not high in the asymptomatic SLE patients. Among the neurophysiological tests, the BR showed the highest abnormality. Our findings may imply a subclinical involvement in the brainstem pathways in at least some of the SLE patients.

SLE is a multisystemic autoimmune disorder affecting many organ systems. The prevalence of the central and peripheral nervous system dysfunction is reported to range from 37% to 95%, depending on the diagnostic criteria and sampling methods used (49-54). The pathogenesis of neuropsychiatric SLE is still unclear, and it is related to a vasculitic process due to autoantibodies and inflammatory mediators (9,10). Peripheral nervous system involvement has been less investigated and is

Table 2. Blink reflexes in patients and control subjects

Blink Reflex		Controls Mean±SD	Patients Mean±SD	p
R1	Latency (ms)	10.71±0.78	10.93±0.69	0.083
iR2	Latency (ms)	30.98±3.57	31.49±3.78	0.407
cR2	Latency (ms)	32.06±3.67	33.69±4.29	0.015
iR2−cR2	Latency difference (ms)	1.08±1.49	2.27±2.02	0.005
LR1−RR1	Latency difference (ms)	0.1±0.68	0.24±0.55	0.314
LiR2−RiR2	Latency difference (ms)	0.26±3.79	0.87±3.56	0.479
LcR2−RcR2	Latency difference (ms)	0.2±3.86	1.01±3.86	0.370

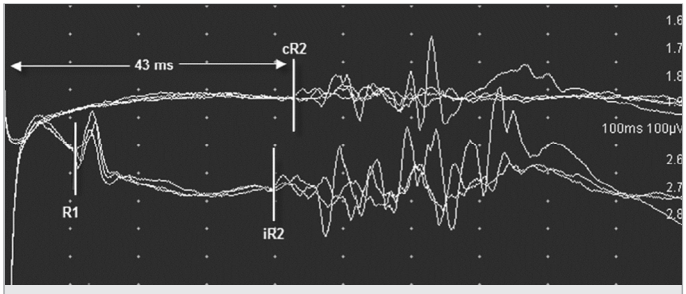

Figure 1. Blink reflex of a patient revealing abnormally prolonged cR2 latency

characterized by a mild form of length-dependent sensory or sensorimotor axonal neuropathy. It is reported to occur in 1.5–27% of patients (11,12,13,14). In our study, approximately 1/3 of the patients had at least 1 abnormal NCS parameter, and only 1 patient (2.6%) was diagnosed with polyneuropathy. This polyneuropathy rate was not higher in asymptomatic SLE patients than the general population (15). The sensory and motor nerves were both affected, and most of these NCS abnormalities suggested an axonal degeneration with reduced nerve action potential amplitudes. Because we studied patients without neurological complaints, we planned to follow up with the patients to determine the electrophysiological changes over time and to observe the clinical correlations of these findings.

Another aim of our study was to detect subclinical central nervous system involvement in SLE patients with brainstem reflex studies. Brainstem reflex studies are easily applied, reproducible and non-invasive investigations. These studies have been evaluated in many diseases, such as trigeminal and facial nerve lesions, polyneuropathy, hemifacial spasm, brainstem lesions, Parkinson's disease and multiple sclerosis, so far (16,17,18,19,20). They are influenced both by lesions in the supranuclear pathways and in the brainstem itself. To the best of our knowledge, our study was one of the first studies assessing the electrophysiological circuits of the central nervous system in SLE patients. Gaber, et al. (21) assessed the presence of asymptomatic cranial neuropathy in SLE patients by evaluating BR and evoked potentials, and they found an association between the abnormal electrophysiological findings and antiribosomal P antibody levels. In our study, the BR recordings demonstrated a significantly delayed cR2 latency and increased iR2−cR2 in SLE patients compared to healthy subjects. This condition was defined as a "crossed type of abnormality" in the study by Cruccu et al. (22), and localizes the topographically bilateral lateral caudal pons and/or bilateral lateral medulla and polysynaptic chain (23). R2 does not usually have a high localizing value as it is affected by suprasegmental influences (cortical and basal ganglia dysfunction, changes in consciousness and cognitive state). However, when only cR2 is affected, as suggested by the crossed type of the abnormality hypothesis, it is better to localize the pathology to the brainstem and restrict it to the caudal pons and medulla oblongata rather than the suprasegmental levels. Therefore, our findings suggest that there is an anomaly that electrophysiologically affects the polysynaptic chains in the medulla oblongata and caudal pons in SLE patients. In addition, the lack of a significant R1 latency prolongation further excludes involvement of the mid-pons. To verify this hypothesis, studies with a greater number of patients should be undertaken, and an anatomical correlation of the findings should be performed using neuroimaging investigations. While performing electrophysiological investigations, the priority is identifying individual abnormalities rather than comparing the groups. In this sense, 60.5% of the SLE patients had abnormalities in at least 1 BR parameter. The most common abnormalities were delayed cR2 latency and prolonged LiR2−cR2 and RiR2−cR2. These findings were consistent with the results obtained from the group comparisons.

MIR, which is elicited by the stimulation of the mental or supraorbital nerves, consists of 2 phases of suppression (SP1 and SP2). The MIR circuit is supposed to extend from the pons to the medulla oblangata. Compared with the controls, our findings demonstrated a significant prolongation of the bilateral SP1 latency in the patient group ($p<0.001$). However, the SP2 latencies did not differ between the 2 groups ($p=0.539$). In terms of the individual abnormalities, SP1 latency prolongation was observed in 11 patients, whereas SP2 latency prolongation was found in 3 patients. The reason for detecting more frequent SP1 latency abnormalities is that the SP1 response is mediated to the ipsilateral trigeminal nucleus through a mono- or oligosynaptic circuit and is therefore quantitatively more sensitive, while the SP2 response is elicited by a more complex circuit with a more caudally located polysynaptic chain of interneurons. In addition, the neurons that mediate the SP2 response are thought to be better protected because of unknown reasons (22,23).

Although our study is limited because of the relatively small sample size, it is, to the best of our knowledge, one of the first studies utilizing brainstem reflexes in SLE patients. Further studies with a prospective design assessing clinical features with electrophysiological and imaging investigations would yield a better neuroanatomical correlation of these findings and would provide more precise topodiagnostic information about CNS dysfunction in SLE patients.

In conclusion, this study shows that both the central and peripheral nervous systems may be affected in SLE patients, even without any clinical neurological manifestations. Brainstem reflex abnormalities suggest that the functional integrity in the lateral caudal pons and lateral medulla oblongata is impaired.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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