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Neurophysiological evaluation of juvenile systemic lupus erythematosus

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Abstract

Background: Peripheral nervous system and the central nervous system involvement in systemic lupus erythematosus (SLE) patients are one of the major causes of morbidity and mortality. The aim of this work was to study the nervous system clinically and electrophysiologically in children with systemic lupus erythematosus.

Results: The study was carried out on thirty-eight children with SLE. Their age ranged from 5 to 16 years. The most encountered neurologic manifestations were tremors. It was observed in 47.4% of children, followed by headache in 39.5%, sensory manifestation as numbness in 23.7%, cerebrovascular stroke in 5.3%, and chorea in 2.6%, which was unilateral mostly in the upper limb, tics, and convulsion had the same percentage. Around 16% of children had positive findings in MRI, such as cerebrovascular disease, minimal hematoma, pseudotumorcerebri, vasculitis, and ectatic ventricles. Subclinical peripheral neuropathy was reported in nearly 52.6% of children, and clinical peripheral neuropathy was reported in 23.6%. Pure sensory subclinical peripheral neuropathy was detected in 13.1% of children, but mixed subclinical peripheral neuropathy was detected in 39.4%. Nearly 53% of studied children had an abnormal somatosensory-evoked potential study of posterior tibial and median nerves.

Conclusion: The current study reported that the clinical neurological manifestations in juvenile SLE is common. Peripheral neuropathy is commonly detected, which could be either clinical or sub-clinical. Somatosensory evoked potential study is of value for early detection of central affection.

So, we recommend more studies to determine the guidelines when to order these informative investigations for children with JSLE.

Keywords: Systemic lupus erythematosus, Nerve conduction study, Neurologic manifestations

Background

Systemic lupus erythematosus (SLE) is an autoimmune, chronic, and multisystemic disease, which is characterized by a wide clinical spectrum. Environmental, hormonal, immunologic, and genetic factors play a role in the pathogenesis, although its etiology is still unknown [1–3].

Diagnosis of SLE in the pediatric age is very difficult due to the similarity of its presentation with other pathologies. The most common presentations are systemic constitutional symptoms such as fatigue, weight loss, and fever; skin involvement, including malar rash and photosensitivity; and musculoskeletal disease, including arthralgia/arthritis, renal, and neuropsychiatric disease [4, 5].

Peripheral nervous system (PNS) and the central nervous system (CNS) involvement in SLE patients are one of the major causes of morbidity and mortality, and it has been the least understood manifestation of the disease and remains a complex diagnostic entity as a result of its multiple clinical presentations. Both are collectively referred to as neuropsychiatric systemic lupus erythematosus (NPSLE) syndromes [6]. The aim of this work was to study the nervous system clinically and electrophysiologically in children with systemic lupus erythematosus

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attending in the Alexandria University Children's Hospital in order to find the subclinical as well as a clinical affection in juvenile SLE.

Methods

A case–control study was carried out on the following:

- Thirty-eight children with juvenile systemic lupus erythematosus (JSLE) attending in the Alexandria University Children's Hospital over a period from May 2017 to April 2018. The children were studied while having a quiescent disease with no clinical or serological signs of activity, through assessment by the SLE disease activity index (SELDAI) [7]. All children were diagnosed with SLE according to the American College of Rheumatology Classification Criteria [8, 9].
- Thirty healthy children of matched age and sex served as a control group for parameters of the electrophysiological study.

Children on corticosteroid with elevated blood sugar were excluded. Also children with known central nervous system disorders or peripheral neuropathy having a cause other than SLE were excluded from the study.

The study was explained to the participants and their parents, and a written consent was taken from the parents of all children included in the study. The study was approved by the local ethics committee of the Faculty of Medicine, Alexandria University.

Children with JSLE were subjected to clinical and neurological examination, and conventional structural magnetic resonance imaging (MRI).

Electrophysiological evaluation was conducted for all children consisting of the following:

1. Peripheral nerve conduction studies (NCSs) [10]: using NIHON KOHDEN (Neuropack 2) electrophysiologic apparatus. All recordings of action potentials were carried out by surface electrodes (8 mm) in diameter, and a ground electrode was placed between the stimulating and recording electrodes. Stimulation was carried out using a bipolar stimulator having a production current ability of 50 mA. The filter setting was between 2 Hz and 10 kHz.
    a Sensory conduction study of the sural, median, and ulnar nerves recording the latency, amplitude, and conduction velocity.
    b Motor conduction study of the median, ulnar, and posterior tibial nerves recording the distal latency, amplitude, and motor conduction velocity.
2. Somatosensory-evoked potentials (SEPs) of the median (recording N 20) and posterior tibial nerve (recording P 40) were done. EEG electrodes were used for recording. We applied an electrical stimulus to the median nerve at the wrist and to the posterior tibial nerve at the ankle. The children lay supine on a bed in a quiet room [11].
- Electromyography (EMG): Standard concentric needle EMG of gluteus medius and tibialis anterior muscles was performed on children with lupus only, not on healthy children [10].

Statistical analysis

Student's t test was used to determine the statistical differences between patients and controls as regards the values of NCSs and SEPs. Normal values for our laboratory were obtained from control children, and abnormal values were defined as 2 standard deviations above/below the normal mean. Significant values were considered at $P \leq 0.05$ [12].

Results

- Clinical assessment: As regards children with JSLE their ages ranged from 5 to 16 years with a mean age of 10.21 ± 2.66 years. Females constituted 81.6%, while males constituted 18.4% from the total number of children with JSLE. There were no statistically significant differences between children with JSLE and healthy children as regards age and sex.

Disease duration was ≤ 5 years in 25 (65.8%) children and > 5 years in 13 (34.2%) children.

As regards treatment, all children were on multi-drug therapy. Thirty-six of the studied children were on triple-drug therapy and only two children were on quadruple drug therapy. All children initially received an oral corticosteroid therapy. About 30% received pulse methylprednisolone. The use of cytotoxic drugs was tried in resistant children according to our unit protocol, and cyclophosphamide was given in 34.2% of the children, azathioprine in 21.1%, mycophenolatemofetil (MMF) in 81.6%, methotrexate in 5.3%, tacrolimus in 15.8%, and hydroxychloroquin in 39.5%.

The clinical neurologic manifestations were reported in 55.2% of the studied children. The most encountered one was tremors on movement. It was observed in 47.4% of children, followed by headache in 39.5%. Sensory manifestation as numbness was presented in 23.7%, while cerebrovascular stroke in 5.3% and chorea in 2.6%, which was unilateral in the upper limb, and tics and convulsion had the same percentage.

Abnormal gait patterns occurred in two children due to proximal muscle weakness in one child and a vascular necrosis of the hip in the other. However, deep reflexes and muscle tone were not affected.

- Radiologically, MRI brain findings were found in 15.8% of children of which 5.3% had an increased cortical signal that reflect cerebrovascular diseases, 2.6% had hypo-intense foci that reflect minimal hematoma, 2.6% had pseudotumorcerebri as slit–like ventricles associated with papilledema, and 2.6% had hyperintense foci due to vasculitis. Ectatic ventricles were documented in 2.6% (Fig. 1).
- Electrophysiological assessment: Statistically significant differences were detected between JSLE children and healthy children in some parameters of the studied motor and sensory nerves (Tables 1 and 2) (Fig. 2).

As a final evaluation of peripheral conduction of the present study, out of 38 studied children, 29 (76.3%) children had peripheral neuropathy either clinical or subclinical, and 9 (23.6%) children did not have peripheral neuropathy (Fig. 3).

We recorded SEP from a posterior tibial nerve in 37 children, as one child had unobtainable responses and was excluded from this statistical analysis (Fig. 4). Statistically significant differences were found between JSLE children and healthy children in some parameters of the studied somatosensory evoked potential from the posterior tibial and median nerves (Table 3).

Nine (23.6%) children had sensory manifestations, and their somatosensory-evoked potential study of the posterior tibial nerve was abnormal with abnormal peripheral sensory conduction study of the median, sural, and ulnar nerves in five of the children.

All children had a normal electromyographic study except one child who had myopathic motor units on volition.

Of 20 children (52.6%) with abnormal findings in the somatosensory-evoked potential study, six children only had positive findings in brain MRI and 14 children had free brain MRI.

Discussion

The neurological manifestation was reported in many studies [13]; however, little was mentioned about the functional subclinical affection whether central or peripheral which was extensively assessed in our study by electrophysiological testing mainly nerve conduction studies, EMG, and somatosensory-evoked potentials.

Although most of our children had a disease duration of less than 5 years, 55.2% of them had clinical neurologic manifestations. This is in agreement with the studies of both Steinlein et al. [14] and Fierro et al. [15], in which neurological manifestations were documented in 43% and 42% of the studied groups, respectively.

The tremor was the most common clinical neurologic JSLE presentation among our children occurring in 47.4% of cases. Robert and R Sunitha [16] reported tremors in 20.51% of their patients. They explained this as part of enhanced physiologic tremor, due to drugs or fatigue because tremor has not been defined in the ACR nomenclature.

Headache is the second most common neurologic manifestation in this study. Headaches are included in

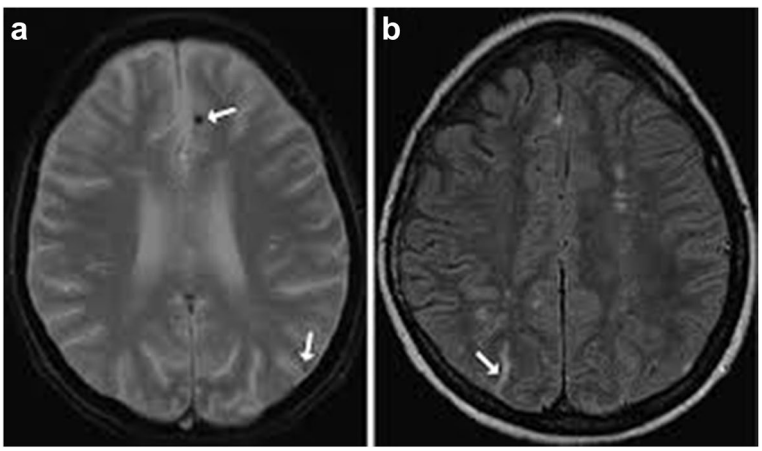

Fig. 1 Brain MRI findings in SLE: hyperintense foci without any restriction of diffusion or any evidence of hemorrhage. They may represent vasculitic changes in the white matter

Table 1 Comparison between the two groups according to motor conduction study

	Motor conduction study	Studied children ($n=38$)	Control group ($n=30$)	*t*	*P*
Median	**Distal latency (ms)**				
	Min. – Max	2.20–3.90	2.40–3.70	0.195	0.846
	Mean ± SD	3.16 ± 0.45	3.18 ± 0.38		
	Median	3.10	3.35		
	Amplitude (mv)				
	Min. – Max	5.73–26.30	6.30–19.0	2.296*	0.025*
	Mean ± SD	13.75 ± 5.29	11.09 ± 3.94		
	Median	13.60	10.50		
	Conduction velocity (m/s)				
	Min. – Max	42.0–80.40	48.0–68.0	1.365	0.177
	Mean ± SD	56.36 ± 9.77	53.68 ± 5.02		
	Median	56.20	52.50		
Ulnar	**Distal latency (ms)**				
	Min. – Max	1.90–3.60	1.90–2.80	1.493	0.140
	Mean ± SD	3.27 ± 3.25	2.38 ± 0.28		
	Median	2.70	2.40		
	Amplitude (mv)				
	Min. – Max	4.40–16.20	6.80–18.0	2.617*	0.010*
	Mean ± SD	10.07 ± 2.76	11.82 ± 2.71		
	Median	10.10	11.50		
	Conduction velocity (m/s)				
	Min. – Max	43.50–93.0	50.0–79.0	0.048	0.962
	Mean ± SD	61.79 ± 11.03	61.91 ± 8.94		
	Median	62.45	60.75		
Post-tibial	**Distal latency (ms)**				
	Min. – Max	2.60–5.60	2.10–4.60	3.701*	< 0.001*
	Mean ± SD	3.97 ± 0.72	3.35 ± 0.64		
	Median	4.0	3.25		
	Amplitude (mv)				
	Min. – Max	7.83–41.70	5.0–23.0	1.749	0.085
	Mean ± SD	18.14 ± 8.31	15.14 ± 4.91		
	Median	17.15	15.25		
	Conduction velocity (m/s)				
	Min. – Max	40.90–88.20	45.0–62.0	0.738	0.463
	Mean ± SD	49.93 ± 8.23	51.20 ± 5.14		
	Median	48.90	49.50		

t Student's *t* test. *P P* value for comparing between the two groups

* Statistically significant at $P \leq 0.05$

the manifestations of NPSLE [17] in both adult and childhood-onset SLE [18, 19].

Although our patients were in the quiescent stage, 39.5% of them complained of headaches. This support the studies that lupus headaches are mostly unrelated to changes in disease activity [20, 21].

The prevalence of stroke due to cerebrovascular disease was low in the present study, occurring in 5.3% of studied children with SLE. This incidence was lower compared to the 7–17% prevalence of cerebral infarction reported in the previous studies [14, 22, 23], but similar to Mohamed et al.'s study [24]. While the exact mechanisms leading to cerebrovascular disease in patients with SLE are unknown, he explains that the cerebrovascular compromise seen in his patients could be secondary to focal thrombus formation as a manifestation of vasculitis [25].

The pathogenesis of CNS lupus is still obscure. Intrathecal IgG and IgM production are observed in 25–66% of all CNS lupus patients. Various specificities of autoantibodies have been observed in the CNS lupus as follows:

Table 2 Comparison between the two groups according to sensory conduction study

	Sensory conduction study	Studied children ($n=38$)	Control group ($n=30$)	*T*	*P*
Median	**Latency (ms)**				
	Min. – Max	2.0–2.90	1.40–3.30	0.341	0.734
	Mean ± SD	2.47 ± 0.27	2.44 ± 0.45		
	Median	2.42	2.40		
	Amplitude (μv)				
	Min. – Max	11.0–168.0	20.70–65.0	1.729	0.089
	Mean ± SD	55.90 ± 36.48	43.57 ± 15.58		
	Median	37.85	46.50		
	Conduction velocity (m/s)				
	Min. – Max	41.70–65.0	49.0–59.0	2.022*	0.047*
	Mean ± SD	49.69 ± 6.29	52.27 ± 3.41		
	Median	47.75	50.50		
Ulnar	**Latency (ms)**				
	Min. – Max	1.06–3.0	1.60–2.50	2.157*	0.035*
	Mean ± SD	2.24 ± 0.34	2.08 ± 0.25		
	Median	2.22	2.05		
	Amplitude (μv)				
	Min. – Max	13.60–142.0	22.0–45.0	3.453*	0.001*
	Mean ± SD	58.08 ± 34.24	35.97 ± 8.28		
	Median	49.95	36.50		
	Conduction velocity (m/s)				
	Min. – Max	39.70–62.50	49.0–64.0	1.831	0.072
	Mean ± SD	50.51 ± 6.61	53.10 ± 4.54		
	Median	49.05	51.50		
Sural	**Latency (ms)**				
	Min. – Max	2.20–4.0	1.70–3.30	4.648*	< 0.001*
	Mean ± SD	3.01 ± 0.43	2.48 ± 0.51		
	Median	3.0	2.40		
	Amplitude (μv)				
	Min. – Max	7.0–92.0	10.0–32.0	0.105	0.917
	Mean ± SD	21.97 ± 19.08	21.17 ± 6.42		
	Median	15.45	20.20		
	Conduction velocity (m/s)				
	Min. – Max	10.60–53.90	44.0–55.0	5.217*	< 0.001*
	Mean ± SD	42.31 ± 6.51	49.40 ± 4.05		
	Median	42.25	49.0		

t Student's *t* test. *P P* value for comparing between the two groups

* Statistically significant at $P \leq 0.05$

anticardiolipin antibodies, low-avidity anti-DNA antibodies, antineuronal antibodies, and lymphocytotoxic antibodies [26].

Peripheral neuropathy (PN) is one of those neuropsychiatric syndromes that affect the peripheral nervous system, according to the criteria of the ACR [27]. Roberta et al. [28] reported that this syndrome is rarely present in children and adolescents with JSLE, and it is usually described as case reports. Studies on the prevalence of this disorder were done with small- or moderate-size populations. Harel et al. [29] described 5/35 (14%) cases of peripheral neuropathy associated with JSLE in Israel. Yu et al. [30] observed an incidence of 3/185 (1.6%) of peripheral neuropathy in patients with JSLE. Benseler & Silverman [31] described a prevalence of 2/91 (2.2%) of peripheral neuropathy in pediatric patients with lupus.

The electrodiagnostic technique especially the peripheral conduction study is an essential

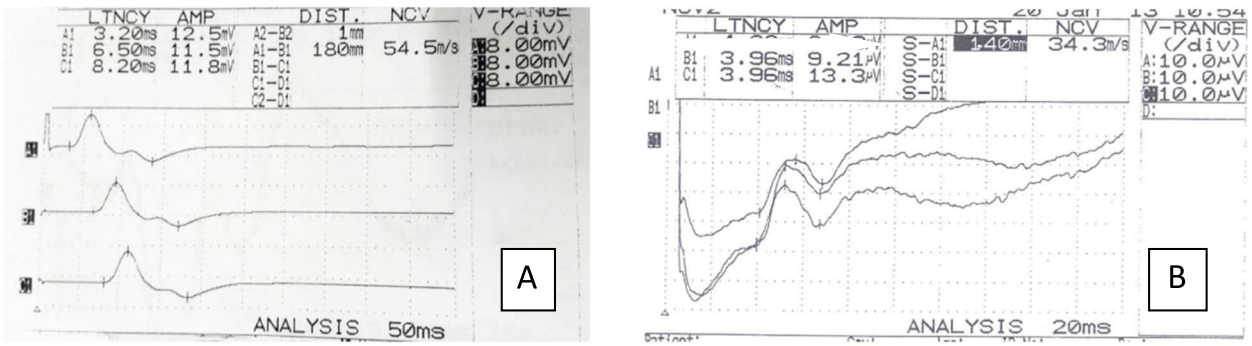

Fig. 2 Motor conduction study of the ulnar nerve showing delayed distal latency, normal amplitude and normal conduction velocity across the elbow (**A**). Sensory conduction study of the sural nerve showing delayed latency with slowing of conduction velocity and normal amplitude (**B**)

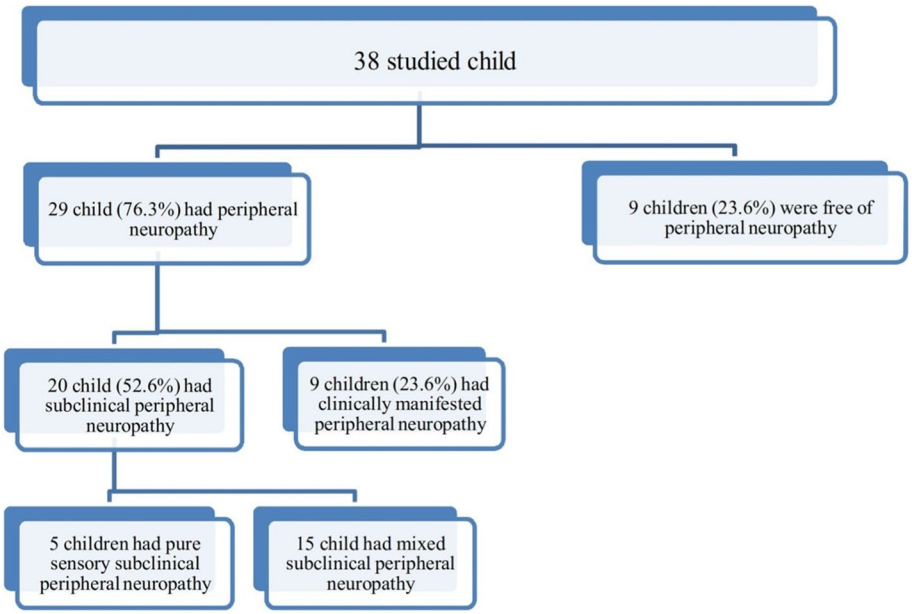

Fig. 3 Distribution of the studied children according to peripheral neuropathy ($n = 38$)

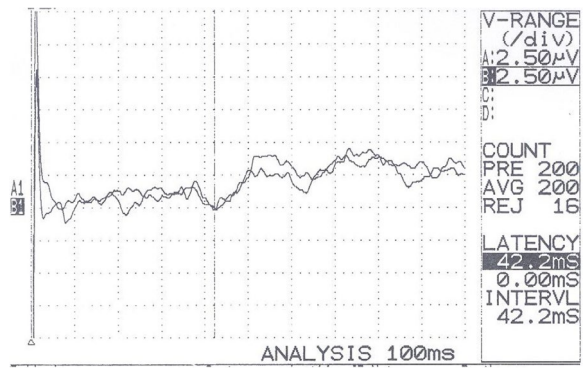

Fig. 4 Somatosensory-evoked potential of the posterior tibial nerve showing a prolonged latency P40 (42.2 ms) cut-off value of 39.25 ms

well-established objective method for the diagnosis and the classification of neuropathies. Many neuropathic syndromes can be suspected on clinical grounds and others cannot. The frequency and pattern of peripheral neuropathy in studied children were evaluated. Although 23.6% of our children had numbness which suggests PN, electrophysiologically, 76.3% had proven to have PN. This suggests that a sizable proportion of JSLE children have subclinical PN. This was supported by previous studies [32, 33]. Peripheral neuropathy can be prevalent in pediatric lupus and rarely diagnosed since those patients can have subclinical manifestations or even non-specific pain that can be mistaken for growing pains.

Table 3 Comparison between the two groups according to somatosensory-evoked potential

	Somatosensory-evoked potential	Studied children	Control group	*t*	*P*
Post-tibial (P 40)	**Latency (ms)**	**(*n* = 37)**	**(*n* = 30)**		
	Min. – Max	29.60–47.80	30.0–37.0	2.409*	0.019*
	Mean ± SD	36.82 ± 4.06	34.83 ± 2.21		
	Median	36.60	33.79		
	Amplitude (μv)	**(*n* = 37)**	**(*n* = 30)**		
	Min. – Max	1.33 – 6.83	3.80 – 13.0	5.785*	< 0.001*
	Mean ± SD	3.77 ± 1.58	6.43 ± 2.18		
	Median	3.75	6.0		
Median (N20)	**Latency (ms)**	**(*n* = 38)**	**(*n* = 30)**		
	Min. – Max	14.40 – 22.20	15.50 – 19.0	1.415	0.162
	Mean ± SD	17.29 ± 1.46	16.87 ± 0.80		
	Median	17.0	17.0		
	Amplitude (μv)	**(*n* = 38)**	**(*n* = 30)**		
	Min. – Max	3.80 – 15.90	6.50 – 18.0	14.634*	< 0.001*
	Mean ± SD	9.14 ± 3.43	9.35 ± 3.46		
	Median	8.88	3.56		

t Student's *t* test. *P P* value for comparing between the two groups

* Statistically significant at $P \leq 0.05$

The incidence of sensory neuropathy in the present study was equal to that of mixed type. Shehata et al. [34] reported axonal neuropathy among SLE patients as they perform only motor conduction studies to their patients.

Also, Khean's study [35] reported that subclinical PN is mainly axonal. Another study on fifty-six SLE patients reported that the pattern of neuropathy in SLE is mainly axonal as 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 [36]. In both studies, the mean age of the patients was 29.9 and 26.9 years, respectively. We raise a question here: Is the type of peripheral neuropathy: axonal or sensory in JSLE differ from that of the adult?

The pathogenesis of PN involves several possible unknown mechanisms. Inflammation and damage of the nerves can be due to autoantibodies, deposit of immune complexes, or direct damage with vasculitis of the "vasa nervorum." This was confirmed by the presence of axonal degeneration and vasculitis in sural nerve biopsies, with higher expression of class II antigens along the fascicular sheath [37]. The other legitimate mechanisms are immunologic effects by a direct antibody aggression, entraining destruction of the peripheral nerve component [38–40]. Xianbin et al. [41] in their study on lupus patients concluded that IgG elevation is an important factor of peripheral neuropathy in SLE. The elevation of IgG is the result of immune dysfunction and reflects B lymphocyte hyperfunction, resulting in the production of autoantibodies and cytokines, activation of T lymphocytes, and the onset of PN. Thus, they propose that the immunological reactions to the nerve tissue may play an important role in the pathogenesis of SLE peripheral neuropathy.

Needle electromyography was normal in all studied children except one child who had myopathic motor units; he was not on corticosteroid at the time of the electrophysiological study. So myopathic motor units may be due to the disease itself as this child was diagnosed with SLE 10 years ago. Previous studies reported neuropathic motor units in 8% of the studied muscles with no myopathic motor units [35].

The somatosensory-evoked potential is an accepted method for evaluating the central nervous system. Statistically significant differences were found as regards amplitude of posterior tibial and median nerves, also as regards distal latency of posterior tibial nerve. Positive findings in somatosensory-evoked potential were recorded in 52.6% of the studied children.

This result was in agreement with Sivri et al. [42] who studied median and posterior tibial nerve SEPs and documented 39.5% of studied lupus patients with SEP abnormalities.

Although, 52.6% of the studied children had positive findings in SEPs, only 15.7% had positive findings in brain MRI. So we can suggest that somatosensory-evoked potential study is more sensitive for early detection of central abnormalities, as it can detect functional

abnormalities but brain MRI can detect structural abnormalities.

The absence of assessment of small fiber neuropathy and lack of assessment of antiphospholipid antibodies are considered as a limitation of this study.

Conclusions

The current study reported that the clinical neurological manifestations in Juvenile SLE are common. The peripheral neuropathy is commonly detected, which could be either clinical or sub-clinical. The somatosensory-evoked potential study is of value for early detection of central abnormalities.

We recommend more studies to determine the guidelines when to order these informative investigations for children with JSLE.

Abbreviations

SLE: Systemic lupus erythematosus; JSLE: Juvenile systemic lupus erythematosus; PNS: Peripheral nervous system; CNS: Central nervous system; NPSLE: Neuropsychiatric systemic lupus erythematosus; SELDAI: SLE disease activity index; MRI: Magnetic resonance imaging; NCSs: Nerve conduction studies; SEPs: Somatosensory evoked potentials; EMG: Electromyography; PN: Peripheral neuropathy.

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Authors' contributions

Study concept and design: AT and HF. Collection of the patients: SE. Examination of the patients: JM and HM. Electrophysiological study of the patients: HM. Analysis and interpretation of data: HF, JM, and HM. Drafting of the manuscript: SE and HM. Critical revision of the manuscript for important intellectual content: AT, HF, JM, and HA. The authors have read and approved the final manuscript.

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Availability of data and materials

Patients were selected from those attending the Alexandria University Children's Hospital over a period from May 2017 to April 2018. All data of the patients are available on reasonal request.

Declarations

Ethics approval and consent to participate

The study was approved by the local ethics committee of the Faculty of Medicine, Alexandria University serial number 01028129. IRB NO: 00012098. FWA NO: 00018699. The study was explained to the participants and their parents, and a written consent was taken from parents of all children included in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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