Original article

Electroneurophysiological evaluation in children and adolescents with collagen diseases.

Background: *Sensorimotor neuropathies have been reported in patients with known or suspected connective tissue disease. It is often difficult to diagnose early neuropathies, and the study of the peripheral neuromuscular system is often made difficult by symptoms resulting from pain in the joints and limitation of movement.*

Objective: *We aimed to investigate the central and peripheral nervous systems involvement in patients with pediatric- onset SLE and juvenile rheumatoid arthritis through clinical assessment and neurophysiological studies (motor nerve conduction velocity (MNCV) of the tibial nerve bilaterally and somatosensory evoked potentials (SSEPs) of the median nerve bilaterally) and to study their relation to clinical data and laboratory investigations.*

Methods: *Nineteen patients with SLE (mean age 14.47± 3.94 years)and fifteen JRA patients (mean age 13.39±3.9 years) were included in the study. Ten healthy, matched subjects served as the control group. In addition to clinical assessment, including complete neurological and psychiatric evaluation, different investigative tools needed for diagnosis as well as assessment of systemic involvement and the degree of activity, were implemented. Both patients and control groups were subjected to neurophysiological studies (Motor nerve conduction velocity (MNCV) of tibial nerve bilaterally and Somatosensory evoked potentials (SSEPs) of the median nerve bilaterally).*

Results: *Definite manifestations of neuropsychiatric involvement attributable to SLE was diagnosed in 37% of SLE patients. Of the SLE patients, 10.5% had abnormal MNCV on the right side, while Erb-N13 interpeak latencies were prolonged in 10.5% and 31.5% of the median nerves studied on the right and left sides, respectively, and N13-N20 was prolonged in 21% and 31.5%, respectively. Neither hypertension nor renal involvement significantly affected the studied parameters; however, SLE patients with cutaneous vasculitis showed slower MNCV of tibial nerve and prolonged Erb-N13 intervals on both sides. Erb-N13 and N13-N20 (on the right side) were positively correlated to the disease activity index (SLE-DAI). Of the JRA patients, 6% had slowed nerve conduction of right tibial nerve, while the interpeak latencies of Erb-N13 were prolonged in 6.6% and 13.3% on the right and left sides, respectively and N13-N20 was prolonged in 6.6% and 20%, respectively. Erb-N13 (on the right side) was negatively correlated to the cumulative dose of steroids.*

Conclusion: *Our study revealed that sensorimotor neuropathies are often more common than expected in patients with collagen disease. Early subclinical neuropathies may be difficult to diagnose where symptoms from joint pain may mask the diagnosis. Widespread vasculitis including vasculitis of the vasa nervora may be the underlying pathology, which stresses the value of steroids in treatment.*

Key words: Collagen disease- neuropathy- somatosensory evoked potentials.

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INTRODUCTION

The central and the peripheral nervous systems are often affected in patients with connective tissue diseases and sensorimotor neuropathies have been reported in patients with known or suspected connective tissue diseases [1].

In systemic lupus erythematosus (SLE), neurological involvement is common and neuropsychiatric lupus erythematosus (NPLE) is recognized to occur in a significant percentage of SLE patients and to be a leading cause of morbidity and mortality [2]. However, manifestations of the peripheral nervous system (PNS) involvement seem to be less prevalent and not so well characterized as compared to the central nervous system (CNS) [3].

In juvenile rheumatoid arthritis (JRA), neurological disorders are reported to occur in 10-15% [4]. The nervous system may be involved by compression neuropathy (e.g. carpal tunnel syndrome), peripheral neuropathy, or occasionally cervical cord compression [5].

It is often difficult to diagnose these slight or early neuropathies, and the study of the peripheral neuromuscular system is often made difficult by symptoms resulting from pain in the joints and limitation of movement. It is nevertheless possible by means of electroneurophysiological studies to show objectively the existence and distribution of even subclinical neuropathies, and give an idea about central nervous system affection [6].

The aim of the study was to investigate the central and peripheral nervous systems' involvement in patients with pediatric-onset SLE and JRA through clinical examination and neurophysiological studies namely motor nerve conduction velocity (MNCV) of the tibial nerve bilaterally and somatosensory evoked potentials (SSEPs) of the median nerve bilaterally and to study their relation to clinical data and laboratory investigations.

METHODS

This study was a case-control one carried out at the Pediatric Allergy and Immunology Outpatient Clinic, Children's Hospital, Ain Shams University. It included 34 patients with SLE and JRA, who were attending the clinic regularly.

The patients were divided into two groups:

Group I:

It included 19 patients with pediatric-onset SLE fulfilling the 1982 American Rheumatism Association Revised Criteria for diagnosis of SLE [7]. They were all females, their ages ranged from 12-18 years, with a mean age of 14.47 ± 3.94 years and a mean disease duration of 5.5 ± 4.15 years.

Group II:

It included 15 patients with JRA fulfilling the 1987 American Rheumatism Association Revised Criteria for diagnosis of rheumatoid arthritis [8], with a male to female ratio of 7:8; their ages ranged from 7-18 years, with a mean age of 13.3 ± 3.9 years, and a mean disease duration of 5 ± 3.9 years.

Exclusion criteria:

Patients with other causes of peripheral neuropathy such as diabetes mellitus, genetically determined neuropathy, and chronic abuse of drugs, apart from those prescribed for JRA and SLE.

Control group (Group III):

A group of 10 clinically healthy children were selected from the same general population to which the patients belong; their ages ranged from 6 to18 years, with a male to female ratio 4:6.

Clinical evaluation

Activity of SLE was measured by the Disease Activity Index (SLE-DAI) score [9].

Neuropsychiatric SLE (NPLE) was defined when a significant and unequivocal change in the baseline neurological and/or psychiatric function was identified by history and physical examination [10]. Evidence of cutaneous vasculitis is included if any of the following skin lesions were present: purpura, ulcers, subcutaneous nodules or livedo reticularis [10].

Laboratory investigations

Including measurement of C3, C4, ANA and anti-DNA, as well as complete blood count (CBC), ESR, complete urine analysis, liver and kidney function tests.

Neurophysiological studies

All the patients and controls were subjected to motor nerve conduction velocity (MNCV) study of the tibial nerve bilaterally and somatosensory evoked potentials study (SSEPs) of the median nerve bilaterally

- MNCV of the tibial nerve :

The apparatus used was counter point MK2 (Dantec, USA). The bipolar stimulator is placed on the anatomical sites of posterior tibial nerve. A maximal stimulus that can be tolerated by the patient without eliciting muscle artifact was applied; distance between site (1) and (2) is measured in cm, then MNCV is calculated. MNCV was considered abnormal if the value was two or more SD below the mean control values.

- SSEPs of the median nerve:

The apparatus used was counterpoint MK2 (Dantec, USA). Recording active and reference electrodes was put in 3 channels:

1. Epi-Epc channel: (Erb's point ipsilateral-Erb's point contralateral).
2. C5SP-Fz channel: (fifth cervical spinous process - mid-frontal zone).
3. Cc-Fz channel: (contralateral somatosensory cortex-mid-frontal zone).

The grounding electrode was placed on the arm just above the stimulating electrode. A series of negative potentials were recorded from Erb's point (N_9), 5th cervical spine (N_{13}), and scalp (N_{20}) using a bipolar stimulating electrode placed on the median

nerve 1cm proximal to the wrist crease (between tendon of flexor carpiradialis and palmaris longus).

The stimulus wave was square pulse 0.2 msec in duration at a rate of 1.5 Hz and delivered with sufficient intensity to cause thumb twitch.

The SSEPs from upper limbs were considered abnormal if the following occur:

1. Prolonged N_{13}-N_{20} inter-peak latency (IPL) i.e. central conduction time (CCT) beyond 2SD of the mean value of the control group.
2. Prolonged Erb-N_{13} inter-peak latency beyond 2SD of the mean value of the control group [11].

Statistical methods

The methods of statistical analysis of the collected data were the following:

1. Mean (x) and standard deviation (SD).
2. The student t-test of significance for comparison between the mean of the different groups of patients.
3. Mann Whitney test (Z test) to compare between non parametric data with wide variability and high standard deviation.
4. Linear regression analysis: the correlation coefficient.
5. Chi-square was used for categorial variables to test differences between groups.

RESULTS

SLE group: On the basis of history and neurological assessment, definite symptoms of neuropsychiatric involvement attributable to SLE disease were found in 7 of the patients (37%), hence considered as affected by NPLE. Neuropsychiatric symptoms included: picture suggestive of peripheral neuropathy (numbness, weak hand grip) in 6 patients (86%), stroke in two (28%), seizures in one (14%), anxiety in one (14%), and depression in one (14%).

Six patients (31.5%) were considered as having lupus nephritis (persistent proteinuria more than 0.5 gm/dl and/ or cellular casts (red blood cell, hemoglobin, granular, tubular or mixed), of whom 2 patients had impaired renal function (Table 1). The SLEDAI score ranged between 12 and 46, with a mean of 19.5 ± 8.6.

MNCV of the tibial nerve bilaterally:

Of the patients with SLE, two (10.5%) had abnormal MNCV (>2 SD below the mean control value) on the right side (Table 2).

The mean values of MNCV of the tibial nerve were lower in patients with SLE, significantly so in right tibial nerve (mean value: 44.3±4.0 m/sec in SLE patients compared to 47.8±4.3 m/sec in the control) ($t=2.16$, $p<0.05$) (Fig 1).

Though there was no significant difference in the MNCV when comparing patients with renal affection or with hypertension to those without, SLE patients with cutaneous vasculitis showed lower mean values of MNCV of tibial nerve bilaterally (42.7±2.79, and 42.8 ± 2.85 on the right and left sides, respectively) , with a statistically significant difference ($t=3.7$, $p= 0.0018$) on the left side when compared to those without cutaneous vasculitis (46.01±4.59 and 47.68±3.1) (Fig 2). On the other hand, SLE patients without neuropsychiatric symptoms had a significantly lower mean value of MNCV of tibial nerve on the left side (43.83± 3.26 m/sec) compared to the symptomatic group (46.64±4.29 m/sec) ($t=2.19$, $p<0.05$). There was a negative correlation between MNCV of left tibial nerve and duration of illness ($r = -0.52$, $p< 0.05$), as shown in Figure (3).

Table (1): Descriptive data of SLE patients (n=19)

Sex (f/m)	19/0
Age (years) Mean ± SD	14.47 ± 3.94
Age at onset (years) Range Mean ± SD	 7-16 10.95 ± 2.3
Disease duration (years) Range Mean ± SD	 1-13 5.53 ± 4.15
Hypertension n(%)	7/19 (37%)
Cutaneous vasculitis n(%)	10/19 (53%)
Neuropsychiatric lupus n(%)	19.53 7 (37%)
Renal involvement n(%)	6/19 (31.5%)
SLEDAI score Range Mean ± SD	 12-46 19.54 ± 8.55
Cumulative dose of steroids (mg/m^2) Range Mean ± SD	 600-64850.3 29316.7 ± 26391.91
Cytotoxic therapy n(%)	5/19 (26%)

Table (2): The frequency of abnormalities in absolute values of electroneurophysiological studies (>2SD of control values)

Study	SLE (Right)	SLE (Left)	JRA (Right)	JRA (Left)
MNCV (m/sec)	2/19 (10.5%)	0/19 (0%)	1/15 (6.6%)	0/15 (0%)
SSEPs (m.sec) Erb-N13	2/19	6/19	1/15	2/15

N13-N20	(10.5%) 4/19 (21%)	(31.5%) 6/19 (31.5%)	(6.6%) 1/15 (6.6%)	(13.3%) 3/15 (20%)

SSEPs of the median nerve bilaterally:

With regards to the SSEP parameters, Erb-N_{13} interpeak latencies were prolonged in 10.5% and 31.5% of the median nerves studied on the right and left sides, respectively, while the central conduction time (N_{13}-N_{20}) was prolonged in 21% and 31.5%, respectively (Table 2). The results of our study revealed no prolongation in the mean values of any SSEPs interpeak latencies in the SLE group when compared to the control group.

Neither hypertension nor renal involvement significantly affected the SSEPs parameters in SLE patients. However, SLE patients with cutaneous vasculitis showed a significant prolongation of Erb-N_{13} interval on right side and left sides (3.61±0.74 and 2.31±1.36 m.sec, respectively) compared to those without (3.03± 0.33 and 3.89±1.29) (t=2.14 and 2.58, respectively, $p<0.05$) (Table 4).

SLE patients exhibiting neuropsychiatric symptoms showed a significant prolongation of the mean value of Erb-N_{13} on the left side (3.99±1.24 m.sec) compared to those without (2.52 ±1.45) (t= 2.24, $p<0.05$)(Table 3).

Table (3): Comparison between SLE patients with neuropsychiatric symptoms (NPLE) and those without (no-NPLE) as regards MNCV of tibial nerve bilaterally.

MNCV **(m/sec)**	**No-NPLE** (n=12)		**NPLE** (n=7)	
	Mean	SD	Mean	SD
Rt.tibial n.	44.38	2.86	44.2	5.82
Lt.tibial n.	43.83	3.26	46.64	4.29 [a]

[a] p< 0.05 (significant).
Rt. = right, Lt. = left, n.= nerve.

There was a positive correlation between Erb-N_{13} and N_{13}-N_{20} on the right side and SLE DAI score (r = 0.52 and p= 0.02, and r = 0.54 and p= 0.01 respectively) (Fig 4).

JRA patients

Demographic characteristic of JRA patients

Only two patients (13%) gave positive history suggestive of peripheral neuropathy (numbness and weak hand grip), however none had abnormal findings on clinical examination or in the results of the studied parameters (Table 5).

MNCV of tibial nerve

Of the patients with JRA, one patient (6%) had slowed nerve conduction of the right tibial nerve >2SD of the control (Table 2), nevertheless, there was no significant difference in the mean values of MNCV of tibial nerve (bilaterally) between JRA patients and control group.

SSEPs of median nerve bilaterally

Regarding SSEPs of median nerve evaluation of JRA patients, the interpeak latency of Erb-N_{13} was prolonged in 6.6% on the right side and 13.3% on the left side, while N_{13}-N_{20} was prolonged in 6.6% and 20% on the right and left sides, respectively (Table 2).

Table (4): Comparison between SLE patients with cutaneous vasculitis and those without as well as between SLE patients with neuropsychiatric symptoms (NPLE) and those without (no-NPLE) as regards parameters of SSEPs of median nerve.

SSEPs of SLE	**Without Cutaneous vasculitis (n=9)**	**With Cutaneous vasculitis (n=10)**	**No-NPLE (n=12)**	**NPLE (n=7)**
(**m.sec)**	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD
Right Erb-N_{13}	3.03±0.33	3.61±0.74 [a]	3.53± 0.74	3.01± 0.20
Right N_{13}-N_{20}	7.63±2.75	5.69±1.01	7.46± 2.55	5.43± 0.87
Left Erb-N_{13}	2.31±1.36	3.89±1.29 [a]	2.52± 1.45	3.99± 1.24 [a]
Left N_{13}-N_{20}	6.82±1.79	6.72±1.56	7.25± 1.64	5.96± 1.39

[a] $p<0.05$ (significant)

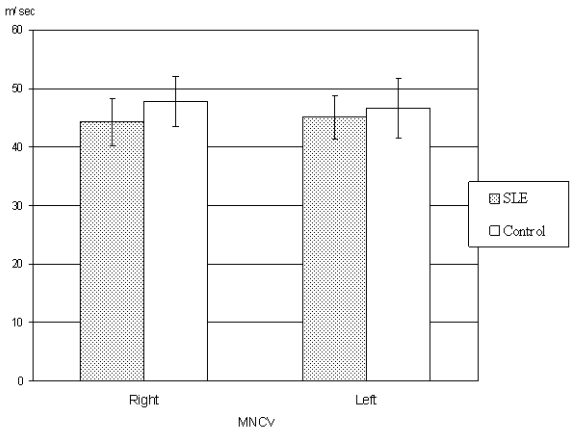
Table (5): Descriptive data of JRA patients (n=15):

Sex (f/m)		8: 7
Age (years)	Range Mean ± SD	7-18 13.3 ± 3.9
Age at onset (years)	Range Mean ± SD	2.5-14 8.3 ± 4.5
Disease duration (years)	Range Mean ± SD	1-14 5 ± 3.9
Hypertension	n (%)	3/15 (20 %)
History suggestive of peripheral neuropathy	n (%)	2/15 (13%)
Steroid therapy	n (%)	10/15 (67%)

Cumulative dose of steroids (mg/m^2)	
Range	0-58500
Mean ±	17037.01 ±
SD	119115.18
Cytotoxic therapy n (%)	6/15 (40%)

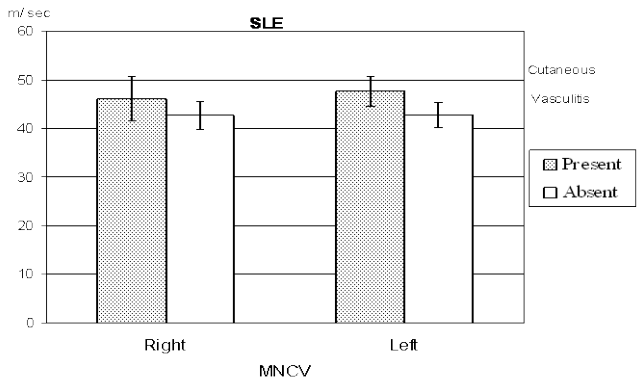
The results of comparison between JRA and control groups revealed no significant prolongation. Similarly, patients with different forms of disease-onset did not show difference in any of the studied parameters.

No significant correlation was found between the neurophysiological studies and the duration of illness. However, a significant negative correlation was found between Erb- N13 (on the right side) and cumulative dose of steroids (r =-0.53, p<0.05) (Fig 5).



p<0.05 on the right side.

Fig(1): Comparison between SLE patients and the control group as regards MNCV (m/sec) of tibial nerve bilaterally.



p< 0.05 on the left.

Figure (2): Comparison between SLE patients with cutaneous vasculitis and those without as regards MNCV of tibial nerve bilaterally.

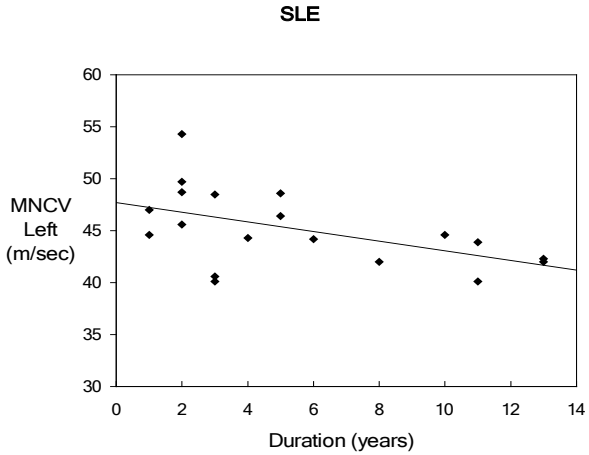


Figure (3): Correlation between MNCV of left tibial nerve and the duration of illness in SLE patients.

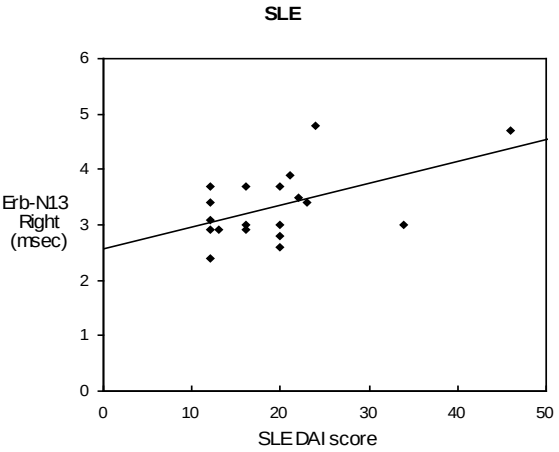


Figure (4): Correlation between Erb-N13 of the right median nerve and SLEDAI score in SLE patients.

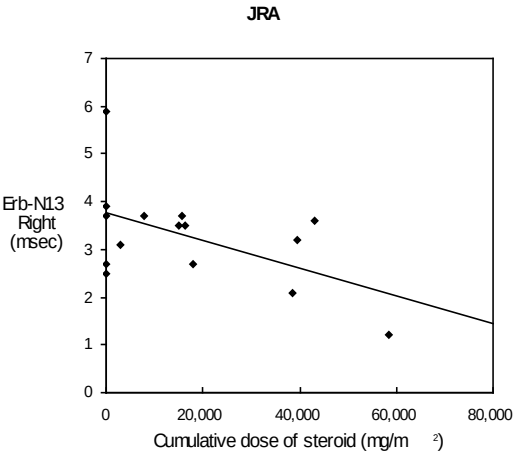


Figure (5): Correlation between Erb-N13 interval of SSEPs of right median nerve and cumulative dose of steroids in JRA patients

DISCUSSION

Studying the neurologic and psychiatric symptomatology in lupus patients, 36% gave positive symptoms and they were referred to as neuropsychiatric lupus (NPLE), this is in agreement with the studies of both Steinlein et al. [12] and Fierro et al. [10], in which NPLE patients represented 43% and 42% of the studied groups, respectively. However, a much higher percentage was found in the study of Schmutzler and colleagues [13], in which NPLE represented 71%.

The most prevalent neuropsychiatric symptoms in our study were symptoms suggestive of peripheral neuropathy (86%), and seizures (78%), while stroke, depression and anxiety were reported each in 14% of patients. This is in agreement with Fierro [9] and associates' study [10] on lupus patients, in which symptoms of peripheral neuropathy were also the most prevalent symptoms (46%), followed by seizures (33%), organic brain syndrome (27%), affective disorders (13%) and lastly stroke in 7%.

Neurophysiological evaluation of SLE patients in our study revealed that MNCV of tibial nerve was delayed (>2SD of the control) in 10.5% of patients. Statistical comparison of MNCV of tibial nerve revealed that their mean values were delayed in SLE patients bilaterally when compared to the control group, significantly so on the right side. These result were in agreement with Omdal et al. [3], and Sivri et al. [14] who reported delay in the NCV of tibial nerve in 15% and 23.6% of their patients, respectively.

In our study SLE patients suffering from cutaneous vasculitis showed delay in the mean values of MNCV of the tibial nerve bilaterally when compared to SLE without cutaneous vasculitis, with a significant difference on the left side. This association was noticed by McNiholl et al. [15], who documented that SLE patients with neurophysiological impairment had a higher frequency of vasculitis, as well as the presence of vasculitis increased the risk of acquiring new neurophysiological abnormalities.

It is of value also to document that the asymptomatic SLE group showed a significant delay in the mean values of MNCV of left tibial nerve when compared to the symptomatic group. This proves that neurophysiological studies can frequently evidentiate subclinical rather than clinical neurological dysfunction in patients with SLE as previously reported by Fierro and colleagues [10].

When correlating MNCV of tibial nerve with clinical data of our lupus patients, there was a negative correlation between MNCV on left tibial nerve and duration of illness. This may represent increased exposure to circulating immune complexes, anti-endothelial and antineuronal antibodies or to other non immune factors as infection, drugs or metabolic derangement. By contrast, in their two studies, Straub and coworkers [1] and Sivri and colleagues [14], found no correlation between NCV and disease duration in lupus.

In our study, the mean values of SSEPs interpeak latencies did not show any significant difference in SLE patients in comparison to the controls. However, Erb-N_{13} latencies were increased above 2SD of the control range in 10.5% on the right side and 31.5% on the left side and N_{13}-N_{20} interval was prolonged in 21.3% on the right side and 31.5% on the left side. By comparison, Fierro et al. study [10], who studied SSEPs only on the right median nerve, found that Erb-N_{13} interval was increased in 25% and N_{13}-N_{20} interval was increased in 28%, while Sivri et al [14], who studied median and tibial nerve somatosensory evoked potential (SSEPs) documented 39.5% of studied lupus patients showing SSEPs abnormalities.

Worth noting is the significant association between cutaneous vasculitis and prolonged Erb-N_{13} interval bilaterally; this was in agreement with the study done by Fierro and coworkers [10]. The evidence of cutaneous vasculitis can suggest a diffuse systemic vasculitis involving the cerebral vessels and vasa-nervora supplying peripheral nerves [16].

The highly significant positive correlation between Erb-N_{13} and N_{13}-N_{20} intervals (central conduction time) on the right side and SLEDAI score proved that SLEDAI scoring can be used to judge CNS involvement in lupus patients as previously suggested by Straub et al.[1].

JRA is a progressive systemic disease that predominately affects the synovial tissues; neurological disorders are registered in 10-15% of cases [4]. The principal neuropathies of RA include nerve compression and a mild distal sensory impairment. These may be manifested only by parasthesia, burning sensation with few objective signs. Patients with prominent joint pain may not specifically complain of additional symptoms such as weakness and parasthesia, which suggest neuropathy[6].

On the basis of history and clinical neurological examination, our study revealed that only two (13%) of our patients with JRA gave neuropathic symptoms, nevertheless careful clinical examination did not support the diagnosis of neuropathy. The MNCV of tibial nerve bilaterally revealed no significant difference when compared to the control group,

however only one patient (6%) had slowed nerve conduction on the right tibial nerve (>2SD of the controls).

In 1986, Puusa et al. [17] studied 129 children with JRA and reported no clinically manifested neuropathy among them. By contrast, Sivri and Guler-Uysal [18], who studied adult patients with RA, documented that symptoms and signs of neuropathy are fairly common in RA. In their study, 6% of patients gave symptoms and signs of carpal tunnel syndrome, while 18% had mononeuritis multiplex. Our results are also much lower than the results of Chang et al.[19], who found 44% acute-subacute mononeuritis multiplex in his RA patient group. The difference from our results may be due to the difference in the age of the included subjects, where these studies were conducted on adults. The suggestion that peripheral neuropathy is more in adult patients with RA than in JRA, may be explained by Puusa et al. [17], who documented that arteritis which involves the arteries supplying the peripheral nerves (vasa-nervora) do not typically occur in JRA even after long period of illness which may be explained by the young age of onset, the prompt and effective initiation of treatment and perhaps a somewhat milder and different clinical picture, compared to adult patients.

As regards SSEPs of median nerve evaluation of JRA patients, though there was no significant difference in the interpeak latencies between the patients and controls, Erb-N_{13} and N_{13}-N_{20} were prolonged in 6.6% on the right side and 13.3% and 20% respectively on the left side.

Few studies have investigated the effect of RA on early somatosensory evoked potential, which reflects spinal cord function and of value in detecting early, sub-clinical lemniscal tract damage [20]. Katz et al. [21] reported that 10 out of 15 RA patients (67%) had abnormalities in SSEPs of the median nerve. Lower percentages were found in the study performed by Naglic et al. [4], who studied 56 patients with RA, all were females and with a mean age of 52 years. They showed increasing N_{13}-N_{20} difference registered in 18%.The difference from our results may again be explained by the different age groups studied in each.

In agreement with Sivri and Guler- Uysal study [18], our study found that neither the mode of disease- onset, nor the type of therapy or the duration of disease did affect any of the studied SSEPs parameters.

However, it is worth reporting the significant negative correlation between cumulative dose of steroids and Erb-N_{13} on right median nerve (pathway from brachial plexus till cervical spinal cord). This implies that the use of corticosteroids in the treatment of neuropathies associated with systemic vasculitis is very efficient [22].

In conclusion, our study revealed that sensorimotor nerves are often more affected than expected in patients with connective tissue disease. Though clinical assessment remains the corner stone of diagnosis, yet by itself, evidently results in under-diagnoses of nervous system involvement especially that early subclinical neuropathies may be difficult to diagnose on clinical basis where symptoms from joint pain and limitation of movements may mask the diagnosis. Widespread vasculitis including vasa nervora supplying peripheral nerves may be the underlying pathology which stresses the value of steroids in the treatment of neurological manifestations due to vasculitis.

We thus recommend routine neurophysiological evaluation of patients with SLE and JRA to detect subclinical neurological dysfunction.

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