Peripheral Neuropathy in Multiple Sclerosis: An Electrophysiologic Study in Iranian Patients

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Abstract- Multiple sclerosis (MS) is the most common cause of disability after trauma in young adults in Northern Hemisphere; it imposes a major burden on the affected young people. A significant association between MS and demyelinating peripheral neuropathy which might be due to common pathogenesis for the central and peripheral nerves demyelination has been reported in several studies. We aimed to assess if there is any peripheral nervous system involvement in a sample of Iranian MS population. Extensive nerve conduction studies (NCS) were conducted in 20 MS patients according to McDonald criteria, and 20 age and gender matched healthy appearing controls. The F-wave ratio was calculated through placing the minimum amount of F-wave proximal latency after 10 stimuli and median or tibial nerves compound motor action potential (CMAP) proximal latency in the corresponding formula. Data were compared between groups. Finally, we found the significantly lower median and tibial nerves conduction velocities (NCV) in MS patients than healthy controls (P=0.008 and 0.003 respectively, Independent Samples t-test). Also, tibial NCV had a significant statistical correlation with Kurtzke's expanded disability scale score (EDSS) as patients with higher EDSS had lower tibial NCV (Pearson's correlation coefficient, r^2=0.8). No statistical relationship was found between MS subtypes and NCS parameters. Although we found some electrodiagnostic abnormalities in Iranian MS patients in comparison to the healthy participants, these differences were small and inconclusive. More extensive well-designed electrodiagnostic studies for evaluation of peripheral nervous system involvement and its probable pattern in these patients seems to be needed.

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Introduction

Multiple sclerosis (MS) is the most common autoimmune inflammatorychronic disease of the central nervous system that is characterized by demyelinization and loss of axonsand the most common cause of disability after trauma in young adults in Northern Hemisphere; it imposes a major burden on the affected young lives. Variable prevalence rate exists in different geographic areas with different races. Possible etiologies include genetic predisposition and environmental factors (1-4). Nowadays, central nervous system involvement is a known problem in MS. Although peripheral nervous system involvement by MS has been suggested for years, different studies have equivocal results, and no specific pattern of peripheral nerve involvement in MS patients has been proved so far.

Pollock *et al.*, (5) found demyelination of the peripheral nerves in the sural nerve biopsy of 10 patients with MS and suggested that the peripheral myelin might be involved in MS. Later, clinicians reported many different cases with concomitant MS and Demyelinating Neuropathy and proposed a significant correlation between MS and demyelinating peripheral neuropathy which might be due to common pathogenesis for the central and peripheral nerve's demyelination (6-9).

In a study of 60 consecutive patients with relapsing-remitting MS, nerve conduction abnormalities suggestive of demyelination were found to be positive just in 5% of the patients. The authors concluded that although the association of chronic inflammatory demyelinating polyneuropathy with MS is not frequent,

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it needs to be recognized as a treatable condition (10).

None of the studies in this field evaluated multiple electro diagnostic parameters including motor and sensory nerves conduction latency and velocity, H-reflex and F ratio simultaneously for assessing peripheral neuropathy. A proximal lesion in the neighborhood of the brachial plexus or root level (the pathology which is common in demyelinating processes like Guillain-Barre syndrome) may be amenable to diagnosis by the use of F-waves (11). The F-wave conduction velocity has been reported to be of value in detecting proximal slowing in various disease states affecting the peripheral nervous system. Because of the potential for distance measurement errors in calculating F-wave conduction velocities, an alternative F-wave technique-F ratio-was developed that does not involve distance. Motor nerve and F-wave conduction velocities may both be abnormal; yet, the F ratio can be within normal limits. This suggests that not only peripheral nerves are conducting slowly over both the distal and proximal segments, but also they are slowed to a similar degree (9).

We aimed to use multiple electro diagnostic parameters paying particular attention to the F ratio to determine if there is any association between MS and peripheral nervous system involvement in Iranian MS cases compared to the age and gender matched healthy appearing controls. The hypothesis is that there may be differences in some nerve conduction parameters between these groups.

Materials and Methods

Patients with the diagnosis of MS according to McDonald criteria referred to our university clinic who said they were interested in participating in the research were included if they didn't have any of the following conditions:

- Having a high degree of disability (Kurtzke's expanded disability scale score (EDSS)>8)
- Having a high degree of weakness (muscle power<4/5)
- Concurrent diabetes mellitus disease
- Using certain medications for neuropathy treatment such as gabapentin, pregabalin, etc.
- Suffering from radicular symptoms (radicular neck or low back pain or positive findings regarding radiculopathy in the cervical and lumbosacral Magnetic Resonance Imaging)
- Having a history of neuropathy before multiple sclerosis

Twenty age and gender matched healthy appearing controls among volunteers working in our hospital were also included. Every participant signed an informed consent form, and the study protocol was approved by our university ethics committee, conforming to the ethical guidelines of the 1975 Declaration of Helsinki. Electro diagnostic tests were performed by a Medelec Synergy electromyography instrument (VIASYS HealthCare, Surrey, UK) with a bar electrode as stimulator, two disposable electrodes as recorder and another disposable electrode as ground. The nerve conduction study consisted of 8 cm trans carpal orthodromic median and ulnar motor nerve latencies and amplitudes, median motor nerve proximal latency from the elbow stimulation and forearm velocity, 14 cm antidromic median and ulnar sensory nerve, superficial peroneal and sural nerves latencies and amplitudes, tibial nerve distal latency and amplitude, tibial proximal latency with stimulation at popliteal fossa, and leg velocity. Also, H-reflex from gastrocnemius muscle and F-Wave proximal latency from the median and tibial nerves (with stimulation at the antecubital and popliteal fossa, respectively) were recorded. Skin temperature during all studies was at least 31° C and all examinations were done in rooms with similar constant temperatures between 23° C and 25° C.

The F-wave ratio was calculated through placing the minimum amount of F-wave proximal latency after 10 stimuli and median or tibial nerves compound motor action potential (CMAP) proximal latency in the following formula(11):

F-ratio= (F-wave latency-CMAP latency-1 ms)/ (CMAP latency×2)

Data were analyzed with SPSS software, version 16. We used Pearson's correlation coefficient and independent samples *t*-test for comparison of the variables between the groups.

Results

Among 20 subjects recruited in each group, 65% were females. The mean age was 32.70±9.02 years for MS patients and 30.20±8.79 years for healthy controls. There was no statistical difference between the two groups regarding the age (P=0.425), gender and height (P=0.358).

Patients had a mean EDSS of 3.12±2.44. The mean duration of the disease was 4.72±3.54 years among these subjects. The most prevalent MS type was the relapsing-remitting with 65% of the patients (13) suffering from this type. Four patients (25%) had primary progressive

MS, two (10%) had secondary progressive type, and one (5%) had progressive relapsing type.

After comparing the CMAP parameters, we found a significantly different median and tibial nerves conduction velocity between the groups as there were lower velocities in MS patients than healthy controls (*P*=0.008 and 0.003 respectively, Independent Samples *t*-test, Table 1).

Table 1. Comparison of the median and tibial nerves CMAP parameters between the groups

	MS patients	Healthy controls	*P*
Median DL(ms)	3.4±0.9	3.3±0.5	0.455
Median AMP(mv)	13.4±0.5	14.1±0.4	0.255
Median CV(m/s)	56.1±3.5	58.3±6.2	0.008
Tibial DL(ms)	4.3±0.7	4.4±0.8	0.245
Tibial AMP(mv)	5.1±0.5	5.9±1	0.159
Tibial CV(m/s)	45.5±3.5	47.1±6.1	0.003

Abbreviations: CMAP: Compound muscle action potential, DL: Distal latency, AMP: Amplitude, CV: Conduction velocity, ms: millisecond, mv: millivolt, m/s: meter/second

Also, tibial nerve conduction velocity (NCV) had a significant statistical correlation with EDSS score as patients with higher EDSS score had lower tibial nerve conduction velocities (Pearson's correlation coefficient, r^2=0.8, Figure 1).

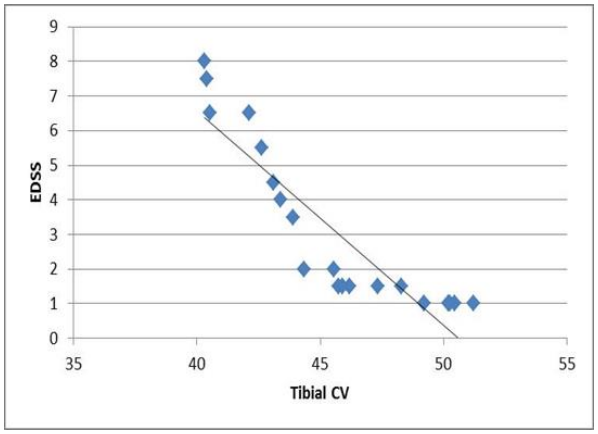

Figure 1. Correlation between Kurtzke's expanded disability scale score (EDSS) and tibial nerve conduction velocity

Other CMAP parameters, sensory nerve action potential (SNAP) parameters, and late responses were measured and after between group analyses no significant statistical difference was found (Tables 2- 4).

No evidence of conduction block or abnormal temporal dispersion was seen in any group. In two young female MS patients (29 and 42 years old), the H-reflex was bilaterally absent. Considering their age might encourage us to emphasize it.

No statistical relationship was found between EDSS and other nerve conduction study (NCS) parameters; also, there was no statistically significant correlation between MS subtypes and NCS parameters.

Table 2. Comparison of the upper limb nerves SNAP parameters between the groups

	MS patients	Healthy controls	*P*
Median DL(ms)	3.23±0.26	3.39±0.41	0.325
Median AMP(mv)	26±1.5	27.1±1.1	0.564
Median CV(m/s)	50.3±7.11	48.35±7.07	0.482
Ulnar DL(ms)	3.1±0.2	3.2±0.2	0.153
Ulnar AMP(mv)	25.5±2.2	26.1±1.9	0.435

Abbreviations: SNAP: Sensory nerve action potential, DL: Distal latency, AMP: Amplitude, CV: Conduction velocity, ms: Millisecond, mv: Millivolt, m/s: Meter/second

Table 3. Comparison of the lower limb nerves SNAP parameters between the groups

	MS patients	Healthy controls	*P*
SPN DL(ms)	2.38±0.3	2.36±0.3	0.517
SPN AMP(mv)	14.5±2	15.4±0.9	0.305
Sural DL(ms)	2.5±03	2.4±0.3	0.568
Sural AMP(mv)	22.1±1.5	23.1±2	0.450

Abbreviations: SNAP: Sensory Nerve Action Potential, DL: Distal latency, AMP: Amplitude, ms: Millisecond, mv: Millivolt

Table 4. Comparison of the median and tibial nerves late responses between the groups

	MS patients	Healthy controls	*P*
H-reflex latency (ms)	29.8±2.2	29.1±2.2	0.321
Median F latency (ms)	21.92±2.019	21.29±1.74	0.147
Tibial F latency (ms)	39.96±1.34	39.55±1.62	0.192
Median F-ratio	1.06±0.2	1±0.18	0.955
Tibial F-ratio	1.02±0.2	1.01±0.11	0.080

Abbreviations: ms: Millisecond

Discussion

We could find just a significant statistical correlation between MS and peripheral motor nerve conduction slowing in the tibial and median nerves; however, the difference between MS and healthy individuals regarding the median and tibial NCV parameters was very little (only 3.92% and 3.51%, respectively). Although bilateral absence of H-reflex can be seen in the normal elderly, observing it in two young MS cases who were recruited after careful investigation to exclude the patients suffering from radiculopathy according to MRI studies or those with a history of neuropathy before multiple sclerosis-compared to the healthy controls besides motor nerve conduction slowing might support the hypothesis of peripheral nervous system dysfunction in this population. Although these limited data are in favour of peripheral nerve involvement even under the circumstance of normal distal latency of the studied nerves, small sample size as well as the small difference between the groups makes this conclusion much difficult because it might be just the result of unintentional enrollment of cases from one end of normal distribution curve and controls from the other.

In a survey by Anlar *et al*., (12), the most frequent electrophysiological abnormalities noted in the patient's group were the low amplitude of the ulnar and sural nerves and slow NCV of the tibial and sural nerves. Another study found nerve conduction abnormalities that fulfilled the criteria of demyelination in three out of 60 MS patients. All of them showed multifocal conduction blocks or abnormal temporal dispersions, and prominent slowing of motor nerve conduction velocities in almost all the nerves examined (10). Although we examined four sensory nerves (median, ulnar, sural and superficial peroneal) in contrast to three motor nerves (median, ulnar and tibial) since sensory nerves are more sensitive to peripheral polyneuropathic changes and according to a previous report regarding the more exaggerated sensory abnormalities than motor ones in multiple sclerosis (13), we could not find a significant difference regarding the sensory nerve electrophysiologic parameters between MS patients and healthy controls. Many other studies have reported either motor or sensory nerve conduction abnormalities (14-16).

A recent study on Iranian patients with a relapsing-remitting or secondary progressive pattern of MS reported some electrodiagnostic abnormalities in these patients, but it had the important limitation of having no control group (17). Authors compared electrodiagnostic parameters findings with the mean of the normal population that was based on previous studies. Thus, this survey is subject to a major bias due to some difference in the nerve conduction parameters in different populations with different races. Therefore, they proposed future studies with matched control groups.

We found a significant statistical relationship between EDSS and tibial nerve conduction velocity, the finding which has not been obtained by Anlar *et al*., (12) who reported that the neurological disability was not associated with the presence of electrophysiological

abnormalities.

Prolonged F wave latency in median, peroneal and tibial nerves has been previously reported by Pogorzelski and colleagues (13). Also, Sarova-Pinhas *et al*., (15) found prolonged F-wave response as one of the most frequent electrophysiologic abnormalities in MS subjects. Argyriou *et al*., (18) reported higher mean and maximum F-wave amplitude values in secondary progressive MS patients with spastic hemiparesis and hand spasticity than controls who were patients with remitting-relapsing MS without any evidence of hand spasticity and 20 age- and gender-matched healthy volunteers. We could not find such results; it might be due to small sample size which made us unable to categorize patients according to muscle tone and compare their F wave parameters between categories.

We used F ratio to assess the pattern of probable peripheral nerve involvement in MS for the first time and although different conduction velocities between groups were seen in the median and tibial nerves and mean F ratio was slightly higher in MS patients, we could not find any statistically significant difference between MS patients and healthy subjects regarding this NCS parameter. Previous studies proposed that co-occurrence of peripheral multifocal demyelinating neuropathies and MS can be due to extending MS lesions beyond the root entry zones and also the frequent involvement of the proximal portions of the spinal and cranial nerve roots (19). Our findings regarding F ratio precluded the further establishment of the theory which suggests more proximal than distal peripheral nerve involvement in MS patients. On the other hand, we cannot negate this theory by such limited study in which small sample size is a major limitation. Another serious limitation is that the patient's group was not a relatively homogenous group with variable disease duration and disease severity which might interfere with the interpretation of the study results.

Although it seems that MS patients have more tendencies for the development of peripheral nervous system pathology according to the electrodiagnostic studies, there are no large epidemiological studies yet to confirm this concept. We recommend performing further well-designed electrodiagnostic studies on this population to provide conclusive evidence regarding the peripheral nervous system involvement and its probable pattern in MS patients.

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