

Research Article

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Axonal Neuropathy in Multiple Sclerosis Patients Treated with Interferon β

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Abstract

Introduction: Peripheral neuropathy has been reported as a rare side effect of interferon α (INF α) but not with interferon β (INF β) treatment.

Objectives: In the current study we aimed at studying the risk of occurrence of neuropathy as well as its pattern in a group of multiple sclerosis (MS) patients receiving INF β .

Methods: We studied the clinical manifestations and electrophysiological pattern of peripheral neuropathy in two groups of multiple sclerosis (MS) patients group I involved 12 patients receiving interferon β and group II involved 28 patients receiving cytotoxic medications.

Results: We revealed electrophysiological abnormalities of nerve conduction suggesting axonal sensory-motor neuropathy in 7 patients (58.3%) out of 12 receiving INF β in contrast to only 5 patients (17.85%) out of 28 patients receiving cytotoxic medications. This was associated with minimal sensory symptoms.

Conclusion: Despite the protective effects of INF β against induced autoimmunity the administration of the drug may trigger auto immune phenomena in immunologically predisposed patients which may interfere with the biosynthetic process of neurons thus inducing dysfunction. We conclude that INF β may cause subclinical axonal neuropathy as a side effect due to autoimmunity.

Keywords: Multiple sclerosis; Neuropathy; Interferon β

Abbreviations: MS: Multiple Sclerosis; CNS: Central Nervous System; PNS: Peripheral Nervous System; MBP: Myelin Basic Protein; MAG: Myelin-associated Glycoprotein; NCS: Nerve Conduction Studies; INF β : Interferon β ; MRI: Magnetic Resonance Imaging; CV: Conduction Velocity; CMAP: Compound Motor Action Potential; SNAP: Sensory Nerve Action Potential; MS: milliseconds; mV: Millivolts

Introduction

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS) [1]. The pathology of multiple sclerosis is the demyelination of central neurons however the patients may have neuropathic pain in distal extremities related to A-delta (myelinated) and C (non myelinated) fiber dysfunction.

The peripheral nervous system (PNS) involvement in MS may be more frequent than is generally assumed. Patients with MS may have very mild peripheral neuropathic symptoms where only subclinical (electrophysiological) signs can be established. Peripheral neuropathy in combination with MS was documented by several authors and it remains unclear if they are part of the same entity (as common antigens between the CNS and PNS, such as myelin basic protein (MBP) and myelin-associated glycoprotein (MAG) were suspected to be pathogens of the coexisting MS and peripheral neuropathy) or coincidental findings. When present they are usually attributed to factors associated with advanced disease, such as malnutrition, immobilization or cytotoxic drugs [2].

In the present study we evaluated the clinical manifestations and the electrophysiological changes with nerve conduction studies (NCS) in 2 groups of MS patients, group taking interferon β (INF β) and other group on cytotoxic drugs (Cyclophosphamide and Corticosteroids).

Patients and Methods

Forty patients diagnosed with definite MS according to the McDonald criteria 2010, were recruited from multiple sclerosis clinic at

Ain Shams University Hospital. Each case was documented by means of MRI examination. Relapsing remittent course of MS was established in all patients. The age of the patients varied between 21 and 50 years. Patients with diseases that can develop neuropathy such as diabetes mellitus, thyroid pathology, renal and hepatic failure, and alcohol abuse were excluded from the study. We grouped patients into two groups; group I involving 12 patients receiving INF β (Rebif®) in a dose of 44 mcg injected subcutaneously three times per week and group II involving 28 patients receiving cytotoxic medications. Cyclophosphamide in a dose of 750 mg/m²/month (maximum dose 1 gram/month) given slowly by intravenous infusion combined with methyl prednisolone 1 gram/month. Regarding the duration of treatment: In Group I, the mean duration of treatment with INF β was 42 months and the maximum duration of treatment was 60 months and for Group II, the duration of treatment with Cyclophosphamide ranged from 6 to 24 months (mean 15.3 \pm 5.5) with the longest duration of treatment (30 months) in only one patient.

The clinical manifestations and electrophysiological pattern of the peripheral neuropathy were studied in all patients by evaluation of neuropathic symptoms and signs, and electrophysiological studies. We performed NCS using the Nicolet® VikingQuest™ Machine from Natus Neurology Incorporated (natus), USA (missing year of manufacture). NCS was done for all patients in the fibers of median, ulnar, common peroneal, posterior tibial and sural nerves. In the NCS we studied the distal latencies, nerve conduction velocities in the motor and

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sensory fibers, amplitude of the compound muscle action potential, and amplitude of the sensory potentials and latency of the F-waves. According to Wang and Robinson Neuropathy is defined by the NCS as either Sural nerve distal latency above 02.55 ± 0.51 milliseconds (ms) or Ulnar nerve sensory distal latency above 02.55 ± 0.51 ms or Ulnar nerve motor distal latency above 02.46 ± 0.32 ms, or Ulnar nerve Conduction Velocity (CV) less than 55.87 ± 3.15 meters per second (m/s) or Tibial nerve motor distal latency above 04.79 ± 0.32 ms, or Tibial nerve CV less than 46.40 ± 2.23 m/s [3]. Axonal affection of the Ulnar nerve is defined by have Compound Motor Action Potential (CMAP) less than 11.14 ± 1.28 Millivolts (mV) and axonal affection of the Tibial nerve is defined by having CMAP less than 06.68 ± 0.71 mV (Table 1).

Results

Mean age of patients in group I (patients receiving INF β) was 34.2 years, while that of patients in group II (patients receiving cytotoxic medications) was 31.8 years; the difference was statistically insignificant ($P>0.05$). Four out of 12 patients (33.3%) in group I and 7 out of 28 patients (25%) in group II had mild symptoms in the form of mild tingling of their feet and hands, yet, with no objective signs suggestive of neuropathy. Electrophysiological signs of subclinical neuropathy were detected rather more often. Electrophysiological changes were established in 7 patients in group I (58.3% of cases), with 4 patients of them (57%) only reporting mild symptoms of tingling and numbness in feet and hands, yet, with no clinical signs (Table 2). On the other hand, electrophysiological signs of subclinical neuropathy were established only in 5 patients in group II (17.85% of cases), with 4 patients (80%) reporting mild symptoms of tingling and numbness in both hands and feet, and again, this was not accompanied by clinical signs (Table 3). This difference was statistically significant ($P<0.05$).

Electrophysiological changes are consistent with axonal neuropathy (reduction in amplitude of CMAPs and sensory nerve action potential SNAPs; with normal distal motor and peak sensory latencies and normal conduction velocities) in all patients in the 2 groups except 1 patient

Nerve	NCS Parameters	Mean \pm SD for males	Mean \pm SD for females
Sural	Distal Latency (ms)	02.47 ± 0.57	02.55 ± 0.51
	Amplitude (mV)	15.63 ± 3.47	15.77 ± 2.23
	Conduction velocity (m/s)	50.02 ± 3.45	50.82 ± 3.95
Ulnar Motor	Distal Latency (ms)	02.44 ± 0.36	02.46 ± 0.32
	Amplitude (mV)	11.38 ± 0.87	11.14 ± 1.28
	Conduction velocity (m/s)	55.58 ± 3.33	55.87 ± 3.15
Median Motor	Distal Latency (ms)	03.53 ± 0.51	02.84 ± 0.72
	Amplitude (mV)	11.82 ± 0.48	11.76 ± 0.71
	Conduction velocity (m/s)	53.62 ± 0.49	53.57 ± 0.71
Ulnar Sensory	Distal Latency (ms)	02.90 ± 0.36	02.91 ± 0.32
	Amplitude (mV)	26.73 ± 0.48	26.69 ± 0.71
	Conduction velocity (m/s)	56.52 ± 0.48	56.47 ± 0.71
Median Sensory	Distal Latency (ms)	03.05 ± 0.55	03.01 ± 0.53
	Amplitude (mV)	35.21 ± 5.46	35.26 ± 6.23
	Conduction velocity (m/s)	56.93 ± 3.47	56.20 ± 3.38
Peroneal Motor	Distal Latency (ms)	04.14 ± 0.36	04.16 ± 0.32
	Amplitude (mV)	05.37 ± 0.97	04.40 ± 0.86
	Conduction velocity (m/s)	49.03 ± 9.01	50.38 ± 6.91
Tibial Motor	Distal Latency (ms)	04.77 ± 0.36	04.79 ± 0.32
	Amplitude (mV)	06.22 ± 0.48	06.68 ± 0.71
	Conduction velocity (m/s)	45.52 ± 3.04	46.40 ± 2.23

ms: milliseconds; mV: Millivolts; m/s: meters per second; SD: Standard Deviation
Table 1: Normal NCS parameters for males and females.

Patients	Age	Type	Nerves	Clinical Symptoms
Patient 1	30	Axonal	Peroneal, Sural	No
Patient 2	22	Axonal	Peroneal, Sural	No
Patient 3	21	Axonal	Peroneal, Sural	Yes
Patient 4	42	Axonal	Peroneal, Sural	Yes
Patient 5	50	Axonal	Peroneal, Sural	No
Patient 6	25	Axonal	Peroneal, Sural	Yes
Patient 7	50	Axonal	Sural, Median (sensory), Ulnar (sensory)	Yes

Table 2: Pattern of electrophysiological abnormalities in patients of group I (receiving INF beta).

Patients	Age	Type	Nerves	Clinical Symptoms
Patient 1	52	Axonal	Peroneal, Sural	Yes
Patient 2	23	Axonal	Peroneal, Median, Sural	Yes
Patient 3	37	Mixed	Axonal: Peroneal, Tibial, Sural Demyelinating: Median, Ulnar (S&M)	Yes
Patient 4	33	Axonal	Peroneal, Sural	Yes
Patient 5	33	Axonal	Peroneal, Tibial, Sural	No

Table 3: Pattern of electrophysiological abnormalities in patients of group II (receiving cytotoxic medications).

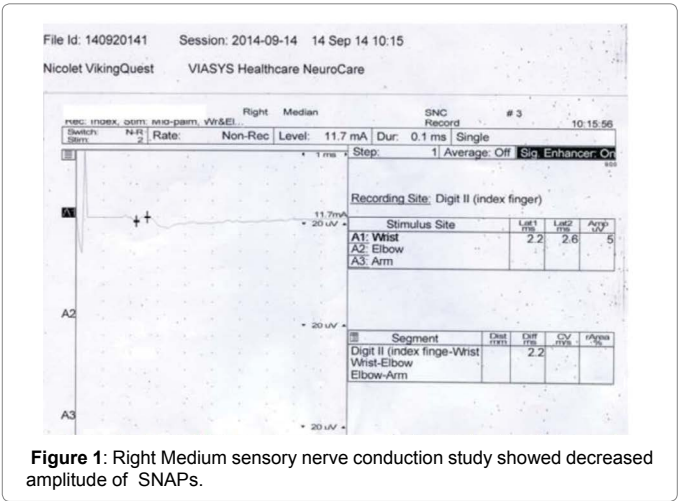


Figure 1: Right Medium sensory nerve conduction study showed decreased amplitude of SNAPs.

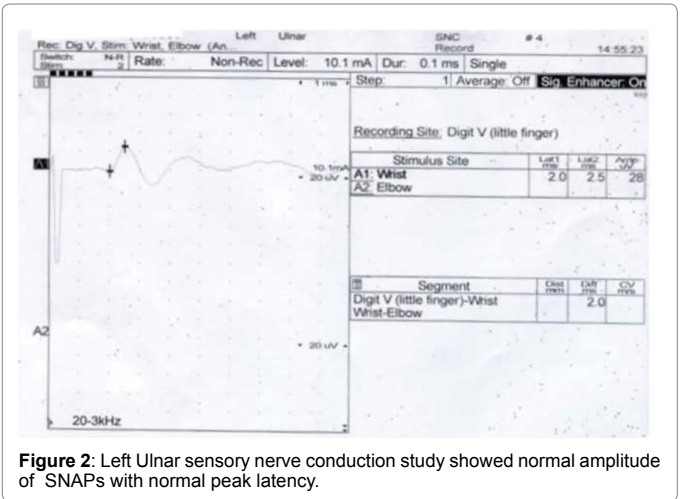
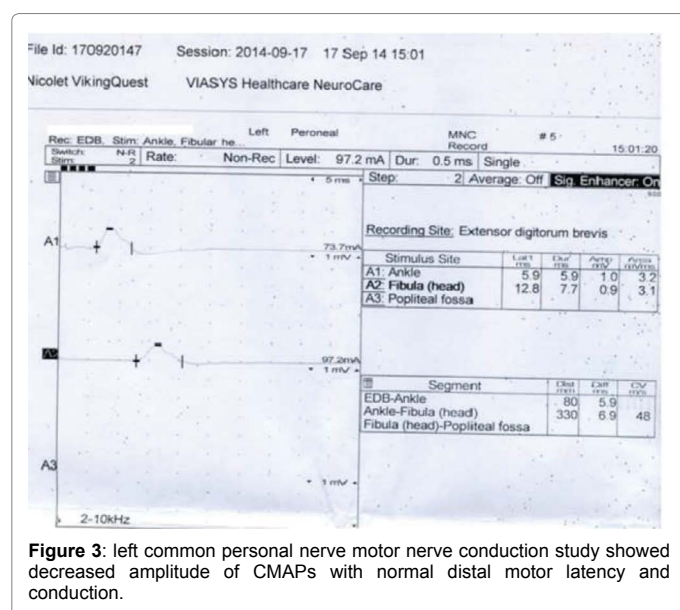


Figure 2: Left Ulnar sensory nerve conduction study showed normal amplitude of SNAPs with normal peak latency.



in group II having mixed (axonal and demyelinating) neuropathy; reduction in amplitude of CMAPs, with prolonged distal motor and peak sensory latencies. Neuropathy involved both motor (Figures 1-3) and sensory fibers. While some patients had normal conduction studies of the nerves of the upper limbs (median and ulnar; sensory and motor) (Figure 2) yet all of them showed affection of the nerves of lower limbs (common peroneal and posterior tibial nerves) which is consistent with length dependent neuropathy.

Discussion

Peripheral neuropathy in combination with MS was documented by several authors and it remains unclear if they are part of the same entity or coincidental findings. It was also reported that patients with neuropathic pain had more severe multiple sclerosis, as assessed by the expanded disability severity score, than those without pain [4].

Peripheral and central myelin have different protein compositions, but they share some proteins such as Myelin Basic Protein and Myelin Associated Glycoprotein therefore an abnormal autoimmune response against a common antigen might cause both MS (Central nervous system demyelination) and Chronic inflammatory demyelinating polyneuropathy (Peripheral nervous system demyelination) [5,6].

Pollock and his colleagues performed sural nerve biopsy on 10 MS, they found a high frequency of abnormal teased fibers and significant reduction of the myelin thickness, suggesting that peripheral myelin may be also involved in MS. Sarova-Pinhas and his colleagues registered electrophysiological abnormalities in 10 out of 22 mildly disabled MS patients [7,8]. In their study, Lisnic and his colleagues revealed clinical signs of neuropathy in 6 patients (12% of cases) out of 50 studied, with electrophysiological abnormalities of nerve conduction suggesting a demyelinating neuropathy in 14 patients (28% of cases) [2]. These findings indicate a high frequency of sensory motor neuropathy in a selected group of MS patients.

Peripheral neuropathy has been reported as a rare side effect of interferon α owing to this drug's ability to increase the anti-inflammatory cytokines, and to decrease TNF- α , also its ability to induce antiganglioside antibodies such as anti-GM1 that is closely associated with various forms of neuropathy like Guillain-Barré

syndrome (subsequent to *Campylobacter jejuni* enteritis) and Multifocal motor neuropathy but not with IFN β treatment. Sural nerve biopsies, performed in some of the cases treated with IFN α , revealed necrotizing vasculitis or axonal degeneration [9-12]. In their study Quattrini and his colleagues revealed axonal polyneuropathy in a man treated with interferon α for chronic hepatitis C [13].

Ekstein and his colleagues assessed six patients with multiple sclerosis who developed polyneuropathy or had exacerbation of previously subclinical neuropathy during treatment with IFN β [14]. In five patients the neuropathy improved after discontinuation of treatment and in two patients it relapsed upon rechallenge. They found that the pattern of neuropathy in their patients is consistent with demyelinating neuropathy in contrast to the fact that toxic neuropathies are rarely demyelinating. This raises the possibility of immune mediated pathogenesis of nerve damage which may result from the pathogenesis of the disease (MS) itself as mentioned before or from the immunomodulatory effects of interferon [13].

In our study, we revealed electrophysiological abnormalities of nerve conduction suggesting axonal neuropathy in 7 patients (58.3%) out of 12 receiving IFN β in contrast to only 5 patients (17.85%) out of 28 patients receiving cytotoxic medications. Neuropathy in our patients was involving sensory and motor nerves, with minimal sensory symptoms.

It has been reported that in vivo and in vitro studies, IFNs amplify auto antibody production and may up regulate gene transcription of class I major histocompatibility complex antigens. Despite the protective effects of the drug against induced autoimmunity, the administration of the drug may trigger autoimmune phenomena in immunologically predisposed patients while suppressing autoimmunity in others. Furthermore, IFNs may also have an inhibitory effect on DNA and RNA synthesis as well as protein metabolism, leading to increased probability of neuronal dysfunction [15].

Finally, we suggest that IFN β may cause subclinical axonal sensory-motor neuropathy which is detected by electrophysiological studies as a result of autoimmunity. Thus screening patients for peripheral neuropathy before starting the treatment with IFN β is important as it may worsen pre-existing neuropathy.

Conclusion

The treatment of MS has come a long way in recent years. Physicians must be aware of possible side effects including peripheral neuropathies in patients who are treated with IFN β as this drug may aggravate pre-existing subclinical neuropathy as well as causing new onset axonal neuropathy.

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