HIGH LIGHT
CME

Polyneuropathy associated with interferon beta treatment in patients with multiple sclerosis

Abstract—Peripheral neuropathy has been reported as a side effect of interferon alpha, but not with interferon beta (IFNβ) treatment. The authors assessed six patients with multiple sclerosis who developed polyneuropathy, or had exacerbation of previously subclinical neuropathy, during treatment with IFNβ. In five patients the neuropathy improved after discontinuation of treatment and in two patients it relapsed upon rechallenge.

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Peripheral neuropathy is a rare adverse effect of interferon (IFN) alpha. Patterns described include chronic inflammatory demyelinating polyneuropathy (CIDP), cranial neuropathy, and mononeuropathy multiplex.[1] In these patients the neuropathy developed either subacutely or with chronic treatment and improved after the discontinuation of IFN. Sural nerve biopsies, performed in some of the cases, revealed necrotizing vasculitis or axonal degeneration.[1] Despite the wide use of interferon beta in patients with multiple sclerosis (MS) only one case of neuropathy caused by local necrosis at the injection site has been reported.[2] We report six patients with MS who developed clinically evident peripheral neuropathy during treatment with interferon beta.

Case descriptions. All patients (table) were diagnosed with clinically definite MS according to Poser's criteria, with a relapsing remitting (RR) or secondary progressive (SP) course. In 3 of 5 checked cases no oligoclonal antibodies were detected in the CSF. Three patients had previously documented mild subclinical peripheral neuropathy and two had had associated immune-mediated diseases (one with a history of ITP and one with alopecia).

We present two illustrative cases. Patient 1 is a woman diagnosed with MS at age 24. The course of her disease was relapsing-remitting (RRMS) for 6 years and then became secondary progressive. At this point, treatment with interferon beta1A-SC (Rebif) was introduced. Six years later, the patient experienced distal hand weakness and atrophy accompanied by weak tendon reflexes. Nerve conduction studies revealed demyelinating sensory-motor neuropathy. The motor distal latency was prolonged (up to 8.2 msec in the right tibial nerve) and the conduction velocities reduced (up to 38.9 m/second in the right tibial nerve). The sensory nerves were even more affected, with conduction velocities as low as 32.3 m/second (in the right ulnar nerve) and less than 38.2 m/second in all the other nerves. EMG showed chronic denervation changes of the right biceps and first dorsal interosseus. Lumbar puncture was normal and after other causes of neuropathy, including thyroid dysfunction, were excluded, interferon treatment was discontinued. Six months later muscle weakness and atrophy improved and the nerve conduction velocities normalized, ranging from 43.7 (left peroneal) to 63.6 m/second (right median). One year after discontinuation of interferon the Achilles tendon deep reflex was still undetectable.

Patient 6 had RRMS since age 24, when she underwent splenectomy for ITP. At age 34, while the course of MS was secondary progressive, interferon beta1A-IM (Avonex) treatment was initiated. Two years later she experienced new onset distal feet weakness, hyporeflexia, and hypoesthesia with "socks"-like distribution. One year later, the nerve conduction study showed demyelination, with distal latencies prolongation (up to 8.4 msec in the right peroneal nerve) and low conduction velocities (as low as 38.1 m/second in the right tibial nerve and up to 42.8 m/second in the right peroneal). At this point, interferon was discontinued. A marked and gradual clinical and electrophysiologic improvement was observed during the 8 months following interferon discontinuation. The conduction velocities in the motor nerves of the legs raised to 42.1 m/second and up to 60.3 m/second (left peroneal nerve). Six months later she had a severe MS relapse. Interferon therapy was readministered (this time IFN beta1B; Betaferon) and again, soon after the initiation of the treatment, distal hypoesthesia was found. In addition a new nerve conduction study, performed 10 months after the initiation of the new treatment, was consistent with the reappearance of peripheral neuropathy: the distal latencies were prolonged (6.7 msec in the right peroneal nerve) and the conduction velocities reduced (42 m/second in the peroneal and 39.7 m/second in the sural nerve).

Discussion. We describe a small series of patients with MS who developed peripheral neuropathy under treatment with interferon beta. A recent study[3] reported an association of neuropathy with interferon treatment in childhood MS. In our series, the neuropathy was at least partially reversible after the discontinuation of the treatment. Moreover, rechallenge with IFN was followed in two patients by reappearance of the symptoms and signs of the neuropathy. Interestingly, the rechallenge caused the relapse of the neuropathy even when a different form of interferon beta (Patient 6) was administered, suggesting that this effect is not specific for only one type of interferon preparation.

The demyelinating pattern of the neuropathy, as demonstrated by the nerve conduction studies in some cases, the high CSF protein in one patient, and the sural nerve biopsy in one patient, together with the fact that toxic neuropathies are rarely demyelinating, raise the possibility of an immune-mediated pathogenesis of the nerve damage, simulating CIDP or acute Guillain-Barré syndrome (GBS). Our findings, although based on a small number of patients, may also indicate that the patients who are more prone to develop neuropathy following treatment with interferon are those with preexisting (subclinical) neuropathy and those with additional immune-mediated diseases.

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Table *Demographic data of the patients and clinical data during IFN beta treatment and after IFN beta discontinuation*

No./sex/ age, y	Course	Neur	Other	OC	IFNβ/yr	On IFN	Off IFN	Rechallenge
1/F/30	RR	No	-	+	1A-SC/6	Distal hands weakness, atrophy, Achilles areflexia, demyelinating signs, chronic denervation on NCS	Improvement in weakness, atrophy, reflexes, almost normal NCS	ND
2/F/41	RR	No	CLL	-	1A-IM, SC/1	Drop-foot, patellar and Achilles areflexia, "socks" hypoesthesia	Recovery of all signs	Reappearance of symptoms signs, demyelinating signs on NCS
3/M/47	SP	Yes	Alopecia	-	1A-IM/3	Severe pain, demyelinating signs on NCS, demyelinating changes in sural biopsy	ND	ND
4/M/54	SP	Yes	-	+	1A-IM/2.5	Distal hands weakness, atrophy, hyporeflexia, mixed signs on NCS	Improvement in atrophy, weakness, NCS	ND
5/F/47	RR	Yes	-	-	1A-IM/1	Foot-drop, distal areflexia, elevated CSF protein, prominent axonal signs on NCS	Improvement in distal weakness and reflexes reappearance	ND
6/F/34	SP	No	ITP	ND	1A-IM, 1B/3	Distal feet weakness, hyporeflexia, "socks" hypoesthesia, demyelinating signs on NCS	Improvement in weakness, reflexes, hypoesthesia, almost normal NCS	Reappearance of symptoms, signs and NCS findings

Neur = previously known neuropathy; OC = oligoclonal bands; IFN = interferon; IFNβ/yr = type of interferon beta/number of years of treatment with interferon before the development of the neuropathy; RR = remitting, relapsing; NCS = nerve conduction study; ND = not done; CLL = chronic lymphocytic leukemia; SP = secondary, progressive; ITP = immune thrombocytopenic purpura.

Interferon alpha has been associated with the aggravation or induction of immune-mediated disorders, such as autoimmune thyroiditis, systemic lupus erythematosus, rheumatoid arthritis, glomerulonephritis, thrombocytopenia, autoimmune hemolytic anemia, sarcoidosis, and psoriasis,[4] putatively by inducing a shift toward the TH2 lymphocyte phenotype. There are also two reported cases of CIDP in patients treated with IFN alpha.[5,6]

Interestingly, few studies reported an association between interferon beta and immune-mediated diseases[7]: these included Raynaud's phenomenon, subacute cutaneous lupus erythematosus, autoimmune hepatitis, and autoimmune thyroiditis. Our findings are in concordance with previous studies suggesting that the induction of immune-mediated diseases by interferon beta occurs mainly in patients with preexisting immune pathology.[7]

The association between MS and peripheral neuropathy in general, and CIDP in particular, has been reported,[8] but its prevalence seems very low and the whole matter remains controversial. In our series, the possibility that the neuropathy represents an incidental finding similar to what is observed in the general MS population cannot be excluded. However, it seems highly unlikely due to the close temporal relationship of IFN treatment and discontinuation with the onset and improvement, respectively, of the clinical and electrophysiologic signs of the neuropathy. Furthermore, a recent article reported an association of neuropathy and interferon beta therapy in children with MS.[3] The neuropathy in these cases responded well to treatment with IVIg, indicating an immune pathogenesis.

Interestingly, interferon beta has been recently successfully applied for the treatment of immune-mediated neuropathies.[9] Is it possible that the same medication may both cause and treat immune-mediated neuropathy? The answer to this question lies within the complicated and delicate balances inside the immune system networks. Immunomodulator agents used for the treatment of an immune-mediated disease may induce or deteriorate the same disease under certain circumstances. For instance, cyclosporin may exacerbate systemic lupus erythematosus (SLE)[10] despite the fact that this medication is among the mainstream treatments of SLE.

Our findings suggest an increased awareness to the development of symptoms or signs indicative of peripheral neuropathy in patients with MS under treatment with interferon beta. Nevertheless, although there are indications in our cases of a causative relation with interferon treatment, a more extensive study is needed

to assess the actual incidence of this important putative side effect of interferon.

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