Exacerbation of Chronic Inflammatory Demyelinating Polyradiculoneuropathy during Interferon β -1b Therapy in a Patient with Childhood-onset Multiple Sclerosis

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Abstract

Interferon β -1b (IFN β -1b) is commonly used for relapsing-remitting multiple sclerosis (MS). We report a 23-year-old woman with childhood onset relapsing-remitting MS treated with IFN β -1b who developed overt chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) immediately after therapy. A baseline conduction study before IFN β -1b therapy revealed decreased motor conduction velocities and prolonged F wave latencies in several nerves, but there was no neurological sign indicating neuropathy. The existence of subclinical demyelinating neuropathy before IFN β -1b treatment was suggested, although the clinical criteria for CIDP were unfulfilled. Following two months of IFN β -1b therapy, numbness of her right upper and lower limbs progressively worsened and all tendon reflexes were depressed. Electrophysiologically, F waves were not evoked in any limbs except for the left ulnar and tibial nerves, which showed marked prolongation of F wave latencies. Moreover, subclinical hyperthyroidism developed in association with high titers of anti-thyroglobulin and anti-thyroid peroxidase antibodies, which were negative before IFN β -1b therapy. These findings indicated that peripheral demyelination worsened at the nerve roots after IFN β -1b therapy. In addition to the development of autoimmune thyroid disease, the patient now fulfilled the criteria for probable CIDP. Along with the results of a previous report demonstrating IFN β -induced CIDP development in patients with childhood MS, this case underscores IFN β as a potential risk factor for CIDP in patients with childhood onset MS.

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Key words: interferon β -1b; chronic inflammatory demyelinating polyradiculoneuropathy; multiple sclerosis

Introduction

The occurrence of multiple sclerosis (MS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in the same subject is uncommon (1–4), yet both are thought to be autoimmune diseases that target myelin. Peripheral nervous system involvement in MS patients has been reported by some authors (5–7). For example, Zee et al (6) conducted a retrospective study on 150 MS patients and found clinical and electrophysiological evidence of radiculopathy in 13 (8%) and peripheral neuropathy in 4 (3%) patients. However, exacerbation of CIDP following IFN β has only been reported by Pirko et al (4). They described three children with MS who responded to interferon- β (IFN β), but developed CIDP that responded to intravenous immunoglobulin (IVIG) administration. It was considered that IFN β treatment somehow contributed to the development of CIDP. This hypothesis is supported by recent reports documenting the onset of CIDP in patients receiving type I IFN (8–10). Here, we report a female patient who developed MS in childhood and underwent interferon β -1b treatment in early adult life, which caused CIDP that was successfully treated by oral corticosteroids.

Case Report

A 23-year-old woman developed left optic neuritis that responded well to IV corticosteroids in 1989 at the age of 10 years. In 1996 she noticed numbness of her right lower limb

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Table 1. Peripheral Nerve Conduction Study of the Patient before and after Interferon β -1b Therapy

	Motor nerve															Sensory nerve					
	MCV (m/s)			DL (ms)			CMAP (mV)			F-No (%)			F-Lat (ms)			SCV (m/s)			SNAP (μ V)		
	Feb	May	June	Feb	May	June	Feb	May	June	Feb	May	June	Feb	May	June	Feb	May	June	Feb	May	June
R. Median	38	37	36	3.4	3.8	3.5	13	13	12	NE	NE	56	NE	NE	44	55	60	61	5	18	23
	(45 ~ 65)			(<4.5)			(4 ~ 25)			(>70%)			(24 ~ 29)			(45 ~ 68)			(10 ~ 60)		
Ulnar	49	47	45	3	2.9	2.8	11	8	6	63	NE	NE	32	NE	NE	48	50	53	8	7	8
	(45 ~ 65)			(<4.0)			(3 ~ 25)						(24 ~ 29)			(45 ~ 65)			(10 ~ 60)		
Tibial	30	46	32	5.1	6	4.8	34	20	25	100	NE	100	53	NE	68	—	—	—	—	—	—
	(40 ~ 60)			(<7.5)									(43 ~ 52)								
Peroneal	47	—	—	6.2	—	—	13	—	—	56	—	—	58	—	—	—	—	—	—	—	—
	(40 ~ 60)			(<7.0)			(7 ~ 40)						(43 ~ 52)								
Sural	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	36	46	40	13	7	12
																			(15 ~ 40)		
L. Median	38	34	37	3.6	3.5	3.3	17	18	17	63	NE	88	32	NE	37	52	61	65	8	20	33
	(45 ~ 65)			(<4.5)			(4 ~ 25)			(>70%)			(24 ~ 29)			(45 ~ 68)			(10 ~ 60)		
Ulnar	45	38	41	3.3	3.5	3	9	10	9	44	100	75	34	37	35	50	52	53	10	3	8
	(45 ~ 65)			(<4.0)			(3 ~ 25)						(24 ~ 29)			(45 ~ 65)			(10 ~ 60)		
Tibial	34	36	35	5.3	4.8	4.1	38	32	27	100	88	100	59	63	61	—	—	—	—	—	—
	(40 ~ 60)			(<7.5)									(43 ~ 52)								
Peroneal	48	40	—	6.1	4.9	—	2.1	4.4	—	44	NE	—	60	NE	—	—	—	—	—	—	—
	(40 ~ 60)			(<7.0)			(7 ~ 40)						(43 ~ 52)								
Sural	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	35	42	44	13	12	9
																(40 ~ 60)			(15 ~ 40)		

MCV: motor conduction velocity, DL: distal latency, CMAP: compound muscle action potential, F-No: F wave evoked frequency, F-Lat: F wave latency, SCV: sensory conduction velocity, SNAP: sensory nerve action potential, NE: not evoked, —: not examined. Normal values are indicated in parentheses.

with mild weakness, which was resolved within 2 months. In May 1999 she developed right facial palsy followed by mild weakness of the right upper and lower limbs. At that time, tendon reflexes in all four limbs were normal. A brain MRI revealed multiple areas of increased signal intensity on T2-weighted images in the periventricular white matter of the bilateral cerebral hemispheres and some showed gadolinium-enhancement. She was thus diagnosed as having MS and she took oral prednisolone (1 mg/kg) with gradual tapering, after which she almost completely recovered except for minimal numbness of her right hand. In March 2002 she once again developed right facial palsy, and again responded well to oral prednisolone, which brought about complete remittance of her symptoms after three weeks of treatment. Eight months later, she developed left followed by right leg numbness. Neurological examination showed mild weakness in the left lower limb with a mild decrease in superficial sensations in both legs. Tendon reflexes were normal in the upper limbs but mildly hyperactive in the lower limbs. The Babinski sign was elicited in her left lower limb. She was once again treated with oral prednisolone, with complete recovery from leg weakness. However, minimal numbness in the distal parts of her left lower limb persisted. Although her illness clinically responded well to prednisolone, a follow-up MRI obtained one month after initiation of corticosteroids

showed new multiple gadolinium-enhancing white matter lesions in the bilateral cerebral hemispheres. From February 2003, she was therefore started on 8×10^6 units of IFN β -1b given subcutaneously every other day. Two months later, she showed a progressive worsening of the numbness in her right upper and lower limbs (Table 1 and Fig. 1).

Neurological examinations revealed temporal pallor of the left optic disc and mild weakness and superficial sensory disturbance in the distal parts of the right upper and lower limbs. Right triceps reflex and both sides ankle jerks were absent, and others were hypoactive. The Babinski sign was elicited bilaterally. Laboratory examinations disclosed an increase of liver enzymes [aspartate transaminase: 46 U/l (normal <33 U/l) and alanine transaminase: 101 U/l (normal <30 U/l)] indicating IFN β -1b-induced liver damage. In February 2003 her baseline thyroid function had been normal [TSH: 2.35 μ IU/ml (0.27<normal<4.20) and free-T4: 1.04 ng/dl (1.00<normal<1.80)] with an upper normal limit of anti-thyroid autoantibody titers. However, at this time, after IFN β -1b therapy, she had subclinical compensated hyperthyroidism (TSH: 0.03 μ IU/ml, free-T4 1.43 ng/dl) and elevated serum autoantibodies against human thyroglobulin (TG) and thyroid peroxidase (TPO) [2,094.5 IU/ml (45 in February 2003) and 167.6 IU/ml (7 in February 2003)]. Anti-ganglioside antibodies and other common autoantibodies

Figure 1. Clinical course of the presented patient.

such as anti-nuclear antibodies, anti-double strand DNA antibodies, anti-RNP antibody, anti-SSA antibody, anti-SSB antibody, anti-Sm antibody and perinuclear and cytoplasmic anti-neutrophil cytoplasmic antibodies were all negative. CSF examination showed 5 nucleated cells/ μ l (all lymphocytes) and an elevated protein level of 81 mg/dl. A baseline conduction study conducted in February 2003 revealed decreased motor conduction velocities and prolonged F wave latencies in several nerves (Table 2), indicating the existence of subclinical demyelinating neuropathy, yet the criteria for CIDP (11) were still not fulfilled. After two months of treatment, however, most of the F waves were not evoked and in the left ulnar and tibial nerves the F wave latencies were markedly prolonged (Table 2). These findings indicated that the demyelinating process had worsened at the nerve roots after IFN β -1b therapy; at this point the patient fulfilled the criteria for probable CIDP (11). As for MS, a brain MRI disclosed multiple small periventricular white matter lesions without gadolinium enhancement (Fig. 2). The number of lesions on the T2-weighted images did not increase compared with those seen in January 2003. A spinal MRI also revealed high signal intensity lesions at the C7 level on the right side and at the T6-7 levels on T2-weighted images (Fig. 2), which were unchanged since February 2003 and not enhanced by gadolinium. Spinal roots including cauda equina were not enhanced by gadolinium. We then discontinued IFN β -1b therapy and treated the patient with oral prednisolone at a dose of 1 mg/kg with a gradual taper. Her weakness was resolved, tendon reflexes were normalized, and sensory

impairment was recovered to her baseline level (Table 1). After corticosteroid therapy, both the F wave evoked frequencies and F wave latencies were markedly improved (Table 2).

Discussion

Although baseline peripheral nerve conduction abnormalities might have partly contributed to the patient's neurologic symptoms prior to IFN β therapy, the preserved tendon reflexes and presence of pathological reflexes together with spinal cord lesions on the MRI suggested that central demyelination was responsible for the earlier neurological symptoms. After IFN β therapy, however, the decreased tendon reflexes and further worsening of peripheral nerve conduction abnormalities suggested that these worsening neurologic symptoms after IFN β therapy were attributable to peripheral demyelination.

The present case is similar to those of Pirko et al (4) in that MS onset occurred in childhood, and that IFN β did not prevent the development of clinically overt CIDP. In their cases, the time lags between the initiation of IFN β and CIDP development were 4 months, 1 year and 4 years, while our patient's CIDP worsened after just 2 months of initiating IFN β therapy, suggesting that in our case IFN β played a role as an exacerbating factor for CIDP. In the present patient, autoimmune thyroiditis also developed after IFN β therapy. IFN β thus appeared to trigger organ-specific autoimmune diseases in our patient. Exacerbation of autoimmune

Figure 2. T2-weighted (A) and gadolinium-enhanced T1-weighted (B) brain MRI and T2-weighted spinal cord MRI (C and D) of the patient at the time of CIDP exacerbation. Note the multiple periventricular lesions without gadolinium enhancement. Arrows show the high signal intensity lesions at the C7 level and at the T6-7 levels. The spinal cord MRI also shows a discrete lesion at the C7 spine level that is not enhanced by gadolinium (not shown).

phenomena has been frequently reported with IFN α (12–15) but not for IFN β (16), but both share a common receptor. Dayal et al (17) reported that IFN- γ secreting cells increased in the early course of IFN β therapy. Moreover, it has been demonstrated by micro-array analysis that IFN β therapy upregulates many Th1 genes (18). In CIDP, CXCL-10 (IP-

10), a chemokine that attracts mainly Th1 cells, has been demonstrated to be elevated in CIDP CSF (19, 20). Moreover, T cells bearing CXCR3, which is a chemokine receptor for CXCL10 and specific for Th1 cells, are shown to mainly infiltrate into the biopsied sural nerves (19). Therefore, in CIDP, Th1 cells are thought to play a crucial

role. Therefore, IFN β might also induce autoimmune diseases targeting peripheral nerve myelin through activation of type 1 cytokines.

The present case together with Pirko's cases (4) suggests that patients with childhood onset MS carry a higher risk of developing CIDP from IFN β administration. Childhood MS reportedly has some distinct clinical and immunological features compared with adult-onset MS, such as a lower frequency of oligoclonal IgG bands in CSF (21), higher CSF cell counts (22), a higher frequency of EEG abnormalities (21), and a higher frequency of relapsing-remitting type (21, 23). Moreover, fever, asthenia, and anorexia are frequently present during the first episode in childhood MS in association with symptoms related to involvement of the spinal cord or cerebellum, suggesting an acute postinfectious autoimmune disorder (22). Such immunological characteristics might also be related to the predisposition for CIDP after IFN β therapy in childhood-onset MS.

The present case further supports the notion that central and peripheral demyelination might have a distinct pathogenic mechanism (4). Although the presence of subclinical peripheral conduction abnormality was uncertain in Pirko's cases (4), initiation of IFN β should be cautiously undertaken in the presence of subclinical demyelinating neuropathy in MS patients, especially in those with childhood onset.

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