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INTERFERON β-1a IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

Case report

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ABSTRACT - Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired immune-mediated neuropathy. It presents with a course of progression which may be slow and steady or step-wise or relapsing. Sensory ataxic polyneuropathy may be the only clinical manifestation of this disease. Treatment with interferon β1a (INF β1a) has been tried with different results in patients who were refractory to other, more conventional, immunomodulatory therapies. Here we report on a patient who had a relapsing form of pure sensory ataxic CIDP and who failed to respond to intravenous human immunoglobulin. He was put on INF β1a for 3 years. During this period he suffered no relapses while his condition stabilized.

KEY WORDS: CIDP, peripheral neuropathy, interferon β (IFN β).

Interferon beta en polineuropatía crónica inflamatoria desmienlinizante: caso clínico

RESUMEN - La polineuropatía crónica inflamatoria desmielinizante (PCID) es una neuropatía inmuno-mediada, que presenta un curso clínico primariamente progresivo o en forma de recaídas. Las manifestaciones sensoriales pueden ser su unica forma de expresión clínica. El tratamiento con interferon beta 1a (IFN β1a) ha sido ensayado en varias oportunidades, con diferentes respuestas terapéuticas, en pacientes refractarios a las terapias inmunomoduladoras convencionales. Nosotros comunicamos un paciente con una forma ataxica recurrente de PCID, que no respondió al tratamiento con inmunoglobulina endovenosa. Posteriormente fue tratado con IFN β 1 a por tres años. Durante el período de seguimiento no mostró nuevas recaídas y su cuadro neurológico se estabilizó.

PALABRAS-CLAVES: neuropatia periferica, interferon beta.

In a recent publication, JM Vallat, et al[1] described the results of using intramuscular (IM) Interferon (IFN) β1a to treat patients with chronic inflammatory demyelinating polyneuropathy (CIDP). The investigators found that this medication had an excellent safety and tolerability profile, and that it lead to a statistically significant improvement in the symptoms of neurological disability in some of their patients, those with pure sensory neuropathy were excluded. CIDP is an acquired immune-mediated neuropathy which presents with a course of progression that may be slow and steady or step-wise or relapsing. Sensory ataxic polyneuropathy may be the only clinical manifestation of the disease[2]. Treatments are designed to modulate the abnormal immune response and to suppress ongoing disease activity. Here we report on a patient who had a relapsing form of pure clinical sensory ataxic CIDP and failed to respond to intravenous human immunoglobulin (IVIg) treatment. He was then put on IFN β1a for a period of three years.

CASE

A 39-year old man presented with a 9-year history of pain, imbalance, and numbness and paresthesias in both feet and hands. The disease presented a relapsing course from the beginning; periods in which the patient´s condition suddenly worsened were followed by others when it stabilized. The patient was suffering one of his relapses when he was first assessed in our clinic. Neurological examination showed normal muscle strength and bulk, while tendon reflexes were absent. Touch and pain sensations were mildly impaired at the distal segments of the four limbs, the sense of vibration had been abolished in both ankles and moderately to severely impaired in the knees and wrists; voluntary movements of the four

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limbs were also partially impaired due to the presence of ataxia; Romberg's sign was present and his gait was ataxic as well. When walking he adopted a wide base, took slow steps, and needed to look at his feet on the floor, characterizing a sensory ataxia gait. His spinal fluid had a protein content of 1.10 g/L (normal: < 0.4 g/L) and was acellular. Protein monoclonal bands were not found in the serum. EMG and nerve conduction studies showed that sensory action potentials were absent in one median and one sural nerve, that the conduction velocity of the motor fibers was slightly diminished in the right peroneal nerve, and that F waves were prolonged in both peroneal nerves as well as in the right median and right ulnar nerves (Table 1).

Given this clinical presentation and such electrophysiological findings, it was not possible to accurately diagnose this patient for CIDP within the criteria of the AAN[3]. We therefore decided to do a nerve biopsy in order to confirm our suspicions. This is what recommended by Vallat et al[4] when they counsel performing a nerve biopsy in cases where CIDP is doubtfull based on clinical and electrophysiological findings.

The biopsy sample revealed severe demyelination and a 35% loss of large diameter myelinated fibers, along with segmental and paranodal demyelination. No signs of axonal degeneration were seen. Some active macrophages, engulfing myelin, could be recognized in electron microscopy.

The patient was given IVIg, 2 g/kg, for 2 days at the time of his first visit and the same on two later occasions, when he suffered two further relapses. After the first course of IVIg there was an improvement which started a week after the treatment was over and which lasted for about four weeks before disappearing. His ataxia was less prominent and, consequently, he could walk with less risk of hurting himself. When, six weeks later, the patient suffered a second relapse, a second infusion of IgIV was administered. Once again his sensorial ataxic condition and ability to walk improved, but not so much as before. This also lasted for about 4 weeks. After this the patient refused to receive a new course of IVIg and returned to his home, far away from the hospital. At home he was treated with nothing more than physiotherapy by the local physician. One year later, when he

Table 1. Nerve conduction studies.

	Patient			Controls		
	R	L	n	x	SD	Range
Motor nerve conduction velocity (m/s)						
Median	57	52	45	57	5.3	50-67
Ulnar	52	66	51	59	4.8	51-72
Peroneal	40	42	45	49	5.7	42-62
Distal Latency (ms)						
Median	3.5	3.0	53	3.0	0.5	2-4
Ulnar	3.1	3.1	48	2,6	0.47	1.5-3.5
Peroneal	5.8	6.4	30	4,2	0.57	3-5
Amplitude						
Median	10	12	56	12.9	5.1	5.5-20
Ulnar	3.1	3.1	80	13.3	5.1	5.2-31
Peroneal	4	3	42	6.4	2.6	2.2-14
F wave latency (ms)						
Median	45	30	33	28.8	2.23	26-32.6
Ulnar	37	32	33	27.4	2.28	25-33
Peroneal	69	71	40	46.2	3.8	34-51
Sensory nerve conduction velocity (m/s)						
Median	AB	58	40	55.1	4.7	44-64
Sural	35	AB	40	46.0	4.7	42-52
Amplitud sensory potential (uv)						
Median	AB	10	40	31.7	13.0	15-85
Sural	4	AB	40	12.4	7.2	9-26

mV: milivolts; ms: milliseconds; uV: microvolts. AB:absent.R: right; L: left; n: number of subjects; x: mean;SD: standard deviation.m/s: meters per seconds; F wave was obtained by stimulating distally.

suffered a new relapse, in the form mainly of a worsening of his ataxia, he returned to our clinic and was again admitted into the ward, where he received a third administration of IVIg. This brought about no improvement. We then decided to put the patient on IM IFN β1a at a weekly dose of 30 μg. Over the next three years his condition stabilized. He recovered the ability to walk without assistance, and his dexterity was adequate for the task of operating a board computer. There were no further relapses and the patient was able to keep his job and social life. No major side effects of the medication were observed during that period.

DISCUSSION

There is an emerging interest in the use of IFN β in patients with CIDP who fail to respond to standard treatments. The use of IFN β has been drawn from the similarities in the cellular and humoral immune responses involved in the pathophysiology of CIDP with its central nervous system counterpart, multiple sclerosis (MS), where IFN β has been shown to be efficacious[5-6-7]. The effectiveness of this therapy in CIDP, as in MS, may be related to its capacity to modify the cytokine network by counteracting the deleterious effects of interferon gamma and TNFα on myelinated fibers, down regulating MHC-II expression in endoneural cells and enhancing the activity of suppressor cells. In addition, IFN β inhibits mRNA expression of regulated upon activation, normal T cell expressed and secreted (RANTES) and macrophage inflammatory protein (MIP-1α) and their receptor CCR5[8]. These chemokines are involved in the trafficking of TH1 proinflammatory cells. Migration of proinflammatory cells toward chemokines is closely associated with recruitment of inflammatory cells at the affected site.

As far as we know, ours is the first reported patient with a clinically pure relapsing sensory CIDP in whom the results, as seen in a long-term follow up, suggest that IFN β1a treatment may be useful. This has also been seen in small pilot studies encompassing sensory-motor, or just motor, progressive or relapsing forms of the disease[9-10].

However, our findings and those of other authors[9-10] are at variance with the results of the unique randomized trial of IFN β1a in CIDP[9] which showed no significant difference between IFN β and a placebo in treated patients, albeit over a shorter follow up period. This difference in the follow up periods might explain the variance in results.

The beneficial effect of IFN β1a has also been reported in a subset of three patients out of nine affected with multifocal motor neuropathy who had previously responded favorably to IVIg treatment[11]. In six patients there was no effect at all. Four patients continued to deteriorate in such a way that treatment with IVIg had to be resumed during the study. Finally, three patients showed an improvement that was more pronounced than when they were on IVIg .

These findings, as well as the results obtained in our own patient, suggest that IFN β 1a may produce beneficial effects in patients with CIDP and might be a useful option for immune-mediated neuropathies which are refractory to conventional therapies.

We cannot deny the possibility that the clinical improvement observed when the patient was on IF β1a might have been a coincidence. The history of his disease, however, shows that the patient's clinical state changed with the treatments. He improved when he received the first course of IVIg as well as when the second course was administered, albeit to a lesser extent, and finally he failed to show any improvement from the third administration of IVIg. His clinical condition stabilized, without any further relapses, when he was put on IFβ1a. This and the other observations already mentioned suggest that further prolonged, controlled, and randomized studies are needed to confirm the long term effectiveness of this novel and potential fruitful treatment.

REFERENCES

1. Vallat JM, Hahn AF, Leger JM, et al. Interferon beta-1a as an investigacional treatment for CIDP. Neurology 2003;60(Supp 3):S23-S28.
2. Villa AM, Molina H, Sanz OP, Sica REP. Chronic inflammatory demyelinating polyneuropathy. Findings in 30 patients. Medicina 1999;59:721-726.
3. AIDS Task Force. Research criteria for diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). Neurology 1991;41:617-618.
4. Vallat JM, Tabaraud F, Magy L, et al. Diagnostic value of nerve biopsy for atypical chronic inflammatory demyelinating polyneuropathy: evaluation of eight cases. Muscle&Nerve 2003;27:478-485.
5. IFNB Múltiple Sclerosis Study Group. Inteferon beta 1b is effective in relapsing-remitting multiple sclerosis: I. Clinical results of a multicenter, randomised, double-blind, placebo-controlled trial. Neurology 1993; 43:655-661.
6. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta 1a for diseases progression in relapsing multiple sclerosis. Ann Neurol 1996;39:285-294.
7. The PRISMS (Prevention of Relapses and Disability by Interferon beta 1a Subcutaneously in Multiple Sclerosis) Study Group. Randomised double-blind placebo-controlled study of interferon beta 1a in relapsing-remitting multiple sclerosis. Lancet 1998;352:1498-1504.
8. Zang YCQ, Halder JB, Samanta AK, Hong J, Rivera VM, Zhang JZ. Regulation of chemokine receptor CCR5 and production of RANTES and MIP-1(alpha) by interferon-(beta). J Neuroimmunol 2001;112:174-180.
9. Hadden RD, Sharrack B, Bensa S, Soudain SE, Huges RA. Randomized trial of interferon beta 1a in chronic inflammatory demyelinating polyradiculoneuropathy. Neurology. 1999;53:57-61.
10. Kuntzer T, Radziwill AJ, Lettry-Trouillat R, et al. Interferon beta 1a in chronic inflammatory demyelinating polyneuropathy. Neurology 1999;53:1364-1365.
11. Van den Berg-Vos RM, Van den Berg RH, Fransen H, Van Doorn PA, Merkies IS, Wokke JH. Treatment of multifocal motor neuropathy with interferon beta 1a. Neurology 2000;54:1518-1521.