Chronic Inflammatory Demyelinating Polyneuropathy after Treatment with Interferon-α

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Abstract

Interferon-α (IFN-α), though widely used for the treatment of chronic viral hepatitis, may be associated with the occurrence of autoimmune disorders. In this case report, a patient with chronic hepatitis C virus infection had chronic inflammatory demyelinating polyneuropathy (CIDP) after the initiation of IFN-α therapy. The neurological symptoms of this patient continued to progress even though the treatment with IFN-α had been withdrawn; the symptoms improved dramatically following treatment with intravenous immunoglobulin. This case may therefore provide an important clue to understand the immune mechanism of CIDP and IFN-α.

Key words: chronic inflammatory demyelinating polyneuropathy, hepatitis C virus, interferon-α

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Introduction

Interferon-α (IFN-α) has been widely used for the treatment of chronic viral hepatitis. However, several reports have suggested that IFN-α may cause certain autoimmune diseases including thyroiditis, systemic lupus erythematosus, hematologic disorders, insulin-dependent diabetes mellitus, and dermatologic diseases (1). Certain neurological disorders have also been reported such as myasthenia gravis, axonal neuropathy, and central nervous system (CNS) demyelination (2, 3). We report a patient with chronic inflammatory demyelinating polyneuropathy (CIDP) associated with the IFN-α treatment which was taken for hepatitis C virus (HCV) infection. Intravenous immunoglobulin therapy improved the symptoms of this case, which resulted in clinical remission without relapse.

Case Report

In April 2005, an otherwise healthy 37-year-old man was diagnosed as having chronic hepatitis C. He was started on a course of treatment comprising IFN-α (3 MIU/day, three times weekly) and ribavirin (600 mg daily) in August 2005; and this resulted in negative conversion of hepatitis C virus (HCV) RNA transcript. After 4 months of treatment, he developed dysesthesia and weakness, which initially involved both feet and then progressed to affect both hands. The IFN-α therapy was discontinued after 2 months; however, the patient continued to note the progression of symptoms, and eventually developed difficulty in walking. In March 2006, he was admitted to our hospital.

On neurological examination, he was found to have hand and foot muscle weakness with 4/5 strength (Medical Research Council scale) bilaterally, and with minimal weakness in the proximal extremities. Deep tendon reflexes were decreased in all limbs. Sensory examination revealed profoundly reduced vibratory sensation affecting mainly the lower limbs, with a slight loss of pain and temperature sensation. A heel-to-shin test revealed slight dysmetria in both legs, and Romberg’s test was positive. He had difficulty in walking as a consequence of ataxia.

Biochemical screening tests, complete blood count, erythrocyte sedimentation rate, and antinuclear antibodies were all normal. There was, however, mild hepatic impairment. Neither anti-ganglioside antibodies nor cryoglobulins were
Table 1. Nerve Conduction Studies

<table>
<thead>
<tr>
<th></th>
<th>Motor nerve</th>
<th>Sensory nerve</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Median (right)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal motor latency (ms)</td>
<td>4.1</td>
<td>3.0</td>
<td>4.2</td>
</tr>
<tr>
<td>Distal CMAP amplitude (mV)</td>
<td>6.2</td>
<td>7.1</td>
<td>17.3</td>
</tr>
<tr>
<td>Proximal CMAP amplitude (mV)</td>
<td>1.9</td>
<td>3.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Conduction velocity (m/s)</td>
<td>18.2</td>
<td>18.7</td>
<td>22.5</td>
</tr>
<tr>
<td>Minimum F-wave latency (ms)</td>
<td>36.9</td>
<td>33.1</td>
<td>50.0</td>
</tr>
<tr>
<td>Distal SNAP amplitude (µV)</td>
<td>30.2</td>
<td>32.1</td>
<td>27.8</td>
</tr>
<tr>
<td>Proximal SNAP amplitude (µV)</td>
<td>51.2</td>
<td>55.7</td>
<td>44.3</td>
</tr>
</tbody>
</table>

CMAP: compound muscle action potential, SNAP: sensory nerve action potential
Proximal CMAP and SNAP amplitude obtained with stimulation below the knee for median and ulnar nerves, and below the knee for peroneal, tibial and sural nerves.

detected. In the cerebrospinal fluid (CSF), the protein content was elevated (153 mg/dL) although the cell count was normal. The results of nerve conduction studies revealed evidence of predominant motor polyneuropathy with prominent demyelinating features, including motor conduction block, low conduction velocity, and prolonged minimum F-wave latency in the bilateral ulnar, median, peroneal, and tibial nerves (Table 1).

In April 2006, intravenous immunoglobulin treatment (IVIg) was administered (0.4 g/kg for 5 days). After 1 month of treatment, both muscle weakness and ataxia were markedly improved, with normal strength in all muscle groups; eventually he could walk without difficulty. Furthermore, his dysesthesia also improved, resulting in minimal dysesthesia in both feet. He has not experienced any relapses and his neurological status has been stable after the treatment.

Discussion

The etiology of polyneuropathy in this patient is considered to be associated with the following factors: 1) polyneuropathy related to HCV, 2) drug-induced polyneuropathy caused by IFN-α, and 3) CIDP triggered by IFN-α.

The features of this case mainly revolved around following points: 1) polyneuropathy developed after negative conversion of HCV-RNA transcript, 2) polyneuropathy developed several months after the initiation of IFN-α treatment, 3) polyneuropathy worsened despite the withdrawal of IFN-α, and 4) the results of nerve conduction studies revealed apparent demyelinating changes. Taken together, it is considered that neither HCV-RNA transcript nor administration of IFN-α was correlated with the clinical course, and that the development of polyneuropathy was triggered by the initiation of IFN-α treatment. In this case, polyneuropathy appeared to be associated with demyelination and satisfied the electrophysiologic criteria for the diagnosis of CIDP proposed by the American Academy of Neurology (4). The prompt response to IVIg also suggests the patient’s neuropathy was caused by an immune-mediation. These findings suggest that the disease of this patient was CIDP triggered by IFN-α.

To date, there have been relatively few case reports of autoimmune neuropathy induced by IFN-α; two cases of CIDP and two cases of motor neuropathy were found (5-8). In cases of CIDP, paresthesia was first noted several months after the initiation of IFN-α treatment, and worsened despite the withdrawal of IFN-α. Neither anti-ganglioside antibodies nor cryoglobulins were detected in these cases (5, 6). Prednisolone and plasma exchange were highly effective, and the condition subsided without residual effects (5, 6). To our knowledge, this is the first report to demonstrate the beneficial therapeutic effects of IVIg against CIDP triggered by IFN-α.

IFN-α is type I interferon, and a leukocyte-derived cytokine that is used for the treatment of chronic HCV infection. Immunomodulatory properties, including activation of natural killer cells and cytotoxic T lymphocytes, upregulation of class I and II major histocompatibility complexes, and terminal differentiation of dendritic cells (DCs), are assumed to be responsible for the antiviral effect (9, 10). On the other hand, it was reported that IFN-α may initiate autoimmune disorders such as SLE (1-3). The mechanism of these actions is not yet fully understood; however, it is suggested that IFN-matured myeloid DCs activate autoreactive T cells, and these cells, together with plasma cytokoid DCs, help expansion of autoreactive B cells (11). IFN-matured DCs also activate cytotoxic CD8+ T cells, possibly increasing apoptotic cell availability (11).

The mechanism of CIDP is not fully understood; however, an important role for DCs in the pathogenesis of inflammatory neuropathies is also suggested by the recent study, which showed that NOD mice deficient in CD86 costimulation develop a spontaneous CIDP-like disease associated with DC and T cell infiltration into peripheral nerve system tissue (12). In CIDP, DCs are probably initially recruited to inflamed spinal nerve roots and adjacent meninges to take up released antigens (13). Then, antigen-loaded DCs may be shed into the CSF, enter CSF-draining lymphatic vessels, and travel to regional lymph nodes, where mature DC interact with T and B cells to induce and modulate myelin-reactive T and B cell responses (13). These findings suggest that IFN-α probably activates autoreactive T and B cells via DCs resulting in CIDP.

We considered the possibility that IFN-α contributed to the development of autoimmune disease in the present patient. However, other factors, particularly HCV infection, could not be ruled out completely since HCV infection is...
also associated with multiple autoimmune manifestations, including the production of autoantibodies and cryoglobulinemia complicated by vasculitis (14). There have been several reports indicating an association between HCV infection and neuropathy (15, 16). The neuropathy is sensory or sensory-motor with a symmetrical or asymmetrical pattern, probably associated with mononeuritis multiplex (17). Neurophysiological and neuropathological findings are compatible with axonal neuropathy with secondary demyelination (17). In very rare cases, the HCV-cryoglobulinemia-associated neuropathy may be demyelinating (18). However, the onset of our patient’s neuropathy was clearly related to the administration of IFN-α, occurred in the absence of HCV-RNA transcript, and responded to intravenous immunoglobulin therapy, which resulted in clinical remission without relapse. Taken together, we emphasize that IFN-α played a major role in the development of autoimmunity in this case.

In conclusion, the present case provides further evidence that treatment with IFN-α might yield neuroimmunological events including CIDP by modifying the immune response. Furthermore, these findings might provide an important clue to understand the immune mechanism of CIDP.

References