New-Onset Type 1 Diabetes Mellitus and Anti-Aquaporin-4 Antibody Positive Optic Neuritis Associated with Type 1 Interferon Therapy for Chronic Hepatitis C

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Abstract

A 60-year-old woman developed type 1 diabetes mellitus and anti-aquaporin-4 antibody positive optic neuritis during type 1 interferon therapies for chronic hepatitis C. The diabetes mellitus was elicited by interferon-α plus ribavirin therapy, while the optic neuritis was induced after interferon-β treatment, followed by interferon-α and ribavirin therapy. It is possible that type 1 interferons lead to the onset of the two autoimmune diseases by inducing disease-specific autoantibodies. Autoimmune disease is an infrequent complication of type 1 interferon treatment; however, once it has occurred, it may result in severe impairments. Patients undergoing type 1 interferon therapy should therefore be carefully monitored for any manifestations of autoimmune diseases.

Key words: aquaporin-4, neuromyelitis optica, chronic hepatitis C, type 1 diabetes mellitus, type 1 interferon


Introduction

Type 1 interferon (IFN) is widely used to treat patients with chronic viral hepatitis and malignant neoplasms. Approximately two million people in Japan are infected with the hepatitis C virus (HCV). Combination therapy with type 1 IFN and ribavirin (RBV) is used in 50,000-100,000 patients annually. Since type 1 IFN has not only antiviral and antiproliferative effects, but also immunomodulatory effects, it can occasionally induce various autoimmune diseases (1). The onset of autoimmune diseases can be attributed to the overproduction of disease-specific antibodies. We herein present the case of a patient who developed type 1 diabetes mellitus (T1DM) and severe optic neuritis with anti-aquaporin-4 (AQP-4) antibodies during treatment with combinations including IFN-α and IFN-β for chronic hepatitis C.

Case Report

A 60-year-old Japanese woman was diagnosed with hepatitis C (type 1b) in 1994 at the age of 42 years. Since the diagnosis, she had received various types of IFN therapy: natural IFN-α, recombinant IFN-α-2b and RBV, recombinant IFN-αcon-1, and pegylated IFN (PEG-IFN)-α-2b and RBV (Fig. 1). From 1994 to 2008, all of the above-mentioned IFN therapies resulted in a transient reduction in HCV-RNA to undetectable levels, but a sustained virologic response (SVR) was not obtained. While undergoing PEG-IFN/RBV treatment, the patient was noted to have hyperglycemia, and she was diagnosed with T1DM in 2008 (Fig. 1). She was found to be positive for anti-glutamic acid decarboxylase (GAD) antibodies, with a titer of 3,440x. The titers of anti-GAD antibodies were decreased to 128x two years after the initiation of insulin treatment.

In January 2009, the patient underwent combination therapy for virus eradication by double-filtration plasmapheresis
(VRAD), intravenous natural IFN-β for 14 days, and PEG-IFN-α-2a plus RBV for 36 weeks to achieve HCV-RNA seronegativity. A SVR was finally achieved with these intensive combination therapies (Fig. 1).

In November 2009, the patient experienced pain when moving her left eye. Her left visual acuity deteriorated to light perception within two weeks. She was diagnosed with left optic neuritis. The IFN therapy was terminated, and triamcinolone was injected locally into the subtenon of the affected side, which was not effective. Serological tests demonstrated that she was positive for AQP-4 antibodies in January 2010, and hence a clinical diagnosis of neuromyelitis optica spectrum disorder (NMOsd) was made (Fig. 1).

To prevent relapse and progression of the optic neuritis, immunosuppressant drug therapy was initiated, with weekly oral methotrexate (MTX) administration at a dose of 2.5 mg. In June 2011, right optic neuritis occurred and the right visual acuity was decreased from normal to finger counting within two weeks. She received two courses of high-dose intravenous methylprednisolone (IVMP) therapy, which were not effective. She was admitted to our hospital for further treatment (Fig. 1).

On admission, her neurological findings were normal, except for the severe visual field defects of 0.02 (20/1,000) in both eyes. The visual field defects were detected by Goldmann perimetry (Fig. 2A). Ophthalmoscopy showed no impairment of the retinal blood vessels. The visual evoked potential indicated no response. The cerebrospinal fluid was normal, with a cell count of less than 1/μL with all mononuclear cells, and a protein concentration of 37 mg/dL. Oligoclonal banding was negative, and the myelin basic protein level was within the normal range. The serum blood sugar level was 196 mg/dL (normal range 70-110), glycosylated hemoglobin was 6.7% (normal range 4.3-5.8), and the anti-GAD antibodies were detected with a value of 9.9 U/mL. The patient’s serum was also found to be positive for anti-AQP-4 antibodies, with a titer of 128x. Anti-nuclear antibodies, anti-SS-A/SS-B antibodies, anti-neutrophil cytoplasmic antibodies, and anti-thyroid antibodies were not detected.

Magnetic resonance imaging (MRI) showed a high signal intensity of the left optic nerve on T2-weighted and fluid-attenuated inversion recovery, and T1-weighted imaging with contrast enhancement, whereas the right optic nerve showed no particular findings (Fig. 2B, C). Brain MRI (Fig. 2D, E) showed a small number of high-intensity spots in the cerebral white matter. No obvious abnormality was observed in the spinal cord MRI.

The patient was treated with eight courses of plasmapheresis. During the treatment, her visual acuity slightly improved and she could read a few written characters. The titer of the anti-AQP-4 antibodies was decreased to 16x. However, the patient’s visual field defect gradually worsened again soon after the discontinuation of plasmapheresis, so we initiated two courses of IVMP therapy, an additional two courses of plasmapheresis, high-dose intravenous immu-
The present patient developed T1DM during IFN-α therapy and anti-AQP4 antibody positive optic neuritis after IFN-β, followed by IFN-α therapy. Her severe visual impairment persisted despite the use of intensive immunotherapy. Several reasons for the intractable disease course can be proposed. For example, the type 1 IFNs or HCV infection may have served as a potent activator of autoimmunity, or the involvement of vasculitis as an extrahepatic manifestation of HCV infection (2) could lead to the clinical deterioration.

The first case of T1DM development during IFN-α therapy for chronic hepatitis C was reported in 1992 (3). New-onset DM among IFN-treated patients has been documented to occur in 0.7% of patients in Japan (4). The mechanism underlying immune-mediated pancreatic β-cell destruction can be attributed to genetic and environmental causes thus leading to the generation of islet cell autoantibodies, i.e., anti-GAD autoantibodies. IFN-α may act as an initiator of the autoimmunity directed against β cells, thus leading to the pathogenesis of T1DM. Likewise, IFN-α can be considered to play a critical role in the pathogenesis of systemic lupus erythematosus.

To date, ten cases of new-onset optic neuritis, multiple sclerosis (MS), MS-like disease, or NMOsd associated with IFN-α therapy for chronic viral hepatitis or malignant neoplasms, have been reported (5-11). There were two cases with seropositivity for anti-AQP4 antibodies (Table); one patient with optic-spinal MS (OSMS) after IFN-α2b and RBV (10), and another patient with NMOsd after PEG-IFN-α and RBV (11). In the remaining eight cases, the presence of anti-AQP-4 antibodies was not examined because they had been reported before the discovery of NMO-IgG (IgG) and anti-AQP-4 (12) antibodies.

IFN-β therapy can also play a role as an initiator of autoimmune diseases involving the central nervous system. A case with new-onset optic neuritis after IFN-β therapy for

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**Figure 2.** The visual impairment and the magnetic resonance images of the present case. The Goldmann visual fields on admission are highlighted (A). The left optic nerve showed high signal intensity on the STIR coronal image (white arrow, B) with marginal contrast enhancement (white arrow, C). The right optic nerve showed no remarkable findings (arrow head, B and C). The brain showed no particular findings except for the optic nerve on FLAIR sagittal (D) and axial (E) images.

**FLAIR:** fluid-attenuated inversion recovery, **STIR:** short inversion time inversion-recovery, **T1-Gd:** gadolinium enhanced T1.
kidney cancer has been reported (13). In addition, a number of exacerbated cases of relapsing-remitting MS (RRMS) have been reported in Japan in patients receiving IFN-β (14). Differentiating between NMO and MS can be achieved based on seropositivity for the anti-AQP-4 antibodies, longitudinally extensive spinal cord lesions, and brain MRI findings not meeting the diagnostic criteria for MS (15). However, before the discovery of this autoantibody, it was difficult to distinguish NMO from MS, especially OSMS, which is common in Asian countries. In 2000, IFN-β therapy was approved in Japan for the prevention of relapse and progression of RRMS, in which patients with OSMS were also included. Consequently, exacerbation of the disease or ineffectiveness of IFN-β was reported among patients with OSMS who underwent IFN-β therapy (14, 16). These cases were later found to be positive for anti-AQP-4 antibodies. Recent articles described that IFN-β treatment was not effective in preventing relapses in NMO patients (17, 18), while strictly defined OSMS showed a response to IFN-β treatment in terms of the prevention of relapses and functional worsening (19).

The mechanism underlying the onset and exacerbation of NMO/NMOsd has not been well understood, but the induction of B-cell activation factors of the tumor necrosis factor (TNF) family by IFN-β is considered to facilitate the production of anti-AQP-4 antibodies (20). For example, Chihara et al. have shown that IL-6-dependent B-cell subpopulations of plasmablasts are involved in the production of anti-AQP-4 antibodies (21). Loss of AQP-4, mediated by immunoglobulins and complements, has been shown in inflammatory lesions of patients with NMO (22). These results indicate that the anti-AQP-4 antibody plays a crucial role in the pathogenesis of NMO, unlike in cases of MS. As another mechanism underlying the development of type 1 IFN-induced NMO/NMOsd, it has been suggested that IFN-β treatment leads to the overproduction of IL-17 from T helper 17 (Th17) cells (23), which is thought to be associated with the pathological feature of NMO.

Type 1 IFN has reciprocal characteristics, with both pathogenic and protective roles in autoimmunity. In general, IFN-β exerts its therapeutic effect on MS by producing anti-inflammatory cytokines and suppressing the proliferation of autoreactive T cells. Both IFN-α and IFN-β bind to a single heterodimeric receptor composed of IFNAR1 and IFNAR2, which can cause similar immunomodulatory effects (24). Hence, it is likely that IFN-α has a similar effect on autoimmunity as does IFN-β, as indicated by the fact that IFN-α has also been developed as a candidate therapeutic agent for MS (25).

Type 1 IFNs served as pathogenic mediators in the present case, inducing T1DM and NMO/NMOsd. Since various types of IFN-α treatment had been carried out intermittently for more than ten years after the onset of chronic hepatitis C, the onset of T1DM was clearly influenced by IFN-α treatment. However, it remains unclear which type of IFN was involved in the induction of NMOsd. We speculate that the combination therapy with IFN-α and IFN-β may have produced synergistic effects to trigger NMOsd in the present case.

The authors state that they have no Conflict of Interest (COI).

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Contributor TK, MA, and MW undertook the clinical management of the patient. MW referred the patient to NCNP and performed the ophthalmological examination. Each of the authors was significantly involved in clinical assessments of the patient. TK and MA equally contributed to this work.

References


Table. The Reported Cases of Newly-onset Anti-AQP-4 Antibody Positive OSMS, and NMOsd Provoked by Type 1 IFN Therapy

<table>
<thead>
<tr>
<th>Patient age, sex</th>
<th>Disease</th>
<th>IFN</th>
<th>ON</th>
<th>SC</th>
<th>B</th>
<th>AQP4-Ab</th>
<th>Duration</th>
<th>References</th>
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<tr>
<td>47, F</td>
<td>Hepatitis C</td>
<td>α-2b/RBV</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1Y</td>
<td>Kajiyama, et al. 200710</td>
</tr>
<tr>
<td>65, F</td>
<td>Hepatitis C</td>
<td>α/RBV</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>2Y10M</td>
<td>Yamasaki, et al. 201211</td>
</tr>
<tr>
<td>60, F</td>
<td>Hepatitis C</td>
<td>α, β, α/RBV</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>α: 15Y β: 9M</td>
<td>Present Case 2012</td>
<td></td>
</tr>
</tbody>
</table>

RBV: ribavirin, ON: optic neuritis, SC: spinal cord lesion, B: brain lesion. Duration: duration between the initiation of type 1 IFN therapy and the onset of OSMS or NMOsd


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