Influenza-associated Monophasic Neuromyelitis Optica

Yoshikazu Nakamura, Ken Ikeda, Yasuhiro Yoshii, Hirono Ito, Takehisa Hirayama, Kiyokazu Kawabe, Osamu Kano and Yasuo Iwasaki

Abstract

Neuromyelitis optica (NMO) is an inflammatory demyelinating disorder characterized by optic neuritis and acute myelitis. A parainfectious pathogenesis may play a partial role in the development of this disorder. Several viral infections are known to cause NMO. Here we report the case of a 15-year-old girl diagnosed with postinfluenza monophasic NMO. The patient developed sudden fever and chills, and the rapid diagnostic test for influenza was positive. She was diagnosed as influenza A and was treated with zanamivir hydrate (10 mg/day, inhalation). Three days later, she complained of dysuria and dysesthesia in the lower extremities. After nine days, she experienced blurred vision bilaterally. Neurological examination revealed visual disturbance, dysuria, dysesthesia and hyperreflexia in the lower extremities. Her visual acuity was counting fingers in OD and 2/100 in OS. Pupillary size was 4.0 mm and light reflexes were sluggish on both sides. Ophthalmoscopy showed marked edema of the optic discs. Serum influenza immunoglobulin M antibodies were elevated and serum anti-aquaporin 4 (AQP4) antibodies were undetectable. Spinal cord magnetic resonance imaging (MRI) displayed longitudinally extensive lesions in the thoracic cord. Brain MRI disclosed three subcortical lesions. The patient fulfilled the revised diagnostic criteria for NMO (2006). After methylprednisolone pulse therapy followed by oral administration of prednisolone, visual dysfunction, dysuria, limb dysesthesia and hyperreflexia were improved. Subsequently, she experienced no attacks for 3 years. This is the first case report of influenza A-associated NMO with such features of postinfectious NMO as a pediatric onset, monophasic course and anti-AQP4 antibody-seronegative status.

Key words: neuromyelitis optica, influenza, parainfection, pediatrics, monophasic course, anti-aquaporin 4 antibody

Introduction

Neuromyelitis optica (NMO) is an inflammatory demyelinating disorder characterized by monophasic or recurrent episodes of bilateral optic neuritis and longitudinal extensive transverse myelitis (1). Recent studies have suggested neurological features of pediatric-onset NMO (p-NMO) patients (2-4). A high frequency of parainfectious or postinfectious NMO has been noted in p-NMO patients compared to adult patients (4, 5). Influenza infection or vaccine rarely causes acute encephalopathy or encephalitis in children and adults (6-8). However, little is known about influenza-associated NMO. Here we report the first case of monophasic postinfluenza p-NMO.

Case Report

A 15-year-old girl developed sudden fever and chills. A rapid diagnostic test for influenza using immunochromatography was positive and she was diagnosed as influenza A. The patient was treated with inhalation of zanamivir hydrate (10 mg/day). Three days later, she complained of dysuria and dysesthesia in the lower extremities. After 9 days, she had visual disturbance in both eyes. Neurological examination revealed bilateral visual impairment, sphincter disturbance, along with dysesthesia and hyperreflexia in the lower extremities. Babinski’s signs were negative. Visual acuity was counting fingers in OD and 2/100 in OS. The pupillary size was 4.0 mm and light reflexes were sluggish on both
Figure 1. (A, B) Ophthalmoscopy showed marked edema in both optic discs. (C, D) After steroid treatment, disc edema was ameliorated markedly.

Ophthalmoscopy showed marked edema of the bilateral optic discs (Fig. 1A, 1B). Central critical flicker fusion frequency (CFF) was impossible to determine in the right eye and it was 15.5 Hz in the left eye (normal ≥29.0). Visual evoked potential (VEP) testing exhibited that P100 latencies were not found in the right side and were delayed in the left side (128 msec). Serum influenza A-immunoglobulin M antibodies were elevated. Anti-aquaporin 4 (AQP4) antibodies measured by indirect immunofluorescence assay using human AQP4-transfected cells (Department of Neurology, Tohoku University Graduate School of Medicine, Sendai, Japan), were undetectable. Cerebrospinal fluid analysis showed a cell count of 3 mononuclear cells/mm³, protein levels of 22 mg/dL and cytology of class I. Myelin basic protein was increased to 344 pg/mL (<102) and oligoclonal immunoglobulin G (IgG) bands were not detected. Spinal cord magnetic resonance imaging (MRI) displayed extensive hyperintensity signal lesions in 4 vertebral segments of the thoracic cord (Fig. 2). Gadolinium enhancement was not observed in the longitudinal lesion. Brain MRI disclosed one enhanced lesion in the right parietal subcortex and 2 non-enhanced lesions in the left parietal and occipital white matter (Fig. 3). These cerebral lesions did not meet the diagnostic criteria for multiple sclerosis (MS). The patient fulfilled the revised diagnostic criteria for NMO by Wingerchuk et al (9). She received two courses of methylprednisolone pulse therapy (1,000 mg/day for 3 days, iv) followed by tapering oral dose of prednisolone (40 mg/day). Eventually prednisolone was discontinued after 40 days. The steroid treatment dramatically improved visual dysfunction, dysuria, dysesthesia and hyperreflexia in the lower limbs. Visual acuity was normalized to 20/16 in OD and OS. CCF was recovered to 37.8 Hz in the right eye and 41.0 Hz in the left eye. Ocular fundus findings were ameliorated (Fig. 1C, 1D). Five months later, follow-up MRI revealed marked shrinkage in the 3 cerebral lesions. Gadolinium enhancement was disappeared in the right parietal lesion (Fig. 4). Subsequently, she has experienced no recurrence of neurological symptoms for 3 years. Finally, we diagnosed her as influenza A-associated monophasic NMO without serum anti-AQP4 antibodies.

Discussion

We reported the first case of influenza-associated p-NMO. In addition to influenza infection, the neurological hallmarks of the present patient were a monophasic course, seronegativity for anti-AQP4 antibodies and excellent response to steroid treatment alone.

Previous studies of p-NMO frequently described cerebral involvement, including acute disseminating encephalopathy (ADEM) or MS-like lesions on brain MRI (2, 10). With respect to serum anti-AQP4 antibodies in p-NMO, Banwell et al (10) analyzed serum NMO-IgG in 17 p-NMO patients. Serum NMO-IgG was positive in 7 of 9 relapsing cases (78%). In contrast, only one of 8 monophasic cases (12.5%) was seropositive for NMO-IgG. Lotze et al (2) reported 9 pediatric patients with NMO spectrum disorders. All patients had recurrent courses, longitudinally extensive spinal cord lesions and brain lesions on MRI. Seven patients (78%) were NMO-IgG-seropositive. These two studies suggested the clinicoradiological aspect of p-NMO patients from North
Figure 2. Spinal cord T2-weighted imaging. (A) Sagittal view showed longitudinal extensive hyperintensity signal areas in the 2nd to the 5th thoracic cord. (B) Axial view of the 4th thoracic cord. Hyperintensity lesions were found in the white matter and the gray matter.

Figure 3. (A-C) Fluid-attenuated inversion recovery (FLAIR) imaging showed hyperintensity lesions in the right parietal, the left occipital and parietal white matter. (D) Gadolinium-enhanced T1-weighted imaging showed marked enhancement in the right parietal lesion. (E, F) Gadolinium enhancement was not found in the left occipital and parietal lesions.

America (2), Canada and Argentina (10). In European populations, a French study showed 12 patients with relapsing p-NMO. Eight patients were seropositive for NMO-IgG. The number of first brain MRI lesions was significantly increased and disability time was prolonged in p-NMO patients compared to adult-onset NMO (3). Another German study addressed contrary aspects of p-NMO patients (4). Of 118 pediatric patients with demyelinating central nervous system disorders, 6 patients (5%) fulfilled the revised NMO diagnostic criteria (9). Two patients had recurrent episodes and 4 had a monophasic course. Only 1 patient with recurrence, who died at 7 years after disease onset, was seroposi-
Figure 4. (A-C) Five months later, subcortical hyperintensity lesions shrunk on FLAIR imaging. (D) Gadolinium-enhanced T1-weighted imaging showed no enhancement in the right parietal lesion.

tive for NMO-IgG. All patients with monophasic NMO were seronegative for NMO-IgG and recovered well, in the similar course to the present patient (4). Other studies have also described low rates of NMO-IgG seropositivity in pediatric or adult patients with monophasic NMO (10, 12). NMO-IgG-seropositive patients had frequent recurrence and severe disabilities compared to seronegative patients (3, 10-12). Therefore, the pathogenesis seems to differ between NMO-IgG-seropositive and NMO-IgG-seronegative p-NMO.

Aside from the clinical course of NMO patients and different sensitivities of various NMO-IgG detection assays, the frequency of NMO-IgG seropositivity has been suggested to depend on ethnicity (9, 12-14). Moreover, there is the possibility that NMO-IgG-seronegative monophasic p-NMO may be a parainfectious disorder (4). A recent report has summarized the characteristics of 11 patients with viral infection-related NMO syndromes (5). Serum NMO-IgG was not detected in those patients. Five patients had pediatric onset (age 5-15 years) and a monophasic course. The causative viruses of parainfectious NMO syndrome revealed varicella zoster virus, human immunodeficiency virus, cytomegalovirus, Dengue virus, Hepatitis A virus and Epstein-Barr virus (5). A previous study of p-NMO also pointed out a viral infection prior to the first attack in 5 of 6 patients (4). Influenza-associated NMO has not been reported previously. Influenza virus is known to cause serious acute encephalopathy or encephalitis (6), and influenza vaccine induces ADEM rarely (7, 8). Concomitant onset of ADEM and bilateral optic neuritis after H1N1 influenza vaccine has been reported in a 2-year-old Canadian boy (7). MRI displayed hyperintensity lesions in the cerebellum, the basal ganglia and the optic nerves. Methylprednisolone pulse treatment ameliorated visual disturbance. However, spinal cord MRI and NMO-IgG were not mentioned in this case (7). It remains unclear whether monophasic p-NMO is present in patients diagnosed with influenza-associated acute encephalitis or ADEM. Further studies are needed to investigate NMO syndrome due to influenza or its vaccination in different racial populations.

In conclusion, we highlighted the first case of postinfluenza A p-NMO. This case was characterized by a monophasic course and seronegativity for anti-AQP4 antibodies. Thus, we should pay more attention to the different profile of parainfectious NMO and anti-AQP4 antibody-seropositive recurrent NMO.

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

Acknowledgement

We gratefully thank Dr. Toshiyuki Takahashi, Department of Neurology, Tohoku University Graduate School of Medicine, Sendai, Japan for measurement of serum anti-AQP4 antibody.

References

5. Sellner J, Hemmer B, Mühlau M. The clinical spectrum and immunobiology of parainfectious neuromyelitis optica (Devic) syn-


