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Short communication

Pontine hemorrhage accompanied by neuromyelitis optica spectrum disorder

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ABSTRACT

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disorder caused by antibody to aquaporin-4 (AQP4). NMOSD can infrequently present as a complication of posterior reversible encephalopathy syndrome (PRES). Moreover, few cases of NMOSD patients with brain hemorrhage have been reported. We report a rare case of PRES together with NMOSD recurrence, subsequent to pontine hemorrhage after intravenous methylprednisolone (IVMP) therapy. A 51-year-old Japanese woman, with a history of hypertension and dyslipidemia, and recurrent episodes of left visual acuity disorder related to AQP4-positive NMOSD, developed blindness in the left eye. Brain MRI showed a hyperintense lesion in pons. She was initially diagnosed with recurrence of NMOSD and 1000 mg of IVMP was administered for 3 days. After the 3rd course of IVMP, she developed left-sided sensory disturbance, and blood pressure was increased to 202/127 mmHg. Brain computed tomography (CT) showed pontine hemorrhage, and she was referred to our hospital again. We diagnosed PRES associated with NMOSD recurrence, along with development of pontine hemorrhage induced by the increase in blood pressure resulting from IVMP. The patient was treated with nicardipine to strictly control blood pressure, and tranexamic acid and glycerol for pontine hemorrhage and PRES. We also extended IVMP for 5 consecutive days in total, followed by plasmapheresis. After therapy, blindness in the left eye improved to light perception. Collectively, anti-AQP4 antibody could induce PRES together with recurrent NMOSD, and pontine hemorrhage could thus be induced by blood pressure increases resulting from IVMP.

1. Background

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune inflammatory demyelinating disease of the central nervous system characterized by recurrent attacks of optic neuritis and myelitis (Lucchinetti et al., 2002). NMOSD can complicate posterior reversible encephalopathy syndrome (PRES), but little is known about its pathological significance (Cheng et al., 2013; Magana et al., 2009). PRES often leads to brain hemorrhage (Hefzy et al., 2009). Here we report a rare case of pontine hemorrhage associated with development of NMOSD recurrence and PRES.

2. Case presentation

A 51-year-old Japanese woman with hypertension and dyslipidemia presented with blindness in the left eye, and was referred to our hospital. She had initially shown impaired left visual acuity to hand movement at 35 years old, and had been diagnosed with optic neuritis. Two courses of intravenous methylprednisolone (IVMP) were administered at 2000 mg/day for 5 days, improving left visual acuity to 20/40 on the Snellen chart. Subsequently, she developed recurrent impairment of left visual acuity and IVMP was performed again at 35 and 40 years old. Visual acuity in the left eye was 20/100 at both of these time points, and 5 mg of oral corticosteroid was continued thereafter. Positive results were obtained for anti-aquaporin-4 (AQP4) antibody, and a hyperintense lesion in the left optic nerve was identified on double inversion recovery image (Fig. 1A, B). NMOSD was therefore diagnosed.

At this time, the patient remained blind in the left eye, and brain MRI showed an isointense area in the pons on diffusion-weighted imaging (DWI), and a hyperintense area on the apparent diffusion coefficient (ADC) map and fluid-attenuated inversion recovery (FLAIR) imaging (Fig. 2A–C). She was admitted to another hospital under a diagnosis of recurrent NMOSD. IVMP was administered at 1000 mg/day

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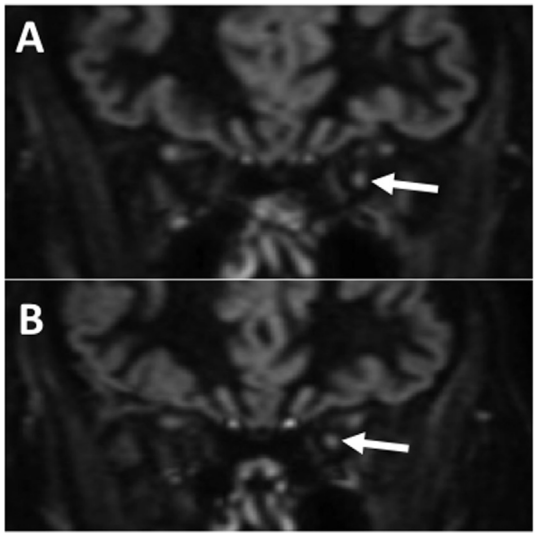

Fig. 1. Recurrent left optic neuritis.
A, B) Representative double inversion recovery images showing left optic neuritis (arrows).

for 3 days, but she suddenly developed left-sided dysesthesia on the final day of steroid pulse therapy. Blood pressure was 202/127 mmHg, and brain CT demonstrated a high-density lesion in the pons (Fig. 2D). She was transferred to our hospital. Blood pressure was 140/80 mmHg under treatment with continuous intravenous nicardipine (7 mg/h). On neurological examination, the patient was alert and well-oriented. She complained of headache, blindness in the left eye, and abducens palsy in the left eye. She had dysarthria, weakness in the left upper limb and both lower limbs, and left-sided sensory disturbance. Cerebellar ataxias were found in the left upper and lower limbs. National Institutes of Health Stroke Scale (NIHSS) score was 10. Brain MRI showed a circumscribed hyperintense area on FLAIR and the ADC map (Fig. 2E, F). Laboratory data showed elevated white blood cells (12.4×10^9/l). Anti-double-stranded DNA antibody, and anti-neutrophil cytoplasmic antibodies (P-ANCA and C-ANCA) and anti-SS-A/SS-B antibodies were within normal ranges. Anti-nuclear antibody was slightly increased (20×), prothrombin time was shortened (international normalized ratio, 0.9) and activated partial thromboplastin time was reduced (25.4 s; control, 35.3 s), possibly owing to IVMP therapy. D-dimer level was < 1 μg/mL. Serum sodium level was 140 mmol/L and glucose level was 154 mg/dL. According to these laboratory data, central pontine myelinolysis (CPM), vasculitis, and other autoimmune diseases were considered unlikely. PRES associated with NMOSD recurrence was diagnosed, with subsequent development of pontine hemorrhage attributed to blood pressure increases from IVMP. We thus treated the patient with nicardipine to strictly control blood pressure, and with tranexamic acid and glycerol for pontine hemorrhage and PRES. At the same time, we extended steroid pulse therapy to 5 consecutive days in total. Moreover, we added immunoadsorption plasmapheresis for 3 days, and double-filtration plasmapheresis for two days. After therapy, blindness improved to light perception. Left-sided sensory disturbance and cerebellar ataxia involving the left upper limb and both lower limbs remained, and final NIHSS decreased to 3.

3. Discussion

The cause of NMOSD is thought to be a specific antibody against the AQP4 water channel located within the optic nerves and spinal cord (Lucchinetti et al., 2002). AQP4 is a membrane protein regulating water balance, and is mainly expressed on capillary blood vessels and glial limiting membrane in the astrocyte foot process (Papadopoulos et al., 2004; Manley et al., 2000). Anti-AQP4 antibody induces inflammatory changes in perivascular lesions and secondary damage to astrocytes implicated in the demyelination seen in NMOSD, which is distinct from the demyelination in multiple sclerosis (Misu et al., 2007). On the other hand, PRES is mainly caused by not only acute blood pressure fluctuations exceeding the ability of cerebral autoregulation, but also by sepsis and autoimmune disease, increasing the permeability of the blood brain barrier (BBB). Disruption of BBB results in vasogenic brain edema, and moreover about 15% of PRES cases are complicated by brain hemorrhage (Hinchey et al., 1996; Hefzy et al., 2009). Importantly, several case series have documented an association between PRES and NMOSD. Disorder of water channels has been speculated to involve the anti-AQP4 antibody, and systemic inflammation could contribute to PRES lesions in NMOSD (Cheng et al., 2013; Magana et al., 2009). In our case, an anti-AQP4-positive NMOSD patient experienced an attack of recurrent NMOSD together with development of PRES in the pons. Furthermore, IVMP increased blood pressure and could thus result in pontine hemorrhage. Considering the diverse mechanisms of pontine hemorrhage, we performed intensive immune

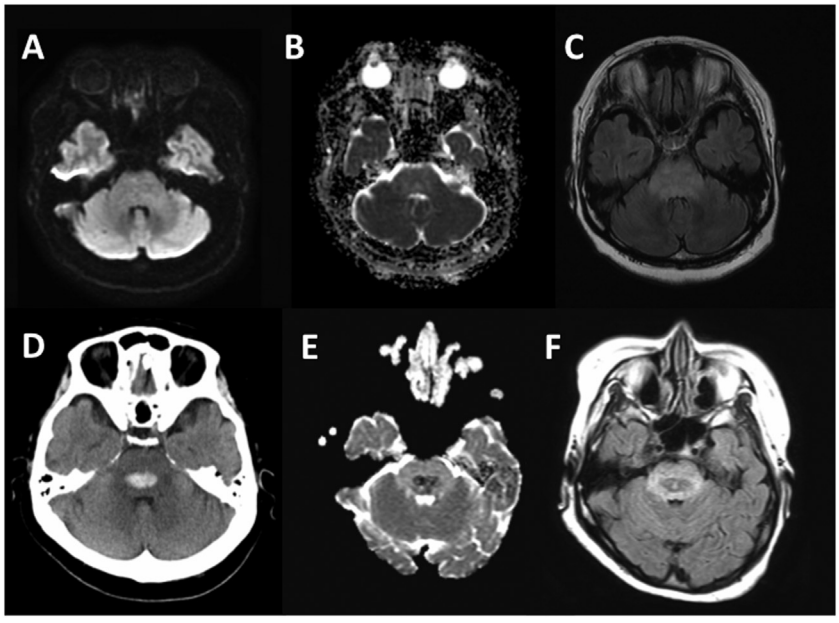

Fig. 2. Posterior reversible encephalopathy syndrome and pontine hemorrhage.
A-C) Representative images from diffusion-weighted imaging, apparent diffusion coefficient (ADC) map and fluid-attenuated inversion recovery (FLAIR) imaging, showing vasogenic edema caused by posterior reversible encephalopathy syndrome. D-F) Representative images of brain CT, and ADC and FLAIR on MRI on day 3 of intravenous methylprednisolone therapy, showing pontine hemorrhage.

Table 1
Epidemiological, clinical, and radiological data from previous and current cases of brain hemorrhage associated with NMOSD.

	Age/Sex	Vascular risk	Diagnosis	NMOSD lesion	Anti-AQP4 antibody	Therapy prior to brain hemorrhage	Complications	Type and location of hemorrhage	Outcome
Case 1 (Shirai et al., 2014)	59/F	–	NMOSD	Medulla oblongata followed by bilateral optic nerve	+	None	Prior recurrent brain hemorrhage	ICH and SAH in right frontal and parietal lobes	Remission
Case 2 (Yaguchi et al., 2017)	48/M	–	NMOSD	Medulla oblongata	+	15 mg of oral corticosteroid	Hypernatremia and increased blood pressure	SAH in the convexity of right parietal lobe	Remission
Our case	51/F	HT, DL	NMOSD	Left optic nerve	+	IVMP	Increased blood pressure and PRES	ICH in pons	Remission

NMOSD = neuromyelitis optica spectrum disorder; AQP4 = aquaporin 4; IVMP = intravenous methylprednisolone; SAH = subarachnoid hemorrhage; ICH intracranial hemorrhage; PRES = posterior reversible encephalopathy syndrome; HT = hypertension; DL = dyslipidemia.

therapy including extension of steroid pulse therapy and plasmapheresis for NMOSD recurrence, together with strict reduction of blood pressure and hemostatic therapy for pontine hemorrhage, resulting in alleviation of symptoms. To the best of our knowledge, this is the first description of pontine hemorrhage associated with PRES in NMOSD in which control of blood pressure and intensive immunotherapy proved effective.

With regard to the relationship between NMOSD and brain hemorrhage, only two cases have been reported (Table 1) (Shirai et al., 2014; Yaguchi et al., 2017). Positive results for anti-AQP4 antibodies were seen in all cases. Prior to brain hemorrhage, Case 1 and our case showed increased blood pressure, while Case 2 displayed recurrent intracranial hemorrhage a few years before the development of NMOSD, for which the etiology was yet to be elucidated in Case 2 (Shirai et al., 2014, Yaguchi et al., 2017). Interestingly, our case showed atherosclerotic vascular risk factors, and represents the first description of a case of PRES with brain hemorrhage in NMOSD.

In conclusion, anti-AQP4 antibody could induce PRES together with NMOSD recurrence, with comorbid pontine hemorrhage associated with increased blood pressure from intravenous steroid pulse therapy, and possibly atherosclerosis in cerebral vessels due to multiple risk factors in our case. For such cases, control of blood pressure and intensive immunotherapy could be effective.

Consent for publication

Written informed consent for publication of this case report and the accompanying images was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Study concept and design: HK and YU. Acquisition of data: HK, YU, MS, NM, KY, and RT. Analysis and interpretation of data: HK, YU, and MS. Drafting of the manuscript: HK and YU. Critical revision of the manuscript for important intellectual content: NH. All authors read and approved the final manuscript.

Availability of data and material

The dataset supporting the conclusions of this article is included within the article.

Ethics approval and consent to participate

The authors declare that ethics approval was not required for this case report.

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