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【 CASE REPORT 】

Neuromyelitis Optica Complicated by Ornithine Transcarbamylase Deficiency Treated Safely with Pulse Steroid Therapy

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Abstract:
Steroid administration to patients with urea cycle disorders can cause hyperammonemia. We encountered a 36-year-old woman with neuromyelitis optica (NMO) complicated by ornithine transcarbamylase (OTC) deficiency. By reducing the doses of steroids and adequate infusion management, we were able to administer pulse steroid therapy without any severe complications. This case indicates the safety of steroid treatment in patients with urea cycle disorders.

Key words: ornithine transcarbamylase deficiency, neuromyelitis optica, pulse steroid therapy, urea cycle disorders

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Introduction

Ornithine transcarbamylase (OTC) deficiency is an X-linked disorder in which the enzyme activity that constitutes the urea cycle (i.e., the metabolic pathway for ammonia) is reduced (1). OTC deficiency is a relatively rare disease with a prevalence rate of 1 in 56,500 at birth (2). Since steroid administration increases protein catabolism in skeletal muscle and increases the levels of amino acids in blood (3), steroid administration to patients with urea cycle disorders can cause severe symptoms of hyperammonemia (4-7). Therefore, the use of steroids in the treatment of autoimmune diseases can be challenging in patients with OTC deficiency.

We herein report a case of OTC deficiency in which pulse steroid therapy was safely administered for the treatment of neuromyelitis optica (NMO) by reducing the doses of steroids and performing adequate infusion management.

Case Report

The patient was a 36-year-old woman. Although no abnormalities had been noted at birth, she weighed slightly less than normal during childhood. She developed symptoms such as abdominal pain and vomiting after eating high-protein food. At 5 years old, hyperammonemia was identified, and OTC deficiency was diagnosed based on high levels of urinary orthoacetic acid, low serum carnitine, and high serum glutamate levels. She subsequently grew up without developing any further symptoms and had stopped her hospital visits.

However, when she was 18 years old, she was frequently hospitalized because of vomiting with elevated serum ammonia levels when she had a cold and was started on L-arginine 4.0 g and phenylbutyrate 1,000 mg. Genetic tests revealed a heterozygous nonsense mutation (c.421C>T) in exon 5 of the OTC gene, which has been reported in OTC deficiency patients (8, 9). Regarding her family history, her mother had symptoms of anorexia and lethargy when she had a cold, but she had not been diagnosed with OTC defi-

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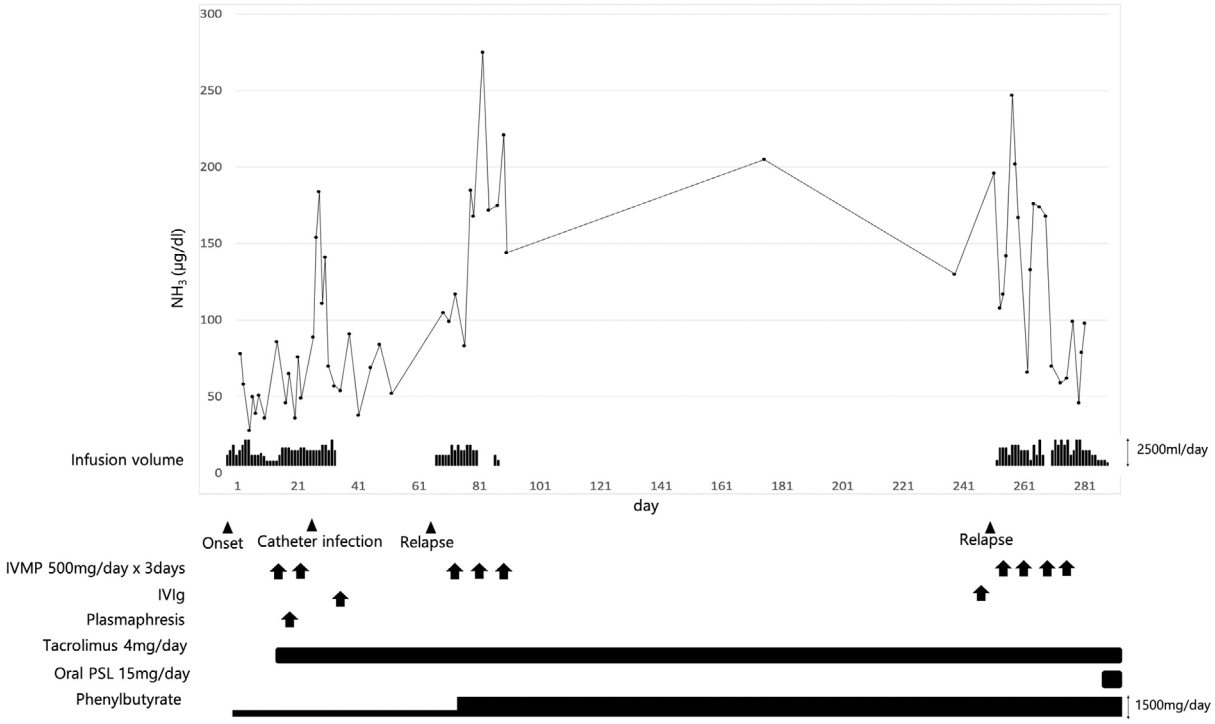

Figure 1. **A Clinical course of this case. IVMP: intravenous methylprednisolone, IVIg: intravenous immunoglobulin, PSL: prednisolone**

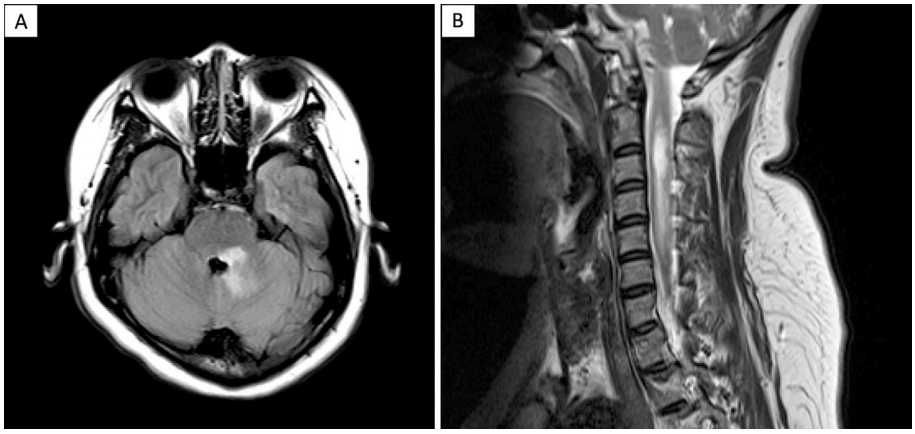

Figure 2. **A: T2-weighted FLAIR image on brain MRI showing a high-intensity area in the left middle cerebellar peduncle. B: T2-weighted imaging on spinal MRI revealing a longitudinally extensive spinal cord lesion from the lower medulla to the C5/6 vertebral level.**

ciency.

The woman was admitted to our hospital because of hypoesthesia of her right limbs and ataxic gait (Fig. 1). Her neurological findings included right gaze directional nystagmus, hypoesthesia in the right face, hypoesthesia in the right upper and lower extremities, dysesthesia in the distal extremities, and truncal ataxia. Other than the neurological symptoms, there seemed to be no physical problems, such as infection, and the elevation of the plasma ammonia levels was slight (62 μg/dL). Therefore, exacerbation of OTC deficiency was not suspected. A cerebrospinal fluid examination showed a slightly elevated cell count (9/μL) and a marked increase in the myelin basic protein level (801 pg/mL). T2-weighted and fluid-attenuated inversion recovery (FLAIR) imaging on brain magnetic resonance imaging (MRI) showed a high-intensity area in the left middle cerebellar peduncle (Fig. 2A). T2-weighted imaging on spinal MRI revealed a longitudinally extensive spinal cord lesion from the lower medulla to the C5/6 vertebral level (Fig. 2B). After admission to the hospital, muscle weakness of the right upper and lower extremities progressed. Since serum anti-aquaporin 4 (AQP4) antibodies were detected by an enzyme-linked immunosorbent assay, a diagnosis of NMO was made.

Two courses of pulse therapy with methylprednisolone (mPSL) were administered every other day for three days.

Table. **Cases of Steroid Therapy to OTC Deficiency.**

Reference	Age (years)	M/F	Primary disease	Steroid	Max NH_3 (μg/dL)	Symptoms, Treatment
(4)	36	M	Sensorineural deafness	Prednisone 60 mg/day	1,185	Tremor, Coma→Intubation
(5)	26	F	Premature delivery	Betamethasone	362	Coma→Intubation, CVVHDF
(6)	56	M	Laryngeal edema	Unknown	320	Coma→Dialysis
(7)	58	F	Asthma attack	IVMP	477	Coma→Intubation

CVVHDF: continuous veno-venous hemodiafiltration, IVMP: intravenous methylprednisolone

The dose of mPSL was reduced to 500 mg/day from the conventional dose of 1,000 mg/day, because the risk of hyperammonemia caused by steroid therapy was a concern. On average, about 2,000 mL of fluid was administered per day during treatment. Because of the limited available steroid dose, plasma exchange (PE) therapy was concomitantly administered from the outset. In addition, we expected that PE therapy would consequently reduce the ammonia levels. However, during the second course of pulse steroid therapy, PE was discontinued because of a catheter infection. Additional intravenous immunoglobulin (IVIg) therapy was administered due to concerns about the immune therapy being insufficient relative to the severity of her NMO. Tacrolimus at 4 mg/day was started to prevent a relapse. Although there was a mild increase in serum ammonia levels after pulse steroid therapy, her neurological symptoms improved without the appearance of serious complications, and she was thus discharged to a rehabilitation hospital.

One month later, the weakness in her right limbs gradually worsened again. Since no possible exacerbation factors for OTC, such as infection, were noted, a relapse of NMO was suspected. Spinal MRI revealed a new NMO lesion at the C1 vertebral level. Three courses of similarly reduced mPSL pulse therapy improved her symptoms. However, after five months, she noticed weakness in the left limbs and paresthesia in her left hand. FLAIR imaging on brain MRI showed a high-intensity area in the left middle cerebellar peduncle. Preceded by one course of IVIg, four courses of pulse steroid therapy were administered for the treatment of NMO. Even during the re-exacerbation of NMO, the treatment with reduced doses of steroids and high-volume infusion resulted in the improvement of neurological symptoms without the appearance of symptoms due to hyperammonemia. To prevent a relapse, oral prednisolone at 15 mg/day was added to her treatment regimen as well as L-arginine 6.0 g and phenylbutyrate 1,500 mg to control ammonia levels. After discharge from the hospital, her serum ammonia levels remained stable. Since then, she has lived for over a year without a recurrence of NMO.

Discussion

We experienced a very rare case of NMO complicated by OTC deficiency. Our experience with this case suggests that pulse steroid therapy can be safely administered to patients with OTC deficiency.

There have been four case reports of patients with OTC deficiency who presented with hyperammonemia resulting in coma due to steroid use (Table) (4-7). In all four of these cases, steroids were administered to patients with undiagnosed OTC deficiency, and there were serious complications, such as coma owing to hyperammonemia. To our knowledge, no cases of the safe administration of pulse steroid therapy to patients with underlying urea cycle disorders have been reported. In the present case, the patient was able to complete her reduced-dose pulse steroid therapy without any serious complications. Adequate supplementation with an isotonic solution was effective in managing serum ammonia levels during pulse steroid therapy. There have been no randomized control trials to investigate the fluid infusion strategy in acute management of hyperammonemia in urea cycle disorders. To prevent the progression of catabolism, we administered a higher amount of glucose through her dietary intake and a glucose-containing infusion than was recommended (6 mg/kg/min) in the guidelines of the Society for the Study of Inborn Errors of Metabolism (10). In the treatment of NMO, it has been shown that a 1,000-mg/day dose of mPLS is more effective than 500 mg/day (11). In our patient however, 500 mg/day pulse steroid therapy also improved her neurological symptoms. We suspect that concomitant PE and IVIg therapies contributed to the successful treatment of NMO in spite of the reduced steroid dose. In particular, while we were unable to complete blood purification therapy due to the catheter infection and the likelihood of the mental stress associated with catheter placement exacerbating the symptoms of OTC deficiency, PE should be considered as an important option for the treatment of similar cases, as blood purification therapy has been reported to be effective in the acute management of both urea cycle disorders (12) and NMO (13).

In the present case, the ammonia levels were able to be controlled even with oral prednisolone at 15 mg/day together with L-arginine 6.0 g and phenylbutyrate 1,500 mg. Of course, since there is a risk of hyperammonemia with steroid administration, it is important to monitor the serum ammonia levels frequently even in the outpatient setting. In recent years, there have been several new effective treatment options for preventing recurrence of NMO, such as eculizu-

mab and satralizumab (14, 15). In particular, since satralizumab monotherapy has been shown to be effective in preventing NMO relapse (15), it can be a an important alternative treatment for OTC deficiency patients with hyperammonemia caused by oral steroids to prevent NMO relapse.

The patient has a known nonsense mutation (c.421C>T) in exon 5 of the OTC gene. This mutation has been reported to change the codon for arginine into a stop codon at position 109 of the OTC protein (8). Since both neonatal- and late-onset cases have been reported with this mutation (8, 9), it may be difficult to predict the severity of OTC deficiency solely based on the genotype (16). In our case, the relatively preserved OTC enzyme activity was a possible factor that led to the success of steroid therapy without exacerbation of OTC deficiency, although the enzyme activity per se was not quantified. Although no cases of OTC deficiency complicated by NMO have been reported, it is necessary to consider the association between the pathogenesis of the two diseases because of their rare comorbidities. Hyperammonemia reportedly increases the expression of AQP4 in astrocytes *in vitro* (17). In addition, it reportedly increases the severity of leakage of the blood-brain barrier *in vitro* (18). However, since there have been no reports of NMO complications in other hyperammonemia-associated diseases, a pathological association between the complications of the diseases in this case was deemed unlikely.

We were able to safely administer pulse steroid therapy to a patient with underlying OTC deficiency by reducing the doses of steroids and performing adequate infusion of an isotonic solution. This experience may provide a basis for therapeutic interventions for patients with urea cycle disorders with comorbid conditions requiring steroid treatment.

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

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