Case Report

Late-onset ornithine transcarbamylase deficiency: a rare cause of recurrent abnormal behavior in adults

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Background: Ornithine transcarbamylase is an enzyme of the urea cycle, which produces urea from ammonia. Although ornithine transcarbamylase deficiency mainly occurs as a severe neonatal-onset disease, a late-onset form that could become symptomatic from infancy to adulthood is also known.

Case presentation: A 34-year-old man presented with sudden onset of abnormal behavior, lethargy, and hyperammonemia (108 μmol/L). He had recently increased daily protein intake, which suggested urea cycle disorder. After initiation of protein-restricted diet and treatment with arginine and sodium phenylbutyrate, his symptoms resolved, along with a decrease in the ammonia level. An R40H(c.119G>A) mutation in the OTC gene was identified.

Conclusion: Awareness of adult onset ornithine transcarbamylase deficiency in a patient with acute psychiatric symptoms due to hyperammonemia is important.

Key words: Ornithine carbamoyltransferase, OTC deficiency

INTRODUCTION

ORNITHINE TRANSCARBAMYLASE (OTC) deficiency is the most common urea cycle disorder (UCD). It is inherited in an X-linked manner and most patients develop severe hyperammonemia in their neonatal period.1 Its severity generally correlates with the residual enzyme activity and the degree of hyperammonemia. Adults with late-onset OTC deficiency (OTCD) show various symptoms triggered by multiple factors such as stress, protein overload, and severe illness.2 Here, we describe a case with abnormal behavior and lethargy who was diagnosed with late-onset OTCD.

CASE REPORT

A 34-YEAR-OLD MAN attended our clinic due to sudden onset of abnormal behavior and lethargy. He was born to non-consanguineous parents and grew up without any health problems, except for well-controlled ulcerative colitis since the age of 32. He graduated from college with above-average grades, has been working for a company, and got married at the age of 28. When he was 30, he suddenly showed abnormal behaviors characterized by screaming and talking to the wall without any reason, and was hospitalized. His symptoms disappeared spontaneously over a few days, and the cause remained unclear and psychosis was suspected. He began to feel fatigued and lethargic after he undertook weight bearing exercises and consumed a high whey-based protein diet, which was later replaced with soy-based diet that improved the symptoms.

On the day of admission, he suddenly started narrating the same story repeatedly while putting two cigarettes at the same time. He complained of lethargy and blurred vision in the emergency room. He was afebrile and fully alert with Glasgow Coma Scale of 15/15 and showed normal findings for vital signs and other physical examinations, except for

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neurological examination, which revealed dysgraphia, acalculia, and fine tremor of his upper limbs.

Hyperammonemia (108 µmol/L) and a relatively low level of blood urea nitrogen (9.4 mg/dL) were detected; all other parameters, including liver enzymes, coagulation ability, and blood glucose were within the normal range. Head computed tomography and magnetic resonance imaging revealed no specific abnormalities. Abdominal ultrasound and contrast computed tomography showed normal liver and spleen findings with no evidence of portosystemic shunt. We also ruled out drug poisoning, central nervous system infection, gastrointestinal bleeding, and urinary tract infection.

Based on clinical findings, we diagnosed him with focal epilepsy and initiated the antiepileptic drug levetiracetam (1000 mg/day). He became asymptomatic except for blurred vision on day 2 and his ammonia level normalized (45 µmol/L). Electroencephalography on day 3 showed diffuse background slowing with delta waves and triphasic waves that suggested a metabolic insult, particularly hyperammonemia. Although his blood ammonia levels increased again on day 7 (173 µmol/L), he was almost asymptomatic except for blurred vision. He was discharged on day 8 on levetiracetam and high protein intake was discouraged.

After discharge, he continued to have occasional blurred vision and disarticulation despite his blood ammonia being within the normal range (39 µmol/L) on day 19.

On day 31, he again presented with lethargy, tremor, and abnormal behaviors. His ammonia level was increased (122 µmol/L), and he was rehospitalized. His medical history revealed “chicken intolerance” and a family history of the early death of his maternal uncle (Fig. 1, II—5) at the age of 2 years due to an unknown cause. As a UCD was suspected, plasma amino acids and urine orotate concentrations were evaluated. Under presumptive diagnosis of UCD, we initiated treatment with protein-restricted diet (40 g/day) and i.v. arginine (12.5 g/day) on day 33. The next day, his symptoms, including blurred vision, disappeared with normalization of serum ammonia level (28 µmol/L). We added oral treatment with sodium phenylbutyrate (4.5 g/day) on day 34. A serum amino acid profile revealed elevated glutamine (925.6 µmol/L; reference range, 422.1–703.8 µmol/L), decreased arginine (51.6 µmol/L; reference range, 53.6–133.6 µmol/L), and normal citrulline levels (20.2 µmol/L; reference range, 17.1–42.6 µmol/L). The levels of urine orotic acid (36.9 mmol/mol Cr; reference range, 0.4–1.2 mmol/L) was increased. These results suggested OTCD (Fig. 2A). The patient was discharged on day 44 (Fig. 3). Since then, there has been no relapse of the symptoms and normal serum ammonia levels have been maintained. An R40H (c.119G > A) mutation in the OTC gene was identified at the Kazusa DNA Research Institute (Kisarazu, Japan).

**DISCUSSION**

Patients with OTC deficiency show variable clinical symptoms such as lethargy, vomiting, ataxia, and seizures due to hyperammonemia. They could also show psychiatric symptoms, mimicking those with psychiatric disorders.
diseases. Patients with certain medical conditions could present with psychiatric symptoms. Differential diagnoses of acute psychosis are endocrine, autoimmune, neurologic, oncologic, and metabolic diseases. We propose that including UCDs in the differential diagnosis is important, particularly in patients with acute psychiatric symptoms.

Many causes including high protein diet, acute stress, major injury, febrile illness, pregnancy, and certain drugs that could induce hyperammonemic episodes in OTCD patients. In our case, a high protein diet and excessive exercise triggered hyperammonemia. Barkovich et al. reported 10 cases in which high protein intake triggered hyperammonemia. They emphasized that a history of recent and remote dietary changes could provide a clue to suspect a UCD. When we encounter patients with hyperammonemia, we should try to obtain a detailed

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Fig. 2. A, Hyperammonemia and orotic acid urea due to ornithine transcarbamylase (OTC) deficiency. B, Arginine supplementation and alternative pathway treatment to manage patients with OTC deficiency.

Fig. 3. Clinical course of our case, a 34-year-old man with ornithine transcarbamylase deficiency. The patient’s symptoms resolved along with decrease in ammonia level.
history to look for the triggers of the event, especially with regards to dietary changes.

In our case, we identified an R40H(c.119G > A) mutation in the OTC gene, which is associated with late-onset OTCD, and there is evidence for a founder effect in northern Kyushu,5 which is the area where the current case was detected. Nishiyori et al. reported that the residual enzyme activity of R40H OTC was 28% of the activity of controls. Our case had a history of increased protein consumption but did not have a simultaneous episode of catabolic stress, which is often associated with a fatal episode of hyperammonemia in patients with OTCD. This might explain a relatively mild clinical course in our patient, although late-onset OTCD can be fatal during the initial episode.6 A protein-restricted diet and adequate nutrition intake to prevent catabolism are essential for management of OTCD patients. When plasma ammonia levels exceed 200 µmol/L, renal replacement therapy is recommended.7 In the present case, blood ammonia levels were below 200 µmol/L, no further rapid increase was observed, and his clinical symptoms were improved with conservative management; therefore, renal replacement therapy was not carried out. Prompt implementation of treatment with arginine, sodium phenylbutyrate, and sodium benzoate is critically important when the diagnosis is suspected,8 as arginine activates the urea cycle and sodium phenylbutyrate and sodium benzoate reduce serum ammonia levels through alternative pathways (Fig 2B).9

CONCLUSION

WHEN ENCOUNTERING A patient with acute psychiatric symptoms due to hyperammonemia, we should consider UCDs and obtain a detailed history, including recent and remote dietary changes that could have triggered episodes of hyperammonemia.

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DISCLOSURE

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Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.
Conflict of interest: None.

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