Case Report

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

Masaoki Hidaka,[1] Eiji Higashi,[1] Takeshi Uwatoko,[1] Kiku Uwatoko,[2] Mayumi Urashima,[3] Hiroshi Takashima,[2] Yoriko Watanabe,[4,5] Takanari Kitazono,[6] and Hiroshi Sugimori[1]

[1]Department of Cerebrovascular Medicine, [2]Department of Neurology, Stroke Center, [3]Department of Pediatrics, Saga Prefecture Medical Centre Koseikan, Saga, [4]Research Institute of Medical Mass Spectrometry, [5]Department of Pediatrics and Child Health, Kurume University School of Medicine, Kurume, and [6]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

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.

Corresponding: Masaoki Hidaka, MD, Department of Cerebrovascular Medicine, Stroke Center, Saga Prefecture Medical Centre Koseikan, Saga 840-8571, Japan. E-mail: masaokihidaka@gmail.com

Received 10 May, 2020; accepted 31 Jul, 2020

Funding information

No funding information provided.

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

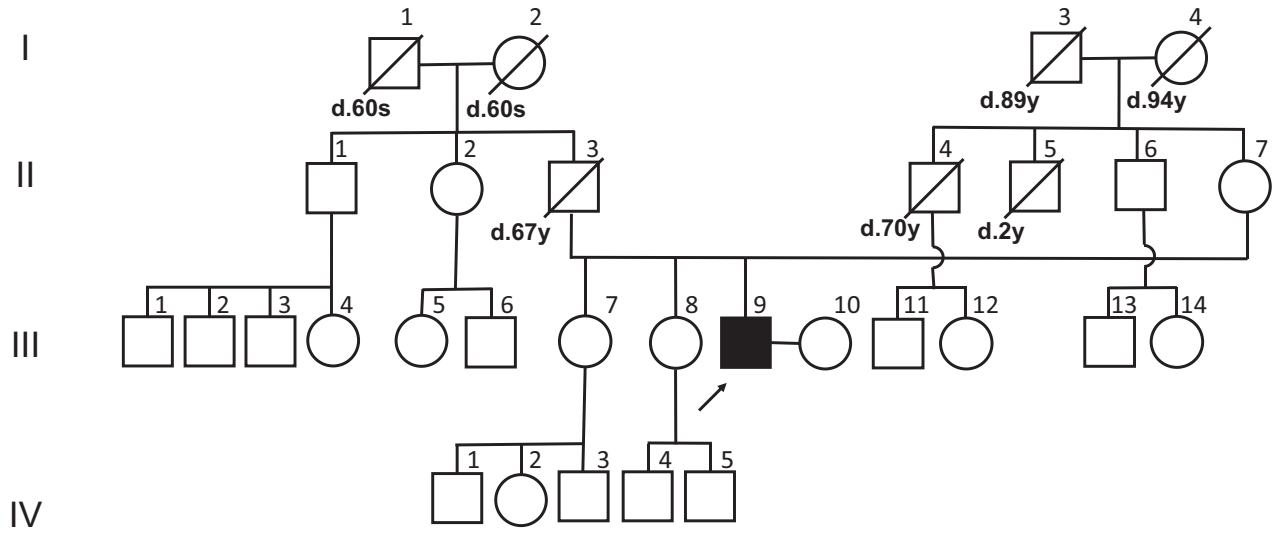

Fig. 1. Family history of our case (III−9; filled square), a 34-year-old man with ornithine transcarbamylase deficiency. An oblique line indicates death (d.). The age at death is also indicated in years (y). His maternal uncle (II−5) died at the age of 2 years. Circle, female; square, male

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 μmol/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.[2] They could also show psychiatric symptoms, mimicking those with psychiatric

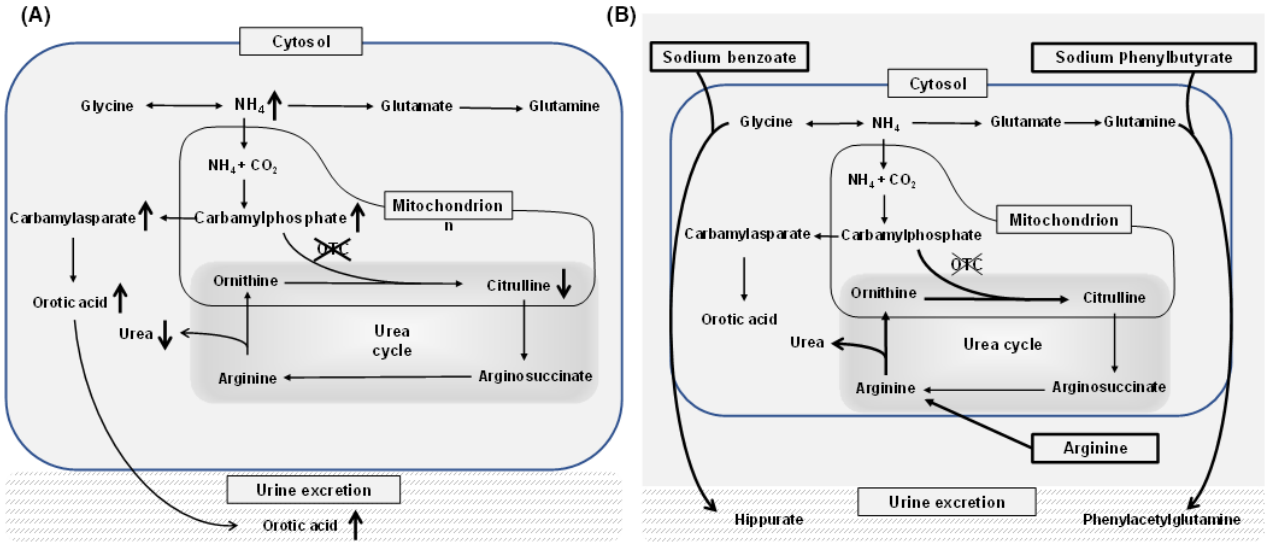

Fig. 2. A, Hyperammonemia and orotic acid urea due to ornithine transcarbamylase (OTC) deficiency. B, Arginine supplementation and alternative pathway treatment to manage patients with OTC deficiency.

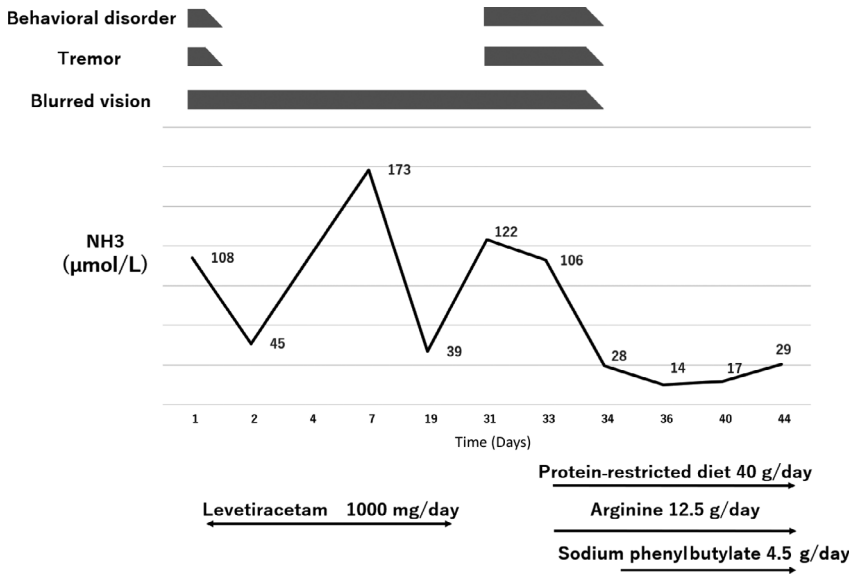

Fig. 3. Clinical course of our case, a 34-year-old man with ornithine transcarbamylase deficiency. The patient's symptoms resolved along with decrease in ammonia level.

diseases. Patients with certain medical conditions could present with psychiatric symptoms.[3] 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.[2] 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.[4] 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

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.

ACKNOWLEDGMENT

NONE.

DISCLOSURE

Approval of the research protocol: N/A.
Informed consent: We obtained written informed consent from the patient.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.
Conflict of interest: None.

REFERENCES

1 Caldovic L, Abdikarim I, Narain S, *et al*. Genotype-phenotype correlations in ornithine transcarbamylase deficiency: a mutation update. J. Genet. Genomics 2015; 42: 181–94.
2 Haberle J, Burlina A, Chakrapani A, *et al*. Suggested guidelines for the diagnosis and management of urea cycle disorders. J. Inherit. Metab. Dis. 2019; 42: 1192–230.
3 Griswold KS, Del Regno PA, Berger RC. Recognition and differential diagnosis of psychosis in primary care. Am. Fam. Physician. 2015; 91: 856–63.
4 Barkovich E, Gropman AL. Late onset ornithine transcarbamylase deficiency triggered by an acute increase in protein intake: a review of 10 cases reported in the literature. Case Rep. Genet. 2020; 2020: 7024735.
5 Nishiyori A, Yoshino M, Kato H, *et al*. The R40H mutation in a late onset type of human ornithine transcarbamylase deficiency in male patients. Hum. Genet. 1997; 99: 171–6.
6 Thakur V, Rupar CA, Ramsay DA, Singh R, Fraser DD. Fatal cerebral oedema from late-onset ornithine transcarbamylase deficiency in a juvenile male patient receiving valproic acid. Pediatr. Crit. Med. 2006; 7: 273–6.
7 Stepien KM, Geberhiwot T, Hendriksz CJ, Treacy EP. Challenges in diagnosing and managing adult patients with urea cycle disorders. J. Inherit. Metab. Dis. 2019; 42: 1136–46.
8 Brusilow SW. Arginine, an indispensable amino acid for patients with inborn errors of urea synthesis. J. Clin. Invest. 1984; 74: 2144–8.
9 Diaz GA, Krivitzky LS, Mokhtarani M, *et al*. Ammonia control and neurocognitive outcome among urea cycle disorder patients treated with glycerol phenylbutyrate. Hepatology 2013; 57: 2171–9.