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CASE REPORT

Late-onset ornithine transcarbamylase deficiency associated with hyperammonemia

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Abstract The urea cycle converts ammonia and produces urea. One form of urea cycle abnormality is ornithine transcarbamylase (OTC) deficiency. This hereditary disorder is associated with hyperammonemia. OTC deficiency commonly appears during neonatal and early childhood life and is rare in adults. We report a 69-year-old man who presented at the local hospital with 3-day loss of appetite, early morning vomiting, and state of confusion. Blood ammonia was 293 μg/dl. At 2–3 h after admission, the patient went into a deep coma. He was intubated and admitted immediately to the intensive care unit. Treatment, including sustained hemodialysis, failed to lower blood ammonia level. His grandchild died of OTC deficiency at 6 year of age. Computed tomography, magnetic resonance imaging and esophagogastroduodenoscopy showed no abnormalities. On admission to our hospital, he complained of vomiting and disturbance of consciousness, hyperammonemia, and normal anion gap. Genetic analysis showed *A208T* mutation. The deceased grandchild with OTC deficiency also had the same mutation. Long-term hemodialysis coupled with administration of L-arginine and lactulose resulted in improvement of blood ammonia level. Early diagnosis and treatment of adult-onset OTC deficiency are essential to avoid serious complications.

Keywords OTC · A208T · Late-onset

Introduction

The urea cycle is the metabolic pathway that counteracts the toxic products of ammonia and produces urea as the final product. Deficiency of the enzyme ornithine transcarbamylase (OTC) is a well-described urea cycle abnormality and clinically associated with hyperammonemia. In Japan, the prevalence of urea cycle abnormalities is 1 in 8,000 people, and the prevalence of OTC deficiency is 1 in 14,000 people. Most cases with OTC deficiency present at birth up to 5 years of age, but approximately 20% of cases appear in patients aged ≥6 years, although onset in people aged ≥18 years is rare [1]. Patients presenting with disturbance of consciousness associated with hyperammonemia should be treated immediately to prevent the development of serious complications. Here, we report a case of OTC deficiency in a 69-year old man who presented with disturbance of consciousness associated with hyperammonemia.

Case report

Clinical history: A 69-year-old man presented with fever of 37 °C, together with loss of appetite for three days. He described vomiting from early morning, and inability to have a conversation. He was admitted to the local hospital. Clinical examination showed normal respiratory and

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cardiovascular systems, but the level of consciousness was labelled as confusion. Blood ammonia level was high at 293 μg/dl. Two to three hours later, the patient went into a deep coma. He was intubated and admitted to the intensive care unit. However, hyperammonemia persisted despite long-term hemodialysis. Accordingly, the patient was transferred to our hospital for further management.

Past history: Type 2 diabetes mellitus, hyperuricemia.
Family history: Grandchild died of OTC deficiency at 6 years of age (Fig. 1).
Symptoms: JCSIII-300.

Laboratory findings: Arterial blood gases while on FiO_2 of 0.4%—pH 7.595, $PaCO_2$ 21.7 mmHg, PaO_2 222 mmHg, HCO_3 21.0 mmol/l, lactate 1.9 mmol/l, BE −0.6 mmol/l.

Complete blood count: Leukocyte count 11,720/μl, erythrocyte count 518×10^4 μl, hemoglobin 15.2 g/dl, hematocrit 44.0%, platelet count 25×10^4/μl.

Biochemical tests: Total bilirubin 1.3 mg/dl, aspartate aminotransferase 46 U/L, alanine aminotransferase 48 U/L, lactic dehydrogenase 296 U/L, alkaline phosphatase 150 U/L, creatine kinase 339 U/L, total protein 6.3 g/dl, albumin 3.0 g/dl, blood urea nitrogen 9.5 mg/dl, creatinine 0.75 mg/dl, C-reactive protein 2.8 mg/dl, Na^+ 137 mEq/l, K^+ 4.0 mEq/l, Cl^- 103 mEq/l, Ca^{2+} 4.0 mEq/l, phosphate 4.4 mEq/l, Mg 2.4 mEq/l, NH_3 231 μmol/l, HbA1c 7.6%, blood glucose 342 mg/dl (Table 1).

Head computed tomography (CT): no particular findings.
Abdomen CT: no particular findings.
Head magnetic resonance imaging: no particular findings.
Esophagogastroduodenoscopy: no polyp, no varicosities.
Diagnosis: Among the diagnostic criteria of urea cycle abnormality, the patient presented with vomiting, disturbance of consciousness and family carriers. Furthermore, the patient also had hyperammonemia with normal anion gap. A definite diagnosis could be made by identification of abnormal orotic acid on urine amino acid analysis, presence of abnormal enzymatic activity, or genetic analysis.

The patient underwent serum and urine amino-acid analyses and urine orotic acid after start of therapy four days later. Citrulline was 10.4 nmol/ml (below the normal level), arginine was 139.0 nmol/ml and glutamine was 437.7 nmol/ml.

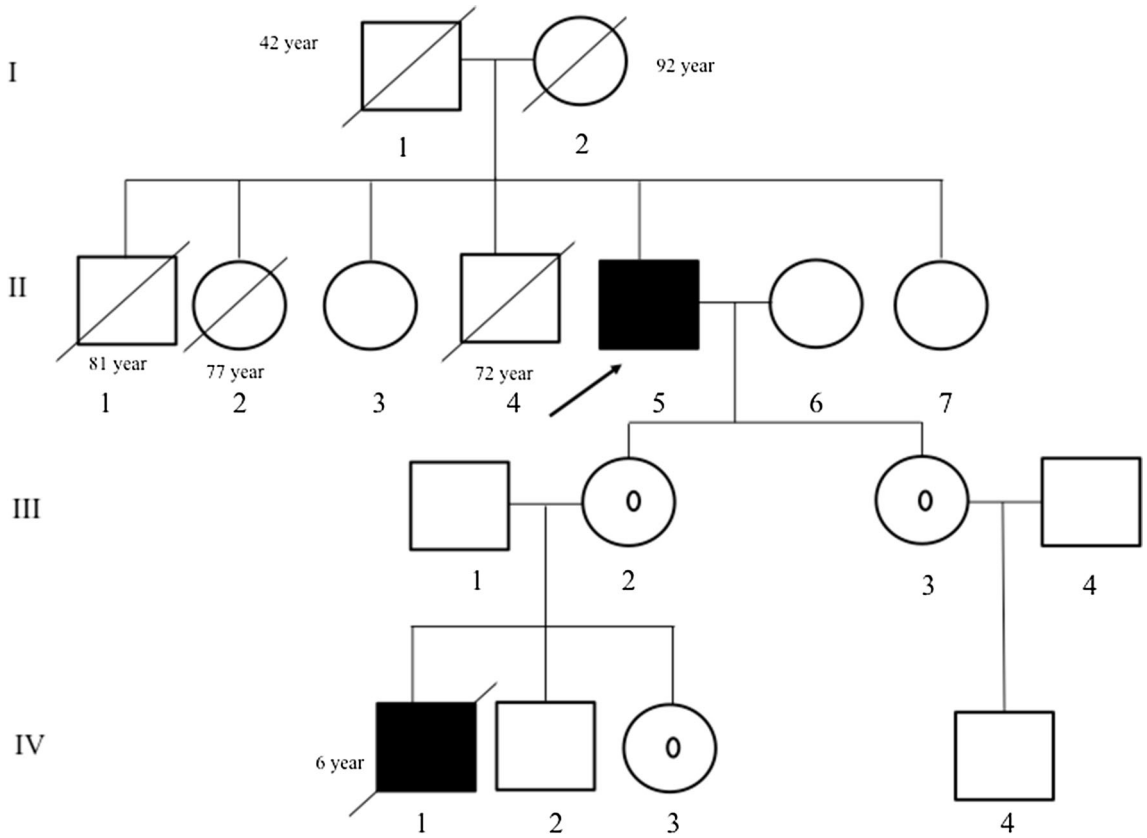

Fig. 1 Pedigree, ◎ female heterozygous for the *A208T* mutation. *Filled square*; male hemizygous for *A208T* mutation

Table 1 Results of laboratory tests

Blood tests						Arterial blood gases	
WBC count	11720/μl	T–bilirubin	1.3 mg/dl	Na	137 mEq/l	pH	7.595
RBC count	518 × 10^4/μl	AST	46 U/L	K	4 mEq/l	pCO_2	31.7 mmHg
Hemoglobin	15.2 g/dl	ALT	48 U/L	Cl	103 mEq/l	pO_2	82 mmHg
Hematocrit	44%	LDH	296 U/L	Ca	4 mEq/l	HCO_3^-	21 mEq/l
Platelet count	25 × 10^4/μl	ALP	150 U/L	P	4.4 mg/dl	SBE^-	−0.6
		CK	339 U/L	Mg	2.4 mg/dl	SaO_2	99.7%
Prothrombin time	70%	Total protein	6.3 g/dl	NH_3	231 μmol/l	Lac	1.9
APTT	41.6 s	Albumin	3 g/dl	HbA1c	7.6%	Total Hb mass	15.4
		BUN	9.5 mg/dl	Glucose	342 mg/dl	CO-Hb	0.9
HBsAg	(−)	Creatinine	0.75 mg/dl			Anion gap	10
HCV antibodies	(−)	C-reactive protein	2.8 mg/dl				
		Citrulline	10.4 nmol/ml				
		Arginine	139.0 nmol/ml				
		Glutamine	437.7 nmol/ml				

APTT activated partial thromboplastin time, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *LDH* lactate dehydrogenase, *ALP* alkaline phosphatase, *CK* creatine kinase, *BUN* blood urea nitrogen

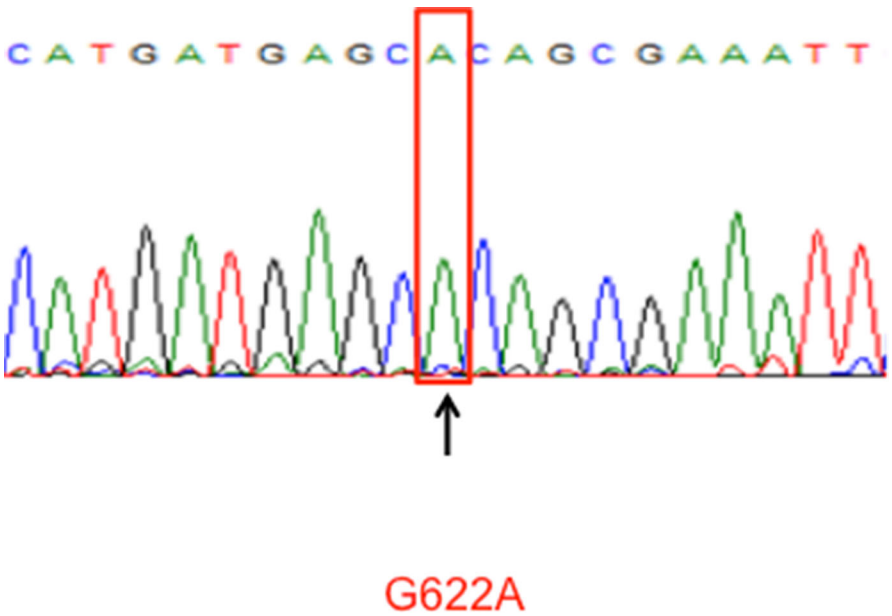

Fig. 2 Genetic diagnosis: the 622nd base guanine of the OTC gene mutated to adenine. A hemizygous variation from the 208th amino acid alanine to threonine was identified

Genetic diagnosis: Genetic analysis showed a mutation in the 622nd base guanine of the OTC gene mutated to adenine, and a hemizygous variation from the 208th amino acid alanine to threonine was identified in the serum. The grandchild who died from OTC deficiency had the same mutation (Fig. 2). The mutant gene was not investigated in hepatocytic cells because the patient refused a liver biopsy.

Clinical course: A definite diagnosis could not be made, but we started treatment assuming the diagnosis of OTC deficiency in a family carrier.

Insulin was administered at a sustained dosage, which improved blood sugar level immediately.

The patient underwent hemodialysis and was treated with L-arginine and lactulose. The above treatment regimen resulted in reduction of blood ammonia level. After termination of artificial ventilation and switching to normal breathing, a high (1800 kcal) calorie diet was provided, together with levocarnitine (Fig. 3). The patient was discharged after nine days of hospitalization. At the last outpatient visit 18 months after discharge from the hospital, the patient was in good condition and remained under treatment with L-arginine, levocarnitine and lactulose.

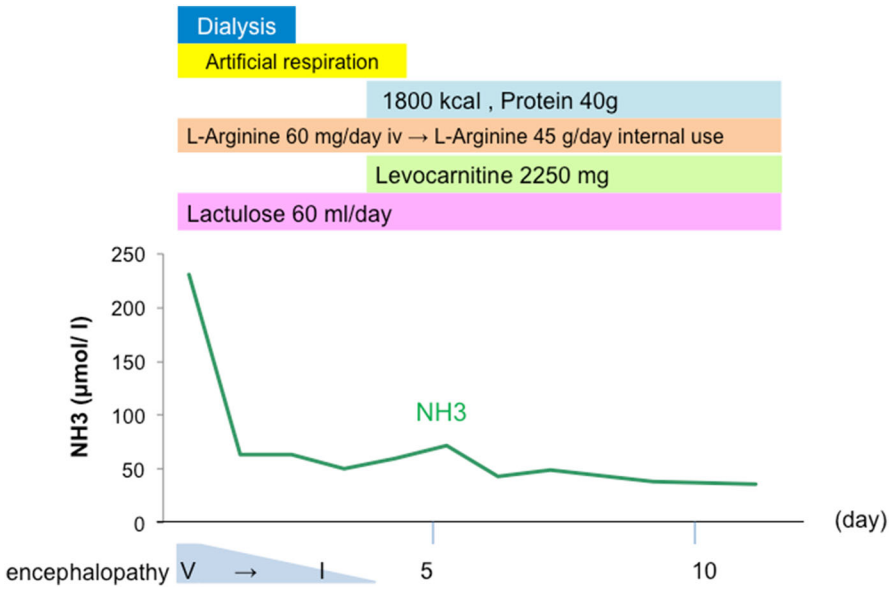

Fig. 3 Clinical course

Table 2 Symptomatic patients aged >40 years reported in the literature

Disease onset (years)	Gender	Mutation	Country	Outcome	References
56	Male	*R40H*	Japan	Died	Matsuda et al. [4]
42	Male	*Y55D*	Japan	Died	Nishiyori et al. [5]
62	Male	*P255T*	USA	Died	Klein et al. [6]
67	Male	*A208T*	Netherland	Died	Bijvoet et al. [7]
69	Male	*A208T*	Japan	Live	Our case

Discussion

In the mitochondria and cytoplasm of hepatocytes, the metabolic pathway of the urea cycle produces urea from ammonia. OTC deficiency is due to abnormality in the OTC enzyme, which catalyzes the combination of carbamyl phosphoric acid and ornithine, both of which are involved in ammonia detoxification. Detoxification of ammonia is hindered in the presence of OTC deficiency, resulting in hyperammonemia [2].

OTC deficiency is an X-linked heredity abnormality, but 10% of the female carriers become symptomatic, and present with various abnormalities that parallel the degree of deflection of the X chromosome [3]. Several publications had described cases with OTC deficiency aged 0–5 years, although approximately 20% of the affected children are aged ≥6 years. To the best of our knowledge, our 69-year-old patient is the oldest reported case [4]. Interestingly, four reports have described OTC deficiency in patients aged >40 years (Table 2).

Matsuda et al. [4] reported a 56-year-old patient with *R40H* mutation. Nishiyori et al. [5] reported a 42-year-old patient with *Y55D* mutation. Klein et al. [6] reported a 62-year-old patient with *P255T* mutation. Although Bijvoet [7] reported a 67-year-old patient with *A208T* mutation, there are no reports of patients with *A208T* mutation in Japan to date. Although Ausems et al. [8] reported a 97-year-old patient with *A208T* mutation, he was asymptomatic and did not present with hepatic coma. With regard to prognosis, 4 of the patients listed in Table 2 died. Thus, our case is perhaps the only Japanese patient who survived symptomatic OTC deficiency with *A208T* mutation.

Why did OTC deficiency appear clinically at an older age in our patient? First, gene mutations such as *R40H*, *P255T*, *Y55D*, and *A208T* were reported previously in patients with late-onset OTC deficiency [4–6, 8]. In this regard, Ausems et al. reported a 10-year-old boy with *A208T* died of late-onset OTC deficiency [8]. To date, >340 gene mutations have been described, and mutations peculiar to each family have also been reported [9]. Detection of mutations by gene analysis confirms the diagnosis of OTC. Second, the severity of OTC deficiency ranges from asymptomatic carrier to death as in newborn babies. In our case, OTC deficiency developed in the grandchild at 6 years of age. However, onset in children is thought to be associated with a milder form of OTC, whereas the typical age of onset of OTC deficiency is the

neonatal period. In this regard, the time of onset and disease severity may be different in siblings with the same gene [8]. Third, late-onset OTC deficiency develops with internal use of valproic acid, starvation, and infection. The disorder could also be associated symptomatically with fever and loss of appetite. The Japanese eating habits greatly changed after the 1980–1990s, with a high increase in protein intake. It is possible that certain diets can delay the appearance of OTC [4].

Treatment of OTC deficiency includes administration of a megadose of glucose to control protein catabolism. Furthermore, arginine and citrulline are also used as medical treatments to lower high blood ammonia levels. The lack of arginine is also associated with sufficient levels of ornithine necessary for the metabolic response of the urea cycle, and removal of excess ammonia becomes difficult. Since arginine is an essential amino acid for the synthesis of proteins, catabolism of the protein is aggravated due to the lack of arginine. Sodium phenylbutyrate and sodium benzoate are used for excretion of surplus nitrogen.

Failure of response to the above treatment requires a switch to hemodialysis or hemofiltration dialysis. Long-term treatment includes diet (protein restriction with sufficient calorie supplementation), medications, and amino acid therapy. Arginine, citrulline, sodium phenylbutyrate, sodium benzoate, L-carnitine, and lactulose are used in the treatment. Another treatment option is liver transplantation, which can achieve satisfactory results especially in patients with medium-grade symptoms [10]. Since the main affected organ is the liver, a successful liver transplantation is expected to improve the quality of life of the patient.

Conclusion

We reported a 69-year-old man with late-onset OTC deficiency who presented with disturbance of consciousness due to hyperammonemia. Symptoms related to urea cycle abnormalities in adults are rare, but early diagnosis and treatment are necessary for early improvement.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

Human/animal rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all patients for being included in the study.

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