Case Reports in Gastroenterology

Case Rep Gastroenterol 2014;8:337–345

DOI: 10.1159/000369131
Published online: November 5, 2014

1662–0631/14/0083–0337$39.50/0
www.karger.com/crg

Antepartum Ornithine Transcarbamylase Deficiency

Hitoshi Nakajima[a] Yosuke Sasaki[a] Tadashi Maeda[a] Masako Takeda[a] Noriko Hara[a] Kazushige Nakanishi[a] Yoshihisa Urita[a] Risa Hattori[b] Ken Miura[c] Tomoko Taniguchi[d]

Departments of [a]General Medicine, [b]Gastroenterology, [c]Neurology and [d]Gynecology, Faculty of Medicine, Toho University, Tokyo, Japan

Key Words
Ornithine transcarbamylase · Ornithine transcarbamylase deficiency · Urea cycle deficiency · Pregnancy

Abstract
Ornithine transcarbamylase deficiency (OTCD) is the most common type urea cycle enzyme deficiencies. This syndrome results from a deficiency of the mitochondrial enzyme ornithine transcarbamylase, which catalyzes the conversion of ornithine and carbamoyl phosphate to citrullin. Our case was a 28-year-old female diagnosed with OTCD following neurocognitive deficit during her first pregnancy. Although hyperammonemia was suspected as the cause of the patient's mental changes, there was no evidence of chronic liver disease. Plasma amino acid and urine organic acid analysis revealed OTCD. After combined modality treatment with arginine, sodium benzoate and hemodialysis, the patient's plasma ammonia level stabilized and her mental status returned to normal. At last she recovered without any damage left.

Introduction

The urea cycle was first described in 1932 by Krebs and Henseleit. Urea cycle deficiency (UCD) result from defects in the clearance of excess nitrogen produced by the breakdown of protein and other nitrogen-containing molecules. These amino acid products are degraded by hepatic transamination and oxidative deamination to produce ammonia. Ammonia is then converted to urea via the five enzymes of urea cycle (carbamoyl phosphate synthetase, ornithine transcarbamylase, argininosuccinic acid synthetase, argininosuccinase and argi-

Hitoshi Nakajima
Department of General Medicine
Faculty of Medicine, Toho University
6-11-1 Omori-Nishi, Ota-ku, Tokyo 143-8541 (Japan)
E-Mail nakaji_ma521@yahoo.co.jp

nase) [1] and excreted by the kidneys. Any disruption to this nitrogen excretion pathway has the potential to cause hyperammonemia and clinical encephalopathy.

Ornithine transcarbamylase deficiency (OTCD) (OMIM 311250), an X-linked genetic disorder, is the most commonly inherited UCD. While hemizygous males typically present with hyperammonemic coma in the neonatal period, unusual female cases sometimes have been reported with late-onset presentations [2].

Here we present the case of a previously healthy 28-year-old woman who developed neurological cognitive abnormality because of undiagnosed OTCD. This case illustrates that UCD can present in adults and can be fatal. Acute neurological decline and hyperammonemia in previously healthy adults should be investigated and managed with this consideration in mind. Our investigation of this patient bears on the potential roles of genetic and environmental factors in the onset of disease expression. We describe a female case of late-onset OTCD presenting as severe acute hyperammonemia with coma, successfully treated with arginine, benzoate and hemodialysis [1]. Treating this previously healthy antepartum OTCD female without delay was very difficult, and we believe this case report could be suggestive and inspire every physician and gastroenterologist.

Case Report

A 28-year-old female visited us with a chief complaint of disturbance of consciousness (Japan Coma Scale 30). She was confirmed to be pregnant in the 16th week and suffered from hyperemesis gravidarum. She could not take enough food. This was her first pregnancy. However, she began to present mild unconsciousness and this symptom could not be explained by the pregnancy-related hyperemesis. At last, she was hospitalized for further examination of unconsciousness of unknown origin. Her unconsciousness was progressive, with an elevated plasma ammonia level and a deteriorated Japan Coma Scale value (table 1). Liver function data were quite normal and other laboratory data were within normal limits. She had no specific past history referring to present illness and she was informed to have no family history.

In the first place, we administered glucose, lactulose and kanamycin sulfate to prevent ammonia level from increasing. However, hyperammonemia deteriorated and we had to lower the plasma ammonia level aggressively and started hemodiafiltration (HDF). Plasma ammonia was temporally lowered just after HDF, but soon after it was elevated again. We thus began continuous HDF, and thereafter the ammonia level could be hold without rising again and went down gradually. Amino acid analysis showed her plasma and urine to be consistent with OTCD, allowing us to explain the etiology of hyperammonemia and cognitive and motor disturbance (table 2). Gene analysis revealed a mutation which confirmed OTCD (fig. 1). There is one report in the literature of an amino acid substitution at the same site in exon 8 (829 C>T, R277W) which was also associated with late-onset symptoms of OTCD [3].

We could follow brain magnetic resonance imaging (MRI) together with illness state during whole disease period (fig. 2). A high-signal area in the white matter of the bilateral frontal lobes was revealed according to her illness. She was gradually getting relieved from encephalopathy along with the lowered plasma ammonia level. She was discharged from the hospital on the 56th hospital day (fig. 3). She recovered completely and fortunately with no damage left.

Discussion

The ornithine transcarbamylase gene *(OTC)* is encoded on the X chromosome and is expressed in the mitochondrial matrix of the small intestine and liver, where it catalyzes the synthesis of citrullin from carbamoyl phosphate and ornithine [4]. OTCD has an estimated incidence of 1 in 14,000 and is the only X-linked urea cycle disorder [4]. Research on the biochemical and molecular bases of OTCD by Tuchman et al. [5] revealed a wide spectrum of genetic defects resulting in different phenotypes. Mutations predicted to abolish all enzyme activity were found in the neonatal-onset group, while mutations causing partial or varying enzyme deficiency were found in the late-onset group [2]. Patients who were asymptomatic until much later in life were almost always heterozygotes and symptom onset coincided with a precipitating factor such as infection, trauma, sodium valproate, surgery, childbirth or physiological stress [6, 7].

OTCD is the most common urea cycle disorder leading to hyperammonemia and substantial cognitive and motor deficit. Neonatal OTCD survivors sustain brain injury with subsequent mental retardation and cerebral palsy [8]. Males with latent-onset OTCD are not as severely affected but show deficit in executive function such as motor planning and working memory. A broad phenotype is also seen in heterozygous females, with symptoms ranging from behavioral and learning disabilities to protein intolerance, stroke-like episodes and hyperammonemic coma [9–14]. Previous autopsy and neuronal approaches revealed substantial brain injury leading to white matter damage [15]. High-signal image in her MRI was supported by the above evidence.

Neurocognitive deficits are a major cause of significant disability in OTCD. Observed cognitive changes that immediately follow hyperammonemia include decreased mental flexibility, impaired attention, poor planning, problems with working memory and increased impulsivity. In our patient, the results of plasma and urine amino acid analyses were compatible with OTCD, allowing us to explain the etiology of her hyperammonemia and neurocognitive deficits.

A diagnosis of OTCD is confirmed when plasma amino acid analysis shows elevated glutamine and alanine levels and a decreased citrullin level and when orotic acid and uridine are found in the urine [4].

There are no definite guidelines as to when to initiate dialysis in patients with hyperammonemia [1]. However, if a patient presents neurocognitive symptom, high-efficiency hemodialysis should be considered to prevent encephalic damage from advancing. The rapid removal of ammonia by hemodialysis is not associated with disequilibrium syndrome because ammonia is a gas and not osmotically active. Our case presented cognitive change in the initial period of her first pregnancy. She had had no previous episode of cognitive disorder. She was not informed about her cousin's history of congenital metabolic disorder. The cousin was male and found to present hyperammonemia 6 months after birth. He was saved by appropriate therapy in childhood, so his medical history was not considered as an important event by any family member. She had been working as a nurse in a general hospital for 5 years and was not worried at all. As a nurse, she had corresponding medical knowledge, but she did not feel any disability during her job.

We could follow the patient's cognitive condition using cerebral MRI. Gropman et al. [15] analyzed 19 adult OTCD patients and showed that diffusion tensor imaging is a useful technique that allows identification of white matter tracts invisible by conventional MRI and provides a quantitative measure of the microscopic characteristics related to the directional organization of the brain. We could show improvement referring to cognitive deficit

over time by conventional MRI. We consider that simple MRI should be useful enough because obvious high-density signals had disappeared 70 days after in our case.

Our patient had no history of liver function damage and this was her first pregnancy. Diagnostic workup revealed hyperammonemia and increased orotic acid levels in urine, as well as an elevated plasma glutamine level and lowered ornithine, citrullin and arginine levels. Suspecting UCD, we started further examination.

Increased nitrogen load of the uterus, placenta and fetus in the antepartum period can partially explain why the urea cycle capability of female *OTC* mutation carriers overloads in the postpartum period. Various triggers, such as trauma, infections, surgery, childbirth, parenteral nutrition and the initiation of sodium valproate therapy, have been reported. Unfortunately, our patient could not avoid abandoning her baby in order to be saved herself.

OTCD should be considered in the differential diagnosis of antepartum and postpartum mental status changes in the presence of normal liver function. Blood ammonia levels should be taken urgently. OTCD may not be excluded if a pathogenetic mutation could not be identified. Unknown mutations in other genes can cause phenocopy of OTCD. A careful and appropriate treatment of the patient and a multidisciplinary team approach can help prevent brain damage, neurological deficits and death.

Acknowledgement

We thank Dr. Okada (National Center for Child Health and Development) and Dr. Hasegawa (Shimane University) for their corporation with gene analysis and amino acid analysis.

Disclosure Statement

No conflict of interest exists.

References

1 Choi DE, Lee KW, Shin YT, Na KR: Hyperammonemia in a patient with late-onset ornithine carbamoyltransferase deficiency. J Korean Med Sci 2012;27:556–559.
2 Tuchman M, Morizono H, Rajagopal BS, Plante RJ, Allewell NM: The biochemical and molecular spectrum of ornithine transcarbamylase deficiency. J Inherit Metab Dis 1998;21(suppl 1):40–58.
3 Finkelstein JE, Francomano CA, Brusilow SW, Traystman MD: Use of denaturing gradient gel electrophoresis for detection of mutation and prospective diagnosis in late onset ornithine transcarbamylase deficiency. Genomics 1990;7:167–172.
4 Brusilow SW, Maestri NE: Urea cycle disorders: diagnosis, pathophysiology, and therapy. Adv Pediatr 1996;43:127–170.
5 Tuchman M, McCullough BA, Yudkoff M: The molecular basis of ornithine transcarbamylase deficiency. Eur J Pediatr 2000;159(suppl 3):S196–S198.
6 Gordon N: Ornithine transcarbamylase deficiency: a urea cycle defect. Eur J Paediatr Neurol 2003;7:115–121.
7 Ellaway CJ, Bennetts B, Tuck RR, Wilcken B: Clumsiness, confusion, coma, and valproate. Lancet 1999;353:1408.
8 Batshaw ML, Brusilow S, Waber L, Blom W, Brubakk AM, Burton BK, Cann HM, Kerr D, Mamunes P, Matalon R, Myerberg D, Schafer IA: Treatment of inborn errors of urea synthesis: activation of alternative pathways of waste nitrogen synthesis and excretion. N Engl J Med 1982;306:1387–1392.
9 Batshaw ML, Hyman SL, Mellits ED, Thomas GH, DeMuro R, Coyle JT: Behavioral and neurotransmitter changes in the urease-infused rat: a model of congenital hyperammonemia. Pediatr Res 1986;20:1310–1315.
10 Christodoulou J, Qureshi IA, McInnes RR, Clarke JT: Ornithine transcarbamylase deficiency presenting with strokelike episodes. J Pediatr 1993;122:423–425.

11 Maestri NE, Brusilow SW, Clissold DB, Bassett SS: Long-term treatment of girls with ornithine transcarbamylase deficiency. N Engl J Med 1996;335:855–859.
12 Maestri NE, Lord C, Glynn M, Bale A, Brusilow SW: The phenotype of ostensibly healthy women who are carriers for ornithine transcarbamylase deficiency. Medicine (Baltimore) 1998;77:389–397.
13 Mamourian AC, du Plessis A: Urea cycle defect: a case with MR and CT findings resembling infarct. Pediatr Radiol 1991;21:594–595.
14 Pridmore CL, Clarke JT, Blaser S: Ornithine transcarbamylase deficiency in females: an often overlooked cause of treatable encephalopathy. J Child Neurol 1995;10:369–374.
15 Gropman AL, Gertz B, Shattuck K, Kahn IL, Seltzer R, Krivitsky L, Van Meter J: Diffusion tensor imaging detects areas of abnormal white matter microstructure in patients with partial ornithine transcarbamylase deficiency. AJNR Am J Neuroradiol 2010;31:1719–1723.

Table 1. Laboratory data on admission, analysis of blood amino acid and analysis of urine organic acid

Blood chemistry		**Blood count**	
TP, g/dl	6.7	WBC/μl	12,500
ALB, g/dl	3.9	N, %	76.3
T-Bil, mg/dl	1.3	Ly, %	18.8
AST, IU	47	Mo, %	4.5
ALT, IU	95	Eo, %	0.2
γ-GTP, IU/l	43	B, %	0.2
ALP, IU/l	104	RBC/μl	458×10^4
LDH, IU	148	Hb, g/dl	13.8
BUN, mg/dl	12	Plt/μl	23.8×10^4
Cr, mg/dl	0.68		
Na, mM	137	**Urinalysis**	
K, mM	4.7	Spec. gravity	1.035
Cl, mM	105	pH	6.0
AMY, IU/l	86	Sugar	(+)
CPK, IU/l	40	Occult blood	(–)
CRP, mg/dl	0.1	Acetone	(3+)
T-CHO, mg/dl	84	Bilirubin	(–)
TG, mg/dl	48	Urobilinogen	(+)
HDL-C, mg/dl	41		
NH_3, μg/dl	268		

Blood coagulation	
PT, %	30
HBsAg	(–)
HCV	0.1
Glu, mg/dl	120
HbA1c, %	4.9

Amino acid	nmol/ml		Normal range
Glutamate	55.3		12.6–62.5
Glutamine	729.2	↑	422.1–703.8
Citrulline	14.4	↓	17.1–42.6
Ornithine	10.0	↓	31.3–104.7
Arginine	23.4	↓	53.6–133.6

Organic acid	Result
Orotic acid	elevated
Uracil	elevated

Table 2. Plasma amino acid analysis and urine organic acid analysis

Amino acid	nmol/ml		Normal range
Glutamate	55.3		12.6–62.5
Glutamine	729.2	↑	422.1–703.8
Citrulline	14.4	↓	17.1–42.6
Ornithine	10.0	↓	31.3–104.7
Arginine	23.4	↓	53.6–133.6

Organic acid	Result
Orotic acid	elevated
Uracil	elevated

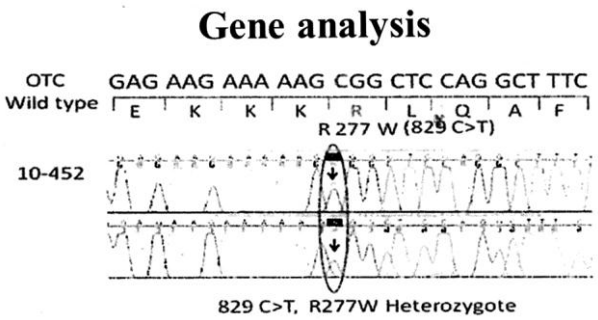

Fig. 1. Gene analysis showed R277W (829 C>T) heterozygote mutation.

DOI: 10.1159/000369131

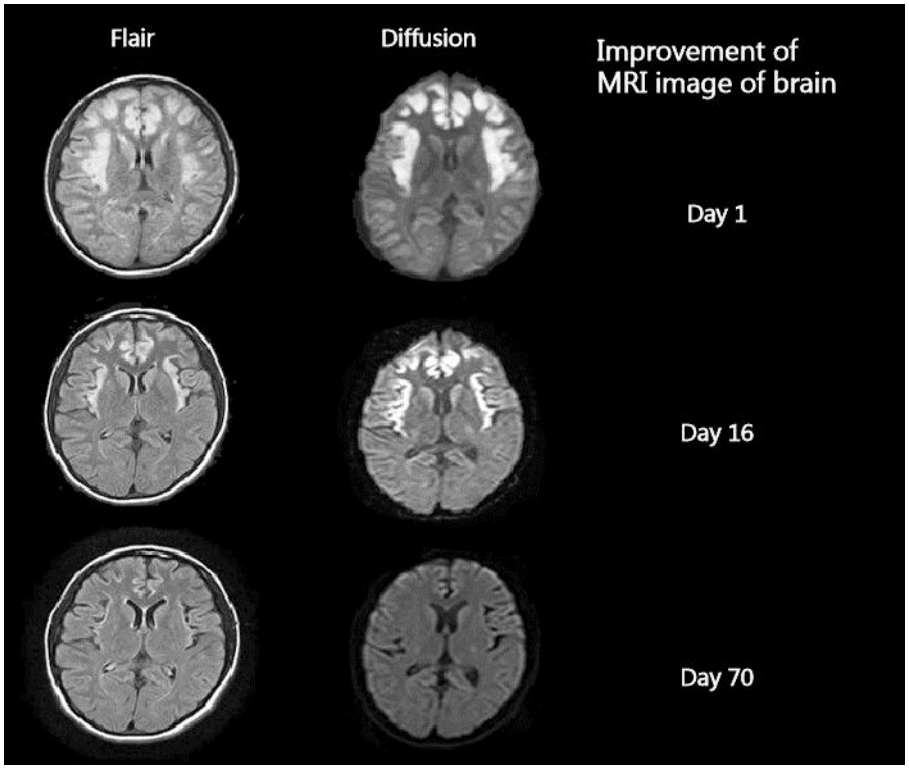

Fig. 2. Brain MRI according to the patient's disease days. The high-signal area in the white matter of the bilateral frontal lobes changed chronologically.

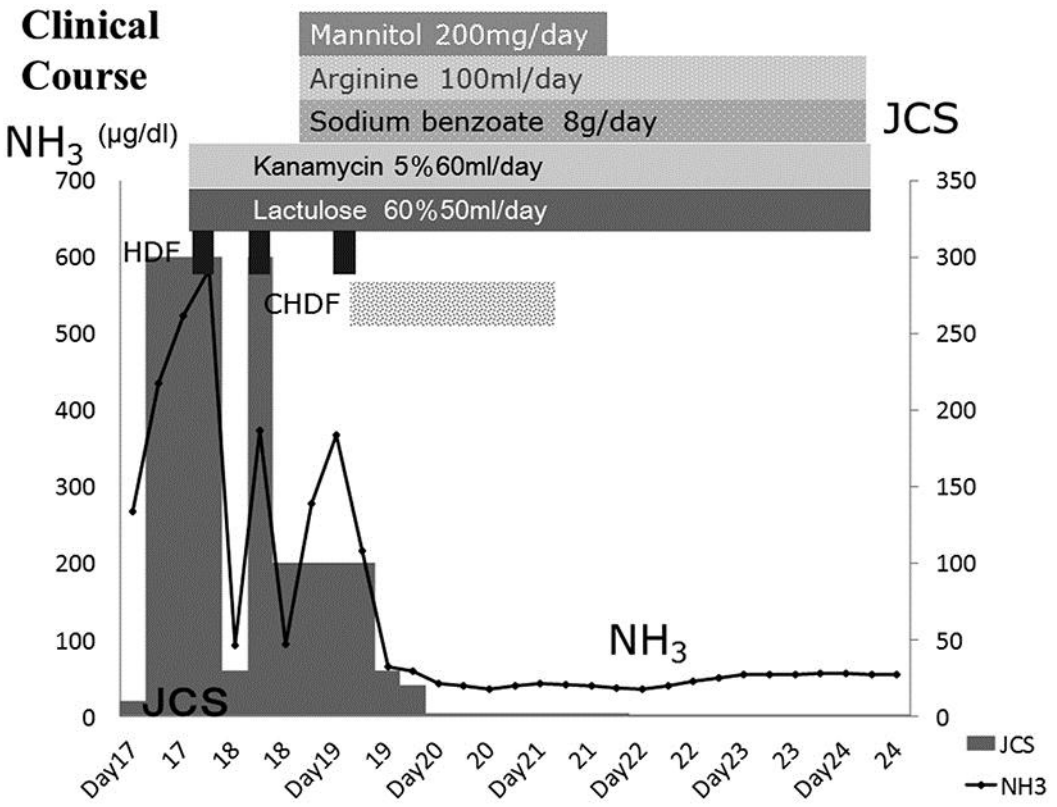

Fig. 3. Care flow data for consciousness level and ammonia titer centering on treatment effectiveness. Consciousness disturbance was progressing, accompanied by ammonia level deterioration. To improve the ammonia level, HDF was started and besides other agents were added. The ammonia level fell gradually after starting HDF, and consciousness recovered almost perfectly. The patient left the hospital on the 37th hospital day. JCS = Japan Coma Scale.