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【 CASE REPORT 】

A 36-year-old Man with Repeated Short-term Transient Hyperammonemia and Impaired Consciousness with a Confirmed *Carbamoyl Phosphate Synthase 1* Gene Monoallelic Mutation

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Abstract:

A 36-year-old man experienced severely impaired consciousness twice after drinking because of hyperammonemia. No abnormal blood tests were found other than ammonia levels. However, magnetic resonance imaging (MRI) showed atrophy of the brain parenchyma. One the second occasion, the patient suffered severe impairment of consciousness, and because of seizures and glossoptosis, mechanical ventilation was started. Urea cycle disorders (UCDs) were assumed to be involved. Genetic testing revealed a monoallelic mutation of the *carbamoyl phosphate synthase 1* (CPS1) gene. When transient hyperammonemia of unknown cause occurs repeatedly in adults, an active investigation for UCDs should be conducted.

Key words: late-onset urea cycle disorders, CPS1 deficiency, hyperammonemia, organic mental disorder

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Introduction

Urea cycle disorders (UCDs) are diseases that present as hyperammonemia due to a genetic disorder in the urea production process of the urea cycle. There have been some cases with a neonatal onset, but an adult onset is rare (1). When seizures and impaired consciousness are caused by hyperammonemia, irreversible neurological damages sometimes persist. In adult-onset cases, the diagnosis and treatment may be delayed due to the low incidence of the disease and clinicians' lack of awareness of this group of inborn errors of metabolism (2). Carbamoyl phosphate synthetase 1 (CPS1) deficiency is a UCD, with an estimated prevalence of 1 in 800,000 births (3).

We herein report a case of transient hyperammonemia with a single-allele mutation of the *CPS1* gene. The purpose of this report is to raise awareness of adult-onset UCDs, including CPS1 deficiency, with repeated short-term transient hyperammonemia.

Case Report

A 36-year-old man (height, 181 cm; weight, 64 kg) experienced difficulty communicating after drinking. Because he was wandering around, he was transported to our hospital by emergency services. He had a personal history of bronchial asthma and no family history of UCDs. He had no siblings, and his only child was healthy. In addition, he had no alcohol dependence or alcoholic liver disease.

Upon arrival, he had severely impaired consciousness, and his plasma ammonia concentration was 517 μg/dL (normal range: 12-66 μg/dL). After 2 hours, the plasma ammonia concentration had improved to 258 μg/dL, and after 6 hours, it had improved to 65 μg/dL, which was within the normal range. The plasma ammonia levels decreased with fluid re-

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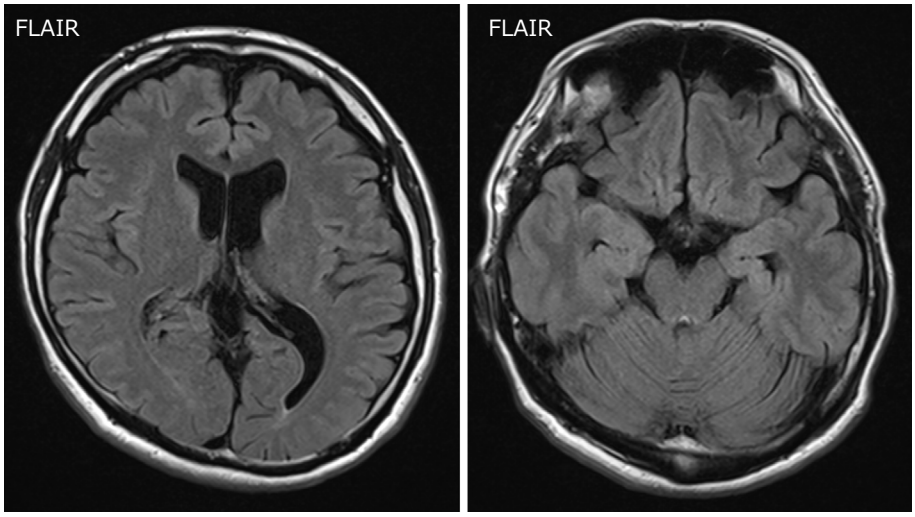

Figure 1. MRI showing atrophy of the left hippocampus and age-inappropriate cerebral atrophy. T2-FLAIR: T2-weighted fluid-attenuated inversion recovery

placement alone, and his consciousness recovered gradually. Since there was no excessive protein consumption, strenuous exercise, or urinary tract infection with urease-producing bacteria that could cause hyperammonemia, it was thought that the hyperammonemia had been triggered by alcohol consumption.

No blood test abnormalities were found other than ammonia levels, and a drug test was normal. However, brain magnetic resonance imaging (MRI) showed atrophy of the left hippocampus and age-inappropriate cerebral atrophy (Fig. 1). After leaving the hospital, he was able to continue with his daily life with almost no problems. However, on returning to work, he began to make mistakes in his computer work, document creation, and accounting.

Sixteen days later, he drank alcohol again and once more experienced difficulty communicating, at which point he was transported to the emergency department. His plasma ammonia concentration was 844 μg/dL. Measurement of vital signs showed a blood pressure (BP) of 111/70 mmHg, a heart rate of 107 beats/min, an SpO_2 of 99%, a body temperature of 37.1 ℃, a Glasgow Coma Scale (GCS) score of 11 (E4, V2, M5), and a pupillary reflex of 3 mm/3 mm. After the patient arrived at the hospital, his level of consciousness gradually decreased, he began to vomit repeatedly, and his pupillary reflex expanded to 5 mm/5 mm. His plasma ammonia concentration was re-examined 90 minutes after his arrival at the hospital, but it was still 648 μg/dL with fluid replacement alone. He developed seizures that included the face and upper right limb and also presented with glossoptosis. Based on the symptoms, cerebral edema and increased intracranial pressure due to hyperammonemia was considered.

The patient had severely impaired consciousness, and because of seizures and glossoptosis, mechanical ventilation was performed. Diazepam and levetiracetam were administered to prevent seizures, glycerin was used to improve cerebral edema, and 10% glucose was used to improve hyperammonemia by preventing a hypercatabolic state. As CPS1 deficiency and ornithine transcarbamylase (OTC) deficiency were considered, arginine infusion and continuous hemodiafiltration (CHDF) were performed. After 4 hours, the plasma ammonia concentration improved to 42 μg/dL, which was within the normal range.

The next day, the patient's consciousness had improved, and he was weaned from the mechanical ventilator. There were no obvious electroencephalogram abnormalities. Somatic computed tomography angiography was performed to identify the vascular shunt that might be responsible for the hyperammonemia. Nothing but mild hepatomegaly was found; thus, we considered the possibility of inborn errors of metabolism that cause hyperammonemia. The results of tandem mass screening using dried blood spots, which did not include UCDs or fatty acid metabolism disorder, were normal, and serum acylcarnitine was within the normal range. An amino acid analysis was performed two days after the second hyperammonemic attack, showing values of 11.3 nmol/mL (normal range: 17.9-48.0 nmol/mL) for blood citrulline, 82.7 nmol/mL (normal range: 12.6-62.5 nmol/mL) for blood glutamate, 595.0 nmol/mL (normal range: 422.1-703.8 nmol/mL) for blood glutamine, and 52.8 nmol/mL (normal range: 53.6-133.6 nmol/mL) for blood arginine. An amino acid analysis was performed two more times at the stable state without medical treatment. The values tended to be similar for blood citrulline and glutamate, but the citrulline value was lower and the glutamate value higher than the normal lower and upper limits, respectively. An amino acid analysis was also performed in the stable state with medical treatment (Table 1). The levels of urinary orotic acid, which are usually high under conditions of OTC deficiency, were normal. The anion gap was 12.5 mEq/L, which was within the normal range. The plasma ammonia concentration increased to 240 μg/dL immediately after the anaerobic exercise stress test, confirming hyperammonemia after exercise. The anaerobic exercise stress is squat jumps for 60 seconds

Table 1. Blood Amino Acid Analysis Findings.

	2 days after the second HA	16 days after the second HA	35 days after the second HA	173 days after the second HA
Citrulline (NR: 17.9-48.0 nmol/mL)	11.3	10.7	11.9	16.1
Glutamate (NR: 12.6-62.5 nmol/mL)	82.7	78.8	82.1	129.7
Glutamine (NR: 422.1-703.8 nmol/mL)	595	611.7	604.6	621.4
Arginine (NR: 53.6-133.6 nmol/mL)	52.8	70.6	133.9	73.1

NR: normal range, HA: hyperammonemic attack

Amino acid analyses performed 16 and 35 days after the second HA were conducted with the patient in a stable state without receiving medical treatment. The amino acid analysis performed 173 days after the second HA were conducted in a stable state with medical treatment of L-carnitine (50 mg/kg/day), L-citrulline (100 mg/kg/day), and L-arginine (130 mg/kg/day).

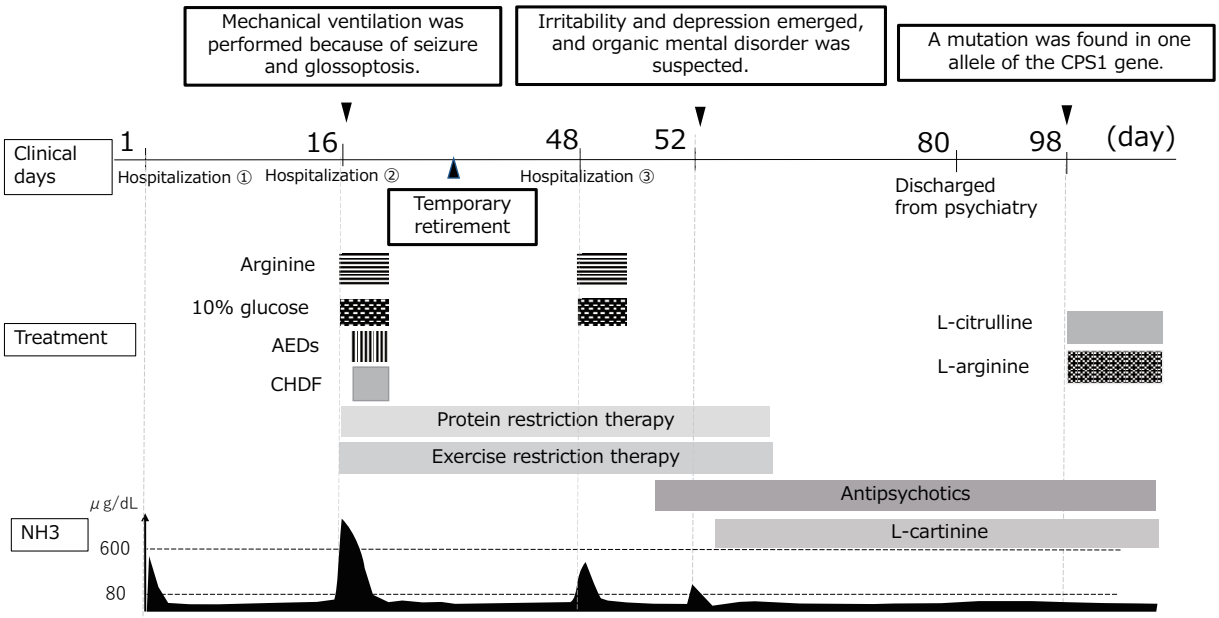

Figure 2. Clinical course. The time course of this patient is shown. NH3: ammonia, AEDs: antiepileptic drugs, CHDF: continuous hemodiafiltration.

before a meal (4). Genetic testing by direct sequencing method for citrullinemia type 2, OTC deficiency, CPS1 deficiency, and N-acetylglutamate synthase (NAGS) deficiency was performed because these inborn errors of metabolism diseases can cause hyperammonemia. A mutation, c.2549G>A (p.Arg850His), was found in one allele of the *CPS1* gene.

Although diet and exercise were restricted to prevent hyperammonemia, the patient experienced repeated hyperammonemia and mildly impaired consciousness after drinking at home, even after the second discharge. Gradual irritability and depression emerged, and because organic mental disorder after hyperammonemia was suspected, the patient was hospitalized again and treated with antipsychotics. After the abovementioned mutation was found in one allele of the *CPS1* gene, L-carnitine (50 mg/kg/day), L-citrulline (100 mg/kg/day), and L-arginine (130 mg/kg/day), which are medicines taken orally for CPS1 deficiency, were used (5). The patient was not advised to restrict his protein consumption or exercise except for being urged to avoid intense physical exercise. Subsequently, severe hyperammonemia did not recur. The course of the patient's disease is described in Fig. 2.

Discussion

The causes of hyperammonemia include liver disease, medication effects, excessive protein consumption, strenuous exercise, and urinary tract infections with urease-producing bacteria (6). However, the present patient showed no findings suggesting any of these causes at the time of the first or second attack. UCDs were thus suspected to be responsible for the hyperammonemia in this patient. Alcohol consumption is known to cause hyperammonemia in patients with UCDs (7).

Based on the results of a blood amino acid analysis, OTC deficiency, CPS1 deficiency, and NAGS deficiency were considered (8, 9). The urea cycle is described in Fig. 3. Genetic testing for these diseases was performed by direct sequencing, and the variation c.2549G>A (p. Arg850His) was found in one allele of the *CPS1* gene (10). The damaging impact of p.Arg850Cys/His mutations is the alteration of the kinetics of the CPS1 enzyme, resulting in decreased enzyme

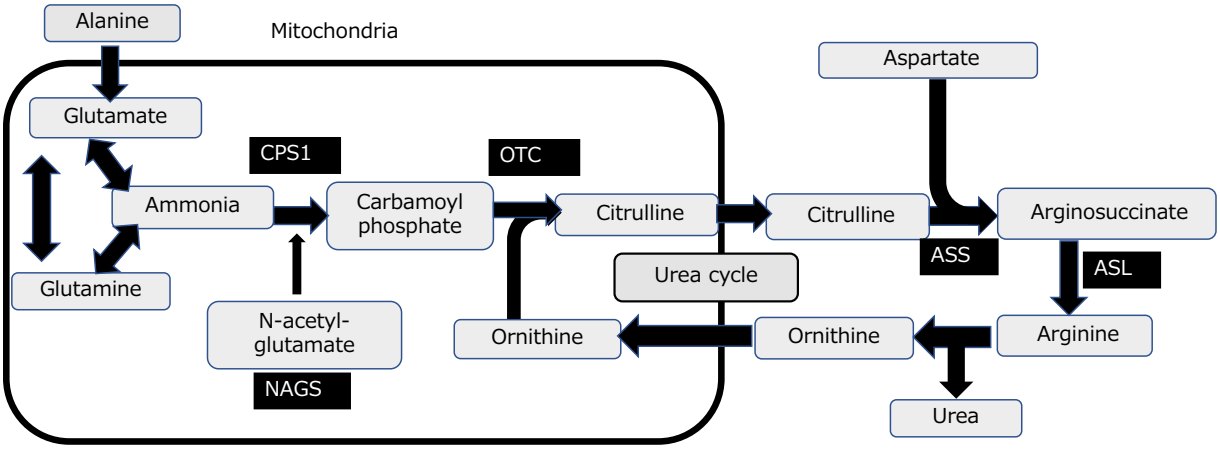

Figure 3. **Urea cycle. A blood amino acid analysis revealed low levels of arginine and citrulline and high levels of glutamate, therefore, OTC deficiency, CPS1 deficiency, and NAGS were considered. CPS1: carbamoyl phosphate synthetase 1, OTC: ornithine transcarbamylase, ASS: argininosuccinate synthase, ASL: argininosuccinate lyase, NAGS: N-acetyl glutamate synthetase**

Table 2. **Summary of the Clinical Presentation and Mutational Analyses of CPS1-deficient Patients.**

Patient	Sex	Age at the onset	Ammonia (μg/dL)	Plasma citrulline (μmol/L)	Outcome	Mutation 1	Mutation 2
Previous study[13,14,15,16,17]							
a[13]	M	Day 1	2,376	8.2	Death on day 20	c.130C>T	c.1312G>C
b[13]	M	Day 3	3,295	NA	Death at 1 year	c.130C>T	c.3969insC
c[13]	F	Day 2	>1,000	18.7	Death on day 2	c.236G>A	c.3584A>C
d[14]	F	**35 years**	224	NA	**Alive**	c.259C>T	c.2407C>T
e[13]	F	**31 years**	3,593	35	Death at 31 years	c.634T>A	c.3308A>G
f[13]	M	Day 1	1,402	NA	Death on day 12	c.840G>C	**Not detectable**
g[13]	F	Day 2	2,320	NA	Death on day 4	c.860delA	c.3643A>G
h[13]	M	Day 1	>1,000	NA	Death on day 4	c.1528delG	c.1528delG
i[13]	F	**13 years**	938	Low	**Alive**	c.1528delG	c.2021A>T
j[15]	F	Day 2	1,404	3.82	Death on day 5	c.1631C>T	c.2896G>T
k[13]	F	Day 3	1,370	5.3	**Alive**	c.1760G>A	c.2494delGinsAA
l[13]	M	Day 1	>400	5.7	Death on day 6	c.1777G>C	c.2494insT
m[13]	F	Day 2	1,001	NA	**Alive**	c.1951G>A	c.2339G>A
n[15]	F	Day 3	823	3.08	Death on day 4	c.1981G>T	c.622-3C>G
o[13,16]	F	Day 3	3,197	6.3	**Alive**	c.2359C>T	c.236+6T>C
p[13]	M	Day 2	>1,000	NA	Death on day 14	c.2359C>T	c.3093C>A
q[17]	M	Day 2	944	NA	**Alive**	c.2359C>T	c.3559G>T
r[13]	F	Day 2	4,400	NA	Death on day 60	c.2548C>T	c.3784C>T
s[13]	M	Day 0	1,960	3.6	Death on day 13	c.2945G>A	c.3723C>A
t[13]	F	Day 2	1,440	8.9	Death on day 36	c.2945G>A	**Not detectable**
This study							
	M	**36 years**	844	11.3	**Alive**	c.2549G>A	**Not detectable**

activity (11). CPS1 deficiency is an autosomal recessive disorder. It presents as repeated episodes of severe hyperammonemia starting at birth. Furthermore, approximately 75% of reported patients die, usually during the neonatal period; patients with this disorder rarely survive to adulthood (12). Therefore, it is likely that the single-allele nature of the mutation of the *CPS1* gene had some relationship with the adult-onset hyperammonemia in this patient.

According to previous studies, a few cases of CPS1 deficiency with only a single-allele mutation have been reported (Table 2) (13-17). Further studies are needed to determine whether or not this patient has mutations in the other alleles that could not be detected through conventional genetic analyses or whether the slightly low CPS1 activity in this patient was further reduced by some acquired factors. In any case, it is likely that the single-allele mutation of the *CPS1*

gene had some clinical significance in this patient.

Fortunately, the hyperammonemia was rapidly improved by CHDF, and MRI after recovery showed no evidence of cerebral edema in this case. Studies of acute liver failure have shown that the plasma ammonia concentration correlates with the development of intracranial hypertension and cerebral herniation; although it is difficult to establish a threshold, cerebral edema is more likely to occur when the plasma ammonia concentration exceeds 340 μg/dL (18). Under hyperammonemia conditions, ammonia is detoxified to glutamine by astrocytes in the brain, but glutamine accumulation increases the osmotic pressure of astrocytes. Ammonia itself is also toxic, activating NMDA receptors and causing astrocyte hyperexcitability. It is presumed that when ammonia levels that exceed the processing capacity of astrocytes are generated by the above mechanism, astrocytes swell, and cerebral edema occurs (19, 20). Cases of respiratory arrest and death due to cerebral edema have also been reported (21, 22). Therefore, in cases of severe hyperammonemia, CHDF should be actively considered in order to prevent cerebral edema, as in the present patient (23).

In our case, brain MRI showed atrophy of the left hippocampus and age-inappropriate cerebral atrophy. Hyperammonemia in childhood due to urea cycle abnormalities can reportedly cause cerebral atrophy and ventricular enlargement; therefore, we believe that the cerebral atrophy in this case was the result of repeated asymptomatic hyperammonemia (24-26).

Furthermore, in the present case, after transient hyperammonemia, the patient had difficulty concentrating and continuing to work, and depression also developed. Chronic encephalopathy, autism, learning disability, hyperactivity, self-injurious behavior, bipolar disorder, and major depression have been reported as delayed symptoms in patients with urea cycle abnormalities (27). Therefore, it is likely that the impaired concentration and psychiatric symptoms in the present case were also complications of a hyperammonemia attack.

Infection, alcohol consumption, exercise, and surgery are known to cause hyperammonemia, and it is important to avoid these factors (8, 28). In this patient, alcohol consumption induced hyperammonemia. No report has yet explained why alcohol consumption induces hyperammonemia in CPS 1 deficiency. However, a plausible mechanism has been posited. Nicotinamide adenine dinucleotide (NAD^+) is essential for the dehydrogenation of acetylaldehyde, which is essential for alcohol metabolism (29). Sirtuin5 (SIRT5), which is an NAD^+-dependent enzyme, can trigger deacetylation and upregulate the CPS1 activity (30). In the present case, alcohol consumption would have reduced the NAD^+ levels. As a result, SIRT5 would no longer be able to trigger an upregulation of CPS1 activity, which was at a slightly low level. Therefore, transient hyperammonemia would have occurred repeatedly after alcohol consumption. In addition, hyperammonemia itself disrupts the function of mitochondria. Impaired mitochondria aggravate hyperammonemia in OTC deficiency (31, 32). It is hypothesized that once a hyperammonemic attack develops, the mitochondrial function recovery takes a long time due to mitochondrial damage. Therefore, a series of hyperammonemic attacks in this patient resulted from continued mitochondrial damage after the first such attack.

Although diet and medication are also used to prevent hyperammonemia, complete prevention can be difficult, and asymptomatic hyperammonemia may lead to progressive brain atrophy, cognitive decline, and worsening of psychiatric symptoms. In the case of childhood-onset UCDs, the survival rate tends to be higher in patients who have undergone liver transplantation than in nontransplant patients (33). Liver transplantation is the definitive treatment for childhood-onset UCDs. However, data are insufficient at present to conclude that liver transplantation for adult-onset UCDs is the definitive treatment. Some patients with adult-onset UCDs are assumed to have a partial or moderate deficiency in a urea cycle enzyme (34). In addition, transplanted patients require long-term immunological therapy and follow-up. Nevertheless, transplantation should be considered in patients with recurrent hyperammonemia or resistance to medical treatment (35). A case of adult-onset CPS1 deficiency resistant to oral medical treatment completely cured by liver transplantation has been reported (36). Therefore, if severe hyperammonemia induces repeat episodes of cerebral edema or impaired consciousness in the future despite alcohol abstinence and the continuation of oral medication for CPS1 deficiency, liver transplantation should be performed in our patient to improve the long-term prognosis in terms of the quality of life and neurological outcome.

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

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