Type II Citrullinemia in an Elderly Patient Treated with Living Related Partial Liver Transplantation

Kiyoyuki TAKENAKA, Ichiro YASUDA, Hiroshi ARAKI, Tomoo NAITO, Yasushi FUKUTOMI, Hiroo OHNISHI, Noriyoshi YAMAKITA*, Takeshi HASEGAWA*, Hirohide SATO*, Yasunobu SHIMIZU*, Hidetoshi MATSUNAMI* and Hisataka MORIWAKI

Abstract

A 60-year-old woman was admitted to our hospital for repeated consciousness disturbance. Blood examination showed hyperammonemia, and plasma amino acid analysis revealed a marked increase in the citrulline level. To establish a diagnosis, a percutaneous needle biopsy of the liver was performed. The determination of the urea cycle enzyme activities revealed a selective marked decrease in argininosuccinate synthetase activity, indicating the final diagnosis of type II citrullinemia. The mean survival period of this disease after the appearance of symptoms has been reported as 26.4 months, and most conservative treatments are not effective. We performed a living related partial liver transplantation. Over the subsequent 13-month follow-up, the patient's condition has remained fairly good. (Internal Medicine 39: 553–558, 2000)

Key words: consciousness disturbance, hyperammonemia, argininosuccinate synthetase.

Introduction

Citrullinemia is an autosomal recessive disease caused by a deficiency of argininosuccinate synthetase (ASS). ASS is the rate-limiting enzyme of the urea cycle, and a deficiency of ASS causes hyperammonemia. Citrullinemia is classified into three types according to the enzyme abnormality and into two forms according to the pathogenesis (1–4). The classical form includes neonatal/infantile onset types I and III. In these cases, the enzyme defect is found in all tissues in which ASS is expressed. The other form is adult-onset, type II citrullinemia with a liver-specific ASS deficiency. It occurs in association with decreased ASS protein with normal kinetic properties in the liver but normal ASS levels in other tissues such as kidney, brain, and

skin fibroblasts (2). This type has been mostly found in Japanese patients (5–43), and it is characterized by the sudden appearance of consciousness disturbance, restlessness, and abnormal behavior. Since most conservative treatments are not effective, the prognosis is very poor. However, brain dead (27, 40) and living related (37, 42, 43) liver transplantations have recently been performed in several patients, and have resulted in the elimination of the metabolic abnormalities, such as hyperammonemia and citrullinemia, and the improvement of clinical symptoms. We report a case of a 60-year-old woman with type II citrullinemia who underwent a living related partial liver transplantation (LRLT). We also review the pertinent Japanese literature.

Case Report

A 60-year-old woman was first admitted to a hospital because of consciousness disturbance in May 1998. She had been healthy until 1997, but thereafter experienced 6 months of restlessness during the day and insomnia at night. She was given a conservative treatment of rest and drip infusions, and the disturbance improved in several days. However, similar symptoms reappeared 3 times in the next 3 months and became more and more serious. On the 4th admission, hyperammonemia was found, but no other liver dysfunction or any abnormalities of the liver imaging were observed.

She was transferred to our hospital for further examination on August 19, 1998. On admission, she was alert and intelligent, but she found it difficult to answer complicated questions and to solve mental calculations. Neurologically, she was almost normal except for a slight hyperreflexia of all extremities. Blood examinations revealed hyperammonemia (193 $\mu\text{g}/\text{dl}$; normal, 25–70), but normal levels of aspartate aminotransferase (15 IU/L; normal, 7–30), alanine aminotransferase (20 IU/L; normal, 7–35), γ -glutamyl transpeptidase (20 IU/L; normal, 0–70), alkaline phosphatase (219 IU/L; normal, 80–300), and total bilirubin (0.6 mg/dl; normal, 0.1–1.0). The serum to-

From the First Department of Internal Medicine, Gifu University School of Medicine and *Matsunami General Hospital, Gifu

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Reprint requests should be addressed to Dr. Ichiro Yasuda, the First Department of Internal Medicine, Gifu University School of Medicine, 40 Tsukasa-machi, Gifu 500-8705

tal protein and albumin levels were low (total protein, 5.9 g/dl; normal, 6.0–8.0; albumin, 2.8 g/dl; normal, 3.9–4.9). The complete blood cell count, erythrocyte sedimentation rate, and serum C-reactive protein level were normal. No autoantibodies were detected. Although carcinoembryonic antigen (CEA) and α -fetoprotein levels were normal, the pancreatic secretory trypsin inhibitor (PSTI) level was increased (20 ng/ml; normal, 4.6–12.2). Serological tests for hepatitis B and C viruses were negative. Plasma amino acid analysis revealed a marked increase in citrulline (463.2 nmol/ml; normal, 17–43) and a slight increase in arginine (159.5 nmol/ml; normal, 54–130).

Abdominal ultrasonography (US) revealed a bright liver, and computed tomography (CT) demonstrated diffuse low density in the liver (Fig. 1), findings which were compatible with the diagnosis of fatty liver. Magnetic resonance imaging (MRI) of the brain showed no abnormalities. An electroencephalogram (EEG) showed diffuse slow waves.

Given these results, we diagnosed the patient with citrullinemia. To further establish the diagnosis, a percutaneous needle biopsy of the liver was performed. Microscopic examination of the biopsied tissue showed steatosis; i.e., over 70% of the liver cells contained small to medium sized fat vacuoles in the cytoplasm, but fibrosis and inflammation were absent (Fig. 2). The urea cycle enzyme activities were measured in the biopsy specimen, and a selective marked decrease in ASS activity was revealed (Table 1). The final diagnosis was type II citrullinemia.

The patient's neurological symptoms were well controlled by a restricted oral protein intake, infusion of branched-chain amino acids, and oral administrations of lactulose and polymixin B sulfate (Fig. 3). Based on our previous reports (see Discussion), however, the prognosis was predicted to be poor. After informed consent was obtained from both the patient and her family, we planned an LRLT using a graft obtained from the patient's healthy 34-year-old son. We also obtained the donor's informed consent to perform a liver biopsy and other preoperative examinations. His ASS activity was confirmed to be almost normal (Table 1) based on the preoperative biopsy of the liver. Approval was obtained from the local ethics committee, and the LRLT was carried out at Matsunami General Hospital on September 22, 1998. The patient's whole liver (volume, 974 ml) was removed, and the left lobe taken from the donor (volume, 490 ml) was transplanted.

Both the patient and the donor recovered without complications. After transplantation, the patient began to receive immunosuppression therapy using FK-506, azathiopurine and prednisolone. Plasma levels of ammonia and citrulline were normalized immediately after transplantation, and her neurological symptoms disappeared. The patient was discharged from the hospital on the 46th day after transplantation, and is now being followed up as an outpatient. Over the now 13-month post-surgical follow-up, her condition has remained fairly good, although she has been readmitted twice, each time for several days, due to mild acute rejection in the 3rd and 6th months (Fig. 3).

Figure 1. Abdominal CT demonstrated diffuse low density in the right lobe of the liver, which was compatible with the diagnosis of fatty liver.

Figure 2. A microscopic examination of the liver showed steatosis. Over 70% of the liver cells contained small to medium sized fat vacuoles in the cytoplasm, but no fibrosis or inflammation was seen (HE stain, $\times 100$).

Table 1. Urea Cycle Enzyme Activities of the Biopsied Liver^a

	Patient	Donor	Controls
Carbamylphosphate synthetase	0.033	0.026	0.036 $\pm$ 0.013 ^b
Ornithine transcarbamylase	0.84	0.58	0.88 $\pm$ 0.35
Argininosuccinate synthetase	0.0023	0.020	0.033 $\pm$ 0.012
Argininosuccinate lyase	0.101	0.060	0.052 $\pm$ 0.025
Arginase	11.1	13.9	15.8 $\pm$ 3.1

^aEnzyme activities are expressed in U/mg protein. ^bValues are expressed as mean $\pm$ SD.

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Figure 3. Clinical course of the patient. Plasma levels of ammonia and citrulline were normalized immediately after LRLT, and her neurological symptoms disappeared. The patient was discharged from the hospital on the 46th day after transplantation. During the 10-month follow-up, her condition was fairly good, though she was admitted twice for several days each due to mild acute rejection in the 3rd and 6th months.

Discussion

Type II adult-onset citrullinemia is caused by selective deficiency of ASS in the liver. ASS is the rate-limiting enzyme of the urea cycle and catalyses the formation of argininosuccinate from citrulline. Much like hepatic encephalopathy, ASS deficiency induces hyperammonemia and consciousness disturbance. The onset of adult-onset citrullinemia is characterized by the sudden appearance of such symptoms as disorientation, restlessness, drowsiness, and abnormal behavior. Generally, however, no characteristic abnormalities other than hyperammonemia are found in routine blood biochemical tests or imaging. The histological findings of the liver vary from normal tissue to fatty change, chronic hepatitis, or cirrhosis (4). Thus, in cases in which the liver is normal in appearance, hyperammonemia may be the sole clue to the presence of this disease.

Citrullinemia is diagnosed by a high concentration of plasma citrulline, a slight increase in plasma arginine, and deficiency of ASS activity in the liver tissue. The majority of previously reported cases of type II citrullinemia have involved Japanese patients (5–43). A MEDLINE search of all pertinent articles, including those written in Japanese, yielded 42 cases of type II citrullinemia (including the present case) (Table 2). The female: male ratio among these cases was 9:33. The mean age of

onset was 34.7 years. The present patient is the oldest among these 42 cases. It remains to be elucidated why the clinical symptoms do not appear until adulthood, when the abnormality of ASS is thought to be genetically inherited and the levels of ASS are not thought to change with age. Since the level of hepatic ASS activity at the onset varies from case to case, there would seem to be no correlation between this level and the prognosis (4).

Once it appears, the encephalopathy generally follows a rapid and progressive course. Thus, fifteen of the twenty-one reported fatalities died within two years of onset. Previously, various conservative therapies have been tried, such as a low protein diet (5, 6, 10–14, 16, 18, 19, 22–24, 30, 32, 33, 35, 36, 38, 39), dietary arginine supplementation (5, 7, 9, 10, 13, 19, 23, 36), sodium citrate (12, 16, 19, 21, 22) or sodium benzoate administration (7, 13, 18, 19, 21, 25, 30, 33, 38), lactulose administration (6, 10, 11, 13, 16, 18, 19, 22, 25, 35, 36, 38, 39, 41), non-absorbed antimicrobial agent administration (6, 13, 18, 39), and branched-chain amino acid infusion (10, 11, 22, 25, 26, 30–33, 35, 38, 39, 41). Peritoneal dialysis (9, 18, 41) or hemodialysis (15, 29) has also been performed in several patients. However, although some of these treatments have contributed to a temporary alleviation of hyperammonemia and consciousness disturbance, they have failed to satisfactorily improve the long-term prognosis. The encephalopathy progresses rapidly, and is followed by decerebral state and deep coma. Most of

Table 2. Reported Cases with Type II Citrullinemia

	Author ^a	Year	Age	Sex	Treatment ^b	Outcome (period after onset)
1	Hara (6)	1981	28	M	conservative	alive (2 month)
2	Yamanaka (7)	1984	28	F	conservative	alive (9 month)
3	Itakura (8)	1984	22	M	conservative	death (9 year)
4	Konishi (9)	1984	14	F	peritoneal dialysis	death (9 month)
5	Ohru (10)	1984	25	M	conservative	death (4 year)
6	Tobo (5)	1985	22	M	conservative	alive (6 month)
7	Ohta (11)	1985	24	M	conservative	alive (8 month)
8	Satomi (12)	1986	32	M	conservative	alive (8 month)
9	Kodama (13)	1986	24	M	conservative	alive (16 month)
10	Kodama (13)	1986	43	F	conservative	alive (7 month)
11	Shoda (14)	1986	21	M	conservative	death (17 month)
12	Yamamoto (15)	1986	46	M	hemodialysis	death (3 year)
13	Ikeda (16)	1987	35	M	conservative	death (16 month)
14	Akiyama (17)	1988	48	M	conservative	alive (15 month)
15	Kitai (18)	1989	47	M	peritoneal dialysis	alive (12 month)
16	Ujihira (19)	1989	44	M	conservative	death (6 month)
17	Muneoka (34)	1989	21	M	conservative	death (16 month)
18	Mutoh (20)	1990	48	M	conservative	death (45 month)
19	Itoh (21)	1991	43	M	conservative	death (11 month)
20	Yuki (22)	1991	29	M	conservative	death (8 month)
21	Arimura (23)	1991	26	M	conservative	death (8 year)
22	Watanabe (24)	1991	28	M	conservative	death (5 year)
23	Wada (25)	1991	43	M	conservative	death (24 month)
24	Shindo (26)	1991	24	M	conservative	death (15 day)
25	Todo (27)	1992	35	M	OLT	OLT (11 month)
26	Tsuda (28)	1992	27	M	conservative	death (3 day)
27	Ishii (29)	1992	41	M	hemodialysis	death (4 month)
28	Tatsumoto (30)	1992	34	F	conservative	death (14 month)
29	Shiohama (31)	1993	19	M	conservative	alive (5 month)
30	Saegusa (33)	1993	29	M	conservative	death (16 month)
31	Saegusa (33)	1993	59	F	conservative	alive (2 month)
32	Tamakawa (32)	1994	52	F	conservative	alive (1 year)
33	Kawase (35)	1995	31	F	conservative	death (16 month)
34	Ohta (36)	1996	27	F	conservative	alive (32 month)
35	Yazaki (37)	1996	25	M	LRLT	LRLT (6 month)
36	Hanazawa (38)	1996	29	M	conservative	alive (12 month)
37	Suenaga (39)	1997	46	M	conservative	alive (1 month)
38	Kawamoto (40)	1997	39	M	OLT	OLT (9 month)
39	Kawamoto (40)	1997	30	M	conservative	death (10 month)
40	Ogawa (41)	1998	57	M	peritoneal dialysis	alive (2 year)
41	Yabe (43)	1998	52	M	APOLT	alive
42	Our case	1999	60	F	LRLT	LRLT (4 month)

^aNumber in parenthesis indicates the reference number. ^bConservative treatments include a low protein diet, dietary arginine supplementation, sodium citrate or sodium benzoate administration, lactulose administration, non-absorbed antimicrobial agent, hypertonic glucose infusion, and branched-chain amino acid infusion. OLT: orthotopic liver transplantation from cadaveric donors, LRLT: living related partial liver transplantation, APOLT: auxiliary partial orthotopic liver transplantation from living donors.

those patients who do not receive liver transplantation die within a few years. Even if a patient survives longer, severe organic brain damage cannot be avoided.

Two patients have previously been treated with orthotopic liver transplantation from cadaveric donors. The first case was performed in the United States by Todo et al in 1992 (27), and

the other in Australia by Kawamoto et al in 1997 (40). The operations resulted in a successful course for both patients. The goal of the treatment of this disease is to correct the metabolic abnormality in the patient before irreversible brain damage occurs. Liver transplantation is a useful option for achieving this purpose, since the initial metabolic disturbance of this dis-

ease is localized in the liver. It is possible that liver transplantation in the early stage of the disease prevents development of organic lesions in the brain due to the metabolic abnormalities.

Recently, various metabolic liver diseases have been treated with liver transplantation. In the United States, 5.3% of liver transplants are applied to metabolic disease (44). But liver transplantations from cadaveric donors have only just begun to be used in Japan, and may not be used widely for some time yet. On the other hand, the first successful case of LRLT was reported by Strong et al in 1990 (45), and was followed by a successful series of LRLTs by Broelsch et al in 1991 (46). In these reports, the LRLT was limited to infants, but its use has steadily increased, and accumulated experiences have extended its indication to adult patients (47, 48). Kawasaki et al (48) reported 13 cases of adult-to-adult LRLT. The liver replacement was successful in all of their patients, and none of them developed liver failure after surgery. While 2 patients with familial amyloid polyneuropathy died due to, respectively, *Aspergillus* pneumonia 2.5 months after transplantation and cerebral embolism 22 months after transplantation, the remaining 11 were reported to be well 2 to 35 months after LRLT. The postoperative course for each of the 13 donors was also uneventful and without significant complication.

For type II citrullinemia, the first patient treated successfully with LRLT was reported by Yazaki et al in 1996 (37). Since the causative genetic disorder of type II citrullinemia has now been elucidated (49), the introduction of a functional complementary DNA into hepatocyte by virus-mediated transfer may be a useful therapeutic option in the near future. In fact, hepatocyte gene therapy was reported to be successful in a neonatal bovine model of citrullinemia (50). However, until the clinical application of this modality, the use of liver transplantation—or in Japan, the use of LRLT in particular—would seem to be the only useful therapeutic approach for this disorder.

Although in a standard LRLT the whole liver is removed from the recipient, an auxiliary partial orthotopic liver transplantation (APOLT) has also recently been applied to a patient with type II citrullinemia (43). APOLT may have advantages over standard orthotopic liver transplantation in cases of a small for size graft, because the remnant native liver can support insufficient graft function until the graft has regenerated sufficiently. Moreover, in patients with non-cirrhotic metabolic liver disease, future gene therapy may still be possible in the preserved native liver. On the other hand, one notable drawback to APOLT is that the portal vein to the native liver must be ligated to prevent portal blood steal and to obtain optimal blood flow to the donor liver (43).

Because the causative disorder is hereditary and the liver graft is generally offered by one of the patient's relatives, as in the present case, we must confirm whether or not the donor has the same disorder, even if there are no symptoms. This is particularly necessary in cases of type II citrullinemia, which is likely to be an autosomal recessive disease (2, 4). The present donor, who was a son of the patient, was at least a heterozygous gene carrier and thus might have been an asymptomatic

patient with type II citrullinemia. Measurement of his ASS activity was therefore necessary. We performed a liver biopsy from the donor, and confirmed that his ASS activity was normal before the operation.

In conclusion, here we reported a case of a 60-year-old woman with type II citrullinemia that was successfully treated with LRLT. At present, LRLT is considered to be a useful and practical option that can fundamentally ameliorate this disorder.

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