降に発症する.

3) アルギニノコハク酸尿症

アルギニノコハク酸分解酵素の欠損による. 血中, 尿中にアルギニノコハク酸が著明に増加し, 血中アルギニンは低値である. 高アンモニア血症による臨床症状のほかに肝腫大, 毛髪のねじれがみられることがある.

4) アルギニン血症

アルギナーゼの欠損により痙性対麻痺と重度の精神運動発達の遅れを特徴とする. この疾患に特徴的な症状は血中アルギニンの高値が原因と考えられる. 治療では蛋白制限を厳格に行い, アルギニンを低下させるが, 知的予後は不良の例が多い.

5) シトリン異常症

シトリン異常症は新生児期には胆汁うっ滞を伴う肝炎を発症し, 幼児期には脂肪肝などを生じるが, 思春期以降では成人発症II型シトルリン血症が典型的な病型である. この病型では肝障害を伴った高アンモニア血症がみられるが, アルギニンの投与で高アンモニア血症は一時的に改善する. 予後不良の例が多く, 肝移植の適応となる. 確定診断には遺伝子診断が行われる.

6) 高オルニチン血症を示す疾患

血中オルニチンの高値を呈する疾患群の中で最も上昇が著明であるのはオルニチンアミノ基転移酵素欠損症である. この疾患は別名 gyrate atrophy of the choroids and retina とも呼ばれ, 緩徐に進行する網膜変性症がある. この疾患は新生児期に軽度の高アンモニア血症を示す. また, HHH(hyperornithinemia hyperammonemia homocitrullinemia)症候群はミトコンドリア膜でのオルニチンの転送障害によって引き起こされる. 高アンモニア血症, 高オルニチン血症と尿中へのホモシトルリンの排泄増加がみられる. 新生児期から成人までいずれの時期においても発症する.

7) リジン尿性蛋白不耐症

二塩基性アミノ酸であるリジン, アルギニン, オルニチンの小腸粘膜上皮および尿細管における吸収(再吸収)が障害され, 尿素サイクルで利用されるアルギニンが減少し, 高アンモニア血症を発症する. 体重増加不良, 嘔吐, 低身長や骨粗鬆症などを呈する. 血中アミノ酸分析ではリジン, アルギニンの低値がみられる.

4. その他の代謝異常症におけるアミノ酸値の異常

a. ピルビン酸脱水素酵素 E1a 欠損症

代謝性アシドーシスと高乳酸血症, 高ピルビン酸血症をきたす. 重症例では出生時に中枢神経系の形態異常を伴っている症例もあり, 出生直後から代謝性アシドーシス, 低血糖がみられる. 軽症例は乳児期, 幼児期に代謝性アシドーシスによる呼吸障害, 嘔吐, 失調症, 筋力低下などで発症する. 血中アミノ酸分析では高アラニン血症がみられる.

b. プロピオン酸血症, メチルマロン酸血症

プロピオン酸あるいはメチルマロン酸が血中で増加し, 重症の代謝性アシドーシスをきたす. 多くは新生児期・乳児期に嘔吐, 意識障害で発症し, 代謝性アシドーシスのほか, 低血糖, 白血球減少, 血小板減少, 高アンモニア血症などが特徴的である. 高グリシン血症を呈することが多く, ケトーシスに伴う高グリシン血症ではこれらの疾患を疑う.

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Liver transplantation in a patient with propionic acidemia requiring extra corporeal membrane oxygenation during severe metabolic decompensation

Sato S, Kasahara M, Fukuda A, Mizuguchi K, Nakagawa S, Muguruma T, Saito O, Karaki C, Nakagawa A, Yoshii K, Horikawa R. Liver transplantation in a patient with propionic acidemia requiring extra corporeal membrane oxygenation during severe metabolic decompensation.
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Abstract: LDLT is an effective treatment modality in patients with congenial metabolic liver disease. PA is a rare autosomal recessive disorder caused by deficiency in propionyl-CoA carboxylase. The present study demonstrates a two-yr-old girl with PA who was admitted for metabolic decompensation and immediately treated with CHD and protein intake restriction at 46 days of age. Two yr later, the patient was readmitted for severe metabolic decompensation with complete atrioventricular block and ventricular fibrillation. CHDF and ECMO were indicated because of progressive metabolic and cardiac deterioration. After full recovery of the ejection fraction, planned LDLT was performed to prevent further metabolic decompensation and fatal cardiac insufficiency. No significant events occurred after the operation and the condition of the patient is stable with continued protein restriction and carnitine supplementation.

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Key words: extra corporeal membrane oxygenation – living-donor liver transplantation – propionic acidemia

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PA, an organic acidemia, is a rare autosomal recessive disorder caused by a deficiency in PCC, a mitochondrial matrix enzyme involved in catabolism, which converts propionyl-CoA to methylmalonyl-CoA before entering the TCA cycle (1). PA is estimated to occur in every 465 000 births in Japan (2). Deficiency in PCC leads to accumulation of toxic substances in the body, that results in severe metabolic decompensation. In two subunits of the PCC gene (PCCA and PCCB), several genetic mutations were reported, that give rise to the varying activity of PCC (3–5). PA is categorized into two forms: an early (neonatal) onset form, in which clinical symptoms are presented within the first 90 days of life, and a late onset form. Clinical features of the early onset form are metabolic decompensation and fatal cardiac events, including cardiomyopathy, whereas those of the late onset form consist of encephalopathy, episodic ketoacidosis, as well as developmental retardation without metabolic decompensation (3). The survival

Abbreviations: CHD, continuous hemodialysis; CHDF, continuous hemo-diafiltration; ECMO, extra corporeal membrane oxygenation; EF, ejection fraction; LDLT, living-donor liver transplantation; LT, liver transplantation; PA, propionic acidemia; PCC, propionyl-CoA carboxylase; TCA cycle, tricarboxylic acid cycle; UCG, ultrasonic cardiography.

period is significantly shorter for the early compared with the late onset form because of metabolic decompensation and fatal cardiac events (4, 6, 7). A study in 17 patients reported a median survival period of eight months in early onset patients and death at age 2.8 and four yr in two late onset patients (4).

Here, we report a LDLT in a patient with early onset PA presenting with severe metabolic decompensation and potentially fatal cardiac insufficiency, which required CHDF and ECMO support.

Case report

A two-yr-old girl, born by normal delivery after a full-term pregnancy and having no significant family disease history, was referred at 46 days of age for hyperammonemia and metabolic acidosis treatment. The patient showed elevated serum ammonia levels at 1123 μg/dL and decreased base excess at −13.2 mmol/L. Treatment by CHD was immediately initiated after admission, and protein administration was restricted to reduce the load on amino acid catabolism. After CHD initiation, serum ammonia levels were gradually corrected. Diagnosis of PA was determined based on urinary organic acid analysis, which revealed elevated levels of 3-hydroxypropionate. In addition, no cardiomyopathy, a life-threatening complication of PA, was detected.

Protein administration was restricted at 0.9 g/kg/day and L-carnitine supplements, which enhance renal excretion of propionyl CoA as propionylcarnitine, were provided. The general condition of the patient appeared stable with no metabolic decompensation, albeit showing a mild developmental delay.

Two yr later, the patient was readmitted for decreased oral intake and general malaise. Serum ammonia and lactate levels were 116 μg/dL and 3.20 mmol/L, respectively, whereas blood gas analysis showed a base excess of −2.1 mmol/L on admission. Despite fluid resuscitation, deterioration of the metabolic acidosis condition was observed (pH 7.078, HCO_3 8.7 mmol/L, Lac 18 mmol/L, B.E. −22.1 mmol/L, NH_3 62 μg/dL). In addition, electrocardiography showed a rapid deterioration of circulation due to complete atrioventicular block and ventricular fibrillation. Cardiopulmonary resuscitation was immediately performed, and recovery of the sinus rhythm followed. However, blood pressure could not be sufficiently maintained and UCG revealed a decrease in EF to 50%. Despite administration of high-dose inotropic agents and CHDF, UCG showed an EF decrease to 10–20% with diffuse hypokinesis. ECMO (veno-arterial ECMO) was initiated based on diagnosis of cardiac insufficiency secondary to severe metabolic decompensation, and a gradual improvement in blood pressure, EF, and oxygenation followed (Fig. 1). Seven days later, EF recovered to 60% and the patient was successfully weaned from ECMO while maintaining optimal blood pressure

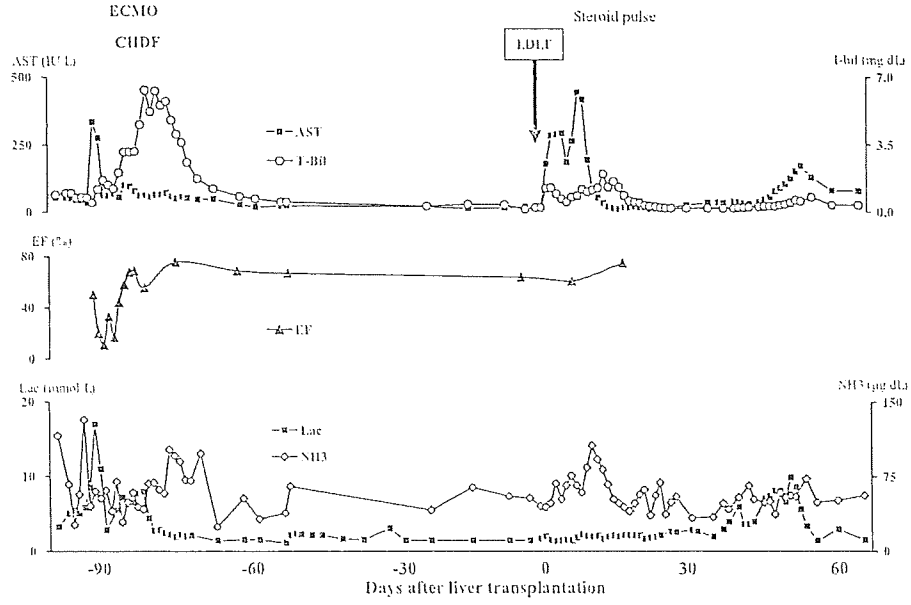

Fig. 1. Clinical course of the patient with propionic acidemia.

and P/F ratio (PaO_2/FiO_2 ratio: oxygenation index). In addition, the patient was weaned from CHDF because of metabolic status improvement.

To avoid further metabolic decompensation and fatal cardiac events, LT was considered and performed three months after cardiac decompensation using the left lateral segment from the father of the patient. Although mild acute rejection was observed after the operation, no metabolic decompensation or cardiac events occurred. Immunosuppressive therapy consisted of tacrolimus and corticosteroid administration. Seven months after LT, metabolic/neurological decompensation and cardiac insufficiency were avoided using mild protein restriction (1.8 g/kg/day) and L-carnitine administration.

Discussion

The medical treatment of PA, consisting of protein restriction, as well as L-carnitine and metronidazole administration, which facilitates the decrease in propionate production by the gut flora, has contributed to survival prolongation (3, 5). Despite medical treatment, life-threatening complications during early-onset PA, namely fatal cardiac events, have frequently occurred. In a study of 19 patients with PA, six (31.6%) were reported to show cardiomyopathy, of which three (50%) died from cardiac insufficiency (6). Electrophysiological investigation by Baumgartner et al. (7) reported a prolonged QTc interval, an independent risk factor for sudden cardiac death, and reduced left ventricular function, detected by UCG, in 70% and 40% of patients with PA, respectively. Given these findings, regular cardiological evaluation of PA patients was recommended. Although still unclear, the causes of cardiomyopathy and QTc prolongation are suggested involvement carnitine deficiency, which possibly induces electromyocardial changes, direct toxic effects of metabolites, which cause prolonged myocardium repolarization, inhibition of oxidative phosphorylation in mitochondria by propionyl CoA, as well as a genetic abnormality (7, 8).

Although LT is indicated for liver-related metabolic disorders, its use in organic acidemias, which are non-liver-related metabolic diseases, is still controversial (9-12). To the best of our knowledge, a total of 11 patients with PA were reported to have undergone LT (Table 1) (5, 10, 13-18). During the neonatal period, metabolic decompensation episodes were observed in all patients, and the median age at LT was two yr, ranging from eight months to nine yr. Livers from seven deceased and four living donors were

Table 1. Worldwide reports of liver transplantation for propionic acidemia

Case	Age at LT	Gender	Graft type	Indication of LT	Post-LT metabolic decompensation	Post-LT protein restriction	Outcome	Reference
1	2 yr	F	Auxiliary	Metabolic decompensation	–	No restriction	Alive, 10 yr	(13, 14)
2	7 yr	M	Deceased (whole)	Metabolic decompensation	+Chronic hyperammonemia	Continued	Died due to PTLD, 15 months	(15)
3	9 yr	F	Deceased (whole)	Metabolic decompensation	–	No restriction	Alive, 5 yr	(15)
4	3 yr	–	Deceased (split-liver)	Metabolic decompensation	Unknown	Unknown	Died, 3 months	(16)
5	2 yr	F	Living	Metabolic decompensation Failure to thrive	+three yr after LT	Unrestricted, then re-initiated because of metabolic decompensation after LT	Alive, 59 months	(10, 17)
6	5 yr	M	Living	Metabolic decompensation	–	Mild	Alive, 30 months	(10, 17)
7	1 yr	M	Living	Metabolic decompensation	–	Mild	Alive, 21 months	(10, 17)
8	8 months	F	Deceased (split-liver)	Metabolic decompensation	–	No restriction	Alive, 12 months	(18)
9	1 yr	M	Deceased (split-liver)	Metabolic decompensation Failure to thrive	–	Mild	Alive, 44 months	(5)
10	2 yr	–	Deceased (whole) Deceased (split-liver)	Metabolic decompensation Failure to thrive Developmental delay	–	Continued	Retransplanted for HAT; Alive, 6 months after initial LT	(5)
11	2 yr 2 months	F	Living	Metabolic decompensation Cardiac insufficiency	–	Mild	Alive, 7 months	Present case

LT, liver transplantation; PTLD, post-transplantation lymphoproliferative disorders; HAT, hepatic artery thrombosis.

used for transplantation. It was reported that LDLT using a graft from a heterozygote donor is an effective treatment modality for PA (10). Indications to perform LT included refractory metabolic decompensation (n = 11), failure to thrive (n = 3), developmental delay (n = 1), and cardiac insufficiency (n = 1). In the present study, LDLT was performed after overcoming severe metabolic decompensation and cardiac insufficiency, which required ECMO. However, from Table 1, previous studies report that case 5 presented with metabolic decompensation after LT (10, 17).

For post-LT protein intake, restriction was partly alleviated in eight patients (72.7%), of which four (36%) returned to normal or near normal protein intake. However, protein restriction was re-initiated in one patient because of metabolic decompensation after transplantation (17). These observations demonstrate the importance of protein restriction and L-carnitine administration after LT. In addition, based on post-transplant data from previous reports, LT for PA patients is considered an effective method to avoid further metabolic decompensation and cardiac insufficiency.

In conclusion, we suggest indicating LT in PA patients with frequent hospitalization for metabolic decompensation and failure to thrive despite conventional medical treatment. Further, LT is a potentially important option in avoiding further fatal cardiac events.

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Liver transplantation for an infant with neonatal intrahepatic cholestasis caused by citrin deficiency using heterozygote living donor

Shigeta T, Kasahara M, Kimura T, Fukuda A, Sasaki K, Arai K, Nakagawa A, Nakagawa S, Kobayashi K, Soneda S, Kitagawa H. Liver transplantation for an infant with neonatal intrahepatic cholestasis caused by citrin deficiency using heterozygote living donor. Pediatr Transplantation 2009. © 2009 John Wiley Sons & A/S.

Abstract: NICCD is an autosomal recessive genetic disorder, characterized by cholestasis, coagulopathy, hypoglycemia, fatty liver and multiple amino acidemia. NICCD develops in the neonatal/infantile period and has been reported as a "naturally curable" disease within one yr of life. Recently, we experienced an infantile NICCD who developed progressive liver failure, and required subsequent LT using a heterozygote living donor at eight months of age. Diagnosis of NICCD was established before transplantation, and donor evaluation included mutation in the SLC25A13 gene for exclusion of individuals with citrin deficiency citrullinemia. LDLT, from blood type identical mother using a left lateral segment graft, was performed without serious complication. Plasma amino acid concentration was normalized rapidly, and the patient was discharged 30 days after transplant. During one yr follow up, the recipient has been doing well without additional medication for NICCD. NICCD should be considered in the differential diagnosis as a cause of neonatal/infantile cholestatic disease. LT using a heterozygote living donor is an effective alternative in countries where a deceased donor is not available.

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Key words: neonatal intrahepatic cholestasis caused by citrin deficiency – living donor liver transplantation – adult-onset type II citrullinemia – heterozygote donor – end-stage liver disease

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Recently, citrin deficiency has been established as an autosomal recessive genetic disorder, and has two phenotypes (1). One is NICCD and the other is CTLN2. NICCD has been reported with SLC25A13 mutations and develops in the neonatal and/or infantile period. Clinical presentations of NICCD are characterized by cholestasis, coagulopathy, hypoglycemia, fatty liver, and multiple amino acidemia; however, these features have been reported to improve spontaneously within one yr of life (2). Therefore, development of end-stage liver disease in NICCD patients is extremely rare. We report our experience of infantile NICCD diagnosed preoperatively that required LDLT because of development of end-stage liver disease. The feasibility of LT using a heterozygote living donor is discussed.

Abbreviations: AFP, alpha-feto protein; CT, computed tomography; CTLN2, adult-onset type II citrullinemia; LDLT, living donor liver transplantation; LT, liver transplantation; NICCD, neonatal intrahepatic cholestasis caused by citrin deficiency; PT-INR, prothrombin time international normalized ratio; T-bil, total bilirubin.

Case

The female neonate was born at 40 wk of gestation, weighing 2679 g, with normal delivery.

She was the first live-born child of unrelated parents with no abnormalities in the family history. At five months old, she was admitted to the hospital because of abdominal distension and an inguinal hernia. Her weight (6370 g) and height (68 cm) were within the limits of the mean and standard deviation of the growth standard. Laboratory data showed an elevated serum T-bil 3.8 mg/dL (normal range: 0.25–0.85 mg/dL), asparate aminotransferase 155 IU/L (24–42 IU/L), alanine aminotransferase 81 IU/L (9–28 IU/L), PT-INR 1.4 (0.64–1.17), and AFP 230 000 ng/mL (normal range at five months of age: 1–20 ng/mL). Abdominal ultrasound and CT revealed a liver tumor of segment 8 (15 mm) (Fig. 1), which was suspected as a hemangioma or hemangioendothelioma by magnetic resonance imaging, without evidence of liver cirrhosis but with massive ascites. Liver function progressively deteriorated within two months, and control of intractable ascites failed. She was referred to National Center for Child Health and Development for possible LT because of end-stage liver disease of unknown etiology. Routine studies to determine the cause of neonatal/infantile end-stage liver disease were performed. As SLC25A13 gene mutation revealed a compound heterozygote of 1638ins23 and S225X, the cause of liver failure was diagnosed as NICCD. Laboratory data before LT showed T-bil 19.5 mg/dL, and PT-INR 2.0 with administration of fresh frozen plasma every other day.

Her mother was evaluated as a potential organ donor for LT. In addition to the routine evaluation for potential donor, mutation in the SLC25A13 gene was examined for exclusion of CTLN2. She did not eat an unbalanced diet, and her liver function was normal including the serum pancreatic secretory trypsin inhibitor 8.0 ng/mL (normal range: 4.6–20.0 ng/mL). DNA diagnosis of donor for the mutated gene revealed an asymptomatic heterozygote for S225X mutation. The ABO blood group identical mother was selected as the organ donor, because of the better graft-to-recipient weight ratio. At eight months old, LDLT was performed using the left lateral segment, weighing 242 g, without complication. The native liver was found to be cirrhotic. Microscopic examination revealed giant cell hepatitis with portal fibrosis of the liver lobules without fatty change, and the tumor was diagnosed as a hemangioendothelioma (Fig. 2). After LDLT, the patient received normal milk and food without protein restriction. Blood amino acid analysis was normal (Table 1), and the serum concentration of AFP, t-bil and total bile acid normalized rapidly. The patient was discharged 30 days after LDLT without serious complication. During one yr follow-up, she has been doing well without additional medication.

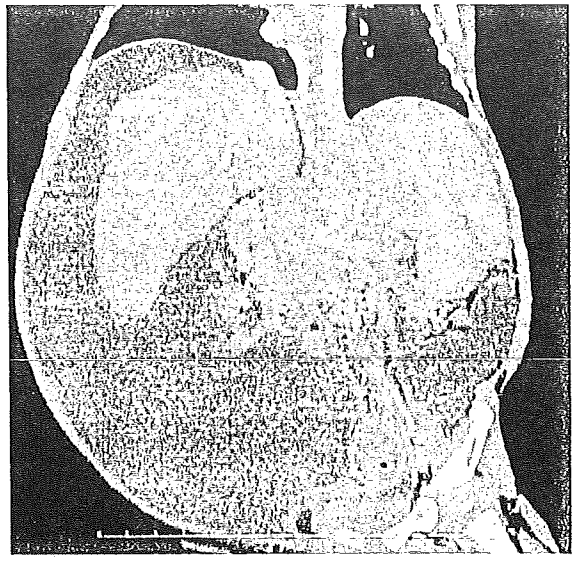

Fig. 1. CT demonstrated the tumor in the liver at segment 8 with massive ascites.

Discussion

Citrin deficiency is an autosomal recessive genetic disorder that results from mutation in SLC25A13 gene on chromosome 7q21.3 (1, 3). SLC25A13 gene encodes a calcium-binding mitochondrial protein, designated citrin, expressed mainly in the liver. Citrin plays an important role in the supply of aspartate from mitochondria to the cytoplasm for synthesis of arginosuccinate.

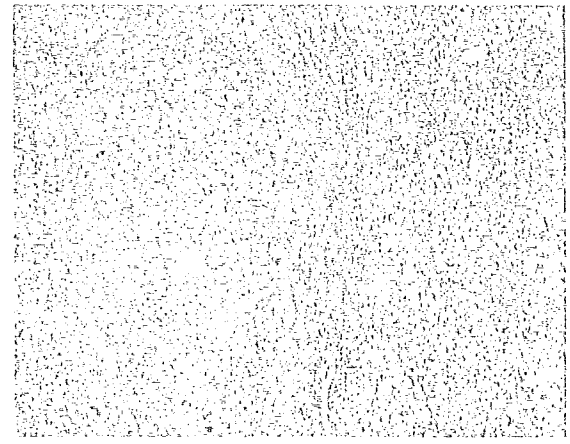

Fig. 2. Histology revealed that liver displayed as giant cell hepatitis with portal fibrosis among liver lobules without fatty change (Masson trichrome stain).

Table 1. Plasma amino acid concentration before and after liver transplant

	Range (nmol/mL)	Post-operative day			
		−107	−28	−11	27
Threonine	66.5–188.9	221.1	270.5	200.5	154.3
Serine	72.4–164.5	195.3	235.2	141.9	85.9
Asparagine	44.7–96.8	39.8	69.5	78.3	55.9
Glutamic acid	12.6–62.5	63.4	69.9	64.9	65.9
Citruline	17.1–42.6	45.2	33.2	25.4	25.5
Methionine	18.9–40.5	40.7	227.8	888	25.8
Leucine	76.6–171.3	122.9	118.3	59.1	130
Tyrosine	40.4–90.3	95	266.2	251.8	65.1
Phenylalanine	42.6–75.7	54.3	92.9	72	53.6
Fisher ratio	2.43–4.40	2.98	1.19	0.77	3.69

Therefore, impairment of citrin could lead to failure in supply of aspirate from mitochondoria to the cytoplasm for synthesis of argininosuccinate, and cause high citrulline and ammonia levels.

In Japan, the frequency of homozygotes with SLC25A13 mutations is estimated to be 1 in 19 000, and the incidence of NICCD could be 1 in 34 000, but it depends on the recognition of this disease entity, owing to the nature of NICCD, which may spontaneously resolve without treatment (2). Ohura et al. (2) reviewed the characteristics of 75 patients with NICCD. Among them, 30 and 45 patients were positive and negative for newborn screening in Japan (hypergalactosemia, hypermethioninemia, and hyperphenylalaninemia), and more than half of negative patients presented before three months with prolonged jaundice, acholic stools, and failure to thrive. Laboratory studies reveal serum transaminase, T-bil, total bile acid concentrations to be mildly elevated. The main characteristic of patients with NICCD is an abnormal amino acid pattern, with significant elevation of citrulline and methionine concentrations; however, it is noteworthy that six newborn screening negative cases did not show any elevation of citrulline. The present case was also negative for newborn screening, but did not present any signs of cholestatic disease during the first five months of age. Moreover, citrulline and methionine were elevated only slightly at her first visit, which made the diagnosis of liver disease attributable to citrullinemia difficult.

Treatment included special lactose-free milk formula enriched with medium chain triglycerides and protein free as well as medical therapy with fat-soluble vitamins, ursodeoxycholic acid, and phenobarbital (2). Four of 75 children with NICCD developed severe liver damage, and required subsequent treatment with fresh-frozen plasma or glucagon-insulin therapy. Seventy-three cases resolved by 12 months; however, two cases progressively developed liver failure and underwent LT before their first birthday. Furthermore, Tamamori et al. (3) reported a case that required LT at 10 months old because of end-stage liver disease. They suspected the cause of end-stage liver disease was tyrosinemia type I before LT, but confirmed the cause as NICCD two yr after LDLT. Moreover, their case was a compound heterozygote of 851del4/IVS11+1G → A, which was different from our case.

LT can offer complete resolution for genetically acquired errors of metabolism originating in the liver. However, LDLT using a heterozygote donor is an important issue to avoid subsequent development of serious complications in donor as well as in recipient. Previously, the safety of using a heterozygote donor has been reported, and concluded that LDLT using parenteral donors can be recommended as an effective treatment for pediatric cases with inheritable metabolic disorders (4). They reported a large series of LDLT for pediatric cases with various inheritable metabolic disorders using parenteral liver grafts, and did not experience mortality and morbidity related to the heterozygote state, as we reported in this manuscript. Thus, LT using a graft from a heterozygote living donor is a feasible alternative for NICCD patients.

In conclusion, we report an LDLT for an infantile case with NICCD who developed intractable ascites and end-stage liver disease. We made a preoperative diagnosis, and successful LDLT was performed using a heterozygote living donor. It is difficult to decide the optimal timing for LT with NICCD because a spontaneous remission can occur; however, LT should be considered when patients develop irreversible liver failure even when only a heterozygote living donor is available.

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IMAGES IN LIVER TRANSPLANTATION

Living Donor Liver Transplantation for Congenital Absence of the Portal Vein with Situs Inversus

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Congenital absence of the portal vein (CAPV) is a rare disorder that may lead to the development of hepatic neoplasms, hepatic encephalopathy, pulmonary hypertension (PH), and hepatopulmonary syndrome (HPS). The portal vein develops by selective involution of the vitelline venous system, and associated abnormalities may result in CAPV. Some patients with CAPV are diagnosed at the time of neonatal screening for hypergalactosemia.[1] The etiology of PH/HPS is an imbalance of vasoconstrictors and vasodilators, either produced or metabolized by the liver, that affect the pulmonary arterioles and capillaries by a portosystemic shunt.[2] A patient whose portal vein is patent and perfuses the liver as well as a shunt vessel (type 2) can be treated by shunt ligation (or graded shunt embolization) without portal hypertension being induced. However, if the liver is not perfused with portal blood and the entire splanchnic blood supply flows through a shunt vessel into a systemic vein (type 1), then either surgical or radiological intervention of the portal vein might be contraindicated. Liver transplantation (LT) is indicated as a curative operation for CAPV in patients with uncontrollable hepatic encephalopathy and PH/HPS. Situs inversus (SI) is also a rare congenital anomaly with a frequency of 0.002% to 0.1%.[3] SI occurs in association with polysplenia syndrome and midgut malrotation, a preduodenal portal vein, an aberrant hepatic arterial supply, and absence of the inferior vena cava (IVC). Consideration, therefore, has to be given to additional vascular reconstruction at LT for CAPV with SI.

A 16-month-old Asian girl weighing 9.5 kg who presented with hyperammonemia (serum NH_3, 150 μmol/L) was admitted to the hospital. The patient was diagnosed to have hypergalactosemia by neonatal metabolic screening. At the time of assessment, a laboratory evaluation showed the following: serum bilirubin, 0.34 mg/dL; aspartate aminotransferase, 72 IU/L; gamma glutamyl transferase, 21 IU/L; albumin, 2.8 g/dL; total protein, 4.8 g/dL; total biliary acid, 126.6 μmol/L; and prothrombin time international normalized ratio, 1.21. Further imaging studies revealed CAPV with SI, polysplenia, and absence of the retrohepatic IVC (Fig. 1). The results of a chest and cardiac examination were unremarkable. Because of recurrent hyperammonemia and progressive hyperintensity in the globus pallidus on magnetic resonance imaging, despite medical treatment and protein restriction, the patient underwent living donor LT.

The donor was her 27-year-old mother, who had the identical blood type. The liver graft, a reduced left lateral sector weighing 154 g and thus representing 1.62% of the graft-to-recipient weight ratio, was procured. The recipient laparotomy showed CAPV, SI, polysplenia, midgut malrotation, and absence of the retrohepatic IVC. The hepatic veins drained directly into the right atrium (Fig. 2A). The right renal vein was patent and

Abbreviations: CAPV, congenital absence of the portal vein; HPS, hepatopulmonary syndrome; IVC, inferior vena cava; LT, liver transplantation; PH, pulmonary hypertension; SI, situs inversus; SMV, superior mesenteric vein; SPV, splenic vein.

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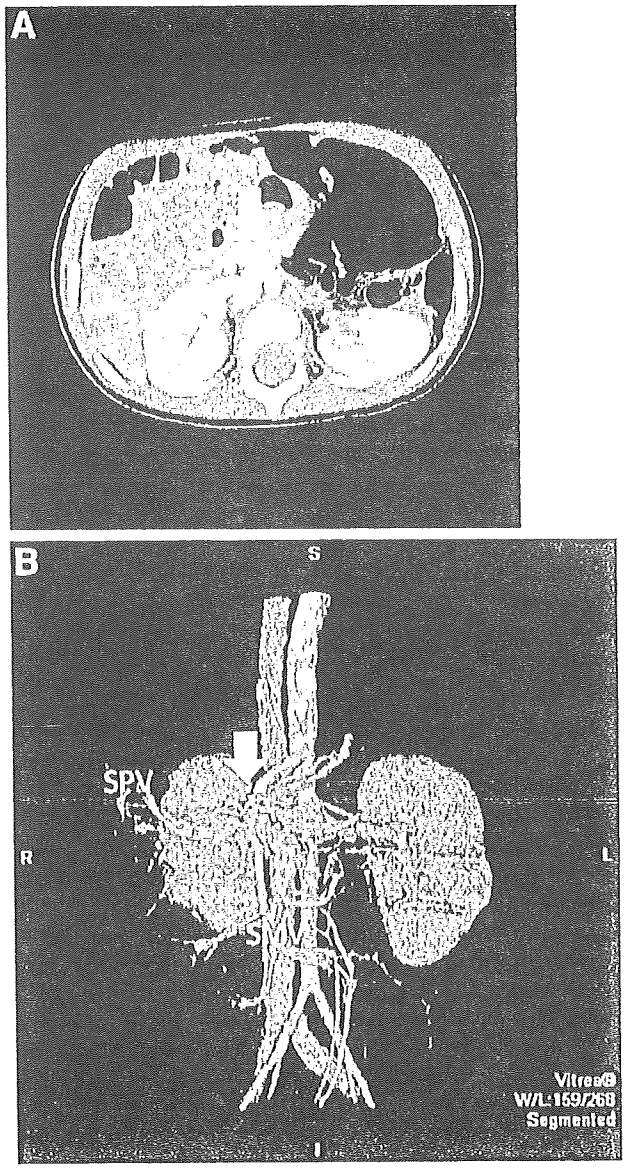

Figure 1. Preoperative computed tomography. The conduit (arrow) of the superior mesenteric vein (SMV) and splenic vein (SPV) drained into the right renal vein without entering the hepatic hilum.

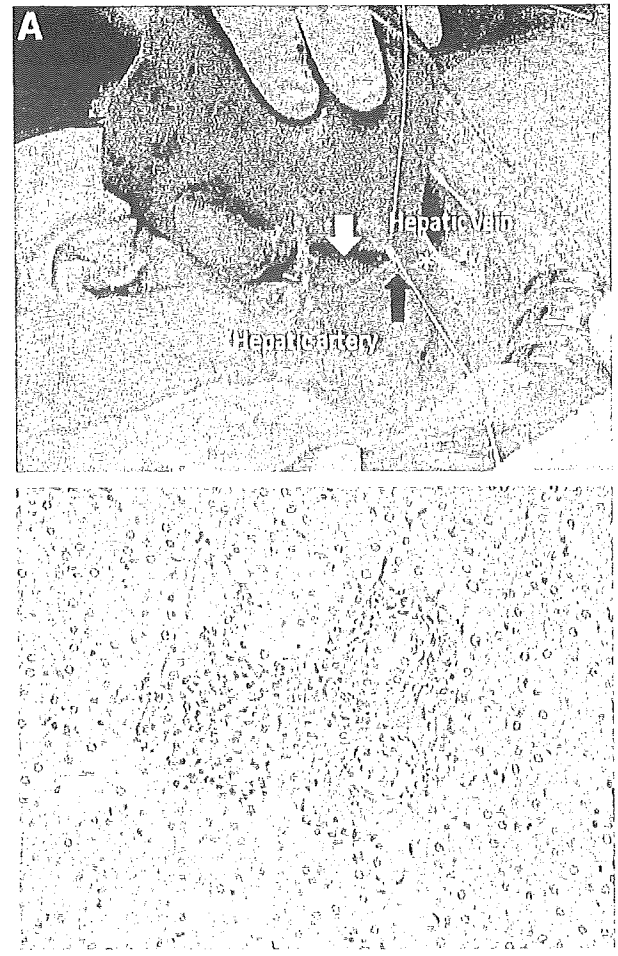

Figure 2. (A) An intraoperative view shows the absence of the retrohepatic inferior vena cava (white arrow) and that the hepatic veins drained directly into the right atrium (asterisk). Note the Arantius ligament (black arrow) and absence of portal branches in the hepatic hilum. (B) A histological examination showed a normal bile duct and hepatic artery and an atrophic portal vein in the portal tract.

drained through the retroperitoneal channels into the azygous system. The recipient hepatectomy was uncomplicated. A histological examination of the 200 g of explanted symmetric native liver, which was 61.6% of the estimated standard liver volume, showed atrophic portal veins visible in the portal tracts (Fig. 2B). The conduit of the superior mesenteric vein and splenic vein drained into the right renal vein without entering the hepatic hilum (Fig. 3A). After the hepatic vein reconstruction to the right atrium, the shunt vessel was divided at its junction with the right renal vein. The stump of the shunt vessels, measuring 3.0 cm in length, was turned upward behind the pancreas and anastomosed directly to the graft portal vein in an end-to-end fashion (Fig. 3B). During the clamping of the portal vein, the portal vein pressure increased from 12 to 32 mm Hg. Mesenteric venous congestion developed, but it was tolerable over the 21 minutes of warm ischemic time. Biliary reconstruction was carried out with a Roux-en-Y choledochojejunostomy. The operation lasted 8 hours 36 minutes, and the blood loss was 520 mL. The postoperative course was uneventful, and the patient was discharged on postoperative day 39. During the 9-month follow-up, the patient did well with normal liver function and normal magnetic resonance imaging findings without hyperammonemia.

The type 1 anomaly seen in the present case is often associated with aberrant malformations, such as biliary atresia, liver tumors, cardiac anomalies, and polysplenia. The present case had 3 additional conditions not reported so far: SI, polysplenia, and absence of the retrohepatic IVC, which are otherwise technically demanding if LT is indicated. The indications for LT in

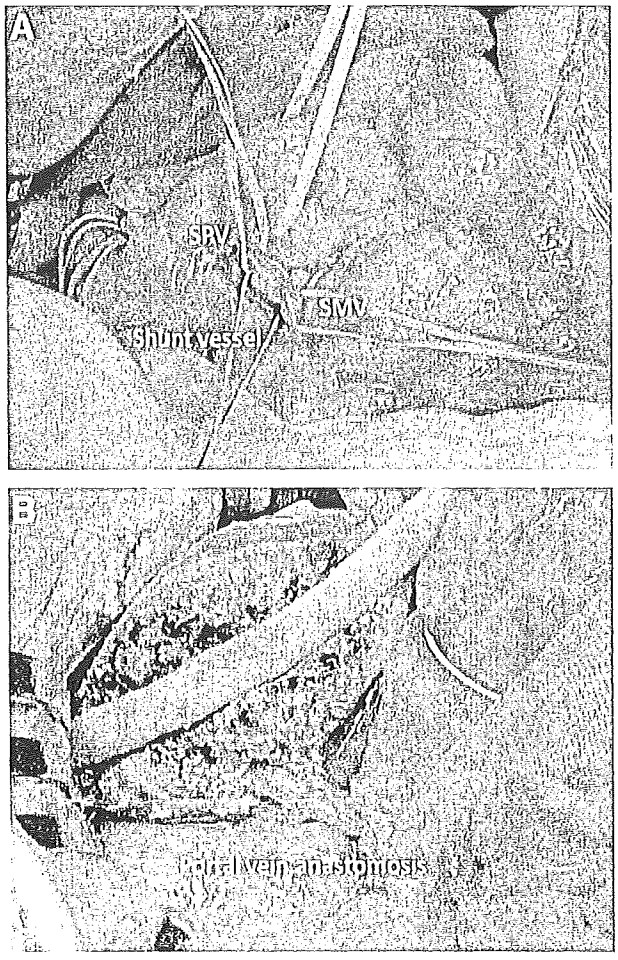

Figure 3. (A) An intraoperative view shows that the shunt vessel, conduit of the superior mesenteric vein (SMV) and splenic vein (SPV), drained into the right renal vein. (B) The stump of the shunt vessel was turned upward behind the pancreas and anastomosed directly to the graft portal vein in an end-to-end fashion.

patients with CAPV have not yet been established. Ten cases of CAPV treated with LT have been reported.[1,4-13] The indications for LT were liver cirrhosis secondary to biliary atresia in 5, an unresectable liver tumor in 3, hyperammonemia in 3, PH in 2, HPS in 1, and hematochezia in 1, and they were resistant to conventional medical treatment. PH was not seen in the present patient; the pathophysiology of PH in CAPV is demonstrated as thromboembolic pulmonary arterial hypertension, and this state can be cured if the shunt vessel can be closed. Recently, preemptive LT for a CAPV patient was performed because LT is the only therapeutic option to prevent regression of progressive PH.[14] In HPS, there is an imbalance between vasodilator and vasoconstrictor substances that have activity in the pulmonary circulation. Pulmonary vasodilation may occur if portocaval shunting impairs the metabolism of vasoactive substances by the liver. Emre et al.[13] reported that HPS could be treated by the routing of the portal flow into the liver with auxiliary LT because it confirms that a major cause of HPS is impaired hepatic clearance of vasoactive substances.

Early LT should therefore be indicated in symptomatic CAPV patients, even in those without impaired liver function, before advanced PH/HPS and/or irreversible brain damage due to hyperammonemia.

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Ⅴ．研究構成員

平成21年度　厚生労働省科学研究費補助金難治性疾患克服研究事業

高チロシン血症を示す新生児における最終診断への診断プロトコールと治療指針の作成に関する研究班

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VI. 遺伝性高チロシン血症の診断治療指針

遺伝性高チロシン血症の診断治療指針

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１．はじめに

遺伝性高チロシン血症は 3 つの病型に分類されている。遺伝形式はいずれも常染色体劣性である。

（1）遺伝性高チロシン血症 I 型:フマリルアセト酢酸ヒドラーゼの欠損によって発症する。

（2）遺伝性高チロシン血症 II 型：細胞質チロシンアミノ基転移酵素の欠損によって発症する。

（3）遺伝性高チロシン血症 III 型：4-ヒドロキシフェニルピルビン酸酸化酵素が欠損することで発症する。またホーキンシン尿症も同じ酵素異常により発症する常染色体優性遺伝性疾患である。

２．臨床症状

（1）遺伝性高チロシン血症 I 型では、進行する肝障害と腎尿細管障害が特徴的である。生後数週から始まる肝腫大、発育不良、下痢、嘔吐、黄疸などが見られる。重症例では肝不全へ進行し、無治療であれば生後 2~3 ヶ月で死亡する。生後数ヶ月から 1 年程度で肝障害を発症する亜急性型や、肝障害の進行は緩やかであるが最終的には肝硬変、肝不全に至る慢性型も存在する。肝臓癌を発生する症例も多く、多発性腫瘍も報告されている。腎臓では尿細管機能障害によって、低リン血症性くる病、ビタミン D 抵抗性くる病などが認められる。

（2）遺伝性高チロシン血症 II 型では、I 型や III 型より血中チロシン値が高い。II 型の皮膚病変はチロシンの針状結晶が析出することによって出現し、手掌･足底に限局した過剰角化、びらんを生じる。また角膜においてもびらん・潰瘍が生じる。血中チロシン濃度が特に高い一部の症例では精神発達の遅れを認めることがある。

（3）III 型の症状は I 型、II 型よりも軽度であり、無症状の症例も存在する。これまでに失調、痙攣、軽度の精神発達遅延などが報告されている。

３．診断指針

上記の臨床症状を呈する患者では、血中アミノ酸分析やタンデムマス検査によって血中チロシン値を測定することがまず必要である。高チロシン血症を呈する患者では遺伝性高チロシン血症 I 型、II 型、III 型以外に、他の原因による血中チロシン値の高値を鑑別する。

（1）遺伝性高チロシン血症 I 型の診断では肝障害の有無が重要である。肝機能障害の結果、血清トランスアミナーゼの上昇や凝固因子の合成低下などを認める。腎尿細管機能障害に

より低リン酸血症、糖尿、蛋白尿などが認められる。また、血清中αフェトタンパクの増加が特徴的である。確定診断のためには、尿有機酸分析をおこないチロシン代謝産物である4-ヒドロキシフェニルピルビン酸、4-ヒドロキシフェニル乳酸、4-ヒドロキシフェニルピルビン酢酸などの増加と、サクシニルアセトンの増加を明らかにする。尿中サクシニルアセトンの増加は診断的な価値が高い。また、酵素診断は肝細胞、培養皮膚線維芽細胞を検体として、フマリルアセト酢酸ヒドラーゼ活性を測定する。

（2）遺伝性高チロシン血症 II 型では皮膚の過剰角化・びらんや角膜のびらん・潰瘍から本症を疑われる。血中アミノ酸分析では血中チロシンは20mg/dl以上と極めて高値である。尿有機酸分析では4-ヒドロキシフェニルピルビン酸、4-ヒドロキシフェニル乳酸、4-ヒドロキシフェニルピルビン酢酸が大量に見出される。細胞質チロシンアミノ基転移酵素活性の測定には肝生検が必要である。

（3）遺伝性高チロシン血症 III 型では臨床症状は特徴的ではない。血中アミノ酸ではチロシンが約 20mg/dl 程度まで増加し、尿中へ 4-ヒドロキシフェニルピルビン酸およびその酸化物が大量に検出される。確定診断では肝 4-ヒドロキシフェニルピルビン酸酸化酵素を測定する。III 型の軽症型であるホーキンシン尿症は尿中ホーキンシンを検出することで診断される。

図1　遺伝性高チロシン血症の代謝障害部位

フェニルアラニン

↓　フェニルアラニン水酸化酵素

チロシン

↓　チロシンアミノ基転移酵素（**高チロシン血症 II 型**）

4－ヒドロキシフェニルピルビン酸

↓　4－ヒドロキシフェニルピルビン酸酸化酵素（**高チロシン血症 III 型、ホーキンシン尿症**）

ホモゲンチジン酸

↓　ホモゲンチジン酸酸化酵素

マレイルアセト酢酸

↓　マレイルアセト酢酸イソメラーゼ

フマリルアセト酢酸

↓　フマリルアセト酢酸分解酵素（**高チロシン血症 I 型**）

フマル酸　＋　アセト酢酸

表１　高チロシン血症の分類

病型	遺伝性	血漿中のチロシン上昇	酵素欠損	主な症状
遺伝性高チロシン血症Ｉ型	常劣	軽度	フマリルアセト酢酸分解酵素	肝細胞障害　尿細管障害 低血糖　ガラクトース代謝異常 神経症状　肝細胞癌
遺伝性高チロシン血症II型	常劣	高度	チロシンアミノ基転移酵素	精神発達遅延　皮膚の異常角化 角膜びらん　潰瘍
遺伝性高チロシン血症III型	常劣	中等度	4ヒドロキシフェニルピルビン酸酸化酵素	失調　けいれん 軽度の精神発達遅延
ホーキンシン尿症	常優	一過性	4ヒドロキシフェニルピルビン酸酸化酵素	一過性発育遅延 食欲不振
肝障害に伴う高チロシン血症	原疾患による	さまざま		原疾患による
新生児一過性高チロシン血症	なし	さまざま		無症状または不活発

４．治療指針

チロシン高値の患者ではＩ型、II型、III型とその他の原因による高チロシン血症の鑑別を対症療法と同時に行う。新生児期には臓器障害がなければ基本的には経過観察する。

（１）Ｉ型では肝障害の進行を早期に防止することが重要であり、ニチシノン（NTBC: 2-(2-nitro-4-trifluoromethyl-benzoyl)-1,3-cyclo- hexanedione)を使用し、低フェニルアラニン・低チロシン食を併用する。治療の効果判定には肝機能検査と血清αフェトタンパク値の測定が有用である。NTBC を使用しない例では肝不全に至ることが多く、肝移植が行われる。NTBC は国内では入手困難であり、個人輸入が必要となる。

（２）II型では低フェニルアラニン・低チロシン食をおこない、血液中のチロシン値を低下させる血中チロシン値を 10mg/dl 以下に保つ。

（3）III 型では II 型と同様に、低フェニルアラニン・低チロシン食による食事療法を行う。

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難治性疾患克服研究事業　研究症例分野

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