Treatment with Lactose (Galactose)-Restricted and Medium-Chain Triglyceride-Supplemented Formula for Neonatal Intrahepatic Cholestasis Caused by Citrin Deficiency

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Abstract Citrin plays a role in the transfer of NADH-reducing equivalent from cytosol to mitochondria as part of the malate–aspartate shuttle in liver. Citrin deficiency may cause an impairment of glycolysis due to an increase in the cytosolic NADH/NAD ratio leading to an energy shortage in the liver. Mutations of the *SLC25A13* gene are responsible for neonatal intrahepatic cholestasis (NICCD) and adult-onset type II citrullinemia (CTLN2). Most patients with NICCD show a resolution of symptoms within the first year of life, but some patients present with severe symptoms and require liver transplantation. We treated four patients including three siblings with NICCD by lactose (galactose)-restricted and medium-chain triglyceride (MCT)-supplemented formula. This formula rapidly improved the clinical condition and laboratory findings. Early treatment was more effective and did not require long-term administration. Lactose (galactose)-restriction can avoid further increase in the cytosolic NADH/NAD ratio in the liver and MCT supplementation can provide energy to hepatic cells by producing an excess of acetyl-CoA in mitochondria. Early treatment with lactose (galactose)-restricted and MCT-supplemented formula is recommended for patients with NICCD and possibly for patients with CTLN2.

Introduction

Citrin, encoded by *SLC25A13*, is a mitochondrial inner membrane aspartate–glutamate carrier that transfers cytosolic NADH-reducing equivalent into the mitochondria as part of the malate–aspartate shuttle in the liver (Kobayashi et al. 1999; Saheki et al. 2010). Human citrin deficiency causes neonatal intrahepatic cholestasis (NICCD: OMIM 603471) and adult-onset type II citrullinemia (CTLN2: OMIM 605814). NICCD presents in the first few weeks of life with prolonged cholestasis, liver dysfunction and metabolic abnormalities including aminoacidemia and galactosemia (Tazawa et al. 2001; Tomomasa et al. 2001). Some patients receive liver transplantation (Tamamori et al. 2002; Shigeta et al. 2010), but in most patients symptoms resolve within the first year of life and they subsequently remain healthy (Ohura et al. 2007). One or more decades later, some of the patients develop neurological symptoms of CTLN2 showing behavioral aberrations, restlessness, disorientation and coma (Kobayashi et al. 1999; Tomomasa et al. 2001; Saheki et al. 2010).

Patients with NICCD complicated with galactosemia or cholestasis have been treated with lactose (galactose)-free formula or one containing medium-chain triglyceride (MCT) supplemented with fat-soluble vitamins (Ohura et al. 2007; Chew et al. 2010). For CTLN2, clinical benefit has been demonstrated with liver transplantation (Saheki et al. 2010). Recently, a favorable result was reported in one patient with therapy using sodium pyruvate and arginine under the low carbohydrate formula (Mutoh et al. 2008).

We now present a promising therapy with lactose (galactose)-restricted and MCT-supplemented formula in four cases including three siblings with NICCD and

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recommend this therapy in order to avoid an increase of cytosolic NADH/NAD ratio and supply an energy source to the mitochondria in liver.

Materials and Methods

Formula

MCT formula supplemented with essential fatty acids (Meiji Milk Product Co., Ltd., Tokyo) contains protein 13.2 g, MCT 20.5 g, linoleic acid 2.0 g, alpha-linolenic acid 0.5 g, soluble polysaccharide 30.5 g, lactose 26.1 g and 504 kcal per 100 g powder. Lactose-free formula (Morinaga Milk Industry Co., Ltd., Tokyo) contains protein 13.0 g, lipids 20.0 g, dextrin 56.8 g, sucrose 5.0 g and 479 kcal per 100 g powder. MCT oil (Kissei Pharmaceutical Co., Ltd., Tokyo) contains MCT 85 g and long chain fatty acid 15 g per 100 g.

Gene Analysis

The Ethics Committee of Yamagata University School of Medicine approved this study. Peripheral blood specimens were used for genomic DNA extraction with written informed consent from the patient's family. *SLC25A13* was analyzed according to previous reports (Tabata et al. 2008; Dimmock et al. 2009).

Patient 1

The patient was a 10-year-and-4-month-old Japanese boy. He was born at 40 weeks gestation after an uneventful pregnancy. His birth weight was 2,520 g (14th percentile) and length was 48.5 cm (40th percentile). He had unrelated and healthy parents and a healthy elder sister. At the age of 3 months, he presented with jaundice and steatorrhea. On physical examination, he weighed 6,740 g (70th percentile) and measured 61.0 cm (40th percentile) in length. His skin and bulbar conjunctiva were jaundiced. His liver and spleen were palpable 5 cm and 1 cm below the costal margin, respectively. Laboratory findings showed hypoalbuminemia, cholestasis and mildly elevated liver transaminases (Table 1). There was no significant change in the complete blood cell count, coagulation tests, blood ammonia, serum alpha-1 antitrypsin, lipoprotein X or urinary coproporphyrin. Plasma amino acid analysis showed an increase in the concentration of citrulline, threonine, methionine, tyrosine and arginine (Table 1). In addition, there was a mild decrease in the concentration of branched chain amino acids, glutamine and alanine. Hepatobiliary imaging by 99mTc-pyridoxyl-5-methyl-tryptophan showed a delay in hepatic clearance, but there was no obstruction of either the common or intrahepatic bile ducts. Liver biopsy

demonstrated macro- and micro-vesicular steatosis, cholestasis, fine sinusoidal fibrosis, small round cell infiltration in the portal region and absence of prominent giant cells. *SLC25A13* analysis demonstrated a compound heterozygous mutation, c.1177+1G>A/c.1750+72_1751-4dup17ins NM_138459.3: 2667 (Tabata et al. 2008). He was treated with MCT formula supplemented with essential fatty acids (Meiji Milk Product Co., Ltd., Tokyo) and arginine supplementation starting at 4 months of age. His condition (cholestasis, jaundice and failure to thrive) and laboratory findings rapidly improved (Fig. 1a). All laboratory findings except for a mild increase in the plasma level of tyrosine had improved to the normal range by 9 months of age. However, the parents changed from the formula containing MCT to ordinary milk for 1 month at the age of 11 months and his condition and laboratory findings worsened. MCT administration was decreased by mixing MCT formula with ordinary milk and finally discontinued at 17 months of age when all abnormal laboratory findings had normalized. At the age of 10 years and 2 months, he weighed 29.3 kg (30th percentile) and was 136.6 cm (50th percentile) tall. He had a preference for protein-and fat-rich food, but he did not have any symptoms or abnormal laboratory findings.

Patient 2

The patient, a younger sister of patient 1, was 2 years and 8 months old. She was born at term after an uneventful pregnancy. Her birth weight was 2,300 g (5th percentile) and length was 48.0 cm (40th percentile). At 2 months of age, she demonstrated cream-colored bulky stools (steatorrhea). On physical examination, she weighed 4,508 g (10th percentile) and had a length of 52.2 cm (below the 1st percentile). There was no apparent jaundice of the skin or bulbar conjunctiva. The liver was palpable 4.5 cm below the costal margin. She showed hypoalbuminemia, cholestasis and mildly elevated liver transaminases. She also had increases in the levels of plasma citrulline, threonine, methionine, tyrosine and arginine, but there was no significant change in the other amino acids, showing a profile consistent with NICCD (Table 1). Blood galactose was elevated to >1.1 mmol/L and was normalized after 2 weeks of treatment with MCT formula supplemented with essential fatty acids (Meiji Milk Product Co., Ltd., Tokyo) and with fat-soluble vitamins and arginine administration. Her condition and laboratory findings were improved and nearly normalized at 7 months of age (Fig. 1b). Fat-soluble vitamins and MCT formula were finally discontinued at 6 months of age and 10 months of age, respectively. She demonstrated the same *SLC25A13* mutation as patient 1. At 2 years and 8 months of age, she weighed 11.4 kg (20th percentile) and measured 85.6 cm (10th percentile) in length.

Table 1 Summary of formula and laboratory data of four patients with NICCD

	Patient 1			Patient 2			Patient 3			Patient 4		
Age at testing (days)	124	155	264	75	104	209	55	76	146	85	110	155
Body weight (g)	6,740	7,600	9,210	4,508	5,410	7,800	3,856	4,786	7,150	5,394	6,520	7,990
<i>Formula</i>												
Protein (g/kg/day)	1.6	2.4	1.9	4.2	4.1	2.6	3.3	2.8	1.8	2.8	2.8	2.2
Carbohydrate (g/kg/day)	10.7	10.4	8.5	20.6	17.6	12.0	16.3	11.8	8.6	18.0	12.3	9.6
Lactose (g/kg/day)	9.5	4.8	6.0	19.7	8.1	9.5	15.3	5.5	8.3	16.1	0	0
Fat (g/kg/day)	5.2	4.6	3.8	9.3	7.8	5.4	7.0	5.2	3.9	8.6	6.5	5.3
MCT (g/kg/day)	0	4.1	3.4	0	7.0	4.8	0	4.7	3.5	0	2.0	1.0
Energy (kcal/kg/day)	96.4	93	75	182	157	106	141	105	76	163	116	85
<i>Laboratory data</i>												
Reference ranges												
Citrulline (μmol/L)	263	24	26	323	43	36	168	32	21	346	29	31
Threonine (μmol/L)	251	75	124	472	129	82	471	191	132	431	149	85
Methionine (μmol/L)	45	16	25	606	53	21	32	48	29	87	77	36
Tyrosine (μmol/L)	120	86	114	102	35	58	27	95	83	151	115	132
Arginine (μmol/L)	91	29	108	294	65	84	148	133	207 ^a	235	73	60
Albumin (g/L)	32	37	46	35	42	46	31	39	40	30	43	48
T. Bil (μmol/L)	124	10	2	54	13	6	20	5	2	90	29	6
D. Bil (μmol/L)	91	7	1	34	7	1	8	1	1	36	17	2
AST (IU/L)	292	164	62	104	109	58	65	50	42	115	51	50
ALT (IU/L)	78	58	57	80	64	49	58	28	40	31	30	43
LDH (IU/L)	401	387	377	354	326	299	285	296	266	330	280	226
ALP (IU/L)	888	476	472	3,322	1,232	859	1,812	796	850	7,289	1,264	873
γ-GTP (IU/L)	53	167	41	251	343	28	163	58	30	335	100	34
ChE (IU/L)	137	299	426	234	366	390	183	404	425	225	374	457
TBA (μmol/L)	717	61	8	230	148	3	174	28	5	399	164	5
NH ₃ (μmol/L)	65	29	36	53	N.D.	N.D.	N.D.	27	N.D.	55	N.D.	N.D.
AFP (ng/mL) ^b	8,128	5,790	10	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	>10,000	4,033	123
PSTI (ng/mL)	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	22	N.D.	N.D.	59	22	19

T. Bil total bilirubin; D. Bil direct bilirubin; AST aspartate transaminase; ALT alanine transaminase; LDH lactate dehydrogenase; ALP alkali phosphatase; γ-GTP γ-glutamyltranspeptidase; ChE cholinesterase; TBA total bile acid; NH₃ ammonia; AFP alpha-fetoprotein; PSTI pancreatic secretory trypsin inhibitor; N.D. not determined

^aSpecimen was obtained after arginine intake

^bNormal range of AFP in adults is <6.2 ng/mL. Infants have four or more orders of magnitudes above normal range, decreasing to the adult range after the first 2 years of life

Patient 3

The patient, a younger brother of patients 1 and 2, was 1 year and 4 months old. He was born at 37 weeks gestation, weighing 2,320 g (5th percentile) and measuring 46.0 cm (10th percentile) in length. He was carefully checked because of his familial history. At 48 days old, there were no apparent problems, but deterioration of his laboratory findings were noted. On physical examination, he weighed 3,632 g (below the 3rd percentile) and measured 51.5 cm (below the 3rd percentile) in length. There was no apparent

jaundice of the skin or bulbar conjunctiva. The liver was palpable 2.0 cm below the costal margin. He showed hypoalbuminemia, cholestasis and a profile consistent with NICCD (Table 1). He was fed MCT formula supplemented with essential fatty acids (Meiji Milk Product Co., Ltd., Tokyo) as well as fat-soluble vitamins and arginine. He quickly improved and received the therapy from 55 days to 76 days of age (Fig. 1c). *SLC25A13* mutation was confirmed. At the age of 1 year and 4 months, he weighed 9,205 g (20th percentile) and measured 76.2 cm (15th percentile) in length.

Fig. 1 (continued)

Fig. 1 Clinical courses of patients showing changes in body weight and laboratory findings. **(a)** patient 1, **(b)** patient 2, **(c)**: patient 3, and **(d)**: patient 4. Each patient received standard daily calorie intake appropriate for his or her age. *Closed circles, triangles and squares* represent body weight, levels of serum cholinesterase (*ChE*), and

levels of serum total bile acids (*TBA*), respectively. *Open circles, triangles and squares* in Fig. 1d represent levels of serum alkaline phosphatase (*ALP*), pancreatic secretory trypsin inhibitor (*PSTI*), and alpha-fetoprotein (*AFP*), respectively. *Arrowheads* indicate the ages at testing of the patients described in Table 1

Patient 4

The patient was a 5-month-old boy. He was born at 39 weeks gestation and weighed 2,580 g (20th percentile) and measured 49.5 cm (60th percentile) in length. He had unrelated and healthy parents and a healthy older brother. At 2 months of age, he was found to have mild bilateral cataracts and was transferred to our department. He weighed 5,374 g (45th percentile) and measured 58.0 cm (45th percentile) in length. Physical examination disclosed

mild jaundice and hepatomegaly, 7 cm below the costal margin. His stool was cream-colored and bulky (steatorrhea). He showed hypoalbuminemia, cholestasis, mildly elevated liver transaminases and typical changes in plasma amino acids, suggesting NICCD (Table 1). He also showed increases in the levels of alpha-fetoprotein, PSTI and blood galactose (4.6 mmol/L). Urine was positive for clintest (reducing sugars), but negative for glucose. *SLC25A13* analysis demonstrated a compound heterozygous mutation, c.1177+1G>A/c.1801G>T. He was diagnosed as hav-

ing NICCD accompanied by cataracts due to galactosemia. MCT oil (13.2 g/day) was administered with a lactose-free formula (Morinaga Milk Industry Co., Ltd., Tokyo) for 2 weeks and then the dosage was decreased to 8.5 g/day. As shown in Table 1 and Fig. 1d, he rapidly responded to therapy, showing an improvement of steatorrhea and laboratory findings.

Results and Discussion

The present series comprised four cases including three siblings with NICCD treated with a lactose (galactose)-restricted and MCT-supplemented formula. Under this formula, all patients except patient 1 proportionally decreased their intake of protein, carbohydrate and fat (Table 1). Patient 1 was breast-fed before treatment and his protein intake increased under the formula. For the three sibling cases (patients 1, 2 and 3), we started the therapy at 4 months of age, 2 months of age and 55 days of age in patients 1, 2 and 3, respectively. The older patients had more severe symptoms, but all patients responded to the therapy and showed steady improvement in both cholestasis and laboratory findings (Fig. 1a–c). Therapy were required until 9 months of age, 7 months of age and 5 months of age in patients 1, 2 and 3, respectively, by which time all laboratory findings were nearly normalized. This

suggests that early treatment is highly effective and long-term administration is not required. Patient 4 presented with mild cataracts possibly due to galactosemia. A favorable outcome was achieved similar to those in patients 1, 2 and 3 by lactose-free formula supplemented with MCT oil (Fig. 1d). These treatments quickly and steadily normalized the markers specific for citrin deficiency, plasma citrulline, serum alpha-fetoprotein and PTSI (Kobayashi et al. 1997).

Lactose (galactose)-free formula has been employed for the treatment of NICCD patients complicated by galactosemia. Lactose (galactose)-restricted and MCT-supplemented formula improved galactosemia in patient 2 after 2 weeks of treatment, however, we administered lactose (galactose)-free formula to patient 4 because of an apparent complication by cataracts. Patients with citrin deficiency likely have an impairment of glycolysis due to an increase in the cytosolic NADH/NAD ratio in liver. As shown in Fig. 2, one molecule of galactose will generate one molecule of NADH at the step of UDP-glucose 4-epimerase reaction in the liver and enter the glycolytic pathway. Naito et al. (2002) described that one NICCD patient with galactosemia, who showed an improvement of his clinical condition following treatment with lactose-free formula beginning at the age of 29 days, deteriorated again when challenged with a lactose-containing formula at the age 56 days, and then improved again after a return to the

Fig. 2 Three NADH shuttles and metabolism of medium chain free fatty acids. Abbreviations: α KG α -ketoglutarate; Asp aspartate; cGPDH cytosol glycerophosphate dehydrogenase; CIC citrate carrier; cyt cytosol; DHAP dihydroxyacetone phosphate; FADH₂ Reduced flavin adenine dinucleotide; Gal galactose; Glc glucose; Glu glutamate; G3P glyceraldehyde 3-phosphate; Mal malate; mit mitochon-

dria; MCFA medium chain free fatty acid; mGPDH mitochondrial glycerophosphate dehydrogenase; NADH reduced nicotinamide adenine dinucleotide; OAA oxaloacetate; OGC α -ketoglutarate/malate carrier; PyC pyruvate carrier; Pyr pyruvate. Dotted lines indicate the malate-citrate shuttle

lactose-free formula. Considering galactose metabolism, a lactose (galactose)-restricted formula should be of value for citrin deficiency.

Formulas containing MCT have been administered to NICCD patients with cholestasis (Ohura et al. 2003). An MCT-containing formula induced rapid improvement in our patients as shown in Fig. 1 and its effect seemed to be extremely different from the effects of MCT on patients with cholestasis due to other causes, such as neonatal hepatitis. These findings suggest that MCT administration improves the basic metabolic impairment in the liver with citrin deficiency. The pathophysiology of citrin deficiency may be an energy shortage in the liver caused by an impairment of glycolysis due to an increased NADH/NAD ratio in cytosol. MCT is quickly hydrolyzed and is absorbed mainly as medium chain free fatty acids (MCFA) (Bach and Babayan 1982). MCFA reach the liver via the portal vein and are metabolized to acetyl-CoA by beta-oxidation, enhance TCA cycle activity and increase ATP levels. As shown in Fig. 2, excess acetyl-CoA is also expected to enhance the activity of the malate–citrate shuttle, which transports citrate from mitochondria to the cytosol and transfers reducing equivalents from the cytosol to mitochondria. However, experiments with ^{14}C -labeled MCT administered intravenously to rats demonstrated that the majority of MCT was retained in the liver and about 90% of the MCT was converted to carbon dioxide within 24 h (Bach and Babayan 1982; Johnson et al. 1990). The effect of MCT therapy on citrin deficiency may not occur via enhancement of the malate–citrate shuttle, but via a supply of acetyl-CoA, FADH_2 and NADH to hepatic cells as energy sources.

The symptoms of NICCD usually start in the neonatal period and resolve within the first year of life (Ohura et al. 2007). This clinical feature may be associated with changes in the energy source of the liver and or maturation of hepatic cells. It is interesting to note that 15–20% of the fatty acids in cord blood have eight or fewer carbon atoms (Pilz 1964). The energy source of the liver may switch from fatty acids to glucose after birth. Neonates with NICCD likely have an impairment of glycolytic pathways due to NADH accumulation in the cytosol. Furthermore, the major carbohydrate of milk is lactose, which is composed of glucose and galactose. Galactose intake may further increase the cytosolic NADH/NAD ratio in liver (Fig. 2) and act as a precipitating factor. It is also interesting to note that citrin-knockout mice do not show any significant phenotype because the mouse liver contains an active glycerolphosphate shuttle, which compensates for the defect of the malate–aspartate shuttle (Sinasc et al. 2004). In the human liver, the glycerolphosphate shuttle is not as active as that in the mouse, but can be expected to compensate to some extent. The activity of liver cytosol

glycerol-3-phosphate dehydrogenase is extremely low in the fetal period and then rises to adult levels during infancy (Sadava et al. 1987). Maturation of hepatic cells and or intake of carbohydrates other than lactose after the weaning period may be associated with a resolution of symptoms within 1 year.

Histological findings in the liver of patients with NICCD showed a combination of mixed macrovesicular and microvesicular steatosis, cholestasis, a necroinflammatory reaction and iron deposition (Kimura et al. 2010). Microvesicular fatty changes are a characteristic feature of Reye syndrome or hepatic mitochondrial DNA depletion syndrome (Becroft 1966; Mandel et al. 2001), suggesting a low energy state of the liver. The pathogenesis of citrin deficiency is likely an energy shortage of the liver due to impaired glycolysis.

Lactose (galactose)-restricted and MCT-supplemented formula can improve energy metabolism of the liver and is recommended for patients with NICCD and possibly for the patients with CTLN2.

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Take-Home Message

Lactose (galactose)-restricted and medium-chain triglyceride-supplemented formula is a promising therapy for neonatal intrahepatic cholestasis caused by citrin deficiency.

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