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ORIGINAL PAPER

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Neonatal intrahepatic cholestasis caused by citrin deficiency: severe hepatic dysfunction in an infant requiring liver transplantation

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Abstract Adult-onset type 2 citrullinaemia (CTLN2) is caused by a deficiency of the citrin protein encoded by the *SLC25A13* gene. Citrin, an aspartate glutamate carrier in mitochondria, is an essential component of the malate-aspartate NADH shuttle. Recently, citrin deficiency has been reported to manifest as neonatal intrahepatic cholestasis. We report here five cases with neonatal intrahepatic cholestasis caused by citrin deficiency. Genetic diagnosis revealed compound heterozygotes of 851del4/IVS11 + 1G→A in two patients, IVS11 + 1G→A/E601X, and IVS11 + 1G→A/unknown in each one patient and homozygote for S225X in one patient. All cases revealed high levels of alpha-fetoprotein, which are not observed in CTLN2 patients. The condition was self-limiting and spontaneously disappeared after 5–7 months of age in four patients. However, one patient developed hepatic dysfunction from the age of 6 months and required a living-related liver transplantation at the age of 10 months. The patient showed complete recovery after transplantation, and now at the age of 3 years, shows normal growth and mental development. *Conclusion:* we report the first case of neonatal intrahepatic cholestasis caused by citrin deficiency with severe hepatic dysfunction requiring a living-related liver transplantation. Patients with this disorder should be followed up carefully, even during infancy.

Keywords Argininosuccinate synthetase · Cholestasis · Citrin · Citrullinaemia · Liver transplantation

Abbreviations *AGC* aspartate glutamate carrier · *ASS* argininosuccinate synthetase · C*TLN1* classical citrullinaemia · *CTLN2* adult-onset type 2 citrullinaemia · *NICCD* neonatal intrahepatic cholestasis caused by citrin deficiency

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Introduction

Citrullinaemia is classified into classical citrullinaemia (CTLN1, OMIM 215700) and adult-onset type 2 citrullinaemia (CTLN2, OMIM 603471). CTLN1 is an autosomal recessive disease caused by argininosuccinate synthetase (ASS) deficiency on chromosome 9q34 [3]. CTLN1 is characterised by neonatal/infantile-onset of severe hyperammonaemia, irritability, lethargy, poor feeding, and tachypnoea. On the other hand, CTLN2 is characterised by late onset (11 to 79 years), frequent attacks of hyperammonaemia, mental derangement, sudden attacks of unconsciousness, and ultimately death within a few years of onset [9, 15]. The CTLN2 locus was identified to chromosome 7q21.3, and the causative gene, *SLC25A13*, has been determined [8]. The *SLC25A13* gene encodes calcium-binding mitochondrial protein, designated citrin. Citrin, an aspartate glutamate carrier (AGC) [13], plays an important role in the malate-aspartate NADH shuttle, urea synthesis, and

gluconeogenesis [10]. Impairment of citrin could lead to failure in supply of aspartate from mitochondria to the cytoplasm for synthesis of argininosuccinate, and cause high citrulline and ammonia levels (Fig. 1). Recently, neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD) has been reported with *SLC25A13* mutations as a new disease entity (OMIM 605814) [12, 16, 18, 21]. Nine different mutations in *SLC25A13* have been detected in CTLN2 and NICCD patients [8, 21, 22].

In previous reports [12, 16, 18], patients with NICCD showed recovery within several months. However, we experienced a patient who underwent living-related liver transplantation at the age of 10 months because of deteriorating liver function. We report here clinical and biochemical features of five NICCD cases including the first infant case with liver transplantation.

Case reports

Case 1

The girl, weighing 3,114 g at birth, was born at 39 weeks of gestation. She was the second live-born child of unrelated parents with no family history. Screening for galactosaemia, homocystinuria, phenylketonuria, and maple syrup urine disease was negative. She received milk-based formulas and breast milk. At 1 month of age, failure to thrive was noted with a body weight of 3,400 g. At 2 months, she presented with jaundice and laboratory tests showed a total bilirubin of 7.7 mg/dl, direct bilirubin of 3.8 mg/dl, aspartate aminotransferase of 162 IU/l, and alanine aminotransferase of 79 IU/l. These tests improved gradually, but worsened again at 6 months of age. She was admitted to Osaka City General Hospital at 7 months. Her weight was 6,610 g. She had light yellow-coloured stools, splenomegaly (3.0 cm below the costal margin), and hypoglycaemia (21 mg/dl) without hyperinsulinaemia (0.0 μU/ml). Biochemical data on admission are shown in Table 1. We suspected tyrosinaemia type 1. Urine analysis showed a significant rise of *p*-hydroxyphenylacetate and *p*-hydroxyphenylpyruvate, but no succinylacetone. The fumarylacetoacetate hydrolase activity in skin fibroblasts was within the normal range. There was no past history of hepatitis A, B and C, cytomegalovirus, herpes virus, or Epstein-Barr virus infection. Biliary tract diseases and cystic fibrosis, glycogen storage disease and α_1-antitrypsin deficiency (185 mg/dl) were excluded. Doppler ultrasound studies did not show abnormalities of the portal vein or a portosystemic shunt. She showed no developmental delay or neurological abnormalities.

Medium-chain triglycerides and a low phenylalanine-tyrosine formula with supplementation of fat-soluble vitamins were administered. However, hepatic dysfunction with hypercitrullinaemia (239 μmol/l) and hypoglycaemia progressed in spite of intensive treatment. She manifested poor feeding and activity. We considered that she had progressive hepatic failure. She underwent living-related liver transplantation at 10 months of age. The histopathological findings of liver specimens included diffuse fatty changes of hepatocytes, cholestasis in lobules with proliferation of bile ducts, portal-to-portal bridging fibrosis, and pseudolobule. At 3 years of age, she was diagnosed with NICCD by genetic analysis, and currently has a normal plasma amino acid pattern, hepatic function, and normal development. Urea cycle enzymes were measured in a postoperative native liver specimen, which was stored for 2.5 years at –80°C (Table 2).

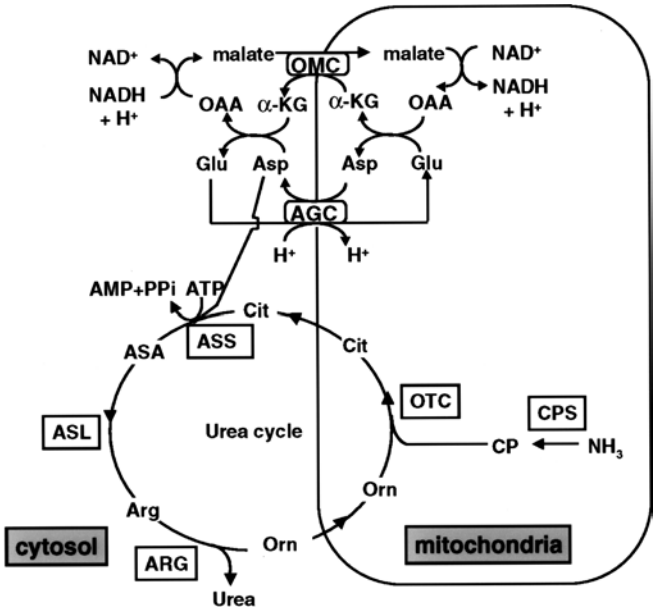

Fig. 1. Metabolic map of the urea cycle and malate-aspartate NADH shuttle. (*AGC* aspartate glutamate carrier; *ARG* arginase; *ASA* argininosuccinic acid, *ASL* argininosuccinate lyase; *CP* carbamylphosphate; *CPS* carbamylphosphate synthetase;*α-KT* α-ketoglutarate; *OAA* oxaloacetic acid; *OMC* α-ketoglutarate/malate carrier; *OTC* ornithine transcarbamylase)

Cases 2–5

These four unrelated patients had healthy parents. Newborn mass screening showed Cases 3 and 4 were positive for phenylalanine (242 and 157 μmol/l, respectively), while Case 5 had high levels of methionine (268 μmol/l) and galactose (1.1 mmol/l). Cases 2–5 had white-cream coloured stools but no hepatosplenomegaly. Cases 2–4 showed mild failure to thrive and Case 5 had hypoglycaemia (31 mg/dl). The laboratory findings are listed in Table 1. Known causes of neonatal cholestasis were eliminated in these patients, including infectious hepatitis, metabolic disease, and biliary tract disease. None showed developmental delay or neurological abnormalities. Without specific treatment other than feeding with medium-chain triglycerides or lactose-free formulas with supplementation of fat-soluble vitamins, biochemical abnormalities in Cases 2–5 improved by the age of 5–7 months.

Control subjects

Seven control newborn subjects were found to have high levels of galactose (0.22–1.4 mmol/l) on newborn mass screening. They did not have the enzyme deficiency for galactosaemia, and surveys of nine different mutations in *SLC25A13* were negative. The cause of mild intrahepatic cholestasis (total bile acid: >40 μmol/l) could not be specified. Biochemical data in control subjects returned to near-normal levels within 2 months.

Methods

The nine known mutations were diagnosed as follows [8, 21,22]: (1) the different length of amplified DNA (851del4 and 1638ins23), (2) the restriction fragments length polymorphisms after DNA amplification with polymerase chain reaction (IVS11+1G→A by Sau3AI digestion, S225X by *Alu* I, IVS13+1G→A by *Pst* I, 1800ins1 by *Tru*1I, R605X by *Bsh*1236 I, E601X by *EcoR* I, and E601K by *EcoR* I), (3) the multiple DNA diagnosis method by using GeneScan/SNaPshot analysis. Informed consent for genetic analysis was obtained from all parents.

Table 1. Biochemical data in five cases of NICCD. (*ALP* alkaline phosphatase, *PSTI* pancreatic secretory trypsin inhibitor)

	Case 1	Case 2	Case 3	Case 4	Case 5	Control subjects	Reference range
Age (months)	7	1	1	1	1	1	
Sex	F	M	M	M	F	M 3, F 4	
Gestational Age (weeks)	39	40	36	38	39	39 ± 1	37–41
Birth weight (g)	3144	2970	2058	2416	1930	3108 ± 39	2164–3928
Total protein (g/dl)	6.0	4.4	4.3	5.6	5.1	5.5 ± 0.4	4.6–7.4
Total bilirubin (mg/dl)	5.9	4.6	6.6	6.3	8.2	2.5 ± 1.7	0.2–1.0
Direct bilirubin (mg/dl)	2.9	3.1	3.4	4.3	2.5	0.7 ± 0.4	0.0–0.4
AST (IU/l)	191	50	64	142	47	45 ± 10	15–55
ALT (IU/l)	78	32	23	67	20	39 ± 14	5–45
γ-GTP (IU/l)	292	78	347	323	219	47 ± 23	5–32
ALP (IU/l)	1774	2444	2849	3889	1530	1005 ± 265	145–420
Total bile acid (μmol/l)	88	265	259	319	220	48 ± 30	5–25
Prothrombin time (%)	29	96	Not determined	63	37	Not determined	75–100
Hepaplastin test (%)	22	Not determined	45	Not determined	32	Not determined	70–130
PSTI (ng/ml)	Not determined	33	107	42	Not determined	32 ± 6	34 ± 12
Ammonia (μg/dl)	67	196	102	166	97	Not determined	18–74
Alpha-fetoprotein (ng/ml)	207000	136000	379000	309000	152570	6400 ± 10460	260–6400[a], 2–55[b]
Threonine (μmol/l)	294	547	962	730	532	179 ± 44	102 ± 20
Citrulline (μmol/l)	87	397	484	611	218	34 ± 8	28 ± 41
Methionine (μmol/l)	246	56	196	705	597	52 ± 19	23 ± 8
Tyrosine (μmol/l)	182	87	139	275	298	125 ± 34	71 ± 23
Arginine (μmol/l)	118	105	206	196	240	107 ± 59	85 ± 13
Phenylalanine (μmol/l)	56	35	41	37	41	70 ± 21	61 ± 14
Fischer ratio	0.76	1.2	1.4	0.36	0.78	1.7 ± 0.4	2.3 ± 0.6
Threonine/serine ratio	2.1	3.8	3.9	3.9	1.9	1.1 ± 0.2	0.8 ± 0.9
Galactose (mmol/l)	Not determined	3.1	5.1	2.9	0.2	0.2 ± 0.2	< 0.06
*SLC25A13*mutation[c]	I/II	II/VIII	I/II	IV/IV	I/-	Negative	

[a]Normal values at 1 month
[b]Normal values at 7 months
[c]*SLC25A13* mutations I, II, IV, and VIII were 851del4, IVS11 + 1G→A, S225X, and E601X, respectively

Results and discussion

We examined our subjects for nine mutations of *SLC25A13,* which had been previously observed in alleles of 92% of patients with early- and late-onset citrin deficiency [21]. These mutations were not present in the control subjects tested. It was therefore presumed that mild intrahepatic cholestasis in our control subjects was not due to citrin deficiency. On the other hand, mutations in *SLC25A13* were detected in both alleles of Cases 1–4 and in a single allele of Case 5, and accordingly were diagnosed as NICCD. The characteristic clinical features (Table 1) of these five paediatric patients are: (1) white coloured or yellow-white coloured stools, (2) poor body weight gain until 1 month after birth, (3) high levels of direct bilirubin, total bile acid, alkaline phosphatase, and γ-glutamyl transpeptidase, (4) high levels of citrulline, tyrosine, methionine, high threonine/serine ratio, low branched-chain amino acids/aromatic amino acid ratio (Fischer ratio), as previously described in CTLN2 patients [14], (5) low levels of vitamin K-dependent coagulation factor, (6) mild hyperammonaemia, and (7) high levels of alpha-fetoprotein, which are characteristic in NICCD since it has not been observed in CTLN2 patients [7,9]. Alpha-fetoprotein in our NICCD patients may have increased due to premature hepatocytes and/or hepatic damage and regeneration. Hepatocyte growth factor was also high (1.57 ng/ml) in Case 1. Pancreatic secretory trypsin inhibitor levels are high in CTLN2 patients [7,9], however, our infant patients (Cases 2 and 4) showed normal levels except for Case 3. Hypoglycaemia was seen in Cases 1 and 5, and was caused by the disturbance of gluconeogenesis. The AGC functions to provide substrates for gluconeogenesis as a part of the pathway for conversion of amino acids to glucose [10].

To date, 22 liver transplantations in CTLN2 adult patients have been performed [1, 5, 6, 7, 9, 17]. Case 1 was the first NICCD case requiring liver transplanta-

tion. The difference between Case 1 and the other four patients is clear if viewed through the progressive changes in cholestasis indices. In Cases 2–5, direct bilirubin, alkaline phosphatase, total bile acid, and alpha-fetoprotein improved with time and the values had nearly normalised by 5–7 months after birth (Fig. 2). In contrast, while cholestasis in Case 1 tended to improve up to 6 months after birth, similar to Cases 2–5, it worsened later, necessitating liver transplantation. The alpha-fetoprotein in Case 1 was also high until liver transplantation was performed. The genotype of Case1 is a compound heterozygote of 851de14 and IVS11 + 1-G→A (Table 1). These two mutations are prevalent, accounting for 33% and 40%, respectively, in Japanese patients with citrin deficiency [21]. Their compound heterozygotes account for 20%. At present, ten patients with the same genotype including our Cases 1 and 3 have developed NICCD [21]. However, two of them, Case1 and a case with NICCD (Hirayama et al., personal communication) required liver transplantation in early infancy, and the condition of the remaining eight patients improved spontaneously [12, 16,18]. Therefore, the relapse of hepatic dysfunction in Case 1 from 6 months after birth is not due to the genotype. At the time of liver transplantation, Case 1 had no infections of hepatitis A, B and C, cytomegalovirus, herpes virus or Epstein-Barr virus, and also had no particular events such as bacterial infection. We could not identify the triggers of relapse after 6 month of age in Case 1. Furthermore, the histological findings at the liver transplantation in Case 1 could not specify the cause of hepatic dysfunction. Adult patients with CTLN2 also do not show pathognomonic histopathological features, but rather were reported to vary from no pathological findings or fatty change to severe pathological lesions such as cirrhosis and chronic hepatitis [1, 5, 6, 9, 17, 20].

Table 2. Activities of urea cycle enzymes in the liver of Case 1. (*ASL* argininosuccinate lyase, *CPS* carbamoylphosphate synthetase, *OTC* ornithine transcarbamylase)

Enzymes	Case 1		Controls[a]
	(U/mg protein)	(%)	
CPS	0.015	56	0.027 ± 0.013 (n = 28)
OTC	0.36	48	0.75 ± 0.29 (n = 23)
ASS	0.005	22	0.023 ± 0.013 (n = 30)
ASL	0.045	82	0.055 ± 0.021 (n = 32)
Arginase	3.0	20	14.9 ± 3.3 (n = 36)

[a]The controls are given as mean ± SD with the number of control samples in parenthesis. The ages of the controls are 3 days to 6 years

The primary cause of CTLN2 is citrin deficiency and low hepatic ASS activity is a secondary effect [22]. The prominent characteristics of CTLN2 are still a quantitative decrease of ASS protein in the liver (13.1 ± 13.3% of control, n = 99; from 0.5% to 79%) [7, 9,22]. On the other hand, three cytosolic enzymes of ASS, argininosuccinate lyase, and arginase in a NICCD patient were within the normal range in the liver biopsy specimens after normalisation of all clinical and biochemical data [16]. The ASS and arginase activities in the resected

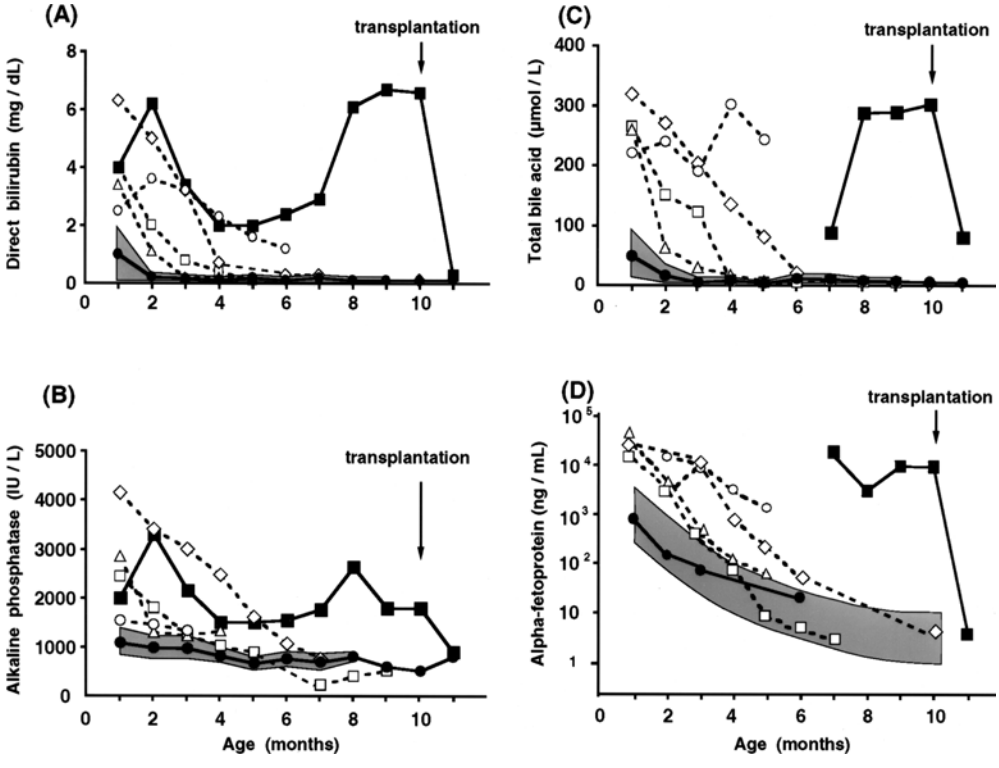

Fig. 2. Serial changes in direct bilirubin (**A**), alkaline phosphatase (**B**), total bile acid (**C**), and alpha-fetoprotein (**D**) in five patients with NICCD. Case 1 (*solid squares*), Case 2 (*open squares*), Case 3 (*open triangles*), Case 4 (*open diamonds*), Case 5 (*open circles*), average data of seven control subjects (*solid circles*). The *shaded* area indicates variation (± SD) of the data values of control subjects (**A**), (**B**) and (**C**) or reference range of alpha-fetoprotein (**D**) [19]

native liver specimen of Case 1 were reduced to 22% and 20% of control, respectively, as shown in Table 2. Several studies have reported decreases of ASS accompanied with carbamoyl phosphate synthetase, argininosuccinate lyase, and/or arginase in patients with CTLN2 [2, 4, 5, 6, 17]. Deterioration of liver tissue results in reduction of activities of all five enzymes of the urea cycle, for example, 36% to 45% in liver cirrhosis [11]. Therefore, the reduced ASS activity in liver specimens of Case 1 is primarily caused by citrin deficiency. In other words, we suspect that deterioration of liver function in Case 1 is primarily caused by citrin deficiency.

Citrin deficiency resulting from mutation of *SLC25A13* is associated with the development of hypercitrullinaemia, followed by intrahepatic cholestasis in infancy. The conditions in most NICCD patients are often self-limiting and spontaneously disappear because of maturation of hepatocytes and/or some adaptations or compensations of other mitochondrial carriers. After 10 or more years, compensatory failure is likely to occur with resultant relapse of the disease in adulthood. However, one of our cases had very severe phenotype of NICCD that required liver transplantation at the age of 10 months. We suspect that some patients with hypertyrosinaemia of an unknown cause may result from NICCD. This severe phenotype of NICCD may not be that rare therefore patients with NICCD should be followed up carefully, even during infancy.

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