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ORIGINAL ARTICLE

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Hypoglycemic attacks and growth failure are the most common manifestations of citrin deficiency after 1 year of age

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Abstract

Citrin deficiency develops in different symptomatic periods from the neonatal period to adulthood. Some infantile patients are diagnosed by newborn mass screening or symptoms of neonatal intrahepatic cholestasis caused by citrin deficiency, some patients in childhood may develop hepatopathy or dyslipidemia as failure to thrive and dyslipidemia caused by citrin deficiency, and some adults are diagnosed after developing adult-onset type 2 citrullinemia (CTLN2) with hyperammonemia or encephalopathy. A diagnosis is needed before the development of severe phenotypic CTLN2 but is often difficult to obtain because newborn mass screening cannot detect all patients with citrin deficiency, and undiagnosed patients often appear healthy in childhood. There are only a few reports that have described patients in childhood. To explore the clinical features of undiagnosed patients with citrin deficiency in childhood, we studied 20 patients who were diagnosed after the first year of life. Of these patients, 45% experienced hypoglycemic attacks in childhood. The acetoacetic acid level during hypoglycemic attacks was lower than expected. Growth failure at diagnosis (45%) was also noted. From the patients' history, fat- and protein-rich food preferences (80%), a low birth weight (70%), and prolonged jaundice or infantile hepatopathy (40%) were identified. To diagnose citrin deficiency in childhood, we should ask about food preferences and a history of infantile hepatopathy for all children with severe hypoglycemia or growth failure and consider the genetic test for citrin deficiency if the patient has characteristic food preferences or a history of infantile hepatopathy.

KEYWORDS

citrullinemia, failure to thrive, SGA, SLC25A13

1 | INTRODUCTION

Citrin deficiency is an autosomal-recessive inherited metabolic disorder caused by biallelic *SLC25A13* (HGNC: 10983) mutations.[1] Citrin deficiency develops in several symptomatic and phenotypic phases: neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD, OMIM #605814), growth failure and dyslipidemia caused by citrin deficiency (FTTDCD), and adult-onset type 2 citrullinemia (CTLN2, OMIM #605814).[2-5] In the neonatal or infantile

periods, some patients with citrin deficiency are diagnosed with NICCD based on a presentation of intrahepatic cholestasis, prolonged jaundice, liver cirrhosis, growth retardation, or coagulation defects.[6] In some neonatal patients, hypercitrullinemia, hyperphenylalaninemia, hypermethioninemia, or galactosemia can be detected through newborn screening (NBS). In adulthood, some patients with citrin deficiency may develop CTLN2, with a disturbance of consciousness, hyperammonemia, fatty liver, hepatoma, or pancreatitis. Some patients need liver transplantation to prevent recurrent hyperammonemic episodes or metabolic failure.[7-10] During NICCD and CTLN2, some patients exhibit an "apparent healthy" period with no obvious symptoms, but other patients may manifest growth failure, hepatomegaly, or dyslipidemia,[5] but the prevalence is unknown.

Not all patients with citrin deficiency diagnosed in the early infantile period. It is known that some patients do not present typical NBS-positive findings or specific symptoms of cholestasis in the neonatal and infantile periods.[11] There are previous reports that patients without citrullinemia or symptoms of NICCD in the infantile period might go undiagnosed until they develop severe symptoms, such as those of CTLN2, later in life.[12,13] Because NICCD symptoms can almost disappear several months after birth,[14] the diagnosis of citrin deficiency becomes even more difficult. With NBS using tandem mass spectrometry, which started being used in 2012 throughout all of Japan, more neonatal patients are expected to be identified through elevations in blood citrulline in the presymptomatic period.

Some case reports have shown that patients in childhood with citrin deficiency exhibit fatigue, hypoglycemia, hyperlipidemia, growth failure, or liver dysfunction.[5,15-18] Nutritional analysis in patients revealed that they have peculiar food preferences, such as a preference for lipid-rich or protein-rich foods and an aversion to high-carbohydrate foods, which might compensate for the metabolic failure caused by citrin deficiency.[19] Okano et al reported that citrin-deficient patients had lower fatigue and quality of life scores during the adaptation and compensation stages than controls.[20] However, there have been few reports about the initial complaints or symptoms of undiagnosed patients with citrin deficiency in childhood.

In this case series, to explore the diagnostic signs of patients with citrin deficiency in early childhood, we investigated the clinical features and illness histories of 20 children with citrin deficiency who were diagnosed after the first year of life. As a result, we found that the most frequent manifestations resulting in a visit to the hospital after 1 year of life were hypoglycemic attacks and growth failure. A peculiar food preference was a good index for children with citrin deficiency. Because undiagnosed citrin-deficient patients might develop CTLN2, and given the poor prognosis of this condition, it is important to understand the characteristics of citrin deficiency in childhood and provide appropriate nutritional or medical management.

SYNOPSIS

We should determine detailed food preferences or a history of infantile hepatopathy as indicators for the genetic test for citrin deficiency when patients in early childhood develop severe hypoglycemia or growth failure.

2 | SUBJECTS AND METHODS

2.1 | Subjects

Patients who were diagnosed with citrin deficiency through molecular genetic tests and met the following criteria were included in this study: (a) presented some clinical phenotype, laboratory abnormality, or familial history that indicated citrin deficiency; (b) had one or two mutations detected through common mutation screening of *SLC25A13*; and (c) were diagnosed after 12 months of age. We excluded patients who presented with the CTLN2 phenotype, such as hyperammonemia or deteriorated consciousness, because the classic initial symptoms of CTLN2 are known. The clinical data of patients who were diagnosed between October 2009 and September 2016 in Japan by screening 11 common mutations were collected.

2.2 | Mutational analysis

We screened patients for the 11 prevalent mutations of *SLC25A13* (NM_014251.3)[21,22] in Asian populations using melting curve analysis by real-time PCR, as described previously with minor revisions.[22] The 11 mutations were as follows: c.852_855del (p.Met285-Profs*2), c.1177+1G>A (p.Ala340_Arg392del), c.1638_1660dup (p.Ala554Glyfs*17), c.674C>A (p.Ser225*), c.1311+1G>A (p.Val411_Cys437del), c.1751-5_ 1751-4ins [TTTTTTTTTTTTTTTT;NM_138459.2:c.-194_ *1573inv; C;1751-21_1751-5], c.1799dup (p.Tyr600*), c.1813C>T (p.Arg605*), c.1801G>T (p.Glu601*), c.1801G>A (p.Glu601Lys), and c.1793T>G (p.Leu598Arg). The allele frequency of the 11 mutations in Japanese patients has

TABLE 1 The characteristics of the 20 patients with citrin deficiency diagnosed after 1 year of life

				Manifestations		Other signs		Past history			
ID	Sex	Diagnosed age	FH	Hypoglycemia (situation), level of blood glucose	Growth failure, SD score	Food pref.	Abnormal lab/data	LBW or SGA (GA, birth weight)	NBS-positive, data	Infantile hepatopathy	Others
1	M	1y 0m	−	−	+*, nd	na	Elevation of Cit, Met, Phe (230, 122, 117 nmol/mL)	+ (38w 1d, 2595 g)	−	+, jaundice and acholic stool at 2 mo	
2	F	1y 7m	−	+*(enteritis since last night), nd	−	na		+ (33w 5d, 1432 g)	Gal, nd	+, elevated TBA at 2 mo, hyperechoic hepatomegaly at 6 mo	Citrullinemia (2 mo)
3	M	1y 7m	−	−	+*, −3 (BW)	+	nd	+ (35w 2d, 2045 g)	−	+, acholic stool, jaundice, elevated liver enzymes at 3 mo	Neonatal hypoglycemia, VSD
4	F	1y 10m	−	+* (during infusion dextrose, several times), 2.5 mmol/L	+, nd	+	Hypertriglyceridemia (262 mg/dL), elevation of AST, ALT (139, 68 U/L)	+ (40w 2d, 2592 g)	−	−	
5	F	2y 3m	−	+* (during infusion dextrose), nd	−	+	Hypertriglyceridemia (180 mg/dL), elevation of AST (62 U/L)	+ (39w 2d, 1888 g)	Cit, 70 nmol/mL	−	Pulmonary artery sling
6	M	2y 9m	−	−	+*, −2	−		+ (38w 6d, 2580 g)	−	+, acholic stool at 1 mo, growth failure and jaundice at 3 mo	Neonatal hypoglycemia
7	M	2y 11m	−	+* (twice, URI and poor oral intake for 2 days), 1.0 mmol/L	+, −2.5 (BH)	+		+ (38w 6d, 2216 g)	Gal, 8.0 mg/dL	−	
8	F	3y 9m	−	+* (4 times, fever or enteritis), 1.38 mmol/L	−	+		−	−	−	
9	F	4y 0m	−	−	+*, nd	+	nd	+, nd	nd	+, cholestasis, elevated liver enzymes	
10	F	6y 11m	−	+* (twice), 2.3 mmol/L	+, nd	+		+ (2416 g)	−	−	General fatigue
11	M	9y 7m	−	+* (enteritis since last night), 1.83 mmol/L	−	+	Elevation of AST, ALT (73, 71 U/L), hypertriglyceridemia (219 mg/dL)	−	−	−	

TABLE 1 (Continued)

				Manifestations		Other signs		Past history			
ID	Sex	Diagnosed age	FH	Hypoglycemia (situation), level of blood glucose	Growth failure, SD score	Food pref.	Abnormal lab/data	LBW or SGA (GA, birth weight)	NBS-positive, data	Infantile hepatopathy	Others
12	M	10y 3m	−	+* (3 times, poor oral intake since last night), 1.66 mmol/L	−	+		−	−	nd	Neonatal hypoglycemia and apnea
13	F	10y 11m	−	−	+, nd	+	Elevation of AST, ALT* (80, 60 U/L), Cit elevation* (170-200 nmol/mL)	−	nd	nd	Hepatomegaly
14	F	3y 2m	+*	−	−	+		+ (39w 1d, 2411 g)	−	+, jaundice at 1 mo	
15	F	3y 2m	+*	−	−	na		nd	−	+, jaundice, elevated liver enzymes at 3 mo	
16	M	3y 8m	+	−	+*, −2.9 (BH)	+		+ (39w 2d, 2084 g)	−	−	
17	M	3y 11m	+*	−	−	+	Elevation of Cit, Phe (52.3, 94.9 nmol/mL)	−	−	+, jaundice at 3 mo	
18	M	5y 1m	+*	+ (enteritis), nd	−	+		+ (39w 5d, 2680 g)	−	−	Hepatomegaly
19	F	6y 0m	+*	−	−	+		+ (37w, 1528 g)	−	nd	
20	F	13y 9m	+*	−	−	+		+ (40w 3d, 2382 g)	−	−	
Total			7	9	9	16		14	3	8	

Abbreviations: *, main manifestations suspected citrin deficiency; ALT, alanine aminotransferase; AST, aspartic aminotransferase; BH, body height; BW, body weight; Cit, citrulline; F, female; FH, family history; Food pref., food preference; GA, gestational age; Gal, galactose; ID, identification; LBW, low birth weight; M, male; Met, methionine; NBS, newborn screening; nd, no data; NICCD, neonatal intrahepatic cholestasis caused by citin deficiency; Phe, phenylalanine; SGA, small for gestational age; TBA, total bile acids; VSD, ventricular septal defect.

TABLE 2 The allele frequency of the subjects diagnosed after 1 year of age

Mutation	Frequency (%, number of allele)		
	This study		
	All	NICCD(−)	Ref. 21
c.852_855del	35.0 (14)	33.3 (6)	33.2
c.1177+1G>A	37.5 (15)	44.4 (8)	37.6
c.674C>A	2.5 (1)	5.5 (1)	5.4
c.1311+1G>A	12.5 (5)	5.5 (1)	8.2
c.1799dup	2.5 (1)	0 (0)	1.3
c.1751-5_1751-4ins[TTTTTTTTTTTTTTTTT; NM_138459.2:c.-194_*1573inv; C;1751-21_1751-5]	7.5 (3)	5.5 (1)	3.6
Others	2.5 (1)	5.5 (1)	10.7

been estimated to be above 95%.[21] If only one mutation was detected, we also performed direct Sanger sequencing on the coding region of *SLC25A13* to detect another mutation. If no other mutation of *SLC25A13* was detected, the patient was excluded.

2.3 | Clinical history and laboratory data collection

We collected information on the current symptoms or complaints at diagnosis, clinical history, and laboratory data of patients who fulfilled all of the above criteria based on a request for genetic analysis sent by the attending doctors. This investigation was approved by the Ethical Board of Tohoku University School of Medicine. All participants' families provided written informed consent.

3 | RESULTS

We performed *SLC25A13* mutation screening for 432 patients who were suspected of having citrin deficiency by their attending doctor, had any symptoms or a family history of NICCD, FTTDCD, and CTLN2, or had positive NBS results (galactosemia or citrullinemia). Of the patients, 198 had one or two mutations in *SLC25A13* detected by screening for the 11 common mutations, and 23 of 198 patients met the inclusion criteria (23/198, 11.6%). All 23 patients were Japanese. Of the 23 patients, we excluded 2 patients who had only one mutation detected through prevalent mutation screening of *SLC25A13* followed by Sanger sequencing and one patient who developed a typical clinical course of citrin deficiency, including neonatal hypoglycemia, galactosemia, citrullinemia, cataracts, and fatty liver, before the studies on NICCD by Ohura and Tazawa were published.[3,4] Finally, 20 patients were included in this study, including 9 males and 11 females (Supporting Information 1). Table 1 shows the characteristics of the participants. The mean age at diagnosis was 4.7 ± 3.2 years (range: 1.0-13.8). Seven subjects had a younger sibling previously diagnosed with NICCD, and the other 13 subjects had no family history of citrin deficiency. Two mutations in *SLC25A13* were detected in all subjects, including six of the prevalent mutations. Supporting Information 2 shows the detected mutations for all subjects. One patient (P4) was verified to be compound heterozygous with a combination of one common and one rare mutation known as disease causing, c.15G>A. The allele frequencies are shown in Table 2.

The most common clinical manifestations of our cohort at diagnosis were hypoglycemic attacks (n = 9) and growth failure (n = 9), followed by family history (n = 7, some overlapped). The patients with hypoglycemic attacks (blood glucose level <2.5 mmol/L) presented with a loss of consciousness, convulsion, sweating, fatigue, or "not doing well" in a catabolic state, which included respiratory infection, gastroenteritis or fever after poor oral intake. The blood glucose levels and hypoglycemic attack details are described in Table 1. These hypoglycemia attacks were recorded 16 times from 16 months of age to 9 years of age (median: 33.5 months of age). Five patients experienced various numbers of recurrent hypoglycemic episodes: four times (n = 1), three times (n = 1), twice (n = 2), and several times (n = 1); four patients had intractable hypoglycemia with resistance to dextrose infusion (overlapping). Table 3 shows the levels of ketone bodies when the patients presented with hypoglycemia (data available for two patients). The level of acetoacetic acid was lower than expected when compared to a previous study[23] and considering the blood glucose level during the hypoglycemic attack. Two patients had data available regarding low

TABLE 3 The profile of blood glucose and ketone bodies at hypoglycemic attack

ID	Age	Blood glucose (mmol/L)	Total ketone bodies (mmol/L)	AcAc (mmol/L)	3-OHB (mmol/L)	3-OHB/AcAc
4	1 y 10 m	2.9	4.14	0.54	3.6	6.7
7	2 y 11 m	1.1	2.499	0.352	2.147	6.1
10	6 y 9 m	2.3	0.94	na	na	
Ref.	1-7 y (n = 27)	2.8-3.8 (mean 3.3)	2.2-5.8 (3.5)		1.7-3.2 (2.5)	2.7-3.5 (2.9)

Note: Reference values (10th-90th percentiles) are based on data from approximately 1- to 7-year-old children in whom no abnormality in the metabolic or endocrine pathway was found after 24 hours of fasting.[23]

Abbreviations: 3-OHB, 3-hydroxybutyric acid; AcAc, acetoacetic acid.

plasma insulin levels during hypoglycemia (immunoreactive insulin <0.3 and 1.0 μU/L, respectively).

The blood laboratory data showed low glucose in nine patients, hypertriglyceridemia (triglyceride >150 mg/dL) in three patients, and AST and/or ALT elevation in four patients. Amino acid analysis data at diagnosis were available for 13 individuals, and citrulline elevation was found in 3 patients. Two of the four patients investigated had a growth hormone deficiency.

From the patients' medical histories, 14 of 20 patients (70%) were born small-for-gestational-age (SGA) or had a low birth weight (LBW <2500 g body weight, mean birth weight: 2377 ± 443 g; range: 1432-3155; mean gestational age at birth: 38 weeks, range: 33 w5d-40 w4d). Additionally, the subjects had infantile hepatopathy or prolonged jaundice (n = 8), neonatal hypoglycemia (n = 3), and transient galactosemia or citrullinemia detected by NBS (n = 3). Focused medical interviews revealed characteristic food preferences (n = 16) with a preference for meat, fish, dairy products, soybean products, or fried chicken, and aversions to rice, noodles, juice, or sweets, as reported in a previous study.[19]

4 | DISCUSSION

To better understand the initial medical conditions of patients with citrin deficiency in childhood, we examined the clinical illness history and laboratory data of those diagnosed with citrin deficiency after 1 year of life. As a result, hypoglycemic attack (blood glucose <2.5 mmol/L) and growth failure were the most frequent manifestations and were detected in 45% (9/20) of citrin-deficient pediatric patients, respectively. These hypoglycemic attacks in the early childhood period (median: 33.5 months of age) often appear after poor oral intake and/or during illness and catabolic states, such as fever, vomiting, or enteritis, and some of these symptoms are repetitive or intractable with dextrose infusion. Thus far, there have been few reports on the symptoms of or diagnostic approaches for citrin deficiency in childhood.[5,15-18] Chong et al reported a characterization of citrin deficiency and that two patients were diagnosed after 1 year of age by family screening the siblings of NICCD infants.[16] Of the two patients, one presented growth failure, and the other had no symptoms. In younger patients with citrin deficiency, low-ketotic hypoglycemia was reported by Otsuka et al[17] and Wada et al.[18] This is the first case series of patients with citrin deficiency in childhood. On the basis of our findings and those of previous studies, we should consider citrin deficiency when individuals experience severe hypoglycemia in childhood.[17,18]

This report included nine patients with symptomatic hypoglycemia, which might indicate failed glucose homeostasis due to citrin deficiency. These attacks were recorded during a catabolic state after 1 year of life but never in infancy, except in neonates. Individuals with NICCD are known to develop hypoglycemia, and NICCD is thought to disturb the glycemic maintenance pathway because citrin plays a role in providing substrates for gluconeogenesis.[24,25] Citrin, aspartate-glutamate carrier 2, is located in the mitochondrial inner membrane and is a component of the aspartate-malate shuttle.[26] The aspartate-malate shuttle transfers the reducing equivalents of NADH into the mitochondrial matrix.[27] This process is involved in redox state balance for gluconeogenesis. In citrin deficiency, cytosolic NADH is increased to excess, and mitochondrial NADH is decreased due to aspartate-malate shuttle failures.[28] Cytosolic NADH/NAD+ elevation is considered to impair gluconeogenesis from lactate,[29,30] and mitochondrial NADH/NAD+ reduction may disturb the beta oxidation pathway, leading to low levels of ketones.[31] Low malate and oxaloacetate due to a citrin deficit also causes gluconeogenesis failure.[29,30] In our cohort, the level of acetoacetic acid was lower than expected on the basis of the blood glucose level during hypoglycemia.[23] Acetoacetic acid production might be disturbed by low NADH/NAD+ in mitochondria. In the adaptation period, because the metabolic failure caused by citrin deficiency could be compensated for by peculiar food preferences such as a high-fat and low-carbohydrate

foods, most patients with citrin deficiency exhibit no obvious symptoms and appear healthy.[19] Latent defects in gluconeogenesis may persist and patients who develop a severe hypoglycemic attack with low levels of ketone bodies cannot compensate for metabolic failure due to citrin deficiency because of decreased energy intake during the catabolic state.

Among undiagnosed citrin-deficient patients, growth failure was also a major symptom observed during clinical evaluation at the hospital. Some patients had growth hormone defects. The exact mechanism of growth failure in citrin deficiency is unknown. Numakura et al reported growth failure in patients with citrin deficiency, which was suggested to be due to lipogenesis failure.[32] To elucidate this mechanism, more studies are needed. Hepatomegaly was detected in two individuals, and noninvasive liver sonography is useful to understand the stage of the disease. Blood tests revealed mild hyperlipidemia or liver dysfunction in four patients. Although citrulline elevation in amino acid analysis might be specific to citrin deficiency, the sensitivity of this test for childhood patients seems low.

Because patients with citrin deficiency in an apparently healthy period might present nonspecific symptoms, such as hypoglycemia, growth failure, hepatopathy, hyperlipidemia, or general fatigue, obtaining a medical history about food preferences or past history is useful. The specific food preferences aligned with those reported in a previous study[19] and were found in 16 of 20 patients (80%). Most of our subjects developed high-fat and high-protein food preferences before 3 or 4 years of age. The other three patients with no food preferences, who were 1 or 2 years of age, might have been too young to declare food preferences. Transient infantile hepatitis (40%), which seemed to be due to cytomegaloviral infection, cholangiectasis, or breast milk jaundice, and galactosemia or citrullinemia as determined by NBS (15%) were also helpful indicators of citrin deficiency. A high prevalence of SGA or LBW (70%) was also found in our cohort. Intrauterine growth failure occurs in fetuses with citrin deficiency,[6,32] although the mechanism is not clear. If the medical information from interviews reveals these findings, genetic analysis should be considered.

The clinical course of these subjects is interesting. There were two groups of patients with or without a history of infantile hepatopathy. A previous study on failure to thrive in citrin deficiency described that patients with NICCD exhibited more severe growth failure than those without NICCD.[32] In this study, we did not state the difference in the degree of growth failure with or without infantile hepatopathy because we did not have adequate data on patient growth. Hypoglycemia seems to be more common in patients without a history of infantile hepatopathy (one of eight patients with hepatopathy vs seven of nine patients without hepatopathy, Table 1), and we considered that patients who were diagnosed because of NBS positivity or NICCD might have been excluded prior to this study. Hypoglycemia in childhood may be the initial manifestation of citrin deficiency in patients who are asymptomatic in the infantile period.

There were no specific mutations for childhood onset. The allele frequencies of the subjects were compatible with those found in a previous Japanese study on NICCD and CTLN2.[21] To the best of our knowledge, the phenotype-genotype correlation remains unclear.

It is important to diagnose patients with citrin deficiency before CTLN2 develops. CTLN2 (prevalence: $1/100\,000$[9]) has a poor prognosis and involves mental disorders, severe hepatic failure, encephalopathy or even death, but these might be preventable with appropriate medical management. However, it is difficult to diagnose all patients with citrin deficiency through NBS. Bloodspot screening or physical examination for infants cannot detect all patients with citrin deficiency because not all patients exhibit abnormalities, such as elevations in citrulline, phenylalanine, methionine, and/or galactose, or prolonged jaundice. The prevalence of citrin deficiency in Japan is predicted to be approximately 1/17 000-20 000, which was calculated using the Japanese carrier frequency.[1,21] In a Japanese pilot study on NBS using tandem mass spectrometry, citrin deficiency was detectable in 5 of 300 000 neonates by elevations in citrulline. In the same cohort, two patients who were diagnosed after NICCD had normal NBS results.[33] The estimated Japanese incidence is approximately $7/300\,000$ ($= 1/43\,000$). These discrepancies suggest that there are patients with citrin deficiency who have been undiagnosed. It is unclear whether other undiagnosed patients develop some symptoms or appear healthy with only food preferences, and more studies are needed to elucidate this information.

We should ask about food preferences and a history of prolonged jaundice in the neonatal period for all children with severe hypoglycemia or growth failure. Most of the patients in this report revealed specific food preferences with an aversion to high-carbohydrate foods and a preference for high-protein or high-fat foods, showing that a detailed questionnaire about food preferences is important for identifying citrin deficiency in those known to have hypoglycemia or growth failure in childhood. From the patients' medical history, 40% of the subjects have developed infantile hepatopathy, which might be chief symptoms of citrin deficiency in infancy. We recommend genetic analysis for citrin deficiency, if the patient has characteristic food preferences or a history of prolonged jaundice which is specific to citrin deficiency. Additionally, a history of low birth weight is also a good index to diagnose patients with citrin deficiency.

Abnormalities in laboratory data, such as elevations of liver enzymes, triglycerides, or citrulline, would support further decision making. We should consider genetic analysis for citrin deficiency to provide proper medical care, and citrin deficiency needs to be diagnosed before CTLN2 develops.

5 | CONCLUSION

Our study showed that in our cohort of 20 patients, the most common clinical manifestations at diagnosis of citrin deficiency in childhood were hypoglycemia and growth failure. These patients exhibited low levels of acetoacetic acid during hypoglycemic attacks. As revealed by focused medical interviews, many patients in childhood had peculiar food preferences with an aversion to high-carbohydrate foods, which might compensate for metabolic failure due to citrin deficiency. To diagnose citrin deficiency, we should determine the past history, food preferences, or family history of patients who exhibit severe hypoglycemic attacks or growth failure, and genetic analysis should be considered. Earlier diagnosis of citrin deficiency in undiagnosed patients through the neonatal and infancy periods can lead to improved prognoses for these patients and prevent CTLN2 development through appropriate medical management.

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CONFLICT OF INTEREST

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INFORMED CONSENT

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients' parent for being included in the study by the attending doctor. Proofs that informed consent are available upon request.

ETHICS APPROVAL

This study was approved by the review boards of Tohoku University School of Medicine (#2006-77, 2011-256, 2015-1-471, 2020-1-310).

ANIMAL RIGHTS

This article does not contain any studies with animal subjects performed by the any of the authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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