Received: 20 April 2023 | Accepted: 14 September 2023

DOI: 10.1002/jpn3.12042

JPGN

REVIEW ARTICLE

Update on the diagnosis and management of neonatal intrahepatic cholestasis caused by citrin deficiency: Expert review on behalf of the Asian Pan-Pacific Society for Pediatric Gastroenterology, Hepatology, and Nutrition

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Abstract

Citrin deficiency is an autosomal recessive metabolic liver disease caused by mutations in the *SLC25A13* gene. The disease typically presents with cholestasis, elevated liver enzymes, hyperammonemia, hypercitrullinemia, and fatty liver in young infants, resulting in a phenotype known as "neonatal intrahepatic cholestasis caused by citrin deficiency" (NICCD). The diagnosis relies on clinical manifestation, biochemical evidence of hypercitrullinemia, and identifying mutations in the *SLC25A13* gene. Several common mutations have been found in patients of East Asian background. The mainstay treatment is nutritional therapy in early infancy utilizing a lactose-free and medium-chain triglyceride formula. This approach leads to the majority of patients recovering liver function by 1 year of age. Some patients may remain asymptomatic or undiagnosed, but a small proportion of cases can progress to cirrhosis and liver failure, necessitating liver transplantation. Recently, advancements in newborn screening methods have improved the age of diagnosis. Early diagnosis and timely management improve patient outcomes. Further studies are needed to elucidate the long-term follow-up of NICCD patients into adolescence and adulthood.

Disclaimer: Although this paper is produced by the APPSPGHAN Working Group on Neonatal Intrahepatic Cholestasis Caused by Citrin Deficiency as a best practice guide, APPSPGHAN is not responsible for the practices of physicians. Diagnosis and treatment are at the discretion of physicians.

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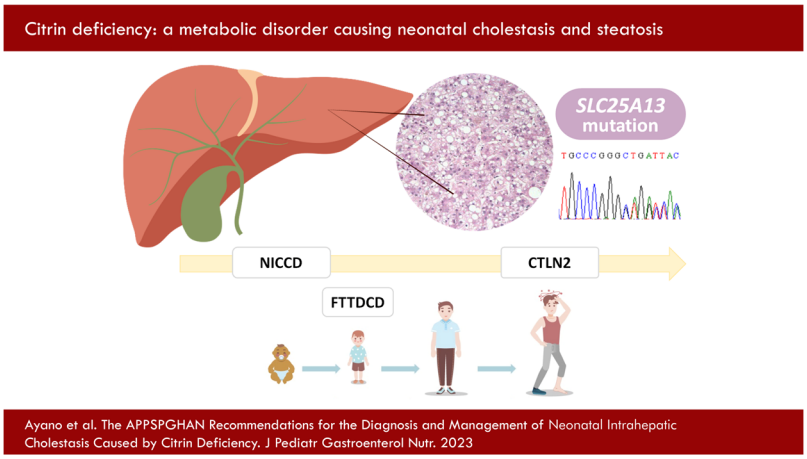
Funding information
The study is supported by the Asian Pan-Pacific Society for Pediatric Gastroenterology, Hepatology and Nutrition



KEYWORDS
citrullinemia, clay stool, jaundice, newborn screening, *SLC25A13*

1 | INTRODUCTION

Citrin deficiency was first described phenotypically in a group of patients with hypercitrullinemia two decades ago. Two forms of hypercitrullinemia associated with hyperammonemia were initially characterized: (1) Type I citrullinemia (CTLN I), an early onset form, caused by argininosuccinate synthase (ASS) deficiency (*ASS1* genetic defect), and (2) Type II citrullinemia (CTLN II), a late-onset form with reduced ASS protein in the liver.[1] In 1999, CTLN II was shown to be caused by defects in the *SLC25A13* gene, designated as a citrin deficiency and registered as an independent autosomal recessive hereditary disease.[2] A case of neonatal hepatitis characterized by steatosis and siderosis,[3] and an infant with hypoproteinemia, hyperbilirubinemia, and fatty liver with fibrosis who developed CTLN II at 16 years old[4,5] were found to have *SLC25A13* mutations, leading to the discovery of a group of cases characterized by neonatal cholestatic jaundice with fatty degeneration. The affected individuals had defects in the *SLC25A13* gene, and the disease was later named neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD).[6,7]

This expert review summarizes the current knowledge of NICCD from the perspective of pediatric hepatologists, conducted by a working group of the Hepatology subcommittee of the Asian Pan-Pacific Society for Pediatric Gastroenterology, Hepatology, and Nutrition (APPSPGHAN). The working group established the scope of this review and collaborated on the task. The final content was approved by the working group members and the Scientific Committee Chair of APPSPGHAN from 2021 to 2023.

What is Known

- Neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD) is an autosomal recessive disorder caused by *SLC25A13* gene mutations that may recover or progress to liver cirrhosis.
- *SLC25A13* gene mutations may have a late-onset phenotype causing neuropsychiatric symptoms in adulthood.

What is New

- Citrin deficiency has been described in several countries beyond Asia and should be considered in the differential diagnosis of all infants with cholestasis and growth failure.
- A genetic diagnosis, which is now widely available, is the most reliable tool to confirm citrin deficiency, given the significant variability in both clinical manifestations and genetic mutations.
- Early diagnosis and treatment results in improved growth and better patient outcomes.

2 | PATHOPHYSIOLOGY

Citrin, encoded by the *SLC25A13* gene, is expressed mainly in the liver. This bipartite protein is located in the mitochondrial inner membrane where it functions as a calcium-binding aspartate–glutamate carrier exporting

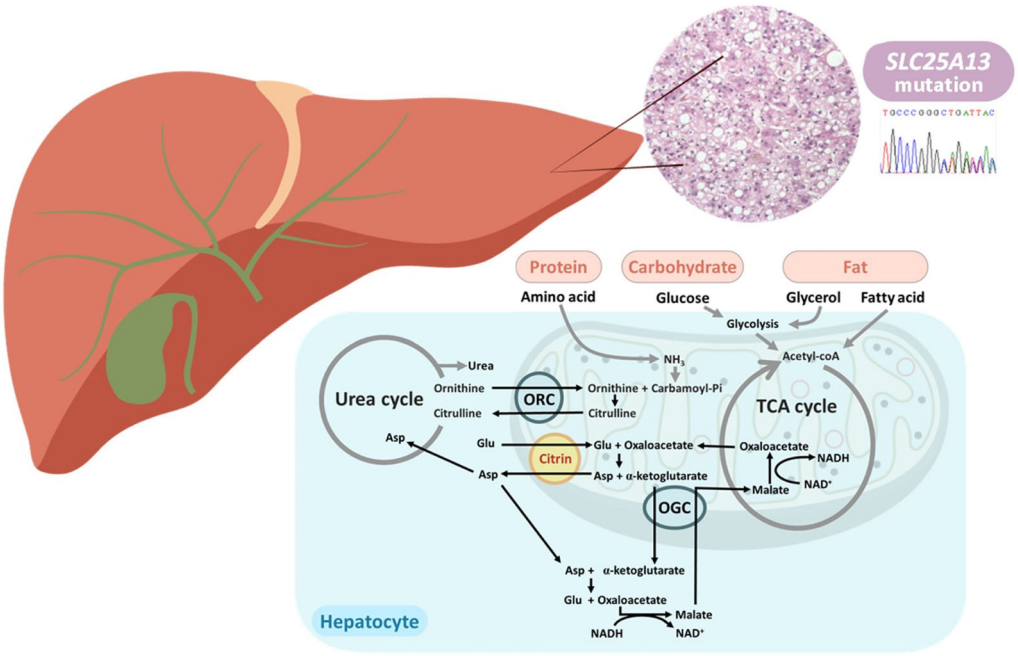


FIGURE 1 Simplified schematic illustrating the pathophysiology of liver disease caused by citrin deficiency. Citrin, a protein located in the mitochondrial inner membrane, functions as a calcium-binding/stimulated aspartate-glutamate carrier and is involved in the malate–aspartate NADH shuttle. Citrin deficiency, caused by genetic variations in the *SLC25A13* gene, leads to disruptions in multiple metabolic pathways, including the urea cycle, aerobic glycolysis, gluconeogenesis, galactose metabolism, and fatty acid synthesis. Liver pathology can manifest as macrovesicular or microvesicular steatosis and cholestasis, and may progress to fibrosis. Asp, aspartate; Glu, glutamate; NADH, nicotinamide adenine dinucleotide hydrogen; OGC, oxoglutarate carrier; ORC, ornithine carrier; TCA cycle, tricarboxylic acid cycle.

aspartate from mitochondria to the cytosol, and cotransport glutamate with a proton into the mitochondrial matrix. Aspartate binds to citrulline in the cytosol to form argininosuccinate catalyzed by ASS and enters the urea cycle. Importantly, citrin is a member of the malate–aspartate (MAS) nicotinamide adenine dinucleotide hydrogen (NADH) shuttle, which functions to transport electrons from the cytosol into mitochondria. This crucial process supplies mitochondria with NADH for ATP production as well as providing NAD+ to the cytosol for the oxidation of nutrients in several metabolic pathways. In citrin deficiency, NADH cannot be oxidized because the mitochondria cannot supply aspartate to the cytosol, and NADH produced in the cytoplasm is not taken up by the mitochondria, thereby increasing the cytoplasmic NADH/NAD ratio.[2,6–9] Collectively, citrin deficiency causes disturbances in multiple metabolic pathways, including the urea cycle, aerobic glycolysis, gluconeogenesis, galactose metabolism, and fatty acid synthesis[10–12] (Figure 1). These disturbances may manifest biochemically as citrullinemia, hyperammonemia, and hypoglycemia with a liver phenotype of mitochondrial hepatopathy. These abnormalities can also affect bile metabolism and transport in the neonatal liver, causing cholestasis.

2.1 | Clinical manifestations

Clinical manifestations of citrin deficiency vary according to the age at presentation.[13] NICCD, failure to thrive and dyslipidemia caused by citrin deficiency (FTTDCD), and adult-onset type II citrullinemia (CTLN2) are manifestations of the disease among neonates/infants, children, and adults, respectively (Figure 2A). The signs and symptoms of NICCD usually resolve spontaneously within the first year of life following appropriate treatment with a lactose-free/medium-chain triglyceride-containing diet. Most patients have high fat and protein food preferences and an aversion to high carbohydrate foods before 3–4 years of age, which might compensate for the metabolic failure caused by citrin deficiency.[15] Some affected individuals might progress directly into FTTDCD, or develop CTLN2 around 10–80 years of age.[4,5,7,16–18] Therefore, ongoing health supervision into adulthood is recommended.

2.1.1 | Hepatic abnormality

Infants with NICCD typically present with prolonged cholestatic jaundice, elevated transaminases, hypoproteinemia, and coagulopathy. Liver histology

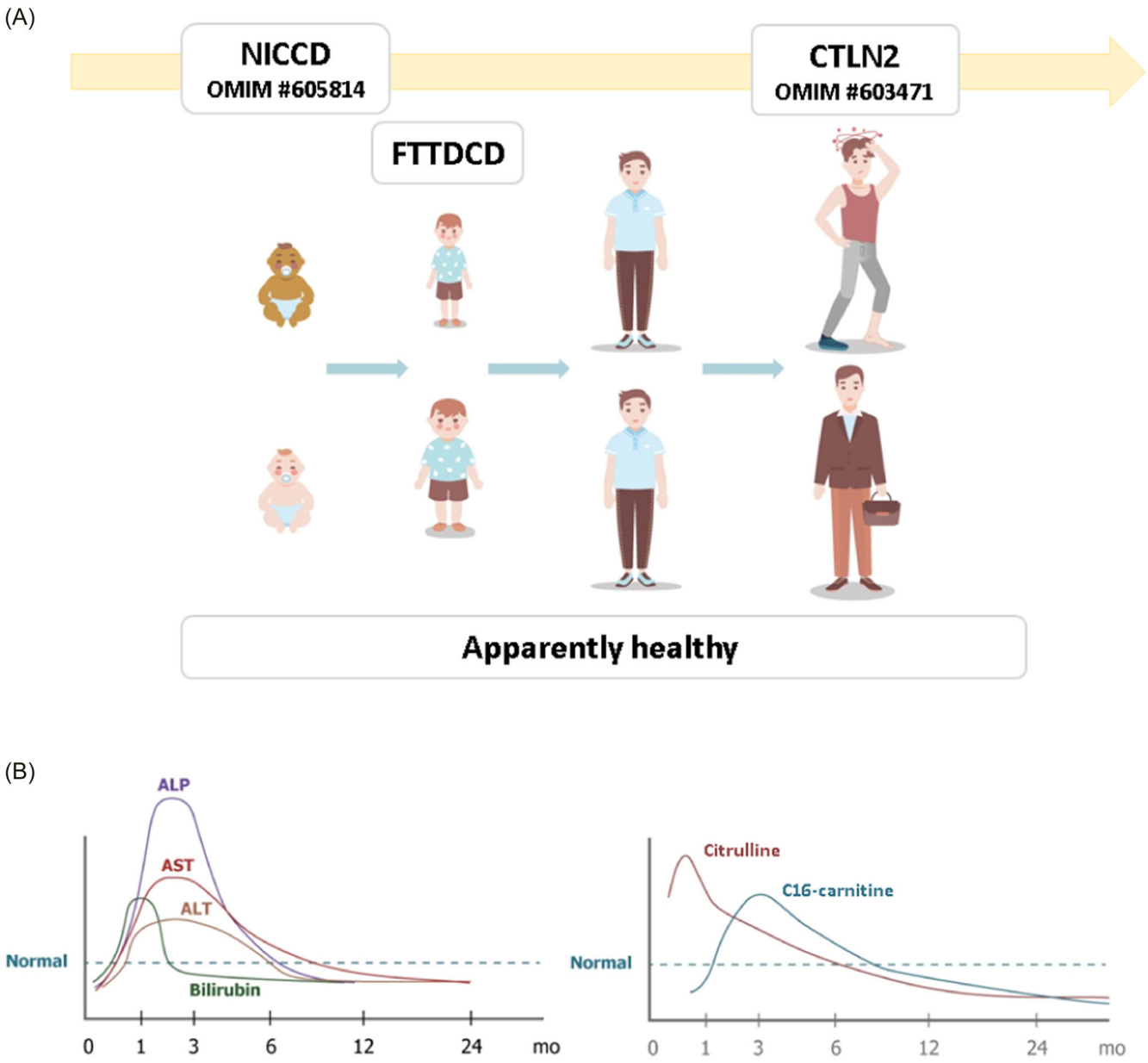


FIGURE 2 (A) Different ages of phenotypic presentation of patients with citrin deficiency with *SLC25A13* mutations. (B) Time course of laboratory parameters in typical NICCD cases. Left: dynamic trends of liver biochemistry markers; Right: the elevations of citrulline and acylcarnitines (with C16-carnitine representing) occurred early in the course of NICCD.[14] ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTLN2, adult-onset type II citrullinemia, usually presents as hyperammonemia and neuropsychiatric symptoms; FTTDCD, failure to thrive and dyslipidemia caused by citrin deficiency; NICCD, neonatal intrahepatic cholestasis caused by citrin deficiency.

may reveal diffuse macrovesicular and microvesicular steatosis, parenchymal cellular infiltration, siderosis, and fibrosis.[3,18–23] Electron microscopy of the liver demonstrates normal mitochondrial and canalicular structure but elevated mitochondrial matrix density and enlarged smooth endoplasmic reticulum.[3]

2.1.2 | Metabolic derangement

Genetic variations of *SLC25A13* cause defective NADH-shuttle leading to disturbance of multiple metabolic pathways including the urea cycle, aerobic glycolysis, gluconeogenesis, galactose metabolism, and fatty acid synthesis. Thus patients may

TABLE 1 Clinical manifestations of 192 neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD) patients sort by frequency according to the 2018–2020 nationwide survey in Japan.

Frequency	Clinical manifestations
Constant (≥66.7%)	Cholestasis,[a] elevated transaminases (>100 U/L)
Frequent (33.3%–66.7%)	Hypoproteinemia, fatty liver, prolonged prothrombin time
Occasional (2%–33.3%)	Short stature (<−2 SD), poor weight gain, hepatomegaly, splenomegaly, hyperammonemia, hypoglycemia, seizure, fatigue, anorexia, nausea/vomiting, intractable diarrhea, hyperlipidemia
Seldom (<2%)	Hyperammonemia coma, abnormal brain MRI/CT, abnormal electroencephalography

Note: Table Modified from Kido et al.[13]

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; NICCD, neonatal intrahepatic cholestasis caused by citrin deficiency.

[a]The frequency of cholestasis was calculated based on analysis from Kido et al.,[13] showing cholestasis was present exclusively among NICCD cases younger than 3 years of age. Typically, patients present with cholestasis in early infancy.

TABLE 2 Diagnosis modalities for NICCD.

	Description	Additional information
Clinical suspicion		
Phenotype	Neonatal cholestasis (jaundice, clay stool, hepatomegaly), chubby face, failure to thrive, idiopathic cirrhosis in infancy	NICCD score[a] ≥ 4 suggesting suspicion of NICCD
Biochemistry		
Liver profile	Elevation of total/direct bilirubin, AST, ALT, ammonia, PT, INR Elevation of AFP in infancy	ALP to ALT ratio > 10 Direct to total bilirubin ratio < 0.67
Mass spectrometry	Multiple aminoacidemia: elevated citrulline, methionine, arginine, tyrosine, phenylalanine, threonine and ornithine	
Liver pathology		
	Hepatic steatosis (mixed macrovesicular and microvesicular fatty change), Siderosis	
Genetic diagnosis		
	SLC25A13 gene mutations (Sanger sequencing, panel-based targeted next-generation sequencing, whole-exome sequencing)	Common mutations found in East Asian countries
Newborn screening		
	Elevated citrulline level on dry blood spot; second-tier genetic analysis	

Abbreviations: AFP, alpha-fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; NICCD, neonatal intrahepatic cholestasis caused by citrin deficiency; PT, prothrombin time.

[a]NICCD score: Patients with four or more features of the following six characteristics is suggestive of NICCD: (1) not having clay-colored stools; (2) a ratio of AST to ALT > 2; (3) a ratio of direct/total bilirubin < 0.67; (4) a ratio of ALP/ALT > 10; (5) a gamma-glutamyl transpeptidase level <300 U/L; and (6) a prothrombin time with the international normalized ratio >1.3.[26]

have diverse metabolic abnormalities, including hypoglycemia, hyperammonemia, citrullinemia, galactosemia, and abnormal acylcarnitine profiles as well as chubby face in early infancy.[9,13,14,18,24] The usual biochemical findings include elevation of blood or plasma ammonia, plasma or serum citrulline, arginine, tyrosine, methionine, threonine, plasma or serum threonine-to-serine ratio, and serum pancreatic secretory trypsin inhibitor.[8,9,14,24] In addition, hypergalactosemia is commonly found in NICCD patients.

2.1.3 | Growth failure

Patients with NICCD are usually small for gestational age and some may fail to thrive in infancy.[13,25] Growth failure persists until 6–9 months of age which is usually the time of diminished energy requirement leading to disease recovery and is caused by cholestasis and defective lipogenesis.[25] Early detection and optimal nutritional intervention may improve growth impairment in such patients.[13] NICCD clinical manifestations and severity can vary markedly and a summary is presented in Table 1.

TABLE 3 Allele frequency of common SLC25A13 mutations in the population.

HGVSc (NM_014251) HGCSp (NP_055066)	dbSNP ID No[a]	MAF (%) World[b]	EAS[b]	SAS[b]	AMR[b]	NFE[b]	AFR[b]	TW[c]	Patients report locations
c.851_854del4 p.Met285fs	rs80338720 [I]	0.033	0.46	0	0	0	0	0.69	CN, HK, IT, JP, KR, MY, TH, TW, VM
c.1177+1G>A	rs80338722 [II]	0.0046	0.065	0	0	0	0	0.033	JP, KR
IVS16ins3kb[d]	NA [XIX]	0	0	0	0	0	0	NA	CN, JP, KR, MY, TH, TW
c.1311+1G>A	rs80338723 [V]	0.0004	0	0.0033	0	0	0	0.033	JP
c.1638_1660dup23 p.Ala554fs	rs80338725 [III]	0.0088	0.12	0	0	0	0	0.13	CN, JP, KR, MY, TH, TW
c.674C>A p.Ser225Ter	rs80338719 [IV]	0.0004	0.0054	0	0	0	0	0	JP, KR
c.1763G>A p.Arg588Gln	rs121908532 [XXIX]	0.0008	0	0.0065	0	0	0	0	KR
c.615+5G>A	rs80338717 [X]	0.01	0.15	0	0	0	0	0.56	CN, TW
c.1801G>T p.Glu601Ter	rs80338727 [VIII]	0	0	0	0	0	0	0	JP
c.1018+1G>A	NA	0	0	0	0	0	0	0	JP
c.1799dupA p.Tyr600Ter	rs80338726 [VI]	0.0024	0	0	0.017	0	0	0	JP
c.1592G>A p.Gly531Asp	rs80338724 [XVI]	0.0004	0.0054	0	0	0	0	0	JP, KR
c.1610_1612delTAGinsAT p.Leu537fs	NA	0	0	0	0	0	0	0	IN, PK
c.1645C>T p.Gln549Ter	rs1364726997	0.0032	0	0	0	0	0.011	0	JP, KR
c.1813C>T p.Arg605Ter	rs80338729 [VII]	0.006	0.011	0.042	0	0	0	0	JP, KR

Abbreviations: AFR, African; AMR, Latino/Admixed America; CN, China; EAS, East Asia; HGVSc, the HGVS coding sequence; HGVSp, the HGVS protein sequence; HK, Hong Kong; IN, India; IT, Italy; JP, Japan; KR, Korea; MAF, minor allele frequency; MY, Malaysia; NA, not available; NFE, Non-Finnish European; PK, Pakistan; SAS, Southern Asia; TH, Thailand; TR, Turkiye (Turkey); TW, Taiwan; UK, United Kingdom; VM, Vietnam.

[a]Mutation number defined by Saheki and colleagues.[7,23,27]

[b]Minor allele frequency from gnomAD v2.1.1.

[c]Minor allele frequency from Taiwan BioBank.

[d]Minor allele frequency from gnomAD SVs v2.1.

3 | DIAGNOSIS

Diagnostic methods have evolved over the past 20 years (Table 2). A typical case of NICCD may present with jaundice, mild hepatomegaly, elevated total, and direct bilirubin (the ratio of direct/total bilirubin is usually lower than other forms of cholestatic liver diseases), mild to moderate elevations of aspartate aminotransferase (AST)/alanine aminotransferase (ALT)/ammonia, and marked elevation of alkaline phosphatase (ALP). Prolonged prothrombin time is frequent and is usually vitamin K responsive.[6,7,18,21] Marked elevation of alpha-fetoprotein (AFP) is frequently noted in young infants. A clinical NICCD score has been proposed to quickly identify patients at the first presentation and facilitate further diagnostic procedures. The scoring parameters include a ratio of direct/total bilirubin < 0.67, AST/ALT > 2, and ALP/ALT > 10.[26]

Diagnosis relies on the presence of clinical/pathological features of neonatal cholestasis and elevated citrulline in the amino acid analysis, and is confirmed by the identification of bi-allele *SLC25A13* genetic mutations.[14,18,23,26–29]

3.1 | *SLC25A13* gene mutations

More than 90 genetic variants/mutations have been reported to cause diseases, with a higher allele frequency of certain genetic variants (hot spots) found in some countries (Table 3). In the past few decades, more cases of NICCD have been reported and genetically confirmed with the advances in genetic testing tools and their increased availability. It is now considered one of the leading causes of neonatal cholestasis in Asia[18–23,26–28,30–34] with increasing cases being reported globally.[35–39] Some patients initially present with symptoms similar to biliary atresia, so the initial evaluation of neonatal cholestasis should consider NICCD. All patients with features suspicious of NICCD should undergo genetic testing to confirm the diagnosis and facilitate genetic counseling. In those populations where hot spot mutations exist, an initial screening of common mutations can be performed but should proceed to full-length analysis when NICCD is suspected and common mutations screening is negative because rare mutations or large insertions have been reported. Other metabolic liver diseases may also present with cholestasis and fatty liver, such as mitochondrial hepatopathy. Whole-exome sequencing (WES) may be considered if genetic analysis of *SLC25A13* is negative in patients with progressive disease.

3.2 | Newborn screening (NBS)

Newborn mass screening to detect citrin deficiency early was introduced in Japan in 2004.[9] Citrullinemia is the initial identifiable biochemical abnormality in neonates with NICCD, with elevated methionine, arginine, tyrosine, phenylalanine, threonine, ornithine, and several citrulline-based ratios, including citrulline/glutamine and citrulline/arginine, being the principal screening markers.[40,41] Citrulline levels may be within normal range soon after birth leading to a significant number of missed NICCD cases.[9,36,42] Indeed, a study in Japan revealed that only 30 out of 75 NICCD patients were detected by NBS based on elevated concentrations of galactose, methionine, and/or phenylalanine reflecting the low sensitivity of NBS.[18] Notably, the citrulline level may be normal or elevated transiently or mildly in infancy, thus the NBS strategy using solely citrulline is not optimal. Modifications of tandem mass spectrometry interpretation and second-tier genetic tests have improved the sensitivity of NICCD detection.[43] Moreover, patients detected by NBS have better outcomes than those identified postnatally with cholestasis, highlighting the importance of early diagnosis.[44]

Taken together, early detection of NICCD by NBS leads to timely therapeutic intervention which can prevent the progression to liver cirrhosis and liver failure. The application of genetic testing and/or other novel methods may improve the performance of the current NICCD NBS program.

3.3 | Natural course and outcomes

The most common clinical features at disease onset are neonatal cholestasis, poor weight gain, fatty liver, and coagulopathy, which tend to improve spontaneously after 6–12 months of age in most patients because of maturation of hepatocytes and/or some adaptation or compensations by other mitochondrial carriers[13] (Figure 2B). Some patients diagnosed after 1 year of age experience hypoglycemic events and growth failure. Low weight and height, and dyslipidemia are frequently noted.[45] NICCD patients usually have a low body weight until 6–9 months of age and are smaller until 11–13 years of age.[25] The final height of NICCD patients may be the same as healthy controls.[13]

Young children are prone to developing hypoglycemia, especially during acute illness and poor intake, because of impaired gluconeogenesis and decreased hepatic glycogen storage due to the energy deficit in hepatocytes. Most patients enter the adaptation/compensation stage in childhood, but a mild fatty liver is persistently observed in a considerable number of post-NICCD patients.

During the follow-up of 75 children with NICCD, 73 recovered by 1 year of age, two progressed to liver failure, and another one patient developed citrullinemia type II at age 16 years.[18] Infrequently, infants diagnosed with NICCD later develop end-stage liver failure requiring liver transplantation.[18,33,46,47] About 20 cases of citrin deficiency-related death have been reported.[41] Most patients died of infections and bleeding associated with liver cirrhosis.

3.4 | Treatment

Early treatment of intrahepatic cholestasis is crucial for NICCD patients to compensate for the disrupted metabolic processes due to citrin deficiency, in particular, hepatic glycolysis, lipogenesis, protein synthesis, and ammonia detoxification.

3.4.1 | Nutritional therapy

The mainstay for NICCD treatment is dietary therapy.[40,41] MCT supplementation is required to provide energy to hepatocytes, and promote lipid production and ammonia detoxification.[48] The use of MCT-supplemented formula for NICCD patients can improve body weight and alleviate cholestasis.[48,49]

In addition, downregulation of peroxisome proliferator-activated receptor alpha suggests that citrin deficiency impairs hepatic de novo lipogenesis coupled with glycolysis, leading to an energy deficit in hepatocytes, hence MCT may be effective in maintaining stable energy levels.[12,48] Galactose metabolism is inhibited in citrin deficiency, so lactose-free formula is used in patients with galactosemia or hypoglycemia.

MCT can be introduced to infants with NICCD by adding MCT to breast milk/formula or using MCT-based formula (MCT oil added to a lactose-free formula in a ratio of 2 mL MCT to 100 mL formula).[48] Breast milk or formula supplemented with MCT can be used if there is no galactosemia. MCT absorption from the intestine does not involve micelle formation or require processing by bile acids so it can be used in cholestatic infants. Medium-chain fatty acids are transported into the mitochondria without carnitine, where they undergo beta-oxidation and are used as an energy source. The use of MCT milk for NICCD can improve the general condition and prevent liver failure.[40,41,49,50]

As most children with NICCD will improve between 6 and 12 months, the infants can be weaned off MCT and lactose-free formula and lactose restriction can be stopped when the cholestasis resolves and liver function is normalized[13,49] However, MCT may be required for longer in patients with prolonged cholestasis.

When solid food is introduced, a high-protein diet and fat-rich foods are preferred supplemented by sufficient carbohydrates to prevent hypoglycemia. The recommended protein, fat and carbohydrate (PFC) ratio is 15%–25%:40%–50%:30%–40%, compared with the ratio in healthy controls, which is 10%–15%:25%–35%:50%–60%. The maintenance of the PFC ratio with high protein and high fat is thought to be a self-protective reaction. Carbohydrate intake increases NADH in the hepatocyte cytoplasm and may further exacerbate metabolic failure.[41]

3.4.2 | Pharmacological therapy including fat-soluble vitamin supplementation

Due to the cholestasis in NICCD, fat-soluble vitamin supplementation including vitamins A, D, E, and K is required. Supplementation should be as per guidelines for neonatal cholestasis and correction monitored by measurement of vitamins A, D, and E, and international normalized ratio (INR) for vitamin K.

Other types of therapy have undergone clinical trials for the childhood and adult manifestations of citrin deficiency but are not usually necessary for treating NICCD. These include arginine (decreases blood ammonia concentration) and sodium pyruvate which may improve growth.[51]

3.4.3 | Liver transplantation in NICCD

NICCD is self-limiting with improvement in late infancy in most children, with only a few children requiring a liver transplant.[18] Some case reports of liver transplants in NICCD predate the establishment of citrin deficiency as a disease entity.[46,47] Only a small number of confirmed NICCD patients with decompensated liver failure or cirrhosis have been described, some of whom have experienced hypoglycemic episodes. There have been concerns cautioning the use of high-volume intravenous glucose infusion in patients with metabolic disturbances.[19,41] Current evidence does not prohibit the use of glucose infusion or parenteral nutrition in patients with citrin deficiency, especially when patients are dehydrated, with hypoglycemia episodes, or cannot eat. Hyperalimentation has been used before transplantation in two cases of CTLN2.[52] We recommend that when intravenous fluids and parenteral nutrition are required, close monitoring and meticulous adjustment of the fluid status and glucose infusion rate are required in patients with liver decompensation and those prepared for liver transplantation.

Late referral, presence of infection, delayed dietary modification, low platelets, low gamma-glutamyl transpeptidase, elevated total cholesterol/blood citrulline level, and high blood ammonia and tyrosine are associated with poor prognosis, and thus, such patients may be potential candidates for liver transplantation.[19] Successful liver transplantation has been reported with both deceased as well as living donor grafts.

3.5 | Long-term follow-up

NICCD is generally considered a mild disease due to the resolution of symptoms by 1 year of age following nutritional therapy with a lactose-free/medium-chain triglyceride-containing diet and fat-soluble vitamin supplementation. Since the long-term prognosis of NICCD is unknown, regular follow-up, at least once a year, is necessary even after an apparently healthy period. Studies of the long-term outcome of cases diagnosed early in infancy, especially neurocognitive function and liver health are warranted.

4 | CONCLUSIONS AND PERSPECTIVES

In conclusion, NICCD should be included in the list of differential diagnoses of patients with infant cholestasis. Genetic analysis and plasma amino acid analysis are important for diagnosis. Proper management involving nutritional treatment is crucial for a good

prognosis in cholestatic patients. Future studies of early screening, mechanisms and factors causing cirrhosis, development of disease-specific therapy, and long-term follow-up of neurocognitive function as well as a potential risk of adult emergent disease are warranted for better patient care.

ACKNOWLEDGMENTS

The authors are grateful to the APPSPGHAN Scientific Committee for initiating this task force. We are grateful for the contributions of Dr. Wan-Hsin Wen and Mr. Bang-Yu Liu and thank Ms. Lily Chen for creating the visual illustrations.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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How to cite this article: Inui A, Ko JS, Chongsrisawat V, et al. Update on the diagnosis and management of neonatal intrahepatic cholestasis caused by citrin deficiency: expert review on behalf of the Asian Pan-Pacific Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr*. 2024;78:178-187. doi:10.1002/jpn3.12042