

ORIGINAL PAPER

A novel form of intrahepatic cholestasis: neonatal sclerosing cholangitis due to *DCDC2* pathogenic variants. Clinical recognition and diagnostic approach

Magda Mekrouda¹, Patryk Lipiński², Łukasz Obrycki³, Elżbieta Ciara⁴, Izabela Mendrek⁴, Irena Jankowska¹, Joanna Ryżko¹, Joanna Cielecka-Kuszyk⁵, Joanna Pawłowska¹

¹Department of Gastroenterology, Hepatology, Feeding Disorders and Pediatrics, The Children's Memorial Health Institute, Warsaw, Poland

²Maria Skłodowska Curie Medical Academy, Warsaw, Poland

³Department of Nephrology, Kidney Transplantation and Hypertension, Children's Memorial Health Institute, Warsaw, Poland

⁴Department of Medical Genetics, Children's Memorial Health Institute, Warsaw, Poland

⁵Department of Pathology, Children's Memorial Health Institute, Warsaw, Poland

ABSTRACT

Introduction: Neonatal sclerosing cholangitis (NSC) caused by pathogenic variants in the *DCDC2* gene is a rare and severe form of cholangiopathy, classified as a ciliopathy. The aim of this study was to analyze the clinical features of seven patients diagnosed with NSC treated in our center and to compare them with previously reported cases in the literature. Particular attention was paid to the similarities and differences between *DCDC2*-related NSC and biliary atresia, as they can present with overlapping features in early infancy. So far, no description of this disease has been found in the Polish literature.

Material and methods: We reviewed clinical, biochemical, and imaging data from seven patients with genetically confirmed NSC caused by biallelic pathogenic variants in the *DCDC2* gene. These data were compared with descriptions of patients diagnosed with NSC published in the literature, taking into account the course of the disease, diagnostic methods, and treatment strategies.

Results: Most patients with NSC present in early infancy with cholestatic jaundice with high γ -glutamyl transpeptidase activity, which usually resolves at the age of 12 months. Subsequently, symptoms such as hepatomegaly and splenomegaly and features of portal hypertension with hypersplenism and gastrointestinal varices begin to dominate. Patients require systematic endoscopic surveillance and repeated sessions of ligation of esophageal varices. So far, one of our own patients and more than half of the patients described in the literature have required liver transplantation.

Conclusions: NSC caused by a biallelic pathogenic variants in the *DCDC2* gene is a rare ciliopathy that can mimic the course of biliary atresia in the neonatal period. In later life, liver fibrosis becomes the predominant manifestation, often leading to the development of portal hypertension. With the development and availability of molecular tests, it should be expected that the group of *DCDC2*-related NSC confirmed by genetic testing will systematically grow.

KEY WORDS:

cholestasis, neonatal sclerosing cholangitis, pathogenic variants, *DCDC2*, liver fibrosis, liver transplantation.

ADDRESS FOR CORRESPONDENCE:

Magda Mekrouda, Department of Gastroenterology, Hepatology, Feeding Disorders and Pediatrics, The Children's Memorial Health Institute, Av. Dzieci Polskich 20, 04-730 Warsaw, Poland, e-mail: magda.mekrouda@gmail.com

INTRODUCTION

The *DCDC2* gene is located on the 6p22.3 chromosome and encodes a ciliary protein known as doublecortin domain-containing protein 2. *DCDC2* protein binds to tubulin, influencing microtubule polymerization. This protein is present in the cilia of cells as well as in the cytoplasm. Recent evidence suggests its role in inhibiting hepatic stellate cell activation and ameliorating liver fibrosis by suppressing Wnt/ β -catenin signaling [1]. According to the Online Mendelian Inheritance in Man (OMIM) database, pathogenic variants in the *DCDC2* gene are associated with three autosomal recessive clinical phenotypes: deafness type 66 (DNFB-66; OMIM #610212), nephronophthisis type 19 (NPHP19; OMIM #616217) and neonatal sclerosing cholangitis (NSC; OMIM #617394).

NSC is classified as a ciliopathy, a group of diseases resulting from molecular defect in genes that encode proteins of the primary cilia and lead to either the absence of the necessary product or its improper function. Primary cilia are found in various organs, including the surface of renal tubular epithelial cells and biliary epithelial cells in the liver. Their proper functioning influences critical signaling pathways during embryogenesis [2]. *DCDC2* has recently been recognized as one of the genes implicated in renal-hepatic ciliopathy.

Liver involvement in ciliopathies occurs as a result of disrupted embryogenesis of the bile ducts. This process includes the remodeling and partial involution of the so-called ductal plate between the 12th and 20th week of pregnancy. Abnormalities at this stage lead to the persistence of numerous embryonic bile duct structures (ductal plate malformation – DPM), which in turn stimulates fibrogenesis. The consequences of disrupted bile duct embryogenesis may include the development of von Meyenburg complexes, congenital hepatic fibrosis, Caroli disease or syndrome, bile duct cysts, or isolated liver cysts.

NSC is a severe form of infantile-onset cholangiopathy, which is characterized by the presence of cholestasis, often pale stools, and elevated γ -glutamyl transpeptidase (GGT) activity, making it a close differential diagnosis to biliary atresia (BA). It is a rare genetic disorder, starting in the neonatal period, that commonly leads to liver transplantation due to end-stage liver disease.

In recent years, an increasing number of patients with either isolated liver disease or combined liver and kidney involvement due to pathogenic *DCDC2* variants have been described [3–12]. Literature data support the association of biallelic pathogenic *DCDC2* variants with NSC [13]. In 2023 we reported the first six Polish patients with *DCDC2*-related NSC and reviewed 28 other patients reported in the literature so far [14]. Up to this moment, few new studies have been published linking clinical phenotype to pathogenic variants in the *DCDC2* gene [13, 15].

In most patients with *DCDC2*-related NSC clinical symptoms of cholestatic jaundice and in some of them

acholic stools appeared in early infancy. Cholestasis usually resolved within a few months. The liver was enlarged and splenomegaly appeared later as the result of liver fibrosis. In less than 30% of reported cases, signs of renal involvement have been documented. Renal manifestations may include nephronophthisis, congenital urinary tract malformations (e.g., ureteral duplication or vesico-ureteral reflux), progression to end-stage renal disease, and thrombotic microangiopathy in some post-transplant patients. In individual patients, intellectual disability has also been described. In an early stage of NSC it may be very difficult to distinguish it from BA and other neonatal cholestatic liver diseases.

The aim of our article is to describe the clinical presentation of our own patients and to compare them with patients with NSC reported in the literature. We also wanted to draw attention to the similarities and differences between patients with *DCDC2*-related NSC and patients with BA and the role of genetic (molecular) tests in the diagnostic process and differentiation of the clinically heterogeneous group of ciliopathies.

MATERIAL AND METHODS

We present a description of the 7 Polish patients with molecularly confirmed diagnosis of NSC caused by biallelic pathogenic variants in the *DCDC2* gene.

Six of them were previously described in the literature [14]. No more cases have been described in Polish literature so far.

Genetic testing was performed in all patients using a genomic DNA sample automatically extracted from the peripheral blood leukocytes with a MagNA Pure instrument (Roche Diagnostics, Rotkreuz, Switzerland) according to the manufacturer's protocol. Next-generation sequencing (NGS) was performed with the TruSight One Sequencing Panel (Illumina, San Diego, CA, USA) as previously reported [14]. The molecular variants were classified according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) guidelines [16]. According to the criteria, benign, likely benign, and variants of uncertain significance (VUS) were filtered out, thereby retaining only pathogenic, likely pathogenic changes. The nomenclature of molecular variants follows the Human Genome Variation Society guidelines (HGVS, <http://varnomen.hgvs.org/>) using the MANE select human *DCDC2* reference sequence: NM_016356.5 (for cDNA) and NP_057440.2 (for protein).

We compared our patients with 28 previously reported patients [3–12] after searching in the PubMed (Medline) database in March 2023, and we added 14 children, from a recently published series [15] and 4 children not included in the previous study [13]. Thus, up to now at least 50 patients have been described.

This was an observational retrospective study approved by the Children's Memorial Health Institute Bioethical Committee, Warsaw, Poland (39/KBE/2020).

RESULTS

In 7 Polish patients (3 girls and 4 boys) from 4 unrelated families, NGS analysis showed the presence of biallelic pathogenic variants in the *DCDC2* gene. The clinical and molecular diagnoses were made at the mean age of 10 years (age range from 9 month to 24 years).

The first clinical presentation in our 6 children was cholestatic jaundice. The onset of jaundice varied from 2 days of life (one patient) to 3 months of age, with most cases occurring in the second month of life. An early diagnosis in patient 2 was possible due to a history of cholestasis in her older sister and the heightened vigilance of the parents.

In 2 of our patients, cholestasis was accompanied by the presence of acholic stools. In all 6 children, the jaundice resolved within 1 year at the mean age of 7 months (range 3–12 months). One patient never presented with cholestatic jaundice and was admitted to the hospital at the age of 7 years due to hepatosplenomegaly and hypersplenism. Two patients had hepatomegaly at the onset of jaundice. None of them had splenomegaly at that time.

Six of our children developed features of portal hypertension with esophageal varices and severe hypersplenism. All of them required esophageal varices ligation (EVL) due to variceal bleeding (4 out of 6) or as a preventive treatment (2 out of 6).

Most of our patients reported pruritus at some point (5 out of 7). In 2 of them, symptoms occurred occasionally.

A detailed clinical presentation of our study group is provided in Table 1.

BIOCHEMICAL, IMAGING AND HISTOLOGICAL FEATURES

The mean value of serum bilirubin (total/direct bilirubin) concentration at presentation and the maximum value of bilirubin in the first year in our patients was 7.2/5.3 mg/dl (range 1.1–10 for total bilirubin and 0.3–7.2 for direct bilirubin) and 8.6/6.3 mg/dl (range 7.3–10 for total bilirubin and 0.3–8 for direct bilirubin), respectively. The mean value of GGT activity at presentation and in the first year was 448 U/ and 815 U/I, respectively.

Abdominal ultrasound revealed an enlarged liver in 3 of 7 patients with a visible gallbladder at presentation, but 6 of our patients had increased liver echogenicity at the age of 6 months. During the observation period the size of the spleen also increased.

Three of our patients underwent magnetic resonance cholangiopancreatography (MRCP), but only 1 (patient 2) showed typical features of intrahepatic cholangiopathy

(narrow, only segmentally visible bile ducts, sectionally widened with irregular lumen).

Five of our patients had at least one liver biopsy. In the initial biopsy at the age of 2–5 months, mild to severe hepatocellular cholestasis, focal or diffuse ductular proliferation, and mild portal inflammation dominated. Portal or porto-portal fibrosis, initially visible in the first biopsy, had progressed in the second biopsy (patients 1 and 6). In 1 patient (patient 1), hepatic explants at the age of 6 years revealed the presence of micronodular cirrhosis.

KIDNEY INVOLVEMENT

Two of our patients presented with features of kidney disease: right vesicoureteral reflux and persistent urachus (patient 2) and nephronophthisis (patient 4).

MOLECULAR ANALYSIS

The five different molecular variants in gene *DCDC2* were identified by NGS in Polish patients: known frame shift deletion c.123_124del p.(Ser42Glnfs*72), novel missense variant c.187A>G p.(Arg63Gly), novel stop-gained variant c.235C>T p.(Gln79*), novel frame shift deletion c.256del p.(Try86Thrfs*17) and known splice-site variant c.705-2A>G p.? (Table 2).

In Polish patients, *DCDC2* analysis was facilitated by an observed homogeneous molecular profile, characterized by the presence of three recurrent variants, including c.123_124del p.Ser42Glnfs*72 in either monoallelic or biallelic form (allele frequency in POLdb = 0.000533, compared to GnomAD v4.1.0 = 0.00001488). The other two variants co-occurred with this deletion in a compound heterozygous pattern (Table 2).

FOLLOW-UP

All patients who remained under our care are alive at the time of writing. One patient transitioned to adult care and was alive at the time of transfer; no further follow-up data are available. One patient underwent liver transplantation (LTx) at 6 years (patient 1), and one has been placed on the active waiting list and is awaiting cadaveric LTx (patient 4). All of the patients with portal hypertension required systematic endoscopic surveillance every 6 to 9 month and repeated sessions of esophageal varices ligation if necessary.

DISCUSSION

Our study investigated *DCDC2*-related ciliopathy by analyzing 7 Polish patients with NSC and reviewing previously reported cases in the literature. An important fact is that the primary clinical manifestation of *DCDC2*-related ciliopathy is a liver disease in the form of NSC.

TABLE 1. Clinical presentation of 7 Polish patients

Factor	1/F	2/F	3/F	4/M	5/M	6/M	7/M
Sibling	–	Sister of Pt 1	–	Brother of Pt 3 and Pt 5	Brother of Pt 3 and Pt 4	Sister died (15 y old)	–
Current age	10 y	3 y	16 y	12 y	7 y	25 y	17 y
Age at first presentation	25 th day of life	2 nd day of life	2 m	2 m	2 m	3 m	7 m
First symptoms	Jaundice, acholic stools, elevated GGT	Jaundice, acholic stools, elevated GGT	Jaundice, elevated GGT	Jaundice, elevated GGT	Jaundice, elevated GGT	Jaundice, elevated GGT	Splenomegaly, hepatomegaly
Hepatomegaly at presentation/latest	No/no	No/no	No/no	Yes/no	No/no	Yes/no	Yes/no
Splenomegaly at presentation/latest	No/splenectomy during LTx	No/yes	No/yes	No/yes	No/yes	No/yes	Yes/yes
TBI/DBil at presentation (mg/dl)	6.8/6.6	10.0/3.3	8.7/6.5	7.3/6.2	8.6/7.2	8.0/7.0	1.1/0.3
TBI/DBil in 1 st year of life (mg/dl)	7.7/6.6	10.0/3.3	8.7/6.5	7.3/6.2	8.6/7.2	9.2/8.0	n/a
GGT at presentation (IU/l)	655	588	623	422	238	445	171
Max. GGT in the 1 st year of life (IU/l)	1366	672	1096	921	312	521	n/a
Resolution of jaundice	7 m	3 m	6 m	6 m	1 y	9 m	Never occurred
PHNH/Age of bleeding/EVL session	Yes/9 m and 2 episodes 5 y/yes	No/never occurred/no	Yes/4 y/yes	Yes/severe anemization at 8 and 13 m/yes	Yes/never occurred/yes	Yes/12 y/yes	Yes/never occurred/yes
PLT latest or before LTx (K/ μ l)	49	147	97	78	68	87 (before admission to adult care)	70
Liver biopsy/age/histology	Yes/2 m and 3.5 y/1 st biopsy – mild fibrosis, severe cholestasis; 2 nd biopsy – severe fibrosis, mild cholestasis	No liver biopsy	Yes/2 m/ mild cholestasis, portal fibrosis	Yes/2 y/ minimal cholestasis, mild portal fibrosis	No liver biopsy	Yes/5 m and 2.5 y/ 1 st biopsy – cholestasis, no fibrosis; 2 nd biopsy – fibrosis	Yes/7 y/ fibrosis, bile duct proliferation, mild cholestasis
Pruritus	Yes – before LTx	Occasionally	No	Occasionally	Occasionally	Yes	No
LTx/age/indication	Yes/6 y/uncontrolled PHTN	No	No	At waiting list for LTx/11 y/PHTN	No	No until 18 y of age	No

F – female, M – male, Pt – patient, y – years, m – months, n/a – not available, GGT – gamma-glutamyl transferase, LTx – liver transplantation, TBI – total serum bilirubin, DBil – direct serum bilirubin, PHTN – portal hypertension, EVL – esophageal varices ligation, PLT – platelet count

TABLE 2. Characteristics of 5 molecular variants identified in a group of 7 probands

Nucleotide change (HGVS) ¹	Amino acid change (HGVS) ¹	Exon (Intron)	Variant type	Variant effect	Zygosity status	Number of patient(s)	Affected alleles	Reported status	MAF ²		Pathogenicity status in databases			ACMG ⁴ status
									gnomAD	POldb	ClinVar ³	LOVD ³	HGMD ³	
DCDC2 NM_016356.5, NP_057440.2, chr6(GRCh38)														
c.123_124del	p.(Ser42Glnfs*72)	1	SNV	frameshift	HET/HOM	6	7	Known	0.00001488	0.000533	P	P	DM	P
c.187A>G	p.(Arg63Gly)	1	SNV	missense	HET	1	1	Novel	0	0	n/a	n/a	n/a	LP
c.235C>T	p.(Gln79*)	1	SNV	nonsense	HET	1	1	Novel	0	0	n/a	n/a	n/a	LP
c.256del	p.(Tyr86Thrfs*17)	1	SNV	frameshift	HET	2	2	Novel	0.000001242	0.0000530	n/a	n/a	n/a	LP
c.705-2A>G	p.?	5	SNV	splice-site	HET	3	3	Known	0.000001254	0.0000537	P	P	DM	P

¹The nomenclature of molecular variants follows the Human Genome Variation Society (HGVS) guidelines (<https://hgvs-nomenclature.org/>) and refers to the Matched Annotation from NCBI and EMBL-EBI (MANE). Select transcript, which aligns with the GRCh38/hg38 reference genome assembly.
²Frequency databases for MAF verification were used: the Genome Aggregation Database (gnomAD v4.1.0, <https://gnomad.broadinstitute.org>), and an in-house database with allele frequencies specific to the Polish population, comprising data from more than 12,000 individuals suspected of having a rare genetic disease (POLdb).
³The novelty of the identified variants was assessed using ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/>), LOVD (the Leiden Open Variation Database, <https://www.lovd.nl/>), and HGMD (the Human Gene Mutation Database, www.hgmd.cf.ac.uk) databases, and, if known, related clinical conditions were confirmed.
⁴According to the ACMG/AMP (the American College of Medical Genetics and Genomics and the Association for Molecular Pathology) and AEGS (the Association for Clinical Genomic Science) criteria.
n/a – not available, P – pathogenic, LP – likely pathogenic, DM – disease-causing, HET – heterozygote, HOM – homozygote, SNV – single nucleotide variant, MAF – minor allele frequency

Furthermore, there is a predominance of early and severe liver disease with mild or no kidney involvement in *DCDC2*-related ciliopathy. Our study also expands the molecular spectrum of pathogenic *DCDC2* variants, and enhances the understanding of *DCDC2*-related NSC, contributing to the improvement in diagnostics and clinical management of affected patients.

The clinical presentation of sclerosing cholangitis with neonatal onset was first described by Amedee-Manesme in 1987 [17] in eight children who presented with cholestasis from the first week of life, followed by early cirrhosis and portal hypertension. However, almost three decades passed before, in 2016, Grammatikopoulos *et al.* [4] and Girard *et al.* [5] linked the disease to a “mutation” in the *DCDC2* gene.

In 2004 Hadj-Rabia *et al.* [18] reported the first case of NSC due to a biallelic pathogenic variant in the *CLDN1* gene (claudin), which is additionally accompanied by ichthyosis.

DCDC2 and *CLDN1* are the only two genes that have been associated with NSC so far. Pathogenic variants in the *DCDC2* gene have also been found in patients with nephronophthisis, non-syndromic recessive deafness, dyslexia, and central nervous system dysfunction without liver involvement.

In the early period, NSC is very difficult to distinguish from BA (Table 3). Cholestatic jaundice, hepatomegaly, elevated activity of serum GGT, and, in some patients, acholic stools suggest obstruction of biliary ducts [19]. However, unlike BA, jaundice resolves by the end of the first year of life. In some patients it may recur in the following years, but to a much lesser extent. The onset of jaundice in patients with *DCDC2*-related NSC, as reported in the literature, varies widely – from a few days after birth to 3.5 years of age (in one patient). However, in the majority of cases, jaundice appears between 2 and 3 months of age.

In one child described by Kaur *et al.* [15] the first clinical symptom was pruritus at the age of 3.5 years and in one variceal bleeding at the age of 9 month. In three infants it was intracranial bleeding at the age 2–4 months.

Laboratory tests usually show hyperbilirubinemia with predominance of the conjugated fraction, increased activity of hepatic tubular enzymes (GGT, alkaline phosphatase), hepatocyte enzymes (ALT, AST) and a high concentration of serum bile acids.

Histopathological findings are not typical, and if the proliferation of bile ducts is present, it may be indistinguishable from BA. What is very important, abdominal ultrasound shows a normal gallbladder. Occasionally, also dilated bile ducts, both intra- and extrahepatic, may be visible. In MRCP, bile ducts may be irregular, dilated, and narrowed, as in patients with primary sclerosing cholangitis.

Treatment of cholestasis is primarily symptomatic, through the use of ursodeoxycholic acid (UDCA), which

TABLE 3. Differences and similarities between biliary atresia and neonatal sclerosing cholangitis due to *DCDC2* mutation

Disease	Biliary atresia	<i>DCDC2</i> -related NSC
Beginning of cholestasis	2–4 weeks neonatal, non-syndromic (~90%) 1–2 weeks fetal, syndromic (~10%)	From few days to 9 months (mean 5 weeks)
Acholic stools	Yes	In about 30% of cases
Hepatomegaly at time of presentation	Yes	Rarely
Splenomegaly at time of presentation	Yes	Rarely
Accuracy of liver biopsy in diagnosis	95%	Not known
Histopathology of liver biopsy	Bile duct proliferation, canalicular and cellular bile stasis, portal or peribiliary edema and fibrosis	Mild to severe cholestasis, portal tract inflammation, ductal proliferation or ductal plate malformation, portal fibrosis
Confirmation of diagnosis	Operative exploration with intraoperative cholangiography	Molecular diagnosis
Treatment	HPE, if not successful liver transplantation	Conservative, pharmacological, if not successful liver transplantation
Portal hypertension with	Yes, very early, even in children with successful HPE	Yes, mainly at the age of few years
Outcome	Without HPE, progressive biliary cirrhosis, hepatic failure and death in first few years of liver	60% of patients require liver transplantation at a mean age of 11 years
Parental consanguinity	No	Often

NSC – neonatal sclerosing cholangitis, HPE – hepatoporenterostomy

can lead to disappearance of jaundice and reduction of itching. As in all cholestatic liver diseases, administration of vitamins A, D, E, and K is important. In the study by Kaur *et al.* [15], more than 90% of patients experienced resolution of jaundice with UDCA treatment at a median age of 11 months. In some patients, jaundice later recurred and persisted until LTx or their most recent follow-up. The main clinical problem of children with *DCDC2*-related NSC later on is progressive, severe portal hypertension with a high incidence of variceal bleeding as a result of hepatic fibrosis. In the largest group of 14 patients described in the literature, 57% of patients had variceal bleeding at a mean age of 3 years (range 1.9 to 5 years).

Pathogenic variants in the *DCDC2* gene influence the ciliogenesis in cholangiocytes, but their involvement in liver fibrosis is still unclear [5]. A study by Liu *et al.* [1] demonstrated decreased expression of *DCDC2* in fibrotic liver tissues from both humans and carbon tetrachloride (CCl₄)-induced mice. They also found that the Wnt/β-catenin signaling pathway played a role in this process. This may elucidate the mechanism for advanced fibrosis and progressive portal hypertension in patients affected by this disease.

Portal hypertension is usually and systematically progressive, and variceal bleeding is reported in up to 50% of patients in the first year of life. Currently, the frequency of gastrointestinal bleeding can be modified by implementing preemptive therapy – sclerotization or ligation of esophageal varices. A good response to endotherapy is the only predictor of long-term native liver survival.

The first endoscopic screening in these patients should be no later than in the first year of life.

So far, one of our own patients and more than half of the patients described in the literature required LTx. The main indication for LTx was the lack of response to endotherapy and recurrent variceal bleeding, severe hypersplenism with very low platelet count and leucopenia, ascites, progressive jaundice, and pruritus.

Unlike other most common ciliopathies such as autosomal dominant and recessive polycystic kidney disease, not all patients with *DCDC2*-related NSC developed renal damage [2]. The most common renal manifestations, described in nearly 30% of patients in the literature, were renal malformations, nephronophthisis, impaired renal function, and end stage renal disease before or after LTx.

Other, fortunately very rare, extrahepatic manifestations are neurological manifestation with developmental delay, dyslexia, learning disabilities, and vascular malformations.

Molecular diagnostics is increasingly relevant in pediatric medicine, particularly with the widespread use of NGS technology. In many cases, it enables precise diagnosis, prognosis, and selection of the most effective therapeutic approach. Molecular confirmation of disease facilitates prenatal diagnosis, recurrence risk assessment, and genetic counselling for affected families.

DCDC2-related ciliopathy follows an autosomal recessive (AR) inheritance pattern, meaning that the disease manifests only in homozygous or compound heterozygous individuals, affecting both sexes equally. Both parents of an affected individual are asymptomatic carriers

(heterozygotes) of the pathogenic *DCDC2* variant. The recurrence risk for an affected child in subsequent pregnancies is 25%, and all children of an affected individual will be carriers of the genetic defect. Autosomal recessive diseases manifest within the same generation, typically among siblings of the proband. Consanguinity is a recognized risk factor for autosomal recessive disorders, often leading to homozygosity for pathogenic variants.

In some instances, molecular testing can replace invasive diagnostic procedures such as liver biopsy or aid in selecting a suitable organ donor who is free of the genetic defect (e.g., asymptomatic carrier parents).

Given the early onset and heterogeneous clinical presentation of *DCDC2*-related ciliopathy, targeted gene sequencing panels associated with liver diseases are often the preferred diagnostic method, enabling a broad differential diagnosis to confirm or exclude a genetic basis for observed symptoms in the shortest time possible. The NGS panel used in our patients is particularly valuable for diagnosing monogenic cholestatic liver disorders, especially when extrahepatic causes have been excluded. NGS has demonstrated the highest diagnostic yield in identifying the molecular etiology of cholestatic liver diseases presenting with a low-GGT progressive familial intrahepatic cholestasis (PFIC) phenotype including a completely new intrahepatic cholestasis: NSC due to *DCDC2* [14].

CONCLUSIONS

DCDC2-related NSC typically presents in infancy as cholestatic jaundice accompanied by elevated GGT activity. As the disease progresses, affected children often develop rapidly advancing portal hypertension, which carries a significant risk of variceal bleeding. A favorable response to endoscopic therapy appears to be the only reliable predictor of long-term native liver survival. Nevertheless, up to 60% of patients ultimately require liver transplantation, most commonly during the second decade of life. The diagnosis of *DCDC2*-related NSC can only be definitively confirmed through molecular genetic testing. With the increasing availability and use of such diagnostic tools, the number of genetically confirmed cases is expected to rise systematically.

DISCLOSURES

1. Institutional review board statement: This was an observational retrospective study approved by the Children's Memorial Health Institute Bioethical Committee, Warsaw, Poland (39/KBE/2020).
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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