Case Report

A case report of intrahepatic bile duct dilatation caused by *WDR19* gene mutation and presented as Caroli syndrome

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Background: Caroli syndrome or Caroli disease is characterized by focal dilation of the intrahepatic bile ducts, with or without congenital liver fibrosis. Mutations in the *WDR19* gene can result in nephropathy, an autosomal recessive cystic kidney disease. However, this genetic mutation is clinically associated with Caroli syndrome or disease. We hypothesize that *WDR19* gene mutations may contribute to extrarenal phenotypes such as Caroli disease or syndrome.

Case Description: The outpatient department received a 1-year-old male patient with persistent dilated bile ducts for over four months. Subsequent ultrasound examination revealed liver cirrhosis, splenomegaly, and cystic dilatation of the intrahepatic bile duct. He was subsequently admitted for comprehensive diagnosis and treatment. Accordingly, we performed computed tomography (CT)-hepatic portal venography, magnetic resonance-cholangiography, and the plain liver scan, the results revealed liver cirrhosis, splenomegaly, cystic dilatation of the intrahepatic bile duct, as well as atypical hyperplasia nodules in the right posterior lobe of the liver and lymphatic hyperplasia and enlargement in the porta hepatis and the space between the liver and stomach. As the possibility of early small liver cancer could not be excluded due to the presence of nodules, surgical resection was performed followed by pathological examination and whole genome exome testing. The pathological findings revealed hepatocyte swelling, hydropic degeneration, and sporadic necrosis. Fibrous tissue hyperplasia was observed in the portal vein area, along with local pseudolobule formation. Also, numerous small bile duct hyperplasia was observed with lymphocyte infiltration, which is consistent with cirrhosis. Moreover, the hepatocytes of the small focal area showed atypical hyperplasia. Considering the above findings, Caroli syndrome was diagnosed. The genetic results showed two heterozygous mutations in the *WDR19* gene, c.2290delC (p.Q764Nfs*29) and c.2401G>C (p.G801R). Therefore, the child's intrahepatic bile duct dilatation and cirrhosis were considered as the manifestations of Caroli syndrome caused by mutations in the *WDR19* gene.

Conclusions: Mutations in the *WDR19* gene can manifest as Caroli disease or Caroli syndrome. For the definite diagnosis of liver diseases of unknown etiology, whole exome sequencing may be more conducive.

Keywords: Caroli syndrome; Caroli disease; nephronophthisis; *WDR19*; case report

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Introduction

Congenital intrahepatic biliary dilatation (Caroli disease), a rare congenital biliary disorder, is characterized by segmental and cystic dilation of nonobstructive intrahepatic bile ducts in the absence of other liver abnormalities. Whereas Caroli syndrome represents marked dilation of the bile ducts with congenital hepatic fibrosis (1,2). Although the clinical manifestations of both are different, they usually display symptoms of fever, cholangitis, jaundice, itchy skin, abdominal pain, pancreatitis, weight loss, vomiting, and diarrhea. In the presence of fibrosis or cirrhosis, portal pressure may also increase (3-5).

Although the cause of Caroli disease is unknown, some researchers believe that it is an autosomal recessive genetic disease related to mutations in the *PKHD1* gene, which affects the fibrocystic protein expressed in multiple organ systems, including renal tubular and hepatic bile duct cells. Mutations in the *PKHD1* gene can lead to fibrocystin abnormalities causing fibrocystic changes in the kidneys and liver. Hence, Caroli disease is often accompanied by autosomal recessive polycystic kidney disease (ARPKD). However, some studies have also reported Caroli disease to be accompanied by autosomal dominant polycystic kidney disease (1). Another study performed exome sequencing in patients with nephronophthisis and identified Caroli disease/syndrome to be a predominant extrarenal phenotype associated with *WDR19* mutations (6). The *WDR19* gene encodes a protein required for ciliary retro transport (7). Pathogenic mutations in the *WDR19* gene are associated with nephronophthisis (NPHP), an autosomal recessive cystic kidney disease, typically progressing to end-stage renal disease (ESKD). Here, we described a case of intrahepatic bile duct dilatation caused by a *WDR19* gene mutation, which was manifested as Caroli syndrome. We present this article in accordance with the CARE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-574/rc).

Highlight box

Key findings

- The present study reports that the child's intrahepatic bile duct dilatation and cirrhosis were considered as manifestations of Caroli syndrome, which is caused by mutations in the *WDR19* gene.

What is known and what is new?

- Pathogenic mutations in the *WDR19* gene have been associated with nephropathy.
- Although the cause of Caroli disease is unknown, some researchers believe that it is an autosomal recessive genetic disease related to mutations in the *PKHD1* gene. But now pathogenic mutations in the *WDR19* gene are also associated with Caroli syndrome or Caroli disease. We hypothesize that mutations in the *WDR19* gene may contribute to the development of extrarenal phenotypes such as Caroli disease or syndrome.

What is the implication, and what should change now?

- The application of whole exome sequencing holds significant value in the diagnosis of liver diseases with unknown etiology. Currently, the patient presents with cirrhosis and abnormal hepatic function, necessitating future liver transplantation treatment.

Case presentation

On August 1, 2022, a 1-year-old boy was admitted to the hospital due to the "discovery of intrahepatic bile duct dilatation for more than 4 months". On March 15, 2022, the child came to our hospital for a follow-up of liver disease. We performed a liver function test, and the results were as follows: alanine aminotransferase (ALT), 25 U/L; aspartate aminotransferase (AST), 109 U/L; total bile acid, 106.9 μmol/L; total bilirubin (TB), 66.2 μmol/L; direct bilirubin (DB), 60.7 μmol/L; γ-glutamyl transpeptidase (γ-GT), 242 U/L. The liver ultrasound showed substantial lesions at the first hilar of the liver, thickened liver parenchymal spot, intrahepatic bile duct dilatation, enhanced Glisson system echo, and intrahepatic cystic lesions. The child was continued under observation without any treatment. After 3 months (June 30, 2022), the patient came to our hospital for further consultation. The liver ultrasound revealed hepatomegaly with diffuse hyperechogenicity and splenomegaly. Additionally, there was dilation of the left hepatic duct and an intrahepatic cystic lesion. Although the child displayed no fever, cough, vomiting, diarrhea, or other discomforts, he developed liver cirrhosis, splenomegaly, and intrahepatic bile duct dilation for unexplained reasons. Therefore, for further diagnosis and treatment of "intrahepatic bile duct dilation", the patient was admitted to the hospital.

Previous history

At the age of 2 months and 28 days, the child was hospitalized in our department due to "jaundice and abnormal liver function for 2 months". Oral medication included ursodeoxycholic acid capsules, bicyclol, and compound glycyrrhizin tablets. The patient was followed up in our hospital many times after discharge. After 2 months, only

bicyclol and compound glycyrrhizin tablets were continued while ursodeoxycholic acid was stopped, and after three months, all of the medications were discontinued. Also, the child had a medical history of polydactyly on the left foot. The physical examination revealed that the liver was positioned 2.5 cm below the right rib, exhibiting moderate quality. The spleen was found to be at the level of the umbilicus, while there were six toes present on the left foot.

Auxiliary examination

White blood cell count, 11.75×10^9/L; neutrophils (%), 33.2%; lymphocytes (%), 54.6%; monocytes (%), 10.6%; hemoglobin, 136.0 g/L; red blood cell count, 5.51×10^{12}/L; platelet count, 127.0×10^9/L. Liver and renal function tests included the following items: creatinine, 25 μmol/L; AST, 52 U/L; uric acid, 149.0 μmol/L; γ-GT, 79 U/L; pyruvate, 46.1 μmol/L. Blood ammonia, 69 μmol/L; urine protein, 1+; virus full set of anti-CMV-IgG, 673.48 AU/mL. The procalcitonin, stool routine, lactic acid, and alpha-fetoprotein (AFP) were found to be normal. Also, ceruloplasmin was 0.435 g/L, the virus full set, the immune full set, the autoimmune hepatitis combination, and hepatitis B surface antigen quantitative tests were negative. Hepatitis C and human immunodeficiency virus (HIV) antibodies (quantitative) were also negative. CT-hepatic portal venography was performed on August 5, 2022, which showed liver cirrhosis, splenomegaly, and abnormally enhancing nodules in the lower segment of the right posterior lobe of the liver, which could be differentiated from focal hyperplastic nodules or atypical tumors (*Figure 1A*). Magnetic resonance-cholangiography (MRCP) (plain scan + water imaging) showed a slightly dilated intrahepatic bile duct, liver cirrhosis, and splenomegaly, with slightly scattered long T2 signal, most of which was distributed along the Glisson's sheath, revealing the possibility of inflammatory lesions. The abnormal signals in the right posterior lobe of the liver indicated tumor lesions, while the abnormal signals in the left lobe of the liver suggested cysts or intrahepatic bile ducts, with the possibility of localized cystic dilatation. Moreover, lymphatic hyperplasia and enlargement were observed in the porta hepatis and the space between the liver and stomach (*Figure 1B*). Cardiac ultrasound revealed a left-to-right shunt at the atrial level, while kidney ultrasound showed slight hydrops in the right kidney.

Diagnosis and treatment process

A discussion was conducted on cirrhosis and bile duct dilatation in children. Abnormally enhanced nodules were observed in the lower segment of the right posterior lobe of the liver, most of which were considered neoplastic lesions, thus, a biopsy was recommended. Low-density lesions in the left lobe of the liver indicated cysts or cystic dilatation of the intrahepatic bile duct. A slightly dilated intrahepatic bile duct and increased lymph nodes in the hilar and liver-gastric space suggested splenomegaly, which led to the recommendation of a needle biopsy. Since the child was young, we needed to consider preoperative anesthesia and operability. Although the nature of the solid lesion in the right lobe of the liver remained unknown, the possibility of a tumor could not be ruled out, considering focal nodular hyperplasia. However, the general condition of the child was good. We communicated with the family members of the child and transferred him to the surgical treatment department. On August 17, 2022, laparoscopic liver tumor resection and liver tissue biopsy were performed in the Pediatric Surgery Department. After the operation, the child, under stable conditions, was transferred to our department for further treatment. First, various indicators were rechecked, which were as follows: white blood cell count, 3.73×10^9/L; neutrophils, 0.71×10^9/L; lymphocytes, 2.50×10^9/L; hemoglobin, 116.0 g/L; platelet count, 165.0×10^9/L; creatine kinase, 36 U/L; ALT, 15 U/L; AST, 26 U/L; γ-GT, 48 U/L; total bile acid, 2.5 μmol/L; lactic acid dehydrogenase, 263 U/L. The liver pathological results are showed in *Figure 2A*. All gray-yellow nodules in the liver were taken for examination and observed microscopically, which showed liver cell swelling, hydropic degeneration, and occasional hepatic cell punctate necrosis. The portal area showed fibrous tissue hyperplasia along with the local pseudolobular formation and a large number of small bile duct hyperplasia, as well as, lymphocyte infiltration, which was consistent with liver cirrhosis. Also, atypical hyperplasia of liver cells was observed in the small focal area. Electron microscopy of the liver tissue showed non-specific inflammatory damage (*Figure 2B*). Furthermore, we sequenced the whole genome exons (*Figure 3*) and found two heterozygous mutations in the *WDR19* gene, namely c.2290delC (p.Q764Nfs*29) and c.2401G>C (p.G801R). One of which was derived from the father and the other from the mother. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent has been obtained from the parents of the

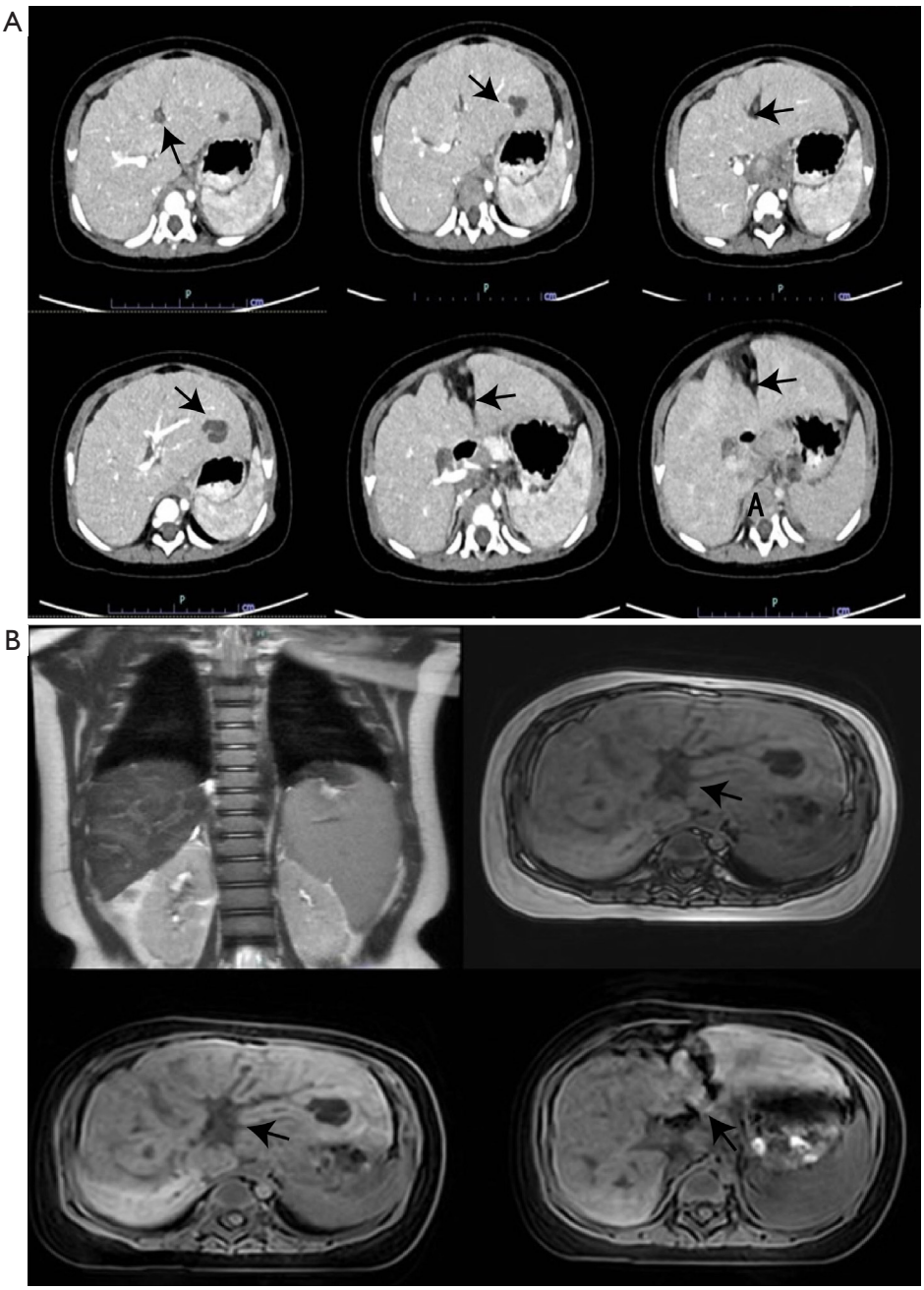

Figure 1 The liver imaging examinations. (A) CT-hepatic portal venography showed liver cirrhosis, splenomegaly, and abnormally enhancing nodules in the lower segment of the right posterior lobe of the liver, which could be differentiated from focal hyperplastic nodules or atypical tumors. (B) MRCP (plain scan + water imaging) showed a slightly dilated intrahepatic bile duct, liver cirrhosis, and splenomegaly, with slightly scattered long T2 signal, most of which was distributed along the Glisson's sheath, revealing the possibility of inflammatory lesions. The abnormal signals in the right posterior lobe of the liver indicated tumor lesions, while the abnormal signals in the left lobe of the liver suggested cysts or intrahepatic bile ducts, with the possibility of localized cystic dilatation. Moreover, lymphatic hyperplasia and enlargement were observed in the porta hepatis and the space between the liver and stomach. Arrows indicate cystic dilated bile ducts and liver lesions. MRCP, magnetic resonance-cholangiography.

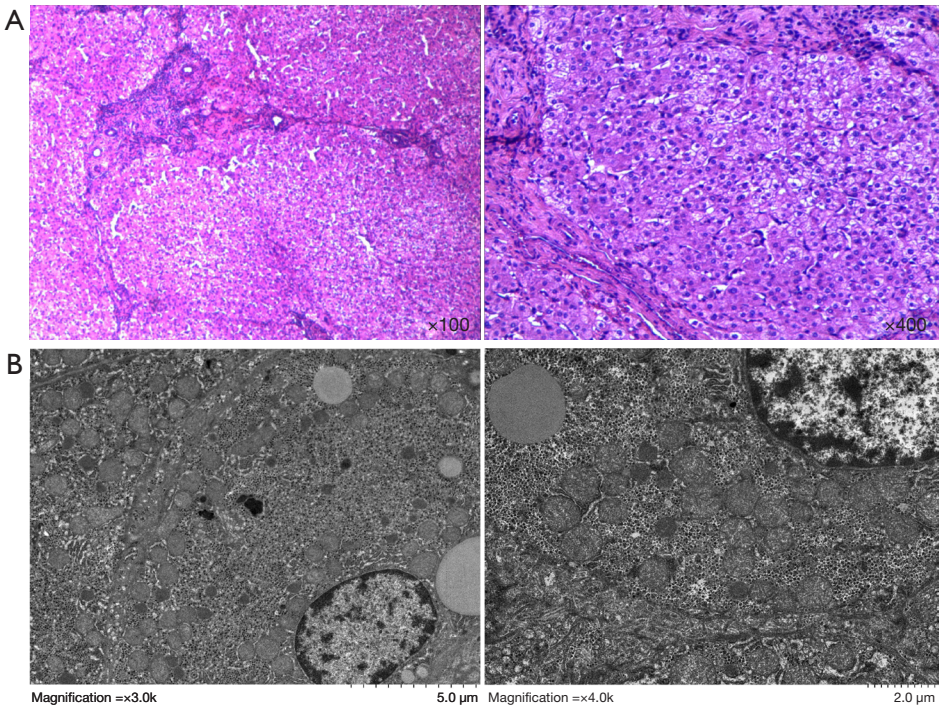

Figure 2 Results of liver pathology and electron microscopy. (A) The liver tissue stained with hematoxylin and eosin revealed hepatocyte swelling, hydropic degeneration, and occasional punctate necrosis of hepatic cells. The portal area exhibited fibrous tissue hyperplasia, local pseudolobular formation, and a significant number of small bile duct hyperplasia. Additionally, lymphocyte infiltration was observed, which is indicative of liver cirrhosis. Furthermore, atypical hyperplasia of liver cells was identified in a small focal area. Special staining showed the following results: reticular fibers (+), PAS (+, positive control +), and PAS + enzyme (–). Whole liver tissue film was used for microscopic examination, which revealed nodular liver cirrhosis. (B) Electron microscopy results showed that hepatocytes were swollen, with no obvious changes in the nuclei, decreased rough endoplasmic reticulum in the hepatocyte cytoplasm, and proliferated and expanded smooth endoplasmic reticulum along with swollen mitochondria. Moreover, the glycogen content was increased in some liver cells, and in some, it was accumulated in flakes as intracellular glycogen. While some liver cells showed a slight increase in the small lipid droplets, a few other liver cells showed a small number of cholestatic pigment granules. Furthermore, hepatic sinusoids were narrow, with swollen sinusoidal endothelial cells. Lymphocytes and Kupffer cells were not increased significantly. Moreover, hepatic stellate cells were easily observed. Regional bundles of collagen fiber deposition were observed in the space of Disse and between hepatocytes. The ultra-thin section showed the edge of the portal area, scattered with infiltration of inflammatory cells, including neutrophils. Electron microscopy of the liver tissue showed non-specific inflammatory damage. PAS, periodic acid-schiff stain.

patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal. The patient's condition was stable, and he was discharged from the hospital. After the discharge, outpatient follow-up visits were performed regularly. The patient's cirrhosis has deteriorated compared to previous assessments, and there is evidence of abnormal liver function. Consequently, a liver transplant will be required at a later stage.

Discussion

The Caroli syndrome is linked to autosomal recessive polycystic kidney disease caused by pathogenic variants in the *PKHD1* gene, which encodes fibrocystin, a large integral membrane protein primarily expressed the kidneys and lower level in the liver (8). Pathogenic mutations in *PKD1* or *PKD2* are associated with autosomal dominant polycystic kidney disease, occasionally accompanied by

Figure 3 Whole-exome sequencing followed by Sanger validation. Two heterozygous mutations, c.2290delC (p.Q764Nfs*29) and c.2401G>C (p.G801R), were identified in the *WDR19* gene; the former was inherited from the mother and the latter from the father.

Caroli's disease (9). Mutations in the *WDR19* gene cause nephronophthisis that often leads to ESKD and Caroli syndrome or disease. NPHP is caused by mutations in a variety of genes encoding the proteins involved in the function of fibrils, basal bodies, and centrosomes, further causing renal disease and extrarenal manifestations, including retinal degeneration, cerebellar ataxia, and hepatic fibrosis (10). The causative gene for about 70% of NPHP cases can be found through molecular genetic screening. Halbritter *et al.* performed whole exome sequencing of patients clinically diagnosed with NPHP and combined it with genetic testing. To date, more than 13 NPHP genes are implied, which account for only about 40% of all cases, including *NPHP1*, *INVS/NPHP2*, *NPHP3*, *NPHP4*, *IQCB1/NPHP5*, *CEP290/NPHP6*, *GLIS2/NPHP7*, *RPGRIP1L/NPHP8*, *NEK8/NPHP9*, *SDCCAG8/NPHP10*, *TMEM67/NPHP11*, *TTC21B/NPHP12*, and *WDR19/NPHP13* (11). The *NPHP13* gene is also called the *WRD19*, *SRDT5*, *ATD5*, or *CED4* gene, and it encodes the IFT144 protein. This gene mutation is present in patients with simple NPHP, NPHP with liver fibrosis, Senior-Loke syndrome, Caroli disease/syndrome, Sensenbrenner syndrome, Joubert syndrome, and Jeune syndrome (6,11-14).

Although the exact mechanism of how multiple NPHP gene defects cause kidney disease is unknown, ciliary dysfunction remains a common mechanism proposed so far. This hypothesis is based on the association between most of the proteins and various human cystic diseases located in the fibrils, basal bodies, and centrosomes, including the nephrocystin protein (15-20). Nephrocystins interact with each other and also with other proteins involved in the cell-cell and cell-matrix signaling (e.g., tensin, filamin, and tubulin) (19,21,22). Some scholars believe that the mutations in the *NPHP* genes change the functioning

of cilia through the defects in the intracellular signaling pathway, resulting in ciliary mechanoreceptors not being able to accurately sense the fluid velocity in the renal cyst cavity. Multiple gene mutations have been found in the patients with NPHP, with their protein products expressed in the primary cilia, basal bodies, and centrosomes. These gene products may play roles in the cell-cell and cell-matrix signaling involved in the sensing of intratubular fluid velocity by ciliary mechanoreceptors (23,24). As abnormal kidney cells fail to sense fluid flow and try to compensate, the genetic defects cause uncontrolled tissue growth and cyst formation (25). The underlying liver disease in ciliopathies is manifested as congenital hepatic fibrosis, Caroli disease, and polycystic liver disease. Targeted exome sequencing (TES) was used to identify a series of nph13 cases, all of which were presented with Caroli syndrome or Caroli disease and characterized by focally dilated intrahepatic bile ducts of the liver associated with or without congenital hepatic fibrosis, respectively. Some clinical cases of nph13 were also reported in four studies (6,7,10,11). Comprehensive analysis showed that 13 of the 27 NPHP patients had liver disease while nine exhibited Caroli disease or syndrome. Since Caroli disease or syndrome may be another major phenotype associated with *WDR19* mutation, screening for the presence of intrahepatic ductal dilatation may be helpful for the diagnosis of NPHP patients.

Caroli disease or syndrome may be the predominant extrarenal phenotype associated with the *WDR19* gene mutation (6). During the follow-up of liver disease in our case, the intrahepatic bile duct was significantly dilated, accompanied by cirrhosis and splenomegaly. Therefore, we considered the diagnosis as Caroli syndrome. The diagnosis of Caroli syndrome does not require a liver biopsy, which is also risky in the case of a cystically dilated biliary system. However, if the patient is presented with an enlarged, firm liver with features of portal hypertension and without biliary dilatation or renal disease, histologic analysis on liver biopsy may be helpful to support the diagnosis. The final genetic results revealed that our patient's disease was not related to the Caroli syndrome gene, but rather an extrarenal manifestation of Caroli syndrome in nephropathy caused by *WDR19* mutations. Mutations in these genes led to extrarenal manifestations of NPHP, including the Caroli disease or Caroli syndrome. Furthermore, Caroli disease, a rare genetic disorder characterized by intrahepatic bile duct dilation, was found to be manifested by two other patients with homozygous *WDR19* mutation (11).

Conclusions

Although the exact mechanism of how the *WDR19* gene defects cause Caroli disease or Caroli syndrome is unknown, ciliary dysfunction remains a common mechanism proposed so far. Also, no specific treatment is available for NPHP. In children with early NPHP and intact renal function, supportive care is given, focusing on maintaining fluid and electrolyte balance, treating anemia, and promoting normal growth. The optimal management in the advanced stages of the disease may entail the consideration of organ transplantation.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-23-574/rc

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-574/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-574/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent has been obtained from the parents of the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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