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CASE REPORT

Hepatology

ZFYVE19 gene mutation: A novel variant of progressive familial intrahepatic cholestasis

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Abstract

A recent nonsyndromic phenotype, newly linked to mutations in the ZFYVE19 gene, is characterized by the appearance of cholestasis accompanied by an increase in serum gamma-glutamyltranspeptidase (GGT) from infancy or early childhood. Affected individuals generally present with hepatosplenomegaly and may develop portal hypertension. The disease is thought to be the result of cholangiocyte-specific ciliary dysfunction, indicating a ciliopathy that appears to be limited to the liver. Here, we describe the case of an infant born to first-degree consanguineous parents, in whom neonatal cholestasis accompanied by elevated GGT led to the discovery of a ZFYVE19 deficiency. The diagnosis was established following an in-depth analysis of the complete exome sequencing.

KEYWORDS

ciliopathy, consanguinity, gamma-glutamyl transpeptidase

1 | INTRODUCTION

Recently, mutations in the ZFYVE19 gene (OMIM: 619849) have garnered attention as a novel area of research in neonatal chronic intrahepatic cholestasis. This discovery opens new avenues for understanding the genetic underpinnings of this condition. It is suggested that ZFYVE19 deficiency is classified as a ciliopathy, which involves an alteration in the pathways associated with cilia.[1–3]

Through this clinical case, we explore the implications of this recent association between ZFYVE19 and intrahepatic cholestasis.

2 | PRESENTATION OF CASE

We report the case of a 3-month-old infant from a first-degree consanguineous marriage, presenting with partial and intermittent cholestasis since 7 days after birth. The history reveals an uncomplicated full-term pregnancy, with a reported death of a sister at the age of 14 months, also for cholestasis that occurred at the age of 3 days, complicated by a generalized hemorrhagic syndrome.

On clinical examination, the child presented with hepatomegaly with the liver's lower margin extending 10 cm below the costal margin and no splenomegaly,

with a weight of 4 kg minus 3 standard deviations, and a height of 56 cm minus 3 standard deviations. Skin abnormalities such as an angioma on the forehead and convergent strabismus were noted. No signs of hemorrhage or neurological disorders were observed. The liver function tests revealed biological cholestasis, with a total bilirubin level of 133 µmol/L, including 110 µmol/L of conjugated bilirubin. Gamma-glutamyl transferase (GGT) values were elevated to 1922 IU/L, while alkaline phosphatase values were 552 IU/L. The prothrombin level was measured at 83%. A significant cytolysis was observed, with aspartate aminotransferase levels reaching 381 IU/L and alanine transaminase at 273 IU/L, exceeding seven times the normal range. The lipid profile revealed high levels of total cholesterol (4.99 g/L) and triglycerides (2.5 g/L). Serologies for toxoplasmosis, Epstein–Barr virus, herpes, parvovirus B19, and human immunodeficiency virus were negative. However, cytomegalovirus immunoglobulin G (IgG) and IgM serology returned positive, with a viral load exceeding 20,000 copies/mL.

Abdominal ultrasound revealed normal morphology of the bile ducts and gallbladder. As cholestasis persisted, intraoperative cholangiography was recommended and excluded biliary atresia. Alagille syndrome (ALGS) was excluded due to the absence of facial dysmorphism, vertebral, renal, or cardiac anomalies characteristic of this syndrome. Sweat tests were normal, ruling out cystic fibrosis.

Protein electrophoresis revealed an alpha 1 peak and excluded a possible alpha 1 antitrypsin deficiency. Alpha-fetoprotein levels were elevated to 2000 ng/mL, and amino acid chromatography returned to normal. Ophthalmological examination identified a right eye esotropia.

A liver biopsy revealed portal spaces enlarged by fibrosis and demonstrating interlobular septa. Biliary neoducts were present, with ductal thrombi and moderate intrahepatocyte cholestasis (Figures 1–3).

Whole-exome sequencing identified a homozygous pathogenic variation in the infant. This variation resulted in a stop-gain (nonsense) mutation in the ZFYVE19 gene (NM_001077268.2: c.547C>T), with the specific mutation as follows: c.547C>T (p. Arg183Ter) (OMIM: 619849).

Therapeutically, the patient was initially treated with vitamin ADEK supplementation and ursodeoxycholic acid (UDCA) at a dose of 20 mg/kg/day. In addition, antiviral treatment with ganciclovir was initiated.

Given the persistence of pruritus at the age of 9 months; it was decided to add rifampicin to the treatment while increasing the dose of UDCA to 25 mg/kg/day. This intervention led to the cessation of itching and enhanced sleep quality.

3 | DISCUSSION

Neonatal cholestasis can result from a number of conditions requiring either medical or surgical treatment. Some forms may be of undetermined origin.[2,4] In a European study, biliary atresia was the most common diagnosis (41%), followed by progressive familial intrahepatic cholestasis (PFIC) and idiopathic cases (around 10% each),[5] representing a small but challenging and important group of disorders. Advanced sequencing methods promise to further increase the diagnostic yield of genetic approaches.[5]

Elevated GGT is a biological characteristic of extrahepatic cholestasis, particularly in biliary atresia and sclerosing cholangitis, as well as obstructions of the main biliary tract. However, in the case of intrahepatic cholestasis, serum GGT levels may help

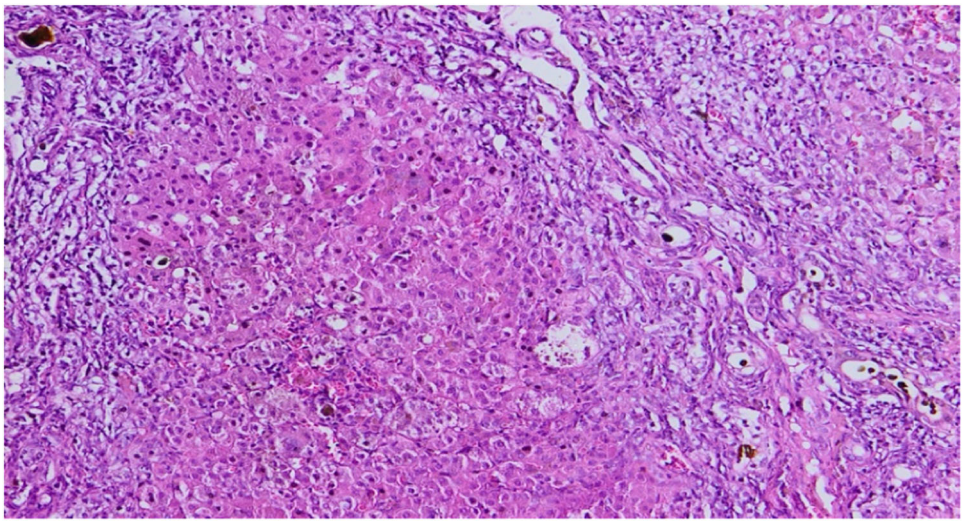

FIGURE 1 Biliary neoductules with presence of canalicular biliary thrombi and intrahepatic cholestasis (under standard H&E staining—magnification × 200). H&E, hematoxylin and eosin.

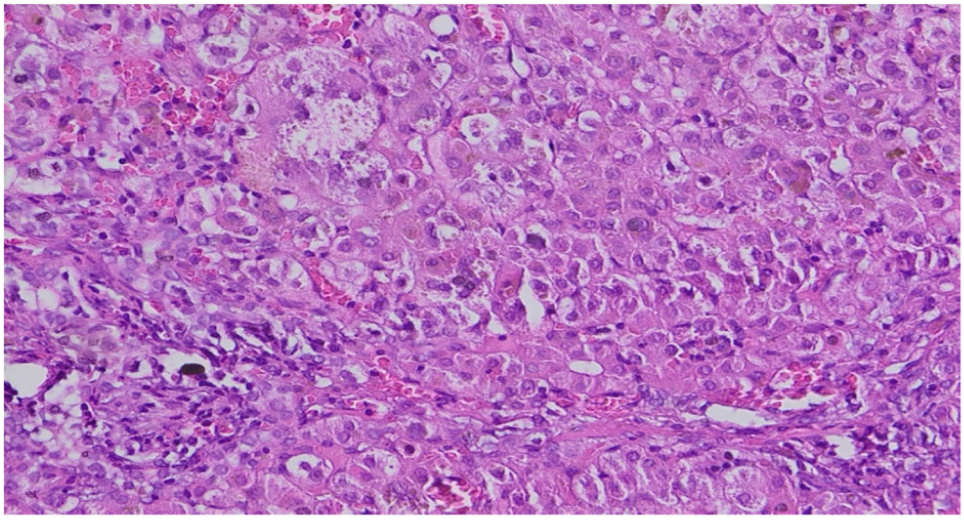

FIGURE 2 Hepatocytes showing a pseudorosette appearance and also taking on the appearance of giant cells (H&E staining—magnification × 400). H&E, hematoxylin and eosin.

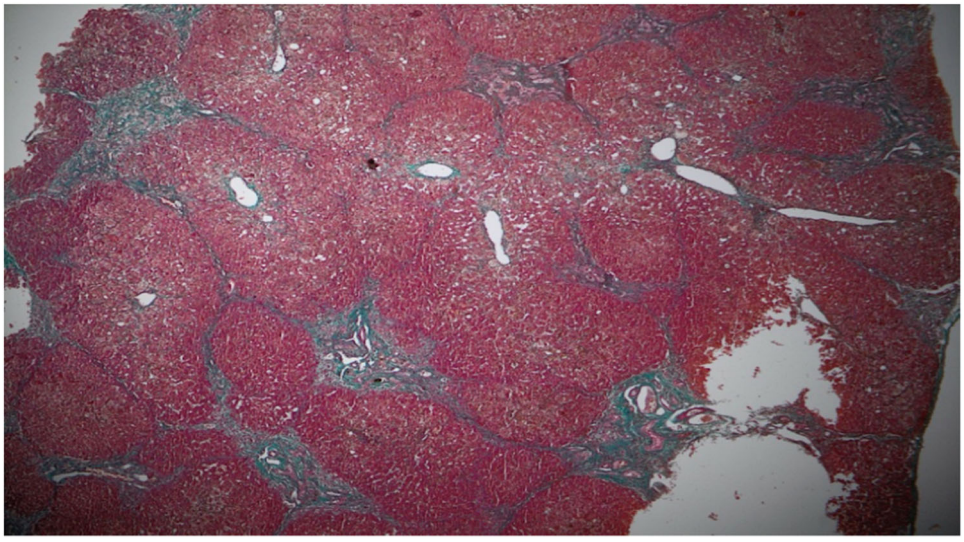

FIGURE 3 Portal spaces enlarged by fibrosis and emitting intralobular septa (under Masson trichrome staining—magnification ×400).

in the differential diagnosis. Low or normal GGT levels are usually seen in PFIC types 1 and 2, or in bile acid synthesis defects. Low GGT levels are also associated with a number of other rare cholestatic conditions. Elevated GGT levels may suggest a range of intrahepatic metabolic/genetic diseases such as α1-antitrypsin deficiency, neonatal sclerosing cholangitis, ALGS, cystic fibrosis, PFIC type 3, and other ductal transport defects.[3,4] In our case, the diagnoses of ALGS and other causes of intrahepatic cholestasis with elevated GGT were subsequently ruled out based on liver histology and genetic studies.

Recently, Luan et al. described a previously unidentified genetic cause of intrahepatic cholestasis, zinc finger FYVE-type containing 19 (ZFYVE19), as a novel cause of elevated GGT cholestasis in a small series of Chinese children with a neonatal sclerosing cholangitis-like phenotype unrelated to the DCDC2 gene.[1]

The ZFYVE19 protein appears to play a role in the control of cytokinesis and resides mainly on centrosomes, important cellular organelles involved in cell division and the formation of primary cilia. Primary cilia are sensory structures located on the membrane of the epithelial cells of the intrahepatic bile ducts, which can detect changes in bile flow.[6,7] As discussed by Pepe et al.,[8] the ZFYVE19 protein plays a crucial role in mediating communication between endosomal sorting complexes for transport- III (ESCRT-III) machinery proteins and the vacuolar protein sorting

4 at the ciliary transition zone, thus influencing ciliogenesis and centrosome duplication. Dysregulation of this process can impact the formation of complex patterns, similar to other hepatic ciliopathies. Additionally, ESCRT-III machinery molecules are essential for the polarized trafficking of the bile salt export pump (BSEP); dysfunction in this mechanism can lead to subapical BSEP retention and result in cholestasis.[8]

Liver-targeted adeno-associated virus vectors containing ZFYVE19 have shown a significant reduction in portal fibrosis, portal tract inflammation, ductular hyperplasia, and hepatobiliary injury markers in ZFYVE19 deficient mouse models, highlighting the crucial role of the ZFYVE19 gene regulating hepatic fibrosis.[6]

Our patient presented with hepatobiliary cholestatic disease accompanied by a significant increase in GGT levels, initially suspected to be related to extrahepatic obstruction such as extrahepatic biliary atresia or sclerosing cholangitis. However, these possibilities were later ruled out. Due to the presence of factors such as family consanguinity and the previous death of her sister, an underlying genetic cause was considered. This discovery underlines the crucial importance of next-generation DNA sequencing in elucidating diagnoses of childhood cholestasis with atypical manifestations and in ruling out common causes of neonatal cholestasis.[7,9–11] In the study conducted by Luan et al.,[1] 25 Chinese patients were included. All were children with undiagnosed intrahepatic cholestasis and elevated GGT levels. In nine children, presumed complete biallelic pathogenic mutations in ZFYVE19 were detected; their clinical presentation was dominated by the presence of portal hypertension. Histopathological examination of these patients revealed portal-tracts widening and fibrosis without interface activity, and ductular reaction.[1] This resembles the histological appearance described in our patient.

Another study conducted by Mandato et al.[2] describes the case of a 5-year-old girl, born to consanguineous Moroccan parents, presenting with cholestatic jaundice, elevated GGT levels, and mild hyperlipidemia. A liver biopsy revealed bile duct proliferation and fibrosis. Treatment with UDCA proved to be partially effective in this patient[2] as the subsequent increase of pruritus required the addition of odevixibat, an inhibitor of the bile acid transporter. Within the first week following odevixibat administration, a significant reduction in serum bile acid levels and pruritic symptoms was observed.[8]

At present, our knowledge of the development and management of this condition remains limited due to the novelty of its discovery and the small number of documented cases.[12,13]

4 | CONCLUSION

Through this clinical fact, we underline the critical importance of next-generation DNA sequencing in elucidating infant cholestasis diagnoses after eliminating common diagnoses that may present with infant cholestasis. In addition, further research is needed to better understand the long-term impact of ZFYVE19 mutations on patients' health and well-being and to develop more specific and effective therapeutic strategies.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

We obtained written consent from the parents to authorize this publication.

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