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Case Report

Progressive familial intrahepatic cholestasis type 2 with trisomy x-reverse Occam's razor: a case report

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ABSTRACT

Progressive familial intrahepatic cholestasis type 2 (PFIC-2) is a rare autosomal recessive liver disorder caused by ABCB11 mutations, leading to severe cholestasis and liver failure. Triple X syndrome (47,XXX) is a sex chromosome aneuploidy with variable clinical features. An 80-day-old female presented with severe neonatal cholestasis and conjugated hyperbilirubinemia. Genetic testing confirmed biallelic ABCB11 variants consistent with PFIC-2 and a supernumerary X chromosome (47,XXX). Despite supportive therapy, she developed intractable ascites and died of septicemia. This case highlights the importance of genomic testing in neonatal cholestasis and the need for multidisciplinary care in complex dual genetic diagnoses.

Keywords: Progressive familial intrahepatic cholestasis type 2, ABCB11 gene, Triple X syndrome, Sex chromosome aberrations, Neonatal cholestasis

INTRODUCTION

Progressive familial intrahepatic cholestasis (PFIC) refers to a heterogeneous group of autosomal recessive disorders that present with intrahepatic cholestasis. PFIC-2 is caused by the mutation in the ABCB11 gene located on chromosome 2 and codes for bile salt export pump (BSEP) protein, a major exporter of primary bile acids.[1,2] It has an incidence of 1/50,000 to 1/1000000 births.[3]

Trisomy X/47 XXX syndrome is a sex chromosomal anomaly with a variable phenotype caused by the presence of an extra X chromosome in females, seen in 1in 1000 female births.[4,5] It was first described in 1959 by Jacobs and coworkers in a woman with ovarian failure. It is not usually suspected at birth or in childhood and is often diagnosed incidentally with prenatal diagnosis or medical testing for infertility.[6,7] Its symptoms vary widely including tall stature, hypertelorism, epicanthal folds, clinodactyly, congenital heart disease, and genitourinary anomalies.[5] Here we present a case of PFIC-2 in a patient who also had trisomy X.

CASE REPORT

An 80-day-old baby girl, born to non-consanguineous parentage, was evaluated for jaundice, high colored urine, and intermittent pale stools from the 4th day of life. She was born at term by a normal vaginal delivery with a birth weight of 3.6 kg following an uneventful pregnancy. There was no history of intrahepatic cholestasis or fever with rash in the mother. She did not have seizures, bleeding manifestations, or unusual urine odor. She was exclusively breastfed and was immunized to date.

Her elder sibling also had a similar illness for which she underwent liver transplantation at 1 year of age but died 4 months after the transplant. The second sibling had congenital hypothyroidism, which was diagnosed at birth through newborn screening.

Examination revealed a relatively well-looking infant with icterus weighing 6.5 kg (±0.57 SD), length of 57 cm (±0.84 SD), and a head circumference of 38 cm (±0.38SD). She did not have dysmorphism, microcephaly, cataract, bleeding manifestations, or signs of chronic liver disease (Figure 1). Her liver was palpable 3 cm below the right costal margin, and was firm and non-tender, the liver span being 8 cm. The left lobe was also palpable 2 cm below the xiphisternum. She also had a 3 cm firm, nontender splenomegaly. There was no free fluid in the peritoneal cavity. Her cardiovascular system was normal. Fundus examination did not show cherry red spots or retinitis pigmentosa. Slit-lamp examination for posterior embryotoxon was negative.

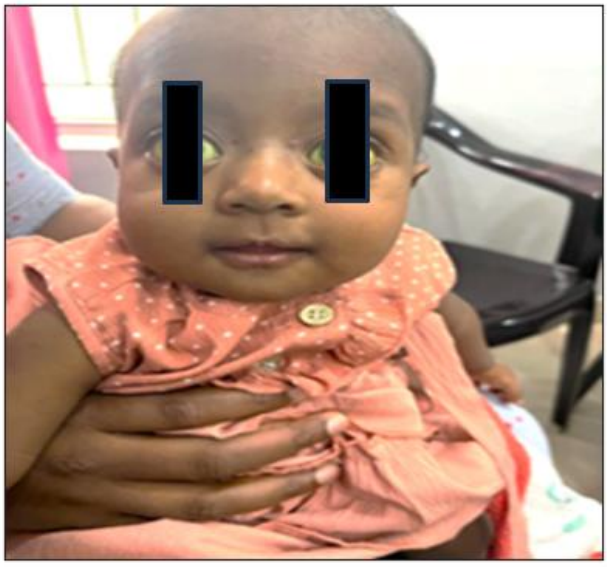

Figure 1: She had icterus and no obvious dysmorphism.

Management and outcome

Hemoglobin was 10 g/dl, total leucocyte count was 8600 cells/ mm^3, and platelet count was 2.6 lakh/mm^3. Her total serum bilirubin was 4.5 mg/dL, conjugated bilirubin 3.5 mg/dl, ALT 952 IU/l, AST 414 IU/l, and alkaline phosphatase 1050 IU/l. Her GGT was 15 IU/l (n: 0-60 IU/l), prothrombin time 15 seconds and INR 1. Blood sugar was 90 mg/dL. Thyroid function tests were normal, serum bile acids were elevated, and serum succinyl acetone were normal. Ultrasonography revealed a normal gallbladder and common bile duct. Intrahepatic biliary radicles were not dilated, and there was no ascites.

A clinical exome study revealed a heterozygous 4 base pair insertion in intron 19 of the ABCB11 gene (chr2: g.168957959_168957960insGTAA; Depth: 114x) that affects the position 4 nucleotides downstream of donor splice site of exon 19 (c.2343+4_2343+5insTTAC; ENST00000650372.1) which was suggestive of PFIC 2. The variant has not been reported in the 1000 genomes or gnom AD. The mutation found was a variant of unknown significance, but parental Sanger sequencing could not be done due to financial constraints. According to bioinformatic prediction tools and short tandem repeat (STR) analysis, the gender was found to be XXX. Karyotype showed 47 XXX (Figure 2). STR was performed in our case as a part of carrier and predictive testing; as the elder sibling who had expired had similar clinical presentation.

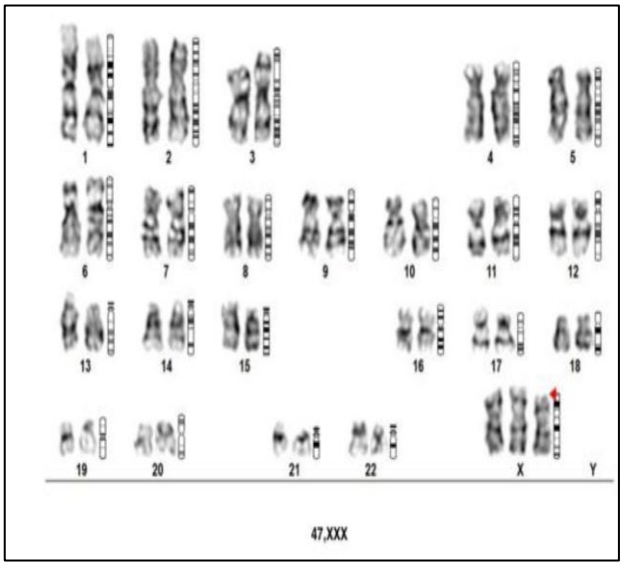

Figure 2: A karyotype showing 47,XXX, indicates triple X syndrome.

*Also called trisomy X), a genetic condition in females where there is an extra X chromosome in each cell, resulting in a total of 47 chromosomes instead of the typical 46.

A provisional diagnosis of PFIC 2 (Byler syndrome) with triple X syndrome was made. She was initiated on ursodeoxycholic acid, parenteral vitamin K and rifampicin. Subsequently, she developed intractable ascites and coagulopathy but her parents were not willing for liver transplantation, and she died of septicemia.

DISCUSSION

PFIC comprises a group of rare autosomal recessive disorders of bile formation resulting from defects in hepatocellular transport proteins. PFIC-2, caused by mutations in the ABCB11 gene encoding the bile salt export pump (BSEP), is associated with early-onset cholestasis, rapid progression to cirrhosis, and increased risk of hepatocellular carcinoma. Advances in genomic diagnostics have significantly improved the identification of PFIC subtypes; however, challenges remain in establishing molecular confirmation, particularly in resource-limited settings.[1]

PFIC should be suspected in children with cholestatic liver disease after excluding more common conditions like biliary atresia, Alagille syndrome, galactosemia, etc. High serum bile acids exclude primary disorders of bile acid synthesis. Serum GGT is low/normal in PFIC-1 and 2, while it is high in PFIC-3. Neonatal cholestasis is rare

in PFIC-3, and they develop cholestasis in infancy, childhood, or even young adulthood.[2]

Deficiency of BSEP in PFIC leads to the accumulation of bile salts in the liver, causing hepatocellular damage.[1,2] In the present case, the clinical phenotype, early-onset cholestasis, low GGT levels, elevated bile acids, family history of severe liver disease, and rapid disease progression was strongly suggestive of PFIC-2. However, genetic testing revealed only a heterozygous intronic variant in ABCB11, classified as a variant of uncertain significance. As PFIC-2 is an autosomal recessive disorder, identification of biallelic pathogenic variants is required for definitive molecular diagnosis. The absence of a second detectable pathogenic variant highlights an important limitation of exome sequencing, which may fail to detect deep intronic variants, large deletions, duplications, regulatory region mutations, or complex structural rearrangements.[8]

This case underscores the critical importance of parental segregation analysis, which could have clarified variant pathogenicity, confirmed inheritance patterns, and strengthened the diagnosis. Unfortunately, parental testing could not be performed due to financial constraints. Additionally, liver histopathology and BSEP immunostaining; valuable diagnostic tools in PFIC-2 were not feasible due to the child's rapid clinical deterioration. These factors collectively limited definitive confirmation of the diagnosis, despite strong clinical suspicion.

Triple X syndrome is a sex chromosomal abnormality, which is not very rare as the majority of such cases go undiagnosed.[6] The incidental detection of trisomy X (47,XXX) adds further complexity. Triple X syndrome is relatively common but frequently undiagnosed due to its variable and often subtle phenotype. In this case, trisomy X appeared to be an incidental finding without an apparent causal relationship to the liver disease. Nevertheless, the coexistence of two rare genetic conditions in a single patient highlights the evolving paradigm of "reverse Occam's razor," wherein multiple genetic diagnoses may coexist and should be considered, particularly with the increasing use of broad genomic testing.

From a management perspective, early genetic diagnosis in neonatal cholestasis is essential for prognostication, timely referral for liver transplantation, consideration of biliary diversion procedures, and accurate genetic counseling. This case also illustrates the emotional and ethical challenges faced by families when advanced therapies such as liver transplantation are declined or not feasible.

CONCLUSION

This case highlights the indispensable role of genetic testing in the evaluation of neonatal cholestasis. At the same time, it illustrates the limitations of exome sequencing, particularly in autosomal recessive disorders where a single heterozygous variant may be insufficient for definitive diagnosis. The case strongly emphasizes the need for parental segregation testing, complementary diagnostic modalities such as liver histology and immunostaining, and a multidisciplinary approach to care.

As genomic testing becomes increasingly accessible, clinicians must interpret results within the broader clinical context and remain cognizant of the possibility of multiple coexisting genetic diagnoses. Early, comprehensive genetic evaluation is essential not only for diagnosis and management but also for informed family counseling and future reproductive planning.

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