ACG CASE REPORTS JOURNAL

CASE REPORT | LIVER

Liver Failure in Neonates With G6PD Deficiency

Milaan Shah, MD[1], and Vani Gopalareddy, MD[2]

[1]*University of South Carolina School of Medicine, Columbia, SC*
[2]*Department of Pediatric Gastroenterology and Hepatology, Levine's Children Hospital, Charlotte, NC*

ABSTRACT

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a commonly inherited enzyme defect that can present with hemolysis, hyperbilirubinemia, and jaundice and may cause kidney and liver dysfunction. G6PD deficiency may serve as a cofactor for chronic liver disease; however, an association with liver failure is not well described. We present the cases of 2 neonates with G6PD deficiency and progressive liver failure resistant to treatment with ursodiol that eventually required liver transplantation. Our cases underscore the importance of monitoring liver function in jaundiced neonates with underlying G6PD deficiency and demonstrate the potential precipitation of liver disease by G6PD deficiency.

INTRODUCTION

Glucose-6-phosphate dehydrogenase (G6PD) is an X-linked genetic disease that is the most common enzyme defect in the world, affecting an estimated 400 million people of mostly African, Asian, and Middle-Eastern ethnicities.[1] G6PD deficiency can cause the onset of hemolysis, hyperbilirubinemia, and/or jaundice in newborns, but these symptoms are usually survivable with medical intervention.

Persistent hemolysis from G6PD deficiency can cause severe hyperbilirubinemia, which can precipitate kernicterus, hearing loss, and mental retardation in severe cases.[2] However, hyperbilirubinemia in neonates with G6PD deficiency is primarily due to reduced hepatic conjugation and excretion, in addition to increased bilirubin production from hemolysis.[3] The presence of G6PD deficiency and liver disease in neonates is well described, with the liver malfunction attributed to G6PD deficiency.[4] An association between G6PD deficiency and liver failure is not established, but the overlap in symptoms and etiology of the 2 diseases warrants further investigation. Thus, we present 2 cases of neonates with G6PD deficiency and concurrent liver failure.

CASE REPORT

Case 1: A 6-week-old African American male child, born at 36 weeks and 5 days gestation, was seen initially for persistent pigmented stools and cholestatic jaundice. His initial laboratory work revealed elevated levels of total bilirubin—6.6 mg/dL, direct bilirubin—4.1 mg/dL, aspartate aminotransferase (AST)—532 IU/L, alanine aminotransferase (ALT)—244 IU/L, and alkaline phosphatase—593 IU/L and a normal gamma glutamyl transpeptidase (GGTP) —25 IU/L. His international normalized ratio (INR) was mildly elevated at 1.7, but it normalized with vitamin K supplementation. The complete blood count was within normal limits. An extensive workup for any primary liver etiology contributing to the cholestatic jaundice was negative.

Workup included a hepatobiliary iminodiacetic acid scan, which noted biliary excretion and bowel activity within 10 minutes, and cytomegalovirus (CMV) polymerase chain reaction, which was noted to be mildly positive with serology suggestive of past infection. An EGL cholestasis gene panel identified a variable of undetermined significance (VUS) in the CFTR gene and a VUS in the PEX12 genes. However, no second variant was identified for either of these recessive genes. Multiple regions of loss of heterozygosity were seen on his single nucleotide polymorphism microarray. Lysosomal enzymes and congenital disorders of glycosylation EBV testing were normal. A subsequent liver biopsy was consistent with idiopathic neonatal giant cell hepatitis with cholestasis and no significant fibrosis (Figure 1). A CMV stain revealed a single inclusion body, and Epstein-Barr virus was negative.

ACG Case Rep J 2022;9:e00845. doi:10.14309/crj.0000000000000845. Published online: August 31, 2022

Correspondence: Milaan Shah, MD (milaan8697@gmail.com).

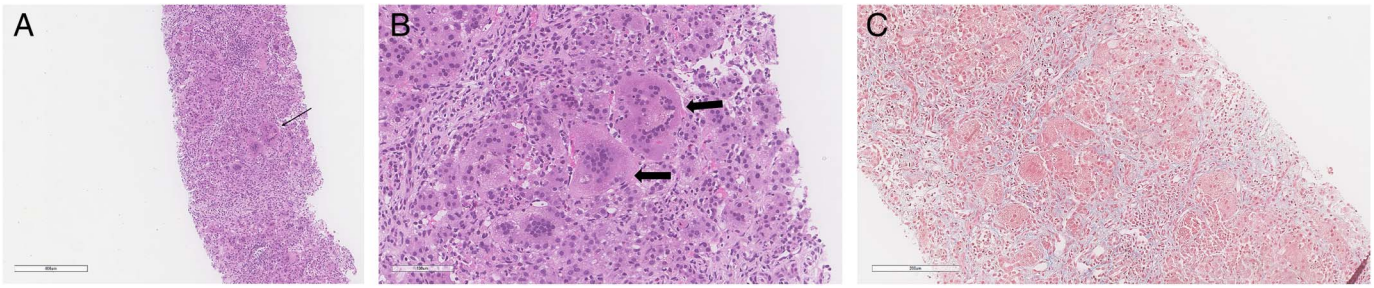

Figure 1. (A) Low-power view of the liver core biopsy showing multiple giant cells present. (B) High-power view of the liver core biopsy showing multiple giant cells with cholestasis, apoptosis, and a background of mixed inflammation with lymphocytes and eosinophils. (C) A trichrome stain of the tissue demonstrating extenuation of the sinusoidal fibrosis.

Serum and urine bile acids were elevated, which was consistent with cholestatic liver disease and severe liver dysfunction, thus excluding bile acid synthetic defects. The urine organic acids and plasma amino acid profiles were also normal. Subsequently, whole exome sequencing of the proband, which was sent for prevention genetics, tested positive for an X-linked G6PD deficiency of homozygous status/pathologic mutation. Of note, the patient's mother had G6PD deficiency.

At birth, he underwent triple phototherapy, but exchange transfusion was not performed. He was started on ursodiol 20 mg/kg/day in divided doses and ADEKs vitamin supplementation. At the age of approximately 6 months, his total bilirubin peaked at 28 mg/dL, with direct bilirubin—18.6 mg/dL, AST—1016 IU/L, and ALT—230 IU/L. His INR peaked at 2.8 and was unresponsive to IV vitamin K. His absolute reticulocyte count remained elevated at 120, and the hemoglobin dropped to 8.0 mg/dL, requiring packed red blood cell transfusion. He remained hyperammonemic with a total ammonia level persistently elevated at 120 μmol/L. He was eventually diagnosed with subacute liver failure and received liver transplantation within the next 2 weeks. On follow-up at 6 months after transplant, the patient was doing well with no recurrence of symptoms.

Case 2: A newborn African American female child, born at 36 weeks gestation, presented with jaundice at birth with total bilirubin—14.1 mg/dL and direct bilirubin—8.5 mg/dL at 9 hours of life. Her LFTs were initially elevated with ALT—108 IU/L and AST—262 IU/L, but her gamma-glutamyl transferase (GGT) was within normal limits. Her hemoglobin was normal on an initial complete blood count at 13.5 mg/dL, and her reticulocyte count was elevated at 19%. A direct Coombs test was negative.

Ursodiol was initiated for treatment, but her stool always remained golden yellow. Further workup, including abdominal ultrasound, urine organic acids, herpes simplex virus test, urine CMV test, soluble IL-2 receptors, and liver biopsy, all returned normal. An Emory genetic cholestasis panel revealed a heterozygous mutation for NOTCH-2 and a nonspecific mutation in CFTR-5T. A further hemolytic anemia panel to ARUP was positive for G6PD deficiency.

She continued to develop worsening jaundice at the age of 6 weeks with total bilirubin—37 mg/dL and direct bilirubin—15.5 mg/dL. Her INR was 1.9, hemoglobin 9.9 mg/dL, platelets 99, and albumin 2.9 g/dL. She developed refractory ascites and required and received a liver transplant within the next 4 weeks. To date, she has been doing well.

DISCUSSION

G6PD deficiency is generally a manageable disease because most afflicted individuals do not experience any negative symptoms with the exception of when they are "triggered" by viral infections, certain medications, and/or fava beans.[5] These triggering events cause significant oxidative damage to the red blood cells resulting in hemolytic anemia, which is the basis for the major medical complications of G6PD deficiency. Severe cases of G6PD deficiency can cause damage to the kidneys and liver, but the mechanism underlying the liver damage is poorly understood.[4,6]

In the 2 cases discussed above, 2 neonates presented with chronic cholestatic jaundice that would not resolve despite ursodiol treatment. It was discovered that both babies had chronic, low-grade hemolysis and compromised liver function in the setting of G6PD deficiency. Of note, in both cases, the neonates had multiple single mutations in various genes. The VUS in the CFTR and PEX12 genes and multiple loses of heterozygosity on single nucleotide polymorphism in case #1 and the mutations in NOTCH-2 and CFTR-5T in case #2 are all of no known clinical significance.

Neonates with G6PD deficiency can have elevated levels of AST, ALT, and INR within 7 days of birth without any significant precipitating hemolytic event and/or trauma.[4] This may suggest that the compromised liver function is attributed to G6PD deficiency. However, the etiology and physiology underlying the impact of G6PD deficiency on the liver is not established and requires further elucidation. If this mechanism is better understood, investigation into the connection between the 2 conditions could potentially reveal causality or lack thereof.

In conclusion, G6PD deficiency can be associated with liver dysfunction, serving as a possible cofactor in the setting of progressive liver failure/chronic liver disease. Although it is not known whether the G6PD deficiency contributes to the development of liver failure, our 2 documented cases suggest that physicians should remain aware of the possibility of

compromised liver function as a complication in this population. Thus, in neonates with G6PD deficiency, it may be particularly important to monitor liver function when jaundice persists for an extended period of time, despite medical intervention. Further studies are warranted to understand the relationship between G6PD deficiency and liver dysfunction in neonates.

DISCLOSURES

Author contributions: M. Shah and V. Gopalareddy wrote and edited the manuscript, reviewed the literature, provided the images, revised the manuscript for intellectual content, and approved the final manuscript. M. Shah is guarantor of the article.

Financial disclosure: None to report.

Previous presentations: This case was presented at the 2021 American Medical Student Association Poster Session, March 6, 2021; Virtual, and the 2021 Discover University of South Carolina Research Day, April 23, 2021; Columbia, SC.

Informed consent was obtained for this case report.

Received June 30, 2021; Accepted July 14, 2022

REFERENCES

1. Frank JE. Diagnosis and management of G6PD deficiency. *Am Fam Phys.* 2005;72(7):1277–82.
2. Washington EC, Ector W, Abboud M, Ohning B, Holden K. Hemolytic jaundice due to G6PD deficiency causing kernicterus in a female newborn. *South Med J.* 1995;88(7):776–9.
3. Iolascon A, Faienza MF, Perrotta S, Meloni GF, Ruggiu G, del Giudice EM. Gilbert's syndrome and jaundice in glucose-6-phosphate dehydrogenase deficient neonates. *Haematologica.* 1999;84(2):99–102.
4. Salomon F, Casimir A, Julien S, et al. Liver function assessment in glucose-6-phosphate dehydrogenase deficient neonates in Benin. *Int J Biomed Res.* 2018;09(06):221–5.
5. Bubp J, Jen M, Matuszewski K. Caring for glucose-6-phosphate dehydrogenase (G6PD)-Deficient patients: Implications for pharmacy. *P T.* 2015; 40(9):572–4.
6. Abdel Hakeem GL, Abdel Naeem EA, Swelam SH, et al. Detection of occult acute kidney injury in glucose-6-phosphate dehydrogenase deficiency anemia. *Mediterr J Hematol Infect Dis.* 2016;8(1):e2016038.