

Bile Acid Synthesis Defect and Hyperinsulinism

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ABSTRACT

Congenital defects of bile acid synthesis are rare disorders that cause progressive liver dysfunction. Prolonged neonatal hyperinsulinism (PNH) is a separate entity that leads to persistent hypoglycemia secondary to stress. We present a 4-month-old infant who presented with liver failure secondary to a bile acid synthesis defect. The patient's liver failure resolved with oral cholic acid therapy. This patient also developed PNH, which slowly resolved over time. This case illustrates a possible relationship between cholestatic liver failure and PNH. This relationship may help define specific stressors that increase the likelihood of developing PNH.

INTRODUCTION

The primary bile acids, cholic acid and chenodeoxycholic acid, are derived from cholesterol in the liver via a series of intermediate steps catalyzed by specific enzymes.¹ Various enzyme deficiencies in this pathway lead to disruption in bile acid synthesis.² When bile acid synthesis is affected, the accumulation of hepatotoxic atypical bile acids and interruption of normal bile flow lead to liver injury and cholestasis.³

Prolonged neonatal hyperinsulinism (PNH) is a rare form of transient hyperinsulinism (HI) that leads to a period of persistent hypoglycemia. PNH is typically confirmed by an insulin level greater than 3 mU/L, a glucagon challenge with a rise in glucose of at least 30 mg/dL, or requiring a glucose infusion rate (GIR) greater than 8 mg/kg/min to maintain euglycemia.⁴ The etiology of PNH is unknown, but stress on a young infant is thought to trigger it.⁵ PNH resolves over time, but resolution may take 6–12 months.

CASE REPORT

A previously healthy 4-month-old female infant presented to the emergency department with a 3-day history of worsening jaundice, lassitude, and poor feeding. Her physical exam was notable for scleral icterus without evidence of hepatosplenomegaly. Laboratory values are presented in Table 1. Her serum glucose was 51 mg/dL (normal 65–150 mg/dL). She was started on intravenous (IV) 10% dextrose, and her hypoglycemia resolved. She was admitted for further evaluation and management of acute liver failure.

An ultrasound with Doppler flow revealed normal size and echogenicity of the liver, with normal patent flow of hepatic vasculature. A percutaneous liver biopsy revealed giant cell hepatitis and minute areas of confluent hepatocellular necrosis (Figure 1). Serum total bile acids were undetectable. Serologies for CMV, EBV, enterovirus, and viral hepatitis A, B, and C were all negative.

Based on the suspicion of a bile acid synthetic defect, oral cholic acid (Cholbam™) was started at 50 mg twice daily (10 mg/kg/dose). The urine bile acid profile obtained prior to starting cholic acid was consistent with a deficiency of the 3β -hydroxy- δ 5-c27-steroid oxidoreductase (HSD3B7) enzyme. Two pathogenic variants were subsequently detected in the *HSD3B7* gene: one copy of a c.45,46delAG and one copy of a c.453delC (p.Y151X). Parents denied consanguinity. The cholestasis and liver function improved with the use of cholic acid for 1 week (Table 1).

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Table 1. Laboratory test results.

	Initial Presentation	1 Week on Cholic Acid	1 Month on Cholic Acid	Normal Range
Total bilirubin, mg/dL	12.2	5.5	1.1	0–1.2
Direct bilirubin, mg/dL	9.2	3.4	0.9	0–0.4
Serum albumin, g/dL	3	3.6	4.5	3.5–5.0
Total protein, g/dL	5.6	5.8	6.5	6.6–8.0
ALP, U/L	587	331	240	145–320
ALTP, U/L	1,514	136	61	12–45
Prothrombin time, s	26.4	12.5	12.2	10.3–13.3
INR	2.24	1.07	1.1	0.9–1.2
GGT, U/L	49	43	38	11–49

ALP: alkaline phosphatase; ALT: alanine aminotransferase; INR: international normalized ratio; GGT: gamma-glutamyl transferase.

However, the patient continued to be persistently hypoglycemic. She was started on IV dextrose with a GIR of 8.7 mg/kg/min to maintain her serum glucose levels above 65 mg/dL. This was slowly weaned down over several weeks, but she was never able to be weaned down further than a GIR of 2.8 mg/kg/min. Complete metabolic evaluation including glycogen storage diseases and disorders of fatty acid oxidation was negative.

During a period of hypoglycemia, her plasma growth hormone was 9.46 ng/mL (0.01–3.61 ng/mL), cortisol 3.3 µg/dL (1.7–14.1 µg/dL), β-hydroxybutyrate 0.23 mmol/L (0.02–0.27 mmol/L), insulin 2.5 mU/L (3–25 mU/L), and C-peptide 0.5 ng/mL (1.1–4.4 ng/mL). Urinalysis was negative for ketones during hypoglycemia. These tests were repeated during four episodes of hypoglycemia with similar results. In a glucagon challenge, serum glucose improved from 35 mg/dL to 55 mg/dL over 30 minutes. Given the presence of serum insulin during hypoglycemia with negative urine ketones, as well as a modest response to glucagon, a diagnosis of HI was made.

She was then started on oral diazoxide. However, she was unable to be weaned completely off of the IV dextrose after 1 week on diazoxide. She did not have any known genetic

mutations associated with HI, including mutations in *ABCC8*, *GCK*, *GLUD1*, *HADH*, *HNF1A*, *HNF4A*, *INSR*, *KCNJ11*, *KDM6A*, *KMT2D*, *PGM1*, *PMM2*, and *UPC2*. Due to persistent hypoglycemia, she was transferred to the HI program at The Children's Hospital of Philadelphia for further evaluation. There she was slowly weaned off IV dextrose over the course of 1 week and remained normoglycemic solely on oral intake. She was discharged home and continues on cholic acid.

DISCUSSION

We present a patient with a very unusual association of a defect in bile acid synthesis due to mutations in *HSD3B7* with PNH. To our knowledge, this association has not been reported previously. A bile acid synthesis defect was suspected in this patient based on serologic evidence of cholestatic liver failure (eg, elevated total and direct bilirubin, low albumin, and elevated international normalized ratio), normal gamma-glutamyl transferase, and undetectable serum total bile acids. The diagnosis was confirmed with mass spectrometric analysis of urine at the Cincinnati Children's Hospital and Medical Center, which revealed a pattern consistent with deficiency of the *HSD3B7* enzyme. Subsequent genetic analysis revealed the underlying pathogenic mutations. *HSD3B7* deficiency was treated with oral cholic acid (Cholbam™), which may reduce the synthesis of abnormal bile acids and may promote bile acid-dependent bile flow via an unknown mechanism.⁶ Our patient had gradual resolution of liver dysfunction with cholic acid and is expected to have an excellent long-term prognosis. Liver transplant is not needed when there is prompt diagnosis with initiation of oral cholic acid to reverse the liver injury, as in this case.

PNH was suspected due to the presence of insulin during a period of hypoglycemia with absent ketones on urinalysis and no evidence of another metabolic disorder. In typical cases of hypoglycemia, ketones are present in the urine and the serum insulin level should be undetectable. Our patient required a

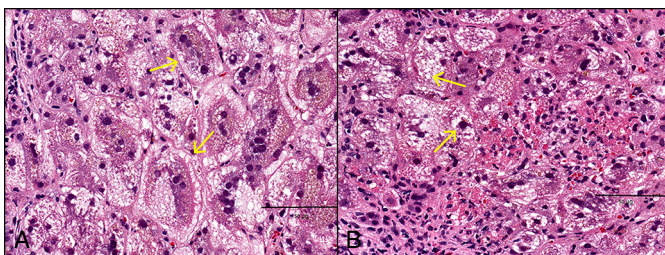


Figure 1. (A) Liver biopsy revealing typical characteristics of a bile acid synthesis defect with giant cell hepatitis, marked canalicular cholestasis, and ductular reaction with fibroedematous expansion of portal areas. (B) Liver biopsy revealing typical characteristics of a bile acid synthesis defect with minute areas of confluent hepatocellular necrosis.

GIR of more than 8 mg/kg/min early in the course, which met diagnostic criteria for PNH. The GIR was gradually decreased over a period of several weeks, which shows that the PNH was improving prior to further investigatory studies. This is why the insulin level, while inappropriately detectable, did not meet strict criteria for classic HI. C-peptide level corresponded well with the insulin level, which excluded exogenous insulin as a cause of patient's hypoglycemia. Negative genetic screening for HI along with the gradual resolution of the hypoglycemia without medication or surgery led to the diagnosis of PNH. Given this patient's underlying bile acid synthesis defect leading to early acute liver failure, it is plausible that this caused enough stress to the patient to cause PNH. The fact that the hypoglycemia gradually resolved after correction of the underlying liver disease further supports this theory.

This case highlights the possibility of persistent hypoglycemia due to PNH in the context of a bile acid synthesis defect that responds to cholic acid. Because the etiology of PNH is unknown, this possible relationship with cholestatic liver failure in a neonate may prove useful in determining more about the specific stressors that increase the likelihood of developing PNH. More understanding of the mechanism of PNH is required going forward.

DISCLOSURES

Author contributions: All authors contributed equally to the manuscript. S Lichtman is the article guarantor.

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Informed consent was obtained for this case report.

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