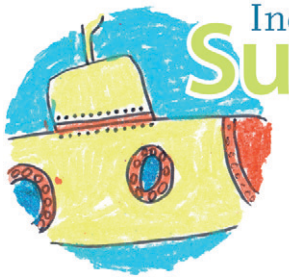

Index of Suspicion

3 Hypoglycemia in an Infant with Cholestasis

Nivedita Patni, MD,* Kathleen Collins, MD,† Perrin White, MD*

*Division of Pediatric Endocrinology, Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX

†Division of Allergy, Immunology, and Rheumatology, Department of Pediatrics, Stanford University, Palo Alto, CA

PRESENTATION

An 8-week-old boy presents with 2 days of worsening jaundice, lethargy, and poor feeding, without fever, vomiting, or diarrhea. At term he weighed 3,400 g (43rd percentile), had hypoglycemia on day 1, and received hyperbilirubinemia phototherapy for 5 days. Physical examination is noteworthy for a lethargic and jaundiced boy weighing 4,300 g (8th percentile). The liver edge is 4 cm below the costal margin. The phallus is 1.7 × 0.7 cm, with no hypospadias, normal scrotum, and descended testes.

Initial laboratory results are as follows: blood glucose, less than 20 mg/dL (<1.11 mmol/L); total/direct bilirubin, 17.8/13.5 mg/dL (304.4/230.9 μmol/L); alanine aminotransferase/aspartate aminotransferase, 258/686 U/L (4.31/11.46 μkat/L); free thyroxine, 0.96 ng/dL (12.4 pmol/L); and thyrotropin, 4.36 μIU/mL (4.36 mIU/L).

An intravenous glucose infusion is started, and the patient is admitted to the hospital. Liver ultrasonography reveals nonspecific coarse echogenicity with gallbladder wall thickening. Liver biopsy shows marked hepatocellular cholestasis, disarray and giant cell transformation, mild portal inflammation and portal fibrosis with early bridging fibrosis, and no abnormal storage material. Testing for herpes simplex virus types 1 and 2, enterovirus, Epstein-Barr virus, cytomegalovirus, adenovirus, human immunodeficiency virus, and hepatitis viruses is negative; levels of urine succinylacetone and organic acids are normal, as are plasma galactose-1-phosphate uridylyltransferase (GALT) and acylcarnitine levels. He is tested for *ATP8B1*, *ABCB11*, *ABCB4*, and *JAG1* mutations. Hypoglycemia continues despite an intravenous glucose infusion rate of 16 mg/kg per minute. After stopping his infusion for 30 minutes, the serum glucose level is 23 mg/dL (1.3 mmol/L). Concurrent laboratory results include insulin, 0.8 μIU/mL (5.6 pmol/L); β-hydroxybutyrate, 0.1 mmol/L; free fatty acids, 0.56 mg/dL (0.02 mmol/L); and growth hormone, 1.55 ng/mL (1.55 μg/L). A low-dose cosyntropin test and brain magnetic resonance imaging (MRI) (Figure) are performed.

DISCUSSION

Differential Diagnosis

Neonatal cholestasis can be caused by obstructed bile flow or functionally impaired hepatic bile secretion secondary to structural, infectious, genetic,

AUTHOR DISCLOSURE Dr Patni has disclosed no financial relationships relevant to this article. Dr Collins has disclosed that she received National Institutes of Health (NIH) training grant 2T32AR050942-11 for a pediatric fellowship research project related to adult and pediatric rheumatology. Dr White has disclosed that he has a grant from Janssen Pharmaceuticals for an NIH-funded clinical drug trial. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

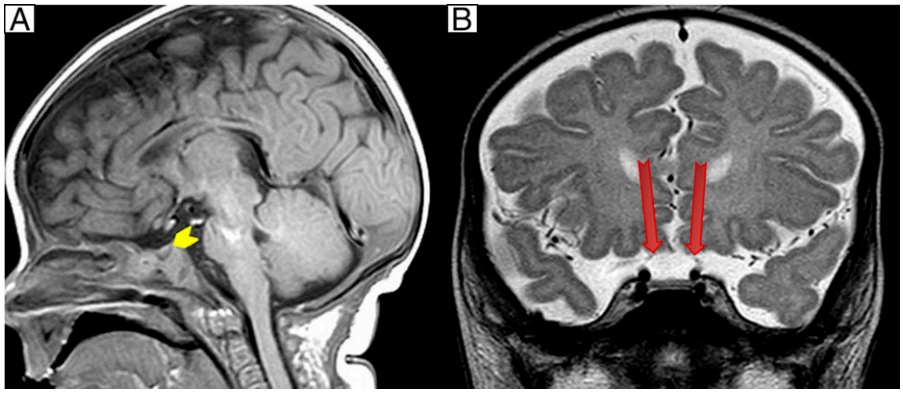

Figure. Brain magnetic resonance imaging. A. Sagittal T1-weighted image. The pituitary gland (yellow arrowhead) is diminutive in size and hypointense. A normal pituitary stalk is not visualized, indicating an ectopic neurohypophysis. B. Coronal T2-weighted image showing optic nerve hypoplasia (red arrows).

metabolic, or endocrine abnormalities. Biliary atresia is a fibro-obliterative disease of the extrahepatic biliary tree that presents with persistent jaundice, pale stools, and dark urine. Key diagnostic findings include ultrasonographic features of abnormal gallbladder size and shape, the "triangular cord" sign, poor gallbladder contractility, and absence of the common bile duct. Hepatobiliary scintigraphy shows lack of tracer excretion from liver to intestines, and liver biopsy demonstrates bile duct proliferation, a small cell infiltrate, portal fibrosis, and absence of sinusoidal fibrosis. (1)

Metabolic conditions such as galactosemia, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (fatty acid oxidation defects), and tyrosinemia type 1 can cause hypoglycemia along with cholestasis; these are usually detected by newborn screening in the United States. Galactosemia may present with vomiting and jaundice within a few days of milk ingestion. Hepatomegaly is often present, and *Escherichia coli* sepsis occurs frequently. Galactosemia is diagnosed by reduced activity of GALT. (2) Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency can present with hypoglycemia and liver disease along with elevated levels of long-chain acylcarnitines. (3) Tyrosinemia type 1, resulting from deficiency of fumaryl acetoacetate hydrolase, usually presents in infancy with severe liver dysfunction, growth failure, rickets, and renal tubular dysfunction. It is characterized by elevated tyrosine, methionine, and phenylalanine levels in plasma; increased succinylacetone levels in the blood and urine; and elevated tyrosine metabolite and δ-aminolevulinic acid levels in urine. Definitive diagnosis is made by measuring fumaryl acetoacetate hydrolyase activity in liver biopsy specimens or cultured fibroblasts. (4)

Progressive familial intrahepatic cholestasis is a group of rare autosomal recessive disorders presenting with intrahepatic cholestasis and features such as hearing loss, diarrhea, and growth failure, and it is caused by mutations in the *ATP8B1*, *ABCB11*, or *ABCB4* gene. (5) Alagille syndrome is an autosomal dominant disorder characterized by conjugated hyperbilirubinemia owing to bile duct paucity; vertebral anomalies; congenital cardiac defects, particularly pulmonary stenosis; ophthalmologic abnormalities such as posterior embryotoxon; and characteristic facial features. Heterozygous inactivating mutations in the *JAG1* gene are found in 94% to 96% of patients. (6)

Biliary atresia was ruled out by liver ultrasonography. A viral hepatitis panel was negative; normal urine succinylacetone and organic acid levels and plasma GALT and acylcarnitine levels ruled out metabolic diagnoses. There were no mutations in the *ATP8B1*, *ABCB11*, *ABCB4*, or *JAG1* genes.

Actual Diagnosis

The infant was diagnosed as having hypopituitarism.

The Condition

The brain MRI (Figure) showed a diminutive pituitary gland (yellow arrowhead), nonvisualization of the normal pituitary stalk, and an ectopic neurohypophysis. The optic chiasm and optic nerves were markedly diminutive (red arrows), and the olfactory bulbs were absent. The cortisol level increased from 1.3 μg/dL (36 nmol/L) to only 6 μg/dL (166 nmol/L) (reference range, >18 μg/dL [>497 nmol/L]) after low-dose cosyntropin stimulation.

Hypoglycemia is best evaluated with additional concurrent blood testing. Patients with hypopituitarism have low free fatty acid, lactate, insulin, cortisol, and growth hormone levels in the setting of hypoglycemia. Hypocortisolism can then be confirmed with a low-dose cosyntropin stimulation test. A brain MRI delineates anatomical causes of hypopituitarism.

A microphallus (ie, penile length <2.5 cm [7]), blunted growth hormone response to hypoglycemia, poor cortisol

response to cosyntropin, and abnormal MRI findings confirmed the diagnosis of hypopituitarism owing to septo-optic dysplasia. Septo-optic dysplasia is a rare congenital syndrome defined by the presence of at least 2 of 3 features: 1) midline forebrain defects such as absence of septum pellucidum or corpus callosum, 2) optic nerve hypoplasia, and 3) hypopituitarism. (8) Hypopituitarism should be suspected in children with hypoglycemia and midline defects such as cleft palate, midface hypoplasia, hypertelorism or hypotelorism, or central incisor; optic nerve hypoplasia presenting with wandering nystagmus or poorly reactive pupils; and microphallus. Newborn boys with hypopituitarism usually have microphallus rather than ambiguous genitalia because in the first trimester, placental human chorionic gonadotropin stimulates testosterone secretion, which promotes differentiation of the external genitalia. Testosterone secretion and consequent penile growth after the first trimester depend on luteinizing hormone secreted by the fetal pituitary gland.

Cholestasis can rarely be a feature of hypopituitarism, (9) the mechanism of which remains unclear. (10) Cortisol modulates bile flow and bile acid synthesis (11); cortisol deficiency might affect hepatic transport of bile acids across bile canaliculi. Growth hormone plays an important role in bilirubin glucuronidation and modulates the biosynthesis and secretion of bile acid in rats (12); and growth hormone deficiency can lead to abnormal biliary cell and bile duct formation. (13) Untreated hypopituitarism has also been linked to congenital hepatic fibrosis. (14) Thyroxine deficiency (not present in this patient) delays maturation of hepatic UDP-glucuronosyltransferase activity and causes unconjugated hyperbilirubinemia. (15)

Patient Course

The patient was treated with hydrocortisone, growth hormone, and testosterone and was closely monitored for diabetes insipidus and hypothyroidism. The cholestasis resolved with growth hormone and hydrocortisone replacement.

Lessons for the Clinician

- Hypopituitarism should be suspected in children with hypoglycemia and midline defects such as cleft palate, midface hypoplasia, hypertelorism or hypotelorism, or central incisor; optic nerve hypoplasia presenting with wandering nystagmus or poorly reactive pupils; or microphallus.
- Cholestasis can be a rare presentation of hypopituitarism.
- Patients with hypoglycemia and conjugated hyperbilirubinemia should undergo endocrine evaluation for hypopituitarism.
- Cholestasis resolves with growth hormone and hydrocortisone replacement.

ACKNOWLEDGMENT

The authors thank the patient's parents for granting permission to publish this information.

References for this article are at http://pedsinreview.aappublications.org/content/40/9/488.

References

1. Lakshminarayanan B, Davenport M. Biliary atresia: a comprehensive review. *J Autoimmun*. 2016;73:1–9
2. Karadag N, Zenciroglu A, Eminoglu FT, et al. Literature review and outcome of classic galactosemia diagnosed in the neonatal period. *Clin Lab*. 2013;59(9-10):1139–1146
3. Sewell AC, Bender SW, Wirth S, Münterfering H, Ijlist L, Wanders RJ. Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency: a severe fatty acid oxidation disorder. *Eur J Pediatr*. 1994;153(10):745–750
4. Sniderman King L, Trahms C, Scott CR. Tyrosinemia type I. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. GeneReviews [Internet]. Seattle, WA: University of Washington, Seattle; 1993–2017. Available at:https://www.ncbi.nlm.nih.gov/pubmed/20301688 Accessed June 6, 2018
5. Amer S, Hajira A. A comprehensive review of progressive familial intrahepatic cholestasis (PFIC): genetic disorders of hepatocanalicular transporters. *Gastroenterol Res*. 2014;7(2):39–43
6. Saleh M, Kamath BM, Chitayat D. Alagille syndrome: clinical perspectives. *Appl Clin Genet*. 2016;9:75–82
7. Feldman KW, Smith DW. Fetal phallic growth and penile standards for newborn male infants. *J Pediatr*. 1975;86(3):395–398
8. Fard MA, Wu-Chen WY, Man BL, Miller NR. Septo-optic dysplasia. *Pediatr Endocrinol Rev*. 2010;8(1):18–24
9. Binder G, Martin DD, Kanther I, Schwarze CP, Ranke MB. The course of neonatal cholestasis in congenital combined pituitary hormone deficiency. *J Pediatr Endocrinol Metab*. 2007;20(6):695–702
10. Copeland KC, Franks RC, Ramamurthy R. Neonatal hyperbilirubinemia and hypoglycemia in congenital hypopituitarism. *Clin Pediatr (Phila)*. 1981;20(8):523–526
11. Dumont M, Erlinger S. Influence of hydrocortisone on bile formation in the rat. *Biol Gastroenterol (Paris)*. 1973;6(3):197–203
12. Gueraud F, Masmoudi T, Goudonnet H, Paris A. Differential effect of hypophysectomy and growth hormone treatment on hepatic glucuronosyltransferases in male rats: evidence for an action at a pretranslational level for isoforms glucuronidating bilirubin. *Biochem Pharmacol*. 1997;53(11):1637–1647
13. DeSalvo D, Pohl JF, Wilson DP, et al. Cholestasis secondary to panhypopituitarism in an infant. *J Natl Med Assoc*. 2008;100(3):342–344
14. Minami K, Izumi G, Yanagawa T, Shimoyamada Y, Yoshikawa N. Septo-optic dysplasia with congenital hepatic fibrosis. *Pediatr Neurol*. 2003;29(2):157–159
15. Labrune P, Myara A, Huguet P, et al. Bilirubin uridine diphosphate glucuronosyltransferase hepatic activity in jaundice associated with congenital hypothyroidism. *J Pediatr Gastroenterol Nutr*. 1992;14(1):79–82

Case 3: Hypoglycemia in an Infant with Cholestasis

Nivedita Patni, Kathleen Collins and Perrin White

Pediatrics in Review 2019;40;488
DOI: 10.1542/pir.2017-0209

Case 3: Hypoglycemia in an Infant with Cholestasis

Nivedita Patni, Kathleen Collins and Perrin White

Pediatrics in Review 2019;40;488
DOI: 10.1542/pir.2017-0209