Clinician's Corner

Vomiting and seizure following circumcision in an infant

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CASE

An ex-27-week premature infant presented at 5 months chronological age to the Emergency Department postcircumcision with one episode of hematemesis, irritability and decreased oral intake. The patient was observed and discharged home after tolerating feeds. He returned after a third episode of emesis with concerns of dehydration and was given a bolus of normal saline. Capillary blood sugar was subsequently found to be 2.9 mmol/L and he had a generalized seizure. He was loaded with phenobarbital, acyclovir, ceftriaxone and vancomycin and made nil per os. Magnetic resonance imaging of the head revealed a nonspecific moderate right-sided subgaleal hematoma. Additional investigations revealed increased echogenicity of the liver, hypoglycemia, hyponatremia and a compensated metabolic acidosis with an elevated lactate.

Further workup showed moderately elevated transaminases, conjugated hyperbilirubinemia, elevated creatinine kinase and markedly elevated triglycerides. Urinary ketones were not detected. Echocardiogram was significant for left ventricular hypertrophic cardiomyopathy.

Past medical history was significant for maternal history of acute fatty liver of pregnancy necessitating early caesarean section. His initial newborn screen had come back positive for very long-chain acyl-CoA dehydrogenase and long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) deficiencies while receiving total parenteral nutrition (TPN). Subsequent repeated acylcarnitine testing and urine organic acids were normal and the screen was deemed a false positive.

CASE DIAGNOSIS: LCHAD DEFICIENCY

Metabolic workup revealed a large increase in all long-chain acylcarnitines including the hydroxylated species consistent with LCHAD deficiency. Urine organic acids were also consistent with this diagnosis. The patient was started on a diet rich in carbohydrates and medium chain triglycerides and restricted in long chain triglycerides. With dietary therapy his encephalopathy and liver function improved. Key pieces in this case that pointed toward an inborn error of metabolism included the history of acute fatty liver in pregnancy, elevated creatine kinase and triglycerides, a mild lactic acidosis and a patient presenting with encephalopathy, cardiomyopathy, liver dysfunction and hypoketotic hypoglycemia.

Inborn Errors of Metabolism (IEMs) can present at various ages and can have consequences if identification and treatment are delayed (1). Over 500 inborn errors have been identified, with acute encephalopathy being the most common clinical presentation (2). Fatty acid oxidation defects together encompass the most common IEMs (3), may manifest clinically following periods of fasting, and should be suspected in any child exhibiting post-fast lethargy particularly in the context of hypoglycemia, hepatomegaly and cardiomyopathy (2).

The enzyme LCHAD catalyzes oxidation of long-chain fatty acids in the mitochondria, such that its absence leads to hypoketotic hypoglycemia in the fasting patient (4). While treatable with timely diagnosis, undetected LCHAD deficiency can lead to irreversible organ failure and high mortality (4,5). It can present from birth to at least 36 months with nonspecific failure to thrive, liver dysfunction, hypotonia and cardiomyopathy, necessitating high suspicion (4). Hints may lie in diet and maternal history and physical examination.

Low-fat diets with night-feeding may mask diagnosis by preventing high-catabolism unwell states; mothers heterozygous for autosomal recessive LCHAD deficiency may present with third-trimester hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome or acute fatty liver of pregnancy (AFLP) syndrome (6). Hypotonia and failure to thrive may be indicative of an underlying metabolic disorder in an otherwise well-appearing neonate/child and should increase suspicion (7). While newborn screening programs increase early diagnosis, their sensitivity and specificity are not absolute, and screen reliability can be clouded by clinical context (3,7). The false positive rate of newborn screening for inborn errors of metabolism is higher in the premature infant than in the term infant due to a combination of higher rates of total parenteral nutrition use and/or immature liver metabolism (8). Our patient was delivered prematurely and was on TPN when the newborn screening sample was collected. These factors

and the normalization of the acylcarnitine abnormalities following cessation of TPN led to the incorrect determination that this was a false positive screen. We hypothesize that the stress of circumcision, combined with poor tolerance of feeds postoperation and prolonged fasting, unmasked his underlying LCHAD deficiency.

Such a wide array of inborn errors with potentially devastating outcomes necessitates front-line provider education and a systematic approach to diagnosis and initiation of corresponding treatment (3). Accordingly, several diagnostic algorithms exist (1,2). However, diagnosis and institution of treatment for suspected IEMs can be difficult as presentations may vary (2). Additionally, patients with LCHAD deficiency can present with episodic hypoketotic hypoglycemic unwell states, leading to missed diagnoses and reaffirming the importance of high suspicion for IEMs and optimal follow-up instruction for seemingly well patients even in the era of neonatal screening (7).

CLINICAL PEARLS

1. Inborn errors of metabolism often present with hypoketotic hypoglycemia.
2. Consider inborn errors of metabolism in infants presenting with seizure or lethargy after a period of fasting.
3. Consider that while there are factors that may lead to false-positive newborn screening results, particularly in the preterm infant, true-positive cases also exist in that same patient population.

References

1. Burton BK. Inborn errors of metabolism in infancy: A guide to diagnosis. *Pediatrics* 1998;102(6):E69.
2. Christodoulou J. Clinical evaluation and emergency management of inborn errors of metabolism presenting in the newborn. *Southeast Asian j Trop Med Public Health* 2003;34(Suppl 3):189–97.
3. Shekawat PS, Matern D, Strauss AW. Fetal fatty acid oxidation disorders, their effect on maternal health and neonatal outcome: Impact of expanded newborn screening on their diagnosis and management. *Pediatr Res* 2005;57(5 Part 2):78R–86R.
4. den Boer ME, Wanders RJ, Morris AA, Ijlst L, Heymans HS, Wijburg FA. Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency: Clinical presentation and follow-up of 50 patients. *Pediatrics* 2002;109(1):99–104.
5. Olpin SE, Clark S, Andresen BS, et al. Biochemical, clinical and molecular findings in LCHAD and general mitochondrial trifunctional protein deficiency. *J Inher Metab Dis* 2005;28(4):533–44.
6. Ibdah JA, Yang Z, Bennett MJ. Liver disease in pregnancy and fetal fatty acid oxidation defects. *Mol Genet Metab* 2000;71(1–2):182–89.
7. Wilcken B. Fatty acid oxidation disorders: Outcome and long-term prognosis. *J Inher Metab Dis* 2010;33(5):501–06.
8. Chace DH, De Jesús VR, Lim TH, Harry Hannon W, Spitzer AR. Tandem mass spectrometric identification of dextrose markers in dried-blood spots from infants receiving total parenteral nutrition. *Clinica Chimica Acta* 2010;411(21–22):1806–816.