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Case 1: Infant With Intrauterine Growth Restriction, Dehydration, and Weight Loss

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Presentation

An infant girl is born by vaginal delivery at 40 weeks' gestation to a gravida 4, para 2012 mother after maternal induction of labor for intrauterine growth restriction (IUGR). Family history is notable for a father and first-child born small for gestational age. Prenatal ultrasonography results at 28 weeks' gestation are normal; fetal weight at that time was in the 43rd percentile for gestational age. Prenatal laboratory findings include negative group B *Streptococcus, Gonorrhea, Chlamydia*, rubella immune, hepatitis B surface antigen nonreactive, and human immunodeficiency virus nonreactive. Her mother has no prior medical conditions; denies substance use, including tobacco smoke and cocaine; and reports not taking anymedications other than prenatal vitamins. The infant's Apgar scores are 9 and 9 at 1 and 5 minutes after birth, respectively, requiring only routine care at delivery. Her initial examination findings are remarkable for depressed fontanelles, and she has no dysmorphic features. Her birth weight is 1,875 g (<3 percentile), length is less than 3 percentile, head circumference is less than 3 percentile, and her Ballard score is 38 (equivalent to 39 weeks' gestation) on admission.

Cord gas analysis results are within the normal range. Glucose levels at ages 5 and 6 hours are 41 and 46 mg/dL (2.3 and 2.6 mmol/L), respectively. After breastfeeding, her glucose level improves to 77 mg/dL (4.3 mmol/L) at 8 hours. Her total bilirubin level at 29 hours is 4.7 mg/dL (80.4 μmol/L). Urine toxicology test results are negative. A quantitative IgM level is within normal limits, and urine cytomegalovirus and viral culture results are negative. Placental pathologic findings are consistent with a third trimester placenta and reveal no evidence of chorioamnionitis. Head ultrasonography findings on day 2 are normal with no signs of calcifications. The genetics department is consulted given the unclear origin

AUTHOR DISCLOSURE

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of her IUGR, and a microarray analysis is performed on day 3. Despite an increase in her feeding volumes and fortifying her formula, she has daily weight loss, worsening depression of her fontanelles, and skin tenting. By day 10, she tolerates daily oral feeds of 145 kcal/kg, has a mean hourly urine output of 7.5 mL/kg, and is 12% below birth weight. Because of polyuria and continued weight loss despite increased caloric intake, blood chemical analyses are performed, which reveal the diagnosis.

Discussion

Diagnosis

Blood chemical analysis findings are notable for the following: glucose, 1,039 mg/dL (57.7 mmol/L); potassium, 5.2 mEq/L (5.2 mmol/L); bicarbonate, 15 mEq/L (15 mmol/L); anion gap, 19; blood urea nitrogen, 27 mg/dL (9.6 mmol/L); and creatinine, 0.8 mg/dL (71 μmol/L). A urinalysis reveals a specific gravity of 1.030, a glucose level of 3+, and a ketone level of 1+. The C-peptide level is low at less than 0.10 ng/mL (<0.03 nmol/L), and the β-hydroxybutyrate level is normal at 0.52 mg/dL (50 μmol/L). These laboratory results reveal hyperglycemia, anion gap metabolic acidosis, and prerenal acute kidney injury. She is diagnosed as having neonatal diabetes mellitus, classified as nothing-by-mouth status, and given an insulin infusion at 0.05 U/kg per hour. Half normal saline and 5 mEq/kg of potassium chloride fluids are administered to give total daily volumes of 200 mL/kg to correct dehydration from hyperosmotic diuresis. Glucose levels are checked every 3 hours. Dextrose fluids (glucose infusion rate, 7 mg/kg per minute) are administered 3 hours later when blood glucose levels start decreasing too rapidly at a rate of greater than 150 mg/dL per hour. To limit the rate of decrease of the glucose and, later, to maintain glucose levels of 100 to 200 mg/dL (5.6–11.1 mmol/L), insulin is adjusted to 0.02 to 0.1 U/kg per hour, and dextrose fluids are titrated. When her anion gap closes and feeds are resumed, the insulin rate is increased by 0.01 U/kg per hour during feeds to maintain glucose goals.

Abdominal ultrasonography is performed and reveals no signs of pancreatic agenesis. Given her paucity of subcutaneous fat, she requires continuous intravenous insulin until 3 weeks after birth when she is able to transition to long-acting subcutaneous insulin. A chromosomal microarray identifies microduplication of chromosome 6 at 6q24, suggesting a diagnosis of transient neonatal diabetes. At 2 months, she exceeds the fifth weight percentile and is successfully weaned off insulin.

The Condition

Neonatal diabetes mellitus is a rare metabolic condition that has an incidence of approximately 1 in 300,000 live births. It is thought to be a nonautoimmune process that results from altered expression of imprinted genes on chromosome 6, causing delayed maturation of pancreatic islets and β-cells. Because insulin normally functions as a fetal growth factor, IUGR is thought to be a result of insulin deficiency from lack of fetal production and failure of maternal insulin to cross the placental barrier. Diagnosis has been defined as hyperglycemia occurring within the first month after birth, lasts for at least 2 weeks, and requires insulin treatment.

Most patients present with low birth weight, failure to thrive, dehydration, low or undetectable C-peptide levels, and negative islet cell antibodies. It can present as transient neonatal diabetes mellitus (TNDM) or permanent neonatal diabetes mellitus (PNDM), depending on the duration of insulin dependence. TNDM occurs more frequently than PNDM (55% vs 45%) and is associated with IUGR and younger age at presentation. PNDM is more often associated with ketoacidosis. Patients with TNDM are on average able to stop insulin therapy at approximately age 3 months. Among infants with TNDM, relapse of diabetes during adolescence or adulthood occurs in 40% of patients and presents with common features of type 2 diabetes. Because recurrence of diabetes can occur after a period of remission, TNDM may be considered a prediabetic state; it is believed to be from a permanent β-cell defect with variable expression during different stages of growth. Roughly half of PNDM cases are associated with mutations in the potassium channel, and some may respond to sulfonylureas. Most of the mutations are de novo, and mutational analysis of chromosome 6 may serve as a tool to identify which patients likely have TNDM vs PNDM.

There are currently no universal guidelines for neonatal diabetes management. Treatment of neonatal diabetes is difficult given the paucity of subcutaneous fat in low-birth-weight infants; therefore, continuous intravenous insulin is the accepted first-line therapy, typically at a rate of 0.02 to 0.1 units/kg per hour. The long-term prognosis is good, and cognitive development is expected to be normal.

Lessons for the Clinician

- In an infant with IUGR, dehydration, and poor weight gain despite adequate caloric intake, reevaluation may reveal conditions such as neonatal diabetes mellitus.
- Treatment of neonatal diabetes mellitus includes continuous intravenous insulin infusion, intravenous hydration, and close monitoring of glucose and electrolytes.
- The diagnosis of transient neonatal diabetes mellitus has long-term implications, such as relapses of hyperglycemia and development of type 2 diabetes mellitus in adolescence.

Suggested Reading

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American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causes, including genetic and autogenic disorders, of neonatal hyperglycemia, including transient diabetes mellitus.
- Know the clinical and laboratory features and approach to therapy of neonatal hyperglycemia, including transient diabetes mellitus.