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Hyperinsulinism in a Neonate

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INITIAL COURSE AT REFERRING HOSPITAL

A male patient was born small for gestational age (SGA) at 33 weeks with a birth weight of 1,663 grams (< 10th percentile) and length 43 cm (10th percentile) to a 38-year-old G5P4 mother by cesarean section due to non-reassuring fetal heart tones. Prior to delivery, his mother experienced decreased fetal movement and decelerations. At birth, he was initially well-appearing and vigorous, with Apgar scores of 7 and 8 at 1 and 5 minutes, respectively. The physical examination was unremarkable — no skin findings, no facial anomalies, good tone, and the anterior fontanelle was soft and flat. The placenta, although noted to be healthy in appearance on prenatal ultrasounds, was atrophic and calcified by gross examination.

The patient developed respiratory distress 1 hour after birth and was found to have a blood glucose level of 24 mg/dL. Following an intravenous (IV) bolus of 10% dextrose in water (D10W) of 2 mL/kg, his glucose was 20 mg/dL. He was started on IV fluids with a glucose infusion rate (GIR) of 7.3 mg/kg/minute, with a subsequent rise in blood glucose to 46 mg/dL. Due to prematurity, respiratory distress, and persistent hypoglycemia, a diagnostic evaluation was initiated for possible sepsis, including a complete blood count with differential and platelet count and blood cultures. The patient was started empirically on IV ampicillin and gentamicin. The patient was subsequently found to have thrombocytopenia,

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hypomagnesemia, and hyponatremia on laboratory evaluation and was transferred to our neonatal intensive care unit (NICU) for further care.

NICU COURSE

After transfer, the patient was found to have a point-of-care (POC) glucose of less than 40 mg/dL on two occasions. Intravenous D10W boluses were given on each occasion, with subsequent rises in blood glucose to 49 mg/dL and 57 mg/dL, respectively; the glucose infusion rate (GIR) was then increased to 10 mg/kg/minute, soon changed from D10W to total parenteral nutrition (TPN). Subsequent blood glucose levels on TPN were 47 mg/dL to 139 mg/dL on a GIR as high as 11 mg/kg/minute. On day 7 after delivery, bolus feeds of breast milk fortified to 24 kcal/oz were initiated at 14 mL/kg/day in addition to TPN. The volume of feedings was gradually increased and TPN decreased accordingly, with pre-prandial blood glucoses of 57 mg/dL to 94 mg/dL during this period. On day 14 of life while taking feeds every 2 to 3 hours, he reached a feeding volume of 122 mL/kg/day, so the TPN was discontinued; however, he remained on IV D10 0.2 NS with GIR of 1.6 mg/kg/min. On day 15 of life, he had feeds every 3 hours and a pre-prandial POC glucose of 42 mg/dL was noted. Finally, on day 18 of life, all IV fluids were discontinued and oral feeds of 24 kcal/oz of fortified breast milk were given as 31 mL every 3 hours (145 mL/kg/day). When not on any IV fluids, however, he continued to experience hypoglycemia with blood glucose levels as low as 35 mg/dL; he was therefore started on continuous nasogastric feeds at a GIR of 7.5 mg/kg/minute. The hypomagnesemia and hyponatremia resolved without special intervention, and it was noted that diuresis increased by day 4 of life. The thrombocytopenia required two platelet transfusions and eventually resolved after treatment with IV immunoglobulin.

CASE DISCUSSION OF INITIAL COURSE AND FURTHER EVALUATION

An initial set of critical laboratory values were obtained at the time of a POC glucose of 44 mg/dL on day 20 of life, which revealed a serum glucose level of 37 mg/dL, serum ketone (beta-hydroxybutyrate) level of 0.37 mmol/L, insulin level of less than 2 uIU/mL, C-peptide level of 0.04 pmol/mL, lactic acid level of 1 mEq/L, free fatty acid level of 0.58 mmol/L, cortisol level of 25.2 mcg/dL, and growth hormone level of 13 ng/mL (Table 1). Several subsequent critical samples sent when serum glucoses were 40 mg/dL to 53 mg/dL also showed insulin levels of less than 2 uIU/mL. Acylcarnitine profile, urine organic acid levels, and thyroid studies were unremarkable. The initial diagnosis was hypoglycemia secondary to low glycogen stores due to prematurity and SGA status, as insulin levels were appropriately suppressed and ketones were detectable during hypoglycemic episodes, and levels of cortisol, growth hormone, and lactic acid were appropriate. Continuous feeds were re-initiated, and a “wait and watch” approach was taken, whereby the patient would presumably gain weight and build up glycogen stores that would prevent hypoglycemia. However, on day 33 of life he had another episode of hypoglycemia with a POC glucose of 47 mg/dL and confirmatory serum glucose of 40 mg/dL while on continuous feeds with GIR of 8.8 mg/kg/min. Given this episode of hypoglycemia occurred while on an adequate GIR, the presumptive diagnosis of poor stores was reconsidered and further evaluation for possible hyperinsulinism was initiated. An intramuscular injection of 0.5 mg glucagon was

administered during the next hypoglycemic episode, with a POC glucose of 37 mg/dL and corresponding serum glucose of 38 mg/dL. Subsequent POC glucose levels assessed at 10, 20, and 30 minutes post-injection were 55 mg/dL, 59 mg/dL, and 71 mg/dL, respectively, with corresponding serum glucose levels of 51 mg/dL, 55 mg/dL, and 65 mg/dL, respectively (total change of +27 mg/dL). An insulin-like growth factor binding protein 1 (IGFBP-1) level drawn during this hypoglycemic episode was 70 ng/mL. The rise in glucose following the glucagon challenge suggested the presence of adequate glycogen stores, whereas the relatively low IGFBP-1 level was consistent with the suppressive effect of insulin. Therefore, the patient was diagnosed with hyperinsulinism (HI), which was thought to be likely transient and associated with perinatal stress.

SUBSEQUENT CLINICAL COURSE

The infant was started on diazoxide 8 mg/kg/day while tolerating fortified breast milk via continuous nasogastric feeds at 14 mL/hr. Four hours after the first dose, and 2 hours off of continuous feeds, the patient's glucose level was 42 mg/dL, so the dose was increased to 10 mg/kg/day; thereafter, he maintained blood glucose levels of greater than 70 mg/dL on every 2-hour and then every 3-hour feeds. After he had been on this dose of diazoxide for 5 days, and was thus likely to be at steady-state levels, a fasting challenge to document safe glucose levels over 8 hours was initiated. POC glucose levels were assessed as follows: 113 mg/dL at 3 hours, 56 mg/dL at 5 hours, 72 mg/dL at 6 hours, 69 mg/dL at 7 hours, and 68 mg/dL at 8 hours. After 8 hours, the serum glucose was 59 mg/dL and serum ketones were 0.23 mmol/L. Given the slightly low glucose level and lack of significant ketone production by the end of the fast, the dose of diazoxide was increased to 12 mg/kg/day, and he was discharged on this dose. At his first outpatient visit, he was maintaining appropriate blood sugars of >70 mg/dl at home on diazoxide with PO ad lib feeding. The future plan was to increase the diazoxide dose only if needed for low blood sugars, otherwise to allow him to outgrow the dose and eventually schedule a repeat fast off of diazoxide to prove resolution of HI.

DISCUSSION

The physiologically normal range of fasting glucose at all ages is 70–100 mg/dL; however a threshold level of blood glucose considered to be sufficiently low to diagnose hypoglycemia and prompt further evaluation has not been universally agreed upon, although most reports in the literature cite levels of 45–55 mg/dL or less.^{1,2} Hypoglycemia in the neonatal period can be caused by sepsis or other hypermetabolic states, glycogen storage diseases, fatty acid oxidation disorders, disorders of gluconeogenesis, deficiencies of pituitary hormones, limited glycogen stores, and hyperinsulinism.^{3,4} Hyperinsulinism can be congenital or transient. The congenital forms result from mutations in at least 8 different genes essential for the regulation of insulin secretion from pancreatic beta-cells, where dominant or recessive mutations in the genes (*ABCC8* and *KCNJ11*) encoding the two subunits of the ATP-sensitive potassium (KATP) channel are most common.⁵ Transient HI is often diagnosed in infants of diabetic mothers but can also occur in association with perinatal stress, which leads to HI by uncertain mechanism(s).^{2–6} Factors associated with perinatal stress HI may include intrauterine growth restriction, cesarean section delivery, and birth

asphyxia.⁷ The placental calcification and atrophy of the placenta in this specific case may have contributed to stress of the newborn by decreased oxygen and nutrient delivery secondary to placental insufficiency.

One set of guidelines lists the following “critical sample” results as suggestive of hyperinsulinism when obtained during hypoglycemia (most often < 50 mg/dL): hyperinsulinemia (plasma insulin > 2 μ U/mL, depending on sensitivity of insulin assay — note that the absence of hyperinsulinemia does not rule out hyperinsulinism); hypofattyacidemia (plasma-free fatty acids <1.5 mmol/L); hypoketonemia (plasma beta-hydroxybutyrate < 2 mmol/L); glycemic response to 1 mg intravenous glucagon (change in glucose >30 mg/dL); and glucose requirement to maintain euglycemia greater than 8 mg/kg/min.⁸ It should be noted that none of these criteria are absolute, but rather all information should be taken together in the context of clinical suspicion. Other guidelines suggest glucose levels of 45 mg/dL to 55 mg/dL or lower as prompting further evaluation by obtaining a critical sample. However, it is worth noting that POC glucose measurements can be 10% to 20% inaccurate; this emphasizes the need for including a serum or plasma glucose level in the critical sample, which is the level that should be used for diagnosis. Most neonates will have a glucose requirement of less than 8 mg/kg/min to maintain euglycemia, but in cases with HI, the GIR can be as high as 20 mg/kg/min or higher. Ketones (best if measured by beta-hydroxybutyrate) and free fatty acid values will depend on the assay being used, but values that are on the lower end of normal or below may indicate HI, even if they are not completely suppressed.

The defining laboratory value of hyperinsulinism is not always a measurable elevation of insulin. Insulin levels fluctuate greatly because of the short half-life of 4 to 5 minutes and because it is rapidly cleared by the liver before it reaches the peripheral circulation. Two important studies documented the level of plasma insulin during hypoglycemic states in large groups of patients with transient HI. The first study noted that 22 of 27 (81%) of infants diagnosed with transient HI had elevated plasma insulin levels.⁴ In the second study, plasma insulin levels were elevated in only 11 of 24 (46%) of neonates with transient HI.⁷ These cases were diagnosed with hyperinsulinism on the basis of other evidence, including lack of ketosis in the setting of hypoglycemia, elevated glucose requirements, and glycemic response to glucagon.

Insulin levels were never documented as elevated during hypoglycemic episodes for the patient presented here. The hypoglycemia was initially felt to be secondary to poor glycogen stores; however, the occurrence of hypoglycemia while receiving continuous feeds with an adequate GIR (> 8 mg/kg/min) made this diagnosis less likely. Furthermore, the patient responded to glucagon with a substantial rise in glucose, suggesting that glycogen stores were present. Although his glycemic response to glucagon did not meet the suggested 30 mg/dL increment in serum glucose, this criterion was established in a population of subjects with congenital hyperinsulinism, which is typically more severe than transient hyperinsulinism. In fact, we noted that the average rise of glucose in response to glucagon was 71 mg/dL in subjects with congenital HI versus 40 mg/dL in subjects with transient HI, indicating that infants with transient HI have a less robust response to glucagon, and the cutoff point to establish a diagnosis of HI may be lower in these patients.^{7,9} Our patient also

responded to diazoxide, which acts to suppress insulin secretion by keeping beta-cell ATP-sensitive potassium channels open. On this medication, the infant showed improved glycemic control, with blood glucose levels consistently higher than 70 mg/dL on regular bolus feeds and relative glucose stability with fasting.

Another useful tool for the investigation of hyperinsulinism is insulin-like growth factor binding protein 1 (IGFBP-1), which is produced by the liver, where its secretion is inhibited by insulin. IGFBP-1 has been found to be greater than 85 ng/mL in patients without HI and less than 125 ng/mL in those with hyperinsulinism in the setting of fasting hypoglycemia.¹⁰ There is overlap in the 85 ng/mL to 125 ng/mL range; however, drawing an IGFBP-1 at the time of hypoglycemia provides strong evidence for HI if it is found to be less than 85 ng/mL and can also be suggestive if less than 125 ng/mL with other evidence of HI. Our patient had an IGFBP-1 level of 70 ng/mL at the time of hypoglycemia, which helped confirm the diagnosis of HI in this case.

In summary, in an infant with recurrent hypoglycemia, it is important to evaluate for possible etiologies by drawing a “critical sample” at the time of hypoglycemia (any time POC glucose is less than 45 mg/dL to 55 mg/dL), including a glucose level, insulin level, serum ketones (beta-hydroxybutyrate), cortisol, growth hormone, lactate, and free fatty acids. If the cortisol level is greater than 20 mcg/dL, and/or the growth hormone level greater than 10 ng/mL on any occasion, these need not be repeated on subsequent critical samples. Other evaluations that may be considered even during times of euglycemia include an ammonia level, acylcarnitine profile, serum amino acids, and urine organic acids. If pituitary hormone deficiencies and inborn errors of metabolism have been ruled out, it is important to consider hyperinsulinism. This remains true even when insulin levels are undetectable in the setting of hypoglycemia, and is especially important if there is a history of perinatal stress. If the insulin level during hypoglycemia is not diagnostic, a glucagon challenge should be initiated, as well as assessment of IGFBP-1 in the setting of hypoglycemia. Diazoxide is the treatment of choice for hyperinsulinism. Treatment should be continued until resolution of hypoglycemia. Resolution may take 18 to 403 days, with a median length of 181 days.⁶

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Table 1

Laboratory results from critical samples done during hypoglycemic episodes.

Day of Life	Serum Glucose (mg/dL)	Serum Ketones (mmol/L)	Free Fatty Acids (mmol/L)	Lactic Acid (mEq/L)	C-peptide (pmol/mL)	Insulin (uIU/mL)	Cortisol (mcg/dL)	GH (ng/mL)
20	37	0.37	0.58	1	0.04	<2	25.2	13.0
24	43	0.26		--	--	<2	12.8	10.6
29	53	0.25		--	--	<2	--	--
33	40	0.23		--	--	<2	--	--
34	38	0.21		--	--	--	--	--