RESIDENT ARTICLE

Hyperinsulinemic Hypoglycemia in an Infant with Partial Trisomy 13

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ABSTRACT

Hyperinsulinemic hypoglycemia is the most common cause of hypoglycemia that persists in infants, though clinical signs of hypoglycemia in this age can be subtle. Persistent hypoglycemia in infants can lead to neurologic consequences if not promptly identified and treated. Hyperinsulinemic hypoglycemia has also been associated with multiple genetic syndromes. A high index of suspicion is required to make the diagnosis of hyperinsulinemic hypoglycemia, as management differs from other causes of hypoglycemia. In this case report, we describe an 8-week-old infant with known partial trisomy 13 with persistent hypoglycemia despite intravenous dextrose boluses, found to have hyperinsulinemic hypoglycemia.

BACKGROUND

Hyperinsulinemic hypoglycemia (HH) is a condition characterized by increased insulin secretion from pancreatic beta-cells, even when blood glucose levels are low (serum glucose < 50 mg/dl). In infants and children, it is considered to be the most common cause of persistent hypoglycemia.[1] If blood glucose levels remain low and there are no other cellular substrates available such as lactate or ketones, there is an increased risk of neurological damage in these patients in the setting of cellular energy failure. HH has been associated with several genetic syndromes like Beckwith-Wiedemann Syndrome, Sotos Syndrome, Simpson-Golabi-Behmel-Syndrome, Kabuki Syndrome, Costello Syndrome, Mosaic Turner Syndrome, and has rarely also been reported in cases of Trisomy 13.[1] Here we present a case of an 8-week-old male born at 37 weeks gestation with partial trisomy 13 due to an unbalanced translocation of chromosome 13 and 17, found to have HH.

Objective: To describe the presentation, pathophysiology, and management of an 8-week-old infant with partial trisomy 13 presenting with apnea and feeding difficulties, found to have hyperinsulinemic hypoglycemia.

SUBJECT PRESENTATION

An 8-week-old male born at 37 weeks gestation following a pregnancy complicated only by multiple urinary tract infections, presented to the emergency department with feeding difficulties and apneic episodes. He had a history of partial trisomy 13 due to an unbalanced translocation between chromosomes 13 and 17, a patent foramen ovale and a small ventricular septal defect, and a brief neonatal ICU admission after birth for hypoglycemia requiring orogastric feeds and intravenous dextrose infusion. The hypoglycemia resolved without any additional evaluation. After discharge, he developed feeding difficulties and often had associated coughing, gurgling, and choking spells. An outpatient swallow study showed silent aspiration. He also developed self-resolving episodes of apnea associated with perioral cyanosis. On initial presentation to the emergency department for these symptoms, his examination was normal except for subtle dysmorphic features, including low set ears, a broad nasal bridge, micrognathia and hypospadias. There were no obvious midline abnormalities, no hepatomegaly and the penile size was normal for age. Complete blood count and comprehensive metabolic panel were normal on admission except a serum glucose of 48 mg/dL. He received intravenous fluids containing 5% dextrose and blood glucose normalized. He had an upper GI series done which showed intestinal malrotation and tracheomalacia. He was started on nasogastric bolus feeds. Several hours after admission he had an episode of left eye deviation, upper extremity stiffening and perioral cyanosis concerning for seizure. Serum glucose was 43 mg/dL at the time of this episode, at which point critical hypoglycemia labs were obtained. He was noted to have an elevated insulin level of 30.7 IU/ml, beta-hydroxybutyrate level 0.27 mmol/L, cortisol level 12.77 mcg/dL and growth hormone level 1.84 ng/ml. Additional evaluation for seizure including prolonged EEG was normal and a MRI brain did not reveal structural brain abnormalities, patient had cavum septum pellucidum and a normal corpus callosum.

Over the next 12 hours, the patient received three 10% dextrose fluid boluses which transiently improved blood glucose levels before hypoglycemia recurred. Pediatric Endocrinology was consulted, and he was diagnosed with HH. He was started on continuous nasogastric feeds and oral diazoxide 10 mg/kg/day divided TID to which he responded well with resolution of hypoglycemia. It was also recommended to avoid additional bolus dextrose infusions to prevent worsening of hypoglycemia, due to increased insulin secretion in response to the sudden exposure to increased glucose concentrations. Additionally, during his hospitalization, he underwent a Ladd's procedure and gastrostomy tube placement for the malrotation and aspiration. A bronchoscopy was done which showed severe tracheomalacia and left bronchomalacia, and he required high-flow-nasal cannula support for persistent apnea episodes. He developed significant generalized edema, a known side effect of diazoxide, treated initially with furosemide. Subsequently, thiazide diuretics were added to his regimen. While his blood glucose levels stabilized with gastrostomy tube feedings and diazoxide, he was ultimately transferred to a specialized children's center for definitive management of recurrent apnea given underlying airway abnormalities.

DISCUSSION

Glucose is one of the body's major energy substrates, and blood glucose concentration is regulated by metabolic hormones. Insulin is the hormone responsible for decreasing blood glucose levels. Blood glucose levels are increased by catabolic hormones including glucagon, cortisol, and catecholamines.[1]

Hyperinsulinemic hypoglycemia is the most common cause of persistent hypoglycemia in infants.[1] In HH, there is an increase in insulin secretion from pancreatic beta-cells, even when plasma glucose concentrations are low. This condition can be potentially life-threatening, leading to significant neurological damage due to the lack of glucose as fuel for neurons.[2]

HH can be transient or permanent in the pediatric population. Transient forms usually resolve within a few days to a week, although in some children it can persist for up to six months.[1] The transient forms of HH have been associated with intrauterine growth restriction, perinatal stress, erythroblastosis fetalis, and maternal diabetes mellitus.[1,3] The permanent form of HH occurs when children continue to require treatment beyond six months of age. The permanent cause is most commonly congenital, to date there have been at least 15 genes associated with congenital hyperinsulinemic hypoglycemia including ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, UCP2, HNF1A, HNF4A, HK1, PGM1, PMM2, FOXA2, CACNA1D, and EIF2S3.[3] There are three histological forms of congenital hyperinsulinemic hypoglycemia (CHH). Focal CHH occurs when one area of the pancreas has abnormal pancreatic beta-cells, diffuse CHH occurs when all pancreatic islets are affected, and atypical CHH occurs when there is a mosaic pattern of focal and diffuse CHH.[1,3]

HH most commonly presents in infancy and childhood. In infancy, HH can present as irritability, jitteriness, or poor feeding.[3] Our patient presented with poor feeding and post-prandial apneic episodes. However, as apnea persisted after stabilization of blood glucose levels, his presenting symptoms were likely multifactorial and also related to aspiration and airway malacias.

HH can become apparent during periods of fasting but may also be precipitated by a meal.[3] Hypoglycemia that occurs while an infant receives an intravenous dextrose infusion is strongly suggestive of hyperinsulinemic hypoglycemia. HH can be diagnosed by the presence of detectable insulin or C-peptide in the setting of hypoglycemia with simultaneous low or undetectable levels of other cellular fuels like ketones.[4]

The management of HH involves achieving normoglycemia acutely with the help of continuous enteral feeds and/or continuous intravenous fluids containing dextrose and if severe, the use of intramuscular or subcutaneous glucagon, and maintaining normoglycemia chronically with the help of medical or surgical interventions. Diazoxide is the first drug of choice. Its mechanism of action is promotion of the opening of potassium-gated ATP channels, thus inhibiting the pancreatic secretion of insulin.[5] Nifedipine and octreotide have been reported to work in diazoxide-unresponsive HH.[3] Long acting somatostatin analogues like lanreotide and mTOR inhibitors like sirolimus have also recently shown to be beneficial in diffuse-CHH.[6] In cases unresponsive to medical management, surgical removal of part of the pancreas in focal-CHH, or near-total pancreatectomy in diffuse-CHH are the treatment modalities of choice.[3]

CONCLUSION

Hyperinsulinemic hypoglycemia is caused by increased insulin secretion by the pancreas in the context of low plasma glucose concentrations. It has been reported in several genetic syndromes to date and there have been reports of the same being managed by continuous glucose infusions and medical management as was done in our patient. The most critical factor in management of HH is the avoidance of wide fluctuations in the serum glucose by avoiding boluses of dextrose or a rapid wean of the supplemental source of glucose, as this can worsen hypoglycemia in response to the surge of insulin secretion. Patients with HH require high diagnostic suspicion and early intervention due to the risk of permanent neurological damage with recurrent hypoglycemia early in life.[2] These patients benefit from home blood glucose monitoring and careful medication dose titrations based on clinical response, and upon discharge from the hospital should be followed closely by a pediatrician and a team specialized in pediatric endocrinology.

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