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Hypoglycemia Due to Hyperinsulinism in Infants and its Conservative Treatment

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Annotation. *Normal brain function depends on a continuous supply of glucose, the principal metabolic fuel of the human brain, from the blood stream. Low plasma glucose concentrations, and as a consequence, low brain glucose availability result in cerebral energy failure, neuronal death, and irreversible brain damage. The developing brain is particularly vulnerable to the deleterious effects of hypoglycemia, as demonstrated by the high frequency of neurodevelopmental deficits in children with congenital hypoglycemia disorders. Thus it is critically important to screen, identify, and treat neonates with persistent hypoglycemia.*

Keywords. *development, facilitated, diffusion*

During fetal development, facilitated diffusion of glucose from the maternal circulation to the fetal circulation guarantees an appropriate supply of glucose to the fetus. The abrupt interruption of maternal glucose transfer to the baby at delivery imposes a need for the newborn infant to independently control plasma glucose concentrations by adjusting insulin secretion and mobilizing counterregulatory responses. These “fasting systems” are intact and functional in the newborn period and provide defense against hypoglycemia when working properly. The “fasting systems” include hepatic glycogenolysis, hepatic gluconeogenesis, and fatty acid oxidation. These processes are all coordinated by endocrine counterregulatory hormones; insulin suppresses these processes whereas glucagon, cortisol, epinephrine, and growth hormone are stimulating. Fasting adaptation’s essential function is to maintain the brain’s fuel supply. The redundancy in hormonal signaling provides for additional layers of security to prevent hypoglycemia. Hepatic glycogenolysis provides energy for only a few hours; beyond that, hepatic gluconeogenesis provides glucose for energy requirements. During extended fasting, lipolysis and fatty acid oxidation mobilize fatty acids and generate ketones as an alternative fuel source for the brain. Hypoglycemia beyond the immediate newborn period is often a consequence of a defect in fasting adaptation.

It is essential to identify neonates with hypoglycemic disorders prior to newborn hospital discharge, because there is a high risk of long-term morbidity. Specifically, persistent and repeated episodes of hypoglycemia in the neonatal period lead to irreversible brain injury and developmental disabilities. In addition to prompt stabilization, early identification of the precise etiology of hypoglycemia allows for tailored interventions to minimize hypoglycemic events and ultimately improve long-term outcomes.

There is a transitional period immediately after birth when mean plasma glucose concentrations fall in normal newborn infants from 70 to 80 mg/dL (close to maternal glucose values) to 55 to 60 mg/ dL. There is evidence that suggests that this transitional period of lower glucose concentrations in normal

newborns is explained by a lower threshold for glucose-stimulated insulin secretion and thus should be considered as “transitional neonatal hyperinsulinism.” This includes observations that during the period that plasma glucose is low in normal newborns, lipolysis and ketogenesis are suppressed and liver glycogen reserves are maintained, as shown by the large glycemic responses elicited by administration of glucagon or epinephrine. An important feature of transitional neonatal hypoglycemia in normal newborns is that the hypoglycemia progressively improves over the first few days of life and the plasma glucose concentration reaches the normal range for older infants and children by the third to fourth day of life. Additionally, the plasma glucose concentration in transitional hypoglycemia is impressively stable and relatively unaffected by initial feeds, which has been demonstrated in multiple studies. Of prime importance, however, is that transitional neonatal hypoglycemia is self-limited, and in the absence of other factors, the hypoglycemia should resolve within the first 3 days of life as the threshold for glucose-stimulated insulin secretion rises and fasting adaptation mechanisms become fully functional.

The process of beta cell maturation after birth may be impacted by perinatal factors resulting in a prolongation of this state of hyperinsulinism. This is a specific entity known as perinatal stress-induced hyperinsulinism, a distinct form of hyperinsulinism that spontaneously resolves within the first few weeks of life, although it sometimes persists for a few months. Perinatal factors associated with perinatal stress-induced hyperinsulinism include birth asphyxia, maternal preeclampsia, prematurity, intrauterine growth retardation, and other peripartum stress. Up to 50% of neonates in these at-risk categories may be affected. Hyperinsulinism secondary to perinatal stress can be as severe as the genetic permanent forms and is also associated with a high risk for neurodevelopmental deficits.

Hyperinsulinism is the most common cause of persistent hypoglycemia in neonates. The biochemical profile of hyperinsulinism includes detectable insulin and C-peptide, suppressed β-hydroxybutyrate and free fatty acids, and an inappropriate positive response to glucagon. Laboratory assays are not always able to detect an elevated insulin level due to the limitations of the assays with the threshold of detection, so obtaining other supportive diagnostic data is imperative. Because neonatal hypopituitarism can closely resemble hyperinsulinism, growth hormone and cortisol assays should be obtained, and if values are insufficient, further provocative simulation testing to assess for central growth hormone and adrenal insufficiency should be pursued if deficiency is suspected. Hyperinsulinism is caused by dysregulated insulin secretion from the pancreatic β-cells and can be the result of perinatal factors (perinatal stress–induced HI), syndromic (as in Beckwith-Wiedemann syndrome), or monogenic, due to mutations in genes important for the regulation of insulin secretion. The most common and severe type of congenital hyperinsulinism is due to inactivating mutations in ABCC8 or KCNJ11, which cause dysfunction in the pancreatic β-cell ATP-sensitive potassium (KATP) channel, resulting in dysregulated insulin secretion. Other causes of congenital hyperinsulinism are mutations in genes encoding different proteins involved in insulin secretion from the β-cells, including activating mutations in glutamate dehydrogenase (GLUD1) and glucokinase (GCK). In addition to monogenic forms of congenital HI, hyperinsulinism is associated with certain syndromes, most notably Beckwith-Wiedemann syndrome. In contrast to genetic congenital etiologies, hyperinsulinism can also be transient, occurring as a result of perinatal stressors. This distinct form of transient HI, known as perinatal stress–induced HI, typically responds to treatment with diazoxide and spontaneously resolves within the first few months of life.5 Hyperinsulinism due to perinatal stress is quite common, affecting up to 50% of at-risk neonates exposed to perinatal stressors. Perinatal stress–induced hyperinsulinism is often perceived as less severe than permanent congenital HI, but children with perinatal stress– induced hyperinsulinism are also at risk for severe hypoglycemia and long-term neurologic sequelae.

Once a diagnosis of hyperinsulinism is established, the short-term goal should be to maintain plasma glucose greater than 70 mg/dL. This can be accomplished with an intravenous glucose infusion.

If high glucose infusion rates are required to maintain normoglycemia, central access should be obtained in order to administer fluids with a higher dextrose concentration and thus minimize fluid overload. In severe cases, a glucagon infusion can be employed, which will temporarily decrease the glucose requirement. There are limited available medical treatments for hyperinsulinism. Diazoxide is the only drug approved by the Food and Drug Administration for the treatment of hyperinsulinism. Diazoxide opens the KATP channel and thereby inhibits insulin secretion. Side effects include hypertrichosis (prevalence, 26%–30%), fluid retention (prevalence, 5.5%–16%), pulmonary hypertension (prevalence, 2.4%–4.8%), bone marrow suppression (prevalence, 15%), and hyperuricemia (prevalence, 5%). To avoid fluid retention, all patients should be started on chlorothiazide at the start of diazoxide treatment, typically at twice the dose of diazoxide, rather than wait for symptoms to occur to begin treatment. Concurrent initiation of chlorothiazide decreases risk of fluid overload and secondary respiratory effects. The PES therapeutic committee has recently published practice guidelines for dosing and monitoring for adverse events in infants treated with diazoxide, which includes tailoring the dose according to the suspected type of hyperinsulinism, i.e., transient versus permanent; a comprehensive evaluation of cardiopulmonary health; and consideration of a baseline echocardiogram. Determining diazoxide responsiveness should be done expeditiously once a diagnosis of hyperinsulinism is established, because the response indicates which infants require a more specialized evaluation. It takes up to 5 days for diazoxide to reach a steady state, and waiting to assess for improved fasting tolerance is recommended, with titration to maximum diazoxide dosing of 15 mg/kg/day, divided twice daily as necessary. Not all forms of hyperinsulinism are diazoxide responsive, and given the side-effect profile, discontinuation of diazoxide is recommended if there is minimal or no response. If a neonate with hyperinsulinism is found to be diazoxide unresponsive, the patient should be transferred to a congenital hyperinsulinism center for further specialized intervention.

Somatostatin analogs are second-line agents used for treatment of hyperinsulinism, due to their insulin inhibitory effects. Octreotide is most commonly used, although treatment failure is not uncommon due to tachyphylaxis. Unfortunately, necrotizing enterocolitis is a concerning known treatment risk, and thus use in neonates is limited. Other side effects of somatostatin analogs include transaminitis, gallstones, hypothyroidism, poor growth, and diarrhea. Glucagon can be used as a short-term agent via continuous infusion of 1 mg per day in infants requiring surgery, to decrease dextrose requirement and thus lessen fluid burden. As a general rule, using feeds to maintain glycemic control is not recommended, because this increases risk for future feeding difficulties, such as oral aversions, and excessive weight gain from overnutrition.

In conclusion, persistent neonatal hypoglycemia is an important cause of long-term morbidity, and thus persistent hypoglycemia disorders should be distinguished from transitional neonatal hypoglycemia. Providers must maintain a high index of suspicion for an underlying hypoglycemia disorder, particularly if hypoglycemia persists beyond the first 2 to 3 days of life or if an infant has risk factors for a hypoglycemia disorder. In the initial days of life, management should be directed toward maintaining glucose stability, and further evaluation with a diagnostic fast should be deferred until after the period of transitional neonatal hypoglycemia is over.

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