Hyperinsulinism

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Hyperinsulinism (HI), the most common cause of hypoglycemia in children, is an excess of insulin secretion from the pancreatic β cells, and it can be congenital or acquired. Congenital HI, which can be transient or persistent, is associated with a risk of permanent brain injury as high as 25% to 50% if there is a delay in diagnosis or inadequate treatment, making early recognition essential. Brain damage occurs because insulin functions to decrease glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis, all of which deprive the brain of its primary and secondary energy sources (glucose and ketone bodies). A plasma glucose (PG) level less than 50 mg/dL (<2.8 mmol/L), a detectable serum insulin level, a low plasma β-hydroxybutyrate level less than 2.0 mmol/L, and low free fatty acid levels less than 42 mg/dL (<1.5 mmol/L) are diagnostic of HI.

The incidence of congenital HI varies between 1 in 50,000 births in Holland and 1 in 2,500 in Saudi Arabia. Sixty percent of patients are diagnosed in the first week of life, 30% in the first year of life, and 10% in adulthood. Because HI often presents in the neonate, it is important to differentiate it from transitional hypoglycemia of infancy, which is a physiologic transition of glucose regulation as infants adapt to extrauterine life. Normally, neonates initially maintain PG levels at 55 to 65 mg/dL (3.1–3.6 mmol/L), which increases to greater than 70 mg/dL (3.9 mmol/L) by 2 to 3 days after birth with little variation in relation to time from last feed. When it occurs, transitional hypoglycemia of infancy lasts 12 to 24 hours, is not associated with brain damage, and usually appears in appropriate-for-gestational age babies who are nondistressed.

Transient HI occurs in certain high-risk infants: premature infants, infants of diabetic mothers or mothers with a history of toxemia, small- or large-for-gestational age infants, and infants who have experienced difficult birth/birth asphyxia. Sulfonylureas or intravenous glucose infusions administered to mothers during labor can also cause transient HI. Symptoms in infants, often subtle, include jitteriness, tachycardia, pallor, hypothermia, lethargy, irritability, poor feeding, cyanosis, tachypnea, apnea, weak/high-pitched cry, floppiness, eye rolling, lip smacking, and seizures. Older children experience tremulousness, anxiety, tachycardia, palpitations, sweating, paresthesia, hunger, and behavioral changes.

In addition to HI, the differential diagnosis for hypoglycemia includes hormonal deficiencies (growth hormone and cortisol), inborn errors of metabolism, fatty acid oxidation defects, exogenous insulin administration, insulinomas, dumping syndrome–associated hypoglycemia, and drug ingestions. Associated clinical features and family history can often help guide the diagnosis: for example, midline facial defects and micropenis suggest hypopituitarism, and hepatomegaly raises concern for a glycogen storage disease. The presence of certain syndromes and hypoglycemia occurring less than 4 to 6 hours from the last feed suggest HI.

The Diagnosis and Management of Hyperinsulinaemic Hypoglycaemia. Rozenkova K, Guemes M, Shah P, Hussain K. *J Clin Res Pediatr Endocrinol*. 2015;7(2):86–97

Perspective on the Genetics and Diagnosis of Congenital Hyperinsulinism Disorders. Stanley CA. *J Clin Endocrinol Metab*. 2016;101(3):815–826

Congenital Hyperinsulinism: Current Status and Future Perspectives. Yorifuji T. *Ann Pediatr Endocrinol Metab*. 2014;19(2):57–68

The most common syndrome associated with HI is Beckwith-Wiedemann syndrome (BWS) (Table), a fetal overgrowth syndrome caused by an imprinting defect in the chromosome 11p15.5 region. HI in BWS, which occurs in approximately 50% of patients, is usually transient but can be persistent and severe, and it is thought to be secondary to loss of function of KATP channels, leading to dysregulated insulin secretion. HI is also associated with Kabuki syndrome, Turner syndrome, and multiple endocrine neoplasia syndromes, as well as Sotos, Costellos, Simpson-Golabi-Behmel, and Usher syndromes, and also trisomy 13 and congenital disorders of glycosylation.

Because plasma insulin levels are often not definitively elevated, the diagnosis of HI depends on obtaining blood at

TABLE. **Genetic Mutations Associated with Hyperinsulinism**

CHANNEL	MUTATION	INHERITANCE	DIAZOXIDE RESPONSIVE	MODY	CLINICAL FEATURES	SYNDROME
KATP/SUR1	ABCC8	AR/AD/sporadic	– or +/– or –		Paternal transmission: resection	
KATP/Kir6.2	KCNJ11	AR/AD/sporadic	– or +/– or –			
GDH	GLUD1	AD	+		Hyperammonemia/leucine sensitive	
GCK	GCK	AD	–	Activating mutation HI/inactivating mutation MODY 2		
SCHAD	HADH1	AR	+			
UCP2	UCP2	AD	+			
HNF4A	HNF4A	AD	+	Type 1	LGA	
HNF1A	HNF1A	AD	+	Type 3		
MCT1	SLC16A1	AD	–		Hypoglycemia triggered by exercise	
HK1	HK1	AD	+			
PGM1	PGM1	AR	–			
KATP	IGF2/H19/ CDKN1C/ KCNQ1	Sporadic	+/–		Omphalocele, macroglossia, macrosomia, renal abnormalities, and visceromegaly	BWS
Kabuki	KMT2D/KDM6A	Sporadic	+/–		Long palpebral fissure, arched eyebrows, eversion of the external one-third of the lower lid, skeletal abnormalities, neurodevelopmental delay and intellectual disabilities, abnormal GH and thyroid levels, and premature thelarche	
CDG1a	PMM2	AR	+			
CDG1b	MPI	AR				

AD=autosomal dominant, AR=autosomal recessive, BWS=Beckwith-Wiedemann syndrome, CDG=congenital disorders of glycosylation, GCK=glucokinase, GDH=glutamate dehydrogenase, GH=growth hormone, HI=hyperinsulinism, HK=hexokinase, HNF=hepatocyte nuclear factor, KATP=potassium adenosine triphosphate, LGA=large for gestational age, MCT=monocarboxylate transporter, MODY=maturity onset diabetes of the youth, PGM1=phosphoglucomutase, SCHAD=short chain 3-hydroxyacyl CoA dehydrogenase deficiency, SUR=sulfonylurea, UCP2=uncoupling protein.

the time of hypoglycemia for pertinent laboratory testing. When the PG level is less than 50 mg/dL (2.8 mmol/L), serum insulin, C-peptide, bicarbonate, lactate, free fatty acid, and β-hydroxybutarate levels should be measured. Cortisol and growth hormone levels are also useful to rule out central hormone deficiency: both should be elevated at the time of hypoglycemia. After the critical sample is drawn, a glucagon stimulation test should be performed by administering 1 mg of glucagon, either intramuscularly or intravenously, and monitoring PG levels every 5 minutes for 30 minutes. A PG level increase of at least 30 mg/dL (1.7 mmol/L) after glucagon administration is consistent with HI.

The normal release of insulin in response to PG is a complex process. Initially, glucokinase in the β cells of the pancreas senses the glucose level. High glucose levels lead to increased expression of glucose transporters (GLUT2) on the β cell, which take up glucose. Glucose is then metabolized, causing an increase in the ratio of adenosine triphosphate (ATP) to adenosine diphosphate (ADP), leading to closure of the ATP-dependent potassium (KATP) channels in the β-cell membrane. The rise in the ATP to ADP ratio causes membrane depolarization and influx of cellular calcium, and leads to fusion and secretion of insulin outside the cell. In addition to the KATP channel, there are other proteins in the β cell that help with normal insulin secretion. A mutation affecting any of these steps can dysregulate insulin secretion, so looking for a genetic etiology in the presence of hyperinsulinemic hypoglycemia has become the standard of care (Table).

Some genes associated with congenital HI can also lead to monogenic diabetes (maturity-onset diabetes of the young). Examples include inactivating mutations in glucokinase or in hepatocyte nuclear factors 1A and 4A, which lead to congenital HI, which then transitions to monogenic diabetes in adulthood. Also, a mutation that activates KATP channel subunits can cause either severe neonatal diabetes or a mildly increased susceptibility to adult-onset diabetes.

Goals of treatment in congenital HI include maintaining a PG level greater than 70 mg/dL (3.9 mmol/L) and establishing a normal feeding regimen with a tolerance for fasting appropriate for age. Acutely, blood glucose levels must be stabilized to prevent brain damage and to allow time for further diagnosis so that specific therapy can be initiated, which may include dietary, medical, or surgical approaches. Parenteral glucose may be necessary, often at rates as high as 15 to 25 mg/kg per minute. If the child with HI also has a feeding disturbance, food aversion, or gastroesophageal reflux disease, food may need to be given via nasogastric tube to maintain euglycemia. With emergent hypoglycemia, glucagon can be administered at a dose of 0.5 to 1.0 mg subcutaneously or intramuscularly.

When possible, the long-term management of HI benefits from the expertise at a tertiary care center (Fig). Treatment depends on whether the patient is diazoxide responsive. Management in diazoxide-unresponsive patients may depend on genetic testing for a mutation underlying the congenital HI. Diazoxide is the first-line treatment for controlling hypoglycemia. It works by causing KATP channels to open, thereby reducing insulin secretion; however, it is ineffective with diffuse disease from inactivating mutations in ABCC8 and KCNJ11 (Table). Diazoxide is started at a dose of 5 to 15 mg/kg per day divided twice per day, to a maximum dose of 20 mg/kg per day. Before a patient is labeled as unresponsive, diazoxide should be given at the maximum dose for 5 days. Adverse effects of diazoxide use include hypertrichosis (reversible once off therapy) and fluid retention, which can be especially problematic in infants, leading to congestive heart failure and pulmonary hypertension. Chlorothiazide (5–10 mg/kg per day in 2 divided doses) is often started at the same time as diazoxide to mitigate fluid retention and has the advantage of also suppressing insulin secretion.

For diazoxide-unresponsive HI, octreotide is a long-acting somatostatin analog that binds the SSTR5 receptor and reduces insulin synthesis in pancreatic β cells. The recommended dose is 5 to 35 μg/kg per day given subcutaneously in divided doses or by continuous infusion. Tachyphylaxis occurs but is transient. Octreotide therapy can have serious adverse effects, including abdominal pain, nausea, diarrhea, hepatitis, long QT, and necrotizing enterocolitis. With severe HI, glucagon can be used in combination with octreotide, both acutely and as a long-term infusion. A recent report describes 2 patients unresponsive to diazoxide and octreotide who were successfully treated with sirolimus, also known as rapamycin. Exendin, a glucagon-like peptide receptor antagonist, may have a role to play in managing hypoglycemia from HI.

Indications for surgery in congenital HI include focal disease confirmed by Fluoro-18-L-Dihydroxyphenylalanine positron emission tomography/computed tomography (18F-DOPA PET/CT) and medically unresponsive diffuse disease. Focal disease is treated with partial pancreatectomy, often performed laparoscopically if the lesion is located in the body or tail of the pancreas.

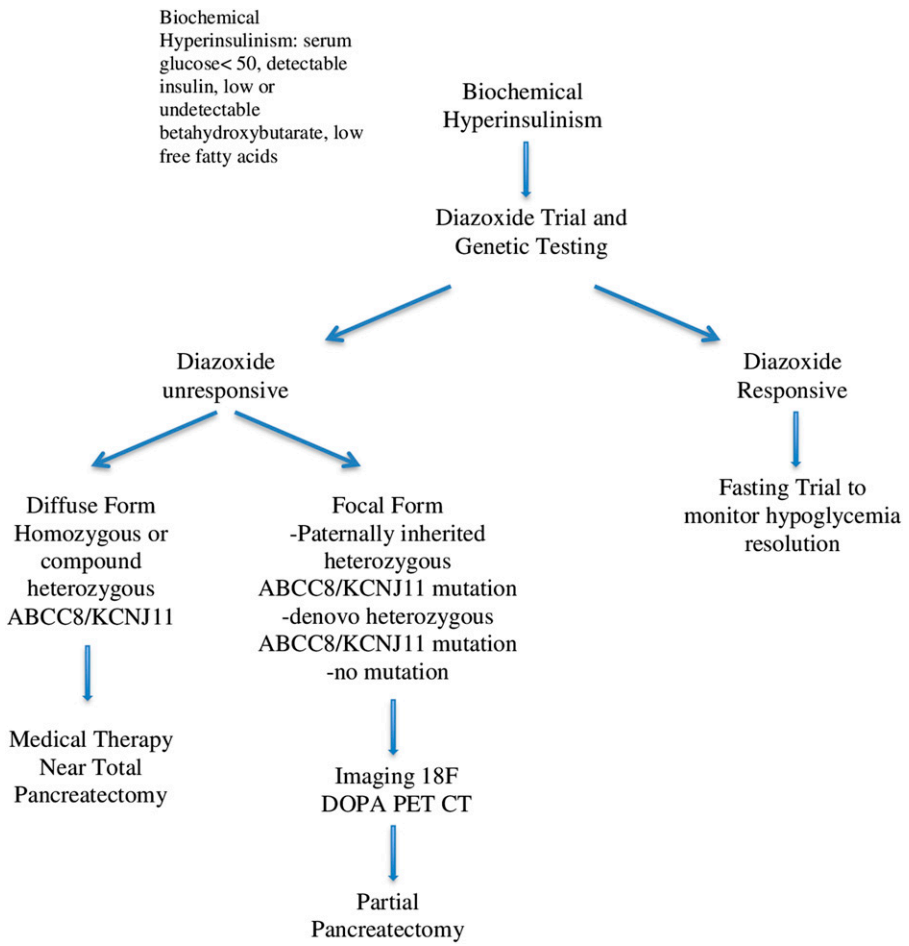

Figure. Algorithm for treatment of hyperinsulinism.

Near-total pancreatectomy is the last resort for medically unresponsive diffuse HI. Patients often continue to experience hypoglycemia even after 95% to 98% pancreatectomy, but the hypoglycemia is likely to be less frequent or severe. Surgery entails a high risk of exocrine pancreatic insufficiency and diabetes mellitus.

COMMENT: With an incidence estimated to be 1 of 13,700 births, BWS is relatively rare, but, as Drs Long and Akhtar report, it is the most common syndrome associated with HI. This interesting syndrome also has multiple other associations, as evidenced by the number of times it is mentioned even in other *In Briefs* that I have personally edited (Abdominal Masses, Apnea, Cushing Syndrome, Growth, Neonatal Hypoglycemia, Tuberculosis, Tumor Markers, Wilms Tumor), as well as in more than a few articles and *Index of Suspicion* pieces. For a rarity, it pops up in *Pediatrics in Review* more often than we would likely expect.

A syndrome of overgrowth resulting from either genomic or epigenetic changes to chromosome 11p15, BWS usually comes without a positive family history: most cases reflect loss of methylation on the mother's chromosome, or uniparental disomy from the father. In addition to hypoglycemia, the syndrome may be marked by macrosomia, hemihypertrophy, macroglossia, visceromegaly, enlargement of the adrenal cortex, kidney abnormalities, and a propensity for embryonal tumor growth, particularly Wilms tumor and hepatoblastoma. Affected children may also have umbilical hernias and abnormal pits or creases of the ear lobe.

– Henry M. Adam, MD
Associate Editor, *In Brief*