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A specialized team approach to diagnosis and medical versus surgical treatment of infants with congenital hyperinsulinism

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Hyperinsulinism (HI) is the most common cause of transient and permanent forms of hypoglycemia in infancy. Establishing the correct diagnosis and initiating appropriate therapy without delay is of utmost importance. Once the diagnosis is made and if medical therapy with diazoxide fails, one should assume that the infant has a K_{ATP} channel defect and may require surgery. In this case, the infant should be referred to a center that specializes in HI with 18-fluoro L-3,4-dihydroxyphenylalanine positron emission tomography scan. This report describes a center specializing in HI with a team of experts consisting of endocrinologists, nurse practitioners, geneticists, radiologists, pathologists, and a surgeon. It describes the center's paradigm for managing severe HI on the basis of more than 250 cases of HI in the past 10 years, including the diagnosis of HI, medical options, genetics of HI, imaging in HI, the surgical approach to HI, and outcomes.

Hyperinsulinism (HI) is the most common cause of both transient and permanent disorders of hypoglycemia in infants and children. Making the diagnosis of HI and initiating the appropriate therapy is crucial. The purpose of this article is to describe the diagnostic process and management of HI in a specialized center established at the Children's Hospital of Philadelphia, based on the past 10 years of experience with more than 250 cases of HI.

Paradigm for congenital HI

The approach to congenital HI requires rapidly establishing a clear diagnosis of HI, then evaluating the potential for controlling hypoglycemia by medical therapy, and determining whether surgery will be required. As shown in Table 1, the process for diagnosis and initiation and evaluation of medical therapy with diazoxide can be done within 5 to 7 days. If a patient does not respond to diazoxide, the possibility of K_{ATP} channel HI exists, and since more than one-half of these cases will have a potentially curable focal lesion, localization with 18-fluoro L-3,4-dihydroxyphenylalanine positron emission tomography (^{18}F-DOPA-PET) scan should be done preoperatively. Genetic testing preoperatively may also help to define the possibility of focal versus diffuse disease. As shown in Figure 1, this paradigm requires a team specialized in the diagnosis, treatment, and management of patients with HI, including endocrinologists, nurse practitioners, geneticists, radiologists, pathologists, and a surgeon.

Genetic forms of HI

As shown in Table 2, mutations in 8 genes have been associated with congenital HI in the newborn period. These

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Table 1 Timeline for diagnosing HI, initiating medical therapy, and referring to specialized center

Day 1	Establish diagnosis of HI (see Table 3)
	Begin 5-d trial of diazoxide
	If HI is severe begin at max dose (15 mg/kg/d)
	If HI less severe/perinatal-stress, start diazoxide at 5-10 mg/kg/d*
	Consider starting a diuretic with diazoxide, especially if on high GIR
Day 2-5	Determine minimum GIR required to maintain blood glucose between 70 and 100
	If HI is severe or GIR is >10 mg/kg/min, send mutation analysis on HI genes for infant and parents
Day 6	Determine fasting tolerance on diazoxide
	Failure to fast >12 h with BS >70 mg/dL indicates diazoxide unresponsiveness
	Diazoxide failure suggests a K_{ATP} channel HI and potential surgical candidate
	Begin arrangements for transfer to a specialized HI center with ^{18}F-DOPA PET scan capability
Day 7	Discontinue diazoxide; consider octreotide, 5 μg kg^{-1} d^{-1} divided every 6-8 h
	Desensitization to octreotide is common after 2-3 doses
	If required, octreotide can be increased to maximum of 15 μg/kg/d
Day 8-14	Evaluate effectiveness of octreotide with fasting test while awaiting transfer of patient

Abbreviations: GIR, glucose infusion rate (mg/kg/min); HI, hyperinsulinism.
*See text for further discussion of tachyphylaxis.

may be divided into disorders that respond to medical therapy with diazoxide, a K_{ATP} channel agonist, and those that are unresponsive and potentially will require surgical intervention. The most common of the HI defects involve the pancreatic beta-cell plasma membrane K_{ATP} channel; because the K_{ATP} channel is the target for diazoxide action, severe defects that completely abolish channel activity are unresponsive to diazoxide. The K_{ATP} channel is composed of 2 subunits: the sulfonylurea receptor 1 (sulfonylurea receptor-1; encoded by *ABCC8*)[1] and the inwardly rectifying potassium channel (Kir6.2; encoded by *KCNJ11*).[2] The second most common HI defect is diazoxide-responsive, dominantly expressed activating mutations of glutamate dehydrogenase (GDH; encoded by glutamate dehydrogenase 1 [GLUD]-1).[3] The third most common mutations are dominantly expressed mutations of glucokinase (GK; encoded by glucokinase).[4] The remaining genetic causes of HI are rare and include short-chain 3-hydroxyacyl-CoA dehydrogenase (short-chain 3-hydroxyacyl-CoA dehydrogenase [SCHAD]; encoded by hydroxyacyl-coenzyme a dehydrogenase [HADH]),[5] ectopic expression on β-cell plasma membrane of monocarboxylate transporter 1 (MCT1; encoded by SLC16A1),[6] hepatocyte nuclear factor 4α (HNF-4α; encoded by HNF4A),[7] and uncoupling protein 2 (UCP2; encoded by UCP2).[8]

Perinatal stress-induced HI

Neonates who are exposed to a variety of perinatal stresses can have a form of HI that persists for a few days to a few months. The etiology of this disorder is not known, but it appears to be acquired and not genetic. Perinatal stress-induced HI can occur in the setting of birth asphyxia, maternal toxemia, prematurity, or intrauterine growth retardation, resulting in prolonged neonatal dysregulation of insulin secretion. Unlike the transient HI seen in the infants of diabetic mothers, which resolves within a day or two after delivery, perinatal stress-induced HI can persist for several days to several weeks. In a series of neonates diagnosed with stress-induced HI persisting after 1 week of age, the median age of resolution was 6 months.[9] The mechanism responsible for the dysregulated insulin secretion is unknown. These infants usually respond well to diazoxide.

Diagnosing HI

Infants with HI often present with large birth weight and with severe and persistent hypoglycemia manifested by lethargy, seizures, apnea, and increased glucose requirements (up to 20-30 mg/kg/min). For diagnosis of HI, it is critical to obtain a blood sample at a time of hypoglycemia (blood glucose < 50 mg/dL) to evaluate the fuel and hormone responses which identify HI (Table 3A). Plasma insulin levels are inappropriately elevated in the setting of hypoglycemia; however, clearly elevated insulin levels are often not present at the time of hypoglycemia with HI. This might be attributable to a variety of factors, including periodic release of insulin that is missed by a single sample or to rapid hepatic clearance so the liver is exposed to high insulin levels which are not reflected in peripheral venous blood. This may also be attributable to the activity of insulin degrading enzymes that are present in hemolyzed samples. Therefore, the diagnosis of HI must frequently be based on other evidence of excessive insulin action, such as suppres-

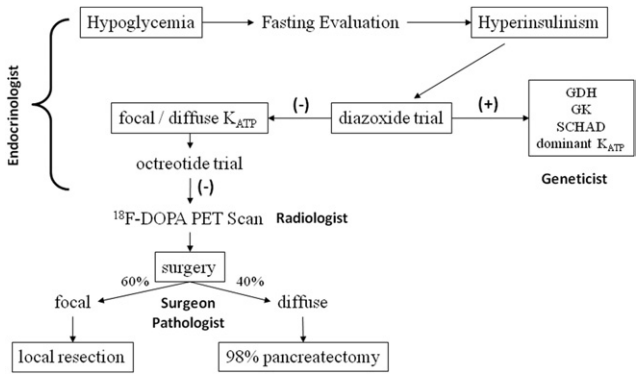

Figure 1 Paradigm for hyperinsulinism at a specialized center. This paradigm requires a team specialized in the diagnosis, treatment, and management of patients with HI, including endocrinologists, nurse practitioners, geneticists, radiologists, pathologists, and a surgeon.