Hiperinsulinismo en el Recien Nacido.

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Introducción.

El Hiperinsulinismo (HI), es la causa más común de hipoglucemia persistente en bebés,

conlleva un alto riesgo de morbilidad a largo plazo. En HI, los resultados de secreción de insulina desregulada en la hipoglucemia grave, la supresión de la respuesta contrarreguladora a la hipoglucemia, y, más significativamente, la supresión de la producción de cuerpos cetónicos, que son combustibles alternativos cruciales para el cerebro. Por lo tanto, la hipoglucemia hipoketótica grave y recurrente resultante de HI, si no se trata, se asocia con daño cerebral irreversible. Los la frecuencia de retrasos del neurodesarrollo en la HI es tan alta como 30% a 50% y, lo que es más importante, esto afecta no solo a los niños con formas congénitas y permanentes de HI sino también a los niños con reconocimiento transitorio HI. La prontitud en el reconocimiento y administración apropiada son fundamental para disminuir el riesgo de estos malos resultados. La dilucidación de la genética molecular de HI y avances en pruebas de diagnóstico, específicamente el uso de 18-fluoro-L-3,4- La PET con dihidroxifenilalanina (F-DOPA) para localizar las lesiones focales ha resultado en una enfoque personalizado del manejo y disminución de la morbilidad.

Le invitamos a leer, la publicación completa de este interesante tema.

Hyperinsulinism in the Neonate

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KEYWORDS

• Hypoglycemia • Neonate • Hyperinsulinism • Insulin • Pancreas • Pancreatectomy

KEY POINTS

- Hyperinsulinism (HI) is the most common cause of persistent hypoglycemia and is associated with high rates of neurodevelopmental deficits.
- Prompt evaluation to establish the diagnosis is important to start appropriate treatment.
- As soon as a diagnosis of HI is established, an initial trial of diazoxide is necessary to identify those who are likely to benefit from specialized evaluation.
- Infants with diazoxide-unresponsive HI require expedited genetic testing for *ABCC8* and *KCNJ11* to determine the likelihood of focal disease.
- The goal of medical therapy is to allow infants to maintain normal feeding patterns and to sustain plasma glucose greater than 70 mg/dL.

INTRODUCTION

Hyperinsulinism (HI), the most common cause of persistent hypoglycemia in infants, carries a high risk of long-term morbidity. In HI, dysregulated insulin secretion results in severe hypoglycemia, suppression of the counterregulatory response to hypoglycemia, and, more significantly, suppression of ketone bodies production, which are crucial alternative fuels for the brain. Thus, severe and recurrent hypoketotic hypoglycemia resulting from HI, if untreated, is associated with irreversible brain damage. The frequency of neurodevelopmental delays in HI is as high as 30% to 50% and, importantly, this affects not only children with congenital and permanent forms of HI but also children with transient HI.[1–3] Prompt recognition and appropriate management are critical to decrease the risk of these poor outcomes. Elucidation of the molecular genetics of HI and advances in diagnostic testing, specifically the use of 18-fluoro-L-3,4-dihydroxyphenylalanine (^{18}F-DOPA) PET to localize focal lesions, has resulted in a personalized approach to management and decreased morbidity.

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EPIDEMIOLOGY

The incidence of congenital HI is approximately 1 in 50,000 live births.[4] In addition to the monogenic forms of congenital HI, HI can be transient and related to perinatal stress or may be part of an underlying syndrome (**Box 1**).[5,6]

Perinatal Stress-Induced Hyperinsulinism

It is well established that plasma glucose concentrations are lower in the first 1 day to 3 days of life in normal newborns, a period of transitional glucose regulation that may be explained by a lower plasma glucose threshold for suppression of insulin secretion.[7] The process of β-cell maturation after birth may be impacted by perinatal factors, resulting in perinatal stress-induced HI, which can be common in these at-risk neonates. In a study of 514 neonates at risk of hypoglycemia, 47% of late-preterm and small-for-gestational-age (SGA) infants were found to have hypoglycemia during the first 48 hours of life[8]; 19% of the babies had recurrent episodes. A majority of infants with perinatal stress HI are diazoxide-responsive, although a subset, in particular those with hypoxic ischemic encephalopathy and liver dysfunction, may fail to respond. Perinatal stress HI resolves within the first 3 months to 6 months of life.[6]

Box 1
Causes of hyperinsulinism

Congenital

- K_{ATP}-HI (*ABCC8, KCNJ11*)
- GDH-HI (*GLUD1*)
- GCK-HI (*GCK*)
- HNF4α-HI (*HNF4A*)
- HNF1α-HI (*HNF1A*)
- SCHAD-HI (*HADH*)
- UCP2-HI (*UCP2*)
- Exercise-induced HI (*SLC16A1*)
- Phosphoglucomutase 1 deficiency (*PGM1*)

Perinatal stress

- Intrauterine growth restriction
- Birth asphyxia
- Maternal preeclampsia/eclampsia
- Congenital heart disease
- Meconium aspiration syndrome
- Prematurity

Syndromic

- Beckwith-Wiedemann
- Turner
- Soto
- Kabuki

These neonates may be at risk for long-term neurologic deficits, however, as demonstrated by the study of a large cohort of neonates at risk followed-up to 4.5 years and found to have a dose-dependent increased risk of poor executive function and visual motor function.[9] Thus, identification and appropriate treatment of these neonates are important to prevent long-term neurologic deficits.

GENETICS

Abnormalities in 10 genes encoding proteins that play an important role in the regulation of insulin secretion are associated with HI (**Fig. 1**). The most common types are discussed.

ATP-Sensitive Potassium Channels–Hyperinsulinism

Inactivating mutations of *ABCC8* and *KCNJ11* that encode SUR1 and Kir6.2, the 2 components of the β-cell ATP-sensitive potassium (K_{ATP}) channels, cause the most common and severe form of congenital HI.[10,11] The mutations result in either lack of channels on the β-cell plasma membrane or channels that are expressed but have impaired function. These channel abnormalities lead to dysregulated insulin secretion, which in a majority of cases is unresponsive to diazoxide, a K_{ATP} channel agonist. Depending on the

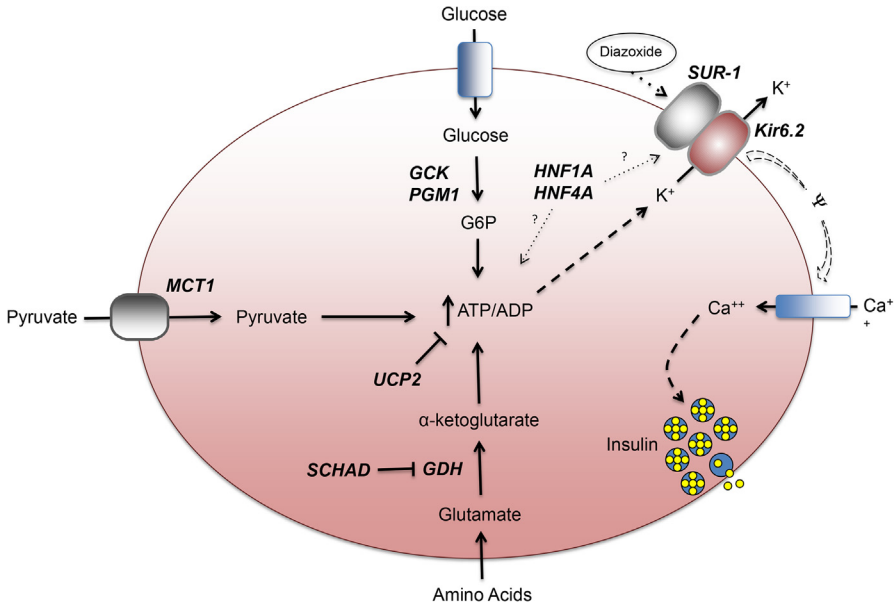

Fig. 1. Insulin secretion by the β cell and site of genetic defects causing HI. Glucose and amino acids are the major fuel signals in the β cell. ATP production from fuel metabolism results in closure of the K_{ATP} channel, which is composed of 2 subunits: SUR-1 and Kir6.2. Closure of the channel results in depolarization of the β cell membrane. The depolarization triggers opening of the voltage-sensitive calcium channels and the subsequent calcium influx leads to insulin secretion. Genetic defects (*bold italics*) in these pathways result in HI. Six are inactivating mutations: SUR-1 (sulfonylurea receptor 1), Kir6.2 (potassium channel), UCP2 (uncoupling protein 2), HNF4A, HNF1A, and SCHAD (short-chain 3-OH acyl-CoA dehydrogenase functioning as inhibitor of GDH through direct protein/protein interaction). Three are activating mutations: GCK, GDH, PGM1 (phosphoglucomutase 1), and MCT1 (monocarboxylate transporter 1). G6P, glucose-6-phosphate.

mutation and its impact on the channel expression and function, K_{ATP}-HI can be recessive diazoxide-unresponsive, dominant diazoxide-unresponsive, or dominant diazoxide-responsive.[12] Infants with diazoxide-unresponsive K_{ATP}-HI present with severe hypoglycemia, large-for-gestational-age (LGA) birth weight, and high glucose infusion rate (GIR) requirements. Infants with the diazoxide-responsive form typically present with milder disease.[13]

K_{ATP}-HI has 2 distinct histologic subtypes: diffuse and focal (**Fig. 2**). In diffuse K_{ATP}-HI, β-cells throughout the pancreas show signs of hyperactivity.[14] In contrast, a discrete area of β-cell proliferation or adenomatosis characterizes the focal form. Diffuse K_{ATP}-HI results from biallelic recessive mutations in the K_{ATP} genes; less commonly, dominant mutations are found. Focal K_{ATP}-HI is the result of a 2-hit mechanism: (1) a paternally inherited recessive mutation in *ABCC8* or *KCNJ11* and (2) somatic loss of the maternally inherited 11p15 chromosomal region, compensated by paternal uniparental disomy.[15,16] The histologic differences in the 2 forms lead to divergent treatment options and outcomes. Patients with focal K_{ATP}-HI are cured with resection of the focal lesion, whereas pancreatectomy for patients with the diffuse form is palliative.

Given these different outcomes, distinguishing between the focal and diffuse forms of K_{ATP}-HI is crucial. Neonates with the diffuse form are more likely to present at birth, whereas those with focal form may fail detection in the neonatal period and present at several weeks to months of life with hypoglycemia seizures.[17] Due to significant overlap in clinical presentation, however, clinical features alone cannot be used to distinguish between the 2 forms. Genetic testing offers the best means of identifying infants with focal K_{ATP}-HI: a single recessive paternally inherited mutation in *ABCC8* or *KCNJ11* has a positive predictive value of 94% for focal HI.[18]

Glutamate Dehydrogenase–Hyperinsulinism

Activating mutations in *GLUD1*, which encodes glutamate dehydrogenase (GDH), cause the second most common form of HI, known as HI/hyperammonemia

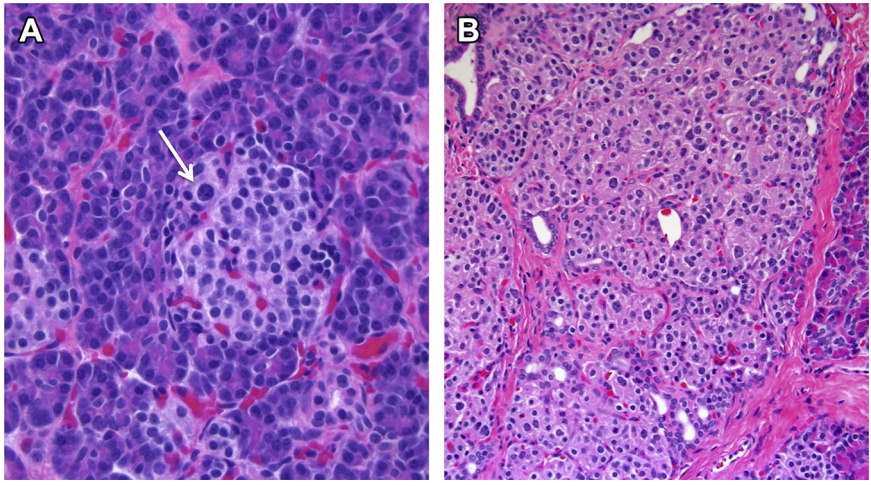

Fig. 2. (*A*) Section of pancreas from a diffuse case showing a pancreatic islet demonstrating β-cell nucleomegaly (*white arrow*), histologic hallmark of diffuse disease (H&E, original magnification × 400). (*B*) Adenomatous lesion from a case of focal HI (H&E, original magnification × 200). Normal pancreas tissue is seen on the right side of the image.

(HI/HA) syndrome.[19] GDH is involved in amino acid–stimulated insulin secretion. Mutations in *GLUD1* most commonly occur de novo (70%), with the remainder inherited in an autosomal dominant manner. Infants with HI/HA syndrome present with fasting and protein-induced hypoglycemia and ammonia levels 3 times to 5 times above the normal range. This form of HI is associated with increased rates of seizures and learning disabilities that may not be directly the result of the hypoglycemia or the HA.[20] Individuals with HI/HA syndrome are responsive to diazoxide.

Glucokinase-Hyperinsulinism

Glucokinase (GCK) is the key enzyme regulating the glucose threshold for insulin secretion.[21] Activating mutations of GCK, encoded by *GCK*, cause an autosomal dominant form of HI, which has variable degrees of severity and diazoxide responsiveness. Although most infants may be managed medically, the severe cases may require near-total pancreatectomy.[22]

Hepatic Nuclear Factor 4 Alpha—Hyperinsulinism

Mutations in the pancreatic transcription factor, hepatic nuclear factor 4 alpha (HNF4α), cause diazoxide-responsive HI.[23] Infants with HNF4A-HI are typically macrosomic and can be treated with low dose diazoxide. The hypoglycemia resolves within the first several years of life. Progressive β-cell failure occurs, however, and results in a monogenic form of early onset diabetes (maturity-onset diabetes of the young [MODY1]).[24] A similar clinical progression (from HI to diabetes) has been described in individuals with mutations in another pancreatic transcription factor, hepatic nuclear factor 1nalpha (HNF1α), which results in MODY3.[25]

DIAGNOSIS

Clinical Presentation

The classic presentation of HI is an LGA infant with a high GIR (>10 mg/kg/min), as is commonly seen in K_{ATP}-HI. The clinical phenotype, however, is a spectrum and some patients present with normal birth weight and minimally elevated glucose requirements. Clinical features can suggest a specific phenotype and guide genetic testing (**Box 2**).

Indications for a Hypoglycemia Evaluation

An expert committee of pediatric endocrinologists and neonatologists recently published guidelines for the evaluation and management of hypoglycemia in neonates, infants, and children.[26] The committee recommended evaluation for a persistent hypoglycemia disorder in neonates unable to consistently maintain plasma glucose concentrations greater than 60 mg/dL by the third day of life, those with severe hypoglycemia (symptomatic hypoglycemia or requiring intravenous dextrose), and those who are at high risk of having a persistent hypoglycemic disorder (LGA, SGA, perinatal stress, maternal diabetes, congenital syndromes, or family history of genetic hypoglycemia disorders).

Laboratory Evaluation

A diagnosis of HI is based on a critical blood sample obtained at the time of hypoglycemia. The critical sample is used to measure plasma concentrations of the hormones and alternative fuels involved in the physiologic response to fasting. To minimize false-positive results, the plasma glucose threshold for obtaining a critical sample is less than 50 mg/dL. This sample may be obtained during a spontaneous episode of

Box 2
Clinical features of hyperinsulinism

High GIR (>10 mg/kg/min)

- All forms
- Highest in K_{ATP}-HI

LGA

- K_{ATP}-HI
- GCK-HI
- HNF4α and HNF1α-HI
- Beckwith-Wiedemann
- Soto

SGA

- Perinatal stress HI

Congenital heart disease

- Perinatal stress HI
- Turner
- Kabuki

Hypertrophic cardiomyopathy

- K_{ATP}-HI

hypoglycemia or during a carefully monitored fast. It is important to confirm the plasma glucose using a laboratory-based assay rather than relying on a point-of-care glucose. In addition to obtaining the critical sample, the glycemic response to glucagon should be assessed.[27] At the time of hypoglycemia (after obtaining the critical blood sample), 1 mg of glucagon is administered and plasma glucoses are monitored every 10 minutes for a total of 40 minutes. For practical reasons, typically, point-of-care meters are used for the measurements of plasma glucose after glucagon is administered. In HI, glucagon administration results in an increase of plasma glucose by greater than 30 mg/dL (**Box 3**). If the plasma glucose does not increase by 20 mg/dL in the first 20 minutes, however, the test should end and the infant should be fed.

The laboratory findings of HI include detectable insulin/C-peptide, suppressed β-hydroxybutyrate and free fatty acids, and an inappropriate glycemic response to glucagon (see **Box 3**). Insulin may not be detectable in a sample taken from peripheral blood (because of hepatic metabolism and/or a hemolyzed sample), so other evidence of insulin actions during hypoglycemia, such as suppression of lipolysis (suppressed free fatty acids), ketogenesis (suppressed β-hydroxybutyrate), and glycogenolysis (glycemic response to glucagon), must be used. Neonatal panhypopituitarism can have an identical biochemical profile to HI. If cortisol and growth hormone levels from the critical sample are not elevated, the appropriate stimulation tests should be performed to evaluate for possible hypopituitarism.[28]

Genetic Testing

Genetic testing should be considered in all patients diagnosed with HI and is available commercially for the known HI genes. By identifying a specific genotype,

Box 3
Diagnostic criteria

When plasma glucose less than 50 mg/dL

- Low β-hydroxybutyrate (<1.8 mmol/L)
- Low free fatty acids (<1.7 mmol)
- Plus/minus detectable insulin/C-peptide
- Positive glycemic response to glucagon (30-point rise in glucose)

Exclude neonatal panhypopituitarism:

- Cortisol greater than 10 μg/dL
- Growth hormone greater than 7 ng/mL

families can be counseled regarding comorbidities and expected duration of treatment, and the genotype result can aid in future family planning. Any infant who fails to respond to diazoxide should have expedited testing (4-day to 7-day turnaround time) of *ABCC8* and *KCNJ11*, because this suggests K_{ATP}-HI. If a mutation in *ABCC8* or *KCNJ11* is found, genotyping the parents is critical to determine parent-of-origin of the mutation and assess the likelihood of focal HI. Rapid identification of infants with the focal form allows the infants to more quickly undergo ^{18}F-DOPA PET and curative surgery.

MANAGEMENT

The goal of treatment in HI is to maintain plasma glucose greater than 70 mg/dL, even during periods of fasting. This goal is initially accomplished using dextrose-containing intravenous fluids. If central venous access is obtained, higher concentration dextrose can be used to minimize fluid overload. Throughout treatment, neonates and infants should be allowed to feed on demand. Nutritional modifications (fortified feedings and continuous feedings) alone are not sufficient to treat HI, and forced feedings or continuous feeds lead to oral aversion and poor feeding skills.

Medical Therapy

There are few medical treatment options for HI, which makes treatment challenging (**Table 1**). The mainstay of therapy is diazoxide, which opens the K_{ATP} channel on the β cell, resulting in inhibition of insulin secretion.[29,30] Side effects of diazoxide include fluid retention; thus, neonates and infants on diazoxide therapy require concomitant therapy with a diuretic, such as chlorothiazide. Diuretic use decreases the risk of fluid overload and respiration compromise, which is frequently seen with neonates receiving diazoxide and large amounts of intravenous fluids.

Octreotide, a somatostatin analog, is the second-line agent used in the treatment of HI.[31] Treatment failure is common, however, due to development of tachyphylaxis. Additionally, safety concerns have significantly limited its use in neonates. Octreotide has been associated with fatal necrotizing enterocolitis and should be avoided during the first 6 weeks to 8 weeks of life.[32,33] A long-acting somatostatin analogue, lanreotide, has been used successfully in children with HI, although dosing limitations restricts its use in the younger patients.[34,35] Finally, glucagon can be used as a continuous intravenous infusion of 1 mg per day to lower dextrose

Table 1
Medications for the treatment of hyperinsulinism in neonates and infants

Name	Dose	Route	Side Effects
Diazoxide	5–15 mg/kg/d, divided twice daily	Oral	Hypertrichosis, fluid retention, bone marrow suppression, decreased appetite
Chlorothiazide (concomitant use in children treated with diazoxide to avoid fluid retention)	20–40 mg/kg/d, divided twice daily	Oral	Hypokalemia
Octreotide	2–20 μg/kg/d, every 6–8 h	Subcutaneous	Elevated liver enzymes, diarrhea, gallstones, growth failure, hypothyroidism, necrotizing enterocolitis
Glucagon	1 mg/d, continuous infusion	Intavenos	Emesis, rash

needs in infants awaiting surgery. Solubility issues have limited its use in the outpatient setting.

Steroids are not effective therapy for HI and expose infants to unnecessary side effects, such as iatrogenic adrenal insufficiency, hypertension, and bone demineralization. Calcium channel blockers, such as nifedipine, also have limited effectiveness in this population and should not be used for treatment of HI.[36] In 2014, sirolimus, a mammalian target of rapamycin inhibitor, was reported as a novel treatment, but subsequent studies have failed to show efficacy.[37,38] Given the risks of increased susceptibility to severe infections associated with sirolimus, its use is not currently recommended.[39]

Assessing Diazoxide Responsiveness

After establishing the diagnosis of HI, a therapeutic trial of diazoxide to determine responsiveness is the crucial first step. Diazoxide is initiated at 5 mg/kg/d to 10 mg/kg/d (or higher in more severe cases) and if there is no improvement in plasma glucose after several days, titrated up to a maximum dose of 15 mg/kg/d. After 5 days on a stable dose of diazoxide, a 12-hour safety fast should be performed to assess responsiveness. Neonates are considered diazoxide-unresponsive if, after 5 days on the maximum dose, they continue to require dextrose support or are unable to maintain plasma glucoses greater than 70 mg/dL while fasting. At that time, the diazoxide should be discontinued and, as discussed previously, expedited genetic testing for *ABCC8* and *KCNJ11* should be sent, because mutations in 1 of these 2 genes account for greater than 90% of cases. These patients require referral to a specialized HI center as possible surgical candidates.

For children with diazoxide-unresponsive diffuse HI, medical therapy can be attempted with continuous enteral dextrose and after the neonatal period, octreotide. In those with severe disease, this approach may be insufficient due to limits on the amount of enteral dextrose that can be safely used as well as side effects from high doses of octreotide. These patients are often referred for surgical intervention. The risks and benefits of the 2 approaches are discussed in more detail later.

18-Fluoro-L-3,4-dihydroxyphenylalanine PET

The recognition that some patients with severe HI were cured after a partial pancreatectomy led to the identification of focal K_{ATP}-HI in the 1980s. Identifying patients

with focal HI and accurately localizing the lesion in the pancreas became 2 of the biggest management challenges for the disease. Understanding the genetic mechanisms of HI led to the recognition that patients with focal HI carry paternally inherited *ABCC8* or *KCNJ11* mutations. Localization of the focal lesion, however, remained a challenge. Conventional imaging, such as ultrasound, CT, and MRI, cannot identify focal lesions, and interventional radiology techniques, such as arterial stimulation venous sampling, were invasive and had poor accuracy at localizing lesions.[40]

The introduction of the ^{18}F-DOPA PET scan was one of the most significant advances in the care of children with HI. Introduced in 2003, it is used to differentiate focal from diffuse disease and to localize focal lesions in the pancreas.[41,42] The tracer, ^{18}F-DOPA, is taken up by neuroendocrine tissue. In focal disease, there is an area of increased tracer uptake in a specific region of the pancreas, corresponding to the area of β-cell adenomatosis (**Fig. 3**). In patients with diffuse HI, the uptake of tracer is uniform throughout the pancreas. In the largest published series to date, 105 infants with HI underwent ^{18}F-DOPA scans, followed by surgery.[43] The sensitivity and specificity for diagnosing focal disease were 85% and 96%, respectively; 100% of lesions were correctly localized in the pancreas.

All infants who have genetics consistent with focal HI require an ^{18}F-DOPA PET scan prior to surgery. Additionally, patients with diazoxide-unresponsive, genetic-negative HI should also undergo an ^{18}F-DOPA PET scan, because they still have the possibility of a focal lesion. Patients who are diazoxide-responsive or those with genetic results known to cause diffuse disease, such as biallelic recessive mutations in *ABCC8* or *KCNJ11* or a *GCK* mutation, do not benefit from imaging.

Surgical Intervention

Surgery is indicated for infants who have a focal lesion or those with diffuse disease who fail medical therapy. Patients with focal lesions should undergo surgery at

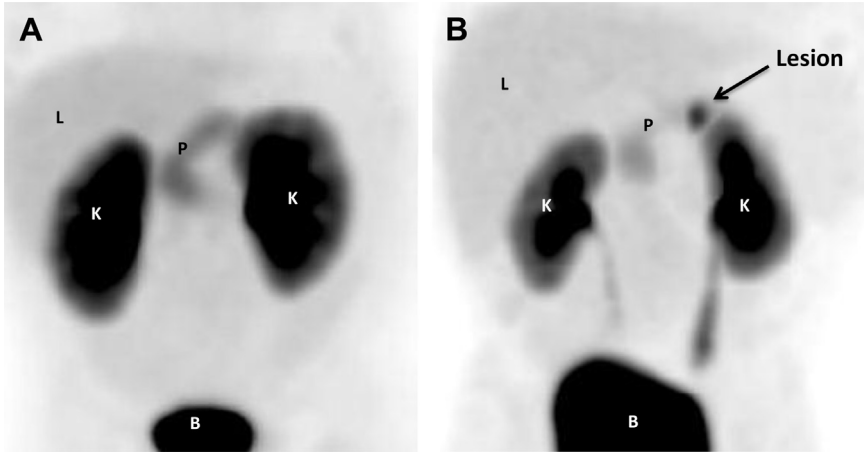

Fig. 3. (*A*) Frontal view of a MIP ^{18}F-DOPA PET image showing a uniform pattern of uptake throughout the pancreas, consistent with diffuse disease. (*B*) Frontal view of a MIP ^{18}F-DOPA PET image demonstrating increased uptake in the tail of the pancreas, consistent with a focal lesion (*black arrow*). Normal liver (L), kidney (K), pancreas (P), and bladder (B) uptake is seen in both images. MIP, maximum intensity projection.

specialized HI centers, which have the multidisciplinary expertise to ensure complete incision of the lesion while minimizing the amount of pancreas resected.[44] At the time of surgery, intraoperative ultrasound can be used to confirm the location of the focal lesion. Frozen section evaluation of biopsies by experienced pathologists allows for confirmation of the focal lesion and guides the extent of pancreatic resection.

Infants with diffuse HI requiring surgical intervention undergo near-total pancreatectomy with gastrostomy tube placement. The gastrostomy tube is necessary for postoperative management because a majority of patients continue to have hypoglycemia, although less severe.[17] For children with diffuse disease, the decision to proceed with surgery is complex and requires careful consideration of the risks and benefits. Surgery decreases the severity of the hypoglycemia and makes it easier to manage medically. This must be weighed, however, against the risk of a surgical procedure as well as the long-term complications of diabetes and pancreatic insufficiency. Medical therapy avoids these complications but carries its own risks with more exposure to hypoglycemia as well as side effects from the high doses of somatostatin analogs that are required.

PROGNOSIS

Surgical Outcomes

A review of 223 surgical cases from the Children's Hospital of Philadelphia found that 94% of infants with focal HI were cured and the majority required less than a 50% pancreatectomy.[17] In contrast, only a quarter of patients with diffuse disease were euglycemic after pancreatectomy. More than 40% of patients required continued treatment of hypoglycemia, and the remainder were treated for hyperglycemia.

Individuals who undergo near-total pancreatectomy in infancy have a high risk of developing diabetes.[2,45] More than 90% of these patients develop insulin-dependent diabetes mellitus during the first 2 decades of life; the median age at diagnosis of diabetes is 8 years.

Neurodevelopmental Outcomes

Despite advances in the field, children with HI continue to have a high risk of neurocognitive abnormalities. Studies have shown that 26% to 48% of children and adults with HI have developmental delays and neurologic issues and 13% to 25% have seizures.[1,46] Poor developmental outcomes are not only limited to children with persistent forms of HI but also involve children with transient forms of HI.[3] Furthermore, the rates of developmental delay and seizures for children treated in the 2000s remain similar to those individuals treated in the decades before.[2] These findings suggest the need for improved screening protocols to identify infants with HI as early as possible to avoid these neurologic sequela.

SUMMARY

With limited medical therapies and a high risk of neurologic damage, HI remains a challenging disorder to treat. Advances in management, such as the ^{18}F-DOPA PET scan, however, have resulted in improved outcomes for the subset of infants with focal HI. Ongoing research into the genetic and molecular basis of HI will hopefully result in novel treatments that benefit those infants with diffuse HI.

Best Practices

What is the current best practice?

- Prompt evaluation of infants with suspected HI
- Early identification of infants with focal K_{ATP}-HI and referral to specialized HI center for ^{18}F-DOPA PET

What changes in current practice are likely to improve outcomes?

- Support plasma glucose with intravenous fluids and allow infants to feed orally on demand
- Use of diuretics in all infants on diazoxide

Major recommendations

- Diagnostic evaluation of neonates who are at high risk of having a persistent hypoglycemic disorder
- Initiate trial of diazoxide as soon as diagnosis of HI is made
- Infants who are diazoxide-unresponsive require expedited genetic testing for *ABCC8* and *KCNJ11*
- The goal of medical therapy is to allow infants with HI to maintain plasma glucose greater than 70 mg/dL while fasting

Summary statement

Early recognition and appropriate treatment of infants with HI are crucial to avoid long-term complications, such as developmental delays and diabetes

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