Hyperinsulinism in Infancy and Childhood: When an Insulin Level Is Not Always Enough

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BACKGROUND: Hypoglycemia in infants and children can lead to seizures, developmental delay, and permanent brain damage. Hyperinsulinism (HI) is the most common cause of both transient and permanent disorders of hypoglycemia. HI is characterized by dysregulated insulin secretion, which results in persistent mild to severe hypoglycemia. The various forms of HI represent a group of clinically, genetically, and morphologically heterogeneous disorders.

CONTENT: Congenital hyperinsulinism is associated with mutations of SUR-1 and Kir6.2, glucokinase, glutamate dehydrogenase, short-chain 3-hydroxyacyl-CoA dehydrogenase, and ectopic expression on β-cell plasma membrane of SLC16A1. Hyperinsulinism can be associated with perinatal stress such as birth asphyxia, maternal toxemia, prematurity, or intrauterine growth retardation, resulting in prolonged neonatal hypoglycemia. Mimickers of hyperinsulinism include neonatal panhypopituitarism, drug-induced hypoglycemia, insulinoma, antiinsulin and insulin-receptor stimulating antibodies, Beckwith-Wiedemann Syndrome, and congenital disorders of glycosylation. Laboratory testing for hyperinsulinism may include quantification of blood glucose, plasma insulin, plasma β-hydroxybutyrate, plasma fatty acids, plasma ammonia, plasma acylcarnitine profile, and urine organic acids. Genetic testing is available through commercial laboratories for genes known to be associated with hyperinsulinism. Acute insulin response (AIR) tests are useful in phenotypic characterization. Imaging and histologic tools are also available for diagnosing and classifying hyperinsulinism. The goal of treatment in infants with hyperinsulinism is to prevent brain damage from hypoglycemia by maintaining plasma glucose levels above 700 mg/L (70 mg/dL) through pharmacologic or surgical therapy.

SUMMARY: The management of hyperinsulinism requires a multidisciplinary approach that includes pediatric endocrinologists, radiologists, surgeons, and pathologists who are trained in diagnosing, identifying, and treating hyperinsulinism. Hypoglycemia in infants and children, if unrecognized, can lead to seizures, developmental delay, and permanent brain damage. There are many causes of neonatal hypoglycemia ranging from transient delays in fasting adaptation in the newborn period to more permanent forms due to endocrine or metabolic diseases. Of these various forms, hyperinsulinism (HI) is the most common cause of both transient and permanent disorders of hypoglycemia. This review focuses on laboratory diagnosis, the genetic disorders underlying congenital HI, and the management of HI.

TERMINOLOGY
HI was first described in 1954 by MacQuarrie (1) as "idiopathic hypoglycemia of infancy." HI has subsequently been referred to by many names, including leucine-sensitive hypoglycemia, islet dysregulation syndrome, and congenital disorders of glycosylation. Laboratory testing for hyperinsulinism may include quantification of blood glucose, plasma insulin, plasma β-hydroxybutyrate, plasma fatty acids, plasma ammonia, plasma acylcarnitine profile, and urine organic acids. Genetic testing is available through commercial laboratories for genes known to be associated with hyperinsulinism. Acute insulin response (AIR) tests are useful in phenotypic characterization. Imaging and histologic tools are also available for diagnosing and classifying hyperinsulinism. The goal of treatment in infants with hyperinsulinism is to prevent brain damage from hypoglycemia by maintaining plasma glucose levels above 700 mg/L (70 mg/dL) through pharmacologic or surgical therapy.

NORMAL INSULIN SECRETION
Insulin secretion by the pancreatic β-cell results from a fuel-stimulated increase in the intracellular phosphate potential (ATP:ADP ratio). Increase in ATP:ADP ratio

1 Nonstandard abbreviations: HI, hyperinsulinism; K<sub>a</sub>, ATP-sensitive potassium; SUR-1, sulfonylurea receptor 1; GK, glucokinase; GDH, glutamate dehydrogenase; SCHAD, short-chain 3-hydroxyacyl-CoA dehydrogenase; MCT1, monocarboxylate transporter 1; IGF2, insulin-like growth factor 2; HA, hyperammonemia; EHHI, exercise-induced HI; BWS, Beckwith-Wiedemann Syndrome; CDG, congenital disorders of glycosylation; AIR, acute insulin response; 18F-DOPA, 18-fluoro-L-3,4-dihydroxyphenylalanine.
inhibits the ATP-sensitive potassium channel (KATP channel), resulting in closure of the channel, depolarization of the membrane, influx of calcium, and release of insulin. Insulin secretion is stimulated by glucose oxidation via glucokinase and by leucine stimulation of glutamate oxidation via glutamate dehydrogenase (Fig. 1).

CONGENITAL HYPERINSULINISM

HI is characterized by dysregulated insulin secretion that results in persistent mild to severe hypoglycemia. The various forms of HI represent a group of clinically, genetically, and morphologically heterogeneous disorders. HI occurs at a frequency of 1 in 30,000 to 50,000 live births (5).

MOLECULAR GENETICS

Mutations in 6 genes have been associated with HI (Table 1): the sulfonylurea receptor 1 (SUR-1; encoded by ABCC8) (6); potassium inward rectifying channel (Kir6.2; encoded by KCNJ11) (7); glucokinase (GK; encoded by GCK) (8); glutamate dehydrogenase (GDH; encoded by GLUD-1) (9); short-chain 3-hydroxyacyl-CoA dehydrogenase (SCHAD; encoded by HADH) (10); and ectopic expression on β-cell plasma membrane of SLC16A1 [encodes monocarboxylate transporter 1 (MCT1)] (11).

HI ASSOCIATED WITH MUTATIONS OF SUR-1 AND Kir6.2

SUR-1 and Kir6.2 combine to form the β-cell plasma membrane K<sub>ATP</sub> channel. The channel is a heterooctameric complex comprising 4 Kir6.2 subunits which form the ion pore, coupled to 4 SUR-1 regulatory subunits. Inactivating mutations in the K<sub>ATP</sub> channel result in constitutive closure of the channel allowing membrane depolarization and calcium influx into the β-cell, resulting in constitutive insulin secretion from the β-cell. These mutations cause K<sub>ATP</sub> channel hyperinsulinism (K<sub>ATP-HI</sub>), the most common and severe form of HI. Electrophysiological studies of islets from infants with K<sub>ATP-HI</sub> show reduction of K<sub>ATP</sub> channel activity and spontaneously active voltage-dependent Ca<sup>2+</sup> channels (12). The K<sub>ATP</sub> channel is normally activated by diazoxide (the main medical treatment for HI), resulting in channel opening, and ultimately, decreased insulin secretion. Because the channel is dysfunctional in K<sub>ATP-HI</sub>, diazoxide is ineffective.

More than 100 mutations of ABCC8 and 20 mutations of KCNJ11 have been found. Channel activity is completely eliminated by some mutations, whereas others alter the density of the channels or their response to nucleotides (13). Most of the ABCC8 and KCNJ11 mutations are recessive, but a few dominantly expressed mutations have been reported (14–17). The dominantly inherited mutations retain responsiveness to diazoxide.

There are two distinct histological forms of K<sub>ATP</sub>-HI, diffuse HI and focal HI. Diffuse HI is inherited in an autosomal recessive fashion. In focal HI, which accounts for approximately 40% to 60% of all cases of K<sub>ATP</sub>-HI, there is a loss of heterozygosity involving a paternally derived mutation of the ABCC8 or KCNJ11 gene and a specific loss of maternal alleles of the imprinted chromosome region 11p15 resulting in a focal lesion (focal adenomatosis) (18). This somatic loss alters the expression of imprinted genes of region 11p15.5, including tumor-suppressor genes. The corresponding paternal allele contains insulin-like growth factor 2 (IGF2), which is a growth-promoting gene. Notably, loss of heterozygosity of the same 11p15 region has been found in some insulinomas (19).

HI ASSOCIATED WITH MUTATIONS OF GDH

Glutamate dehydrogenase HI is the second most common form of HI. It is also known as the hyperinsulinism and hyperammonemia (HI/HA) syndrome (reviewed by Stanley (20)). It is caused by activating
mutations in GDH, a mitochondrial enzyme (9), and a key regulator of amino acid and ammonia metabolism in β-cells, liver, and brain. GDH is normally activated by leucine and ADP and allosterically inhibited by GTP and ATP. Sirtuin 4 (SIRT-4) has recently been found to inhibit GDH by ADP-ribosylation (21). Leucine stimulates insulin secretion in β-cells by allosterically activating GDH to increase oxidation of glutamate to α-ketoglutarate, increasing the ATP:ADP ratio and triggering insulin release via the KATP-channel.

In GDH-HI, missense mutations of GDH occur in the GTP binding site, hence reducing the sensitivity of the enzyme to allosteric inhibition by GTP. The loss of inhibitory control of GDH in β-cells results in excessive insulin release. Isolated islets from transgenic mice expressing mutated human GDH exhibit normal glucose-stimulated insulin secretion but enhanced leucine-stimulated and amino-acid–stimulated insulin secretion (22). In the liver, increased GDH activity leads to increased ammonia production and impaired urea synthesis. The result of increased GDH activity in the brain is unclear, but might explain the lack of toxic effects of hyperammonemia in affected children. De novo (80%) and dominantly inherited (20%) mutations have been reported in the GTP-inhibitory allosteric binding site or in an antenna region of the enzyme, which has a role in communicating with adjacent enzyme subunits (2).

GDH-HI presents with recurrent episodes of fasting and postprandial hypoglycemia that are less severe than in KATP-HI, and can be precipitated by a protein-rich meal (23). Despite persistently increased plasma ammonia levels, patients with GDH-HI are asymptomatic. Plasma ammonia levels are typically 2–5 times the upper limit of normal and stable with fasting and protein meals. As these patients do not typically present with hypoglycemia at birth, they are frequently not diagnosed until several months of age. Children with GDH-HI can present with an unusual pattern of generalized seizures (24). The hypoglycemia in patients with GDH-HI is easily controlled with diazoxide.

HI ASSOCIATED WITH MUTATIONS OF GK
GK-HI, a rare form of HI, is caused by activating mutations in GCK, which encodes glucokinase (8), a hexokinase that acts as a glucose sensor in pancreatic β-cells and seems to have a similar role in entero-endocrine cells, hepatocytes, and hypothalamic neurons. In β-cells, GK controls the rate-limiting step of glucose metabolism and is responsible for glucose-stimulated insulin secretion (25). In GK-HI, activating mutations result in increased affinity of glucokinase for glucose, resulting in an increase in the ATP:ADP ratio in the pancreatic β-cell, closure of KATP channel, and inappropriate insulin secretion. The β-cell glucose threshold for glucose-stimulated insulin secretion in children

### Table 1. Classification of genetic forms of congenital hyperinsulinism.

<table>
<thead>
<tr>
<th>Genetic form</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Inheritance</th>
<th>Clinical features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>K&lt;sub&gt;ATP&lt;/sub&gt;-HI</td>
<td>ABCC8, KCNJ11</td>
<td>11p15</td>
<td>Diffuse: AR Focal: loss of heterozygosity with paternal mutation</td>
<td>Severe hypoglycemia; unresponsive to medical therapy</td>
<td>Pancreatectomy or “conservative” therapy with octreotide and continuous feedings</td>
</tr>
<tr>
<td>Dominant K&lt;sub&gt;ATP&lt;/sub&gt;-HI</td>
<td>ABCC8, KCNJ11</td>
<td>11p15</td>
<td>AD</td>
<td>Milder hypoglycemia; responsive to diazoxide</td>
<td>Diazoxide</td>
</tr>
<tr>
<td>GDH-HI (HI/HA)</td>
<td>GLUD-1</td>
<td>10q</td>
<td>AD</td>
<td>Fasting and postprandial hypoglycemia; less severe than K&lt;sub&gt;ATP&lt;/sub&gt;-HI; protein sensitivity; asymptomatic hyperammonemia</td>
<td>Diazoxide</td>
</tr>
<tr>
<td>GK-HI</td>
<td>GCK</td>
<td>7p</td>
<td>AD</td>
<td>Variable phenotype: can range from easy to manage with medical therapy to very difficult to control</td>
<td>Diazoxide; pancreatectomy</td>
</tr>
<tr>
<td>SCHAD-HI</td>
<td>HADH</td>
<td>4q</td>
<td>AR</td>
<td>Mild to severe hypoglycemia; abnormal acylcarnitine profile</td>
<td>Diazoxide</td>
</tr>
<tr>
<td>MCT1 (EHII)</td>
<td>SLC16A1</td>
<td>1p</td>
<td>AD</td>
<td>Exercise-induced hypoglycemia, especially anaerobic</td>
<td>Carbohydrate intake during exercise; limit exercise</td>
</tr>
</tbody>
</table>

AR, autosomal recessive; AD, autosomal dominant.
with GK-HI may be as low as 270 mg/L (27 mg/dL), whereas the normal glucose threshold is maintained close to 900 mg/L (90 mg/dL) (2). The activating mutations seen in GCK are inherited in an autosomal dominant manner. Five mutations in GCK have been reported (26). Age of onset and severity of symptoms vary markedly (8, 27–29). Some mutations have a mild phenotype with fasting hypoglycemia that is responsive to medical treatment; others lower the glucose threshold further and might be more difficult to treat (29).

**HI ASSOCIATED WITH MUTATIONS OF SCHAD**

A mutation in HADH, the gene encoding the mitochondrial enzyme SCHAD, is associated with HI (10, 30, 31). SCHAD catalyzes the third of 4 steps in the mitochondrial fatty acid oxidation pathway by catalyzing the oxidation of short-chain substrates. SCHAD-HI is characterized by fasting hypoglycemia due to insulin dysregulation. The HADH mutation is inherited in an autosomal recessive pattern and has been reported in 3 families (32). The biochemical markers, in addition to those of increased insulin action, are increased levels of plasma 3-hydroxybutyrylcarnitine and increased levels of 3-hydroxyglutarate in urine.

Unlike all other defects in fatty acid oxidation, children with SCHAD-HI have no signs of hepatic dysfunction, cardiomyopathy, or effects on skeletal muscle (30). The clinical presentations of SCHAD-HI are varied, ranging from late onset of mild hypoglycemia to severe onset of hypoglycemia in the neonatal period. The hypoglycemia of SCHAD-HI is responsive to medical therapy with diazoxide. Multiple potential mechanisms have been postulated as the cause of dysregulated insulin secretion in SCHAD deficiency (33); however, the mechanism remains unclear.

**HI ASSOCIATED WITH MUTATIONS OF SLC16A1: UPREGULATION OF MCT-1**

Exercise-induced HI (EIHI) has been associated with mutations in MCT1, a plasma-membrane protein expressed in low levels in β-cells and involved in the transport of pyruvate into the β-cell. Mutations have recently been reported in the promoter of SLC16A1, the gene encoding MCT1 (11). These mutations lead to increased gene transcription and increased MCT1 expression, selectively in β-cells. Increased MCT1 expression leads to increased transport of pyruvate into the β-cell, increasing the ATP:ADP ratio and stimulating insulin release via the K<sub>ATP</sub> channel pathway. EIHI is inherited in an autosomal dominant pattern and is characterized by inappropriate insulin secretion during exercise, particularly during anaerobic exercise (34). Patients with EIHI display a positive response to pyruvate-stimulated insulin secretion compared with controls (35).

**OTHER FORMS OF HYPERINSULINISM**

HI can also occur in the setting of perinatal stress such as birth asphyxia, maternal toxemia, prematurity, or intrauterine growth retardation, resulting in prolonged neonatal hypoglycemia. Unlike the transient HI seen in the infants of diabetic mothers, 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 (36). The mechanism responsible for the dysregulated insulin secretion is unknown. These infants usually respond well to diazoxide.

**HI MIMICKERS**

**Neonatal panhypopituitarism.** Neonatal panhypopituitarism can present with severe hypoglycemia due to deficiencies of the counterregulatory hormones cortisol and growth hormone. Presentation is similar to perinatal stress–induced HI, including suppressed ketones and fatty acids and a glycemic response to glucagon. These patients are treated with growth hormone, cortisol, and thyroid hormone replacement. Clues to this diagnosis include midline defects and micropenis (37). Ketotic hypoglycemia is seen in older children with panhypopituitarism.

**Drug-induced hypoglycemia.** Surreptitious insulin administration must always be suspected in patients presenting with hypoglycemia consistent with HI. These patients may have increased insulin levels as well as other markers of excessive insulin effects; however, they will have inappropriately low C-peptide levels relative to their insulin level. Surreptitious insulin administration in neonates and children is almost always a result of Munchausen-by-proxy syndrome.

Other drugs with the potential to induce hypoglycemia include sulfonylureas, β-blockers, ethanol, and terbutaline (38).

**Insulinoma.** Insulinomas must also be a consideration in children presenting with hypoglycemia that is consistent with HI. These patients typically present at an older age with varying degrees of symptoms. A diagnosis of multiple endocrine neoplasia syndrome type 1 should be considered in a patient with a pancreatic islet cell tumor (39).

**Anti-insulin and insulin receptor–stimulating antibodies.** Although exceedingly rare, insulin antibodies and insulin receptor–stimulating antibodies are worth mentioning as a potential cause of HI-like symptoms (40).
**Beckwith-Wiedemann syndrome.** Beckwith-Wiedemann syndrome (BWS) is a clinically and genetically heterogeneous disorder characterized by macrosomia, macroglossia, hemihypertrophy, transverse creases of the ear lobes, hypoglycemia, and predisposition to childhood tumors. Hypoglycemia occurs in up to 50% of patients with BWS (12), and it can vary from mild and transient to severe and persistent. The underlying mechanism of hyperinsulinism in these patients is unclear. The response to medical therapy in BWS is variable; some patients are well controlled with pharmacologic medical therapy, and others require partial pancreatectomy. Most cases of hypoglycemia resolve spontaneously for reasons that are unknown (41).

**Congenital disorders of glycosylation.** Congenital disorders of glycosylation (CDG; formerly known as carbohydrate-deficient glycoprotein syndrome) are inherited metabolic diseases caused by defects in the biosynthesis or transfer of lipid-linked oligosaccharides to the nascent protein chain (type I) or compromised processing of protein-bound oligosaccharides (type II). Hypoglycemia with features of HI has been reported in cases of CDG-Ia (42), CDG-Ib (43, 44) and in a case of CDG-Id (45). The underlying mechanism behind the dysregulated insulin secretion in these conditions is unknown. Some patients have been successfully treated with diazoxide.

**DIAGNOSIS**

At the time of hypoglycemia [defined as a blood glucose <50 mg/L (50 mg/dL)], it is important to obtain a “critical” blood sample to evaluate the counterregulatory fuel and hormone responses to hypoglycemia and to identify diagnostic markers of specific disease entities (Fig. 2). Infants with HI present with severe and persistent hypoglycemia manifested by lethargy, seizures, apnea, and increased glucose requirements (up to 20–30 mg/kg/min). Plasma insulin levels are inappropriately increased in the setting of hypoglycemia; however, clearly increased insulin levels are often not present at the time of hypoglycemia with HI. This might be due to periodic release of insulin, which is missed by a single sample, or to rapid hepatic clearance so that the liver is exposed to high insulin levels which are not reflected in peripheral venous blood (46). This may also be due to the activity of insulin degrading enzymes that are present in hemolysed samples (47). Therefore, the diagnosis of HI must frequently be based on evidence of excessive insulin action, such as suppression of plasma β-hydroxybutyrate and free fatty acid levels. An inappropriate glycemic response to glucagon >300 mg/L (30 mg/dL) at the time of hypoglycemia is consistent with excess insulin action and is useful for confirming the diagnosis (48). Additional laboratory tests for specific forms of HI include plasma ammonia levels (increased in GHD-HI) and a plasma acyl-carnitine profile (3-hydroxybutyrylcarnitine) and urine organic acids (3-hydroxybutyrate) (both of which are increased in SCHAD-HI).

**Fig. 2. Results from the critical blood sample obtained at the time of hypoglycemia serve as the basis for distinguishing 4 categories of disease: impairment of gluconeogenesis, normal and abnormal forms of ketotic hypoglycemia, defects in fatty acid oxidation and ketogenesis, and impairment of lipolysis and ketogenesis.**

<table>
<thead>
<tr>
<th>Glycemic response</th>
<th>Ketones</th>
<th>FFA</th>
<th>FAO defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperinsulinism</td>
<td>↑</td>
<td>↓</td>
<td>Ketones</td>
</tr>
<tr>
<td>HI Mimickers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acidemia</td>
<td>↑</td>
<td>↓</td>
<td>Ketones</td>
</tr>
<tr>
<td>No acidemia</td>
<td>↓</td>
<td>↑</td>
<td>FFA</td>
</tr>
</tbody>
</table>

**GENOTYPE AND PHENOTYPE TESTING**

Genetic testing is available through commercial laboratories for 4 of the 6 genes known to be associated with HI (ABCC8, KCNJ11, GCK, GLUD-1). In addition, acute insulin response (AIR) tests are useful in phenotypic characterization: patients with diffuse $K_{ATP}$-HI display abnormal positive responses to calcium, abnormal negative response to the $K_{ATP}$-channel antagonist tolbutamide, and impaired responses to glucose (49, 50). Focal and diffuse HI are clinically indistinguishable and AIR tests do not reliably differentiate between the two (51, 52). Infants with GDH-HI demonstrate an increased response to leucine (53). For infants with prolonged stress-induced HI, AIR testing shows that, in general, the patterns of insulin response to calcium, tolbutamide, glucose, and leucine resemble those of normal controls (36).

**IMAGING IN HI**

The ability to distinguish focal and diffuse HI is of paramount importance, in that focal HI is curable by partial pancreatectomy. Interventional radiology studies, such as transhepatic portal venous insulin sampling
(54) and selective pancreatic arterial calcium stimulation (51), have been used to localize focal lesions. Both have only modest success and are technically difficult and highly invasive. More recently, PET scans with 18-fluoro-L-3,4-dihydroxyphenylalanine (18F-DOPA) have been shown to accurately discriminate focal HI from diffuse HI (55–57). In a recent study including 50 patients with HI, the positive predictive value of 18F-DOPA in diagnosing focal adenomatosis was 100% and the negative predictive value was 81% (58). It has been previously shown that β-cells take up 1-DOPA (59) and that DOPA decarboxylase is active in pancreatic islet cells (60). In children with focal HI, there is local accumulation of 18F-DOPA, and coregistration of PET and CT images allows the anatomical localization of the lesion. Diffuse pancreatic accumulation of 18F-DOPA is consistent with diffuse HI.

**HISTOLOGY**

In diffuse HI, β-cells throughout the pancreas are functionally abnormal and have characteristic enlarged nuclei in about 2%–5% of cells. Focal HI lesions are usually <10 mm in diameter and are characterized by the presence of a confluent proliferation of islet-cell clusters (focal adenomatosis) (18). Some of the β-cells within the focal lesion contain enlarged nuclei, but the absence of abnormal or enlarged islet cell nuclei in pancreas that is not adjacent to the focal lesions is essential to the classification as focal rather than diffuse HI (2). In GK-HI, descriptions of islet cell morphology vary, with normal-appearing islets in some cases (28) and enlarged islet size in others (29). Histological studies have described diffuse islet cell “hyperplasia” in CDG-Id-HI (45) and islet cell “hyperplasia” and “hypertrophy” in BWS (61). It is important to mention neidobiolastosis to dispel its continued association with HI. Nesioblastosis describes the persistence of diffuse proliferation of islet cells budding from pancreatic ducts and was thought to be of pathologic significance in children with HI (3); however, it is now recognized as a normal feature of the pancreas in early infancy (4).

**MANAGEMENT**

The goal of treatment in infants with HI is to prevent brain damage from hypoglycemia by maintaining plasma glucose levels above 700 mg/L (70 mg/dL).

**MEDICAL THERAPY**

First-line pharmacologic therapy in patients with HI is diazoxide, a KATP channel agonist. Because a functional KATP channel is required for diazoxide to exert an effect, patients with recessive focal or diffuse KATP-HI do not respond to therapy with diazoxide. Patients with GDH-HI, SCHAD-HI, and perinatal stress–induced HI typically respond well to diazoxide. Patients with GK-HI have a variable response to diazoxide. The dose of diazoxide is 5–15 mg/kg/day, given orally once or twice per day. The side effects of diazoxide include sodium and fluid retention and hypertrichosis. Should it occur, fluid retention can be managed with concomitant diuretic therapy.

Second-line medical therapy for infants unresponsive to diazoxide is octreotide. Octreotide is a long-acting somatostatin analog that inhibits insulin secretion distal to the KATP channel by inducing hyperpolarization of β-cells, direct inhibition of voltage-dependent calcium channels, and more distal events in the insulin secretory pathway. Octreotide is administered either subcutaneously every 6–8 h or via continuous infusion at 5–20 μg/kg/day. The initial response to octreotide is good in most cases of HI, but tachyphylaxis develops after a few doses, rendering therapy inadequate for long-term use.

Glucon can be given as a continuous intravenous infusion of 1 mg/day to help maintain euglycemia in infants awaiting surgery.

**SURGICAL THERAPY**

The decision to operate is based on a laboratory evaluation consistent with HI, medical responsiveness, genetic testing, and imaging. Surgical therapy is indicated in patients that cannot be managed medically or who are thought to have focal HI that can be surgically cured. A preoperative diagnosis is not always accurate despite the diagnostic modalities available. Genetic testing is useful in differentiating focal from diffuse HI; however, a child with a paternally derived mutation and assumed to have focal HI may also have a maternal mutation that was not found on genetic testing (or the parent-of-origin mutational analysis may not be available at the time of surgery). An 18F-DOPA PET scan may not identify a focal lesion and be interpreted as diffuse disease. With the potential for ambiguity of the preoperative diagnosis, it is critical to have a surgeon experienced in pediatric pancreatic surgery as well as pathologists trained in evaluating intraoperative frozen sections to identify focal lesions, which aid in guiding the extent of the surgery (62). Infants with diffuse disease will normally require a near-total pancreatectomy (95%–98%) to control the HI and might require additional therapy with diazoxide, octreotide, and/or frequent feedings to maintain euglycemia.

**PROGNOSIS AND OUTCOME**

Children with HI are at risk for neurodevelopmental disabilities and must be screened. In a series of 90 patients with HI, severe mental retardation was found in 8%, with less severe disability in 18%. Psychomotor retardation was found to be more common in patients...
with neonatal hypoglycemia than in those with onset of hypoglycemia during infancy (63). Patients with HI requiring surgical therapy have a higher incidence of neurodevelopmental problems than patients responsive to medical therapy (64). The risk of developing diabetes has been attributed to pancreatectomy (65); however, it has been observed that patients who did not have surgery can still develop diabetes later in life. In a series of 114 patients with HI, the incidence of diabetes was as high as 27% after pancreatectomy, and the highest rate (71%) was in patients who had undergone more than one surgical resection (66).

Conclusions

With the expanding identification of genetic mutations that cause HI and the ability of imaging to differentiate focal and diffuse disease, management goals can be better geared toward maximizing medical treatment of nonsurgical patients or surgical cure of focal disease. Many patients with diffuse disease require a near-total pancreatectomy and continued postoperative medical treatment for HI. Hopefully, with a better understanding of the molecular genetics, effective medical therapies for patients with diffuse HI will be developed in the coming years. Lastly, it is important to emphasize that the management of HI requires a multidisciplinary approach that includes pediatric endocrinologists, radiologists, surgeons, and pathologists who are trained in diagnosing, identifying, and treating HI. With advancements in diagnosis and disease-specific treatments, it is essential to refer a child with HI to a specialized center that is equipped to manage the disease.

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References

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