Abstract

Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) is the most common cause of recurrent hypoglycemia in neonates and infants. It is a disorder of glucose homeostasis characterized by unregulated hyperinsulinemia and profound hypoglycemia. PHHI may be differentiated from other causes of hypoglycemia by demonstrating the persistence of inappropriately high insulin levels regardless of blood glucose concentration. Prompt recognition and treatment of PHHI is critical because uncorrected hypoglycemia in the newborn period is associated with permanent damage to the central nervous system and subsequent mental retardation. The aim of therapy is to maintain euglycemia to protect the developing brain from possible damage. Despite recent advances in medical treatment, subtotal pancreatectomy is often necessary. This article will review the function of insulin, glucagon, and somatostatin, pathophysiology of hyperinsulinism, clinical manifestations, differential diagnosis, management, and reported neurologic outcomes of newborns and infants with PHHI.

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Persistent Hyperinsulinemic Hypoglycemia in Infants

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Persistent hyperinsulinism is a genetically heterogeneous condition associated with excessive insulin production and, although rare, it is the most common cause of severe, persistent hypoglycemia beyond the immediate neonatal period.^{1–3} It is referred to as persistent hyperinsulinemic hypoglycemia of infancy (PHHI). PHHI was first described more than 40 years ago by McQuarrie⁴ and usually presents between birth and the first 3 months of life.^{1,2} In a noninbred White population, the estimated frequency is 1 in 50,000 live births^{5,6} but in certain populations, such as Saudi Arabia, where approximately 50% of births occur to parents who are first or second cousins, the incidence rises sharply to 1 in 2700 live births.^{7–9} Previously there was a lack of unifying hypothesis regarding the pathophysiology of the condition, making diagnosis difficult and management strategies problematic. There is increasing evidence, however, that the disorder frequently has a genetic rather than a sporadic origin. Recent investigations suggest that the pathophysiology is commonly caused by genetic defects in the regulation of insulin secretion and generalized beta-cell dysfunction.^{10,11} In some infants, recessively inherited mutations have been found in the gene for the plasma membrane sulfonyleurea receptor (SUR1) or its associated inwardly rectifying potassium channel (KIR6.2) of the beta cells.^{5,12–14} Mutations of SUR1 have been found in Ashkenazi Jews and in residents of Saudi Arabia.^{7,15,16} Other cases have described a milder, dominantly inherited form of hyperinsulinism that is not linked to the SUR1 locus but is thought to be a mutation in the glucokinase gene.^{17,18} A third group of described cases have an unusual combination of congenital hyperinsulinism and hyperammonemia.^{10,19} Additionally, several studies have now clearly demonstrated the existence of two forms of hyperinsulinism: *diffuse* involvement of the pancreatic beta cells or *focal* adenomatous islet cell hyperplasia.^{12,20–23} However, many sporadic and familial cases of hyperinsulinism remain unexplained.²⁴

Patients affected with any of the various forms of hyperinsulinism are at high risk for seizures and permanent brain damage. Early treatment and diagnosis are essential to prevent long-term neurologic sequelae. The aim of therapy is to maintain euglycemia to protect the developing brain from possible damage. Because the cerebral glucose concentration approaches zero when plasma glucose concentration decreases to below 40 mg/dL, blood glucose should be maintained above this level. Traditionally, management has involved initial high rates of glucose infusion (>12 to 15 mg/kg/min) followed by the addition, if needed, of antihypoglycemia medications. Treatment is then dependent on diagnosis. If medical management fails, surgical exploration and nearly total pancreatectomy are indicated.⁶

Fig 1. The pancreas and endocrine cells. Alpha cells secrete glucagon and beta cells secrete insulin.

Physiology

All tissues use glucose as a source of energy, but the brain and formed elements of blood have an obligatory glucose requirement. The brain cells are permeable to glucose and can utilize glucose without the intermediation of insulin. In addition, the brain is able to metabolize ketone bodies, acetoacetate, and beta-hydroxybutyrate for up to two-thirds of its energy requirements in the absence of glucose.^{25–27}

The pancreas secretes two important hormones that regulate glucose, lipid, and protein metabolism: glucagon and insulin. It is composed of two major types of tissues: the acini, which secrete digestive juices into the duodenum, and the islets of Langerhans, which secrete the hormones insulin and glucagon directly into the blood. The islets of Langerhans contain three types of hormone-secreting cells: the alpha cells, which secrete glucagon, the beta cells, which secrete insulin, and the delta cells, which secrete somatostatin and/or gastrin. (Fig 1) Additionally, several other hormones are active in glucose homeostasis. The endocrine system plays an important role in modulating the process of glucose utilization: glycogenolysis (breakdown of hepatic glycogen yielding glucose), gluconeogenesis (the production of glucose from noncarbohydrate precursors), lipolysis, and ketogenesis.^{24,28} The anterior pituitary secretes growth hormone (GH) and adrenocorticotropin (ACTH). The latter causes the adrenal cortex to secrete cortisol, which has multiple functions for control of metabolism.^{25,26} The effects of insulin, growth

hormone, cortisol, epinephrine, and glucagon in metabolism are summarized in Table 1.

Blood glucose concentration is a reflection of the balance between glucose input into the circulation from food intake and glucose extraction from blood for consumption by the tissues. Glucose input includes sugars and carbohydrates in the diet, glucose release from glycogen stores, and gluconeogenesis. Pathways of glucose extraction include glucose storage as glycogen in the liver and muscles, glucose conversion to lipid, and glucose oxidation.^{27,29,30}

During feeding, increased blood glucose and amino acid levels, as well as gut hormones, stimulate insulin secretion and suppress glucagon release. The main action of insulin is in the liver, where it stimulates conversion of glucose to glycogen and decreases gluconeogenesis and glycogenolysis.^{25–27} Glucose is also stored as glycogen in the muscles. It is oxidized in the muscle and adipose tissue and converted to lipid in the liver and adipose tissue. Insulin stimulates amino acid incorporation into protein and fatty acid incorporation into lipids.

During periods of fasting, the source of energy shifts from the oxidation of glucose to the oxidation of fat. Early in fasting, glucose is supplied by the breakdown of hepatic glycogen stimulated by epinephrine and glucagon. After hepatic glycogen stores are depleted, the body depends on new glucose produced from precursors in muscle and adipose tissue. Gluconeogenesis is stimulated by growth hormone and cortisol. With prolonged fasting, adipose tissue is broken down into free fatty acids (FFA) and glycerol. FFA can be used directly as a fuel by tissues and are oxidized in the liver to provide energy with resultant formation of ketone bodies (acetoacetate and β -hydroxybutyrate).^{29,30} Ketone bodies can be used as an alternate fuel as previously mentioned.

To summarize, the maintenance of normal blood glu-

Table 1. Hormone Regulation of Glucose Homeostasis^{25–28,35}

Insulin	↑ Glucose oxidation	↓ Glycogenolysis
	↑ Glycogen synthesis	↓ Gluconeogenesis
	↑ Lipogenesis	↓ Lipolysis
	↑ Protein synthesis	
Growth hormone	↑ Protein synthesis	↓ Glucose oxidation
	↑ Gluconeogenesis	
	↑ Lipolysis	
Cortisol (ACTH)	↑ Gluconeogenesis	
	↑ Proteinolysis	
Epinephrine	↑ Glycogenolysis	
	↑ Lipolysis	
Glucagon	↑ Glycogenolysis	↓ Glycogen synthesis
	↑ Gluconeogenesis	
	↑ Lipolysis	

Table 2. Classification of Hypoglycemia in Infants^{3,25,28}

Transient	Persistent
<ul style="list-style-type: none"> ■ Decreased production <ul style="list-style-type: none"> ● Premature and SGA infants ■ Increased utilization-hyperinsulinism <ul style="list-style-type: none"> ● Infant of a diabetic mother ● Erythroblastosis fetalis ● Improper UA catheter placement ● Rapid discontinuation of IV glucose ● β Cell hyperplasia ■ Decreased production and increased utilization <ul style="list-style-type: none"> ● Fetal distress (asphyxia, toxemia) ● Cyanotic heart disease 	<ul style="list-style-type: none"> ■ Decreased production or release of hepatic glucose <ul style="list-style-type: none"> ● Defects in gluconeogenesis ● Defects in glycogenolysis ■ Decreased alternate fuel production <ul style="list-style-type: none"> ● Defects in fatty acid oxidation ● Defects in ketogenesis ■ Decreased production and/or limited substrate <ul style="list-style-type: none"> ● Hormone deficiencies ■ Increased utilization <ul style="list-style-type: none"> ● Hyperinsulinism — endogenous ● Exogenous

cose during fasting is dependent on both the ability to produce adequate glucose (glycolysis and gluconeogenesis) and the ability to utilize alternative sources of energy via fatty acid oxidation. It is essential that the blood glucose level be maintained above a critical level. When blood glucose levels fall below 40 mg/dL, cerebral glucose concentration approaches zero and symptoms of hypoglycemia develop, characterized by irritability, seizures, and eventual comatose state.^{26,29}

Pathophysiology

Exaggerated insulin secretion occurs in a variety of different states in the neonate with resultant hypoglycemia.^{1–3,11,31} Hypoglycemia may be classified according to duration of symptoms and organized into transient or persistent states (Table 2). These states can be further divided into five major categories of glucose metabolism disruption: 1) failure to receive or absorb nutrients; 2) decreased production or release of hepatic glycogen; 3) limited substrate for gluconeogenesis; 4) decreased alternate fuel production; and 5) increased utilization of glucose. Of these five major categories, neonates will usually fall into three of the transient states or four of the persistent states. In general, transient forms of hypoglycemia usually correct within 3 to 7 days of life and require glucose infusions equal to normal glucose production rates. Persistent forms of hypoglycemia are more protracted and severe than transient forms and require prolonged treatment. Infants with a disorder in any of these categories will present with hypoglycemia as the primary problem.^{29–31}

PHHI consists of persistent hyperinsulinemia for more than several weeks and is characterized by inappropriately high insulin secretion that is not suppressed during hypoglycemia.³² An elevated insulin concentration makes the reduction of glucose for utilization by insulin-dependent

tissues impossible. The increased insulin level also suppresses glucose release from hepatic glycogen, whereas the levels of alternative substrates such as free fatty acids and ketone bodies are already low. In addition, the elevated insulin level is believed to suppress glucagon activity, resulting in a further decrease of glycogenolysis and gluconeogenesis.^{25,33}

Clinical Manifestations

Newborns and infants with hyperinsulinemia will have severe and recurrent or persistent hypoglycemia. The symptoms are generally present from the first few hours of life, although low blood glucose levels may not be discovered immediately. Many infants cannot tolerate even 1 to 2 hours of fasting, while others become hypoglycemic despite support with IV glucose. The signs and symptoms are related to neurogenic stimuli with autonomic discharge of catecholamines and acetylcholine and/or profound decreases in blood glucose with resulting brain glucose deprivation.²⁹ Severe and prolonged hypoglycemia may cause permanent brain damage in a pattern that is similar to that caused by severe asphyxia.³ In the infant, signs and symptoms of hypoglycemia are nonspecific but may include seizures and can be as severe as sudden death.^{29,30,34,35} Milder symptoms, such as tremors and jitteriness, hypotonia, feeding problems, irritability, tachycardia, sweating, cyanosis, and occasionally hypothermia may be present^{29,36} (Table 3).

Until recently, there were no reports of distinguishing physical findings of hyperinsulinism; however, de Lonlay and coworkers, reported 17 patients with hyperinsulinemic hypoglycemia and consistent facial features.³⁷ These patients presented with high forehead, small nasal tip, and short columella, smooth philtrum, and a thin upper lip. Four patients had, in addition, a square appearance of the face. This study suggests that the facial alterations are

Table 3. Signs and Symptoms of Hypoglycemia in Infants^{3,28,29,34,35}

● Abnormal high-pitched cry	● Apathy
● Apnea or irregular breathing	● Poor feeding
● Lethargy	● Cyanosis
● Jitteriness	● Sweating
● Tremors	● Hypothermia
● Hypotonia	● Seizures
● Tachypnea	● Cardiac arrest

likely related to fetal intoxication by insulin.³⁷ Additionally, infants with PHHI are often large for gestational age due to increased adiposity^{2,30} and many are often plethoric.²¹ The clinical features of hyperinsulinism are listed in Table 4.

Differential Diagnosis

The differential diagnosis for hypoglycemia is long and complex.^{38,39} A list of disorders that can cause infantile hypoglycemia must include all congenital metabolic and endocrine disorders in addition to more common pathologies, such as growth restriction or infants of diabetic mothers (Table 5). Initial diagnostic testing should determine which category the hypoglycemic infant is most likely to fall within. This distinction is usually possible from measurements of the plasma glucose, serum insulin, cortisol, growth hormone, lactate, free fatty acids, and β -hydroxybutyrate (ketones) at times of hypoglycemia.^{2,11,38} The diagnosis is established when there is an inappropriately elevated serum insulin level despite hypoglycemia^{9,24,39} and a brisk lycemic response to glucagon. Table 6 shows the critical blood and urine samples that should be obtained for measurement of hormones, metabolic substrates, and serum chemistries, and Table 7 provides diagnostic laboratory values. Recent discovery of hyperinsulinism/hyperammonemia syndrome suggests that serum ammonia levels should be included during the diagnostic evaluation.^{19,24} Fig 2 illustrates how the determination of blood specimens is used in the differential diagnosis of hyperinsulinism. In addition, the first voided urine following a hypoglycemic episode should be tested

Table 4. Clinical Features of Hyperinsulinism^{3,30,40}

- Usually less than 12 months of age at time of presentation
- Hypoglycemia soon after feeding (0-5.5 hours, average $\approx$ 2 hours)
- Serum insulin measurable with blood glucose < 40 mg/dl
- Brisk lycemic response to glucagon > 30 mg/dl
- Parenteral glucose to maintain normoglycemia

Table 5. Differential Diagnosis of Hypoglycemia^{3,15,25,29,30,34,35}

- Transient hypoglycemia
 - Infants of diabetic mothers
 - Prematurity
 - Hypothermia
 - Intrauterine growth restriction (IUGR)
 - Small for gestational age (SGA)
 - Septicemia, asphyxia/birth depression
 - Erythroblastosis fetalis
 - Beckwith–Wiedemann syndrome
- Persistent hypoglycemia
 - Hyperinsulinemia
 - PHHI
 - Beta-cell adenoma
 - Exogenous insulin administration
 - Sulfonylurea use
 - Hormone deficiency
 - Growth hormone
 - Adrenal insufficiency
 - Glucagon
 - Hypothyroidism
 - Panhypopituitarism
 - Errors of metabolism
 - Carbohydrate metabolism disorders
 - Fat metabolism disorders
 - Amino acid metabolism disorders
- Ketotic hypoglycemia
- Reye's syndrome
- Intoxication (salicylate, ethanol)

for the presence of ketones, reducing sugars, and glucose.¹¹ Most causes of hypoglycemia not listed in the categories of Table 2 are either readily apparent (eg, infant with diabetes on insulin therapy) or are part of a complex metabolic clinical picture (eg, Galactosemia, Maple Syrup Urine Disease).

Plasma glucose is measured to confirm hypoglycemia. Normally, in the presence of hypoglycemia, the insulin level should be unmeasurable. If the insulin is high, hyperinsulinemia is likely, however, insulin levels should be measured repeatedly because insulin secretion is pulsatile and is not always elevated at the time it is obtained.^{27,30} If the growth hormone is not above 8 ng/mL or the cortisol is not above 20 μ g/mL in the presence of hypoglycemia, a hormonal deficiency is suggested. If the lactate is elevated, a defect in gluconeogenesis is indicated. Normally, β -hydroxybutyrate will rise when an infant is fasted and becomes hypoglycemic.³⁸ A relatively low level is found in hyperinsulinemia because insulin inhibits fatty acid mobilization and infants with hyperinsulinemia usually become hypoglycemic before ketosis develops. If the infant has hypoglycemia with appropriate hormone, lactate,

Table 6. Critical Blood/Urine Samples in Unexplained Hypoglycemia^{3,10,28,69}

Blood				Urine
Metabolites	Insulin secretion	Counterregulation	Fatty acid oxidation	Ketones
<ul style="list-style-type: none"> ● Glucose ● Lactate/pyruvate ● Alanine, amino acids ● Ammonia 	<ul style="list-style-type: none"> ● Insulin ● C-peptide ● Proinsulin 	<ul style="list-style-type: none"> ● Growth hormone ● Cortisol ● Glucagon ● Epinephrine 	<ul style="list-style-type: none"> ● Free fatty acids ● β-OHB/AcAc ● Carnitine (free/total) ● Plasma acylcarnitins 	<ul style="list-style-type: none"> ● Reducing sugars ● Organic acids ● Acylcarnitines ● Acylglycine

Note: β -OHB/AcAc are β -hydroxybutyrate and acetoacetate.

and β -hydroxybutyrate levels, then ketotic hypoglycemia is the likely diagnosis.²⁸ Of note, the serum C-peptide concentration is low or undetectable when hyperinsulinism is caused by exogenous insulin administration. An extraordinarily high serum insulin concentration with low C-peptide concentration suggests factitious disease caused by exogenous administration of insulin, a rare case of child abuse.^{1,3,11,30}

Although fasting is a useful diagnostic procedure, it must be done with caution. Infants with defects in fatty acid oxidation may suffer cardiac arrest during a fasting stress. An alternative approach is to first exclude a defect in fatty acid oxidation by measuring serum carnitine, urine acylcarnitines after a carnitine load, and urine acylglycines.⁴⁰

The differential diagnosis of the hypoglycemic infant with an appropriately suppressed serum insulin concentration and ketosis can be further delineated depending on whether the liver is large. A large liver suggests a glycogen storage disease or disorder of gluconeogenesis. The liver is normal in size in patients with ketotic hypoglycemia,

cortisol/ACTH deficiency, GH deficiency, glycogen synthetase deficiency, panhypopituitarism, and amino acidopathies/organic acidemias.^{3,41}

Management

The goal of management for PHHI is to stabilize serum glucose to prevent the harmful effects of hypoglycemia while minimizing the treatment-associated complications. Controversy continues regarding the choice of therapy, and no single strategy has proved effective. There is consensus however about treatment modalities and most plans are directed toward suppressing insulin production, using drugs to antagonize the effects of insulin, and reduction of beta cell mass by surgical resection.^{25,29,42} Some infants with significant hypoglycemia will improve markedly if they can be maintained with medical therapy^{2,11,28} and spontaneous remission has been described by Kubota and coworkers, in a small number of infants.⁴³

Treatment is divided into several phases. For acute management, stabilization of blood glucose may require

Table 7. Diagnostic Serum Lab Values for Hyperinsulinism^{11,16,28}

Hyperinsulinism (normal serum values)	
● Glucose	● <40 mg/dl = 2.2 mmol/L (>40 mg/dl)
● Insulin	● >13 μ U/ml (13 μ U/ml)
● Insulin:glucose ratio	● >0.3 (<0.3)
● Cortisol	● >20 μ g/dl (5–20 μ g/dl)
● Growth hormone	● >7–10 ng/mL
● β -Hydroxybutyrate	● <1 mmol/L (>2 mmol/L)
● Free fatty acids	● <1 mmol/L (>1.5 mmol/L)
● Glycemic response to glucagon	● >30 mg/Dl (<30 mg/Dl)
● IGFBP1	● <100 ng/mL (>100–400 ng/mL)

Note: IGFBP, insulin-like growth factor binding protein (peptides that regulate growth and cellular proliferation).

* β OH Butyrate is β -hydroxybutyrate (ketones)

Fig 2. Flow chart for differential diagnosis of hypoglycemia.^{2,11,28,29}

an intravenous glucose infusion rate up to 20 or 30 mg/kg/min, well above the usual 6 to 8 mg/kg/min needed by most infants. As previously mentioned, the hypoglycemia must be corrected immediately to prevent irreversible brain damage. Such volume and concentration of glucose frequently requires central venous access.^{34,35} Glucose polymers can also be added to increase the carbohydrate intake but care must be taken because too high an osmolar load can predispose the infant to necrotizing enterocolitis.^{30,42}

During the next phase of treatment, attempts are made to decrease the parenteral fluid by adding a combination of drugs, which includes diazoxide, octreotide (somatostatin analog), nifedipine, glucagon, and glucocorticoids⁹ (Table 8). Diazoxide is one of the most effective drugs in controlling hypoglycemia and acts to inhibit insulin secretion. It has been suggested that it may also exert a direct effect on hepatic glucose production.^{25,44,45} Side effects include fluid retention, and a diuretic medication such as hydrochlorothiazide or lasix is sometimes used with Diazoxide in anticipation of this.^{6,42,44} Octreotide is a long-acting somatostatin analog that also acts to inhibit insulin secretion by activating the beta cell potassium channels, but it involves the possibility of suppression of growth hormone^{28,44,46–48} abdominal distention, and gallstones.⁶ Nifedipine is a calcium channel blocking agent and acts to decrease insulin secretion by closing the ATP potassium channels in the pancreatic beta cells.^{49–51} Glucagon is used as a temporizing agent and antagonizes insulin action by mobilizing hepatic glycogen stores, thereby decreasing the glucose requirement of the infant with PHHI. It is most effective as a holding therapy while the infant is prepared for surgery.²⁹ Finally, glucocorticoids have also been shown to be effective in managing hypoglycemia, but their use is minimal. Although several glucose-producing functions are enhanced by steroids, their primary effect is likely stimulation of gluconeogenesis from protein sources.²⁵ Ehara and coworkers reported effective control of hypoglycemia using a high dextrin formula that contained 31% of calories as dextrin, 40% as glucose, and 19% as amino acids in addition to conventional medical therapy.⁵² Dextrin is a glucose polymer that is a slow release form of glucose, therefore it can maintain normoglycemia for longer periods. Frequent carbohydrate-rich feedings used to treat infants with glycogen storage disease type I have also been used successfully to treat two infants with PHHI.^{21,53} Cornstarch or tapioca starch has resulted in longer euglycemia in some patients^{11,28} but is reported to be most effective when used in combination with nifedipine.⁵³ Side effects of raw cornstarch include abdominal distention and obesity. In addition, a low protein diet may help some infants because protein stimulates insulin secretion.^{11,19}

Table 8. Treatment Options for Hyperinsulinemia^{6,11,27,29,33,35,42,50,70,71}

Drug	Diazoxide	Octreotide	Nifedipine	Glucagon	Hydrocortisone
Action	<ul style="list-style-type: none"> • Opens the K⁺ ATP channels, ↑ hepatic glucose production 	<ul style="list-style-type: none"> • Activates beta cell K⁺ channels and inhibits insulin secretion 	<ul style="list-style-type: none"> • Ca channel blocker, ↓ insulin secretion 	<ul style="list-style-type: none"> • ↑ Hepatic glycogenolysis and gluconeogenesis 	<ul style="list-style-type: none"> • Short acting glucocorticoid promotes gluconeogenesis
Administration route	<ul style="list-style-type: none"> • Orally 	<ul style="list-style-type: none"> • Intravenously • SQ injection 	<ul style="list-style-type: none"> • Orally 	<ul style="list-style-type: none"> • Intravenously • Intramuscularly 	<ul style="list-style-type: none"> • Intravenous • Orally
Usual dose	<ul style="list-style-type: none"> • 5–20 mg/kg/day 	<ul style="list-style-type: none"> • Continuous SQ injection • 5–40 µg/kg/day 	<ul style="list-style-type: none"> • 0.3–0.8 mg/kg/day 	<ul style="list-style-type: none"> • 0.2 mg/kg bolus • 48–300 µg/kg/day 	<ul style="list-style-type: none"> • 5–8 mg/kg/day
Side effects	<ul style="list-style-type: none"> • Hypertrichosis • Vomiting • Fluid retention • Cardiomyopathy • Intractable vomiting • Cholelithiasis • Facial changes • Hypotension 	<ul style="list-style-type: none"> • GH, TSH (thyroid stimulating hormone), ACTH suppression • Steatorrhea • Abdominal distention 	<ul style="list-style-type: none"> • Hypotension • Tachycardia 	<ul style="list-style-type: none"> • Nausea • Growth restriction • ? Ileus • Hypokalemia 	<ul style="list-style-type: none"> • Hypoglycemia • Glucosuria • Acute adrenal insufficiency • Fluid/electrolyte disturbance

Fig 3. Algorithm for treatment of neonatal hypoglycemia. Adapted from Cowett RM, Lougheed JL: Neonatal glucose metabolism: Differential diagnosis, evaluation, and treatment of hypoglycemia. Neonatal Network 2002;21:9-19.

Although medical management is a more conservative approach, surgical intervention is often necessary. Many infants who are treated medically, gradually improve and therapy can be withdrawn. Others remain dependent on medical therapy with significant dietary restrictions and possible side effects of drug therapy.

It is important to ensure that conservative therapy will consistently maintain normoglycemia (>60 mg/dL). During the final phase of treatment, a pancreatic resection is performed when it is clear that hypoglycemia cannot be controlled by diet and oral medication alone. Previous data suggest that 95% pancreatectomy is the optimal resection for early-onset PHHI, and partial pancreatectomy (65 to 80%) may be adequate for late-onset disease.⁵⁴ Based on a review of the literature, Shilansky and coworkers reported that 97% resolution of hypoglycemia in patients following a 98% pancreatic resection, 64% resolution in the 95% pancreatectomy group, and 54% resolution of hypoglycemia in the group who had a subtotal (<95%) resection.⁵⁵ Re-

searchers further suggest that partial pancreatectomy is sufficient to treat infants with the focal form of hyperinsulinemia, and near total pancreatectomy is the procedure of choice to treat the diffuse lesions.^{22,41,56-58} However, although the ultimate goal of surgery is cure, pancreatectomy may only reduce beta cell mass enough to allow for more effective medical management and diet and drugs may still be needed to achieve euglycemia.⁵⁹ Repeat surgeries may also be needed. A number of researchers have reported a high incidence of diabetes after a 95% pancreatectomy and, according to several studies, it seems that the incidence increases with more extensive surgery.^{55,60,61} Additionally, diabetes has been reported to be related to age and increases or develops most at puberty.^{59,62} One of the most common surgical complications is injury to the common bile duct (Fig 1), which can be corrected with a choledochoduodenostomy. Adhesions with intestinal obstruction can occur within several months of surgery.³⁰ Recently, Blakely and coworkers performed a laparoscopic pan-

createctomy in a newborn infant and suggest that, in patients with PHHI in whom further surgery is likely, this technique is the ideal initial surgical approach.⁶³

Outcome

The severity of hypoglycemic episodes and the form of hyperinsulinemia influence prognosis. Neurologic sequelae are the major concern with severe hypoglycemia during infancy. Psychomotor retardation, learning disability, seizures, and diverse neurologic sequelae have been reported in many children at follow up.^{62,64} In addition to learning disabilities, stroke-like symptoms or cerebral palsy can occur. Strabismus or blindness may also be caused by hypoglycemia.⁶⁵ Even with rapid diagnosis and appropriate management, up to 20% of infants will suffer permanent damage and up to 50% of children will have brain damage if their condition is not recognized or if treatment is ineffective.^{66,67} As noted previously, infants with PHHI are especially vulnerable because they do not produce ketone bodies during hypoglycemia.⁶⁸

Some infants with PHHI are reported to be in clinical remission and the antihypoglycemic treatment may be tapered or discontinued. Although surgery results in postoperative control of hypoglycemia, in long-term follow-up, development of diabetes mellitus and exocrine failure remain significant problems.^{1,49,50} This type of diabetes appears to resemble type II because these adolescents rarely develop diabetic ketoacidosis. Some may be managed with diet alone, but most require insulin therapy to control blood glucose. Additionally, failure to absorb food may be a problem due to loss of the enzymes produced by the pancreas for digestion. These children may require long-term enzyme replacement in addition to antihypoglycemic medication.⁶⁶

Unfortunately, the pathogenesis of PHHI is not well understood. There is increasing evidence, however, to suggest that genetic evaluation before surgery will be a useful tool to determine the optimal surgical strategy.⁵⁹ Perhaps the combination of less severe pancreatectomy and intensive medical therapy may help to avoid the occurrence of diabetes and pancreatic dysfunction. There are no large studies with long-term follow-up of medically managed patients without surgical intervention. In addition, there are not enough patients who have been treated with surgical intervention and followed through puberty to assess outcome.¹ At present, it is believed that an alternate treatment strategy is needed, since pancreatectomy fails to prevent hypoglycemia and increases the risk of development of diabetes in a minimum of two-thirds of infants treated.⁵⁵

Recognition of infants at risk for hypoglycemia and appropriate screening is an essential nursing function

when caring for newborns. Guidelines for care and various management algorithms/protocols that provide direction for treatment should be present in all newborn and special care nurseries. Cowett and Loughheed published an algorithm for treatment of hypoglycemia in 2002.²⁹ They provide a clear and comprehensive approach to early intervention for caregivers to follow (Fig 3). In addition to screening, the nursing role includes monitoring for further complications and close surveillance of glucose levels.

Conclusion

Persistent hyperinsulinemic hypoglycemia is a highly complex disorder that requires aggressive treatment. Excessive insulin release from pancreatic beta islet cells results in profound unremitting hypoglycemia. Prompt recognition and correction of hypoglycemia are necessary to prevent damage to the developing brain. Failure to do so early in the course of the disease may result in mental retardation, permanent neurological defects, and even death.^{55,65} The diagnosis of PHHI is likely in hypoglycemic infants with detectable serum insulin levels. Low serum ketone body concentrations, low serum fatty acid concentrations, and a glycemic response to glucagon in the presence of low serum glucose concentrations support the diagnosis of PHHI and rules out errors of metabolism and hypopituitarism as causes of hypoglycemia.² Despite the etiology, the goal of therapy is rapid control of hypoglycemia. Even if the newborn appears to be asymptomatic, hypoglycemia may still result in neurologic damage and therefore must be managed as aggressively as in a symptomatic neonate.^{1,11}

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Objectives: At the end of this article the reader will be able to: 1) Describe the pathophysiology of hyperinsulinism. 2) Discuss the clinical manifestations of hyperinsulinism. 3) Identify risk factors for hyperinsulinism. 4) Outline a management plan for the infant and family experiencing hyperinsulinism.

Article: Persistent Hyperinsulinemic Hypoglycemia in Infants

- Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) usually presents
 - at birth
 - in the first week of life
 - by 3 months of life
- The estimated incidence of PHHI in high-risk populations such as Saudi Arabians is 1 in
 - 2,700 live births
 - 27,000 live births
 - 50,000 live births
- According to recent studies, PHHI is a genetic disorder that results in beta-cell dysfunction and alterations in the regulation of
 - glucagon uptake
 - insulin secretion
 - lipolysis
- Newborns affected with PHHI are at high risk for
 - intracranial hemorrhage
 - periventricular leukomalacia
 - seizures
- Cerebral glucose levels approach zero when the neonate's plasma glucose concentration decreases to less than
 - 40 mg/dL
 - 50 mg/dL
 - 60 mg/dL
- Body tissues that have an obligatory requirement for glucose as a source of energy are
 - hepatocytes
 - neurons and red blood cells
 - pancreatic beta cells
- Delta cells of the pancreas secrete
 - glucagon
 - insulin
 - somatostatin
- Alpha cells of the pancreas secrete
 - gastrin
 - glucagon
 - insulin
- According to Table 1, the hormone responsible for a decrease in glucose oxidation is
 - cortisol
 - growth hormone
 - insulin
- According to Table 1, the hormone responsible for an increase in protein production is
 - cortisol
 - epinephrine
 - insulin
- The main action of insulin occurs within the
 - liver
 - pancreas
 - small intestine
- In periods of fasting, an alternative fuel to glucose is
 - acetoacetate
 - brown fat
 - glycogen
- A persistent cause of hypoglycemia in the newborn is
 - cyanotic heart disease
 - defect in ketogenesis
 - small for gestational age (SGA)
- A symptom of hypoglycemia in neonates is
 - hypertonia
 - seizures
 - tachycardia
- Transient causes of hypoglycemia usually correct within
 - 7 days
 - 10 days
 - 13 days
- Infants with PHHI are usually term and
 - appropriate for gestational age (AGA)
 - large for gestational age (LGA)
 - small for gestational age (SGA)

17. The suggested mechanism for facial alterations (square face, high forehead, smooth philtrum, etc.) common in infants born with PHHI in the de Lonlay study is
 - A. fetal intoxication by insulin
 - B. genetic abnormality
 - C. placental deficiency
18. Critical blood studies for PHHI should include serum
 - A. ammonia level
 - B. electrolytes
 - C. lactose dehydrogenase
19. A newborn infant presents with hypoglycemia. The first voided specimen from this infant should be tested for the presence of
 - A. blood
 - B. proteins
 - C. reducing substances
20. In the presence of hypoglycemia, a newborn's insulin level should be
 - A. markedly elevated
 - B. nearly zero
 - C. within normal limits
21. Fasting for diagnostic procedures should be avoided in the infant with defects in fatty acid oxidations because of the risk for
 - A. cardiac arrest
 - B. hypoxemia
 - C. profound hypertension
22. Hepatomegaly in the newborn with persistent hypoglycemia suggests
 - A. glycogen storage disease
 - B. ketotic hypoglycemia
 - C. panhypopituitarism
23. Management of the infant with PHHI may require an intravenous glucose infusion rate of
 - A. 5 mg/kg/min
 - B. 15 mg/kg/min
 - C. 25 mg/kg/min
24. The most effective drug for controlling hypoglycemia in the newborn is
 - A. cortisol
 - B. diazoxide
 - C. nifedipine
25. Octreotide is a drug analog for
 - A. glucagon
 - B. insulin
 - C. somatostatin
26. The drug that decreases insulin secretion by closing adenosine triphosphate (ATP) potassium channels in pancreatic beta cells is
 - A. diazoxide
 - B. nifedipine
 - C. octetrotide
27. Dietary control of hypoglycemia in the infant with PHHI is best achieved with a formula that is high in
 - A. calories
 - B. dextrin
 - C. lactose
28. The goal of conservative therapy for the infant with PHHI is to maintain the serum glucose greater than
 - A. 45 mg/dL
 - B. 60 mg/dL
 - C. 75 mg/dL
29. The percentage (%) of the pancreas removed for optimal surgical treatment is
 - A. 65-80%
 - B. 81-95%
 - C. 95%
30. During adolescence, individuals with surgically treated PHHI are at high risk for developing
 - A. Cushing's syndrome
 - B. diabetes insipidus
 - C. diabetes mellitus