Contemporary Endocrinology
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Diva D. De León-Crutchlow
Charles A. Stanley *Editors*

Congenital Hyperinsulinism

A Practical Guide to Diagnosis and Management

Humana Press

Contemporary Endocrinology

Series Editor

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We dedicate this book to the "sugar" babies and their families. Their strength and perseverance inspire us every day to continue our efforts to improve the understanding of the disease, to develop new therapies, and to look with optimism to the possibility of a cure in the future.

We thank our colleagues that dedicated many hours to write these chapters and our families that patiently support us to continue our work.

Diva D. De León-Crutchlow
and Charles A. Stanley

Series Editor Foreword

Insulin is perhaps the most potent anabolic hormone in mammals. Because of its pleiotropic characteristics, the term "symphony of insulin action" has been used to describe both the power and the multitude of insulin's effects. Although insulin's power is life-sustaining, it may turn into a lethal weapon when uncontrolled. This is indeed the case with a number of conditions collectively called "congenital hyperinsulinism." If not diagnosed and treated rapidly, congenital hyperinsulinism can produce devastating consequences, including permanent brain damage and even death.

It is because of the above considerations that the current volume in the Contemporary Endocrinology series is an extremely important book. An international group of experts led by Drs. Diva D. De León-Crutchlow and Charles A. Stanley discuss the causes (including genetics) of congenital hyperinsulinism, its clinical manifestations, its diagnosis (which is often not straightforward), medical and surgical therapeutic options, and long-term care of children affected by this condition.

Guided by this information and these recommendations, neonatologists, pediatricians, pediatric endocrinologists, and other physicians taking care of the "sugar babies" (the term used by the editors to describe their patients) will undoubtedly help save and dramatically improve the quality of many lives.

New York, NY, USA — Leonid Poretsky, MD

Preface

Congenital hyperinsulinism is the most difficult endocrinologic emergency of infants and children for pediatricians to diagnose and manage. The importance of this problem was first recognized in 1953 by Dr. Irvine McQuarrie in his Presidential Address to the American Pediatric Society. He stressed the fact that he had encountered too many "cases…of irreparable brain damage" due to "severe spontaneous hypoglycemia in infants who were victims of delayed diagnosis and inadequate early therapy." At the time Dr. McQuarrie called the disorder idiopathic hypoglycemia of infancy, because it was thought that hypoglycemia due to endogenous hyperinsulinism could only occur in adults with insulinomas; that the underlying disorder was hyperinsulinism did not become recognized for another decade when Yalow and Berson discovered the insulin radioimmunoassay.

Over the past 60 years, it has become appreciated that congenital hyperinsulinism is the most common form of hypoglycemia in children, that the risk of permanent brain injury in these children is high, and that most cases are caused by genetic mutations in pathways controlling insulin release in the pancreatic beta cells. Currently, over a dozen genes have been associated with congenital hyperinsulinism, and additional loci continue to be identified. The most important of these hyperinsulinism genes are the two subunits of the beta-cell ATP-dependent K_{ATP} channel, encoded by two adjacent genes, *ABCC8* and *KCNJ11*, on the short arm of chromosome 11 which are the most common targets for mutations causing hyperinsulinism. Defects in these K_{ATP} channel genes may result in diffuse hyperinsulinism involving all of the pancreas or may cause isolated focal lesions that can be cured by surgical excision. The diagnosis of infants who can be cured by surgery has been dramatically improved by the recent development of technologies for rapid mutation analysis and for preoperative localization of focal lesions using 18fluorodopa PET scans. Medical therapies for children with congenital hyperinsulinism have been limited for many years to a single drug, diazoxide, that was first introduced in 1964. Apart from the introduction of octreotide in the 1980s and longer-acting versions of octreotide in the past 5–10 years, there has been little improvement in the treatment of congenital hyperinsulinism. Fortunately, the several investigational

drugs for hyperinsulinism that are under investigation give hope for major improvements in treatment in the near future.

Given the importance of congenital hyperinsulinism and other transient forms of hyperinsulinism, such as transitional neonatal hypoglycemia and perinatal stress-induced hyperinsulinism, it is essential that pediatricians, pediatric endocrinologists, and neonatologists be able to rapidly diagnose and effectively manage these children to prevent the high risk of "irreparable brain damage." The purpose of this book is to provide a practical guide to diagnosis and treatment of hyperinsulinism in infants and children and, especially, in newborn infants.

Philadelphia, PA, USA

Diva D. De León-Crutchlow, MD, MSCE
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Chapter 1
Approach to the Diagnosis of Neonates and Infants with Persistent Hypoglycemia

Paul S. Thornton and Charles A. Stanley

Introduction

The approach to diagnosing patients with persistent hypoglycemia focuses on two simultaneous processes: (1) evaluating the history of the episode, performing clinical exam for classical features of hyperinsulinism (HI) or alternate explanations, and drawing the critical sample during hypoglycemia and (2) rapidly raising the glucose to >70 mg/dL in order to prevent the risk of brain damage from prolonged and severe hypoglycemia. In this chapter, we review these processes with a particular focus on the role of the fasting study and the diagnosis and clinical phenotyping of the specific forms of hyperinsulinism.

Diagnosis of HI: Fasting Test and "Critical Samples"

The diagnosis of hyperinsulinism in neonates and infants is usually straightforward if one remembers two important characteristic features of the disorder. First, as in most hypoglycemia disorders in infants and children, hypoglycemia in hyperinsulinism almost always means *fasting hypoglycemia*. Second, the pathophysiology of hyperinsulinism is not characterized by "over-secretion" of insulin but rather by a

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failure to appropriately "suppress insulin" before fasting hypoglycemia develops. For this reason, insulin levels are not always elevated sufficiently to make a diagnosis in infants and children with hyperinsulinism. Thus, the diagnosis of hyperinsulinism relies heavily on demonstrating inappropriate effects of insulin on fasting adaptation, i.e., inappropriate suppression of lipolysis and ketogenesis and inappropriate preservation of liver glycogen reserves as hypoglycemia develops [1, 2]. The fasting test essentially allows a presumptive diagnosis of hyperinsulinism to be rapidly made at the bedside using simple point of care meters while awaiting confirmatory results from the laboratory. The fasting test also provides an important opportunity to exclude other disorders that can mimic hyperinsulinism, especially multiple pituitary hormone deficiencies in newborn infants.

Increased glucose utilization is another important hallmark of hyperinsulinism. Rates greater than 10 mg/kg/min (normal glucose utilization in newborns is 4–6 mg/kg/min) almost always indicate hyperinsulinism, except for the rare circumstance of multiple pituitary hormone deficiencies in newborns.

Diagnosis of Hyperinsulinism Using the Closely Monitored Fasting Test

The goal of the fasting test is to evaluate fuel and hormone responses during the development of fasting hypoglycemia. The test procedure is outlined in Table 1.1 and should be performed on a unit with medical and nursing staff trained in the procedure. The patient should have intravenous access for obtaining blood specimens (at least at the end of the test). Plasma glucose and, if possible, plasma beta-hydroxybutyrate should be monitored at the bedside at 2–3 h intervals and more frequently as the plasma glucose falls below 70 mg/dL. A plasma glucose concentration of 50 mg/dL is usually taken as the "critical time" for terminating the fasting challenge and obtaining the "critical samples" for diagnosis. However, the test may need to be ended early if the patient becomes excessively symptomatic or appears distressed (especially important if prior tests of plasma free and total carnitine, acylcarnitine profile, and urine organic acids have not been done to exclude a possible fatty acid oxidation defect). For purposes of diagnosing hyperinsulinism, the "critical samples" obtained at the end of the test should include plasma glucose, insulin, beta-hydroxybutyrate (the predominant ketone), and free fatty acids. Additional laboratory tests can be added to the "critical samples," as desired, to exclude mimickers of hyperinsulinism (especially multiple pituitary hormone deficiencies in neonates).

In practical terms, the patient's previous history should be evaluated to estimate how many hours after starting the fast the patient is likely to develop hypoglycemia and try to time this to occur between 08:00 in the morning and 17:00 in the evening when experienced staff are available and the laboratory is prepared to process samples. In patients on a high glucose infusion rate (GIR), regular feedings should continue, and the GIR should be reduced by 10–20% each feed until hypoglycemia

Table 1.1 Fasting test protocols

A. Diagnostic fasting test:
Perform test on a unit with trained medical/nursing staff
Place 1–2 blood-drawing IV lines and have IV access for emergency resuscitation
Have D10% available for immediate use
Measure glucose and BOHB (POC meter) every 2–3 h until glucose <70 mg/dL; then every 2 h until <60 mg/dL; then hourly until </=50 mg/dL
When glucose <60 mg/dL (POC meter), send specimen for laboratory confirmation of plasma glucose
When plasma glucose ≤50 mg/dL, draw blood for the following:
(1) Essential: glucose, insulin, BOHB, FFA
(2) Important: ammonia, plasma cortisol, GH, lactate, acylcarnitine profile, urine organic acids
(3) Special circumstances: C-peptide, proinsulin, sulfonylurea screen, toxicology screen
B. Glucagon stimulation test (may be done once "critical samples" are obtained)
(1) Measure glucose (POC meter) and then give glucagon 0.5–1 mg either IM or IV push
(2) Monitor glucose (POC meter) every 10 min for 40 min
(3) Terminate prematurely if 30 min glucose is still below 50 mg/dL
(4) After 40 min, may feed and resume treatment to maintain plasma glucose >70 mg/dL
C. Safety/cure fasting test
(1) Have blood-drawing IV line available
(2) Check glucose and BOHB (POC meter) every 2–3 h until glucose <70 mg/dL; then every 2 h until <60 mg/dL; then hourly until </=50 mg/dL. When glucose <60 mg/dL (POC meter), send specimen for laboratory confirmation of plasma glucose
(3) Terminate fast when
(a) Plasma BOHB >2 mmol/L on two separate samples
(b) Plasma glucose <50 mg/dL
(c) Duration of fasting >18 h in <1 year old or >30–36 h in older children

develops. If hypoglycemia does not occur during the weaning, the fasting test should commence with a meal.

The fasting test should be completed with a glucagon stimulation test to assess liver glycogen reserves as another physiologic effect of excessive insulin [3]. A pharmacologic dose of glucagon is preferable (1 mg IM or IV, 0.5 mg in small neonates), because smaller, more physiologic doses (e.g., 0.03 mg/kg) may not produce an adequate response.

Evidence of hyperinsulinism includes an inappropriately detectable insulin level (typically >1–3μU/mL, the detection limit for most laboratories), inappropriately suppressed beta-hydroxybutyrate (typically <1.0 mM) and free fatty acids (typically <1.0 mM), and inappropriately large glycemic response to glucagon (delta glucose >30 mg/dL within 15–30 min). Table 1.2 provides recently reported cutoff values for differentiating between HI patients and ketotic hypoglycemia patients from Ferrara et al. [1]. As noted in this report, 20% of patients with hyperinsulinism had an undetectable insulin level; in these cases, an elevated C-peptide level may be helpful. Measurement of C-peptide is also helpful for differentiating between endogenous and exogenous insulin as a cause of hypoglycemia, such as the possi-

Table 1.2 Interpretation of critical sample results: hyperinsulinism [1]

Plasma glucose	<50 mg/dL
Plasma insulin	>lower limit of detection (~1–2 μU/mL)
Plasma free fatty acids	<1.5 mmol/L
Plasma beta-hydroxybutyrate	<1.8 mmol/L
Glycemic response to glucagon	>30 mg/dL (when initial plasma glucose <50 mg/dL)

bility of surreptitious exogenous insulin administration ("Munchausen syndrome by proxy").

Diagnosis of Hyperinsulinism Based on a Random "Critical Sample"

Whenever possible, the "critical sample" to measure levels of circulating fuels and hormones can be obtained during a spontaneous episode of hypoglycemia (e.g., presentation to an emergency room with symptomatic hypoglycemia) and interpreted as above. An important caveat, however, is that relying solely on the "critical sample" without having intermediate measurements of beta-hydroxybutyrate and free fatty acids can occasionally be misleading. For example, if a hyperinsulinism patient is allowed to be hypoglycemic for a prolonged period, adrenergic stimulation may produce a "breakthrough" rise in free fatty acid and ketone levels. Similarly, in the case of hyperinsulinism due to glucokinase gain-of-function mutations, patients tend to develop a stable level of hypoglycemia at plasma glucose levels between 50 and 65 mg/dL and over 8–12 h may gradually show an increase in beta-hydroxybutyrate levels to greater than 2–2.5 mM. Conversely, in situations where the plasma glucose concentration falls too rapidly to permit turn-on of lipolysis and ketogenesis (such as an abrupt discontinuation of intravenous dextrose leading to sudden hypoglycemia or post-fundoplication surgery), a false diagnosis of hyperinsulinism may be made. Thus, a careful history surrounding the circumstances of the critical sample is important in making a diagnosis of the etiology of hypoglycemia. Note that ammonia levels are elevated in GDH-HI at all times and are not dependent on hypoglycemia; thus, plasma ammonia may be measured at any time to assist in clinical recognition of this form of congenital hyperinsulinism [4].

Table 1.3 Oral protein tolerance test (oPTT)

Have blood-drawing IV available and have D10% available for immediate use
Measure baseline plasma glucose (or POC meter) and insulin
Administer 1 g/kg protein[a] orally or via intragastric tube over 5–15 min
Measure plasma glucose and insulin every 30 mins for 3 h
If plasma glucose drops to <60 mg/dL, may terminate the test with IV dextrose bolus or carbohydrate drink and recheck glucose until >70 mg/dL

[a]Resource Beneprotein® (Nestle Health Sciences). If unavailable, may substitute food protein (e.g., eggs, meat, and cheese)

Other Tests Used to Define Specific Phenotypes of Hyperinsulinism

Oral Protein Tolerance Test (oPTT)

Patients with several of the common genetic forms of congenital hyperinsulinism are predisposed to developing hypoglycemia following either an oral protein load or an oral leucine load [4]. Testing for protein sensitivity can help indicate the possible underlying genetic etiology of hyperinsulinism and is also useful in adjusting the diet to avoid provoking episodes of hypoglycemia. Table 1.3 outlines the method for the oPTT. An abnormal response is defined as a drop in plasma glucose of more than 10 mg/dL with a nadir below 70 mg/dL within 1–2 h [4]. Normal individuals show little change in glucose or have a decrease of less than 10 mg/dL and should not drop below 70 mg/dL. Interpretation of the response is focused on the decrease in plasma glucose concentration during the first 2 h. The insulin response to oral protein load is not helpful in differentiating protein-sensitive and normal individuals—this may reflect the fact that glucagon responses to hypoglycemia are impaired in both K_{ATP}-HI and GDH-HI. Careful monitoring of plasma glucose during the oPTT is necessary, and having rescue intravenous glucose on hand is advisable because patients who are highly protein sensitive can quickly develop symptomatic hypoglycemia within 15–20 min. Protein-sensitive hypoglycemia is associated especially with GDH-HI, SCHAD-HI, and the various forms of K_{ATP}-HI. Patients with GCK-HI are not protein sensitive. There is little information about other rarer forms of HI, although patients with HNF-4A and HNF-1A HI might be suspected to be protein sensitive, since their hyperinsulinism has been suggested to be due to impaired expression of the K_{ATP} channel genes. GDH-HI and SCHAD-HI have both protein- and leucine-sensitive hypoglycemia, because leucine is an allosteric activator of GDH-stimulated insulin secretion in both of these disorders. Protein sensitivity in K_{ATP}-HI occurs by a different mechanism that does not involve leucine or GDH [5].

Table 1.4 Oral glucose tolerance test (oGTT)

Place blood-drawing IV
Measure plasma insulin and glucose
Administer 1.75 g/kg glucose orally or via intragastric tube
Measure plasma insulin and glucose every 30 mins for 3–5 h
Terminate test if plasma glucose <60 mg/dL

Oral Glucose Tolerance Test (oGTT)

Oral glucose tolerance test (oGTT) (for suspected postprandial hypoglycemia: "late dumping syndrome" due to gastric bypass surgery for obesity or fundoplication for gastroesophageal reflux): Glucose tolerance tests provide no useful information in the workup of most forms of hypoglycemia in children, where the problem is chiefly a disorder of fasting adaptation. The exception is patients who have postprandial hypoglycemia secondary to gastric surgery [6] sometimes called "late dumping syndrome" (in infants and children, primarily gastric fundoplication for gastroesophageal reflux; in adults, primarily gastric bypass surgery for obesity). Testing separately for fasting and postprandial hypoglycemia is often essential in patients who have previously had gastric surgery or feeding tubes and might actually have two separate forms of hypoglycemia. Table 1.4 outlines the procedure for a 4 h oGTT; similar information can be obtained with a mixed meal tolerance test, but the oGTT is better standardized. The characteristic abnormality in affected infants and children is a very dramatic rise in plasma insulin (often >100–200 μU/mL) 30–60 min following ingestion of glucose, followed by the development of hypoglycemia at 2–4 h after the glucose load. Often, there is also a marked hyperglycemic spike at 1–2 h after the glucose load (rise >50 mg/dL) and before hypoglycemia develops, but this does not always occur and is not the cause of the hypoglycemia. The underlying mechanism is activation of intestinal incretin hormones by the sudden transit of glucose past the stomach which leads to excessive amplification of the insulin response to the glucose load mediated by GLP-1 [7].

Acute Insulin Response (AIR) Tests

Infants and children with various genetic forms of hyperinsulinism have been shown to have distinctive abnormalities in AIR to different agents that stimulate insulin release, including calcium, leucine, glucose, and tolbutamide [8]. Although AIR tests are not routinely performed now that genetic testing is widely available, there may be circumstances where phenotyping islet responses may be useful in suggesting the underlying defect. The tests are done by rapid intravenous infusion of each agent at intervals of 30 min or greater and following the increase in plasma insulin at 1 min intervals for 5 min. Calcium stimulates insulin release when the beta-cell calcium channels are opened (K_{ATP}-HI); leucine stimulates insulin release when GDH is activated (GDH-HI, SCHAD-HI) [9]; glucose stimulates insulin release in normals, but the response is blunted in K_{ATP}-HI and accentuated in GCK-HI and

PGM1-HI; tolbutamide stimulates insulin release in normals and in most forms of HI, but cases of K_{ATP}-HI show an impaired response.

Genetic Testing in Neonates and Children with Hyperinsulinism

Genetic testing for mutations in the known HI genes provides information that is important for both the diagnosis of HI and planning appropriate treatment. As described in later chapters, the finding of a paternally derived recessive K_{ATP} channel mutation is highly predictive of a potentially curable focal lesion. Therefore, as soon as a diagnosis of congenital HI is suspected, specimens should be sent for mutation analysis on the patient. Importantly, specimens from both parents should be sent at the same time to determine the parent of origin for any disease-causing mutations that may be found. This ensures that there is no delay in being able to interpret the genetic tests and should, in most cases, provide results in less than 7 days.

Important Mimickers to Exclude in the Diagnosis of Hyperinsulinism

Multiple Pituitary Hormone Deficiencies in Neonates

In the newborn period, congenital hypopituitarism can mimic all of the features of congenital hyperinsulinism, including increased glucose utilization, elevated insulin levels, suppressed beta-hydroxybutyrate and free fatty acids, and an inappropriately large glycemic response to glucagon. This contrasts with older infants and children, in whom deficiencies of the counter-regulatory hormones (cortisol and growth hormone) can cause fasting hypoglycemia, but with hyperketonemia. Sometimes, severe hypoglycemia in neonates with pituitary deficiency is associated with cholestatic liver disease. The diagnosis of pituitary deficiency may also be suggested by physical findings, such as midline facial defects (blindness, cleft lip or palate, single central incisor) or, in males, by microphallus or small normal phallus. It is very important to exclude pituitary deficiency in the diagnosis of congenital hyperinsulinism, since the hypoglycemia and liver dysfunction associated with pituitary deficiency resolve quickly with hormone replacement therapy. For this reason, it is often convenient to include determination of plasma cortisol, growth hormone, and free T4 in the "critical sample" at the point of hypoglycemia (see Table 1.1). If levels of these hormones are not sufficiently high to exclude pituitary deficiency (cortisol >17–20 μg/dL, growth hormone >7.5–10 ng/mL, free T4 >0.8 ng/dL), formal provocative testing should be considered.

AKT2

This rare condition has been described in less than a half-dozen patients and is caused by post-zygotic, mosaic, gain-of-function mutations in AKT2. The AKT2 serine/threonine kinase has an important role in the post-receptor actions of insulin; e.g., activation of AKT2 causes translocation of Glut-4 to the plasma membrane to increase Glut-4 action and produce hypoinsulinemic hypoglycemia. Distinctive physical features of affected patients include asymmetric hypertrophy of subcutaneous adipose tissue with reduction in visceral adipose fat, ocular ptosis, and proptosis [10]. In affected children, hypoketotic hypoglycemia occurs in the absence of elevated insulin or C-peptide, and a glycemic response to glucagon is retained during hypoglycemia. Glucose utilization rates are typically much lower than those found in classic hyperinsulinism.

Autoimmune Hypoglycemia

Autoimmune Hypoglycemia (anti-insulin autoantibodies, Hirata disease; anti-insulin receptor activating antibodies): These two rare hyperinsulinism mimickers are usually reported in older children and adults; they may occur as early as the first year of life, but beyond the neonatal period. The first disorder, insulin autoimmune syndrome (IAS), is a condition in which anti-insulin antibodies develop in a patient not previously exposed to exogenous insulin. First described in Japan by Hirata and further delineated by Uchigata [11], IAS is commonly associated with a history of autoimmune disease and antibodies to other organs, in addition to insulin, including Graves' disease and treatment by methimazole, but has occurred due to exposure to other drugs, particularly those with a sulfhydryl group. The disorder manifests as hypoketotic hypoglycemia, often with markedly elevated insulin levels (depending on the specific insulin assay method). The mechanism of hypoglycemia is thought to involve delayed clearance of insulin due to binding by the endogenous antibodies and usually occurs in the postprandial state as free insulin is released. Spontaneous remission occurs when drug exposure is removed in 80% of cases.

The second form of autoimmune hypoglycemia is caused by activating antibodies against the insulin receptor (analogous to thyroid-stimulating antibodies in Graves' disease). In this disorder, hypoketotic hypoglycemia occurs in the absence of elevated insulin levels. A possible clue to the diagnosis is the failure of acute injection of octreotide to induce a hyperglycemic response. Various forms of antiimmune therapy have been tried in this form of autoimmune hypoglycemia, which can be very severe. Some patients have responded to monthly infusions of intravenous immunoglobulin.

Surreptitious Insulin Administration

This condition is a common presentation of Munchausen syndrome in adolescents or Munchausen syndrome by proxy in younger children. It may occur in adolescents with insulin-dependent diabetes who inject insulin surreptitiously to "demonstrate" they no longer need treatment because they are having low glucose levels without insulin. The typical history reveals hypoglycemic symptoms occurring intermittently and with a timing not fitting with typical fasting hypoglycemia. The critical sample may reveal very high plasma levels of insulin, but with suppressed C-peptide levels (which differentiates exogenous insulin from endogenous production), in addition to suppressed concentrations of FFA and beta-hydroxybutyrate. It is important to note that some insulin analogues may not be detected by specific insulin assay methods, and if there is a high clinical suspicion, details about the type of insulin and the insulin assay method should be discussed with the laboratory.

Insulin Secretagogues

The sulfonylurea class of antidiabetic medications, such as glyburide, acts on the beta cell to stimulate insulin release by closing plasma membrane K_{ATP} channels. In hypoglycemia due to exogenous sulfonylureas, both insulin and C-peptide levels will be elevated (differentiating this from surreptitious insulin administration). Thus, drug testing of plasma or urine for sulfonylureas is the only way to differentiate between endogenous hyperinsulinism due to defects in insulin secretion, insulinomas, and surreptitious or accidental ingestion of sulfonylureas. Testing for sulfonylureas is generally not considered necessary with the typical neonatal presentation of HI; however, in older children with atypical presentation of hypoglycemia, the possibility of accidental ingestion or surreptitious administration of sulfonylureas should be considered.

Insulinoma

Acquired insulin-secreting pancreatic tumors are a rare cause of hypoketotic hypoglycemia occurring in 1–4/1,000,000 of the adult population [12]. The majority of insulinomas occur in adults but may occur in children as young as 2–5 years of age [13]. In children, insulinomas are often associated with mutations in Menin, the gene causing multiple endocrine neoplasia type 1 (MEN1). Clinically, insulinomas present with episodes of symptomatic hypoglycemia that fulfill Whipple's triad (symptoms of hypoglycemia, associated with low plasma glucose, and responsive to glucose administration). Symptoms may be predominantly neuroglycopenic (e.g., confusion), and neurogenic symptoms (tachycardia, sweating,

and tremulousness) are often not apparent due to hypoglycemia-associated autonomic failure (HAAF). The critical sample at the time of hypoglycemia shows results which are similar to that seen with the genetic forms of HI. Some investigators emphasize the finding of an elevated proinsulin to insulin molar ratio, which in insulinoma is typically >20% (note the need to convert insulin into same units as proinsulin to calculate the ratio) [14]. Prior to localization procedures and surgery, it is important to exclude the possibility of oral hypoglycemic medications by testing plasma or urine for sulfonylureas at the time of hypoglycemia. Localization of an insulinoma may be difficult, but it is important to not operate on a suspected insulinoma until the location of the lesion (or possible multiple lesions) has been visualized. Mutation testing for MEN1 mutations and cascade testing of family members should be done since MEN 1 patients will need ongoing surveillance for the development of recurrent insulinomas or other endocrine tumors.

Table 1.5 Clinical signs and symptoms of hypoglycemia

A. Newborn
Jitteriness
Irritability
Lethargy
Hypothermia
Poor suck, loss of interest in feeding
Increased hunger
High-pitched cry
Sweating
Apnea
Seizures
Unresponsiveness
B. Older infants and children
Neurogenic symptoms
Pallor
Shakiness, tremulousness
Sweating
Tachycardia
Anxiety
Hunger
Hypothermia
Neuroglycopenic symptoms
Confusion, delirium
Lethargy or irritability
Impaired cognition
Erratic behavior
Loss of consciousness
Seizures or stroke-like episodes (Todd's paresis)

Signs and Symptoms of Hyperinsulinism in Neonates and Children (See Table 1.5)

Neonates

As shown in Table 1.5, the signs and symptoms of hypoglycemia in the newborn infant are relatively nonspecific and may easily go unrecognized. Essentially, any unusual behavior (excessive lethargy to excessive irritability), difficulty feeding (from over-vigorous to disinterest), unexplained tachycardia or sweatiness due to adrenergic stimulation, hypothermia, and various neurologic signs including jitteriness and seizures should suggest the possibility of hypoglycemia. Specific features suggesting possible hyperinsulinism in the neonate include excessive glucose utilization (GIR > 10 mg/kg/min). Large for gestational age (LGA) birthweight is an important clue (since insulin is a major fetal growth factor), although not all neonates with congenital HI are LGA and neonates with perinatal stress hyperinsulinism may be small for gestational age (SGA). LGA with hemihypertrophy, macroglossia, umbilical hernia, or ear creases may suggest hyperinsulinism due to Beckwith-Wiedemann syndrome. The possibility of perinatal stress-induced hyperinsulinism should be considered in infants of diabetic mothers, infants with evidence of intrauterine growth retardation (SGA infants), infants born to mothers with hypertension or preeclampsia, and infants with perinatal asphyxia. A particularly important sign of neonatal hyperinsulinism which requires careful follow-up is a history of hypoglycemia or unexplained seizure disorder or sudden infant death in first-degree relatives or in more distant relatives that might suggest either a recessive or dominantly transmitted genetic form of hyperinsulinism.

Infants and Children

Infants and children <5 years of age often will exhibit only neuroglycopenic symptoms of hypoglycemia, and so the absence of classical neurogenic symptoms of hypoglycemia in a toddler does not rule out hypoglycemia (Table 1.5). Children older than 5 years of age are more dependable in being able to express and report the neurogenic symptoms of hypoglycemia but may have hypoglycemia unawareness due to repetitive hypoglycemic episodes that blunt autonomic responses. Any neonate, infant, or child demonstrating neuroglycopenic symptoms deserves glucose screening. In older infants and children with possible hyperinsulinism, it is important to evaluate the timing of hypoglycemic episodes relative to the last feeding and also to attempt to determine if the hypoglycemia is induced by fasting or by meals. Hyperinsulinism typically manifests short but highly variable duration of fasting tolerance. The physical examination may suggest syndromic forms of hyperinsulinism (e.g., Kabuki syndrome, Turner syndrome, and Beckwith-Wiedemann syndrome). Since glucose utilization is often not as markedly elevated in older infants and children compared to neonates with hyperinsulinism, the differential

diagnosis may need to be larger and include disorders of glycogenolysis and gluconeogenesis, as well as defects in fatty acid oxidation and intoxications or Munchausen syndrome by proxy.

Fasting Test to Evaluate Efficacy of Treatment ("Safety Fast" and "Cure Fast")

All neonates and children with hyperinsulinism require a fasting test prior to discharge to evaluate the effects of treatment and to determine whether a patient is safe to go home. The definition of "safe to go home" depends to some extent on the intensity of current therapy and what further options are for therapy. For details, see Chap. 2, Diazoxide-Responsive Forms of HI, and Chap. 3, Diazoxide-Unresponsive Forms of HI. The "safety" fast is carried out as a modification of the diagnostic fasting test protocol (Table 1.1), by monitoring plasma glucose and beta-hydroxybutyrate at frequent intervals until some pre-defined end point is reached (e.g., the development of hyperketonemia (beta-hydroxybutyrate >2–2.5 mM) or hypoglycemia or the duration of fasting predetermined to be adequate for safe care at home). In some cases, it may be important to determine whether the hyperinsulinism has been completely cured (e.g., resection of a focal HI lesion) or has otherwise resolved (e.g., a patient with perinatal stress HI or HI caused by a mutation in the genes for HNF-4A or HNF-1A). For the "cure" fasting test, the duration of fasting is extended until either hyperketonemia develops (beta-hydroxybutyrate >2.0–2.5 mM), or the patient develops hypoglycemia, or the length of fast exceeds 16–18 h (in a young infant) or 30–36 h (in an older infant or child). Developing hypoglycemia without elevation of plasma beta-hydroxybutyrate concentrations >1.8 mM indicates the presence of ongoing hyperinsulinism [1].

Conclusion

It is critical to make a rapid diagnosis of the etiology of hypoglycemia in order to implement specific therapy and prevent ongoing hypoglycemia. Once hyperinsulinism is confirmed, evidence from the timing and the pattern of the hypoglycemia, the presence or absence of hyperammonemia, the response to substrate challenge tests, and results of genetic testing can specify the type of hyperinsulinism. This knowledge will allow one to implement the correct therapy and determine if the patient is a candidate for curative surgical approach such as is possible in focal K_{ATP}-HI and insulinomas.

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Chapter 2
Diazoxide-Responsive Forms of Congenital Hyperinsulinism

Daphne Yau and Charles A. Stanley

Introduction

One of the critical distinguishing features of children with congenital hyperinsulinism (HI) is whether their hypoglycemia responds to treatment with the drug, diazoxide (Proglycem®). This K_{ATP} channel agonist was originally introduced for the treatment of hyperinsulinism in 1964 and for many years was the only medication available for the disorder [1]. In those failing to respond to diazoxide, the only option was near-total pancreatectomy, and surgery is still the only option for many children [2]. However, for children whose hyperinsulinism is responsive to diazoxide, it is possible to safely control hypoglycemia and avoid surgery. This chapter will outline criteria for defining diazoxide responsiveness and review the most common diazoxide-responsive forms of hyperinsulinism. Dominant mutations of the two K_{ATP} channel genes, *ABCC8* and *KCNJ11*, which are sometimes responsive to diazoxide therapy, are discussed separately in Chap. 3. Of note, only 35% of diazoxide-responsive hyperinsulinism patients have an identifiable mutation in one of the currently known hyperinsulinism genes (Fig. 2.1), so other genes or genetic mechanisms may be involved in many diazoxide-responsive cases. This may include syndromic forms of hyperinsulinism, discussed in Chap. 4.

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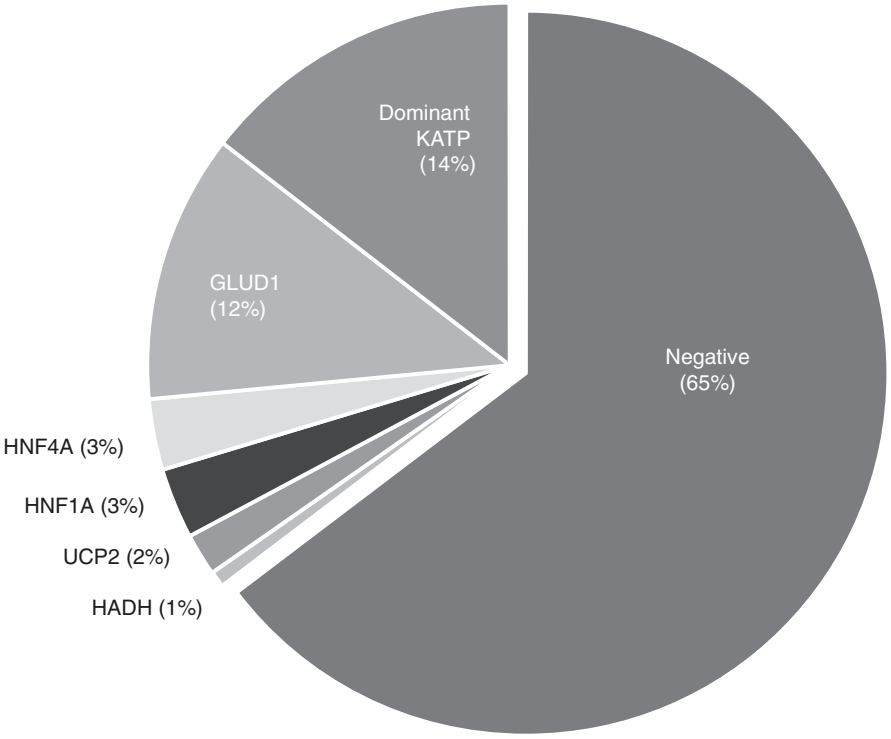

Fig. 2.1 Frequency of genetic causes of diazoxide-responsive hyperinsulinism. Data were collected from 317 patients over a 20-year period from the Children's Hospital of Philadelphia. Cases of transient, including perinatal stress, and syndromic hyperinsulinism were excluded. Note the large proportion of persistent, diazoxide-responsive hyperinsulinism with no mutations detected (65%). Of the cases without a mutation, 85 were screened for *ABCC8*, *KCNJ1*, *GLUD1*, and *GCK*, and 120 were screened for all genes. The dominant K_{ATP} group includes 33 with *ABCC8* and 13 with *KCNJ11* mutations

Definition of Diazoxide Responsiveness

There has been confusion among centers treating children with congenital hyperinsulinism in how "diazoxide responsiveness" is defined. Some centers have defined responsiveness as being able to maintain normoglycemia on a feeding schedule that is appropriate for the age of the patient. However, this definition lacks precision and varies markedly with age, since the length of a normal overnight fast changes from 3 to 4 h in early infancy to 8–10 h or longer later. In addition, the duration of fasting tolerance is not a fixed value in children with congenital hyperinsulinism. An affected child who has fasted for 6–8 h before becoming hypoglycemic on one occasion may develop hypoglycemia within only 1–2 h after a meal when tested again. It is easy for such patients to be misclassified as diazoxide-responsive in the

hospital, only to be discharged and suffer a hypoglycemic seizure at home. In addition, children with some forms of congenital hyperinsulinism can have not only fasting hypoglycemia but also hypoglycemia in response to specific foods. Thus, the definition of diazoxide responsiveness must take into account its potential for preventing both fasting and feeding-related hypoglycemia.

A more reliable definition of diazoxide responsiveness is to demonstrate that the cardinal abnormality of hyperinsulinism, i.e., fasting hypoketotic hypoglycemia, is corrected while on treatment. In addition, any susceptibility to postprandial hypoglycemia (e.g., protein-sensitive hypoglycemia) should also be corrected. In practical terms, this requires monitoring of both plasma glucose and plasma beta-hydroxybutyrate (BOHB) during a provocative fasting test to demonstrate that appropriate hyperketonemia (plasma BOHB >2.0 mmol/L) develops *before* the plasma glucose falls below 2.8–3.3 mmol/L (50–60 mg/dL). Meters for bedside monitoring of BOHB are readily available and are sufficiently accurate to demonstrate the large rise in plasma BOHB that normally occurs during prolonged fasting. In most normal infants and young children, plasma BOHB rises from 0.1 mmol/L at baseline to >2.0 mmol/L within 12–18 h of fasting, well before hypoglycemia develops [3]. In cases of uncertainty, a glucagon stimulation test can be done when the plasma glucose reaches 2.8–3.0 mmol/L (50–55 mg/dL) to confirm that hepatic glycogen reserves have become appropriately depleted (see Chap. 1).

Criteria for Defining Diazoxide-Responsiveness
While on diazoxide treatment (≤15 mg/kg/day):

- Correction of fasting hypoketotic hypoglycemia:
  - Plasma BOHB >2.0 mmol/L *before* plasma glucose drops below 2.8–3.3 mmol/L (50–60 mg/dL)
    OR
  - Able to fast ≥18 h with plasma glucose >3.9 mmol/L (>70 mg/dL) with some increase in BOHB
- Correction of food-induced hypoglycemia if present (e.g., protein-sensitive hypoglycemia in GDH-HI, K_{ATP}-HI, SCHAD-HI; carbohydrate-induced hypoglycemia in UCP2-HI)

Perinatal Stress-Induced Hyperinsulinism

An increased risk of severe and/or prolonged hypoglycemia in neonates with various forms of perinatal stress has been recognized for more than five decades [4]. The list includes both maternal (preeclampsia, maternal diabetes) and fetal conditions (small for gestational age (SGA)/intrauterine growth restriction (IUGR), birth asphyxia) (Table 2.1). Perinatal stress-induced hyperinsulinism is very common, with hypoglycemia occurring in 50% of SGA infants in the first 48 h of life and lasting beyond 10 days of life in an estimated 10% of these infants [5, 6].

Table 2.1 Risk factors for perinatal stress-induced hyperinsulinism

Maternal diabetes
SGA/IUGR
Preeclampsia/maternal hypertension
Birth asphyxia
Prematurity
Erythroblastosis fetalis

Pathophysiology Although there has been speculation that the mechanism of perinatal stress-induced hypoglycemia might involve immaturities of hepatic metabolism or inadequate glycogen reserves, there is compelling evidence that it is due to hyperinsulinism: (1) insulin is frequently inappropriately detectable at the time of hypoglycemia; (2) glucose infusion rates as high as 20–30 mg/kg/min may be needed to support plasma glucose levels; (3) plasma ketones and free fatty acids are suppressed; and (4) there is often a glycemic response to glucagon as a marker of inappropriate preservation of hepatic glycogen reserves [7–9].

The cause of perinatal stress-induced hyperinsulinism is not known. It may represent an exaggerated and prolonged form of normal transitional neonatal hypoglycemia, in which the fetal pattern of immature insulin regulation, characterized by a lower glucose threshold for insulin release, is more pronounced and takes longer to resolve after delivery [10]. *ABCC8* and *KCNJ11* sequence analysis has not identified any underlying defects, and the functional responses to insulin secretagogues are similar to controls without hyperinsulinism [7, 11]. In most neonates, hypoglycemia resolves within 1–2 weeks, although hyperinsulinism can be more severe and persist for several months [7, 11]. Most infants with perinatal stress-induced hyperinsulinism have an obvious underlying condition around the time of delivery, although a predisposing stressor may not be obvious in all cases [7, 11].

Clinical Features and Management Hypoglycemia in perinatal stress-induced hyperinsulinism can be quite severe and prolonged with high risk of seizures or permanent brain injury in affected neonates [13]. For this reason, infants with any of the conditions in Table 2.1 need to be considered at high risk. The Pediatric Endocrine Society guidelines recommend close glucose monitoring of at-risk neonates and, importantly, careful evaluation for persistent hypoglycemia prior to discharge home [14].

The features of perinatal stress-induced hyperinsulinism are similar to other forms of hyperinsulinism, persistent hypoglycemia with increased glucose requirement. Physical features of hyperinsulinism, such as large-for-gestational-age birthweight, are not present, except with maternal diabetes, because the onset of hyperinsulinism reflects the type of stress, such as birth asphyxia, which is usually close to the time of delivery. However, cardiomyopathy, seen in some neonates with genetic forms of hyperinsulinism, may also occur in cases of perinatal stress-induced hyperinsulinism, such as maternal diabetes. There are no laboratory features specific to perinatal stress-induced hyperinsulinism, although it has been suggested that most cases have elevated erythroblast counts immediately after delivery as a marker

of stress [15]. Genetic testing is not indicated if the hyperinsulinism resolves quickly but should be considered in cases of persistent hypoglycemia .

In milder cases, where resolution within a week or two is anticipated, temporary use of dextrose infusions to maintain normal plasma glucose (>3.9 mmol/L, >70 mg/dL) may be sufficient. However, medical therapy is often required when hypoglycemia fails to resolve by the time of discharge home and/or to aid in controlling hypoglycemia if reducing or eliminating intravenous dextrose is desired. Most cases respond well to low doses of diazoxide (5–10 mg/kg/day), but severe cases may not be well controlled, even on high doses of diazoxide (15 mg/kg/day), and can require continued dextrose support or octreotide. As in other forms of hyperinsulinism, it is important to begin a diuretic prior to initiating diazoxide, to minimize the risk of fluid retention and pulmonary hypertension in infants who are on intravenous fluids [16, 17]. A potent diuretic such as furosemide is preferred over thiazides, which should be reserved for chronic treatment once intravenous dextrose is no longer required. Because diazoxide has a half-life of 9–24 h in children, evaluating the response to therapy may require up to 5 days of treatment [18].

Prior to discharge, control of hypoglycemia should be confirmed by a provocative fasting test to ensure that plasma glucose concentrations >3.9 mmol/L (>70 mg/dL) can be maintained for a minimum of 8–12 h. Families should be taught to monitor plasma glucose prior to feeds several times daily and, if stable, at least once a day, especially during illnesses. Note that severe *hyper*glycemia can occur acutely due to over-suppression of insulin secretion during severe illness.

Since perinatal stress-induced hyperinsulinism is expected to eventually resolve, withdrawal of diazoxide may be considered after 1–2 months of stable plasma glucose concentrations. This can be done either gradually over several weeks under close monitoring at home or rapidly by abrupt discontinuation under observation in the hospital. In either case, complete resolution should be documented by a fasting test demonstrating an appropriate hyperketonemic response occurs before the onset of hypoglycemia, i.e., BOHB >2.0 mmol/L within 12–18 h of fasting (see section "Definition of Diazoxide-Responsiveness"). This "cure fast" is necessary, because children with apparently normal fasting plasma glucoses after stopping diazoxide have subsequently had symptomatic hypoglycemia, demonstrating persistence of their hyperinsulinism and an ongoing need for therapy.

Glutamate Dehydrogenase Hyperinsulinism (Hyperinsulinism/Hyperammonemia Syndrome)

Glutamate dehydrogenase hyperinsulinism (GDH-HI, also known as hyperinsulinism/hyperammonemia syndrome) is one of the most common and easily identifiable causes of diazoxide-responsive hyperinsulinism on account of the combination of hypoglycemia and hyperammonemia [2]. Patients have persistent, mild elevations of plasma ammonia and are markedly susceptible to protein and leucine-induced hypoglycemia (Table 2.2).

Pathophysiology *GLUD1* encodes glutamate dehydrogenase (GDH), a mitochondrial enzyme that catalyzes the reversible oxidative deamination of glutamate to alpha-ketoglutarate (2-oxoglutarate) and ammonia [19]. Alpha-ketoglutarate is further oxidized in the tricarboxylic acid (TCA) cycle, generating ATP and stimulating insulin release (Fig. 2.2). GDH is tightly regulated by several allosteric effectors,

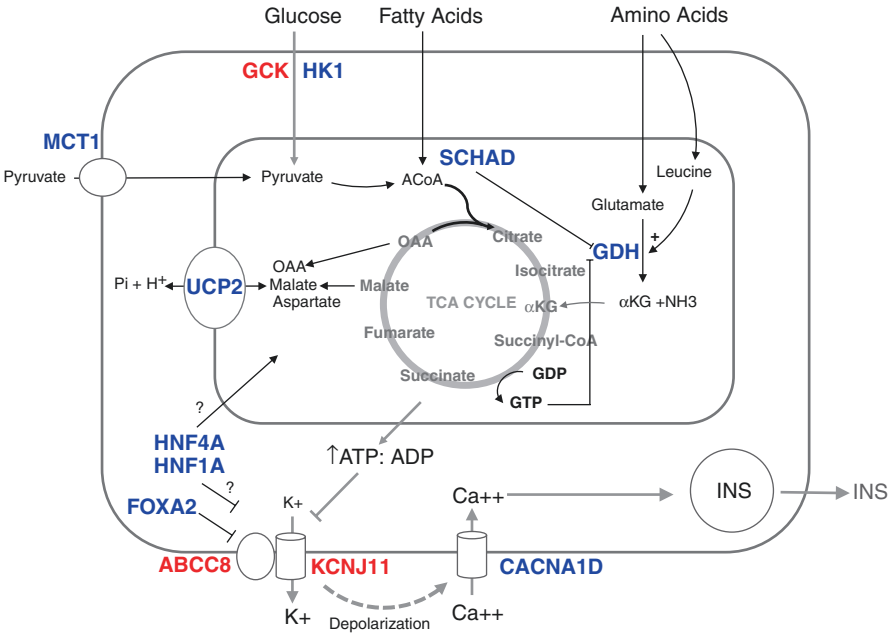

Fig. 2.2 Sites of genetic defects in diazoxide-responsive forms of hyperinsulinism. The canonical pathway of insulin secretion is shown: from the *upper left*, glucose enters the beta cell, is phosphorylated by glucokinase (*GCK)*, and is converted to pyruvate through glycolysis. Pyruvate enters the TCA cycle and increases ATP production. The increase in ATP/ADP ratio closes K_{ATP} channels (KIR6.2 and SUR1 subunits, encoded by *KCNJ11* and *ABCC8*, respectively), leading to membrane depolarization and opening of voltage-gated calcium channels (CACNA1D). The calcium influx triggers insulin (INS) release (bottom right). Genes affected in diazoxide-responsive forms of hyperinsulinism are shown in *blue*, and genes responsible for diazoxide-unresponsive forms are shown in red. Dominant gain-of-function mutations in *GCK* and mutations permitting expression of *HK1*, normally disallowed, result in HI through increased glucose phosphorylation. Dominant gain of function mutations in *GDH* lead to leucine-stimulated insulin release and, thus, protein-induced hypoglycemia, through the formation of alpha-ketoglutarate (*α*KG), which enters the TCA cycle and induces a rise in ATP. Short-chain L-3-hydroxyacyl-CoA dehydrogenase (SCHAD) loss-of-function mutations increase GDH activity and enhance insulin secretion by removing the inhibitory effect of SCHAD protein on GDH activity. Uncoupling protein 2 (UCP2) transports four-carbon intermediates out of the mitochondrial matrix in exchange for phosphate and protons; UCP2 loss-of-function mutations increase insulin release through enhanced flow of glucose into mitochondrial oxidation. The mechanism of hepatocyte nuclear factor (HNF) 4A/1A hyperinsulinism is unclear but likely involves alterations in transcription of key beta-cell genes such as Kir6.2. Expression of the "disallowed" MCT1 gene *SLC16A1* in beta cells permits pyruvate to enter the beta cell and stimulate insulin release during anaerobic exercise, leading to exercise-induced hypoglycemia. NH3 ammonia, OAA oxaloacetate

including leucine, an activator, and GTP, a potent inhibitor [18, 23]. GDH is also inhibited by protein-protein interaction with short-chain L-3-hydroxyacyl-CoA dehydrogenase (SCHAD), the enzyme affected in *HADH*-HI, a rare form of protein-sensitive hyperinsulinism without hyperammonemia (see below) [20].

In patients with GDH-HI, missense mutations in *GLUD1* impair GTP-mediated inhibition of GDH, enhancing both basal insulin secretion and insulin responses to leucine stimulation, thus resulting in both fasting and protein-induced hypoglycemia [21–23]. GTP is generated in the TCA cycle from the GDP-dependent isoenzyme of succinyl-CoA synthase, providing a mechanism that tightly links glucose oxidation to downregulation of amino acid oxidation [24]. In islets with activating GDH mutations, glucose can suppress the increased insulin response to leucine via increased production of GTP; in a similar manner, carbohydrate preloading may help control protein-induced hypoglycemia in GDH-HI patients [25, 26].

In addition to pancreatic beta cells, GDH is highly expressed in the kidneys, liver, and brain. The kidneys, rather than the liver, appear to be responsible for the hyperammonemia in GDH-HI since activation of GDH increases renal ammonia production [27]. For this reason, therapies used to treat hyperammonemia in hepatic urea cycle enzyme disorders have little or no effect in GDH-HI. Unlike the urea cycle defects, hyperammonemia in GDH-HI does not appear to cause clinical symptoms, and treatments such as protein restriction or alternate pathway drugs are ineffective in reducing hyperammonemia [28–31]. As noted below, patients with GDH-HI have a markedly increased risk of a specific type of generalized epilepsy, atypical absence seizures, and increased risk of behavioral problems and developmental delay presumably due to increased GDH activity in the brain [29, 32]. These neurologic manifestations of GDH-HI do not appear to be due to hypoglycemic episodes and might reflect depletion of glutamate, a key neurotransmitter, due to the increased brain GDH activity.

Clinical Features and Management In 70% of GDH-HI cases, the mutations in *GLUD1* are de novo, while familial cases show an autosomal dominant pattern. Birth weight in GDH-HI is not increased, in contrast to the higher birth weights commonly seen in children with K_{ATP}-HI [22, 33]. Hypoglycemia tends to be recognized later in GDH-HI than in K_{ATP}-HI, at an average age of 4–11 months [22, 29, 33]. Affected children may have relatively mild fasting hypoglycemia but have striking sensitivity to protein exhibiting severe hypoglycemia shortly after eating a protein-rich meal resulting from enhanced leucine-stimulated insulin secretion (Table 2.2) [26, 31]. GDH-HI is usually easily recognized by a mild, persistent hyperammonemia in the range of 60–150 μmol/L (102–255 μg/dL). Because plasma ammonia levels in GDH-HI are not affected by feeding, fasting, protein intake, or plasma glucose levels, hyperammonemia can be readily demonstrated using random blood samples. As noted above, hyperammonemia does not respond to treatments used in urea cycle disorders.

Neurodevelopmental problems are common, observed in at least 70% of GDH-HI patients. Epilepsy is the most frequent feature, with atypical absence seizures, a form of generalized epilepsy, being predominant [29, 32]. Brain imaging, in the absence of injury from hypoglycemia, is normal. No correlation has been observed between the degree of hyperammonemia and the development of epilepsy.

Developmental delay and behavioral problems, such as attention deficit disorder and poor social interaction, are also common, and half to three-quarters of patients may have mild to moderate cognitive impairment [22, 29, 33].

Most cases of GDH-HI respond well to moderate doses of diazoxide, approximately 10 mg/kg/day, with good control of both fasting and protein-induced hypoglycemia. Protein restriction is not usually required, but patients should be advised to take some carbohydrate prior to eating protein at mealtimes in order to diminish the leucine-induced insulin response (see above). Diazoxide does not affect the hyperammonemia or neurodevelopmental abnormalities.

HNF4A and HNF1A Hyperinsulinism

Inactivating mutations in two hepatic nuclear factor (HNF) transcription factor genes, *HNF4A* and *HNF1A*, are well-recognized causes of maturity onset diabetes of youth (HNFA-MODY, formerly MODY1, and HNF1A-MODY, formerly MODY3). In the last decade, it has been recognized that the phenotype of HNF4A-MODY and HNF1A-MODY patients can also be biphasic, with some affected individuals presenting with congenital hyperinsulinism at birth and subsequently evolving to diabetes in adolescence and early adulthood (Table 2.2) [34].

Pathophysiology The HNF transcription factors control the expression of multiple pathways in the pancreatic islets, liver, and kidney, including reciprocal control of each other [35]. In both HNF4A-MODY and HNF1A-MODY, affected adults have impaired insulin responses to glucose and progressive glucose intolerance leading to diabetes in the second to fourth decades of age [36]. Why a subset of individuals carrying *HNF4A* and *HNF1A* mutations will have hyperinsulinism in early life is unknown. Mice with beta cell-specific deletion of *Hnf4a* have hypoglycemia, possibly due to reduced expression of the Kir6.2 subunit of the K_{ATP} channel and/or impaired channel activity [34, 37, 38]. As discussed in Chap. 3, K_{ATP}-HI patients are "glucose blind" which results in hypoglycemia in early life but may also manifest as glucose intolerance in adulthood [39, 40]. Thus, there may be similarities between islet dysfunction caused by HNF mutations and inactivating mutations of the K_{ATP} channel subunits. Of note, penetrance of the hyperinsulinism phenotype in *HNF4A* mutation carriers is incomplete, with reported rates of recognized neonatal hypoglycemia in two large cohorts of only 6–15% and the duration of hyperinsulinism lasting from a few days up to several years [38, 41, 42]. The reasons for this variable penetrance require further investigation.

While congenital hyperinsulinism due to *HNF4A* mutations is a well-established disorder, questions have been raised about whether mutations in *HNF1A* can be responsible for hyperinsulinism. The major reason for this concern is that large-for-gestational-age birthweight, a cardinal finding in some types of hyperinsulinism, is common in infants carrying *HNF4A* mutations, but does not appear to be as frequent in infants with *HNF1A* mutations [34]. Despite such reservations about *HNF1A*, both genes should be considered as candidate loci for congenital hyperinsulinism,

particularly in families with histories suggesting dominantly inherited, early-onset adult diabetes.

One particular *HNF4A* mutation p.Arg76Trp (sometimes reported as p.Arg63Trp; c.226C3T) has been described in ten patients to have a unique phenotype involving additional derangements of the liver and kidneys. The renal abnormalities include Fanconi syndrome, which may occur without acidosis, in addition to renal impairment and hypercalciuria [44–46]. The liver abnormalities occur less consistently and resemble the Fanconi-Bickel syndrome, including hepatomegaly, glycogen storage, and elevated transaminases. The mechanism may relate to decreased renal and hepatic expression of the GLUT2 glucose transporter, the genetic locus for Fanconi-Bickel syndrome and a known target gene of HNF4A [47].

Clinical Features and Management The typical phenotype of HNF4A-HI is neonatal hypoglycemia occurring in a large-for-gestational-age infant. Mean birth weight is increased 750–790 g compared to family members without mutations, and 60% of infants are classified as macrosomic (>4 kg). Hypoglycemia is often noted in the first 1–2 days of life, and its severity and persistence are variable: some cases have only mild, transient hypoglycemia in the neonatal period, while others may continue to require treatment for hypoglycemia into late childhood [48, 49]. Similarly, although fewer cases have been reported, HNF1A-HI tends to present in the neonatal period and can persist into early childhood [50]. Although the proportion of *HNF1A* and *HNF4A* mutation carriers with congenital hyperinsulinism may be under 20%, all infants born to mutation carriers warrant careful monitoring for hypoglycemia after birth. Furthermore, testing for *HNF1A* and *HNF4A* mutations should be considered in patients with diazoxide-responsive hyperinsulinism, because family history can be negative in up to 64% of HNF4A-HI cases [51].

HNF4A-HI and most cases of HNF1A-HI respond well to diazoxide therapy at usual doses (5–10 mg/kg/day) (Table 2.2). However, for reasons that are unknown, some cases of HNF1A-HI mutations have demonstrated only a partial response to diazoxide and required additional therapy [50]. In cases that have resolution of the hypoglycemia, diazoxide therapy can be withdrawn. The section on perinatal stress-induced hyperinsulinism in this chapter outlines recommended procedures for withdrawing treatment and follow-up testing to prove that diazoxide is no longer required.

Rarer Forms of Diazoxide-Responsive Hyperinsulinism

Short-Chain L-3-Hydroxyacyl-CoA Dehydrogenase Hyperinsulinism

L-3-Hydroxyacyl-CoA Dehydrogenase (SCHAD) is responsible for the penultimate step in fatty acid beta-oxidation [52]. SCHAD converts short- and medium-length 3-hydroxyacyl-CoA esters into their corresponding 3-ketoacyl-CoA esters, with the highest activity for 3-hydroxybutyryl-CoA. Recessive mutations in *HADH*,

the gene encoding SCHAD, were first reported as a cause of hyperinsulinism in 2001 [53]. Subsequent reports indicate a phenotype of diazoxide-responsive hyperinsulinism with protein-/leucine-induced hypoglycemia and abnormal metabolic profiles, including elevations of 3-hydroxybutyrylcarnitine in plasma and 3-hydroxyglutaric acid in urine (Table 2.2) [53–57].

The mechanism of hyperinsulinism in SCHAD deficiency was initially thought to involve abnormal fatty acid metabolites. However, the finding of protein-induced hypoglycemia in a patient with SCHAD-HI led to the demonstration of direct protein-protein interactions between GDH and SCHAD which showed that SCHAD is an inhibitor of GDH [20, 54, 57]. Under normal circumstances, SCHAD restrains GDH activity in pancreatic islets. But with loss of this inhibition, GDH activity is increased and, similar to GDH-HI, results in leucine-/protein-induced hypoglycemia and fasting hypoglycemia (Fig. 2.2). Unlike GDH-HI, ammonia levels are normal in SCHAD-HI. This is presumably due to the higher ratio of SCHAD to GDH protein levels in islets, rendering islets more sensitive to the SCHAD defect than the kidney, the source of hyperammonemia in GDH-HI (see above).

The phenotype of SCHAD-HI contrasts with other genetic defects in fatty acid oxidation, which present with non-hyperinsulinemic hypoketotic hypoglycemia, Reye-like syndrome, cardiomyopathy, or exercise-induced myopathy. SCHAD-HI cases have presented with both fasting and protein-induced hyperinsulinemic hypoglycemia, ranging from the early neonatal period to 14 months [58]. Birth weight is not increased. Ammonia levels are normal, unlike GDH-HI, but the unique features of elevated blood 3-hydroxybutyrylcarnitine and urinary 3-hydroxyglutarate may be present (Table 2.2). Testing for SCHAD-HI should be considered in diazoxide-responsive HI even if metabolite profiles are normal, since the elevations are often only minimal; newborn screening tests should not be relied upon for diagnosis. In one series, SCHAD-HI was found in up to 10% of diazoxide-responsive cases of congenital hyperinsulinism; thus, SCHAD-HI should be considered when recessive inheritance is suspected [57, 59–61]. Reported cases of SCHAD-HI have been diazoxide-responsive at doses in the range of 5–10 mg/kg/day. Of the two adults with SCHAD-HI reported, one continued to require treatment, while the other appeared to have a decline in the severity with age [60, 62].

Uncoupling Protein 2 Hyperinsulinism

Uncoupling protein 2 (UCP2) is an inner mitochondrial membrane protein that exports intramitochondrial TCA cycle intermediates, oxaloacetate and malate, in exchange for phosphate and hydrogen ions, thereby regulating the balance between oxidation of glucose and amino acids (Fig. 2.2) [63]. Evidence for a role for UCP2 in insulin secretion comes from rodent models demonstrating enhanced glucose-stimulated insulin secretion in Ucp2 knockout mice and reductions in both insulin secretion and ATP generation with overexpression of UCP2 [64, 65]. This inverse

relationship between UCP2 activity and glucose-stimulated insulin secretion led to the recognition of dominant, heterozygous *UCP2* mutations in two patients with diazoxide-responsive hyperinsulinism in 2008 [66]. In vitro studies of these loss-of-function mutations in a rodent cell line showed reduction in transport activity and enhanced insulin secretion [66, 68]. The *UCP2* loss-of-function mutations presumably increase the availability of TCA cycle intermediates leading to increased glucose-stimulated insulin secretion (Fig. 2.2). Following the initial report, seven additional patients have been identified, although there has been controversy as to whether some of these mutations are disease-causing due to their relatively high frequency in certain populations [2, 67, 68]. Thus, *UCP2*, like *HNF1A*, remains a candidate genetic locus for causing congenital HI.

The small number of UCP2-HI cases reported have tended to be older than children with K_{ATP}-HI at presentation, with a median age of 7 weeks, ranging from 2 days to 8 months [66, 68]. Large-for-gestational-age birthweight has not been a feature. Studies of older children suggest that fasting hypoglycemia is relatively mild, occurring after 18–20 h, but postprandial hypoglycemia occurring 3–4 h following a carbohydrate load can be severe [68]. Family members carrying UCP2-HI mutations have shown a similar phenotype with hypoglycemia several hours after an oral glucose load and fasting plasma glucoses declining toward 3.9 mM (70 mg/dL) after 24 h (Table 2.2). Most children with UCP2-HI have responded to moderate to high doses of diazoxide (10–15 mg/kg/day). Although initial reports suggested resolution of hyperinsulinism by age 1–2, subsequent cases suggest that ongoing treatment is required into the second decade of life or beyond [68].

Monocarboxylate Transport Protein 1 Hyperinsulinism

Mutations in *SCL16A1,* encoding monocarboxylate transport protein 1 (MCT1), cause a rare form of hyperinsulinism triggered by anaerobic exercise with normal fasting tolerance. MCT1 is the plasma membrane transporter for pyruvate, lactate, and ketone bodies; normally it is not expressed in beta cells to prevent these substrates from stimulating insulin release. MCT1-HI was first reported in older children and adults from three families in Finland and Germany [69, 70]. Their unique phenotype of exercise-induced hypoglycemia led to the observation of pyruvate-induced insulin secretion and the discovery of dominant mutations in the promoter region of *SLC16A1* in affected individuals [71].

Under normal circumstances, pyruvate, the end product of muscle glycolysis during anaerobic exercise, is prevented from entering the beta cell because *SLC16A1* expression is silenced. However, in individuals with exercise-induced hyperinsulinism, MCT1 promoter mutations lead to expression of the transporter in the beta cell and allow pyruvate to inappropriately stimulate insulin secretion during vigorous exercise (Fig. 2.2).

The age at presentation of MCT1-HI has ranged from 11 months to adolescence and adulthood. Most individuals report the onset of hypoglycemia symptoms with physical exertion in childhood. The hypoglycemia is only triggered by anaerobic activity of at least moderate intensity (i.e., sufficient to induce a mild lactic acidemia); mild aerobic exercise is generally well-tolerated. Uncommonly, hypoglycemia with prolonged fasting has been reported [69]. Exercise protocols to test for exercise-induced hyperinsulinism exist [70, 79]; these should only be performed with close monitoring and guidance from an expert in hyperinsulinism. Diazoxide treatment is not effective in preventing exercise-induced episodes of hypoglycemia. Some cases have benefited from intake of glucose or rapid-acting carbohydrates during or immediately after exercise.

Additional Rare Forms of Diazoxide-Responsive Hyperinsulinism

Other rare forms of diazoxide-responsive HI have been reported in only a limited number of cases; the phenotype of these disorders described below is, therefore, somewhat tentative.

Hexokinase 1-Associated Hyperinsulinism Noncoding variants in hexokinase 1 (*HK1*) were recently identified in one of the families first described as "idiopathic hypoglycemia of infancy" by MacQuarrie in 1954. In what is now a large kindred, affected children have a dominant, non-syndromic, diazoxide-responsive mild form of HI, often not recognized at birth. Hypoglycemia occurs both with fasting and after glucose loading [72]. The mechanism is presumed to reflect inappropriate expression of HK1 in beta cells. Like MCT1, HK1 is normally forbidden from beta cells since it has a higher affinity for glucose than glucokinase and expression of HK1 would result in glucose phosphorylation and insulin release at abnormally low-plasma glucose concentrations (Fig. 2.2).

FOXA2 **Hyperinsulinism** Forkhead box protein A2 (*FOXA2*), also known as hepatocyte nuclear factor 3-beta (*HNF-3B*), is a member of the forkhead class of nuclear transcription factors involved in embryonic development and tissue-specific gene expression [73]. Two reports have described infants with heterozygous inactivating mutations of *FOXA2* associated with HI and additional multi-system syndromic features [74, 75]. Both cases presented with neonatal hypoglycemia which was initially thought to be secondary to congenital hypopituitarism based on deficiencies of cortisol and growth hormone and pituitary abnormalities on MRI. After hypoglycemia persisted despite hormone replacement, HI was documented. One case was responsive to diazoxide; diazoxide was discontinued in the other case due to fluid overload and managed with continuous enteral feedings. Additional syndromic fea-

tures included facial dysmorphia in one case; the second case had midline facial defects, pulmonary stenosis, and hepatic fibrosis. As suggested by findings in a beta cell-specific *Foxa2* knockout mouse model, the mechanism of HI due to *FOXA2* deficiency may reflect reduced expression of target genes including *KCNJ11*, *ABCC8*, and *HADH* [74, 75].

***CACNA1D* Hyperinsulinism** One case has been reported with neonatal-onset HI due to a de novo heterozygous activating mutation of CACNA1D, the voltage-gated L-type beta cell calcium channel involved in triggering insulin release (see Fig. 2.2). The HI presented shortly after birth and responded to a moderate dose of diazoxide; the child was able to discontinue treatment at age 5 years [76]. Mutations of *CACNA1D* are associated with aldosterone-producing adenomas, and one case with transient neonatal hypoglycemia treated with diazoxide and hydrocortisone was included in a case series of adenomas due to *CACNA1D* mutations [77]. The *CACNA1D*-activating mutations cause calcium channels to open at a lower membrane potential, as well as impairing channel closure. As a result, there is inappropriate calcium influx which triggers insulin secretion. There is speculation that HI due to *CACNA1D* activation might be responsive to calcium channel closing compounds, such as nifedipine [76].

Phosphoglucomutase 1 Deficiency Hyperinsulinism PGM1 is responsible for the interconversion of glucose-6-phosphate and glucose-1-phosphate in the pathway of glycogen synthesis and degradation. Recessive inactivating mutations of *PGM1* cause a congenital disorder of glycosylation syndrome that is associated with two distinct forms of hypoglycemia [78]. In the beta cell, deficiency of PGM1 is thought to impair conversion of glucose-6-phosphate to glucose-1-phosphate and cause postprandial HI due to increased flux through glycolysis and insulin release (Fig. 2.2). In addition, in the liver, impairment of glycogenolysis from decreased conversion of glucose-1-phosphate to glucose-6-phosphate results in fasting hyperketonemic hypoglycemia. Diazoxide is not effective in controlling the postprandial hyperinsulinemic hypoglycemia in PGM1 deficiency. Other common manifestations of this disorder include elevated transaminases, bifid uvula, growth retardation, short stature, skeletal myopathy, and cardiomyopathy.

Other syndromic forms of diazoxide-responsive HI include some patients with Beckwith-Wiedemann syndrome, Kabuki syndrome, and Turner syndrome which are described in detail in Chap. 4.

Table 2.2 Phenotypes of diazoxide-responsive hyperinsulinism

Type	Inheritance	Diazoxide dose (mg/kg/day)	Food sensitivity	Other features
Perinatal stress HI [7, 9, 12, 13]	Acquired	5–10	–	–
GDH (HI/HA syndrome) [22, 29, 31–33]	Dominant	10	Protein	Hyperammonemia Absence epilepsy Learning disorders
K_{ATP}-HI	Dominant	5–10	Protein	Discussed in Chap. 3
SCHAD [53–62]	Recessive	5–15	Protein	Elevated plasma 3-hydroxybutyrylcarnitine and urinary 3-hydroxyglutaric acid
HNF4A [34, 36, 41, 42, 44–47, 50, 51]	Dominant	5–10	?	Diabetes in second to fourth decades (HNF4A-MODY)
HNF1A [43, 50]	Dominant	5–10	?	Diabetes in second to fourth decades (HNF1A-MODY)
UCP2 [66–68]	Dominant	10–15	Glucose	–

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Chapter 3
Diazoxide-Unresponsive Forms of Congenital Hyperinsulinism

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Abbreviations

18F-DOPA	18Fluoro-dihydroxyphenylalanine
GCK	Glucokinase
GCK-HI	Glucokinase hyperinsulinism
HI	Congenital hyperinsulinism
HI	Hyperinsulinism
K_{ATP}	ATP-sensitive potassium channel
Kir6.2	Inwardly rectifying potassium channel subunit (encoded by *KCNJ11*)
LINE	Localized islet cell nuclear enlargement
PET	Positron emission tomography
SUR1	Sulfonylurea receptor 1 (regulatory subunit encoded by *ABCC8*)

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Introduction

Long-term management of patients with congenital hyperinsulinism (HI) depends to a great extent on the responsiveness to medical therapy with diazoxide, the only FDA-approved drug for the treatment of HI. As outlined in Chap. 2, the definition of diazoxide responsiveness should be based on the demonstration that the cardinal abnormality of hyperinsulinism, i.e., fasting hypoketotic hypoglycemia, can be corrected on treatment. In addition, any susceptibility to postprandial hypoglycemia (e.g., protein-sensitive hypoglycemia) should also be corrected. This chapter will focus on the pathophysiology, clinical manifestations, and management of diazoxide-unresponsive HI. In non-syndromic patients, this is most frequently due to inactivating K_{ATP} channel mutations and less frequently to activating *GCK* mutations. In a small percentage of diazoxide-unresponsive cases (10%), which we refer to as "atypical HI," the underlying molecular defect is not found by the analysis of peripheral blood DNA. It is also important to add that some cases of syndromic HI, such as Beckwith-Wiedemann syndrome, Turner syndrome, and Kabuki syndrome, as well as some neonates with perinatal stress-induced HI, may not respond to therapy with diazoxide.

K_{ATP} Hyperinsulinism

Inactivating mutations in *ABCC8* or *KCNJ11*, the two adjacent genes on chromosome 11p that encode the two subunits (SUR1 and Kir6.2, respectively) of the beta cell plasma membrane K_{ATP} channel, are the most common causes of hyperinsulinism and are responsible for 80–90% of the diazoxide-unresponsive cases [1, 2].

Pathophysiology

In the pancreatic beta cell, the K_{ATP} channels play a major role in coupling glucose metabolism to insulin secretion. Glucose oxidation leads to a rise in ATP/ADP ratio and closure of K_{ATP} channels on the plasma membrane of the beta cell. This, in turn, depolarizes the cell membrane and leads to opening of voltage-gated Ca^{2+} channels and subsequent influx of Ca^{2+} ions and release of insulin granules (see Fig. 2.2) [3]. Inactivating mutations affecting the K_{ATP} channel result in reduced or absent channel function and dysregulated insulin secretion [3]. Therefore, the effect of the mutations on channel expression and function determines the clinical phenotype, particularly the response to diazoxide, a K_{ATP} channel opener.

As described in Table 3.1, K_{ATP}HI can be classified into three subtypes based on genetic defect and diazoxide responsiveness: (1) diazoxide-unresponsive disease due to recessive K_{ATP} channel mutations, (2) diazoxide-unresponsive disease due to autosomal dominant K_{ATP} channel mutations, and (3) diazoxide-responsive disease due to autosomal dominant K_{ATP} channel mutations [3].

Table 3.1 K_{ATP} channel mutations leading to hyperinsulinism

K_{ATP} channel mutations	Diazoxide responsiveness	Mode of inheritance	Histology	Birth weight	Time of hypoglycemia presentation	Treatment
Recessive	Unresponsive	Paternally inherited recessive mutation with somatic loss of heterozygosity for the maternal 11p region → paternal isodisomy	Focal disease	Lower likelihood of LGA compared to diffuse disease	Days to weeks after birth	Curative limited pancreatectomy
		Biallelic recessive mutations	Diffuse disease	LGA	Birth to within few days of birth	Medical therapy, if unresponsive may need subtotal pancreatectomy
Dominant	Unresponsive	Autosomal dominant mutations	Diffuse disease	LGA	Birth to within few days of birth	Medical therapy, if unresponsive may need subtotal pancreatectomy
	Responsive	Autosomal dominant mutations	Diffuse disease	LGA	Asymptomatic to mild disease that presents days to weeks after birth	Diazoxide

LGA large for gestational age

Diazoxide-Unresponsive HI due to Recessive K_{ATP} Channel Mutations

The majority of diazoxide-unresponsive HI cases are due to recessive K_{ATP} channel mutations causing either focal (affecting a limited number of ß cells) or diffuse (affecting all the beta cells of the pancreas) disease.

Focal K_{ATP}HI is caused by a "two-hit" mechanism: first, a paternally inherited recessive *KCNJ11* or *ABCC8* mutation and, second, somatic loss of the maternally inherited chromosomal region 11p15, compensated by paternal uniparental disomy (Chap. 5). This results in an imbalanced expression of imprinted genes encoded in this region in the affected ß cells. The loss of maternally expressed genes involved in tumor suppression (*H19* and *CDKN1C*) explains the "tumor-like" area of focal adenomatosis found on histologic inspection. Focal K_{ATP}HI can therefore be cured by targeted resection of affected tissue.

Unlike focal K_{ATP}HI, diffuse disease caused by inheritance of biallelic recessive mutations results in complete loss of K_{ATP} channel function in all beta cells of the pancreas, thereby causing diffuse pancreatic disease. Molecularly, the recessive mutations are either null mutations or amino acid substitutions that interfere with expression of K_{ATP} channels or trafficking of the channels to the plasma membrane of the beta cells, thus leading to persistent plasma membrane depolarization, constitutively opened calcium channels, increased cytosolic calcium, and insulin secretion that is independent of plasma glucose concentration [4].

Diazoxide-Unresponsive HI due to Dominant K_{ATP} Channel Mutations

A smaller subset of diazoxide-unresponsive K_{ATP}HI cases are due to autosomal dominant mutations of K_{ATP} channels, usually involving the SUR1 subunit. These mutations do not affect channel formation/trafficking but result in severely dysfunctional channels at the beta cell membrane [5]. This is in contrast to *autosomal dominant diazoxide-responsive disease*, in which the channel function is not as severely compromised [6].

Clinical Features and Management

Infants with diazoxide-unresponsive K_{ATP}HI are often large for gestational age with initial presentations characterized by severe hypoglycemia in the neonatal period, requiring high glucose infusion rates (frequently 4–5 times that of normal) to achieve normoglycemia. In addition to severe fasting hypoglycemia due to failure to suppress insulin secretion, patients with K_{ATP}HI also have impaired glucose-stimulated insulin secretion [7] that results in postprandial hyperglycemia and in older individuals may be confused with "glucose intolerance" or "prediabetes." In

contrast to the impaired glucose-stimulated insulin secretion, amino acids trigger insulin release and cause protein-induced hypoglycemia [3].

Up to 15% of infants with HI who demonstrate hypoglycemia within the 1st week of life also have symptomatic hypertrophic cardiomyopathy due to prenatal exposure to high insulin concentrations. While this cardiomyopathy is often reversible, administration of high fluid volumes to treat the hypoglycemia can exacerbate symptomatic hypertrophic cardiomyopathy or even unmask asymptomatic hypertrophic cardiomyopathy [3].

In all cases of HI, assessing responsiveness to diazoxide after at least 5 days of treatment with doses of up to 15 mg/kg/day is of foremost importance. This information is used to determine the management approach because additional therapeutic options are limited but, more importantly, because among the diazoxide-unresponsive group, approximately 50% of cases are focal and can be cured by surgical excision of the lesion [3]. The management approach for diazoxide-unresponsive patients is summarized in Fig. 3.1.

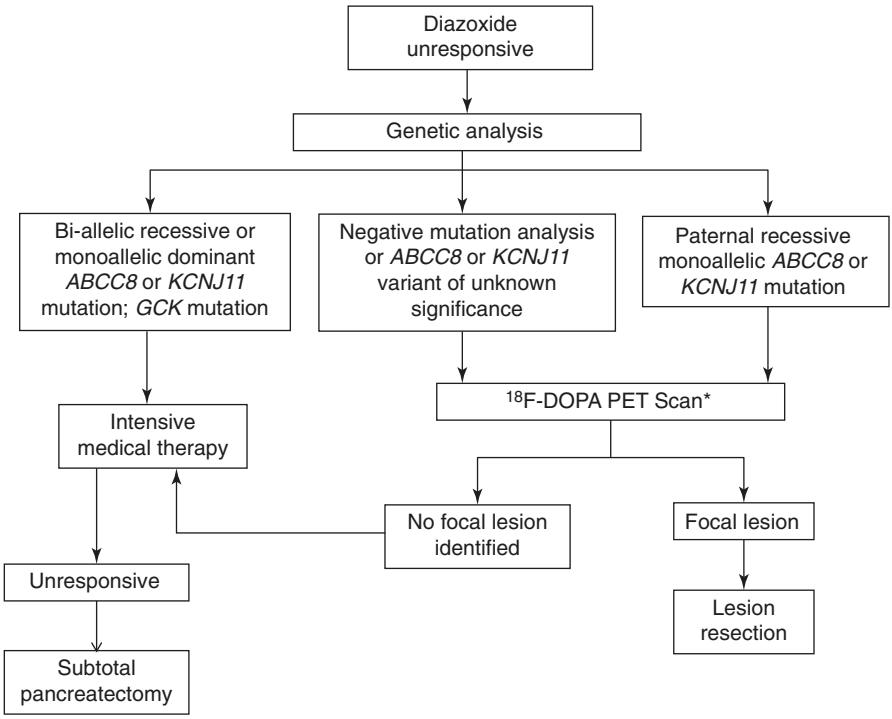

Fig. 3.1 Management approach to children with diazoxide-unresponsive hyperinsulinism. * In approximately 15% of focal cases, ^{18}FDOPA PET fails to identify the focal lesion; therefore, surgical exploration should be considered in cases with genetic analysis results suggestive of focal disease (paternal monoallelic recessive mutation) even if the ^{18}FDOPA PET is negative for focal disease

Focal K_{ATP} Hyperinsulinism

While the severity of hypoglycemia and glucose requirements overlap in both focal and diffuse diazoxide-unresponsive diseases, those with focal disease are more likely to present at a slightly older age (median of 0.3 months vs. 0 months) and with seizures, according to a retrospective chart review of 223 children treated at our center [8]. However, because it is impossible to differentiate focal from diffuse disease solely based on clinical features, genotyping and ^{18}fluoro-l-dihydroxyphenylalanine positron emission tomography (^{18}F-DOPA PET) imaging are critical to identify children with focal HI and to localize the lesion prior to surgery (Chap. 7). The sensitivity of mutation analysis for predicting focal HI based on finding a monoallelic recessive K_{ATP} mutation is 97%, and demonstration of paternal origin has a positive predictive value for focal HI of 94% [2] (Chap. 5). In children with suspected focal HI, noninvasive imaging with ^{18}F-DOPA PET should be performed preoperatively to identify the location of the lesion. This test has a sensitivity and specificity of 85% and 96%, respectively, which is superior to other imaging modalities, and it is less invasive than the formerly used calcium arterial stimulation with venous sampling; surgical resection of the lesion results in resolution of the hyperinsulinemic hypoglycemia.

Biallelic Recessive Diazoxide-Unresponsive K_{ATP}HI

According to the same retrospective chart review of 223 cases, newborns with recessive diazoxide-unresponsive K_{ATP}HI were more likely to be large for gestational age, to have hypoglycemia at birth, and to require higher glucose infusion rates when compared to those with focal disease. Molecular analysis indicating biallelic inheritance of recessive mutations is indicative of diffuse disease. ^{18}F-DOPA PET imaging is not indicated in these cases.

A large percentage of infants with diffuse K_{ATP}HI may require a subtotal pancreatectomy. Prior to considering a subtotal pancreatectomy, effectiveness of alternative medical therapies such as somatostatin analogues and enteral supplemental glucose should be assessed (reviewed in Chap. 6). If hypoglycemia persists despite maximal medical therapy or if severe adverse effects are observed, subtotal pancreatectomy should be considered as the next step of management [3]. In contrast to focal HI, a pancreatectomy is palliative in children with diffuse disease, and more than 40% of children continue to have persistent hypoglycemia after a near-total pancreatectomy, although usually the hypoglycemia is easier to manage.

Dominant Diazoxide-Unresponsive K_{ATP}HI

While dominant K_{ATP}HI was traditionally associated with diazoxide responsiveness, it is now being recognized that a small subset of patients with dominant mutations are not responsive to diazoxide. The clinical phenotype of children with dominant diazoxide-unresponsive K_{ATP}HI is indistinguishable from that of children with

diffuse disease caused by the more common K_{ATP} recessive mutations. These children are often born large for gestational age (LGA), with a median age of presentation of hypoglycemia that is more similar to individuals with recessive disease than those with diazoxide-responsive dominant disease. The majority require subtotal pancreatectomy, while a minority can be managed with somatostatin analogues and frequent feeds or continuous overnight dextrose through a gastrostomy [5].

Dominant Diazoxide-Responsive K_{ATP}HI

The phenotype of individuals with congenital hyperinsulinism due to dominant diazoxide-responsive K_{ATP} channel mutations is milder when compared to that of the diazoxide-unresponsive subtypes of the disease. The age of presentation is usually later than that of the recessive form. The severity of the hypoglycemia can vary among members of the same pedigree, and some mutation carriers may be asymptomatic [9]. Protein-induced hypoglycemia may be the dominant feature in older individuals with dominant diazoxide-responsive K_{ATP} channel mutations [10]. Diazoxide is the treatment of choice for these cases. Typically, the severity of the disease ameliorates with age, and treatment can be discontinued around pubertal years; however, some cases need treatment through adulthood.

Complications

Brain injury due to hypoglycemia is particularly high in K_{ATP}HI due to the severity of the hypoglycemia, especially during a crucial period of brain development. When compared to the better controlled diazoxide-responsive patients, patients with K_{ATP}HI requiring surgical therapy have a higher incidence of neurodevelopmental problems [11].

After 95–98% pancreatectomy, additional complications include persistent hypoglycemia and/or diabetes. Most children undergoing a pancreatectomy for diffuse HI may also require a gastrostomy tube placement. Because the remaining 2–5% of beta cells are still affected, complete resolution of the hypoglycemia is not always possible. Up to 40% of individuals continue to have hypoglycemia but may be more responsive to medical therapy. In some cases, the hypoglycemia may be so severe that additional pancreatectomy is required. The majority of children that undergo near-total pancreatectomy develop diabetes in the second decade of life [12, 13].

Glucokinase Hyperinsulinism

Glucokinase hyperinsulinism (GCK-HI) is less common than K_{ATP} HI with an estimated prevalence in pooled HI patient cohorts of (8/734) 1% [2, 14–16]. The GCK-HI mutations cause activation of glucokinase enzymatic activity which leads

to increased glucose phosphorylation at a lower glucose threshold than normal for beta cell glucose-stimulated insulin release. In addition, there is activation of glucokinase in the liver that leads to increased glucose clearance and contributes to hypoglycemia. A total of 18 different activating *GCK* mutations have been reported in 61 patients of 27 families. The reported phenotype varies considerably in terms of severity, clinical onset, and clinical course. Treatment for GCK-HI includes dietary interventions, because medical treatment with diazoxide and octreotide often has been insufficient to ensure normoglycemia. Near-total pancreatectomy has been required in the most severely affected patients; partial resection was used in one patient with atypical HI appearing to affect a limited portion of the pancreas due to a mosaic, somatic *GCK* mutation.

Pathophysiology

GCK-HI is caused by dominant, activating missense mutations in *GCK*, located on chromosome 7p15.3-p15.1 and coding for glucokinase (GCK, hexokinase IV). Glucokinase converts glucose to glucose 6-phosphate and functions as the "glucose sensor" of the beta cell [17, 18]. In the liver, glucokinase acts as a pacemaker for conversion of glucose to glycogen in response to insulin stimulation [3]. Glucokinase action in the liver, but not the beta cells, is subject to inhibitory regulation by glucokinase regulatory protein (GKRP). Although at least 99% of the body's full complement of glucokinase is located in hepatocytes, glucokinase is also expressed in several other cell types with importance for glucose homeostasis, including the hypothalamus and pancreatic alpha cells [19–21].

Mutations in *GCK* alter the kinetics of glucokinase by increasing the enzyme affinity for glucose and cause hypoglycemia by lowering the threshold for glucose-stimulated insulin secretion (GSIS) in the beta cell [22–24]. In contrast, heterozygous inactivating *GCK* mutations lead to maturity-onset diabetes of the young type 2 (MODY 2) [25]; homozygous inactivating *GCK* mutations are a cause of permanent neonatal diabetes [26]. While more than 700 inactivating *GCK* mutations associated with diabetes have been reported, only 18 activating *GCK* mutations have been identified in GCK-HI.

Activating GCK Mutations

Table 3.2 lists the different activating *GCK* mutations that have been reported [14, 15, 22, 23, 27–41]. All but three of the activating *GCK* mutations [28, 29, 40] are located in the allosteric binding site of the enzyme for inhibition by GKRP. The glucokinase allosteric site has been a target for development of drugs for the treatment of type 2 diabetes. Small-molecule glucokinase activators (GKAs) reduce plasma glucose by lowering the threshold for beta cell GSIS and increasing glucose phosphorylation in the liver [42, 43]. Liver-specific small-molecule GKAs have

Table 3.2 Activating *GCK* mutations in HI patients

Mutation		Reference	Functional properties[a]		Patients	Clinical data		
Nucleotide change	Amino acid change		GSIR threshold, mmol/L (wild type 5.0 mmol/L)	Relative activity index (wild type 1.0)	(*n*)	Diazoxide response[b]	Octreotide response[b,c]	Pancreatic surgery (patient *n*)
c.191C>A	p.Ser64Tyr	[14]	1.4	22	1	Yes	–	0
c.194C>T	p.Thr65Ile	[14, 15, 34]	3.1	9.8	3	Partial; yes	–	1
c.203G>T	p.Gly68Val	[41]	1.9	16	8	Yes, combined		0
c.271G>T	p.Val91Leu	[15, 36]	1	30	3	No; yes	No	2
c.295T>C	p.Trp99Arg	[14, 34]	2.8	6.4	4	No; partial; yes	Partial	0
c.295G>T	p.Trp99Leu	[40]	2.2	8.9	1	Partial	–	0
c.297G>T	p.Trp99Cys	[15]	–	11.7	1	Yes	–	0
c.308c>G	p.Thr103Ser	[29]	2.9	8.4	6	Yes	–	0
c.591G>T	p.Met197Ile	[39, 40]	3.5	3.1	2	Yes	–	0
c.590T>C	p.Met197Thr	[38]	–	4.4	3	–	–	0
–	p.Ile211Phe[d]	[35]	–	–	1	Partial		1
c.641A>G	p.Tyr214Cys	[32]	0.8	130	1	No	–	1
c.1165G>C	p.Val389Leu	[29, 30]	2.9	6.0	7	Partial; yes	No	0
c.1324G>A	p.Glu442Lys	[15, 28]	4.1	3.3	4	Partial; yes	n/a	0
c.1354G>C	p.Val452Leu	[27, 37]	1.9	10.8	2	Partial	Partial combined with diazoxide	0
c.1361_1363dupCGG	Ins454A	[40]	1.1	26	1	No	Partial	0
c.1363G>A	p.Val455Met	[23]	2.5	5.2	5	Yes	–	0
c.1367C>T	p.Arg456Val	[14, 22, 31, 33]	1.4–1.5	34–37.9	8	Partial	Partial; yes	0

GCK gene according to NM 000162.3
Abbreviations: *GSIR* Glucose-stimulated insulin release
[a]Values from different laboratories
[b]According to different definitions
[c]Including long-acting release and lanreotide
[d]Somatic mutation

been developed in an effort to avoid complications of hypoglycemia that are associated with beta cell GCK activation [44]. Liver-specific GKAs inhibit the binding of GKRP to GCK and hence inhibit GCK sequestration. The development of GKA drug stands as an example of how research in HI can lead to increased understanding of beta cell function and development of novel potential treatments for diabetes.

Activating *GCK* mutations are kinetically characterized by a higher affinity for glucose and in some – but not all mutations – a higher maximal enzyme velocity (K_{cat}) [34]. Based on GCK enzyme kinetic parameters, a relative activity index (RAI) compared to wild-type GCK can be calculated [25, 45]. The increased glucose affinity in patients with activating *GCK* mutations leads to increased rates of glucose oxidation, increased ATP/ADP ratio, K_{ATP} channel closure and, hence, hypersecretion of insulin through the beta cell triggering pathway. The lower glucose threshold for GSIS predicts a phenotype with stable, but not progressively declining, fasting hypoglycemia, since glucose responsiveness is preserved, but with switching off of insulin secretion only at a lower than normal glucose threshold.

Several papers have reported de novo mutations in GK-HI [15, 31, 32, 34, 37, 40]. This relatively high incidence of de novo mutations is common in dominantly inherited disorders (e.g., hyperinsulinism-hyperammonemia syndrome due to dominant mutations of GLUD1; see Chap. 2) and has sometimes been interpreted to suggest reduced reproductive capacity due to the devastating consequences of severe hypoglycemia [34, 40].

One unique GK-HI patient had a somatic, mosaic *GCK* mutation, p.Ile211Phe, that involved only a part of the pancreas and was cured after partial pancreatectomy [35]. This girl appeared to have a focal type of hyperinsulinism based on pancreatic venous sampling; however, histology revealed a mosaic pattern with only some regions showing increased islet nucleomegaly [46]. A known GCK-HI mutation was identified in this region of the pancreas, but was not detectable in the blood or in the normal-appearing part of the pancreas. Functional studies of the p.Ile211Phe mutation showed the highest relative activity index of all known GCK mutations and suggested that the defect as a germline mutation might not be compatible with life [3]. However, in the mosaic form the affected patient had a milder disease than predicted in case of germline p.Ile211Phe mutation.

Clinical Features and Management

The reported phenotypic spectrum of GK-HI is extremely broad, ranging from asymptomatic [15, 22, 30], over attacks of seizures and loss of consciousness [15, 22, 29, 34] to permanent severe hypoglycemia [32]; a clinical onset in the neonatal period [15, 28, 34, 40] to late adulthood up to 77 years [30]; and a relapsing [14, 22, 27, 40] or persistent course [14, 15, 32]. When formally tested, asymptomatic patients revealed to have repeat episodes of low plasma glucose [31], in keeping with the concept of hypoglycemia unawareness with hypoglycemia-associated

autonomic failure (HAAF) [47] and hence lack of adrenergic and cholinergic symptoms and signs (e.g., tremor, pallor, palpitations, anxiety, sweating, hunger, paresthesia). Many newly identified patients have been overweight or obese [14, 23, 30, 31, 41], suggesting increased eating behavior to avoid unrecognized hypoglycemia symptoms. In some of the obese patients, hypoglycemia was diagnosed only after severe clinical attacks following a trial of slimming, demonstrating the importance of regular food intake to avoid hypoglycemia [31].

Of note, not only fasting leads to hypoglycemia in GCK-HI. Oral or i.v. glucose stimulation can also lead to hypoglycemia after 60–150 min in some, but not all, with preceding excess insulin response [22, 23, 30, 31, 34, 37]. The hypoglycemia after OGTT may be more profound than fasting hypoglycemia with plasma glucose values down to 25–38 mg/dL (1.4–2.1 mmol/L). Others have reported hypoglycemia after high-carbohydrate meals or exercise [40]. In contrast, leucine stimulation test and i.v. calcium stimulation have not lead to (aggravation of) hypoglycemia [32, 40].

In most described families with dominant inherited GCK-HI, the reported phenotype is highly variable within the family suggesting additional genetic or environmental factors [15, 22, 28–30, 34, 41]. Adults aged 42–75 years with activating *GCK* mutations have developed diabetes with no documentation of autoimmune etiology [23, 29, 41], potentially as the result of adverse genetic background [29], obesity, or "beta cell exhaustion" from chronic hyperinsulinism due to the mutation itself [23, 41].

In conclusion, the variable phenotype in GCK-HI may reflect unrecognized hypoglycemia and delay of diagnosis, as well as differences in the mutations' severity, germline vs. mosaic somatic mutations, genetic background, and the effects of age, diet, exercise, and obesity.

Dietary Treatment

A diet with avoidance of prolonged fasting and meals with balanced carbohydrate had some benefit in many patients [15, 33, 38], although clearly not in all. Others have been treated with frequent feeding day and night [40] or continuous carbohydrate feeding through gastric tube at night with some success [40, 41]. A seemingly high occurrence of disease onset, relapse after neonatal hypoglycemia, or worsening hypoglycemia around 14–15 years of age can be deducted from several patient reports [14, 22, 23, 40]. This may be the consequence of lifestyle change during the teenage years, supporting the importance of diet in GK-HI. Frequent low-carbohydrate meals, and eventually continuous night feeding, should be considered in any patient with GK-HI.

Medical Treatment

Given an intact K_{ATP} channel, diazoxide is predicted to have some effect in the treatment of GCK-HI, acting as a K_{ATP} channel opener downstream the triggering pathway of the beta cell with inhibition of the glucose sensitivity for insulin

secretion. This is indeed the case as reported in the majority of patients with GCK-HI, as listed in Table 3.2. However, the diazoxide responsiveness was only partial or variable for many mutations at closer inspection. Taken together, much of the reported diazoxide responsiveness in the literature may in fact represent an overestimation with disregard of the importance of hepatic glucose clearance and dietary treatment. Lastly, but perhaps most importantly, diazoxide responsiveness was not defined in majority of published studies of GCK-HI. In one recent study, diazoxide response for doses up to 20 mg/kg/day was defined as maintained normoglycemia with plasma glucose levels >60 mg/dL (>3.3 mmol/L) in conjunction with a normal feed volume and frequency and appropriate fasting tolerance for age [15]. A clear definition of diazoxide responsiveness is warranted in future publications.

Treatment with octreotide or long-acting octreotide or lanreotide has been reportedly effective, or partially effective, in a few patients [31, 40], but not on others [30, 36].

Surgery

Pancreatic surgery has been performed in some GCK-HI patients [15, 32, 34–36]. In all reported cases a trial of conservative, medical treatment had failed, however in some with unreported or reported low medication doses [15, 32, 35]. Partial and even near-total pancreatectomy had no effect in the two most severe cases with the p.Tyr214Cys mutation, whereas the patient with somatic p.Ile211Phe mutation was cured after resection of the pancreatic tail and body [46]. Reported histology ranged from normal appearance [34, 40, 41] to diffuse hyperinsulinism [36], in keeping with the disease severity, with the exception of atypical mosaicism in the patient with the somatic p.Ile211Phe mutation [35].

Diazoxide-Unresponsive HI with Unknown Genetics

Ten percent of diazoxide-unresponsive cases are of unknown etiology [3]. Research efforts are undergoing to elucidate the molecular mechanisms on these cases. Unique non-syndromic patients may have somatic mutations with mosaic distribution in the pancreas. These rare atypical forms are not homogenous and have formerly included segmental mosaic forms and extensive focal forms [48]. Different terms have been used to refer to this group of patients, which likely represent varied pathophysiology, including atypical HI and localized islet cell nuclear enlargement (LINE). This latter term describes the histopathological findings, which includes features of diffuse disease (nucleomegaly) that are confined to a specific region of the pancreas, while the rest of the pancreas looks normal. The findings are distinct from focal HI in that there is no ß cell mass expansion (see Chap. 8).

At the Children's Hospital of Philadelphia, the cohort of children with LINE includes 16 patients. Patients with LINE usually present with hypoglycemia late

in infancy, at a median age of approximately 4 months (range day of life 1–7 months), and do not usually respond to diazoxide or octreotide. On imaging with ^{18}F-DOPA PET scan, diagnosis of focal vs. diffuse is usually unclear. Surgical removal of histologically abnormal tissue [median surgical removal of 71% of the pancreas (range 15–98%)] resulted in resolution of the hyperinsulinism in 82% of patients.

Conclusions

Diazoxide-unresponsive HI is a severe form of hyperinsulinism that is most commonly caused by inactivating mutations in the genes encoding the K_{ATP} channel and less commonly by activating mutations in *GCK*. Determining diazoxide responsiveness is of utmost importance, because the majority of patients who are diazoxide-unresponsive have inactivating K_{ATP} channel mutations, and of these, 50–60% have focal disease, which can be cured by limited pancreatectomy. In cases of diffuse or nonfocal HI, a trial of aggressive medical therapy is warranted, as a subtotal pancreatectomy is palliative and is often followed by persistent hypoglycemia and future development of diabetes. Prevention of hypoglycemia are the goals of medical and surgical therapy, so as to prevent poor neurodevelopmental outcomes and provide better quality of live.

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Chapter 4
Syndromic Causes of Congenital Hyperinsulinism

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Congenital hyperinsulinism (HI) has been linked to a number of specific genes, but in the past few years, it has become increasingly clear that not all children with HI have a genetic cause linked to these HI genes. Several genetic syndromes are also associated with HI, most commonly Beckwith-Wiedemann syndrome (BWS), Kabuki syndrome (KS) [46], Sotos Syndrome (SS), and Turner syndrome (TS) (Fig. 4.1). These syndromes should be considered in all cases of HI both with and without an identified mutation in an HI gene since management both for HI and the other manifestations of the syndrome are needed to optimize care for these patients. It is important to note that all four of these syndromes can present with features that are more subtle than the classically described syndromes, so careful clinical evaluation for syndromic causes should be considered in all HI patients.

Beckwith-Wiedemann Syndrome

Beckwith-Wiedemann syndrome (BWS) is an overgrowth and cancer predisposition syndrome with an incidence of 1 in 10,500 [36] initially characterized in the 1960s by J. Bruce Beckwith and Hans Wiedemann. It is classically characterized by

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macroglossia, omphalocele, organomegaly, and increased risk for embryonal tumors [8, 36]. Distinct facial features include glabella and/or eyelid nevus simplex, infraorbital creases, and ear pits or creases (Fig. 4.1a–c). Additional features that can be recognized prenatally include polyhydramnios and mesenchymal dysplasia. Histologic findings include adrenal cytomegaly and pancreatic islet adenomatosis. It has recently been recognized that there is a spectrum of clinical phenotypes in BWS and that some children only present with subtle features such as lateralized overgrowth or hemihypertrophy [8, 22]. This is due to the fact that the genetic and epigenetic changes in BWS occur in a mosaic fashion such that there is a mixture of normal and BWS cells [24]. In some cases, HI may be the only presenting feature of BWS [9, 23].

Approximately 50% of children with classical BWS have hypoglycemia due to hyperinsulinism at birth, and about 5% of these have severe persistent hyperinsulinism (HI) [14, 35]. In addition, a recent report of a large HI cohort found that BWS was the cause of HI in 5–10% of cases [23].

Fig. 4.1 Syndromic HI. (**a**, **b**) Beckwith-Wiedemann syndrome (BWS) due to paternal uniparental isodisomy for chromosome 11. (**c**) BWS due to loss of methylation at imprinting control region 2. (**d**) Kabuki Syndrome. (**e**) Sotos Syndrome. (**f**) Turner syndrome. (Photos courtesy of Dr. Jennifer M. Kalish, Children's Hospital of Philadelphia)

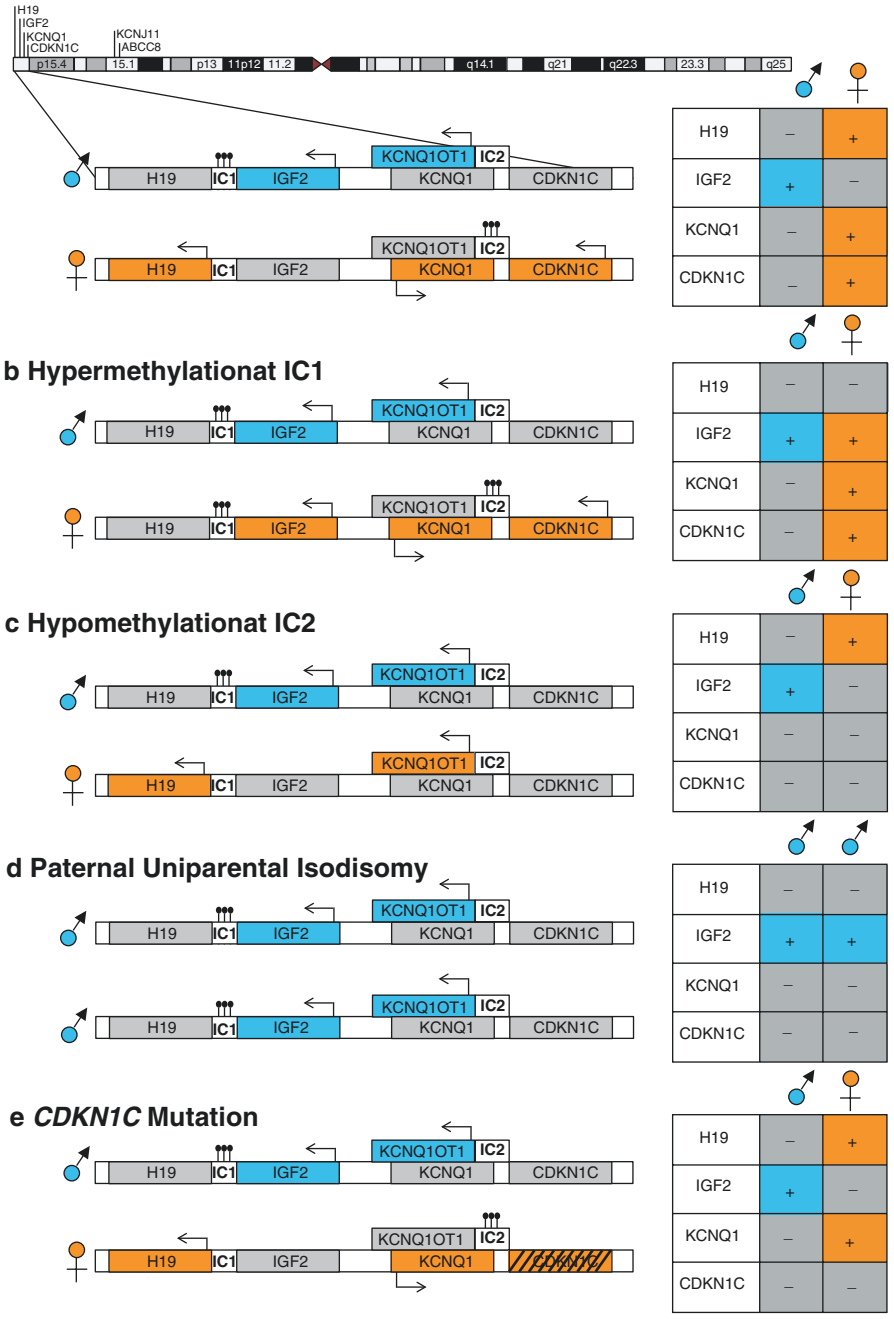
BWS is due to genetic or epigenetic changes involving two imprinting control centers (IC) on chromosome 11p15.5 (Fig. 4.2a). This locus includes *IGF2*, a growth-promoting protein; *H19*, a long noncoding RNA growth suppressor; and *CDKN1C*, a cell cycle regulator and growth inhibitor. Methylation at the two imprinting control centers (IC1 which regulates *H19* and *IGF2* and IC2 which regulates *CDKN1C*) leads to parent of origin-specific gene expression. In addition, *KCNQ1*, a potassium-repolarizing channel, is controlled from IC2. BWS occurs through loss of methylation at IC2 in about 50% of cases [8] (Fig. 4.2b). About 20% of BWS is due to paternal uniparental isodisomy for part or all of chromosome 11 (Fig. 4.2c); 5% are due to gain of methylation at IC1 (Fig. 4.2d); 5% are due to maternally inherited mutations in *CDKN1C* (Fig. 4.2e); and ~6% are due to chromosome rearrangements leading to deletions or duplications of the 11p15.5 region [8].

Notably, the most common genetic cause of HI involves recessive inactivating mutations in the sulfonylurea receptor 1 or the inwardly rectifying potassium subunit of the plasma membrane ATP-sensitive potassium channel (encoded by *ABCC8* and *KCNJ11*, respectively), which are located on chromosome 11p15.1, in close proximity to the BWS region [3, 38, 51, 52]. The mechanism of focal HI is paternally inherited mutations in one of these subunits coupled with a localized paternal uniparental isodisomy event for chromosome 11 (pUPD11), leading to biallelic loss of one of the channel subunits [13]. Because the mechanism of action of diazoxide involves activation of this channel, patients with focal HI are unresponsive to diazoxide.

HI has also been reported in BWS patients caused by loss of methylation (LOM) at IC2. These patients are usually diazoxide responsive, because the K_{ATP} channel is not affected [21, 23, 45]. In BWS patients with pUPD11, the severity of the HI and management strategies vary based on the co-occurrence of a K_{ATP} mutation and/or the size of the pancreatic region affected [23]. In the absence of a paternally inherited K_{ATP} mutation, HI due to pUPD11 may be responsive to diazoxide; however, even in the absence of a K_{ATP} mutation, some cases can be more severe and require treatment with somatostatin analogues or subtotal pancreatectomy [23]. Both short- and long-acting forms of somatostatin analogues have been used in some cases of BWS [4, 23]. Given the phenotypic spectrum of BWS and the range of management of HI, it is important to consider BWS in all HI patients.

Kabuki Syndrome

Kabuki makeup syndrome (KS) is increasingly recognized as one of the most frequent causes of syndromic HI [31]. Kabuki syndrome was discovered in 1981 by Niikawa and Kuroki, who named it after the specific facial dysmorphia of the patients, which resembles the makeup worn by actors in the Japanese Kabuki


a Normal
H19
IGF2
KCNQ1
CDKN1C
KCNJ11
ABCC8
p15.4
15.1
p13
11p12
11.2
q14.1
q21
q223
23.3
q25
KCNQ1OT1
IC2
IC1
b Hypermethylationat IC1
c Hypomethylationat IC2
d Paternal Uniparental Isodisomy
e CDKN1C Mutation
CDKN1C
H19 – +
IGF2 + –
KCNQ1 – +
CDKN1C – +
H19 – –
IGF2 + +
KCNQ1 – +
CDKN1C – +
H19 – +
IGF2 + –
KCNQ1 – –
CDKN1C – –
H19 – –
IGF2 + +
KCNQ1 – –
CDKN1C – –
H19 – +
IGF2 + –
KCNQ1 – +
CDKN1C – –

theater [26, 41]. The initial description included five cardinal features: facial dysmorphism (Fig. 4.1d), skeletal abnormalities, dermatoglyphic abnormalities, intellectual disabilities, and postnatal growth retardation. However, the disease is far more polysystemic and may involve virtually all body systems.

The prevalence of KS was estimated in Japan at 1/32,000 living births [40]. The genetic causes were discovered by Ng and Miyake in 2010: in about two-thirds of the patients, mutations are found in the *KMT2D* gene, formerly called *MLL2* (autosomal dominant, predominantly de novo), while *KDM6A* gene mutations (X-linked) represent less than 10% of patients [33, 34, 39]. The products of these two genes function by either adding an activating methyl group (in the case of *KMT2D*) or removing a repressive methyl group (in the case of *KDM6A*) from specific amino acid residues in a protein called histone H3. Although the two enzymes are doing opposite activities, the result is the same – repressing the open chromatin state of the H3 histones and subsequently silencing various genes. Thus, KS is a disease of the epigenetic machinery.

Up to 10% of KS neonates present with hypoglycemia; however, the mechanism of the hypoglycemia may be multifactorial: besides HI, growth hormone deficiency (GHD) is observed in up to 8% of patients [15, 49]. HI is a feature in up to 6% of KS patients [53]. HI is present from birth, is usually diazoxide-responsive, and often appears to resolve during the first decade of life. Clinical recognition of the facial dysmorphism of KS is difficult in the neonate. Therefore, KS should be considered in all patients with neonatal HI, by a careful clinical exam; the association of failure to thrive with poor sucking and heart and/or bone malformation can lead to the diagnosis. In about one-third of patients, prenatal ultrasound identified unspecific abnormalities, such as a thickened nuchal fold during pregnancy, growth retardation, or malformation (heart, urinary tract, facial clefts) [44].

Fig. 4.2 Mechanisms of Beckwith-Wiedemann syndrome (BWS). Chromosome 11 includes the BWS region and the KATP genes. Expressed genes are noted with a surrounding bold box. Maternally expressed genes are in orange, and paternally expressed genes are in blue. Imprinted genes that are not expressed are in gray. Closed circles indicate methylation. The K_{ATP} channel genes *KCNJ11* and *ABCC8* are biallelically expressed. (**a**) 11p15 contains two adjacent imprinting control regions that are altered in BWS. Normally, imprinting control region 1 (IC1) is methylated on the paternal allele resulting in paternal expression of *IGF2* and unmethylated on the maternal allele resulting in maternal expression of *H19*. Imprinting control region 2 (IC2) is methylated on the maternal allele resulting in *KCNQ1* and *CDKN1C* (p57) expression and unmethylated on the paternal allele. (**b**) Hypermethylation at IC1, a rarer cause of BWS, leads to biallelic *IGF2* expression and loss of *H19* expression. (**c**) Hypomethylation at IC2 in which IC2 is unmethylated on both alleles leads to loss of *KCNQ1* and *CDKN1C* expression. (**d**) In paternal uniparental isodisomy (pUPD11), IC1 is methylated on both alleles resulting in biallelic *IGF2* expression and loss of *H19* expression. IC2 is unmethylated on both alleles, resulting in loss of *KCNQ1* and *CDKN1C* expression. (**e**) Maternally transmitted *CDKN1C* mutations can occur. Additionally, rare deletions or duplications of the imprinted region(s) can also lead to BWS

During the first year of life, the facial dysmorphism becomes increasingly typical: patients have long palpebral fissures, with an eversion of the external third of the lower lid. They may also have arched eyebrows, arched palates, and dental agenesis.

At least 90% of KS patients present with other dysmorphic features: hands are almost always involved (fetal pads at the extremities of fingers, absent distal interphalangeal creases of the third and fourth fingers, brachymesophalangy of the fifth finger, abnormal dermatoglyphics, etc.); skeleton (about 90% of patients exhibit vertebral and costal malformation, scoliosis, hip dislocation, microcephaly, etc.), heart (about 50% of patients have septal defects, conotruncal heart defects, etc.), kidney, and urinary tract malformations (about 30); cryptorchidism; anorectal malformations; and chronic diarrhea [2, 29, 32]. Besides HI and GHD, other endocrine conditions have also been described: premature thelarche and hypothyroidism.

Mild to moderate cognitive impairment has been found in 75% of KS patients. In some cases, the delay is obvious from the neonatal period onward because of hypotonia and failure to thrive. Some patients may present with microcephaly, epilepsy, or brain malformation. The neurocognitive development may also be impacted by neurosensory impairments (about half of the patients), perception or transmission deafness, and refractive errors (myopia, astigmatism, etc.). About one-third of the patients are born small for gestational age and have subsequent postnatal growth delay. After an early infancy marked by failure to thrive, obesity can be observed from 8 years of age in 25% of the patients [55].

Sotos Syndrome

Sotos syndrome (SS) is classically characterized by pre- and postnatal overgrowth with height and/or head circumference ≥2 standard deviations above the mean, distinctive facial features (frontal bossing, broad and prominent forehead, sparse frontotemporal hair, prominent jaw, malar flushing, and down-slanting palpebral fissures) (Fig. 4.1e), and learning disabilities, including early developmental delay and/or mild to severe intellectual impairment. These three cardinal features are present in >90% of individuals diagnosed with Sotos syndrome [28, 50]. Other clinical features may include maternal preeclampsia, cardiac defects, advanced bone age, cranial abnormalities, renal anomalies, scoliosis, seizures, neonatal hypotonia, neonatal jaundice, and hyperlaxity [28, 50].

Sotos syndrome is caused by haploinsufficiency of the nuclear receptor-binding SET domain 1 gene (*NSD1*). *NSD1* is located at chromosome 5q35 and encodes a histone methyltransferase implicated in the regulation of chromatin [1, 50]. Transient HI in the neonatal period has been reported in eight patients with Sotos syndrome; most had microdeletions of *NSD1* [10–12, 20, 30, 37, 50]. It is speculated that alterations or microdeletions in *NSD1* lead to downstream disruption of the regulation of insulin secretion, but the mechanism is currently unclear [30].

Turner Syndrome

Turner syndrome (TS) was discovered by Henry Turner in 1938 and is the consequence of complete or partial loss of the X chromosome. Its prevalence is about 1 in 2500 female live births. All TS karyotypes are mosaic, and the proportion of cytogenetic abnormality differs among patients and among their tissues. About half of the patients have a 45, X/46,XX karyotype, while 40–50% carry other kinds of anomalies (delXp, delXq, isoXq, etc.); about 6% of patients have a ring X chromosome with the karyotype 45,X/46,X,+r(X) [18].

The clinical spectrum of TS is broad, ranging from a typical phenotype combining many physical symptoms (Fig. 4.1f) to patients with minimal features and even normal appearance. At birth, half of TS patients are small for gestational age. Some may present with fetal cystic hygroma, hydrops, or dysmorphic features (20–60%) such as down-slanted palpebral fissures, epicanthal folds, low-set anomalous pinnae, micrognathia, narrow palate, short broad neck, and pterygium colli. Congenital heart defects affect up to 40% of patients, obstructive left-sided defects being the most typical (bicuspid aortic valve, coarctation, aortic stenosis, mitral valve anomalies, and hypoplastic left heart syndrome). Madelung deformity and kidney malformations are also frequent.

Later in life, growth restriction affects 95% of patients. The growth velocity decreases, usually from the age of 18 months, and the average final height is about 20 cm less than the average of the general population, despite normal growth hormone secretion. Growth hormone treatment, even without GH deficiency, has shown positive effects on linear growth. Delayed puberty, amenorrhea, or infertility due to hypergonadotropic hypogonadism often provides an opportunity for diagnosis. The majority of TS women have a normal cognitive development; however, 10% have intellectual disabilities [18]. A ring X chromosome is associated with the highest risk for intellectual disability [25].

TS patients are prone to metabolic syndrome and diabetes [6]. Conversely, the occurrence of hypoglycemia in TS is rare: it was observed in only 2/594 cases in a Danish epidemiological study. However, the risk ratio of hypoglycemia in TS patients appeared to be 3.5 times higher than expected [19]. Screening for hypoglycemia is not included in current TS guidelines [18, 27].

Hypoglycemia in TS has been rarely reported in the literature and has been attributed to growth hormone deficiency [7], unknown mechanisms [17], or primarily due to HI [5, 16, 42]. HI has been reported to occur 50 times more often than expected in TS; it was diagnosed because of symptomatic hypoglycemia at birth or later during the first year of life and was usually responsive to treatment with diazoxide [16]. These patients were reported to have either facial dysmorphism, heart malformation, or uterus and ovarian hypoplasia.

Interestingly, the first reported HI-TS patients, including the patient reported by Goto, had a ring X chromosome, which confers a risk of intellectual disability, as well as a Kabuki-like phenotype (e.g., eversion of the external part of the lower lid)

[43, 47, 48, 54]. In contrast, the recent series of 13 HI-TS patients by Gibson found only 3 cases of a ring X [16]. Interestingly, *KDM6A*, one of the two genes associated with Kabuki syndrome, is carried on the X chromosome. Studies of isolated islets from HI-TS patients showed alterations in insulin secretion that were similar to those of control islets treated with a *KDM6A* inhibitor. Thus, it is suggested that haploinsufficiency for *KDM6A* due to mosaic X chromosome monosomy may be responsible for hyperinsulinism in Turner syndrome.

This chapter has described only the four most common syndromic forms of HI. Given the prevalence of syndromes which may cause HI, it is important that every patient with HI should be carefully assessed for features suggestive of these syndromes.

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Chapter 5
Molecular Diagnosis of Congenital Hyperinsulinism

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Genetic Heterogeneity of Congenital Hyperinsulinism (HI)

HI has been associated with pathogenic mutations in nine genes [1]. By far the most common genetic cause of HI is inactivating mutations in *ABCC8* and *KCNJ11*, which encode the two subunits of the pancreatic beta cell ATP-sensitive K^+ (K_{ATP}) channel [2, 3]. As shown in Table 5.1, mutations in these genes represent 86% of mutation-positive cases at the Children's Hospital of Philadelphia and 82% of those at the University of Exeter.

The majority of patients with mutations in *KCNJ11* and *ABCC8* are diazoxide unresponsive and may require pancreatic surgery. It is extremely important to understand both the mode of inheritance and parent of origin of the mutation(s) as these will provide information on the pancreatic histological subtype (i.e. focal vs diffuse). Focal HI represents a localized area of islet cell adenomatosis and is caused by a single paternally inherited recessive K_{ATP} channel mutation followed by a somatic loss of the maternal chromosome 11p15 region [4, 5]. Diffuse K_{ATP} HI

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involves the whole pancreas and is caused by either two loss-of-function recessive mutations, one inherited from each parent, or by a single dominant negative mutation. The latter, dominant K_{ATP} channel mutations, may result in either diazoxide-responsive or diazoxide-unresponsive HI, depending on the degree of residual channel activity [6–8]. Dominant mutations may be inherited from a parent or can arise spontaneously (i.e. de novo). In cases where the dominant mutation is inherited, variable penetrance is often observed within the family [7–9].

Mutations in seven additional genes (*GCK*, *HADH*, *GLUD1*, *HNF4A*, *HNF1A*, *SLC16A1*, *UCP2*) are relatively rare, accounting for just 14% and 18% of the University of Pennsylvania and University of Exeter's mutation-positive cases, respectively (Table 5.1). Although *UCP2* is included on many commercial genetic test panels, debate is ongoing as to whether or not mutations in this gene are causative for HI [10–12]. *HK1* has also been implicated in the pathogenesis of HI but is not included on genetic testing panels; additional evidence is needed to prove the association of *HK1* mutations with HI [13]. The majority of children with a mutation in one of these seven rare genes are typically responsive to diazoxide. However, exceptions include some children with *GCK*, *UCP2* and *HNF1A* mutations who are diazoxide unresponsive. See "Diazoxide-Unresponsive Hyperinsulinism" and "Diazoxide-Responsive Hyperinsulinism" chapters in this book. A genetic diagnosis can inform on the protein-sensitive nature of the HI (e.g. *ABCC8*, *KCNJ11*, *GLUD1*, *HADH*) or give important information on prognosis (e.g. increased risk of adult-onset diabetes in individuals with *HNF1A* and *HNF4A* mutations) [14–17]. Clues as to the most likely underlying genetic aetiology can in some cases be gleaned by phenotypic characteristics. For example, the presence of hyperammonaemia suggests a *GLUD1* mutation, and exercise-induced HI indicates the possibility of an *SLC16A1* mutation [18, 19].

For the majority of patients diagnosed with HI, hypoglycaemia and its associated sequelae are the only manifestations of the disease. However hyperinsulinism can occur as part of a multisystem disorder with the most common example being

Table 5.1 Children with positive mutation analysis in nine HI genes in both the University of Pennsylvania (UoP) and University of Exeter (UoE) cohorts. The UoP cohort represents children treated at the Children's Hospital of Philadelphia. The modes of inheritance of each genetic subtype and the functional consequence of the reported mutations are also provided for each gene

Gene	Mode of inheritance	Functional consequence	UoP cohort (n = 562)	UoE cohort (n = 1308)
ABCC8	Recessive/dominant/*de novo*	Loss of function	434 (77.5%)	938 (71.7%)
KCNJ11	Recessive/dominant/*de novo*	Loss of function	47 (8.5%)	135 (10.3%)
GCK	Dominant/*de novo*	Gain of function	15 (2.6%)	31 (2.4%)
GLUD1	Dominant/*de novo*	Gain of function	38 (6.8%)	78 (6.0%)
HADH	Recessive	Loss of function	2 (<1%)	68 (5.2%)
HNF4A	Dominant/*de novo*	Loss of function	10 (1.7%)	58 (4.4%)
HNF1A	Dominant/*de novo*	Loss of function	10 (1.7%)	0
UCP2	Dominant/*de novo*	Loss of function	6 (1%)	0
SLC16A1	Dominant/*de novo*	Gain of function	0	0

a form of Beckwith-Wiedemann syndrome due to 11p uniparental isodisomy [20, 21]. Paternally inherited recessive K_{ATP} channel mutations are present in some children with 11pUPD BWS [21]. These children tend to have more severe HI that is diazoxide unresponsive. Other children with HI associated with BWS are diazoxide responsive. In addition, HI has been reported in some children with Kabuki syndrome due to mutations in *KMT2D* or *KDM6A* and in Turner syndrome [22–25]. See "Syndromic Hyperinsulinism" chapter in this book.

Strategies for Genetic Screening

A rapid and accurate clinical and genetic diagnosis of HI is particularly important in children who are unresponsive to diazoxide. In these cases, the genetic results will indicate whether diffuse or focal HI is most likely and consequently whether a 18F-DOPA PET-CT scan is required prior to surgery (see "Surgical Management of Hyperinsulinism" chapter of this book). Mutation analysis is an excellent tool in predicting the presense of focal HI. When a single recessive K_{ATP} channel mutation is identified, focal HI is predicted with 97% sensitivity [25]. Demonstration of paternal origin provides a small increase in specificity. Preoperative genetic diagnosis of focal HI is of great importance in clinical decision-making since a lesionectomy is likely to be curative in these patients. This need for rapid genetic testing has led many laboratories to adopt a two-tier testing strategy for the molecular diagnosis of HI. Patients who are diazoxide unresponsive should be sent for tier 1 testing which includes Sanger sequencing of the coding and flanking intronic regions of *ABCC8*, *KCNJ11* and, in some laboratories, *GCK* and *GLUD1*, as well as exonic dosage analysis of *ABCC8* and *KCNJ11*, with results available within 5 days of sample receipt. In cases of diazoxide-unresponsive HI, mutation analysis is successful in 90% of cases with the majority of mutations being identified in *ABCC8* and *KCNJ11* and a small number being identified in *GCK* (Fig. 5.1a). If no mutation is identified, testing should reflex to tier 2 testing.

Patients who are responsive to diazoxide should be sent for tier 2 testing which involves targeted next-generation sequencing of the coding exons and flanking intronic regions of all known HI genes except *SLC16A1*. Only the promoter and upstream regions of *SLC16A1* are sequenced because mutations associated with exercise-induced HI have been restricted to this region [18]. In addition, tier 2 testing should include analysis for partial/whole gene deletions or insertions of all genes. In diazoxide-responsive patients, the majority of mutations are identified in *ABCC8*, *KCNJ11* or *GLUD1* (Fig. 5.1b). Mutation analysis is less successful in patients with diazoxide-responsive HI as only about 36% are found to have a mutation (Fig. 5.1b) [25, 26].

Because the interpretation of genetic results is often reliant on the inheritance pattern, it is crucial that samples from both parents are collected and sent along with the patient sample for either tier 1 or 2 testing. Parent-of-origin testing is especially crucial for identifying possible focal HI and should always be included as part of tier 1 testing.

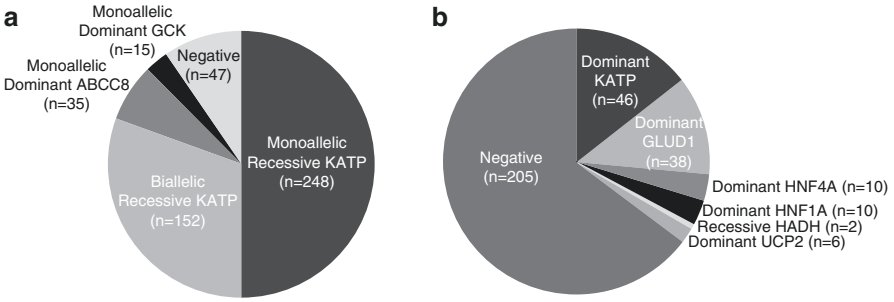

Fig. 5.1 (**a**) Diazoxide-unresponsive HI (n = 497). (**b**) Diazoxide-responsive HI (n = 317). Distribution of identified mutations in children with diazoxide-unresponsive HI (a) and diazoxide-responsive HI (b) treated at the Children's Hospital of Philadelphia. Mutations are identified in 90% of diazoxide-unresponsive patients and in only 35% of diazoxide-responsive patients

Interpretation of Genetic Test Results

Once a variant(s) is identified in a causative gene, substantial effort and expertise are required to interpret the clinical impact of the change. For HI genes this is not a trivial task, given that they are extremely polymorphic [over 800 variants have been identified in *ABCC8* alone [25, 27] (Flanagan, Ganguly unpublished data)], that there is often variable penetrance and expressivity and that multiple genetic mechanisms of disease have been reported [25, 27]. For novel variants evidence must be sought to determine how likely it is that the genetic change is causative of the disease. Whilst common founder mutations have been reported in Israeli Ashkenazi [3, 28], Hispanic [29], Bedouin [30], Spanish [31], Irish [32], Finnish [33] and Turkish [32] populations, the majority of mutations are novel and have not been published in the literature. The introduction of targeted next-generation sequencing has also added complexity with more variants being identified as a result of testing multiple genes simultaneously in each individual. To help mitigate these issues, laboratories rely heavily on internal knowledge bases of previously identified variants and the phenotypes of individuals in which they were found.

The publication of the American College of Medical Genetics (ACMG) guidelines for variant interpretation has helped in standardizing approaches for classification [34]. Variants are classified as "pathogenic", "likely pathogenic", "variant of unknown significance", "likely benign" or "benign" based on different levels of evidence. The strongest evidence for a "pathogenic" classification is the identification of a null variant (i.e. nonsense, frameshift, splicing mutations) in a gene where loss of function is a known mechanism of HI. However, if a missense mutation is identified, some level of literature support, such as functional studies or an overrepresentation of the variant in individuals with HI, is required to achieve a "pathogenic"

Table 5.2 Types of *ABCC8* and *KCNJ11* mutations including associated inheritance patterns and predicted responsiveness to diazoxide

Type of mutation	Inheritance pattern	Diazoxide responsiveness
Missense	Dominant or recessive	Diazoxide unresponsive (recessive or dominant) or diazoxide responsive (dominant)
Nonsense	Recessive	Diazoxide unresponsive
Frameshift	Recessive	Diazoxide unresponsive
Intronic splicing	Recessive	Diazoxide unresponsive
Insertion/deletion	Recessive	Diazoxide unresponsive

classification. The absence of the variant in control populations is evidence for pathogenicity, but if a variant is found to have an allele frequency within the general population above what is expected given the estimated incidence of HI, the variant will typically be evaluated as "benign" or "likely benign" [35]. Correlation of the genetic report with the clinical characteristics of the patient is crucial in determining the significance of identified variants.

Of particular difficulty in terms of classification are novel missense variants that are identified in *ABCC8* or *KCNJ11*. Unlike nonsense, frameshift and intronic splicing mutations, which are clearly recessive loss-of-function mutations, missense variants can be either recessive or dominant (Table 5.2). If dominant, they can result in either diazoxide responsive or diazoxide unresponsive HI [6–8]. Variant classification using the ACMG guidelines is not useful in distinguishing recessive from dominant missense mutations. Additionally, missense mutations in *ABCC8* and *KCNJ11* that result in a gain of function are a cause of diabetes.

Careful review of the interpretation section on each genetic report is important. Key aspects of the report include details on the zygosity of the variant, whether it is expected to be dominant or recessive, evidence of pathogenicity including whether the variant has been published previously and whether a recurrence risk has been calculated.

Cascade Family Testing

When a mutation is identified, it is important to consider cascade testing of at-risk family members, especially when a dominant mutation is identified. Phenotypic heterogeneity is common in dominant forms of HI, with many adult carriers being clinically unaffected or having subclinical features which are often only recognized following provocative testing (e.g. fasting, oral protein tolerance tests or glucose tolerance tests). For these individuals, identifying a mutation will allow for accurate counselling on recurrence risk and importantly may prevent hypoglycaemia-related morbidities.

The recurrence risk of HI when a parent carries a dominant mutation is 50%. When both parents carry a recessive mutation, as in diffuse HI caused by recessive K_{ATP} channel mutations and HADH HI, the recurrence risk is 25%. The risk for focal HI in a child carrying a paternal-recessive K_{ATP} channel mutation is estimated to be 1:270 [36].

Negative Genetic Test Results

For approximately 40–50% of individuals with HI, a mutation in a known gene is not identified by routine testing [25, 26]. For these individuals, it is important to understand the testing limitations of the laboratory. For example, promotor or deep intronic mutations may be missed if the laboratory does not sequence the non-coding and regulatory regions of genes. Similarly, it is important to recognize whether the test methodology includes dosage analysis to determine whether a whole or partial gene duplication or deletion is present. De novo mosaic mutations have also been reported in a number of the HI genes, and it is possible that these could be "missed" if they are at a level lower than the threshold of detection for the assay or if the mutation is not present in the tissue being tested (e.g. the mutation is confined to the pancreas) [37]. For patients without a genetic diagnosis, mutations in novel disease-causing genes are also possible. Finally, it is possible that the causative mutation is in a gene associated with a syndrome which is not sequenced routinely. Extra-pancreatic features can help to guide genetic testing in patients who are suspected to have a syndromic form of HI.

Factors to Consider when Choosing Where to Send Samples for Genetic Testing

When choosing a laboratory for genetic testing, several factors are important to consider. Whilst cost will inevitably be a major influence in the decision-making process, one must also consider what types of samples are accepted by the laboratory (i.e. saliva, blood), the testing strategy and the expected turnaround time. It is also important to consider the additional tests that are offered including prenatal testing or testing for syndromic forms of HI.

The experience of the laboratory should also be a key factor given that variant interpretation is heavily dependent on the expertise of the molecular geneticist issuing the report and in-house databases of previously reported variants.

Conclusions

Genetic testing is crucial for effective management of HI. A genetic diagnosis can provide information on histological subtype, prognosis, response to treatment and, importantly, recurrence risk within families. Rapid Sanger sequencing of *ABCC8*, *KCNJ11* and *GCK* is essential for individuals with diazoxide-unresponsive HI whilst targeted next-generation sequencing of a panel of genes is recommended in those with medically manageable HI or, as a second-line test, for those without a K_{ATP} channel or *GCK* mutation.

The recent adoption of next-generation sequencing has revolutionized the way in which one can now screen for HI and has resulted in a significant reduction in the cost of genetic testing. Further reducing these costs is of the utmost importance as this will make testing more accessible to larger numbers of individuals with HI who will in turn reap the benefits that a genetic diagnosis brings.

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Chapter 6
Medical Management of Hyperinsulinism

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Introduction

Children with congenital hyperinsulinism (HI) can present with a wide spectrum of clinical severity, ranging from very mild hypoglycemia requiring minimal treatment to very severe neonatal-onset hypoglycemia, in which maintaining normoglycemia is difficult despite a combination of therapies. In the latter patients, near-total pancreatectomy is often considered. While selective curative partial pancreatectomy is indicated for focal HI, pancreatectomy for diffuse HI is likely to result in insulin-dependent diabetes. Because hypoglycemia in patients with diffuse HI tends to become less severe in latter childhood, there have been efforts to manage the disease with various combinations of medications and intragastric feedings [1–4].

Medical management of hyperinsulinism has two objectives:

1. To rapidly correct hypoglycemia and restore plasma glucose concentrations to the normal range. Because insulin inhibits all of the mechanisms for protection against hypoglycemia, including production of ketones as an alternative fuel for the brain and hepatic glycogenolysis, hyperinsulinemic hypoglycemia is particularly likely to cause brain damage [5–7].

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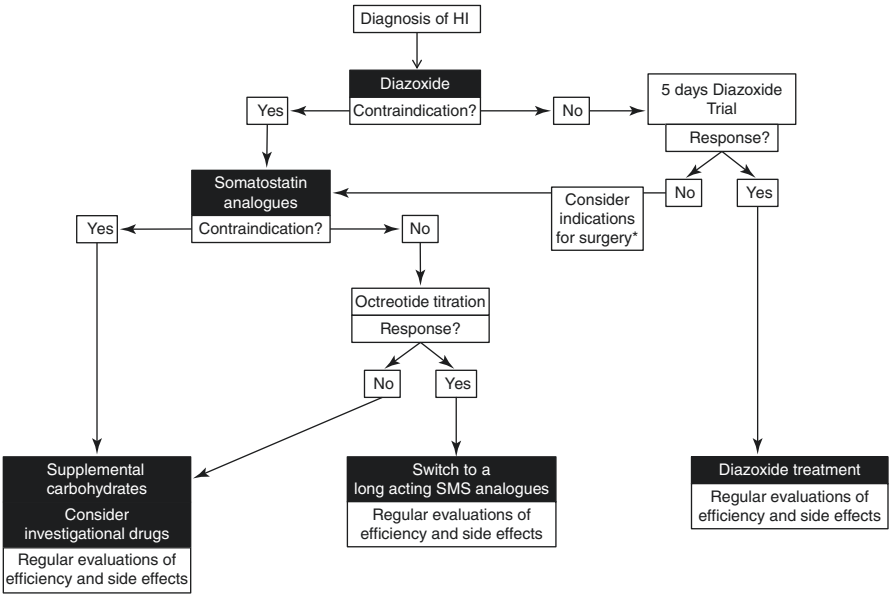

Fig. 6.1 Medical management. SMS somatostatin. * Indications for surgery: see Chap. 9

2. To maintain normoglycemia long term while carefully taking into consideration the burdens of treatment on quality of life for affected children and their families. This is especially difficult for patients with diazoxide-unresponsive forms of hyperinsulinism that are not amenable to cure by surgical excision.

The goal of this chapter is to review the drugs which are currently available for medical management of children with congenital hyperinsulinism (Fig. 6.1 and Table 6.1).

Initial Correction and Stabilization of Hypoglycemia

As soon as hypoglycemia is detected, especially in neonates, treatment should be promptly initiated to prevent irreversible brain damage [8, 9]. Dextrose, 200 mg/Kg, should be given intravenously to rapidly correct hypoglycemia (e.g., 10% dextrose, 2 mL/Kg IV), followed by continuous dextrose infusion to maintain plasma glucose concentrations above 70 mg/dL. If an intravenous line is not available, glucose, 200 mg/Kg, can be given orally as liquid or as glucose gel and repeated at 5–10 min intervals to maintain normoglycemia. If hyperinsulinism is known to be the cause of the hypoglycemia, glucagon can also be used as emergency treatment to normalize plasma glucose concentrations (some recommend a dose of 0.3 mg/Kg, whereas others suggest a dose of 1 mg regardless of body weight; the dose may be given

Table 6.1 Side effects of treatments

	Diazoxide	SMS analogues	mTOR inhibitor
Side effects	Hypertrichosis	Gallbladder stones	Elevated blood lipids
	Fluid retention	Elevated liver enzymes	Bacterial infections
	Bone marrow suppression	Reduced growth velocity (rare)	Diarrhea
		Injection site reaction	Aphtosis
		Nausea, diarrhea, steatorrhea	Noninfectious pneumonitis
			Thrombopenia, anemia, neutropenia
			Delayed wound healing
			Hypokalemia, hypophosphatemia
			Hypersensitivity reactions
Side effects before 4 months old	Pulmonary hypertension	Necrotizing enterocolitis (NEC)	
Contraindications	Pulmonary hypertension	Drug-induced hepatitis (if severe)	Scheduled surgery within 30 days
	Patent ductus arteriosus	Neonates: concomitant risk factor for NEC	Sirolimus-induced severe side effect

SMS somatostatin analogues

intravenously, intramuscularly, or subcutaneously). In infants with severe hyperinsulinism, rates of dextrose infusion required to maintain normoglycemia may exceed the physiological needs of normal neonates by severalfold (>8 mg/Kg/min); thus, placement of a central intravenous line to administer highly concentrated dextrose is usually required [10]. It is especially important to remember that treatment with glucocorticoids such as cortisol or prednisone is not effective and is never appropriate for treating hypoglycemia due to hyperinsulinism. Continuous infusion of glucagon (1–2 mg/24 h or 2.5–10 μg/kg/h, either intravenously or subcutaneously) may be used when hypoglycemia remains unstable despite high rates of continuous dextrose infusion (e.g., >15–20 mg/Kg/min).

Diazoxide: The First-Line Drug for Children with Congenital Hyperinsulinism

In neonates with hypoglycemia persisting beyond 1–2 weeks of age and in older children diagnosed with hyperinsulinism, specific treatment for HI must be initiated. In the absence of contraindications, the first line of treatment of choice is oral *diazoxide* 2–15 mg/Kg/day (brand name, Proglycem). Diazoxide (7-chloro-3-methyl-1,2,4-benzothiadiazine-1,1-dioxide) was initially developed in the early 1960s as a non-diuretic, rapidly acting antihypertensive agent, derived from

antibacterial sulfonamides. Because its side effect of hyperglycemia prevented chronic oral use of diazoxide for hypertension [11, 12], it was formerly marketed for the intravenous treatment of hypertensive emergencies (Hyperstat) – and is still under evaluation for the acute treatment of severe preeclampsia and eclampsia [13]. The vasodilating effects of diazoxide are mediated by its binding and activation of SUR2-containing ATP-sensitive K (K_{ATP}) channels resulting in membrane hyperpolarization and reduced Ca^{2+} influx in arterial smooth muscle cells [14, 15]. In 1964, based on its diabetogenic side effect, diazoxide was shown to be an effective treatment for children with hyperinsulinism [16] and, since then, has been used widely as a first-line treatment for hyperinsulinism.

The hyperglycemic effect of diazoxide relies primarily on its binding to the SUR1 subunit of the beta-cell plasma membrane K_{ATP} channel and activating (opening) the channel to hyperpolarize the plasma membrane and inhibit insulin release [17, 18]. Diazoxide also has off-target effects that may inhibit insulin release to some extent and might be responsible for the partial improvements in hypoglycemia sometimes noted in children with hyperinsulinism due to K_{ATP} channel defects. These include (1) decreasing ATP synthesis through opening of the mitochondrial K_{ATP} channels and inhibition of the respiratory chain complex II [19–21] and (2) rescue of plasma membrane K_{ATP} channel trafficking, as suggested in some mutations of the SUR1 subunit of the K_{ATP} channel, encoded by *ABCC8* [22].

It has recently been shown that, in addition to the beta-cell K_{ATP} channel, diazoxide can activate K_{ATP} channels in peripheral tissues which contain the SUR2 subunit. This may account for many of the off-target side effects of diazoxide, including salt and water retention, hypertrichosis, bitter taste, and, rarely, pulmonary hypertension. Many of these side effects of diazoxide are seen as consequences of activating mutations of SUR2 in patients with Cantu syndrome [23].

In neonates and infants with hyperinsulinism, an echocardiogram before and after initiation of diazoxide is advisable, because of the risk of pulmonary hypertension; this is especially indicated in premature infants and in children with syndromic forms of hyperinsulinism up to 4 months of age [24–26]. The risk of fluid retention and edema or congestive failure and pulmonary hypertension is greater with doses above 10 mg/Kg/day [27]. Higher doses may induce nausea and poor feeding or vomiting; in two cases with diazoxide-unresponsive diffuse HI due to K_{ATP} channel mutations, diazoxide appeared to cause a paradoxical worsening of HI [28]. A predictable side effect in children treated with diazoxide is hypertrichosis (vellus hair, therefore, not hirsutism). This appears to be more severe in young children than in adults and is dose-dependent. Excessive hair may be removed by shaving and is reversible after several months off the drug; occasionally hypertrichosis may be distressing enough to motivate discontinuation of diazoxide.

It is particularly important to note that salt and water retentions are common with diazoxide treatment and, especially at higher doses, can cause edema and cardiovascular side effects such as congestive heart failure. Consequently, diuretic therapy is recommended, at least during the initiation of treatment. For infants on high rates of intravenous fluids for management of hypoglycemia, it is recommended to begin diuretics at the initiation of treatment with diazoxide (or even

prior to the first dose). Although thiazide diuretics usually suffice for children on chronic treatment with diazoxide, more potent diuretics (such as furosemide) may be preferable when initiating diazoxide in patients on high rates of fluid administration.

Diazoxide is highly protein-bound and has a long half-life (estimated at 24–36 h in younger children). Therefore, diazoxide responsiveness should be assessed after 5 days of treatment by the following criteria: absence of hypoglycemia while feeding a normal diet for age and during an overnight 8–12 h fast. A strict definition of diazoxide responsiveness is complete reversal of hyperinsulinism both during fasting (as evidenced by appropriate fasting hyperketonemia) and following meals (absence of protein-sensitive hypoglycemia) (see Chap. 2). If these criteria are not met, the hyperinsulinism is classified as diazoxide-unresponsive, and diazoxide treatment should be discontinued while further treatment is considered.

The efficacy and requirement for ongoing treatment with diazoxide should be re-evaluated on a regular basis, at least annually. Since most genetic forms of hyperinsulinism do not disappear with age, these children are likely to require lifelong therapy with diazoxide. Exceptions include children with HNF1A and HNF4A mutations, who often transition to insulin-insufficient diabetes later in life (see Chap. 3); some syndromic forms of hyperinsulinism, such as Beckwith-Wiedemann syndrome (see Chap. 5); and infants with perinatal stress hyperinsulinism (see Chap. 2). If diazoxide is discontinued, a fasting test to evaluate fasting tolerance and to clearly demonstrate evidence of resolution should be carried out.

Few data are available in humans exposed to diazoxide in utero. When diazoxide was used in the 1960–1980s for the treatment of hypertensive emergencies in pregnancy during the second and third trimester, it was reported to cause reversible alopecia or hypertrichosis in the newborn [29]. However, animal embryos exposed in vitro or in vivo to diazoxide at early stages of development were reported to have variable defects, including fetal resorption and heart and skeletal malformations [30, 31]. Thus, caution should be taken in women with hyperinsulinism disorders to consider discontinuing diazoxide before and during pregnancy.

Second-Line Treatment: Somatostatin Analogues

Somatostatin analogues are considered the second-line treatment for those HI patients that do not respond to diazoxide or experience significant side effects. A major disadvantage of somatostatin analogues for treatment of HI is that they are not approved for this indication in any developed country.

Somatostatin is a cyclic polypeptide that binds to specific membrane receptors called somatostatin receptors (SSTR1-SSTR5) [32] and is found throughout the nervous and gastrointestinal system. In the pancreas, somatostatin has inhibitory effects on the release of glucagon and insulin from the pancreatic islet cells, and it also suppresses the incretin glucagon-like peptide 1 (GLP-1) [33]. In the central nervous system, somatostatin inhibits growth hormone and thyroid-stimulating

hormone secretion. Other actions of somatostatin include inhibition of gastrointestinal motility, gallbladder contractility, and splanchnic blood flow [34].

Clinical use of somatostatin is limited because of its short half-life of less than 3 min [32, 35, 36]. Octreotide, a somatostatin analogue with a prolonged half-life (90 min), is labeled for use in the treatment of acromegaly, carcinoid tumors, and vasoactive intestinal peptide tumors [37]; its off-label use for the treatment of HI was first described in 1989 by Glaser et al. [38]. Since then, octreotide has been widely used as a second-line treatment for hyperinsulinism and as first-line treatment in parts of the world where diazoxide is not available [39–41]. Octreotide is usually initiated at a dose of 5–10 μg/Kg/day given every 6–8 h and titrated up progressively every 48 h if the response is insufficient or if tachyphylaxis occurs. There is no agreement regarding the recommended maximal dose of octreotide; however, because of dose-dependant side effects, in USA dose higher than 20 mcg/Kg/day are usually not recommended, while higher doses are currently used in other countries.

The major limitations in the use of octreotide are the short half-life and tachyphylaxis. An approach to avoid the need for multiple injections has been the use of subcutaneous pumps for continuous administration of octreotide (e.g., off-label use of insulin pumps filled with octreotide) [42]. A different approach limits dosing of octreotide to twice a day used in combination with continuous overnight dextrose through a gastrostomy in an effort to avoid tachyphylaxis [43]. The safety profile of octreotide in children with HI has not been systematically evaluated. The most frequent side effects reported are transient elevation of liver enzymes (46.4%), gallbladder pathology (12–30%), and growth hormone suppression (reviewed in [44]). More serious side effects have also been reported, including necrotizing enterocolitis [45–47]. Because of this association, octreotide's use in infants less than 4 weeks of age or infants with other risk factors should be avoided.

More than 10 years ago, the long-acting formulations of somatostatin analogues octreotide-LAR (O-LAR) and lanreotide autogel (Lan-ATG) were introduced for the treatment of adult patients with hormonal disease given intramuscularly and as deep subcutaneous injections, respectively, at variable doses every 4 weeks [48]. The use of lanreotide in children with HI was first reported in 2006 [49]. O-LAR or Lan-ATG reach their stable blood concentration 1–2 months after their initiation; thus, in severe cases, it might be necessary to continue subcutaneous octreotide during the 1st month (Lan-ATG) or 2 months (O-LAR) of long-acting somatostatin analogues. Today long-acting somatostatin analogues are widely used in children with HI [50–52]. Their use in younger children has been limited because dosing cannot be easily titrated with current formulations. Recently, a report described the use of Lan-ATG in four infants as young as 2 months old without severe adverse effects [53]; however, long-term data is needed before this approach is widely adapted for the treatment of diffuse diazoxide-unresponsive hyperinsulinism. If effective, monthly injections of Lan-ATG or O-LAR provide higher flexibility in everyday life than octreotide.

For most patients, some substantial effect is seen after initiation of somatostatin analogues; however, fasting tolerance is not normalized: only about 57% of HI patients would have a complete response to octreotide during the neonatal period

[54]. This makes concomitant nutritional treatment necessary, which may include high caloric feeding or even continuous carbohydrate supply by nasogastric or gastric tube with the most severe patients continuing to present recurrent episodes of mild hypoglycemia [in the range of 54–70 mg/dL (3–3.8 mmol/L)]. A recent study found an insufficient response to octreotide in particular in patients without a mutation in the K_{ATP} channel genes [55].

Based on the experiences available, the efficacy of somatostatin analogues is limited, but for infants with diazoxide-unresponsive diffuse hyperinsulinism, they may represent a better alternative than near-total pancreatectomy. Close monitoring for side effects is recommended. The most concerning adverse effect is an increased risk for NEC during the neonatal period. It is recommended to start somatostatin analogues only in clinically stable patients without other risk factors for NEC. Treatment should be immediately stopped once any signs of NEC are present. In addition to NEC, the risk of gallbladder pathology should be considered. This risk might be reduced by concomitant use of ursodeoxycholic acid, but its prophylactic effect in patients on octreotide or lanreotide treatment requires further assessment. Other adverse effects are mostly transient. Growth does not seem to be severely affected in HI patients treated with somatostatin analogues. Dose should only be decreased if marked growth deceleration becomes evident, as in most of the children the decrease in growth velocity is transient. Monitoring during treatment with somatostatin analogues should include measurements of blood count and liver enzymes and routine gallbladder ultrasound [4].

Third-Line Treatments: Calcium Channel Blockers and Investigational Drugs

Note that the following potential medical therapies for congenital hyperinsulinism mostly consist of repurposed drugs with marketing authorization for various other medical conditions. Their off-label use in HI should follow legal and ethics requirements for investigational use, as well as strict clinical cautions.

Calcium Channel Blockers (Nifedipine)

Insulin secretion by pancreatic beta cells depends on the activation of L-type calcium channels to increase cytosolic calcium concentrations and signal release of insulin from storage granules. L-type calcium channel blockers such as nifedipine, nimodipine, verapamil, diltiazem, and isradipine have been shown to inhibit the secretion of insulin in isolated islets [56–58] and to reversibly block calcium-dependent action potentials in islets isolated from an infant with persistent HI [59]. In vivo, inhibition of the L-type calcium channel in rats and dogs with diltiazem does not impair glucose-stimulated insulin secretion [57], but

intravenous verapamil inhibits insulin responses to oral glucose, oral glibenclamide, or intramuscular glucagon injection in normal humans. Diltiazem and verapamil were reported to reduce the frequency of hypoglycemia in patients with insulinoma [60].

There are at least 11 single case reports of nifedipine used for the treatment of hyperinsulinism (reviewed in [61]). In some, nifedipine was introduced to avoid side effects of other medications (e.g., diazoxide, octreotide, etc.) or with a concomitant antihypertensive purpose [59]. Case reports on the use of nifedipine in patients with hyperinsulinism have lacked important details such as the genetic cause, assessment of fasting response, side effects, and follow-up. Only one study [61] has assessed the effectiveness of nifedipine therapy in a relatively large cohort of patients with mutations in the *ABCC8* gene. They found that there was no positive glycemic effect in any patient and that it was not possible to wean intravenous glucose infusions or reduce any of the concomitant medications. In fact, there was no improvement in the plasma glucose levels at all in any patient, despite nifedipine doses up to a maximum of 2.5 mg/kg/day. It is conceivable that K_{ATP} channel gene defects might alter the function of the L-type calcium channel, thus rendering it unresponsive to therapy with nifedipine. However, there is no clear evidence that calcium channel blockers are actually effective in any of the other genetic forms of hyperinsulinism. Thus, there is lack of evidence to support the use of calcium channel blockers as a treatment for hyperinsulinism, and most centers with experience in managing children with congenital hyperinsulinism no longer consider calcium channel blockers as potential treatment.

mTOR Inhibitors (Sirolimus)

Sirolimus is a mammalian target of rapamycin (mTOR) inhibitor. mTOR is a serine and threonine protein kinase which regulates cellular growth by stimulating protein synthesis by increasing RNA translation initiation and the capacity of the ribosomal protein machinery [62]. Reports suggest that there is constitutive activation and overexpression of p-mTOR on the plasmalemmal aspect of the acinar cells, and activation of p-mTOR on the plasmalemmal aspect of the ductal cells in the diffuse variant of congenital HI [63] raised the possibility of using mTOR inhibitors to treat HI.

A number of autocrine growth factors like insulin-like growth factor 1 (IGF-I), vascular endothelial growth factor (VEGF), and epidermal growth factor receptor (ErbB), as well as glucose, fatty acids, and amino acids, activate the mTOR pathway [62]. Upregulation of mTOR leads to increased insulin production in the pancreatic β-cells [64]. Conversely, inhibition of mTOR with rapamycin inhibits insulin secretion as well as β-cell growth [65].

In 2014, sirolimus emerged as a potential alternative to pancreatectomy for infants with severe diazoxide-unresponsive hyperinsulinism. The first report described the successful treatment of four infants with sirolimus without major side effects [66]. Following the first reported experience, several other case reports

indicating the successful use of sirolimus have been published [67–70]. However, in a multinational study evaluating the efficacy of sirolimus in ten patients with diazoxide-unresponsive congenital HI, mTOR inhibition was shown to have limited efficacy, with only three patients (30%) responding and a significant rate of side effects [71]. The most common adverse effects were stomatitis, increased risk of infection, immunosuppression, renal dysfunction, fatigue, pneumonitis, and increased serum aminotransferase or lipid levels. Thus, there is insufficient evidence to support the use of sirolimus or other mTOR inhibitors in the treatment of HI outside a well-designed clinical trial [72].

Conclusion

The long-term management of children with severe diffuse HI is challenging, particularly during the first few years of life. During childhood progressive amelioration of the disease severity allows for some of the therapies to be weaned; thus, the current approach is to maximize medical therapy instead of performing subtotal pancreatectomy. Hopes are rising from emerging therapies, actually under evaluation, which might repel further the need for pancreatectomy and for continuous enteral feeding: exendin-(9–39) (a GLP1 receptor antagonist) [73], XOMA358 (insulin receptor antibodies) [74, 75], and soluble glucagon.

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Chapter 7
18F-DOPA PET

Lisa J. States and Klaus Mohnike

Introduction

The 18-F-L-3,4-dihydroxyphenylalanine [18F]-DOPA PET/CT scan has been incorporated into the algorithm for the evaluation of congenital hyperinsulinism (HI) and is the standard of care for the localization of a clinically suspected focal lesion [1–3]. Ideal candidates for the [18F]-F-DOPA PET/CT are patients with documented HI who are unresponsive to standard treatment with diazoxide and require high glucose infusion rates to maintain a safe glucose level and are being considered for surgical pancreatectomy. Genetic analysis prior to scanning can aid in the selection of patients who benefit from a PET scan. The detection of a paternally inherited recessive K_{ATP} mutation in either of the two genes encoding the K_{ATP} channels, *ABCC8* and *KCNJ11*, has a positive predictive value of 94% for focal disease (Chap. 5). An [18F]-DOPA PET scan is not indicated in patients with a genetic defect consistent with diffuse HI, such as biallelic recessive K_{ATP} channel mutations, glutamate dehydrogenase HI, or glucokinase HI. If genetic testing is not diagnostic of diffuse or focal disease, a PET scan is indicated in a patient who does not respond to medical therapy.

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Imaging Techniques

Since 2003, at least 550 [18F]-DOPA PET/CT scans and 12 [18F]- DOPA PET/MRI scans have been performed at CHOP and DTZ Berlin for the investigation of the ability to detect and accurately localize a focal lesion. Conventional imaging techniques, including computed tomography or magnetic resonance imaging, are unable to detect these lesions. The findings by Otonkoski in Finland were initially reported at the European Society for Pediatric Endocrinology in Ljubljana, September 2003. The first experiences with [18F]-DOPA PET in infants with HI were published by researchers from Finland and France [4, 5]. The preliminary report from Otonkoski et al. found that [18F]-DOPA PET scans could image focal lesions in congenital HI, and comparison with PVS was made [5]. Subsequent studies have demonstrated it to be superior to ASVS (arterial calcium stimulation with hepatic venous sampling) or PVS (portal venous sampling) in locating focal lesions and also safer and less invasive. Multiple published studies with a total of 286 histologically proven cases have found [18F]-DOPA has sensitivity ranging from 75% to 100% for detecting a focal lesion [5–14]. These studies showed that when a focal lesion was detected, the [18F]-DOPA PET scan was 91–100% accurate in identifying the anatomic location of the focal lesion and thus provided an important guide to successful surgical resection. Although considered standard of care worldwide, in the United States, [18F]-DOPA is not approved by the Food and Drug Administration (FDA) and can only be used under an Investigational New Drug (IND) license. In Germany, institutions equipped with a cyclotron must obtain a manufacturing license for [18F]-F-DOPA applications. In France, [18F]-DOPA was approved for use by the European Medicines in 2007 [15].

The mechanism of [18F]-DOPA uptake is based on the affinity of neuroendocrine cells for taking up amino acid precursors. Normal islet cells of the p*ancreas take up L-DOPA*: *convert it to L-dopamine*, *using the enzyme DOPA decarboxylase* (*DDC*); and store it in vesicles [16]. This same mechanism allows uptake, conversion, and storage of [18F]-F-DOPA as 18F-dopamine in vesicles, allowing islet cells to be imaged. Focal lesions appear as a "bright spot" of intense radioactivity against the background of low-level activity in the surrounding normal pancreas. The mechanism of increased activity seen in a small focal lesion of *β*-cell adenomatosis likely reflects simply *β*-cell crowding [18] but has also been suggested to reflect increased insulin production [17, 18] and/or beta-cell overactivity. Carbidopa, a DOPA decarboxylase inhibitor used in the evaluation of other neuroendocrine tumors, blocks the conversion of L-DOPA to dopamine and has been found to block pancreatic uptake of [18F]-F-DOPA [4]. Carbidopa is not recommended in the evaluation of HI. Other organs that have increased [18F]-DOPA uptake are the liver, due to high amounts of DOPA decarboxylase, and the kidneys, due to high DOPA decarboxylase and excretion of radiotracer [17]. If the patient is imaged beyond 50 min from injection of [18F]-DOPA, uptake can also be seen in

the gallbladder, biliary tree, and duodenum due to liver excretion of radiotracer. Since the duodenum and jejunum can be a site of ectopic focal HI lesions [19, 20], imaging prior to 60 min is recommended to avoid this confounding effect. Uptake can also be seen in the growth plates of the ribs, spine, and extremities.

Protocol

In 2006, Mohnike et al. proposed a standardized protocol for [18F]-DOPA PET imaging. Since then, publications have used dynamic imaging protocols starting 5–20 min after injection with 10 min acquisition times for up to 50–60 min [7–14, 21].

The [18F]-DOPA is manufactured on the day of the scan using established procedures for electrophilic or nucleophilic labeling by a nearby cyclotron facility. Due to the 110 min half-life of fluorine-18, the delivery time of the radiotracer should be within 2–3 h of production. Depending on the synthesis method used, electrophilic versus nucleophilic, and specific activity of the radiotracer, the expiration time can vary from 6 to 12 h [22]. As part of patient preparation, the patient is NPO for 6 h, and medications that could potentially interfere with pancreatic beta-cell function, such as octreotide and glucagon, are discontinued, although they have not been shown to interfere with uptake. Rates of intravenous (IV) glucose infusion are adjusted to maintain plasma glucose levels greater than 70 mg/dl (3.9 mmol/L) during the [18F]-PET/CT scan. Intravenous hydration is used to promote urinary excretion of isotope and decrease radiation dose to the bladder. Patients typically undergo general anesthesia by a pediatric anesthesiologist, although light sedation with chloral hydrate has been used [13]. A dose of 3–6 MBq/kg (0.08–0.16 mCi/kg) is administered by slow intravenous injection [23]. A typical scanning protocol using hybrid PET/CT protocol will begin with a low-dose non-contrast CT scan of the abdomen, with 3 mm slices, for attenuation correction. PET emission scanning of the abdomen at a single bed position is started within 10–15 min of injection, and dynamic acquisitions are performed in 10 min increments over 50 min. At the end of the PET acquisition, a low-dose contrast-enhanced CT is performed using 3 mm slice thickness in the portal venous phase for simultaneous opacification of the portal venous system and the arterial system. MRI can also be used for image co-registration for anatomic localization. Hybrid imaging with PET/MRI is a promising technique that is currently limited to a small number of nuclear medicine facilities. Protocols using PET/MRI will use similar timing with simultaneous MRI acquisitions including volumetric sequences, fluid-sensitive sequences for visualization of the biliary and pancreatic ducts, and diffusion-weighted imaging for possible lesion detection. Contrast enhancement with gadolinium-based macrocyclic contrast agents may provide added value for surgical planning.

Image Interpretation

Review of images is performed by a nuclear medicine physician or radiologist with experience in nuclear medicine. Images are first reviewed in 3-D mode for the best visualization of the pancreas which cannot be viewed in a single plane. This first impression helps to guide review of the fused CT or MRI and PET images in 2-D in the axial, coronal, and sagittal planes. The contrast-enhanced images fused with the attenuation-corrected PET images are used to show the position of a focal lesion with respect to the splenic artery and vein, portal vein, superior mesenteric vein and artery, common bile duct, and duodenum to create a road map for the surgeon.

Laje et al. review of lesions that were not detected by [18F]-DOPA PET revealed errors due to the size or shape of the lesion or physician interpretation error. Retrospective review of images revealed the focal lesion in some, but not all cases. Lesions that were not identifiable due to size or shape included a flat leaf-like lesion on the surface of the pancreas and a large lesion that involved most of the pancreas. Other undetectable lesions ranged in size from 2 to 13 mm in diameter. Lesions that could be identified in retrospect were small lesions adjacent to the upper pole of the left kidney [12]. Lesions adjacent to the kidney can be best visualized on the images performed at 50 or 60 min due to clearance of radiotracer from the cortex of the kidneys. One of the pitfalls of interpretation is due to greater activity in the pancreatic head with respect to the rest of the pancreas. Increased activity in the head may be related to the larger volume of tissue in the pancreatic head compared to the rest of the pancreas (Fig. 7.1) or be due to a small focal lesion in the head (Fig. 7.2). In some cases, mild increased in the activity in the head is seen in the setting of a focal lesion in the body or tail. Increased activity in the pancreatic head requires a more careful search for a focal lesion in the tail or body (Fig. 7.3). The pattern for diffuse disease can be either uniformly homogeneous, minimal increased activity in the head with respect to the rest of the pancreas, or patchy with nonuniform uptake with areas of higher activity in the head, body, and tail simulating multiple lesions to the inexperienced reader (Fig. 7.4). Quantitative analysis using the ratio of activity in

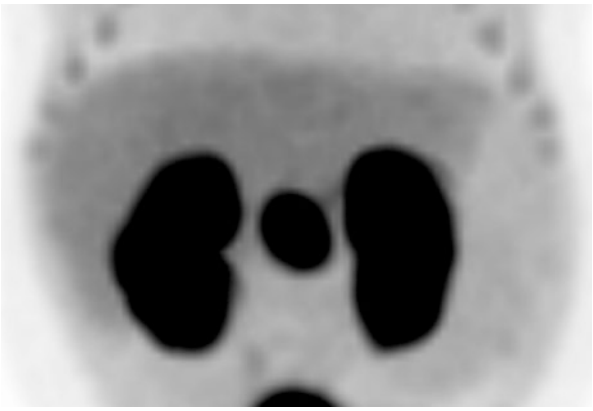

Fig. 7.1 A 6-week-old with severe HI and heterozygous recessive *ABCC8* mutation with large focal lesion. Patient underwent 50% pancreatectomy and Roux-en-Y pancreaticojejunostomy

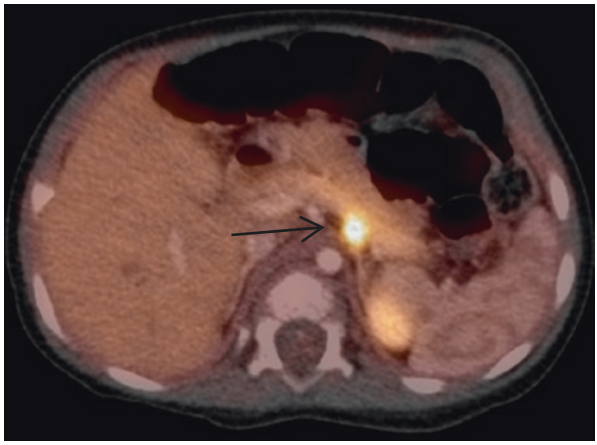

Fig. 7.2 A 5-month-old with heterozygous recessive *ABCC8* mutation with focal lesion. Axial fused PET/CT image shows an exophytic lesion (arrow) arising from posterior aspect of the pancreatic body. A 5% pancreatectomy was performed and resulted in cure

Fig. 7.3 A 3-month-old with heterozygous *ABCC8* mutation with biopsy-proven diffuse disease. The 3-D MIP demonstrates heterogeneous uptake with mild uptake in the head, body, and tail. This can be confused with multiple lesions. A 98% pancreatectomy was performed

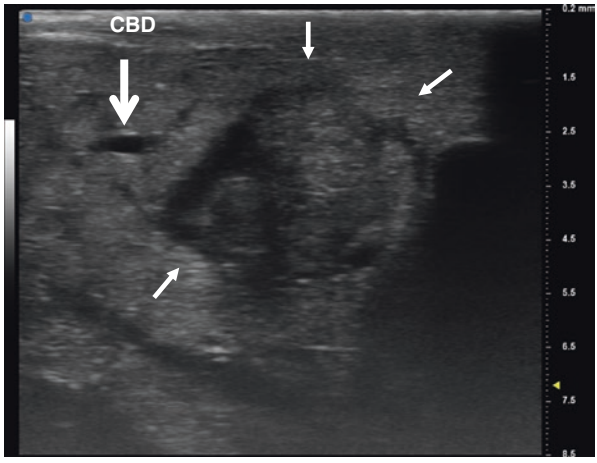

Fig. 7.4 A 6-week-old with severe HI and heterozygous recessive *ABCC8* mutation with small focal lesion in the head. Intraoperative ultrasound was used to locate the lesion using a high-resolution 50 MHz transducer. Axial ultrasound image of the pancreatic head shows anechoic common bile duct (CBD) and 4 mm heterogeneous focal lesion. A 2% pancreatectomy resulted in cure

the lesion to background pancreatic activity has been suggested as an aid to diagnosis of a focal lesion and can be used to increase diagnostic confidence. For quantification, a standardized uptake value (SUV) ratio can be calculated using the formula SUVmax of the lesion divided by SUVmax of the "normal" pancreatic tissue. An SUVmax ratio of ≥1.5 [5] or 1.2 [24] has been suggested as diagnostic for a focal lesion. The intensity and distribution of activity do not always predict the size of the lesion. An SUV percentage analysis has also been proposed by Masue et al. [10]. In most cases, visual analysis is adequate for interpretation and localization of a focal lesion. A good rule of thumb for interpretation is that a focal lesion is always a single lesion, which is seen in two or more acquisitions. In equivocal cases, any areas of concern should be communicated to the surgeon. Accurate identification and localization of a focal lesion can lead to a cure with a very limited pancreatic resection, as little as 2% for a lesion in the tail of the pancreas.

Safety

A review of safety data at CHOP revealed no adverse events related to the isotope, [18F]-DOPA, in 330 subjects (unpublished data) or in 220 patients at DTZ "Berlin-Frankfurter Tor" and therefore is thought to pose little risk to the subjects. The [18F]-DOPA PET/CT scan involves exposure to radiation. Based on a dose 3.7–5.92 MBq/kg (0.16 mCi/kg) and a patient weight of 10 kg, the estimated effective radiation dose (ED) is 0.3 ± mSv/MBq [25]. Due to excretion of radiotracer by the kidneys, the radiation dose to the bladder is ten times greater than that received by any other organ or tissue. Therefore, adequate hydration is essential for minimizing dose to the bladder [26, 27]. The dose of the low-dose CT of the abdomen is 100 mrem. This gives an average dose much lower than 10,000 mrem, the level of radiation known to increase the long-term risk of developing cancer [28]. MRI, as an alternative to CT, avoids additional radiation and has been proposed to provide additional visualization of the common bile duct and pancreatic duct (Fig. 7.5) to guide surgery in the vicinity of a focal lesion.

In cases where a focal lesion is not detected by [18F]-DOPA PET/CT and intraoperative biopsies reveal normal pancreatic tissue, intraoperative high-resolution sonography may be helpful in localization of a focal lesion. Characteristic

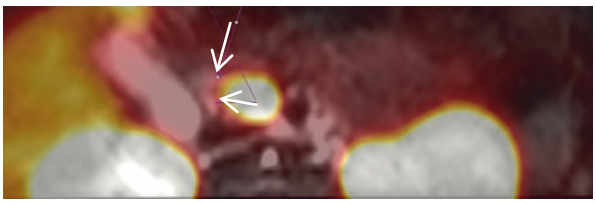

Fig. 7.5 Pancreatic head focal lesion on axial fused PET/MR image shows the common bile duct anterior to gastroduodenal artery (arrows) medial to the focal lesion. The gallbladder, focal lesion, kidneys, and liver have increased 18F-DOPA uptake, and the vessels have bright MR signal

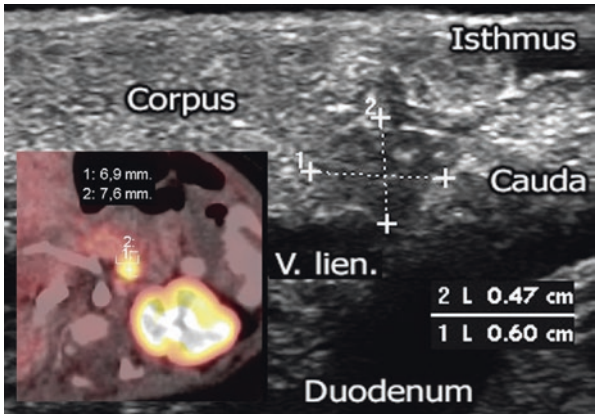

Fig. 7.6 A 14-month-old with heterozygous recessive paternal *ABCC8* mutation. Axial contrast-enhanced CT fused with PET shows focal bright focus in the posterior pancreatic body measuring less than 1 cm in size. A high-resolution intraoperative ultrasound shows a focal hypoechoic lesion with poorly defined margins. The splenic vein (v. lien.) is seen posterior to the lesion

sonographic features include hypoechogenicity or variable homogeneous and inhomogeneous texture; blurred, irregular margins; filiform or lobular processes; and insular dispersal into the surrounding tissue as well as visualization of the pancreatic duct [29] (Fig. 7.6). Contrast-enhanced ultrasound is also a promising technique that may prove useful in the localization of a focal lesion and evaluation of the pancreatic duct after lesion resection.

Summary

The [18F]-DOPA PET scan has become the "GPS" (global positioning system) for directing the surgeon to the location of a focal lesion that cannot be seen or palpated. The published data from centers in the United States, Europe, and Japan support the hypothesis that [18F]-DOPA PET/CT imaging provides a clinically useful guide to surgical resection of focal lesions. It is indicated in all infants with medically unresponsive HI in whom genetic tests are not consistent with diffuse disease since surgery offers a chance of cure in patients with a focal lesion. However, some focal lesions cannot be detected by [18F]-DOPA PET/CT. Intraoperative sonography may be helpful for intraoperative detection of a focal lesion in this situation and ultrasound especially useful in locating the bile duct and pancreatic duct.

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Chapter 8
Histopathology of the Pancreas in Congenital Hyperinsulinism

Tricia R. Bhatti and Eduardo D. Ruchelli

Introduction

In the years since the initial histologic descriptions of the pancreas in patients with congenital hyperinsulinism, there has been an increase in the ability to incorporate molecular and functional data into the existing morphologic characterizations. In addition, it has become ever more obvious that the morphologic changes previously ascribed to "nesidioblastosis," including enlarged and clustered islets as well as budding of islet cells from duct structures, are features seen in pancreatic tissue from both symptomatic and non-affected individuals.

Molecular diagnosis has become an essential component of the clinical evaluation of patients with congenital hyperinsulinism and defines the underlying molecular alterations which, in turn, are associated with typical histologic changes within the pancreas. Current genotype-phenotype correlations still largely depend on the histologic study of pancreases resected from those patients who are medically unmanageable. In the majority of these cases, the hyperinsulinism is caused by inactivating K_{ATP} channel mutations; far fewer of the cases that require surgery involve mutations in other genes of the insulin secretion pathway or islet overgrowth syndromes [1, 3].

It is now well-recognized that hyperinsulinism resulting from loss of function of the β-cell K_{ATP} channel can be associated with three different types of genetic mechanisms involving either the high-affinity sulfonylurea receptor 1 regulatory subunit

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(SUR1, encoded by *ABCC8*) or the inwardly rectifying potassium ion pore subunit (Kir6.2, encoded by *KCNJ11*). These three mechanisms include bi-allelic recessive mutations, paternally inherited recessive mutations with somatic loss of maternal 11p, and dominant mutations. These underlying genetic alterations are associated with characteristic changes in the morphology of affected endocrine tissue that can be recognized intraoperatively by examination of frozen sections of surgical specimens [1, 2].

Diffuse HI

Homozygous (bi-allelic) recessive mutations and, less commonly, dominant mutations in K_{ATP} genes result in diffuse HI, which is characterized by normal-appearing islets displaying rare nucleomegaly of individual islet cells within the context of intact lobular architecture (Fig. 8.1). An overall increase in endocrine

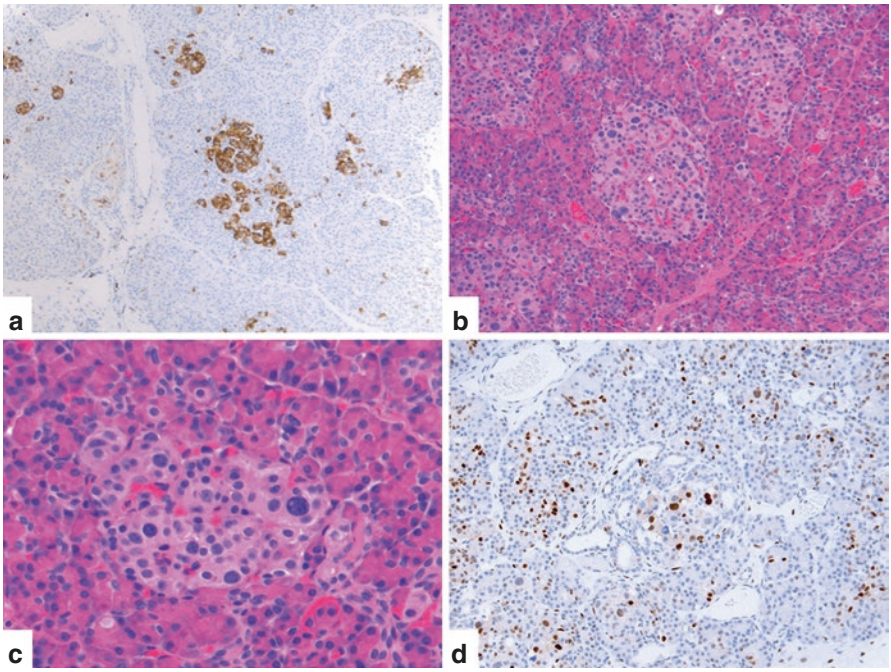

Fig. 8.1 Histology of diffuse HI due to K_{ATP} channel mutation. (**a**) Normal quantity and distribution of endocrine tissue without islet expansion (immunohistochemical stain for chromogranin, original magnification ×100). (**b**) Endocrine tissue with occasional islet cell nucleomegaly observable at medium power (hematoxylin and eosin stain, original magnification ×200). (**c**) At higher magnification, affected nuclei are at least three times as large as adjacent non-involved endocrine cell nuclei (hematoxylin and eosin stain, original magnification ×400). (**d**) Endocrine cell nuclei, and those within neighboring acinar cells and ducts, show retained nuclear immunoreactivity for p57 in contrast to islet cells within a focal lesion (original magnification ×200)

cell volume is not typically present. Criteria for islet cell nucleomegaly have been defined by the identification of an increased number of islet cell nuclei which are at least three times the size of the nuclei of adjacent islet cells [4] and four times the size of acinar cell nuclei [5]; this takes into account the expected degree of endocrine cell nuclear pleomorphism (Fig. 8.1c). Intranuclear invaginations of cytoplasm resulting in nuclear pseudo-inclusions can also be seen. Typically, the islet nucleomegaly is distributed in sections from throughout the pancreas; however, the quantity and distribution of enlarged islet cell nuclei can vary both between islets and between different areas of the pancreas. Other findings in pancreases with diffuse HI include enlarged septal islets and ductular-insular complexes. The latter are characterized by persistent islet cell budding from duct structures; these can be seen infrequently in diffuse HI but, as described above, can also be present in the normal neonatal pancreas. This feature of islet cell budding has been shown to have no association with overall beta-cell volume or proliferation [2].

In one study, disorganization of islets was identified in cases of diffuse HI together with an increase in NKX2.2 expression in δ-cells, resembling the immature functional profile of fetal pancreas [6]. Similar to prior studies, this study found an increase in β-cell proliferation, as measured by Ki-67, as well as a concomitant increase in apoptosis, but no net increase in the quantity of β-cells [6, 7]. As a point of caution, islet cell nucleomegaly has also been found in the pancreas of patients without K_{ATP} mutations and in normal areas of patients with focal HI but is reported as being more prominent in patients with diffuse K_{ATP}-HI where >45% of islets were found to contain two or more enlarged nuclei [8].

Hyperinsulinism is less frequently caused by dominant mutations in *ABCC8* and *KCNJ11* which produce subunits with amino acid substitutions that act in a dominant-negative fashion. Depending on the specific mutation, the hyperinsulinism may be milder and diazoxide-responsive, but some of the dominant defects may be as severe and diazoxide-unresponsive as hyperinsulinism caused by biallelic recessive K_{ATP} mutations [9]. Investigations of the underlying molecular alterations in the latter patients with dominant diazoxide-unresponsive mutations have identified heterozygous missense mutations in *ABCC8* that result in normal trafficking of channels to the plasma membrane but form channels that have impaired opening responses to diazoxide and MgADP [10, 11]. Histology of the resected pancreas in these cases shows features typical of diffuse HI illustrated in Fig. 8.1.

Hyperinsulinism can also be caused by mutations in other genes in the pathways of insulin secretion, including SCHAD (short-chain 3-OH acyl-CoA dehydrogenase), GDH (glutamate dehydrogenase), GCK (glucokinase), MCT1 (monocarboxylate transporter 1), UCP2 (uncoupling protein 2), and HNF4-α and HNF1-α (hepatic nuclear transcription factor 4-alpha and 1-alpha). These defects are rarer, and surgical specimens from affected patients are less commonly seen. When reviewed, histology from the involved pancreatic tissue shows features typical of diffuse HI with more infrequent islet cell nucleomegaly compared to that present in K_{ATP} channel diffuse HI (Fig. 8.2).

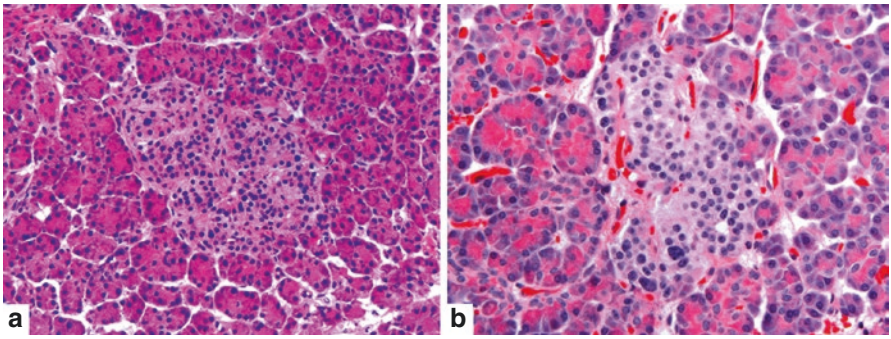

Fig. 8.2 Histology of hyperinsulinism due to non-channelopathies showing rare islet cell nucleomegaly similar to other cases of diffuse K_{ATP}-HI. (**a**) Pancreas from patient with glutamate dehydrogenase mutation (hematoxylin and eosin stain, original magnification ×200). (**b**) Pancreas from patient with glucokinase mutation (hematoxylin and eosin stain, original magnification ×400)

Focal HI

Focal HI results from the combined "two hits" of a paternally transmitted recessive mutation in one of the two K_{ATP} channel genes (*ABCC8* or *KCNJ11*), coupled with somatic loss of heterozygosity of the adjacent Beckwith-Wiedemann syndrome (BWS) region on maternal 11p15. The loss of normal control of cell growth by the imprinted genes in the BWS region results in a localized proliferation of endocrine tissue (adenomatosis) which histologically characterizes the focal lesion (Fig. 8.3). The focal HI lesion is predominantly composed of β-cells but also includes proliferation of other endocrine cell types, including α-and δ-cells, in a distribution similar to that present in the normal pancreas [2]. Also present in the focal lesion are variable proportions of acinar cells and duct structures whose presence facilitates histologic distinction between focal HI and acquired, well-differentiated pancreatic endocrine tumors such as insulinoma [12]. Insulinoma tumors are typically bounded by a fibrous capsule, which is not a usual feature of focal HI. In our experience, some focal lesions can present as polypoid structures with a plane of loose fibrovascular tissue at the interface between the lesion and adjacent normal pancreas, but more commonly they blend in an irregular fashion into the adjacent normal pancreas. Endocrine cells within the focal lesion can also demonstrate nucleomegaly similar to diffuse HI; while nucleomegaly is sometimes helpful for distinguishing the lesion from background pancreas, it is not as critical for diagnosis as it is in diffuse HI. One of the imprinted genes in the BWS region on 11p15 located adjacent to the K_{ATP} genes that is normally expressed from the maternal allele is *CDKN1c*, which encodes the growth-inhibiting factor, $p57^{kip2}$. Immunostaining for $p57^{kip2}$ will demonstrate loss of nuclear reactivity in a focal HI lesion and can be helpful in confirming maternal loss of heterozygosity of the 11p15 gene region within lesional β-cells.

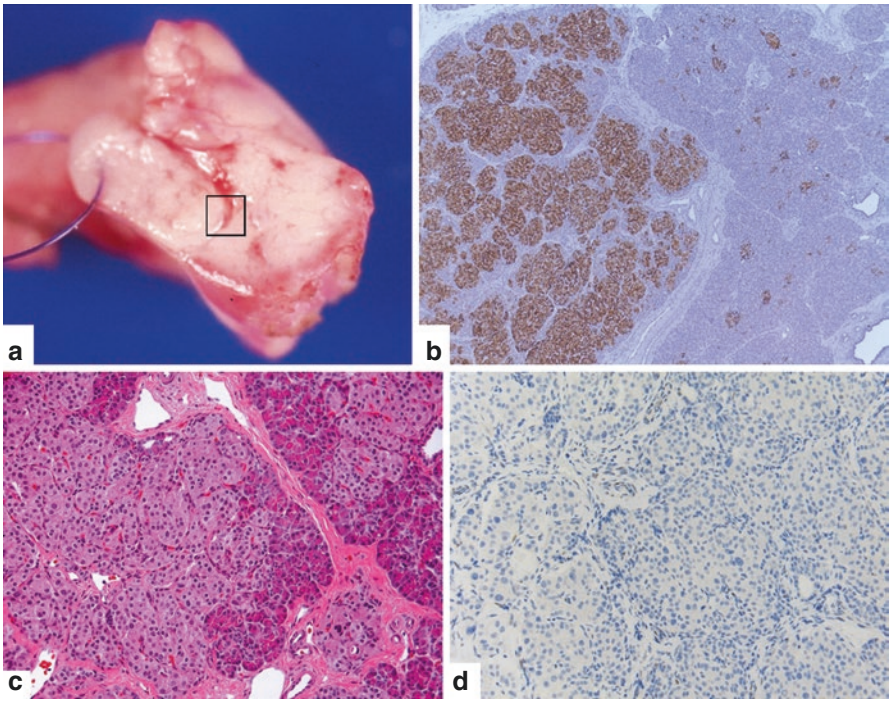

Fig. 8.3 Histology of focal HI due to K_{ATP} channel mutation with loss of maternal 11p15. (**a**) Focal lesion largely indistinguishable from adjacent parenchyma on cut section of the pancreas. (**b**) Inset from A showing immunostaining with chromogranin highlighting the mass-like proliferation of endocrine tissue which is demarcated from normal pancreatic lobules. Unstained areas represent intermixed acinar tissue within the focal lesion (immunohistochemistry for chromogranin A; original magnification ×200). (**c**) Lesion is largely composed of endocrine tissue with acinar cells at the periphery of the lobule; nucleomegaly can be present but is not required for diagnostic purposes (hematoxylin and eosin stain, original magnification ×200). (**d**) Immunostaining with p57 shows loss of nuclear immunoreactivity in lesional nuclei but is retained in occasional duct epithelial cells

The possibility of potentially curing a child afflicted with congenital HI by localized excision of a focal lesion rather than by near-total pancreatectomy makes identification of patients with focal HI a clinical imperative. Routine use of PET imaging with fluorine-18-L-3,4-dihydroxyphenylalanine ([^{18}F]-DOPA), which is preferentially taken up by β-cells, has dramatically facilitated the localization of focal lesions prior to surgery [13]. The technique has also facilitated the identification of rare ectopic lesions outside of the pancreas [14, 15]. Intraoperative frozen sections have the ability to further tailor the surgical approach: i.e., the identification of islet cell nucleomegaly in more than two areas of the pancreas would suggest diffuse HI versus the finding of a localized area of islet adenomatosis characteristic of a focal lesion in which margin involvement can also be assessed to insure adequate excision [5, 16].

Syndromic HI

As the identification of patients with hyperinsulinism and 11p overgrowth/Beckwith-Wiedemann syndrome (BWS) continues to increase, so has our appreciation of the spectrum of morphologic changes within the pancreas of affected patients. Overall, as in the initial descriptions, BWS patients show an increase in the volume of endocrine tissue throughout the pancreas [17]. At one end of the spectrum in BWS-HI, the increase of endocrine tissue manifests as variable degrees of islet expansion, without significant alterations to the lobular architectural pattern of the parenchyma (Fig. 8.4). In many of these cases, the islet expansion is accompanied by an accentuation of the trabecular arrangement of islet cells imparting a prominent gyriform or ribbon-like pattern which is best appreciated at low to medium power and further facilitated by immunostaining with neuroendocrine markers such as chromogranin or synaptophysin. Hormone-producing cells show a pattern of distribution similar to that present within normal islets (and focal HI) with centrally located β-cells, α-cells arranged at the periphery, and δ-cells scattered within the islets [18]. In the majority

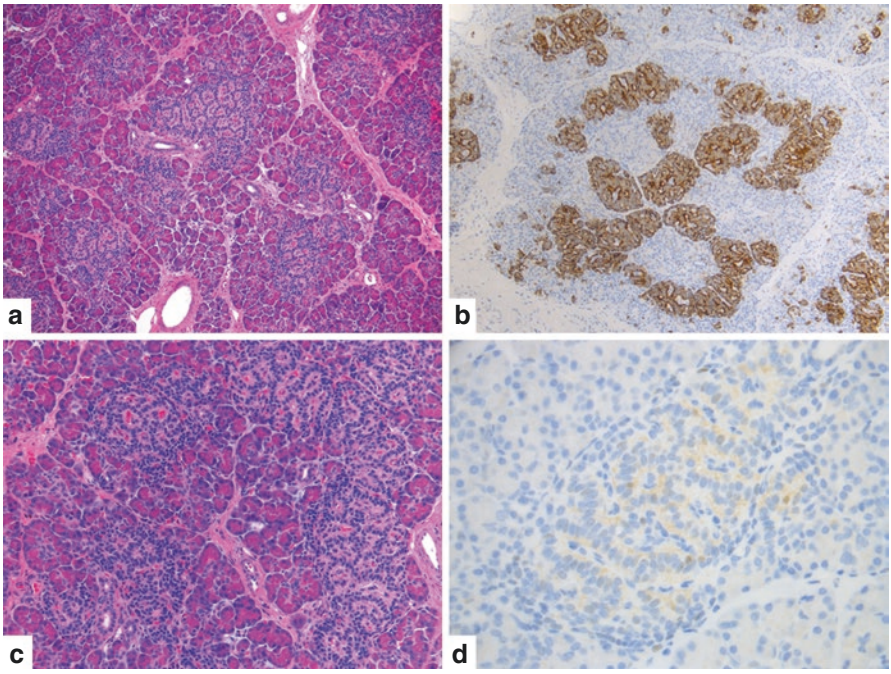

Fig. 8.4 Histology of hyperinsulinism in 11p overgrowth/Beckwith-Wiedemann syndrome. (**a**, **b**) Markedly expanded endocrine tissue involving majority of lobules is present throughout the pancreas (**a** hematoxylin and eosin stain; **b** immunohistochemistry for chromogranin **a**; both at original magnification ×100). (**c**) Affected endocrine tissue demonstrates prominent trabecular architectural pattern of islet cell nuclei (hematoxylin and eosin stain, original magnification ×200). (**d**) Similar to focal HI, affected endocrine cells show loss of nuclear immunoreactivity for p57 reflecting loss of the maternal 11p15 (original magnification ×400)

of cases, endocrine tissue expansion is present throughout the pancreas, although the degree of involvement can be variable and, in some cases, has been strikingly heterogeneous, most likely reflecting the underlying mosaic nature of the genetic defect. In some cases the expansion of endocrine tissue can be so severe as to cause marked distortion of the normal lobular architecture of the pancreas leaving only small foci of residual acinar cells and ducts. As shown in Fig. 8.4b, similar to focal HI, affected endocrine tissue in the majority of BWS-HI cases shows loss of nuclear $p57^{kip2}$ expression, indicating their shared mechanism of maternal loss of heterozygosity of 11p15 [19]. Loss of $p57^{kip2}$ expression has also been demonstrated in β-cells of many pediatric insulinomas, which further suggests an important role of 11p15 in the regulation of islet cell growth in both the neoplastic and the embryonic developmental endocrine lesions [12].

Other syndromes that have less commonly been associated with congenital HI include Turner [20], Kabuki, Costello, Sotos, and Usher syndromes. At our institution, pancreases from patients with Turner-HI have shown intact lobular architecture with islet cell nucleomegaly similar to that seen in patients with diffuse K_{ATP}-HI. Hyperinsulinism in patients with Costello syndrome has manifested as an incidental focal lesion discovered at autopsy [21] with evidence of 11p15 pUPD in lesional tissue similar to that seen in BWS-HI [22].

Atypical HI

Cases of symptomatic congenital HI that do not demonstrate the typical focal or diffuse histologic patterns have also been described. In our experience, a subset of patients with diffuse HI have shown islet cell nucleomegaly that is confined to a limited region within the pancreas, a pattern which we have referred to as localized islet cell nuclear enlargement (LINE). In contrast to children with diffuse HI, LINE-HI patients have usually presented with symptomatic hypoglycemia at a slightly older age, and most appear to have been cured of their hyperinsulinism following limited resection of the involved area(s) of the pancreas [23].

Variability in islet composition and morphology has also been reported by Sempoux and Rahier [24]. They described the presence of two types of islets including hyperfunctional islets which were large in size and contained β-cells with abundant cytoplasm, occasional large nuclei, and low insulin content as well as small hypofunctional islets with relatively small β-cells with abundant insulin and limited proinsulin content by immunohistochemistry [25]. Similar to our LINE-HI patients, their "atypical HI" patients had normal birth weight, later clinical onset, were relatively diazoxide-sensitive, and had no detectable mutations in *ABCC8*, *KCNJ11*, and *GCK*, and most were cured by limited pancreatectomy [24]. In a few cases, functional studies of insulin secretion by the "hyperfunctional" islets isolated from surgical specimens were shown to have abnormally low thresholds for glucose-stimulated insulin secretion and were found to have somatic mutations of *GCK* [25]. Others have described atypical HI cases showing morphologic heterogeneity of islets composed of "active" and "resting/quiescent" islets that also showed increased

NKX2.2 expression suggestive of a more immature immunophenotype [26]. Further studies of these cases with LINE-HI or atypical HI are necessary to understand the underlying genetic mechanism(s) and best strategies for histopathologic diagnosis and management.

Summary

As understanding of the mechanisms for congenital HI on the molecular level continues to grow, careful clinic-pathologic correlation remains an essential part of accurate diagnosis and patient care. A thorough understanding of the genetic, radiographic, and surgical impressions is necessary for the appropriate interpretation of the histologic findings in any given patient which allows for optimal care as well as providing opportunities to direct further research into the pathobiology of the disease process.

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Chapter 9
Surgery for Congenital Hyperinsulinism

N. Scott Adzick

Preoperative Management

The most important aspect of the preoperative planning is to determine whether the patient has diffuse or focal disease, because the surgical strategy is radically different between the two, as is the clinical outcome. Genetic testing is the first step. Ideally, either a known disease-causing K_{ATP} channel mutation is found on both alleles (one from each parent) confirming recessive diffuse HI, or only one disease-causing mutation is found in the paternal allele, suggesting focal disease. The identification of a mutation in the paternal line does not exclude the rare possibility of a disease-causing postzygotic mutation on the maternal line resulting in diffuse HI not reflected in peripheral blood leukocytes [1]. There are situations in which the genetic analysis is difficult to interpret, for example, (1) no known mutations are found, or (2) a previously unknown genetic variant is found but is impossible to determine if it is a new disease-causing mutation or simply a rare polymorphism.

Patients with genetically confirmed recessive K_{ATP}-related diazoxide-resistant diffuse HI do not need preoperative imaging studies and should undergo a near-total pancreatectomy if medical treatment fails – the resection of less than 95–98% of the pancreas is associated with a much greater need for further resection and is not recommended [2]. When the genetic background is unknown or unclear, the patient must undergo imaging studies to determine if it is a case of focal or diffuse HI. Patients with genetic studies suggestive of focal HI must undergo imaging studies to confirm focal disease and localize the suspected lesion.

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Imaging Studies

Conventional noninvasive imaging studies such as ultrasound, computerized tomography, and magnetic resonance have been used to try to distinguish between focal and diffuse HI and to localize genetically suspected focal lesions without success. Invasive interventional tests (arterial stimulation/venous sampling and transhepatic portal venous sampling) were developed in the late 1980s and were used in at the Children's Hospital of Philadelphia (CHOP) until 2004 [3, 4]. They take several hours to be performed and are technically very demanding, and their sensitivity and specificity for distinguishing between focal and diffuse HI are limited [5]. They have been replaced by what is now considered the gold standard imaging study: ^{18}Fluoro-L-3-4 dihydroxyphenylalanine positron emission tomography merged with a low-radiation computerized tomography (^{18}F-PET/CT). The study was originally developed in the late 1990s for the detection of tumors of neuroendocrine origin in adults and has been used in HI patients since 2004 [6–8]. Islet cells of the pancreas take up L-dihydroxyphenylalanine (L-DOPA), convert it to L-dopamine by the enzyme DOPA decarboxylase, and store it in vesicles. Similarly, these cells can take up ^{18}fluoro-L-3-4 dihydroxyphenylalanine (18F-DOPA), convert it into ^{18}fluoro-dopamine, and store it in vesicles that can be tracked by their gamma radiation. At CHOP, the isotope ^{18}F-DOPA is administered under an FDA-approved Investigational New Drug (IND) protocol and the approval of the Institutional Review Board. The isotope has a half-life of 110 min and is manufactured on the day of the study in the Cyclotron Facility of the University of Pennsylvania. The study is done under general anesthesia in a PET/CT hybrid scanner that initially captures the radioactive signal and then generates a low-radiation CT scan of the abdomen without moving the patient. Focal lesions (which represent hyperplastic adenomatosis of beta cells) are seen as bright spots over a dark background due to the high concentration of the tracer, whereas in cases of diffuse disease, the tracer is homogeneously distributed throughout the organ. In a recent review of 105 consecutive studies performed at CHOP on a single scanner and read by a single nuclear medicine physician, we found that the sensitivity of the ^{18}F-PET/CT to detect a focal lesion was 85% and the correlation between the location on the images and the location at surgery was 100% [9]. The ^{18}F-PET/CT is also sensitive in the detection of the very rare ectopic focal lesions [10, 11].

Surgical Management

The operation is done through a transverse supraumbilical laparotomy [5]. The pancreas is completely exposed by an extended Kocher maneuver, entry into the lesser sac, and mobilization of the inferior border. The pancreas is inspected with 4× loupe magnification and carefully palpated in an attempt to identify a focal lesion. Focal lesions often have subtle differences in appearance and/or texture compared to

normal tissue (focal lesions are firmer). If no focal lesion is identified, biopsies are taken with sharp scissors (cautery causes artifact that affects the pathology interpretation and should be avoided) from the pancreatic head, body, and tail for intraoperative frozen section analysis. Patients with intraoperative confirmation of diffuse HI undergo near-total pancreatectomy. A near-total pancreatectomy involves the resection of the entire pancreas leaving only a tiny residual piece of pancreatic tissue between the common bile duct (CBD) and the duodenal wall. The intrapancreatic segment of the CBD must be identified and skeletonized for a true near-total pancreatectomy to be performed. To help with the identification and dissection of the CBD, I place a vessel loop around the extrapancreatic section of the CBD above the duodenum and then swing that within the duodenal C-loop. This maneuver is not needed if the CBD follows a visible course completely posterior to the pancreatic head, but gentle retraction with a vessel loop facilitates CBD dissection.

In babies with diffuse disease, I place a gastrostomy tube for long-term enteral access. When the intraoperative biopsies demonstrate normal pancreatic histology, a further search for the focal lesion is conducted.

The preoperative PET/CT study greatly facilitates the search. Intraoperative high-resolution ultrasound can sometimes help in localizing focal lesions, and we routinely arrange for intraoperative ultrasound if the genetics suggest a focal lesion but the PET/CT does not show a focal lesion (true for 15% of our focal lesion cases) [12]. I have been able to identify by visualization with 4× loupe magnification and/or palpation (focal lesions are often firmer than surrounding normal pancreas) in more than two-thirds of all focal lesions. Focal lesions that are buried within the pancreatic tissue can be impossible to see or feel, so it is necessary to patiently take additional biopsies of suspicious areas for frozen section analysis until the lesion is found. Expert pediatric anatomic pathology interpretation is crucial [13–15].

Focal lesions are generally less than 10 mm in diameter but can be much larger. They are irregularly shaped and frequently have octopus-like tentacles, which makes the intraoperative frozen section confirmation of clear margins imperative. Once the focal lesion is identified, a partial pancreatectomy is performed (free-of-disease margins must be confirmed before concluding the surgery). Small and superficial lesions in the body or tail can be treated by simple resection. Deep periductal lesions in the body and tail are treated by distal pancreatectomy. Intraoperative ultrasound can identify the 0.4-mm-diameter pancreatic duct and facilitate operative planning since injury to the pancreatic duct should be avoided. Superficial and small lesions in the head of the pancreas can also be treated by simple resection. On the other hand, deep lesions of the pancreatic head can be tricky to excise with clear margins without causing damage to the CBD and pancreatic duct. To ensure a complete resection of the lesion in these challenging cases, I remove almost all the pancreatic head and construct a Roux-en-Y pancreaticojejunostomy to drain the remaining pancreatic body and tail, preserving the endocrine and exocrine functions of the pancreas. In my experience, this approach has been required in about 30% of focal lesions located in the pancreatic head [16]. The end of a retrocolic, 25-cm-long Roux-en-Y jejunal limb is meticulously anastomosed to the capsule of the pancreatic body (just beyond the cut surface of the pancreas) with fine interrupted

monofilament suture to tuck the cut end of the pancreas into the jejunal lumen (Fig. 9.1). The omentum is then wrapped around the anastomosis to help seal potential leaks. Rarely, a focal lesion in the head will extend into the duodenal wall in which case a Whipple procedure may be needed. In cases of near-total and pancreatic head resections, it is crucial to preserve the gastroduodenal artery all as the vessels supplying the third and fourth portion of the duodenum (superior/inferior posterior/anterior pancreaticoduodenal arteries) if possible to avoid duodenal ischemia. I do not use drains after any pancreatic resection for HI.

Laparoscopic surgery can be used in HI patients with focal disease of the pancreatic body or tail. The surgery is done via three or four 3–5 mm ports, and to facilitate pancreatic exposure, the stomach is tacked up to the anterior abdominal

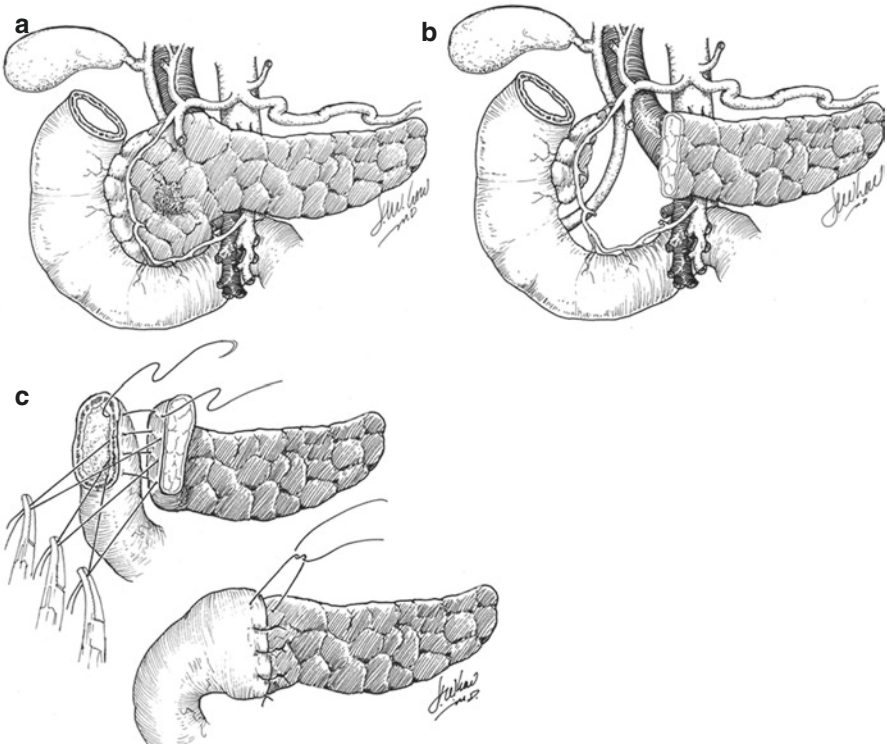

Fig. 9.1 (**a**) Focal lesion in the head of the pancreas that has octopus-like tentacles that extend into the normal tissue. (**b**) Near-total pancreatic head resection. The common bile duct (CBD) is skeletonized, and the duodenal vasculature is preserved. A tiny portion of the pancreatic head is left between the CBD and the duodenal wall. (**c**) Pancreaticojejunostomy. Fine interrupted monofilament stitches are placed from the end of the jejunal limb (full thickness) to the capsule of the pancreas just beyond the cut edge so that the cut end of the pancreatic body is tucked into the jejunal lumen. The posterior aspect of the anastomosis is performed first, with all sutures placed first and then tied serially leaving the knots on the inside of the anastomosis. The anterior aspect is performed in the same manner, but leaving the knots on the outside

wall with two to three transabdominal-transgastric stitches near the greater curvature. However, a major drawback to the laparoscopic approach is the limited tactile feedback to help palpate a non-visible focal lesion and the inability to apply an ultrasound probe directly on the pancreas to identify the pancreatic duct. Accordingly, laparoscopic resections for tail or body lesions by necessity lead to distal pancreatectomy, whereas open resections can often remove much less pancreas. The dissection and resection of the pancreatic head are significantly more technically demanding than for the distal pancreas. A high rate of CBD injury has been observed in cases of true laparoscopic near-total pancreatectomies (in which the CBD is identified and dissected laparoscopically). Recent reports claim a lower rate of CBD injuries, but a detailed analysis reveals that in those cases, the CBD is neither identified nor dissected and the pancreatectomy ends just beyond the superior mesenteric vessels, which means that those cases are not near-total but rather distal pancreatectomies [17, 18]. I have had to reoperate on babies with diffuse disease who had an inadequate laparoscopic pancreatectomy performed at other hospitals.

In addition to the focal and diffuse forms of HI, there are rare cases that do not fit in any of the two categories and are called atypical. Among those are cases with remarkable endocrine hyperplasia in the context of Beckwith-Wiedemann syndrome and patients with features of diffuse HI restricted to a single area of the pancreas distributed in a mosaic pattern which we term localized islet nuclear enlargement (LINE). Patients with atypical forms of HI are clinically heterogeneous and require a medical and surgical treatment plan that is individually crafted according to the severity of each case. For those patients with atypical HI who require surgery, intraoperative frozen sections are crucial to determining the extent of pancreatectomy [19].

Postoperative Management

Postoperative pain after open pancreatectomy is managed by an epidural catheter or intravenous narcotics. Patients are kept NPO until bowel function resumes. The intravenous glucose infusion is restarted immediately after the operation at a very low GIR (2 mg/kg/min) in part because the stress of the surgery induces hepatic glycogenolysis. The GIR is advanced to 5 mg/kg/min 12–18 h after the surgery and to 8 mg/kg/min (equivalent to the physiological hepatic glucose release during fasting periods) 24–36 h after the surgery. Plasma glucose levels are measured hourly in the beginning and spaced out as they become stable. The immediate postoperative oscillations in the plasma glucose levels are not reflective of the eventual long-term outcome, because factors like surgical stress and pain can alter glucose homeostasis. When bowel function is evident, enteral feedings are started and advanced gradually, and simultaneously the GIR is gradually weaned off. When patients are exclusively on enteral feeds, a “cure” fasting test is performed. If patients are able to maintain euglycemia for 18 h with plasma ketones appropriately

increasing during fasting, they are considered completely cured. If the time to hypoglycemia is less than 18 h, the next step is to determine a regimen of frequent feeds and short fasting periods that will allow the patient to be managed safely at home. Patients who cannot be weaned from the intravenous GIR are obviously not cured and will need further assessment to determine if additional surgery is required.

Outcomes After Surgery

From December 1998 to May 2018, 500 patients with HI underwent pancreatectomy at CHOP: 246 for focal disease, 202 for diffuse disease, 37 for atypical HI (16 for localized islet nuclear enlargement [LINE]; 21 for Beckwith-Wiedemann syndrome), and 15 for insulinoma. The focal HI patients (ages 1 week to 14 months; median age = 7 weeks) were treated with partial pancreatectomy. Since 2004, the focal lesion was found using preoperative 18-fluoroDOPA PET/CT scan and multiple pancreatic biopsies with frozen section analysis, followed by partial pancreatectomy. Patients with diffuse disease who failed medical management underwent biopsies to confirm the diagnosis then near-total (98%) pancreatectomy. The vast majority of pancreatectomies for focal HI were <50% (range 2%–98%), and many were local excisions of 2–10%. Fifty-five percent of patients had involvement of the pancreatic head or neck with the focal lesion. Forty lesions required pancreatic head resection with Roux-en-Y pancreaticojejunostomy (including two Whipple procedures) to preserve the normal body and tail. Lesions of the body or tail were treated with local resection or distal pancreatectomy. Intraoperative ultrasound was useful for delineating the course of the pancreatic duct. Ninety-seven percent of patients had a complete response to surgery and are cured. For diffuse disease patients, near-total pancreatectomy resulted in 31% having well-controlled blood glucoses, 20% requiring insulin, and 49% requiring treatment for hypoglycemia (Fig. 9.2). The incidence of diabetes has increased with long-term follow-up.

The overall surgical complication rate after pancreatic surgery for HI is low. General postoperative complications are bowel obstruction due to adhesions and small intestine-to-small intestine intussusception [20]. Specific complications of pancreatic surgery such as chylous leaks and pancreatic leaks are very rare in my experience. CBD complications (intraoperative injury or postoperative stricture) have been reported to occur in up to 17% of pancreatectomies involving the pancreatic head [21]. However, in my experience of more than 200 near-total pancreatectomies and 135 focal lesions involving the pancreatic head or neck, I had only 5 CBD complications.

These CBD complications were treated by choledochoduodenostomy. With our splenic vessel-sparing pancreatectomy approach, no splenectomies have been required [22].

Our approach to patients with focal HI can distinguish focal from diffuse disease, localize focal lesions, and permit partial pancreatectomy with cure in almost all patients. Surgery does not cure diffuse disease but can help prevent hypoglycemia and brain damage.

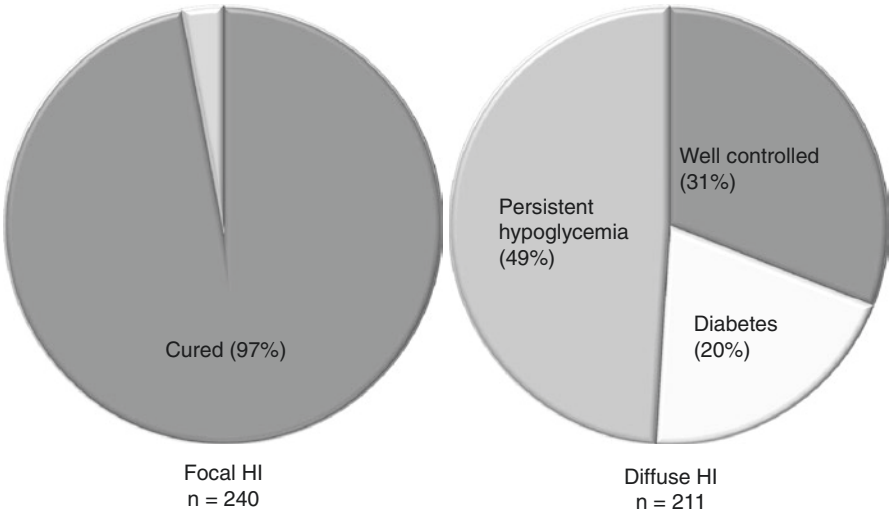

Fig. 9.2 Surgical outcomes in 240 focal cases and 211 diffuse cases

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Chapter 10
Perioperative Management of Hyperinsulinism

Katherine Lord, Melissa Duran, and Natalie Rintoul

Introduction

Indications for surgical intervention include all patients with the focal form of hyperinsulinism and those with diffuse disease whose hypoglycemia is unable to be controlled with medical therapy [1]. A standardized perioperative process ensures optimal plasma glucose control, nutritional support, and pain management and aids in patient recovery [2]. The postoperative course of patients with diffuse HI is different than those with focal HI. Children with diffuse disease, having undergone a near total (98%) pancreatectomy, may require an insulin infusion following surgery. They will have a gastrostomy tube placed at the time of pancreatectomy to facilitate medical management of the hyperinsulinism following recovery from surgery. In contrast, children with focal HI usually have a smaller pancreatic resection, do not

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require gastrostomy tube placement, and are unlikely to require insulin after surgery. Additionally, pancreatic head resection may require a Roux-en-Y pancreaticojejunostomy for adequate pancreatic duct drainage [3].

Preoperative Management

Patients with HI undergoing pancreatectomy require central venous access for infusion of high dextrose concentration intravenous fluids preoperatively and total parenteral nutrition (TPN) postoperatively (Table 10.1). Peripheral intravenous (PIV) access should also be obtained, either prior to transport to the operating room (OR) or upon arrival by anesthesia, for volume replacement with lactated ringers (LR) solution or drug administration. Prior to surgery, patients are placed on a "two-bag" system with a dextrose-containing fluid and an electrolyte solution without dextrose (Table 10.1). This allows for administration of adequate fluid volumes during surgery and allows for rapid titration of the glucose infusion rate (GIR) to maintain euglycemia. Plasma glucose levels increase in response to general anesthesia and surgery. Reducing the dextrose infusion to 50% of the preoperative rate with induction of anesthesia is recommended [4].

Table 10.1 Pre-/intraoperative management

Preoperative	
Access	Indwelling double lumen central catheter
	Infusion of high-dextrose concentration fluid
	Peripheral IV
	Administration of medications and volume replacement
Monitoring	Hemoglobin/hematocrit
	Type and screen
	Point-of-care glucose every 1–3 h
Intravenous fluids	"Two-bag" system
	Dextrose 30% in water (D30W) at current glucose infusion rate (GIR)
	0.45 normal saline (NS) at rate to achieve maintenance fluid goal
	Non-potassium-containing fluids
Pain control	Consider placement of epidural catheter
Intraoperative	
Monitoring	Point-of-care glucose every 30 min
	Do not draw from central line
Intravenous fluids	Reduce GIR by 50% at induction of anesthesia
	Titrate D30W and 0.45NS as needed to maintain glucose target of 80–180 mg/dL
	Do not decrease GIR below 2 mg/kg/min

Intraoperative Management

The intraoperative management of infants undergoing pancreatectomy is challenging and requires close monitoring of plasma glucose concentration (every 30 min). To avoid hyperglycemia and maintain adequate hydration, the "two-bag system" allows 0.45 normal saline to be titrated up as the dextrose-containing fluids are weaned. Fluid replacement and flushes should be LR or normal saline (NS) without added glucose. By the end of surgery, the GIR is typically ~2 mg/kg/min. To avoid the possibility of hypoglycemia, discontinuation of all dextrose-containing fluids is not recommended.

Postoperative Management

On return from the operating room, the patient remains NPO and is continued on the intravenous fluid infusions (Table 10.2). Plasma glucose concentration is followed hourly with a target goal of 80–180 mg/dL. Patients should have gastric decompression with a Salem sump to low continuous suction; in those patients with a gastrostomy tube (GT), the tube should be placed to gravity.

On postoperative day (POD) 1, the GIR is increased, and the 0.45 normal saline is adjusted as needed to maintain the calculated total fluid limit and adequate hydration. In the event of increasing plasma glucose concentrations, the GIR should not be weaned since the goal is to optimize nutrition. Plasma glucose concentrations greater than 250 mg/dL can be tolerated for 6–8 h postoperatively before starting insulin. If plasma glucose concentration is >250 mg/dL during the immediate 6–8 h postoperative period, plasma ketones should be measured. If plasma glucose concentrations are persistently >250 mg/dL after 6–8 h postoperatively, a low-dose insulin infusion is initiated. The majority of patients who have undergone a near total pancreatectomy will require an insulin infusion (Table 10.2).

Total parenteral nutrition (TPN) is initiated on POD 1. The TPN GIR is increased to 8 mg/kg/min, where it should remain until feeds are restarted. In addition, the Salem sump should remain on suction until bowel function resumes. Return of bowel function is signified by a resolution of bilious Salem sump output, a marked reduction in volume of output, and a resumption of stooling. In patients with a gastrostomy tube, the tube will begin to drain well when bowel function resumes. Patients with limited intraoperative manipulation of the duodenum will require the Salem sump for the shortest period of time.

A sepsis evaluation (blood culture and urine culture) should be considered for persistent hyperglycemia or hypoglycemia past the acute postoperative period.

Table 10.2 Postoperative management day 0–1

Day 0	
Access	Indwelling double lumen central catheter
	Peripheral IV
	Salem sump
	Low continuous suction
	+/− Gastrostomy tube (GT)
	Gravity
Monitoring	Point-of-care (POC) glucose hourly
	Check serum potassium if glucose >300 mg/dL
Intravenous fluids	"Two-bag" system
	Dextrose 30% in water (D30W) at glucose infusion rate (GIR) of 2 mg/kg/min
	0.45 normal saline (NS) at rate to achieve total fluid limit (TFL) of 80–100 mL/kg/day
Pain control	+/− Epidural
	Morphine/nalbuphine PRN
	+/− Continuous opioid infusion
	Acetaminophen
Diet	NPO
Medications	Antibiotics for 24 h
Day 1	
Monitoring	POC glucoses every 1–3 h
	More frequent monitoring may be needed if requiring an insulin infusion
Intravenous fluids	Adjust fluids
	D30W GIR to 5 mg/kg/min
	0.45 NS TFL to 100–120 ml/kg/day
	Initiate total parenteral nutrition (TPN) with GIR 8 mg/kg/min
	Discontinue other fluids with start of TPN
Diet	NPO
Medications	Insulin
	Initiate if persistent hyperglycemia (>250 mg/dL)
	Regular insulin infusion at 0.005 units/kg/hr
	Titrate to maintain glucose 80–180 mg/dL

Postoperative Pain Management

Pain control in patients undergoing pancreatectomy is essential. Plasma glucose concentration can become elevated by inadequate pain management. Establishing an effective pain management regimen early in the postoperative period minimizes discomfort and aids recovery; therefore, a postoperative pain algorithm with involvement of a dedicated pain team should be developed (Table 10.2). Epidural analgesia has been shown to be both safe and effective in neonates/infants undergoing laparotomies [5]. However, in many cases epidural analgesia alone is not sufficient for optimal pain management in infants after pancreatectomy. The addition of a continuous opioid infusion, specifically morphine, is often needed. Intermittent

doses of morphine and nalbuphine can be given, as needed, for breakthrough pain. Non-opioid medications, such as acetaminophen and ketorolac, are also used frequently as adjuvant therapy. Because of bleeding risk, the decision to use ketorolac must be made with the surgeon's input.

Postoperative Feeding Regimen and Other Considerations

When bowel function resumes as indicated by passage of stool, enteral feedings can be reintroduced (Table 10.3). Bowel function usually returns at approximately 5–7 days postoperatively. Return of bowel function takes longer if significant manipulation of the duodenum occurred intraoperatively or following a Roux-en-Y pancreaticojejunostomy procedure. Enteral feedings are started at 1/3 of the estimated total daily requirement by gastrostomy tube or by mouth, depending on the patient's oral skills preoperatively. As feeds are advanced over 3 days, the TPN is weaned (Table 10.3). For infants requiring an insulin infusion, the rate should be adjusted to maintain plasma glucose in the range of 80–180 mg/dL during the feed advancement. Infants who still require an insulin infusion after discontinuation of parental nutrition should be transitioned to subcutaneous insulin dosing (Chap. 12).

A minimal amount of emesis is not uncommon as feeding is advanced. Postoperative pancreatectomy patients often will require anti-reflux medications. If

Table 10.3 Postoperative management day 2 – return of bowel function

Day 2 to return of bowel function	
Monitoring	POC glucose every 1–3 h
Intravenous fluids	TPN with GIR 8 mg/kg/min
Pain control	+/− Epidural
	Morphine/nalbuphine PRN
	+/− Continuous opioid infusion
	Acetaminophen PRN
	+/− Ketorolac ATC for 48–72 h
Diet	NPO
Return of bowel function	
Access	Indwelling double lumen central catheter
	Remove Salem sump
	Clamp GT
Monitoring	POC glucose every 1–3 h
Intravenous fluids	Wean TPN as enteral feedings advance
	Day 1, GIR 5 mg/kg/min
	Day 2, GIR 2 mg/kg/min
	Day 3, off
Diet	Feeding advance (oral or via GT)
	Day 1, 1/3 volume
	Day 2, 2/3 volume
	Day 3, full volume

there is a concern for postoperative bowel obstruction, as evidenced by bilious emesis or intractable pain, an abdominal ultrasound should be obtained to evaluate for an intussusception. Postoperative intussusception has been observed after either partial or near total pancreatic resections [6]. It usually occurs within the first 2 postoperative weeks and involves the small bowel. The outcome after surgical correction of the intussusception is usually uneventful.

Transition from the Intensive Care Unit

Patients can be transitioned from the intensive care unit (ICU) to the general ward once they are on full enteral feeds and have discontinued parental nutrition. The removal of the central venous catheter should be considered once the infant is tolerating full-volume feedings. Patients with focal HI who are euglycemic without dextrose support should have their catheters removed prior to transfer from the intensive care unit (ICU). Patients with diffuse HI may require use of a central catheter for several days after the transition to full feeds in order to provide continuous dextrose support.

Conclusion

Infants and children undergoing pancreatectomy for hyperinsulinism have unique needs. A standardized approach to their perioperative care ensures optimal glucose control, pain management, and nutrition as well as aiding in their recovery.

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Chapter 11
Management of the Child with Persistent Hypoglycemia After Surgery

Amanda M. Ackermann and Diva D. De León-Crutchlow

Introduction

Following pancreatectomy for congenital hyperinsulinism (HI), regardless of underlying diagnosis, patients must be reevaluated to determine whether their HI has been cured or is persistent. Patients with resolved HI may need no medical management, or they may require treatment for insulin-deficient diabetes (DM type 3c [1]) depending on the extent of the pancreatic resection. Patients with persistent HI may have sufficient improvement to allow for medical management and discharge home, or they may require additional resection of pancreatic tissue. This chapter will discuss the potential postsurgical outcomes, specifically in regard to glucose homeostasis, and the available treatment modalities for patients with persistent congenital HI.

Post-pancreatectomy Outcomes

Only a few studies have systematically evaluated patient outcomes following pancreatectomy for congenital HI (Table 11.1). These studies vary substantially in the number and characteristics of the patients included in the study cohort, the rigor of pre- and postoperative evaluations performed, and the length of follow-up. In

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Table 11.1 Post-pancreatectomy outcomes

Study	HI etiology	Px extent	Follow-up time	Repeat Px for HI	Persistent HI after final Px	Diabetes	No glycemic management
Jacobs et al. (1986) [2]	Diffuse (5)	85–99%	1–6 years	25% (3/12)	0% (0/12)	17% (2/12)	58% (7/12)
	Focal (6)						
	Unknown (1)[a]						
Al-Rabeeah et al. (1995) [3]	Diffuse[a]	90%	4 months – 6 years	0% (0/22)	27% (6/22)	0% (0/22)	73% (16/22)
Leibowitz et al. (1995) [4]			6.5–21 years			75% (6/8)	
Soliman et al. (1996) [5]	Diffuse (5)	95–98%	2.5–7 years	0% (0/7)	0% (0/7)	43% (3/7)	57% (4/7)
	Focal (2)[a]						
Cade et al. (1998) [6]	nd[a]	85–95%	0.9–12.7 years	0% (0/6)	50% (3/6)	17% (1/6)	33% (2/6)
Rother et al. (2001) [7]	Diffuse (non-focal)[a]	~95%	8–15 years	20% (3/15)	13% (2/15)	13% (2/15)	53% (8/15)
Meissner et al. (2003) [8]	Diffuse and focal	≤95%	1–27 years	27% (17/63)	46% (29/63)	27% (17/63)	27% (17/63)
Cherian and Abduljabbar (2005) [9]	nd[a]	95%	1–20 years	0% (0/10)	0% (0/10)	100% (10/10)	0% (0/10)
Beltrand et al. (2012) [10]	Diffuse	95%	1–19 years	17% (10/58)	0% (0/58)	91% (53/58)	9% (5/58)
	Focal	≤66%	0–17 years	4% (2/47)	2% (1/47)	0% (0/47)	94% (44/47)
Lord et al. (2013) [11]	Diffuse	15–100%	<1 year	nd	41% (40/97)	36% (35/97)	23% (22/97)
	Focal	1–100%	<1 year	nd	4% (5/114)	2% (2/114)	94% (107/114)
Lord et al. (2015) [12]	Diffuse	75–99%	3–50 years	nd	nd	63% (37/59)	nd
	Focal	1–98%	3–50 years	nd	nd	11% (6/54)[b]	nd

Outcomes determined based on end of follow-up period
Px pancreatectomy, *nd* no data
[a]No genetic testing was performed
[b]All six patients in this study with focal HI who developed diabetes had ≥97% pancreatectomy

addition, differences due to advances in genetic diagnostics, radiographic imaging-assisted preoperative planning, intraoperative biopsy evaluations, and surgical approach also contribute to variations in reported outcomes.

A recent study of short-term outcomes following pancreatectomy found that 94% of patients with focal HI were cured of their HI and were normoglycemic at the time of discharge from the hospital, while only 4% had persistent HI that was medically manageable, and 2% had diabetes requiring insulin [11]. Importantly, all of the patients with focal HI who developed diabetes immediately after pancreatectomy had ≥97% of their pancreatic tissue resected. A similarly high cure rate of 94% was found after long-term follow-up (up to 17 years) of patients who underwent partial (≤66%) pancreatectomy for focal HI [10]. These results highlight the importance of preoperative imaging and intraoperative biopsy histological analyses for guiding a limited pancreatic resection for focal HI [13, 14].

Our group also evaluated the short-term surgical outcomes of patients with diffuse HI, most of whom had a more extensive pancreatectomy than did the patients with focal HI (median 98% versus 27%) [11]. At the time of discharge from the hospital, 41% had persistent HI requiring medical management, 36% had diabetes requiring insulin treatment, and 23% were normoglycemic. Longer-term follow-up studies show that the risk of diabetes after near-total pancreatectomy for diffuse HI increases substantially over time (to 63–91%) and that most patients develop diabetes by adolescence [10, 12]. Therefore, most cases of postsurgical persistent HI eventually evolve into diabetes, often with components of both dysregulated insulin secretion and insulin deficiency.

Other forms of severe congenital HI may also be treated with pancreatectomy. For example, some patients with severe persistent HI associated with Beckwith-Wiedemann syndrome have benefited from subtotal (75–95%) pancreatectomy [15]. For best outcomes, the extent of resection should be guided by preoperative imaging and intraoperative biopsy histology.

Determination of Post-pancreatectomy Outcomes

As discussed in the previous chapter on postoperative management, hypoglycemia or hyperglycemia may be readily apparent in the immediate postoperative period. It is important to provide acute management of hypo- or hyperglycemia as clinically indicated while recognizing that such hypo- or hyperglycemia may be transient, related to perioperative stress, illness, or parenteral nutrition. Once the patient is on a stable feeding regimen for several days, their glycemic status should be reassessed in preparation for determining a safe management plan prior to discharge.

Normoglycemic Patients

For focal HI patients with apparent normoglycemia (plasma glucose 70–140 mg/dL) post-pancreatectomy, a "Cure Fast" should be performed prior to discharge (Table 11.2). The goal of the Cure Fast is to determine whether the patient's HI persists, indicating that abnormal beta cells are still present in the remnant pancreas. In this respect, a Cure Fast is similar to an initial Diagnostic Fast (see Chap. 1), with extended fasting time ending early if hypoglycemia occurs with plasma glucose <50 mg/dL, and laboratory evaluation for HI including a limited critical sample and a glucagon stimulation test.

During a Cure Fast, the plasma glucose concentration (and if possible plasma beta-hydroxybutyrate concentration) should be measured every 3 h while >70 mg/dL, then every 1 h until <60 mg/dL, and then every 30 min until <50 mg/dL. When the plasma glucose is confirmed to be <50 mg/dL, then the limited critical labs [glucose, beta-hydroxybutyrate, insulin, C-peptide, nonesterified fatty acids, and insulin-like growth factor-binding protein 1 (IGFBP1)] should be drawn. The plasma glucose should then be immediately rechecked, and if still <50 mg/dL, a glucagon stimulation test should be performed by administering 1 mg of glucagon intravenously (IV) or intramuscularly (IM), and plasma glucose should be rechecked every 10 min. A positive glucagon stimulation test result in which plasma glucose increases by ≥30 mg/dL within 40 min, or a negative result in which plasma glucose increases by ≤20 mg/dL within 20 min, is an indication to end the test and feed the child.

In addition to information regarding persistence of HI, the Cure Fast also provides data regarding length of fasting tolerance for those patients that are not cured. Parents and caregivers should be informed and given anticipatory guidance

Table 11.2 Fasting studies performed after pancreatectomy

	Cure	Safety
Duration		
<1 month old	18 h	8–12 h
1–12 months old	24 h	12 h
>12 months old	36 h	18 h
Other ending criteria		
Plasma glucose *or* significant symptoms	<50 mg/dL	<60–70 mg/dL
Critical labs to draw at end	Glucose	Glucose
	Beta-hydroxybutyrate	Beta-hydroxybutyrate
	Insulin	
	C-peptide	
	Nonesterified fatty acids	
	IGFBP1	
Glucagon stimulation test	Yes	No

regarding how long the patient is able to maintain plasma glucose >70 mg/dL, which should inform their sleeping, feeding, and glucose checking regimens. It is also important to keep in mind that fasting tolerance is often substantially shorter when ill.

Hyperglycemic Patients

Patients who develop persistent hyperglycemia (plasma glucose recurrently >200 mg/dL) after pancreatectomy require insulin management. Patients receiving insulin therapy do not require a fasting test prior to discharge. However, it is important to note that patients with diffuse HI who require insulin after pancreatectomy are still at risk of hypoglycemia due to dysfunctional remaining beta cells, in addition to exogenous insulin administration. For more details of insulin management for these patients, see Chap. 12.

Hypoglycemic Patients

For patients with persistent hypoglycemia (plasma glucose recurrently <70 mg/dL) after pancreatectomy, the first determination that needs to be made is whether the hypoglycemia is medically manageable or not. If not medically manageable, then a repeat pancreatectomy should be considered. Options and strategies for medical management are discussed in more detail in the next section, but they may include continuous enteral dextrose and/or octreotide. Once a therapeutic regimen is established, then the effectiveness of that regimen should be evaluated with a "Safety Fast" prior to discharge (Table 11.2).

Similar to a Safety Fast for nonsurgical patients on diazoxide therapy, the goal of a Safety Fast is to determine the length of time that the patient can maintain their plasma glucose ≥70 mg/dL without feeding while receiving their medical interventions. Therefore, the protocol for a Safety Fast includes continuing their medical therapies (including continuous enteral dextrose, if appropriate) while fasting; during which time, the plasma glucose (and ideally beta-hydroxybutyrate) is assessed every 3 h until it decreases to <70 mg/dL. It is helpful to obtain laboratory measurements of glucose and beta-hydroxybutyrate at the end of the fast to confirm persistence of hyperinsulinemic hypoglycemia. No other laboratory tests, nor a glucagon stimulation test, are necessary, because the diagnosis of hyperinsulinism is pre-established.

The information obtained during a Safety Fast regarding how long the patient is able to maintain plasma glucose ≥70 mg/dL should be shared with the parents and caregivers to guide their child's sleeping, feeding, and glucose checking regimens while remembering that illness often significantly shortens the patient's fasting tolerance.

Management of Persistent Hyperinsulinemic Hypoglycemia After Pancreatectomy

Treatment of persistent HI following pancreatectomy requires an individualized approach, although some general principles should be followed. Often, a combination of therapies is required to achieve a suitable regimen that can safely and reasonably be carried out at home.

Repeat Pancreatectomy

Patients with focal HI, based on genetic and histologic analyses, should be cured if the lesion has been completely excised. Although focal HI is often characterized by a discrete area of abnormal endocrine tissue within the pancreas, some cases can have irregular borders or be multifocal [16], leading to incomplete resection despite intraoperative biopsy histological analysis. Therefore, repeat more extensive pancreatectomy, in particular with an experienced surgeon and team, should be strongly considered in these cases. Regardless of the ability to medically manage these patients' persistent HI, the potential for cure is almost always preferred.

Repeat pancreatectomy may also be indicated in patients with diffuse or other forms of HI, if the initial pancreatectomy does not improve the patient's hypoglycemia

Table 11.3 Medical management options for persistent HI after pancreatectomy

Therapy	Maximum dose	Side effects	Monitoring
Somatostatin Analogs Octreotide LAR octreotide Lanreotide	20 mcg/kg/day 10 mg/month 60–90 mg/month	Transaminitis Biliary sludging Hypothyroidism Growth suppression NEC	Liver enzymes q6m Gallbladder US q12m TFTs q6m IGF1, IGFBP3 q6m Stool output, abdominal girth
Enteral dextrose	10 mg/kg/min	Diarrhea	Stool output
Diazoxide	15 mg/kg/day	Sodium/fluid retention Hyperuricemia Bone marrow suppression Hypertrichosis Appetite suppression	BMP q3m Uric acid q12m CBC q12m
Glucagon	1 mg/day	Nausea Erythema necrolyticum migrans	HgbA1c q12m

q6m every 6 months, *US* ultrasound, *q12m* every 12 months, *TFTs* thyroid function tests (TSH, Free T4), *IGF1* insulin-like growth factor 1, *IGFBP3* insulin-like growth factor-binding protein 3, *NEC* necrotizing enterocolitis, *BMP* basic metabolic panel, *q3m* every 3 months, *CBC* complete blood count, *HgbA1c* hemoglobin A1c

sufficiently to allow for a reasonable medical management. When weighing the pros and cons of available treatment options, the increased risk of diabetes with repeat pancreatectomy must be taken into consideration, although, in general, management of diabetes is somewhat more predictable and less risky than management of HI. Furthermore, most patients who initially had a near-total (≥95%) pancreatectomy already have a high risk of developing diabetes in childhood/adolescence, so a repeat pancreatectomy likely would only hasten the inevitable.

When pursuing a repeat pancreatectomy, it is important to take into consideration the timing in relation to the initial pancreatectomy. It is recommended that a repeat pancreatectomy be performed within 2 weeks of the initial pancreatectomy, to avoid complications associated with fibrosis from the first procedure interfering with the surgeon's ability to biopsy or resect pancreatic tissue without damaging nearby structures. These patients are best served by a surgeon and clinical team with extensive experience in performing repeat pancreatectomies and managing patients with persistent HI.

After pancreatectomy or repeat pancreatectomy, the treatment options for persistent HI are essentially the same as they were preoperatively discussed in more detail in Chap. 6, although lower doses may be sufficient. The comparison of the patient's pre- versus postoperative glucose infusion rate (GIR) required to maintain normoglycemia is helpful for determining the degree of residual HI and the potential efficacy of additional therapies.

Somatostatin Analogs

Because patients who underwent pancreatectomy should have preoperatively been trialed on and failed treatment with diazoxide, it is generally recommended to start treatment with somatostatin analogs in patients with persistent post-pancreatectomy HI. These medications act on endocrine cells to indirectly inhibit voltage-gated calcium channels and thus reduce secretion of endocrine hormones (e.g., insulin) [17].

Octreotide has been in clinical use since the 1980s and has a relatively short biologic half-life of approximately 90 min [18]. It can be given subcutaneously via injection or continuous infusion, or intravenously, although only subcutaneous routes should be considered in patients after pancreatectomy, as the goal of therapy is to achieve a regimen that can be administered at home. Most patients require two to four subcutaneous injections per day to prevent hypoglycemia. Unfortunately, tachyphylaxis is quite common [19], in which subsequent doses lose effectiveness, necessitating higher doses and extended time in between doses to attempt to recover efficacy.

To circumvent the need for frequent injections, long-acting somatostatin analogs have been developed, although not yet approved by the FDA for use in HI (their primary use is for acromegaly). LAR (long-acting release) octreotide has been clinically available since the 1980s and is administered IM monthly as a depot injection [20]. Lanreotide has only been available since 2007 and is administered in deep

subcutaneous tissue monthly [21]. A recent study found that 89% of patients with HI treated with a long-acting somatostatin analog achieved adequate glucose control [21]. It is generally recommended that octreotide injections be continued during the 1st month of transitioning from octreotide to LAR octreotide or lanreotide, although the evidence for this in HI is anecdotal. No comparison studies have yet been performed to evaluate the relative efficacies of the different somatostatin analogs for patients with HI.

In general, these long-acting alternatives carry the same risks as octreotide. The most concerning side effect of somatostatin analogs is necrotizing enterocolitis (NEC), likely due to reduced splanchnic blood flow [22]. Because the highest risk of this complication is in neonates and patients at general increased risk for NEC (preterm, history of cardiac abnormalities, etc.), most patients after pancreatectomy are good candidates for octreotide. Other side effects of somatostatin analogs include transaminitis, biliary sludging, and reduced secretion of multiple endocrine hormones resulting in hypothyroidism and growth hormone insufficiency [23–25]. Therefore, routine evaluation of transaminases, thyroid function tests, and growth factors (IGF1 and IGFBP3) is recommended every 6 months, along with annual ultrasound imaging of the gallbladder [26].

Continuous Enteral Dextrose

Octreotide alone is usually insufficient to maintain normoglycemia long term. Thus, patients often also require a continuous source of glucose, either just overnight while not feeding or around the clock. In some cases in which octreotide is contraindicated or resulted in substantial tachyphylaxis, or in mild persistent HI, continuous enteral dextrose may be used alone as monotherapy [27]. The solution consists of 10–20% dextrose mixed with sterile water and administered through a feeding tube; patients who have undergone a pancreatectomy for diffuse disease should have all had a gastrostomy tube placed for this purpose. A maximum enteral GIR of 10 mg/kg/min is recommended to avoid complications of intolerance and vascular compromise associated with high volume and osmotic load.

Diazoxide

If a combination of somatostatin analog and enteral dextrose is insufficient to prevent hypoglycemia, then all other treatment modalities should be considered. Depending on the patient's genetic diagnosis (or lack thereof), it may be worthwhile to retrial maximum-dose diazoxide therapy (15 mg/kg/day divided twice daily). Some patients who had a marginal response to diazoxide treatment prepancreatectomy may have a more substantial response postoperatively. Even a marginal response may be sufficient to allow safe doses of octreotide and enteral

dextrose to be used in combination to achieve normoglycemia. However, patients with focal HI or diffuse HI due to recessive mutations in the ATP-gated potassium (K_{ATP}) channel will not benefit from diazoxide treatment in any circumstance, as diazoxide functions by binding to and opening the K_{ATP} channel.

Common side effects of diazoxide include sodium and water retention, hypertrichosis, and appetite suppression. Other less common side effects of diazoxide include hyperuricemia (due to decreased urinary excretion of uric acid) and bone marrow suppression. To counteract the sodium and water retention side effects, co-administration of a diuretic is recommended for all young infants receiving diazoxide, as well as any patient with additional risk factors for fluid overload. Routine lab monitoring of electrolytes, uric acid, and complete blood count is recommended every 6 months while on diazoxide therapy [28].

Continuous Glucagon

Other medical therapies including continuous subcutaneous glucagon [29] may be utilized in the management of persistent HI after pancreatectomy, although current glucagon formulations require daily changing of the administration cartridge due to precipitation.

Follow-Up and Monitoring of Patients with Persistent HI After Pancreatectomy

In addition to the laboratory and imaging evaluations described above and in Table 11.3, patients with persistent HI following pancreatectomy require repeat assessments of their HI treatment regimen, as well as screening for development of diabetes. As previously discussed, the natural course of post-pancreatectomy HI is to eventually regress and evolve into diabetes, usually by adolescence. In general patients with milder post-pancreatectomy HI are at higher risk of developing diabetes sooner than patients with more severe post-pancreatectomy HI. Routine screening of hemoglobin A1c is recommended.

While patients display evidence of persistent HI, it is recommended that they undergo annual inpatient evaluation consisting of repeat Safety Fast and modification of treatment regimen as needed. Sometimes this may involve reducing enteral dextrose or octreotide doses, as the HI improves. However, not infrequently, medication regimens must be increased due to worsening HI, for example, by increasing octreotide dose and/or frequency, transitioning to a long-acting somatostatin analog, and/or increasing enteral dextrose GIR or length of administration. Post-pancreatectomy HI can be particularly difficult to control due to several factors: (1) these patients had more severe HI to begin with; (2) in addition to their underlying dysregulated insulin secretion, there is some degree of insulin insufficiency that

contributes to intermittent hyperglycemia, especially in the setting of octreotide administration, that results in widely fluctuating glucose concentrations; and (3) pancreatectomy removed most of the alpha cells, so there is also insufficient glucagon production to help counteract hypoglycemia.

Summary

Pancreatectomy provides a cure for most (94%) patients with focal HI, without significant risk of complications including diabetes. However, pancreatectomy is only palliative for patients with diffuse HI, as the evidence shows that the most effective management of HI is achieved by near-total (≥95%) pancreatectomy, which results in only 23% of patients achieving normoglycemia and is associated with a very high likelihood (~63% to 91%) of developing diabetes over the next 10–20 years. Best outcomes are achieved when an experienced team of pediatric endocrinologists, pediatric surgeons, geneticists, radiologists, and pathologists are involved in the patient's care. A large proportion (41%) of patients with diffuse HI have persistent HI following near-total pancreatectomy and thus require additional management including possible repeat pancreatic resection, somatostatin analogs, and continuous enteral dextrose. It is imperative that the medical regimen be challenged prior to discharge from the hospital by a fasting study. Additionally, because of the variability of post-pancreatectomy persistent HI and its evolution into diabetes over time, annual reassessment of fasting tolerability and adjustment of the medical regimen, in addition to screening for treatment-related complications, is indicated.

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Chapter 12
Management of Diabetes and Pancreatic Insufficiency After Pancreatectomy

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Introduction

Disruption of the endocrine and exocrine function of the pancreas may occur following surgery to treat hyperinsulinism. Clinicians have to evaluate and manage endocrine and exocrine insufficiency postoperatively, in the short and longer term. In this section, we will address pancreatic and hepatobiliary complications of pancreatic surgery and discuss management principles and practices.

Surgical Management of Hyperinsulinism

A large proportion of patients with K_{ATP} HI are diazoxide unresponsive and may require surgery to control hypoglycemia. Historically, near total pancreatectomy was performed for all those unresponsive to diazoxide; however, since the early descriptions of focal HI [1], discovery of the genetic mechanism causing it [2] and the development of surgical techniques to remove only that affected portion of the

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pancreas have dramatically changed outcomes for focal HI [3]. Together, preoperative genetic testing [4] and preoperative pancreatic imaging with 18F-DOPA PET may enable the clinician to identify those with focal HI and locate the lesion [5]. Cure rates following local resection of the lesion focal disease have been reported to be 85–95%.

For those with diffuse disease and failure of diazoxide therapy, the current approach is to attempt to maintain the glucose in the normal range with a complex feeding program typically consisting of continuous enteral feeds or intragastric glucose administration in combination with pharmacologic therapy (see Chap. 6 on medical management). However, in patients in whom the enteral glucose infusion rate (GIR) needed to maintain euglycemia is >10 mg/kg/min, surgery may be indicated. When contemplating 98% pancreatectomy for diffuse disease, the physicians and family must be familiar with the likely outcome post-surgery. This includes ongoing hypoglycemia, the short- and long-term risks of diabetes, and the occurrence of exocrine pancreatic insufficiency.

In patients with diffuse disease undergoing 98% pancreatectomy, immediate post-op outcomes include persistent hypoglycemia in about 60% of patients [6], persistent diabetes in 20%, and transient diabetes followed by hypoglycemia in the remainder. Beltrand et al. [7] found that 48% of patients had diabetes by 8 years and 91% by 14 years. Since the development of focal surgery, Beltrand reports no diabetes occurring in focal patients [7].

Management of Diabetes in the Immediate Postoperative Period

Transient diabetes progressing to hypoglycemia may be difficult to manage. The physiological stress of the surgery combined with transiently impaired blood flow to the remaining 2–3% of the pancreas often results in immediate hyperglycemia. Initially fluids should be adjusted to reduce the glucose infusion rate (GIR), and if glucose persists >250 mg/dL, then continuous insulin by infusion is recommended to prevent diabetic ketoacidosis (see Chap. 10). Alternatively, subcutaneous insulin bolus therapy may be started every 4–8 h if it is likely that enteral feeding may soon start. Starting with a low dose is recommended to prevent hypoglycemia. Resolution of transient diabetes may take 2–3 days or as much as 4–6 weeks. If patients need to go home on insulin, various approaches may be undertaken including continuous subcutaneous infusion (CSI) insulin with pump therapy using either U-100 or U-10 insulin.

Transient diabetes can also occur in patients with focal disease treated by diazoxide until the day of surgery. In this case, removal of the lesion results in cure, but due to the half-life of diazoxide in the system, complete inhibition of insulin secretion

can occur in the remaining normal tissue until 3–5 days post discontinuation of diazoxide. In these cases, lowering the GIR to 0–4 mg/kg/min and judicious use of subcutaneous rapid-acting insulin will usually suffice until the diazoxide has cleared the system in 3–5 days.

Persistent Diabetes in Infancy and Early Childhood

The management of insulin-dependent diabetes in infants presents a unique set of challenges. Infants require small, accurate doses of insulin which should be administered for all carbohydrates ingested. Insulin pump therapy is the best way to attempt to mimic physiologic insulin dosing for an infant. Dilute insulin in a subcutaneous insulin pump allows for small doses with appropriate timing based on the infant's schedule and feeding regimen [8, 9]. Dilute insulin by syringe also allows for precise dosing of subcutaneous insulin. Dilute insulin is diluted with normal saline [10] or manufacturer-provided diluent [11] to 1 unit of insulin in 10 units/cc (U-10) rather than the standard insulin which is 100 units/cc (U-100). U-10 insulin allows for doses as small as 0.1 units/dose with syringe and 0.01 units with pump therapy.

Dilute insulin has been found to decrease the amount of hypoglycemia in young children as the ability to give minute doses allows dosing for what children eat rather than getting them to eat for the amount of insulin they need to receive [8]. It has also been noted that there are less pump alarm occlusions when dilute insulin is utilized compared to using very small doses of U-100 insulin [10]. Dilute insulin is not without challenges as it does need to be mixed every 7–14 days [8]; however, the benefits of accurate dosing outweigh the risks. Typical starting doses of insulin are 0.5 units/kg/day with 50% as basal and 50% as bolus with adjustments made from there.

While dilute insulin does allow for increased accuracy in dosing, it does present certain risks both while the patient is hospitalized and at home. Nurses are familiar with standard U-100 insulin. Extreme caution must be taken in order to prevent overdosing the infant. Orders must specify U-10 insulin, the dose to be drawn up, and the dose to be given. An example would be this: "please give 0.3 units (0.03 ml) of U-10 insulin and have a 2-nurse check." A "2-nurse check" must be mandated. Families tend to have fewer safety issues with dilute insulin as this is the only type of insulin they are familiar with, and parents/caregivers do not generally have prior knowledge of U-100 insulin. However, they do need to be told to tell everyone they meet in future medical settings that they are on "special" insulin and only their home insulin may be used. Families must be instructed to bring their home insulin to all medical appointments and emergency care visits.

Late-Onset Diabetes

Children with hyperinsulinism status post 98% pancreatectomy may require continued treatment for hypoglycemia until approximately the age of 3–8 years, and then they may have a period of relative euglycemia. The onset of diabetes often disrupts the first period of euglycemia that children and families have experienced. The idea of needing to give insulin, the hormone that was overproduced for so long, may be daunting for children and caregivers as also is the idea of restricting carbohydrates when they have been lifesaving thus far.

Management of the postoperative patient during childhood and early adolescence should focus on the early identification of a rising trend in blood glucose. Screening HbA1c should be done yearly until >6.2% and then every 6 months or if home glucose monitoring starts to show fasting glucose >100 mg/dL or random >200 mg/dL. Once this occurs, there should be a weaning of anti-hypoglycemic medications and a lowering of the carbohydrate supplementation.

One of the most difficult issues in the early development of diabetes is the time when the patient has what appears to be postprandial hyperglycemia (diabetes) and fasting hypoglycemia (hyperinsulinism). There are several approaches to solving this problem. One can wait and watch until the HbA1c rises >7.0% as one is unlikely to do better than that with insulin therapy. Another approach is to start with moderate carbohydrate restriction and correction factor during the day (but not at night). In some patients, using a basal insulin during the day that does not have such a large effect at night, such as low-dose insulin detemir given before breakfast, will prevent the daytime highs and minimize the nighttime lows. Once the A1C is >7.5%, a full-fledged MDI or CSI insulin program should be initiated.

Pancreatic Insufficiency and Biliary Complications of Surgery

Exocrine pancreatic insufficiency (EPI) may be a consequence of partial or subtotal pancreatectomy. EPI may be subtle and can be difficult to diagnose after subtotal pancreatic resection. In children, long-term data is limited by the infrequency of pancreatic resection and a paucity of studies examining long-term exocrine function outcomes, especially for children with resection due to hyperinsulinism. Most of the data discussed below regarding EPI diagnosis and management emanates from the literature regarding cystic fibrosis, the prototypical disorder associated with EPI in children.

Clinical Features

EPI after pancreatectomy is a result of reduced pancreatic secretion of digestive enzymes, hormones, and electrolytes (especially bicarbonate). The primary clinical features of EPI result from fat malabsorption, secondary to decreased lipase quantity and activity in the lumen of the small bowel. The consequences of fat malabsorption specifically include risk for essential fatty acid (EFA) deficiency and fat-soluble vitamin deficiency in addition to fecal energy loss. Loss of pancreatic bicarbonate secretion results in incomplete alkalization of the duodenal lumen, the consequences of which include impaired pancreatic enzyme activity, and potentially adverse effects on vitamin B_{12} digestion and absorption [12]. Other nutrients at risk for malabsorption related to impaired bicarbonate secretion and duodenal alkalinization may include calcium, magnesium, iron, zinc, and selenium. Zinc is a cofactor in EFA metabolism, and zinc and EFA deficiency may manifest similarly.

Steatorrhea and malnutrition are often the most striking symptoms of EPI, frequently accompanied by gas, bloating, or abdominal distension. Decline in growth trends, suboptimal weight gain, and weight loss can be observed [13]. Patients may have biochemical evidence of EPI prior to manifestation of clinical features [14]. Given the number of nutrients at risk for deficiency, the clinical consequences are numerous and can be subtle or profound, with the degree of malabsorption and duration of deficiency potential risk factors for deficiency states and presentation. The potential nutritional consequences of EPI are summarized in Table 12.1.

Diagnosis

Testing for EPI may be performed through direct or indirect methods. Currently, direct measures of exocrine pancreatic function are either invasive or lack standardization; thus, indirect methods are more commonly used for practical diagnosis. Direct pancreatic stimulation testing can measure bicarbonate output, pancreatic enzyme output, or both and has been standardized by the Dreiling tube method [15, 16]. Endoscopic pancreatic stimulation testing has been standardized in adults but not in pediatrics.

The gold standard for indirect measurement of pancreatic function is the coefficient of fat absorption (CFA), obtained by a 72-h fecal fat collection concurrent to a 3-day dietary intake record, with recommended amounts of dietary fat intake for the study and analyzed by the gravimetric method. The more commonly utilized indirect method of screening for EPI is the fecal elastase monoclonal assay[17]. Elastase is secreted by the pancreas, binds to bile acids, and is not degraded in the digestive tract. This test was validated in patients with cystic fibrosis. While there is universal agreement that >500 ug/g stool is normal and that <15 ug/g stool is abnormal, dif-

Table 12.1 Exocrine pancreatic insufficiency: indirect surrogate nutritional markers

Nutrient	Functions	How/what to measure clinically	Deficiency	Toxicity[a]
Vitamin A and the carotenoids	Vision, gene expression, reproduction, growth, immune function, bone health	Serum retinol [μmol/L], expressed in relationship to retinol binding protein and to transthyretin (normal ratio 1:1:1) Should also measure retinyl esters [% of total retinol] Esters in fasting state are concerning for potential toxicity	Vision, impaired dark adaptation, xerophthalmia, Bitot's spots, corneal xerosis	Birth defects (1st trimester supplementation)
			Hematological: anemia	Risk for hepatitis, hepatic fibrosis
			Immune: increased susceptibility to measles and risk for diarrheal diseases, infant mortality	Bone mineral loss and increased risk for fracture
				Headaches; increased intracranial pressure
Vitamin D	Intestinal absorption of calcium and phosphorous, cellular function, immune function	Serum 25 [OH] vitamin D Measured in ng/mL and nmol/L. Serum levels may relate to clinically important outcomes Deficiency <20 ng/mL (<50 nmol/L) Insufficiency: <21–29 ng/mL (52.5–72.5 nmol/L) Optimal range: > 30–99 ng/mL (75–247.5 nmol/L) Risk for toxicity: >100 ng/mL (>250 nmol/L)	Bone health	Polyuria, polydipsia; hypercalciuria; tissue calcification; nephrolithiasis; impaired renal function
			Immune function	
			Increased risk for certain cancers	
Vitamin E	Antioxidant, CNS functions	Serum alpha tocopherol and gamma tocopherol serum Recommended to obtain fasting labs and to express as a function of total cholesterol or to total lipids (functional compartment)[b]	Peripheral neuropathy; spinocerebellar ataxia; myopathy; retinopathy; RBC fragility	Potentially hemorrhagic toxicity and diminished blood coagulation and also vitamin K deficiency

Vitamin K	Coenzyme for blood coagulation and bone metabolism	Serum PIVKA-II (*p*rotein expressed *i*n the absence of *v*itamin *K*), *currently unavailable*	Easy bruising; prolonged bleeding. Decreased bone mineralization	No known toxicity
		Percent undercarboxylated osteocalcin, bone marker; research tool		
		Prothrombin time (PT)/INR: currently the most commonly used tool. Liver disease may complicate interpretation. Factor V is not related to vitamin K status		
Vitamin B_{12}	Coenzyme for 1-methyl metabolism, essential for normal hematological and neurological function	Serum vitamin B_{12} and methylmalonic acid; high MMA is suggestive of B_{12} deficiency Deficiency can be masked with folate supplementation Elevated serum levels of B_{12} can be observed with: Increased intake/supplementation Renal disease Liver disease Bone marrow disease Cancer	Glossitis	No known toxicity
			Megaloblastic anemia	
			Atrophic gastritis	
			Myelopathy and neuropathy; dementia can be irreversible	
Essential fatty acids	2 essential fatty acids: linoleic acid (LA; omega or n6) Alpha linolenic acid (ALA; omega or n3)	Fatty acid profile Levels of LA, ALA expressed as mol% or μmol/L; triene/tetraene Zinc is a cofactor in the metabolic pathway	Alopecia	Not known; balance of dietary fats may influence inflammation
			Bruising	
			Gingival bleeds	
			Seborrhea	
			Impaired growth, short stature	

Otten et al. [23]
Ross et al. [24]
Rifai et al. [25]
[a]Primarily from supplementation
[b]Huang et al. [26]

ferent labs cite different cutoff points of 100 and 200 ug/g stool. The test is highly sensitive and specific (98% and 80%, respectively), though its sensitivity is lower in patients with mild EPI. Fecal elastase testing can detect decline in exocrine pancreatic function prior to the appearance of steatorrhea [18]. The monoclonal antibody test is preferred, as the monoclonal antibodies do not react with bacterial antigens or porcine-derived pancreatic enzyme supplements to yield false positives, as is the case with the polyclonal assay [19]. Fecal elastase testing may also be falsely positive due to dilution when stool is watery, so a formed sample is required for an accurate test.

Outside of the United States, the ^{13}C-mixed triglyceride breath test may be used to diagnose EPI. This test measures exhaled $^{13}CO_2$ as dietary triglycerides are hydrolyzed by pancreatic lipase. The accuracy of this test may be affected by the rate of gastric emptying, mucosal absorption of CO_2, and other factors [17].

Recommended Screening for EPI

The incidence and prevalence of EPI after pancreatectomy in patients with hyperinsulinism are not well defined. As such, screening for any patients who have had pancreatic resections may be reasonable. The frequency of surveillance labs has not been determined for this population of patients. Assessment of surrogate markers of nutritional status susceptible to EPI and fecal elastase screening may be reasonable approaches. We suggest screening if there are clinical symptoms, and in the asymptomatic patient who is at risk based on surgical intervention, with baseline screening prior to discharge and every 6–12 months thereafter.

Treatment

The main principle underlying treatment of EPI is to minimize energy and micronutrient losses in stool and to also prevent overcorrection/potential toxicity. At this time, there is insufficient data to support firm recommendations supporting biochemical evidence over clinical evidence when deciding to initiate therapy for EPI [6]. Pancreatic enzyme replacement therapy (PERT) is the mainstay of this approach. PERT is available in multiple forms, including delayed-release capsules, tablets, and as an in-line cartridge for tube feedings. PERT is generally dosed based on lipase units per kilogram of body weight per meal, with a maximum of 10,000 lipase units/kg of body weight per day. See Table 12.2 below for more general principles of PERT dosing. Despite taking PERT, fat-soluble vitamin supplementation may be necessary [20]. There is an upper limit to PERT dosage, above which the risk of fibrosing colonopathy increases [21]. Adding an acid blocker may enhance PERT efficacy [22]. The principle underlining PERT and vitamin supplementation is to prevent deficiency and avoid toxicity/adverse effects.

Table 12.2 Management of exocrine pancreatic insufficiency

Product	Details and dosing	Use/monitoring	Cautions/troubleshooting
Pancreatic enzyme replacement therapy (PERT)	Dosing is based on lipase units Two dosing modalities: 1. By grams of fat in the meal/formula feed (For infants and young children; also can be used for overnight supplemental enteral tube feeding) 2000–4000 lipase units/120 ml breastmilk/standard formula Increase as needed to 4000 lipase units/g fat ingested 2. By weight (in kg) a. Per meal; usually half as much with snacks b. By weight per day c. Age considerations <4 years of age: 1000 units lipase/kg/meal ≥4 years of age: 500 units lipase/kg/meal Dose adjustments: Increase up to 2000–2500 lipase units per kg per meal and not to exceed 10,000 lipase units per kg per day	Start at the lower end of the dose range and follow clinical signs and symptoms as well as indirect/nutritional surrogate markers; adjust accordingly For formula-fed infants and children as well as patients treated with supplemental enteral tube feeding, non-enteric-coated products may be preferable and can be added to feeds. Clogging of feeding tubes can occur. Alternatively, PERT can be given at the beginning and toward the end of tube feeding Timing enzymes at the beginning of a meal is generally recommended. Doses can be divided for meals lasting >20 min	PERT does not improve malabsorption of carbohydrates PERT has a shelf life and may be temperature sensitive PERT should not be chewed, as oral ulcers may occur Exceeding the maximal dose (2500 lipase units/kg/meal or 10,000 lipase units/kg/d) may increase risk for fibrosing colonopathy Other variables involved in fat absorption may include GI motility, pH, and enzyme efficacy; small bowel bacterial overgrowth Acid blockers may enhance efficacy of PERT
Enteral in-line feeding cartridge (EFIC)	Intended for liquid nutrition primarily as a continuous feed Contains bacteriophage-derived liprotamase adhered to inert beads Triglycerides are lysed to 2 free fatty acids and a monoglyceride	Each EFIC device can process 500 ml of fluid EFIC can be connected in serial to proceed 1000 ml of formula	EFIC filters could clog with high fiber formulas

Sinaasappel et al. [27]
Cystic Fibrosis Foundation et al. [28]
Sermet-Gaudelus et al. [29]

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Chapter 13
Feeding Problems in Congenital Hyperinsulinism

Caroline Hall and Indraneel Banerjee

Introduction

Congenital hyperinsulinism (HI) is a rare and complex disease of hypoglycemia in children due to excessive and dysregulated insulin secretion from the pancreas. HI is associated with a high prevalence of adverse neurodevelopment, occurring in a third to a half of patients affected. The cornerstone of clinical management of HI is prompt recognition and correction of hypoglycemia, which prevents and ameliorates the risk of neuroglycopenia on the developing brain.

Feeding is an essential activity for all children, providing them with nutrition and preventing hypoglycemia. Feeding is a pleasurable and satisfying experience for parents, encouraging parent-child bonding and oromotor development. It is not surprising that adequate feeding is a key part of the clinical strategy to prevent hypoglycemia in HI.

Feeding behavior is often abnormal in patients with HI; feeding problems in varying proportions are commonly associated with HI and are more frequent in those with greater disease severity. Feeding difficulties including problems with sucking, swallowing, vomiting, and food refusal have been reported in up to one third of children with HI at diagnosis [17]. A significant majority of infants may require feeding support through the use of nasogastric tube feeding (75%), and 93% may require anti-reflux medication for gastroesophageal reflux. Feeding problems may persist up to 12 months after diagnosis in more severe cases, suggesting a continuing and tenacious problem with no easy solution (Fig. 13.1). It is important to address feeding problems to improve the well-being of the child and family with HI.

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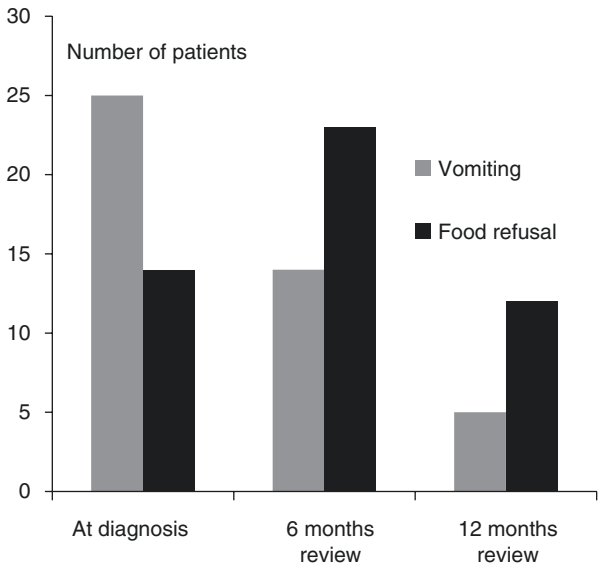

Fig. 13.1 Vomiting and food refusal are present at the time of diagnosis of HI and may persist in follow-up assessment, suggesting that the main components of feeding problems are long term. (Figure adapted from Banerjee I et al., Front Endocrinol 2016)

Normal Infant Feeding Milestones

Feeding a newborn baby is an instinctive first step for a mother. Although an entirely natural process in normal children, successful feeding involves complex coordination of the suck-swallow-breathe mechanism [1], processes that develop from reflex behaviors in the postnatal period prior to the influence of higher cortical control [12].

The development of effective feeding skills does not occur in isolation but is part of the baby's overall development incorporating physical, sensory, and social skills. Effective feeding is also dependent on and affected by environmental factors. There is increasing recognition of the importance of early relationships on developing effective feeding patterns, linked to positive outcomes for babies and children [2].

Normal infant feeding starts at birth with early reflexive behaviors: rooting and sucking, progressing in the first 2 years to self-feeding and acceptance of a wide range of textures within a normal mealtime routine. Disruption of these complex and coordinated processes can be detrimental to the development and establishment of effective feeding and may contribute to aversive feeding patterns persisting well into mid-childhood.

Disruption to Feeding Milestones: Causes

A number of medical conditions in the neonatal period have been correlated with food refusal behaviors, for example, prematurity. Disruption of feeding development may be due to illness and clinical management in intensive care such as

intubation and ventilation. Recurrent exposures to unpleasant sensory stimuli and frequent use of feeding tubes may impede the natural evolution of feeding behavior [9]. These early negative experiences can significantly alter the infant's facial/oral sensitivity and thus early feeding experiences; it is reported that nasogastric tube feeding over periods exceeding 3 weeks may be particularly deleterious [32]. In children with significant early-life adversity, feeding in later life may continue to be problematic. However, in many children, feeding recovery occurs with illness resolution and re-engagement of social, emotional, and sensory stimuli. An optimistic outcome is not always observed in patients with extreme prematurity and prolonged ventilation. Likewise feeding problems can be persistent in infants who undergo cardiac surgery and have prolonged postoperative recovery periods [29].

Analogous to patients with neonatal illnesses, feeding problems are also common in children with HI; in both conditions, severity of disease is a major determinant of feeding problems. In both conditions, feeding issues prolong the duration of hospital stay, which can in turn further compound and reinforce aversive feeding patterns. It is not clear if clinical circumstances, the pathophysiology of disease, or treatment choices in HI make feeding success particularly resistant to standard feeding interventions than other conditions. It remains the case that feeding problems in HI cause considerable stress and anxiety for parents and clinicians [7].

Presentation of Feeding Problems in HI

The true incidence of feeding problems in HI is not known, but parents and families often list feeding as a major problem, a stumbling block to successful management of HI at home. In a relatively large prospective cohort, the incidence of feeding problems was present in a third, with preponderance in those with greater severity [17]. This observation correlates with a food aversion incidence of 45% in children from another cohort, the majority of who were treated by subtotal pancreatectomy for diffuse HI [7]. In the former cohort, patients with significant neurodevelopmental delay in whom abnormal swallow and feeding difficulties have greater preponderance were excluded, thereby limiting the true prevalence. Thus feeding problems in HI are likely to be more pervasive than reported.

Feeding problems often start at the point of diagnosis when infants presenting with HI are admitted to the hospital and treated with intravenous fluids to stabilize plasma glucose levels. Depending on the severity of HI, as well as any other concomitant illness, intravenous fluids may be continued for an extended period of time and prioritized over oral feeding, which may take time to build up.

In early life, vomiting is the predominating symptom with 93% of infants being affected [17]. Gradually interest in oral feeding deteriorates, with reduced acceptance progressing to overt food refusal behavior.

As a result of inadequate milk volumes secondary to feeding problems, nasogastric tube feeding is frequently required to supplement oral feeding. The most severe presentations may require gastrostomy tube insertion due to the persistence of

feeding problems extending beyond 6 months. The insertion of feeding tubes positioned for a long duration may not encourage oral feeding. However, feeding tubes ensure carbohydrate delivery and may be critical in preventing hypoglycemia-induced brain injury. Therefore, the insertion and maintenance of a feeding tube is often a trade-off between hypoglycemia prevention and exacerbation of feeding problems.

Feeding problems can also manifest at the time of weaning from liquid to solid food. Most children with severe hypoglycemia often have complex medical needs, which may delay initiation of weaning. During hospital stay, the timing of medications, tube feeding, ward rounds, and procedures such as blood sampling interfere with the normal mealtime experience of feeding. The timing of surgical procedures, particularly pancreatic surgery, can also disrupt suitable weaning. The postoperative period is characterized by periods without food or drink by mouth, which impede attempts to commence oral feeding. Recurrently disrupted oral feeding, pain associated with gastroesophageal reflux, and discomfort from abnormal gastrointestinal motility compound the problem. Sometimes it is not the initiation but the progression of weaning that is problematic. Even if full oral feeding is achieved, it is not uncommon to have poor texture progression and restriction of the range of foods accepted by the child.

Perspectives on Feeding Problem Causation

Feeding problems associated with HI are complex and multifactorial. Although not typically described in patients with HI, a large proportion is expected to have some degree of behavioral etiology. It is well recognized that children with feeding problems usually present with coexisting medical, behavioral, psychological, and developmental problems [26] with 48–85% having two or more such conditions at the same time [19], suggesting a complex interplay of contributory factors. While we acknowledge multifactorial causation, it is often impossible to clearly delineate factors impacting on feeding; it is not surprising that the overlapping nature of the problem makes management complex and challenging.

Medical:

- HI disease severity may play a causal role in feeding problems [17]. Feeding problems have greater association with mutations in the ATP-sensitive potassium channel genes *ABCC8* and *KCNJ11*, acting as potential surrogate markers of disease severity. Importantly, there is clear reduction of aversive feeding patterns after improvement of disease severity, implying a role for the disease process in the pathophysiology of feeding problems.
- The link between HI severity and feeding problems is recognized but not explained. One possibility is that excessive endogenous insulin secretion may have a detrimental effect on feeding centers in the hypothalamus. Insulin and insulin receptors are present in the rodent hypothalamus [24], leading to the

speculation of similar neural insulin pathways in human brains. The finding of such pathways may explain the existence of a brain-pancreatic axis [3], modulating appetite control and food interest in several clinical scenarios [8, 35] including HI.

- Diazoxide, the first-line treatment for HI [14], has a bitter aftertaste [22], which may contribute to the suppression of appetite. However, diazoxide treatment per se has not been confirmed to suppress feeding in HI [17], and there is no evidence from studies published from different centers that feeding problems are directly attributable to diazoxide dose and duration. Therefore, the rationale to delay diazoxide to prevent feeding problems if hyperinsulinism is proven is unfounded. Delaying the introduction of diazoxide could potentially increase the reliance on high-concentration dextrose delivered through central venous catheters and the introduction of octreotide, usually a second-line drug, administered by subcutaneous or intravenous routes and complicated by major side effects such as hepatitis [15]. Further, a significant proportion of children with HI respond successfully to diazoxide and are transient in duration [16, 34], a group in which feeding problems are less likely to occur. Therefore, individual adverse feeding impact aside, diazoxide treatment should not be deferred.
- Ghrelin is a gut hormone that stimulates appetite through its effects on specific areas of the brain [36]. In contrast to endogenous insulin, ghrelin has negative correlation with activation of the hypothalamus. Although ghrelin levels have not been investigated in HI, it is possible that opposing actions of ghrelin and insulin are important for appetite regulation in HI. In the context of another state of hyperinsulinism mediated by gastric bypass surgery for severe obesity, ghrelin secretion to food appears to be altered and possibly reduced [30], implying similar insulin-ghrelin dynamics may occur in HI.
- Although there is scant published evidence, gastroesophageal reflux is considered common in children with HI and often treated with medications that reduce gastric acid secretion and increase gastric motility [17]. Gastroesophageal reflux is more likely in those with hypoglycemic brain injury in keeping with similar associations in children with neurological disease [33].

Environmental:

- Initial stabilization of hypoglycemia in HI often relies on continuous intravenous fluids comprising of concentrated dextrose solutions, creating an immediate disruption to the normal hunger drive. Once glycemic stability is achieved, enteral feeding is commenced. Most infants are acutely ill at this time and rarely take to oral feeding seamlessly. To ensure adequate enteral carbohydrate intake, nasogastric feeding is frequently required. In the initial phases, nasogastric feeding is continuous as tolerance to feeds is better with continuous than with intermittent bolus feeds. Although gastric tolerance is better, continuous feeds disrupt normal hunger drive required for the establishment of feeding. Length of time on intravenous fluids and upward titration of enteral feeds can be highly variable and dependent on the individual and on the severity of disease. The greater the feeding disruption, the longer the time taken to re-establish feeds.

- Once full enteral feeding is established, it is not uncommon for children to have episodes of infections, central venous catheter insertion, and surgery, causing further disruption in the form of multiple periods of non-oral feeding.
- The consequence of continuous feeding and disrupted hunger drive is diminished feeding cues. If such disruption continues over prolonged periods of time, the normal feedback loop between hunger, satiety, and feeding urge is extinguished.
- Tube feeding is a useful tool to provide calories to prevent hypoglycemia but may discourage oral feeding and prevent satisfactory feeding progress. Some centers rely on nasogastric and gastrostomy tube feeding to deliver glucose reliably, particularly overnight. Although tube feeding is not recommended for long durations, this may be the only feasible way to achieve satisfactory glycemic status and thereby prevent brain damage. On a more optimistic note, the evidence that nasogastric tube insertion is the primary cause for feeding problems is meager. Although there is some evidence of prolonged nasogastric tube feeding impacting on feeding development, the correlation in patients with HI is less clear [17]. While a strategy to reduce reliance on nasogastric tube feeding is reasonable, zealous avoidance of nasogastric feeding support cannot always be justified. In the short term, nasogastric tube top-up may be considered in the early stages when assessing treatment options and response.
- Hospitals are "sanitized" environments which do not replicate the smell of cooking and food at home. Hedonic food behavior, partly mediated through olfactory stimulation, is an important trigger for orexigenic hypothalamic pathways [27]; it is conceivable that bland environments downregulate and desensitize the olfactory-hypothalamic loop, adding to feeding problems. In very preterm babies, introduction of smell and taste of milk prior to milk feeds improved milk tolerance [18], an observation that could be valuable to the treatment of feeding problems in HI infants.

Developmental:

- Prolonged periods of hospitalization are not conducive to normal development, including the development of coordination to suck feed. Without regular practice, reliance on reflexive neonatal sucking behavior is not sufficient to generate and sustain interest in feeding [28].
- Infants often experience periods of prolonged bed rest without being handled during feeds, and without the opportunity to develop and practice movements against gravity, leading to poor overall postural tone. Lack of movements against gravity and handling during normal feed times leads to missed oral and facial stimulation through normal hand-mouth play. Additionally, lack of varied sensory stimuli to the hands within the clinical environment may reduce an infant's understanding of texture established through hand exploration and hand-mouth play, thus impacting on sensory development of feeding.
- Infants with HI are subject to unnatural and sometimes painful sensory experiences, e.g., passing nasogastric tubes, application and removal of adhesives on the face, and frequent heel-prick blood testing. These negative experiences are

counterproductive to the normal pattern of neonatal development relying on positive experiential learning [21].

Psychosocial:

- Feeding in the newborn period is an instinctive process that allows the baby to bond with the mother in a way that exceeds all other opportunities. Illness and hospitalization due to HI denies the mother this unique opportunity, fracturing early bonding possibilities. Undermining of parental bonding and responsibility leads to parental anxiety, helplessness, and guilt. Many mothers are unable to breastfeed, affecting their mental health and predisposing them to postpartum depression [20].
- Feeding in hospitals where parents cannot be present for all oral feed attempts is often a responsibility for nurses, who are time restricted and are unable to offer verbal, physical, or psychological stimulation to enhance the feeding experience. While parents quickly learn and respond to their infant's cues, preferred feeding technique and position, nursing practices can vary and be confusing to the baby.
- The medicalization of feeding to "treat" hypoglycemia distorts the normal function of feeding and parental attitude to feeding. The focus rapidly shifts from a fulfilling and enjoyable opportunity to that of an anxiety-provoking ritual that seeks only to normalize glucose levels. It is not surprising that parents describe living with HI "one feed at a time."

Treatment Strategies

Feeding problems in HI continue to persist despite improvement in standards of medical management. Earlier focus had targeted physical illness factors [11], with optimal medical management expected to improve feeding practices. However, the notion that feeding problems are wholly secondary to physical illness is simplistic and unhelpful to provide holistic treatment options. Monotherapy with drugs such as cyproheptadine [31] which stimulate appetite does not ameliorate feeding problems; approaches targeted at restoration of disrupted developmental processes yield more sustainable results, although such strategies are time-consuming and rely on gradual "relearning" of feeding behavior. A treatment plan should consider feeding strategies that are individualized, acceptable, and rational while minimizing disruption and discomfort. An early approach is preferred to prevent feeding problems [4, 5].

Historically, infant feeding within hospital settings has been dependent on a scheduled interval model, with feeds being offered within a timed, volume-driven routine. Within this model, emphasis is placed on completing feeds and achieving set volumes irrespective of infant feeding behaviors. Similar practices in HI patients are likely to compound feeding problems; a need for a behavior-focused feeding plan is required to achieve gradual and sustained benefit.

Recent research in preterm and ill infants recommends responsive feeding strategies [10], although the current published evidence remains scant [13]. Nonetheless, it is reasonable to allow babies to develop feeding skills at their own pace, gradually building on the mutual pleasurable experiences of the child and parents [6].

As the roots of feeding problems are multifactorial, treatment strategies covering medical, developmental, and psychosocial domains are required. Thus management needs to be addressed within a multidisciplinary context around the child and family, involving expert HI medical teams, specialist nurses, dietitians, speech and language therapists, and clinical psychologists. Treatment strategies are best individualized to the child, akin to strategies utilized in neonatal dysphagia [25].

Feeding problems tend to occur rapidly within the first few days and weeks of diagnosis of HI. In contrast, treatment response is slow and requires significant and sustained multidisciplinary input, highlighted in Fig. 13.1. It is important to maintain feeding strategies, even if resolution does not seem imminent. Therefore a long-term strategy should be discussed and parents be made aware of an expected slow pace of improvement (Fig. 13.2).

Practical strategies to improve infant feeding should start right from the diagnosis of HI. Focus should be on feeding as a pleasurable experience with necessary support given to parents to help understand the nature of the problem. Although in the hospital, the infant's medical needs remain a priority, active feeding plans should be encouraged and discussed with the family. There is no one-size-fits-all approach to feeding problems as causation is multifactorial and individual to the patient. A range of potential causative factors should be identified and feeding strategies aimed at these factors developed in a clear and coherent feeding plan. In Table 13.1, we

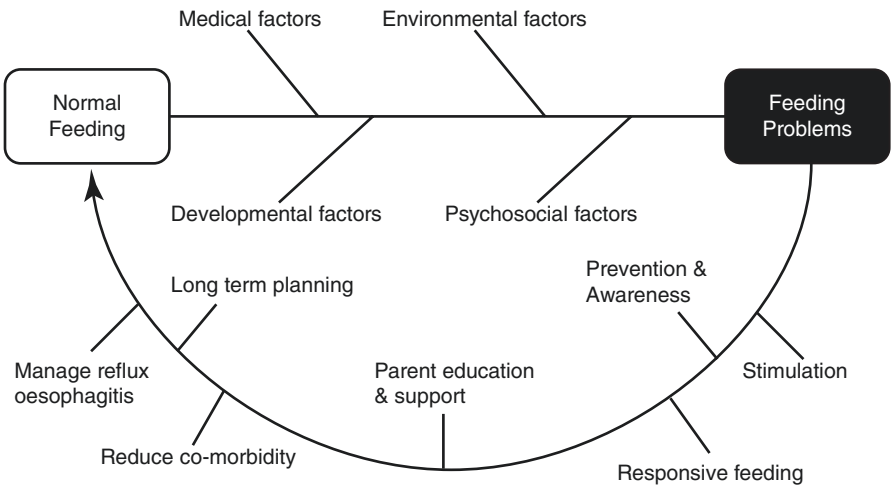

Fig. 13.2 Fish bone diagram of feeding problems in children with HI. Various factors impede and disrupt normal feeding over a relatively short period of time. A number of direct and indirect strategies have to be implemented to revert to normal feeding

Table. 13.1 A list of direct and indirect strategy choices to improve feeding practices in HI patients; this list is an overview and needs to be individualized by a multidisciplinary team of HI experts

Strategies prior to feed establishment	
Direct	**Indirect**
Provide appropriate stimulation through: Non-nutritive sucking Positive facial touch: encourage positive/pleasant oral experiences Skin-skin contact: encourage development of normal feed-seeking behaviors Mouth cares Appropriate positioning to enable normal oral experiences; achieve hand-mouth stimulation during nasogastric tube feeds	Provide support to parents through: Emotional support: recognize the impact of disrupted feeding on normal bonding processes Education: recognize and respond to emerging feeding and stress cues Support to continue frequent and effective breast milk expression: discuss advice/plan, consider provision of appropriate hospital-grade breast pump
Strategies during feeding establishment	
Direct	**Indirect**
Ensure safety of swallow to reduce the risk of aspiration prior to commencing oral feeding trial if any comorbidity is likely Manage vomiting and gastroesophageal reflux: reduce impact of unpleasant sensory experiences Normalize feeding regime: allow to feed in response to emerging feeding cues Appropriate positioning to enable continued normal oral experiences: feed in flexion, allow normal hand-mouth stimulation Supplement oral feeding attempts: to reduce pressure/expectations on infant, allow appropriate responses to stress cues Consideration of early weaning where indicated/if extended length of stay: establish weaning within developmentally appropriate critical period, minimize impact of delayed weaning on later texture progression	Support expectations: recognize lengthy process to establish full oral feeding, support understanding of progress Empower parents to recognize their infant's cues/behavioral responses: help understand baby's stress responses and know when to stop offering oral food Education: early involvement in nasogastric feeding to include parents within feeding process Education: recognize continuum of normal/abnormal feeding, manage and prevent feed-related parental anxiety Planning: consider early gastrostomy insertion if suspecting longer-term feeding problems, reduce negative oral sensory experiences

have described a list of the timing and types of interventions commonly utilized in such a plan.

Feeding plans should extend beyond the duration of hospital stay as feeding problems are likely to continue when the child is discharged home. For children with persistent feeding problems, it is likely that parents will require ongoing access to support and advice from the multidisciplinary team in the period after discharge from the hospital. Where possible, drop-in sessions in feeding clinics could be considered. Long-distance specialist advice, either by telephone contact or by electronic communication from the HI center, may be required with concomitant input from local services and resources.

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Chapter 14
Neurodevelopmental Outcomes

Katherine Lord and Diva D. De León-Crutchlow

Introduction

Neurological damage is a well-known consequence of hypoglycemia. In children with hyperinsulinism (HI), plasma ketone levels are suppressed during hypoglycemia, making them particularly vulnerable to hypoglycemia-induced brain damage. This insult leads to long-term sequela of developmental delays, learning disabilities, and epilepsy. Importantly, neurological dysfunction occurs in both transient and congenital forms of hyperinsulinism [1]. Given the high risk of neurological damage, children with HI should have periodic developmental assessments and be quickly referred for treatment if abnormalities are found.

Pathophysiology

Glucose is the primary fuel used by the brain for cellular metabolism. The brain has minimal glycogen stores and is dependent on a steady source of glucose from the circulation to maintain normal function, accounting for more than one-half of total glucose consumption. During periods of fasting, the ketone bodies, beta-hydroxybutyrate and acetoacetate, can be utilized as alternative energy sources [2]. In animal studies, lactate, pyruvate, amino acids, and free fatty acids have also been shown to support cerebral metabolism during the newborn period [3].

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The developing brain is more vulnerable to neurological injury from hypoglycemia. This vulnerability results from the important role that glucose plays in brain development. Growth in brain volume during infancy and childhood coincides with dramatic increases in cerebral glucose usage [4]. By the end of the first decade of life, glucose utilization by the brain is double that of an adult. Interruption of the brain's primary energy source during this crucial period has severe implications. Studies have shown that children with diabetes mellitus who experienced severe hypoglycemia had smaller brain volumes compared to those who did not [5].

Hypoglycemia results in both gray and white matter damage. In 1967, Anderson examined the brains of six severely hypoglycemic infants and found widespread neuronal injury in multiple regions of the brain [6]. Subsequently, Larroche demonstrated periventricular leukomalacia in infants who died from hypoglycemia [7]. More recently, neuroradiology has confirmed these pathologic findings. A study of 35 term infants with severe symptomatic hypoglycemia found white matter abnormalities on MRI in 94% of the infants [8]. Additionally, the MRI findings correlated with developmental outcomes.

Children with HI are more vulnerable to neurologic injury during hypoglycemia than children with other hypoglycemic disorders, because they are unable to generate ketone bodies, depriving the brain of a crucial alternative fuel. Infants with perinatal hypoxic ischemic injury may carry even additional risk of neurologic damage from hypoglycemia. Studies show worse outcomes in anoxic animals exposed to hypoglycemia compared to those who remain normoglycemic [9]. Therefore, infants with hypoxic ischemic encephalopathy and perinatal stress HI may be at highest risk for poor neurologic outcomes.

Outcomes

The risk of poor neurological outcomes in children with HI has long been recognized. In 1971, Harken et al. found that six out of ten infants with severe hypoglycemia requiring pancreatectomy had "significant retardation of neurological development" [10]. Thomas's 1977 review paper summarized the 84 cases of hypoglycemic infants who underwent pancreatectomy since 1935 and reported that "more than half were regarded as mentally retarded" [11]. In the subsequent decades, larger and more rigorous studies from multiple centers confirmed the high prevalence of neurological deficits in the HI population (Table 14.1).

In 2001, Menni et al. described the neurological outcomes of 90 infants with HI, 63 of whom were treated surgically and 27 medically [12]. Twenty-six percent of subjects had intermediate to severe psychomotor delay, and those that required surgery were more likely to have severe delays compared to those treated medically. Steinkrauss et al. found similar results in a 2005 study consisting of 68 children, with 31% subjects of scoring low to very low on a developmental assessment tool [13]. Children treated surgically were more likely to score in the "very low" range.

Other studies show even higher rates of neurological deficits. A 2003 retrospective study from Germany of 114 children with HI found that 44% had psychomotor or mental retardation and 26% epilepsy [14]. In 2017, Ludwig et al. published a prospective study of 60 German patients with HI who underwent standardized psychometric testing [15]. Forty-seven percent had developmental delays with motor delays being the most common, followed by speech delays.

In 2013, Lord et al. reported on the neurodevelopmental outcomes of 121 individuals with surgically treated HI [16]. Neurobehavioral problems were reported in 48% of the study population with psychiatric/behavioral problems and speech delays being the most common abnormalities (Table 14.2). Twenty-seven percent of subjects scored abnormally on developmental and behavioral screening tests. The study also divided the cohort into those diagnosed before 2004 and those diagnosed after 2004. Surprisingly, between the two groups, there were no differences in the

Table 14.1 Major studies of neurocognitive outcomes in individuals with hyperinsulinism

Year published	Reference #	Patient cohort (years treated)	Country	# of subjects by treatment type	Neurodevelopmental deficits (%)	Seizures (%)
2001	[12]	1982–1998	France	63 surgical 27 medical	26	18
2003	[14]	1975–2002	Germany	65 surgical 49 medical	44	26
2003	[19]	1972–1998	Australia	30 surgical 25 medical	45	29
2005	[13]	1980–2000	USA	35 surgical 25 medical 7 transient	31	N/A
2013	[16]	1960–2008	USA	121 surgical	48	13
2017	[15]	2008–2013[a]	Germany	22 surgical 38 medical	47	N/A
2017	[18]	2013–2016[a]	Denmark Russia	25 surgical 50 medical	47	20

[a]Recruited

Table 14.2 Prevalence of reported neurobehavioral abnormalities

Type	Individuals with HI (%) [16]	USA population (%) [20–22]
Psychiatric/behavioral	21	13
Speech delay	18	8
Learning disability	16	8
Seizures	13	1
Physical disability	11	5
ADHD	10	7
Autism	2	0.5

proportion with a reported neurobehavioral problem or scores on the screening assessments. This finding suggests that the neurological insult occurs in the first several days of life before diagnosis and treatment, and thus, even infants with focal HI who can be cured of the disease are at risk if diagnosed late.

Abnormal neurological outcomes are not solely limited to children with congenital forms of HI. Studies indicate that those with transient HI are at risk of developmental delays as well. In the study by Steinkrauss et al., 43% of the transient HI subgroup scored in the low to very low range on their assessment tool [13]. In 2013, Avatapalle et al. compared the neurodevelopmental outcomes of 33 children with permanent HI to 34 with transient HI [1]. Overall, 39% of the children had abnormal development. The proportion with abnormal development in subjects with transient HI (30%) was not statistical different from the proportion in those with permanent HI (47%). These results speak to importance of screening all children with HI, regardless of type, for developmental delays.

Risk Factors

The risk factors for neurocognitive deficits in the HI population remain poorly defined. As described above, two studies found higher rates of developmental delays in individuals treated surgically as compared to those treated medically [12, 13]. These findings are likely a reflection of the severity of the hypoglycemia in children that require surgery and not an indication of the treatment itself increasing risk. Other factors examined include age at presentation, genotype, histology, and time to treatment, but the studies found either negative or conflicting results [1, 15, 17–19]. For example, Avatapalle et al. reported that abnormal development was associated with presentation before 7 days of life [1]. However, two other large studies found no association between abnormal development and age at presentation [15, 17]. In the absence of identifiable risk factors for neurological deficits, all children with HI require developmental screening.

Assessment and Intervention

Given the increased risk of neurocognitive deficits in children with HI, early identification and treatment is essential. All children with HI should have periodic developmental assessments (Fig. 14.1) and, if abnormalities are identified, be quickly referred for therapy. Unfortunately, despite the high risk of abnormal development, children with HI are not being appropriately screened. Lord et al. reported that only 24% of individuals in their study had undergone formal developmental assessment [16].

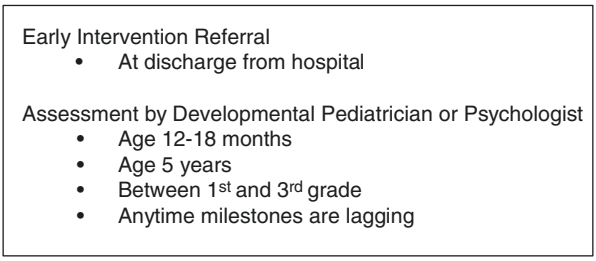

Fig. 14.1 Recommended developmental screening

Conclusions

Despite significant advancements in the field over the past several decades, neurocognitive deficits remain a cause of significant morbidity for the HI population. While published studies are mostly retrospective, include a small number of subjects, and have not been consistent in terms of the neurodevelopmental assessment tools, the frequency of neurodevelopmental deficits are surprisingly similar across the major HI centers and independent of the mode of therapy. Importantly, children with both transient and congenital forms of HI are at risk of developmental delays, learning disabilities, and seizures. Appropriate developmental screening and early referral for intervention is essential to improve long-term neurological outcomes for children with hyperinsulinism.

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