Chapter 1
Approach to the Diagnosis of Neonates and Infants with Persistent Hypoglycemia

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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, acyl-carnitine 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 anti-immune 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 auto-nomic 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 investiga-tors 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 sur-gery, 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 ongo-ing 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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