Hypoglycemia

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Key Points

- Hypoglycemia disorders in children are rare but may have severe consequences if they are unrecognized or inappropriately managed.
- Evaluation for hypoglycemia disorders is recommended for:
  - Neonates with plasma glucose <60 mg/dL after the first 48 h of life
  - Infants and young children if plasma glucose concentrations are documented to be <60 mg/dL on laboratory quality assays
  - Older children and adolescent with documented Whipple's triad (symptoms/signs of hypoglycemia, a documented low plasma glucose, and relief of signs/symptoms when plasma glucose is restored to normal)
- The therapeutic plasma glucose goal for neonates, infants, and children with a hypoglycemia disorder is >70 mg/dL

30.1 Introduction and Background

Hypoglycemia is a medical emergency that may result in seizures, permanent brain damage, or even sudden death. Hypoglycemia can be the presenting sign of a large list of pathologies, and therefore it is necessary to have a comprehensive and systematic strategy for diagnosis and therapy. This chapter presents an approach to disorders of hypoglycemia based on the metabolic and endocrine systems involved in successful adaptation to fasting. This "fasting systems" approach takes advantage of the fact that almost all of the hypoglycemia problems in infants and children involve fasting. Since the integrity of these fasting systems is reflected in plasma levels of major fuels and counter-regulatory hormones at the time of hypoglycemia, the most important specimens for diagnosis are the ones obtained at the time of hypoglycemia, which is known as the "critical sample."

Within 1–2 h after birth, plasma glucose concentrations in newborns decrease to a nadir of 55–60 mg/dL and then steadily increase to reach a mean concentration of 80 mg/dL by 72 h of life [1]. Thus, the physiological plasma glucose range in neonates after the first 3 days of life is not different than for older children and adults (70–100 mg/dL). When plasma glucose decreases below this threshold, the glucose counter-regulatory systems are activated. A critical sample obtained when plasma glucose is <50 mg/dL reflects the metabolic response to hypoglycemia and allows the determination of the underlying cause of hypoglycemia.

30.2 Etiology

In infants and children, hypoglycemia, with few exceptions, is almost always fasting hypoglycemia. The physiology of normal successful fasting adaptation provides a useful framework that encompasses the diagnosis and treatment of potential hypoglycemia disorders [2].

Three metabolic systems regulate the physiologic response to fasting: (1) hepatic glycogenolysis, (2) hepatic gluconeogenesis, and (3) hepatic ketogenesis. These three metabolic systems are coordinated by the (4) endocrine system, which consists of suppression of insulin and production of counter-regulatory hormones that activate one or more of the three metabolic systems: glucagon (glycogenolysis), epinephrine (glycogenolysis, gluconeogenesis, ketogenesis, and suppression of insulin), cortisol (gluconeogenesis), and growth hormone (ketogenesis, via increased lipolysis) (Figs. 30.1 and 30.2).

The essential function of fasting adaptation is to maintain fuel supply to the brain, since the brain has no fuel stores of its own. As shown in

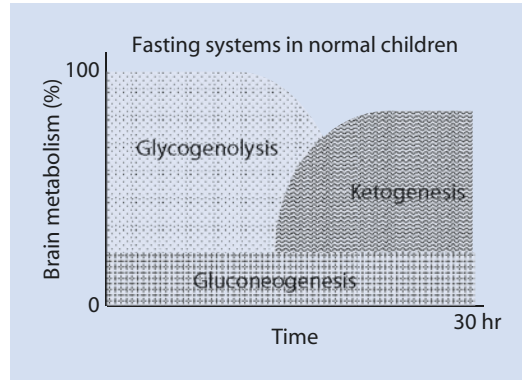

Fig. 30.1 Contribution of major fasting systems to brain metabolism over time in a typical normal infant. Note that glycogen stores are depleted by 8–12 h and that ketogenesis becomes the major fuel source for brain substrate by 24–36 h

Fig. 30.2 Hormonal regulation of fasting metabolic systems

Hormonal control of fasting systems

	Glycogenolysis	Gluconeo-genesis	Lipolysis	Ketogenesis
Insulin	–	–	–	–
Glucagon	+	+		
Epinephrine	+		+	+
Cortisol		+		
Growth hormone			+	

Fig. 30.3 Changes in plasma concentrations of major substrates during the course of fasting in a normal infant

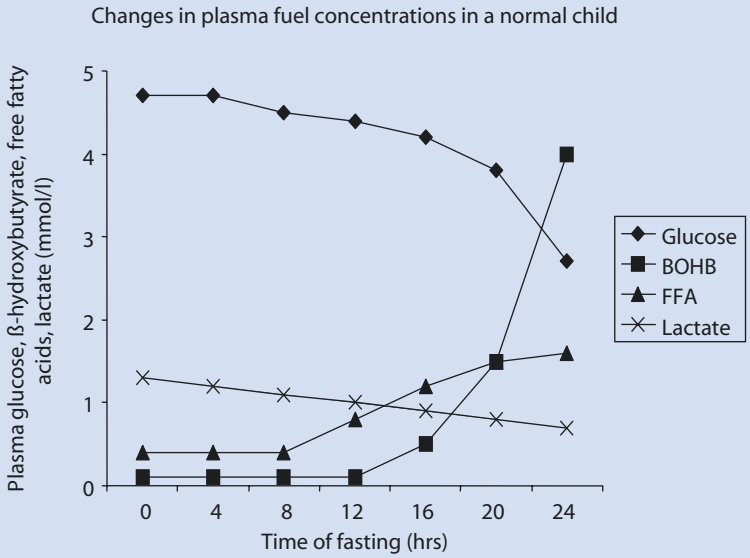

Fig. 30.1, early in fasting, glucose is the primary brain fuel and accounts for over 90% of total body oxygen consumption. Glucose is provided chiefly from hepatic glycogenolysis, supplemented by hepatic gluconeogenesis utilizing amino acids released by muscle protein turnover. After 12–16 h in normal infants (24–36 h in adults), glucose production declines, since the supply of liver glycogen is limited and the rate of gluconeogenesis from amino acids remains constant. At this time, a transition to fat as the major fuel for the body begins, with accelerated adipose tissue lipolysis and increased fatty acid oxidation in muscle and ketogenesis in liver. The brain cannot utilize fatty acids directly; therefore, ketones (β-hydroxybutyrate and acetoacetate) provide an alternative fat-derived fuel for the brain and permit a reduction of brain glucose consumption and the drain on essential muscle proteins. In late stages of fasting adaptation, fatty acid oxidation and ketone utilization account for 90% of total oxygen consumption.

The circulating levels of certain key fuels and hormones at the time of hypoglycemia reflect the integrity of these metabolic and hormonal systems of fasting. As shown in Fig. 30.3, in a normal infant fasted until hypoglycemia approaches at 24–30 h, i.e., at a plasma glucose of 50 mg/dL, (1) glycogen stores are exhausted (no glycemic response to glucagon) [3]; (2) gluconeogenic

substrate levels have declined modestly compared to the fed state (lactate <1.5 mM); (3) free fatty acids (FFA) have tripled (to 1.5–2.0 mM) and beta-hydroxybutyrate (BOHB), the major ketone, has risen 50–100-fold (to between 2 and 5 mM); and (4) insulin has declined to undetectable levels (<2 uU/mL). A comparison of these normal expected values to the values from a patient obtained at the "critical" time when fasting adaptation fails and the plasma glucose falls below 50 mg/dL provides the information "critical" to diagnosing the underlying cause.

30.3 Specific Disorders

30.3.1 Insulin-Mediated Hypoglycemia

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Insulin is the most important regulatory hormone, and dysregulated insulin secretion with failure to suppress insulin during fasting is the most common cause of persistent hypoglycemia in infants and children. This can be due to a genetic defect affecting the various steps involved in fuel-stimulated insulin secretion, or in the high-risk neonate precipitated by perinatal stress (IUGR, infants of mothers with preeclampsia, etc.), or an insulin-producing tumor in older children and adolescents; but the possibility of exogenous insulin administration or hypoglycemic agents should also be considered.

30.3.1.1 Congenital Monogenic Hyperinsulinism (HI) [4, 5]

Caused by dysregulated insulin secretion of the pancreatic beta cells, HI presents with severe hypoglycemia, very short fasting tolerance, and a high GIR requirement (>10 mg/kg/min), although more mild forms exist. Diagnosis is based on evidence of excessive insulin effects on the metabolic systems, as insulin levels may not be elevated even at the time of hypoglycemia. Laboratory results consistent with the diagnosis are suppressed BOHB and FFA and a positive glycemic response to glucagon (>30 mg/dL rise in glucose) [3]. Mutations in ten genes are known to cause HI (◘ Fig. 30.4). The most common genetic forms are discussed in more detail below.

Recessive loss-of-function mutations of K_{ATP}-channel genes (*ABCC8*, encoding SUR1, sulfonylurea receptor; *KCNJ11*, encoding Kir6.2, potassium ion pore) [6, 7]. K_{ATP}-HI features include severe neonatal onset, LGA birthweight, protein-induced hypoglycemia, diazoxide unresponsiveness, and very high glucose requirement (up to 20–30 mg/kg/min).

Dominant loss-of-function mutations of ABCC8 and KCNJ11 [8]. Unlike the severe disease often associated with recessive mutations of SUR1, hypoglycemia in these cases is milder and typically responsive to treatment with diazoxide, although some mutations do not respond. Dominant *ABCC8* and *KCNJ11* mutations are also associated with protein-induced hypoglycemia [9].

Focal hyperinsulinism [10, 11]. This is a consequence of focal loss of heterozygosity for maternal 11p and expression of a paternally transmitted recessive K_{ATP}-channel mutation (either *ABCC8* or *KCNJ11*). The phenotype is very similar to recessive diffuse K_{ATP}-channel HI, and focal HI accounts for 40–60% of cases of severe diazoxide-unresponsive HI [12]. Preoperative localization of the lesion by 18F-fluoro-L-DOPA PET scan and resection of the lesion can result in cure of the hyperinsulinism [13, 14].

Dominant gain-of-function mutations of glutamate dehydrogenase (*GLUD1*): hyperinsulinism/hyperammonemia (HI/HA) syndrome [15–17]. Children with HI/HA typically present within the first year of life but may not be diagnosed in the neonatal period as they have normal weight at birth and can fast longer than neonates with K_{ATP}-HI. HI/HA is characterized by fasting and protein-induced hypoglycemia which is diazoxide-responsive and a persistent mild hyperammonemia (plasma ammonium, 50–200 micromols/L). They also have increased rates of seizures (typically absence) and learning disabilities, which are unrelated to the hypoglycemia [18].

Dominant gain-of-function mutations of glucokinase (*GCK*) [19]. Gain-of-function mutations in *GCK* result in a lower glucose threshold for insulin release. Children with GCK-HI have hypoglycemia of variable degrees of severity and are not usually diazoxide-responsive [20].

Recessive loss-of-function mutations of HADH (encoding SCHAD, the mitochondrial enzyme short-chain 3-hydroxyaxyl-CoA dehydrogenase) [20, 21]. In addition to its function in fatty acid oxidation, in the pancreatic beta cell, SCHAD functions as a negative regulator of glutamate dehydrogenase.

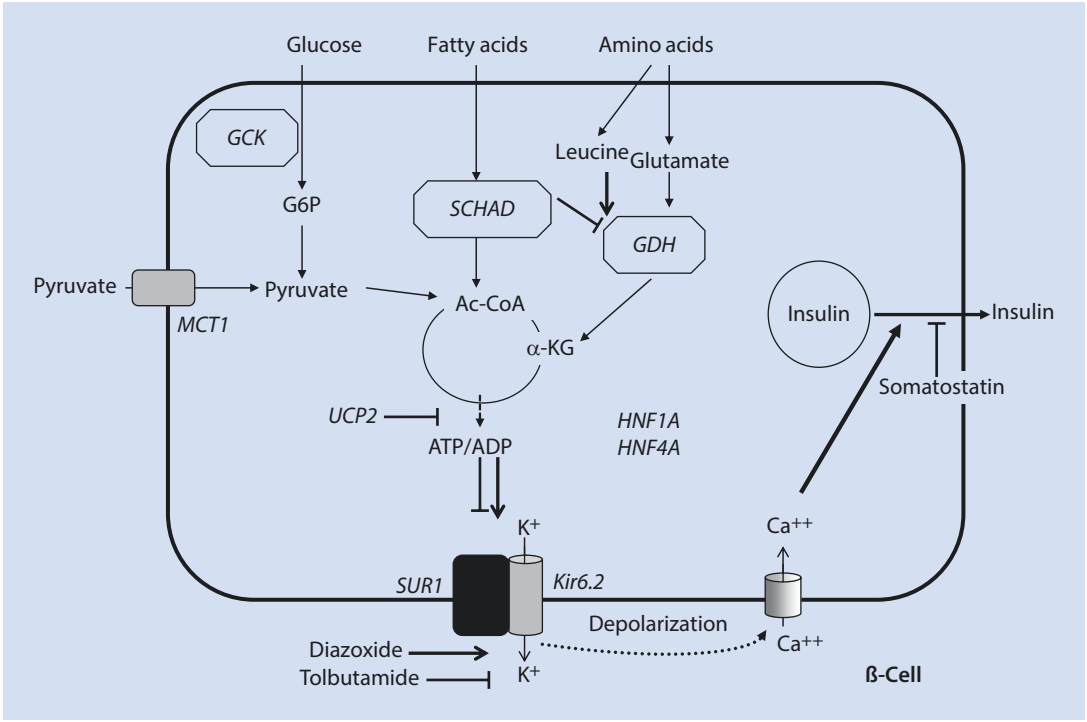

Fig. 30.4 Pathways of pancreatic beta-cell insulin secretion. Glucose and amino acids stimulate insulin secretion via an increase in ATP/ADP ratio which leads to inhibition of plasma membrane ATP-dependent potassium channels, membrane depolarization, and activation of voltage-gated calcium channels with the subsequent influx of calcium triggering insulin exocytosis. Note that leucine stimulates insulin secretion by allosteric activation of glutamate oxidation via glutamate dehydrogenase. Drugs may stimulate or inhibit insulin secretion by activation or inhibition of the plasma membrane ATP-sensitive potassium channel (e.g., diazoxide or tolbutamide) or by downstream inhibition of insulin release (e.g., octreotide). The known gene defects associated with hyperinsulinism are shown in italics. Abbreviations: GCK glucokinase, G6P glucose-6-phosphate, MCT1 monocarboxylate transporter 1, UCP2 uncoupling protein 2, SCHAD short-chain 3-OH acyl-coA dehydrogenase, Ac-CoA acetyl CoA, α-KG alpha-ketoglutarate, SUR1 sulfonylurea receptor 1, Kir6.2 potassium channel, GDH glutamate dehydrogenase, HNF1A hepatocyte nuclear factor 1A, HNF4A hepatocyte nuclear factor 4A

Thus, similar to HI/HA, SCHAD-HI presents with fasting and protein-induced hypoglycemia, which is responsive to diazoxide therapy, but without the hyperammonemia. The biochemical hallmark, in addition to markers of increased insulin action, is increased levels of 3-hydroxybutyryl-carnitine in plasma and increased levels of 3-hydroxyglutarate in urine.

Dominant loss-of-function mutations of hepatocyte nuclear factor 4 (HNF4A) and hepatocyte nuclear factor 1 (*HNF1A*) [22–24]. These transcription factors are well known causes of familial monogenic diabetes (MODY3 and MODY1, respectively). More recently, it has been recognized that the phenotype in individuals with these mutations is biphasic with neonatal hypoglycemia due to hyperinsulinism and diabetes later in life. The hyperinsulinism phase can last from a few weeks to up to 8 years. Children with these forms of HI respond well to diazoxide.

Dominant mutations of monocarboxylate transporter 1 (MCT1, encoded by *SLC16A1*) [25, 26]. Mutations in the promoter region of *SLC16A*1 result in aberrant expression of MCT1 in the beta cells and cause a rare form of HI, which is triggered by exercise. Characterized by episodes of hypoglycemia at the time of anaerobic exercise, MCT1-HI has been primarily identified in the Finnish population. The degree of hypoglycemia in response to exercise is variable.

Dominant mutations of uncoupling protein 2 (*UCP2*) [27]. Loss-of-function mutations in *UCP2*, which encodes an inner mitochondrial membrane carrier, result in a diazoxide-responsive form of HI.

30.3.1.2 Transient Neonatal Hyperinsulinism

Infant of diabetic mother. Maternal hyperglycemia triggers insulin hypersecretion by the fetal pancreatic beta cells, resulting in larger birth weight and hypoglycemia due to hyperinsulinism that typically resolves in 2–3 days.

Perinatal stress-induced hyperinsulinism [28, 29]. It is associated with SGA birth weight, birth asphyxia, and maternal toxemia. The mechanism is unknown. It can be clinically indistinguishable from the monogenic forms with high glucose requirements to maintain euglycemia (up to 20–30 mg/kg/min) and is diazoxide-responsive. The age of resolution is typically a few weeks to up to 2–3 months.

30.3.1.3 Syndromic Hyperinsulinism

Hypoglycemia due to HI can be the presenting symptom in children with Beckwith-Wiedemann syndrome (BWS), an overgrowth syndrome due to genetic or epigenetic abnormalities in the imprinted region of chromosome 11p. The severity of the HI in BWS is variable; infants with paternal UPD11p-associated HI have a persistent and severe HI phenotype compared to transient hypoglycemia of BWS patients caused by other etiologies [30]. Other syndromes associated with HI include Turner syndrome, Kabuki syndrome and congenital disorders of glycosylation (CDG).

30.3.1.4 Insulinoma

These are typically benign islet cell tumors, which are rare in the pediatric population. After diagnostic testing confirms evidence of insulin excess, imaging should be performed to localize the lesion. Multiple modalities (MRI, endoscopic ultrasound) may be necessary given the difficulty in localization. Resection is curative. Genetic testing for multiple endocrine neoplasia type 1 (MEN1) should be done in any child with an insulinoma.

30.3.1.5 Munchausen by Proxy

Induced hypoglycemia by administration of either insulin or hypoglycemic agents should be considered in the differential of insulin-mediated hypoglycemia. The clinical presentation can be undistinguishable from endogenous forms of hyperinsulinism; however, the abrupt onset of hypoglycemia of unpredictable pattern in an otherwise healthy child may trigger further investigation.

30.3.2 Hormone Deficiencies (Isolated Cortisol and Growth Hormone Deficiencies) and Panhypopituitarism

Hypoglycemia from growth hormone deficiency occurs primarily during infancy and presents as ketotic hypoglycemia. However, in the neonate, features may mimic hyperinsulinism, including high glucose requirement, low FFA and BOHB and a glycemic response to glucagon. This diagnosis should be suspected in neonates with the phenotype of HI but who also have midline malformations, microphthalmia, micropenis or cholestatic liver disease. Low growth hormone and cortisol levels obtained at the time of hypoglycemia are not diagnostic and prior to starting hormone replacement, appropriate stimulation tests should be performed to confirm the diagnosis [31], in addition to a brain MRI. The hypoglycemia resolves with replacement of the missing hormones.

30.3.3 Disorders of Gluconeogenesis

The most common disorder of gluconeogenesis is glucose-6-phosphatase deficiency (type Ia and type Ib glycogen storage disease) [32] (◘ Fig. 30.5). Infants present after feedings are spaced out longer than 3–4 h with failure to thrive, protuberant abdomen, and hepatomegaly. Shunting of glucose-6-phosphate to alternative pathways leads to markedly elevated blood lactate, triglycerides, and uric acid. Administering glucagon after a feed results in increased lactate levels with no change in plasma glucose. Diagnosis is straightforward based on these characteristic biochemical abnormalities and can be confirmed by genetic testing. GSDIb patients also have cyclic neutropenia. Fasting beyond 3–4 h in infants or 4–6 h in older children or adults results in a life-threatening metabolic acidosis.

30.3.4 Glycogen Storage Disorders (GSD)

Glycogen storage disorders include glycogen synthase (0), debrancher (III), liver phosphorylase (VI), or phosphorylase kinase deficiencies (IX)

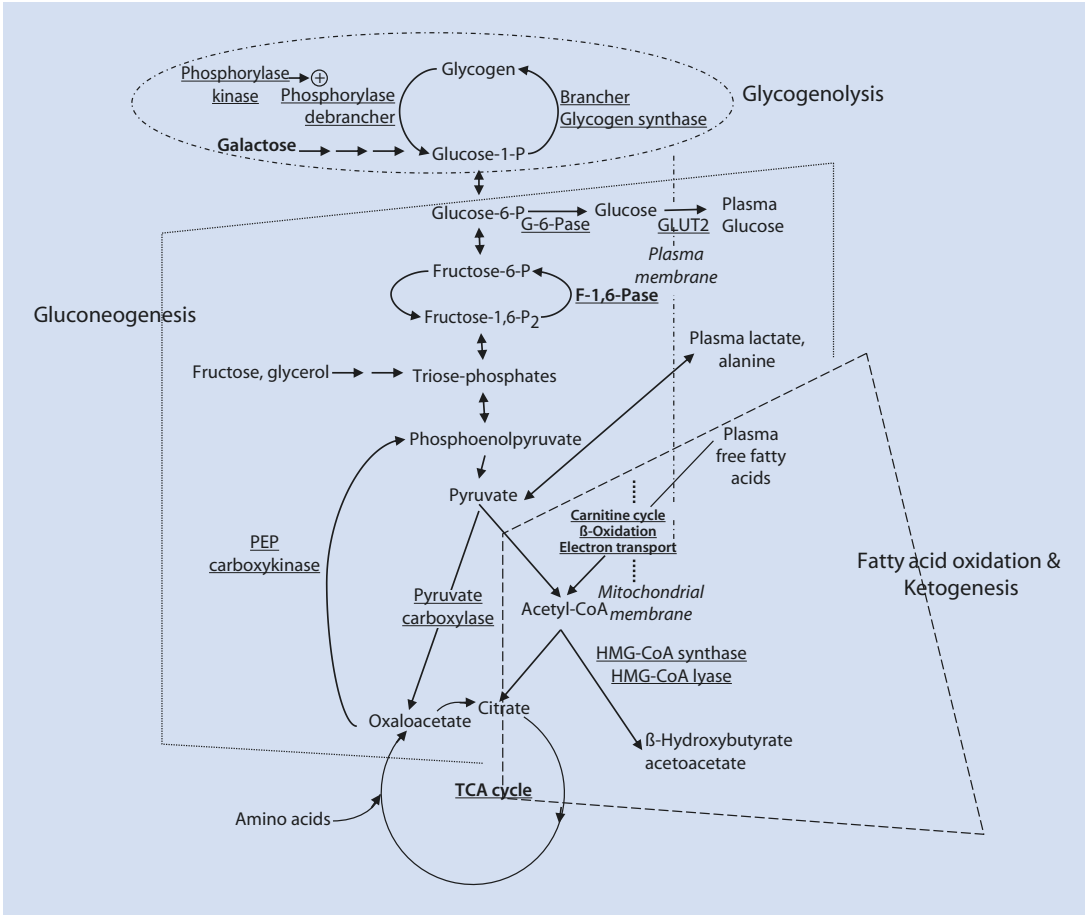

Fig. 30.5 Metabolic pathways of fasting adaptation. Sites of genetic defects are underlined

(Fig. 30.5). The hepatic GSDs are a heterogeneous group of disorders, which have varying severity of fasting hypoglycemia and hepatomegaly. GSD type III has the most severe presentation with failure to thrive, impressive hepatomegaly, hypertriglyceridemia, elevated liver transaminases, and cardiomyopathy. In contrast, GSD types VI and IX present with hypoglycemia following overnight fasting, milder hepatomegaly and growth retardation, and minimal metabolic and hepatic abnormalities. Liver biopsy as the gold standard for diagnosis has been replaced by genetic mutation testing.

30.3.5 Fatty Acid Oxidation Defects

The most common defect is due to medium-chain acyl-CoA dehydrogenase deficiency (MCAD) (Fig. 30.6) [33, 34]. These infants present with acute life-threatening episodes of illness, which are provoked by fasting stress beyond 8–14 h. Hypoketotic hypoglycemia, often with elevated liver transaminases, uric acid, or ammonia, but nearly normal levels of bicarbonate, is typical. The presentation mimics Reye syndrome [35]. Cardiac and skeletal muscle involvement occurs in the more complete defects. Most (but not all) can be diagnosed from plasma acyl-carnitine profiles by tandem mass spectrometry [36].

30.3.6 Ketotic Hypoglycemia

These are children, usually 1–4 years of age, with episodes of symptomatic fasting hypoglycemia, but do not have any identifiable metabolic or endocrine defect. In most instances, this can be thought of as merely a quantitative rather than a specific, qualitative abnormality of fasting

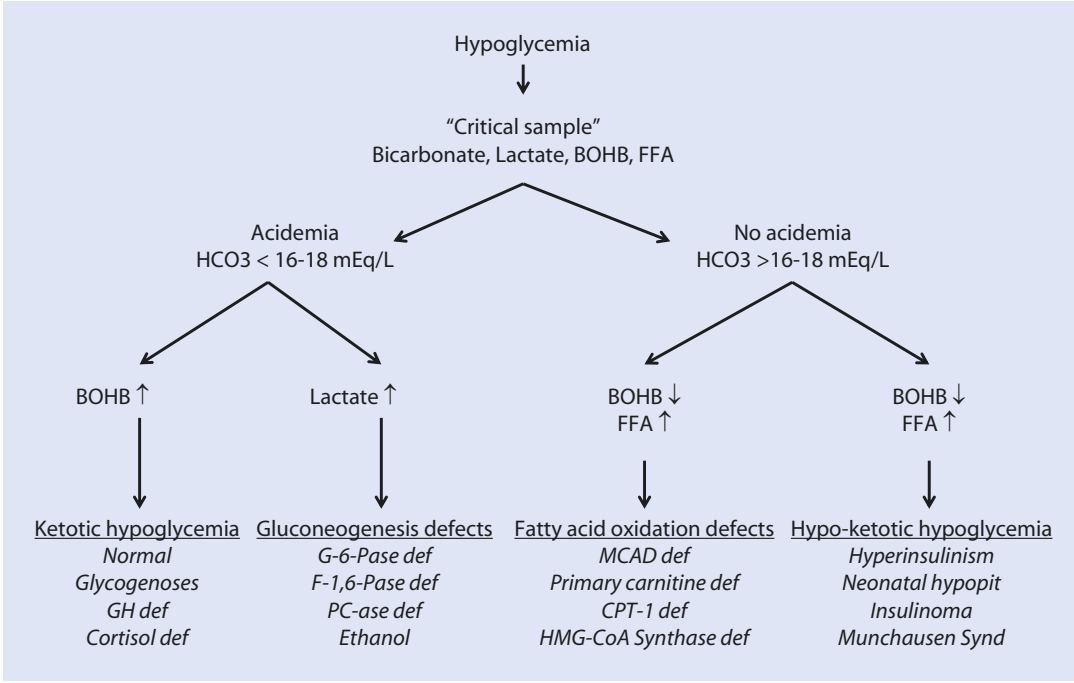

Fig. 30.6 Algorithm for diagnosis of hypoglycemia based on specimens obtained at time of fasting hypoglycemia

adaptation. These children may simply represent the lower end of the normal distribution of fasting tolerance. Note, however, that the features of abbreviated but otherwise normal fasting response are shared by the milder glycogenoses. Some cases of "ketotic hypoglycemia" have been found to have a mild GSD or inactivating mutations of monocarboxylate transporter 1 (MCT1) [37, 38].

30.3.7 Post-Fundoplication Hyperinsulinemic Hypoglycemia

This may occur in infants following fundoplication surgery for gastroesophageal reflux and may be severe enough to cause seizures and brain damage [39]. The mechanism involves rapid emptying of a meal into the small intestine, with early hyperglycemia followed by an exaggerated insulin surge and subsequent hypoglycemia, usually 1–2 h after the feed or meal. Increased secretion of the potent insulinotropic hormone, glucagon-like peptide-1 (GLP-1), by the small bowel after a meal may, at least in part, be responsible for the postprandial hyperinsulinemia [40]. The diagnosis is made by demonstration of the typical plasma glucose and insulin patterns in response to a mixed meal or formula tolerance test. Treatment includes feeds of longer duration, reduced high glycemic index foods, and inhibitors of gastric motility; the alpha glucosidase inhibitor, acarbose, may be useful as a means to delay digestion and absorption of complex carbohydrates [41].

30.4 Clinical Presentation

Older children and adults manifest Whipple's classic triad: neurogenic and neuroglycopenic symptoms/signs of hypoglycemia, a confirmed low plasma glucose value, and resolution of the symptoms/signs when the glucose level is restored to normal. However, neonates, infants, and younger children may not reliably demonstrate and/or lack the ability to communicate such symptoms. Hypoglycemic symptoms may be subtle and difficult to recognize in these age groups and include poor feeding, sweating, somnolence, apnea, and irritability. Myoclonic jerks and seizures may occur with severe hypoglycemia.

Hypoglycemia: the critical sample

	Hours	Lactate	BOHB	FFA	Response to glucagon
GSD I	2–4	↑	±↑	↑	–
GSD III	4–8	↓	↑	↑	–
F-1,6-pase	8–12	↑	↓	↑	–
MCAD	12–16	N	↓	↑	–
Hyperinsulinism	0–?	N	↓	↓	↑
Hypopituitarism	12–16	N	±↑	±↑	–

Fig. 30.7 Differential diagnosis of hypoglycemia disorders based on the "critical sample" obtained at a time of fasting hypoglycemia

30.5 Diagnostic Evaluation

Guidelines published by the Pediatric Endocrine Society detail which infants and children require evaluation for hypoglycemia disorders [42]. High-risk neonates (LGA, SGA, perinatal stress, maternal diabetes, those with congenital syndromes and family history of genetic hypoglycemia disorders) with plasma glucoses <60 mg/dL after the first 48 h of life should undergo additional evaluation prior to discharge. Evaluation should also occur in infants and young children if plasma glucose concentrations are documented to be <60 mg/dL on laboratory quality assays and in older children only if Whipple's triad is documented.

As outlined above, the integrity of the fasting systems can be evaluated by a critical sample obtained during a formal fasting test or during a spontaneous episode of hypoglycemia to establish the underlying cause of hypoglycemia (Fig. 30.7).

30.5.1 Formal Fasting Test Protocol

The success of the fasting test requires an experienced team of nurses and physicians, a blood-drawing IV, and rapid and accurate plasma glucose monitoring (N.B. Standard bedside glucose meters are not accurate enough). The fast usually begins with the 8 p.m. bedtime snack but may be adjusted later if very short fasting tolerance is suspected (consider monitoring for 24 h on usual diet before starting the fasting test to assess glucose stability). From the beginning of the fast, monitor plasma glucose and BOHB closely (e.g., every 3 h until <70 mg/dL, every 1 h until <60 mg/dL, then every 30 min to end). End the test at plasma glucose <50 mg/dL or when bedside measurement of BOHB indicates values >2.5 mM (or large urinary ketones in 2 subsequent occasions) or a specific duration has been reached (18 h if <1 month; 24 h if 1–12 months; 36 h if >1 year; 48–72 h for adolescents) or in case of any worrisome symptoms. At the end of the fast, obtain "critical sample" labs, which should include the basic metabolic panel, lactate, ammonia, insulin, c-peptide, BOHB, FFA, GH, cortisol, plasma acyl-carnitine profile, plasma total and free carnitine, and urinary organic acid profile. If considering hyperinsulinism (low BOHB during the fast), perform the glucagon stimulation test, 1 mg IV, to test liver glycogen reserve (at plasma glucose <50 mg/dL, appropriate glycemic response is <30 mg/dL within 15–30 min after glucagon administration; glycemic response above 30 mg/dL is consistent with hyperinsulinism) [3]. *Caution*: fasting tests are potentially hazardous provocative tests that, like the water deprivation test, must be closely monitored for patient safety. Sudden deaths during fasting tests have been reported in patients with fatty acid oxidation defects. Patients with fatty acid oxidation defects may develop life-threatening symptoms before plasma glucose levels fall below 60–65 mg/dL, including progressive lethargy, nausea, vomiting, or unexplained tachycardia; fasts should be terminated in these cases without waiting for plasma glucose to reach 50 mg/dL.

The serum bicarbonate from the critical sample allows segregation of the hypoglycemia disorders into two groups (Fig. 30.6), with and without acidemia (HCO3 < 16–18 vs. >16–18 mEq/L). The groups are then further divided based on the presence or absence of ketones and lactate:

1. Acidemia due to lactate accumulation typifies defects in hepatic gluconeogenesis: glucose-6-phosphatase deficiency (GSD type I), GLUT2 deficiency, fructose-1,6-diphosphatase deficiency, hereditary fructose intolerance, and ethanol ingestion.
2. Acidemia due to ketone accumulation typifies normal children, ketotic hypoglycemia (likely normal, but with shortened fasting tolerance), defects in glycogenolysis (GSD types 0, III, VI, IX), growth hormone and/or cortisol deficiencies, and ketone utilization defects.
3. No acidemia with ketones and free fatty acids both suppressed: congenital hyperinsulinism, prolonged neonatal hypoglycemia or "perinatal stress-induced" hyperinsulinism," insulinoma, exogenous administration of insulin or oral hypoglycemics, and neonatal hypopituitarism.
4. No acidemia with suppressed ketones but elevated free fatty acids: genetic defects in fatty acid oxidation and ketogenesis.

30.5.2 Other Tests

30.5.2.1 Plasma Acyl-Carnitine Profile

This test using tandem mass spectrometry measures the different fatty acids bound to carnitine to detect many (but not all) of the genetic defects in fatty acid oxidation. The method is now employed in most newborn screening programs using filter paper blood spots to screen for 20 or more inborn errors of metabolism. Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is particularly common (1/5000) and easily detected by this method [36].

30.5.2.2 Genetic Testing

Genetic testing for the most common forms of hyperinsulinism is available in commercial laboratories and should be obtained as soon as the diagnosis is confirmed. This is particularly important for infants with diazoxide-unresponsive hyperinsulinism as >90% of these cases will have a K_{ATP} channel defect and, therefore, an approximately 50% likelihood of having focal hyperinsulinism. Mutation screening is useful for glucose-6-phosphatase deficiency, since 80% of patients have one of five common mutations. Ninety percent of MCAD patients have the common A985G mutation. In addition, for children with repeated episodes of "ketotic hypoglycemia," genetic testing may identify those with an underlying defect in glycogenolysis or ketone utilization.

30.5.2.3 Cultured Cells

Lymphoblasts or fibroblasts are useful for diagnosis of some inborn errors of metabolism (such as fatty acid oxidation disorders) and as sources of DNA for mutation analysis for other genetic defects.

30.6 Outcomes

Severe or recurrent hypoglycemia results in neurologic dysfunction and, in rare cases, death. Therefore early recognition and treatment are essential to avoid neurologic damage and later risk of learning disabilities and epilepsy. Long-term studies of HI patients have found rates of neurodevelopmental abnormalities between 26% and 48% and epilepsy between 13% and 43% [43–45]. Despite a better understanding and recognition of the disease, individuals diagnosed with HI in the last 20 years have not demonstrated substantially improved outcomes compared to older individuals with HI [46]. This suggests that the neurologic insult from hypoglycemia occurs in the first several days of life and speaks to the importance of screening high-risk infants for hypoglycemia.

30.7 Treatment

The management of children with hypoglycemia should be guided by the following goals: (1) prevention of brain damage from recurrent hypoglycemia, (2) establishment of a specific diagnosis and therapy, and (3) encouragement of normal feeding behavior while assuring safe fasting tolerance.

To minimize the risk of brain damage, aim to maintain plasma glucose >70 mg/dL [42]. Ideally, treatment should maintain normoglycemia on a normal feeding schedule for age. It is advisable to periodically reassess efficacy of treatment in any form of hypoglycemia by a formal fasting study on treatment. Figure 30.8 depicts the management approach for children with hyperinsulinism and other causes of hypoglycemia.

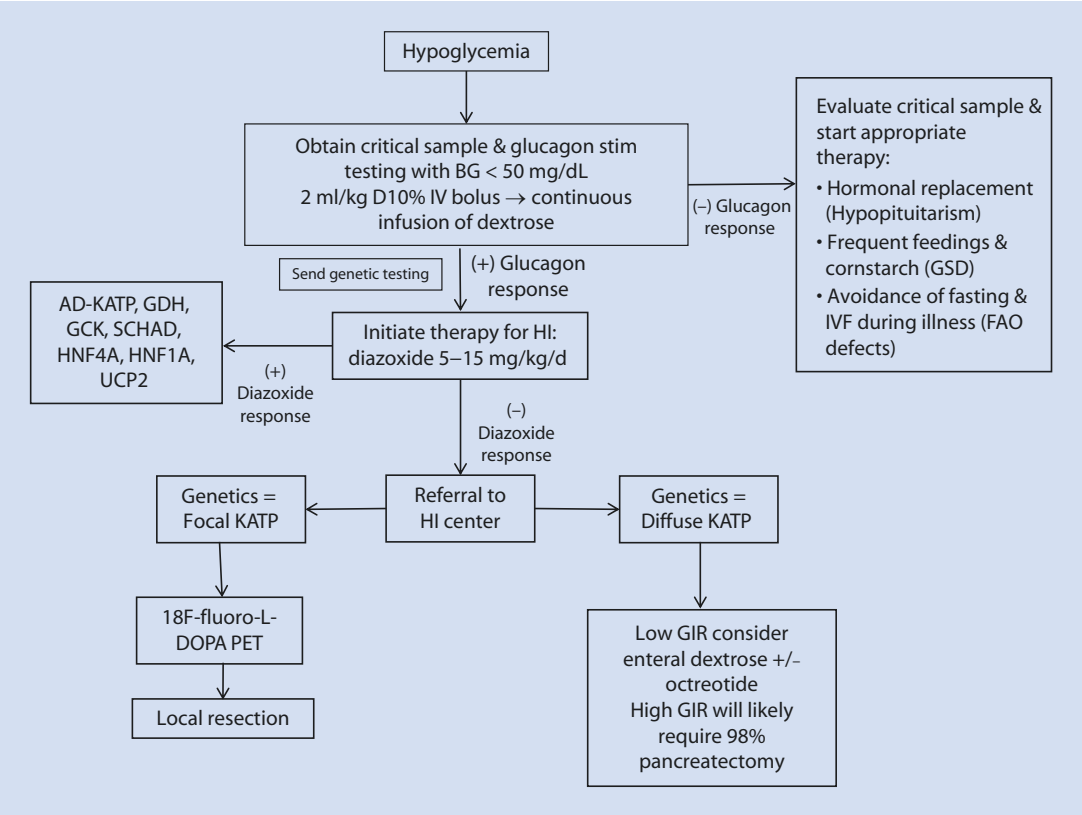

Fig. 30.8 Management approach to the child with hypoglycemia

30.7.1 Selected Drugs for Hypoglycemic Disorders

1. Dextrose (emergency Rx): IV 0.2 gm/kg bolus (2 mL/kg of D10), followed by D10 administered continuously. The glucose infusion rate is adjusted to maintain plasma glucoses greater than 70 mg/dL. Children with HI may need infusion rates of glucose as high as 20–30 mg/kg/min. Continuous dextrose (20%) can be given enterally as home management for GSD type I and certain forms of diazoxide-unresponsive HI.
2. Glucagon (emergency Rx only in case of insulin-induced hypoglycemia): 1 mg IM or IV. This can also be used as a continuous intravenous infusion in HI as a temporary measure to reduce glucose requirements, while the infant is in the hospital.
3. Diazoxide. 5–15 mg/kg/day divided into two oral doses for HI. The starting dose should be 5–10 mg/kg/day based on the severity, increasing to a maximum of 15 mg/kg/day if necessary. Fasting tolerance should be assessed after five full days of therapy (since the half-life is 24–36 h) [47]. The major side effects are fluid retention and hypertrichosis. Concomitant or preemptive use of a diuretic should be considered, especially in infants receiving intravenous fluids, to prevent congestive failure or pulmonary hypertension.
4. Octreotide: 5–15 mcg/kg/day SQ divided q 6–8 h. Tachyphylaxis is commonly encountered. Because of recent concerns about necrotizing enterocolitis in neonates treated with octreotide [48] and given the lack of a lasting response in most cases, we advise against its use in infants less than 2 months old. For older children who respond to octreotide, long-acting somatostatin analogs that can be dosed once a month are now available.
5. Cornstarch: 1.6 g/kg every 3–4 h for GSD type I [32]. This may also be used at bedtime for other forms of GSD or for young children with abbreviated fasting tolerance.

Case Study

A full-term baby boy with a birth weight of 4500 gm (LGA) was found to have a plasma glucose of 25 mg/dL shortly after birth. Due to persistent pre-feed plasma glucose values in the 30s, on DOL #2 he was started on dextrose containing IVF, which were subsequently weaned off over the next several days. His hypoglycemia was declared "resolved," and he was discharged home with no further evaluation. At 2 months of age, he had a generalized tonic clonic seizure and EMS was called. His plasma glucose was 30 mg/dL. He was admitted to the hospital where he was found to have persistent hypoglycemia. He underwent a fasting test, during which he fasted only 3 h with plasma glucoses above 50 mg/dL. His critical sample showed the following: glucose 45 mg/dL, HCO3 24 mmol/L, BOHB 0.1 mM, lactate 0.5 mmol/L, insulin 2 uU/mL, FFA 0.15 mmol/L, cortisol 18 mcg/dL, and GH 12 ng/mL. Glucagon 1 mg was given when his plasma glucose was 45 mg/dL and increased to 90 mg/dL by 20 min. He was diagnosed with hyperinsulinism and was started on diazoxide at a dose of 15 mg/kg/day. After 5 days, he continued to require a GIR of 16 mg/kg/min and could not be weaned off his IVF. Diazoxide was discontinued. Genetic testing of the HI genes had been sent on him and his parents and showed a paternally inherited autosomal recessive mutation of *ABCC8*. He underwent an 18F–fluoro-L-DOPA PET scan, which demonstrated focal uptake of the tracer in the tail of the pancreas. He was taken to surgery and underwent a 15% partial pancreatectomy after analysis of frozen samples confirmed focal HI histology. After recovery from surgery, he underwent another fasting test during which he was able to fast for 24 h with plasma glucose levels >70 mg/dL.

30.8 Summary

Hypoglycemia disorders are rare but have potentially severe consequences for children if unrecognized. An understanding of normal fasting adaption and a systematic approach to the interpretation of the critical sample allows for narrowing of the differential diagnosis and timely diagnosis and appropriate treatment.

Review Questions

1. A 9-month-old male presents to the emergency department with new onset seizures and a plasma glucose of 38 mg/dL. A critical sample obtained at presentation showed bicarbonate = 20 mmol/L, FFA = 0.82 mmol/L, BOHB = 0.95 mmol/L, plasma insulin = 3 uU/mL, lactate = 1 mmol/L, GH = 0.48 ng/mL, cortisol = 4.14 ug/dL, and ammonia = 120umol/L.

   What additional test would help establish the underlying cause of hypoglycemia?

   A. Arginine/clonidine GH stimulation test
   B. Fed glucagon stimulation test
   C. CRH stimulation test
   D. Glucagon stimulation test
   E. Both A and C

2. A 6-month-old female is referred for evaluation of poor growth and hypoglycemia. Laboratory testing ordered by the pediatrician showed a plasma glucose of 49 mg/dL, bicarbonate = 14 mmol/L, lactate = 6.8 mmol/L, AST = 120 U/L, ALT = 100 U/L, triglycerides = 800 mg/dL, and hemoglobin = 9 g/dL.

   The diagnosis is best confirmed by which of the following results?

   A. Following injection of glucagon 1 mg IV, the plasma glucose rises from 49 mg/dL to 80 mg/dL after 30 min.
   B. Following injection of glucagon 1 mg IV, the blood lactate rises from 6.8 mmol/L to 10 mmol/L after 20 min.
   C. Following ingestion of an oral protein supplement, 1.5 g/kg, the plasma glucose falls from 70 mg/dL to 40 mg/dL after 30 min.
   D. Following ingestion of oral glucose, 1.75 g/kg, the plasma glucose rises to 250 mg/dL at 1 h. and then falls to 35 mg/dL at 2 h.
   E. Following injection of galactose, 1 g/kg IV, the plasma glucose rises from 80 to 150 mg/dL after 30 min.

3. You are consulted to evaluate a 2-week-old male with persistent

hypoglycemia. He was born by emergency cesarean section due to non-reassuring fetal heart rate at 35 weeks of gestation and was SGA at birth. His initial plasma glucose was 10 mg/dL. He was on intravenous fluids with dextrose for 1 week and fortified formula every 3 h. Pre-feeding glucoses are now 55–60 mg/dL.

The most appropriate next step in the management of this infant is:

A. To initiate therapy with hydrocortisone 10 mg/m2/day.
B. No further evaluations are required since plasma glucose is now above 50 mg/dL.
C. To perform a diagnostic fasting test.
D. To recommend feeding the infant every 2 h.
E. To add cornstarch 1 g/kg to the formula.

Answers

1. (D) The findings of suppressed β-hydroxybutyrate and free fatty acids and a positive response to glucagon (> 30 mg/dL) at the time of hypoglycemia are diagnostic of hyperinsulinism. It is not unusual to find that insulin is not elevated in cases of hyperinsulinism; therefore, low plasma insulin at the time of hypoglycemia does not rule out the diagnosis. Accordingly, the diagnosis must often be based on the examination of other physiologic manifestations of excessive insulin secretion, such as suppression of glycogenolysis, lipolysis, and ketogenesis, which can be inferred by the finding of a glycemic response to glucagon and the suppression of plasma free fatty acids and β-hydroxybutyrate concentrations during hypoglycemia. The late presentation and the elevated ammonia are characteristic of GDH hyperinsulinism, or the hyperinsulinism hyperammonemia syndrome, caused by an activating mutation in *GLUD1*. Note that frequently GH and cortisol levels are not elevated in the critical sample in HI patients; also, except for the immediate postnatal period, deficiencies of these two hormones do not cause hypo-ketonemic, hypo-fatty acidemic hypoglycemia.
2. (B) The clinical picture of growth failure, hypoglycemia, hypertriglyceridemia, elevated liver enzymes, and lactic acidemia suggests glycogen storage disease type I (deficiency of glucose 6-phosphatase). The diagnosis can be confirmed by a fed glucagon stimulation test, which will show failure of glucose to rise and elevation of lactate as result of increased glycogenolysis.
3. (C) The finding of persistent hypoglycemia (beyond 2–3 days after birth) in this high-risk neonate suggests an ongoing problem with glucose regulation. The history suggests perinatal stress-induced hyperinsulinism that has not yet resolved. Prompt evaluation with a diagnostic fasting test will help determine the underlying cause and initiate appropriate therapy.

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