Review Article

Approach to hypoglycemia in infants and children

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Abstract: Hypoglycemia is a heterogeneous disorder with many different possible etiologies, including hyperinsulinism, glycogen storage disorders, fatty acid disorders, hormonal deficiencies, and metabolic defects, among others. This condition affects newborns to adolescents, with various approaches to diagnosis and management. This paper will review current literature on the history of hypoglycemia, current discussion on the definition of hypoglycemia, as well as etiologies, diagnosis, and management.

Keywords: Endocrinology; hypoglycemia; children

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Introduction

Hypoglycemia may be caused by various defective pathways in the production and metabolism of glucose, as well as defective pathways to maintain euglycemia. This review will discuss pertinent literature as it relates to the normal pathways for glucose utilization, history of hypoglycemia, select etiologies and approach to management.

Pathophysiology

Throughout gestation, increasing glucose requirements by the growing fetus lead to transport of glucose through the placenta. This is performed by facilitated diffusion as the primary source of energy through the family of glucose transporter proteins (GLUT), primarily glucose transporter type 1 (GLUT1) through a concentration gradient which favors the fetus (1-3). Fetal glucose is mostly provided by maternal glucose supply (1,4-6), while fetal insulin functions primarily for growth (7). Although uterine glucose uptake is regulated by maternal glucose, utero-placental glucose consumption is primarily regulated by fetal glucose levels (8). Fetal hepatic glycogen stores increase during the latter stages of gestation. Although the fetal pancreas matures throughout pregnancy, it maintains a relative immaturity to secrete glucagon and insulin and does not substantially change fetal glucose concentrations until the neonatal period (1). Plasma glucose levels are maintained at ~55–60 mg/dL after birth, and then increase to 70 mg/dL at approximately 2 days of life (9). A glucagon surge occurs shortly after birth to maintain glucose levels and then decreases, insulin levels decrease, and ketone production occurs along with gluconeogenesis. However, chronic hyperglycemia (as seen among infants of diabetic mothers) can lead to increased insulin secretion (1). The newborn period is reflected by a plasma glucose requirement of approximately 6 mg/kg/min, which changes relative to prematurity and increasing age (10). Premature or growth restricted infants may have reduced ability to maintain euglycemia, due to reduced glycogen stores, increased metabolic needs, or poor counter-regulatory response to hypoglycemia (11).

In response to feeding, glucose is absorbed through the gastrointestinal tract through glucose transporters, including but not limited to SGLT1 (Na^+/glucose co-transporter), glucose transporter type 2 (GLUT2), GLUT5 (fructose transporter), and also mediated by calcium and potassium channels (12,13). Regulatory physiologic processes are then activated, including increased plasma insulin levels, glycogen synthesis, and triglyceride synthesis. Gluconeogenesis, ketogenesis and lipolysis are inhibited, and there is relative increase in peripheral glucose uptake through glucose transporter type 4 (GLUT4) (10,14). Glucose supply to the brain is controlled by plasma glucose levels, GLUT1, and glucose transporter type 3 (GLUT3)

transporter proteins (6).

Conversely, as declining plasma glucose levels occur, insulin levels start to decrease at plasma glucose levels of approximately 80–85 mg/dL. Counter-regulatory glucagon and epinephrine pathways are elicited, which can stimulate hepatic glycogenolysis and gluconeogenesis, lipolysis, and ketogenesis; this may occur at plasma glucose levels as early as 68 mg/dL. Cortisol and growth hormone (GH) release then occur at even lower plasma glucose levels (14). Glycogenolysis is usually the first process to occur during hypoglycemia prior to gluconeogenesis and lipolysis while disorders of fatty acid oxidation and gluconeogenesis may manifest at a later age as feedings become less frequent (14).

As children grow, liver glycogen stores increase and fasting periods with available glucose can increase from 4 hours during early infancy up to 24 hours in older children (14).

Definition of hypoglycemia

Historically, neonatal hypoglycemia was only discernible through clinical symptoms including, but not limited to, lethargy, coma, and seizures. These clinical criteria determined the definition of clinically significant hypoglycemia (15,16). Many approaches have been utilized to clarify hypoglycemia, but one of the well-known early definitions among adults involved Whipple's triad, which states that one must have: (I) symptoms consistent with hypoglycemia; (II) low plasma glucose concentration; and (III) resolution of symptoms with normal plasma glucose levels. Utilizing this triad may become problematic in infants as they may not be able to communicate symptoms consistent with hypoglycemia and further testing may be necessary (11,15). With the advent of technologic advances, it became possible to discover etiologies of hypoglycemia and its counter-regulatory mechanisms. Generally, some main approaches to defining hypoglycemia have included: (I) hypoglycemia relative to presence of clinical manifestations; (II) using population data of values to determine a cutoff based on standard deviation; (III) hypoglycemia at which neurological function is impaired; and (IV) hypoglycemia at which physiologic metabolic and hormonal processes occur (16,17), but these approaches have been problematic for a myriad of reasons. This may suggest that hypoglycemia may be more of a continuum of hormonal abnormalities and clinical manifestations, and a single plasma glucose value has become difficult to associate with neurological outcome, as it could depend on the degree and duration of the hypoglycemia (11,16). In addition, a newborn infant may be asymptomatic, and these clinical symptoms could be attributed to other pathologic conditions (16). However, among older children and adolescents, utilizing Whipple's triad before undertaking an intervention may be reasonable (11).

Longstanding discussion and research continues in order to define clinical hypoglycemia. This can be defined as a plasma glucose level below 68 mg/dL, the cutoff glucose value for when counter-regulatory processes can occur (14). Furthermore, a plasma glucose level approximately at or below 50 mg/dL has been regarded as sufficient to undergo testing to define an etiology of hypoglycemia, as many counter-regulatory responses occur at this level (10,11,14). However, other studies and guidelines have proposed various plasma glucose cutoff values which could be associated with increased risk for long-term adverse outcomes (16). Official guidelines and others have noted that among infants who are symptomatic, plasma glucose level less than 50 mg/dL (<48 hours of life), and less than 60 mg/dL (>48 hours of life) should be evaluated. Additionally, among asymptomatic infants at risk, infants whose plasma glucose levels are less than 25 mg/dL (<4 hours of life), less than 35 mg/dL (4–24 hours of life), less than 50 mg/dL (24–48 hours of life), and less than 60 mg/dL (>48 hours of life) warrant intervention (5,18). Due to these diverse guidelines, available studies have investigated the long-term outcomes of hypoglycemia among patients utilizing a certain plasma glucose level. Some of these studies have noted that maintaining at-risk infants above a plasma glucose level of 47 and 45 mg/dL was not associated with neurologic deficits at follow-up (19,20). Moreover, results noted in various studies are not consistent and require further investigation for clarity (21-23).

Symptoms of hypoglycemia can occur through neuroglycopenic or autonomic pathways. Autonomic symptoms, which result in sympathetic activation, can include, but not limited to, tachycardia, anxiety, tremors, sweating, nausea/vomiting, and hypothermia. Neuroglycopenic symptoms due to effects of decreased glucose availability to the central nervous system involves manifestations such as headaches, lethargy, and motor/sensory/visual disturbance, among others (14). These symptoms, along with counter-regulatory responses, can be affected by clinical status, age, gender, and medication use, among others (24-26). With chronic hypoglycemia, blunted counter-regulatory responses may occur. This is termed hypoglycemia associated autonomic failure or, "hypoglycemia unawareness" and this should be identified and evaluated if this occurs (14,27).

Causes of hypoglycemia

Hyperinsulinism

Hyperinsulinism has been regarded as the most common cause of hypoglycemia during infancy. This condition typically occurs shortly after birth, although it can present later in infancy as feedings become less frequent.

This condition is manifested by inappropriate levels of insulin and c-peptide respective to the plasma glucose level, decreased levels of free fatty acids, beta-hydroxybutyrate (BOHB), and insulin growth factor binding protein 1 (IGF-BP1) (due to *IGF-BP1* gene transcription suppression by insulin). Another diagnostic test for hyperinsulinism is an increase in plasma glucose levels of greater than 30 mg/dL in response to glucagon administration during hypoglycemia. A glucose infusion rate above 6–8 mg/kg/min to maintain normoglycemia is typical of this condition. Hyperinsulinism can be classified into two types: transient and persistent forms.

Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) may have an underlying identifiable cause in about 50% of patients (28). Defects in K-ATP channels, which regulate insulin secretion from pancreatic beta cells, are the most frequent cause of permanent congenital hyperinsulinism and account for approximately 90% of all congenital hyperinsulinism cases. Defects in two genes, *ABCC8* (which encodes the SUR1 subunit of K-ATP channel) and *KCNJ11* (which encodes the Kir6.2 subunit of the K-ATP channel), can cause increased secretion of insulin. Diffuse forms may involve the inheritance of two autosomal recessive K-ATP mutations, whereas focal disease can involve certain cells possessing the inheritance of the paternal mutation and loss of the normal maternal allele (14).

K-ATP associated hyperinsulinism can be managed medically or surgically. Typical medical management begins with the administration of diazoxide. Other therapies can be considered, as discussed further. Diazoxide binds to the SUR1 subunit, causing opening of the K-ATP channels and inhibition of insulin secretion (9,29). Diffuse forms of hyperinsulinism due to autosomal recessive inactivating mutations of *ABCC8* or *KCNJ11* are not typically diazoxide responsive, whereas the dominant inactivating mutations are usually milder and diazoxide responsive (29,30). Diazoxide doses range from 5–20 mg/kg/day divided into three doses, although the lowest possible dose should be used to achieve euglycemia (29). Responses are usually seen within 48 hours after dose initiation. Other interventions should be considered if no response is seen after 5 days of therapy (31). Possible side effects include hypertrichosis, fluid retention (in some cases, chlorothiazide therapy may be necessary), gastrointestinal symptoms (nausea, vomiting), decreased IgG, and/or neutrophil concentrations (32,33).

Octreotide is a somatostatin analogue that inhibits insulin secretion, through decreased calcium transfer and insulin promoter gene activity, as well as affecting the K-ATP channel. This therapy can increase plasma glucose levels but its effectiveness may wane after 24–48 hours of therapy (34). Some side effects of octreotide include nausea, abdominal pain, long QT syndrome, necrotizing enterocolitis, hepatitis, and suppression of other hormones such as GH and thyroid stimulating hormone (TSH) (29,35,36).

Nifedipine is a calcium channel blocker and can inhibit insulin secretion. However, studies have not shown a very effective response and therefore its use has been generally limited in hyperinsulinism (29,37,38).

The mammalian target of rapamycin (mTOR) inhibitor is a possible downregulator of cellular growth, and could reduce beta cell proliferation, and therefore inhibit insulin production (29,34,39). Initial reports showed some promise among patients with hyperinsulinism who were unresponsive to diazoxide and octreotide therapy (40). Evidence has shown that the mTOR inhibitor has shown limited aid with achieving normal plasma glucose levels and reduced need for other adjunctive therapy in congenital hyperinsulinism (41). Additionally, lung, renal, and liver function, and mucocutaneous side effects must be monitored (42).

Other studies have shown that glucagon-like peptide 1 (GLP-1) receptor antagonists have been shown to increase glucose levels in K-ATP associated hyperinsulinism but use at this time is limited (43).

^{18}F-dihydroxyphenylalanine positron emission tomography (^{18}F-DOPA PET) imaging is available to localize lesions, as islet cells take in L-DOPA, and convert it to dopamine by DOPA carboxylase, which is present in pancreatic islets (9,14,29,35). Partial or near total pancreatectomy can be undertaken if medical therapy is not successful. However, there are some children who remain hypoglycemic despite a near total pancreatectomy. In these cases, medical therapy post surgery with diazoxide may be helpful. These hypoglycemia episodes have been shown to be milder and can be more intermittent with increasing age. A second attempt at surgery may be necessary (29,44). In patients who undergo near total pancreatectomy, it is important to monitor for hyperglycemia leading to diabetes

or exocrine pancreatic insufficiency (29,44,45).

Another form of hyperinsulinism is caused by activating mutation of the *GLUD1* gene, which encodes for glutamate dehydrogenase. The activating mutations cause exaggerated production of ATP, triggering insulin secretion independent of glucose levels and exacerbated by protein ingestion. There is also a conversion of glutamate to α ketoglutarate, producing ammonia. Decreased availability of glutamate in the liver can lead to defective urea synthesis as well (14). Therefore, the findings of hyperinsulinism coupled with increased ammonia levels, as well as hypoglycemia incited by protein intake, should prompt consideration of this diagnosis. The hyperinsulinism may be less severe than K-ATP mutation associated conditions and typically presents later in infancy. Clinical manifestations may be variable, ranging from altered mental status secondary to hypoglycemia in the early neonatal period to mild hypoglycemia presenting later in life (14). Treatment of this condition includes diazoxide, and dietary therapy (46,47).

Glucokinase regulates the conversion of glucose to glucose 6 phosphate, which in turn controls glucose metabolism (29,34). Activating mutations of the glucokinase gene may lead to a lower set-point for glucose induced insulin secretion, and may result in mild hypoglycemia (48). There may be a positive family history of hypoglycemia associated with this condition (14). Treatment with diazoxide therapy may not be effective and surgical treatment may be required (9,34,49).

Additionally, a mutation involving hepatocyte nuclear factor 4α (HNF4A), which is an important factor for beta cell development, can cause increased insulin secretion and neonatal hypoglycemia. This condition can be diazoxide responsive and transient. Conversely, inactivating glucokinase and *HNF4A* mutations can also cause monogenic diabetes (MODY2 and MODY1, respectively) (14,34).

A less common form of congenital hyperinsulinism has been shown to be caused by a dominant inactivating mutation in uncoupling protein 2 (*UPC2*), which increases glucose oxidation and increases insulin secretion. Those affected may or may not be diazoxide responsive (31,34,50,51).

Short chain 3-hydroxacyl-CoA dehydrogenase (SCHAD) is an enzyme involved with fatty acid oxidation. SCHAD mutations can dysregulate glutamate dehydrogenase enzyme function and result in hyperinsulinism, as this enzyme is present in the pancreas as well. There are typically no features of hyperammonemia. Diazoxide treatment has been shown to be effective (14,34).

Exercise induced hyperinsulinism can be associated with mutations in solute carrier family 16 member 1 (SLC16A1), which encodes the monocarboxylate transporter protein (9,29). This mutation can induce insulin secretion independent of the glucose level. These children may or may not respond to diazoxide therapy (34).

Insulinomas are pancreatic adenomas. These adenomas may be solitary or multiple and not commonly malignant (14,52). Supervised hypoglycemia fasting studies will display a clinical picture of hyperinsulinemic hypoglycemia. Surgery is usually the treatment modality of choice with adjunctive medical therapy such as diazoxide. Insulinomas typically display biochemical features of hyperinsulinism, a therefore imaging may be helpful to confirm the diagnosis. Various imaging approaches may be used. However, ultrasound, computed tomography (CT) scan and magnetic resonance imaging (MRI) may not be able to identify the tumor (14). Other imaging modalities such as F-DOPA PET, pancreatic arterial stimulation with calcium and venous insulin sampling, and/or intra-operative ultrasound are available for use. More recent imaging techniques have utilized ^{68}Ga-DOTATE PET/CT with some success (53). Children with insulinomas should be screened for multiple endocrine neoplasia type 1 (MEN1), which may have adenomas in the pituitary gland, parathyroid, and pancreas (14).

Hypoglycemia can also occur after gastrointestinal surgeries, such as Nissen fundoplication. This is noted to be due to excessive release of glucagon like peptide-1 (GLP-1) resulting in excessive insulin secretion. Hypoglycemia typically occurs post-prandially and can be aided by adapting dietary habits such as providing fat and protein with carbohydrates, or adding uncooked cornstarch or acarbose (alpha glucosidase inhibitor which slows carbohydrate digestion) (14). GLP-1 receptor antagonists have been used for treatment of post-prandial hypoglycemia caused by increased insulin secretion (54).

Hypoglycemia may also be associated with diabetes mellitus and its treatment. In this case, hypoglycemia may occur due to incorrect insulin administration, poor oral intake, or excessive exercise coupled with inaccurate insulin and carbohydrate intake. Emerging technologies are aiding the detection and possible prevention of this condition, including continuous glucose monitors (CGM). It is also important to rule out adrenal insufficiency if a child with type 1 diabetes has persistent hypoglycemia. Adrenal insufficiency can be associated with type 1 diabetes as cortisol deficiency has been associated with increased insulin sensitivity (14).

Other causes of hyperinsulinemic hypoglycemia can be drug induced (certain beta blockers, oral anti-hyperglycemics, antiviral or anti-arrhythmic medications) (32). Hyperinsulinism can also be associated with Beckwith Wiedemann syndrome, Kabuki syndrome, Costello syndrome, and Turner syndrome, among others (31,32,55).

Glycogen storage disease (GSD)

GSD encompass a subset of disorders that involve defects of enzymes that are involved with glucose transport, glycogen synthesis, and glycogenolysis. The following is information on GSD selected for discussion; all GSD are not described.

GSD type 0 (glycogen synthase deficiency)

This condition is marked by inhibition of the process that converts glucose into glycogen, caused by a mutation in the *GSY2* gene. Clinical characteristics include fasting hypoglycemia, ketosis, and no hepatomegaly. Lactic acidosis may also be seen. Post-prandial hyperglycemia may occur due to inability to store glycogen in the liver (56,57). Counter-regulatory hormone response is typically appropriate. Glucagon response in the fed state produces a glucose response but does not occur during fasting. Treatment can include frequent feeding regimens, uncooked cornstarch, and/or protein rich meals. Children should also be advised to avoid prolonged fasting (14).

GSD 1a and 1b (glucose-6-phosphatase deficiency)

GSD 1a (von Gierke disease) is caused by deficiency of glucose-6-phosphatase. This inhibits the conversion of glucose-6-phosphate to glucose, which can impair glycogenolysis and gluconeogenesis (14). These children typically have hypoglycemia, which can occur at birth but sometimes occur at 1–2 years of age. This is associated with hepatomegaly, metabolic acidosis, failure to thrive, hypertriglyceridemia/hypercholesterolemia (possibly causing xanthomas and pancreatitis), delayed puberty, among other symptoms (14,58). These children can also display hyperuricemia, due to increased production and decreased renal clearance. Renal complications can occur due to the deposition of glycogen, such as proteinuria and hypertension, among other symptoms (14). These children may or may not display typical symptoms of hypoglycemia, as their brain may have adapted to other sources of energy such as lactate, producing lactic acidosis. Additionally, they may have blunted counter-regulatory responses due to the chronic hypoglycemia, but hormone levels (such as GH and cortisol) are appropriately increased, along with a suppressed insulin level (14).

GSD 1b is caused by deficiency of transporter of glucose-6-phosphate. This condition is similar to the clinical manifestations of type 1a but also can exhibit neutrophil deficiency and chronic enteritis. Genetic testing can also be performed as well for these conditions. Treatment modalities to help hypoglycemia can include frequent or continuous feedings, and/or uncooked cornstarch (14). Typically, as plasma glucose is maintained within the normal range, the other abnormalities that are seen, such as hypertriglyceridemia, lactic acidosis, can improve, although adjunctive therapy may be undertaken (14).

GSD type 3 (amylo-1,6-glucosidase deficiency)

GSD type 3 exhibits an impaired ability to degrade glycogen, causing a partial defect in glycogenolysis. This can affect the muscle and liver, and children can have hepatomegaly, transaminitis, failure to thrive, fasting ketotic hypoglycemia, and hyperlipidemia. Myopathies and cardiac issues can occur as well, causing an elevated creatine kinase level. Hypoglycemia is usually not as severe as some other GSD, as children are still able to undergo gluconeogenesis. Studies have also shown reduced bone mineral density (59). Diagnosis can be made with genetic testing. Treatment modalities involve frequent feedings, and/or uncooked cornstarch. A high protein diet has been suggested, enhancing gluconeogenesis to maintain normal plasma glucose levels (14,60).

GSD type 6 (liver phosphorylase deficiency) and GSD type 9 (phosphorylase kinase deficiency)

GSD type 6 is caused by mutations involving the gene encoding for hepatic phosphorylase, which is required for glycogenolysis. GSD type 9 occurs from mutation arising from genes for phosphorylase kinase, which is required to activate phosphorylase, and ultimately glycogenolysis. These children present with less severe hypoglycemia, hepatomegaly, transaminitis, and growth failure. Lactic acidosis may be present and lipid levels may be elevated. Diagnosis can be confirmed by genetic testing. Treatment generally includes frequent feedings and intake of carbohydrate rich foods (14,61).

Congenital disorders of glycosylation (CDG)

This disorder is marked by a glycosylation defect and may present with various types and phenotypic features. CDG

type 1b involves a deficiency of phosphomannose isomerase and features hyperinsulinemic hypoglycemia. Those afflicted with this condition typically present with failure to thrive, enteropathy, and liver fibrosis (14,62,63). The hypoglycemia may not be evident due to the frequent feedings being given due to their gastrointestinal manifestations (62,63).

Galactosemia

This condition can be caused by various defects in metabolism of galactose. Galactose is formed (along with glucose) from lactose breakdown during energy utilization. The most common defect is galactose-1-phosphate uridyl transferase (GALT) deficiency (64,65). These patients may present with hypoglycemia, which may be post-prandial due to accumulation of galactose-1-phosphate. Other common manifestations include hepatomegaly, transaminitis, hyperbilirubinemia, cataracts, neurologic deficits, and increased urine amino acids (66). They also may have growth delays and ovarian failure (67,68). Newborn screening programs in the United States screen for this disorder. The newborn screen may measure levels of galactose, galactose-1-phosphate, and/or GALT enzyme activity, and differ according to location in which it is performed. However, newborn screening may also misclassify classic galactosemia due to other forms of galactosemia (69). Treatment includes avoidance of galactose (66).

Fructose intolerance

This disorder is marked by a deficiency of fructose-1-phosphate aldolase isoenzyme b, which inhibits gluconeogenesis through accumulation of fructose-1-phosphate. These children can present with hypoglycemia when fructose or sucrose is introduced into the diet. Additionally, they may have hepatomegaly, failure to thrive, hyperuricemia, and lactic acidosis. Diagnosis may be undertaken through genetic testing or through nuclear magnetic resonance spectroscopy. Therapy includes avoidance of dietary fructose, sucrose, and sorbitol, which can be successful in the management of the many clinical manifestations of the disease. Untreated fructose intolerance may lead to progressive renal and liver failure (14,70).

Fatty acid oxidation defects

Free fatty acid oxidation defects include medium chain acyl-CoA dehydrogenase (MCAD) deficiency, carnitine defect/deficiency, beta-oxidation defects, and fatty acid mobilization defects, among others. Hypoglycemia can occur after prolonged fasting or low carbohydrate diet. Additionally, these patients may manifest with low ketonemia, elevated free fatty acid levels, abnormal plasma acylcarnitine and urine organic acid levels, hepatomegaly, cardiac abnormalities, transaminitis, myopathy, or neurologic deficits (which may or may not resolve after hypoglycemia). Diagnosis can be made by liver tissue samples or gene sampling. Treatment includes a high carbohydrate diet to maintain euglycemia and to avoid prolonged fasting or stress induced states (such as illness or trauma). Additionally, carnitine supplementation can be used for specific fatty acid oxidation disorders (14,71).

GH deficiency and adrenal insufficiency

Cortisol and GH are important counter-regulatory hormones involved with hypoglycemia. GH is related to insulin resistance and increased lipolysis during prolonged fasting that could aid in euglycemia (14,72). Low GH values during hypoglycemia may be suggestive of this condition and further evaluation with a GH stimulation test may be indicated (14).

Inadequate cortisol production (due to primary or secondary adrenal insufficiency) can cause decreased gluconeogenesis causing hypoglycemia. Additional manifestations may include hypotension, weight loss, and fatigue. These symptoms may be more pronounced in younger children, or during times of illness or stress. These children have low cortisol responses to hypoglycemia and dynamic adrenocorticotropic hormone (ACTH) testing. Should a secondary adrenal insufficiency be identified, children should be imaged for brain abnormalities and screened and tested for other pituitary hormone deficiencies. It is also important to note that pan-hypopituitarism can present clinical picture similar to a stress induced hyperinsulinism (73).

Ketotic hypoglycemia

This condition typically presents during the toddler years, and is not as common after middle childhood (after 9–10 years of age). The exact specificities are not clear, as there does not seem to be obvious defects in metabolism but it is important to rule out other causes of hypoglycemia that can also produce ketosis (74). It is believed that limited hepatic

glycogen stores, coupled with limited glucose production, and possibly limited amino acid utilization may contribute to this disorder. Biochemical findings include low insulin levels, appropriate cortisol and GH levels, elevated free fatty acid and ketone levels, negative response to glucagon stimulation testing during fasting hypoglycemia, normal thyroid hormone levels, and reassuring metabolic panels which rule out other defects (including plasma acylcarnitine profile, urine organic acids, and serum amino acids). It is also important to exclude other conditions that may contribute to hypoglycemia such as metabolic defects, adrenal insufficiency, or GH deficiency. Treatment measures include avoidance of prolonged fasting, uncooked cornstarch at bedtime, and/or close monitoring of oral intake when in stressed states (such as illness) to avoid hypoglycemia (14).

Other possible causes of hypoglycemia

Fructose-1,6-bisphosphatase deficiency presents with a defect in gluconeogenesis from amino acids. This can result in hypoglycemia, failure to thrive, ketosis, lactic acidemia, hyperlipidemia, and increased uric acid levels. The findings of hepatomegaly may be variable. Genetic testing can be undertaken for diagnosis. Treatment includes frequent feedings and avoidance of prolonged fasting (14,75). Pyruvate carboxylase deficiency prevents a step-in gluconeogenesis. Clinical manifestations may include hypoglycemia (which is variable), hepatomegaly, lactic acidosis, and/or encephalopathy. Treatment includes frequent feeding and additional glucose support in times of illness (14). Phosphoenolpyruvate carboxykinase (PEPCK) deficiency affects gluconeogenesis and can cause hypoglycemia, failure to thrive, lactic acidosis, and lipid accumulation in the kidney and liver. Genetic testing can be confirmatory (14).

Organic and amino acid defects include propionic acidemia, methylmalonic acidemia, glutaric acidemia type 1, and tyrosinemia, among others. These children can present with severe metabolic acidosis, failure to thrive, and hypoglycemia (especially in times of stress or illness) (14).

Diagnostic considerations

When children present with symptoms of hypoglycemia, it is important to thoroughly investigate potential etiologies. As stated previously, plasma glucose concentrations <70 mg/dL should prompt evaluation, and plasma glucose levels approximately at or below 50 mg/dL should be sufficient to delineate an etiology. Plasma glucose levels should be utilized, as whole blood glucose levels may be 10–15% lower than plasma glucose concentrations (14). Plasma glucose levels should be evaluated as soon as possible as delayed separation can cause red cell glycolysis and artificially decreased glucose levels by up to 6 mg/dL/hour (11). Additionally, placing samples in ice slurry with rapid separation can produce an accurate value, however this is not always feasible. Various other methods have also been utilized to obtain the most accurate glucose levels. Studies comparing citrate and fluoride containing samples showed that samples containing citrate produced higher diagnostic accuracy of glucose levels, although some recent tube preparations have a combination of these (76-79). Also, studies have shown that utilizing various tubes for glucose concentrations do not produce interchangeable glucose values (80). Glucose meters offer the convenience of measuring glucose levels rapidly in clinical context. However, there can be up to 20% variance from plasma glucose levels, and there can be up to 10% variance in consecutive measurements and should be confirmed with a plasma glucose level (10,14). Furthermore, the accuracy of glucose values during hypoglycemia is limited to 10–15 mg/dL with glucose meters (11).

Evaluation should begin when an infant has persistent hyperglycemia past 48 hours of life as transitional hypoglycemia can occur. However, studies are mixed on whether long-term effects occur with hypoglycemia during this transitional time (6,11,81). It becomes important to identify high-risk infants after the transitional period, and this can include infants with symptoms of hypoglycemia, infants who are large or small for gestational age, those with midline malformations or physical defects, perinatal stress, prematurity, family history concerning for hypoglycemic syndromes, or certain congenital syndromes (11,18). Among these infants, it may be necessary to perform a supervised 6–8 hours safety fast to ensure normal glucose concentrations prior to going home from the nursery or neonatal intensive care unit (NICU) (11).

When obtaining a history, certain factors should be noted to delineate a possible etiology. Young infants are more prone to have inborn errors of metabolism, and ingestions or ketotic hypoglycemia can occur during the toddler years. Hormone deficiencies can occur at nearly every age. Additionally, dietary history at a young age can be important as well, as certain foods can cause hypoglycemia for some metabolic conditions. Certain states, such as chronic disease, other associated systemic conditions (such

as gastrointestinal symptoms), or acute illness or trauma should be documented as well. Physical exam should document any developmental delay, midline or other physical defects, or possible syndromes that can contribute to hypoglycemia (Turner syndrome, Beckwith Wiedemann syndrome, or Kabuki syndrome, among others) (31,82-85).

Aside from clinical evaluation, it is extremely helpful to obtain a "critical sample" at time of hypoglycemia identified with a glucose meter. This involves obtaining a confirmatory plasma glucose level, as well as levels of BOHB, free fatty acids, insulin, c-peptide, GH, and cortisol levels. This should be followed by administration of glucagon to document glucose levels after administration. Liver function testing, electrolyte panel, lipid levels, creatine kinase levels, ammonia, and lactate can aid in diagnosis. Additionally, obtaining acylcarnitine profile, serum amino acid profile, and urine organic acid profile can identify other etiologies as well. If a "critical sample" cannot be obtained, a supervised hypoglycemic fasting study may need to be undertaken to obtain a critical sample when plasma glucose levels are below 50 mg/dL and glucagon can be administered, in a controlled medical environment. These testing methods should be done in coordination with a pediatric endocrinologist if possible (11).

An exaggerated glucose response (glucose increment of >30 mg/dL) after glucagon administration, inappropriate levels of insulin and c-peptide respective to a low plasma glucose level, low IGF-1 level, low levels of BOHB and free fatty acids, and elevated glucose infusion rate (as stated previously) points towards hyperinsulinism. At times, insulin levels are not always low at time of hypoglycemia and require multiple samples or other diagnostic tests for confirmation (73,86).

Additionally, a low c-peptide level with high insulin level can be due to exogenous insulin administration causing hypoglycemia. However, not all insulin assays may be able to detect different types of insulin preparations (11). If hyperinsulinism is identified and it is not thought to be transient in nature, genetic testing can be performed to elucidate strategies in management. A fatty acid disorder is due to the inability to utilize free fatty acids and can be detected by elevated free fatty acid levels and minimal ketosis (BOHB). A low cortisol level during and shortly after hypoglycemia points towards adrenal insufficiency, and an ACTH stimulation test should be performed to evaluate for this condition. A low GH level during hypoglycemia points towards possible GH deficiency and stimulated GH testing may be necessary. It is important to perform a brain MRI and screening for other pituitary deficiencies if ACTH or GH deficiency is diagnosed. A suggested algorithm is seen in *Figure 1* (note: algorithm is not inclusive of all disorders). Findings specific to other metabolic conditions have been discussed individually above (11). If the etiology cannot be identified through preliminary testing, a referral to an endocrinology or metabolic specialist may be needed, along with other possible testing.

Acute management of hypoglycemia includes oral carbohydrate intake or intravenous fluids containing dextrose (18), in addition to treatment of the underlying disease. These methods should be maintained to achieve euglycemia. Glucose levels should be monitored closely, however, it is unclear how often this should be done (87). The American Academy of Pediatrics guidelines for neonatal hypoglycemia noted that among infants at risk, blood glucose should be checked within 1 hour of life, half hour after the feeding, and with continuous glucose checks before feeds (18).

If hyperinsulinism is suspected, glucagon may be useful but should be used as adjunctive therapy as its effect is transient. There has been some research in identifying CGM as a technological tool to identify hypoglycemia. Although some infants were briefly hypoglycemic through CGM but resolved prior to intervention, it could potentially prevent the need for treatment of hypoglycemia. However, it was also noted that some patients were hypoglycemic without symptoms and could leave to overtreatment of these infants, with more research needed to clarify the risks and benefits (87). Studies investigating dextrose gel have shown that while it improved hypoglycemia among at-risk infants and prevented NICU admissions for hypoglycemia (88), it did not significantly change overall cognitive impairment at follow-up (89,90). It also did not impair subsequent feeding (91). However, more studies are needed so that they may be more generalizability to the entire newborn population.

If transient hyperinsulinism is suspected, methods to maintain euglycemia are undertaken, such as promoting enteral feeds and intravenous fluids containing dextrose if medically able. If hypoglycemia is noted to be persistent, medical therapy can be initiated. Additionally, ^{18}F-DOPA PET scan may be performed to localize disease in these patients, as the pancreatic islet typically takes ^{18}F-DOPA, although newer methods have been introduced, as described above (29,53).

Conclusions

Hypoglycemia is a heterogeneous disorder with many

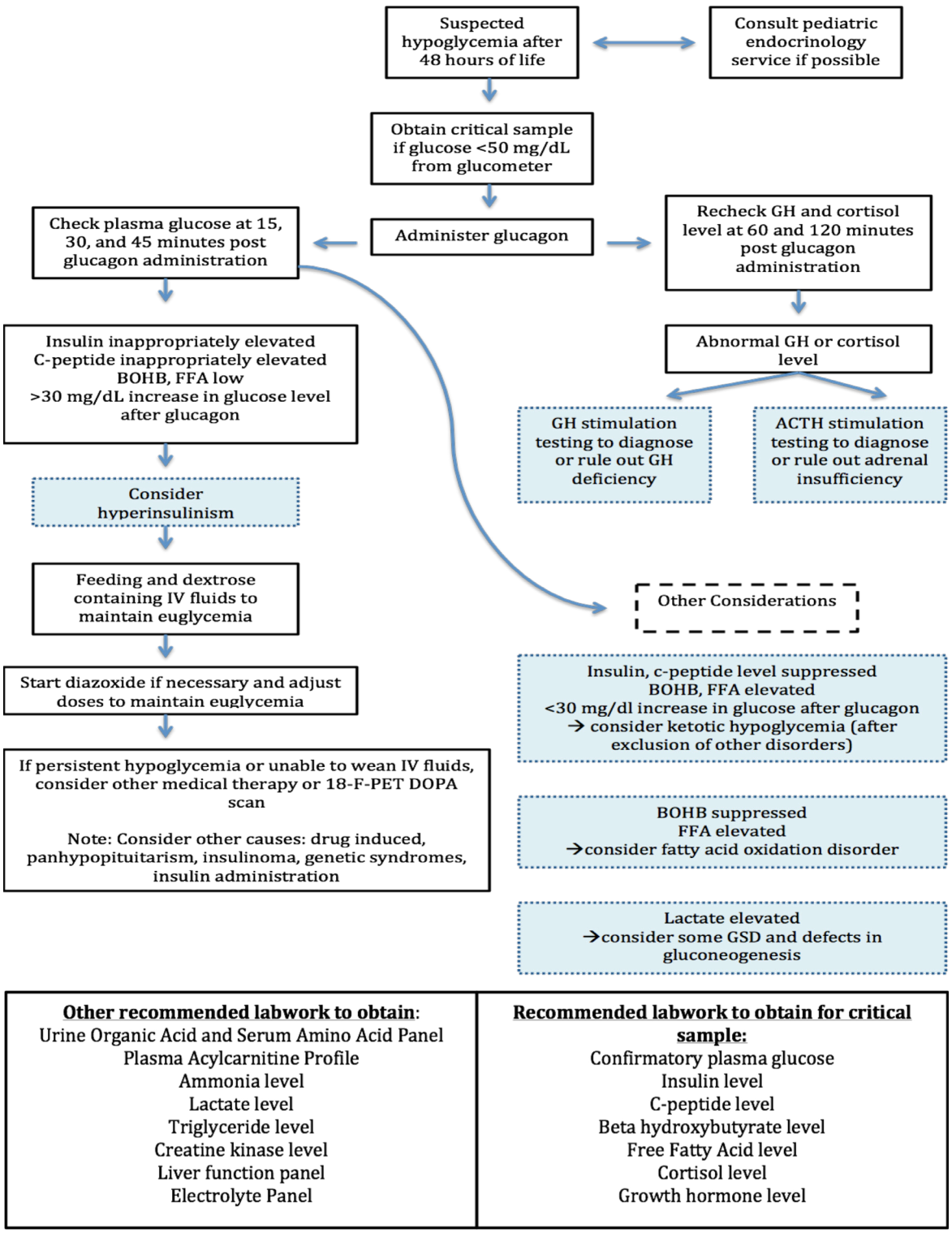

Figure 1 Suggested hypoglycemia algorithm. BOHB, beta-hydroxybutyrate; FFA, free fatty acid; ACTH, adrenocorticotropic hormone; GH, growth hormone; IV, intravenous; GSD, glycogen storage disease; DOPA, dihydroxyphenylalanine; PET, positron emission tomography.

possible etiologies, and a multidisciplinary approach is ideal in caring for these infants and children with this condition. Research advances have better elucidated the complex pathophysiology, diagnosis, and management of this disorder. Ongoing research involves further advances on diagnosis, genotypic analysis and more accurate imaging and surgical approaches, in the hope of further developing specific management approaches among these infants and children with hypoglycemia.

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Footnote

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References

1. Melmed S, Polonsky K, Larsen PR, et al. Williams Textbook of Endocrinology. 12th edition. Philadelphia: Elsevier/Saunders, 2011.
2. Rao PN, Shashidhar A, Ashok C. In utero fuel homeostasis: Lessons for a clinician. Indian J Endocrinol Metab 2013;17:60-8.
3. Zeng Z, Liu F, Li S. Metabolic Adaptations in Pregnancy: A Review. Ann Nutr Metab 2017;70:59-65.
4. Kalhan SC, D'Angelo LJ, Savin SM, et al. Glucose production in pregnant women at term gestation. Sources of glucose for human fetus. J Clin Invest 1979;63:388-94.
5. Stanley CA, Rozance PJ, Thornton PS, et al. Re-evaluating "transitional neonatal hypoglycemia": mechanism and implications for management. J Pediatr 2015;166:1520-5.e1.
6. Hay WW Jr, Raju TN, Higgins RD, et al. Knowledge gaps and research needs for understanding and treating neonatal hypoglycemia: workshop report from Eunice Kennedy Shriver National Institute of Child Health and Human Development. J Pediatr 2009;155:612-7.
7. Hattersley AT, Beards F, Ballantyne E, et al. Mutations in the glucokinase gene of the fetus result in reduced birth weight. Nat Genet 1998;19:268-70.
8. Hay WW Jr. Placental-fetal glucose exchange and fetal glucose metabolism. Trans Am Clin Climatol Assoc 2006;117:321-39; discussion 339-40.
9. Stanley CA. Perspective on the Genetics and Diagnosis of Congenital Hyperinsulinism Disorders. J Clin Endocrinol Metab 2016;101:815-26.
10. Kappy MS, Geffner ME, Allen DB. Pediatric Practice: Endocrinology. 2nd edition. McGraw-Hill Education/ Medical, 2014.
11. Thornton PS, Stanley CA, De Leon DD, et al. Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. J Pediatr 2015;167:238-45.
12. Chen L, Tuo B, Dong H. Regulation of Intestinal Glucose Absorption by Ion Channels and Transporters. Nutrients 2016;8. pii: E43.
13. Drozdowski LA, Thomson AB. Intestinal sugar transport. World J Gastroenterol 2006;12:1657-70.
14. Sperling MA. editor. Pediatric Endocrinology. 3rd edition. Philadelphia: Elsevier/Saunders, 2008.
15. Whipple AO, Frantz VK. Adenoma of Islet Cells with Hyperinsulinism: A Review. Ann Surg 1935;101:1299-335.
16. Cornblath M, Hawdon JM, Williams AF, et al. Controversies regarding definition of neonatal hypoglycemia: suggested operational thresholds. Pediatrics 2000;105:1141-5.
17. World Health Organization. Hypoglycaemia in the Newborn: Review of the Literature. 1997. Available online: http://apps.who.int/iris/bitstream/10665/63362/1/WHO_CHD_97.1.pdf
18. Committee on Fetus and Newborn, Adamkin DH. Postnatal glucose homeostasis in late-preterm and term infants. Pediatrics 2011;127:575-9.
19. McKinlay CJ, Alsweiler JM, Ansell JM, et al. Neonatal Glycemia and Neurodevelopmental Outcomes at 2 Years. N Engl J Med 2015;373:1507-18.
20. Goode RH, Rettiganti M, Li J, et al. Developmental Outcomes of Preterm Infants With Neonatal Hypoglycemia. Pediatrics 2016;138. pii: e20161424.
21. McKinlay CJ, Alsweiler JM, Anstice NS, et al. Association of Neonatal Glycemia With Neurodevelopmental Outcomes at 4.5 Years. JAMA Pediatr 2017;171:972-83.
22. Kaiser JR, Bai S, Gibson N, et al. Association Between Transient Newborn Hypoglycemia and Fourth-Grade Achievement Test Proficiency: A Population-Based Study. JAMA Pediatr 2015;169:913-21.
23. Mahajan G, Mukhopadhyay K, Attri S, et al. Neurodevelopmental Outcome of Asymptomatic Hypoglycemia Compared With Symptomatic Hypoglycemia and Euglycemia in High-Risk Neonates. Pediatr Neurol 2017;74:74-9.
24. Davis SN, Shavers C, Costa F. Differential gender

responses to hypoglycemia are due to alterations in CNS drive and not glycemic thresholds. Am J Physiol Endocrinol Metab 2000;279:E1054-63.
25. Fujii S, Tamai H, Kumai M, et al. Impaired glucagon secretion to insulin-induced hypoglycemia in anorexia nervosa. Acta Endocrinol (Copenh) 1989;120:610-5.
26. Kerr D, Sherwin RS, Pavalkis F, et al. Effect of caffeine on the recognition of and responses to hypoglycemia in humans. Ann Intern Med 1993;119:799-804.
27. Cryer PE. Mechanisms of sympathoadrenal failure and hypoglycemia in diabetes. J Clin Invest 2006;116:1470-3.
28. Fournet JC, Junien C. The genetics of neonatal hyperinsulinism. Horm Res 2003;59 Suppl 1:30-4.
29. Rozenkova K, Guemes M, Shah P, et al. The Diagnosis and Management of Hyperinsulinaemic Hypoglycaemia. J Clin Res Pediatr Endocrinol 2015;7:86-97.
30. Pinney SE, MacMullen C, Becker S, et al. Clinical characteristics and biochemical mechanisms of congenital hyperinsulinism associated with dominant KATP channel mutations. J Clin Invest 2008;118:2877-86.
31. De Leon DD, Stanley CA. Congenital Hypoglycemia Disorders: New Aspects of Etiology, Diagnosis, Treatment and Outcomes: Highlights of the Proceedings of the Congenital Hypoglycemia Disorders Symposium, Philadelphia April 2016. Pediatr Diabetes 2017;18:3-9.
32. Arnoux JB, Verkarre V, Saint-Martin C, et al. Congenital hyperinsulinism: current trends in diagnosis and therapy. Orphanet J Rare Dis 2011;6:63.
33. Yildizdas D, Erdem S, Kucukosmanoglu O, et al. Pulmonary hypertension, heart failure and neutropenia due to diazoxide therapy. Adv Ther 2008;25:515-9.
34. Demirbilek H, Rahman SA, Buyukyilmaz GG, et al. Diagnosis and treatment of hyperinsulinaemic hypoglycaemia and its implications for paediatric endocrinology. Int J Pediatr Endocrinol 2017;2017:9.
35. Hussain K. Diagnosis and management of hyperinsulinaemic hypoglycaemia of infancy. Horm Res 2008;69:2-13.
36. Laje P, Halaby L, Adzick NS, et al. Necrotizing enterocolitis in neonates receiving octreotide for the management of congenital hyperinsulinism. Pediatr Diabetes 2010;11:142-7.
37. Darendeliler F, Fournet JC, Bas F, et al. ABCC8 (SUR1) and KCNJ11 (KIR6.2) mutations in persistent hyperinsulinemic hypoglycemia of infancy and evaluation of different therapeutic measures. J Pediatr Endocrinol Metab 2002;15:993-1000.
38. Guemes M, Shah P, Silvera S, et al. Assessment of Nifedipine Therapy in Hyperinsulinemic Hypoglycemia due to Mutations in the ABCC8 Gene. J Clin Endocrinol Metab 2017;102:822-30.
39. Alexandrescu S, Tatevian N, Olutoye O, et al. Persistent hyperinsulinemic hypoglycemia of infancy: constitutive activation of the mTOR pathway with associated exocrine-islet transdifferentiation and therapeutic implications. Int J Clin Exp Pathol 2010;3:691-705.
40. Senniappan S, Alexandrescu S, Tatevian N, et al. Sirolimus therapy in infants with severe hyperinsulinemic hypoglycemia. N Engl J Med 2014;370:1131-7.
41. Szymanowski M, Estebanez MS, Padidela R, et al. mTOR Inhibitors for the Treatment of Severe Congenital Hyperinsulinism: Perspectives on Limited Therapeutic Success. J Clin Endocrinol Metab 2016;101:4719-29.
42. Sankhala K, Mita A, Kelly K, et al. The emerging safety profile of mTOR inhibitors, a novel class of anticancer agents. Target Oncol 2009;4:135-42.
43. Calabria AC, Li C, Gallagher PR, et al. GLP-1 receptor antagonist exendin-(9-39) elevates fasting blood glucose levels in congenital hyperinsulinism owing to inactivating mutations in the ATP-sensitive K+ channel. Diabetes 2012;61:2585-91.
44. Beltrand J, Caquard M, Arnoux JB, et al. Glucose metabolism in 105 children and adolescents after pancreatectomy for congenital hyperinsulinism. Diabetes Care 2012;35:198-203.
45. Arya VB, Guemes M, Nessa A, et al. Clinical and histological heterogeneity of congenital hyperinsulinism due to paternally inherited heterozygous ABCC8/KCNJ11 mutations. Eur J Endocrinol 2014;171:685-95.
46. Hsu BY, Kelly A, Thornton PS, et al. Protein-sensitive and fasting hypoglycemia in children with the hyperinsulinism/hyperammonemia syndrome. J Pediatr 2001;138:383-9.
47. Huijmans JG, Duran M, de Klerk JB, et al. Functional hyperactivity of hepatic glutamate dehydrogenase as a cause of the hyperinsulinism/hyperammonemia syndrome: effect of treatment. Pediatrics 2000;106:596-600.
48. Glaser B, Kesavan P, Heyman M, et al. Familial hyperinsulinism caused by an activating glucokinase mutation. N Engl J Med 1998;338:226-30.
49. Sayed S, Langdon DR, Odili S, et al. Extremes of clinical and enzymatic phenotypes in children with hyperinsulinism caused by glucokinase activating mutations. Diabetes 2009;58:1419-27.
50. Ferrara CT, Boodhansingh KE, Paradies E, et al. Novel Hypoglycemia Phenotype in Congenital Hyperinsulinism Due to Dominant Mutations of Uncoupling Protein 2. J

Clin Endocrinol Metab 2017;102:942-9.
51. Gonzalez-Barroso MM, Giurgea I, Bouillaud F, et al. Mutations in UCP2 in congenital hyperinsulinism reveal a role for regulation of insulin secretion. PLoS One 2008;3:e3850.
52. Janem W, Sultan I, Ajlouni F, et al. Malignant insulinoma in a child. Pediatr Blood Cancer 2010;55:1423-6.
53. Nockel P, Babic B, Millo C, et al. Localization of Insulinoma Using 68Ga-DOTATATE PET/CT Scan. J Clin Endocrinol Metab 2017;102:195-9.
54. Calabria AC, Charles L, Givler S, et al. Postprandial Hypoglycemia in Children after Gastric Surgery: Clinical Characterization and Pathophysiology. Horm Res Paediatr 2016;85:140-6.
55. Alexander S, Ramadan D, Alkhayyat H, et al. Costello syndrome and hyperinsulinemic hypoglycemia. Am J Med Genet A 2005;139:227-30.
56. Aynsley-Green A, Williamson DH, Gitzelmann R. Hepatic glycogen synthetase deficiency. Definition of syndrome from metabolic and enzyme studies on a 9-year-old girl. Arch Dis Child 1977;52:573-9.
57. Bachrach BE, Weinstein DA, Orho-Melander M, et al. Glycogen synthase deficiency (glycogen storage disease type 0) presenting with hyperglycemia and glucosuria: report of three new mutations. J Pediatr 2002;140:781-3.
58. Bandsma RH, Smit GP, Kuipers F. Disturbed lipid metabolism in glycogen storage disease type 1. Eur J Pediatr 2002;161 Suppl 1:S65-9.
59. Melis D, Rossi A, Pivonello R, et al. Reduced bone mineral density in glycogen storage disease type III: evidence for a possible connection between metabolic imbalance and bone homeostasis. Bone 2016;86:79-85.
60. Dagli A, Sentner CP, Weinstein DA. Glycogen Storage Disease Type III. In: Adam MP, Ardinger HH, Pagon RA, et al. editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle, 1993-2017.
61. Dagli AI, Weinstein DA. Glycogen Storage Disease Type VI. In: Adam MP, Ardinger HH, Pagon RA, et al. editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle, 1993-2017.
62. Sparks SE, Krasnewich DM. Congenital Disorders of N-Linked Glycosylation and Multiple Pathway Overview. In: Adam MP, Ardinger HH, Pagon RA, et al. editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle, 1993-2017.
63. de Lonlay P, Cuer M, Vuillaumier-Barrot S, et al. Hyperinsulinemic hypoglycemia as a presenting sign in phosphomannose isomerase deficiency: A new manifestation of carbohydrate-deficient glycoprotein syndrome treatable with mannose. J Pediatr 1999;135:379-83.
64. Jumbo-Lucioni PP, Garber K, Kiel J, et al. Diversity of approaches to classic galactosemia around the world: a comparison of diagnosis, intervention, and outcomes. J Inherit Metab Dis 2012;35:1037-49.
65. Coelho AI, Rubio-Gozalbo ME, Vicente JB, et al. Sweet and sour: an update on classic galactosemia. J Inherit Metab Dis 2017;40:325-42.
66. 66. Berry GT. Classic Galactosemia and Clinical Variant Galactosemia. In: Adam MP, Ardinger HH, Pagon RA, et al. editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle, 1993-2017.
67. Panis B, Gerver WJ, Rubio-Gozalbo ME. Growth in treated classical galactosemia patients. Eur J Pediatr 2007;166:443-6.
68. Spencer JB, Badik JR, Ryan EL, et al. Modifiers of ovarian function in girls and women with classic galactosemia. J Clin Endocrinol Metab 2013;98:E1257-65.
69. Pyhtila BM, Shaw KA, Neumann SE, et al. Newborn screening for galactosemia in the United States: looking back, looking around, and looking ahead. JIMD Rep 2015;15:79-93.
70. Baker P II, Ayres L, Gaughan S, et al. Hereditary Fructose Intolerance. In: Adam MP, Ardinger HH, Pagon RA, et al. editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle, 1993-2017.
71. Vishwanath VA. Fatty Acid Beta-Oxidation Disorders: A Brief Review. Ann Neurosci 2016;23:51-5.
72. Moller N, Jorgensen JO. Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. Endocr Rev 2009;30:152-77.
73. Palladino AA, Bennett MJ, Stanley CA. Hyperinsulinism in infancy and childhood: when an insulin level is not always enough. Clin Chem 2008;54:256-63.
74. Ghosh A, Banerjee I, Morris AA. Recognition, assessment and management of hypoglycaemia in childhood. Arch Dis Child 2016;101:575-80.
75. Li N, Chang G, Xu Y, et al. Clinical and Molecular Characterization of Patients with Fructose 1,6-Bisphosphatase Deficiency. Int J Mol Sci 2017;18. pii: E857.
76. Daly N, Flynn I, Carroll C, et al. Comparison of Citrate-Fluoride-EDTA with Fluoride-EDTA Additives to Stabilize Plasma Glucose Measurements in Women Being Screened during Pregnancy with an Oral Glucose Tolerance Test: A Prospective Observational Study. Clin Chem 2016;62:886-7.

77. Carta M, Montagnana M, Cascio CL, et al. Glucose sampling: importance of citrate. Ann Clin Biochem 2016;53:715-6.
78. Sacks DB, Arnold M, Bakris GL, et al. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Diabetes Care 2011;34:e61-99.
79. Dimeski G, Yow KS, Brown NN. What is the most suitable blood collection tube for glucose estimation? Ann Clin Biochem 2015;52:270-5.
80. Saracevic A, Dukic L, Juricic G, et al. Various glycolysis inhibitor-containing tubes for glucose measurement cannot be used interchangeably due to clinically unacceptable biases between them. Clin Chem Lab Med 2017. [Epub ahead of print].
81. Vannucci RC, Vannucci SJ. Hypoglycemic brain injury. Semin Neonatol 2001;6:147-55.
82. Kalish JM, Boodhansingh KE, Bhatti TR, et al. Congenital hyperinsulinism in children with paternal 11p uniparental isodisomy and Beckwith-Wiedemann syndrome. J Med Genet 2016;53:53-61.
83. Genevieve D, Amiel J, Viot G, et al. Atypical findings in Kabuki syndrome: report of 8 patients in a series of 20 and review of the literature. Am J Med Genet A 2004;129A:64-8.
84. Alkhayyat H, Christesen HB, Steer J, et al. Mosaic Turner syndrome and hyperinsulinaemic hypoglycaemia. J Pediatr Endocrinol Metab 2006;19:1451-7.
85. Cappella M, Graziani V, Pragliola A, et al. Hyperinsulinemic Hypoglycaemia in a Turner Syndrome with Ring (X). Case Rep Pediatr 2015;2015:561974.
86. Ferrara C, Patel P, Becker S, et al. Biomarkers of Insulin for the Diagnosis of Hyperinsulinemic Hypoglycemia in Infants and Children. J Pediatr 2016;168:212-9.
87. Rozance PJ, Hay WW Jr. New approaches to management of neonatal hypoglycemia. Matern Health Neonatol Perinatol 2016;2:3.
88. Harris DL, Weston PJ, Signal M, et al. Dextrose gel for neonatal hypoglycaemia (the Sugar Babies Study): a randomised, double-blind, placebo-controlled trial. Lancet 2013;382:2077-83.
89. Hegarty JE, Harding JE, Gamble GD, et al. Prophylactic Oral Dextrose Gel for Newborn Babies at Risk of Neonatal Hypoglycaemia: A Randomised Controlled Dose-Finding Trial (the Pre-hPOD Study). PLoS Med 2016;13:e1002155.
90. Harris DL, Alsweiler JM, Ansell JM, et al. Outcome at 2 Years after Dextrose Gel Treatment for Neonatal Hypoglycemia: Follow-Up of a Randomized Trial. J Pediatr 2016;170:54-9.e1-2.
91. Weston PJ, Harris DL, Harding JE. Dextrose gel treatment does not impair subsequent feeding. Arch Dis Child Fetal Neonatal Ed 2017. Lancet 2013;382:2077-83.

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