Chapter 5

Neonatal Hypoglycemia

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Abstract

Hypoglycemia is the most frequent metabolic abnormality in the newborn, but no consensus exists on what level of blood glucose is able to protect the brain and influence the child's neural development and which is the best course of management in cases labeled as hypoglycemia. Early diagnosis, urgent treatment, and prevention of future episodes of hypoglycemia are the cornerstones of management, now supported by recent advances in molecular genetics and in our understanding of the pathophysiology of neonatal hypoglycemia, particularly the pathogenesis of congenital hyperinsulinemic hypoglycemia.

Keywords: hypoglycemia, newborn, molecular mechanisms, hyperinsulinemia, actual treatment

1. Introduction

Hypoglycemia is the most frequent metabolic abnormality in the newborn, and although it is the most common biochemical disorder in this age group [30], it is still a source of clinical concern and controversy, as no consensus exists on what level of blood glucose is able to protect the brain and influence the child's neural development [6, 22, 53] and which is the best course of management in cases labeled as hypoglycemia. Early diagnosis, urgent treatment, and prevention of future episodes of hypoglycemia are the cornerstones of management, now supported by recent advances in molecular genetics [48] and in our understanding of the pathophysiology of neonatal hypoglycemia, particularly the pathogenesis of congenital hyperinsulinemic hypoglycemia [12].

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Hypoglycemia occurs in 1.3–4.4 per 1000 full-term newborns and 15–55 per 1000 preterm newborns. This suggests that gestational age has enormous influence on its onset; in certain groups, adaptive mechanisms are not adequately developed, which predisposes them to increased risk of hypoglycemia. According to current evidence, the prevalence of hypoglycemia is approximately 10% in full-term neonates [45]; 6.5% in appropriate for gestational age (AGA), 8% in large for gestational age (LGA), and 15% in small for gestational age (SGA) newborns; and 15.5% in late-preterm infants [7].

2. Metabolic aspects

The maintenance of physiological concentrations of glucose in newborns plays important roles, including protecting the brain from damage caused by insufficient glucose intake and preventing the consequences of hyperosmolarity caused by high glucose concentrations. Although glucose is the preferred energy source of neurons, other sources, such as lactate and ketone bodies [23], seem to exert a neuroprotective effect. However, in hypoketotic states, such as hyperinsulinism or fatty acid oxidation disorders, ketone and lactate concentrations are not high enough to replace glucose, and the risk of a cerebral energy deficit is greater [60, 61].

It is known that, during fasting, several metabolic systems are activated to prevent hypoglycemia, which may be seen as a failure in one of these systems or as an abnormality affecting one or more of the hormones that control these systems [24].

As the brain mass of newborn infants in relation to body size is larger than that of adults, the rate of glucose utilization per kg body weight in newborns is two- to threefold than that of adults (4–6 mg/kg/min) [61].

2.1. Maternal provision of glucose to the fetus

The first half of pregnancy is characterized by marked anabolism. In early pregnancy, increased caloric intake not only supports fetal development but also facilitates fat deposition in the mother in preparation for the second half of pregnancy, a period of accelerated fetal growth in which maternal stores are mobilized to meet the needs of the fetus. To this end, increased insulin secretion also occurs in early pregnancy, as a way to store energy.

From the midpoint of pregnancy onward, high levels of circulating maternal insulin are also observed, but high levels of anti-insulin factors override this effect, ensuring the provision of nutrients to the fetus during the postprandial period. Thus, in pregnant women with preexisting diabetes, the effects of these anti-insulin factors are potentiated, causing excess provision of glucose and other energy sources to the fetus and thus triggering the abnormalities observed in infants born to diabetic mothers.

In the expectant mother, glucose is found at levels 25–30% higher than in the fetus, and it is transported to the fetus by concentration gradients and simple diffusion and through the action of transporters. In the fetus, the predominant transporter is GLUT-1, which has a high affinity for glucose and facilitates its passage through tissues [28].

Most glucose in the fetus undergoes oxidation to supply its energy needs, while another part contributes significantly to a buildup of glycogen, protein, and fat in triglyceride form. Glucose is the most important source of energy for the fetus and the major substrate for brain metabolism.

2.2. Glucose uptake in the newborn

At birth, the fetus becomes dependent on itself to obtain energy and meet the metabolic needs of its vital organs, particularly the central nervous system (CNS). Each mole of oxidized glucose provides 38 moles of adenosine triphosphate (ATP) [54].

Cerebral glucose transport takes place through a facilitated diffusion process, which is dependent on glycemia and is not regulated by insulin. Protection against hypoglycemia is coordinated by the autonomic nervous system by means of hormones that stimulate the production of glucose (through glycogenolysis and gluconeogenesis) and limit peripheral glucose utilization [54].

Glycogen is the only glucose storage medium in the body. Its deposits are found in the liver, striated muscle tissue (including cardiac muscle), kidneys, bowel, brain, and placenta.

The fetal liver contains a complete enzyme system for the synthesis and breakdown of glycogen, levels of which are low in early pregnancy but rise slowly and steadily from gestational weeks 15–20, before peaking in the third trimester. At this time, fat deposition also increases. Thus, part of the energy and substrates used for fetal growth is redirected for storage, which will play an important role in the peripartum and postpartum periods.

Hepatic glycogenolysis is the major mechanism of glucose release in the immediate neonatal period, which leads to depletion of glycogen stores. It is induced by an increase in glucagon and catecholamines and a reduction in insulin. This exhaustion of glycogen stores promotes activation of gluconeogenesis, which occurs largely as a result of free fatty acid oxidation in the liver.

Glucose homeostasis will thus depend on glucose intake; gluconeogenesis; glycogen, protein, and fat stores; and hormonal and neural factors.

Glucose produced from the breakdown of dietary lactose into galactose and glucose, for instance, is not taken up by the liver in the neonatal period; the newborn is thus dependent on hepatic gluconeogenesis to sustain glucose production.

Once glycogen stores are low, gluconeogenesis induced by glucagon, catecholamines, cortisol, and growth hormone mobilizes fat and protein substrates. Insulin, thyroid hormone, cortisol, and glucagon systematically promote induction of specific enzymes, thus adapting the neonate to the abrupt cessation of the supply glucose that was provided continuously before birth.

Upon clamping the umbilical cord, the maternal glucose supply, which was 54 mg/dL during pregnancy, ceases abruptly, and the neonate's blood glucose levels decline rapidly and precipitously—from a concentration similar to that of the mother to approximately 41 mg/dL within the first 6 h of life. Physiologically, glucose concentration decreases to approximately 30 mg/dL in the first 2 h after birth, subsequently rises, and plateaus at approximately 45 mg/dL 12 h after birth.

3. Definition

Current evidence is still unable to define a specific glucose concentration that is safe to prevent acute neurological damage or chronic, irreversible neurological injury in the neonate. Weight and gestational age, as well as the age at onset, severity, duration, and number of episodes of hypoglycemia, are all determinants of the blood glucose level most appropriate for protection of the neonatal brain [54]; thus, doubts persist as to whether any single level may represent a red flag for neurological safety.

A plasma glucose level below 30 mg/dL (1.65 mmol/L) in the first 2 h of life or below 45 mg/dL (2.5 mmol/L) after these first 2 h has been considered diagnostic of hypoglycemia [54].

Various situations can influence the appropriateness of a blood glucose level for use as a cutoff point for treatment initiation, including nutritional timing and the presence and absence of symptoms [64]. Thus, in 2011, the American Academy of Pediatrics proposed that neonatal hypoglycemia be defined as a blood glucose level of 2.5 mmol/L before routine feeding [1, 20]. Other studies suggest a limit of 2 mmol/L in asymptomatic newborns and 2.5 mmol/L in symptomatic neonates [42]. Although cutoff values below 2.6 mmol/L have been cited in various studies as defining of neonatal hypoglycemia, there is no guarantee that such a concentration is the most appropriate choice for establishing a diagnosis of this disorder and prompting initiation of treatment. An important finding reported by McKinlay et al. [34] has encouraged neonatologists to consider a glucose concentration >47 mg/dL as the level at which no impairment of appropriate neurological development was observed at age 2 years.

These proposed levels serve to provide a margin of safety until additional data are available to support a more accurate definition. However, the potential risk of neurologic sequelae has led many authors to consider blood glucose values <50 mg/dL in infants as the limit beyond which treatment should be instituted [61].

In practice, blood glucose levels below 50 mg/dL as measured by a glucometer should warrant careful monitoring, and plasma glucose levels below 45 mg/dL should prompt initiation of diagnostic measures and immediate treatment.

4. Etiology and pathogenesis

Overall, neonatal hypoglycemia is caused by one of the three main mechanisms: situations associated with hyperinsulinemia, situations associated with low or depleted glycogen stores, and situations associated with excessive glucose consumption. These mechanisms may also be compounded by the effects of certain drugs used in pregnancy.

4.1. Situations associated with hyperinsulinemia

4.1.1. Infant born to a mother with diabetes

Offspring of diabetic mothers may be abnormally large at birth (LGA), even when the mother was able to keep blood glucose within normal or near-normal range throughout pregnancy.

The risk of birth defects is two to four times higher in fetuses of pregnant women with diabetes, particularly when the disorder is poorly controlled during the period of fetal organ development (i.e., gestational weeks 6–7), and the neonatal mortality rate is fivefold than that of infants born to women without diabetes.

Intermittent maternal hyperglycemia causes fetal hyperglycemia, which, in turn, stimulates excess insulin production by the fetal pancreas. On the one hand, this increased fetal insulin synthesis stimulates excess organ growth (except of the brain and liver, which are not dependent on insulin supply for growth), thus causing fetal macrosomia. On the other hand, it is associated with a high incidence of neonatal hypoglycemia and marked lipolysis during the first few hours after birth. Hyperinsulinism and hyperglycemia may also cause fetal acidosis, which results in an increased rate of stillbirths. Although hyperinsulinemia is probably the leading cause of hypoglycemia, reduced epinephrine and glucagon responses can also be contributing factors. Levels of cortisol and growth hormone are normal [11].

Increased levels of glycated hemoglobin in fetal blood appear to precipitate tissue hypoxia, as this form of hemoglobin has high affinity for oxygen molecules.

Furthermore, chronic fetal hyperinsulinemia increases metabolic rates, thus increasing oxygen consumption and inducing relative hypoxemia; this, in turn, boosts red blood cell production, causing polycythemia and, consequently, hemolysis and neonatal hyperbilirubinemia. Severe hypoxemia can ultimately lead to fetal death.

After birth, the supply of glucose to the fetus is cut off, but hyperinsulinemia persists, speeding both exogenous glucose utilization and endogenous glucose production; this phenomenon may last approximately 3 days, until normal insulin secretion is established. Hypoglycemia may manifest in the intervening period.

4.1.2. Large for gestational age status

LGA neonates may also develop hypoglycemia [44], through the same mechanism observed in infants born to diabetic mothers; however, in these infants, blood glucose reaches normal levels within the first few hours of life [32].

4.1.3. Congenital hyperinsulinemic hypoglycemia

Hypoglycemia associated with congenital hyperinsulinism (CHH), also known as persistent hyperinsulinemic hypoglycemia of infancy (PHHI), is the result of inappropriate insulin secretion or hyperinsulinism. In infants with this disease, hypoglycemia is triggered by fasting and is always accompanied by an increase in plasma insulin concentrations, which are usually inappropriately high for the concomitant low blood glucose concentration. The disease appears to be more closely related to an increase in global endocrine functional activity of the pancreas rather than an increase in the number of pancreatic beta cells.

CHH is an important etiology that should be considered in cases of persistent and difficult-to-control hypoglycemia. It is a medical emergency that requires precise etiological diagnosis and represents a serious therapeutic challenge. The term PHHI was first proposed by Glaser in 1989 [19] and has since come to replace the now-outdated terms nesidioblastosis and islet-cell

dysmaturity syndrome to describe pancreatic abnormalities associated with hypoglycemia and hyperinsulinism.

Most cases of CHH are sporadic (1:40,000–50,000 live births), but a higher prevalence has been described in communities with a high degree of consanguinity. This familial form associated with inbreeding may occur in up to 1:2500 live births. Thus, an autosomal recessive inheritance pattern has been posited to explain it. There is no evidence of sex predominance, and the maternal history is generally negative; however, a careful history may reveal prior neonatal deaths or unexplained seizures or mental retardation in other siblings.

Patients with CHH are mostly LGA, as a consequence of hyperinsulinism, but without significant hepatomegaly. They exhibit persistent symptoms of hypoglycemia, including hypotonia, cyanosis, apnea, and difficult-to-control seizures, as early as the neonatal period. Sudden infant death is also seen in patients with CHH. Although the condition is rare, the high frequency of brain damage and developmental delay as a result of severe, treatment-refractory hypoglycemia in these patients justifies the need for early etiologic diagnosis and immediate treatment.

Currently, the most accepted etiogenic hypothesis for the dysfunction of CHH is inappropriate insulin secretion by pancreatic beta cells. The molecular basis of congenital hyperinsulinism involves defects in key genes that regulate the complex mechanism of insulin secretion control [12]. Nine genes have been identified and classified within the potassium channelopathies (ABCC8, KCNJ11) and metabolic disorders (GLUD1, GCK, HNF4A, HNF1A, SLC16A1, UCP2, HADH) [47, 52]. Genetic defect mutations involving the ABCC8/KCNJ11 genes, which encode the SUR1/Kir 6.2 components of the ATP-sensitive potassium channels (K_{ATP}) in pancreatic beta cells, are the most common [13, 27]. In normal cells, the K_{ATP} channels remain open or closed in response to variation in blood glucose levels, which leads to changes in the action potential of the cell membrane. An increase in blood glucose raises the rate of glucose metabolism in beta cells, resulting in increased adenosine triphosphate (ATP) and decreased adenosine diphosphate (ADP) within the cell, triggering closure of K_{ATP} channels and subsequent depolarization of the beta-cell membrane. This change in potential opens voltage-dependent calcium channels and leads to calcium influx. The subsequent increase in the cytosolic calcium concentration stimulates exostosis of insulin secretory granules; thus, insulin is released continuously.

The potassium channel is a complex of two proteins: SUR1, a receptor with high affinity for sulfonylureas, and Kir 6.2, which forms the inner pore of the channel and maintains its alignment [39, 58, 59]. The regulatory genes of the sulfonylurea receptor and potassium channels were recently mapped to region 11p15.1 of chromosome 11. Individually; none of these proteins has the ability to act as a potassium channel. Depending on the type of mutation affecting the genes that regulate these proteins, CHH may manifest with three distinct phenotypes. The first represents the familial form, with truncation of SUR1 and the absence of K_{ATP}. These patients have the most severe form of CHH and, in most cases, respond poorly or not at all to clinical treatment. In the second type, which accounts for sporadic cases, there is loss of K_{ATP} function but partial response to clinical treatment, due to formation of new potassium

ion channels. In the third type, onset is delayed and severity is mild, as these patients have functional K_{ATPs} and respond to clinical treatment.

A diagnosis of CHH is usually considered when hypoglycemia develops shortly after birth and requires glucose infusion at high rates, usually exceeding 10 mg/kg/min and occasionally up to 15–20 mg/kg/min. Typically, these infants have high blood levels of insulin, sometimes exceeding 10 μU/mL, and the insulin (μU/mL)-to-glucose (mg/dL) ratio is 1:4 or higher.

Beta-cell adenomas are characterized by marked, early onset hyperinsulinemia. These tumors require surgical removal or partial pancreatectomy. They are uncommon in the neonatal period. Definitive diagnosis can only be established through histopathology, and immunohistochemical study may be required.

4.1.3.1. Beckwith-Wiedemann syndrome

Beckwith-Wiedemann syndrome is one of the most common overgrowth disorders and can be identified in more than 75% of neonates above the 90th percentile for weight and length. It is estimated to occur in 1 in 13,700 births, but mild cases may lead to underestimation of its true frequency [31]. There is no gender predominance. The syndrome is characterized by gigantism, omphalocele, and macroglossia, a triad that occurs in over 80% of cases. Other abnormalities that occur less frequently include earlobe creases and posterior helical ear pits, microcephaly, wide fontanels, a prominent occipital protuberance, facial nevus flammeus, nonspecific cardiac defects, abdominal wall defects (umbilical hernia, diastasis recti), visceromegaly, and hyperplasia of the kidneys, pancreas, adrenal cortices, gonadal interstitial cells, and pituitary [50].

Neonatal hypoglycemia occurs in at least 50% of cases of Beckwith-Wiedemann syndrome. It is generally serious and may be associated with future mental retardation. Thus, early diagnosis is important for proper treatment of low serum glucose levels, to prevent neurological damage. It is believed that hypoglycemia in this syndrome is secondary to hyperinsulinism caused by beta-cell hyperplasia and hypertrophy, but glucagon deficiency and a reduction in somatostatin-producing delta cells have also been documented.

There is a clear evidence of genomic influence in the development of Beckwith-Wiedemann syndrome. A mutation in 11p15.5, a region that encompasses multiple gene loci, has been implicated [37].

4.1.3.2. Congenital hyperinsulinemic hypoglycemia and other syndromes

CHH has been described in other diseases and syndromes, including congenital hypothyroidism [29], Sotos syndrome [4], Costello syndrome [21], Donohue syndrome [63], and Kabuki syndrome [62].

4.2. Situations associated with low or depleted glycogen stores

Prematurity and intrauterine growth restriction are among the situations that can influence neonatal blood glucose levels [35].

4.2.1. Prematurity

As very low-birth-weight preterm infants have limited glycogen stores, gluconeogenesis is their main source of glucose production. Gluconeogenesis is induced by decreased glucose intake, as well as by high cortisol, catecholamine, and glucagon levels.

Increased neurologic morbidity is particularly common in children with severe, recurrent hypoglycemia. Experimental observations have stressed the resistance of the immature brain to damage caused by hypoglycemia. This resistance is a consequence of compensatory increase in blood flow to the brain, reduced energy needs, increased endogenous carbohydrate stores, and ability to take up and consume alternative organic substrates while saving glucose for energy production [36].

4.2.2. Intrauterine growth restriction

As a result of intrauterine growth restriction, SGA neonates may exhibit several abnormalities shortly after birth, including increased susceptibility to infections, pulmonary hemorrhage, hyperbilirubinemia, and hypoglycemia. The widely varying incidence of the latter may reflect the different etiologies of intrauterine growth restriction (e.g., poor maternal nutrition, mothers with advanced age, uteroplacental insufficiency, derangements in maternal metabolism, or fetal infection). Furthermore, polycythemia and fetal and neonatal hypoxemia, which are often seen in SGA infants, can themselves contribute to development of hypoglycemia [49].

SGA infants are most at risk of hypoglycemia. Of those who do develop it, 65% are premature and 25% are post-term. Hypoglycemia can be asymptomatic or symptomatic and is generally observed in the first 24 h of life.

The factors contributing to low blood glucose levels include inadequate hepatic glycogen stores due to the high brain-to-body-mass ratio of SGA infants, the glucose-dependent nature of cerebral oxidative metabolism, and high overall metabolic rates. Furthermore, a reduction in rates of gluconeogenesis is probably responsible for 1% of episodes of prolonged hypoglycemia in SGA infants, as these infants exhibit high concentrations of gluconeogenesis precursors (such as alanine); this suggests an inability to convert these exogenous precursors into glucose.

Hypoglycemia combined with asphyxia is more damaging to the immature brain than either condition alone.

4.3. Situations associated with increased glucose consumption

Various situations can increase glucose consumption in the neonate. These include severe birth asphyxia [9], severe respiratory distress, and sepsis.

Perinatal asphyxia may initially feature hyperglycemia secondary to cortisol and catecholamine release; this is followed by hypoglycemia secondary to depletion of hepatic glycogen stores, mobilized in response to this excess glucose consumption. The association of hypoglycemia with transient hyperinsulinism has been described [18].

The association of severe respiratory distress, from various causes, and hypoglycemia caused by increased glucose consumption has often been described.

Neonatal sepsis is defined as a clinical syndrome characterized by systemic signs of infection and bacteremia (detected by positive blood cultures) during the first month of life. It is becoming increasingly important due to the reduction of neonatal mortality among the most premature newborns and to the prolonged care of these infants in neonatal units.

Decreased glycogen stores, impaired gluconeogenesis, and increased peripheral glucose utilization appear to be the factors responsible for hypoglycemia associated with sepsis, although the usual response to sepsis observed in animal models has been an increase in the rates of glucose *turnover* and gluconeogenesis, as the result of a counter-regulatory hormonal response [33]. Blunting of this process is observed only during the final stage of illness and serves as a marker of fulminant sepsis [38].

4.4. Drugs used in pregnancy

Drugs such as beta-adrenergic agonists [57], corticosteroids, thiazide diuretics, oral antidiabetics, propranolol, labetalol [3], valproic acid [10], antidepressants (SSRIs) [40], phenytoin, and terbutaline [55], among others, can cause hypoglycemia in infants.

B. Zhu et al. (2016) [67] reported an association between metformin use by diabetic patients during pregnancy and a reduction in incidence of neonatal hypoglycemia when compared to mothers who used insulin. Metformin has proven an effective alternative for use in this patient population, although it can cross the placenta.

5. Manifestations and clinical diagnosis

In most cases, infants—even those at risk—are asymptomatic. Nevertheless, an infant who is apathetic and refusing feeds and has a feeble cry should heighten suspicion of hypoglycemia. In high-risk infants, major findings include fine tremors, acrocyanosis, seizures, and apnea; if left untreated, coma and death may follow.

After birth, neonates born to mothers with diabetes develop complications related to their hyperinsulinemic state. In the first 3 days of life, these infants may exhibit episodes of irritability, tremor, and hyperexcitability or may present with hypotonia, lethargy, and weak suckling—manifestations consistent with early development of hypoglycemia and late onset of hypocalcemia. However, one must bear in mind that these infants are sometimes asymptomatic and the absence of symptoms should not delay testing for hypoglycemia.

The presence of tachypnea in the first days of life may be a transient manifestation of hypoglycemia, hypothermia, polycythemia, heart failure, cerebral edema secondary to traumatic delivery (particularly in macrosomic infants), or asphyxiation. The incidence of respiratory distress syndrome is high in these infants, since hyperinsulinemia may alter fetal lung maturation, inhibiting the development of enzymes required for the synthesis of pulmonary surfactant.

6. Laboratory diagnosis

Glucometry is the method of choice for initial screening of glucose levels, due to its use and minimal blood sample required; however, levels should be confirmed through laboratory measurement in plasma, especially when the glucometer reading is very low, as this method is rather imprecise at the lower limit of detection. Several factors can affect the values obtained by glucometry, such as the expiration date of the test strip, ambient temperature and humidity in the storage environment, the presence of sugars other than glucose, metabolic acidosis, high PO_2, hyperbilirubinemia, high hematocrit, and edema, among others [25, 66]. Several devices have been tested with the aim of demonstrating that their results may be unreliable and influence the management indicated by a reading [14].

7. Diagnostic imaging

A particular vulnerability of the occipital lobe to hypoglycemia has been observed on MRI [16], with no plausible explanation. Other authors have raised the possibility that variant anatomy of the circle of Willis and occipital lobe infarct may be implicated in these cases [2].

8. Treatment

As mentioned previously, there are still no clearly set values to define hypoglycemia in the first 2 h of life. It is known that, in the healthy, full-term neonate, blood glucose levels are lowest between 30 and 60 min of life and rise thereafter to normal baseline values of 60–90 mg/dL between 90 and 180 min of life. This threshold should be considered the physiological goal or therapeutic target at which blood glucose levels should be maintained.

Although one may consider a diagnosis of hypoglycemia when plasma glucose levels are below 45 mg/dL, this is not an absolute cutoff. Depending on the etiology of hypoglycemia and, consequently, on the availability of alternative pathways for gluconeogenesis, patients may be symptomatic in the 45–60 mg/dL range, as in cases of fatty acid oxidation defects.

SGA and late-preterm infants should be fed every 2–3 h and screened before each feeding in the first 24 h. After 24 h, screening needs only be continued in those whose glucose levels remain below 50 mg/dL.

8.1. Newborns asymptomatic in the first 2 h of life

The need for treatment in these children has been called into question, as hypoglycemia may be transient and may resolve spontaneously through stimulant counter-regulatory mechanisms. In general, if the infant is asymptomatic, to start early breastfeeding without the need to draw blood for glucose measurement, formula feeding, or other special care.

However, in some newborns, this physiological process may fail, which may facilitate the development of hypoglycemia; therefore, the American Academy of Pediatrics suggests that

in the first hour of life, asymptomatic at-risk infants should have a glucose check 30 min after feeding; if the blood glucose level remains below 25 mg/dL and the infant is asymptomatic, it should be fed again and blood glucose reassessed 1 h after the first check [67].

8.2. Asymptomatic high-risk newborns

Late-preterm, LGA, SGA, and intrauterine growth restriction (IUGR) infants, as well as those born to diabetic mothers, are at particular risk of hypoglycemia. However, they are often asymptomatic. Breastfeeding followed by repeated glucose measurement has been the standard of care. However, if hypoglycemia persists despite frequent feedings, continuous intravenous infusion of glucose may be indicated.

A dextrose infusion rate of 3–5 mg/kg/min may be used in infants born to diabetic mothers, both to prevent overstimulation of glucose secretion and because of the greater fat mass of these infants. A dextrose infusion rate of 4–7 mg/kg/min may be used in most full-term and late-preterm neonates. In IUGR neonates, a glucose infusion rate of 6–8 mg/kg/min is often necessary. A study in an animal model of IUGR revealed increased peripheral insulin sensitivity, which may be associated with increased glucose infusion requirements. However, some children with IUGR should be followed closely, especially preterm infants, who may develop hyperglycemia due to reduced insulin secretion and less muscle mass for glucose utilization. Continuous intravenous glucose infusion, usually preceded by an IV bolus of dextrose (200 mg/kg over 5 min), is also indicated if these newborns develop symptomatic hypoglycemia. However, the need for such massive glucose administration is hotly contested due to the risk of undesirable effects, particularly in very-low-birth-weight preterm infants. Complete or partial resolution of symptoms once glucose concentration is corrected is considered definitive proof that symptoms were caused by hypoglycemia. Nevertheless, IV dextrose infusions are not an entirely appropriate treatment; they cause discomfort to the infant, which is made worse by the need for placement of a deep IV catheter, the need for NICU admission, and physical separation of the newborn from the mother, which hinders timely initiation of breastfeeding. However, when administered safely so as to prevent these complications, IV infusion of dextrose at low concentrations can be beneficial even in asymptomatic high-risk neonates.

8.2.1. Dextrose gel

Oral administration of glucose in gel form has been considered appropriate and should be part of any protocol to prevent episodes of hypoglycemia in asymptomatic newborns [41]. Current studies have shown that oral administration of 40% dextrose gel may reduce the occurrence of neonatal hypoglycemia by up to 70% [5] and should thus be considered as the first-line treatment in these patients [65].

8.3. Symptomatic newborns

8.3.1. Glucose

Symptomatic neonates should be treated with glucose intravenously, not orally. A 200 mg/kg bolus of glucose should be administered over 1 min (10% dextrose at 2 mL/kg). This should be followed by IV infusion at 6–8 mg/kg/min. Glucose levels should be monitored after 30–60 min,

with a therapeutic target of >45 mg/dL. Control measurements should be obtained every 1–2 h. Once levels are stable, they can be reassessed every 4–6 h. If values do not reach a normal range, the rate of glucose infusion is increased by 1–2 mg/kg/min every 3–4 h. In cases of hyperinsulinism, a rate of 15–30 mg/kg/min may be necessary. Oral feedings should only resume once blood glucose levels have been stable for 6 h.

High glucose concentrations (20–25%) may be necessary to maintain a rate of infusion of 15–30 mg/kg/min; concentrations above 12.5% will require a central venous catheter [56].

8.3.2. Glucocorticoids

Physiologically, glucocorticoids promote increased resistance to insulin action, reduce the secretion of insulin, and activate enzymes involved in gluconeogenesis, mobilizing amino acids for this purpose. Thus, although such effects should theoretically induce an increase in blood glucose, there is no evidence to support glucocorticoid therapy in the treatment of hypoglycemia other than that caused by primary or secondary adrenal insufficiency.

Except in cases of hypoglycemia of self-limiting etiology (e.g., infants born to diabetic mothers), blood and urine samples should be drawn at the time of hypoglycemia for investigation of possible changes in energy and hormone metabolism (lactate, free fatty acids, ketones, insulin, cortisol, growth hormone, urinary organic acids) before any specific medications are administered.

8.3.3. Glucagon

Endogenous glucagon is the counter-regulatory hormone of insulin, secreted by pancreatic beta cells. Physiologically, hypoglycemia induces glucagon secretion to raise glucose levels [43]. The administration of glucagon has proven to be quite effective in full-term and preterm neonates without hyperinsulinism. Serum sodium levels should be monitored during glucagon infusion. Hyponatremia, thrombocytopenia, and a rare paraneoplastic phenomenon, called necrolytic migratory erythema, have been associated with continuous infusion of glucagon. Hypertonic saline solution (3% sodium chloride) may be indicated to treat glucagon-associated hyponatremia.

A dose of 0.02 mg/kg/dose has been recommended [43]. A 24-h continuous infusion has been used at doses of 20–40 μg/kg/h up to a maximum of 1 mg/day. A 50% rise in blood glucose is expected in normal infants. The effect is transient. Long-acting preparations are employed in patients with glucagon deficiency and, in combination with somatostatin, in the treatment of congenital hyperinsulinism. When the expected rise in blood glucose does not occur, the diagnosis of hepatic glycogen storage disease should be suspected.

8.3.4. Diazoxide

This agent is indicated in cases of hypoglycemia associated with hyperinsulinism.

Diazoxide is a benzothiazine derivative that acts by opening ATP-sensitive potassium channels, causing inhibition of insulin secretion by pancreatic beta cells. Therefore, patients with

genetic defects that affect SUR1 and Kir 6.2, the constituent proteins that form the ATP-sensitive potassium channel, may not benefit from administration of this drug. The recommended dose ranges from 10 to 15 mg/kg/day, divided in two or three oral doses, up to a maximum dose of 30 mg/kg/day. It promotes an increase in hepatic glucose production and decreases peripheral glucose utilization. Most of the drug is eliminated by glomerular filtration, and 90% of diazoxide is bound to albumin. Sodium and water retention, plasma volume expansion, edema, thrombocytopenia, anorexia, vomiting, ketoacidosis, and hyperuricemia are possible complications of the use of this drug [17].

When the drug is effective, blood glucose levels will return to normal range within 2–4 days. Any trial of diazoxide therapy should last at least 1 week before the possibility of treatment failure is considered. Onset of action occurs within 1 h of administration, and the duration of action is approximately 8 h, as long as renal function is normal.

Failure of diazoxide therapy suggests an abnormality in ATP-sensitive potassium channels. In these cases, a course of octreotide therapy, which acts further downstream on the insulin secretion pathway, is advised.

8.3.5. Octreotide

Octreotide was the first somatostatin analogue approved for clinical use, due to its more prolonged effect. This substance inhibits the secretion of glucagon, insulin, growth hormone, and thyrotropin, as well as the exocrine secretions of the bowel. Due to its ability to inhibit hormones, this drug can be used in infants with congenital hyperinsulinemic hypoglycemia [19]. A dose of 5–35 mcg/kg/day via subcutaneous injection has been recommended.

8.3.6. Sirolimus (rapamycin)

The management of diffuse hyperinsulinemic hypoglycemia, which does not respond to diazoxide, is a major therapeutic challenge. The successful use of sirolimus, both alone and as adjunctive therapy with octreotide, appears to be a potential alternative to subtotal pancreatectomy. Sirolimus is an immunosuppressant that inhibits the activation and proliferation of T lymphocytes, with effects *downstream* of the IL-2 receptor and other T-cell growth factor receptors.

In a study involving four patients with diffuse hyperinsulinemic hypoglycemia [46], therapy with sirolimus allowed discontinuation of intravenous infusions of dextrose and glucagon in all for patients and maintenance treatment with octreotide alone. At the end of the first year of life, the four patients continued to receive sirolimus and were normoglycemic, without any apparent major adverse events. Sevim Ünal et al. [63] reported the use of sirolimus in a neonate with CHH due to a KCNJ11 gene mutation who had already failed treatment with continuous infusions of glucose (14 mg/kg/min) and prednisone (2 mg/kg/day). Addition of intensive therapy with multiple medications (diazoxide, chlorothiazide, octreotide, glucagon, and nifedipine) also failed to produce an adequate response. However, before partial pancreatectomy was attempted, at age 30 days, sirolimus therapy was instituted at a dose of 0.5 mg/m^2/day.

Improvements in glycemic control were achieved, enabling progressive dosage reduction of the other drugs. At the time of publication, at age 5 months, the infant was on minimal doses of hyperglycemic agents and continued to receive twice-daily sirolimus at a dose of 0.3 mg/m^2/day, without any complications.

8.3.7. Exendin

Recently, exendin-(9-39), a GLP-1 receptor antagonist that raises blood glucose levels in adults, has been introduced as a possible novel therapy for management of hypoglycemia in patients with CHH. However, further studies on its effectiveness and safety are needed [8].

8.3.8. Other drugs

Growth hormone is used in cases of hypoglycemia associated with deficiency of this hormone or with hypopituitarism.

In cases of hypoglycemia due to persistent hyperinsulinemic hypoglycemia that does not respond to treatment with diazoxide, glucose, and sirolimus, partial pancreatectomy may be indicated.

9. Consequences

Recurrent or sustained hypoglycemia can cause neurological damage, mental retardation, epilepsy, and personality disorders [54]. Transient episodes of hypoglycemia are also associated with deficits in math learning around age 10 years [26].

Severe hypoglycemia can lead to impairment of cardiovascular function and is associated with high rates of neonatal mortality in very low-birth-weight infants [15].

Permanent brain damage is found in 25–50% of patients with recurrent severe symptomatic hypoglycemia under age 6 months. Furthermore, hypoxemia and ischemia may potentiate the permanent damage caused by hypoglycemia. The pathological changes described include gyral atrophy, reduced white-matter myelination, and cerebral cortical atrophy. It bears noting that the cerebral infarctions characteristic of hypoxic-ischemic processes are absent in hypoglycemia-associated brain injury [51].

10. Final considerations

Newborns with risk factors for neonatal hypoglycemia or those which, although not considered at risk, exhibit poor suckling or inadequate breast milk intake should receive follow-up monitoring and care after hospital discharge, so as to prevent possible undetected hypoglycemia.

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