

Neonatal Hypoglycemia

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OBJECTIVES

After completing this article, readers should be able to:

1. Describe the most common cause of prolonged neonatal hypoglycemia.
2. List the signs of hypoglycemia.
3. Describe the condition that has been implicated as a mechanism of hypoglycemic brain injury.

Case Study

A term male infant was born after an uneventful pregnancy to a 28-year-old gravida I woman who had no evidence of hyperglycemia and no chronic diseases. The infant had Apgar scores of 7 and 9 at 1 and 5 minutes, respectively. His growth parameters were in the normal range, with weight at the 60th percentile, head circumference at the 50th percentile, and length at the 50th percentile. The baby was taken to the well baby nursery, examined and bathed, and then taken to the mother for nursing at about 2 hours of age. He appeared slightly jittery at that time and was not very interested in nursing or very aware. A blood glucose concentration of 1.39 mmol/L (25 mg/dL) was obtained using a One Touch[®] instrument. The baby was fed 25 mL of 5% dextrose in water. The blood glucose concentration obtained 1 hour later was 2.22 mmol/L (40 mg/dL), and the baby nursed for about 5 minutes at each breast with apparent satisfaction. Jitteriness and “lack of interest” were improved.

Normal nursery routine was followed, with no comment in the chart by the nursing staff about the infant’s feeding or behavior until the second day of life when he again appeared jittery and fussy. Glucose concentration at that time was 1.11 mmol/L (20 mg/dL). The infant was fed by breast or bottle (routine 20 kcal/oz house formula) alternating every 2 hours, and clinical signs

improved. One Touch[®] glucose concentrations obtained over the next 24 hours were variable, but overall the concentration increased, with a predischarge, preprandial value of 2.78 mmol/L (50 mg/dL).

The family failed to return to the hospital clinic the next day, but did see their primary care physician on the fifth day of life at which time the infant acted hungry, was noted to be “very active,” and weighed 113.4 g more than birthweight. At 2 weeks of life, the parents noted the infant to be very fussy and jittery and to experience staring spells. At a local emergency department, he was noted to have lost weight, appeared somnolent but fussy when aroused, and started having tonic-clonic jerking movements of all extremities. A “glucose concentration” was less than 0.55 mmol/L (10 mg/dL). The infant was treated with intravenous glucose, and the apparent seizure resolved. Over the next several weeks, the infant returned to the emergency department several times with similar episodes.

When finally examined by the primary care physician, the infant had gained 283.5 g and appeared “puffy.” An “office glucose concentration” was 1.94 mmol/L (35 mg/dL). The infant was referred to a pediatric endocrinologist, who noted that the infant’s weight was approaching the 90th percentile, there was definite hepatomegaly, and the infant appeared “apathetic.” In the hospital, several serum glucose concentrations were measured at less than 2.22 mmol/L (40 mg/dL), with plasma insulin concentrations all greater than 144 pmol/L (20 mcU/mL).

The infant was treated with diazoxide with only limited success over the next 3 months. Development continued but was “slow.” He was treated in the local emergency department three times for tonic-clonic seizures, all requiring intravenous glucose to correct severe hypoglycemia. At 5 months of age, the infant underwent a subtotal pancreatectomy. While recovering, he had a severe, prolonged seizure and was noted to be in shock, requiring two rounds of resuscitation. *Escherichia coli* meningitis was diagnosed and treated successfully.

At 1 year of age, the infant showed little developmental gain from 6 months of age. At 5 years of age, he exhibited extremely poor growth, had diabetes mellitus that necessitated insulin treatment, and required pancreatic enzyme replacement with feedings to treat malabsorptive diarrhea. He was almost completely deaf and had marked developmental delay. His parents sought legal counsel, claiming that the treating physicians in the birth hospital failed to diagnose a “hyperinsulinism” condition that then led to delayed diagnosis and treatment, followed by severe neurologic damage.

Questions to consider (feel free to send in your answers to these questions and any questions of your own for the “experts” to consider and discuss about this case):

1. What is the likely diagnosis for this infant’s hypoglycemia?
2. What diagnostic tests could have been done in the birth hospital to determine whether the infant had

ABBREVIATIONS

AGA:	appropriate for gestational age
ATP:	adenosine 5'-triphosphate
IDM:	infant of a diabetic mother
IUGR:	intrauterine growth retardation
LGA:	large for gestational age
NMDA:	N-methyl-D-aspartate
SGA:	small for gestational age

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transient or persistent hypoglycemia?

3. What could have been done prior to discharge from the birth hospital to provide evidence of the infant's ability to maintain a normal blood glucose concentration with a normal feeding schedule?

4. What did the pancreatic pathology examination likely show at the time of subtotal pancreatectomy?

5. How would you assess the clinical outcome in relation to the primary diagnosis and its complications versus the *E coli* meningitis and shock?

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Introduction

Glucose is the major source of energy for organ function. Although all organs can use glucose, the human brain uses it almost exclusively as a substrate for energy metabolism. Because cerebral glycogen stores are limited, maintenance of adequate glucose delivery to the brain is an essential physiologic function. The high brain-to-bodyweight ratio in the newborn results in a proportionately higher demand for glucose compared with the capacity for glucose production than that encountered in the adult, with cerebral glucose use accounting for as much as 90% of total glucose consumption. Although alternate fuels, such as lactate and ketone bodies, can be used as a substrate for energy production, the newborn's immature counterregulatory response limits the availability of these molecules. Thus, newborns are extremely susceptible to any condition that impairs the establishment of normal glucose homeostasis during the transition from intrauterine to independent extrauterine life.

Glucose Homeostasis in Utero

Glucose is one of the major substrates for fetal metabolism. Under normal conditions (ie, normal maternal glucose levels), virtually all of the glucose used by the fetus is supplied from the maternal circulation via facilitated diffusion across the

placenta. This results in a fetal blood glucose concentration of approximately 70% of the maternal value. Although the enzymes necessary for both gluconeogenesis and glycogenolysis are present in the human fetus by the end of the first trimester, several studies have demonstrated that there is no significant glucose production in the fetus unless there is a sustained decrease in umbilical glucose uptake. Glucose utilization rates in the fetus have been estimated at 4 to 6 mg/kg per minute. Approximately 60% to 70% of fetal glucose utilization is accounted for by oxidation of glucose carbon to CO₂, with the remainder available for synthesis of glycogen and other macromolecules. In the human fetus, oxidation of glucose accounts for approximately 80% of fetal oxygen consumption, demonstrating that glucose is the major substrate for fetal oxidative metabolism.

The rate at which the fetus uses glucose is primarily a function of glucose concentration, although changes in insulin concentration may have a modest influence as well. Studies have demonstrated that levels of fetal pancreatic insulin secretion correlate with changes in fetal glucose concentration, but the pancreatic response is blunted compared with the newborn or adult. Insulin secretion in response to fetal hyperglycemia increases glucose utilization and oxidation rates, but it has little effect on fetal metabolic rate or the rate of oxygen consumption, suggesting that oxidation of other substrates is reduced under these conditions. Decreased oxidation of substrates such as amino acids and lactate results in increased availability of those substrates for tissue accretion and may account in part for the increased somatic growth associated with fetal hyperinsulinemia.

In animal models, administration of glucagon does not appear to have a direct effect on fetal glucose metabolism. However, the ratio of insulin to glucagon in the fetal circulation plays a critical role in regulating the balance between glucose consumption and energy storage. The high insulin:glucagon ratio in the fetal circulation results in activa-

tion of glycogen synthesis and suppression of glycogenolysis by regulating the activity of the hepatic enzymes used for these processes. Predominance of insulin maintains glycogen synthase in its active form and glycogen phosphorylase in its inactive form via cAMP-dependent effects on specific protein kinases and phosphatases, thus enhancing glycogen synthesis and minimizing glycogenolysis. In most species, including humans, hepatic glycogen stores accumulate slowly during early and midgestation, with a rapid increase in hepatic glycogen content occurring during the last 30% of fetal life. The marked increase in glycogen synthesis during this period is associated with an increase in circulating concentrations of both insulin and cortisol. Because the increase in cortisol seems to be necessary for maximal activation of glycogen synthase, fetal adrenal dysfunction may limit hepatic glycogen accumulation late in gestation. Under conditions associated with decreased fetal glucose concentrations and increased glucagon secretion, such as chronic hypoglycemia or hypoxemia, glycogen phosphorylase is activated, and synthase is converted to its inactive form, thereby suppressing glycogen synthesis and stimulating glycogenolysis with subsequent depletion of fetal glycogen stores. The high insulin:glucagon ratio also suppresses lipolysis, which allows for additional energy to be stored in the form of subcutaneous fat. Thus, the fetal hormonal and metabolic milieu establishes a ready substrate supply that can be used during the metabolic transition from fetus to newborn.

Glucose Homeostasis in the Newborn

The relative dependence of the fetus on a constant supply of maternal glucose necessitates significant changes in regulation of glucose metabolism at birth following the abrupt interruption of umbilical glucose delivery. Although the exact trigger is unknown, a number of physiologic changes equip the newborn for maintenance of glucose homeostasis. Increased catechol-

amine concentrations immediately following delivery stimulate glucagon secretion, with a subsequent decrease in the insulin:glucagon ratio. Glycogen synthase is inactivated and glycogen phosphorylase is activated, leading to stimulation of glycogenolysis and inhibition of glycogen synthesis. Release of glucose from glycogen provides a rapidly available source of glucose for the newborn in the first few hours postpartum. However, it has been estimated that term infants have only enough hepatic glycogen to maintain the glucose supply for about 10 hours. Therefore, other mechanisms are required to maintain glucose homeostasis. The high glucagon:insulin ratio postpartum also induces synthesis of the enzymes required for gluconeogenesis. With the combination of the release of fatty acids stimulated by the high catecholamine concentrations that leads to a marked increase in glycerol availability and the availability of free amino acids in the circulation, the infant becomes capable of significant gluconeogenesis by 4 to 6 hours of life. However, enzyme activities do not reach adult levels until 1 to 2 weeks of age.

Basal glucose utilization rates in the newborn infant are 4 to 6 mg/kg per minute, almost twice the weight-specific rates in adults. During the first few hours of life, blood glucose concentrations fall from the fetal value, which reflects the mother's blood glucose concentration, to as low as 1.7 mmol/L (30 mg/dL) before the infant attains the metabolic transition to independent glucose production and establishes postnatal glucose homeostasis. Until an exogenous supply of substrate is provided, either by enteral feedings or administration of intravenous fluids, hepatic glucose output serves as the most significant source of glucose to meet metabolic demands. To maintain normal levels of hepatic glucose production, the infant must have adequate stores of glycogen and gluconeogenic precursors (eg, fatty acids, glycerol, amino acids, and lactate), appropriate concentrations of the hepatic enzymes required for gluconeogenesis and glycogenolysis, and a normally functioning endocrine system. Absence

of any of these requirements leads to disruption of glucose homeostasis, most commonly resulting in neonatal hypoglycemia.

Incidence, Diagnosis, and Clinical Presentation

INCIDENCE

Estimates of the incidence of hypoglycemia in the newborn depend both on the definition of the condition and the methods by which blood glucose concentrations are measured. The overall incidence has been estimated at 1 to 5 per 1,000 live births, but it is higher in at-risk populations. For example, 8% of large-for-gestational-age infants (primarily infants of diabetic mothers [IDMs]) and 15% of preterm infants and infants who have intrauterine growth retardation (IUGR) have been reported as having hypoglycemia; the incidence in the entire population of "high-risk" infants may be as high as 30%.

LABORATORY DIAGNOSIS

The concentration of blood glucose at which the diagnosis of neonatal hypoglycemia should be made has been highly controversial. Hypoglycemia in term infants has been defined as a blood glucose value of less than 2.0 mmol/L (<35 mg/dL) or as a plasma glucose value of less than 2.2 mmol/L (<40 mg/dL). However, a recent survey of pediatricians in the United Kingdom demonstrated no consensus as to the level of blood glucose that they considered "hypoglycemia". They cited concentrations ranging from 1 mmol/L (20 mg/dL) to 4 mmol/L (70 mg/dL) as the lower limit of normal. Further, definitions of hypoglycemia are based primarily on population studies of blood or plasma glucose concentrations during the first 48 to 72 hours of life, with hypoglycemia being defined as a blood glucose level more than 2 standard deviations below the population mean. Such definitions have only limited physiologic significance.

Physiologically, hypoglycemia is present when glucose delivery is inadequate to meet glucose demand

and can occur over a range of glucose concentrations, depending on the status of the infant. For example, a 2-hour-old healthy infant who has a blood glucose of 1.7 mmol/L (30 mg/dL) might not demonstrate impaired organ function, but a stressed infant might demonstrate physiologic hypoglycemia at a blood glucose concentration of 2.8 mmol/L (50 mg/dL) if the rate of glucose delivery to specific organs (eg, the brain) is less than the rate of glucose utilization. No studies to date have established an absolute blood glucose concentration at which short- or long-term organ dysfunction invariably occurs, although animal studies suggest that concentrations less than 1 mmol/L (<20 mg/dL), if sustained over a number of hours, may be associated with inevitable brain injury. Without specific evidence to support an absolute threshold value, no single blood glucose value can be used to define physiologic hypoglycemia.

The definition of "normal" blood glucose concentrations for a given population of newborns also depends on the feeding practices in that population. For example, the mean value for normal blood glucose concentrations in term infants determined from studies 30 years ago was significantly lower than values determined in the past 10 years. This is not because of a change in neonatal physiology, but because pediatricians no longer follow the practice of withholding feedings from healthy newborns for a prolonged period after delivery. Rather than reflecting "normal" neonatal glucose homeostasis, these early values demonstrated the effects of the interference of medical practitioners in the normal transition to postnatal metabolism. Similarly, early data that demonstrated lower blood glucose values in populations of preterm infants compared with term infants was interpreted erroneously to mean that low-birthweight infants tolerated hypoglycemia better than normal-weight neonates. In fact, these data reflected failure of hepatic glucose production in preterm infants in response to an inadequate supply of exogenous substrate. At that time, standard feeding practices had not been established for

this population, and reliable intravenous (IV) nutrition was not available. Finally, the time at which the blood glucose concentration is measured affects the value considered “normal”; blood glucose concentrations increase over the first 24 to 48 hours of life in healthy term infants, probably as a result of both the increasing volume of enteral feeding and initiation of gluconeogenesis. Thus, a value that would be considered “low normal” at 3 hours of life might be termed “hypoglycemic” at 18 hours.

Making a firm diagnosis of hypoglycemia is complicated further by the limitations of methods used to measure blood glucose concentrations rapidly. Although the “gold standard” remains the hexokinase method used by many diagnostic laboratories, this approach is impractical as a screening tool because of the time required to process the sample and to perform the assay. Furthermore, if the sample is not transported rapidly to the laboratory and processed quickly, the glucose will be metabolized by red blood cells, thereby falsely decreasing the glucose concentration. Placing the specimen in a tube that contains a glycolytic inhibitor such as sodium fluoride can prevent this problem, but such tubes are either not readily available or simply not used.

Most nurseries use glucose oxidase/peroxidase chromogen test strips to screen high-risk newborns for low blood glucose concentrations. A drop of blood placed on the reagent-impregnated paper strip for the specified time will induce a color change that correlates with blood glucose concentration. The actual blood glucose concentration can be estimated by comparison with a standard chart or determined more precisely by “reading” the color of the strip with a reflectance colorimeter that has been calibrated using a standard solution. Although use of a reflectance colorimeter to read the test strips improves precision, multiple studies comparing various methods have found that the correlation between “real” blood glucose values and values obtained using test strips remains highly variable. This is especially true at low blood glucose concentrations.

Reagent test strip results also are susceptible to variations in the technique used to obtain the sample (eg, variability in the amount of blood applied to the strip or contamination of the sample by residual isopropyl alcohol on the skin). It has been estimated that screening with reagent strips will detect approximately 85% of cases of hypoglycemia, although the false-positive rate may be as high as 25%. Thus, to ensure accurate detection of low blood glucose concentrations, a confirmatory sample should be sent to a central laboratory if a test strip value is consistent with hypoglycemia or if the test strip result is in the normal range but clinical findings raise the suspicion of hypoglycemia.

CLINICAL PRESENTATION

Although hypoglycemia often is classified as “symptomatic” or “asymptomatic”, these terms actually reflect the presence or absence of physical signs that accompany a low blood glucose concentration. A variety of signs may be seen in cases of severe or prolonged hypoglycemia and in infants who have mild-to-moderate hypoglycemia and are otherwise physiologically stressed. Most findings are nonspecific and result from disturbances in one or more aspects of central nervous system function. These include abnormal respiratory patterns, such as tachypnea, apnea, or respiratory distress; cardiovascular signs, such as

tachycardia or bradycardia; and neurologic findings, including jitteriness, lethargy, weak suck, temperature instability, and seizures. Many of these signs can result from other common neonatal disorders, including sepsis, hypocalcemia, and intracranial hemorrhage. Hypoglycemia always must be considered in an infant who exhibits one or more of these signs because untreated hypoglycemia can have serious consequences, and the treatment is fast, relatively easy, and has limited side effects. However, given current standards for newborn care, most cases of hypoglycemia in the neonate are diagnosed during routine screening of infants considered to be at risk but who appear physiologically normal at the time of evaluation.

Etiology

PREMATURITY AND IUGR

The causes of neonatal hypoglycemia can be categorized according to associated disturbances in one or more of the processes required for normal hepatic glucose production that may lead to transient or prolonged episodes of hypoglycemia (Table 1). Hepatic glycogen stores are limited in both preterm infants, who have not experienced the period of rapid glycogen accumulation during late gestation, and small-for-gestational age (SGA) infants, who have not had adequate substrate supply available for glycogen synthesis,

TABLE 1. Etiologies of Neonatal Hypoglycemia

ETIOLOGY	DURATION OF HYPOGLYCEMIA
Prematurity, intrauterine growth retardation	Transient*
Asphyxia, hypothermia	Transient
Sepsis	Transient
Infant of diabetic mother	Transient
Erythroblastosis fetalis	Transient
Exposure to beta-agonist tocolytics	Transient
Familial hyperinsulinism	Prolonged
Inborn errors of metabolism	Prolonged
<i>*Generally <7 d duration.</i>	

which puts these newborns at risk for hypoglycemia. IUGR due to placental insufficiency with preservation of normal head size puts an added demand on the infant's already low glycogen stores because of the increased brain-to-bodyweight ratio. Postterm infants and infants of multiple gestations also may be at risk because of the presence of relative placental insufficiency. In addition to decreased glycogen availability, studies in preterm and IUGR infants have found altered patterns of insulin secretion, substrate metabolism, and hormonal responses to changes in blood glucose concentration compared with appropriate-for-gestational age (AGA) term infants.

Infants who have experienced perinatal stress due to asphyxia or hypothermia or who have increased work of breathing due to respiratory distress may have "normal" glycogen stores, but the amount of glycogen available may be inadequate to meet their increased requirement due to higher-than-normal levels of glucose utilization. Hypoglycemia may occur in these infants once available glycogen has been used to meet the initial postnatal metabolic demands, particularly if there has been a period of hypoxemia with associated rapid consumption of glucose via anaerobic metabolism.

It is uncommon for inadequate levels of gluconeogenic precursors to be a limiting factor in hepatic glucose production in the newborn because even preterm infants appear to have sufficient fatty acids, glycerol, amino acids, lactate, and pyruvate available. However, gluconeogenic enzymes are induced more slowly in preterm infants. Further, production of ketone bodies is relatively diminished in response to hypoglycemia. Term infants may have augmented release of ketone bodies when blood glucose decreases, but the concentrations of ketones correlate poorly with the degree of hypoglycemia. As a result, the contribution of gluconeogenesis to hepatic glucose production may be limited in some newborns.

IDMS

Several groups of infants are at increased risk for hypoglycemia due

to alterations in hepatic enzyme functions that impair glycogenolysis, gluconeogenesis, or both. Hepatic function can be affected by a number of endocrine and metabolic disturbances, the most common being hyperinsulinism. IDMs may have increased secretion of pancreatic insulin because of exposure to increased maternal glucose concentrations in utero. Placental glucose transport is increased, leading to fetal hyperglycemia, which in turn stimulates secretion of insulin by the fetal pancreas. IDMs also have exaggerated pancreatic insulin secretion in response to a given glucose load compared with nonIDMs. Other diabetes-induced alterations in maternal metabolism, such as changes in serum amino acids, may play a role in the metabolic alterations found in IDMs.

After delivery, increased blood glucose concentrations no longer are present, but the hyperinsulinemia persists, thus maintaining a high insulin:glucagon ratio postnatally. As a result, glycogenolysis and lipolysis are inhibited, gluconeogenic enzymes are not induced, and hepatic glucose production remains at low levels in the face of decreasing blood glucose concentrations. Insulin also increases peripheral glucose utilization in insulin-sensitive tissues such as skeletal muscle, contributing to rapid depletion of available glucose. The combined effects of increased glucose utilization and inhibited hepatic glucose production result in hypoglycemia, which may persist for 24 to 72 hours before insulin secretion patterns normalize.

ERYTHROBLASTOSIS FETALIS AND BETA-AGONIST TOCOLYTIC AGENTS

Although maternal diabetes is the most common cause of hyperinsulinism in the newborn, postnatal insulin secretion may be abnormal due to several other disorders. Infants who have erythroblastosis fetalis have increased levels of insulin and an increase in the number of pancreatic beta cells. The mechanism for this development is unclear, but one possibility is that glutathione released from hemolyzed red cells inactivates insulin in the circulation, which trig-

gers more insulin secretion and upregulates the beta cells. Exchange transfusions may exacerbate the problem because transfused blood usually is preserved with a combination of dextrose and other agents. During the exchange, the infant receives a significant glucose load, with subsequent exaggerated insulin response from the hyperplastic pancreas. At the end of the exchange, the rate of dextrose administration returns to baseline, but insulin levels remain elevated, leading to further hypoglycemia.

Use of beta-agonist tocolytic agents such as terbutaline also is associated with hyperinsulinemia in the newborn, especially if the agent was used for more than 2 weeks and was discontinued less than 1 week prior to delivery. Affected infants also appear to have reduced glycogen stores, which further aggravates the hyperinsulinemia and its effects on decreasing glucose concentrations.

HYPERINSULINISM

Hypoglycemia that persists for more than 5 to 7 days is uncommon and most often is due to hyperinsulinism. Some infants who have IUGR or perinatal asphyxia demonstrate hyperinsulinemia that may persist for as long as 4 weeks, but such cases are relatively rare, and the underlying mechanism is unclear. Several types of congenital hyperinsulinism have been described and are said to be the most common cause of hypoglycemia persisting beyond the first week of life.

The autosomal recessive form of congenital hyperinsulinism has been linked to a defect in the sulfonylurea receptor or K^+ -ATP channel. A single mutation on the short arm of chromosome 11 has been described in the Ashkenazi Jewish population, but cases in other ethnic groups have been associated with a number of other mutations in the same region. An autosomal dominant form of hyperinsulinemia also has been described. The mutation(s) responsible for the autosomal dominant form of hyperinsulinism has not yet been identified, but the disorder differs from the autosomal recessive form in that it does not appear to result

from abnormal sulfonylurea receptor function. A syndrome of congenital hyperinsulinemia and asymptomatic hyperammonemia associated with mutations in the glutamate dehydrogenase gene also has been described. Beckwith-Weidemann syndrome is associated with hyperplasia of multiple organs, including the pancreas, with consequent increased insulin secretion. Rarely, hyperinsulinemia may result from localized islet cell adenomas within an otherwise normal pancreas.

INBORN ERRORS OF METABOLISM

Inborn errors of metabolism may affect either the availability of gluconeogenic precursors or the function of the enzymes required for production of hepatic glucose. Metabolic defects that may present with hypoglycemia include some forms of glycogen storage disease, galactosemia, fatty acid oxidation defects, carnitine deficiency, several of the amino acidemias, hereditary fructose intolerance (fructose-1,6-diphosphatase deficiency), and defects of other gluconeogenic enzymes. Finally, endocrine disorders such as hypopituitarism and adrenal failure also can result in hypoglycemia because of the absence of the appropriate hormonal response to hypoglycemia and subsequent failure to activate hepatic glucose production. However, these conditions are very rare and should be considered after ruling out more common etiologies.

DETERMINING ETIOLOGY

Obtaining a careful perinatal history is the first step in determining the etiology of hypoglycemia in the newborn. The presence of risk factors, such as abnormal results on a maternal glucose tolerance test, maternal administration of drugs associated with neonatal hypoglycemia, or prematurity, makes the diagnosis relatively simple. Growth parameters should be plotted to establish if the infant is SGA, AGA, or LGA. Sepsis should be suspected strongly in the term infant who has hypoglycemia but no other apparent risk factors. If hypoglycemia persists for more than 1 week, the possibilities of hyperinsulinemia, other endo-

crine disorders, and inborn errors of metabolism should be investigated, especially if the hypoglycemia is refractory to standard treatment.

Unfortunately, it often is difficult to document hyperinsulinemia because insulin levels must be drawn during episodes of hypoglycemia to demonstrate the presence of inappropriate insulin secretion. Levels of the binding protein for insulin-like growth factor 1 (IGFBP-1) are decreased in the presence of hyperinsulinemia, making measurement of serum levels of IGFBP-1 useful in confirming the diagnosis of hyperinsulinemia. Serum and urine tests for specific metabolic and endocrine disorders, such as serum amino acid profiles and measurement of cortisol and growth hormone levels, also may be necessary to elucidate the etiology of neonatal hypoglycemia.

Management

The goals in treating the infant who has hypoglycemia are to normalize blood glucose concentrations as quickly as possible and to avoid further episodes of hypoglycemia by providing adequate substrate until normal glucose homeostasis can be established. The method chosen to achieve this goal is a function of both the clinical status of the infant and the suspected etiology of the hypoglycemia.

ENTERAL FEEDING

In term infants who have asymptomatic mild hypoglycemia, an initial attempt at enteral feeding may be successful in reaching target blood glucose values. Although a prompt increase in blood glucose concentrations can be achieved following a feeding with a 5% dextrose and water solution, the dextrose is metabolized rapidly, and hypoglycemia may recur before normal feedings can be established. Use of a standard infant formula will provide not only carbohydrate in the form of lactose but also protein and fat, which are metabolized more slowly and, therefore, will provide a sustained supply of substrate. Fat intake also decreases cellular glucose uptake and stimulates gluconeogene-

sis, further contributing to a restoration of normal glucose homeostasis. It is estimated that blood glucose concentrations should increase by approximately 1.67 mmol/L (30 mg/dL) within the first hour after a feeding of 30 to 60 mL of standard infant formula.

IV THERAPY

Infants whose blood glucose concentrations normalize following an enteral feeding should continue to have blood glucose concentrations checked before each feeding for 12 to 24 hours. If the postprandial concentration is normal, but the value before the next feeding is again in the hypoglycemic range, enteral feeding should be considered a failure, and the infant is a candidate for IV therapy. Prompt provision of IV glucose in these circumstances will avoid repeated episodes of preprandial hypoglycemia. This may be important because follow-up studies of infants who have recurrent hypoglycemia indicate that multiple episodes of low blood glucose concentrations are more likely to be associated with adverse neurodevelopmental outcomes than a single episode.

IV therapy should be the first treatment modality used in symptomatic infants, infants unable to tolerate enteral feedings, and those in whom the disturbance in glucose homeostasis is severe or is expected to last more than a few hours. The latter category includes preterm infants, infants who have IUGR, infants of women who have poorly controlled diabetes, and infants who have underlying etiologies for hypoglycemia, such as sepsis, known or suspected inborn errors of metabolism or endocrine defects, or erythroblastosis.

Administration of an initial bolus of 200 mg/kg of 10% dextrose and water (2 mL/kg of D₁₀W) should be followed by continuous infusion of dextrose calculated to deliver 5 to 8 mg/kg per minute of glucose (ie, a rate equivalent to the glucose utilization rate of a healthy infant). The "mini-bolus" approach has been shown to return blood glucose concentration to normal more rapidly than a constant infusion alone. The

“mini-bolus” dose also is designed to avoid overshooting the desired glucose concentration. By limiting the amount of glucose given as a bolus, it is possible to avoid inducing iatrogenic hyperglycemia, which might stimulate excess insulin secretion and induce rebound hypoglycemia. The blood glucose concentration should be checked approximately 30 minutes after the bolus, then every 1 to 2 hours until stable and in the normal range. If a subsequent value falls in the hypoglycemic range, the bolus should be repeated and the infusion rate increased by 10% to 15%. It is not uncommon for infants who have transient or sustained hyperinsulinemia to require as much as 12 to 15 mg/kg per minute of IV glucose to maintain normoglycemia. In such cases, it may be necessary to place an umbilical venous catheter or a peripheral central venous catheter (so-called PIC line) to allow administration of IV solutions with dextrose concentrations greater than 12.5%.

Unless there are concerns about fluid overload or the ability to tolerate enteral nutrition, infants requiring IV therapy for hypoglycemia should be permitted to continue feedings. There are several benefits to this practice. First, it will allow an easier transition from a parenteral to an enteral source of carbohydrate once blood glucose concentrations have stabilized. Second, providing some carbohydrate as galactose (one of the sugars that comprise lactose) may be useful in IDMs and other infants who have hyperinsulinemia;

studies have shown that the pancreatic insulin response to galactose is less than the response to an equivalent amount of glucose. When a normal blood glucose concentration has been established and the requirement for IV glucose has been stable for 12 to 24 hours, the infant can be weaned from this therapy by measuring preprandial blood glucose concentrations and decreasing the infusion rate by 10% to 20% each time the blood glucose is greater than 2.8 to 3.4 mmol/L (>50 to 60 mg/dL). Failure to tolerate weaning from IV glucose indicates the presence of a pervasive disorder, such as a metabolic defect or idiopathic hyperinsulinemia, and should prompt further evaluation.

OTHER AGENTS

Several other agents have been used to treat refractory hypoglycemia, most often encountered in one of the hyperinsulinemic states (Table 2). Corticosteroids (hydrocortisone, 5 to 15 mg/kg per day in two to three divided doses, or prednisone, 2 mg/kg per day) are associated with decreased peripheral glucose utilization and increased blood glucose concentrations, but they have a variety of other metabolic effects that must be considered. Administration of corticosteroids as an adjunct to IV glucose may be useful when glucose requirements are greater than 15 mg/kg per minute.

Glucagon will produce a rapid rise in blood glucose in infants who have adequate glycogen stores, but this is only a transient effect, and

caregivers must be prepared to manage hypoglycemia when it recurs. Preterm infants and infants who have IUGR have limited glycogen stores and are unlikely to experience an increase in blood glucose concentration following administration of glucagon. An initial dose of 30 mcg/kg may produce a response in some infants, but those who have hyperinsulinemia may require a 10-fold higher dose to overcome the effects of high circulating insulin levels and stimulate glycogenolysis. Administration of glucagon is most useful in those infants who have severe hypoglycemia as a temporizing measure until stable IV access can be obtained (eg, while awaiting the arrival of a transport team).

Several other agents may be valuable for management of infants in whom the diagnosis of hyperinsulinemia is confirmed and who remain persistently hypoglycemic in spite of administration of IV glucose at 15 to 20 mg/kg per minute. Diazoxide at a dose of 5 mg/kg every 8 hours will inhibit pancreatic insulin secretion. Somatostatin or its long-acting analogue octreotide also inhibits insulin release as well as growth hormone and glucagon secretion and is used most often preoperatively in infants requiring pancreatectomy for refractory hypoglycemia and hyperinsulinemia. Subtotal (95%) or near-complete pancreatectomy may be required to manage cases of hyperinsulinemia due to gene mutations or islet cell adenomas. However, hypoglycemia recurs in up to 33% of surgically treated patients, and 40% to 60%

TABLE 2. Adjunct Therapies for Hypoglycemia

THERAPY	EFFECT	DOSAGE
Corticosteroids	Decrease peripheral glucose utilization	Hydrocortisone 5 to 15 mg/kg per day or Prednisone 2 mg/kg per day
Glucagon	Stimulates glycogenolysis	30 mcg/kg if normal insulin 300 mcg/kg if increased insulin
Diazoxide	Inhibits insulin secretion	15 mg/kg per day
Somatostatin (long-acting: octreotide acetate)	Inhibits insulin and growth hormone release	5 to 10 mcg/kg every 6 to 8 h
Pancreatectomy	Decreases insulin secretion	—

develop diabetes mellitus later in life.

Consequences of Hypoglycemia

HYPOGLYCEMIC BRAIN INJURY

Although hypoglycemia is associated with a number of physiologic changes, the most profound effects are seen in the brain, where glucose is the major substrate for energy metabolism and both local energy stores and the supply of alternate substrates are limited. Severe hypoglycemia in the newborn is associated with selective neuronal necrosis in multiple brain regions, including the superficial cortex, dentate gyrus, hippocampus, and caudate-putamen. The initiating events in hypoglycemic encephalopathy still are not understood completely, but brain injury appears to result from a number of processes that are initiated when blood glucose concentrations decrease (Figure). A moderate reduction in blood glucose concentration is associated with compensatory increases in cerebral blood flow that have been assumed to represent

a means of maintaining delivery of cerebral glucose. In preterm newborns, such changes in cerebral blood flow may predispose to intraventricular hemorrhage and may have little effect on neuronal glucose supply because transfer of glucose across the blood-brain barrier depends on the activity of the glucose transporters on the vascular endothelium and cell membranes. Glucose transporter levels are decreased in the fetus and newborn compared with older infants and may be rate-limiting for cerebral glucose uptake.

If glucose supply to the brain is not maintained, there may be a decrease in cerebral electrical activity, membrane breakdown with release of free fatty acids, and altered amino acid metabolism, including increased production of glutamate. Glutamate, which is one of the excitatory amino acid neurotransmitters found only in the central nervous system, is believed to play a major role in the pathophysiology of hypoglycemic brain injury. Hypoglycemia is associated with increased glutamate concentrations

in the synaptic cleft, most likely due to a combination of increased glutamate release from presynaptic neurons and decreased adenosine 5'-triphosphate (ATP)-dependent glutamate uptake by glial cells. Glutamate binds to postsynaptic receptors, triggering release of second messengers via the metabotropic glutamate receptors and changes in transmembrane ion fluxes via the ionotropic glutamate receptors. Although there are several types of ionotropic receptors, the *N*-methyl-D-aspartate (NMDA)-type glutamate receptor, which is associated with an ion channel that transports sodium and calcium into the cell and potassium out of the cell, predominates in immature brain. In all species studied, including humans, the number of functional NMDA receptors increases during brain development, subsequently decreasing to adult levels.

The increased number of NMDA receptors in the late fetal and early newborn periods most likely reflects the role of the receptor as one of the primary mediators of long-term potentiation, a process that is associated with synaptogenesis and mem-

ory formation. NMDA receptor activity also may be involved in regulating the process of apoptosis, or programmed cell death, via changes in cytoplasmic and nuclear calcium concentrations. In the human fetus, the third trimester of fetal development and early neonatal period are characterized by active formation and modification of synaptic connections and arborization of dendrites associated with increased NMDA receptors. Thus, normal levels of NMDA receptor activity are critical to the development of the immature brain. However, excess activation of NMDA receptors by glutamate increases cytoplasmic concentrations of

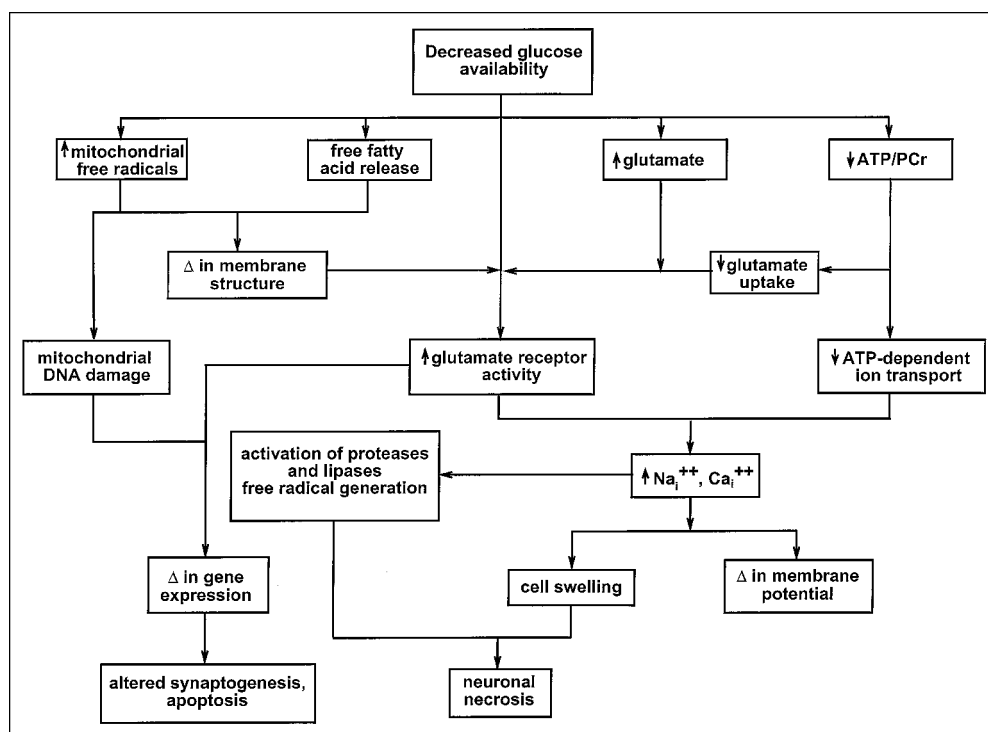


FIGURE. Proposed mechanism for the pathogenesis of hypoglycemic brain injury in the newborn. ATP = adenosine 5'-triphosphate; PCr = phosphocreatine. Used with permission of Ross Products Division, Abbott Laboratories Inc., Columbus, OH 43216. From Semin Neonat Nutr Metab. 1997; 4, Ross Products Division, Abbott Laboratories Inc.

sodium and calcium to levels that exceed the capacity of neuronal homeostatic mechanisms, thereby altering transmembrane ion gradients. Hypoglycemia specifically increases the sensitivity of NMDA receptors to activation by glutamate, which may result in a lower threshold for glutamate-induced excitotoxicity. During hypoglycemia, energy-dependent mechanisms for restoring normal transmembrane gradients of sodium and calcium cannot operate because of the depletion of ATP and phosphocreatine associated with hypoglycemia. Excess calcium influx activates cellular phospholipases and proteases, alters mitochondrial metabolism, triggers free radical formation, changes patterns of synaptic transmission, and eventually may result in selective neuronal necrosis.

There is increasing evidence that specific changes in mitochondrial function may play a significant role in the early events leading to hypoglycemic encephalopathy. Decreased fluxes of substrate through the tricarboxylic acid cycle results in decreased availability of reducing equivalents in mitochondria. As a result, there is incomplete reduction of molecular oxygen within mitochondria and increased formation of oxygen free radicals, which damage both mitochondrial membranes and mitochondrial DNA. Fragmentation of mitochondrial DNA interferes with synthesis of electron transport chain enzymes, such as subunits of cytochrome oxidase and nicotinamide adenine dinucleotide (NADH)-dehydrogenase that are coded for by the mitochondrial genome. Thus, the ability of the cell to restore ATP levels is impaired. Local depletion of high-energy phosphates as well as changes in the mitochondrial membranes lead to decreased sequestration of calcium by the mitochondria as cytoplasmic calcium. Mitochondrial dysfunction also may contribute directly to neuronal necrosis by initiating the process of apoptosis. Recent studies have indicated that release of cytochrome c from mitochondria is required to activate the enzymes that trigger apoptosis and that cytochrome c is released as oxidative phosphorylation fails.

Hypoglycemia also could exacerbate brain injury during periods of cerebral hypoxia in immature brain. As in hypoglycemia, cerebral hypoxia is associated with depletion of high-energy phosphates, increased extracellular glutamate concentrations, activation of ionotropic glutamate receptors, and increased intracellular sodium and calcium. In addition, anaerobic glycolysis during hypoxia accelerates depletion of glucose in the brain. Thus, the combination of hypoglycemia and hypoxia might be expected to act synergistically in producing neuronal injury. Although hypoglycemia appears to be neuroprotective during cerebral ischemia in adults, studies in immature animals have demonstrated that concurrent hypoglycemia exacerbates hypoxic-ischemic brain injury, possibly by accelerating depletion of high-energy phosphates. Hypoglycemia also abolishes hypoxic vasodilatation of cerebral blood vessels, thus impairing compensatory mechanisms that might otherwise improve oxygen delivery to the brain during periods of hypoxemia. Although further investigation is necessary, these results indicate that maintenance of normoglycemia is especially critical in infants at risk for episodes of hypoxemia, such as those who have significant respiratory distress.

CLINICAL CONSEQUENCES

The physiologic disturbances associated with acute hypoglycemia in the newborn result in a stress response, with release of catecholamines and glucagon and subsequent lipolysis and glycogenolysis in an attempt to increase substrate availability for normal metabolic processes. Thus, even in asymptomatic hypoglycemia, there are significant short-term effects on the infant that may result in depletion of endogenous substrate, leaving the infant unprepared to handle subsequent physiologic stress. In term infants, a brief period of increased sympathetic activity and altered hepatic metabolism usually is tolerated well. However, in the preterm or SGA infant, the added physiologic stress associated with a low blood glucose concentration may be sufficient to precipitate cardiorespiratory instability and

complicate acute management significantly. Prompt, rapid normalization of low blood glucose concentrations is required to minimize the hormonal and metabolic derangements. If a normal blood glucose concentration can be achieved in a timely manner, the acute effects of a single episode of hypoglycemia can be minimized.

The long-term effects of neonatal hypoglycemia remain controversial. Repeated episodes of symptomatic hypoglycemia, as are seen in infants who have persistent hyperinsulinism, have been associated with selective neuronal necrosis and long-term impairment of cognitive and motor function. Early studies also reported poor neurodevelopmental outcomes in IDMs. However, more recent data suggest that hypoglycemia alone does not alter long-term outcome in IDMs; rather, adverse outcomes were related to the presence of congenital anomalies.

Very few data are available regarding the long-term outcome in the vast majority of hypoglycemic infants who have asymptomatic hypoglycemia that is detected on routine screening and is treated promptly. Studies in normal adults have shown that cognitive function is impaired during mild insulin-induced hypoglycemia (blood glucose values < 3.4 mmol/L [<60 mg/dL]). Adult diabetics who have a history of recurrent episodes of hypoglycemia have been found to have persistent cognitive deficits as well as mild cortical atrophy, findings that have not been observed in diabetics who have not experienced significant hypoglycemia.

Most studies in newborns, although unavoidably limited in scope, have failed to demonstrate any long-term sequelae in term infants who have experienced brief episodes of hypoglycemia. Changes in brainstem auditory evoked responses (BAERs) were reported in several infants (1 to 5 d old) during episodes of hypoglycemia of unspecified etiology. Abnormal BAERs were detected at blood glucose concentrations ranging from 0.7 to 2.5 mmol/L (12 to 45 mg/dL), and in two infants they remained abnormal for several hours after glucose had been administered. How-

ever, no long-term follow-up was reported on these infants. A second study, which analyzed factors affecting outcome at 18 months of age in a cohort of preterm infants, found that those who had at least one blood glucose value less than 2.6 mmol/L (46 mg/dL) on 5 or more days had significantly lower scores on standardized tests of mental and motor development and a threefold higher incidence of cerebral palsy than those who had fewer episodes of hypoglycemia or those who had experienced a single episode of more severe hypoglycemia. The differences remained significant when other risk factors such as birth-weight and intraventricular hemorrhage were accounted for. Thus, there is evidence to suggest that mild-to-moderate hypoglycemia may affect outcome, at least in high-risk infants.

Conclusion

Disturbances of glucose homeostasis that result in hypoglycemia are com-

mon among newborns. Awareness of risk factors that predispose infants to hypoglycemia allows for screening of those at risk so that clinically undetectable hypoglycemia can be treated promptly, thereby preventing the development of severe or symptomatic hypoglycemia, which is associated with adverse outcomes. However, management of high-risk infants is complicated by the lack of a consensus on the blood glucose value that constitutes hypoglycemia as well as the inaccuracies in methods used to measure blood glucose values. A further unresolved issue is whether asymptomatic hypoglycemia is associated with permanent effects on brain function in the newborn. No conclusive studies demonstrate long-term effects of asymptomatic hypoglycemia in term infants, but it is likely that hypoglycemia contributes to abnormal neurodevelopmental outcome in infants who have other risk factors for brain injury, such as prematurity or hypoxic-ischemic brain injury. In these

infants, maintaining blood glucose concentrations well above the threshold for hypoglycemia may improve neurologic outcome. Further studies are necessary to determine the consequences of hypoglycemia in term infants.

SUGGESTED READING

- Aynsley-Green A. Glucose, the brain, and the pediatric endocrinologist. *Horm Res.* 1996;46:8–25
- Kalhan S, Saker F. Metabolic and endocrine disorders, part one: disorders of carbohydrate metabolism. In: Fanaroff AA, Martin RJ, eds. *Neonatal-Perinatal Medicine: Diseases of the Fetus and Newborn*. 6th ed. St. Louis, Mo: Mosby-Year Book Inc; 1997
- Stanley CA. Hyperinsulinism in infants and children. *Pediatr Clin North Am.* 1997;44:363–374
- Williams AF. *Hypoglycemia in the Newborn: A Review*. WHO Publications #5778, 1997

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