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Hypoglycemia in Children Attending the Critical Care Medicine in Developing Countries

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1. Introduction

Hypoglycemia is a biochemical symptom, which refers to the presence of an underlying cause. As glucose is the fundamental energy currency of the cell, disorders that affect its availability or its use can cause hypoglycemia (DePuy et al., 2009, Schaefer-Graf et al., 2002). Glucose is a source of energy storage in the form of glycogen, fat, and protein and hypoglycemia is the most common metabolic problem among pediatric patients in the critical care medicine (DePuy et al., 2009, Tita et al., 2009, Adamson et al., 1995, Alkalay et al., 2006). The lower limit of the accepted normal value of blood glucose level in newborn infants with associated illness especially in presence of hypoxemia and ischemia that already impairs the cerebral metabolism has not been determined (Sperling et al., 2008, Alkalay et al., 2006). Moreover, there are controversies regarding the definition of hypoglycemia (Cornblath et al., 2000). However, some reasonably accepted definitions of hypoglycemia for the purpose of the clinical management of the entity are in practice. In children, a blood glucose value of less than 40 mg/dL (2.2 mmol/L) represents hypoglycemia (Tita et al., 2009, Guideline, 2004, Jain et al., 2008). A plasma glucose level of less than 30 mg/dL (1.65 mmol/L) in the first 24 hours of life and less than 45 mg/dL (2.5 mmol/L) thereafter constitutes hypoglycemia in the newborn (DePuy et al., 2009, Tita et al., 2009, Daly et al., 2003, Guideline, 2004, Cornblath et al., 2000). However, in children with severe acute malnutrition (SAM) the cutoff value is a bit high, and, a blood glucose value of less than 54 mg/dL (3.0 mmol/L) represents hypoglycemia (WHO, 1999, Ahmed et al., 1999).

2. Incidence of hypoglycemia

Incidence of hypoglycemia varies with the definition, population, method and timing of feeding, and the type of glucose assay (Guideline, 2004). The age is also helpful in assessing the probable diagnosis of hypoglycemia. The incidence is highest in the immediate post neonatal period (Halamek et al., 1997a, Cornblath and Ichord, 2000). The incidence decreases with increasing age (Halamek et al., 1997a, DePuy et al., 2009).

The overall incidence of symptomatic hypoglycemia in newborns varies from 1.3-3 per 1000 live births (Cranmer, 2009, Guideline, 2004). Serum glucose levels are higher than whole blood values (Cowett and Loughead, 2002, Deshpande and Ward Platt, 2005). The incidence of hypoglycemia is greater in high-risk neonatal groups (DePuy et al., 2009, Guideline, 2004, Cornblath and Ichord, 2000). Hypoglycemia is more common in premature neonates especially born at less than 37 weeks of gestation and in those especially born at more than 40 weeks gestation, with incidence rates of 2.4% in neonates born at 37 weeks' gestation, 0.7-1.8% in neonates born at 38-42 weeks of gestation (Tita et al., 2009, Narchi and Skinner, 2009, Cornblath and Ichord, 2000). The incidence of hypoglycemia in children older than 6 months in a large urban critical care department was 0.034% (Daly et al., 2003). In a recent Japanese study, more than 80% of admissions from the nursery to the neonatal ICU after birth were due to apnea or hypoglycemia in neonates born at 35-36 weeks' gestation (Ishiguro et al., 2009). Incidence of hypoglycemia among 1-5 years old children with acute gastroenteritis and dehydration was found 9.2% (Reid and Losek, 2005). However, study conducted among the hospitalized malnourished children in the critical care medical units of the developing countries, 16-39% were found to be hypoglycemic on admission (Bennish et al., 1990, Huq et al., 2007, Chisti et al., 2010).

Early feeding decreases the incidence of hypoglycemia (Wight, 2006, Meier et al., 2007, Chertok et al., 2009). The incidence of inborn errors of metabolism that lead to neonatal hypoglycemia are rare but can be screened in infancy (Schwartz, 1997b, Guideline, 2004, Cranmer, 2009):

Common inborn errors of metabolism:

- Carbohydrate metabolism disorders (>1:10,000)
- Fatty acid oxidation disorders (1:10,000)
- Hereditary fructose intolerance (1:20,000 to 1:50,000)
- Glycogen storage diseases (1:25,000)
- Galactosemia (1:40,000)
- Organic acidemias (1:50,000)

Uncommon inborn errors of metabolism:

- Phosphoenolpyruvate carboxykinase deficiency
- Primary lactic acidosis

3. Objectives

- To develop a guideline for the physicians and nurses working at the critical care medicine in the developing countries for the bed side diagnosis and prompt management of hypoglycemia and
- To evaluate its role as a predictor of fatal outcome in children with SAM.

4. Options

- Clinical assessment
- Bed side testing
- Prompt bed side management
- Empirical antimicrobial therapy according to cause

5. Benefits of this chapter

- Increase awareness for the rapid diagnosis of hypoglycemia in children with SAM, and those with dehydrating diarrhea
- Better utilization of the available diagnostic equipments
- Understanding the value of rapid management of hypoglycemia in children with SAM
- Understanding the need for antimicrobial therapy according to cause
- Decreased morbidity and mortality due to hypoglycemia
- Increase the awareness of the causes of pediatric hypoglycemia
- Immediate diagnosis
- Prompt treatment
- Reduced cost associated with unnecessary investigations and complications due to inappropriate treatment

6. Importance of the chapter

Health professionals in developing countries often rely on clinical signs to predict the severity of disease in hospitals with limited facilities, which is often reliable in children with better nutritional status (WHO, 2005, Chisti et al., 2009c) but severely malnourished children often have severe infection (Chisti et al., 2010) and die without any prior overt clinical signs, which may prevent their appropriate and timely management (Suskind and Suskind, 1990, Morgan, 1997). Laboratory investigation, an essential alternative measure of suppressed clinical signs, often involves many efforts, time and cost, as in blood culture. Availability of pertinent laboratory investigations in resource poor settings is very limited. Furthermore, data on simple, less time-consuming and inexpensive laboratory diagnostic tool(s) that can predict the outcome of such infants are scarce. However, limited data for predicting factors of fatal outcome in severely malnourished children in pediatric critical care medicine revealed that hypoglycemia, measured by a simple portable bedside glucose test, is significantly associated with fatal outcome especially in children presenting with SAM (Chisti et al., 2010, Huq et al., 2007). It may be a useful rapid diagnostic test, allowing prompt comprehensive management of such children following WHO guidelines (WHO, 2005), thus reducing deaths even in resource poor settings.

7. Associated factors of hypoglycemia

Hypoglycemia is common in critically ill children and is associated with increased mortality rates in critically ill nondiabetic children (Faustino and Bogue, Cornblath and Ichord, 2000, Reid and Losek, 2005). A recent study by Faustino et al. showed that hypoglycemia was associated with worsening organ function (Faustino and Bogue) and concluded that it may be a marker of severity of illness. He also suggested that further investigations are needed to establish the mortality risk with hypoglycemia due to the effect of insulin compared to spontaneous hypoglycemia (Faustino and Bogue). One recent study revealed that infants with serious illness such as sclerema requiring admission to critical care medicine in an urban diarrhea hospital were significantly associated with hypoglycemia (Chisti et al., 2009a). Another study from the same center revealed that patients with enteric encephalopathy having fatal outcome more often presented with hypoglycemia compared to those who survived (Chisti et al., 2009b).

A most recent study from the critical care ward of Dhaka hospital of ICDDR,B revealed that among all relatively rapid laboratory investigations in neonates, hypoglycemia was the independent predictor of fatal outcome (Table 1). The study revealed that to predict death, the sensitivity, specificity, and positive predictive value of hypoglycemia with their 95% confidence intervals were 40% (14–73%), 88% (75– 95%), and 40% (14–73%), respectively (Chisti et al., 2010). The study concluded that most of the laboratory markers used to predict fatal outcome in diarrheal infants with SAM take several hours to become available, except a bedside glucose test, which takes less than a minute but is inexpensive. The study suggested that presence of hypoglycemia, measured by a portable bedside glucose test, is significantly associated with fatal outcome with high specificity in infants presenting with diarrhea and SAM (Chisti et al., 2010). It may be a useful rapid diagnostic test allowing prompt detection followed by comprehensive management of such infants according to WHO guidelines, which would help in reducing deaths even in resource poor settings (WHO, 2005). The findings of the study was also supported by another previous study from the same country where children with hypoglycemia more often had bacteremia (Huq et al., 2007).

Variable	Death N = 10 (%)	Survivor N = 51 (%)	Non-adjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Hypoglycemia	4 (40)	6 (12)	5.0 (1.01 - 29.8)	0.027	5.0 (1.1 - 23.0)	0.039
Abnormal WBC count	6 (60)	36 (71)	0.6 (0.1 - 3.1)	0.710	0.5 (0.1 – 2.5)	0.438
Higher S. CRP level	9 (90)	33 (65)	4.9 (0.6 - 111.7)	0.151	4.5 (0.5 - 39.5)	0.179
Hyponatremia	3 (30)	14 (28)	1.1 (0.2 - 6.0+)	1.00	0.8 (0.2 - 4.2)	0.813
Hypokalemia	4 (40)	25 (49)	0.7 (0.1 - 3.3)	0.735	2.2 (0.3 - 14.4)	0.409
Hypocalcemia	4 (40)	11 (22)	2.4 (0.5 - 12.4)	0.243	1.8 (0.3 - 10.2)	0.529
Hypomagnesemia	0 (00)	2 (4)	0.0 (0.0 - 23.5)	1.00	0.0 (0.0 - unidentified)	1.0

OR: odds ratio, CI: confidence interval, S: serum, CRP: C-reactive protein.
Illustrated from the Tropical Medicine and International Health by Chisti et. al. (2010)

Table 1. Comparison of the characteristics of severely malnourished infants with fatal outcome and those who survived

8. Hypoglycemia and glucose metabolism

Malnutrition is a major risk factor for death in children in developing countries (Faruque et al., 2008), and the mortality risk is higher in infants when they present with severe form of malnutrition (Pelletier et al., 1994, Naheed et al., 2009, Chisti et al., 2009c), especially in a set up with critical care medicine (Elusiyan et al., 2006). It has not received enough attention in developing countries. The primary therapy is very simple by immediate infusion of intravenous glucose. The occurrence of hypoglycemia is directly related to energy balance and determined by the availability of glucose, free fatty acids and ketone bodies in the tissue (Nuoffer and Mullis, 2005, Fluck et al., 2003, Mohnike and Aynsley-Green, 1993). An intact energy balance and maintenance of normal blood sugar concentration is dependent upon: an adequate caloric and qualitative dietary intake; a functionally intact hepatic glucogenolytic and gluconeogenic enzyme system; an adequate supply of endogenous

gluconeogenic substrates (lactate, amino acids and glycerol); an adequate energy supply provided by the beta-oxidation of fatty acids to synthesize glucose and ketone bodies and a normal endocrine system (insulin, glucagon, catecholamines and growth hormone) for integrating and modulating these processes (Nuoffer and Mullis, 2005, Mohnike et al., 1993). Disturbances in each of these factors may lead to hypoglycemia. Glucose has an essential and fundamental importance for the brain metabolism. The major contribution of the brain to the basal metabolic rate is an important factor contributing to the frequency and severity of a hypoglycemic syndrome in the pediatric age (Nuoffer and Mullis, 2005, Mohnike et al., 1993). Cerebral glucose uptake occurs through a glucose transporter molecule and these molecules are carrier mediated and facilitate diffusion process that is dependent on blood glucose concentration but cerebral and cerebrospinal fluid (CSF) glucose uptake are not regulated by insulin (Sperling et al., 2008). Paucity of glucose transporter molecule can result in seizures due to reduced cerebral and CSF glucose concentrations although there might have normal blood glucose levels (Sperling et al., 2008, Mohnike et al., 1993). Thus, hypoglycemia should be considered as a medical emergency and treated very aggressively especially in children with other associated illnesses such as SAM, severe sepsis, septic shock, febrile neonates, prematurity and low birth weight in the critical care medicine ward.

9. Pathophysiology of hypoglycemia

Normal blood glucose is very narrowly regulated, usually from 4.4-5 mmol/L. Glucose levels increase transiently after meals to 6.6-7.7 mmol/L. Feedback systems return the glucose concentration rapidly back to the preprandial level, usually within 2 hours after the last absorption of carbohydrates (Fleisher, 2000, Halamek and Stevenson, 1998, Reid et al., 2003, Sperling et al., 2008).

Insulin and glucagon are the important hormones in the immediate feedback control system of glucose (Sperling et al., 2008). When blood glucose increases after a meal, the rate of insulin secretion increases and stimulates the liver to store glucose as glycogen (Halamek et al., 1997b). When cells (primarily liver and muscle) are saturated with glycogen, additional glucose is stored as fat (Reid et al., 2003).

When blood glucose levels fall, glucagon secretion functions to increase blood glucose levels by stimulating the liver to undergo glycogenolysis and release glucose back into the blood (Sperling et al., 2008, Halamek et al., 1997b).

In starvation, the liver maintains the glucose level via gluconeogenesis (Sperling et al., 2008). Gluconeogenesis is the formation of glucose from amino acids and the glycerol portion of fat. Muscle provides a store of glycogen and muscle protein breaks down to amino acids, which are substrates utilized in gluconeogenesis in the liver (Narayan et al., 2001). Circulating fatty acids are catabolized to ketones, acetoacetate, and B-hydroxybutyrate and can be used as auxiliary fuel by most tissues, including the brain (Fleisher, 2000, Sperling et al., 2008).

The hypothalamus stimulates the sympathetic nervous system, and epinephrine is secreted by the adrenals causing the further release of glucose from the liver (Haninger and Farley, 2001). Over a period of hours to days of prolonged hypoglycemia, growth hormone and cortisol are secreted and decrease the rate of glucose utilization by most cells of the body (Halamek and Stevenson, 1998).

In the newborn, serum glucose levels decline after birth until 1-3 hours due to an abrupt transition from the intrauterine life, then they spontaneously increase, ultimately

characterized by the autonomous ability to maintain euglycemia. Liver glycogen stores become rapidly depleted within hours of birth, and gluconeogenesis, primarily from alanine, can account for 10% of glucose turnover in the newborn infant by several hours of age (Halamek and Stevenson, 1998).

Neonatal hypoglycemia (Halamek and Stevenson, 1998, Sperling et al., 2008)

- Inappropriate changes in hormone secretion
- Inadequate substrate reserve in the form of hepatic glycogen
- Inadequate muscle stores as a source of amino acids for gluconeogenesis
- Inadequate lipid stores for the release of fatty acids

Hypoglycemia in older infants and children (Sperling et al., 2008, Reid et al., 2003)

- The pathophysiology of hypoglycemia is analogous to that in adults.
- Glucose homeostasis is maintained by glycogenolysis in the immediate post feeding periods and by gluconeogenesis several hours after meals.

Hypoglycemia in severely malnourished children:

The pathophysiology of the hypoglycemia is poorly understood although there is popular belief that it is mainly due to severe infection in severely malnourished children. There is decreased endogenous glucose production (EGP) in severely malnourished children which is related to the degree of hypoalbuminemia and oxidative stress (Bandsma et al.). Severe malnutrition is associated with impaired glucose absorption and decreased glucose absorption correlates with oxidative stress in sick children who needs admission to the pediatric critical care medicine (Bandsma et al.). This potentially explains the etiology of hypoglycemia in severely malnourished children. Severe malnutrition in infants often causes depressed cell-mediated and humoral immune responses, associated with impairment of IgA production, chemotaxis, reduced mature T cells, and compromised phagocytic activity (Suskind and Suskind, 1990, Morgan, 1997). As a result, patients become highly susceptible to infectious disease, predominantly diarrhea, which is often associated with prolonged anorexia and vomiting (Feign. R and Garg, 1987). Failure of gluconeogenesis in such infants is a common phenomenon (Butler et al., 1989, Bennish et al., 1990) and potentially responsible for the development of fatal hypoglycemia.

10. Causes/etiology of hypoglycemia

Hypoglycemia events are usually accompanied by an increased heart rate with bounding pulse due to increased epinephrine secretion (Dubois et al., 1995). This leads the infant to be irritable, tremulous, and cranky (al-Rabeeah et al., 1995). In any case the brain energy supply is severely impaired; the mental status of the children is likely to be impaired with extreme inappropriate effect and mood, lethargy, seizure, or coma. Large body size for age in the neonate or older child suggests hyperinsulinism, although some children with hyperinsulinism are born prematurely and are small for gestational age (de Lonlay-Debeney et al., 1999, Stanley, 1997). Decreased subcutaneous fat as in severe malnutrition such as in severe wasting suggests inadequate glucose stores (de Lonlay-Debeney et al., 1999, Dubois et al., 1995). Poor linear growth may point to growth hormone deficiency, and midline facial and cranial abnormalities suggest pituitary hormone deficiencies (Dunne et al., 1997). Liver size should be assessed for evidence of glycogen-storage diseases. Etiology of hypoglycemia includes the following:

10.1 Hyperinsulinemia

Potential causes of hyperinsulinism in children include maternal diabetes in pregnancy, persistent hyperinsulinemic hypoglycemia of infancy, insulin-producing tumors, and child abuse (Stanley, 1997). Hyperinsulinism causes excess glucose use primarily by stimulating skeletal muscle to uptake glucose. This is aggravated by insulin-induced suppression of hepatic glycogenolysis and gluconeogenesis (al-Rabeeah et al., 1995, Stanley, 1997).

In neonates

Hyperinsulinism is the most common cause of hypoglycemia in neonates. However, in addition to hyperinsulinism, or persistent hyperinsulinemic hypoglycemia of infancy (PHHI), hypoglycemia occurs due to limited glycogen stores (eg, prematurity, intrauterine growth retardation), depleted glycogen stores (eg, stress in perinatal asphyxia, starvation), in ketotic hypoglycemia, easily depleted glycogen stores, in combination with inadequate production of glucose through gluconeogenesis, contribute to hypoglycemia (Cranmer, 2009, Guideline, 2004). Thus, fatty acid oxygenation is required to provide substrate for gluconeogenesis and ketogenesis. Ketones, the byproduct of fatty acid metabolism, are found in urine and represent the starved state. Increased glucose use (eg, hyperthermia, polycythemia, sepsis, growth hormone deficiency), decreased glycogenolysis, gluconeogenesis, or use of alternate fuels (eg, inborn errors of metabolism, adrenal insufficiency) (Cranmer, 2009, Guideline, 2004).

In infants

Hyperinsulinemia may be due to various genetic defects that cause a loss of glucose regulation of insulin secretion (Cosgrove et al., 2004, Tornovsky et al., 2004). This disorder is known as endogenous-persistent hyperinsulinemic hypoglycemia of infancy (previously termed nesidioblastosis) (Cosgrove et al., 2004, Stanley, 1997). No genetic defect is identified in 50% of patients with hyperinsulinism although unusual single nucleotide polymorphisms defects have been found that may be responsible in some infants (Di Candia et al., 2009).

Infants of mothers with diabetes also have high insulin levels after birth due to the high glucose exposure in utero; the poorer the glucose control during pregnancy, the greater the likelihood of hyperinsulinism in the infant (Stanley, 1997). In older children, hyperinsulinemia is rare, but an insulin-producing tumor is the most common cause (Stanley, 1997). Exogenous administration of insulin or oral hypoglycemic agents, either accidental or due to abuse, must be considered (Di Candia et al., 2009).

Overall criteria for the diagnosis of hyperinsulinism in the infant (Sperling et al., 2008)

- Hyperinsulinemia (plasma insulin > 2 μU/mL)
- Hypofattyacidemia (plasma free fatty acids < 1.5 mmol/L
- Hypoketonemia (plasma β-hydroxybuterate < 2.0 mmol/L)
- Inappropriate glycemic response to glucagon, 1 mg IV (delta glucose > 40 mg/dl))

10.2 Disorders of glucose underproduction

This includes inadequate glucose stores which are associated with prematurity, infants who are small for gestational age, SAM, and ketotic hypoglycemia (Di Candia et al., 2009).

Among them, children with SAM who need admission to the critical care medicine have paramount importance. We will focus our discussion at the later part of the chapter.

After insulin treatment in diabetes, the above mentioned disorders are the most common causes of hypoglycemia. These disorders are largely diagnoses of exclusion made after other causes of hypoglycemia are ruled out. Prematurity, infants who are small for gestational age, and SAM should be readily apparent based on the clinical situation. Ketotic hypoglycemia, which usually affects children with SAM and aged 18 months to 6 years, is usually due to disrupted food intake (Di Candia et al., 2009).

Glycogen-storage disease type 0 (due to glycogen synthase deficiency) is associated with fasting hypoglycemia because of the liver's inability to store glucose in the immediate postprandial state. Thus, the glucose load from the meal is anaerobically used rather than stored for later use. In this disorder, plasma glucose and lactate levels are high in the immediate postprandial state (Di Candia et al., 2009).

Glycogen-storage disease type I (Due to disorders of hepatic glucose production include glucose-6-phosphatase deficiency), glycogen-storage disease type III (due to debrancher deficiency), and glycogen-storage disease type VI (due to hepatic phosphorylase deficiency), galactosemia, hereditary fructose intolerance, and maple syrup urine disease interfere in glucose production through various defects, including blockage of glucose release or synthesis or blockage or inhibition of gluconeogenesis. Children with these diseases may adapt to their hypoglycemia because of its chronicity (Di Candia et al., 2009).

Hormonal abnormalities include panhypopituitarism, growth hormone deficiency, and cortisol deficiency (primary or secondary). As described above, growth hormone and cortisol play important roles in generating alternative fuels and stimulating glucose production. Because they are easily treatable abnormalities, early recognition is important (Di Candia et al., 2009).

Toxins and other illnesses (ethanol, salicylates, propranolol, malaria) also cause hypoglycemia. Ethanol inhibits gluconeogenesis in the liver and can thus cause hypoglycemia. This is particularly true in patients with insulin-treated diabetes who are unable to reduce insulin secretion in response to developing hypoglycemia. Salicylate intoxication causes both hyperglycemia and hypoglycemia. The latter is due to augmentation of insulin secretion and inhibition of gluconeogenesis (Di Candia et al., 2009).

11. Clinical features of hypoglycemia

Glucose usually provides the primary source for brain energy. Clinical manifestations are broad and can be from a combination of adrenergic stimulation or from decreased availability of glucose for the CNS. Unlike older children, infants are not able to verbalize their symptoms and are particularly vulnerable to hypoglycemia (Cranmer, 2009). Symptoms of hypoglycemia occur through two main clinical pathways. The first one is caused by activation of the autonomic nervous system, which causes symptoms such as anxiety, tremulousness, diaphoresis, tachycardia, pallor, hunger, nausea, and vomiting (Dunne et al., 2004). The symptoms of second one is due to neuroglycopenia (hypoglycorrhachia) and consists of headache, mental confusion, staring, behavioral changes, difficulty concentrating, visual disturbances (eg, decreased acuity, diplopia), dysarthria, seizures, ataxia, somnolence, coma, stroke (hemiplegia, aphasia), paresthesias,

dizziness, amnesia, decerebrate or decorticate posturing (Dunne et al., 2004). There are other nonspecific symptoms which include dry mouth, mouth tingling, headache, nausea, and blurred vision (Dunne et al., 2004).
During the first or second day of life, symptoms vary from asymptomatic to CNS and cardiopulmonary disturbances (Guideline, 2004).

Following high risk groups does need screening for hypoglycemia in the first hour of life (Guideline, 2004, Feign. R and Garg, 1987, Fleisher, 2000)

- Newborns who weigh more than 4 kg or less than 2 kg
- Large for gestational age infants who are above the 90th percentile, small for gestational age infants below the 10th percentile, and infants with intrauterine growth restriction
- Infants born to insulin-dependent mothers or mothers with gestational diabetes
- Gestational age less than 37 weeks
- Newborns suspected of sepsis or born to a mother suspected of having chorioamnionitis
- Newborns with symptoms suggestive of hypoglycemia, including jitteriness, tachypnea, hypotonia, poor feeding, apnea, temperature instability, seizures, lethargy

In addition, consider hypoglycemia screening in infants with following conditions: (Guideline, 2004).

- Significant hypoxemia
- Perinatal distress
- 5-minute APGAR scores less than 5
- Mother on terbutaline, beta-blockers, or oral hypoglycemic agents
- Isolated hepatomegaly
- Microcephaly
- Anterior midline defects
- Gigantism
- Macroglossia or hemihypertrophy; or any possibility of an inborn error of metabolism

The onset of hyperinsulinemia is from birth to 18 months (al-Rabeeah et al., 1995, de Lonlay-Debeney et al., 1999, Dubois et al., 1995, Dunne et al., 2004, Dunne et al., 1997).

- Insulin concentrations are inappropriately elevated at the time of documented hypoglycemia.
- Transient neonatal hyperinsulinism occurs in macrosomic infants of diabetic mothers who have diminished glucagon secretion and endogenous glucose production is significantly inhibited. Clinically, these infants are macrosomic and have increasing demands for feeding, intermittent lethargy, jitteriness, and frank seizures.
- Infants with prolonged neonatal hyperinsulinism can be described by small for gestational age, patients with perinatal asphyxia, neonates born to mothers with toxemia, have high rates of glucose use and often require dextrose infusion for a prolonged period of time

Ketotic hypoglycemia is an uncommon but dramatic illness. It is observed in children younger than 5 years who usually become symptomatic after an overnight or prolonged fast, especially with illness and poor oral intake. Children often present inexplicably

lethargic or frankly comatose, having only marked hypoglycemia with ketonuria (Cranmer, 2009).

The symptoms often vary according to age of the children as follows (de Lonlay-Debeney et al., 1999, Daly et al., 2003, al-Rabeeah et al., 1995, Dubois et al., 1995, Schwartz, 1997b, Schwartz, 1997a, Luber et al., 1998):

In neonates-

- Restlessness
- Hypothermia
- Tremulousness
- Brisk Moro reflex
- Compromised activity
- Poor feeding
- Hypotonia
- Lethargy
- Apathy
- Jitteriness
- Seizures
- Congestive heart failure
- Respiratory difficulty
- Apnea
- Bradycardia
- Convulsion
- Coma and
- Sudden death

In older children-

- Dizziness
- Hunger
- Anxiousness
- Sweating
- Lethargy
- Poor feeding
- Confusion
- Irritability
- Convulsion
- Coma and
- Sudden death

Clinical signs of hypoglycemia in SAM

A large number of patients with hypoglycemia may not have any symptoms or may present with severe CNS and cardiopulmonary disturbances. However, in children with SAM who need the admission in the pediatric critical care medicine, the most common clinical manifestations can take account as

- Altered level of consciousness,
- Seizure,
- Vomiting,

- Unresponsiveness, and
- Lethargy.

Any child with SAM and acute illness should be evaluated for hypoglycemia, especially when history reveals lesser oral intake (Chisti et al., 2010). Persistent or repetitive hypoglycemia in infants and children has a major impact on normal brain development and function (al-Rabeeah et al., 1995, Bennish et al., 1990). Evidence suggests that hypoxemia potentiate hypoglycemia, causing brain damage that may permanently impair neurologic development (Bennish et al., 1990).

Hypoglycemia is often a sign of severe infection (Bennish et al., 1990). The child should be tested for hypoglycemia on admission or whenever lethargy, convulsions or hypothermia are found (Butler et al., 1989). If blood glucose cannot be measured, all children with SAM suspected to have hypoglycemia should be treated accordingly (Ahmed et al., 1999). Otherwise the children with severe malnutrition and hypoglycemia may die within few minutes (Chisti et al., 2010, Huq et al., 2007).

12. Differential diagnosis of hypoglycemia in children (de Lonlay-Debeney et al., 1999, Daly et al., 2003, al-Rabeeah et al., 1995, Dubois et al., 1995, Schwartz, 1997b, Schwartz, 1997a, Wyngaarden et al., Cosman et al., 1989, Stuckey et al., Wall, 2000, Olry, 2002, Belay et al., 1999, CDC, Dellinger et al., 2008)

- Adrenal Insufficiency and Adrenal Crisis
- Hypopituitarism
- Hypothyroidism and Myxedema Coma
- Munchausen Syndrome
- Reye Syndrome
- Plant Poisoning, Hypoglycemics
- Shock, Septic
- Toxicity, Alcohols
- Toxicity, salicylates

13. Laboratory studies

A bedside glucose level is a very cheap rapid diagnostic test, although it may lead to over treatment of hypoglycemia (Cranmer, 2009).

Serum or plasma glucose levels (Serum glucose level is higher than whole blood glucose level) (Cranmer, 2009)

- Arterial and capillary samples may overestimate the plasma glucose concentration by 10% in non-fasting patients.
- Whole blood estimation of glucose may underestimate the plasma glucose concentration by approximately 10-15% because RBCs contain relatively low concentrations of glucose.

Serum insulin: when blood glucose is less than 40 mg/dL, plasma insulin concentration should be less than 5 and no higher than 10 microunits/mL (Cranmer, 2009).

Urine (first voided urine dipstick for ketones) (Sperling et al., 2008, Reid et al., 2003)

- Absence of large ketones with hypoglycemia suggests that fat is not being metabolized from adipose tissue (hyperinsulinism) or that fat cannot be used for ketone body formation (enzymatic defects in fatty acid oxidation).
- Consider urine for organic acid analysis.

Newborn screening (Sperling et al., 2008, Schwartz, 1997b):

- Aminoacidemias
- Urea cycle disorders
- Organic acidurias and
- Fatty acid oxidation disorders by electrospray ionization-tandem mass spectrometry.

First and prompt recognition of these inborn errors of metabolism has the potential to reduce morbidity and mortality rates in these infants.

Imaging studies (Sperling et al., 2008):

- Celiac angiography to detect adenomas has limited success. There is potential risk of causing vascular trauma in infants younger than 2 years.

14. Consequencess associated with hypoglycemia (Schwartz, 1997b, Guideline, 2004, Cranmer, 2009)

Hypoglycemia is the most common metabolic problem in neonates. Still, the level or duration of hypoglycemia that is harmful to an infant's developing brain is not known. Major long-term sequelae include:

- Neurologic damage resulting in mental retardation
- Recurrent seizure
- Respiratory distress
- Developmental delay
- Heart failure and
- Personality disorders.

Some evidence suggests that severe hypoglycemia may impair cardiovascular function.

15. Management

In children without severe malnutrition (Cranmer, 2009, Cornblath and Ichord, 2000):

In the critical care ward, supportive therapy includes oxygen, establishing an intravenous (IV) line, and monitoring.

- If convulsion, unresponsive to correction of hypoglycemia should be managed with appropriate anticonvulsants.
- If there is marked acidosis (pH < 7.1) suggestive of shock or serious underlying disease and should be treated appropriately.
- The goal of treatment is to maintain a blood glucose level of at least 45 mg/dL (2.5 mmol/L).
- Children who drink but has intact airway protective reflexes, nasogastric administration of oral liquids containing sugar may be performed.

15.1 Medication

Hypoglycemia should be treated as soon as possible to prevent complications of neurologic damage. Early feeding of the newborn with breast milk or formula is

encouraged. For those unable to drink, a nasogastric tube can be used. The mainstay of therapy for children that is alert with intact airway protection. For those who cannot protect their airway or are unable to drink, nasogastric, intramuscular, intraosseous, or intravenous (IV) routes can be used for the following drugs used to raise glucose levels (Sperling et al., 2008, Reid et al., 2003):

- Dextrose
- Glucagon
- Diazoxide and
- Octreotide

Case reports have shown that nifedipine may help maintain normoglycemia in children with persistent hyperinsulinemic hypoglycemia of infancy (PHHI) (Cranmer, 2009).

Cortisol should not be used because it has minimal acute benefit and may delay the diagnosis of the cause of hypoglycemia. Cortisol stimulates gluconeogenesis and causes decreased use of glucose, which leads to overall elevated blood glucose and may mask the true cause of hypoglycemia (Cranmer, 2009).

Anti-hypoglycemic agents (agents elevate blood glucose levels)

Dextrose

Choice of treatment as it is absorbed from the intestine resulting in rapid increase in blood glucose concentration when administered PO (Reid et al., 2003). Give IV dextrose to infants of diabetic mothers with transient neonatal hyperinsulinemia for several days until hyperinsulinemia abates (Sperling et al., 2008). Avoid hyperglycemia evoking prompt insulin release, which may produce rebound hypoglycemia. SGA infants and those with maternal toxemia or perinatal asphyxia require dextrose IV infusion rates >20 mg/kg/min to control levels (Halamek and Stevenson, 1998). Treatment may be necessary for 2-4 week .

Diazoxide

Aim to increase blood glucose by inhibiting pancreatic insulin release, and possibly through an extrapancreatic effect. Hyperglycemic effect starts within an hour and usually lasts a maximum of 8 h with normal renal function (Halamek and Stevenson, 1998, Sperling et al., 2008, Shirland, 2001).

Octreotide

Long-acting analog of somatostatin that suppresses insulin secretion for short-term management of hypoglycemia (Cranmer, 2009, Fontaine et al., 1972).

Glucagon (Glucagon Emergency Kit)

May be used to treat hypoglycemia secondary to hyperinsulinemia and administered to patients without initial IV access. Each mL contains 1 mg (ie, 1 unit). Maximal glucose concentration occurs between 5-20 min for IV administration and about 30 min for IM administration (Cranmer, 2009, Stanley, 1997).

Surgical opinion

If hypoglycemia is diagnosed in an infant younger than 3 months, surgical intervention may be necessary. Surgical exploration usually is undertaken in severely affected neonates who

are unresponsive to glucose and somatostatin therapy (Halamek and Stevenson, 1998, Sperling et al., 2008).

In one most recently conducted study revealed that once the diagnosis is made and if medical therapy with diazoxide fails, one should assume that the infant has a K(ATP) channel defect and may require surgery (Palladino and Stanley). In this case, the infant should be referred to a center that specializes in 18-fluoro L-3,4-dihydroxyphenylalanine positron emission tomography scan. This report describes a center specializing in 18-fluoro L-3,4-dihydroxyphenylalanine positron emission tomography scan with a team of experts consisting of endocrinologists, nurse practitioners, geneticists, radiologists, pathologists, and a surgeon. It describes the center's paradigm for managing severe cases of congenital hypersplenism (H1) with surgery (Palladino and Stanley). On the other hand another indicated that in absence of response to the medical treatment with diazoxide a limited pancreatectomy permits to cure focal HI, while a diffuse HI requires a subtotal pancreatectomy with high risk of subsequent diabetes mellitus (Giurgea et al., 2005). However over all recommendation with risk benefit from the peer reviewed publications and text book are as follows (Halamek et al., 1997b, Sperling et al., 2008, Reid et al., 2003)

- Near total resection of 85-90% of the pancreas is recommended.
- Risks include the development of diabetes.

If hypoglycemia first manifests in infants aged 3-6 months, a therapeutic trial of octreotide, diazoxide, steroids, and frequent feedings can be attempted for as long as 2-4 weeks.

Management of hypoglycemia in children with SAM:

If the child is conscious and blood glucose is <3mmol/l or 54mg/dl:

50 ml bolus of 10% glucose or 10% sucrose solution (1 rounded teaspoon of sugar in 3.5 tablespoons water) is given orally or by nasogastric (NG) tube. The starter diet F-75 or "milk suzi" in children above 6 months of age / expressed breast milk (EBM) or "infant formula" for children under the age of 6 months of age is given every 30 min for two hours (giving one quarter of the two-hourly feed each time) (WHO, 1999, Ahmed et al., 1999). Thereafter, two-hourly feeds are continued for first 24-48 hours (Ahmed et al., 1999).

If the child is unconscious, lethargic or convulsing:

Sterile 10% glucose (5ml/kg) or 25% dextrose (2ml/kg) is given IV, followed by 50 ml of 10% glucose or sucrose by NG tube. Then the starter diet F-75 or "milk suzi"/EBM or "infant formula" is given as above (Ahmed et al., 1999, WHO, 1999). A number of studies revealed that continuous intravenous dextrose might require in case of uncontrolled hypoglycemia (Lilien et al., 1977, Lilien et al., 1980). One of the studies revealed that the treatment of neonatal hypoglycemia by constant infusion of glucose at the rate of 8 mg/kg/minute was studied in 22 hypoglycemic neonates. In that study, 18 neonates glucose levels rose above the hypoglycemic range within ten minutes of infusion and in three, within 30 to 50 minutes of infusion. The remaining neonate had hyperinsulinemia and responded only to diazoxide. Thus, constant glucose infusion was found to be useful therapeutically for neonatal hypoglycemia (Lilien et al., 1977). Results from the another study from India revealed that symptomatic hypoglycemia should always be treated with a continuous infusion of parenteral dextrose. Neonates needing dextrose infusion rates above 12 mg/kg/m should be investigated for refractory causes of hypoglycemia. Hypoglycemia has been linked to poor neuro-developmental outcome and therefore they recommended aggressive screening and treatment with continuous infusion of glucoes (Narayan et al., 2001).

Follow up (Cranmer, 2009, Cornblath and Ichord, 2000):
Any child with documented hypoglycemia not secondary to insulin therapy should be admitted in a critical care unit for careful monitoring and diagnostic testing.

16. Prognosis

The prognosis is good in asymptomatic neonates with hypoglycemia of short duration. Hypoglycemia recurs in 10-15% of infants after adequate treatment (Sperling et al., 2008). However, there are no published data on the prevalence of hypoglycemia in severe PEM after adequate treatment although it has been thought that it will be more than that of in infants. Rebound hypoglycemia is more common if intravenous fluid are extravasated or discontinued too early or do not offer oral glucose after IV infusion of glucose especially in case SAM (Sperling et al., 2008, Ahmed et al., 1999). Remission of congenital hyperinsulinism generally does not occur, but the severity of the disease may decrease with time. The prognosis of intellectual function could be worse if the symptoms stay for prolong duration and usually associated with neurological sequele (Sperling et al., 2008).

17. Patients care giver education

Provide genetic counseling for families with affected children, including information about a possible 25% risk of recurrence (DePuy et al., 2009).

18. Conclusion

Hypoglycemia in children especially in neonates and SAM is a medical emergency and should be tested for hypoglycemia on admission or whenever lethargy, convulsions, hypoxemia or hypothermia are found. IV infusion of glucose should be given very urgently in order to prevent life threatening consequences. If blood glucose cannot be measured, all neonates and children with SAM suspected to have hypoglycemia should be treated accordingly.

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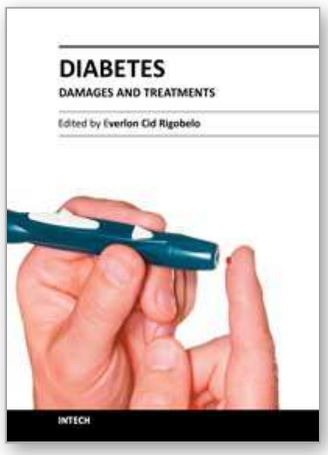

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Over the last few decades the prevalence of diabetes has dramatically grown in most regions of the world. In 2010, 285 million people were diagnosed with diabetes and it is estimated that the number will increase to 438 million in 2030. Hypoglycemia is a disorder where the glucose serum concentration is usually low. The organism usually keeps the serum glucose concentration in a range of 70 to 110 mL/dL of blood. In hypoglycemia the glucose concentration normally remains lower than 50 mL/dL of blood. Hopefully, this book will be of help to many scientists, doctors, pharmacists, chemicals, and other experts in a variety of disciplines, both academic and industrial. In addition to supporting researcher and development, this book should be suitable for teaching.

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