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An Update on Neonatal Hypoglycemia

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1. Introduction

Glucose is the predominant source of energy for the fetal and neonatal brain. During the process of adaptation from a continuous supply of glucose in-utero to an intermittent supply after birth, the neonate is prone to periods of low blood glucose. Transient mild decreases in blood glucose levels are a common feature of perinatal adaptation. This period is characterized by an up-regulation of hormonal and metabolic pathways of gluconeogenesis, hepatic glycogenolysis and ketogenesis. However, in some neonates, these may be delayed and hypoglycemia may get prolonged or severe. Persistent, recurrent or severe hypoglycemia may cause irreversible injury to the developing brain. Hence, the neonatologist needs to be proactive in suspecting, diagnosing and treating hypoglycemia in the newborn.

The normal range of blood glucose is different for each newborn and depends upon birth-weight, gestational age, body stores, feeding status, availability of energy sources as well as the presence or absence of disease. Population based meta-analyses have revealed that the blood glucose levels rise with increasing post natal age. Although, there are controversies surrounding the definition, a blood glucose <40 mg/dL is considered as the operational threshold to treat hypoglycemia in all neonates in first few days of life, irrespective of gestation. Hypoglycemia is the most common metabolic disorder in the neonatal intensive care unit. The reported incidence of hypoglycemia varies with the definition, population, glucose measurement technique and feeding schedule. Preterm infants and those with intrauterine growth retardation are at a high risk of developing hypoglycemia in the first week of life because of lack of sufficient glycogen and fat stores, which are normally accumulated in the third trimester. In some preterm infants, developmental delays in the postnatal up-regulation of enzymes of glucose homeostasis may persist even at the time of discharge from hospital. Large for gestational age infants and infants of diabetic mothers are the other important high risk groups because of relative hyperinsulinemia. A proportion of small for gestational age infants also have high insulin levels which contribute to hypoglycemia and can persist for few weeks to months. Recently, late preterm ($34^{0/7}$ to $36^{6/7}$weeks) infants have been identified as another important group prone to hypoglycemia. In addition, any sick newborn warrants screening for low blood glucose. Term healthy infants without any risk factors need not be monitored routinely. All asymptomatic, at-risk neonates should be screened at two hours after birth and surveillance should be continued 4-6 hourly thereafter, until feedings are well established and glucose values have normalized; which may take 48-72 hours. Monitoring before 2 hours may be

required if mother has been starving or vomiting. The maximum risk for hypoglycemia is in first 24 hours but usually persists till 72 hours.

The prevention of hypoglycemic brain injury requires early detection in infants considered 'at risk' and appropriate timely intervention. Detection and treatment of hypoglycemia requires accurate, rapid and reliable measurement of blood glucose. This is usually done on the bedside by glucose reagent strips. If the values are low, a blood sample is sent to the laboratory for confirmation by glucose oxidase or glucose electrode method. The treatment should be given on the basis of screening test and not await laboratory results. Most of the point-of-care strip based glucometers are however unsuitable for neonates because they were primarily developed to measure higher blood glucose levels in diabetic patients. Their accuracy in low blood glucose ranges is not good. Current blood gas machines incorporate a glucose sensor which is more accurate but may require a larger blood volume. Treatment of hypoglycemia should be based upon 'operational thresholds' and clinical assessment. Symptomatic hypoglycemia with neurological signs requires more urgent treatment by intravenous route, as compared to the 'asymptomatic' baby, irrespective of blood glucose value. Supervised and measured volume milk feeding may be an initial treatment option for asymptomatic hypoglycemia in healthy infants. However, symptomatic hypoglycemia should always be treated with a continuous infusion of parenteral dextrose. Intravenous dextrose infusion should be started in babies with asymptomatic hypoglycemia if the blood glucose is <25 mg/dL, blood glucose remains below 40 mg/dL despite one attempt of feeding milk, enteral feeding is contraindicated or if the baby becomes symptomatic. If there is no contraindication to feeding, oral feeds of breast or formula milk should be continued along with and their proportion increased as the intravenous infusion is tapered. Oral feeding ensures a more stable glycemic control.

Symptomatic hypoglycemia, especially if manifesting as seizures, is associated with abnormal neurodevelopmental outcomes in 50% of infants. Moderate asymptomatic hypoglycemia persisting for 3 to 5 days is also associated with 30% to 40% incidence of neurodevelopmental sequelae. Neuroimaging in infants with severe hypoglycemia shows involvement of the occipital lobes in 82%. Occipital brain injury can cause visual impairment, epilepsy and long-term disability. Cortical visual deficits are seen in a significant proportion of infants with recurrent hypoglycemia and correlate significantly with low mesial occipital apparent diffusion coefficient values on diffusion weighted MRI. All infants with hypoglycemia should be followed up for neurodevelopmental sequelae.

Refractory or persistent hypoglycemia should be suspected and investigated if the glucose infusion requirement is >12 mg/kg/min or the hypoglycemia persists >5-7 days, respectively. Hyperinsulinemic hypoglycemia is the most important cause of severe and persistent hypoglycemia after initial few days. The risk for brain injury and subsequent neurodevelopment handicap is significantly greater with hyperinsulinemic hypoglycemia. Hyperinsulinemic hypoglycemia may persist for many weeks to months and then remit spontaneously, particularly in growth retarded and stressed neonates. In such infants, the hypoglycemia nearly always responds to medications like diazoxide. Several forms of congenital hyperinsulinism also present with hypoglycemia in neonates that does not remit. Depending on the type of genetic mutation, hypoglycemia in these infants with congenital hyperinsulinism may be controlled medically or may require surgery. The extent of surgery required in infants with ATP-dependent potassium channel mutations unresponsive to diazoxide is dependent upon whether the histological subtype is focal or diffuse. Advances

in molecular genetics, positron emission tomography scanning and minimally invasive surgery have completely changed the clinical approach to these infants.

Certain clinical practices can help prevent the occurrence of hypoglycemia. These include support and promotion of early exclusive breastfeeds within first hour of life in all healthy newborns. Delayed initiation of breast feeds is an important risk factor for hypoglycemia. Maintenance of thermoneutral environment in small infants helps prevent hypoglycemia and skin to skin contact with mother should be encouraged as a strategy for temperature maintenance. Oral dextrose solutions should not be used as a substitute for breast milk. Plain dextrose feeding can induce vomiting and will cause increased insulin secretion, decreased glucagon, delayed gluconeogenesis and rebound hypoglycemia. In infants receiving intravenous infusions, it should be ensured that there is no interruption in the glucose infusion by maintaining a good intravenous access and using a syringe infusion pump to deliver at a steady rate.

In this chapter, we discuss the controversies behind the definition of hypoglycemia, glucose metabolism in fetal and neonatal brain, biochemical derangements during hypoglycemia, clinical correlates and pathological manifestations of hypoglycemia, management issues and the rare entity of persistent hypoglycemia of infancy.

2. Definition

The literal meaning of hypoglycemia is low level of glucose in blood. The 'low level' is however difficult to define in neonates due to the several reasons. First, their nervous system does not have sufficient maturity and capacity to manifest the signs and symptoms of hypoglycemia in a consistent fashion, below the 'low level' of blood glucose. The 'critical limit' of blood glucose required for normal integrity of neonatal brain function is currently not fully understood. Secondly, the 'low blood glucose' levels often occur in association with other biological insults. In presence of these insults, the 'low blood glucose level' limits are likely to be higher as compared to isolated cases of hypoglycemia. These insults e.g. hypoxemia, ischemia, asphyxia, acidosis etc. might have a role in potentiating hypoglycemic brain injury in the vulnerable sick newborn (Volpe, 2008). Hence, the 'normal' range of blood glucose is different for each newborn and depends upon birth-weight, gestational age, body stores, feeding status, availability of energy sources as well as the presence or absence of disease.

2.1 Clinical definition

In early nineteenth century, clinical manifestations (lethargy, tremor, sweating, cyanosis, jitteriness, hypotonia, coma, and seizures) were recognized as the only responses to hypoglycemia. Working definition of hypoglycemia was the 'low blood glucose levels' at which the clinical manifestations were noticed (Hartmann et al., 1960; Brown & Wallis 1963; Cornblath et al., 2000). These clinical manifestations are however nonspecific and can occur with many other neonatal illnesses e.g. sepsis, hypothermia, hypoxic-ischemic brain injury etc. Certain signs like jitteriness can be present even in normal healthy neonates. Therefore clinically significant hypoglycemia is diagnosed if Whipple's triad (Whipple & Frantz 1935) is present. Whipple's triad is defined as: (a) the presence of characteristic clinical manifestations, (b) clinical manifestations occurring in presence of low plasma glucose concentrations, and (c) the clinical signs resolve within minutes to hours, after normalization of blood glucose. It is possible to make clinical diagnosis confidently when all three requirements are met.

However, there are several limitations with this clinical definition. The levels of blood glucose at which clinical manifestations appear may be different from the levels at which biochemical injury occurs leading to long term neurological sequelae. This clinical definition does not take into account clinically asymptomatic neonates who have 'low blood glucose' i.e. "asymptomatic hypoglycemia". Asymptomatic hypoglycemia can also cause hypoglycemic brain injury (Griffiths, 1968; Griffiths & Bryant, 1971; Lucas et al., 1988). The presence or absence of such signs cannot be used reliably to discriminate between normal and low blood glucose levels. Nevertheless presence of clinical signs of encephalopathy such as decreased level of consciousness or seizures should alert the physician for possibility of cerebral fuel deficiency.

2.2 Metabolic definition

Low blood glucose concentrations stimulate counter-regulatory hormonal response in order to increase the blood glucose. With the decrease in blood glucose levels, plasma insulin levels decrease and plasma glucagon levels increase (Sperling et al., 1974). There is increase in serum levels of cortisol, epinephrine, and growth hormone levels as well. The concentration of alternative brain fuels e.g. lactate and ketone bodies also increase in presence of low blood glucose (Persson et al., 1972; Adam et al., 1975; Vannucci et al., 1981). The concentration of blood glucose at which counter-regulatory hormonal response is elicited, may be utilized to define 'acceptable' lower limit of blood glucose. However, there is little information available for the thresholds levels of blood glucose in neonates for the counter-regulatory hormonal stress response, autonomic and neuroglycopenic signs, as well as impaired cognitive function; which have been described in adults (Mitrakou et al., 1991; Ward Platt & Deshpande, 2005). Additionally, preterm neonates are unable to mount a mature counter-regulatory response to low blood glucose levels, making this judgment unsuitable for this population (Hawdon et al., 1992).

2.3 Neurophysiological definition

With fall in blood glucose levels, there may be changes in neurophysiological functions, which can be recorded in form of evoked potentials. Few authors have attempted to measure neurophysiological changes in response to neuroglycopenia. Koh et al. described abnormalities of brain-stem auditory or somatosensory evoked potentials in some children having blood glucose less than 2.6 mmol/L (Koh et al., 1988). None of the children with blood glucose concentrations of ≥2.6 mmol/L showed changes in neurophysiological functions. The authors suggested that 2.6 mmol/L of blood glucose may be taken as a safe threshold in neonates and children. However, there were only five term neonates included in this study. The concentrations of alternative fuels were not measured consistently during this study. Moreover, researchers failed to reproduce distinct threshold to diagnose hypoglycemia on the basis of evoked potentials in both term and preterm babies (Pryds et al., 1988; Cowett et al., 1997).

Positron emission tomography has been utilized to study changes in cerebral blood flow during hypoglycemia among preterm newborn infants (Koh et al., 1988; Pryds et al., 1988). However, resolution of these abnormalities in response to glucose administration needs to be documented to attribute these abnormalities to significant hypoglycemia. Pryds et al. compared hypoglycemic infants (N=13, mean birth weight - 1,500 g) and normoglycemic controls (N=12, mean birth weight - 1,310 g) for the cerebral blood flow and plasma

epinephrine and norepinephrine responses. Hypoglycemia was defined as a blood glucose less than 30 mg/dL. Cerebral blood flow and plasma epinephrine concentrations were increased among hypoglycemic infants. There was no difference in norepinephrine levels. Among hypoglycemic neonates, cerebral flow decreased by 11% after correction of blood glucose. The data suggests that counter-regulatory mechanisms are stimulated below blood glucose values of less than 30 to 45 mg/dL (Pryds et al., 1990).

2.4 Neurodevelopmental approach to define hypoglycemia

Clinical risk of hypoglycemia can be correlated with neurodevelopmental outcome. In a follow-up study of 661 infants weighing less than 1850 g at birth, Lucas et al identified a significantly strong association between the number of days (≥5d) on which blood glucose concentrations of <2.6 mmol/L(<47 mg/dL) were found and lower Bayley developmental scores at 18 months of age (Lucas et al., 1988). The major limitations of this study were non-standardized monitoring of blood glucose, and effect of unidentified confounders with the result that the 'safe' plasma glucose concentrations still cannot be reliably extrapolated. The low plasma glucose concentrations may have been a proxy for extreme illness because such protracted hypoglycemia lasting for 5 days is rare. At 8 years, however, this association was not sustained, and another study in a different large cohort has also failed to replicate this finding (Cornblath & Schwartz, 1999; Williams, 2005).

2.5 Statistical definition

Conventionally, hypoglycemia is defined by a value lying outside the 'normality distribution of the range of values obtained in a healthy population'. 'Low' is arbitrarily defined as a value, 2-standard deviations (SD), below the mean of the population. The major caveat is this approach is that the blood glucose concentrations in a cohort of normal population represent a continuum, and it is not possible to pick a single value that could represent a threshold of abnormality. Those 'minus 2-SD' cutoff value would vary with the gestational age, postnatal age, type of feeding and physiological state e.g. post or pre-feed (Srinivasan et al., 1986; Hawdon et al., 1992; de Rooy & Hawdon, 2002). Moreover, this 'statistical' abnormality cannot be taken as 'biological' abnormality. Technical issues, including discrepancy between values obtained from whole blood and plasma, and the low sensitivity of reagent strip for hypoglycemic range of blood glucose, are also deterrent for such an approach. This may partly explain the lack of consensus between physicians and standard texts in the field. A major criticism of the 'normal range' approach to deriving a treatment yardstick is that it does not consider the complexities of the metabolic milieu, the availability of alternative substrates and the clinical condition of the baby (Koh et al., 1988; Williams, 1997; Williams, 2005).

2.6 Operational thresh-holds

Cornblath et al have suggested a pragmatic way to give cut-off values of blood glucose on which the action should be taken (Cornblath et al., 2000). An "operational threshold " is not diagnostic of a disease, but an indication for action. These recommendations are conservative approximations of designating the lower level of normoglycemia that one can safely tolerate in specific infants, at specific ages and under established conditions. It is difficult to define significant hypoglycemia by a single cut-off value that can be applied universally. Rather, it is characterized by a value(s) that is unique to each individual and

varies with both their state of physiologic maturity and the influence of pathology. It can be defined as the concentration of glucose in the blood or plasma at which the individual demonstrates a unique response to the abnormal milieu caused by the inadequate delivery of glucose to a target organ (for example, the brain).

The operational thresholds may not be applicable to breastfed infants as they have higher concentrations of ketone bodies than formula-fed infants despite having lower blood glucose concentrations (Hawdon et al., 1992; Swenne et al., 1994). The production of ketone bodies among breastfed infants is directly proportional to postnatal weight loss. These data suggest that the provision of alternate fuels constitutes a normal adaptive response to transiently low nutrient intake during the establishment of breastfeeding. These infants may well tolerate lower plasma glucose levels without any significant clinical manifestations or sequelae. However any symptomatic infant with clinical signs consistent with low blood glucose concentration should be treated if the blood glucose levels are <45 mg/dL (2.5 mmol/L). Operational thresh-holds are different among neonates, who are at risk of hypoglycemia as a result of alteration in maternal metabolism, intrinsic neonatal problems, or anticipated or perceived endocrine or metabolic disorders. If the plasma glucose concentration is less than 36 mg/dL (2.0 mmol/L), a close surveillance should be maintained, and intervention is recommended if plasma glucose remains below this level, if the level does not increase after a feed, or if abnormal clinical signs develop. At very low glucose concentrations (<20–25 mg/dL, 1.1–1.4 mmol/L), intravenous glucose infusion aimed at raising the plasma glucose levels above 45 mg/dL (2.5 mmol/L) is indicated. The higher therapeutic goal is chosen to include a significant margin of safety in the absence of any data evaluating the correlation between glucose levels in this range and long-term outcome in full-term infants. The operational thresh-hold suggested for the infants on parenteral nutrition is 45 mg/dL (Cornblath et al., 2000).

It is clear from the above discussion that it is very difficult to give a single value to define hypoglycemia. The approach for the diagnosis and treatment of hypoglycemia should take into account the gestational age as well as sickness level of the baby.

3. Fetal glucose metabolism and metabolic adaptation at birth

In the in-utero life, the fetus is dependent largely on maternal circulation for transplacental transfer of nutrients including glucose. However fetus is capable of endogenous glucose production during placental insufficiency and maternal starvation (Hay & Sparks, 1985). The fetal blood glucose concentrations are lower than but close to those of mother (Bozzetti et al., 1988). Glucose crosses the placenta by facilitated diffusion along a concentration gradient. Human liver contains glycogenic enzymes as early as 8 weeks of gestation, and glycogen deposition begins in early pregnancy. Hepatic glycogen content increases from only 3.4 mg/g at 8 weeks of age to 50 mg/g by term (Capkova & Jirasek, 1968; Williams, 2005). In humans, the enzymes for gluconeogenesis develop by 2 months of gestational age. However under normal physiological circumstances, the gluconeogenesis is not expressed in-utero (Kalhan et al., 1979). Only 40-50% of the maternal glucose taken up by the placenta is transferred to the fetus and rest is utilized by the placenta, which converts it to lactate. This lactate is released into the fetal and maternal circulation in a ratio of 1:3. Fetal lactate uptake is about half of the fetal glucose uptake and provides a major substrate for both oxidative and non-oxidative (such as glycogen synthesis) fetal metabolism. Glucose, however, remains the principal energy substrate for the human fetus under physiological conditions (Williams, 2005).

The blood glucose concentration in the umbilical venous blood is 80-90% of that in the maternal venous blood at the time of birth. Clamping of the umbilical cord causes rapid decrease in neonatal glucose concentration, reaching a nadir by 1 h of age and then increasing to stabilize by 3 h of age even in the absence of any exogenous nutritional intake (Fig. 1) (Srinivasan et al., 1986; Heck & Erenberg, 1987). The cascade of events in successful adaptation to extrauterine life includes metabolic changes such as hepatic glycogenolysis, lipolysis, fatty acid β-oxidation with generation of ketone bodies, and proteolysis that generates lactate and other substrates for gluconeogenesis.

These changes in glucose concentration are modified by a number of factors, including prior fetal glucose homeostasis influenced by antepartum and peripartum events, umbilical concentrations of glucose, plasma insulin concentrations, and the onset of neonatal glucose production from glycogenolysis and gluconeogenesis. There is considerable variability in glucose concentrations during this early postnatal period, both within individual neonates and among groups of neonates of different gestational ages and growth patterns. During this period, plasma insulin levels fall and plasma glucagon levels markedly rise from the baseline levels (Bloom & Johnston, 1972; Sperling et al., 1974). The stress of the birth process causes catecholamine surge. Growth hormone concentration also increases markedly after birth. However its physiological significance is not clear. The initial glucagon surge with low insulin/glucagon molar ratio is the key hormonal adaptation in the newborn infant (Ward Platt & Deshpande, 2005).

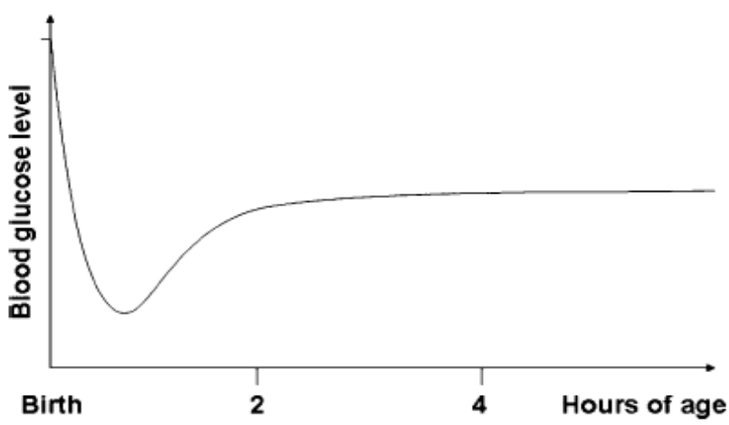


Fig. 1. Profile of blood glucose concentrations in the immediate postnatal period (Srinivasan et al., 1986)

Ketone bodies and lactate serve as alternative fuels with glucose-sparing effects, and are important in maintaining cerebral energy supply. Oxidative metabolism of glucose in fasting human newborns can only supply 70% of the estimated energy needs of the brain (Denne & Kalhan, 1986). Alternative energy substrates such as ketone bodies and lactate are required during fasting for energy production in brain. The capability of newborn brain to utilize ketone bodies is about 5-40 fold greater than that of infant or adult brain (Persson et al., 1972). Even in regularly fed newborn infants, ketogenesis and ketone body consumption provide around 12% of the cerebral oxygen consumption in neonates after a 6-h fast (Hawdon et al., 1992; Ward Platt & Deshpande, 2005). Lactate appears to be an important energy substrate for the infant in the immediate postnatal life. It is metabolized via oxidation by lactate

dehydrogenase in the brain. Although the lactate pool is small (2.4 mM), the concentrations tend to be higher in the crucial first 2-3 postnatal hours (Kalhan et al., 2001).

In the post-natal life, blood glucose concentrations depend upon the feeding practices. Postnatal age and blood glucose concentrations are positively correlated, with the lowest values usually found on day-1 of life (Hawdon et al., 1992; Ward Platt & Deshpande, 2005). The rate of glucose production in the human neonate during the first few postnatal days is estimated to be 4-6 mg/kg/min. Approximately one-third of glucose is produced by glycogenolysis (Shelley & Neligan, 1966). Gluconeogenesis is important for continued glucose supply at this time. The activity of cytosolic phosphoenolpyruvate carboxykinase (PEPCK), which is responsible for gluconeogenesis, markedly increases after birth. Its secretion is stimulated by a fall in the plasma insulin/glucagon molar ratio. The concentrations of gluconeogenic precursors such as alanine and lactate are higher in term neonates as compared to older children or adults (Stanley et al., 1979; Hawdon et al., 1992). It may be due to slow postnatal maturation of PEPCK enzyme, or may be due to catabolic status of the neonate. Gluconeogenesis starts as early as 2 h after birth in the term human neonate (Kalhan et al., 1980). Long-chain fatty acids are required for the postnatal induction of enzymes of mitochondrial fatty acid β-oxidation (Pegorier et al., 1998). Owing to the limited capacity for hepatic ketogenesis in the immediate postnatal life, newborn infants have low plasma ketone body concentrations despite adequate levels of precursor free fatty acids (FFAs) in the first 8 h after birth (Stanley et al., 1979). From 12 h of age onwards, healthy term infants have high ketone body turnover rates (12-22 mmoL/kg/min) (Hawdon et al., 1992). The vigorous ketogenesis appears to be an integral part of extrauterine metabolic adaptation in the term human neonates.

Among preterm neonates, blood glucose levels have a greater fall after birth as compared to term infants. Circulating levels of gluconeogenic substrates are higher in preterm infants (Hawdon et al., 1992). However, the activity of microsomal glucose-6-phosphatase (the final enzyme of glycogenolysis and gluconeogenesis) in preterm infants is extremely low as compared to term infants (Hume & Burchell, 1993). In contrast to these findings, Sunehag et al. showed that preterm infants (25-26 weeks gestation) can have glucose production rates similar to the term neonates (Sunehag et al., 1993; Ward Platt & Deshpande, 2005). Similar observations were reported in preterm infants of 26-31 weeks gestational age. Preterm infants, however, cannot mount mature counter-regulatory ketogenic responses to low blood glucose levels in the first week after birth. The preterm infants demonstrate a positive relationship between blood ketone body concentrations and the volume of enteral feed (Hawdon et al., 1992). This immaturity of counter-regulatory ketogenesis is shown to persist during first 8 postnatal weeks. It may persist even till 2-6 months of postmenstrual age. Preterm neonates have a higher basal insulin secretion (plasma immunoreactive insulin concentrations at low blood glucose levels) as compared to term infants or children. The basal insulin concentrations have been shown to decrease with increasing maturity, however, they remained persistently high in the longitudinal evaluation of metabolic counter-regulation in preterm infants (Ward Platt & Deshpande, 2005).

4. Glucose metabolism and brain

Glucose and oxygen are the principle substances required for energy production in brain. To understand the injury caused by hypoglycemia it is essential to understand the metabolism of glucose in human brain.

4.1 Glucose uptake

Glucose supply to the brain is regulated by the plasma glucose concentration and mediated through a process of facilitated diffusion utilizing glucose transporter 1 (GLUT1) and glucose transporter 3 (GLUT3) proteins. This transport is not energy dependent. The levels of these proteins are relatively low in immature neonates and are a limiting step for glucose transfer and utilization (Koh et al. 1988; Cornblath et al., 2000; Volpe, 2008). GLUT1 is expressed in the blood-brain barrier endothelial cells, astrocytes, oligodendrocytes and choroid plexus while GLUT3 is expressed primarily in neurons and their synaptic membranes (Mantych et al., 1993; Kalhan et al., 2001). The brain glucose transporter is concentrated in capillaries and the concentration increases with maturity. The limiting factor for the passage of glucose to the brain tissue is the concentration of glucose transporters rather than the affinity of the receptors. The number of available endothelial receptors in human premature neonates is one third to half as compared to the adult brain (Powers et al., 1998; Volpe, 2008).

4.2 Glucose utilization in brain

Glucose is acted upon by hexokinase to form glucose-6-phosphate. It may be utilized via glycolytic pathway to produce energy (ATP), Hexose mono-phosphate (HMP) shunt to produce reducing equivalents or conversion to glycogen. Glycogen thus formed is stored in astrocytes and is used for energy production later on during periods of low blood glucose levels. Reducing equivalents from HMP shunt are required for lipid synthesis and nucleic acid synthesis. Glucose utilization is highest in brainstem gray matter structures, declining in a caudal to rostral manner, to the cerebral cortex. Cerebral glucose utilization in the human studies was found to be highest in the sensorimotor cerebral cortex, thalamus, mid-brain-brainstem, and the cerebellar vermis. By 3 months of age, glucose metabolic activity in the human infants had increased in the parietal, temporal, and occipital cortices and in the basal ganglia. Subsequently it increased in frontal and various association regions of cerebral cortex by 8 months. Little further change was observed between 8 and 18 months of postnatal age (Vannucci & Vannucci, 2000). Glucose acts as a primary metabolic fuel in the mature and immature brain. The studies in the newborn dogs indicate that glucose consumption accounts for 95% of the cerebral energy supply (Volpe, 2008). If the glucose supply to the brain is limited, alternative substances such as lactate and ketone bodies can be utilized to protect the brain functions and structure. Ketone bodies can be taken up by carrier mediated transport system, converted to acetyl CoA and metabolized to produce energy. Ketone bodies account for approximately 12% of total cerebral oxygen consumption after 6-hr fasting in newborns. However, availability of ketone bodies in such circumstances depends on the liver's capacity to deliver them in blood. The role of exogenous ketone bodies as a source of energy in settings of hypoglycemia is yet to be explored (Plecko et al., 2002). Lactate uptake from the blood also increases during periods of low blood glucose levels and it gets oxidized to pyruate by lactate dehydrogenase. The activity of lactate dehydrogenase in perinatal animal models is higher than adults (Lehrer et al., 1970; Wilson, 1972; Nehlig & Pereira de Vasconcelos, 1993). The association of increased lactate utilization and relative sparing of neonatal brain is strong but the exact role is yet to be explored. It is argued that the lactate utilization in perinatal animal could be an adaptive response to increased lactate levels in blood in perinatal period to avoid lactic acidemia (Volpe, 2008).

5. Biochemical alterations during hypoglycemia

In the event of low blood glucose, certain biochemical changes occur in the neonatal brain. With continuing hypoglycemia, changes secondary to hypoxia, ischemia and seizures may add to the insult. These combined effects are of major concern as it increases the chances of brain injury even if individual insults are not of sufficient magnitude to cause injury by themselves (Volpe, 2008).

5.1 Initial changes

The initial response to the low blood glucose levels is an increase in cerebral blood flow so as to increase glucose supply to brain. This effect has been shown in adult models (Siesjo, 1988), neonatal animal models (Anwar & Vannucci, 1988; Mujsce et al., 1989), and human infants (Pryds et al., 1988, 1990; Pryds, 1991; Skov & Pryds, 1992). In human infants, a sharp increase in cerebral blood flow has been observed below a blood glucose of 30 mg/dL (Pryds et al., 1990). Initial biochemical changes include metabolic attempts to preserve cerebral energy status by utilizing alternatives to glucose. Glycogenolysis starts to provide glucose to brain tissue. Researchers have noticed that initially there is not much change in cerebral oxygen consumption. This discrepancy between falling blood glucose levels and relatively preserved oxygen utilization in initial phases of hypoglycemia implies that alternative substrates like lactate and ketone bodies might be sufficient to meet cerebral energy needs (Norberg & Siesio, 1976; Ghajar et al., 1982). Amino acids may be other alternative substrates as a sharp decrease in brain concentrations of most amino acids occurs along with increase in brain ammonia levels (Volpe, 2008).

There is dissociation between cerebral energy metabolism and brain functions during hypoglycemia. The changes in level of consciousness (from alert state to depressed state) and from normal EEG to slowing can occur with relatively little change in levels of ATP in various regions of brain (Siesjo, 1988; Vannucci et al., 1981; Vannucci & Vannucci, 2000; Volpe, 2008). This phenomenon can be attributed partially to metabolic changes happening during early periods of hypoglycemia. The concentration of ammonia goes up as the levels of amino acids decrease so as to preserve ATP production. The level of ammonia production is considered sufficient to produce stupor in adult hypoglycemic animals. Mature rats, who were made hypoglycemic, displayed impaired acetylcholine synthesis in early phase of hypoglycemia (Gibson & Blass, 1976; Ghajar et al., 1982). Only modest hypoglycemia was able to decrease acetylcholine levels by 20-45%. Moreover there was 40-60% decrease in synthesis of this neurotransmitter in cortex and striatum (Ghajar et al., 1982). The likely mechanism for the dissociation between cerebral energy metabolism and brain functions during hypoglycemia, is decrease in acetyl-coA concentration secondary to low blood glucose and hence glycolysis (Volpe, 2008). However in newborn animal models, hypoglycemia severe enough to deplete glucose from brain is accompanied by some preservation of glycolytic intermediates such as pyruate and lactate; and almost complete preservation of ATP levels. Newborn animal models showed resistance to neurological deterioration even at plasma glucose levels of 15 mg/dL when maintained for a period of 2 hours (Vannucci & Vannucci, 1978). In newborn dog, the EEG slowing was observed only below 20 mg/dL (Vannucci et al., 1981). There are various reasons for the relative resistance of newborn brain towards neuronal injury to hypoglycemia. These include lower cerebral energy requirements, marked increase in cerebral blood flow in early phases of hypoglycemia, increased capacity of neonatal brain to utilize lactate as an alternative brain

fuel and relatively less effect on cardiovascular system as compared to adults due to abundant endogenous carbohydrate stores (Volpe, 2008).

5.2 Later changes

If hypoglycemia continues, generation of fatty acids increases due to phospholipid degradation, to provide additional source of energy. However, this energy source is not sufficient to provide for the deficit of high energy phosphate compounds and prevent clinical and EEG deterioration (Ghajar et al., 1982; Siesjo, 1988). In advanced phases of hypoglycemia, there are changes in intracellular Ca^{++} and extracellular K^+ concentration (Agardh et al., 1981; Wieloch et al., 1984; Siesjo, 1988). The neuron loses its ability to maintain normal ionic gradients. The failure of energy dependent Na^+/K^+ ATPase is the likely reason responsible for these changes. With energy failure, Na^+ accumulates intracellularly and K^+ accumulates in extracellular space leading to sustained membrane depolarization. Increase in intracellular Na+ would lead to activation of Na^+/Ca^{2+} exchange system and intracellular accumulation of Ca^{2+} ions. There is also failure of energy dependent Ca^{2+} transport across the cell membrane, which again leads to intracellular accumulation of Ca^{2+} ions. The increased concentration of cytosolic Ca^{2+} ions leads to phospholipase activation and cellular injury. This explanation is supported by the observed corresponding decline in phospholipid concentration and increase in fatty acid levels with increase in intracellular Ca^{2+}. Additionally, the increase in cytosolic calcium concentration causes increase in release of excitatory amino acids (e.g. aspartate and glutamate) from synaptic nerve endings and reduced uptake secondary to failure of glutamate transport. Antagonists of N-Methyl-D-Aspartate type of glutamate receptors have been shown to attenuate neuronal injury in cultured neurons and in vivo models (Wieloch, 1985; Volpe, 2008). The excess cytosolic Ca^{2+} also leads to increase in reactive oxygen and nitrogen species. These free radical species result in DNA damage and as a consequence DNA repair enzyme, poly (ADP-ribose) polymerase-1 (PARP). Excessive activation of PARP, leads to apoptosis. PARP inhibitors have been shown to protect neurons from hypoglycemic injury in in- vivo and in-vitro models (Suh et al., 2003; Volpe, 2008).

6. Pathological changes in hypoglycemic brain injury

It is difficult to define exact neuropathology in newborns suffering from hypoglycemia as it almost always coexists with other morbidities. However the literature suggests that the topography of the hypoglycemic brain injury is peculiar and is different from that of hypoxic ischemic brain injury. Adolescent monkeys when exposed to blood glucose of <20 mg/dL for more than 2 hours showed neuronal injury predominantly in the regions of parieto-occipital cortex. Less commonly involved regions were hippocampus, caudate nucleus, and putamen. The injury was most severe in regions contiguous to cerebrospinal fluid such as superficial cerebral cortical layers (Agardh et al., 1980; Auer et al., 1984, 1985; Kalimo et al., 1985; Siesjo, 1988). Similar topographical distribution of neuropathology was observed in premature infants using autopsy studies, computed tomography, magnetic resonance imaging and single photon emission computed tomography blood flow scans (Anderson et al., 1967; Spar et al., 1994; Chiu et al., 1998; Volpe, 2008). The hypoglycemic brain injury primarily involves neurons but glia are also affected (Anderson et al., 1967). Studies of oligodendrocyte precursor cells and cerebellar slice cultures showed that

hypoglycemia induces apoptotic cell death and inhibits differentiation and myelination (Yan & Rivkees 2006). Additionally hypoglycemia alone if not severe enough to cause neuronal injury, may contribute to the injury caused by other insults. The sequelae of hypoglycemic brain injury include microcephaly, widened sulci and atrophic gyri, diminished cerebral white matter and dilated lateral ventricles. The pathological effects of marginal hypoglycemia with or without other concomitant insults are not known.

7. Clinical profile

Hypoglycemia is a concomitant finding in variety of neonatal disorders. The incidence of hypoglycemia depends upon the proportion of term and preterm in a given population, type of milk feeding, the pattern of feeding, screening timings and methods, temperature, sickness level and definition used for the diagnosis of hypoglycemia. In a large series of 661 preterm neonates with birth weight <1850 g, 10% had at least one value of blood glucose <0.6mmol/L (<10mg/dL approximately), 28% had at least one value <1.6mmol/L (<30mg/dL approximately), and 66% had at least one value of blood glucose <2.6 mmol/L (<45mg/dL approximately) (Lucas, Morley et al. 1988). Among breastfed healthy term neonates, approximately 17% of the neonates had plasma glucose value of <2.16mmol/L (<40 mg/dL) at 3 hours of postnatal life. Ten percent of neonates had similar values at 72 hours of life (Diwakar & Sasidhar, 2002).

The clinical manifestations of hypoglycemia are largely related to central nervous system. Common clinical signs include jitteriness, irritability, varying degree of altered consciousness, seizures, tachypnea, apnea and hypotonia. It is important to realize that there might be no symptoms in presence of biochemical evidence of hypoglycemia (Asymptomatic hypoglycemia)(Volpe, 2008). Neonates with 'symptomatic hypoglycemia' can be classified into four categories according to the clinical setting of hypoglycemia, time of presentation, and severity of presentation (Volpe, 2008):

7.1 Early transitional adaptive hypoglycemia

It occurs in first 6-12 hours of life, after sudden withdrawl of maternal nutrient supply due to cord clamping. This manifests in neonates, who fail to mount adequate metabolic adaptive response in the face of falling blood glucose levels, in immediate postnatal life. If the mother receives excess glucose in intravenous fluids during intrapartum period, the glycolytic and gluconeogenic responses of the neonate are blunted and insulin secretion increases in immediate postnatal period. Large for gestational age infants born to diabetic (IDM) or non-diabetic mothers, neonates who experience hypothermia or asphyxia are at risk for very early hypoglycemia. This type of hypoglycemia lasts for brief duration, is mild in severity and responds rapidly to treatment. The prognosis depends largely on the underlying cause.

7.2 Secondary associated hypoglycemia

This can occur as an associated finding with a variety of illnesses. It is often seen in appropriate for gestational age (AGA) term and preterm neonates, and is associated with illnesses particularly involving central nervous system e.g. birth asphyxia, intracranial hemorrhage, congenital anomalies and systemic disorders. The association with brain disorders is of particular interest as these may have adverse impact on regulation of hepatic glucose production. This variety of hypoglycemia is also characterized by short duration, mild severity and rapid response to treatment (Volpe, 2008).

7.3 Classic transient neonatal hypoglycemia

This group encompasses predominantly small for gestation (SGA) term infants, who may also have polycythemia concomitantly. The onset of hypoglycemia is in later part of first day. Hypoglycemia is usually moderate to severe, duration can be prolonged and often high glucose infusion rates are required to maintain euglycemia.

7.4 Severe recurrent hypoglycemia

Recurrent and persistent hypoglycemia is the hallmark of this variety. This type occurs in term AGA neonates who have either hyperinsulinism or endocrinopathies or hereditary metabolic defects. The hypoglycemia is variable in onset according to the underlying cause, usually severe, difficult to treat, prolonged and invariably symptomatic. The prognosis depends on the timely detection of the disorder, institution of specific therapy, and the ability to maintain normal blood glucose levels.

8. Monitoring of blood glucose

8.1 Who should be monitored?

All preterm and SGA neonates merit blood glucose screening as they have decreased body stores of glycogen and they often harbor co-morbidities putting them at risk for hypoglycemia. The large for gestation age infants and IDM neonates usually have excess insulin secretion in the immediate neonatal period putting them at risk of hypoglycemia. All 'unwell' neonates should also be routinely monitored for hypoglycemia. (Deshpande & Ward Platt 2005). The indications of monitoring blood glucose in neonatal age group are shown in Figure 2.

Due to maternal indications	Neonatal indications
• Maternal drug ingestion eg β-blockers, oral hypoglycemics, β-sympathomimetics • Insulin dependent diabetic mothers • Gestational diabetic mothers • Massively obese mothers • Mothers given large amounts of parenteral glucose during labor and delivery • Mothers given parenteral glucose too rapidly prior to delivery	• Prematurity • Small or large for gestational age • Hypothermia • 'Sick looking' or 'unwell' neonate • Sepsis • Hypoxia ischemia • Polycythemia • Congenital heart diseases • Total parenteral nutrition • Blood exchange transfusion • Suspected inborn errors of metabolism

Fig. 2. Indications of monitoring blood glucose

8.2 What should be the monitoring schedule?

The neonates in whom there is increased consumption of glucose because of increased insulin levels become symptomatic very early in postnatal life. It is also evident that the levels of alternative 'brain fuels' would also be less due to presence of anabolic hormone insulin. Hence IDM and severely intrauterine growth retarded neonates can become symptomatic very early in life and merit screening right from cord blood. Some severely IUGR infants may develop hypoglycemia in-utero (Soothill et al., 1987; Economides &

Nicolaides, 1989) and would not be expected to achieve normal metabolic adaptation soon after birth. These neonates merit cord blood glucose estimation and routine screening in the postnatal life at least for initial 48 hours. The neonates with low body glycogen stores like preterm and IUGR neonates should get first screening within 1 hour of life. All neonates who are symptomatic should get blood glucose levels checked immediately. Many textbooks and guidelines recommend blood glucose monitoring at pre-fixed time periods after birth, such as at 1 h, 2 h, 3h,6h and then 6 hourly till 48-72 hours by when feeding is likely to be established. Blood glucose estimation should be done immediately before a feed, as the purpose of screening is to identify the minimum blood glucose level (Lucas et al., 1981).

8.3 How should blood glucose be measured?

An ideal diagnostic method should be precise, rapid, inexpensive, available at bedside, and should require small blood volume. At beside, the blood glucose measurements are done by point of care glucose meters. They measure blood glucose within few seconds and require small sample volumes (as small as 0.3 µL). For treatment decisions, the clinical practices are dependent on point of care measurements rather than laboratory estimations. The small volume of blood required by such approach has been shown to reduce the need for blood transfusions (Madan et al., 2005). Apart from the devices used, the estimation of blood glucose levels can also be affected by the properties of sample used for analysis.

8.3.1 Devices for screening of blood glucose

Since the introduction of reagent strip blood glucose tests in the 1970s for blood glucose screening in newborn infants, the world has witnessed dramatic developments in point of care devices for blood glucose measurements. Dextrostix was the first dry reagent, which was interpreted with change in color and hence was dependent on subjective interpretation. Then came the era of photometric devices (reflectance meters). In this method, the blood was required to be placed on the strips for specific time periods, wiped and then inserted into a meter . Sources of error in glucose estimation while using these methods are possible contamination by alcohol skin-cleansers, not covering the whole surface of the test-pad with blood, and failure to time the reaction accurately before wiping the strip. The paper-strip methods tend to underestimate the neonatal blood glucose values even when these precautions are adopted. The common glucose strips used in neonatal practice were Dextrostix (Ames Co., Slough, England) (Chantler et al., 1967; Wilkins & Kalra 1982; Williams, 1997), BM-test-Glycemie (Boehringer Mannheim, Mannheim, Germany) (Wilkins & Kalra, 1982; Reynolds & Davies, 1993), and Chemstrip bG (Boehringer Mannheim, Mannheim, Germany) (Kaplan et al., 1989; Holtrop et al., 1990). Recently, point of care testing is being done by glucose meters, which utilize enzyme reactions (glucose oxidase or glucose dehydrogenase) to generate electric signals, which are measured by a meter. The size of the current is proportional to the amount of glucose in the blood sample leading to increased accuracy (Beardsall, 2010).

However it is important to know that these methods were primarily designed for diabetic patients and not for the glucose screening of newborns. The sensitivity of these methods is likely to be highest at blood glucose levels in diabetic range and may drop at extreme values. In intensive care units, a number of potential inaccuracies may arise because of presence of metabolic acidosis (Tang et al., 2000), hypoxia (Tang et al., 2001), hypoperfusion

(Atkin et al., 1991) or edema (Critchell et al., 2007). If the devise uses glucose oxidase method, it may give abnormally low glucose values at high blood oxygen levels (Tang et al., 2001). High hematocrit levels in preterm and IUGR neonates might display falsely low glucose levels with these methods and this effect is most marked at low blood glucose levels (Kaplan et al., 1989; Tang et al., 2000). High bilirubin levels can also interfere with some analyzers (Jain et al., 1996). The data of their use in neonatal age group is limited. In a study comparing five glucometers namely Reflolux S (Boehringer), Advantage and Glucotrend (Roche); Elite XL (Bayer) and Precision (Abbott) with plasma glucose measured in the laboratory (Aeroset; Abbott); none of the five glucometers was satisfactory as the sole measuring device. For detection of glucose concentrations <2.6 mmol/L, the Precision glucometer had the highest sensitivity (96.4%) and negative predictive value (90%). For lower glucose concentrations (<2.0 mmol/L), the Glucotrend glucometer performed even better (sensitivity 92.3%, negative predictive value 96.3%) (Ho et al., 2004). A recent retrospective study compared three meters (Elite™ XL, Ascensia™ Contour™ and ABL 735) with laboratory hexokinase reference method. All three POCT systems tended to overestimate glucose values. The Elite XL appeared to be more appropriate than Contour to detect hypoglycemia, however with a low specificity. Contour additionally showed an important inaccuracy with increasing hematocrit. The sensitivity to detect hypoglycemia with a cutoff value <2.5 mmol/L was 86% and 43% for Elite XL and Contour respectively (Beardsall, 2010).

With modern blood gas and electrolyte analyzers, it is possible to directly measure blood glucose levels by electrochemical biosensors. The comparative data for glucose biosensor technology versus traditional methods of blood glucose estimation in the neonatal age group is sparse. In a recent study, an amperometric electrode with glucose oxidase membrane incorporated in a multi-analyte analyzer was compared with hexokinase/glucose-6-phosphate dehydrogenase method. It showed a sensitivity and specificity of 55% and 100% respectively below a cutoff of <2.5mmol/L and 89% and 95% respectively below a cutoff of <3.0mmol/L of laboratory reference value (Beardsall 2010). Another study compared blood glucose measurements obtained by point-of-care testing using an AVL Omni 9 blood gas analyzer with those obtained in the central laboratory using a DADE Dimension RXL analyzer. There was a good correlation (r = 0.92) between the two for glucose values <3 mmol/L. The limits of agreement for the AVL Omni 9 when compared with the DADE Dimension RXL analyser were -0.1 +/- 0.5 mmol/L. (Newman et al., 2002). Laboratory analyses are done by a number of different enzymes which measure glucose e.g. glucose oxidase, hexokinase or glucose dehydrogenase. Glucose measured by these methods is the most practical method for measurement of glucose levels. The plasma glucose levels measured by these enzymes are less affected by interference by metabolites and are not affected by hematocrit (Beardsall, 2010).

8.3.2 Continuous glucose monitoring

Continuous glucose monitoring is possible by placement of subcutaneous glucose monitoring sensors. This glucose oxidase based platinum sensor catalyzes interstitial glucose and an electrical current is produced every 10 seconds. This current is recorded by a monitor and displayed as real time trend. The glucose value is averaged for past 5 min and thus profile of glucose trend is generated. This displays trend of tissue glucose levels over time, like continuous saturation monitors. The glucose levels in newborns can fluctuate

widely especially those requiring intensive care. This means that by periodic spot monitoring we may miss undetected periods of hypoglycemia as well as hyperglycemia (Beardsall et al., 2005). Their use in management of adults and children with diabetes has led to stringent control over blood glucose levels, with reduction in episodes of hyperglycemia and hypoglycemia. Commercial devices are available such as CGMS Gold or Guardian (Medtronic Watford UK) or Free Style Navigator (Abbott Maidenhead, Berks, UK). The initial devices could not display real time trends limiting their clinical potential. However it is possible with more recent models, which have been successfully used to monitor post-cardiac surgery pediatric patients. During the management of infants with neonatal diabetes, these can be linked to subcutaneous insulin pumps (Corstjens et al., 2006). Their clinical application can be extended to the management of preterm and sick neonates who are at risk of hypoglycemia and hyperglycemia. However the benefits and risks need to be fully evaluated before their introduction into clinical care. Microdialysis is another method of continuous glucose monitoring. A semi-permeable dialysis fiber or double lumen catheter with micro-holes is placed in subcutaneous tissue. Isotonic glucose free fluid passes through the device collecting dialysate of interstitial fluid. Thus the dialysate contains glucose equal in concentration to that of interstitial fluid. Commercial devices are available such as the CMA Microdialyses catheter (Solna Sweden), which can be used in neonates. However these devices are expensive, invasive, need calibration, and there is a significant lag time in collection and measurement. Although they have been used as research tool, their routine clinical use is limited (Baumeister et al., 2001). In a recent study comparing Continuous Glucose Monitor Sensor (CGMS system gold, Medtronic, MiniMed, Northridge, California) with glucose oxidase method in blood gas analyzer (Radiometer, ABL800Flex, Copenhagen, Denmark), 81% of total 265 episodes of low interstitial glucose concentrations were not detected with blood glucose measurement (Harris et al., 2010). The non-invasive devices utilizing optical sensors (spectrophotometry) or transdermal devices using reverse iontophoresis are being evaluated for possible clinical utilization. They are in early phase of development and their clinical potential is yet to be evaluated in neonates (Beardsall, 2010).

Thus, at present, there is no reliable and accurate point-of-care method for blood glucose estimation in the low ranges of blood glucose encountered in newborn infants. Laboratory systems that provide timely results may be the preferred option; these facilities require certification by the institutional clinical pathology services and other accrediting agencies, as well as initial and ongoing assessment and maintenance of instrument function, technical training of the users, and data quality monitoring. Thus far, there are no satisfactory methods for noninvasive monitoring of glucose or alternate substrates. Such monitoring devices, however, would have a major impact on clinical decision making. Continuous glucose monitoring with subcutaneous perfusion devices has been used to a limited extent.

8.3.3 Properties of the sample and sources of error

Arterial blood has a slightly higher glucose concentration than venous, while the capillary blood has intermediate values. This difference is usually not clinically significant. The difference of blood glucose levels between arterial and venous blood depends upon tissue glucose demands and is greatest in anaerobic conditions. In presence of peripheral circulatory failure, capillary sampling is unreliable as the blood flow is reduced. The blood sample must be a free-flowing sample and squeezing the tissues to get blood causes hemolysis. The glucose estimations performed with 'squeezed' sample are not true values

and deproteinization is required to get true values. Contamination by the alcohol antiseptic solutions during skin preparations might give erroneously high values (Grazaitis & Sexson 1980; Togari et al., 1987). The sample should be analyzed immediately or it should be deproteinized (e.g. using perchloric acid) and chilled to avoid glycolysis. Sodium fluoride added to blood inhibits glycolysis and gives freedom to process sample after some time. But the fluoride is not able to completely prevent glycolysis, thus getting falsely low blood glucose values in samples sent to a distant laboratory (Elimam et al., 1997). Commercially available sodium-fluoride coated tubes do not always ensure a fluoride concentration sufficient to inhibit glycolysis (Joosten et al., 1991). Chan et al. observed that glucose levels in blood fall about 0.3–0.34 mmol/L over the first hour, in samples collected into either heparin or sodium fluoride containing tubes (Chan et al., 1989). High hematocrit values may be associated with falsely low blood glucose estimation. Red blood corpuscles contain less proportion of water than an equivalent volume of plasma. Thus in equal volume of blood and plasma, the glucose concentration is expected to be higher in plasma, on average by about 18% (Aynsley-Green, 1991). Furthermore, the diffusion of plasma into the testpad of the strip is impeded due to higher sample viscosity. This problem can be tackled by estimating plasma glucose after getting plasma from a heparinized microhaematocrit tube (Kaplan, Blondheim et al. 1989). Presence of hemolysis also gives falsely low values. The presence of hemoglobin or release of reduced glutathione competes with the chromogen for hydrogen peroxide released in the assay. Deproteinization of the sample reduces the interference with blood glucose estimations by hemolysates, uric acid, and bilirubin (Williams, 1997).

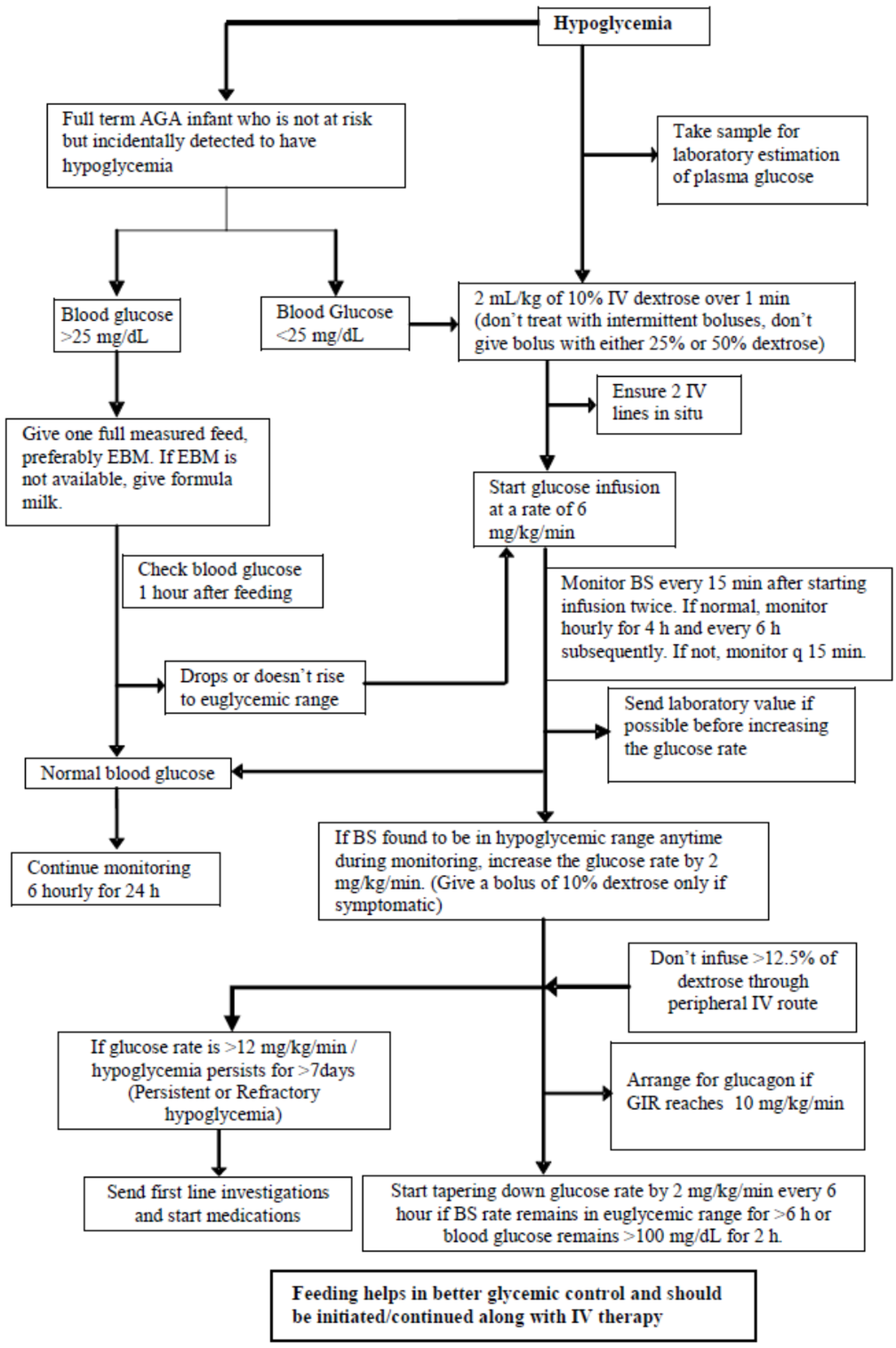
9. Prevention

The earliest and common cause of low blood glucose levels is delay in the normal metabolic adaptation after birth. Hence oral feeds within half hour of life should be promoted in healthy appropriately grown term infants. In preterm infants of <32 weeks gestation or those with asphyxia or respiratory distress or any illness interfering with enteral nutrition, intravenous dextrose infusions should be started. Glucose delivery through intravenous infusions should match the amount of glucose production by endogenous hepatic output. For most well-grown preterm infants, it is approximately 6 mg /kg/ min (around 90 mL 10% dextrose/kg per day (Sunehag et al., 1993). The occurrence of hypoglycemia should be unusual with such fluid regimens, in these preterm infants, (Hawdon et al., 1992) and enteral feeds can be gradually increased along with. Near-term infants of 33-36 weeks gestational age require careful nursing as they may not be able to establish good feeding due to physiological handicaps and increased demands. Supplementary feeds may be required if breastfeeding is not fully established. If possible first option should be expressed breast milk, and formula milk can be used if breast milk is unavailable or inadequate. In neonates who remain hypoglycemic despite an adequate enteral intake, or for those unable to tolerate milk, an intravenous dextrose infusion is necessary. Some IUGR infants require glucose intake in excess of 10 mg/kg/min. Hyperinsulinism may be the likely mechanism of such high glucose requirements (Collins et al., 1990) and these babies may have insulin values above those seen in healthy term babies (Hawdon et al., 1993a, 1993b). They may be described as 'functionally' hyperinsulinemic as they also demonstrate increased insulin sensitivity (Bazaes et al., 2003).

10. Treatment of neonatal hypoglycemia

A 'symptomatic' neonate should be treated with intravenous dextrose and this should be instituted as early as possible if the blood glucose concentrations are below 45-50 mg/dL (Volpe, 2008). Glucose 'minibolus' (200 mg glucose/kg, 2 mL/kg of 10% dextrose) is effective in rapidly correcting neonatal hypoglycemia. A minibolus should be given when blood glucose concentration needs to be raised quickly, such as in a symptomatic neonate with neurological signs in association with a low blood glucose concentration. A minibolus should always be followed by intravenous glucose infusion. The glucose infusion should be started at an infusion rate of 6-8 mg/kg per min (Lilien et al., 1980). The glucose infusion rate (GIR) should then be titrated with repeated blood glucose estimations. Blood glucose should be frequently monitored until it stabilizes. After commencing intravenous infusion, blood glucose should be repeated with in half an hour. The glucose infusion rate should be hiked by 2 mg/kg per min if the repeat screen is also in 'hypoglycemic' range. Once blood glucose levels are stabilized, preprandial blood glucose may be monitored at 4 to 8 hour intervals (Cornblath & Ichord, 2000). Boluses of hypertonic glucose solution should be avoided as they can precipitate rebound hypoglycemia. Baby should be offered enteral feeds if clinically there is no contraindication. Amino-acids like alanine promote gluconeogenesis and help to maintain blood glucose levels. Breast milk in particular promotes ketogenesis (de Rooy & Hawdon, 2002). After 12-24 hours of intravenous glucose infusion, addition of sodium 1 to 2 mEq/kg/day is indicated to prevent iatrogenic hyponatremia. After 24-48 hours, 1 to 2 mEq/kg/day of potassium should be added to the parenteral fluids (Cornblath & Ichord, 2000). If baby remains symptomatic or if plasma glucose concentrations cannot be maintained over 45 mg/dL (2.6 mmol/L), even at glucose infusion rate of 12 mg/kg/min, hydrocortisone (5 mg/kg intravenously every 12 hours) should be added to the regimen (Volpe, 2008). If the concentration of glucose infusion exceeds 12.5% to 15% through peripheral vein, a PICC (peripherally inserted central catheter) line should be placed, as concentrated solutions can cause injury to peripheral veins. If the rate of glucose infusion exceeds 10-12 mg/kg/min or the hypoglycemia is present after 5 to 7 days, the infant may have refractory or persistent hypoglycemia (Cornblath & Ichord, 2000).

Once the blood glucose levels are maintained in euglycemic range of 70-100mg/dL, the glucose infusion should be tapered by 2mg/kg/min every 6 to 12 hourly. The gradual reductions in the rate of intravenous glucose infusion should be attempted as they avoid wide swings in blood glucose concentrations. The glucose infusion rate should be reduced while increasing oral intake (Williams, 1997) and glucose levels should be closely monitored to keep them >50mg/dL (Volpe, 2008). Intramuscular glucagon (see below) may act as a temporary measure to raise blood glucose, if there is difficulty in placing intravenous line quickly. Glucagon promotes early neonatal glycogenolysis from liver and also stimulates gluconeogenesis and ketogenesis (Milner & Wright, 1967). An intramuscular bolus dose of 200 µg/kg increases the blood glucose level (Hawdon et al., 1993c). It has been used successfully to treat hypoglycemia in infants of diabetic mothers (Wu et al., 1975) and growth-restricted infants (Carter et al., 1988). Side-effects of glucagon include vomiting, diarrhea, and hypokalemia; at high doses it may stimulate insulin release. Controlled studies of the relative efficacy of glucagon and the more conventional alternative of glucose infusion at concentrations >6mg/kg per min are needed (Williams, 1997). An algorithm for the management of a neonate with hypoglycemia is presented in Figure 3 (Narayan & Wazir, et al. 2010).



GIR: Glucose Infusion Rate BS:Blood Sugar(Glucose)

Fig. 3. Management algorithm for neonatal hypoglycemia

11. Refractory or persistent neonatal hypoglycemia

Refractory or persistent hypoglycemia can be defined as the persistent requirement of a glucose infusion rate more than 12 mg/kg/min to maintain normoglycemia or persisting or hypoglycemia beyond first 5 to 7 days of life. The causes of refractory or persistent hypoglycemia are related to endocrine or metabolic disturbances (Table 1)

Hormone Deficiencies	Multiple Endocrine Deficiency	Congenital Hypopituitarism Anterior pituitary "aplasia" Congenital optic nerve hypoplasia
	Primary Endocrine Deficiency	Isolated growth hormone deficiency Adrenogenital syndrome Adrenal hemorrhage
Hormone Excess with Hyperinsulinism		Beckwith-Wiedemann syndrome Hereditary defects of pancreatic islet cells
Hereditary Defects in Carbohydrate Metabolism		Glycogen storage disease Fructose intolerance Galactosemia Glycogen synthase deficiency Fructose, 1-6 diphosphatase deficiency Ketogenetic and ketolytic defects
Hereditary Defects in Amino Acid Metabolism		Maple syrup urine disease Propionic acidemia Methylmalonic acidemia Tyrosinosis
Hereditary Defects in Fatty Acid Metabolism		3-OH-3-methyl glutaryl CoA lyase deficiency Acyl CoA dehydrogenase--medium, long chain deficiency Mitochondrial/3-oxidation & degradation defects

Table 1. Causes of Refractory or Persistent Hypoglycemia

The most common cause of persistent or refractory hypoglycemia is congenital hyperinsulinism, also called as persistent hyperinsulinemic hypoglycemia of infancy (PHHI). Although a glucose infusion rate exceeding 12 mg/kg per min suggests hyperinsulinism, the diagnosis is confirmed by the presence of-

1. Hyperinsulinemia (plasma insulin >2 μU/mL, depending on sensitivity of insulin assay), in presence of documented laboratory hypoglycemia (<50 mg/dL)
2. and/or evidence of excessive insulin effect
   a. Increased glucose consumption rate (>8 mg/kg/min)
   b. Hypofattyacidemia (plasma free fatty acids <1.5 mmol/L)
   c. Hypoketonemia (plasma β-hydroxybutyrate <2.0 mmol/L)
   d. Glycemic response to 1 mg IV glucagon 50 μg/kg (max 1mg) (increase in glucose >30 mg/dL)

Insulin level should be obtained only during presence of hypoglycemia. Simultaneous measurement of blood glucose level may be done to find out the insulin-glucose ratio. Elevated insulin-glucose ratios are found in hyperinsulinemic states (normal - up to 0.2; elevated - >0.4). A 'normal' level of insulin is abnormal if it occurs in the face of hypoglycemia, especially in the context of high glucose requirement to maintain normoglycemia.

PHHI results from an inappropriate insulin secretion by the β-cells of pancreatic islets of Langerhans (Arnoux et al., 2010). Insulin decreases plasma glucose concentration by inhibiting glucose release from the liver (by glycogenolysis and gluconeogenesis), and by increasing glucose uptake in muscle and adipose tissues. It also inhibits lipolysis and hence production of fatty acids and ketone bodies is markedly reduced. Hence, the brain is unable to get alternative fuels in presence of hypoglycemia and thus is particularly vulnerable to hypoglycemic injury.

PHHI presents as severe hypoketotic hypoglycemia. There is a risk of neonatal seizures and brain damage if it is left untreated. Hypoglycemia occurs early within 72 h after birth and half of the patients become symptomatic in the form of seizures. Majority of neonates are macrosomic. The affected neonates may present with abnormal movements as tremulousness, hypotonia, cyanosis, hypothermia or a life-threatening event. On external examination, they may have mild hepatomegaly. Sometimes typical facial features in form of high forehead, large and bulbous nose with short columella, smooth philtrum and thin upper lip can be appreciated. However, hyperinsulinism can be associated with syndromes such as Beckwith–Wiedemann syndrome (BWS), Perlman syndrome, Kabuki syndrome, Sotos syndrome, congenital disorders of glycosylation type Ia or Ib (CDG) (de Lonlay et al., 1999), or Usher syndrome type Ic. Hypoglycemia may be detected in such neonates by routine measurement of blood glucose. The hypoglycemia is severe and rates of intravenous glucose administration to maintain euglycemia are usually in excess of 12 mg/kg per min. Subcutaneous or intramuscular administration of glucagon can be used to raise blood glucose concentrations transiently.

Hyperinsulinemia in the neonatal age group may also be seen for transient periods in conditions like acute fetal distress, small weight for gestational age and gestational diabetes. The severity is usually mild in such cases. These neonates respond to diazoxide, and hyperinsulinemia resolves spontaneously within several days or weeks. All neonates with hyperinsulinemia should be screened for hyperammonemia to diagnose hyperinsulinemia hyperammonia (HI/HA) syndrome (GLUD1 gene), urine organic acids to diagnose short chain hydroxyacyl-CoA dehydrogenase (SCHAD) deficiency (HADH gene) and plasma acylcarnitines chromatographies, for CDG syndromes, as these 3 diseases may present in the neonatal period as apparently isolated hyperinsulinism (Arnoux et al., 2010). Other genes which can be suspected are SLC16A1 gene (Otonkoski et al., 2003) and HNF4A gene when the newborn is macrosomic with a family history of maturity onset diabetes of young (Pearson et al., 2007). Finally, familial forms or consanguinity and syndromic forms have to be checked as these are associated with diffuse HI (Arnoux et al., 2010).

The treatment of such a condition should be aggressive as the glucose levels are very low and there is deficiency of alternative brain fuels in hyperinsulinemic neonates. Majority of these neonates are already on intravenous glucose administration when the diagnosis of hyperinsulinemia is established. Medical management consists of drugs such as Diazoxide,

Nifedipine and Octreotide. Diazoxide blocks insulin secretion by activating (opening) the SUR1 receptors. Transient and persistent hyperinsulinemia (involving genes other than those encoding SUR1 and Kir6.2) respond to diazoxide. However, most of neonatal and isolated persistent HI is resistant to diazoxide. Diazoxide is tolerated well by neonates except in premature neonates because of sodium and fluid retention, which may lead to edema, pulmonary hypertension or heart failure. The most frequent adverse effect of prolonged use is hypertrichosis. Hematological side effects are very rare in routine doses. Diazoxide unresponsiveness is defined by the occurrence of 2 episodes of hypoglycemia [<54 mg/dL (<3 mmol/L)] in 24-hour period. In such cases, Octreotide must be tried before considering surgery (Thornton et al., 1993). Doses vary from 10 to 50 µg/kg/day intravenously, administered continuously or subcutaneously every 6 or 8 h. Higher doses may worsen hypoglycemia by suppressing both glucagon and growth hormone. Some patients may have vomiting and/or diarrhea and abdominal distension after starting therapy, which spontaneously resolves within 7–10 days. Gallbladder sludge or stones may appear during therapy. The dose of octreotide should be progressively increased according to the weight gain of the baby, to prevent recurrence of hypoglycemia. Other drugs such as calcium channels blockers (nifedipine, 0.5– 2 mg/kg/day in 2 oral doses) can be tried. Surgery is the other treatment option if medical management fails. Patients requiring surgical treatment must be assessed for histological form of HI (Shilyansky et al., 1997; Rahier et al., 1998). HI has two histological forms (focal form and diffuse form) and the choice of surgery is different for each form. The focal form is defined by focal adenomatous hyperplasia of islets β-cells within the pancreatic tissue and it requires partial and selective pancreatectomy (Goossens et al., 1989; Arnoux et al., 2010). However all the β-cells of the pancreas are abnormal in diffuse form, so that a subtotal pancreatectomy may improve the patient's condition. Positron emission tomography (PET) utilizing 18F-fluoro-L-DOPA isotope localizes the focal lesion (Ribeiro et al., 2007; Barthlen et al., 2008) and differentiates between the two histological forms. Pancreatic catheterization with pancreatic venous sampling was previously used to distinguish the two forms but now it has been replaced by PET scan (Arnoux et al., 2010).

12. Summary

Neonatal hypoglycemia is a common metabolic disorder and the operational threshold values of blood glucose <40 mg/dL (plasma glucose< 45 mg/dL) should be used to guide management. All "at risk" neonates and sick infants should be monitored for blood glucose levels. Term healthy AGA infants without any risk factors need not be monitored routinely. Screening for hypoglycemia can be done by point of care devices but confirmation requires laboratory estimation of blood glucose levels. Treatment however should not be delayed while awaiting laboratory confirmation. Asymptomatic hypoglycemia can be managed with a trial of measured oral feed if blood glucose is >25 mg/dL and there is no contraindication to feeding. Symptomatic hypoglycemia should be treated with a mini-bolus of 2 ml/kg 10% dextrose followed by continuous infusion of 6-8 mg/kg/min of 10%dextrose. Refractory or persistent hypoglycemia should be suspected and investigated if the glucose infusion requirement is consistently more than 12 mg/kg/min or the hypoglycemia persists more than 5-7 days. Babies with hypoglycemia should be followed up for neurodevelopmental sequelae.

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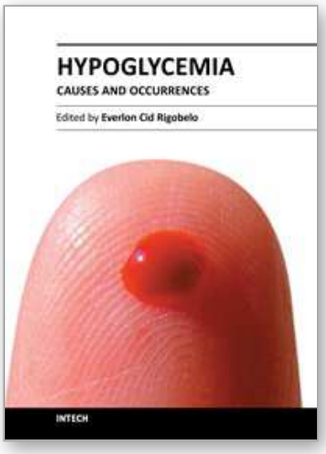

Hypoglycemia - Causes and Occurrences
Edited by Prof. Everlon Rigobelo

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Glucose is an essential metabolic substrate of all mammalian cells being the major carbohydrate presented to the cell for energy production and also many other anabolic requirements. Hypoglycemia is a disorder where the glucose serum concentration is usually low. The organism usually keeps the glucose serum 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. This book provides an abundance of information for all who need them in order to help many people worldwide.

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