A Perspective on Neurological Aspects of Neonatal Hypoglycaemia

Nihan Hilal Hosagasi, Mustafa Aydin

ABSTRACT

Cerebral metabolism is mainly dependent upon glucose utilization. In newborn infants, low blood glucose levels cause to neuronal and glial cell death, and hence associated with long-term neurodevelopmental handicaps. Occipital and parietal lobes are most severely affected regions of the brain on imaging techniques in infants suffered from brain damage as a result of neonatal hypoglycaemia. On neurodevelopment follow up, the mental and psychomotor developmental indexes of the children who suffered from hypoglycaemia during newborn period are significantly low. Hence, early diagnosis and treatment of neonatal hypoglycaemia is mandatory to prevent the long-term neurological sequelae.

Key words: Hypoglycaemia; Diagnosis; Treatment; Neuroimaging; Neurodevelopment; Newborn

THE DEFINITION OF HYPOGLYCAEMIA

Although hypoglycaemia is determined by the low blood glucose level that affects the neurological and developmental prognosis, the numerical definition is extremely complicated and contradictory. Hypoglycaemia in newborns is mostly asymptomatic because the newborns’ brain is not mature enough. Studies which have tried to identify the lowest level of blood glucose in determining asymptomatic hypoglycaemia are not sufficient to form a consensus[7]. The most frequently used limit value of blood glucose < 47 mg/
Hosagasi NH et al. Hypoglycemic Neuronal Injury

L (< 2.6 mmol/L) was generally accepted after a comprehensive study which evaluated the neurodevelopmental results\(^6\)-\(^10\). There is a consensus about the treatment of symptomatic hypoglycaemic infants and especially those with neurological symptoms who should be treated immediately. Whereas the limit value of blood glucose for hypoglycaemia in these infants was 45-47 mg/dL (2.5-2.6 mmol/L) according to most authors, the guidelines of the AAF published in 2011, defined the limit as < 40 mg/dL\(^{[3,5,6,11]}\).

**Clinical approach**

The clinical approach determines the blood glucose levels where clinical symptoms are seen. This approach can be summarized by whipple triad; (1) Characteristic clinical findings; (2) Low blood glucose levels evaluated concurrently in a sensitive and correct manner; (3) Improvement in clinical symptoms after normoglycaemia.

However, this definition is inadequate for asymptomatic hypoglycaemic infants because the symptoms of hypoglycaemia are not seen in certain infants with the low glucose levels. In this way, it is not certain whether confirmed glucose levels can cause neurological damage or not\(^{[7,9]}\).

**Epidemiological approach**

Hypoglycaemia can be defined as those glucose levels not included in the normal glucose levels of the healthy population. Empirically, the values -2 standard deviation (SD) under normal distribution are accepted as hypoglycaemia. Alkatay et al evaluated the plasma glucose threshold of 723 healthy term newborns by metaanalysis. They evaluated the 5. percentile values of plasma glucose concentration (PGC) as 27 mg/dL for 1-2nd hours, 40 mg/dL for 3-23rd hours, 41 mg/dL for 24-47th hours, 48 mg/dL for 48-72nd hours\(^{[12]}\). In fact these values represent only one of the continuous glucose levels of those infants who are at the metabolic adaptation period and are strongly associated with the feeding type, feeding time, gestation age and postnatal age. This approach does not consider the complex metabolic status of the infants or any alternative energy sources. Most importantly, there is no correlation between this approach and clinical result\(^{[10]}\).

**Neurophysiological approach**

According to this approach, the glucose level for hypoglycaemia is the value that hormonal changes and counter regulatory mechanisms, like an increase in blood flow in the brain, are seen or the value at which neurophysiological abnormalities begin. Pryds et al found an increase in the compensatory cerebral blood stream in 10 hypoglycaemic newborns when the glucose level was under 30 mg/dL (1.7 mmol/L); in fact they found that the visual evoked potentials (VEP) and the amplitude-integrated electroencephalography (EEG) were normal\(^{[13]}\). In addition, the effects of these values on neurodevelopment as well as the importance of these values to determine hypoglycaemia are not known.

**The approach according to long term neurological results**

This approach is more readily accepted because it is supported by clinical research. In fact the results of the studies about the effect of hypoglycaemia on neurodevelopment conflict with each other. After an empirical study which found that average level hypoglycaemia in asymptomatic preterm infants caused developmental disorders; a cohort study was conducted with 566 preterm infants and no neurodevelopmental disorders were found in 47 hypoglycaemic cases between the ages of 2 and 15\(^{[14,15]}\). Cornblath et al improved a new definition called ‘operational threshold’, based on the assumption that a single hypoglycaemic value for all patients can be never defined. Operation threshold is defined as the blood or plasma glucose concentration when clinicians have to intervene. Although it is a pragmatic approach, it creates a safe area for patients. Operation threshold and target glucose levels are completely different. According to Cornblath et al, the operational threshold of term infants with impaired metabolic adaptation is 36 mg/dL, whereas the target glucose level should be 45 mg/dL\(^{[14,15]}\).

**GLUCOSE METABOLISM IN THE BRAIN**

Neurons and erythrocytes do not oxidise fatty acids and they are glucose dependent. Therefore glucose is essential for brain metabolism as is oxygen. Glucose is not only used to energize, it also plays a role in their biosynthetic process. The major part of glucose utilization occurs in the brain during the early newborn period. The newborn’s brain mass is relatively bigger. This is explained by their having 2-3 times more hepatic glucose reproduction than adults\(^{[15]}\).

The glucose transportation of the brain is dependent on the blood glucose concentration as well as glucose transporter proteins which transport the glucose with facilitated diffusion from the blood-brain barrier\(^{[15,17]}\). Glucose transporter-1 (GLUT-1) which is located in the blood-brain barrier and glia are also commonly located in the fetal brain from an early time. GLUT-3 is the second most common glucose transporter, located in neuron membranes, and has a similar localization with glucose utilization distribution. These transporter proteins are commonly located infratentorially in the early infant period. In fact these proteins are located supratentorially in mature brains\(^{[18]}\). The energy generation of the brain is shown in Figure 1\(^{[15]}\).

Ketone bodies (β-hydroxybutyrate, acetocacetate) and lactate which are alternative energy sources, are used instead of glucose in hypoglycaemic status to prevent the immature brain from negative effects\(^{[15,17]}\). *In vitro* studies about alternative substrats in rats, shown that the lactate and β-hydroxybutyrate concentrations of newborn rat brains was two times higher than in adult rats and in fetal rats it is six and two times higher than in adult rats respectively\(^{[18]}\). A study of newborn dogs showed that 95% of energy sources in normoglycaemia status were made up of glucose, 4% lactate, 0.5% ketone. In hypoglycaemia induced with insulin, 48% glucose and 52% lactate were used. In this study there was no significant difference concerning the use of ketone\(^{[19]}\).

One of the end products of lipolysis are keton bodies which are important, because the brain can not use free fatty acids to energize in hypoglycaemia. Consequently keton bodies are used to energize the brain\(^{[19]}\). An increase in ketone bodies was shown in the early neonatal period in Howdon’s study. In fact this increase was inadequate in preterm infants even with low glucose concentrations. The same study showed that term infants who were given breast feeding had higher ketone levels\(^{[20]}\). The use of ketone bodies in the brain is shown in Figure 2\(^{[19]}\). There is no problem as regards the metabolic adaptation of normal birth weight term infants, if there is no problem with hormonal regulation. Nevertheless the risk of hypoglycaemia is higher in low birth weight preterm infants who have a lack of glucogen and fat storage, immature enzymes and are inadequate in reproducing alternative energy.

**IMPAIRED METABOLIC ADAPTATION**

Hypoglycaemia is seen when the consumption of glucose is higher
than glucose production. That occurs with two mechanisms; (1) Ensuring inadequate glucose: inadequate glucogen storage; impaired glucose production; (2) An increase in glucose consumption.

The reasons for impaired metabolic adaptation are shown in Table 1[21].

Those newborns who have potential deficiency in the basic mechanism of metabolic adaptation are determined as being at risk. The groups that were at risk in the guidelines published in 2011 by the American Academy of Pediatrics Fetus and Newborn Committee were as follows[5]; (1) Late preterm; (2) Small for gestational age; (3) Infants of diabetic mothers; (4) Large for gestational age.

ETIOLOGY OF HYPOGLYCAEMIA AND RISK FACTORS

The most important typical feature in determining the etiology and risk factors is to decide whether hypoglycaemia is transient or persistent. Transient hypoglycaemia is seen in less than 3-5 days; persistent hypoglycaemia is seen in more than 5-7 days[23]. The reasons for persistent hypoglycaemia are shown in Table 2[23].

The reasons for transient neonatal hypoglycaemia are[22,24,25]; (1) Inadequate glucose production: Prematurity; Intrauterine growth restriction; Postmaturity; Sepsis; Perinatal asphyxia. (2) Excessive glucose use: Infants of diabetic mothers; Intrauterine growth restriction; Perinatal asphyxia; Sepsis; Cyanotic heart disease or congestive heart disease; Erythroblastosis fetalis; High umbilical artery catheter; Polycythemia; Drugs used by the mother (beta-sympathomimetics, oral antidiabetics); Large for gestational age; Infant of toxemic or preeclamptic mothers; Hypothermia; Interruption of intravenous fluid fast.

THE SYMPTOMS OF HYPOGLYCAEMIA IN THE NEWBORN PERIOD

Hypoglycaemia in the newborn period is commonly seen to be asymptomatic. The findings of symptomatic hypoglycaemia are often faint and nonspecific; and so a suspect is needed to identify these signs. The symptoms are caused by the activation of the adrenergic system in the neurological system or decreased glucose and oxygen (Table 3)[25,26]. The most common symptoms are light-to-moderate impaired consciousness such as irritability and lethargy; these symptoms recover when blood glucose is regulated. Respiratory depression, hypotony, coma may be seen in severe and elongated hypoglycaemia and these symptoms may not recover immediately with glucose supplementation[25-28]. Convulsion is commonly seen after elongated or recurrent hypoglycaemia and rarely seen in the early periods; it is correlated with the severity of the hypoglycaemia. Jitteriness is one of the most common symptoms of hypoglycaemia, it is not suitable to determine hypoglycaemia because it may be seen in healthy term infants[22,24].

THE EFFECTS OF HYPOGLYCAEMIA IN THE BRAIN

The brain of a newborn is more resistant to hypoglycaemia than the brain of an adult.
the brain of an adult. Firstly, the newborn’s brain is immature so that energy utilization rate is 30% lower. Secondly blood flow in the brain increases even in intermediate hypoglycaemia. Glucose metabolism rate decreases and alternative glucose substrates are used to control brain energy levels in severe and prolonged hypoglycaemia.

The early effects of hypoglycaemia in brain metabolism

Glucose needed for brain metabolism depends on the plasma glucose concentration and the brain blood stream in order to transport it to the brain. When blood glucose concentrations decrease, the brain blood flow increases as a first compensation mechanism. It has been shown that when the plasma glucose concentration of preterm infants is < 30 mg/dL, the brain blood stream increases; when hypoglycaemia is regulated the blood flow returns to its normal rate. In a study into newborn dogs, a significant brain blood stream increase was found when insulin induced hypoglycaemia occurred. This increase was locally differentiated as being 172-250% higher than in the control group. On the other hand the glucose consumption rate did not vary[15,24,29,30].

The glucose metabolism rate decreases and alternative glucose substrates are used to control brain energy levels in severe and elongated hypoglycaemia. The metabolism rate of notably lactate, ketone bodies and aminoacids increases. The levels of excitator and inhibitor aminoacids change and brain ammonia levels increase. Acetyl-Coa syntheses and acethylcoline levels decrease because of the lack of glucose[15].

The late term effects of hypoglycaemia in brain metabolism

The effects of hypoglycaemia in immature brains in relation to the damage in gray and white matter have not been defined clearly. Studies into this subject are mostly conducted as animal experiments and cell culture tests.

Biochemical effects start to be observed in brain metabolism when alternative energy substrates are finished in hypoglycaemia. It is accepted that toxic excitator aminoacids cause necrosis in hypoglycaemia. It was found that extracellular concentration of excitator aminoacids (aspartate, glutamate) increased and the activation of N-metil-D-aspartate (NMDA) type glutamate receptor antagonists fixed neuronal damage. NMDA type glutamate receptors are seen commonly in immature brains as are other ionotrophic receptors. Their numbers decrease in inverse proportion...
to brain maturity. Synaptic functions degenerate and excitator aminoacids are excreted massively based on a lack of energy. ATP-dependent glutamate uptake in glial cells also decreases and glutamate increases in the presynaptic gap stimulating NMDA associated ion channels. Ca and Na are ingested to cells, then a cascade of intracellular activities which cause neuronal necrosis and apoptosis are triggered. The energy dependent transmembrane gradient of Na and Ca is not provided because of the low ATP levels caused by hypoglycaemia; then Ca and Na accumulate in the cells. Calcium activates cellular phospholipase and protease and changes the mitochondrial metabolism, causing free radical formation and even selective neuron necrosis. Na increases in cells cause edema with varying transmembrane potential.

Reduced substrates are not sufficiently ensured for mitochondria in hypoglycaemia and so free oxygen radicals occur because molecular oxygen in mitochondria can not be reduced. This is another mechanism which causes hypoglycaemic encephalopathy. Increased free oxygen radicals cause oxdant damage in the mitochondrial proteins and DNA. Damage to the mitochondrial DNA blocks the enzyme transcription of the electron transport chain and ATP reproduction of the cell is interrupted. The brain effects of hypoglycaemia are shown in Figure 3. McGoven et al found that superoxide and hydrogen peroxide levels in the brain increased when insulin induced hypoglycaemia was performed on newborn pigs. In another study intermediate and severe glucose inhibition occurred in the hippocampus cells and it was concluded that free oxygen radical formation in intracellular Ca accumulation could or could not be avoided with NMDA receptor antagonists. Ca accumulation and free oxygen radical formation could be avoided in intermediate glucose inhibition whereas they could not be avoided in severe glucose inhibition. This result was observed to be a free radical formation which causes neuron damage associated with excitotoxins and intracellular Ca accumulation in intermediate hypoglycaemia. In severe hypoglycaemia it is associated with a lack of energy, not excitotoxins.

Brain damage is increased because of the synergic effect of a combination of hypoglycaemia and hypoxia. Anaerobic glycolyses during hypoxia cause glucose to be used rapidly. Although the biochemical damage caused by hypoxia or hypoglycaemia has similar characteristics, there are some differences in the affected localizations. Hypoxic-ischemic encephalopathy (HIE) is commonly seen with cerebral infarctus, in fact selective neuronal necrosis is seen in hypoglycaemic brain damage. It was found with screening methods and postmortem studies that some of the significant brain areas are more sensitive to hypoglycaemia. The occipital lobe, dentate gyrus of the hippocampus and basal ganglions are sensitive to hypoglycaemia, whereas the cerebral trunk and cerebellum affected in HIE are resistant to hypoglycaemia.

**THE NEUROLOGICAL EFFECTS OF HYPOGLYCAEMIA**

Although there are many studies into the neurological effects of newborn hypoglycaemia there is no common concensus about the neurodevelopmental effects of hypoglycaemia. Hypoglycaemia and other brain damage factors such as hypoxia are commonly seen together so that explaining the effects of hypoglycaemia in neurodevelopmental prognosis is more complicated. There is insufficient information about below which level of glucose concentration, in which infant and in what time period central nervous system damage occurs. Despite the conflicting available clinical data certain generalizations about hypoglycaemia can be made. When excessive and persistent low glucose concentration (0-18 mg/dL) is continuous for 1-2 hours and severe neurological symptoms (coma and convulsion) are observed, without accompanying central nervous system pathology (HIE, intracranial bleeding, infection, etc.) neurologic damage due to hypoglycaemia may be diagnosed.

Williams summarized the minimum requirements in order to attribute neurological sequel to hypoglycaemia in his article about the legal dimensions of hypoglycaemia: brain damage pattern defined by neuropathological literature has to be observed along with diagnostic screening methods and Whipple triad must be satisfied.

A retrospective multicenter study into glucose concentrations, hypoglycaemia incidence and the effects of hypoglycaemia in Bayley motor and mental scale were researched in 661 preterm infants who were under 1850 g. Intermediate hypoglycaemia (PGC < 2.6 mmol/L or 47 mg/dL) was seen in 433 infants. Many factors affecting neurodevelopment were considered and a strong relationship was found between the number of days that hypoglycaemia had been seen and the Bayley motor and mental scale. Hypoglycaemia above 5 or more days decreased the Bayley motor and mental scales by 13 and 14 points in corrected 18th months, respectively. The incidence of neurological defects such as cerebral palsy and developmental retardation (mental-motor scale ≤ 70 vs) increased 3.5 times. These data were described as prolonged and recurrent hypoglycaemia increases the risk of neurodevelopmental damage. On the other hand, when the patients were examined at the age of 7.5-8, only arithmetic and motor test results were found to be low so it was understood that the abnormalities recorded previously were temporary.

The effects of transient hypoglycaemia were studied (first hour after birth < 2.2 mmol/L, after < 2.5 mmol/L) in large for gestation age infants to their neurodevelopment at the age of 4; the Denver developmental scale results of 60 hypoglycaemic infants and 15 normoglycaemic infants were compared, the negative effects of mild transient hypoglycaemia about psychomotor development were not shown. The study which researched the long term effects of hypoglycaemia in the small for gestation age preterm infants found a strong relationship between recurrent mild hypoglycaemia (< 2.6 mmol/L or 47 mg/dL), low head circumference percentile and low psychomotor scores at the age of 5. Stenning et al compared the eighth year motor and developmental results of 13 infants of diabetic mothers who had PGC < 1.5 mmol/L (27 mg/dL), 15 normoglycaemic infants of diabetic mothers and 28 healthy infants. Children who had neonatal hypoglycaemia, had minimal brain disfunction concerning attention, motor control and perception, when compared with normoglycaemic infants of diabetic mothers and the healthy group. Developmental retardation and neonatal morbidities were studied using a community-onset questionnaire conducted among the parents of gestation age 32-36 week preterm infants. 832 children were evaluated in this study. It was found by multivariate analyses that hypoglycaemia increased developmental retardation at a ratio of 2.1.
Hosagasi NH et al. Hypoglycaemic Neuronal Injury

It was found that hypoglycaemia is associated with increased risk for brain injury and adverse neurodevelopmental outcome in newborn infants whom have risk for encephalopathy. A recent study including 94 HIE cases with hypoglycaemia (blood glucose < 46 mg/dL) in postnatal 24 hours found that concomitant neonatal hypoglycaemia increased corticospinal damage 3.7 times and decreased the motor and mental scores on the Bayley Scales of Infant Development Test[51]. Burns et al reported that brain damage caused by symptomatic hypoglycaemia was more various than known and early MRI was more directive than the hypoglycaemia stage and duration in predicting the neurodevelopmental prognosis. According to this study white matter abnormalities were found at a rate of 94%, posterior lobe was affected predominantly in 29% of cases. Of the cases, 51% had cortical abnormalities, 30% white matter haemorrhage, 40% lesions of the basal ganglion and thalamus and 11% internal capsule abnormalities[49]. Tam et al demonstrated that restricted diffusion in the occipital lobe was present in half of 16 term infants of 25 newborns who were screened by diffusion weighted MRI within 6 days after hypoglycaemia had been determined. This sign was not found in preterm infants. Occipital restricted diffusion was not demonstrated in any MRI taken 6 days after hypoglycaemia. It was found that restricted diffusion was associated with abnormal cortical VEP[50]. It should be particularly noted that these neuroimaging studies included those infants who had severe and prolonged hypoglycaemia and encephalopathy. There is no screening evidence

Figure 3 Effects of hypoglycaemia on brain.
concerning brain damage in short and mild hypoglycaemia or asymptomatic hypoglycaemia at any time[30].

In conclusion, hypoglycaemia is the most common metabolic problem in neonates. It is considered as very harmful to a newborn infant’s developing brain which causing to long-term neurological handicaps. Accordingly, prompt diagnosis and early management is extremely imperative, which could lead to less morbidity and mortality.

CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

REFERENCES

Hosagasi NH et al. Hypoglycaemic Neuronal Injury

86: 1768-1780.

Peer reviewers: Masashi Kameyama, Division of Nuclear Medicine, Department of Radiology, School of Medicine, Keio University, 35 Shinanomachi Shinjuku-ku, Tokyo, 160-8582, Japan; Hui Liu, MD, PhD, Department of Radiological Sciences, Washington University School of Medicine, 4566 Scott Blvd, Room 254, McDonnell Sciences Bldg, St. Louis, MO, USA.