Niger J Paediatr 2016; 43 (2):70 –77

REVIEW

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Hypoglycaemia in children: Review of the literature

DOI:http://dx.doi.org/10.4314/njp.v43i2.2

Accepted: 16th March 2016

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Abstract*:* Hypoglycaemia is a common metabolic condition in children. It often presents urgent and therapeutic challenges and it has been documented to affect many childhood conditions. Its clinical presentation is not classical and requires a high index of suspicion for an early diagnosis and prompt management. Undiagnosed or undertreated hypoglycaemia has been found to increase mortality in children when it is present. This review sought to review the subject of hypoglycaemia in children and calls for testing for it in all sick and admitted children.

Introduction

The term hypoglycaemia refers to blood glucose level below normal. Most of the time low blood glucose concentration is not associated with the development of the classic clinical manifestations of hypoglycaemia. The absence of clinical symptoms does not indicate that glucose concentration is normal or has not fallen below optimal level for maintaining brain metabolism.[1] Hypoglycaemia in the paediatric age group is a common clinical finding and is associated with a wide variety of disorders[2]. Even in the Tropics, there is a growing awareness that hypoglycaemia can complicate many childhood illnesses.[3] This has necessitated several recent work on the problem of Hypoglycaemia among Nigerian children.[4-6] The condition often presents urgent diagnostic and therapeutic challenges.[7]

The major long-term sequelae of severe, prolonged hypoglycaemia are neurologic damage resulting in mental retardation, transient cognitive impairment, neurological deficit and recurrent seizure activity.[8] Subtle effects on personality are also possible but have not been clearly defined.[9,10] Moderate hypoglycaemia has been shown in neonates to be associated with a considerable increase in adverse neurodevelopmental effects.[10]

Definition of hypoglycaemia

Although there is a general agreement on the need to maintain blood glucose concentrations above a 'critical' level in young children and neonates, there is no agreement among practising paediatricians and authors as to the lowest safe concentration of blood glucose.[11] The difficulty with the definition is understandable in view of the lack of reliable clinical signs when the blood glucose concentrations fall in newborn infants and young children and in view of the continuing controversy over whether 'asymptomatic' hypoglycaemia causes neurological dysfunction and damage or not.[10]

The plasma glucose concentration is normally maintained within a relatively normal range of 3.9 to 8.3mmol/L (70 to 150mgdl), despite wide variations in glucose influx and efflux such as those that follow meals and occur during exercise[11]. There is however general agreement that a value of blood glucose that is less than 2.2mmol/L (40mgdl) represents hypoglycaemia and most of the work on hypoglycaemia[3,12-14] in the literature are based on this cut-off value. Two factors which are frequently overlooked when interpreting the glucose concentrations are the analytic method used and whether whole blood or serum (plasma) was examined. When whole blood is used, the value of blood sugar below 2.2mmol/L represents hypoglycaemia as opposed to 2.5mmol/L if plasma (or serum) sample is used. This is because in individuals with a normal haematocrit, fasting whole blood glucose concentration is approximately 8 to 15% less than plasma glucose due to the fact that the water content of plasma (93%) is approximately 12% higher than that of whole blood.[15-17] In most clinical laboratories plasma or serum is used for most glucose determination whereas most bedside methods for self-monitoring of glucose use whole blood.

Epidemiology

Hypoglycaemia is said to occur more commonly in paediatric patients than in adults.[18]There are many studies on neonatal hypoglycaemia probably engendered by the increased vulnerability of the immature neonatal brain to damage by hypoglycaemia.[19,20]

Hypoglycaemia has also been reported in children beyond the neonatal period[3-6,21]. It has been found to also complicate many emergency paediatric admissions.[3-6,21] The prevalence of hypoglycaemia in emergencies varies

from one practice to another.
In Birmingham[21], a rate of 6.54/100,000 visits was found among children seeking care at the emergency department while Solomon et al[3] found a rate of 7.1% in Mozambique. More recent studies done in paediatric emergency admissions of some West African countries equally documented the occurrence of hypoglycaemia.[22-24.] Prevalence rates of 6.4% in Ile-Ife by Elusiyan et al[22] and 5.6% in Lagos by Oyenusi et al[23]both in Nigeria and a rate of 13% by Ameyaw et al[24] in Kumasi, Ghana respectively were reported. Other studies such as that done by Osier et al[25] reported a prevalence of 7.3% among paediatric admissions in Kenya while a prevalence rate of 18.6% was documented by Wintergerst et al[26] among patients admitted to a paediatric intensive care unit of a tertiary hospital in California, United States.

Some authors reported the prevalence of hypoglycaemia in studies designed to investigate specific disease entities rather than cohorts ofchildren presenting to the emergency room or admitted into the wards with diverse problems. For instance, Familusi and Sinnette[27] documented aprevalence rate of 13% in children presenting with febrile convulsions at the emergency ward in Ibadan, Nigeria. Among children with diarrhoea, the prevalent rates of hypoglycaemia reported were 4.5% by Bennish et al[13] and Bhattacharya et al[28]40%, respectively in Asia while in Nigeria, Ntia et al[29] and Onyiriuka et al[30] reported prevalence rates of 4% and 4.9% respectively.

Another clinical condition in which the prevalence of hypoglycaemia has been widely investigated ismalaria. Comparable prevalence rates of hypoglycaemia between 16-17% were documented by English et al[12] in Kenya, Genton et al[31] in New Guinea and Nwosu et al[32] in Lagos, Nigeria among children with severe malaria. However, Onyiriuka et al[33] in Benin, Nigeria and White et al in Gambia[14] reported higher prevalence rates of 18.3% and 32% respectively in children with severe malaria.

Pathophysiology

Glucose plays a central role in mammalian fuel economy and is a source of energy derivable from glycogen, fats and protein.[34]Glucose is an immediate source of energy providing 38 moles of ATP/mole of glucose oxidized.[34] Blood glucose level reflects a dynamic equilibrium between the glucose input from dietary sources plus that released from the liver and kidney and the glucose uptake that occurs primarily in the brain, muscle, adipose tissue and blood elements.[11,34] Hypoglycaemia thus represents a defect in one or several of the complex interactions that normally integrate glucose homeostasis during feeding and fasting.

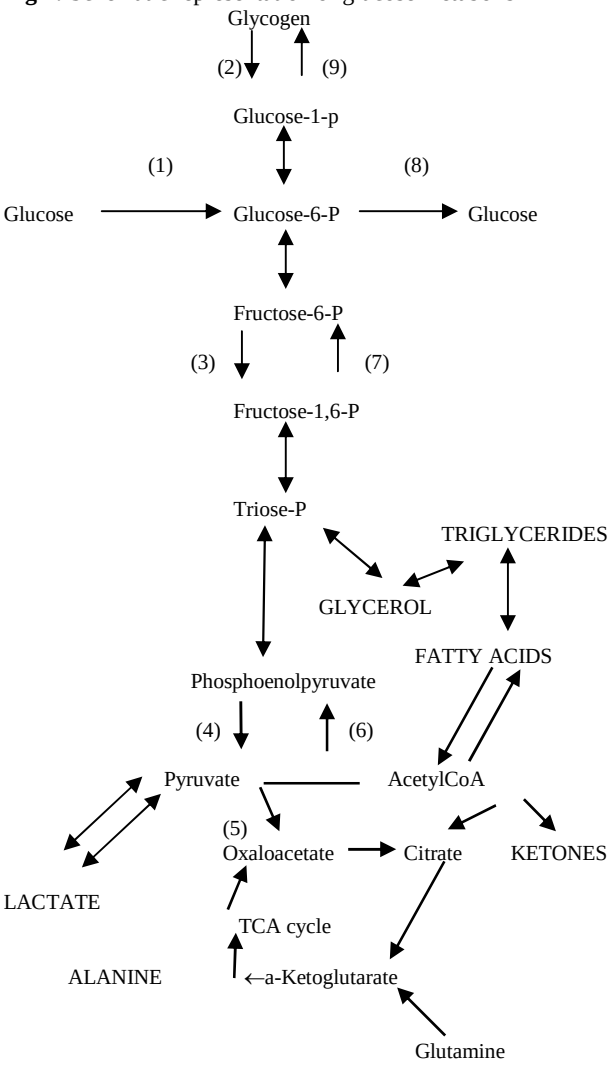
The maintenance of the plasma glucose concentration is critical to survival because plasma glucose is the predominant metabolic fuel utilized by the central nervous system (CNS) under most conditions. The CNS can neither synthesize glucose nor store more than a few minutes' supply of glucose.[11] Glucose metabolism by the brain accounts for almost 100% of total basal glucose turnover making most of the endogenous glucose production (EGP) in infants and young children accounted for by brain metabolism[1], unlike in neonates where EGP provides approximately one third of glucose needs.[35] Thus brief hypoglycaemia may cause profound brain dysfunction, while prolonged severe hypoglycaemia may eventuate in brain death.[11] Therefore, to maintain normal blood glucose concentration and prevent precipitous falls to levels that impair brain function, humans have evolved an elaborate gluco-regulatory system.[11] The prolonged interval between onset of symptoms and correct diagnosis reported in most studies indicates that the possibility of symptomatic spontaneous hypoglycaemia has not received proper consideration early in the course of many clinical situations. Therefore, whenever repetitive, episodic, bizarre manifestations occur at any time, whether after a fast, after an acute illness or shortly after meals, a blood glucose level should be obtained at the time of the symptoms. Only in this way can the diagnosis be established and therapy instituted early, thus avoiding the sequelae of prolonged hypoglycaemia.[36]

Elucidation of the physiology of glucoregulation in general and of glucose counter regulation in particular has provided major insights into the pathophysiology of hypoglycaemia in humans. Nevertheless, there are major gaps in our understanding of the causes, mechanisms and management of many hypoglycaemic states.[11] In the fasted individual, the maintenance of a normal blood glucose level is dependent upon (1) adequate supply of endogenous gluconeogenic substrates like amino acids, glycerol, and lactate (2) functionally intact hepatic glycogenolytic and gluconeogenic enzyme systems, and (3) a normal endocrine system for integrating and modulating these two processes. The adult human being is quite capable of maintaining a normal blood glucose level even when totally deprived of calories for weeks or, in the case of obese subjects, for months. In contrast, the normal child exhibits a progressive fall in blood glucose to hypoglycaemic levels when fasted for even short periods (e.g. 24 to 48 hours).[2,37] The reasons for the difference are not clear, but it may be that the young individual, when fasting, is unable to supply sufficient glucose to meet the obligatory demands of the body for glucose.
Although most tissues have the enzyme systems required to synthesize glycogen (glycogen synthase) and to hydrolyse glycogen (phosphorylase), only the liver and kidneys contain glucose-6-phosphatase, the enzyme necessary for the release of glucose into the circulation[11]. The liver and kidneys also contain the enzymes necessary for gluconeogenesis (including the critical enzymes pyruvate carboxylase, phosphenol pyruvate carboxykinase, and fructose-1,6- bisphophatase).[11] This shows the importance of these organs in glucose homeostasis, particularly with gluconeogenesis. In diseased states affecting these organs, hypoglycaemia will be a major problem unless adequate intake of glucose is maintained.

There are multiple potential metabolic fates of glucose

transported into cells[11] It may be stored as glycogen majorly. It may undergo glycolysis to pyruvate, which in turn can be oxidized to carbon-dioxide and water via the tricarboxylic acid cycle, converted to fatty acids (and stored as triglycerides), or utilized for ketone bodies (acetoacetate, B-hydroxylbutyrrate), or cholesterol synthesis (Fig.1).[11] Finally, glucose may be released into the circulation for the immediate metabolic need of the body.[11] External losses are normally negligible.

Fig 1: Schematic representation of glucose metabolism[11]



1. Hexokinase/Glucokinase
2. Glycogen synthase
3. Phosphofructokinase
4. Pyruvate kinase
5. Pyruvate carboxylase
6. Phosphoenol pyruvate carboxylkinase
7. Fructose-1,6-Bisphosphatase
8. Glucose-6-phosphatase
9. Phosphorylase

Mechanisms of hypogyclaemia

Several mechanisms are known to cause hypoglycaemia in children. Theoretically hypoglycaemia could result from excessive glucose efflux (excessive glucose utilization or external losses), deficient glucose influx (deficient endogenus production), or both.[11,38] There are conditions in which glucose utilization is increased markedly (e.g. exercise, large tumours, infections) and in which renal losses occur at physiological plasma glucose concentration (i.e. renal glycosuria)[11]. However, because of the normal capacity of the liver to increase glucose production several fold, clinical hypoglycaemia is rarely the result of excessive glucose efflux alone.[11] Rather, it is commonly the result of hepatic glucose production that is either decreased absolutely or inappropriately low relative to the rate of glucose utilization[11].
In African children with malaria and other infections, an impairment in hepatic gluconeogenesis in the presence of adequate levels of precursors has been considered the most likely mechanism[12,14,39].

Other suggested possible mechanisms of hypoglycaemia in malaria include accelerated tissue metabolism;[40] the metabolic requirements of the parasites and malabsorption of glucose probably secondary to changes in splanchnic blood flow owing to a heavy parasite load in vessels[41,42]. Sequestration of parasitized red cells in the venules and capillaries of deep tissues may impair local circulation[43,44]. This may necessitate a transition to anaerobic glycolysis releasing lactate and increasing glucose consumption[45]. High serum lactate levels in patients with malaria is thought to indicate lactate production by the malaria parasites and anaerobic glycolysis in tissues where the blood vessels have a heavy parasite infestation[39,43,46]. Impaired hepatic gluconeogenesis could also lead to high lactate levels from the Cori cycle[45]. Furthermore, the reduced dietary intake and the associated vomiting as well as the increased metabolic requirement caused by fever in malaria are other suggested mechanisms of hypoglycaemia[14].

Mechanisms of hypoglycaemia in infections

Hypoglycaemia in other infective process like pneumonia and septicaemia has been attributed to the increased metabolic requirement caused by fever as stated earlier resulting in increased peripheral glucose utilization.[47] Studies have also shown that increased peripheral utilization of glucose appears to be the primary mechanism for hypoglycaemia in neonates with bacteraemia[48,49]. Inhibition of gluconeogenesis is considered to be primarily responsible for the hypoglycaemia in septicaemia in a report by Filkins and Cornell.[50] Endotoxins produced by organisms in infectious processes have also been known to stimulate increased insulin secretion causing hypoglycaemia[47,50,51]. These toxins can also cause hypoglycaemia by contributing directly to depletion of hepatic glycogen stores[47]. Hypotension and decreased tissue perfusion in septic shock increase peripheral utilization of glucose because the shift to anaerobic from aerobic metabolism requires 18 times more glucose to produce the same amount of energy (ATP)[52].

Mechanisms of hypoglycaemia in diarrhoeal disease

Various factors ranging from hyperinsulinaemia, hypoxia, fasting, malnutrition, ketosis and impairment

of gluconeogenesis have been suggested as the mechanisms of hypoglycaemia in diarrhoeal diseases[13,50,53]. Bennish et al[13]noted that plasma levels of counter-regulatory hormones (glucagon, epinephrine and norepinephrine) were appropriately elevated while gluconeogenic substrates were inappropriately low in the children with diarrhoea and hypoglycaemia suggesting that the hypoglycaemia observed in such patients is often due to the failure of gluconeogenesis.[13]

Mechanisms of hypoglycaemia in malnutrition

During severe malnutrition, gluconeogenic substrates such as alanine and lactate are significantly reduced[2,54]. The capacity to generate glucose by gluconeogenesis is markedly diminished and alternate fuels such as ketones or lactate are also reduced[2,54]. The resultant fatty infiltration of the liver causes glycogen and gluconeogenic substrate depletion. There is also defect in glycogenolytic pathways and limited lipolysis[55].

Mechanisms of drug-induced hypoglycaemia

Hypoglycaemia can also be caused by medications administered to patients in the course of an illness. Drug therapy for malaria particularly quinine, may cause hypoglycaemia by stimulating insulin release[57-59]. The use of other cinchona alkaloids like quinidine has also been associated with hypoglycaemia[60]. Drug intoxications in children can also cause hypoglycaemia. Excessive doses of salicylates (4 to 6g/day) can distort multiple biochemical reactions to produce metabolic acidosis, hypoglycaemia or hyperglycaemia[61,62]. Accelerated utilization of glucose due to augmentation of insulin secretion by salicylates and possible interference with gluconeogenesis may both contribute to hypoglycaemia[62].
Accidental ingestion of ethanol is a common cause of poisoning in children in our environment.[63] In ethanol intoxication, the liver metabolizes ethanol as a preferred fuel, and generation of reducing equivalents during the oxidation of ethanol alters the NADH/NAD ratio that is essential for certain gluconeogenic steps[15]. As a result, gluconeogenesis is impaired and hypoglycaemia may ensue if glycogen stores are depleted[15]. Three to five percentage of children with alcohol intoxication will have hypoglycaemia[64]. Overdosage of other drugs such as insulin and oral hypoglycaemic agents can also cause hypoglycaemia[65,66].

Cow's urine concoction (CUC) is a mixture consisting of cow's urine, tobacco leaves, garlic leaves, basil leaves, lemon juice, rock salt and bulbs of onion[67]. It is commonly used in Western Nigeria in the belief that it controls convulsions or prevents febrile convulsions in children but it is known to cause severe hypoglycaemia[27,63,67]. This could be due to the hypoglycaemic activity of onions[68,69] and garlic[70] contained in the mixture.

Common aetiology of hypoglycaemia in Neonates[1]

A) Transient 0-7 days

1. Hyperinsulinism – Infant of Diabetic mothers, erythroblastosis, discontinuation of intravemous glucose.
2. Exact cause unknown – Small for gestational age, fetal distress, any sick newborn Neonatal sepsis, Neonatal tetanus etc.

B) Persistent (Neonatal, Infancy and early child hood 0 -2yrs)

1. Hyperinsulinism – Islet cell hyperplasia, Nesidioblastosis, Islet cell adenoma, leucine sensitivity, Beckwith – Wieldeman syndrome
2. Glycogen Storage disease
3. Defect in gluconeogenesis
4. Hormone deficiency – Congenital Adrenal Hyperplasia, hypothyroidism etc.
5. Miscellaneous – Galactosaemia, Fructose – intolerance, salycylate intoxication, Reye syndrome, hepatitis

Older Children 1-18 years: The predominant conditions complicated by hypoglycaemia as seen in the tropics include severe malaria, septicaemia, pneumonia and protein-energy malnutrition.[22-25] Other cause include side effects of drugs or drug overdosages, use of traditional concoctions as mentioned earlier amongst others. Hyperinsulinism, secondary to therapy of diabetes or islet cell adenoma is also an important cause of hypoglycaemia.

Persistent hypoglycaemia

There are few examples of persistent hypoglycaemia in children. These include persistent hyperinsulinaemic hypoglycaemia and ketotic hypoglycaemia. It must be pointed out that these classes of hypoglycaemia are rarely reported in the tropics probably due to problems with diagnosis.

Hyperinsulinaemic hypoglycaemia is a heterozygous condition in which insulin secretion becomes unregulated and its production persists despite low blood glucose levels[15]. It is the most common cause of severe and persistent hypoglycaemia in neonates and children[1,15]. This could be monogenic or syndromic.Congenital hyperinsulinism (HI) has been described under various terms in the past including "idiopathic hypoglycaemia of infancy," "leucine-sensitive hypoglycemia," or "nesidioblastosis."[71] It has now become apparentt that HI is caused by genetic defects in the pathways that regulate pancreatic β-cell insulin secretion[71]. Several candidate genes mutations have been identified as responsible for CHI including ABCC8, KCNJ11, GLUD1, GCK, HADH1[71]. In a cohort from Turkey,mutations in the ABCC8 gene were found to be the most common cause of CHI[72]. Management of HI is very difficult as current facilities for genetic diagnosis and appropriate imaging are limited only to very few centres in the world and frequently requires difficult choices, such as near-total pancreatectomy and/or highly intensive care with continuous tube feedings[71,73] Some patients may respond to treatment with diazoxide, a KATP channel agonist while others may also develop diabetes in later life following the surgery.
Ketotic hypoglycaemia is said to be the most common

form of childhood hypoglycaemia[74]. It is also referred to as ketotic hypoglycaemia of infancy and classically manifest between the ages of 18 months and 5 years and may remit spontaneously before the age of 10 years.[74] Typical history is of a child who may miss a meal due to an infection usually an upper respiratory tract infection and then develops hypoglycaemia[74] form of childhood hypoglycaemia[74]. It is also referred to as ketotic hypoglycaemia of infancy and classically manifest between the ages of 18 months and 5 years and may remit spontaneously before the age of 10 years.[74] Typical history is of a child who may miss a meal due to Convulsion may occur at the time of hypoglycaemia and a presumptive diagnosis is made by documenting a low blood sugar in association with ketonuria, ketonaemia and typical symptoms of hypoglycaemia. Ketotic hypoglycaemia is prevented by limiting the duration of fasting and maintaining a high glucose intake during illnesses.[74]

Clinical features of hypoglycaemia

The clinical manifestations of hypoglycaemia are non-specific[11]. In addition, they vary among individuals and may vary from time to time in the same individuals[11] form of childhood hypoglycaemia[74]. It is also referred to as ketotic hypoglycaemia of infancy and classically manifest between the ages of 18 months and 5 years and may remit spontaneously before the age of 10 years.[74] Typical history is of a child who may miss a meal due to Clinical manifestations of hypoglycaemia fall into two categories.[1] The first category includes features associated with the activation of the autonomic system and epinephrine release usually seen with a rapid decline in blood glucose.[1,15], These features are sweating, trembling, anxiety, nervousness, weakness, hunger, nausea and vomiting.[1,15] The second category includes features due to decreased cerebral glucose utilization usually associated with slow decline in blood glucose level or prolonged hypoglycaemia.[15,16] These features are headaches, visual disturbances, lethargy, lassitude, restlessness, irritability, difficulty in thinking, inability to concentrate and mental confusion. Others include somnolence, stupor, prolonged sleep, loss of consciousness, coma, hypothermia, twitching, convulsion and bizarre neurological signs (motor and sensory), loss of intellectual ability, personality changes and outbursts of temper. There could also be psychological disintegration with manic behaviour, depression, psychosis, permanent mental or neurological damage[1,15].
Therefore it is important to consider the possibility of hypoglycaemia in any situation in which the signs or symptoms are compatible with an inadequate supply of glucose to the brain[75].

Diagnostic work up

Any child that is sick enough to be admitted to the hospital should be screened for presence of hypoglycaemia. This is very important because most times, hypoglycaemia is asymptomatic and when symptoms are present, they are non-specific. Bedside meters have been validated and found to be highly sensitive and specific for diagnosing hypoglycaemia in studies by the authors[76,77]. A brand of glucometer was found to have a sensitivity of 96.00% (95% CI =81.81%-99.80%) and a specificity of 96.46% (95% CI=94.17%-98.02%).[76] The predictive index of a positive test of 64.9% and the predictive index for a negative test of a 97.72%.[76] An equally high specificity (99.8%) and moderate sensitivity (75%) of another brand of glucometer were observed with high positive predictive and negative predictive values of 94.7% and 98.7% respectively[77]. However it remains imperative that at least, a sample should be sent to the laboratory for confirmation. Furthermore, in newborns, hypoglycaemia should be tested for in all infant of diabetic mothers irrespective of weight at birth and gestational age and in all babies born with a birth weight of 4kg and above[78]. Children on *nil per oris* too should also have regular blood glucose monitoring. Once hypoglycaemia is diagnosed, blood glucose should be determined frequently 30 minutes after initial correction and then hourly, 2 hourly and 4 hourly after obtaining two normal readings[78] form of childhood hypoglycaemia[74]. It is also referred to as ketotic hypoglycaemia of infancy and classically manifest between the ages of 18 months and 5 years and may remit spontaneously before the age of 10 years[74]. Typical history is of a child who may miss a meal due to
Another benefit of bedside determination of blood glucose is to prevent hyperglycaemia which may be caused by unnecessary glucose administration to children that are normoglycaemic or may even be hyperglycaemic[24,25,79,80].

Treatment of hypoglycaemia

The primary objective of treatment is to restore the blood glucose concentration to the normal range.[75] The hypoglycaemic child should receive an immediate bolus of 0.25g/kg of dextrose as a concentrated solution (10-25%) over a minute[1,15,22,23,75,81]. This should be followed by a continuous dextrose infusion at 8-10mg/kg/min in order to avoid rebound hypoglycaemia which may occur within 30 minutes of the bolus injection[1,15,22,75]. Glucose level should be determined at 15 minutes after the bolus has been given and while the maintenance glucose infusion is running. If hypoglycaemia recurs at this time, a bolus of 0.5g/kg of glucose may be given and the
glucose infusion increased by 25-50% until normoglycaemia is achieved[15,75]. High volume rates carry the risk of fluid overload manifest in pulmonary oedema and/or heart failure. This can be minimized by the use of a central venous catheter and concentrated solutions[75]. Enteric feeding is encouraged if there are no contraindications. The glucose infusion and blood glucose determination are discontinued after two consecutive normal blood glucose levels measured 30 minutes apart and patient is eating well[22,23]. Infant of diabetes mothers should be fed within 30 minutes of birth by the most possible route[78].

Complications of hypoglycaemia

A strong association between hypoglycaemia and increased mortality and morbidity has been documented

by several authors[3,22-26,82]. Hypoglycaemia appears to be a function of the severity of illness in childhood and more severely ill children will be more likely to die than less severely ill ones.[22,23] Hypoglycaemia is also a major indicator of a poor prognosis in different disease entities like cerebral malaria and gastrointestinal infections[13,29-33,39,83,84]. Hypoglycaemia has been shown to be independently associated with speech and language impairments and impairment of non-verbal functioning.[83] Nwosu et al[32] reported that neurological sequelae were about twice as common in children with cerebral malaria and concomitant hypoglycaemia. The most frequently occurring sequelae were cortical blindness, monoparesis, aphasia, hemiparesis, generalized hypotonia, decerebrate syndrome and cerebellar ataxia[33,39].

In a retrospective multicentre study, Lucas et al[10] found that moderate hypoglycaemia (<2.6mmol/L) may have serious developmental consequences if present for five or more days during the first two months of life. This provides compelling evidence that even asymptomatic hypoglycaemia could be harmful[85]. Menniet al[86] reported that hyperinsulinaemic hypoglycaemia was associated with psychomotor retardation, learning disability, seizures and diverse neurological sequelae. The authors[86] further noted that the hypoglycaemia of hyperinsulinism is particularly dangerous because it is associated with total absence of all brain fuels (low plasma lactate, ketones and glucose) and thus more easily predisposes the individual to brain damage[86]. The risk of brain damage from hypoglycaemia is highest when the hypoglycaemia is prolonged or recurrent and the effects have been shown to be more in the younger child[75].

Conclusion

Hypoglycaemia is a common complication of many childhood diseases with varied pathophysiological mechanisms. It is amenable to treatment but can cause permanent neurological sequelae if prolonged or not treated promptly. Children who present in emergency are at special risk of hypoglycaemia. A high index of suspicion should be maintained when evaluating very sick children for early detection and subsequent prompt and aggressive management.

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