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Neonatal Hypoglycemia - Current Concepts

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1. Introduction

Hypoglycaemia is a common problem in the neonatal period, and it frequently reflects difficulties in adapting to extra uterine life. Strategies to facilitate this physiological adaptation should be enhanced. (Sem fetal neo del 2005)

Incidence is variable depending on the definition criteria used in different studies, but according to Cornblath (Cornblath et al 1993, 2000 as cited by Fernández Loranzo et al 2011) it varies from 5-7% in term newborns and from 3.2 to 14.7% in preterm infants. Respective to weight, it occurs in 8% of Large for Gestational Age (LGA) and up to 15% of Small for Gestational Age (SGA) infants.

There is still no universal consensus on how to define hypoglycaemia. Establishing a universal cut-off glucose value is difficult and considerations must be made regarding the measuring device used, type of sample (blood, serum or plasma), moment of measurement after birth, duration and degree of hypoglycaemia and characteristics of the newborn. Based on the World Health Organization (WHO) recommendations (WHO 1997 as cited by Fernández Lorenzo et al 2011) thresholds would be:

Sick newborn, (signs of illness): <2.5mmol/L or 45 mg/dL

Healthy term / preterm (feeding well): < 1.1 mmol/L or < 19.8 mg/dL

Most expert authors support the cut-off value of 36mg/dL for asymptomatic healthy newborns, rather than the WHO suggested threshold, and some authors even suggest that values down to 1.7mmol/L should be accepted in an otherwise healthy term infant (Fugelseth 2001). In a recent review on neonatal hypoglycaemia, operational thresholds of less than 40mg/dL (2.2mmol/L) during the first 24 hours and less than 50mg/dL (2.8mmol/L) thereafter are suggested (Chan 2011). Other definitions have been suggested such as using an epidemiological concept: considering hypoglycaemia when glucose levels are 2 standard deviations below the mean value for infants of the same age (which would be around 20-30mg/dL). However, this value does not seem like the optimal threshold, so this definition is rarely used in clinical practice or for study purposes.

Experts agree that the neurological disabilities associated to neonatal hypoglycaemia depend on gestational and chronological age and associated risk factors such as Hypoxic-Ischemic Encephalopathy (HIE) and that they frequently result after situations of persistent and severe hypoglycaemia (Fernández Lorenzo et al 2011). What is more, the vast majority of healthy term newborns with isolated glucose levels under the target of 45 mg/dL will have a normal neurological prognosis. (Hay et al 2009)

Recent consensus workshop (Straussman & Levitsky 2010) results reveal that there has been little progress in establishing a clear numerical definition for hypoglycaemia, but

understanding of underlying pathogenic mechanisms (specially in persistent hypoglycaemias), new information in genetic causes and promising information based on neuroimaging to define neurological outcomes, help define new strategies in preventing and treating hypoglycaemia in newborns (Chan, 2011).

2. Glucose metabolism physiology in the term and preterm newborn

Glucose is the most important foetal energy substrate (mainly for brain metabolism). Foetal glucose needs are met thanks to the continuous transplacental glucose transfer, and although the necessary enzyme systems needed for gluconeogenesis develop early during pregnancy, the foetus only produces its own glucose in extreme conditions such as maternal starvation. (Gustaffson 2009). The foetal glucose level is 60-80% of that of the mother's.

In order to provide the foetus with glucose, the mother undergoes different metabolic changes throughout gestation, such as increase in hepatic glucose production. Also, during the first trimester, the mother has a higher sensitivity to insulin that leads to fat depot formation. Later on, on the third trimester, when the baby has its own fat depots, the mother metabolizes these depots via lypolisis for her own needs under the influence of specific hormone changes therefore saving glucose for foetal use only.

The foetus is exposed to high insulin concentrations, as it has a very important anabolic action. During the third trimester, insulin stimulates fat deposition and increases energetic stores in the form of glycogen.

At birth, the constant placental supply is interrupted. Healthy term infants are prepared to adapt to this new situation thanks to a series of metabolic and hormonal changes that will ensure that the newborn's glucose demands (Central Nervous System (CNS) in particular) will de adequately met in the first 48 hours, while sufficient enteral feeding is being established. It has been demonstrated that early, frequent, breastfeeding together with skin to skin contact, promote adequate transition and meet the needs of healthy full-term infants. (Wight, 2006; Achoki et al, 2010).

First, an increase in glucagon and catecholamine levels and a decrease in insulin levels occur. This induces hepatic glucose production, (which in a healthy full term baby is 4-6micrgo/kg/min, three times that of an adult). This rate of hepatic glucose production is proportional to the baby's estimated brain weight. During the first 10 hours of life, it occurs by glycogenolisis. After, it takes places via gluconeogenesis (production of glucose "de novo" from alanine, pyruvate, lactate and glycerol). To further help in neoglucogenesis, lypolisis is stimulated (to levels comparable to an adult fasting), due to an increase in TSH levels after birth, which generates glycerol and free fatty acids. These free fatty acids play an important role as they promote further neoglucogenesis, and together with ketone bodies and lactate, are used as an alternative energy substrate for the brain. (Gustaffson, 2009; Mitanchez, 2007))

After birth, an adequate balance between tissue consumption of glucose, hepatic glucose production and exogenous glucose supply is necessary to establish glucose homeostasis. Glucose levels in the newborn decrease in the first two hours, but steadily rise afterwards and thereafter remain constant. Hypoglycaemia occurs when this equilibrium fails, and is usually transient.

In the presence of persistent hypoglycaemia, three main possible scenarios must be considered: depletion of energetic storage (prematurity and intra-uterine growth restriction), increase tissue energetic consumption and foetal hyperinsulinism. (Mitanchez, 2008; Wight, 2006; Ward Platt & Desphande 2005).

Preterm and intrauterine growth restricted (IUGR) newborns have different patterns of adaptation to that of a full-term neonate: they both have limited energy depots, and they have a higher risk of impaired compensatory ketogenesis. (Ward Platt & Desphande 2005). These babies are capable of neoglucogenesis and lypolisis, with some differences and restrictions.

Preterm infants have limited energy stores plus immature metabolic pathways to ensure an adequate glucose production, that lead to a larger fall in blood glucose in the first hours after birth. Because they have limited glycogen liver storage depots (since this takes place mainly during the third trimester), glycogenolisis is limited, therefore neoglucogenesis (from glycerol, alanine and lactate) is the main pathway for glucose production. Because neoglucogenesis requires some time to begin, in the absence of adequate glycogenolisis, hypoglycaemia in these "babies is hard to" avoid if exogenous glucose is not administered (Mitanchez, 2007), although some authors suggest that though neoglucogenesis occurs at slower rates in these infants than in term newborns, it may be just sufficient to prevent hypoglycaemia in the first hours of life (Gustafsson, 2009). Lypolisis occurs. However, the depot fat in an infant born after at 28 weeks is only 2% of total body weight (7 times less than in term infants) therefore the degree of lypolisis is decreased (Gustafsson, 2009; Diderholm , 2009).

Preterm infants are therefore at higher risk for hypoglycaemia because of their limitations for adequate glucose metabolism, but also because other clinical conditions which are associated with hypoglycaemia are common in this population, such as perinatal asphyxia, hypoxia, sepsis, and hypothermia. Preterm infants are less capable of compensating these glucose alterations than term infants are, being the final goal to ensure sufficient energy substrate for the brain to use, and even moderate hypoglycaemia can lead to an adverse neurodevelopmental outcome. Enteral feeding is a stimulus for postnatal metabolic adaptation. Thus, early milk feeding should be encouraged as soon as possible when tolerated, even at a minimal level (Mitanchez, 2007).

On the other hand, preterm infants (particularly those less than 30 weeks of gestational age (GA)) frequently have impaired insulin – glucose balance, leading to hyperglycaemia during the first weeks of life. This occurs because processing of pro-insulin in the pancreatic beta-cells is deficient, therefore preterm infants are partially resistant to insulin. Exogenous insulin infusion is efficient and may be used with caution. (Mitanchez, 2008). These patterns of metabolic adaptation are further influenced by feeding practices. (Ward Platt & Desphande, 2005)

As mentioned before, compared to adequate for gestational age (AGA), infants with IUGR have smaller energy depots. Gluconeogenesis has been shown to occur effectively from glycerol in these infants (50% of glycerol is converted to glucose and this rate increases in babies who do not receive extra parenteral glucose infusion) and from pyruvate. Ketogenesis is severely limited in preterm infants. Lypolisis also occurs but is limited because it correlates with birth weight (that is: the rate of lypolisis depends on the amount of stored fat), and it is therefore reduced in IUGR babies (Gustafsson, 2009, Mitanchez, 2007).

Infants born to diabetic mothers are at risk for hypoglycaemia, due to increased levels of insulin in the baby. This increase occurs due to increased maternal glucose levels throughout the pregnancy. Despite insulin normally reducing lypolisis, this does not happen in these babies, probably as a compensation for the lower level of glucose production seen in these newborns (Gustafson, 2009).

There is limited information on metabolism in newborn LGA infants. These babies tend to have increased lypolisis rates (partly due to higher body and brain weight) and variable

degrees of insulin resistance (as happens with obese children in later periods of life) (Gustafsson, 2009).

3. Defining aetiology and risk factors

When considering aetiology and risk factors in hypoglycaemia, the differentiating marker is whether it is transient (< 3-5 days) or persistent (> 5-7 days). (Fernández Lorenzo et al, 2011; Cloherty & Stark, 2009; Polin & Yoder 2007; Chan 2011).

3.1 Transient hypoglycaemia

Low endogenous glucose production or low glycogen deposits.

This occurs in situations where glucose metabolic pathways are impaired or immature such as in preterm infants, intrauterine growth retardation (IUGR) and small for gestational age (SGA) newborns and in situations of insufficient calorie intake (feeding difficulties, problems with breastfeeding or intolerance of enteral feedings etc…).

Increase in glucose use or diminished exogenous administration.

Exposure to situations with high energy consumption rates such as perinatal stress (asphyxia, sepsis, respiratory distress, hypothermia, congenital cardiopathy…). In these situations, anaerobic glycolisis occurs due to decreased tissue perfusion and low oxygen blood content. When polycythemia occurs, the higher number of red blood cells consume glucose at higher rates than normal, as would happen during and after an exanguinotransfussion procedure. An abrupt cease in intravenous glucose administration may induce transient hypoglycaemia that is normally reverted reinitiating the glucose infusion.

RISK FACTOR	MECHANISM
Preterm and Intrauterine Growth Restriction	Low glycogen deposits Restriction in fluids / energy Hormonal and enzymatic immaturity Feeding difficulties
Diabetic mother Beckwith-Wiedemann Syndrome RH haemolytic disease	Transient hyperinsulinism
Pancreatic islets dysregulation Syndrome Pancreatic islets adenoma	Persistent hyperinsulinism
Perinatal stress; asphyxia, sepsis Polycythemia, hypothermia	Low glycogen deposits Hyperinsulinism Feeding difficulties Fluid / energy restrictions
Maternal drugs: propanolol, oral antidiabetic preparations	Altered cathecolamin response
Adrenal insufficiency Hypothalamic / Hypopituitaric deficiency	Counter-regulatory hormone deficiency
Inborn errors in metabolism	Enzyme defects, altered glucogenolisis, neoglucogenesis or fatty acid oxidation.

Table 1. Risk factors and physiopathological mechanisms that cause hypoglycaemia

Transient hyperinsulinemic hypoglycaemia

There are many situations where the newborn is exposed to intra-uterine hyperinsulinism, rendering the infant prone to hypoglycaemia after birth, when that hyperinsulinism persists until pancreatic beta cells commence to work and regulate insulin secretion, but the constant transplacental glucose supply has been terminated.

Diabetic mothers (specially those needing insulin during gestation, which implies worse glucose regulation), big for gestational age neonates, erytroblastosis, misplaced umbilical arterial line (near the pancreas) or if the mother receives intrapartum Pre-par* or other beta-sympaticomimetics that interrupt glycogenolisis, tiazides, clorpropamide, anti-hyperglycaemic agents or glucose infusion rates of more that 10g/h before birth, may develop transient hyperinsulinemic hypoglycaemia. In the Beckwith-Wiedemann Syndrome (LGA newborn, macroglosia, onphalocele and visceromegaly), hypoglycaemia occurs secondary to transient hyperinsulinism due to pancreatic beta cells hypertrophy.

3.2 Persistent hypoglycaemia

When persistent hypoglycaemia occurs (that is, need for glucose infusion for more than 5-7 days, in particular when high rates are required) other clinical scenarios must be ruled out and specific diagnostic procedures must be started.

Prolonged neonatal hyperinsulinemic hypoglycaemia may occur as a result of nesidioblastosis, pancreatic adenoma or beta cell hyperplasia, that is, clinical situations that increase insulin production at the pancreatic beta cell. However, up to 30-40% of **persistent hyperinsulinism cases are congenital or genetic**, with increasing knowledge of genetic mutations in specific calcium channels that control insulin secretion. This will be further explained.

Other causes of persistent hypoglycaemia are syndrome such as **Usher Syndrome** (hearing loss and retinitis pigmentosa), **endocrine disorders** (pituitary hormone deficiencies or primary adrenocortical insufficiency) and **inborn errors of carbohydrate metabolism** (glucogenosis, hereditary fructose intolerance and galactosemia) **or amino-acid metabolism** (methylmalonic and glutaric acidemias, leucinosis (MUSD), carnitine deficiency and others…) and **defects in fatty acid beta-oxidation.**

4. Clinical manifestations of hypoglycaemia in the neonatal period

These are unspecific and may resolve within minutes-hours after normoglycaemia is restored, unless cerebral damage has occurred.

Neurological symptoms such as irritability, tremor, jitteriness, hypotonia, exaggerated Moro reflex, and weak cry may appear gradually and progress towards seizures, acute encephalopathy, lethargy and coma. Altered state of consciousness is a common finding, with alternate jitteriness and stupor (Chan, 2011).

Jitteriness is not very specific of hypoglycaemia though a frequent form of presentation, as it may be present in up to 44% of healthy term infants (Alkalay et al, 2005). In some cases, it may be pathological, resembling a brainstem release reflex (impaired function of superior cortical inhibitory structures that normally control the brainstem). As for tremor, it is also frequent in healthy term newborns, and only normally correlates to hypoglycaemia or hypocalcaemia when it persists despite suckling stimulation, rather than stopping as it does in healthy babies. As for seizures, these may present very early after hypoglycaemia

appears, but normally occur after persistently or recurrently low glucose values over at least 12 hours.

Other clinical manifestations include tachypnea, cyanosis (due to apnea, autonomic response or decreased pulmonary flow) or apnea spells. Difficulty to suck and feeding problems may also occur. Autonomic alterations are frequent, such as hypothermia or unstable temperature, pallor, profuse sweating or bradycardia (Alkalay et al, 2005).

5. Monitoring glucose levels and how to do so?

In the presence of asymptomatic newborns with any of the known risk factors (preterm, IUGR, SGA and LGA infants; newborns with diabetic mothers; perinatal stress situations; maternal drugs before or during labour, infants requiring intensive care, those with polycythemia and syndromes such as Beckwith-Wiedemann) glucose must be closely monitored. Blood glucose should also be monitored in infants receiving long duration parenteral nutrition, even when stable. Healthy asymptomatic newborns without risk factors do not need routine evaluation. **Chan 2011**

Glucose determination must be done at the first hour of life, and afterwards, depending on different guidelines (Fernández Lorenzo et al, 2011) every 2-4 hours for the first 8 hours of life, and every 6-8 hours for the following 24 hours of life. The main point however, is to carefully assess glucose metabolism during the more vulnerable stages of transition. Normally, if glucose levels are maintained in the first hours of life (when hypoglycaemia is most likely), they rarely fall afterwards. Nevertheless, periodic measurements (more or less frequently depending on glucose values and associated risk factors) must be performed during at least the first critical 24 hours.

Specifically, suggested controls in newborns of diabetic mothers would imply: glucose testing in the first hour of life, and afterwards, every 6-12 hours, since hypoglycaemia is most probable around the first six hours of life. These controls may be suspended after 12 hours of normal glucose values.

In preterm and SGA infants however, controls should be more frequent, every 2-4 hours depending on glucose values: are they normal, just on the limit or actually low? Do they require clinical management that must be monitored?

On the other hand, whenever a newborn presents with clinical symptoms that could be due to hypoglycaemia, particularly if the newborn has risk factors for hypoglycaemia, rapid glucose determination is imperative, as early treatment is essential to prevent brain damage. This implies having a wide scope of suspicion in any situation, as symptomatic hypoglycaemia con vary from very unspecific clinical symptoms such as discrete irritability to more alarming and obvious presentations such as seizures, and recognition is determinant.

6. Diagnosis

In order to diagnose hypoglycaemia, a cut-off value has to be established. There is still no evidence of what that numerical value is, and it probably differs amongst different babies (term, preterm, IUGR, asphyxiated, septic…) as tolerance thresholds of glucose values are probably different in each of these scenarios (sick babies are probably more susceptible to hypoglycaemia than healthy term newborns, specially if hypoglycaemia persists or is severe). Therefore, in order to diagnose hypoglycaemia, operational guidelines exist, and

diagnosis is normally made in the presence of blood glucose concentration <45mg/dL (<2.5mmol/L) in the first hours – days of life. (Fugelseth, 2001). Later on, a certain degree of glucose control is expected and hypoglycaemia is diagnosed with glucose levels < 50-55 mg/dL. (Chan , 2011).

Accurate measurement of blood glucose levels in the newborn is important in order to prevent and treat hypoglycaemia effectively, therefore reducing the risk of adverse neurological outcomes. Commonly used Point of care (POC) glucose testing provides immediate results with small sample volumes. This enables treatment, when necessary, to start fast and permits the necessary modifications according to the infants´ clinical situation. These devices are perfected constantly, and yet, they still lose accuracy at the limits of both low and high glucose values (hypoglycaemia with blood glucose <2.0 mmol/l or <2.6 mmol/l and hyperglycaemia with blood glucose >10 mmol/l). Knowing these limitations is important and so strictly speaking, these devices cannot be completely relied on for an accurate diagnosis. However, as a screening tool, they are essential, and when accuracy is doubtful, laboratory confirmation is necessary. This will require intermittent blood samples and results are somewhat delayed. Less invasive and continuous methods of glucose monitoring are under development. These devices provide constant information and being increasingly used for control and care of patients with diabetes mellitus, but they are not currently in use in neonates (Beardsall, 2010). Continuous interstitial glucose monitoring has been tested on newborns thought to be at risk for hypoglycaemia, and though apparently reliable, it is still not known how to best interpret the results, and therefore more studies are needed before implementation of this technique. (Harris et al, 2010; Hay et al , 2010 as cited in Chan, 2011).

When using laboratory measurement of glucose, it is important to know what sample is used. Glucose concentration in whole blood is up to 15% lower than that in plasma and may be even lower in the presence of a high hematocrit. Once the sample has been taken, analysis should be performed rapidly, as glucose values in blood can decrease by 15 to 20 mg/dL per hour in blood samples at room temperature. (Chan, 2011).

Diagnosis of hypoglycaemia begins with determining low glucose levels in the presence or not of clinical symptoms. It should be emphasized that surveillance and intervention thresholds are not the same: when treating hypoglycaemia, the desired range for normoglycaemia should be 72-90 mg/dL (4-5 mmol/L), as opposed to the diagnostic suggested thresholds of <46mg/dL (<2.6mmol/L) (Kalhan & Peter-Wohl, 2000).

This is normally a transient problem in adaptation in a newborn with frequently recognisable risk factors or other treatable underlying causes such as sepsis, insufficient exogenous glucose administration or errors in administration. However, when hypoglycaemia is persistent (at least more than 72 hours, and specifically more than the first week of life), and high rates of iv glucose (some times up to 12 mg/kg/min) are required to maintain normal glucose levels, specific laboratory test must be begun to rule out causes of persistent hypoglycaemia in order of frequency (Chan, 2011): prolonged neonatal hyperinsulinemic hypoglycaemia, congenital hyperinsulinemic hypoglycaemia, endocrine disorders and inborn errors of metabolism.

The diagnostic algorithm requires defining ketone body production, and plasma levels of both free fatty acids and of lactic acid. With these three parameters, we can establish which diagnosis is most probable:
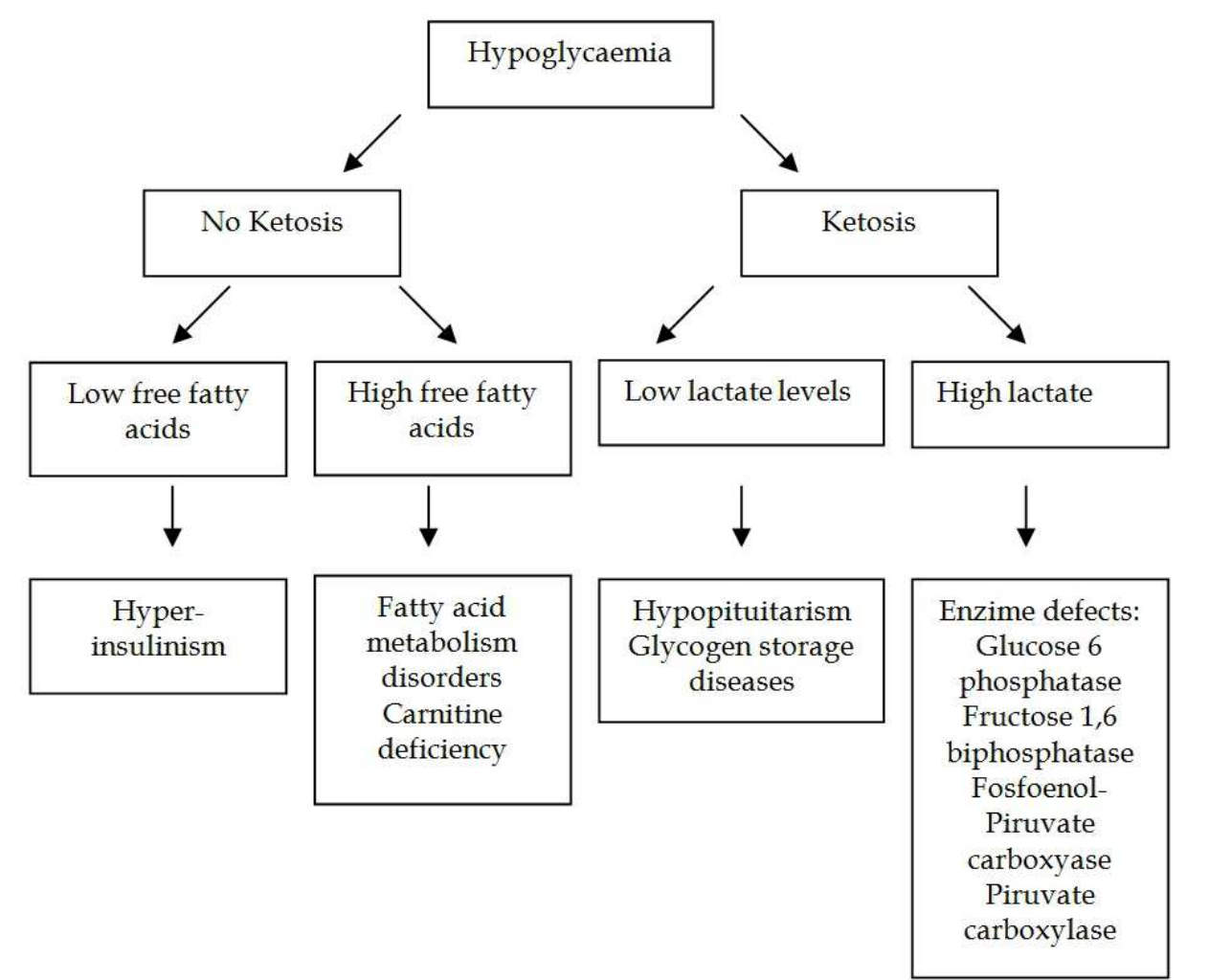
Fig. 1. Algorithm for hypoglycaemia diagnosis

Ketone body production is the normal alternative pathway to obtain energy in the absence of sufficient glucose supply. Free fatty acids are oxidized to obtain ketone bodies, which are an important energy substrate for the heart, muscle and brain. In this scenario, high levels of lactic acid suggest a defect in neoglucogenesis, whereas low lactic levels suggest glycogen storage disease or hypopituitarism.

On the other hand, in the absence of ketone body production and with low free fatty acid levels, hyperinsulinism must be suspected, as insulin inhibits glycogenolisis (turning glycogen stores into glucose), neoglucogenesis (de novo glucose production from non-carbohydrate sources such as lipids and proteins) lipolysis and therefore ketogenesis. No ketosis with high levels of free fatty acids in the setting of hypoglycaemia suggests fatty acid oxidation defects, because free fatty acids cannot be used to produce ketone bodies as an alternative energy substrate in the presence of hypoglycaemia.

First level laboratory tests:

Glycaemia / Insulinemia ratio

Ketone bodies in urine (3 beta hidroxybutiric acid)

Lactate / Piruvate ratio

Plasmatic insulin higher than 13mU/ml when plasmatic glucose is lower than 40mg/dL (that is, a glucose/insulin rate < 3:1) without ketosis and low free fatty acids is

patognomonic of hyperinsulinism: excessive insulin levels despite having low glucose levels without the normal alternative energy ketone body production.

Second level laboratory tests:

Ketone bodies and organic acids in blood

Organic acids in urine

This is a first step towards diagnosing possible inborn errors in metabolism, specially specific enzyme defects found in organic acidemias.

Third level laboratory tests:

Thyroid hormones (T4, TSH)

Glucagon

Cortisol / ACTH (poner nombre entero) / Growth Hormone (GH)

Amino-acids in blood and in urine

Growth hormone and Cortisol are counter-regulatory hormones that normally rise with hypoglycaemia. If there are low levels of GH (< 7-10 ng/mL) or of cortisol (<20 microg/dL) this suggests an isolated hormone deficiency or hypopituitarism.

Glucagon basal levels are suggestive, but specifically, an increase in plasma glucose of more than 30 mg/dl after glucagon administration suggests that the hepatic glycogen stores are not depleted, which is also characteristic of hyperinsulinism.

Diagnostic criteria to define hyperinsulinism are:

Glucose < 40mg/dL

Insuline > 13 microU/mL

Glucose/insuline ratio < 3:1

Glucose intravenous needs > 6-8 mg/kg/min

Negative ketone bodies in plasma and urine (3-beta-hidroxi-butiric acid < 1mmol/L)

Low free fatty acids (< 1 mmol/L)

Cortisol > 20 microg/dL

GH > 7-10 ng/mL

Glucemic reaction to glucagon administration > 30 mg/dL (ie: positive response)

7. Persistent hypoglycaemic hyperinsulinism

When hypoglycaemia persists for more than 5 days, initial laboratory tests must commence to rule out other possible causes of persistent hypoglycaemia. In this scenario, persistent hypoglycaemic hyperinsulinism is a frequent entity and deserves a mention of its own, as it is a major cause of hypoglycaemic brain injury and mental retardation. (Kapoor et al, 2009a; 2009b).

In normal conditions, the pancreatic islet beta cells produce insulin that is secreted outside the cell via an ATP sensitive potassium channel (ATP-K). Genetic mutations that produce altered proteins that form part of different sub units of this channel explain the dysregulation of insulin secretion (that is: excess secretion even in the presence of low plasma glucose levels).

It has two main characteristics: high glucose needs to maintain normoglycaemia and responsiveness to exogenous glucagon. Hypoglycaemia occurs due to a dysregulated insulin secretion with defects in the normal counter-regulatory hormones (cortisol or GH). It is possible that there may be an increased insulin sensitivity in these patients, although this has not been proven. The excess insulin secretion leads glucose into the insulin sensitive tissues (mainly skeletal muscle, adipose tissue and liver) so hypoglycaemia occurs. On the other hand,

insulin inhibits glycogenolisis (turning glycogen stores into glucose), neoglucogenesis (de novo glucose production from non-carbohydrate sources such as lipids and proteins) lipolysis and therefore ketogenesis (oxidation of fatty acids to produce alternative energy substrate ketone bodies). As was mentioned before, the normal counter-regulatory cortisol and glucagon responses are blunted, so hypoglycaemia persists. In this scenario, the brain is being deprived of any form of energy substrate, as glucose (its main energy source) is depleted in plasma, but also, alternative energy sources (ketone bodies and lactate) are characteristically low in these cases, so the risk for brain damage is increased greatly.

Understanding this is crucial, as management to prevent brain damage will differ from other underlying processes. Initially, 2.6 mmol/l was suggested as definition for hypoglycaemia based on the neurophysiological changes associated to hypoglycaemia, but these were established under conditions of non-hyperinsulinism, that is, the brain does have alternative energy fuel. Later, "operational thresholds" were suggested for different groups of neonates (Cornblath, 2000), since there is still uncertainty as to what levels of hypoglycaemia and for what duration, promote brain injury. And though many centres have accepted 2.6mmol/L as the operational threshold for hyperinsulinism, based on the complete absence of alternative energy sources for the brain in a crucial moment (intense development in the neonate and during infancy), a higher threshold of at least 3.5-6 mmol/L is necessary in order to prevent cerebral glycopenia, as the brain will be completely dependant on glucose plasma levels for an adequate glucose intake (Hussain et al, 2007).

There is great variability in terms of clinical presentation, histology, genetics and treatment response and hyperinsulinism can be classified according to three main characteristics: (Giurgea et al, 2005)

Onset of hypoglycaemia: neonatal period or later during infancy
Histological lesion: focal or diffuse
Genetic transmission: sporadic recessive or less frequently, dominant

Hyperinsulinism may be isolated or may be part of a more complex syndrome. The former tends to present early in the neonatal period and is frequently severe as compared to syndromic hyperinsulinism which commonly has later onset during infancy, with a milder presentation. Severity is evaluated considering the exogenous glucose administration rate required for normoglycaemia and the response to medical treatment which may be highly variable amongst individuals. (Cloherty & Stark, 2009; Chan, 2011; Arnoux et al, 2010).

Over the past decades, there is increasing information on the genetic aspects of hyperinsulinism. Congenital hyperinsulinism is caused by mutations in genes involved in regulation of insulin secretion. To date, seven genes involved have been identified (ABCC8, KCNJ11, GLUD1, CGK, HADH, SLC16A1 and HNF4A). These genes encode glucokinase, glutamate dehydrogenase, the mitochondrial enzyme short-chain 3-hydroxyacyl-CoA dehydrogenase plus the proteins that form the subunits of the ATP-K channel (which are the most common underlying mechanisms). Severe forms of congenital hyperinsulinism, that is, those with early neonatal presentation, are caused by mutations in these ATP-K channel subunits: ABCC8 or sulfonylurea receptor gene (SUR1) and KCNJ11 or inward-rectifying potassium channel gene (KIR6.2), both located in the 11p15.1 region. Mutations in HNF4A, GLUD1, CGK, and HADH lead to transient or persistent hyperinsulinism, whereas mutations in SLC16A1 cause exercise-induced hyperinsulinism.

In focal pancreatic islet-cells hyperplasia, mutations of the ABCC8 or the KCNJ11 genes are inherited from the father, with a loss of the maternal allele specifically in the hyperplasic islet cells. In diffuse isolated hyperinsulinism, genetic inheritance is heterogeneous and may

be recessive (ABCC8 and KCNJ11) or dominant (ABCC8, KCNJ11, GCK, GLUD1, SLC16A1, HNF4A and HADH). Syndromic hyperinsulinism is always diffuse and genetic inheritance depends on the specific syndrome. (Arnoux et al, 2010 ; Giurgea, 2005 ; Kapoor et al, 2009a) Despite the increasing amount of genetic information already available, there are still up to 50% of the cases where no known genetic alteration can be identified.

Therefore, defining the histological forms of hyperinsulinism is particularly important as they involve different genetic mutations and inheritance but most importantly, because they have different treatment options. Focal hyperplasia consists of a focal adenomatoid hyperplasia of islet cells, while diffuse forms involve all the pancreatic beta cells of the whole pancreas. Infants suffering from ATP-K hyperinsulinism present shortly after birth with severe and persistent hypoglycaemia, and the majority do not respond to medical treatment. Up to 40-60% of the children with ATP-K hyperinsulinism have focal lesions in the pancreas and are candidates for local resection which is effective while avoiding the long-term complications of near-total pancreatectomy such as diabetes-mellitus. Diffuse hyperinsulinism however, when resistant to medical treatment (octreotide, diazoxide, calcium antagonists and continuous feeding) may require subtotal pancreatectomy.

To distinguish between focal and diffuse forms, trans-hepatic catheterisation with pancreatic venous sampling has been used, but is being replaced by [(18)F] Fluoro-L-Dopa PET scan, which is easier to perform, and is not only a diagnostic tool, but may also be used to guide laparoscopic surgery. Therefore, rapid genetic analysis combined with an understanding of these histological features (focal or diffuse disease) and the introduction of (18)F Fluoro-L-Dopa PET scan, have totally transformed the clinical approach to this complex metabolic alteration (Arnoux et al, 2010; Kapoor et al 2009).

Treatment options:	Diazoxide	Octreotide	Ca antagonist	Glucagon
Mechanism	Opens K channel Stimulates CA production	Opens K channel: inhibits insulin secretion	Inhibits Ca channel	Increases glucogenolisis & neoglucogenesis
Doses	10-15 mg/kg/day every 8h (maximum of 25mg/kg/day)	10 microg/kg/day subcutaneous every 4-6h	0.25-0.7 mg/kg/day every 8h oral	0.2 mg/kg im fast Maintenance infusion of 2-10 microg/kg/h iv
Indications & effectiveness	Fist line 20-50%	Second line 20-80%	Not enough experience	Emergency treatment and stabilization
Adverse effects	Liquid retention Hypertrichosis Hyperglycaemia Cetoacidosis Hypertension Leucopenia Trombopenia Hyperuricemia	GH, TSH and glucagon suppression Steatorrhea Cholestasis	Hypotension	Increases myocardial contractility Lowers Ca & K Lowers gastric acid and pancreatic enzymes Frequently nauseas and vomiting

Table 2. Medical treatment options in hyperinsulinemic hypoglycaemia.

Before considering possible surgical treatments (once the diagnosis of hyperinsulinism has been made), medical treatment must be started, with the goal of maintaining glucose values within a normal target range. Initially exogenous glucose administration will be required and glucagon infusion may be useful in certain emergency situations. In terms of specific medical treatment, oral diazoxide is the first line option. If the infant does not respond, somatostatin analogues and calcium antagonists may be considered. Except for ATP-K channel defects hyperinsulinism (ABCC8 and KCNJ11), most forms are sensitive to diazoxide.

In conclusion, there are two main points that sum up the management of hyperinsulinism cases: prevention of brain damage by normalizing glycaemia and screening for focal forms as they may be definitively cured after a limited pancreatectomy. (Arnoux et al, 2010).

8. Treatment for hypoglycaemia

When treating hypoglycaemia, there are two mains aspects that must be considered and that will define a different approach: first, whether the neonate is symptomatic or not and secondly, the initial glucose values. (Fernández Lorenzo et al, 2011; Chan, 2011).

8.1 Asymptomatic hypoglycaemia

When glucose levels are under 46mg/dl (2.6mmol/L) but higher than 30mg/dL, and the baby has no feeding intolerance or difficulty, breastfeeding is the first option, together with supplementation either with extracted mothers´ milk or adapted infant formula if necessary. This provides a higher glucose intake than offering plain 5% glucose solution orally. Capillary glycaemia controls are needed every 20-30 minutes after intake. If normoglycaemia has been achieved, normal feedings can be established (preferably breastfeeding ad libitum, that is, as often as the baby needs, but at least every two-three hours), and considering adding supplements of the mothers´ extracted breast milk or adapted formula if necessary).

If there are feeding difficulties or intolerance, or if glucose levels are below 30mg/dL, intravenous exogenous glucose administration must be considered. 10% glucose infusion at a rate of 5-8 mg/kg/min will be required as a starting point. As feeding tolerance recuperates, oral feedings must begin, promoting the physiological fractioned enteral feeding pattern that will better regulate insulin secretion. As glucose levels are maintained, parenteral glucose administration must be tapered until complete and exclusive fractioned enteral nutrition has been established.

In some cases, if an intravenous line is difficult to obtain, or if a baby is persistently hypoglycaemic but asymptomatic despite fractioned enteral feedings, continuous enteral feeding may be considered, which provides a continuous glucose intake, but requires adequate gastrointestinal tolerance.

8.2 Symptomatic hypoglycaemia

When hypoglycaemia persists (less than 46 mg/dL or 2.6mmmol/L) and symptoms are present, rapid glucose correction is warranted. An intravenous bolus of 10% glucose must be administered at a dose of 2ml/kg/dose (200mg/kg/dose). Higher glucose concentrations should not be used, in order to avoid the possible insulin peak secretion that may occur in response to the bolus. In the presence of seizures, higher doses of 4ml/kg/dose (400mg/kg/dose) must be considered. In any case, after bolus administration, a continuous

glucose perfusion must be started to prevent rebound hypoglycaemia due to peak insulin secretion; again, around 5-8 mg/kg/min to begin with.
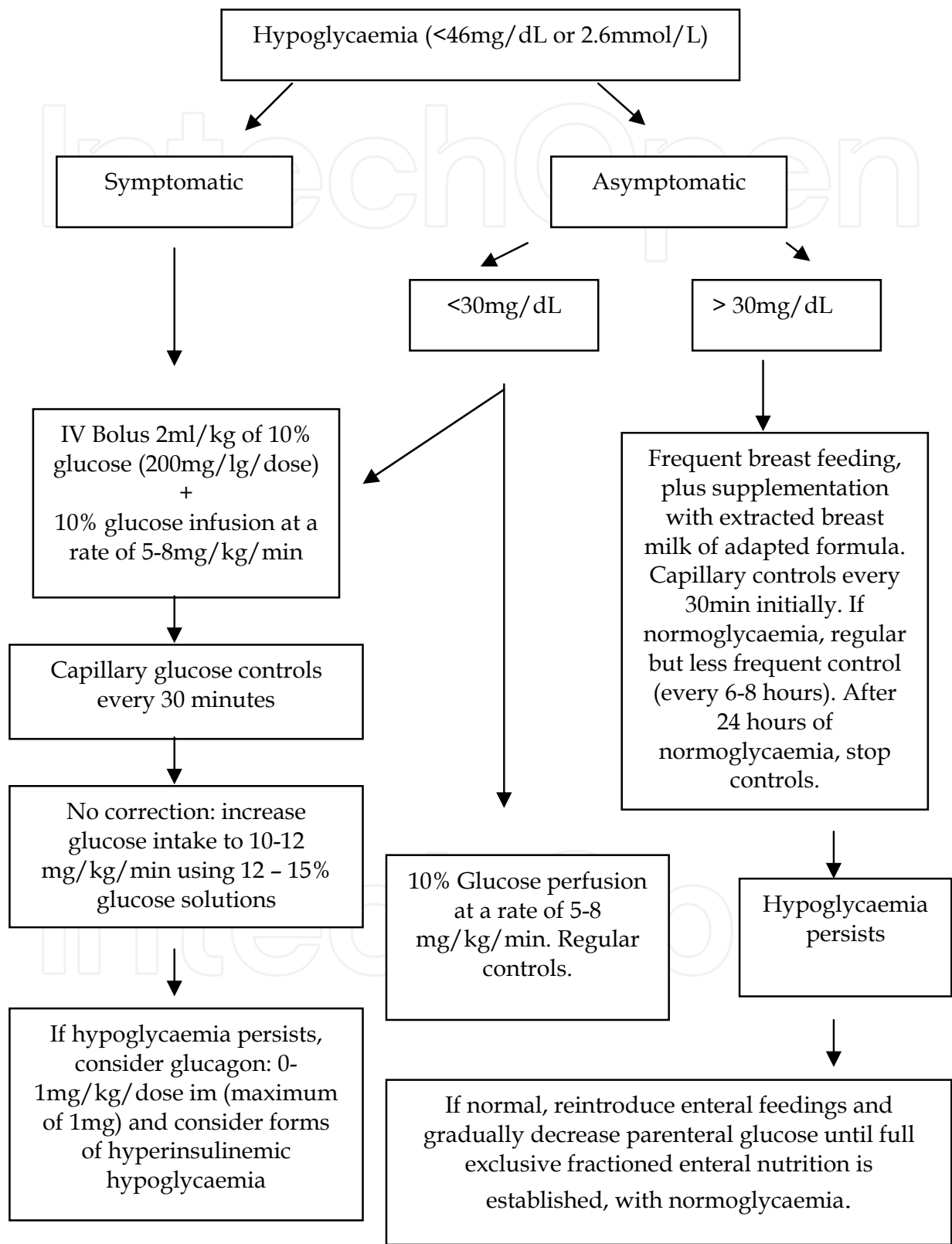

Fig. 2. Treatment algorithm for neonatal hypoglycaemia

Depending on glycaemia control afterwards, the exogenous glucose intake may be increased further either initially increasing perfusion rate (up to a maximum volume intake the baby will tolerate according to gestational age, weight and clinical status) or, more frequently, increasing the glucose concentration using 12% or 15% glucose solutions. This implies a central line must be placed, as with increasing concentration, osmolarity increases and peripheral lines risk extravasation. In this case, it is preferable not to use umbilical lines, specifically to avoid using the umbilical artery, as malposition of this artery line may cause hyperinsulinism due to direct pancreatic stimulus, and further hypoglycaemia.

When glucose needs exceed 12mg/kg/min, glucocorticoid therapy is an option,, due to stimulation of neoglucogenesis and reduction in peripheral glucose utilization. Hydrocortisone (5mg/kg/day divided in two doses orally or intravenously) or prednisone (2mg/kg/day orally or intravenously) are used over several days until glycaemia recovers and doses can be gradually decreased. In this scenario (persistently high needs of exogenous glucose administration, despite glucocorticoid treatment) or in emergency situations where glucose bolus alone is not effective or cannot be administered rapidly enough, glucagon is an alternatively, though infrequently used. A wide rang of initial bolus doses have been reported, but in a recent review, the suggested   initial dose is 0.2-0.3 mg/kg (either intramuscular administration or as a slow intravenous push over one minute) with a maximum doses of 1mg. Blood glucose should rise in the next 20-30 minutes. If not, another does can be administered, and if there is still no response, glycogen store disorders must be ruled out. This is only a temporary option, while interventions are planned to provide sufficient glucose and to start diagnosis of hyperinsulinism which may prompt use of diazoxide or somatostatin as mentioned earlier (Chan, 2011).

9. Neurological outcome

There is increasing concern about neurodevelopment after hypoglycaemia and many studies have tried to establish a correlation between hypoglycaemia and brain damage, dating since the 1960´s. But, to date there is still not sufficient adequate information to define a precise cut-off glucose value, below which irreversible brain damage occurs, at a specific moment or for a defined period of time, in a given infant or in a subset of specific infants. There seems to be consensus that it is after recurrent, protracted, severely low glucose concentrations (less than 18-20mg/dL (< 1mmol/L) for more that 1-2 hours) specially when accompanied by severe neurological symptoms such as seizures or coma, that adverse neurological outcome is to be expected (Rozance & Hay,2006; Cornblath, 2000; Alkalay, 2005; Vannuci, 2001). There is also consensus that in order to define CNS injury as a consequence of hypoglycaemia, other obvious CNS lesions must be absent (such as hypoxia-ischemia, intracranial haemorrhage, infection, etc.). Other conditions such as confirmed or suspected hyperinsulinemic hypoglycaemia in the presence of seizures, for example, contribute to the diagnosis of hypoglycaemic injury (Rozance & Hay, 2006).

Because we do not know what the absolute threshold value is, operational thresholds have been suggested, where clinical guidance is compulsory, so an infant with neurological symptoms will need more urgent evaluation than an asymptomatic newborn, regardless of the glucose value (Williams, 2005).

In the preterm population, there are no conclusive studies regarding neurological outcome in case of hypoglycaemia, but they suggest that even mild but repeated hypoglycaemia could be detrimental on brain development. Retrospective data from a multicenter trial of

nutrition in premature infants found lower Bayley mental and psychomotor scores at 18 months in infants with at least five confirmed hypoglycaemia events, with a higher rate of developmental delay and cerebral palsy, but however failed to confirm these findings at 7.5 and 8 years of age (Lucas et al, 1988; Cornblath, 1999 as cited in Chan, 2011).

Considering the innate risk for adverse neurodevelopment in the preterm infant, emphasis must be put on monitoring glucose levels in these infants to avoid further possible CNS injury (Wayenberg & Pardou, 2008).

It is worth pointing out that the physiopathological mechanisms that promote injury in hypoglycaemia vary from injury mechanisms in HIE, with some areas being more sensitive to deprivation of glucose and others to deprivation of oxygen and a greater tendency towards selective neuronal necrosis in hypoglycaemic babies. Also, concurrent hypoglycaemia and HIE have worst prognosis than either condition individually, therefore extreme caution must be taken to maintain normoglycaemia in an HIE setting (Vannuci, 2001; Garg & Devaskar, 2006).

Neonatal hypoglycaemia can lead to reduced head circumference at follow-up, lower psychomotor scores, motor deficit and mental retardation. Specifically neonates with recurrent episodes had lower psychomotor scores than those with a single episode. (Lucas, 1988; Nunes, 2000; Greery, 1966 as cited in Alkalay 2005).

Hypoglycaemia episodes with seizures have worse outcomes than hypoglycaemia episodes alone. At follow-up, many of those that had hypoglycaemia and seizures develop epilepsy of different types such as infantile spasms and partial seizures. Electroencephalographic recordings do not show specific patognomonic features that may result diagnostic (Alkalay, 2005).

Parieto-occipital diffusion restriction seen on MRI scans have been reported associated with neonatal hypoglycaemia and can result in long-term disability, epilepsy, and visual impairment (Finlan et al, 2006; Tam et al, 2008). The aetiology of this pattern of injury is unclear; however, transient hyperinsulinism may be an independent risk factor. Magnetic resonance brain imaging can help define the extent of brain injury and guide follow-up. In a 23 case follow-up, with severely low and persistent or recurrent glucose values, abnormal brain imaging findings were associated with profound hypoglycaemia and involved occipital lobes in 82% the cases. Half of these infants had visual impairment (Alkalay et al, 2005b).

In relation to this, a cohort of 45 neonates with diffusion-weighted MRI studies after hypoglycaemia was studied retrospectively to determine whether hypoglycaemic injury, as indicated by diffusion restriction in the occipital lobes, correlated with visual evoked potentials and long-term cortical visual dysfunction. They saw that diffusion-weighted imaging studies performed within 6 days after initial hypoglycaemia were sensitive in term (50% had restricted diffusion in occipital lobes) but not in preterm neonates (none had this alteration), as opposed to those performed after, and were associated with abnormal visual evoked potentials detected within 1 week after birth. Cortical visual impairment happened in a significant proportion of patients with recurrent hypoglycaemia and correlated significantly with low mesial occipital apparent diffusion coefficient values. They concluded that diffusion restriction, with low apparent diffusion coefficient values, in the mesial occipital poles, may indicate poor visual outcomes in acute settings after neonatal hypoglycaemia (Tam et al, 2008).

While occipital lobe injury patterns have been widely described, other brain injury patterns have also been identified when studying MRI scans performed on term neonates with

symptomatic hypoglycaemia and compared to neurologically normal infants. White matter abnormalities occurred in 94% of the infants (43% of theses were severe lesions), with predominant posterior lobe alterations in 29% of the cases. Cortical abnormalities were identified in 51% of infants; 30% had white matter haemorrhage, 40% basal ganglia and or thalamic lesions, and 11% had an abnormal posterior limb of the internal capsule. Three infants had middle cerebral artery territory infarctions. It was noted that early MRI findings predicted neurodevelopmental outcomes better than the severity or duration of hypoglycaemia: 65% of these infants had impaired neurologic development at 18 months, which were related to the severity of white matter injury and involvement of the posterior limb of the internal capsule (Burns et al, 2008).

10. Prevention

Despite controversy and gaps in knowledge as to what level of hypoglycaemia and for how long, brain injury occurs, it is clear that hypoglycaemia can and must be prevented. In the majority of healthy newborn infants, if hypoglycaemia occurs, it is merely a transient adaptation process. However, although the majority of term newborns without risk factors will adapt correctly, there is up to 10% of these infants that will have significant hypoglycaemia in the first 3-4 hours of life, and will probably be asymptomatic. Helping these infants adapt is best achieved when promoting early skin to skin contact as soon as the baby is born (this promotes mother-child bonding, more effective breast feeding and better temperature control) and early and frequent breast feeding. On the other hand, infants with risk for hypoglycaemia are more vulnerable and may not adapt as easily as a healthy newborn, despite applying these strategies. Preventing significant hypoglycaemia in this subset population implies controlling these infants at risk in the first hours of life and thereafter periodically depending on the infants' clinical status and glucose levels, and adapting treatment options to the babies' situation.

11. Conclusions

Hypoglycaemia in the neonatal period is a frequent problem. In the majority of cases, in healthy term newborns, it is merely a transient adaptation process from intra-uterine life to extra-uterine conditions. However, there are infants who for different reasons are at risk of more significant and persistent hypoglycaemia, that will have less capacity to adapt to extra-uterine life and that will require frequent monitoring and treatment when necessary.

The goal is to maintain normoglycaemia in order to assure an adequate energy substrate for all organs but most importantly for the brain in order to prevent brain injury. To achieve this, many cut-off values have been proposed, and perhaps the most accepted concept is that of defining specific "operational thresholds" for different groups of infants at risk, that is, the glucose value for a given infant where treatment is required, the point where we must intervene. There is consensus in the need of preventing hypoglycaemia, which means looking out for it in infants at risk, and promptly treating it if present (from more frequent feeding to parenteral glucose infusion to glucagon if necessary).

Hypoglycaemic induced brain damage occurs when hypoglycaemia is severely low in a persistent or recurrent manner, and is more likely when acute neurological symptoms such as seizures are present. Occipital lobe affectation has been widely described, but recent research opens the scope of brain injury to white matter and to vascular lesions as well.

In the setting of persistent hypoglycaemia, persistent hyperinsulinemic hypoglycaemia, inborn errors of metabolism and endocrine disorders must be ruled out. Specifically, when considering persistent hyperinsulinemic hypoglycaemia, innovations in diagnosis at a molecular and radiological level have been particularly important in terms of differentiating focal from diffuse forms, which, if unresponsive to medical treatment may be candidates for curative partial pancreatectomy.

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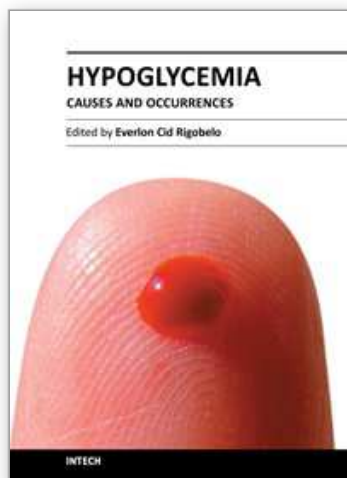
Hypoglycemia - Causes and Occurrences

Edited by Prof. Everlon Rigobelo

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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