Postnatal metabolic adaptation and neonatal hypoglycaemia

JM Hawdon

Abstract

Blood glucose levels fall in the hours after birth in all babies but for most babies the normal process of neonatal metabolic adaptation mobilises alternative fuels (e.g. ketone bodies) from stores so that the physiological fall in blood glucose is tolerated. However, some babies are at risk of impaired neonatal metabolic adaptation and for these babies it is important to prevent hypoglycaemia, to recognise clinically significant hypoglycaemia, and to treat it without causing unnecessary separation of mother and baby or disruption of breast feeding. This article aims to provide paediatricians with an understanding of the science underpinning best practice and offers a plan of investigation for babies in whom hypoglycaemia is persistent, resistant or unexpected.

Keywords alternative fuels; blood glucose monitoring; breast feeding; hypoglycaemia; neonatal metabolic adaptation

Introduction

Much debate surrounds neonatal hypoglycaemia in terms of the definition of the condition, its clinical significance and its optimal management. This is in part because there is a continuum between the normal postnatal metabolic changes, with a physiological fall in blood glucose after birth accompanied by protective metabolic responses, and the more worrying situations where there is delay or failure of the normal metabolic adaptation to birth. Therefore, hypoglycaemia cannot strictly be applied as a pathological diagnostic term and it is preferable to consider a diagnosis of impaired metabolic adaptation. Invariably "neonatal hypoglycaemia" is used as a shorthand term for this. It is important to prevent potentially damaging hypoglycaemia in vulnerable babies, but this must be balanced against the risks of overly invasive management – separation of mother and baby, placing at risk the establishment of breast-feeding, and unnecessary administration of formula or intravenous glucose which in turn impair metabolic adaptation to postnatal life.

Metabolic changes at birth

During pregnancy, the human fetus receives from its mother via the placental circulation a supply of substrates necessary for growth, for the deposition of fuel stores which are essential after birth, and for energy to meet the basal metabolic rate and requirements for growth. When the continuous flow of nutrients from the placenta is abruptly discontinued at birth, immediate postnatal metabolic changes preserve fuel supplies for vital organ function. The newborn infant must adapt to the fast-feed cycle and to the change in major energy source, from glucose transferred across the placenta to fat released from adipose tissue stores and ingested with milk feeds. After birth, plasma insulin levels fall and there are rapid surges of catecholamine and pancreatic glucagon release. These endocrine changes switch on the essential enzymes for glycogenolysis (the release of glucose stored as glycogen in liver, cardiac muscle and brain), for gluconeogenesis (glucose production from 3-carbon precursor molecules by the liver), lipolysis (release of fatty acids from adipose tissue stores), and ketogenesis (the β oxidation of fatty acids by the liver). Some tissues, for example the kidney, are obligate glucose users but others burn fatty fuels to provide energy. Of the organs that utilise alternative fuels to glucose, the brain is the most important in that, it takes up and oxidises ketone bodies at higher rates than seen in adults, and the neonatal brain uses ketone bodies more efficiently than glucose. Lactate has also been identified as an alternative fuel.

In clinical terms, low blood glucose concentrations are commonly found during the first postnatal days in healthy appropriate weight for gestation age (AGA) term neonates, particularly those who are breast-feed. However, these infants have high ketone body levels when blood glucose concentrations are low, and it is likely that these alternative fuels protect them from neurological injury.

Clinical significance of impaired metabolic adaptation

In some circumstances (see below), such as following preterm delivery, intrauterine growth restriction, perinatal hypoxia –ischaemia or suboptimal control of diabetes in pregnancy, there may be impaired glucose and ketone body production and in these babies hypoglycaemia must be prevented, diagnosed and treated effectively.

No study has yet satisfactorily addressed the duration of absent or reduced availability of metabolic fuels which is harmful to the human neonate. Animal studies indicate that hours (rather than minutes) of hypoglycaemia are required to cause injury, and that injury is unlikely to occur if there are no abnormal clinical signs. For babies in whom prolonged neonatal hypoglycaemia has been associated with abnormal clinical signs (most usually hypotonia, reduced level of consciousness or fits) adverse long-term outcomes have been reported. There is evidence from case reports that profound and prolonged hypoglycaemia is associated with both transient and permanent structural changes in the brain. Grey matter injury is most commonly reported with the parieto-occipital regions being most affected.

Causes of impaired neonatal metabolic adaptation

Insufficient availability of glucose and alternative fuels

Preterm birth: the preterm baby has not had sufficient time in utero to lay down glycogen and adipose tissues stores. In addition, hormonal and enzyme adaptive responses may by immature or the baby may have systemic conditions which affect hepatic function and glucose production, e.g. severe infection.

Intrauterine growth restriction (IUGR): it is important to use this term rather than "small for gestational age" because not all

J M Hawdon *MA MBBS MRCP FRCPCH PhD is Consultant Neonatologist and Clinical Academic Group Director, Women's and Children's Health, Barts Health NHS Trust, London, UK.*

IUGR infants will have birthweights on a low centile. Conversely, not all small for gestational age infants will have been subject to placental insufficiency – they may be constitutionally small and will not experience impaired postnatal metabolic adaptation. The baby who has experienced IUGR has reduced stores of carbohydrate and fat, these fuels were required for metabolism in fetal life. Therefore, the IUGR baby is at risk of hypoglycaemia prior to the successful establishment of milk feeds and may have reduced availability of alternative fuels for cerebral metabolism. However, it has been shown that healthy breast fed IUGR babies can mount a ketogenic response, and that excessive formula milk supplementation is associated with a suppressed response.

Perinatal hypoxia–ischaemia: the high metabolic requirement for anaerobic metabolism will reduce endogenous fuel stores if the fetus is exposed to significant hypoxia–ischaemia. In addition, hypoxic liver damage will reduce the activity of the counterregulatory metabolic responses. Although concurrent hypoglycaemia and hypoxia–ischaemia are more damaging than either insult alone, there is no evidence that hypoglycaemia following cessation of a hypoxic-ischaemic insult worsens hypoxic–ischaemic injury.

Systemic conditions: any condition which increases metabolic demands (e.g. hypothermia, systemic infection), affects adequacy of feeding, or affects perfusion or function of the gut or liver places the baby at risk of impaired metabolic adaptation. If hypoglycaemia is diagnosed, there must be urgent investigation for underlying conditions and appropriate management of these.

Inborn errors of metabolism and endocrine insufficiency: these conditions are rare, but for affected individuals frequently present in the neonatal period when nutrient intake is low. The most common metabolic disorders presenting at this time are defects of β oxidation of fatty acids. The most common congenital endocrine disorders presenting with neonatal hypoglycaemia are defects in cortisol production.

Maternal medication: maternal beta blocker therapy has been associated with impaired neonatal metabolic adaptation, although passage across the placenta and in breast milk is variable. This is not a contraindication to breast feeding (NICE). Often, the baby of the mother with hypertension also has IUGR, thus increasing the risk.

Prolonged starvation: as described above, various factors affect the sufficiency of endogenous fuel stores at the time of birth. If exposed to prolonged inadequacy of nutrient intake, even the healthy well grown baby will run out of endogenous stores and metabolic adaptation will fail.

Neonatal hyperinsulinism

If the fetal insulin levels are raised and do not fall after birth, or if there is excessive insulin release from the neonatal pancreas, the actions of insulin are to increase glucose uptake into cells, suppress endogenous glucose production, and suppress release of fat from adipose tissue stores. In these circumstances the baby is at risk of hypoglycaemia and an absence of alternative metabolic fuels. Clinical features are that glucose requirements to maintain normoglycaemia are high, in excess of 8 mg/kg/minute, as compared to the 4–6 mg/kg/minute usually required by neonates, and the infant may be macrosomic if hyperinsulinism was of fetal origin.

Maternal diabetes mellitus: for babies born after diabetes in pregnancy which has not been well controlled, the postnatal fall in blood glucose concentration is more prolonged than for the healthy term neonate and may become clinically significant. Fetal and neonatal hyperinsulinism may occur after pre-pregnancy type 1 or type 2 diabetes or diabetes whose onset is in pregnancy, and is the result of increased placental transfer of glucose and other nutrients stimulating increased fetal insulin secretion. For affected babies, plasma insulin levels usually fall to normal within 12–24 hours of birth and this form of hypoglycaemia presents early and is self limiting.

Congenital hyperinsulinaemic hypoglycaemia (HH): although a rare condition, this is the most common cause of recurrent and persistent hypoglycaemia in infancy and childhood. There are a number of underlying pathologies and the molecular and genetic basis of these are becoming clear. HH is usually associated with macrosomia and high glucose requirements. The condition may be self-limiting in the neonatal period or extend beyond this time. As there is no protective ketone body response to hypoglycaemia, there are usually neurological signs and the risk of brain injury is high. Therefore, urgent treatment is required (see below).

Beckwith–Wiedemann syndrome: this condition is characterised by exomphalos, macroglossia, visceromegaly, earlobe abnormalities and an increased later incidence of malignancies. Hyperinsulinism is a common but not invariable feature which usually resolves in the days after birth.

Other causes: transient hyperinsulinism has also been reported in association with perinatal hypoxia–ischaemia, intrauterine growth restriction and rhesus haemolytic disease, although the mechanisms for this have not been determined. Maternal thiazide diuretic use may cause neonatal hyperinsulinism.

Iatrogenic or factitious hyperinsulinism: hyperinsulinism may result from erroneous or malicious administration of insulin. Although rare, these circumstances should be suspected if hypoglycaemia is unexpected, profound or resistant to treatment.

Diagnosis of clinically significant hypoglycaemia

Much controversy and confusion has surrounded the definition of hypoglycaemia. Factors which should be considered are the blood glucose concentration considered to be the minimum safe level, the duration beyond which the low blood glucose level is considered to be harmful, the presence of clinical signs, the group of infants studied, the consideration of alternative fuel availability, the conditions of sampling and the assay methods. Most of these have not been adequately addressed in scientific studies. Therefore, a pragmatic approach based upon thresholds for intervention has been proposed. If there are neurological signs in association with low blood glucose levels there should be urgent investigation for underlying cause (Table 1) and