Hyperinsulinaemic hypoglycaemia: biochemical basis and the importance of maintaining normoglycaemia during management

Khalid Hussain, Oliver Blankenstein, Pascale De Lonlay and Henrik T Christesen

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Central to the decision making process is a proxy judgement of an individual’s quality of life. This is very tricky to ascertain in children in any case, and how often do attempts to measure this reveal a significant divergence of opinion between children and their parents. It is surely not surprising that children adapt better to adversity than their parents give them credit for. Quality of life is an important and emotive issue which should colour our decision making, yet tools for its objective measurement are very crude. However, that should not preclude us from at least trying to make an assessment.

So, having debated the rights and wrongs of intervening in pubertal development, what about the thorny issue of growth limitation? We spend considerable energy prescribing measures to promote growth in disabled children, such as accelerated nutrition or growth hormone, since failure to thrive is often regarded as a failure of parental and clinical care. So then, when we are faced with the opposite request, to limit growth to facilitate long-term care, what should our response be? The extent of growth failure is now well appreciated as being in proportion to the severity in conditions such as cerebral palsy, so much so that reference standards are now available. Thus children with the most severe psychomotor retardation grow the least well. This is the situation even in the absence of other distortions such as pathological precocious puberty. The onset of early sexual development curtails prepubertal growth significantly, and as transit through puberty is accelerated, resultant adult stature is even further reduced as a result of premature growth cessation. Therefore, if this can be predicted by expert opinion and is expected, why the need for intervention, especially if treatments such as high-dose oestrogens may have physical and psychological complications? Treatment with high-dose sex steroids to accelerate puberty and promote premature epiphyseal fusion in constitutionally tall children is only modestly successful with reported reductions in adult height of at most 6 cm. Advocating surgical intervention to control the complications of such treatments brings us right back to the debate about autonomy and consent, and also whether any medical treatment is necessary at all. We also need to recognise that a high-dose oestrogen treatment regimen is rarely used nowadays in girls in favour of inducing an early onset and rapid transit through puberty using physiological oestrogen doses.

We find ourselves on the horns of a dilemma. Pioneering new clinical developments is fundamentally important, yet we must be certain that the rights of the vulnerable are not violated. We must also be absolutely certain of our facts about the nature of certain particular clinical situations before claiming definite benefits from any interventions. We do have the duty to support carers, but our overriding responsibility as paediatricians is to the child and their wellbeing, and that may well put us in an unenviable position while we advocate for what we believe is right.

Hyperinsulinaemic hypoglycaemia

Hyperinsulinaemic hypoglycaemia: biochemical basis and the importance of maintaining normoglycaemia during management

Khalid Hussain, Oliver Blankenstein, Pascale De Lonlay, Henrik T Christesen

In patients with suspected hyperinsulinaemic hypoglycaemia, blood glucose concentrations should be maintained within the normal range during routine management

Hyperinsulinaemic hypoglycaemia (HH) is a major cause of recurrent and persistent hypoglycaemia in infancy and childhood. Rapid diagnosis, avoidance of recurrent and repeated episodes of hypoglycaemia and prompt management of the hypoglycaemia are vital in preventing brain damage and mental retardation. Unfortunately, a large proportion of children with HH still develop brain damage as a consequence of delayed diagnosis and subsequent management. HH can be either congenital or secondary to certain risk factors (such as intrauterine growth retardation). Congenital hyperinsulinism involves either defects in the genes ABCC8 and KCNJ11 (encoding for the two proteins SUR1 and KIR6.2 of the pancreatic β cell KATP channel, respectively) or abnormalities in the enzymes glucokinase, glutamate dehydrogenase and short chain acyl-CoA dehydrogenase (SCHAD). Loss of function mutations in the genes ABCG8 and KCNJ11 cause the most severe forms of HH which are usually medically unresponsive. HH is also observed in newborns with intrauterine growth retardation, in infants with perinatal asphyxia, in infants

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of diabetic (gestational and insulin dependent) mothers, in some infants with Beckwith-Weidemann syndrome and, more recently, in infants with no predisposing factors. In most of these conditions, the HH is a transient phenomenon and resolves spontaneously. However, some small for gestational age and appropriate for gestational age infants can have prolonged hyperinsulinaemic hypoglycaemia which requires treatment with diazoxide, persists for several months and then resolves spontaneously. Recognition of this group of patients is important as they are fully responsive to treatment with oral diazoxide. The underlying mechanisms of the HH in these patient groups are unclear at present.

**BIOCHEMICAL BASIS OF HYPERINSULINAEMIC HYPOGLYCAEMIA**

The biochemical basis of HH (congenital and secondary) involves dysregulated insulin secretion with defects in glucose counter-regulatory hormones. It is also possible that there is increased insulin sensitivity in some of these patients (for example, those with intrauterine growth retardation), although this has not been proven directly. The unregulated insulin secretion drives glucose into the insulin sensitive tissues, especially skeletal muscle, adipose tissue and liver, causing profound hypoglycaemia. This is compounded by the fact that insulin simultaneously inhibits gluconeogenesis (glucose breakdown), gluconeogenesis (glucose production from non-carbohydrate sources), lipolysis and ketogenesis (hypoketotic). The normal physiological glucagon and cortisol counter-regulatory hormonal responses to hypoglycaemia are blunted further, exacerbating the hypoglycaemia. This biochemical milieu is a recipe for depriving the brain of its most important fuel, namely glucose.

The associated brain glucoseaemia is accompanied by a lack of alternative substrates such as ketone bodies and lactate. It is under these conditions that the risk of brain damage is highest. The importance of ketone bodies as an alternative substrate for brain utilisation in patients with HH was illustrated in a study by Plecko et al. Two patients with congenital hyperinsulism were administered oral beta-hydroxybutyrate and using magnetic resonance spectroscopy Plecko et al were able to show an increased uptake in the brain of beta-hydroxybutyrate with a concomitant reduction in the glucose infusion rate. This uptake of ketone bodies by the brain was proportional to the circulating concentration of beta-hydroxybutyrate.

Recent advances in understanding brain glucose sensing, the role of intrahypothalamic insulin and KATP channels in glucose regulation have further highlighted the potential complex central mechanisms that may contribute to the increased risk of hypoglycaemia in patients with HH. Pancreatic b cell KATP channels play a pivotal role in regulating insulin secretion by transducing metabolic signals to electrical changes in membrane potential. These KATP channels are also present in the hypothalamus and are similar to those in the pancreas. Animal studies have shown that hypoglycaemia is sensed in several areas of the brain, especially in the ventromedial hypothalamus (VMH) in which KATP channels play an important role in mediating responses to hyper- and hypoglycaemia. Closing of KATP channels in the VMH (much like the b cell) impairs defence mechanisms against glucose deprivation and therefore could contribute to defects in glucose counter-regulation. In rats intrahypothalamic infusions of insulin can suppress hepatic glucose production by inhibiting glucogenesis. This action of insulin is mediated by hypothalamic KATP channels via the vagus nerve. As patients with HH have raised serum insulin levels (and presumed raised CSF insulin levels as insulin can cross the blood–brain barrier), it is conceivable that hepatic glucose production is suppressed not just by the peripheral actions of insulin but also by the central actions of insulin. Hence several potentially defective mechanisms (peripheral and central) of glucose homeostasis may be contributing to the hypoglycaemia in patients with HH.

**Practical implications for managing patients with HH**

Confusion and controversy surrounds the definition and management of hypoglycaemia in infancy and especially in the newborn period. However, regardless of the definition used, it is recognised that hypoglycaemia can cause neonatal encephalopathy resulting in permanent brain injury. Even transient HH secondary to intrauterine growth retardation and maternal diabetes mellitus can lead to neonatal seizures and occipital brain injury. A blood glucose concentration of 2.6 mmol/l was suggested by Koh et al. as the definition of hypoglycaemia based on the neurophysiological changes associated with hypoglycaemia. It is important to remember that these studies were performed in infants who were not hyperinsulinaemic and thus were able to generate alternative fuels such as ketone bodies in response to hypoglycaemia. Cornblath et al. have recently suggested using “operational” thresholds (blood glucose levels at which clinical interventions should be considered) in different groups of individuals. For most patients it difficult to define a blood glucose level that will require intervention (especially in neonates) since there is uncertainty over the level and duration of hypoglycaemia that can cause neurological damage. Many centres accept a blood glucose level of 2.6 mmol/l as the operational threshold for neonates and infants with HH.

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**Table 1** Serum insulin, total ketone bodies and lactate measurements in seven patients with different forms of HH and at different blood glucose concentrations

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cause of HH</th>
<th>Gestation (weeks)</th>
<th>Age at testing (days)</th>
<th>Blood glucose (mmol/l)</th>
<th>Serum insulin (mU/l)</th>
<th>Total ketone bodies (mmol/l)</th>
<th>Plasma lactate (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Congenital (ABCC8)</td>
<td>39</td>
<td>14</td>
<td>2.1/3.9/5.3</td>
<td>4.2/12.4/15.4</td>
<td>1.0/0.05/0.05</td>
<td>1.1/2.1/2</td>
</tr>
<tr>
<td>2</td>
<td>Congenital (ABCC8)</td>
<td>40</td>
<td>12</td>
<td>2.6/3.8/5.1</td>
<td>13.2/5.6/9.3</td>
<td>2.0/0.05/0.05</td>
<td>1.3/0.1/1</td>
</tr>
<tr>
<td>3</td>
<td>IUGR (2.3 kg)</td>
<td>39</td>
<td>9</td>
<td>2.4/3.5/5.2</td>
<td>7.3/12.4/11.6</td>
<td>1.0/0.05/0.05</td>
<td>1.2/1.3/1.1</td>
</tr>
<tr>
<td>4</td>
<td>IUGR (2.1 kg)</td>
<td>38</td>
<td>10</td>
<td>2.3/3.6/5.5</td>
<td>7.5/8.4/8.7</td>
<td>0.05/0.05/0.05</td>
<td>1.3/0.1/1</td>
</tr>
<tr>
<td>5</td>
<td>Maternal DM</td>
<td>38</td>
<td>2</td>
<td>2.0/3.5/5.5</td>
<td>6.3/9.5/11.4</td>
<td>0.05/0.05/0.05</td>
<td>1.4/1.0/1.0</td>
</tr>
<tr>
<td>6</td>
<td>Maternal DM</td>
<td>39</td>
<td>2</td>
<td>1.9/3.7/5.8</td>
<td>7.8/9.4/9.7</td>
<td>0.05/0.05/0.05</td>
<td>1.3/1.5/1.2</td>
</tr>
<tr>
<td>7</td>
<td>BWSS</td>
<td>39</td>
<td>2</td>
<td>2.1/4.0/5.5</td>
<td>23.4/10.4/8.3</td>
<td>0.05/0.05/0.05</td>
<td>1.2/1.4/1.2</td>
</tr>
</tbody>
</table>

BWSS, Beckwith-Weidemann syndrome; Congenital (ABCC8), congenital hyperinsulinaemia due to mutations in the ABCC8 gene; DM, diabetes mellitus (insulin dependent); HH, hyperinsulinaemic hypoglycaemia; IUGR, intrauterine growth retardation.

Total ketone bodies were undetectable in all patients (<0.05 mmol/l). Ketone bodies and lactate were measured at three different blood glucose concentrations (<3 mmol/l, 3–5 mmol/l and >5 mmol/l). Serum ketone bodies were undetectable in all patients at all blood glucose concentrations. The serum lactate remained within the normal range of 1–2 mmol/l.
Patients with HH are clearly very different and the definition of an operational threshold of hypoglycaemia should be re-evaluated in this group of patients. Given the biochemical basis (hypoketotic and hypofattyacidaemia) of the hypoglycaemia, maintaining blood glucose concentrations below the normal range (3.5–6 mmol/l) will lead to brain glucopaenia. As discussed above, this brain glucopaenia will be compounded by the fact that there are no alternative substrates (ketone and lactate) for the brain to use. In these patients the brain is constantly dependent on a normal circulating blood glucose concentration as the oxidative fuel for neuronal function. There are no studies in this group of patients to suggest that the brain is able to compensate for the glucopaenia either by reducing brain glucose utilisation, increasing cerebral blood flow, increasing the fractional extraction of glucose from the circulation or using glycogen stored in the astrocytes. On the contrary, as insulin is able to cross the blood–brain barrier, it is conceivable that the breakdown of stored glycogen in astrocytes will be inhibited. Insulin stimulates glucose uptake and enhances glycogen accumulation in neonatal rat brain astrocytes preventing glucose release.20

Table 1 shows the total serum ketone bodies (acetoacetate and beta-hydroxybutyrate) and lactate concentrations in seven patients with different forms of HH. These serum ketone bodies were measured at three different blood glucose concentrations (<3 mmol/l, 3–5 mmol/l and >5 mmol/l) in all seven patients. The different blood glucose concentrations were maintained by increasing or decreasing the intravenous glucose infusion rate. As is shown, serum insulin concentrations are detectable at all three blood glucose concentrations in each patient and serum ketone bodies are concurrently suppressed at all time points. The serum lactate level remained within the normal range in all patients. These simple observations reinforce the fact that glucose is the only substrate available for brain utilisation in patients with HH.

Hence these principles have important implications for managing patients with HH. It is therefore recommended that in patients with suspected HH blood glucose concentrations should be maintained within the normal range (3.5–6 mmol/l) during routine management. This is to avoid the neurological consequences of neuroglycopenia and its long-term complications. Neonatologists and paediatricians should have a high index of suspicion of diagnosing HH in any patient who has persistent hypoglycaemia.

Given the complex management issues with these patients, in the UK and in some other European countries the development of designated regional referral centres is being considered. Referring paediatricians and neonatologists will be able to seek advice about diagnosis, treatment and transfer of patients with HH to regional centres. The increased awareness, early diagnosis and transfer of patients with severe forms of hyperinsulinaemic hypoglycaemia to dedicated centres will not only improve the quality of care delivered to these patients but more importantly the long-term neurological outcome.

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