particularly when medical or social factors are exceptional.

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.[7] 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 expend considerable energy prescribing measures to promote growth in disabled children, such as accelerated nutrition or growth hormone,[8] 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.[9] 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 epiphysial fusion in constitutionally tall children is only modestly successful with reported reductions in adult height of at most 6 cm.[10] 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 natural history of 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.

Arch Dis Child 2007;**92**:567–568.
doi: 10.1136/adc.2007.116327

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Competing interests: None.

REFERENCES

1 **Albanese A**, Hopper NW. Suppression of menstruation in adolescents with severe learning disability. *Arch Dis Child* 2007;**92**:629–32.
2 **Gunther DF**, Diekma DS. Attenuating growth in children with profound disability. *Arch Pediatr Adolesc Med* 2006;**160**:1013–17.
3 Ashley's blog. http://ashleytreatment.spaces.live.com/blog/ (accessed 28 March 2007).
4 Mental Capacity Act 2005, chapter 9. Available at http://www.opsi.gov.uk/acts/acts2005/20050009.htm (accessed 28 March 2007).
5 **Dyer C**. The Gillick judgement. *BMJ* 1985;**291**:1208–9.
6 **Lansdown J**. Listening to children: have we gone too far (or not far enough)? *J R Soc Med* 1998;**91**:457–61.
7 **Sheppard L**, Eiser C, Davies HA, *et al*. The effects of growth hormone treatment on health-related quality of life in children. *Horm Res* 2006;**65**:243–9.
8 **Shim ML**, Moshang T Jr, Oppenheim WL, *et al*. Is treatment with growth hormone effective in children with cerebral palsy? *Dev Med Child Neurol* 2004;**46**:569–71.
9 **Stevenson RD**, Conaway M, Chumlea WC, *et al*. North American Growth in Cerebral Palsy Study. *Pediatrics* 2006;**118**:1010–8.
10 **De Waal WJ**, Greyn-Fokker MH, Stijnen T, *et al*. Accuracy of final height prediction and effect of growth-reductive therapy on 362 constitutionally tall children. *J Clin Endocrinol Metab* 1996;**81**(3):1206–16.

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.[1] 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.[2] 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 K_{ATP} channel, respectively) or abnormalities in the enzymes glucokinase, glutamate dehydrogenase and short chain acyl-CoA dehydrogenase (*SCHAD*). Loss of function mutations in the genes *ABCC8* 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

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

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

BWS, Beckwith-Weidemann syndrome; Congenital (ABCC8), congenital hyperinsulinism 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.

of diabetic (gestational and insulin dependent) mothers, in some infants with Beckwith-Weidemann syndrome and, more recently, in infants with no predisposing factors.[3–6] 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.[7 8] 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.[9–11] 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 glycogenolysis (glycogen 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.[10 11] This biochemical milieu is a recipe for depriving the brain of its most important fuel, namely glucose.

The associated brain glucopaenia 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*.[12] Two patients with congenital hyperinsulinism 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 K_{ATP} 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 β cell K_{ATP} channels play a pivotal role in regulating insulin secretion by transducing metabolic signals to electrical changes in membrane potential. These K_{ATP} channels are also present in the hypothalamus and are similar to those in the pancreas.[13] Animal studies have shown that hypoglycaemia is sensed in several areas of the brain, especially in the ventromedial hypothalamus (VMH)[14] in which K_{ATP} channels play an important role in mediating responses to hyper- and hypoglycaemia. Closing of K_{ATP} channels in the VMH (much like the β 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 gluconeogenesis.[15] This action of insulin is mediated by hypothalamic K_{ATP} 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.[16] Even transient HH secondary to intrauterine growth retardation and maternal diabetes mellitus can lead to neonatal seizures and occipital brain injury.[17] A blood glucose concentration of 2.6 mmol/l was suggested by Koh *et al*[18] 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*[19] 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.

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 hypofattyacidaemic) 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 neuroglycopaenia 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.

Arch Dis Child 2007;**92**:568–570.
doi: 10.1136/adc.2006.115543

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Competing interests: None.

REFERENCES

1 **Hussain K**. Congenital hyperinsulinism. *Semin Fetal Neonatal Med* 2005;**10**(4):369–76.
2 **Menni F**, de Lonlay P, Sevin C, *et al*. Neurologic outcomes of 90 neonates and infants with persistent hyperinsulinemic hypoglycemia. *Pediatrics* 2001;**107**(3):476–9.
3 **Collins JE**, Leonard JV. Hyperinsulinism in asphyxiated and small-for-dates infants with hypoglycaemia. *Lancet* 1984;**2**(8398):311–13.
4 **Sperling MA**, Menon RK. Infant of the diabetic mother. *Curr Ther Endocrinol Metab* 1994;**5**:372–6.
5 **Hussain K**, Cosgrove KE, Shepherd RM, *et al*. Hyperinsulinemic hypoglycemia in Beckwith-Wiedemann syndrome due to defects in the function of pancreatic beta-cell adenosine triphosphate-sensitive potassium channels. *J Clin Endocrinol Metab* 2005;**90**(7):4376–82.
6 **Yap F**, Hogler W, Vora A, *et al*. Severe transient hyperinsulinaemic hypoglycaemia: two neonates without predisposing factors and a review of the literature. *Eur J Pediatr* 2004;**163**(1):38–41.
7 **Hoe FM**, Thornton PS, Wanner LA, *et al*. Clinical features and insulin regulation in infants with a syndrome of prolonged neonatal hyperinsulinism. *J Pediatr* 2006;**148**(2):207–12.
8 **Fafoula O**, Alkhayyat H, Hussain K. Prolonged hyperinsulinaemic hypoglycaemia in intrauterine growth retarded newborns. *Arch Dis Child Fetal Neonatal Ed* 2006;**91**(6):F467.
9 **Aynsley-Green A**, Hussain K, Hall J, *et al*. The practical management of hyperinsulinism in infancy. *Arch Dis Child Fetal Neonatal Ed* 2000;**82**:F98–F107.
10 **Hussain K**, Bryan J, Christesen HT, *et al*. Serum glucagon counter regulatory hormonal response to hypoglycemia is blunted in congenital hyperinsulinism. *Diabetes* 2005;**54**:2946–51.
11 **Hussain K**, Hindmarsh P, Aynsley-Green A. Neonates with symptomatic hyperinsulinaemic hypoglycaemia generate inappropriately low serum cortisol counter-regulatory hormonal responses. *J Clin Endocrinol Metab* 2003;**88**(9):4342–7.
12 **Plecko B**, Stoekler-Ipsiroglu S, Schober E, *et al*. Oral beta-hydroxybutyrate supplementation in two patients with hyperinsulinaemic hypoglycaemia: monitoring of beta-hydroxybutyrate levels in blood and cerebrospinal fluid, and the brain by in vivo magnetic resonance spectroscopy. *Pediatr Res* 2002;**52**(2):301–6.
13 **Ashford ML**, Sturgess NC, Trout NJ, *et al*. Adenosine-5′-triphosphate-sensitive ion channels in neonatal rat cultured central neurones. *Pflugers Arch* 1988;**412**(3):297–304.
14 **Evans ML**, McCrimmon RJ, Flanagan DE, *et al*. Hypothalamic ATP-sensitive K+ channels play a key role in sensing hypoglycemia and triggering counter regulatory epinephrine and glucagon responses. *Diabetes* 2004;**53**:2542–51.
15 **Pocai A**, Lam TK, Gutierrez-Juarez R, *et al*. Hypothalamic K(ATP) channels control hepatic glucose production. *Nature* 2005;**434**:1026–31.
16 **Vannucci RC**, Vannucci SJ. Hypoglycemic brain injury. *Semin Neonatol* 2001;**6**:147–55.
17 **Filan PM**, Inder TE, Cameron FJ, *et al*. Neonatal hypoglycemia and occipital cerebral injury. *J Pediatr* 2006;**148**(4):552–5.
18 **Koh THHG**, Aynsley-Green A, Tarbit M, *et al*. Neural dysfunction during hypoglycaemia. *Arch Dis Child* 1988;**63**:1353–8.
19 **Cornblath M**, Hawdon JM, Williams AF, *et al*. Controversies regarding definition of neonatal hypoglycemia: suggested operational thresholds. *Pediatrics* 2000;**105**(5):1141–6.
20 **Schwartz MW**, Figlewicz DP, Baskin DG, *et al*. Insulin in the brain: a hormonal regulator of energy balance. *Endocr Rev* 1992;**13**(3):387–414.