Transient hyperinsulinism associated with macrosomia, hypertrophic obstructive cardiomyopathy, hepatomegaly, and nephromegaly

A Mehta, K Hussain

CASE REPORT

Transient hyperinsulinism (HI) has been reported in infants born to mothers with diabetes mellitus, in infants subjected to perinatal asphyxia, or intrauterine growth restriction, in those born with Beckwith-Weidemann syndrome (BWS), and in those with rhesus haemolytic disease. The aetiology and mechanisms that underlie transient HI in some of these conditions remain poorly understood. Little is known of the histopathology and membrane physiology of pancreatic β cells in these patients, since the HI is most often transient, not requiring a pancreatectomy. In comparison there has been an explosion of knowledge in the past five years about persistent HI. Mutations in five different genes have been implicated to date. These mutations affect the ionic control of insulin secretion from the pancreatic β cell. The most common form of persistent HI is associated with mutations in the SUR1 (ABCC8) and KIR6.2 (KCNJ11) genes, which cause loss of function of the K\_\text{ATP} channel in the β cell membrane with unregulated secretion of insulin from the pancreatic β cell.

We report two cases of transient HI associated with macrosomia, severe hypertrophic obstructive cardiomyopathy (HOCM), hepatomegaly, and nephromegaly. One of the babies had evidence of a microcolon. There was a history of mild maternal gestational diabetes requiring no treatment in one patient, while the maternal oral glucose tolerance test in the second patient was normal. These cases represent an atypical form of severe transient HI.

CASE 1

A male infant (birth weight 5.6 kg) was born by emergency caesarean section because of cephalopelvic disproportion. There was no history of maternal diabetes mellitus and serial antenatal ultrasound scans were normal. A previous sibling had died of sudden infant death syndrome at the age of 7 weeks with a probable diagnosis of viral pneumonia at postmortem examination.

The baby developed profound hypoglycaemia within the first few hours of birth, with a true blood glucose concentration of 1.5 mmol/l, requiring increased glucose requirements of 12 mg/kg/min to maintain normoglycaemia (blood glucose >2.6–3.0 mmol/l). On examination, he had marked macrosomia, with hepatomegaly and nephromegaly noted on ultrasound examination. There were no other features suggestive of BWS.

He was hypotensive, requiring ventilatory support and high volume replacements to maintain a normal blood pressure. An echocardiogram showed evidence of severe HOCM with outflow tract obstruction (fig 1A). He responded to an infusion of a β adrenergic blocking agent and was slowly weaned off the ventilatory support.

A diagnostic fast was conducted in order to determine the aetiology of his hypoglycaemia. He was found to be hypoglycaemic within 20 minutes of the fast (see table 1). He was commenced on octreotide (10 µg/kg/day) and glucagon (1 µg/kg/h) combination therapy by continuous subcutaneous infusions to control the hypoglycaemia. Diazoxide treatment was not indicated in view of cardiomyopathy and risks associated with fluid retention. He showed a dramatic clinical response and his glucose requirement was reduced to 7 mg/kg/min within 24 hours.

Enteral feeding was commenced, once stabilised, but caused persistent symptoms of vomiting and retching. An electrogastrogram (EGG) performed in view of the gastrointestinal symptoms confirmed an intestinal dysmotility, which is a well recognised finding in patients with HI.

Figure 1 Echocardiographic findings. (A) Case 1: evidence of severe HOCM with outflow tract obstruction. (B) Case 2: symmetrical HOCM but no obstruction.

Abbreviations: BWS, Beckwith-Weidemann syndrome; EGG, electrogastrogram; HI, hyperinsulinism; HOCM, hypertrophic obstructive cardiomyopathy; OGTT, oral glucose tolerance test
Complete withdrawal of the dextrose support and full enteral feeding was only established at the age of 3 weeks. He was subsequently weaned off octreotide and glucagon infusions and remained stable with no recurrence of hypoglycaemia. A repeat fast conducted prior to discharge from hospital was well tolerated for six hours, with a blood glucose concentration of 3.7 mmol/l at the end of the test. He was discharged on three-hourly bottle feeds. Apart from oral propranolol for cardiomyopathy, he was off all other medications. A repeat echocardiogram, carried out at 6 weeks of age, showed improvement, with mild residual left ventricular hypertrophy but no outflow tract obstruction.

An oral glucose tolerance test (OGTT) conducted on his mother, postnatally, again failed to reveal any abnormalities.

CASE 2
A male child was born following an emergency caesarean section at term, with a birth weight of 5.7 kg. He was noted to be floppy and cyanosed, requiring immediate resuscitation with ventilatory support.

His mother was asymptomatic throughout pregnancy. She was diagnosed to have gestational diabetes mellitus in late pregnancy (32 weeks), requiring no treatment. An OGTT had shown a peak glucose concentration of 14 mmol/l at 30 minutes.

Macrosomia with hepatomegaly and nephromegaly on ultrasound examination were again noted. No other dysmorphic features suggestive of BWS were found. An echocardiogram showed marked symmetrical HOCM, but no critical outflow tract obstruction. An EGG study, performed because of persistent vomiting and failure to tolerate enteral feeds, showed profoundly abnormal gut motility. He was entirely dependent on parenteral nutrition and continuous infusions of glucagon and octreotide until the age of 4 weeks, when he was successfully weaned off all support. A repeat echocardiogram performed at 3 months of age was normal with complete resolution of the cardiomyopathy (fig 2). He tolerated a repeat fast of six hours without any hypoglycaemia.

DISCUSSION
Transient HI is a poorly defined term with no consensus on the duration permitted for HI. It may persist for days, weeks, or in some cases even months. Mechanisms responsible for transient HI in conditions such as BWS and intrauterine growth restriction remain unclear. On the other hand, in persistent HI, mutations have been found in the genes controlling transient HI in conditions such as BWS and intrauterine growth restriction remain unclear. On the other hand, in persistent HI, mutations have been found in the genes controlling the function of two components of the KATP channel, in the β cell membrane. Our first case presented with marked macrosomia, HOCM, hepatomegaly, nephromegaly, and HI. There was no evidence of maternal diabetes mellitus and this was confirmed by a normal OGTT. In case 2, although it is feasible that the HOCM may be related to the mild maternal gestational diabetes, the severity and morphology of HOCM was atypical.

The HOCM, in both our patients was global, involving both the septum and the ventricular walls, unlike that seen in infants born to diabetic mothers who have an asymmetrical hypertrophy with thickening of the interventricular septum. The latter is usually benign, needing no treatment, and more likely to occur with poorly controlled maternal diabetes. Massin and colleagues reported a progressive form of hypertrophic cardiomyopathy in a neonate with “focal” HI which was only resolved with a partial pancreatectomy. The precise pathophysiology of HOCM, in both persistent and transient HI, still remains to be understood.

Both infants showed features of a hyperinsulinaemic, hypofattyacidaemic, hypoketonaemic hypoglycaemia, which are the hallmarks of HI. The hypoglycaemia persisted for more than seven days and required treatment with octreotide and glucagon infusions, in contrast to milder hypoglycaemia seen in infants born to diabetic mothers. The latter group, in the vast majority, have a transient asymptomatic hypoglycaemia at 1–4 hours after birth, with a spontaneous increase in blood glucose. Some may show a more prolonged period of symptomatic hypoglycaemia, and a minority develop delayed hypoglycaemia after an initial asymptomatic period. However, in all patients, normoglycaemia is regained within the first few days after birth.

### Table 1 Results of the diagnostic fast

<table>
<thead>
<tr>
<th>Metabolite/hormone</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose (mmol/l)</td>
<td>2.4</td>
<td>2.2</td>
</tr>
<tr>
<td>Plasma insulin (mU/l)</td>
<td>9.1</td>
<td>22.1</td>
</tr>
<tr>
<td>C peptide (mU/l)</td>
<td>401</td>
<td>1466</td>
</tr>
<tr>
<td>Non-esterified fatty acids (mmol/l)</td>
<td>0.06</td>
<td>0.21</td>
</tr>
<tr>
<td>β-hydroxybutyrate (mmol/l)</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Serum cortisol (mmol/l)</td>
<td>293</td>
<td>500</td>
</tr>
<tr>
<td>Serum growth hormone (mU/l)</td>
<td>94.7</td>
<td>38</td>
</tr>
<tr>
<td>Serum ammonia (µmol/l)</td>
<td>16</td>
<td>30</td>
</tr>
</tbody>
</table>

![Figure 2](http://adc.bmj.com/ on April 7, 2017 - Published by group.bmj.com)
BWS is characterised by exomphalos, macroglossia, visceromegaly, gigantism, and hyperinsulinaemic hypoglycaemia. Ear lobe anomalies are of pathognomonic value. Symptomatic hypoglycaemia occurs in up to 50% of cases, most often transient, although prolonged and severe hypoglycaemia lasting several months is known.1

Cardiac involvement is mostly limited to a mild cardiomegaly, with HOCM being very rare.3 Although these patients have visceromegaly, macroglossia, gigantism, and adrenal cytomegaly, no significant myocardial changes have been described. Recent developments in molecular genetics have mapped the syndrome to chromosome 11p 15.4, the same region implicated in families with autosomal recessive HI involving the sulphonylurea receptor gene. The most common genetic abnormality in BWS is the loss of heterozygosity with uniparental disomy. Both our cases were negative for the loss of uniparental disomy, apart from macrosomia and the finding of hepatomegaly and large kidneys, there were no other definitive features to diagnose BWS in our cases. The hepatomegaly seen in our patients probably reflects the stored glycogen as the anabolic effects of insulin predominate. This has been previously noted in infants born to mothers with diabetes mellitus and in BWS. The cause of the transient nephromegaly in our cases is unclear.

Gastrointestinal dysmotility, observed in both patients, is well recognised in patients with HI.11 The disturbed gastrointestinal peristalsis can clinically present with vomiting, retching, and gastro-oesophageal reflux. On the other hand, gastrointestinal symptoms are rare in infants born to mothers with diabetes mellitus, and this again distinguishes our cases. Some patients with persistent HI have a severe form of enteropathy because of a contiguous gene deletion on chromosome 11p15.1.12

In summary, we present two babies with marked macrosomia, organomegaly (hepatomegaly, nephromegaly), and hyperinsulinaemic hypoglycaemia. The combination of features suggests a prenatal onset of HI. The reasons triggering the onset of HI are as yet unclear, as are the mechanisms that underlie dysregulated insulin secretion.

REFERENCES

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