

## CURRENT TOPIC

## Hyperinsulinism and Beckwith-Wiedemann syndrome

C F J Munns, J A Batch

Beckwith-Wiedemann syndrome (BWS) is a congenital overgrowth syndrome first described by Beckwith in 1963.<sup>1</sup> The incidence of BWS is about 1:13 700 births, with an equal sex distribution.<sup>2</sup> It is a clinically and genetically heterogeneous disorder. Table 1 outlines the major clinical features. The existence of milder forms of BWS probably underestimates this incidence.<sup>1</sup> Developmental delay in BWS has been associated with chromosomal duplication, prematurity, and hypoglycaemia.<sup>3</sup> The long term survival in BWS is favourable,<sup>1</sup> although surveillance for tumours is required.<sup>4</sup> The phenotype of BWS is likely to result from an imbalance of a number of critical genes at chromosome 11p15. At this location, genetic imprinting with the loss of maternally expressed tumour and/or growth suppressor genes—for example, p57<sup>KIP2</sup> and H19—or duplications and unipaternal disomy of paternally expressed growth promoter genes—for example, insulin-like growth factor II—have been implicated in BWS.<sup>2</sup> In BWS, 85% of cases are sporadic and 15% are autosomal dominant.<sup>2</sup> Identified causes of autosomal dominant BWS include p57<sup>KIP2</sup> mutations and 11p15 duplications and translocations.<sup>2</sup> About 30% of the sporadic cases result from p57<sup>KIP2</sup> mutations, unipaternal disomy, or 11p15 duplications and translocations, while 70% have no identified cytogenetic or DNA abnormality.<sup>2</sup>

### BWS and hypoglycaemia

The incidence of hypoglycaemia in BWS is about 50%.<sup>3,5</sup> In one BWS hypoglycaemia series, 80% were reported as mild and asymptomatic, requiring extra feeds or intravenous dextrose only. In 20%, the hypoglycaemia was

prolonged (duration greater than one week) and difficult to control.<sup>3</sup> Hypoglycaemia has been documented into the third year of life.<sup>5</sup> Intellectual impairment was associated with hypoglycaemia.<sup>3</sup>

Hyperinsulinism and BWS Hyperinsulinism is the cause of both transient and prolonged hypoglycaemia in BWS. A number of case reports provide data on the metabolic aspects of BWS.<sup>6–11</sup> There is little uniformity between the different reports. The individual authors have undertaken different investigations, making it difficult to draw conclusions. There have been some consistencies with regard to the characterisation of the serum glucose and insulin responses to  $\beta$  cell secretagogues, and these will be discussed below. Owing to the limited data available, the underlying  $\beta$  cell abnormality associated with the hyperinsulinism remains unclear. Therefore conclusions that can be drawn at this time are speculative. The unifying feature of all the case reports of hypoglycaemia in BWS is hyperinsulinism, with inappropriate insulin secretion in the presence of hypoglycaemia. Exaggerated and sustained insulin response and/or reactive hypoglycaemia in response to a glucose load were often reported.<sup>6–11</sup> Rates of glucose disappearance were elevated in the three cases in which they were examined.<sup>9–11</sup> Glucagon has been shown to both raise<sup>8,9</sup> and lower<sup>6</sup> blood glucose concentrations. The lowering of the glucose concentrations resulted from sustained hyperinsulinism.<sup>6</sup> Tolbutamide administration led to a lowering of serum glucose concentration resulting from an immediate and sustained high insulin response.<sup>6</sup> The effects of arginine<sup>6</sup> and leucine<sup>6,9,10</sup> on the  $\beta$  cell were found to be normal. Combs *et al*<sup>6</sup> described three infants with BWS. The infants were successfully treated with diazoxide, cortisol, or glucagon as monotherapy. One infant was off medication by 10 weeks of age, and the other two were still receiving medication at 8 and 20 months of age. Schiff *et al*<sup>6</sup> performed the most comprehensive set of investigations on a male infant with BWS. Glucose, glucagon, and tolbutamide produced an exaggerated and sustained rise in serum insulin concentrations and a fall in blood glucose concentrations. Leucine and arginine did not provoke this insulin response. The authors concluded that the different

Table 1 Features of Beckwith-Wiedemann syndrome

Feature	Frequency (%)
Macroglossia	93
Pre or postnatal growth >90th centile	88
Abdominal wall defects	80
Ear creases or pits	76
Facial naevus flammeus	62
Renal abnormalities	59
Hypoglycaemia	50
Hemihypertrophy	24
Cardiac malformation	7
Intestinal malrotation	5
Neoplasia	4
Mental retardation	4

Department of  
Endocrinology and Diabetes,  
Royal Children's Hospital,  
Herston Road, Herston,  
4029 Brisbane, Queensland,  
Australia  
j.batch@mailbox.uq.edu.au

secretagogues caused insulin release by different mechanisms. Hyperinsulinism requiring treatment continued into the third year of life and was successfully managed with a combination of diazoxide, adrenaline (epinephrine), and regular feeds. In 1973 Goltin<sup>11</sup> reported on a female infant with BWS and hyperinsulinaemic hypoglycaemia. The infant continued to have hyperinsulinaemic hypoglycaemia until 10 months of age despite diazoxide treatment. Insulinopenic responses were shown to oral glucose and intravenous glucagon while the child was receiving diazoxide. Roe *et al*<sup>10</sup> described a female infant with BWS, who required an 80% pancreatectomy at 24 days of age for hyperinsulinaemic hypoglycaemia. The hypoglycaemia could not be managed with 20% dextrose, corticotrophin, hydrocortisone, methylprednisolone, adrenaline, or diazoxide. At 32 weeks of age the infant was shown to have fasting hypoglycaemia (< 2.2 mmol/l) and an abnormal oral glucose tolerance test. There was a peak serum glucose concentration of 10.4 mmol/l at 90 minutes and reactive hypoglycaemia at five hours. Insulin concentrations showed minimal change. Serum growth hormone response to hypoglycaemia was normal. Throughout this period, regular four hourly feeds maintained normoglycaemia. Roe *et al*<sup>10</sup> concluded that partial pancreatectomy was successful in the treatment of hyperinsulinism in BWS. The blunted insulin response to glucose and leucine after pancreatectomy was attributed to a reduction in pancreatic mass. Moncrieff *et al*<sup>6</sup> reported on a male infant with BWS. Despite treatment with diazoxide and prednisolone, the infant had persistent hyperinsulinaemic hypoglycaemia until 14 weeks of age. This improved to allow withdrawal of medication by 28 weeks of age. In the final report, Gerver *et al*<sup>7</sup> described a male infant with BWS and hypoglycaemia. This patient showed suboptimal counter-regulatory hormone response to hypoglycaemia. The authors concluded that somatostatin with regular feeding successfully treated the hyperinsulinaemic hypoglycaemia of BWS, although the infant was at greater risk of hypoglycaemia because of the suboptimal counter-regulatory hormone response. In the cases described by Moncrieff *et al*<sup>6</sup> and Goltin<sup>11</sup>, medical treatment did not prevent asymptomatic hypoglycaemia until 14 weeks and 10 months of age respectively. In the light of recognition of the adverse neurological effects of asymptomatic hypoglycaemia,<sup>12</sup> more aggressive medical management with or without surgery may be considered today.<sup>13</sup>

### **BWS as a cause of neonatal hypoglycaemia**

BWS is a relatively uncommon cause of neonatal hyperinsulinaemic hypoglycaemia.<sup>1 2</sup> To improve our understanding of hypoglycaemia in BWS, a comparison of this condition with the more well defined causes of neonatal hyperinsulinism was carried out. The other causes of neonatal hyperinsulinism can be divided into (a) persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI), (b) hyperinsulinism hyperammonaemia syndrome (HHS),

and (c) transient hyperinsulinaemic hypoglycaemia.<sup>14</sup> There are many similarities between the hyperinsulinaemic hypoglycaemia of BWS and other forms of neonatal hyperinsulinism.

### **PRESENTATION**

Infants with BWS normally develop hypoglycaemia in the first few days of life.<sup>6-11</sup> The same is true in PHHI, HHS, and transient hypoglycaemia.<sup>13 14</sup> Macrosomia may be common to all the conditions.<sup>1 2 13 14</sup> Children with BWS may have other distinguishing phenotypic features (table 1).<sup>1</sup>

### **CLINICAL COURSE**

Hypoglycaemia in BWS can be divided into mild, moderate, and severe depending on the duration and treatment requirements. A similar classification can be made for other forms of congenital hyperinsulinism. Mild cases of hypoglycaemia in BWS and transient hyperinsulinaemic hypoglycaemia often only require extra dextrose to maintain normoglycaemia.<sup>3 15</sup> Moderate cases of hypoglycaemia in BWS<sup>6-9 11</sup> and most cases of PHHI can be managed medically as described by Aynsley-Green *et al*.<sup>13</sup> Severe hypoglycaemia in both BWS and PHHI may require partial pancreatectomy to obtain blood glucose control<sup>10 13</sup>. Both the hyperinsulinaemic hypoglycaemia of BWS and PHHI tend to improve with time, allowing the withdrawal of medication, although some children require prolonged drug treatment.<sup>6-9 11 13 16</sup>

### **HISTOLOGY**

Understanding the pancreatic histology in BWS is limited to the severe cases in which the patient has died or had partial pancreatectomy.<sup>9 10 17</sup> The histological evidence is consistent with the diffuse picture described by de Lonlay-Debeney *et al*,<sup>23</sup> with islet and  $\beta$  cell hyperplasia and hypertrophy.<sup>9 10 18 19</sup> A reduction in somatostatin-producing cells has been noted.<sup>7</sup>

### **METABOLIC ABNORMALITIES**

$\beta$  cell dysregulation is the cause of hyperinsulinism in BWS, PHHI, and HHS.<sup>6 8-11 15 20</sup> There have been no reports of plasma ammonium concentrations in patients with BWS and hyperinsulinism. Normal concentrations would exclude HHS as a possible cause.<sup>21</sup>

### **CAUSES**

The cause of PHHI is becoming more defined, although in most cases the mechanism of the hyperinsulinism remains unclear.<sup>22</sup> With the information available on PHHI, it is possible to speculate on the cause of the hyperinsulinaemic hypoglycaemia in BWS. The diffuse form of PHHI can result from an abnormality of the sulphonylurea receptor type 1 (SUR1), the gene for which is located on chromosome 11p15.<sup>22 23</sup> The focal form of PHHI may result from an abnormality of the SUR1 gene in combination with a loss of the maternally imprinted tumour suppressor genes (H19 and p57<sup>KIP2</sup>), also located on chromosome 11p15.<sup>22 23</sup> Loss of these same tumour

suppressor genes may cause BWS.<sup>2</sup> It is not surprising therefore that BWS is associated with hyperinsulinaemic hypoglycaemia. Mild hyperinsulinaemic hypoglycaemia in BWS may result from hyperplasia of normally functioning  $\beta$  cells that are downregulated postnatally. The moderate forms of BWS hyperinsulinaemic hypoglycaemia, which respond well to treatment with diazoxide and octreotide, may be secondary to a more widespread loss of maternal tumour suppressor genes or greater up-regulation of paternal growth promoter genes—for example, insulin-like growth factor II—on chromosome 11p15. The response to diazoxide and octreotide suggests that SUR1, the site of action of these medications,<sup>13</sup> is functional. Infants resistant to medical treatment may have an SUR1 gene mutation and complete loss of the maternal tumour suppressor genes. The use of calcium channel blockers has been successful in controlling the hypoglycaemia of HHS.<sup>20</sup> Use of these agents has not been reported in the treatment of hypoglycaemia associated with BWS.

#### OUTCOME

Continuing  $\beta$  cell dysregulation has been found in BWS and PPHI.<sup>6 7 12 13 16 24</sup> The progression of PPHI to type 1 diabetes is well described.<sup>16 24</sup> No such progression has been documented for BWS, although Roe *et al*<sup>10</sup> found an abnormal oral glucose tolerance test in an infant with BWS and hyperinsulinaemic hypoglycaemia at 32 weeks of age after a partial pancreatectomy. Aynsley-Green *et al*,<sup>13</sup> in a review of PPHI, concluded that a diabetic glucose tolerance test and persistent inappropriate insulin secretion in the face of hypoglycaemia results from a reduction in the mass of abnormally functioning  $\beta$  cells secondary to apoptosis.

#### Conclusion

BWS is an uncommon cause of hyperinsulinaemic hypoglycaemia in the neonatal period.<sup>10</sup> The hypoglycaemia, although usually mild or asymptomatic, may be severe, requiring medical and occasionally surgical treatment.<sup>3 5-11</sup> Severe hypoglycaemia and persistent asymptomatic hypoglycaemia may result in an impaired neurological outcome.<sup>12</sup> In most patients with BWS, long term survival is normal,<sup>1</sup> making it paramount to ensure that cognitive function is not adversely affected by poorly controlled neonatal hypoglycaemia. The treatment of hyperinsulinaemic hypoglycaemia in BWS should therefore be prompt, with vigilant control of blood sugar levels. We recommend the hierarchical approach to management outlined recently by Aynsley-Green *et al*.<sup>13</sup> Thus adequate carbohydrate should be provided (oral and intravenous), followed by oral agents such

as diazoxide, chlorothiazide, and nifedipine. The use of parenteral agents such as glucagon and octreotide may be necessary if oral treatment fails. Finally pancreatic surgery may be required if maximum medical treatment fails to control the hypoglycaemia.

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