Syndrome of the month

Beckwith-Wiedemann syndrome

Margaret Elliott, Eamonn R Maher

In 1963 Beckwith1 presented the necropsy findings of three unrelated children with exomphalos, macroglossia, hyperplasia of the kidneys and pancreas, and adrenal cytomegaly, and suggested that this might represent a new syndrome. In 1964 Wiedemann2 published a case report of three sibs with exomphalos, macroglossia, and overgrowth. Subsequently more than 300 cases have been reported and the incidence of Beckwith–Wiedemann syndrome (BWS) has been estimated at 0·07 per 1000 births.3,4

Clinical features and natural history

The clinical features of BWS are listed in the table which is derived from the personal experience of one of the authors (ME) of 69 cases in the UK and 22 cases from the other large clinical study published.5 Anterior abdominal wall defects, macroglossia, pre- or postnatal overgrowth, and characteristic facial dysmorphism occur in most cases (figs 1–3). Other common features are neonatal hypoglycaemia, organomegaly, renal anomalies, and hemihypertrophy. Neoplasia, developmental delay, and cardiac malformations may cause significant morbidity but are infrequent. The overall mortality rate is about 10% with most deaths occurring early secondary to congenital malformations or prematurity. Histopathology characteristically shows diffuse adrenal cytomegaly, pancreatic β islet cell hyperplasia, and nephroblastomatosis.6 There are no fixed diagnostic criteria for BWS and no one feature is obligatory in making the diagnosis, but we have found the following definition covers most cases: either (1) three major features (anterior abdominal wall defect, macroglossia, pre- or postnatal overgrowth) or (2) two major features plus three minor features (ear creases or pits, fetal naevus flammaeus, hypoglycaemia, nephromegaly, hemihypertrophy). The craniofacial dysmorphic features are most apparent before the age of 3 years, and after the age of 5 years there is often only minor dysmorphism. It is helpful to consider the complications of BWS by the age at presentation.

Prenatal

Exomphalos complicates approximately half the cases of BWS and will usually be picked up on prenatal ultrasonography, but BWS is a rare cause of exomphalos (<3% of all cases).6 Prenatal diagnosis of BWS has occasionally been reported after ultrasonographic detection of a combination of abdominal wall defect, polyhydramnios, nephromegaly, and macroglossia.7 BWS pregnancies are frequently complicated by premature onset of labour. The risk of prematurity is associated with an increased incidence of polyhydramnios but not with fetal overgrowth alone. Multiple births are more common in BWS, with an excess of both monzygotic and dizygotic twins. Twin pairs are invariably discordant for BWS, though the second twin may occasionally show minor features. There is an excess of female monzygotic twins pairs among twin pairs with normal chromosomes (13 female, one male).8,9

Neonatal

Many BWS children will require surgery for exomphalos in the neonatal period and this is generally well tolerated. Hypoglycaemia also occurs in the majority of BWS patients, but this is usually mild and transient. In severe cases hypoglycaemia may persist for months, and early detection and treatment of hypoglycaemia is important to prevent neurological damage. Prematurity related pulmonary disease and congenital heart disease are the leading cause of early death in BWS, although congenital cardiac defects only occur in <10% of BWS patients.

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Clinical features of Beckwith–Wiedemann syndrome

<table>
<thead>
<tr>
<th>Compliations</th>
<th>Frequency (%)</th>
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<tbody>
<tr>
<td>Macroglossia</td>
<td>99</td>
</tr>
<tr>
<td>Pre- or postnatal gigantism (growth &gt; 90th centile)</td>
<td>87</td>
</tr>
<tr>
<td>Abdominal wall defect (exomphalos, umbilical hernia, or diastasis recti)</td>
<td>77</td>
</tr>
<tr>
<td>Ear creases or posterior helical ear pits</td>
<td>75</td>
</tr>
<tr>
<td>Renal abnormalities (nephromegaly, multiple calyceal cysts, or hydronephrosis)</td>
<td>62</td>
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<tr>
<td>Facial naevus flammaeus</td>
<td>62</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>59</td>
</tr>
<tr>
<td>Hemihypertrophy</td>
<td>23</td>
</tr>
<tr>
<td>Congenital cardiac malformations</td>
<td>9</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>4</td>
</tr>
<tr>
<td>Moderate/severe mental retardation</td>
<td>4</td>
</tr>
<tr>
<td>Polydactyly</td>
<td>3</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>3</td>
</tr>
</tbody>
</table>
Beckwith-Wiedemann syndrome

**Figure 1** An 8 month old boy with BWS. Macroglossia, maxillary hypoplasia, and facial hemihypertrophy are present.

**Figure 2** A 5 year old girl with BWS after tongue reduction. Mild prognathism is present but dysmorphic features are much less apparent.

**Figure 3** Ear lobe creases and ear pits in BWS: posterior helical pits and pits on the posterior aspect of the ear lobe can be seen.

**CHILDHOOD**

The most frequent problems during childhood are related to macroglossia, overgrowth, hemihypertrophy, urological anomalies, and concerns about the risks of embryonal tumours and psychomotor retardation.

Macroglossia is the most frequent manifestation of BWS, and may cause feeding difficulties, speech delay secondary to articulation problems, and obstructive apnoea (during sleep or feeding). Surgical tongue reduction is performed in up to 50% of cases (usually at 2
and urinary tumour, in galactogly, this has the prognosis. Tumours for sonography is frequently advocated."

"An experience reported in ADULTHOOD is that about 15% of BWS patients have a positive family history, and familial BWS is inherited as an autosomal dominant trait with incomplete penetrance. Parent of origin differences in penetrance are well described, such that penetrance is more complete if the mother is the transmitting parent. Genetic linkage studies have mapped the BWS gene to chromosome 11p15.5. The parent of origin effects in familial BWS and patients with chromosome 11 aberrations suggest that the BWS gene(s) is imprinted. Further evidence for genomic imprinting is the observation that about 20% of patients with sporadic BWS have uniparental isodisomy of chromosome 11p15.24 (unpublished observations). Detailed analysis has shown that (1) uniparental disomy in BWS patients arises as a postzygotic mitotic event so that affected persons are mosaic for normal and disomic cell lineages, and (2) the critical region of paternally disomic includes chromosome 11p15.5. There is a strong association between uniparental disomy and hemihypertrophy (and possibly Wilms' tumour) in BWS, and the hemihypertrophy presumably reflects the variation in the proportion of disomic cells between the two sides of the body. Although not proven, it is hypothesised that monozygotic twins discordant for BWS may reflect differing degrees of mosaicism for UPD. The excess of female monozygotic twins might result from the delayed development of female compared to male embryos.

**Genetics**

The genetics of BWS are complex and are the subject of much current interest. Imprinted genes in chromosome 11p15 have been implicated in the pathogenesis of familial and sporadic BWS. A small number of patients (2 to 3%) have cytogenetic abnormalities of chromosome 11p15. Paternally derived duplications of chromosome 11p15 and maternally inherited inversions or balanced translocations may be associated with BWS. Approximately 15% of BWS patients have a positive family history, and familial BWS is inherited as an autosomal dominant trait with incomplete penetrance. Parent of origin differences in penetrance are well described, such that penetrance is more complete if the mother is the transmitting parent. Genetic linkage studies have mapped the BWS gene to chromosome 11p15.5. The parent of origin effects in familial BWS and patients with chromosome 11 aberrations suggest that the BWS gene(s) is imprinted. Further evidence for genomic imprinting is the observation that about 20% of patients with sporadic BWS have uniparental isodisomy of chromosome 11p15.24 (unpublished observations). Detailed analysis has shown that (1) uniparental disomy in BWS patients arises as a postzygotic mitotic event so that affected persons are mosaic for normal and disomic cell lineages, and (2) the critical region of paternally disomic includes chromosome 11p15.5. There is a strong association between uniparental disomy and hemihypertrophy (and possibly Wilms' tumour) in BWS, and the hemihypertrophy presumably reflects the variation in the proportion of disomic cells between the two sides of the body. Although not proven, it is hypothesised that monozygotic twins discordant for BWS may reflect differing degrees of mosaicism for UPD. The excess of female monozygotic twins might result from the delayed development of female compared to male embryos.

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**Differential diagnosis**

BWS should be distinguished from Simpson-Golabi syndrome (SGS), Perlman syndrome, and overgrowth disorders such as Sotos and Weaver syndromes. The most common misdiagnosis is with SGS, an X linked recessive condition characterised by overgrowth, mild macroglossia, umbilical and inguinal herniae, cleft palate, cardiac malformations, an
Beckwith–Wiedemann syndrome

Aetiology
Candidate BWS genes from chromosome 11p15 should be imprinted. BWS could be explained by (1) an excess of an imprinted growth promoter expressed from the paternal allele, or (2) a deficiency of an imprinted growth suppressor expressed from the maternal allele.34 In BWS patients with duplications of chromosome 11p15 only the former mechanism would fit, while either or both mechanisms could be operative in disomic persons. Maternally inherited chromosome 11 inversions and balanced translocations would appear to involve a loss of function mutation in an imprinted growth suppressor which is expressed from the maternal allele, but could cause BWS by disrupting normal imprinting of a growth promoter so that there was now activation of the silenced maternal allele. Familial BWS could result from similar mechanisms. Comparative studies in man and mice have identified two genes (IGF2 and H19) within the target region (distal chromosome 7p in the mouse and chromosome 11p15 in man are homologous) which are imprinted in both species. Insulin-like growth factor 2 (IGF2) is an imprinted growth promoter which is expressed from the paternal allele.26-28 Mice with inactivating mutations of the paternal IGF2 allele are small,29 and chimeric mouse embryos with paternally disomic distal chromosome 7p are larger than controls.37 H19 is widely expressed during embryonal development, is closely linked to IGF2, but is oppositely imprinted to IGF2 (H19 is expressed from the maternal allele) in man and mouse.30-32 Determining the function of H19 has been enigmatic and the absence of a conserved open reading frame between mouse and man suggests that H19 may not encode a protein product.33 However, a recent study suggests that H19 expression can suppress growth in an embryonal tumour cell line and suppress tumour formation in nude mice.34 Both IGF2 and H19 have been suggested as candidate BWS genes. BWS patients with paternally derived chromosome 11 duplications and paternally UPD would be predicted to have increased expression of IGF2 (the minimally duplicated/disomic region includes IGF2), and recently Weksberg et al35 have reported four non-disomic BWS patients in which there was disruption of maternal repression of IGF2 resulting in biallelic IGF2 expression. These findings clearly implicate IGF2 overexpression in the pathogenesis of a subset of patients with BWS, but whether this results from mutations in the IGF2 gene or in an imprinting control gene is not known. Relaxation of IGF2 imprinting has been reported in sporadic Wilms tumour,36,37 and supports the concept that IGF2 overexpression would promote cellular growth and predispose to tumour development. Familial BWS could result from mutations which directly or indirectly disrupt normal imprinting of the IGF2 gene leading to expression of the maternal IGF2 allele. Such families would only be expected to show maternal transmission of the disease phenotype. An alternative explanation involves maternally inherited inactivating mutations of a paternally repressed growth suppressor gene such as H19. Molecular mapping of the balanced translocation and inversion breakpoints associated with maternally inherited BWS have identified two breakpoint cluster regions.38 The most telomeric is close to IGF2 and might disrupt normal IGF2 imprinting, while the other (at chromosome 11p15.4) might indicate the presence of a second BWS gene.39 Alternatively, it is conceivable that the translocation would have a long range effect on IGF2 imprinting.

A variety of genetic mechanisms may produce BWS. Overexpression of IGF2 appears to be the primary abnormality in some patients with BWS. However, the report of a patient with gigantism, Wilms' tumour, and biallelic expression of IGF2, but no other evidence of BWS suggests that other factors may be involved.39 Further research should elucidate whether IGF2 is the cause of BWS in all cases, and whether other genes, such as H19, are involved. Furthermore, such studies should identify the molecular mechanisms underlying the loss of repression of the maternal allele of IGF2 in BWS.

We thank Dr Anne Ferguson-Smith for helpful advice, and the many families and their doctors who have helped with our research.

1 Beckwith JB. Extreme cytoplasmic of the adrenal fetal cortex, omphalocele, hyperplasia of the kidneys and pancreas, and Leydig cell hyperplasia—another syndrome? Presented at the Annual Meeting of Western Society for Pediatric Research, Los Angeles, California, 11 November 1963.


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