Syndrome of the month

Beckwith-Wiedemann syndrome

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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 one 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.⁴

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, facial naevus flammeus, hypoglycaemia, nephromegaly, hemihypertrophy). The craniofacial dysmorphological

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 monozygotic 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 monozygotic 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

Complications	Frequency (%)
Macroglossia	99
Pre- or postnatal gigantism (growth > 90th centile)	87
Abdominal wall defect (exomphalos, umbilical hernia, or diastasis recti)	77
Ear creases or posterior helical ear pits	75
Renal abnormalities (nephromegaly, multiple calyceal cysts, or hydronephrosis)	62
Facial naevus flammeus	62
Hypoglycaemia	59
Hemihypertrophy	23
Congenital cardiac malformations	9
Neoplasia	4
Moderate/severe mental retardation	4
Polydactyly	3
Cleft palate	3

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

to 3 years of age, but earlier if there are significant feeding problems or apnoea). Untreated macroglossia that does not regress spontaneously may lead to prognathism, open anterior bite, and dental problems.

Growth patterns are very variable in BWS. Often rapid growth occurs in early childhood and bone age is advanced. Growth rate tends to slow down during late childhood and although detailed information on adult height is sparse, most reported cases are 2 to 3 SD above the mean.

Hemihypertrophy occurs in up to 25% of cases, is usually evident at birth, and often becomes more marked as the child grows. Mild asymmetry may require physiotherapy and conservative orthopaedic management (for example, shoe raises). In more severe cases, surgical intervention (to shorten the hypertrophied side or lengthen the non-hypertrophied side) may be performed at puberty.

Organomegaly is common with nephromegaly in 65%. In up to half of these cases there may be an associated renal malformation and approximately 25% of children have recurrent urinary tract infections. Inguinal herniae and undescended testes are common in males.

Neoplasia is generally estimated to occur in 7.5% of cases,¹⁰ although this may be an overestimate. The most common tumour is Wilms' tumour, followed by adrenocortical carcinoma, hepatoblastoma, and neuroblastoma. Screening for tumours by three monthly abdominal ultrasonography is frequently advocated.¹¹ However, this has not yet been proven to improve the prognosis. Although the requirement for regular ultrasonography has been questioned, it is generally agreed that weekly abdominal palpation by parents can be helpful in detecting Wilms' tumours. Tumours rarely develop after the age of 10 years, but the risk of neoplasia appears to be increased in children with hemihypertrophy.¹⁰

Most children with BWS develop normally, and the major risk factors for psychomotor retardation are an unbalanced translocation, ineffective treatment of hypoglycaemia, and severe prematurity related complications.

ADOLESCENCE AND ADULTHOOD

Less information is available, but it seems that new complications are infrequent after childhood. An increased incidence of infertility has been reported in males with BWS, in some cases possibly related to cryptorchidism.¹² Personal experience suggests an apparent excess of endocrinopathies, but further information is required.

Differential diagnosis

BWS should be distinguished from Simpson-Golabi syndrome (SGS), Perlman syndrome, and overgrowth disorders such as Sotos and Weaver syndromes.¹³ 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

increased risk of neoplasia, and a characteristic craniofacial dysmorphism.^{14,15} As the penetrance of familial BWS is more complete when the mother is the transmitting parent,^{12,16} the family history in BWS may occasionally resemble X linked inheritance. Features to consider in the differential diagnosis of BWS and SGS include the different facial dysmorphism, relative macrocephaly, and mild macroglossia in SGS, and the infrequency of exomphalos in SGS. Umbilical and inguinal herniae, and nephromegaly and renal malformations are common to both. Cardiac malformations, cleft palate, glandular hypospadias, polydactyly, and accessory nipples are seen occasionally in BWS, but are much more common in SGS. Perlman syndrome is a rare autosomal recessive disorder with a high neonatal mortality, characteristic facies, a high incidence of renal malformations and Wilms' tumour, hypoglycaemia, and mental retardation.¹⁷ Exomphalos and macroglossia are not reported, and although there may be macrosomia at birth, postnatal overgrowth does not occur.

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.¹⁸⁻²⁰ 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.^{12,16} Genetic linkage studies have mapped the BWS gene to chromosome 11p15.5.^{21,22} 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 unipaternal isodisomy of chromosome 11^{23,24} (unpublished observations). Detailed analysis has shown that (1) unipaternal 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 paternal isodisomy includes chromosome 11p15.5. There is a strong association between unipaternal 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.²⁵ 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.

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.²⁵ 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 paternal disomy of distal chromosome 7p are larger than controls.²⁷ 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 paternal UPD would be predicted to have increased expression of IGF2 (the minimally duplicated/disomic region includes IGF2), and recently Weksberg *et al*³⁵ 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 invokes maternally inherited inactivating muta-

tions 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. The proximal breakpoint cluster (at chromosome 11p15.4) might indicate the presence of a second BWS gene.³⁸ 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.

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