Beckwith-Wiedemann Syndrome

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Abstract
Beckwith-Wiedemann Syndrome (BWS; OMIM 130650) is an overgrowth disorder characterized by macrosomia, macroglossia, organomegaly and developmental abnormalities (in particular abdominal wall defects with exomphalos). Its incidence is estimated to be 1 per 13,700 live births. BWS patients are prone to the development of embryonal tumors (most commonly Wilms' tumor or nephroblastoma). BWS is a multigenetic disorder caused by dysregulation of gene expression in the imprinted 11p15 chromosomal region. Various 11p15 defects have been implicated and epigenetic defects account for about two thirds of cases. The management of patients with BWS involves the surgical cure of exomphalos and monitoring of hypoglycemia in the neonatal period. It also involves the treatment of macroglossia and the screening for embryonal tumor that can be facilitated by genotyping. A recent series of reports suggested that assisted reproductive technology (ART) may increase the risk of imprinting disorders, and BWS in particular.

Keywords
Overgrowth syndrome, Beckwith-Wiedemann syndrome, 11p15 region, *IGF2* gene, *H19* gene, *KCNQ1OT1* gene, *CDKN1C* gene, embryonal tumor, imprinting, methylation, epigenetic change, assisted reproductive technology

Disease name and synonyms

Beckwith-Wiedemann syndrome (BWS)
Exomphalos-Macroglossia-Gigantism syndrome (EMG syndrome)

Definition

BWS is an overgrowth disorder involving developmental abnormalities. This multigenic disorder is caused by dysregulation of the expression of imprinted genes in the 11p15 chromosomal region.

Diagnosis criteria

(for references see: Wiedemann HR, 1964; Pettenati MJ *et al.*, 1986; Elliott M *et al.*, 1994; DeBaun MR *et al.*, 1998)

The phenotypic expression of BWS is variable and diagnosis is still based on clinical signs. Recent improvements in the molecular diagnosis of BWS and other overgrowth disorders suggest that in the next few years, BWS will be defined molecularly.

It is generally accepted that diagnosis of BWS requires at least 3 clinical findings including at least 2 major findings:

Major clinical findings

- Macroglossia (present in more than 95% of patients).
- Macrosomia or overgrowth, defined as pre- and-/-or postnatal growth greater than the 97th percentile (present in about 80% of patients). The trend to increased size continues through early childhood but becomes less dramatic with increasing age.
- Abdominal wall defects (exomphalos, umbilical hernia, diastasis recti; 65% of patients).
- Organomegaly involving principally abdominal organs: kidneys, liver, spleen, pancreas and adrenal glands (present in 50% of patients).

Minor clinical findings

- Hypoglycemia in the neonatal period (occurs in about 40% of patients), mostly mild and transient.
- Renal abnormalities: malformations, medullary dysplasia.
- Ear creases and pits (30% of patients).
- Facial nevus flammeus (30% of patients).
- Hemihyperplasia (30-35% of patients).
- Embryonal tumors: about 7.5% of BWS patients develop tumors (Wilms' tumor, neuroblastoma, adrenal carcinoma, hepatoblastoma, rhabdomyosarcoma), most commonly in the first 6 years of life.
- Polyhydramnios.

Differential diagnosis

Clinically, BWS must be distinguished from other overgrowth syndromes:

- Simpson-Golabi-Behmel syndrome (OMIM 312870) is an X-linked disease caused by mutations in the gene encoding glypican-3, an extracellular proteoglycan known to play an important role in growth control in embryonal mesoderm tissues, in which it is selectively expressed. This proteoglycan binds IGF2, reducing its availability to the type 1 IGF-receptor (Pilia G *et al.*, 1996; Neri G *et al.*, 1998).
- Perlman syndrome (OMIM 267000), which is often more severe, has a high perinatal mortality rate. Its pathogenesis is still unknown (Grundy RG *et al.*, 1992; Henneveld HT *et al.*, 1999).
- Sotos syndrome (OMIM 117550) is caused by mutations in the gene encoding NSD1 and should be considered for differential diagnosis because of the clinical overlap with BWS (Baujat G *et al.*, 2004).

BWS must also be recognized in its incomplete forms (Sotelo-Avila C *et al.*, 1980) and in related forms, such as non-syndromic IGF2 overgrowth disorder (Morison IM *et al.*, 1996). Some cases of isolated hemihyperplasia are also related to abnormalities in the 11p15 region and are associated with a risk of tumor (Hoyme HE *et al.*, 1998).

Prevalence

The incidence of BWS (1 per 13,700 livebirths) has been reported in only one study (Thorburn MJ *et al.*, 1970) and is probably underestimated.

Etiology

BWS is caused by imprinting errors in the 11p15 chromosomal region (Maher ER *et al.*, 2000; Reik W *et al.*, 2001) This region includes genes encoding growth factors and tumor suppressor genes. The paternally expressed genes (maternally imprinted) have growth enhancing activity and the maternally expressed genes (paternally imprinted) have growth suppressing activity. The 11p15 region is organized into two domains: a telomeric domain including the *IGF2* and *H19* genes and a centromeric domain including the *CDKN1C* (Cyclin Dependant Kinase Inhibitor 1C), *KCNQ1* (Potassium voltage-gated channel, subfamily Q, member 1) and *KCNQ1OT1* (KCNQ1-Overlapping transcript 1) genes. Each domain is controlled by its own imprinting center (IC1 and IC2 for the telomeric and the centromeric domains, respectively) (Reik W *et al.*, 2001).

BWS is a multigenic disorder involving various molecular abnormalities in the 11p15 region (Engel JR *et al.*, 2000; Bliek J *et al.*, 2001; Gaston V *et al.*, 2001; Weksberg R *et al.*, 2001; DeBaun MR *et al.*, 2002).

- Cytogenetic abnormalities account for 1-2% of cases and consist of maternally inherited translocations or inversions and trisomy with paternal duplication.
- The genetic abnormalities described in BWS are:

- 11p15 paternal uniparental disomy (UPD) of both the centromeric and telomeric domains. In paternal UPD, the maternal allele is lost and the paternal allele is duplicated. This occurs in approximately 20% of cases.
- Mutations in the *CDKN1C* gene (also known as *p57KIP2*) encoding a maternally expressed cell-cycle regulator, found in about 5% of patients (Lam WW *et al.*, 1999). Patients with *CDKN1C* gene mutations have a typical BWS phenotype, with a very high frequency of exomphalos.

Mutations in the *CDKN1C* gene are much more frequent in familial BWS and about 60% of familial BWS cases are caused by mutation of the *CDKN1C* gene.

- The epigenetic abnormalities described in BWS are:

- Hypermethylation of the *H19* gene, a maternally expressed untranslated RNA with tumor suppressor function, found in 10% of cases.
- Demethylation of *KvDMR1*, a differentially methylated region at the 5' end of the *KCNQ1OT1* gene, involved in 55-60% of patients. The *KCNQ1OT1* gene (also known as *LIT1* or *KvLQT1-AS*) encodes an antisense transcript within intron 10 of the *KCNQ1* gene and is normally expressed from the paternal allele (Lee MP *et al.*, 1999; Smilinich NJ *et al.*, 1999). This gene may be involved in regulating imprinting of the centromeric domain (Cleary MA *et al.*, 2001; Fitzpatrick GV *et al.*, 2002).
- It was recently shown that microdeletions within *IC1* (*H19 DMR*) (Sparago A *et al.*, 2004) or *IC2* (Niemitz EL *et al.*, 2004) account for a low percentage of BWS cases with hypermethylation of *H19* or demethylation of *KCNQ1OT1*. However, the exact frequency of these microdeletions is still unknown.

Genotype/phenotype correlations

The clinical expression of BWS may differ between patients with similar molecular abnormalities, due to the mosaicism distribution for most known molecular defects. This is well-illustrated for 11p15 UPD (Itoh N *et al.*, 2000).

Other genotype/phenotype correlations have also been observed, providing evidence that aspects of the BWS phenotype may be correlated with the involvement of specific imprinted genes (Engel JR *et al.*, 2000; Gaston V *et al.*, 2001; DeBaun MR *et al.*, 2002). Indeed, exomphalos is more frequent in patients with a defect of the centromeric domain (demethylation of *KCNQ1OT1* and mutation of *CDKN1C*). Hemihyperplasia and organomegaly are more frequent in patients with hypermethylation of *H19* or 11p15 UPD.

About 7.5 to 10% of BWS patients will develop a tumor. Wilms' tumor is the most common tumor found in patients with BWS (60% of all tumors), but other solid childhood tumors also are found. Previous studies (Engel JR *et al.*, 2000; Bliek J *et al.*, 2001; Gaston V *et al.*, 2001; Weksberg R *et al.*, 2001; DeBaun MR *et al.*, 2002) have clearly shown that 11p15 UPD and *H19* hypermethylation are strongly associated with tumor risk in BWS patients. Wilms' tumor is only found in BWS patients with molecular lesions in the telomeric domain and is the only type of tumor found in patients with *H19* hypermethylation (Bliek J *et al.*, 2004). Patients with molecular lesions in the centromeric domain (demethylation of *KCNQ1OT1* or mutation of *CDKN1C*) have a low risk of tumor and these patients develop a different spectrum of tumors, including hepatoblastoma, rhabdomyosarcoma and gonadoblastoma (Weksberg R *et al.*, 2001, Bliek J *et al.*, 2004). The only tumor reported in patients with mutation of *CDKN1C* is neuroblastoma (Lee MP *et al.*, 1997; Gaston V *et al.*, 2001).

Diagnostic methods

Careful cytogenetic analysis of the 11p15 region and fluorescent *in situ* hybridization (FISH) can be used to recognize the rare translocations, inversions and trisomies.

Molecular diagnosis is difficult, mostly because of the large spectrum of genetic and epigenetic abnormalities. Molecular tests must differentiate the various abnormalities in the 11p15 region: patients with 11p15 paternal UPD, patients with hypermethylation of the *H19* gene, patients with demethylation of the *KCNQ1OT1* gene and patients with a mutation in the *CDKN1C* gene.

As demethylation of the *KCNQ1OT1* gene is never associated with abnormal methylation of the *H19* gene except in patients with 11p15 paternal UPD, analysis of the methylation status of both the *KCNQ1OT1* and *H19* genes leads to the diagnosis of more than 90% of 11p15 defects:

- Isolated demethylation of the *KCNQ1OT1* gene.
- Isolated hypermethylation of the *H19* gene.

It is not yet possible to determine precisely the percentage of cases with epigenetic defects displaying a microdeletion of *IC1* or *IC2*.

Hypermethylation of the *H19* gene associated with demethylation of the *KCNQ1OT1* gene is indicative of 11p15 paternal UPD, which should be confirmed by analysis of markers of the 11p15 region and of parental DNA. 11p15 paternal UPD always occurs as mosaicism and, because tissue distribution of mosaicism is variable, tissue from a second source (such as fibroblasts) may be helpful.

If the methylation status of the *KCNQ1OT1* and *H19* genes is normal, then sequencing of the *CDKN1C* gene is indicated, particularly in patients with exomphalos and/or a family history of BWS.

Management of BWS patients

Neonates with exomphalos should undergo abdominal wall repair soon after birth.

Hypoglycemia during the first few days of life can be anticipated by monitoring glycemia in newborns with BWS every six hours for the first few days. Serious neurological sequelae can therefore be prevented.

Macroglossia should be treated by a maxofacial surgical team.
Assessing tumor risk is the main difficulty in patients with BWS. Between 7.5% and 10% of all BWS patients will develop a tumor, mostly during the first 6 years of life. The severity of the phenotype, hemihyperplasia and organomegaly (of the kidneys in particular) have been shown to be associated with an increase in the relative risk of cancer (Schneid S *et al.*, 1997; Beckwith JB, 1998; DeBaun MR *et al.*, 1998; Gaston V *et al.*, 2001) but none of these clinical features can identify with certainty patients likely to develop tumors. Based on molecular analysis, it is now possible to discriminate between BWS patients with high and low tumor risks. It is also possible to predict whether patients are at risk of developing Wilms' tumor. Different screening protocols could therefore be offered to BWS patients, based on molecular diagnosis. In BWS patients with a telomeric defect (30% of cases), tumor management should involve abdominal ultrasound scans every 3 months, with clinical examination at alternate consultations, during the first 6 years of life. In BWS patients with a centromeric defect (70% of cases), tumor management should involve monthly clinical examinations during the first year, with a reference abdominal ultrasound scan at 3 months, followed by a clinical examination every 3 months for 6 years.
Plasma alpha-fetoprotein (AFP) levels have been put forward as a possible marker for routine tumor screening in children with BWS. AFP levels should be interpreted with a normal curve established specifically for BWS as AFP concentration is higher in patients with BWS than in healthy infants and children (Everman DB *et al.*, 2000; Clericuzio CL *et al.*, 2003).

Genetic counseling
Most of BWS are sporadic (85%) but about 15% BWS cases correspond to familial forms. The risk of recurrence in a family depends on the genetic cause of BWS in the proband.
Cytogenetic abnormality:
The risk to siblings of patients with BWS is up to 50% in case of a maternal 11p15 translocation or inversion. This risk is not clearly defined in BWS patients with an 11p15 duplication inherited from a father carrying a balanced translocation involving chromosome 11p15.
CDKN1C mutation:
The risk to siblings of patients with BWS is up to 50% if the mother has the mutated *CDKN1C* gene. The children of a woman with a *CDKN1C* mutation have a 50% risk. The children of a man with a *CDKN1C* mutation have a theoretical risk of 0%, but with 50% of them will carry the mutation and the disease may be transmitted by girls to the next generation.
11p15 UPD:
The risk of recurrence is very low in cases of paternal UPD, as UPD results from a post-zygotic event.
Epigenetic abnormalities:
Although rare, there are familial forms of BWS involving demethylation of *KCNQ1OT1*, which are maternally transmitted. A microdeletion of the *KCNQ1OT1* gene has been identified in one of these familial forms (Niemitz EL *et al.*, 2004). A few patients with hypermethylation of *H19* have also been shown to display a maternally-inherited microdeletion within *IC1* (Sparago A *et al.*, 2004). The recurrence risk for siblings and offspring of BWS patients with demethylation of *KCNQ1OT1* or hypermethylation of *H19* is probably low. However, the frequency of microdeletions of imprinting centers is unknown and it is therefore difficult to generate an accurate figure for risk estimation.

Antenatal diagnosis
Prenatal diagnosis by ultrasound scan can be used to assess fetal growth and to detect abdominal wall defects, thereby helping to prevent neonatal complications.
Cytogenetic testing is appropriate for the diagnosis of translocation, inversion or duplication. Molecular diagnosis is also possible for 11p15 paternal UPD or *CDKN1C* gene mutation.
The reliability of testing for epigenetic modifications is unknown.

Beckwith-Wiedemann syndrome and assisted reproductive technology
Syndromes involving epigenetic alterations have recently been reported to occur in animals and humans conceived by ART. These include large offspring syndrome (LOS) in ruminants (Young L *et al.*, 2001), BWS (DeBaun M *et al.*, 2003; Gicquel C *et al.*, 2003; Maher ER *et al.*, 2003; Halliday J *et al.*, 2004) and Angelman syndrome (Cox GF *et al.*, 2002; Orstavik K *et al.*, 2002) in humans. Various genetic and epigenetic mechanisms are involved in BWS and Angelman syndrome, but, following ART, the molecular defect in these imprinting disorders, always involves a loss of methylation of a maternally-imprinted methylated gene (demethylation of *KvDMR1*/*KCNQ1OT1* in BWS) suggesting that ART impairs the acquisition or maintenance of methylation marks on maternal imprinted genes. No specific procedure has yet been implicated in the epigenetic risk of ART-conceived patients. Indeed, ART-conceived Angelman syndrome and BWS patients were conceived by various procedures including classical IVF, ICSI, embryo cryopreservation, early or late embryo transfer, the use of various culture media (Cox GF *et al.*, 2002; Orstavik K *et al.*, 2002; DeBaun M *et al.*,

2003; Gicquel C *et al.*, 2003; Maher ER *et al.*, 2003; Halliday J *et al.*, 2004; Chang AS *et al.*, 2005). Large-scale and long-term outcome studies in children born as a result of ART should make it possible to estimate the exact risk of imprinting disorders after ART and to identify the underlying cause of this association.

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