The Clinical Course of an Overgrowth Syndrome, From Diagnosis in Infancy Through Adulthood: The Case of Beckwith–Wiedemann Syndrome

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Beckwith–Wiedemann syndrome (BWS) is the most common genetic overgrowth syndrome, and it is frequently clinically recognizable because of characteristic features. These features include macrosomia, hemihypertrophy, macroglossia, facial nevus flammeus, earlobe creases and pits, omphalocele, and organomegaly. The most common molecular cause is hypomethylation of the maternal imprinting control region 2 (ICR2) in 11p15. Other molecular causes include hypermethylation of the maternal ICR1 in 11p15, mutations in CDKN1C, mosaic uniparental disomy 11p15, and chromosomal abnormalities involving 11p15. Some of these abnormalities are testable, and DNA methylation tests of 11p15 confirm about 60% of cases with BWS. The main management issues in pediatrics are hypoglycemia at birth, macroglossia, and surveillance for embryonal tumors, especially Wilms and hepatoblastoma.

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Introduction

Among the genetic overgrowth syndromes, Beckwith–Wiedemann syndrome (BWS) is the most common, 1:13,700 births.[1,2] Babies with BWS are large at birth, and either symmetric or asymmetric overgrowth continues throughout childhood. Characteristic features include eye proptosis with periorbital fullness, mid-glabellar capillary malformation (nevus flammeus), earlobe creases and pits, large mouth with large tongue (macroglossia), organomegaly, and omphalocele. Frequently, macroglossia is the sign that prompts the diagnosis in the nursery. Main pediatric management issues are hypoglycemia/hypocalcemia at birth and the risk for embryonal tumors (primarily Wilms tumor, hepatoblastoma, neuroblastoma, and rhabdomyosarcoma). The hypoglycemia can be persistent in infancy and sometimes hard to treat. The risk for tumors is about 7.5% till 8 years of age and then gradually declines close to general population risk.[2,3] This risk is addressed with tumor surveillance by abdominal ultrasound and peripheral blood alpha-fetoprotein levels every 3 months till 8 years of age. Most children have normal mental capabilities; the risk for developmental delays is slightly above the general population risk. The overgrowth is a feature of childhood with normal or slightly above normal adult height and weight. The diagnosis is clinical in many children with BWS since the common genetic tests have about 60% sensitivity and extensive genetic testing can reach about 80%.[2–4]

Clinical Diagnosis

Beckwith and Wiedemann in 1969[5] described a syndrome with three cardinal features: exomphalos (omphalocele), macroglossia, and gigantism (EMG). The syndrome was renamed Beckwith–Wiedemann syndrome (BWS) and the associated phenotype expanded. BWS is quite variable and EMG is seen in some but not all of the children who have the BWS diagnosis. Clinical criteria have not been established. BWS experts including Dr. J Bruce Beckwith and Dr. Rossana Wecksberg published criteria in GeneReviews in 2010.[3] Three major or one major and two minor criteria are diagnostic (Table).

Differential diagnosis includes many overgrowth syndromes discussed by Yachelevich,[6] as well as diabetic embryopathy. Boys with the rare X-linked recessive Simpson–Golabi–Behmel syndrome can present similarly to BWS and only molecular testing can provide the diagnosis.[7]

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TABLE. Major and Minor Findings Associated With Beckwith–Weidemann Syndrome (BWS)

Three major findings or one major and two minor findings are required to make the clinical diagnosis
Caution: A child with isolated macroglossia or macrosomia or hemihypertrophy can be mosaic for a BWS related molecular abnormality and at risk for tumor similar to children with BWS diagnosis.
Major findings
Positive family history (one or more family members with a clinical diagnosis of BWS or a history or features suggestive of BWS)
Macrosomia (traditionally defined as height and weight >97th centile)
Anterior linear earlobe creases/posterior helical ear pits
Macroglossia
Omphalocele (also called exomphalos)/umbilical hernia
Visceromegaly involving one or more intra-abdominal organs including liver, spleen, kidneys, adrenal glands, and pancreas
Embryonal tumor (e.g., Wilms tumor, hepatoblastoma, neuroblastoma, and rhabdomyosarcoma) in childhood
Hemihyperplasia (asymmetric overgrowth of one or more regions of the body)
Cytomegaly of the fetal adrenal cortex ascertained by pathology (It is pathognomonic and hence quite helpful in pathological analysis of abortuses[16])
Renal abnormalities including structural abnormalities, nephromegaly, nephrocalcinosis, later development of medullary sponge kidney
Cleft palate (rare in BWS)
Placental mesenchymal dysplasia[10]
Cardiomegaly
Cardiomyopathy (rare in BWS)
Minor findings
Pregnancy-related findings including polyhydramnios and prematurity
Neonatal hypoglycemia
Facial nevus flammeus, other vascular malformations
Characteristic facies, including midface hypoplasia, and infraorbital creases
Structural cardiac anomalies
Diastasis recti
Advanced bone age (common in overgrowth/endocrine disorders)

Molecular Abnormalities Associated With BWS and Genetic Testing

BWS is due to genetic or epigenetic abnormalities (epimutations) involving 11p15.[8] The segment 11p15 is imprinted, which means that different genes are expressed or silenced in the maternal segment than those in the homologous paternal segment. 'Maternal' and 'paternal' refer to the parental origin of the chromosome and not to patterns that exist in the chromosomes of the parents, i.e., the paternal chromosome of the mother loses paternal imprinting and becomes maternal in her offspring. Imprinted segments of the genome like 11p15 include imprinting control regions (ICR) that are chromosomal regions that regulate the expression or silencing of imprinted genes. There are two ICRs in 11p15; ICR1 and ICR2. Epigenetic abnormalities in ICR1 and ICR2 account for most of the known causes of BWS. Epigenetic abnormalities are DNA modifications, usually methylation or histone modification, which do not change the DNA sequence but can change gene expression. The epigenetic abnormality in 11p15 involves loss or gain of DNA methylation that causes aberrant silencing or activation of gene expression without a change in the DNA sequence. Loss of methylation in the maternal ICR2 is the most common molecular cause of BWS.[8–10]

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ICR2 loss of methylation (hypomethylation) on the maternal chromosome, found in 50% of persons with BWS, leads to reduced expression of *CDKN1C*.[2,10] The *CDKN1C* gene is translated to the cyclin-dependent kinase (CDK)-inhibitor 1C (CDKN1C) protein that negatively regulates cell proliferation.[8] Conceivably, reduced expression of *CDKN1C* upregulates cell proliferation underlying overgrowth in BWS.[8,9] Loss-of-function mutations in *CDKN1C* are seen in 50% of familial BWS (about 15% of all cases are familial[2,3]) and about 5% of the sporadic BWS.[8] Interestingly, gain-of-function mutations in *CDKN1C* also have clinical significance, as they are seen in the short-stature