# Beckwith-Wiedemann Syndrome





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## Continuing Education Activity

Beckwith-Wiedemann Syndrome is the most common overgrowth syndrome. It is a genetic imprinting disorder, and it can present as a wide and varied clinical spectrum with a predisposition to developing tumors during early childhood. Thus, early recognition of the condition in the prenatal or neonatal period is critical for monitoring and timely treatment of complications. This activity reviews the evaluation and management of Beckwith-Wiedemann syndrome and highlights the role of the interprofessional team in improving care for patients with this condition.

**Objectives:**

- Identify the etiology of Beckwith-Wiedemann syndrome.
- Review the evaluation of a patient with Beckwith-Wiedemann syndrome.
- Summarize the management considerations for patients with Beckwith-Wiedemann syndrome

## Introduction

Beckwith-Wiedemann Syndrome (BWS) is the most common overgrowth syndrome. The condition was named after American pediatric pathologist John Bruce Beckwith in 1963, and German pediatrician Hans-Rudolf Wiedemann in 1964, reported the syndrome independently.[1] Etiologically, BWS is a human imprinting disorder caused by genetic and epigenetic changes affecting the regulation of genes on chromosome 11p15 region. It presents with a wide and varied clinical spectrum, which can make the diagnosis challenging in some cases. Among the clinical signs, macrosomia, macroglossia, and abdominal wall defects stand out as the most common features. BWS is also a cancer predisposition syndrome. Thus, early recognition of the condition in the prenatal or neonatal period is critical for monitoring and timely treatment of complications.[2][3]

## Etiology

The etiology of Beckwith-Wiedemann Syndrome is complex. About 80-90% of patients have a known molecular aberration that affects the regulation of a group of imprinted genes implicated in cell cycle progression and somatic growth control located in the chromosome 11p15.5. Genomic imprinting is an epigenetic-regulated process by which only one copy of a gene is expressed depending on the sex of the parent carrying the allele. Two imprinting control regions (IC1 and IC2) regulate the gene expression from the 11p15 region. Normally, methylation (silencing of gene expression) occurs in the paternal allele at IC1 and the maternal allele at IC2. In an individual with BWS, the molecular defects more commonly described are:[2][3][4]

- Loss of methylation at IC2 on the maternal allele in 50 to 60% of cases
- Paternal uniparental isodisomy of 11p15 in 20 to 25% of cases
- The gain of methylation at IC1 on the maternal allele in 5 to 10% of cases
- Autosomal dominant maternal point mutations in CDKN1C (regulated by IC2) in 5% of sporadic cases and 40% of familial cases
- Chromosomal rearrangements (duplications, translocations, deletions or inversions) in less than 1% of cases
- The unknown molecular defect in 10 to 15% of cases

## Epidemiology

The incidence of BWS is estimated in 1:10,000 to 13,700 live births, a number that is likely underestimated due to subtle phenotypes. It affects all ethnic groups with a 1:1 sex ratio. There is a known positive correlation with assisted reproductive techniques with a 10-fold increase risk of BWS.[2][5][6]

## History and Physical

BWS is a complex multisystem disorder that presents in a wide and varied clinical spectrum. For a better understanding of the historical features and physical findings likely to encounter in BWS patients, this section is divided according to the presentation of the syndrome in the different stages of life.

- **Prenatal stage:** common complications in pregnancies with BWS fetuses usually start after the 22 weeks of gestation with gestational hypertension, pre-eclampsia, gestational diabetes mellitus, vaginal bleeding, polyhydramnios, macrosomic fetus, increased alpha-fetoprotein, and ultrasonographic findings of organomegaly. During birth, patients may present with macrosomia-related complications (e.g., cephalohematoma, brachial plexus injury), premature birth, and placentomegaly. A positive family history of BWS is another important consideration since approximately 15% of cases could be attributed to familial transmission, although it is important to point out that most cases are sporadic.[2][5]
- **Neonatal period:** neonates with BWS may present with macrosomia, whole body hemihypertrophy, limb length discrepancy, distinctive facial appearance, abdominal wall defects (omphalocele, umbilical hernia, or diastasis recti), organomegaly (could involve liver, kidneys, spleen, pancreas, thymus, heart, and adrenal glands), nephrological abnormalities (kidney malformations +/- hydronephrosis), cardiac anomalies (patent ductus arteriosus, patent foramen ovale, and congenital long QT syndrome), and hypotonia. Typical dysmorphic facies in BWS include prominent eyes, infraorbital creases, midfacial hypoplasia, macroglossia (most common feature), prognathism, anterior earlobe creases, posterior helical pits, and nevus flammeus at the glabella. Other physical findings are cleft palate, supernumerary nipples, polydactyly, and genital abnormalities (cryptorchidism). Neonatal BWS is also characterized by hypoglycemia, most likely secondary to islet cell hyperplasia and hyperinsulinism.[2][5][7]
- **Infancy, childhood, and Adolescence:** typical features of BWS facies are usually lost in later childhood. Regarding growth parameters, height and weight usually remain around the 90th percentile while head circumference remains around the 50th percentile. Development is, most of the time, not affected unless specific 11p15.5 duplication or perinatal complications were present. Nephrocalcinosis, nephrolithiasis, renal cysts, and recurrent urinary tract infections are common nephrological complications that could develop during infancy to adolescence. Predisposition to embryonal tumors development is one of the most fear characteristics of BWS, for which long-term monitoring is warranted. The most common malignancies reported are Wilms tumor and hepatoblastoma, while others include neuroblastoma, adrenocortical carcinoma, and rhabdomyosarcoma.[2][5][7]
- **Adulthood:** Most of the features derived from their pediatric phenotype. Adult height usually ends in the normal range, although some studies report an increased mean adult height in the BWS population. Limb length discrepancy can persist or even worsen, leading to scoliosis. Fertility issues have been reported in males as a primary testicular dysfunction or consequence of cryptorchidism; insufficient data is available for females.[5][8]

## Evaluation

The diagnosis of BWS is established based on clinical criteria and may be confirmed by molecular/cytogenetic testing. However, given the heterogeneous presentation of this disorder, no consensus exists, and most experts agree that these criteria should not replace clinical judgment on a case-by-case basis. In the same line, negative diagnostic testing cannot rule out BWS.

### Clinical Diagnosis

There are several published diagnosis criteria for BWS.[9][10][11][12][13][14] Recent reviews consider it acceptable to guide the clinical diagnosis based on the presence of major and minor findings of BWS. The presence of at least three major findings, or two major and one or more minor findings would support the diagnosis of BWS.[2][5][7]

### Major Findings

- Abdominal wall defect: omphalocele or umbilical hernia
- Macroglossia
- Neonatal macrosomia (birth weight more than 90 percentile)
- Postnatal overgrowth (height/length more than 90 percentile)

- Embryonal tumors (Wilms tumor, hepatoblastoma, adrenal tumors, neuroblastoma)
- Outer ear malformations (anterior ear creases, posterior helical pits)
- Visceromegaly
- Cytomegaly of the adrenal fetal cortex
- Hemihypertrophy
- Anomalies of the kidney and ureter (e.g., medullary dysplasia, nephrocalcinosis, medullary sponge kidney, and nephromegaly)
- Positive family history of BWS
- Cleft palate

### Minor Findings

- Polyhydramnios
- Enlarged placenta, placental mesenchymal dysplasia
- Thickened umbilical cord
- Prematurity
- Neonatal hypoglycemia
- Nevus flammeus at the glabella
- Distinctive facies
- Cardiomegaly, cardiac anomalies, hypertrophic cardiomyopathy
- Diastasis recti
- Polydactyly
- Supernumerary nipples
- Advanced bone age

Novel diagnostic criteria consider the predictive value of each BWS feature. Brioude *et al.* (2018) proposed a clinical scoring system based on cardinal features (macroglossia, omphalocele, lateralized overgrowth, bilateral Wilms tumor, hyperinsulinism, adrenal cytomegaly or placental mesenchymal dysplasia) and suggestive features (birth weight greater than two standard deviations above the mean, facial nevus simplex, polyhydramnios or placentomegaly, ear creases or pits, transient hypoglycemia, embryonal tumors, nephromegaly or hepatomegaly, and umbilical hernia or diastasis recti). The scoring consist of adding 2 points for each cardinal feature present, and 1 point for each suggestive feature. A total score of 4 or more would confirm a diagnosis of BWS even without the need for testing. A score of 2 or 3 would warrant genetic testing. Finally, a score of less than two would not meet the criteria for testing.[3][15]

### Molecular Diagnosis

As previously stated, given the wide variety of molecular aberrations that are behind the etiology of BWS, as well as the mosaicism affecting different tissues in the same individual, the molecular diagnosis of this condition requires a multistep approach, and a negative test cannot exclude the diagnosis. Testing is usually performed on DNA derived from blood-leukocytes; however, samples from buccal swabs, skin fibroblasts, or mesenchymal-derived cells from surgical resections and/or excisions of hyperplastic tissues, could be used to improve the detection. Different testing approaches have been recommended. The most widely used tests are the following:[3][7]

- Methylation analysis: consider first-line testing since methylation alteration could be detected in most cases of BWS with known molecular etiology. Further studies such as copy number variant (CNV) testing might be needed to determine the exact molecular mechanism.
- Sequencing analysis, or gene-targeted sequencing: test to be considered if methylation analysis is negative. Useful in the detection of pathogenic variants of genes in the 11p.15 region, specially CDKN1C mutations.
- Chromosomal microarray, SNP array, or microsatellite analysis: could detect microdeletions, microduplications, or length of paternal uniparental disomy region of chromosome 11.
- Karyotype or FISH: could detect chromosomal defects associated with BWS such as duplication, inversion, or translocation of 11p15.5.

### Prenatal Diagnosis

If there is a positive family history of BWS or the presence of prenatal features, genetic counseling is warranted, and testing could be offered. Methylation analysis and CDKN1C sequencing are the preferred diagnostic tests in these situations. Regardless of any positive or negative result, postnatal testing is needed for confirmation.[2][7]

## Treatment / Management

The management of patients with BWS entails a qualified lead health-care provider to oversee the coordination for the care of the patient, following a holistic approach. Once a diagnosis of BWS is made or even suspected, anticipatory medical management is required, as well as a comprehensive plan that includes standard supportive medical and surgical care, as necessary. Given the high heterogenicity and the variable degree of the features when present, treatment indications should be customized for each specific patient.[3][5][7][15]

- **Prenatal management**: in suspected or confirmed cases, it is important to anticipate possible fetal or maternal complications (maternal pre-eclampsia, congenital anomalies, macrosomia-related complications, postnatal hypoglycemia), and provide adequate care. Delivery should be planned to occur in an institution with a neonatal intensive care unit.

- **Management of hypoglycemia**: glucose monitoring should be performed for the first 48 hours of life. If hypoglycemia is detected, the newborn should be transferred to a neonatal intensive care unit for management as per general guidelines. If no hypoglycemia is detected, fasting tests, including glucose, insulin, and ketones, are recommended at 48 hours of life and prior to nursery discharge. Severe persistent hyperinsulinism warrants further investigation.
- **Management of growth anomalies**: growth should be routinely monitored using growth charts specifically modified for BWS patients. Interventions for possible tall stature could be considered. Lateralized overgrowth should be monitored clinically, at least once a year. If a leg-length discrepancy is encountered, referral to a pediatric orthopedic surgeon is warranted; on the contrary, an arm-length discrepancy is generally monitored clinically with no indication for surgical correction.
- **Management of macroglossia**: feeding problems require the involvement of feeding specialists and dietitians. For suspected airway obstruction, careful evaluation, including sleep studies and consultations to pulmonologist and ear, nose, and throat specialists, are needed. Tongue-reduction surgery is indicated if there are macroglossia-related complications such as feeding difficulties, persistent drooling, speech difficulties, dental malocclusion, and appearance-related psychosocial problems, usually performed after the age of 1 year, or earlier in cases of severe airway obstruction.
- **Management of abdominal wall defects**: there are no additional specific recommendations than the general guidelines for these conditions.
- **Management of cardiac anomalies**: a baseline clinical cardiovascular examination is necessary at diagnosis. If anomalies are detected or suspected, referral to a cardiologist specialist for assessment and echocardiography is required. Annual evaluation and electrocardiogram are recommended for patients with a known molecular aberration involving the IC2 region.
- **Management of renal complications**: clinical and ultrasonographic evaluation for nephrological anomalies is needed at diagnosis and at the time of adult transition. If anomalies are detected, referral to a nephrologist and urologist is necessary. Nephrocalcinosis and renal stones should also be monitored along with abdominal surveillance for tumor screening.[12][13]
- **Management and monitoring of embryonal tumors**: BWS is a recognized cancer predisposition syndrome, with an estimated tumor risk of 8 to 10% in the first decade of life, with the highest incidence during the first 2 years of life. Different tumor screening protocols have been proposed with common goals of early detection, reducing morbidity, and increasing survival. The protocol of tumor surveillance used in the USA includes the performance of abdominal ultrasound and serum alpha-fetoprotein (AFP) at diagnosis, then every 3 months until age 4 years. Thereafter, only ultrasound screening should be continued every 3 to 4 months until the age of 7 years. Abdominal ultrasound screening covers the most common associated tumors, including Wilms tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma, and adrenal carcinoma. AFP is specifically used for monitoring hepatoblastoma; however, it has been involved in recent controversies due to the presence of higher levels of this marker in BWS infants which obscure its interpretation, and the implications of repeated venipuncture. Even though certain molecular defects have more predisposition to certain types of cancer, it is recommended to apply the protocol to all BWS patients regardless of the molecular subtype.[14]
- **Management of neurological features**: cognitive development is usually normal, but monitoring by a pediatrician is recommended, especially if perinatal complications (prematurity, birth trauma, neonatal hypoglycemia) or chromosomal anomalies are present.
- **Monitoring of late-onset complications**: a comprehensive evaluation at age 16 to 18 years is recommended to detect any complication that would require follow-up by adult health-care services. Genetic counseling should be offered for family-planning advice.
- **Psychological and counseling aspects**: at the time of diagnosis, families should be offered contact information of BWS support groups. Psychological evaluation and support, specialist counseling, and family support services should be included as part of the plan of care. [16][17]

## Differential Diagnosis

BWS is one of the multiple overgrowth syndromes along with isolated hemihyperplasia (IH), Sotos, Simpson-Golabi-Behmel, Costello, Perlman, Weaver, NF1-microdeletion, and Proteus syndromes, among others. The diagnosis is usually achieved with a comprehensive clinical assessment, including family history detailed documentation of physical findings, and confirmation with genetic/molecular analysis if needed. A particular consideration in the differential diagnosis of BWS should be isolated hemihyperplasia since they could share similar epigenetic alterations in 11p15, but this condition should not be reclassified as BWS solely on this finding.

Many other genetic syndromes and endocrine diseases may also share features with BWS, including mosaicism for trisomy 8, congenital hypothyroidism, mucopolysaccharidosis (Hurler, Hunter, and Maroteaux–Lamy syndromes), gangliosidosis, and Pompe disease which should be included in the differential diagnosis.

In the neonatal period, the finding of macrosomia, macroglossia, and hypoglycemia, should prompt a comprehensive evaluation, including maternal diabetes mellitus.

In children considered to have BWS and developmental delay with no chromosomal abnormalities, and no history of prematurity, birth trauma, or neonatal hypoglycemia, other causes of developmental delay need to be considered.[2][5][18]

## Prognosis

The prognosis varies depending on the severity of the clinical presentation, the molecular subtype, and the timely diagnosis of the condition. In general, most patients with BWS would have a normal life expectancy. Adults with BWS would present features related to their pediatric phenotype, with a good prognosis provided an early recognition of the disease, proper anticipatory guidance, and management of complications if they were to develop.[2][8]

## Complications

The following are some of the complications seen in patients with BWS:[2][5][7]

- Perinatal complications: gestational hypertension, pre-eclampsia, gestational diabetes mellitus, vaginal bleeding, polyhydramnios, prematurity, and macrosomia-related complications (cephalohematoma, brachial plexus injury, or other birth trauma).
- Neonatal complications: increased risk for mortality mainly as a result of complications of prematurity, macroglossia (breathing and feeding difficulties), hypoglycemia, and, rarely, cardiomyopathy.[8]
- Other complications: speech issues related to macroglossia, cognitive impairment related to specific chromosomal anomalies and/or perinatal complications, high risk to develop embryonal tumors (especially Wilms tumor and hepatoblastoma), nephrocalcinosis, nephrolithiasis, renal cysts, recurrent urinary tract infections, scoliosis related to the leg-length discrepancy, fertility issues from cryptorchidism, and psychosocial issues related to the fear for the condition and complications.[8][5]

## Deterrence and Patient Education

Patients and their families should be offered counseling, education, support, and guidance since the moment of diagnosis. As part of the holistic approach to the management of patients diagnosed with BWS, providers must facilitate contact information for BWS support groups and resources, including the entries on Beckwith-Wiedemann syndrome at the National Organization for Rare Disorders (NORD), the Beckwith-Wiedemann Children's Foundation International (BWCFI), among others.

## Pearls and Other Issues

Beckwith-Weidemann syndrome (BWS) is a heterogeneous syndrome that could affect one or multiple systems. Classic features may or may not be obvious at birth. The etiology of BWS is complex. Most cases are sporadic molecular alterations of genes in the chromosome 11p15 region. The index of suspicion should be high when evaluating a case of BWS, with strong consideration of the use of genetic/molecular testing to confirm the diagnosis. Anticipatory guidance of the complications is fundamental in the care for these patients, with special consideration of a tumor protocol surveillance given the high risk of developing embryonal tumors during infancy and childhood. Early diagnosis and a holistic management approach with a multidisciplinary team are also indispensable to ensure a good prognosis for the patient.

## Enhancing Healthcare Team Outcomes

In the management of BWS patients, it is fundamental to include different specialists to provide the best possible care. In order to coordinate this, an experienced lead health-care provider should work closely with the patients and their families to ensure the continuous monitoring and follow-up needed in this specific population. Specific treatment indications, including supportive medical and surgical care, should be personalized for each specific case depending on the clinical presentation and molecular subtype if known. Periodic evaluations and proper transition to adult health-care services are also tasks that the primary care provider should arrange.[15]

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