Beckwith-Wiedemann Syndrome in a Three-Month-Old Child

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Abstract

Beckwith-Wiedemann syndrome (BWS) is the most common pediatric overgrowth syndrome. The reported prevalence ranges from 1/10,000 to 1/13,700.

Most cases of BWS are sporadic with a recurrence risk of less than 1% in the family, but depending on the genetic mutation, the recurrence risk may be as high as 50%.

Patients with BWS have an increased risk of neonatal hypoglycemia and the development of embryonal tumors during childhood.

We present the case of a 3-month-old child who presented to the general pediatrics department with macroglossia and hemifacial hypertrophy. Molecular genetics revealed an abnormal methylation pattern at 11p15.5 region confirming the diagnosis of BWS.

Introduction

Beckwith-Wiedemann syndrome (BWS) is a complex medical condition characterized by a range of distinct clinical features. It is a genetic disorder marked by excessive tissue growth, predisposition to tumors, and congenital malformations.

The syndrome was first identified in 1963 by the American pathologist John Bruce Beckwith, who presented three postmortem cases exhibiting a range of anomalies including macroglossia, omphalocele, fetal corticoadrenal cytomegaly, renal medullary dysplasia, and visceromegaly. Concurrently, in 1964, the German geneticist Hans-Rudolf Wiedemann reported three siblings with similar clinical features, along with diaphragmatic anomalies and hypoglycemia (1).

This syndrome presents with typical manifestations, including neonatal hypoglycemia (present in 50% of cases), macroglossia, birth macrosomia, omphalocele, and anterior abdominal wall anomalies. Table 1 provides a summary of the frequency of major and minor manifestations observed in BWS (2) (5).

Table 1: Frequency of manifestations observed in Beckwith-Wiedemann Syndrome.

Clinical signs	Frequency
Macroglossia	90 %
Macrosomia	45 – 65 %
Ears anomalies (anterior earlobe creases or posterior helical ear pits)	63 %
Prenatal polyhydramnios	53 %
Facial nevus	52 %
Kidney anomalies	52 %
Neonatal hypoglycemia	30 – 60 %
Omphalocele	44 %
Visceromegaly	44 %
Umbilical hernia or diastasis recti	22 – 44 %
Hemihyperplasia	37 – 65 %
Embryonal tumor	8 %
Cardiac anomalies	13 %
Clef palate	3 %

The prevalence of this syndrome is low, estimated to be between 1/10,000 and 1/13,700 births. However, it is one of the most frequently encountered congenital overgrowth syndromes (3).

The overall prevalence is likely to be underestimated given the existence of undiagnosed individuals with milder phenotypes.

The majority of BWS cases are sporadic, with a recurrence risk of less than 1% within the family. However, depending on the genetic alteration (such as copy number variation at 11p15.5 or a *CDKN1C* pathogenic variant), the recurrence risk may be as high as 50% (4).

A greater prevalence of BWS has been observed in the population of children born through assisted reproductive technology (ART).It affects both boys and girls (5).

This genetic syndrome originates from an alteration in the expression of genes in the 11p15.5 region. This region encompasses two imprinting control regions: imprinting center 1 (IC1) and imprinting center 2 (IC2). Methylation occurs in the paternal allele of IC1 and in the maternal allele of IC2. Alterations in parental imprinting result in BWS (4). The clinical diagnosis is based on the association of at least 3 major criteria or 2 major criteria and 3 minor criteria (Table 2) (5).

Molecular analysis allows confirmation of the diagnosis (4).

Figure 1. Typical macroglossia of our patient with BWS

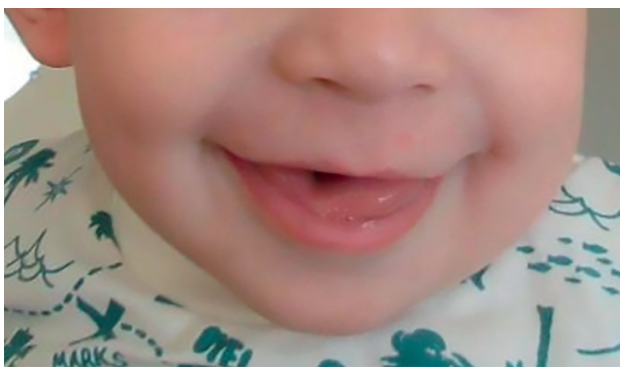

Table 2: Major and Minor Criteria Associated with Beckwith-Wiedemann Syndrome

Clinical signs	Minor Criteria
Major Criteria	
Abdominal wall defect : omphalocele or umbilical hernia	
Macroglossia	Pregnancy-related anomalies : polyhydramnios, hypertrophic placenta and/or thickened umbilical cord, threatened preterm labor
Macrosomia (birth weight greater than 90th percentile)	Neonatal hypoglycemia
Anterior lobe ear creases and/or posterior helical pits (bilateral or unilateral)	Port-wine stain
Visceromegaly of one or more intra-abdominal organs (liver, kidneys, spleen, pancreas, and adrenal glands)	Cardiac anomalies : cardiomegaly, cardiomyopathy
Embryonal tumor in childhood	Diastasis recti
Hemihyperplasia	Advanced bone age
Fetal adrenal cortex cytomegaly, typically diffuse and bilateral (pathognomonic)	
Renal anomalies (medullary nephrosclerosis)	
Family history of Beckwith-Wiedemann Syndrome	
Cleft palate	

Case report

A male infant was referred to the general pediatrics department at the age of three months due to macroglossia. (Figure 1). The infant was born at 31 weeks and 6 days of gestation, via vaginal delivery, following spontaneous rupture of the amniotic membrane, resulting in premature labor.

It was a dichorionic diamniotic twin pregnancy, resulting from in vitro fertilization with sperm donation. The patient is the second twin. Macrosomia had already been suspected antenatally, with no other ultrasound abnormalities observed.

The mother had pre-existing type 2 diabetes treated with insulin. At 27 weeks and 2 days gestation, she experienced threatened preterm labor, for which complete pulmonary maturation was performed.

At birth, the patient had a weight of 2360 grams (95th percentile), while his twin brother had a weight of 1820 grams. The patient was placed on non-invasive ventilation with continuous positive airway pressure for a period of two weeks due to the presence of hyaline membrane disease. His blood glucose levels remained within the normal range. However, he experienced feeding difficulties due to a large and asymmetrical tongue. Additionally a patent foramen ovale was identified, without hemodynamic repercussion. Hemihypertrophy gradually became apparent.

He was hospitalized at 3 months of age for a cyanotic spell in the setting of gastroesophageal reflux confirmed by pH-impedance monitoring. There have been no subsequent recurrences of spells.

The patient has a normal neurological development.

Tongue ultrasound and ophthalmologic examination were unremarkable. Abdominal ultrasound showed hepatomegaly without other organomegaly. Cardiac ultrasound revealed a structurally and functionally normal heart. Electrocardiogram was unremarkable. Laboratory tests (complete blood count, renal function, liver enzymes, coagulation, and thyroid function) were normal. Alpha-fetoprotein was 28.7 µg/L at the time of diagnosis confirmation when the patient was 10 months old.

Genetic testing included molecular karyotyping, which returned normal. Hypomethylation of IC2 at 11p15.5 confirmed the diagnosis of BWS.

The patient is currently 20 months old and has no major developmental abnormalities.

He experienced feeding difficulties related to macroglossia, which are now resolved. He has a growth delay with a weight below the 5th percentile. Alpha-fetoprotein was normalized (6.8 µg/L) at the last check-up (18 months old). Hepatomegaly remains stable on multiple ultrasound examinations. Macroglossia did not require surgical intervention.

Follow-up for this patient includes a multidisciplinary approach to monitor and manage potential complications associated with Beckwith-Wiedemann syndrome. Regular abdominal ultrasounds will continue every 3 months until 8 years of age to screen for abdominal tumors, particularly Wilms tumor and hepatoblastoma. Alpha-fetoprotein levels will be measured periodically until 4 years of age for early detection of hepatoblastoma. In addition, the patient will undergo regular assessments by a pediatric endocrinologist to monitor growth and metabolic parameters, and an orthopedic specialist will evaluate any progression of hemihypertrophy. Given the history of feeding difficulties, ongoing nutritional assessments and consultations with a dietitian are also planned. The patient's development will be closely monitored by a pediatric neurologist to ensure early intervention in the event of delays or abnormalities.

The patient's initial referral to the pediatrician was made by a stomatologist, who had identified and managed the macroglossia. A stomatologist will continue to play a crucial role in the follow-up care, with regular evaluations to monitor and address any dental or maxillofacial anomalies that may arise. This includes surveillance of the development of the teeth and jaw structure, as well as any necessary interventions to manage or correct abnormalities.

Discussion

Although rare, BWS remains the most common etiology of overgrowth with a prevalence of 1/10,000 to 1/13,700 births. This prevalence is increased in the population of children conceived through ART (6).

The severity of this condition correlates with the risk of hypoglycemia and the development of embryonal tumors (5 to 10% of cases), for which genotyping assists in screening (7).

In our case, there were no reported antecedents of BWS.

Epigenetic mechanisms play a key role in the regulation of gene expression. Genomic imprinting refers to the molecular processes that modulate gene expression depending on the parental origin of the gene. Several genes involved in embryonic and fetal growth are subject to genomic imprinting (8).

In the majority of cases, BWS results from epigenetic alterations that disrupt the parental imprinting of genes located at 11p15.5. These alterations are diverse, and some have been identified to be linked with different tumor risks (9).In our case, genetic analysis reveals hypomethylation of IC2 and a normal methylation of IC1 at the 11p15.5 locus.

The prevalence of BWS is increased in the population of ART children, as the methodologies used could have an influence on epigenetics (6). Prenatal genetic diagnosis is rarely performed because the majority of BWS cases occur sporadically. However, it can be beneficial in cases of

familial BWS with a known genetic alteration or when BWS is strongly suspected based on antenatal ultrasound findings (omphalocele, macrosomia, organomegaly, enlarged placenta, and polyhydramnios).

The challenge in establishing the diagnosis lies in the existence of milder forms, which may lead to delays due to certain clinical signs lacking pathognomonic features (8).

Patients with BWS have an increased risk of developing certain embryonal tumors, with Wilms tumor, neuroblastoma and hepatoblastoma being the most common (2). Precise identification of the genetic alteration can point towards certain tumors, mainly in case of paternal unidisomy 11p15.5 or hypermethylation of the imprinting center (4).

Surveillance is performed by abdominal ultrasounds. Other, less common tumors include rhabdomyosarcoma, and corticoadrenal carcinoma. The risk of these tumors is greatest in the first 8 years of life. Alpha-fetoprotein levels can be measured periodically up to 4 years of age for early detection of hepatoblastoma (4).

Multidisciplinary follow-up is recommended for patients with BWS.

When considering a diagnosis of Beckwith-Wiedemann syndrome, it is important to differentiate it from other overgrowth syndromes that may present with overlapping features. Differential diagnoses include Sotos syndrome, which is characterized by a distinctive facial appearance, advanced bone age, and learning disabilities; Simpson-Golabi-Behmel syndrome, which presents with congenital malformations and an increased risk of tumors; and Perlman syndrome, a rare condition associated with nephroblastomatosis and a high neonatal mortality rate. Other considerations might include mosaic overgrowth syndromes such as Klippel-Trénaunay syndrome, which involves vascular malformations and limb asymmetry, and Proteus syndrome, known for asymmetric overgrowth and skin abnormalities (5). Accurate genetic and clinical assessment is essential to differentiate BWS from these conditions, as management and surveillance strategies may differ significantly.

Conclusion

The diagnosis of BWS is challenging because of the existence of milder forms and because some clinical signs are not pathognomonic of the disease. However, it is essential to consider the condition because of its association with increased tumor risk. It requires an approach integrating clinical, genetic, and radiologic aspects. Close coordination between pediatricians, stomatologists, geneticists, radiologists, and other specialists is essential for optimal screening and management of patients with this syndrome.

Patient consent

Oral consent was obtained from the patient's parents for anonymized patient information to be published in this article.

Conflict of interest

The authors report no conflict of interest and no financial disclosures.

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