Beckwith-Wiedemann syndrome. Clinical and etiopathogenic aspects of a model genomic imprinting entity

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ABSTRACT

The Beckwith-Wiedemann syndrome is the most common genetic entity in overgrowth, with an approximate incidence of 1 in 10 000-13 700 births. Its broad clinical spectrum includes pre- and postnatal macrosomia, macroglossia, pinna abnormalities, abdominal wall defects, visceromegaly, and hyperinsulinemic hypoglycemia. This syndrome predisposes to childhood cancer and is caused by diverse genetic and/or epigenetic disorders that usually affect the regulation of genes imprinted on chromosome 11p15.5. The knowledge of (epi) genotype-phenotype correlations has prompted recommendations to propose different health care strategies, including tumor surveillance protocols based on molecular classification, aimed at standardizing clinical practice. The objective of this article is to describe the current status of the Beckwith-Wiedemann syndrome, a model of genomic imprinting.

Key words: *Beckwith-Wiedemann syndrome, neoplasias, genetic predisposition to disease, genomic imprinting, genotype-phenotype correlations.*

http://dx.doi.org/10.5546/aap.2018.eng.368

To cite: Cammarata-Scalisi F, Avendaño A, Stock F, et al. Beckwith-Wiedemann syndrome. Clinical and etiopathogenic aspects of a model genomic imprinting entity. *Arch Argent Pediatr* 2018;116(5):368-373.

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Funding:
None.

Conflict of interest:
None.

Received: 10-18-2017
Accepted: 3-8-2018

INTRODUCTION

The Beckwith-Wiedemann syndrome (BWS, OMIM #130650) is the most common genetic entity in overgrowth.[1-9] It was first described by Beckwith in 1963 and Wiedemann in 1964.[5] It is a panethnic syndrome with a 1:1,[2] sex ratio and an approximate incidence of 1 in 10 000-13 700 births.[1,2,8] Such incidence may be underestimated in mild phenotypes and most likely increases due to a positive correlation with assisted reproductive techniques.[8]

CLINICAL FEATURES AND FOLLOW-UP

The clinical spectrum is wide and varied and includes a history of polihydramnios[7] and prenatal macrosomia.[2-7] At a later stage, it is characterized by postnatal overgrowth,[5] hypotonia,[7] hemangiomas, nevus flammeus of the forehead,[1,4,5,8-11] infraorbital fold,[11] midfacial hypoplasia,[8,11] macroglossia,[1-11] cleft palate,[4,8,9,11] ptyalism, prognathism,[8,11] pinna abnormalities (ear lobe creases and posterior helical ear pits, *Figure 1*),[1,4,8,11] dyspnea,[8] heart anomalies[4] (cardiomegaly and, rarely, long QT syndrome),[8] supernumerary nipples,[11] abdominal wall defects (omphalocele, umbilical hernia,[1-9] and diastasis recti),[8,10] visceromegaly[3,5,8,10,12] (liver, pancreas, spleen or kidneys),[3,12,13] medullary sponge kidney,[12] malformations of the kidney and ureter,[3,4,5] whole-body hemihypertrophy,[1-3,5,6,9,10,13] which is commonly evident at birth,[8] polydactyly,[4,11] and hyperinsulinemic hypoglycemia,[8,10] among other phenotypic features,[3,6,9] although psychomotor development is usually normal.[11]

The diagnosis is based on clinical signs, and the presence of three major signs or two major and one minor sign may guide clinical diagnosis (*Table 1*).[1,4,10,11]

In the presence of macrosomia, there may be a greater risk for trauma among newborn infants, such as cephalohematoma, brachial plexus injury, respiratory distress syndrome, and even death. Such potential complications increase the probability

of choosing to perform a cesarean section, and an association has been established with preterm birth.[11]

On its side, macroglossia is the most common feature. It may be observed in up to 97% of patients (*Table 1*). It is the most easily identifiable feature of BWS[11] and a risk factor for obstructive sleep apnea. Surgical reduction management has been successful in macroglossia, although it is necessary to better understand which individuals may benefit from this procedure[14] and its impact on breathing,[15] language, and swallowing.[14,15] It also involves other aesthetic aspects, such as open mouth posture, increased interdental space, and prognathism, which may have negative consequences in relation to body image and an altered psychological well-being.[15] Infrequently, conductive hearing loss may occur, which should be managed to avoid learning disorders.[8]

In the case of hypoglycemia, hyperinsulinemia and nesidioblastosis should be ruled out, so an assessment by the Pediatric Endocrinology Service and an early drug treatment should be considered,[16] in order to reduce seizures that may lead to developmental delay.[17]

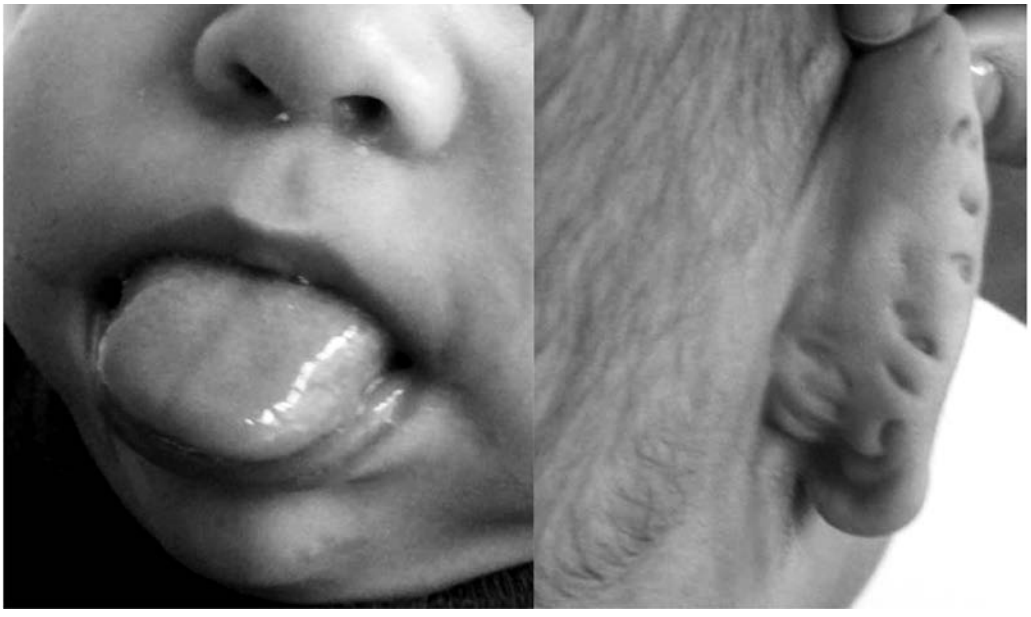
BWS predisposes to childhood cancer, compared to the general population,[1-3,5,7,9,10] with an estimated risk for malignancy of 4-21% (~7.5%).[2,4,8] The risk is higher at birth and reaches the general population's baseline before

TABLE 1. *Diagnostic criteria of Beckwith-Wiedemann syndrome*[1,4,10,11]

Findings	Frequency (%)
Major	
Abdominal wall defect	80
Macroglossia	97
Macrosomia	84
Embryonal tumors	~7.5
Outer ear malformations	63
Visceromegaly	41.4
Hemihypertrophy	63.8
Anomalies of the kidney and ureter	28-61
Positive family history of BWS	-
Cleft palate	5.5
Minor	
Prematurity	50
Neonatal hypoglycemia	> 50
Nevus flammeus of the forehead	54
Distinctive facies	-
Placentomegaly	50
Polihydramnios	50
Cardiomegaly, hypertrophic cardiomyopathy	20
Diastasis recti	27.6
Polydactyly	-
Supernumerary nipples	-
Advanced bone age	-

BWS: Beckwith-Wiedemann syndrome.

FIGURE 1. *Macroglossia and pinna abnormalities (posterior helical ear pits)*



puberty.[1] Tumors mainly include embryonal histiotypes, such as Wilms tumor[1,2,4,6,8,13] and hepatoblastoma, among the most common ones,[1,4] in addition to neuroblastoma,[4,8] adrenocortical carcinoma,[4,18] pheochromocytomas,[19] and rhabdomyosarcomas.[6,8] However, the risk for tumors is significantly different from the abnormal expression of a group of genes imprinted on chromosome 11p15.[5,3,4]

The early recognition during the prenatal or neonatal period is critical because it facilitates medical-surgical interventions that may cover any observed complication, while starting long-term monitoring for the neoplasias mentioned above, which allows to educate parents on the different treatments available.

PRENATAL DIAGNOSIS

Prenatal assessment is recommended when there is a positive family history or certain BWS clinical features are diagnosed. It is confirmed by the presence of two major features (macroglossia, macrosomia, abdominal wall defects, such as omphalocele, placentomegaly) or one major and two minor features (polihydramnios, nephromegaly, adrenal dysplasia or cytomegaly). These may be explored by ultrasound around 18-20 weeks of gestation and then confirmed at 25-32 weeks of gestation.[8] For this reason, it is necessary to consider performing a morphogenetic assessment of the fetus using ultrasound to establish the status of its abdominal and craniofacial regions, including the measurement of solid organs. In addition, high serum alpha-fetoprotein levels are associated with the presence of omphalocele.[16]

Chorionic villus sampling in the first trimester or an amniocentesis in the second trimester may help to determine the different molecular alterations that will become exposed subsequently. During gestation, there may be a higher risk for hypertension and proteinuria (suggestive of preeclampsia), and gestational diabetes mellitus.[8]

RISK FACTORS

The frequency of monozygotic twins among patients with BWS is higher than in the general population (2.5% compared to 0.3-0.4%)[8,9] and it is more common in the monochorionic diamniotic type.[9] It predominates among female individuals[8] and twins, where one has the BWS phenotype and the other one has a normal or partial phenotype.[9]

Since the first BWS case conceived using assisted reproductive techniques in 1995,[10] it has been associated with a higher risk when using these tools and the presence of genomic imprinting defects.[7] The incidence of BWS in the population conceived using these techniques is approximately 1 in 4000 births.[1] During early embryonic development, the epigenetic mechanism may alter methylation patterns, after the blastocyst implantation until the end of the embryo development, when deoxyribonucleic acid (DNA) methylation marks are added in regulation-susceptible regions. Without distinction, patients with fertility problems, either treated or not, have a higher frequency of imprinting disorders; for this reason, it has been suggested that these techniques are a risk factor.[7]

DIFFERENTIAL DIAGNOSES

There are other overgrowth entities, including the Sotos, Simpson-Golabi-Behmel, Costello,[8,20,21] and Perlman syndromes,[20,21] which may hinder the possibility of establishing the difference in the prenatal period. Other endocrine diseases, such as congenital hypothyroidism, metabolic alterations with facial dysmorphism, such as mucopolysaccharidosis (Hurler, Hunter, and Maroteaux–Lamy syndromes), besides gangliosidosis and Pompe disease, should be ruled out.[1]

ETIOPATHOGENESIS

BWS is caused by a variety of genetic and/or epigenetic alterations that usually affect the regulation of genes imprinted on chromosome 11p15.5[2,6] which may result in an heterogeneous clinical spectrum. Therefore, it is a paradigm of congenital abnormalities associated with genomic imprinting,[1,5] a process that consists in a specific gene expression of parental origin. Up to 90% of cases are caused by an alteration in the expression of genes involved in cell cycle progression and somatic growth control, regulated by two independent imprinting centers (IC1 and IC2),[1,6,7,22] which cover approximately 1 Mb.[7]

Across the entire genome, there are approximately 120 imprinted genes associated with 44 imprinting centers. In addition to BWS, other disorders have been well characterized, such as the Prader-Willi, Angelman, Temple, Kagami-Ogata, and Silver-Russell syndromes, together with transient neonatal diabetes mellitus and pseudohypoparathyroidism.[7]

Imprinting refers to the preferential or

exclusive expression of the paternal or maternal allele of an imprinted gene. The imprinting gene expression is regulated by epigenetic mechanisms. The most common one is DNA methylation in the imprinting centers rich in CpG islands, which make up an important percentage of gene promoters.[2] IC1 and IC2 are characterized by different methylation patterns of the maternal and paternal alleles,[1] and, in normal conditions, IC1 of the paternal allele and IC2 of the maternal allele are methylated.[5]

The main cause is the loss of methylation in IC2 –in 50-60% of cases (*Table 2*)–, which is located centromeric to IC1.[1,2,4,5,9,10,22] It results in a reduced expression of the cyclin dependent kinase inhibitor 1C (*CDKN1C*) gene,[1,22] which works as a tumor suppressor gene and a negative regulator of fetal growth,[2] normally expressed by the maternal chromosome.[1,22] Individuals who carry this genetic alteration tend to develop macroglossia,[14] hepatoblastoma, neuroblastoma, and adrenal tumors.[12]

In addition, maternal point mutations in the *CDKN1C* gene account for 5-10% of cases[1,4-6,9,10] and are responsible for 5% of sporadic cases[1,4] and half of the cases with a positive family history,[1,6,7] preferably maternal and with an autosomal dominant inheritance pattern.[21] For this reason, most BWS cases are rare.[10,21] Polydactyly, supernumerary nipples, and cleft palate are most commonly observed in this type of gene alteration.[11]

Omphalocele occurs more frequently in patients with hypomethylation of IC2[2,6] or point mutations in the *CDKN1C* gene.[2,6,13] However, the risk for tumors is significantly lower in these two situations,[2,6] and multiple studies have concluded that the loss of methylation of IC2 does not imply a higher risk and, therefore, does not require screening for Wilms tumor.[2]

In addition, 5-10% of cases are caused by hypermethylation of IC1,[1,4,5,10,17] which results in the regulation of the biallelic expression of the insulin-like growth factor 2 (IGF2), normally expressed in the paternal allele, and the non-coding ribonucleic acid (RNA) of the oncosuppressor *H19* gene, normally expressed in the maternal allele.[1,2,4,22] The presence of macrosomia,[4] omphalocele,[13] and a higher risk for Wilms tumor is more commonly associated with this type of epigenetic alteration.[4,13]

The alteration in IC1 and IC2 methylation is explained by mosaic paternal uniparental disomy, which occurs in 20-25% of cases[1,2,5,6,9,10] and is

TABLE 2. *Etiopathogenic factors in Beckwith-Wiedemann syndrome, frequency and associated findings*[1,2,4-7,9-13,17,31,32]

Mechanism	Frequency (%)	Related clinical findings
Hypomethylation of IC2	50-60	Macroglossia Omphalocele Hepatoblastoma Neuroblastoma Adrenal tumors Does not require screening for Wilms tumor
Mosaic paternal uniparental disomy	20-25	Hemihypertrophy Higher risk for tumor development: Wilms tumor Hepatoblastoma
Mutations in the *CDKN1C* gene*	5-10	Cleft palate Supernumerary nipples Omphalocele Polydactyly Lower risk for tumor
Hypermethylation of IC1	5-10	Macrosomia Omphalocele Increased risk for Wilms tumor
Chromosomal rearrangement	< 1	
Undetectable	10-15	

* Autosomal dominant.
IC1: independent imprinting center 1.
IC2: independent imprinting center 2.

associated with additional phenotypic features,[1] such as hemihypertrophy[4,13] and a higher risk for tumor development, especially Wilms tumor[2,6,12] and hepatoblastoma.[13,23]

In general, less than 1% of cases are caused by chromosomal rearrangements, such as duplications, translocations, inversions, deletions, which encompass IC group genes,[1,5,22] and approximately 10-15% of clinically diagnosed individuals do not have a detectable molecular defect, even if they have an evident phenotype.[1,2,5,6]

TUMOR SURVEILLANCE PROTOCOLS

Although all these mechanisms play a role in the pathogenesis of BWS that remains unknown,[6] the knowledge of (epi)genotype-phenotype correlations has prompted recommendations to propose different health care strategies, including tumor surveillance protocols based on molecular classification, aimed at standardizing clinical practice.[5,11]

In view of the genetic findings described above, an abdominal ultrasound should be done (every 3-4 months during childhood to rule out Wilms tumor[6,23] and neuroblastoma). Other studies that may be part of this screening include an annual chest X-ray and an abdominal computed tomography in the case of nephromegaly or any suspected observation.[16] Besides, serum alpha-fetoprotein levels (every 2-3 months in the first 4 years) should be measured to screen for hepatoblastoma.[6,16,23] Likewise, chorionic gonadotropin and catecholamine values should be determined to detect germ cell tumors and neuroblastoma, respectively. A urinalysis should also be done annually as part of the assessment. An early detection may warrant an adequate management of high-risk malignancies.[16] Screening for tumors should be encouraged, especially for those with paternal uniparental disomy.[23]

GENETIC COUNSELING

As discussed here, most cases of BWS are rare; therefore, the studied case is, in general, the only one affected in the family group. Except when a point mutation in the *CDKN1C* gene is observed, which shows an autosomal dominant inheritance pattern; those with this genetic alteration have a 50% risk for recurrence. The prognosis varies depending on the clinical presentation of this disease, which may be different even among family cases.

For this reason, follow-up and management of these patients should be done in an early and individual manner so as to minimize the complications that may arise and provide available treatment.

The objective of this article is to describe the current status of BWS, learn how to make a diagnosis based on clinical features, and rule out differential diagnoses. The etiopathogenic causes vary; it is necessary to understand them to guide interdisciplinary medical surveillance protocols, which should be customized to each patient and include timely family genetic counseling.■

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