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Case Report

Ultrasound and molecular prenatal diagnosis of Beckwith-Wiedemann syndrome: Two case reports ☆,☆☆

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ABSTRACT

Beckwith-Wiedemann syndrome (BWS) is a rare genetic disease, characterized by macrosomia, congenital malformations and tumor predisposition, associated with genetic and epigenetic alterations in the 11p15 region. Most cases are diagnosed after birth, with prenatal diagnosis being difficult and depending on the identification of specific ultrasound anomalies, namely macrosomia, macroglossia, omphalocele and renal dysplasia. Case 1: Ultrasound diagnosis at 13 weeks of isolated omphalocele with normal array. At 20 weeks, there were shortened fetal long bones, foot deformity, macroglossia, corpus callosum hypoplasia and bilateral nephromegaly. Due to the polymalformative syndrome, a termination of pregnancy (TOP) was performed. The anatomopathological study of the placenta identified mesenchymal dysplasia. The search for the methylation pattern of the 11p15 region by MS-MLPA was normal and the molecular study of the *CDKN1C* gene identified a likely pathogenic variant, inherited from the mother. Case 2: Morphological ultrasound at 21 weeks revealed macrosomia, macroglossia, omphalocele, bilateral renal dysplasia, and hydramnios. The cytogenetic study, after amniocentesis, was normal (46,XX karyotype). TOP was performed. The anatomopathological study of the fetus confirmed the described malformations and the one concerning the placenta identified placentomegaly. The search for the methylation pattern of the 11p15 region by MS-MLPA revealed abnormal methylation. These results confirmed the diagnosis of BWS in both cases. Prenatal ultrasound suspicion of this pathology is extremely important to guide the conduct in pregnancy and/or the prevention of perinatal complications. Shortened fetal long bones and foot deformity complement the broad spectrum of this syndrome. Positive molecular tests allow confirming the diagnosis, assessing the risk of recurrence and guiding the surveillance of future pregnancy.

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Introduction

Beckwith-Wiedemann syndrome (BWS) was first reported in 1963 by Beckwith and in 1964 by Wiedemann that described a unique syndrome in newborns, including omphalocele, macroglossia, overgrowth, renal hyperplasia, medullary dysplasia, adrenal cytomegaly, pancreatic islet hyperplasia, facial nevus flammeus, and hypoglycemia. Further others authors report maternal polyhydramnios in 50% of cases [1,2]. BWS has an incidence of 1 in 10,300-13,700 live births, with similar prevalence in females and males [3,4].

BWS exhibits etiological molecular heterogeneity. It usually occurs sporadically (85%), but familial transmission occurs in approximately 15% of cases. Different mechanisms can originate BWS by epigenetic and/or genomic alterations leading to abnormal methylation at 11p15.5 (loss of methylation on the maternal chromosome at imprinting center 2 (IC2) in 50% of affected individuals; paternal uniparental disomy in 20% and gain of methylation on the maternal chromosome at imprinting center 1 (IC1) in 5%) [5,6].

The syndrome presents a large clinical heterogeneity, generally including omphalocele, macroglossia, and macrosomia [2]. In the prenatal period, macrosomia, and hydramnios are the most frequent findings, and it is also associated with placental abnormalities [7].

There are few cases reported in the prenatal period, due to its difficult diagnosis, and those that do exist are old and poorly documented in terms of ultrasound images associated with the syndrome.

These 2 cases, in addition to being rare, demonstrate the correct diagnostic approach, ultrasonographic and molecular, in the prenatal period, in case of suspected BWS. Furthermore, the identification of shortened fetal long bones and foot deformity in one of the cases complements the broad spectrum of this syndrome.

Case presentation

Case 1: 38-year-old pregnant woman, Gravida III Parity I (one full term delivery by cesarean section, with male newborn (NB) weighing 3770 g, healthy; one early pregnancy loss), with no relevant personal history. She denied consanguinity or a family history of birth defects.

Pregnancy was early monitored in the hospital and primary health care. The analytical study of the first trimester did not show alterations, with all serologies being negative (immune to rubella, immune to toxoplasmosis, nonimmune to Cytomegalovirus, negative Hepatitis B and HIV).

She was referred for prenatal diagnosis at 13 weeks and 3 days for omphalocele and nuchal translucency greater than the 95th percentile for gestational age.

Chorionic villus sampling was performed. QF-PCR did not detect aneuploidies of chromosomes 13, 18, 21, and X and chromosome microarray analysis did not identify clearly pathogenic alterations.

Morphological ultrasound was performed at 20 weeks and 4 days, which revealed omphalocele (Fig. 1A), macroglossia (Figs. 1B and C), prefrontal edema (7 mm, Fig. 1D), corpus callosum hypoplasia (14.9 mm, <5th percentile, Fig. 1E), shortened long bones at 5th percentile (humerus with 28.2 mm, femur with 30.1 mm; Fig. 2), foot deformity with medial curvature of its longest axis (Fig. 1F), not in relation to the tibia/fibula, and bilateral nephromegaly (right kidney measuring 19 × 19 × 33 mm, corresponding to 6.2 cm^3 and left kidney measuring 21 × 22 × 29 mm, with 7 cm^3).

The hypothesis of BWS was raised and amniocentesis was performed to determine the methylation status of the 11p15 region by MS-MLPA, which was normal.

Due to polymalformative syndrome, termination of pregnancy (TOP) was requested by couple. The observation and anatomopathological study of the fetus confirmed the ultrasound findings, with partial agenesis of the corpus callosum, pancreas and large ovaries and cytomegaly of the adrenal glands.

The anatomopathological study of the placenta identified mesenchymal dysplasia.

For this reason, we carry out the molecular study of the *CDKN1C* gene, which identified a heterozygous probably pathogenic variant, c.479del [p. (Pro160Argfs*112)], inherited from the unaffected mother, which molecularly confirms the diagnosis of BWS.

Case 2: 35-year-old female, healthy, Gravida I Parity I a delivery by cesarean section, male NB, 3290 g, healthy), with no family history of congenital malformations. The pregnancy was monitored, without complications. The analytical study and ultrasound in the 1st trimester (12s+6d) showed no changes, with nuchal translucency below the 95th percentile (1.9 mm). The couple was not consanguineous.

She was referred to the prenatal diagnosis at 21 weeks and 6 days due to macrosomia (estimate fetal weight 642 g, >95th percentile), macroglossia, omphalocele, bilateral nephromegaly (right kidney with 29 × 21 × 50 mm, 15.9 cm^3 and left with 34 × 28 × 50 mm, 25.4 cm^3, both above the 95th percentile) and hydramnios (deepest vertical pocket of 7.3 cm) (Fig. 3).

Amniocentesis was performed at 22s+6d, and the cytogenetic study was normal (46, XX karyotype). The couple requested TOP, which was performed at 23 weeks. The anatomopathological study of the fetus confirmed the ultrasound findings, having identified left hemihypertrophy, macrostomia, omphalocele containing intestine, adrenal glands with bilateral cortical cytomegaly, large gallbladder, pancreatic hyperplasia, and the study of the placenta identified placentomegaly.

The search for the methylation status of the 11p15 region by MS-MLPA (methylation of KCNQ10T1 and H19 genes) revealed abnormal methylation, having confirmed the existence of loss of methylation in the imprinting center 2 (IC2) and methylation gain in the imprinting center 1 (IC1). These results confirmed the diagnosis of BWS.

Discussion

BWS is a rare disease, whose prenatal diagnosis requires a strong suspicion and knowledge of the key clinical findings.

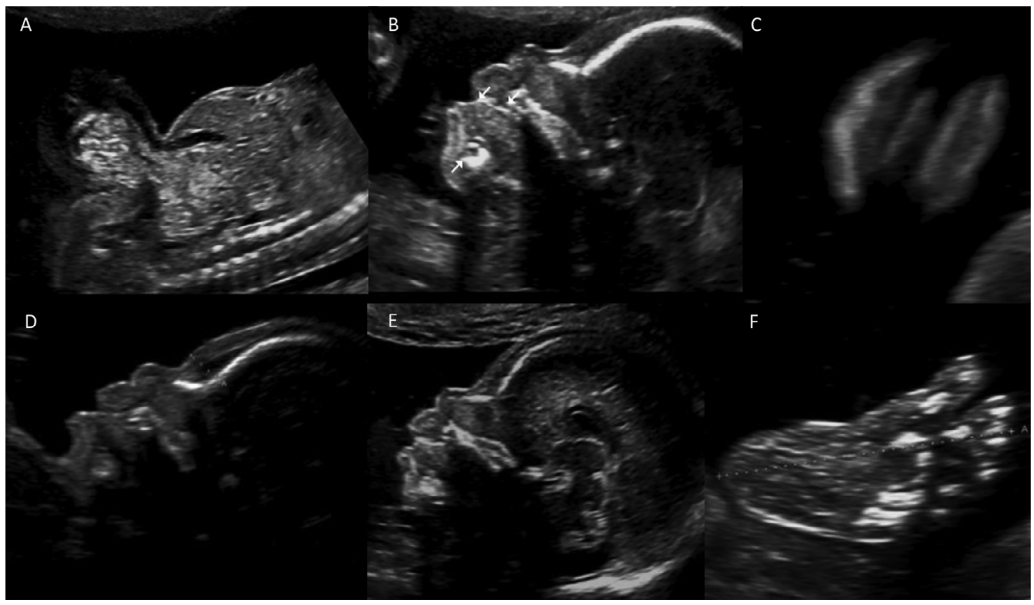

Fig. 1 – (A) Omphalocele containing intestine (sagittal plane at the level of the fetal abdomen); (B) macroglossia (midsagittal plane of the face); (C) macroglossia (coronal view of upper lip); (D) prefrontal edema (sagittal plane of the face); (E) corpus callosum hypoplasia (midsagittal plane of the face); (F) foot deformity with medial curvature of its longest axis (transverse plane).

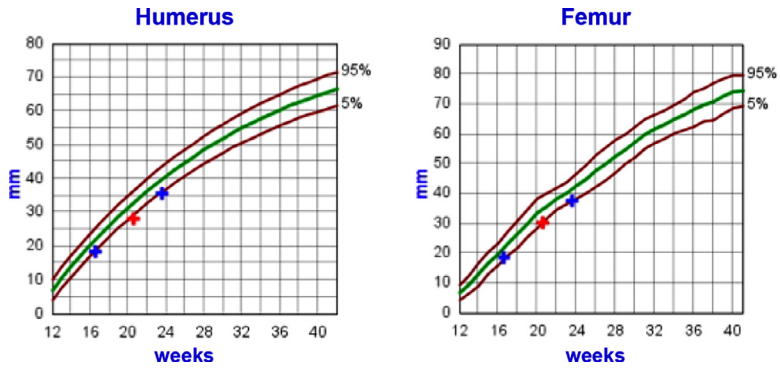

Fig. 2 – Femur and humerus growth curves, persistently at the 5th percentile or below.

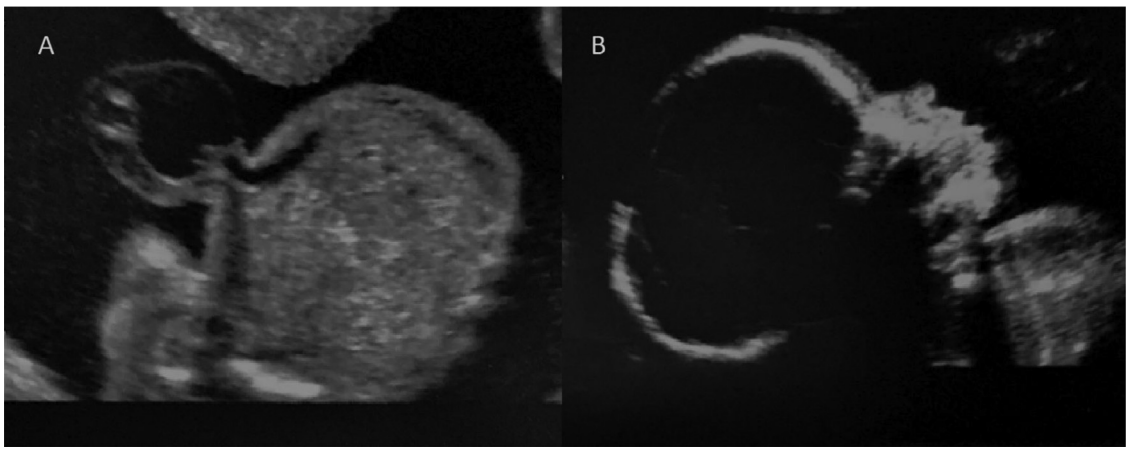

Fig. 3 – (A) Omphalocele (transverse plane of the abdomen); (B) macroglossia (midsagittal plane of the face).

Table 1 – Diagnostic criteria of Beckwith-Wiedemann syndrome.

Cardinal features (2 points per feature)	Suggestive features (1 point per feature)
Macroglossia	Birth weight >2 SDS above the mean
Exomphalos	Polyhydramnios and/or placentomegaly
Hemihyperplasia	Nephromegaly and/or hepatomegaly
Multifocal and/or bilateral Wilms tumor or nephroblastomatosis	Umbilical hernia and/or diastasis recti
Hyperinsulinism (lasting beyond 1 week and requiring escalated treatment)	Ear creases and/or pits
Pathology findings: adrenal cortex cytomegaly, placental mesenchymal dysplasia or pancreatic adenomatosis	Hypoglycemia
-	Facial nevus simplex
-	Typical BWS tumors (unilateral Wilms tumor rhabdomyosarcoma, neuroblastoma, hepatoblastoma, adrenocortical carcinoma or pheochromocytoma)

There is no universal approach to the diagnosis of this pathology. Classically, the clinical diagnosis of BWS in postnatal is based on the presence of 3 major features (anterior abdominal wall defect, macroglossia, macrossomia) or 2 major and 3 minor features (ear creases on the lobes or postauricular pits, prominent facial nevus flammeus, nephromegaly, hemihyperplasia, or hypoglycemia) [8].

A recent international consensus, from 2018, created new diagnostic criteria based on cardinal and/or suggestive characteristics of the syndrome (Table 1).

According to this new classification, for the diagnosis of BWS a score $\geq$ 4 is required, with no need for genetic confirmation. Patients with scores greater than 2 require genetic testing for further investigation [9]. Some of these findings can be found in the prenatal period, but most are only detected after birth.

Ultrasound is a valuable tool in the prenatal detection of characteristic findings associated with BWS. The first prenatal diagnosis was made in 1980, after ultrasound description of fetus larger than expected with increased amniotic fluid, bilateral cystic kidneys and an apparent omphalocele [10].

Previous case reports suggest that the prenatal diagnosis of BWS can be made during pregnancy through the following findings: macrosomia, macroglossia, omphalocele, hydramnios, increased waist circumference, nephromegaly, or hepatomegaly [11].

Some authors have proposed criteria for prenatal diagnosis of BWS. However, the samples are small and the criteria used include anatomopathological data, so they are not very useful in clinical practice, especially if TOP is not an option for the couple [12].

Macrosomia was a consistent finding in both cases. It appears to occur in over 50% of fetuses diagnosed with BWS [8].

Macroglossia was a facial anomaly detected in both situations. It is one of the most frequent clinical features of the syndrome, with an incidence of 82%-98% [3,13]. It is usually only detected in the postpartum period, because it can appear later in fetal life or, according to some authors, because in the past, correct evaluation of the fetal face was not routinely performed [14,15].

The existence of an abdominal wall defect was another common feature among the cases. Omphalocele affects about half of BWS cases, but only 3% of omphalocele are associated with this syndrome [16].

Renal abnormalities associated with BWS are nephromegaly and pyelectasis [17]. In these cases, both fetuses had bilaterally enlarged kidneys.

Brain malformations, namely hydrocephaly, Chiari malformation and posterior fossa abnormalities have been reported associated with this pathology [18,19]. However, to our knowledge, anomalies of the corpus callosum have only been reported twice in the literature: a dysgenesis of the corpus callosum associated with a Dandy-Walker malformation and a hypoplasia of the corpus callosum [20].

Shortened long bones, below the 5th percentile, were found in the first case described. This is interesting, as this syndrome is associated with overgrowth. Although there is a case report in the literature with a short femur, there does not seem to be one with short humerus and femur [21]. To the best of our knowledge, this is the first clinical case with shortened long bones in BWS. Foot deformity with medial curvature of its longest axis does not seem to have been previously reported either.

Hydramnios is the most consistent finding reported in the literature. It usually appears in the second trimester; hence, it was not seen in the first case. Its association with this syndrome may be as high as 50%.

Placental mesenchymal dysplasia and placentomegaly, present in cases 1 and 2, respectively, are findings strictly associated with BWS. Placental mesenchymal dysplasia is manifested by a hydropic placenta with multiple cyst-like villi and absence of trophoblastic hyperplasia. This placental anomaly, despite occurring in pregnancies with normal fetuses, in about 25% of cases is associated with BWS [22,23].

The etiology of placental mesenchymal dysplasia is unknown, but some authors suggest that it may be a complex mechanism caused by a mosaicism of uniparental disomy, which would explain its link to BWS [24].

After identifying these anomalies, namely at the ultrasound level, it is essential to review the parental family history. Diagnosis can be confirmed by molecular/cytogenetic tests. The genetics of BWS is complex and may be associated with epigenetic and/or genomic alterations in 2 imprinted domains on chromosome 11p15.5 (also known as the BWS critical region), which regulation may be disrupted by any one of numerous mechanisms. The BWS critical region includes 2 domains: imprinting center 1 (IC1) regulates the expression of *IGF2* and *H19* in domain 1; imprinting center 2 (IC2) regulates

the expression of *CDKN1C, KCNQ10T1, and KCNQ1* in domain 2. Genomic imprinting is a phenomenon whereby the DNA of the 2 alleles of a gene is differentially modified and only one parental allele is normally expressed [25]. Differential methylation of IC1 and IC2 is associated with expression of specific genes on the paternal and maternal alleles in unaffected individuals. In more than 80% of individuals with BWS, genetic testing can detect alterations in 1 of the 5 following situations: loss of methylation of IC2 on the maternal chromosome, gain of methylation of IC1 on the maternal chromosome, paternal uniparental disomy of 11p15.5, genomic imbalances involving chromosome 11p15.5 (duplications, inversions or translocations visible in conventional cytogenetic or copy number variants as microduplications or microdeletions of 11p15.5 region identified by chromosome microarray analysis and a heterozygous pathogenic variant in gene *CDKN1C* on maternal allele [26]. Methylation changes may be associated with all, except for pathogenic variants on the maternal *CDKN1C* allele [27].

Choosing the appropriate test requires understanding the mechanism of disease, as well as having a sufficient knowledge about limitation of the each test.

Prenatal identification of this pathology allows adequate gestational counseling: informing parents about the possibility of TOP, risk of malignancy; determine the best mode of delivery; determine the best approach to potentially fatal neonatal complications such as airway obstruction, hypoglycemia, or congestive heart failure.

This pathology is usually associated with prematurity due to macrosomia and hydramnios. Delivery planning is extremely important, as there is an increased risk of dystocia due to macrosomia. BWS also appears to be associated with an increased risk of postpartum hemorrhage [3].

In addition, families must obtain correct genetic counseling, making it possible to plan a future pregnancy.

In the first case, the molecular study of the *CDKN1C* gene revealed a likely pathogenic variant, inherited from the mother. The absence of signs and symptoms of BWS in the mother presupposes that the variant is present in the paternal allele, which is silenced by the normal process of imprinting. Therefore, in the first case, the mother had a 50% chance of transmitting the variant to the offspring, with recurrence of BWS, although the phenotype can be variable. In this context, there is room to discuss future reproductive options, such as molecular prenatal diagnosis and preimplantation genetic diagnosis. Other family members, specifically her sisters, whom have a 50% of probability to be carriers are at risk of affected descendants. Her brothers have the same probability to be carriers but there is no risk of affected offspring. However, there is risk of grandchildren affected (offspring of daughters). In this context genetic counselling is essential.

In case 2, the search for the methylation status of the 11p15 region by MS-MLPA revealed abnormal methylation, having confirmed the existence of methylation loss in imprinting center 2 and methylation gain in imprinting center 1, compatible with uniparental disomy. The occurrence of uniparental disomy is a generally somatic and post-zygotic event, therefore the probability of recurrence is very low or even negligible, with no risk for other family members [28].

Conclusions

Prenatal diagnosis of BWS is extremely important for gestational counseling, perinatal approach and postnatal care, despite its prenatal detection can be challenging.

These cases demonstrate the ultrasound findings existing in this syndrome, as well as the correct diagnostic approach in case of suspicion of this pathology.

The detection of macrosomia, macroglossia, omphalocele, nephromegaly, hydramnios, and placental changes should alert to the possibility of BWS. Furthermore, hypoplasia of the corpus callosum, shortened long bones and foot deformities complement the broad fetal phenotypic spectrum of this pathology.

Positive molecular tests allow to confirm the diagnosis, assess the risk of recurrence, which will vary depending on the causal mechanism, guide reproductive options and surveillance of future pregnancy.

Patient consent

Informed consent was obtained from all subjects involved in the study.

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