Case Report

Beckwith–Wiedemann Syndrome Diagnosed in the Early Second Trimester in Two Fetuses with Isolated Omphalocele

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Abstract

Beckwith–Wiedemann syndrome (BWS) is an imprinting disorder caused by various genetic or epigenetic alterations involving growth regulatory genes located on chromosome 11p15.5 region. Conventionally, most cases of BWS are diagnosed during the neonatal period or early childhood. Early prenatal diagnosis is very important because it provides information regarding the prognosis, guidance of delivery preparation, and postnatal care plan. We report two cases of BWS diagnosed in utero using exome sequencing (ES) after the early identification of fetal omphalocele and normal findings of microarray and methylation analyses. Case 1 carried a *de novo CDKN1C* c.694C>T (p.Gln232*) variant. Case 2 carried a familial *CDKN1C* c.827_828delinsAA (p.Phe276*) variant; another member in the family presented with features of BWS. In both cases, no macrosomia and visceromegaly were demonstrated. Although fetal omphalocele was identified in the first trimester, invasive testing was delayed to the early second trimester for methylation in the two cases. Fetal omphalocele should not be regarded as just an abdominal wall defect. When a fetal omphalocele was identified, a detailed family history, especially with searching for the signs of BWS in familial members, should be undertaken. For an omphalocele, ES is an option for patients after normal microarray and methylation analyses.

Keywords: Beckwith–Wiedemann syndrome, CDKN1C, omphalocele, prenatal diagnosis

Introduction

Beckwith–Wiedemann syndrome (BWS) is an imprinting disorder, with various genetic or epigenetic alterations which involve growth regulatory genes located on 11p15.5.[1] Classic BWS is characterized by macrosomia, macroglossia, neonatal hypoglycemia, abdominal wall defects, lateralized overgrowth, and increased risk of embryonal tumors during early childhood. Although some features can be detected prenatally, they usually develop late in gestation, for example, macrosomia, organomegaly, macroglossia, and polyhydramnios.[2] Therefore, early prenatal diagnosis is difficult if the diagnosis is only based on clinical criteria.[3] In this study, we report two cases of BWS diagnosed *in utero* using exome sequencing (ES) after the identification of fetal omphalocele in the first trimester.

Case Reports

Case 1

A 28-year-old G2P1 woman came for a routine first-trimester scan. She was healthy, and her medical history and familial history were unremarkable. Her 3-year-old girl (II-1) was healthy. The ultrasound examination showed a single live fetus with a crown-rump length (CRL) of 68 mm and nuchal translucency (NT) of 1.0 mm. However, an omphalocele (2.9 mm × 2.0 mm × 2.0 mm) was observed [Figure 1a]. The patient was referred to a senior sonographer who had extensive sonographic experience in the first-trimester structural ultrasound. Further detailed scans showed a normal appearance of the head, face, heart, stomach, bladder, limbs, and placenta. Isolated omphalocele was the temporary diagnosis.

At 16 weeks, amniocentesis reported a normal karyotype and array result, and methylation-specific multiplex ligation-dependent probe amplification for 11p15.5 region

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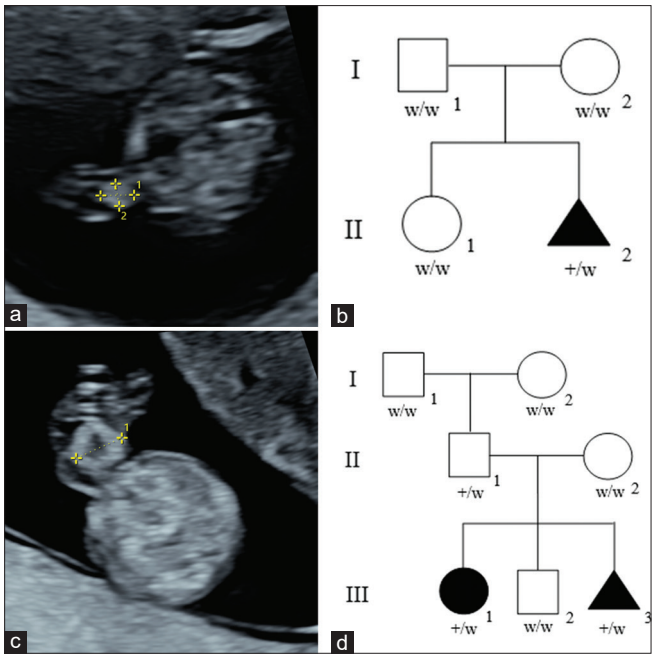

Figure 1: Prenatal ultrasounds of omphalocele in the first trimester and family pedigrees. (a) first-trimester omphalocele of Case 1; (b) family pedigree of Case 1; (c) first-trimester omphalocele of Case 2; (d) family pedigree of Case 2. W: Wild allele, +: Mutant allele

methylation was negative. A repeat ultrasound at 18 weeks still showed an isolated bowel-containing omphalocele. The parents decided to pursue further testing, and trio ES identified a *de novo* pathogenic nonsense variant, c.694C>T (p.Gln232*), in the *CDKN1C* (NM_000076.2) gene. The healthy sibling (II-1) was confirmed negative for this variant [Figure 1b].

The pregnancy continued to 38 weeks with no macrosomia and visceromegaly. A male infant weighing 3025 g (22th centile) was delivered, with an omphalocele, facial naevus simplex, ear lobe creases, and wide nipple. His palate was intact. There was no macroglossia or lateralized overgrowth. No hypoglycemia was reported during the neonatal period. Primary closure of the abdominal defect was undertaken. His psychomotor development seemed normal, but overgrowth was reported on the last follow-up at the age of 12 months. Based on these clinical presentations, BWS is the diagnosis of this patient. He was under surveillance for tumor occurrence during his growth.

Case 2

A 32-year-old G3P2 woman was referred for further investigation because of a fetal omphalocele. The detailed structural ultrasound performed by a senior sonographer showed a single live fetus with CRL of 70 mm and NT of 1.5 mm. Except for a bowel-containing omphalocele (5 mm × 7 mm × 6 mm) [Figure 1c], the fetus had normal morphology of the face, heart, stomach, bladder, and limbs. The woman was healthy with an unremarkable medical history. The 2-year-old brother (III-2) was healthy. The 6-year-old sister (III-1) had normal intelligence, but her height and weight were greater than those of her peers. The sister's prenatal duration was unremarkable, and the neonatal period was uneventful. The girl (III-1) had a birthweight of 3100 g (38th centile) and a cleft palate which was repaired at 12 months. She was currently undergoing treatment for precocious puberty. Considering these clinical features, the sister was suspected to have BWS, although she had normal microarray and methylation analyses which ruled out the common molecular mechanisms causing BWS. Because *CDKN1C* sequencing was not a routine practice at our centre, and other monogenic conditions could not be excluded from the study, trio ES was chosen, which detected a likely pathogenic nonsense variant c.827_828delinsAA (p.Phe276*) in *CDKN1C* (NM_000076.2) in the girl, inherited from the mother. Family analysis showed that the grandparents (I-1; I-2) and the brother (III-2) did not carry this variant [Figure 1d]. At 16-week gestation, amniocentesis was performed, and target testing of this variant confirmed the presence of it. Fetal karyotype by cell culture was normal. After genetic counseling, the patient opted for pregnancy termination at 17 weeks.

Discussion

Omphalocele may be a part of many syndromes.[4] Detailed targeted ultrasound of all fetal organs is mandatory in these cases. For example, the most common chromosomal abnormality was trisomy 18, where omphalocele was always associated with other major structural abnormalities. Therefore, for fetuses with omphalocele identified at the time of NT examination, a detailed structural scan should be conducted by senior sonographers to search for other anomalies. In the prenatal period, omphalocele is the only feature of BWS that can be observed in the first trimester. Because CVS cells might not reflect the (epi) genetic constitution of the fetus,[5] in our clinical practice, we delay the invasive testing to ≥15 weeks for microarray and methylation analysis in those with isolated omphalocele, considering methylation alterations in 11p15.5 accounts for more than 80% of BWS patients.[6] In contrast, CVS will be offered to those with nonisolated omphalocele who have a higher risk of chromosomal abnormalities.

Recent studies found that the frequency of BWS among isolated omphaloceles was estimated at 19%–37.5%.[7,8] These findings highlight the importance of offering BWS testing for all prenatally diagnosed isolated omphaloceles. The decision to pursue further testing through ES in isolated omphalocele depends on a variety of factors, such as the patient's desire for more information, family history, or cost. Currently, the exact utility of using ES in cases of omphalocele remains unclear, although ES is increasingly being used in the prenatal setting with structurally anomalous fetuses, which can have a diagnostic yield as high as 80% for certain ultrasound findings.[9,10] We believe that the principles of reproductive autonomy and informed decision-making determine individual patients' primacy in deciding which tests they opt for, particularly after a risk-related invasive procedure has been done, even in the situation of isolated omphalocele. After genetic counseling, both the current two families had opted for ES. The two (likely) pathogenic *CDKN1C* variants,

c.694C>T (p.Gln232*) and c.827_828delinsAA (p.Phe276*), which are associated with BWS, contributed to the cause of prenatal BWS phenotype (omphalocele) in the two families, respectively. Indeed, BWS patients carrying *CDKN1C* variants have a higher frequency of abdominal wall defects than BWS patients carrying other molecular defects.[11]

In conclusion, we reported two fetuses of omphalocele identified in the first trimester which led to a detection of BWS, one of which had a previously unknown familial inheritance. Our report supports that BWS testing should be considered early in the diagnostic workup for isolated omphaloceles. Early prenatal diagnosis is critical, as the information is very useful for counseling of prevention of neonatal hypoglycemia, parents concerning the risk of developing embryonic tumors in childhood, and even options of pregnancy termination of previable fetuses.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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