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Case Report

Omphalocele and macroglossia: a case of Beckwith-Wiedemann syndrome

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ABSTRACT

Beckwith-Wiedemann syndrome (BWS) is a pediatric overgrowth disorder which predisposes to tumor development. The following case study examined a prenatal finding of omphalocele with postnatal findings of macroglossia and cutaneous hemangioma, ultimately leading to a diagnosis of BWS. This case highlighted the features of BWS, the diagnostic principles and the importance of a multidisciplinary team approach to its management.

Keywords: Beckwith-Wiedemann syndrome, Omphalocele, Macroglossia

INTRODUCTION

Beckwith-Wiedemann syndrome (BWS) is a pediatric growth disorder which predisposes to tumor development. Around 85% of cases occur sporadically while cases that are inherited follow an autosomal dominant inheritance pattern with incomplete penetrance and variable expression.[1]

Omphalocele and macroglossia are associated with BWS.

An omphalocele is a rare midline birth defect of the anterior abdominal wall occurring at the base of the umbilical cord. It typically contains herniated abdominal contents. It is the second most common congenital abdominal wall defect after gastroschisis. The worldwide prevalence of omphalocele is 2.6 per 10,000 births.[2]

Macroglossia is present in 90% of BWS cases and may present at birth or have postnatal onset.[3] It is a true enlargement of the tongue and is generalized. Symptoms include drooling, speech impairment, difficulty eating, stridor, and airway obstruction.

CASE REPORT

A 38-year-old female in a non-consanguineous marriage presented to her primary health care center during her second pregnancy. Her first pregnancy resulted in a healthy child delivered by lower segment caesarian section (LSCS). There was no known family history of genetic disorders.

Prenatal obstetric ultrasonography carried out at 12 weeks revealed a single live uterine pregnancy. However, a 19 week anomaly scan revealed a small omphalocele containing small bowel. No further structural abnormalities were identified.

She was transferred to a tertiary care center where following prenatal counselling she underwent amniocentesis.

Giemsa banding chromosome analysis revealed normal karyotype 46, XX. Genome wide array comparative genomic hybridization (aCGH) analysis did not identify any DNA copy number changes. Fluorescence *in situ* hybridization (FISH) analysis for rapid detection of the

copy number of chromosomes 13, 18, 21 and X detected no abnormality.

Subsequent obstetric ultrasound scans showed normal growth, amniotic fluid and blood flow with no change in omphalocele size.

A baby girl, weighing 3.9 kg was delivered by emergency LSCS at gestation 38 weeks and 2 days following uterine contractions. No other physical findings were noted, and she underwent surgery for omphalocele repair the following day.

A peripheral blood sample taken from the child was tested and aCGH yielded normal hybridization pattern for the genomic DNA and did not identify any DNA copy number changes.

The baby was discharged and next seen in her primary health care center for her first routine vaccinations at age 8 weeks. She was noted to be breastfeeding with normal weight gain, development, and hearing. Examination revealed a surgical abdominal scar, macroglossia, a 6×6 cm scalp hemangioma and a facial nevus flammeus (port wine stain). No other abnormality was detected.

The child was referred to pediatric specialist services due to the finding of macroglossia and further genetic testing revealed loss of methylation in the IC2 region of chromosome 11p15 consistent was a diagnosis of BWS.

She was last seen in her primary healthcare center aged 7 months, for her routine 6-month vaccination where no developmental concerns were noted. Despite macroglossia, under the supervision of occupational therapists she was able to feed herself and was maintaining height and weight above the 50th centile.

She remains under the care of pediatric specialists.

DISCUSSION

Omphalocele

Small omphaloceles are less than 4 cm in size and usually contain only small bowel. Giant omphaloceles are greater than 4 cm in size and usually contain most or all the liver with or without other abdominal organs.[4] Small omphaloceles can be closed within days of birth.

Omphaloceles may be isolated in 42-44% of cases.[5,6] The remaining cases had at least one concomitant structural abnormality and in 61% of these cases there were chromosomal anomalies present.[5]

Coexisting anomalies include cardiac (11%), gastrointestinal (7%), genitourinary (6%), central nervous system (4%), pulmonary (3%) and genetic (15%). The four most common genetic disorders identified were BWS (6%), trisomy 13 (3%), trisomy 18 (2%), and trisomy 21 (1%).[7]

Syndromes frequently associated with omphalocele include Schisis association, BWS, Pentalogy of Cantrell, OEIS complex (omphalocele-bladder exstrophy-imperforate anus-spinal defects), Donnai-Barrow syndrome and Shprintzen-Goldberg omphalocele syndrome. Syndromes infrequently associated with omphalocele include Melnick-Needles syndrome, Carpenter syndrome and trisomy, 13, 18 and 21.[8]

The size of the defect and the severity of any associated anomalies impact the pre and postnatal morbidity and mortality. The overall mortality rate is 32% with most deaths occurring during the neonatal period and in children with multiple anomalies or syndromic omphalocele.[2] However, the survival rate of an isolated omphalocele with normal karyotype was as high as 96%.[9]

There is a very high rate of termination of pregnancy (30-52%) due to the presence of associated anomalies and spontaneous abortion.[4]

BWS

There was no consensus on the clinical diagnostic criteria. BWS should be suspected in individuals who had one or more of the following findings and it had been proposed that a diagnosis be established if three major findings, or two major and one minor finding were present.[10]

Table 1: Findings associated with BWS.[10]

S. no.	Major findings associated with BWS	Minor findings associated with BWS
1.	Macrosomia (weight and length/height >97th centile)	Pregnancy-related findings including polyhydramnios and prematurity
2.	Macroglossia	Neonatal hypoglycemia
3.	Hemihyperplasia (asymmetric overgrowth of one or more regions of the body)	Vascular lesions including nevus simplex or hemangiomas (cutaneous or extracutaneous)
4.	Omphalocele or umbilical hernia	Structural cardiac anomalies or cardiomegaly
5.	Embryonal tumor in childhood (e.g. Wilms tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma)	Characteristic facies including midface retrusion and infraorbital creases

Continued.

S. no.	Major findings associated with BWS	Minor findings associated with BWS
6.	Visceromegaly involving one or more intra-abdominal organs including liver, spleen, kidneys, adrenal glands, and/or pancreas	Diastasis recti
7.	Cytomegaly of the fetal adrenal cortex (pathognomonic)	Advanced bone age (common in overgrowth/endocrine disorders)
8.	Renal abnormalities including structural abnormalities, nephromegaly, nephrocalcinosis, and/or later development of medullary sponge kidney	
9.	Anterior linear ear lobe creases and/or posterior helical ear pits	
10.	Placental mesenchymal dysplasia	
11.	Cleft palate (rare in BWS)	
12.	Cardiomyopathy (rare in BWS)	
13.	Positive family history (≥1 family members with a clinical diagnosis of BWS or a history or features suggestive of BWS)	

However, since BWS is a clinical spectrum, it cannot be ruled out using this diagnostic method.

The diagnosis can also be determined by finding an epigenetic or genomic alteration leading to abnormal methylation at 11p15.5 or a heterozygous BWS causing pathogenic variant in CDKN1C in the presence of more clinical findings.[10]

In the above case, there was a finding of a small isolated omphalocele on the obstetric ultrasound. At 8-weeks macroglossia, cutaneous hemangioma and facial nevus flammeus were noted in the baby. Omphalocele and macroglossia were two major findings associated with BWS while cutaneous hemangioma and facial nevus flammeus were simple vascular lesions that are minor findings associated with BWS. The clinical findings supported a diagnosis of BWS which was later confirmed by more specific genetic testing that revealed loss of methylation in the IC2 region of chromosome 11p15.

The incidence of BWS is particularly high in fetuses with isolated omphalocele. After excluding aneuploidy, and after subsequent clinical evaluation and/or molecular testing, BWS was identified in 20-37.5% of isolated, and 5% of non-isolated omphaloceles.[11,12] Omphaloceles were small to moderate in size and contained bowel only.[11]

Children with BWS are at increased risk of mortality due to neoplasia especially in the first decade of life. Malignancy risk is estimated between 5% and 10% overall but as low as 1% and as high as 45% in certain molecular subgroups.[1] Wilms tumor (WT) and hepatoblastoma (HB) are the most common tumor types reported. Other tumors reported include neuroblastoma, rhabdomyosarcoma, pheochromocytoma, and adreno-cortical carcinoma. The median age at which BWS individuals develop cancer is 24 months for WT and 12 months for HB.[13]

Tumor surveillance should be carried out by cancer predisposition specialists. In North America, tumor surveillance for WT is generally undertaken by three-monthly renal ultrasound from birth (or time of diagnosis) until age eight years. For HB, full abdominal ultrasound and serum alpha-fetoprotein measurements are advised every 3 months from birth (or time of diagnosis) until age five years.[14] Annual or biannual renal ultrasound thereafter has been suggested, as has annual ECG and cardiac assessment, as well as periodic chest radiography in appropriate cases.

CONCLUSION

Routine prenatal screening in the first and second trimester can diagnose abdominal wall defects and associated anomalies. Early detection is important as it allows for prenatal counseling, abortion, and safe delivery in an appropriate setting under the care of a multidisciplinary team including obstetricians, neonatologists, and pediatric surgeons.

BWS is a genetic disorder that may be suspected based on several clinical findings made in primary care. These may come to light during the prenatal period and include obstetric ultrasound findings of omphalocele, structural abnormalities, macrosomia, and polyhydramnios, or in the postnatal period and include macroglossia and vascular lesions such as cutaneous hemangiomas. The expectant mother or child should be referred to a specialist obstetrician or pediatrician respectively for consideration of genetic testing to aid diagnosis. Small omphaloceles can be closed within days of birth. Treatment of macroglossia depends upon severity and ranges from speech therapy in mild cases to surgical reduction.

BWS is a tumor predisposing disorder and appropriate tumor surveillance by cancer predisposition specialists should take place in the first decade of life.

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