Elevated maternal serum α–fetoprotein level in a fetus with Beckwith-Wiedemann syndrome in the second trimester of pregnancy

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Summary

Background: Beckwith-Wiedemann syndrome (BWS) is a rare disorder characterized by macrosomia, macroglossia, visceromegaly, and omphalocele and an increased risk of growing tumors. Prenatal and postnatal high levels of serum alpha-fetoprotein are associated with several diseases and neoplasms including hepatoblastomas and other hepatic tumors. The diagnosis of BWS is usually made in the postnatal period on the basis of physical exam features and hypermethylation of the H19 gene.
Case: A 30-year-old woman gravida 3, para 2, underwent maternal serum screening at 15 weeks' gestation. The screening was negative for Down's syndrome (risk 1/6085), but positive for NTDs. Further ultrasound examination at 20 and 30 weeks' evidenced a fetal overgrowth and a 3-D scan at 33 weeks' gestation presented a protruding tongue, and a fixed opened mouth caused by macroglossia.
Conclusions: BWS was suspected on the basis of clinical features, and molecular analysis of critical region 11p15.5 revealing the hypermethylation of H19 gene supported the diagnosis.

Key words: maternal serum screening, Beckwith-Wiedemann syndrome, prenatal diagnosis.

Case report

Beckwith-Wiedemann syndrome (OMIM 130650) (BWS) is a rare disorder characterized by a number of clinical features as macrosomia, macroglossia, visceromegaly, omphalocele, hypoglycemia, unusual linear fissures in the earlobe. Approximately 5-10% of the patients develop intra-abdominal embryonal malignancies: most commonly Wilms tumor, hepatoblastoma and adrenal cortical carcinoma (1, 2). Less frequently, patients are affected by gonadoblastoma, rhabdomyosarcoma and neuroblastoma (2). BWS is caused by mutation or deletion of imprinted genes within the chromosome 11p15.5 region. Specific genes involved include p57, H19, and LIT1 (1). Prenatal and postnatal high levels of serum alpha-fetoprotein (AFP) are associated with several diseases such as ataxia telangectasia, hepatobiliary problems, hypothyroidism and neoplasms including hepatoblastomas and other hepatic tumors (2). AFP is routinely dosed during second trimester Downs' syndrome serum screen. Elevated serum levels of AFP in pregnant women (MS-AFP) are associated with neural tube defects (NTDs), and poor maternal/fetal outcome as spontaneous abortion, preterm delivery, gestational hypertension, preeclampsia, preterm premature rupture of membranes (3). The diagnosis of BWS is usually made in the postnatal period in almost all cases on the basis of physical exam features (4). Definition of BWS is based on the description of either three major features (anterior abdominal wall defect, macroglossia, pre- or post-natal overgrowth) or two major features plus three minor features (ear creases, post-auricolar pits, prominent facial nevus flammeus, hypoglycemia, nephromegaly, or hemyhyperplasia) (5). Some of these features and other findings like polydramnios can be detected prenatally (6).
Here we describe a fetus presenting elevated levels of MS-AFP at second trimester serum screen and diagnosed at 33 weeks' gestation by a 3D/4D scan of being affected by BWS.
A 30-year-old woman gravida 3, para 2, underwent maternal serum screening at 15 weeks' gestation. Serum analyte levels were 93.2 IU/ml for AFP (3.05 multiples of the median) (MoM), 43011 mIU/ml for human chorionic gonadotropin (hCG) (1.17 MoM), and 8.55 nmol/L for unconjugated estriol (uE_3) (1.51 MoM). The screening was negative for Down's syndrome (risk 1/6085), but positive for NTDs. Further ultrasound examination at 20 and 30 weeks' evidenced a fetal overgrowth and a 3-D scan at 33 weeks' gestation presented a protruding tongue (Fig. 1a, 1b) and a fixed opened mouth caused by macroglossia. Hepatomegaly (Fig. 1c), nephromegaly (Fig. 1d), cardiomegaly (Fig. 1e) and polyhydramnios were visualized, and BWS was suspected. After extensive counselling the couple decided to have genetic text only after delivery.

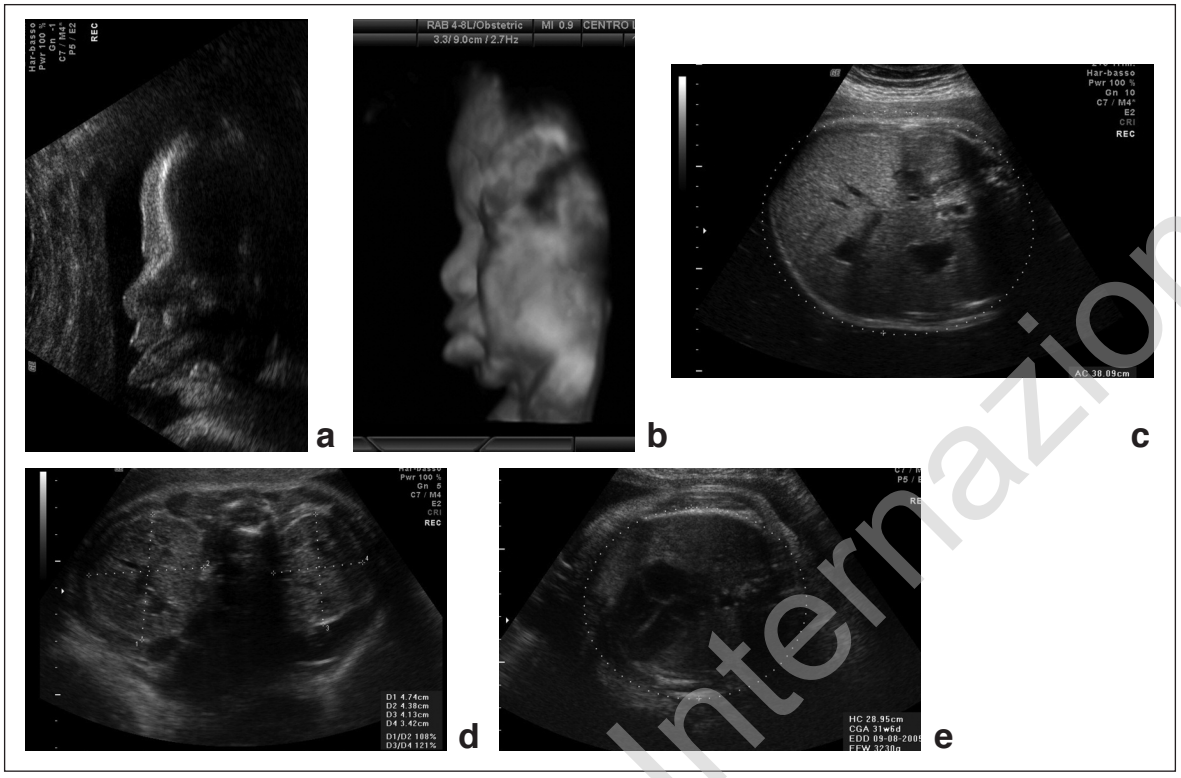

Figure 1. Ultrasound scan at 33 weeks' gestation demonstrating a) protruding tongue at 2-D ultrasound; b) protruding tongue at 3-D ultrasound; c) hepatomegaly; d) nephromegaly; e) cardiomegaly.

The newborn was delivered by cesarean section at 37 weeks' gestation. Clinical examination revealed a birth weight of 3,800 grams (>97° centile), a length of 50 cm (90° centile), macroglossia, diastasis recti, left ear creases, clitoromegaly, large left kidney. The liver scan revealed hepatomegaly with no evidence of liver tumors. Patient karyotype was normal but the molecular analysis of critical region 11p15.5 revealed the hypermethylation of H19 gene supporting the diagnosis of BWS. The AFP level was of 103,963 IU/ml at the date of birth. After 3 months the dosage was 4,817 IU/ml, 785 IU/ml after 6 months, and 59 IU/ml after 12 months. A surgical tongue reduction was performed.

Discussion

Prenatal diagnosis of BWS occurs sporadically with almost all cases being diagnosed at birth (4).
In our case, no ultrasonographic findings associated with BWS were depicted in the second trimester. The feature detectable during second trimester was an abnormal triple screen due to elevated AFP without evidence of NTDs or abdominal wall defects. Anomalies of triple screen in BWS fetus has been previously reported (5), presenting elevated values of AFP and human chorionic gonadotropin (hCG). In the present case hCG and uE3 levels were within normal range and only AFP presented high values with increased NTDs' risk. Elevated AFP has been described in fetuses affected by BWS (6). Elevated AFP and BWS is a well-known sign derived from abnormal liver function. In BWS children liver function abnormalities, albeit known, is related to liver neoplasm, and AFP is suitable for oncologic monitoring.
A fetal overgrowth was evidenced at 20 and 30 weeks' gestation but only at 33 weeks' some of the prenatal features of BWS were observed, and genetic counselling was addressed to a specific syndrome. Considering the advanced gestational age the couple opted to perform a specific only after delivery.

Conclusion

Our case suggests that BWS should be included as differential diagnosis, while performing a genetic sonogram in the second trimester of pregnancy with unexplained elevated AFP at second trimester serum triple screen. This case further highlights the potential of maternal serum screen for revealing maternal-placental-fetal disorders.

References

1. Online Mendelian Inheritance in Man. Center for Medical Genetics, Johns Hopkins University (Baltimore, MD) and National Cancer for Biotechnology Information, National Library of Medicine (Bethesda, MD) 1999. URL:http://www.ncbi.nlm.nih.gov/omim.
2. DeBaun MR, Tucker MA. Risk of cancer during the first four years of life in children from The Beckwith-Wiedemann Syndrome Registry. J Pediatr. 1998; 132:398-400.

3. Anfuso S, Soncini E, Bonelli P, Piantelli G, Gramellini D. Second-trimester maternal serum alpha-fetoprotein elevation and its association with adverse maternal/fetal outcome: ten years experience. Acta Biomed. 2007;78:214-219.
4. Everman DB, Shuman C, Dzolganovski B, O'Riordan MA, Weksberg R, Robin NH. Serum alpha-fetoprotein levels in Beckwith-Wiedemann syndrome. J Pediatr. 2000;137:123-7. Clericuzio CL J Pediatr. 2003;143:270-272.
5. Aagaard-Tillery KM, Buchbinder A, Boente MP, Ramin KD. Beckwith-Wiedemann syndrome presenting with an elevated triple screen in the second trimester of pregnancy. Fetal Diagn Ther. 2007;22:18-22.
6. Eliott M, Bayly R, Cole T, Temple IK, Maher ER. Clinical features and natural history of Beckwith-Wiedemann syndrome: presentation of 74 new cases. Clin Genet. 1994;46:168-172.