CASE REPORT

Elevated Alpha-fetoprotein in a 3-month-old Infant: The Significance in a Patient With Beckwith-Wiedemann Syndrome

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ABSTRACT

A 3-month-old female infant with omphalocele, posterior cleft palate and bilateral hydronephrosis was inadvertently discovered to have macroglossia, hepatomegaly, and facial nevus flammeus during hospitalisation for community-acquired pneumonia. A clinical diagnosis of Beckwith-Wiedemann syndrome (BWS), a disease with a higher predisposition to developing embryonal tumours was made. A liver ultrasound revealed a haemangioma at section VIII with the absence of hepatoblastoma. A serum alpha-fetoprotein (AFP) of 413 IU/mL was initially a concern given it was 60 times higher than the stated reference interval but was noted to be age-appropriate and related to the patient's underlying disease. This case report highlights the importance of reporting an AFP age-specific reference interval as well as the necessity of monitoring AFP in a child with BWS due to the higher risk of hepatoblastoma.
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INTRODUCTION

Beckwith-Wiedemann syndrome (BWS) is an overgrowth disorder characterised by a wide spectrum of clinical features including macrosomia, macroglossia, visceromegaly, abdominal wall defect, hypoglycaemia and a higher likelihood of developing embryonal tumours (1). The disease is associated with genetic and epigenetic alterations in chromosome 11p15. BWS is rare, with a prevalence of 1 in 10340 live births, which is probably underestimated as mild phenotypes may not be detected (2).

The risk of embryonal malignancies is a major concern with the highest risk occurring in the first two years of life. Wilms tumour (52%) and hepatoblastoma (16%) are the two most common tumours, followed by neuroblastoma (10%), rhabdomyosarcoma (5%) and adrenocortical carcinoma (3%) (2). Molecular studies have shown that patients with a gain of methylation at imprinting control region 1(IC1 GOM) on the maternal allele are predisposed to Wilms tumour, while patients with loss of methylation at imprinting control region 2 (IC2 LOM) on the maternal allele of chromosome 11p15 are more likely to develop hepatoblastoma. Both tumours occur with similar frequencies in patients with paternal uniparental isodisomy (pUPD) of chromosome 11p15 (2).

Alpha-fetoprotein (AFP) is increased in more than 95% of patients with hepatoblastoma and hence has been used to screen those at high risk (3). It is expressed at high concentrations during foetal development with the levels decreasing after birth until normal adult levels are achieved.

CASE REPORT

A 3-month-old female infant with omphalocele (primary closure of exomphalos minor performed at day two of life), posterior cleft palate (planned for surgery after the age of one year) and bilateral hydronephrosis presented to the paediatric clinic for a routine follow-up, upon which the mother complained that the child had been having rapid breathing. A physical examination revealed a respiratory rate of 54 breaths per minute and mild subcostal recession whilst a chest x-ray showed left upper zone consolidation. Her initial laboratory studies were unremarkable except for leukocytosis (16.12 x 10^9/L; reference interval, 4 – 10 x 10^9/L) and thrombocytosis (772 x 10^9/L; reference interval, 210 – 650 x 10^9/L). She was hence admitted for treatment of community-acquired pneumonia.

The child was born at term by spontaneous vaginal delivery to a mother with gestational diabetes mellitus on metformin. She has a 6-year-old sister with no underlying medical illness. There was also no family history of genetic disorders or malignancy in the family. During the morning ward round, a paediatrician noted several physical findings such as macroglossia, hepatomegaly (4-finger breadth below right costal margin), anterior linear earlobe creases and facial nevus flammeus which in combination suggested BWS. There was also an ejection systolic murmur and an umbilical hernia.

Echocardiography revealed moderate secundum atrial septum defect of 9 mm, mildly dilated right atrium, mild-to-moderate proximal right pulmonary artery stenosis, mild valvular pulmonary stenosis and mild tricuspid regurgitation. Otherwise, there was no evidence of pulmonary hypertension. An abdominal ultrasound showed presence of a hyperechoic lesion in segment VIII of the liver, which was likely a haemangioma with no evidence of hepatoblastoma. Her serum alpha-fetoprotein (AFP) concentration measured using the ADVIA Centaur AFP assay was 413 (reference interval <6.7 IU/mL). Although the parents were concerned about the elevated AFP, the paediatric onco-haematologist reassured them that the AFP was acceptable given the patient's age. The paediatric gastroenterologist confirmed that no treatment was required for the haemangioma apart from regular monitoring with liver function test, AFP and ultrasound abdomen. Considering that this child has a structural heart defect, close monitoring for heart failure or possibly Kasabach-Merritt syndrome was also recommended. The child was discharged after completing five days of intravenous antibiotics with negative findings of the nasopharyngeal aspirates for virology and blood culture. Molecular testing was not done on this patient.

DISCUSSION

Diagnosis of BWS

An international consensus scoring system is used to establish a clinical diagnosis of BWS and to determine if molecular testing should be pursued (1). A minimum of four points is required for its clinical diagnosis, with two points for each cardinal feature and one for each suggestive feature. This infant had a total of eight points; four points from cardinal features (macroglossia, exomphalos) and the remaining points from suggestive features (facial naevus simplex, ear creases, nephromegaly/hepatomegaly, umbilical hernia). Genetic testing is merit for patients with a clinical score of two or greater whilst a score ≥4 fulfils a diagnosis of classical BWS, even without molecular confirmation (2). Hence, genetic testing is not required for a confirmatory diagnosis of BWS in this patient.

Significance of AFP measurement in patients with BWS

AFP is considered an excellent indicator of hepatoblastoma (2). It has been recommended that all patients with BWS have a liver ultrasound and AFP performed every three months due to the 2280 times greater risk of developing hepatoblastoma than the general population, thus allowing for early detection, better treatment options and prognosis (3). AFP levels are also used to monitor response to treatment whereby a decreasing trend suggests a successful response to treatment. However, the international BWS consensus did not include AFP in their tumour surveillance recommendations as its interpretation in the general paediatric population is challenging. Various factors such as prematurity, comorbidities, and gender can affect its levels. Interpretation may be more difficult in BWS patients, as AFP levels tend to be higher and decrease at a slower rate compared to unaffected populations. Duffy et. al., reported AFP reference intervals (RIs) specifically for patients with BWS with values for a 3-month-old stated as 702 IU/mL (95% confidence interval 506 – 972). The study also showed a statistically significant difference in AFP levels between premature and non-premature BWS patients. An AFP of 459 IU/mL (95% confidence interval 309 – 681) and 1220 IU/mL (95% confidence interval 715 – 2080) was obtained for non-premature and premature BWS patients (3).

A serum AFP of 413 IU/mL in this patient although 60 times higher than the stated RI, was in fact age and disease appropriate for her underlying condition. The Canadian Laboratory Initiative on Paediatric Reference Intervals (CALIPER) study of healthy newborns to 18 years of age reported an upper limit of normal AFP level on four analysers (Abbott Architect, Beckman Coulter DxI 800, Ortho Vitros 5600 and Roche Cobas) (4). Of the four analysers, the Ortho Vitros 5600 had the lowest upper limit of normal (430 IU/mL) and the Beckman Coulter had the highest upper limit of normal (2479 IU/mL) in 3-month-old females. The variances are contributed by methodologies and reagent specificity; hence the importance of reporting assay-specific RI. AFP in our laboratory is measured on ADVIA Centaur AFP assay, a two-site sandwich immunoassay using direct chemiluminometric technology.The laboratory is in the process of reporting age-specific AFP RIs.

Association of BWS with Hepatic Haemangioma

Vascular tumours are uncommon and not typically associated with BWS. In this patient, a haemangioma at section VIII of the liver was noted. Infantile Hepatic Haemangioma (IHH) is a benign vascular tumour commonly seen in infants below six months of age. It can be focal, multifocal or diffuse, but are most often multiple and bilobar. Due to the significant risk of bleeding, a biopsy of the lesion is neither appropriate nor necessary to determine the diagnosis, which is

consistent with conservative management in this case. No treatment was administered other than regular monitoring of blood tests and ultrasonographic imaging. IHH often regresses spontaneously. The presence of both hepatoblastoma and IHH in infants with BWS is even rarer but has been reported, where differentiation between the two is important as the management differs (5).

Although patients with IHH have been reported to have elevated serum AFP, the levels are never as high as those with hepatoblastoma. The AFP levels should be assessed at diagnosis and during follow-up. An increasing AFP trend should raise concerns about hepatoblastoma or malignancy change (5).

CONCLUSION

In summary, this case report highlights the importance of an age-specific AFP RI for the paediatric population. It also raises the awareness that AFP tends to be raised in BWS and hence, the importance of serial AFP monitoring in these patients due to the higher risk of hepatoblastoma. The establishment of a local RI that reflects age, sex and ethnicity using assay methodology in the local hospital setting will unquestionably aid the clinician in managing the patient.

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