HHS Public Access

Author manuscript

Am J Med Genet A. Author manuscript; available in PMC 2018 May 01.

Published in final edited form as:

Am J Med Genet A. 2017 March ; 173(3): 581–584. doi:10.1002/ajmg.a.38068.

The Utility of Alpha-Fetoprotein Screening in Beckwith-Wiedemann Syndrome

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Abstract

Beckwith-Wiedemann syndrome (BWS) is one of the most common cancer predisposition disorders. As a result, BWS patients receive tumor screening as part of their clinical management. Until recently, this screening has been employed uniformly across all genetic and epigenetic causes of BWS, including the utilization of ultrasonography to detect abdominal tumors and alpha-fetoprotein (AFP) to detect hepatoblastoma. The advancements in our understanding of the genetics and epigenetics leading to BWS has evolved over time, and has led to the development of genotype/phenotype correlations. As tumor risk appears to correlate with genetic and epigenetic causes of BWS, several groups have proposed alterations to tumor screening protocols based on the etiology of BWS, with the elimination of AFP as a screening measure and the elimination of all screening measures in BWS patients with loss of methylation at the KCNQ1OT1:TSS-DMR 2 (IC2). There are many challenges to this suggestion, as IC2 patients may have additional factors that contribute to risk of hepatoblastoma including fetal growth patterns, relationship with assisted reproductive technologies, and the regulation of the IC2 locus.

Keywords

Beckwith-Wiedemann Syndrome; Tumor screening; Alpha-fetoprotein; Hepatoblastoma

INTRODUCTION

Advancements in genetic testing and the understanding of epigenetics have led to the classification of subgroups of patients with Beckwith-Wiedemann syndrome (BWS): loss of methylation at KCNQ1OT1:TSS-DMR (IC2); gain of methylation at H19/IGF2:IG-DMR (IC1); paternal uniparental isodisomy of chromosome 11 (pUPD); *CDKN1C* mutations; chromosome abnormalities and translocations; and those with no molecular defects identified. Until recently, all children with a clinically or molecularly confirmed diagnosis of BWS or isolated hemihypertrophy (IHH) have been advised to regularly screen for the development of tumors. While the exact frequency of screening has varied among institutions, it has generally been accepted that children should receive screening for the development of hepatoblastoma by serial serum alpha-fetoprotein (AFP) measurements

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every six weeks to three months until the age of four years, and screening for abdominal tumors by ultrasonography until the age of seven to eight years.

Screening protocols specific to epigenetic and genetic subtypes have recently been suggested, as tumor risk varies between these subgroups, with tumor screening focused on patients at higher risks. The specific surveillance protocols have varied in the literature, but a common element is the question of whether screening is warranted in patients with IC2 alterations, as they have a lower tumor risk compared to the other subgroups.

Maas et al. [2016] recently presented a pooled cohort of tumor frequencies reported within the IC2, IC1, pUPD, *CDKN1C*, and no molecular defect identified subgroups. The authors proposed that due to the low occurrence of hepatoblastoma in the BWS population, the invasiveness of screening, and the difficulty in interpreting AFP measurements, patients should only be screened by ultrasonography. Furthermore, they stated that screening is not indicated at all in IC2 patients. A similar protocol was suggested by Brioude et al. [2013].

Previously, it was proposed that pUPD and IC2 patients may benefit the most from hepatoblastoma screening [Cooper et al., 2005; Mussa et al., 2011]. These suggestions were recently amended, as Mussa et al. [2016a] concluded that AFP screening is recommended in pUPD patients and comment further in response to Maas et al. [2016] [Mussa and Ferrero, AJMG letter in review 2016]. Within this discussion, the utility of AFP screening in other BWS patients should be considered as well, as additional analysis and observations supports the use of AFP screening in BWS patients with IC2 alterations. Mussa et al recently suggested that pUPD patients should be screened and for non-pUPD patients screening should be offered and discussed [Mussa and Ferrero, AJMG letter in review 2016] and we are providing further evidence to support this assertion.

HEPATOBLASTOMA OCCURS IN SIMILAR RELATIVE FREQUENCIES IN IC2 AND pUPD PATIENTS

Among the types of tumors developed by IC2 and pUPD patients, the percentage of hepatoblastoma as the type of tumor developed is comparable between these subgroups, with a slightly higher percentage in the IC2 group. Based on the pooled data of frequencies of tumor development by epigenetic/genetic subgroup presented by Maas et al. [2016], there were 26 tumors developed in 26 patients in the IC2 subgroup and 67 tumors developed in 59 patients in the pUPD subgroup [Gaston et al., 2001; Weksberg et al., 2001; DeBaun et al., 2002; Bliek et al., 2004; Brioude et al., 2013; Ibrahim et al., 2014; Maas et al., 2016; Mussa et al., 2016c]. Hepatoblastoma was responsible for 7 of the 26 tumors in the IC2 group (26.9%) and 13 of the 67 tumors in the pUPD group (19.4%). In the cohort reported by DeBaun et al. [2002], the specific types of tumors developed were not specified. If the DeBaun cohort is removed from the pooled cohort, hepatoblastoma represented similar percentages in the IC2 and pUPD subgroups (28.0% and 20.0%, respectively). Hepatoblastoma was the most common tumor type developed in the IC2 group, while Wilms tumor was the most common type to develop in the pUPD group. This suggests that while IC2 patients are at an overall lower risk of tumor development compared to other genetic subgroups, if a patient with IC2 develops a tumor, it is more likely to be a hepatoblastoma.

THE ROLE OF THE IC2 REGION IN HEPATOBLASTOMA DEVELOPMENT

Hepatoblastoma has primarily been reported in subgroups with IC2 and pUPD, suggesting the IC2 region may play a role in its development. Of interest, in the pooled data cohort presented by Maas et al. [2016], only one patient in the no defect subgroup developed a hepatoblastoma and no patients in the IC1 and *CDKN1C* subgroups developed hepatoblastoma. It has been suggested previously that the IC1 region may play a role in the development of Wilms tumor, as the majority of BWS patients that develop this type of tumor have IC1 and pUPD defects [Brioude et al., 2013]. Using this same rationale, it can be hypothesized that the IC2 region may play a role in the development of hepatoblastoma, as patients with IC1 defects and *CDKN1C* mutations have normal methylation in this region. It is important to note that while hepatoblastoma primarily develops in IC2 and pUPD patients, there has been one patient with an IC1 defect reported who developed this tumor type [Mussa et al., 2016b]. This rare occurrence is similar to the reported two patients with IC2 defects who developed Wilms tumors [Maas et al., 2016].

The role of IC2 in the development of hepatoblastoma is suggested by the methylation analysis at imprinted loci in hepatoblastoma tissue compared to normal tissue [Rumbajan et al., 2013]. In this analysis of 12 hepatoblastoma samples reported, one patient was identified with BWS due to pUPD. However, among the non-BWS samples, loss of methylation (LOM) at IC2 was detected in an additional three tumors. In two cases the LOM at IC2 was isolated and in one additional case LOM at IC2 was seen in conjunction with gain of methylation at IC1, suggesting pUPD. While this study was small, it suggests a possible role of IC2 in the mechanism of hepatoblastoma formation.

Multiple methylation defects at imprinted genes have also been found in hepatoblastoma, suggesting other imprinted regions besides 11p15 may play a role in its development and some of these genes may serve as markers for tumor histology, outcome, recurrence, and age of onset [Tomlinson and Kappler, 2012; Rumbajan et al., 2013]. In patients diagnosed with an imprinting defect resulting in BWS, multi-locus methylation defects (MLMD) were found only in patients with loss of methylation at IC2, and accounted for approximately 20–25% of patients [Rossignol et al., 2006; Azzi et al., 2009; Bliek et al., 2009; Eggermann et al., 2014]. Perhaps MLMD patients are at an increased risk for tumors. Additionally, there may be other, as yet undefined, modifier genes predictive of hepatoblastoma risk in these patients.

ADDITIONAL RISK FACTORS FOR HEPATOBLASTOMA

Assisted reproductive technology (ART), prematurity, and low birth weight are among the risk factors for hepatoblastoma [Ross and Gurney, 1998; Ansell et al., 2005; McLaughlin et al., 2006; Allan et al., 2013; Heck et al., 2013; Tulla et al., 2015]. ART conceived children are three to nine times more likely to have BWS and the BWS subtype is usually IC2 [DeBaun et al., 2003; Maher et al., 2003; Halliday et al., 2004; Rossignol et al., 2006; Tee et al., 2013; Tenorio et al., 2016]. IC2 patients as a result of ART may be at higher risk for hepatoblastoma.

Additionally, more than three-quarters of premature births observed in BWS are in infants with IC2 alterations and the IC2 subgroup is less likely than the others to be large for gestational age [Mussa et al., 2016d]. As low birth weight and preterm birth are risk factors for hepatoblastoma, the fetal growth patterns of IC2 patients could provide increased risks for hepatoblastoma development. It is difficult to assess if prematurity alone is a risk factor for hepatoblastoma, further study is needed in both the general population and the BWS population.

EARLY DETECTION OF HEPATOBLASTOMA IMPROVES OUTCOME

The prognosis and event-free survival rates for hepatoblastoma remain significantly lower compared to Wilms tumor and other embryonal tumors [Tulla et al., 2015]. Tumor stage and surgical resection are independent predictors of survival in hepatoblastoma patients and despite advancements with chemotherapy and other treatment options, complete tumor resection remains the cornerstone of treatment [Herzog et al., 2000; von Schweinitz, 2012; Allan et al., 2013]. Patients with lower stage, localized tumors can most often have tumors fully resected and achieve survival rates reported between 80–100%, while patients with later stage tumors face a poorer prognosis, with survival rates between 40–65% and event-free survival of 20–30% [Herzog et al., 2000; Katzenstein et al., 2002; Perilongo et al., 2004; von Schweinitz, 2012; Allan et al., 2013; Czauderna et al., 2014].

Given that lower stage tumors have much higher success rates compared to later stage tumors, there is a clear need for early detection of these tumors. Although ultrasonography can detect hepatoblastoma, AFP has been shown to detect these tumors before abdominal imaging, in some cases with multiple normal scans after AFP elevation [Clericuzio et al., 2003; Zarate et al., 2009; Mussa et al., 2011]. Trobaugh-Lotrario et al. [2014] provided further evidence of the effectiveness of AFP screening, as all patients diagnosed through screening techniques had localized tumors and were alive at the conclusion of the study, while patients that did not receive screening had later stage tumors and only half survived [Trobaugh-Lotrario et al., 2014; Mussa and Ferrero, 2015].

SUMMARY

Despite an overall lower risk of tumor development in IC2 patients compared to other molecular subgroups of BWS, these patients have a number of factors that may increase their risk of hepatoblastoma. These risks include prematurity, lower birth weights compared to other BWS subgroups, conception through ART, and the possible role of the IC2 region itself. Further investigation of these potential co-factors in IC2 risk is warranted.

In light of recent recommendations suggesting that ultrasonography may not be warranted in the IC2 subgroup of BWS patients, we advise caution in the decision to also discontinue serial AFP monitoring. Without any screening, it is likely that the IC2 patients who do develop hepatoblastoma will have a later stage of the disease and face a much poorer prognosis.

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