HHS Public Access

Author manuscript

Am J Med Genet A. Author manuscript; available in PMC 2018 May 02.

Published in final edited form as:

Am J Med Genet A. 2016 September ; 170(9): 2261–2264. doi:10.1002/ajmg.a.37881.

Tumor Screening in Beckwith-Wiedemann Syndrome – To Screen or Not to Screen?

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Abstract

Beckwith-Wiedemann syndrome (BWS) is the most common imprinting disorder and consequently, one of the most common cancer predisposition disorders. Over the past 20 years, our understanding of the genetics and epigenetics leading to BWS has evolved and genotype/phenotype correlations have become readily apparent. Clinical management of these patients is focused on omphaloceles, hypoglycemia, macroglossia, hemihypertrophy, and tumor screening. Until recently, the need for tumor screening has been thought to be largely uniform across all genetic and epigenetic causes of BWS. As tumor risk correlates with genetic and epigenetic causes of BWS, several groups have proposed alterations to tumor screening protocols based on the etiology of BWS. However, there are many challenges inherent in adapting screening protocols. Such protocols must accommodate not only the risk based on genetic and epigenetic causes but also the medical cost-benefit of screening, the psychological impact on families, and the social-legal implications of missing a treatable tumor.

Keywords

Beckwith-Wiedemann Syndrome; Tumor screening; 11p Overgrowth

INTRODUCTION

Beckwith-Wiedemann syndrome (BWS) is an overgrowth and tumor predisposition disorder that affects at least 1 in 11,000 children [Hennekam RCM, 2010; Mussa et al., 2016a]. In many cases the clinical features are variable, which can make clinical and molecular diagnosis challenging. The range of clinical features is due to genetic and epigenetic changes on chromosome 11p15, leading to the use of the term "11p Overgrowth Spectrum." Due to the increased tumor risk for children with these genetic and epigenetic changes, tumor screening guidelines have been developed [Beckwith, 1998; DeBaun and Tucker, 1998; Cooper et al., 2005; Lapunzina, 2005; Rump et al., 2005; Scott et al., 2006; Tan and Amor, 2006; Clericuzio and Martin, 2009; Weksberg et al., 2010; Teplick et al., 2011; Mussa et al., 2016a] along with modified recommendations [Brioude et al., 2013; Mussa et al., 2016a; Mussa et al., 2016c].

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As we have developed a better sense of the correlations between phenotype and (epi)genotype [Eggermann et al., 2016], there has also been a stratification of tumor risk. Most comprehensively, Maas et al. [Maas SM, 2016] in this issue has presented some genotypes and epigenotypes that lead to an elevated risk (up to 28%) while other epigenotypes lead to a lower risk (as low as 2.8%). Contemporaneously with the Maas et al. publication discussed herein, Mussa et al. [Mussa et al., 2016b] published a meta-analysis of an overlapping historical dataset and proposed a slightly different (epi)genotype-specific screening protocol.

Maas et al. very elegantly presented their current Amsterdam/UK data combined with a meta-analysis of previously published work on tumor risk within each genotype/epigenotype and offered thoughtful suggestions on how best to update the current screening protocol [Maas SM, 2016]. This work now raises the challenge of how to use these data to implement screening protocols for 11p Overgrowth Spectrum patients in a practical manner. In particular, the medical, societal and legal environments, which may vary both nationally and regionally, need to be considered in implementing screening guidelines.

CURRENT RECOMMENDATIONS

Current tumor screening recommendations do not differ based on the genetic cause of BWS, although some practitioners may follow the children in the higher risk groups more closely or react to abnormalities more urgently. Ultrasounds are recommended every 3 months until age 8 years and alpha-fetoprotein (AFP) measurements are recommended at intervals ranging from 6 weeks to 3 months until age 4 years [Weksberg et al., 2010; Teplick et al., 2011]. Interpretation of results by radiologists, geneticists, and/or oncologists familiar with BWS likely lowers the incidence of false positive results. Patients with *CDKN1C* mutations are screened for neuroblastoma using urine HVA/VMA screening as well.

RECENTLY PROPOSED RECOMMENDATIONS

Maas et al. recommend stratifying tumor screening in BWS based on the genetic/epigenetic cause of BWS [Maas SM, 2016]. They recommend screening only for patients in the highest risk groups. Specifically, such groups include patients with paternal uniparental disomy of 11p15 (pUPD11) and gain of methylation at imprinting center 1 (IC1), who carry tumor risks as high as 16% and 28% respectively. Their recommendations suggest screening with abdominal ultrasounds every three months until age 5 years, based on a risk of less than 5% after that age. They consider screening patients with *CDKN1C* mutations with ultrasounds and urine screening as well. Of note, they propose no screening for patients with loss of methylation at imprinting center 2 (IC2), which carries a 2.6% risk of tumor formation. Maas et al. also state that AFP screening for hepatoblastoma presents challenges with interpretation of variable results, the frequency of screening required to make the test useful, and the anxiety that blood draws cause for children and families and disagree with its use [Maas SM, 2016]. The recent meta-analysis by Mussa et al. [Mussa et al., 2016b] reported similar findings regarding tumor risk and (epi)genotypes and proposed screening, except that they propose continuing to screen IC1 and pUPD11 patients for Wilms tumor beyond age 5 years.

MULTIPLE INFLUENCES AFFECT IMPLEMENTATION OF MEDICAL PRACTICE

Maas et al. have built their model based on the clinical features and molecular diagnosis, medical management, and frequency of adverse outcomes in the 11p Overgrowth Spectrum [Maas SM, 2016]. Very often, however, the medical context in which patient care occurs is influenced heavily by patient and societal financial considerations, parental and patient anxiety as well as potential legal ramifications due to a missed diagnosis. These medical, molecular, financial and societal implications together influence the implementation of tumor screening into medical practice.

PATIENT AND SOCIETAL FINANCIAL IMPLICATIONS OF RARE DISORDER SCREENING

The overall societal impact of tumor screening in rare disorders is quite different from population-based screening programs like those for breast cancer. This difference in scale suggests that most cost-benefits analyses will likely favor the benefits of screening over the adverse outcomes of not screening [McNeil et al., 2001]. In evaluating the financial cost of screening, the context of private versus public insurance needs to be considered. Private insurance usually covers the cost of screening, but public insurance, particularly universal health care, may not cover the cost of screening. Therefore private health care plans may prefer to screen at a lower cost per patient and reduce the likelihood of a large cost given an undetected tumor. Under universal health care, however, the occasional larger cost due to a later detected tumor may outweigh the cost of regular screening for the larger population.

PARENTAL AND PATIENT ANXIETY ABOUT A MISSED DIAGNOSIS

Many previous studies have only evaluated screening by ultrasound based on cost and did not account for parental anxiety regarding tumor screening or patient anxiety around the blood draws for AFPs. The parent and patient anxiety brings us to consideration of the family microenvironment in which tumor screening occurs. How does one quantify the anxiety a parent feels waiting by the phone for the screening results? Does the screening reassure or merely provoke additional anxiety?

Screening can improve the emotional well being of families, by giving parents a sense of control and continued reassurance with negative results [Beckwith, 1998; Tan and Amor, 2006; Teplick et al., 2011]. In accordance with this theory, some parents choose to continue screening past the recommended eight years [McNeil et al., 2001]. Others argue that screening creates a burden on families as a result of frequent screening visits, the invasiveness of AFP draws, and the anxiety associated with false-positive results [Beckwith, 1998; Choyke et al., 1999; Lapunzina, 2005; Tan and Amor, 2006; Clericuzio and Martin, 2009; Zarate et al., 2009; Mussa et al., 2016a]. These factors are thought to contribute to poor adherence to screening [Zarate et al., 2009]. It has been suggested that the opinions of families should be considered in the decision to discontinue screening in patients and that families may be more anxious if screening is stopped [Scott et al., 2006].

Most of the current data regarding parental attitudes and anxiety towards cancer screening have been in regards to testing of children with familial cancer predisposition syndromes [Gopie et al., 2012]. Screening was associated with good psychological outcomes, as most participants viewed screening programs positively and felt that screening both offered security and gave participants a sense of control. Individuals compliant with screening reported less fear, but screening was still associated with increased distress and lower quality of life overall [Gopie et al., 2012]. These data are applicable to the situation of BWS families, but distinct in that BWS families face a graded risk ranging from <2.8% to 28% depending on the genetic cause and the tumor type.

LEGAL RAMIFICATIONS OF MISSED DIAGNOSIS

Just as accessibility to care varies between countries and even between regions, liability and legal ramifications vary greatly as well. For example, the malpractice lawsuit payment rate in Pennsylvania is twice the rate in Illinois, despite the fact that the populations are similar [Services, 2014]. Therefore, to effectively implement a screening protocol, this variation must be accommodated.

Maas et al. use an acceptable risk model of 5% in determining which epigenetic subtypes to screen and at which age to stop screening for Wilms tumor [Maas SM, 2016]. In other pediatric practice contexts, the risk of disease may be much lower and screening remains standard practice. For example, in the well-studied management of a child with fever and petechiae, the risk for meningococcemia is 1.6%, with practice guidelines recommending CBC, antibiotics and treatment [Mandl et al., 1997]. If a similar acceptable risk cutoff of 1% were applied to the 11p Overgrowth Spectrum, one would recommend screening all patients for Wilms tumor until 8 years of age, AFP screening, and screening IC2 patients despite the comparative lower risk of tumor development.

LIMITATIONS OF PROPOSED MODEL ACCESS TO GENETIC TESTING

One of the challenges of stratifying screening by genetic testing is that in order to implement guidelines based on genetic testing results, patients need to have access to reliable genetic testing. Insurance companies or universal health care need to be willing to pay for that testing as part of necessary medical care. Additionally, the proposed tumor-screening model is designed for patients with a clear clinical diagnosis followed by a molecular diagnosis. When molecular and clinical diagnoses overlap, this screening paradigm could be implemented though there are concerns regarding some of the specifics of the Maas et al. [Maas SM, 2016] proposal. That being said, the proposed model does not address the subtler end of the 11p Overgrowth Spectrum without a confirmed molecular diagnosis.

EFFECTIVE AFP SCREENING

It is well documented that early detection of hepatoblastoma can lead to a more timely diagnosis and better outcome for patients. Alpha-fetoprotein screening can aid with early detection prior to radiological findings. An elevated AFP with radiological evidence can prompt the start of treatment with the need for a biopsy [Perilongo et al., 2004; Clericuzio

and Martin, 2009; Zarate et al., 2009; Mussa et al., 2011; Ricafort, 2011; Trobaugh-Lotrario et al., 2014]. Without the rise in AFP values to prompt clinical suspicion and more frequent imaging studies, many cases would likely have gone undiagnosed until the later stages of tumor development.

AFPs need to be performed in a patient- and family-sensitive manner. This testing can be reassuring but sporadic testing is difficult to interpret. We have found regular AFPs to be incredibly useful for detection of early hepatoblastomas. Accordingly, accurate data tables for AFPs are key to making AFP results easier to interpret.

Because of both historical and ongoing utility of AFPs in detecting hepatoblastomas, it is important to carefully evaluate the role of AFPs in screening in 11p Overgrowth Spectrum before discontinuing the use of AFP in tumor surveillance recommendations. Maas et al. [Maas SM, 2016] may have misinterpreted the 2015 letter to the editor by Mussa and Ferrero, as “the usefulness of AFP screening should be doubted” when the authors stated that “we could debate whether screening of all BWS patients for hepatoblastoma is worthwhile, but, in our opinion, screening the UPD ones is mandatory [Mussa and Ferrero, 2015].” Despite its widespread use, there is a need to establish better AFP reference values in this population to enable better interpretation. A study on the cost-effectiveness of AFP screening versus hepatoblastoma treatment could better clarify the utility of screening as well. Finally, the effect of AFP screening on either creating or calming family anxiety should be better characterized to assist in developing tumor surveillance recommendations.

LENGTH OF WILMS TUMOR SCREENING

In the Wilms tumor literature, the average age of diagnosis for a unilateral Wilms tumor is 38 months, which suggests that in a much larger cohort of children (far beyond the numbers available for BWS), the risk for Wilms tumor is well beyond 5 years of age [Breslow et al., 1993]. According to the Children’s Oncology Group, 75% of Wilms tumors occur before age 5, but that leaves 25% occurring at an older age [Davidoff, 2009]. Therefore, basing guidelines on a smaller and relevant dataset needs to be balanced with the much larger datasets available through the Wilms tumor literature.

HOW TO IMPLEMENT TUMOR SCREENING GUIDELINES FOR BWS

The challenge as a clinician is how to best apply recent medical publications and recommendations to our patients especially when such recommendations are not yet consensus-based from a recognized expert body. We must consider the cost to patients and their families—not simply the dollar amount, but also the burden on a family to screen (time off from work, anxiety, etc.), as well as the burden of not screening and potentially missing a treatable tumor. Screening recommendations must balance all of these considerations, along with the anxiety that tumor screening can cause for a family. How do we apply data to clinical practice? Do we initiate screening for new patients? Do we cease screening for current patients? What do we say to the families in the lower-risk category whose children have nonetheless developed tumors? In order to take further action to implement new guidelines, we need to not only account for the current data set forth by Maas et al. [Maas

SM, 2016], but we also need to gather data across several countries to assess the burden of screening on families and to best allow us to implement or modify these guidelines.

SUMMARY

Given the risk stratification presented by Maas et al [Maas SM, 2016] and Mussa et al. [Mussa et al., 2016b], it is clear that there are variable risks based on the genetic and epigenetic causes of BWS. Furthermore, to effectively alter the current screening guidelines, it is necessary to gather more data on how such guidelines can be implemented into clinical practice. Comprehensive guidelines should also include development of international cost-benefit analysis paradigms to compare the impact that altering tumor screening pathways would have on patients and families within a given country. While the data assessment by Maas et al. [Maas SM, 2016] is insightful, it may not apply universally. To best accomplish strategies tailored to unique medical systems, further data are necessary in order to build models that allow us to implement these recommendations.

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