VIEWPOINT

Should testing for mosaic genome-wide paternal uniparental disomy in Beckwith-Wiedemann spectrum (BWSp) be implemented in diagnostic testing?

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INTRODUCTION

Beckwith-Wiedemann syndrome (BWS; OMIM #130650), is an overgrowth disorder mainly characterized by macrosomia, macroglossia, and abdominal wall defects. Diagnosis is made based on a clinical scoring system and because the phenotype can be variable the term Beckwith-Wiedemann spectrum (BWSp) is recently introduced [1]. Approximately 80–85% of the clinically diagnosed patients have (epi)genetic aberrations in the imprinting center regions ICR1 and ICR 2 on 11p.15 leading to the perturbed expression of monoallelic expressed (imprinted) genes. There are three most common molecular subtypes: loss of methylation at *KCNQ1OT1*:TSS-DMR (IC2 LOM; ~50% of patients), gain of methylation at *H19/IGF2*:IG-DMR (IC1 GOM; 5–10% of patients), and paternal uniparental isodisomy of chromosome 11 (patUPD11; ~20% of patients). A small number of patients have an intragenic mutation in the *CDKN1C* gene. In ~15% of BWS cases, no (epi)genetic aberrations in the primary BWS-associated region 11p15 can be detected [1]. In these patients molecular testing in other tissues can be considered as somatic mosaicism can vary between different tissues [1, 2].

Patients with BWSp have an increased risk of developing embryonal tumors depending on the genetic subgroup. Patients with pUPD11 have an overall tumor risk of 16%, mainly Wilms tumor (7.9%) and hepatoblastoma (3.5%) [1, 3]. With some differences in mean age at diagnosis depending on tumor types, the overall cancer risk is highest in the first 2 years of life and then declines progressively. Therefore tumor screening until the age of seven is carried out in all genetic subgroups except IC2LOM, who are not screened at all [1].

MGWpatUPD in BWS

Mosaic genome-wide paternal uniparental disomy (MGWpUPD) is a rare genetic condition in which alleles are inherited solely from the father in part of the cells. The majority of patients present with a BWSp phenotype and occasionally features that are associated with other imprinting disorders that are caused by paternal UPD [4, 5]. Also homozygosity for pathogenic variants in the isodisomic cells can have an effect on the phenotype [5]. Reports of percentages of patients with BWSpUPD carrying a mosaic GWpUPD vary from 2–3 to 16% [6, 7]. At this moment standard procedures for molecular testing in BWS are confined to the 11p15 region, leaving MGWpUPD undetected.

The risk of developing tumors is suggested to be higher for patients with MGWpUPD compared to patients with pUPD11 and tumors in patients with MGWpUPD are also reported later in life [5, 8]. Extended data on lifelong tumor risk of patients with MGWpUPD are not available. In large cohort studies on tumor risk of patients with BWS, tumor risk calculated in patients with pUPD comprehends the risk for patients with MGWpUPD [3, 9]. Data on tumor risk in patients with MGWpUPD are only available from a limited number of case reports as reviewed by Postema [8]. In these 19 case reports, typical BWS tumors which are screened for according to the current screening protocol for pUPD patients, all appeared within the recommended screenings period. In total, 37% of the patients developed one or more malignant tumors of variable nature after the screening period. Higher tumor risk might be explained by homozygosity of paternal mutations in tumor suppressor genes but this has not been evaluated yet.

Numbers are small and data might be biased as in most adult cases MGWpUPD is detected only after the development of malignancies. Most of the patients described were young, so data on lifelong tumor risk are incomplete.

Data of adult patients with BWS in general are limited. Gazzin et al. studied 34 adult patients with BWSp and reported no tumors at an adult age in the pUPD11 group (5 cases) [10]. Tumors that were reported occurred in the other molecular groups. This report implicates that tumor risk in adult patients may not be necessarily associated with pUPD or hidden MGWpUPD although the patient group is small. Collecting these data for patients with MGWpUPD is hampered by the fact that most of the patients with BWSp are lost for follow-up at an older age. Additionally, case control studies comparing the tumor risk of patients with MGWpUPD, following all patients until adult age, with the other molecular subgroups have not yet been described.

IMPLICATIONS FOR SCREENING

At this moment testing of MGWpUPD in patients with pUPD11 is not recommended in the international consensus guidelines [1].

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Molecular diagnostic tools for the detection of MGWpUPD are available and could be implemented in routine diagnostics.

The consequence of the molecular diagnosis of MGWpUPD on clinical care and monitoring tumor development in BWSp patients remains to be resolved. In recent publications a more stringent and extensive screening protocol is recommended for the patients with MGWpUPD [4, 5, 11]. However, Wilms tumor and hepatoblastoma all occurred before the age of seven in the reported patients with MGWpUPD and are therefore detected in the recommended screening protocol for patients with pUPD11. The variability of the nature of the other tumors and the age at which these tumors developed in the reported patients with MWGpUPD make effective surveillance very complicated.

Before changing clinical care and screening protocols it is crucial to have more knowledge about the exact risk of developing tumors in all molecular BWSp subgroups. The age at which the tumors developed (especially above the age of 7 years) and its nature should be taken into account. Testing for MGWpUPD in patients with pUPD11 should be started initially in a research setting. After collecting these data, it will be possible to decide whether the implementation of diagnostic tests for MGWpUPD in patients with pUPD11 is needed.

International collaboration in this research is needed to obtain sufficient data.

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AUTHOR CONTRIBUTIONS

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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