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Genetic forum

Recommendations of the Scientific Committee of the Italian Beckwith–Wiedemann Syndrome Association on the diagnosis, management and follow-up of the syndrome

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ABSTRACT

Beckwith–Wiedemann syndrome (BWS) is the most common (epi)genetic overgrowth-cancer predisposition disorder. Given the absence of consensual recommendations or international guidelines, the Scientific Committee of the Italian BWS Association (www.aibws.org) proposed these recommendations for the diagnosis, molecular testing, clinical management, follow-up and tumor surveillance of patients with BWS. The recommendations are intended to allow a timely and appropriate diagnosis of the disorder, to assist patients and their families, to provide clinicians and caregivers optimal strategies for an adequate and satisfactory care, aiming also at standardizing clinical practice as a national uniform

Abbreviations: αFP, alpha-fetoprotein; ART, Artificial Reproductive Techniques; BWS, Beckwith–Wiedemann syndrome; *CDKN1C*, Cyclin-Dependent Kinase Inhibitor 1C gene; CGH, Comparative Genomic Hybridization; CoBRA, Combined Bisulsulphite Restriction Analysis; IC, imprinting center; IC2-LoM, loss of methylation at imprinting center 2; IC1-GoM, hypermethylation of the imprinting center 1; *IGF2*, Insulin-like Growth Factor 2; HELLP, hemolysis, elevated liver enzyme levels and low platelet count; IHH, isolate hemihyperplasia; MS-MLPA, methylation-sensitive multiple ligation probe amplification; PAPP-A, Pregnancy-Associated Plasma Protein A; SNP, Short Nucleotide Polimorphimsms; UPD, chromosome 11p15.5 uniparental paternal disomy.

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approach. They also highlight the direction of future research studies in this setting. With recent advances in understanding the disease (epi)genetic mechanisms and in describing large cohorts of BWS patients, the natural history of the disease will be dissected. In the era of personalized medicine, the emergence of specific (epi)genotype–phenotype correlations in BWS will likely lead to differentiated follow-up approaches for the molecular subgroups, to the development of novel tools to evaluate the likelihood of cancer development and to the refinement and optimization of current tumor screening strategies. Conclusions: In this article, we provide the first comprehensive recommendations on the complex management of patients with Beckwith–Wiedemann syndrome.

1. Background

Beckwith–Wiedemann syndrome (BWS) (OMIM #130650) results from the variable association of overgrowth, abdominal wall defects (omphalocele, umbilical hernia, *diastasis recti*), macroglossia, nephrourologic malformations, hemihyperplasia, hyperinsulinaemic hypoglycaemia, ear anomalies (lobe creases or helical pits), capillary malformations (hemangioma and *nevus flammeus* at the glabella), and organomegaly (Eggermann et al., 2014; Weksberg et al., 2010). The syndrome entails the predisposition to embryonal tumor development in infancy: malignancy risk is estimated as high as 10% during the first decade of life and the histotype spectrum typically includes Wilms' tumor and hepatoblastoma besides other rarer histotypes. Specific molecular anomalies at chromosome 11p15.5 are found in 75–80% of BWS patients, but the diagnosis is clinical (Rump et al., 2005, Ibrahim et al., 2014).

Isolated hemihyperplasia (IHH, OMIM #235000), namely localized overgrowth of a part of the body, is considered the mild end of BWS spectrum as it is caused by the same molecular anomalies and entails the same implications for cancer development (Niemitz et al., 2005).

Currently, no consensual recommendations or international guidelines are available for the management of BWS. The Scientific Committee of the Italian Beckwith–Wiedemann Syndrome Association (www.aibws.org), proposes these recommendations as a national uniformed approach for the diagnosis, management and follow-up of patients with BWS/IHH, notwithstanding molecular tests results. These recommendations are intended to allow a timely and appropriate diagnosis of the disorder, to assist patients and their families, to provide clinicians and caregivers optimal strategies for an adequate and satisfactory care, and aims to standardize clinical practice.

2. Epidemiology

BWS is the commonest genetic overgrowth condition. The prevalence estimate for cases with clear-cut diagnosis is about 1 in 10,500 live births (Mussa et al., 2013), but this figure may be an underestimation as recent research has revealed that the typical molecular anomalies can be found in atypical cases lacking full diagnostic criteria or with only minor ones. The prevalence is almost equal in the two sexes, the distribution is panethnic, and there is no demonstrated risk factor although accumulating evidence indicates that BWS is more frequent among children conceived by Artificial Reproductive Techniques (ART). BWS registries show that the proportion of BWS patients conceived using ART is at least 4% (DeBaun et al., 2003; Gicquel et al., 2003; Maher et al., 2003) and that the prevalence of BWS in ART cohorts may reach 1 in 4000 live births (Hiura et al., 2012, Vermeiden and Bernardus, 2013).

3. (Epi)genetic causes and molecular subtypes

BWS is a paradigm of congenital disorders of genomic imprinting, a process consisting in a parent-of-origin-dependent gene expression. A cluster of imprinted genes associated with BWS is present at chromosome 11p15.5. Both growth inhibitory, such as Cyclin-Dependent Kinase Inhibitor 1C (*CDKN1C*) and *H19*, and growth-promoting genes, such as Insulin-like Growth Factor 2 (*IGF2*), are present in the 11p15.5 region. The 11p15.5 gene cluster is functionally divided in two domains each controlled independently by an imprinting center (IC) that is methylated on only one parental chromosome in a parent-of-origin manner. At the centromeric domain, the IC (IC2) is normally methylated only on the maternal chromosome; its methylation inhibits the expression of a long non-translated RNA (*KCNQ1OT1*) that in turn allows the expression of the maternal *CDKN1C* allele. At the telomeric domain, the methylation of the IC (IC1) is paternal; this leads to *IGF2* expression and *H19* repression on the paternal chromosome and to *IGF2* repression and *H19* activation on the maternal chromosome, *H19* expressed. Therefore, in normal conditions, the telomeric domain expresses the paternal allele of *IGF2* and the maternal allele of *H19* (Mussa et al., 2015b).

The molecular defects resulting in BWS are heterogeneous but in about 80% of the cases affect the 11p15.5 region and lead to unbalanced expression of imprinted genes (Choufani et al., 2010; Mussa et al., 2015b; Shuman et al., 2000). The vast majority of molecularly confirmed BWS cases (>90%) are sporadic, while the remaining 10% show autosomal dominant inheritance with parent-of-origin dependent penetrance (Lubinsky et al., 1974, Shuman et al., 2000). In approximately 50% of the cases, the molecular defect consists in loss of methylation of IC2 on the maternal chromosome (IC2-LoM) leading to reduced expression of *CDKN1C*. About 10% of the cases are associated with gain of methylation of IC1 on the maternal chromosome (IC1-GoM) resulting in biallelic expression of *IGF2* and silencing of *H19* that in turn cause a double stimulus to cell proliferation. Uniparental Paternal Disomy (UPD) of the 11p15.5 region is present in 20% of BWS cases and lead to both reduced *CDKN1C* and *H19* expression and biallelic expression of *IGF2*. All patients with UPD have somatic mosaicism. Most of the cases with IC1-GoM and IC2-LoM are sporadic; the rare familial cases are associated with microdeletion/duplications or point mutation involving either one of the two ICs (Chiesa et al., 2002; Demars et al., 2010; Sparago et al., 1994). Chromosomal rearrangements associated with BWS are found in 1–3% of cases and consist mostly in paternal 11p15.5 duplications or trisomies (Shuman et al., 2000; Weksberg et al., 2010). Approximately 5–10% of BWS cases are associated with inactivating mutations of the *CDKN1C* gene on the maternal allele and may cause familial transmission of the phenotype (Hatada et al., 1997; Romanelli et al., 2010). Finally, approximately 20% of the clinically diagnosed cases have no detectable molecular defect in spite of a clear-cut phenotype.