Lateralized and Segmental Overgrowth in Children

Subjects: Oncology | Pediatrics

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Lateralized overgrowth (LO), or segmental overgrowth, is defined as an increase in tissue growth of various origins (skeletal, muscular, fibrous, vascular, adipose, or any association of these) in any region of the body.

Lateralized overgrowth (LO) cancer screening

1. Background

Congenital disorders of lateralized or segmental overgrowth (LO) are heterogeneous conditions with increased tissue growth in a body region. LO can affect every region, be localized or extensive, involve one or several embryonic tissues, showing variable severity, from mild forms with minor body asymmetry to severe ones with progressive tissue growth and related relevant complications. Recently, next-generation sequencing approaches have increased the knowledge on the molecular defects in LO, allowing classifying them based on the deranged cellular signaling pathway. LO is caused by either genetic or epigenetic somatic anomalies affecting cell proliferation. Most LOs are classifiable in the Beckwith–Wiedemann spectrum (BWSp), PI3KCA/AKT-related overgrowth spectrum (PROS/AROS), mosaic RASopathies, PTEN Hamartoma Tumor Syndrome, mosaic activating variants in angiogenesis pathways, and isolated LO (ILO). These disorders overlap over common phenotypes, making their appraisal and distinction challenging.

2. Beckwith–Wiedemann Spectrum (BWSp)

2.1. Overview

BWSp (OMIM # 130650) is the most common congenital overgrowth disorder with a prevalence approaching 1:10,000 live births in the general population [1] and of 1:1100 in children conceived by assisted reproduction techniques [2]. Its clinical features include fetal macrosomia, postnatal overgrowth, abdominal wall defects, LO, macroglossia, auricular anomalies (indentations in the ear lobes and helix of the pavilion), organomegaly, nephro-ureteral malformations, hyperinsulinism with hypoglycemia, and oncological predisposition. The malformations can be variably associated and have different degrees of severity, thus resulting in a widely variable clinical spectrum. LO in BWSp can rarely be identified prenatally, not even in particularly severe forms [3][4][5][6]. BWSp diagnosis is clinical and based on criteria that have been refined over time and recently reviewed by leading experts in pathology [7] (**Table 1**). BWSp includes typical Beckwith–Wiedemann syndrome (BWS) cases (when several of the diagnostic criteria are present with a score ≥ 4 points, with or without associated genetic anomalies), atypical BWS

(when typical molecular anomalies are found in patients with few diagnostic criteria and score is <4 points), and cases with ILO and associated molecular BWSp abnormalities (**Figure 1**) [8].

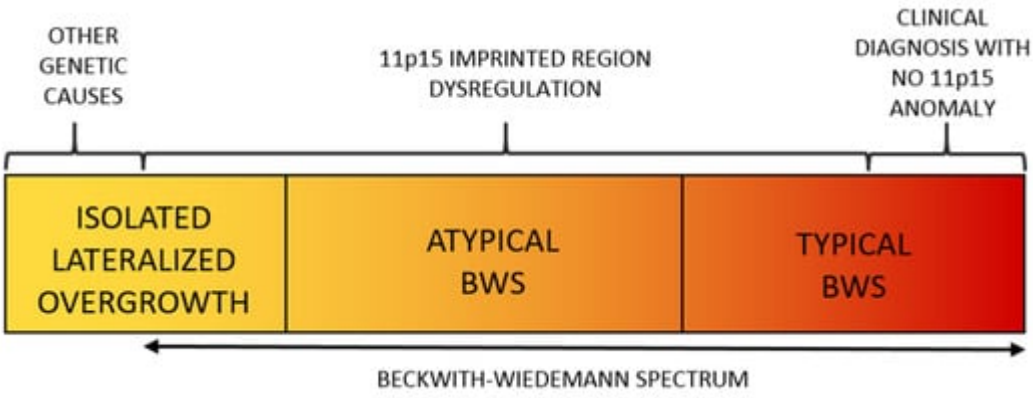

Figure 1. The Spectrum of the Beckwith–Wiedemann Syndrome (BWSp) includes (1) patients with "typical Beckwith–Wiedemann syndrome (BWS) with a clinical diagnosis (score ≥ 4 points) with or without an (epi)genetic change at 11p15.5 imprinted region, (2) patients with "atypical forms" (defined as those with a score < 4 points) *plus* an (epi)genetic change at the BWS locus, and (3) patients with isolated lateralized overgrowth (ILO) plus an (epi)genetic change at the 11p15.5 locus.

Table 1. Cardinal and suggestive clinical features of Beckwith–Wiedemann spectrum (BWSp). Features of BWSp are classified into cardinal ones (2 points each) and suggestive ones (1 point each). Molecular testing is indicated with ≥2 points or positive family history and inheritable 11p15 anomaly. The clinical diagnosis of BWSp can be made in cases with ≥4 points. From Brioude et al. [7].

Cardinal Features (2 Points Each)	Suggestive Features (1 Point Each)
Macroglossia	Macrosomia (height/Birth Weight > +2SD)
Exomphalos	Facial naevus simplex
Lateralized overgrowth	Polyhydramnios/Placentomegaly
Multifocal/bilateral Wilms tumor or Nephroblastomatosis	Ear creases/pits
Hyperinsulinism	Transient hypoglycemia/hyperinsulinism
Pathology findings:	Typical BWSp tumors (neuroblastoma, rhabdomyosarcoma, unilateral WT, hepatoblastoma, adrenocortical carcinoma, phaeochromocytoma)
Adrenal cortex cytomegaly	Nephromegaly/Hepatomegaly
Placental mesenchymal dysplasia	Umbilical hernia/Diastasis recti
Pancreatic adenomatosis	

imprinting defects. While most human genes are expressed by both maternal and paternal alleles, genes subject to genomic

imprinting are expressed monoallelically based on parental origin. This differential expression mechanism is regulated epigenetically by the differential methylation of parental alleles at the differentially methylated regions (DMR) of two imprinting centers (ICs) at 11p15.5 in BWSp. IC1 and IC2 regulate the transcription of two clusters of genes involved in cell cycle progression. Epigenetic anomalies of these regions are found in nearly 85% of cases of BWSp. **Figure 2** details the molecular mechanisms of the syndrome: (a) Loss-of-Methylation (LoM) in IC2 occurring in more than 50% of cases, (b) Gain-of-Methylation (GoM) in IC1 detected in 5–10% of cases, (c) paternal uniparental disomy of chromosome 11 (UPD(11)pat) identified in 20–25% of cases, (d) inactivating mutations of the *CDKN1C* gene, observed in 5% of cases, and responsible for about half of heritable cases [7][9].

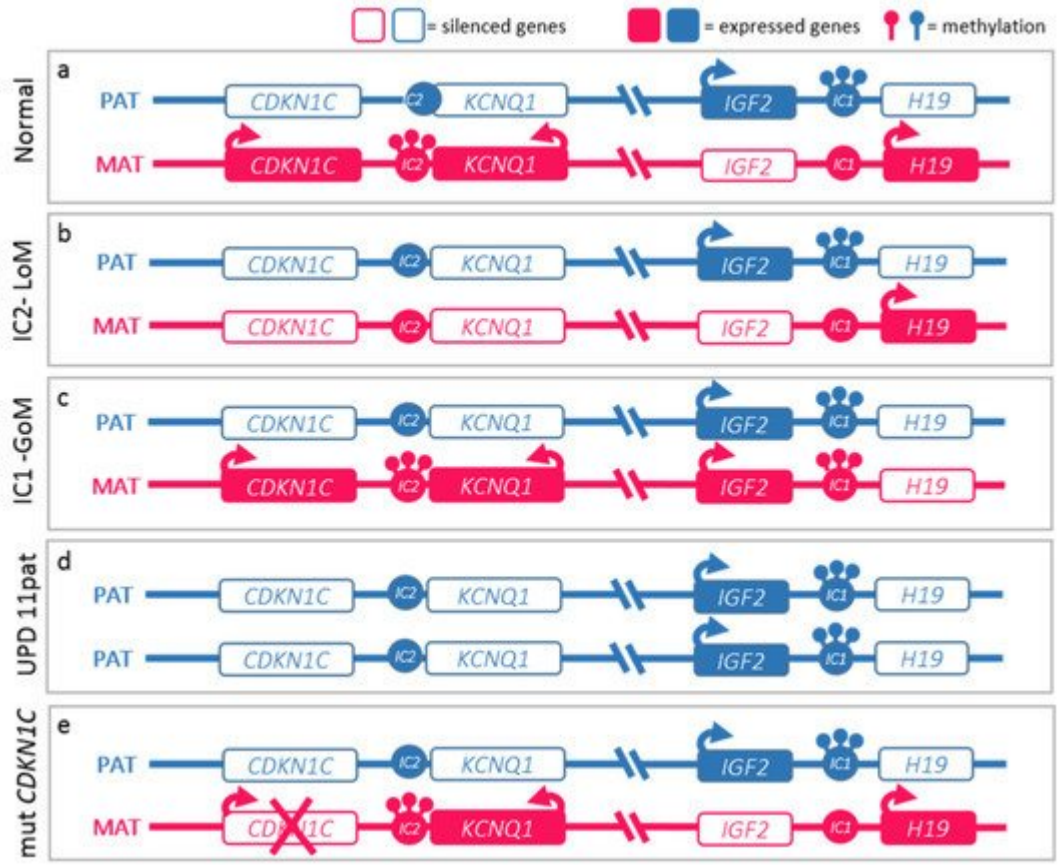

Figure 2. Molecular defects in Beckwith–Wiedemann spectrum (BWSp). (**a**) Normal functioning of the paternal (blue) and maternal (red) 11p15 imprinted domains. The centromeric domain is regulated by the imprinting center 2 (IC2) which methylation regulates the expression of *KCNQ1*, *KCNQ1OT1* (*KCNQ1 Opposite Strand/Antisense Transcript 1*), and *CDKN1C* expression. Normally, *KCNQ1* and *CDKN1C* are expressed by the maternal alleles and silenced on the paternal ones, while *KCNQ1OT1* is expressed only by the paternal one. The telomeric domain is regulated by the IC1: methylation on the paternal chromosome silences *H19* and allows *IGF2* expression. BWSp can be caused by: (**b**) IC2 loss of methylation (IC2-LoM) on maternal chromosome leading to reduced expression *CDKN1C*; (**c**) gain of methylation at maternal IC1 (IC1-GoM) leading to biallelic *IGF2* and reduced *H19* expression; (**d**) chromosome 11 paternal uniparental disomy (UPD(11)pat), leading to both expression anomalies seen in IC2-LoM and IC1-GoM; (**e**) *CDKN1C* loss-of-function mutations on the maternal chromosome. The latter are dominant and lead to BWSp phenotype only when inherited from the mother.

2.3. Lateralized Overgrowth in BWSp

LO is one of the cardinal features of BWSp and mild BWSp can be evident with ILO (**Figure 3**). LO is present in approximately one-third of BWSp patients. Although LO can be found in patients with each of the molecular subtypes of BWSp [10], this feature shows a strong association with UPD(11)pat: in this group, its prevalence is around 60–80%, while it is less common in the IC2-LoM (25%) and the IC1-GoM (35%) groups, and very rare in *CDKN1C* mutation cases (less than 5% of cases) [11][12]. LO is the feature of BWSp showing the strongest association with cancer development [12][13][14][15]. LO has a mild trend in worsening during growth, especially if compared to other conditions with segmental overgrowth [16]. Mainly the more severe LLD tend to have worse evolution. Despite orthopedic interventions and epiphysiodesis being effective in correcting the LLD, the LO and LLD remain a significant cause of disability and morbidity in adulthood [17].

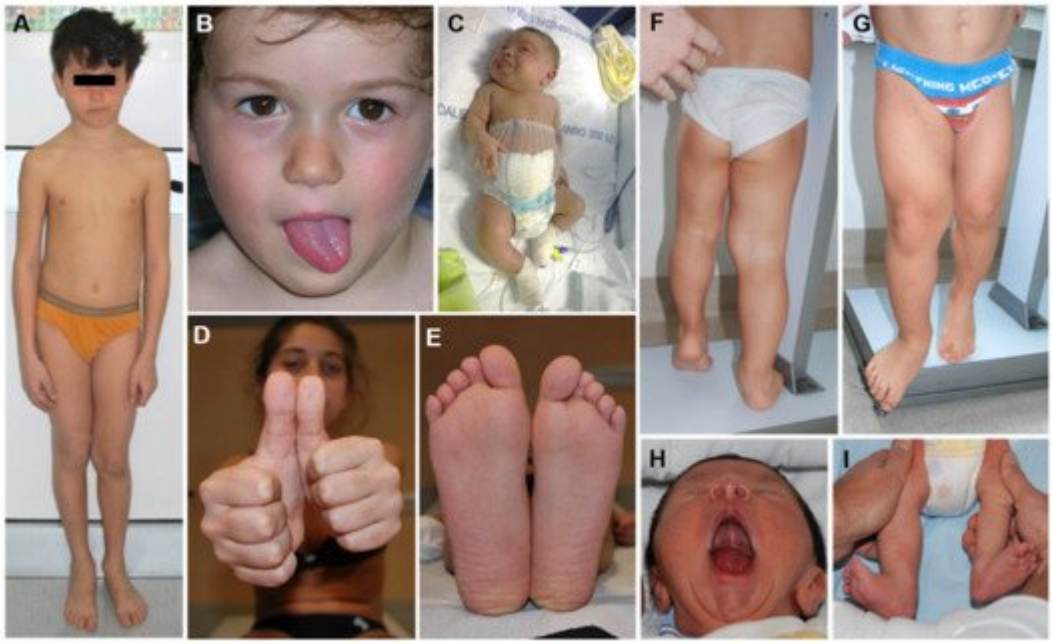

Figure 3. Lateralized Overgrowth (LO) in patients within the Beckwith–Wiedemann spectrum (BWSp). Isolated LO with Imprinting Center 2 Loss of Methylation (IC2-LoM, (**A**)), paternal uniparental disomy of chromosome 11 (UPD(11)pat) (**B**,**H**,**I**), and IC1 Gain of Methylation (IC1-GoM, (**D**,**E**)); severe LO in patients with BWSp clinical criteria and UPD(11)pat (**C**,**F**,**G**).

2.4. Cancer Screening

Cancer surveillance represents the most delicate and controversial aspect of the clinical management of patients with BWSp. The (epi)genotype-phenotype correlation studies allowed us to stratify the oncological risk with respect to the different molecular subgroups. For the majority of patients, those affected by IC2-LoM, the tumor risk is low (about 2%) and mostly encompasses hepatoblastoma or rhabdomyosarcoma. On the opposite, the risk is relevant in patients with UPD(11)pat (about 15%) and these patients develop any kind of tumor seen in BWSp, mainly

Wilms tumor (WT) and hepatoblastoma, but also adrenal carcinoma and pheochromocytoma. The highest risk is seen in patients with IC1-GoM and approaches 25%, almost exclusively for WT [18][19].

The cornerstones of surveillance in BWSp are abdominal ultrasound (US) for early detection of WT [20] and the serum alpha-fetoprotein assay [21][22][23] used for early diagnosis of hepatoblastoma. The US can detect also hepatoblastoma at advanced stages with respect to alpha-fetoprotein [24][25], as well as other rarer abdominal neoplasms. The US up to 8 years of age and alpha-fetoprotein assay up to 4 years of age are repeated quarterly based on tumor growth data [26]. There is a currently unanimous consensus on performing quarterly ultrasound (US) WT screening up to the eighth year of age in patients with IC1-GoM, UPD(11)pat and negative molecular tests [26]. The position of experts on US screening in patients with IC2-LoM and on screening for hepatoblastoma by means of the alpha-fetoprotein assay, on the other hand, appears varied [26][27]. In many European countries, the IC2-LoM group is not screened as it has almost no risk for WT and alpha-fetoprotein screening is not adopted given the overall low-risk of hepatoblastoma (less than 5%) [26]. On the other hand, in the USA, adopting a lower risk threshold (~1%) the IC2-LoM group is screened and the alpha-fetoprotein assay screening is suggested [28]. However, epidemiology suggests that most tumors in patients with IC2-LoM and hepatoblastoma cases occur within the first 2 years of life, therefore, we adopt the US in IC2-LoM and alphafetoprotein assay every 3 months up to 24–30 months of age for all patients [29]. A rare epigenetic subtype of BWSp, androgenetic chimerism, is characterized by severe features and very high cancer risk and needs a more frequent and intense screening protocol that can be extended to young adulthood [30].

Management of the adrenal masses in children with BWSp has been reviewed by MacFarland et al. [31].

It is common that children with WT are diagnosed within the BWSp secondarily to cancer diagnosis [32]. Moreover, it has been recently demonstrated that up to one-third of children with WT or hepatoblastoma have a 11p15.5 epimutation detectable in the blood [33] and suggested that this testing might be included among those by a sequencing-based approach to screen for a cancer predisposition in children with such tumors [33].

3. Lateralized Overgrowth Syndromes with Vascular Anomalies

Diffuse capillary malformation with overgrowth (DCMO) is a clinical diagnosis identifying patients with multiple and extensive capillary malformations (CM) associated with overgrowth of a body segment, usually an entire hemisome or limb. CM in DCMO are typically reticulate, pale, extensive, and diffuse, characterized by multiple anatomic regions contiguously stained [34]. The absence of deep venous varicosities, the persistence of embryonic vessels or lymphatic components differentiate DCMO from KTS, together with being virtually free of major complications and limited evolution over time. DCMO is an entity recently described: confusion still exists in the clinical definition of many conditions characterized by overgrowth and vascular anomalies and many of such conditions are identified as yet with definition and as syndromes dating back to the pre-NGS era. Currently, the classification of vascular anomalies with overgrowth is rapidly evolving thanks to massively parallel sequencing. Somatic variants in *GNAQ* and *GNA11* have been found in DCMO as well as in overlapping disorders, such as Sturge–Weber syndrome [35].

More recently, it has been highlighted that DCMO can also be caused by pathogenetic variants in *PIK3CA*: molecular testing is, therefore, necessary to correctly categorize and characterize cases of DCMO.

4. Isolated Lateralized Overgrowth (Not Belonging to Other Overgrowth Disorders)

4.1. Overview

The diagnosis of ILO is made clinically when segmental overgrowth is not attributable to a specific multiple developmental disorder and shows no associated anomaly or malformation. Diagnosing this clinical entity can be tricky for two reasons. First, it is not trivial to distinguish overgrowth of a region of the body from contralateral hypoplasia/hypotrophy, both because the mechanisms involved in the pathogenesis are different, and because of the profound differences in clinical management. An example is represented by segmental undergrowth/hemyhypoplasia that can be seen as an isolated feature in mild forms of Silver–Russell syndrome [36]. The latter is the mirror phenotype of BWS and is caused by the opposite (epi)genetic changes of BWS [37]. ILO, therefore, implies the differential diagnosis with causes of isolated undergrowth of a body area [38], as it is not easy to distinguish which of the body part is normal and which is affected by an over/under-growth condition. In this view also acquired congenital asymmetries, not of genetic origin must be considered: examples are vascular disruption during fetal life or iatrogenic limb hypoplasia consequent to vascular damage following central lines positioning. Correctly framing the clinical presentation is key to requesting appropriate molecular tests and setting up a correct management approach and follow-up.

4.2. Molecular Bases

The etiopathogenetic mechanisms at the basis of ILO include somatic mosaicisms for genetic or epigenetic mutations responsible for an alteration of the cell growth mechanisms of the affected tissues. The most frequently identified molecular anomalies fall within those of BWSp, mostly UPD(11)pat, and pathogenic variants in the PI3K/AKT/mTOR signaling pathway. Recently, high depth NGS approaches have increased dramatically the knowledge on the molecular defects causing these disorders, allowing classifying many of them into groups based on the cellular signal pathway involved. Indeed, when a specific molecular anomaly is found, ILO can be actually reclassified as a mild phenotype of the corresponding overgrowth disorder. However, currently few studies have evaluated what percentage of ILO cases is attributable to these specific genetic causes. Genetic testing carried out on the affected tissue (i.e., skin or muscle biopsy) rather than on leukocyte-extracted DNA allows increasing the rate of a molecular diagnosis in a relevant percentage of ILO cases [39]. Molecular tests include MS-MLPA for anomalies of the 11p15.5 region, SNP array and high-depth NGS of genes of the PI3K/AKT/mTOR and RAS/MAPK pathways; 11p15.5 methylation status testing on blood-extracted DNA allows to classify less than 6% of ILO cases as BWSp [39]. This is likely related to both a mosaicism level lower than the sensitivity limits of the analytical method, and to an inadequate sampling of the affected tissue or a combination of both factors. The rate of positive MS-MLPA test increased to 40% testing tissues other than blood [8]. It also appears likely that the ILO may have molecular bases still to be unraveled and require further studies on large case studies.

4.3. Cancer Risk and Surveillance

The identification of one of the typical molecular lesions makes it possible to include the ILO in a specific spectrum of disorders and to adopt related clinical guidelines. In the case of negativity to all molecular tests, a prudential clinical follow-up is adopted for such patients taking into consideration the possibility of low-expression forms of the molecular anomalies of the BWSp (i.e., the form with the highest oncogenic risk) and the related oncological implications. However, the literature indicates that ILO has a lower tumor risk than that of BWSp, with a risk ranging from 1.1% to 6% [39][40][41][42]

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