 UNDER-DIAGNOSED BECKWITH-WIEDEMANN SYNDROME AMONG EARLY-ONSET OBESE CHILDREN
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Introduction: 
- Beckwith-Wiedemann syndrome (BWS) is a clinical and genetically heterogeneous entity encompassing overgrowth with a widely variable clinical phenotype that attenuates with age. Although there is no complete consensus, proposed criteria to warrant clinical suspicion for BWS are the presence of at least 3 major or 2 major plus 1 minor features. Obesity can be a feature associated with macrosomia, but it is not considered a criterion.
- Early diagnosis of BWS is crucial due to the increased risk for developing embryonal malignancies (mainly below 5 years of age).
- Several genetic and epigenetic aberrations affecting the imprinted 11p15 locus can cause BWS, all of them leading to the down-regulation of maternally expressed genes and/or the up-regulation of paternally expressed genes. Two of the genes in these regions, IGF2 and CDKN1C, contribute to growth regulation and are directly related to the pathogenesis of BWS. (Figure 1A)

Objective: 
- We aimed to determine the presence of underdiagnosed BWS in early-onset “non-syndromic” obese children in our department.

Patients and methods: 
- We studied 159 children (95 males/64 females) diagnosed with early-onset (<5 years) severe (BMI-SDS >3 SDS) obesity.
- A custom-made methylation-specific multiple-ligand-probe- assay (MS-MLPA), with HhaI as a methylation-sensitive restriction enzyme, was used to analyze blood cell DNA methylation at the 11p15.5 region. The assay contains 11 probes, including one for the imprinting-center-1 (IC1) locus (H19) and one for IC2 (KCNQ1). Probes located at fully unmethylated loci were included as technical controls, as wells as probes without the HhaI recognition site for methylation quantification.
- Hypomethylation at the KCNQ1 locus was identified in two of the 157 patients. The same MS-MLPA assay was useful to discard unbalanced genomic rearrangements or uniparental disomy at this 11p15.5 region, considering that the methylation level at H19 was within the reference range.
- A decrease of 60% in the methylation level at KCNQ1 locus was detected in patient 1, while in patient 2 the reduction was approximately 33% (Figure 1B). The different percentage of methylation reduction suggests different degrees of mosaicism for the alteration in the two samples. Both patients with 11p15.5 epimutations had been referred to our Pediatric Endocrinology clinic due to severe childhood obesity. Neither of them fulfilled the minimum criteria for clinical diagnosis of BWS (Table). Kidney ultrasound and plasma alpha-fetoprotein levels (after diagnosis) were normal in both girls.
- Patient 1, with a higher degree of methylation impairment, presented no single criteria for diagnosis of BWS. She had suitable birth anthropometry, height, and bone age according to target height and chronological age and her obesity was ameliorating as age progressed (Figure 2).
- Patient 2, with a lesser degree of methylation impairment, had one major [pre- (birth length and weight 53 cm and 4.0 kg, respectively) and post-natal macrosomy (height +2.7 SDS)] and two minor criteria [gastropulmonary and advanced bone age (+ 2 years over chronological age)]. She presented a more severe predominantly abdominal obesity (BMI >8 SDS) while in adolescence (Figure 3).

Conclusions: 
- Some overgrowth syndromes, particularly BWS, can present clinically as early-onset obesity, with mild or no prenatal overgrowth and no other features, leading to misdiagnosis and misclassification as “common” obesities.
- Genetic testing for BWS should be considered in early-onset obesity. MS-MLPA is an useful and efficient diagnostic tool.