A 4 MONTH-OLD BOY WITH BECKWITH WIEDEMANN SYNDROME (BWS)

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No conflict of interests.

Background

Beckwith-Wiedemann syndrome (BWS), an overgrowth and tumor predisposition syndrome is clinically heterogeneous. It is characterized by macrosomia, macroglossia, visceromegaly, embryonal tumors (Wilms tumor, hepatoblastoma, neuroblastoma, and rhabdomyosarcoma), omphalocele, hypoglycemia in 30-50% of neonates, ear creases/pits, adrenocortical cytomegaly, and renal abnormalities (medullary dysplasia, nephrocalcinosis, medullary sponge kidney, and nephromegaly)[1].

Growth rate slows around age seven to eight years. Hemihyperplasia may affect segmental body regions or selected organs and tissues. Early death may occur from complications of prematurity, hypoglycemia, cardiomyopathy, macroglossia, or tumors. Previously reported mortality of 20% is likely an overestimate due to enhanced treatment options and better recognition of the disorder.

Case Report

- A **4 month-old boy with overgrowth and longitudinal hemi-hypertrophy of tongue and left cheek** delivered with (ELSC) Elective Section Cesarean due to fetal macrosomia;
- **Birth weight** was 4600grams **(+3.0 SDS)**, **98.6th** percentile and **birth length** 53cm **(+1.25 SDS)**, **90th** percentile;
- **Auxology parametars**: **weight 9.9 kg (+3.5 SDS)** and height, **68cm (+2.3 SDS)** at **4 months**, both at **99th** percentile, at **20 months**, **17kg (+3,35 SDS)** and **88 cm (+1,2 SDS) and BMI 21,95 kg/m² (+3,3 SDS)**;
- There is **a difference of 1cm circumference between his left and right leg**, but not in their length or in arms;
- **The behavior, intelligence and development were also normal.**

Abstract

Background: Beckwith Wiedemann Syndrome (BWS) is an overgrowth disorder with variable phenotype (hemihypertrophy, macroglossia, visceromegaly, malformations, hypoglycemia in 30-50%) and predisposition for tumors, during the second part of pregnancy and first few years of life.

Aims and objectives: Molecular characterization of a patient with BWS was performed to ensure adequate clinical management. This analysis revealed the most common form of BWS due to loss of methylation in KvDMR1 in presence of a normal *H19*-DMR methylation.

Methods: We present a 4 month-old boy with overgrowth and longitudinal hemi-hypertrophy of tongue and left cheek delivered with (ELSC) Elective Section Cesa-rean due to fetal macrosomia. His birth weight was 4600grams (+3.0 SDS), 98.6th percentile and birth length 53cm (+1.25 SDS), 90th percentile. The boy had 9.9 kg (+3.5 SDS) and high, 68cm (+2.3 SDS) at 4 months, both at 99 percentile. There was a difference of 1cm circumference between his left and right leg, but not in their length or in arms. Diagnostic assessment was achieved according to clinical features, ultrasound survey, biochemical and molecular analysis.

Results: Performed tongue, cardiac, abdominal and renal ultrasound scans (USS) showed: longitudinal left hemihypertrophy of tongue tissue, round heart shape with mild aortal valve stenosis, mild hypertrophy of liver and moderate hypertrophy of kidnies, especially left one. A brain ultrasound was uneventful, but on MRI were prominent both frontoparietal subarachnoideals more than 5mm. Karyotype was normal male, 46, XY. No evidence of clinical or biochemical parameters for hypoglycemia. Molecular analysis revealed hypomethylation of KvDRM1 (LIT1) in chromosome 11p15 region and normal methylation pattern for *H19* with estimated tumor risk of 1-5%.

Conclusions: We present a patient with BWS phenotype associated with molecular confirmation of loss of function in specific gene in the imprinting cluster and low risk of embryonal tumors. The overall estimation will predict his clinical management.

Key words: Beckwith Wiedemann Syndrome (BWS), overgrowth, hypomethylation, embryonal tumors

Methods

Ultrasound scan (USS) survey :

- **Tongue – longitudinal left hemihypertrophy of tongue tissue,**
- **Cardiac – round heart shape with mild aortal valve stenosis,**
- **Abdominal – mild hypertrophy of liver,**
- **Kidney – moderate hypertrophy of kidnies, especially left one;**
- **Brain – uneventful.**

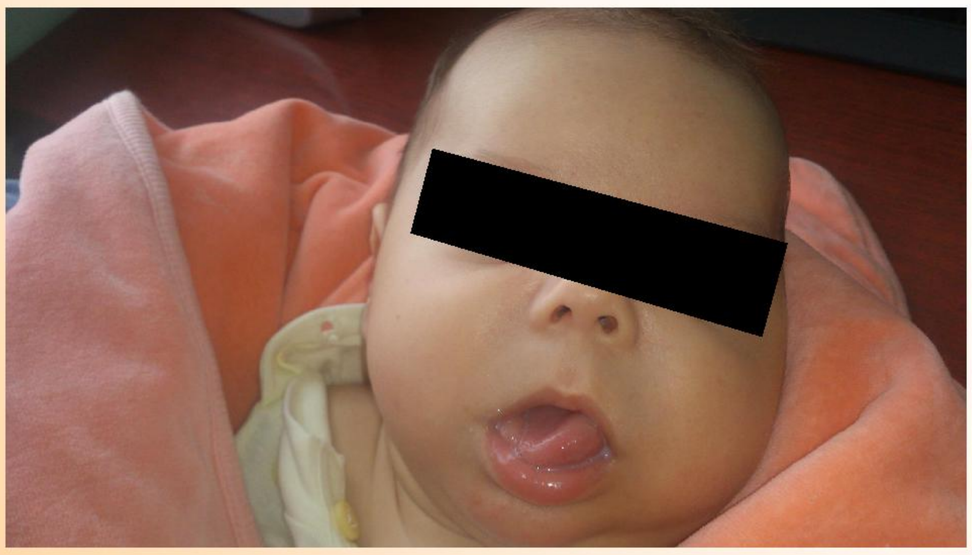
Brain MRI: prominent both frontoparietal subarachnoideals more than 5mm.

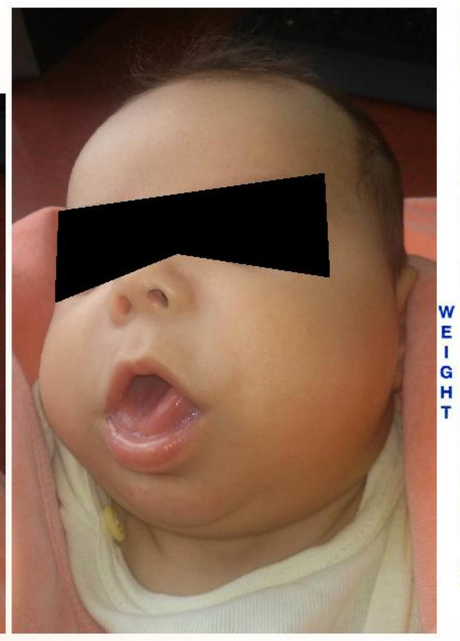
Karyotype: normal male, 46 XY

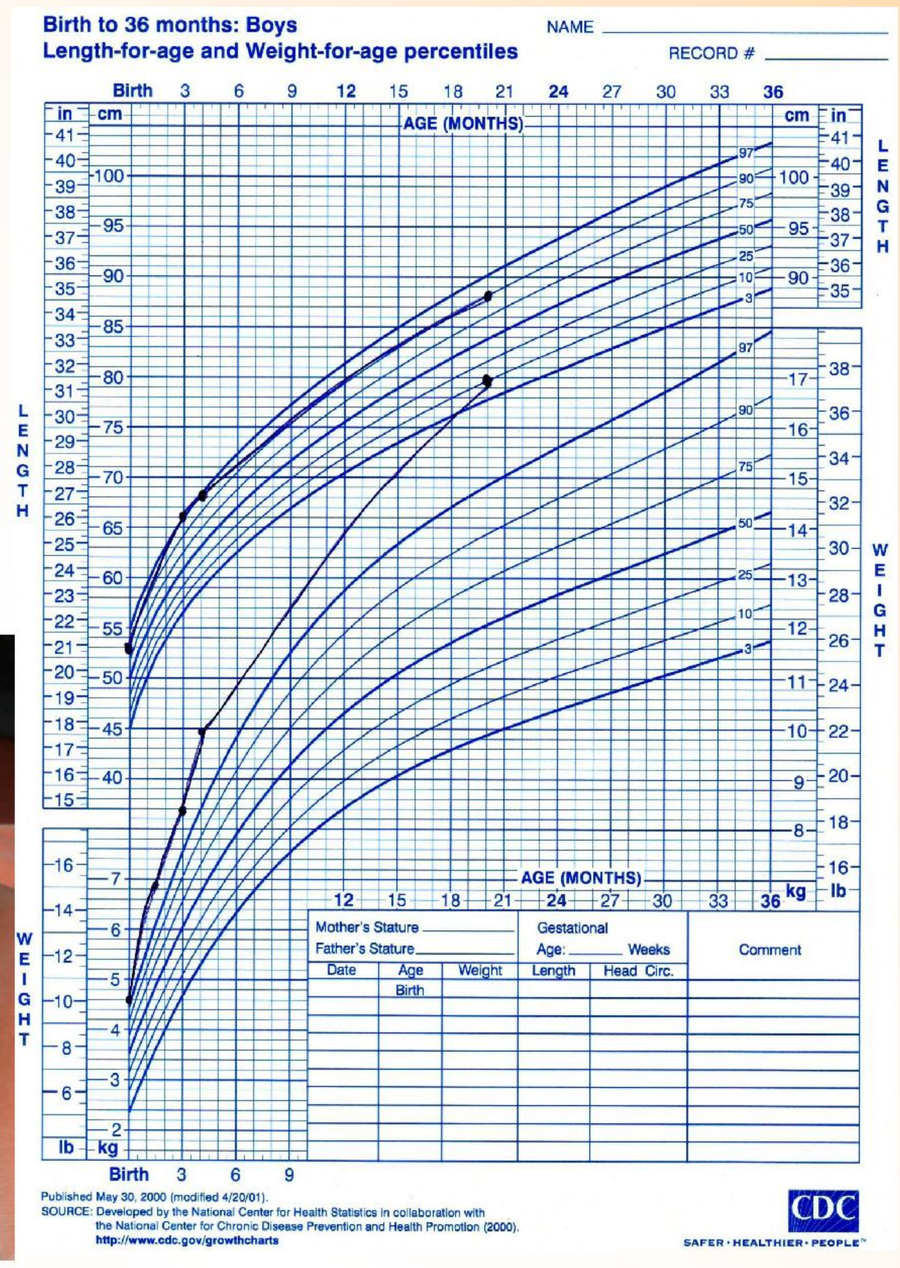
Biochemical and hormonal analyses: no evidence of hypoglycemia, others in normal range for his age and sex.

Molecular genetic deletion /duplication analyses of BWS/SRS critical region 11p15 (MLPA)[2]:

- **hypomethylation of KvDRM1 (LIT1) in chromosome 11p15 region;**
- **normal methylation pattern for *H19*-DMR with estimated tumor risk of 1-5%.**







Discussion

- No consensus diagnostic criteria for Beckwith-Wiedemann syndrome (BWS) exist, although the presence of several findings (three major or two major and one minor) is often used to confer a clinical or provisional diagnosis.
- Beckwith-Wiedemann syndrome is associated with abnormal regulation of gene transcription in the imprinted domain on chromosome 11p15.5. Most individuals with BWS are reported to have normal chromosome studies or karyotypes [3].
- Most BWS cases are sporadic, 85% have no family history of it and result from loss of maternal methylation at imprinting center 2 (IC2), gain of maternal methylation at imprinting center 1 (IC1) or paternal uniparental disomy (UPD)[4].
- Nearly 10-15% have a family history consistent with autosomal dominant transmission of BWS [3].
- ***Treatment of manifestations:*** tongue reduction surgery for macroglossia in infancy or early childhood, craniofacial surgery will benefit patients with facial hemihyperplasia, neoplasia should be treated using adequate pediatric oncology protocols [3].
- ***Prevention of secondary complications:*** Annual renal ultrasound examination for affected children between age eight years and mid-adolescence to identify those with nephrocalcinosis or medullary sponge kidney disease [3].
- ***Surveillance:*** Monitor for hypoglycemia, especially in the neonatal period; screen for embryonal tumors by abdominal ultrasound examination every three months until age eight years; monitor serum alpha-fetoprotein (AFP) concentration every two to three months in the first four years of life for early detection of hepatoblastoma [5].
- ***Prenatal screening:*** It is possible by chromosome analysis for families with an inherited chromosome abnormality or by molecular genetic testing for families in which the molecular mechanism of BWS has been defined.

Conclusions

Determination of impairment in a patient with an overgrowth and confirmed molecular diagnosis is crucial for establishment the concept of his further follow up and expected complications.

We present a patient with BWS phenotype associated with molecular confirmation of loss of function in specific gene in the imprinting cluster and low risk of embryonal tumors. The overall estimation will predict his clinical management.

Molecular analysis enabled genetic advice in this family. This implicates an importance of the prenatal diagnosis and its impact on quality of life in children.

References

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