sciendo

ПРИЛОЗИ. Одд. за мед. науки, XXXIX 2–3, 2018 МАНУ
CONTRIBUTIONS. Sec. of Med. Sci., XXXIX 2–3, 2018 MASA

10.2478/prilozi-2018-0052

ISSN 1857-9345
UDC: 616-056.7-053.2

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

Aleksandra Janchevska[1], Velibor Tasic[1], Nevenka Laban[1], Momir Polenakovic[2], Zoran Gucev[1], Nadine Bachmann[3], Carsten Bergmann[3]

[1] Medical Faculty, Skopje, Republic of Macedonia

[2] Macedonian Academy of Sciences and Arts, Skopje, Republic of Macedonia

[3] Center for Human Genetics, Bioscientia Institute for Medical Diagnostics Ingelheim, Germany

Corresponding author: Aleksandra Janchevska, MD, Medical faculty Skopje, 50th Division, 1000 Skopje, Republic of Macedonia, Mob. Tel: +389 70 305 685, e-mail: dr.sasha1969@yahoo.com

ABSTRACT

Objectives: Molecular characterization of a patient with BWS.

Clinical presentation and intervention: A 4-year-old boy with overgrowth (weight above 99th and height at 99th percentile) had longitudinal hemihypertrophy of the tongue and left cheek. In addition, there was a difference of one centimeter in the circumference of the left and right leg. Molecular genetic analysis revealed hypomethylation of KvDRM1 (LIT1) in the imprinting control region-2 (ICR2) on chromosome 11p15.5 and a normal methylation pattern of the *H19*-differentially methylated region (*H19*-DMR) in the ICR1. The estimated tumor risk was 1-5%.

Conclusion: This patient with clinical characteristics of BWS has an imprinting defect associated with a low risk of embryonal tumors.

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

INTRODUCTION

Beckwith-Wiedemann syndrome (BWS/ MIM 130650), an overgrowth syndrome with tumor predisposition, is clinically very heterogeneous. It is characterized by macrosomia (weight and height more than the 97th percentile for the patient's age and sex), macroglossia, visceromegaly (in one or more intra-abdominal organs), 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). The overall estimated BWS occurrence is about 1/13 in 700 healthy individuals [1, 2, 3].

Prematurity, macroglossia, hypoglycemia, tumors or cardiomyopathy may be the cause of death in infancy. A mortality of 20% was reported [4]. However, this seems to be exaggerated as there are improved treatment options and BWs tends to be earlier diagnosed.

CLINICAL PRESENTATION AND INTERVENTION

We present a now 4-year-old boy, with overgrowth and longitudinal hemihypertrophy of the tongue and left cheek, delivered with elective Cesarean section due to fetal macrosomia. His birth weight was 4600 grams (+2.9 SDS), 99.8th percentile and birth length 53cm (+1.83 SDS), 96.6th percentile. The boy was initially referred at the age of 1.5 months with weight of 6.9 kg (+2.7 SDS) and length of 61cm (+2.1 SDS) (Fig.1 and Fig.2). At the age of four years his height was at the 99.6th (+2.12 SDS) percentile, weight was above the 99th percentile (+4.42 SDS) and BMI z-score was 2.86 (above the 99th percentile) (Fig. 3). There was a difference of one centimeter in the circumference between his left and right leg, but not in their length or in the circumference or length of his arms.

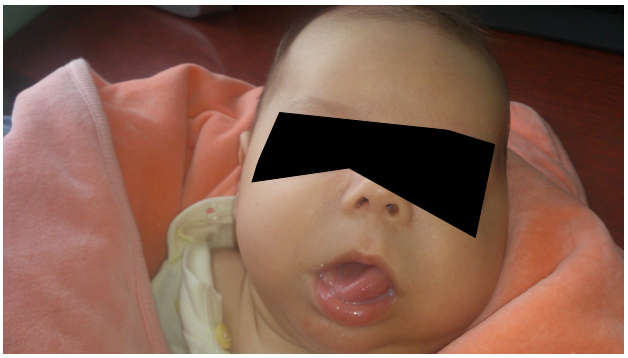

Fig. 1. *Boy's facial appearance*

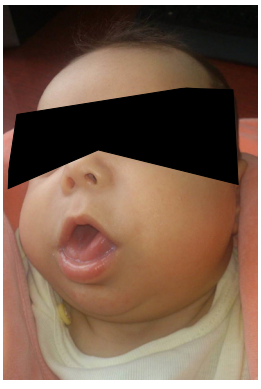

Fig. 2. *Boy's facial appearance*

Ultrasound scan found aortal valve stenosis, mild hypertrophy of the liver, moderate hypertrophy of the kidneys, especially the left one. The brain US was uneventful. Karyotype was 46, XY. There was no evidence of hypoglycemia.

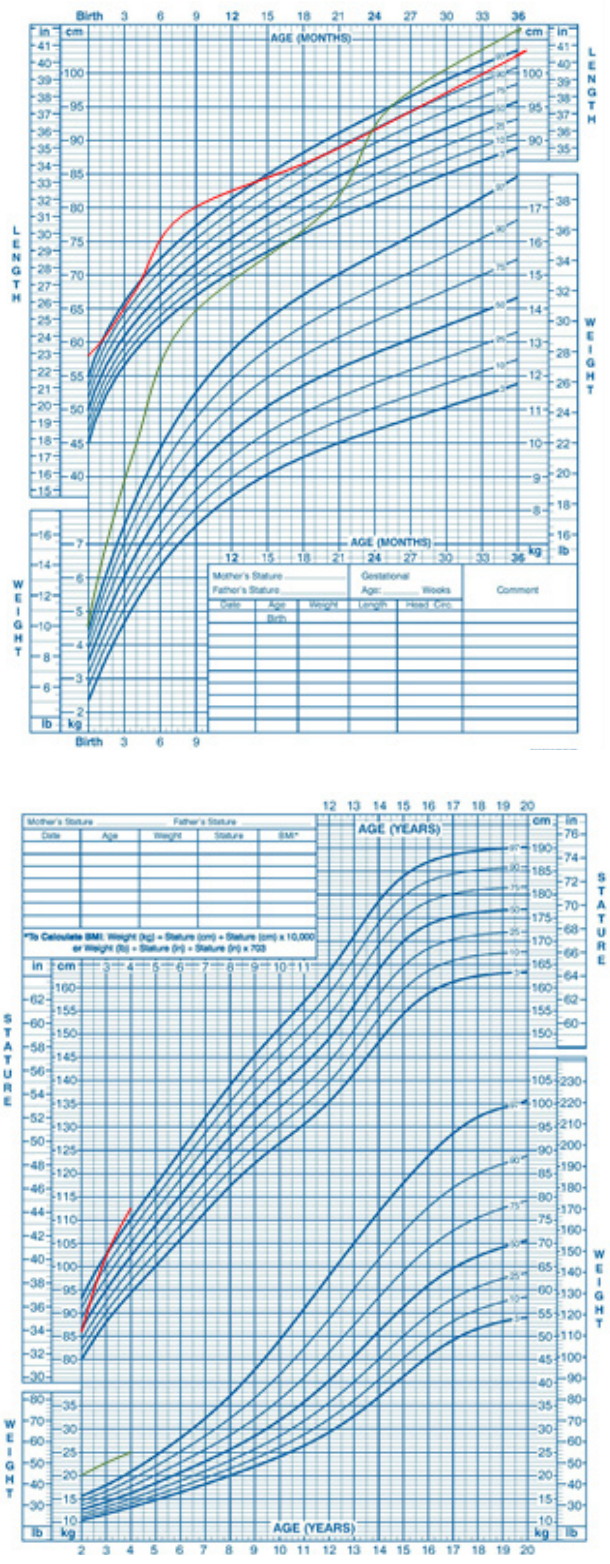

Fig. 3. *Boy's growth curves*

Molecular genetic deletion/duplication analysis of the BWS/SRS critical region 11p15 and analysis of the methylation status of *H19*-DMR (differentially methylated region) and KvDRM1 (LIT1) in 11p15.5 was performed with MLPA (multiplex ligation-dependent probe am-

plification) using the SALSA ME030-C3 BWS/SRS DV29 kit [5]. There was a normal methylation pattern for *H19*-DMR and hypomethylation of KvDRM1 (LIT1) in the chromosome 11p15.5 region with an estimated tumor risk of 1-5%.

A written informed consent was obtained from his parents for the analysis of the blood samples, DNA extraction, medical photography and publishing.

DISCUSSION

The presence of three major or two major and one minor feature is used to assign a clinical or working diagnosis of BWS [2].

Normal karyotypes were found in most patients with BWS [4]. Nevertheless in ~1% patients there are chromosomal abnormalities. Our patient had normal male karyotype.

BWS is usually sporadic.

Several abnormalities of the regulation of gene transcription in the imprinted domain on the chromosome 11p15.5 region have been observed: loss of methylation at imprinting control region-2 (ICR2) (KvDMR1) on the maternal chromosome, gain of methylation at imprinting control region-1 (ICR1) (H19-DMR) on the maternal chromosome or paternal uniparental disomy of chromosome 11(UPD (11)) [6]. Some 10-15% of BWS patients have a positive family history for BWS [4], mostly caused by maternally transmitted mutations in the growth suppressor gene CDKN1C, but also due to copy number variations in the chromosomal region 11p.15 [6].

The higher prevalence of malignancies in BWS has been recognized requiring a close follow-up. An established hypothesis that tumor predisposition in BWS patients is related to the imprinting status of the H19-DMR and KvDMR1 on chromosome 11p15.5 was confirmed by Rump et al. 2005 in a meta-analysis of five studies [7]. He revealed a strong association between a loss of imprinting (LOI) of the H19-DMR and higher tumor risk, especially development of Wilms tumor in these patients. The highest risk (35-45%) can be recognized in children with a normal methylation pattern of the KvDMR1 and hypermethylation of the H19-DMR. In addition, patients with paternal UPD have more susceptibility to cancer, but also hemihypertrophy and neonatal hypoglycemia.

The BWS Registry [8] was used to confirm the hypothesis that different epigenetic alterations could be associated with particular phenotypes in BWS patients. Hypomethylation of KvDRM1 (LIT1) in 11p15.5 is the most common cause for BWS and it can be detected in nearly 50% of patients with this syndrome [7]. The risk for BWS patients with hypomethylation of KvDRM1 to manifest embryonal tumors is estimated to be 1-5%. In our boy, the detected hypomethylation of KvDRM1 is the most likely molecular cause for its BWS phenotype.

There was no evidence of severe neonatal or early childhood manifestations in our patient although he fulfilled clinical criteria of the disease. Hemihyperplasia may affect separate body regions or selected organs and tissues in these patients and is due to an increased cell number in those parts of the body. Our boy had mild liver and moderate left kidney hypertrophy confirmed on US accompanied with left longitudinal tongue hemihypertrophy. Tongue reduction in severe macroglossia should be done during infancy or early childhood from the 2nd till the 4th year.

Growth rate acceleration BWS starts in the second half of pregnancy and early infancy, and slows around the age of seven or eight years, the final height remains at the upper range for their age and sex. Our boy was growing at the 99th percentile and he was obese for his height (weight +4.42 SDS and BMI z-score 2.86).

Three monthly monitorings of serum glucose and alpha-fetoprotein (AFP) concentrations were within normal range. We continued the follow up with abdominal US every three months until the age of eight years [2, 7, 9, 10]. We will continue with annual kidney ultrasound after the age of eight years to mid-adolescence for prevention of nephrocalcinosis or medullary sponge kidney disease as secondary complications [4].

Prenatal screening is possible with chorionic villi sampling (CVS) for families with an inherited chromosome abnormality, or by molecular genetic testing for families in which the molecular mechanism of BWS has been defined.

CONCLUSION

We present a patient with a BWS phenotype and molecular genetic detection of hypomethylation in the KvDMR1 in the imprinted

chromosomal region 11p15.5, indicating a low risk of embryonal tumors. Clinical management is strongly influenced by the type of genetic abnormality observed. Determining the molecular defect made the genetic counseling possible. Children with clinical features of BWS should undergo specific molecular analysis.

REFERENCES

1. Weksberg, R, Shuman C, Beckwith JB. Beckwith-Wiedemann syndrome. Europ J Hum Genet. 2010; 18: 8–14.
2. Firth HV, Hurst JA, Hall JG. Beckwith-Wiedemann syndrome (BWS). In: Oxford desk reference: Clinical genetics. Oxford desk reference, 278–279. Oxford University Pres, 2005.
3. Mussa A, Russo S, Larizza L, Riccio A, Ferrero GB. (Epi)genotype-phenotype correlations in Beckwith-Wiedemann syndrome: a paradigm for genomic medicine. Clin Genet 2016; 89: 403–415.
4. Shuman C, Beckwith JB, Smith AC, et al. Beckwith-Wiedemann Syndrome. 2000 [Updated 2010 Dec 14]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2015.
5. Schouten JP, McElgunn CJ, Waaijer R, Zwijnenburg D, Diepvens F, Pals G. Relative quantification of 40 nucleic acid sequences by multiplex ligation-dependent probe amplification. Nucleic Acids Res. 2002.
6. Baskin B, Choufani S, Chen YA, Shuman C, Parkinson N, Lemyre E, Micheil Innes A, Stavropoulos DJ, Ray PN, Weksberg R. High frequency of copy number variations (CNVs) in the chromosome 11p15 region in patients with Beckwith-Wiedemann syndrome. Hum Genet. 2014; 133(3): 321–30.
7. Rump P, Zeegers MP, van Essen AJ. Tumor risk in Beckwith-Wiedemann syndrome: A review and meta-analysis. Am J Med Genet A. 2005; 136(1): 95–104.
8. DeBaun MR, Niemitz EL, McNiel DE, Brandenberg SA, Lee MP, Feinberg AP. Epigenetic Alterations of H19 and LIT1 Distinguish Patients with Beckwith-Wiedemann Syndrome with Cancer and Birth Defects. Am J Hum Genet. 2002; 70: 604–611.
9. Martinez-y-Martinez R, Martinez-Carboney R, Ocampo-Campos R, Rivera H, Gomez Plascencia y Castillo J, Cuevas A, Martin Manrique MC. Wiedemann-Beckwith syndrome: clinical, cytogenetical and radiological observations in 39 new cases. Genet Counsel. 1992; 3: 67–76.
10. Clericuzio CL, Martin RA. Diagnostic criteria and tumor screening for individuals with isolated hemihyperplasia. Genet Med. 2009; 11: 220–222.

Резиме

ЧЕТИРИГОДИШНО МОМЧЕ СО БЕКВИТ ВИДЕМАН СИНДРОМ (БВС)

Александра Јанчевска[1], Велибор Тасиќ[1], Невенка Лабан[1], Момир Поленаковиќ[2], Зоран Гучев[1], Надин Бахман[3], Карстен Бергман[3]

[1] Медицински факултет, Скопје, Република Македонија

[2] Македонска академија на науките и уметностите, Скопје, Република Македонија

[3] Центар за хумана генетика, Институт за медицинска дијагностика Биосциенција, Ингелхајм, Германија

Цели: Молекуларна карактеризација на пациент со BWS.

Клиничка презентација и интервенција: Четиригодишно момче со прекумерен раст (тежина над 99-тиот и висина на 99-иот перцентил) имаше надолжна хемихипертрофија на јазикот и на левиот образ. Покрај тоа, имаше разлика од еден сантиметар во обемот на левата и десната нога. Молекуларната генетска анализа откри хипометилација на KvDRM1 (LIT1) во импринтинг-контролниот регион 2 (ICR2) на хромозомот 11p15.5 и нормален модел за метилација на *H19*-диференцирачки метилиран регион (*H19*-DMR) во ICR1. Проценетиот ризик за појава на тумори изнесуваше 1–5 %.

Заклучок*:* Опишаниот пациент со клинички карактеристики на БВС има вроден/импринтинг дефект, кој е асоциран со низок ризик од ембрионални тумори.

Клучни зборови: Беквит Видеман синдром (БВС), прекумерен раст, хипометилација, ембрионални тумори