SHORT COMMUNICATION

TWO INFANTS WITH BECKWITH-WIEDEMANN SYNDROME

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ABSTRACT

Beckwith-Wiedemann syndrome (BWS; OMIM 130650) is an overgrowth disorder characterized by macrosomia, macroglossia, organomegaly and developmental abnormalities (in particular abdominal wall defects with exomphalos) and a multi genetic disorder caused by dysregulation of genes expressed in the imprinted 11p15 chromosomal region. We report two unrelated male Moroccan firstborn infants who were hospitalized for macroglossia with breathing difficulties associated with other malformations indicative of BWS.

Keywords: Beckwith-Wiedemann syndrome (BWS), Newborn, Macroglossia, Overgrowth, Imprint

INTRODUCTION

Beckwith-Wiedemann syndrome (BWS, OMIM 130650) is a rare congenital growth disorder characterized by macrosomia, macroglossia, visceromegaly, embryonal tumors, midline abdominal wall defects, neonatal hypoglycemia and ear creases or ear pits, adrenocortical cytomegaly, and renal abnormalities [1-4]. It is estimated that BWS affects 1 in 13,700 newborns [5]. Most affected children do not have all of these symptoms, while other children have different findings such as hemihypertrophy, moderate/severe developmental delay, congenital heart defects, polydactyly and cleft palate [3]. Beckwith-Wiedemann syndrome is a multi genetic disorder caused by dysregulation of gene expression in the imprinted 11p15 chromosomal region [6,7]. We report on two male Moroccan newborn infants hospitalized for macroglossia and breathing difficulties associated with other malformations characteristic of BWS.

CASE REPORTS

Patient 1. A 2-day-old male, firstborn infant of 25-year-old non consanguineous parents, was referred for medical genetics consultation because of multiple malformations. There was no family history of congenital anomalies. The mother had given birth prematurely by cesarean section at 34 weeks gestation because of hydramnios. The infant was intubated and ventilated for respiratory distress. He was macrosomic (>97th percentile) for length and weight, had facial dysmorphism of one infraorbital crease, mid

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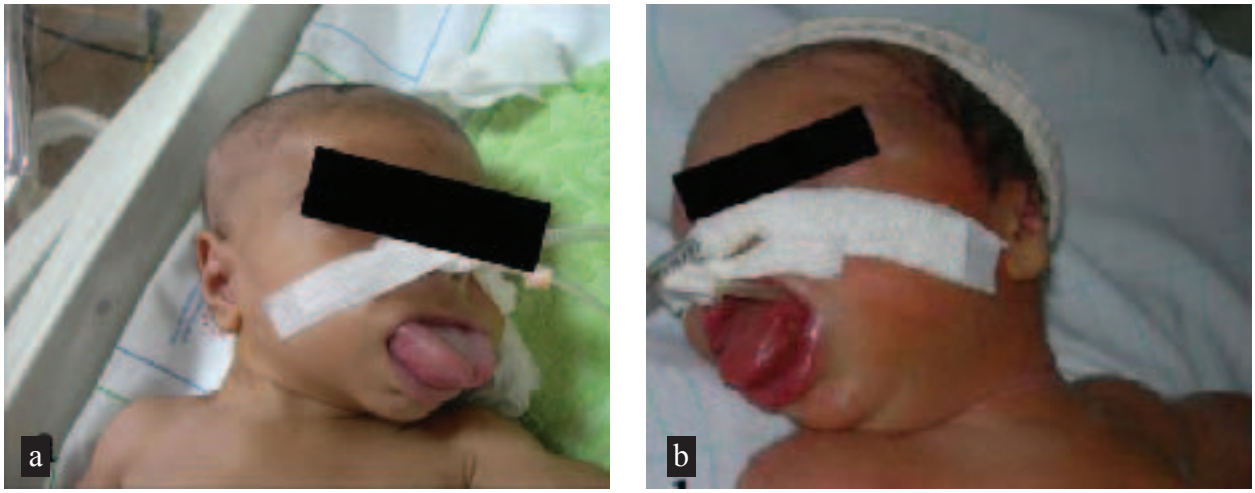

Figure 1: Photos of patient1 (a) patient 2 (b) with dysmorphic face and macroglossia.

face hypoplasia, macroglossia, low-set ears, distended abdomen and cryptorchidism (Figure 1a).

An abdomino-renal ultrasonography revealed nephromegaly with normal structure. All laboratory examinations were within normal limits, including blood glucose levels. The parents were healthy and appeared normal. We concluded from the association of hydramnios, prematurity, characteristic facies, macroglossia, overgrowth, and nephromegaly that the infant had BWS. Due to respiratory distress, the infant died when he was 7 days old.

Patient 2. A newborn male was hospitalized for multiple malformation syndrome and macroglossia responsible of respiratory distress. He was the first-born of a healthy consanguineous couple (second degree), the mother being 20 years old and the father 27 years old at the time of birth. There was no relevant family history. The infant had been delivered by cesarean section at term because of suspected hydramnios. He had the same dysmorphic features as patient 1. All laboratory examinations were within normal limits, including blood glucose levels. The chromosomal investigation revealed a normal male karyotype, 46 XY. We concluded that he had BWS because of the hydramnios, overgrowth (>97th percentile for length and weight), macroglossia and bilateral ureterohydronephrosis (Figure 1b).

DISCUSSION

Beckwith-Wiedemann syndrome is an overgrowth multiple malformation disorder [3] with a predisposition for developing embryonal tumors (most commonly Wilms' tumor or nephroblastoma). Its estimated prevalence [5] may be too low because of the marked variability in the syndome's presentation and the difficulties in diagnosis when the clinical features are less prominent and likely to be ignored [8]. Consensus diagnostic criteria for BWS do not exist, although it is generally accepted that diagnosis requires the presence of at least three characteristic findings, two major and one minor [3] (Table 1). Our patient 1 had three major and three minor signs, while patient 2 had two major and three minor signs. None of our patients had neonatal hypoglycemia, which is a minor criterion. Clinically, BWS must be distinguished from other overgrowth disorders, particularly the Simpson-Golabi-Behmel, the Sotos, the Weaver and the Perlman syndromes, each of which is characterized by distinctive facial features and other signs [9].

Eighty-five percent of BWS cases are sporadic, while 15% result from vertical transmission. Beckwith-Wiedemann syndrome is associated with abnormal transcription and regulation of genes in the imprinted domain on chromosome 11p15.5 [6,7,10], which includes genes encoding growth factors and tumor suppressor genes. The paternally expressed genes (maternally imprinted) have growth enhancing activity and the maternally expressed genes (paternally imprinted) have growth suppressing activity. This region is organized into a telomeric domain which includes the *IGF2 (Insulin Growth Factor II)* and *H19* genes, and a centromeric domain that includes the *CDKN1C* (Cyclin DependEnt Kinase Inhibitor 1C), *KCNQ1* (potassium

voltage-gated channel, subfamily Q, member 1) and *KCNQ1OT1* (KCNQ1-Overlapping transcript 1) genes. Each domain is controlled by its own imprinting center (IC1 and IC2 for the telomeric and centromeric domains, respectively) [7].

Beckwith-Wiedermann syndrome can be caused by a variety of defects. Cytogenetic abnormalities account for 1-2% of the cases and consist of maternally inherited translocations or inversions and trisomy with paternal duplication. Various molecular abnormalities in the 11p15 region have been reported [11-14]: ***1)*** 11p15 paternal uniparental disomy (UPD), the maternal allele is lost and the paternal allele is duplicated. This occurs in approximately 20% of cases. ***2)*** Mutations in the *CDKN1C* gene for a maternally expressed cell-cycle regulator occur in about 5% of patients [15]. The phenotype is typical and includes a very high frequency of exomphalos. Mutation of the *CDKN1C* gene account for 60% of familial BWS cases.

Epigenetic abnormalities also occur in BWS: ***1)*** hypermethylation of the *H19* gene is found in 10% of cases. ***2)*** Demethylation of *KvDMR,* a differentially methylated region at the 5' end of the *KCNQ1OT1* gene, is involved in 55 to 60% of patients. The *KCNQ1OT1* gene (also known as *LIT1* or *KvLQT1-AS*) encodes an antisense transcript of the *KCNQ1* gene and is normally expressed from the paternal allele [15-19]. ***3)*** Microdeletions within IC1 (H19 DMR) [20] or IC2 (Intermediate Chain 2) [21] account for some BWS cases with hypermethylation of H19 or demethylation of KCNQ1OT1.

Management of patients with BWS requires the surgical cure of exomphalos, monitoring and eventual treatment of hypoglycemia in the neonatal period, treatment of macroglossia, and screening for embryonal tumor. For patient 2, we recommended surgical treatment for his macroglossia at a future time and screening for an embryonal tumor. The risk of recurrence in a family depends on the genetic cause of BWS present in the proband.

Table 1. Diagnostic criteria for Beckwith-Wiedemann syndrome [4].

The Presence of At Least Two Major and One Minor From the Following Features
Major:
Positive family history (one or more family members with a clinical diagnosis of BWS, or suggestive history and features)
Macrosomia
Anterior linear ear lobe creases/posterior helical ear pits
Macroglossia, omphalocele/umbilical hernia
Visceromegaly involving one or more intra-abdominal organs including liver, spleen, kidneys, adrenal glands, and pancreas
Embryonal tumor (*e.g.,* Wilms' tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma) in childhood
Hemyhyperplasia
Adrenocortical cytomegaly
Renal abnormalities including structural abnormalities, nephromegaly and nephrocalcinos
Cleft palate
Minor:
Polyhydramnios
Prematurity
Neonatal hypoglycemia
Facial nevus flammeus
Hemangioma
Characteristic facies including midfacial hypoplasia and infraorbital creases
Cardiomegaly, structural cardiac anomalies, cardiomyopathy (rare)
Diastasi recti
Advanced bone age
Monozygotic twinning disorder

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