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Urological Findings in Beckwith-Wiedemann Syndrome With Chromosomal Duplications of 11p15.5: Evaluation and Management

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Abstract

Beckwith-Wiedemann Syndrome (BWS) is an overgrowth disorder with various congenital anomalies. Although the most classic constellation includes macrosomia, macroglossia, and omphalocele, nephrourological findings are commonly associated with BWS. Clinical presentation is highly variable because of its complex molecular heterogeneity, which involves changes in DNA methylation and disruption of growth regulatory genes. We report 3 pediatric patients, ages 13 months to 3 years old, who presented with clinical features consistent with BWS. A variety of nephrourological abnormalities were also noted, including posterior urethral valves, hydroureteronephrosis, and undescended testes. Genetic testing for all 3 patients revealed duplication of the region chromosome 11p15.5.

Beckwith-Wiedemann Syndrome (BWS) is a genetic overgrowth syndrome that affects infants and children without sexual predilection. Commonly associated features include macrosomia, macroglossia, omphalocele, hemihypertrophy, and an increased risk of embryonal tumors. The population incidence is estimated to be 1 in 11,000.¹ BWS has a wide molecular heterogeneity with genetic changes occurring in mosaic patterns, resulting in a variety of clinical manifestations involving multiple organs. Here we describe 3 patients with rare confirmed paternally inherited duplications or unbalanced translocations resulting in BWS, their associated genitourinary (GU) anomalies, and a brief literature review of BWS-associated GU manifestations.

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PATIENT PRESENTATIONS

Case 1

Clinical Scenario—A 13-month-old male was born at 31 weeks by cesarean section. Pregnancy was complicated by polyhydramnios. At delivery, he was noted to have macrosomia, macroglossia, an umbilical hernia, cardiac anomalies, and severe pulmonary hypertension. Genital abnormalities were absent. On day-of-life 1, a renal bladder ultrasound revealed left hydroureteronephrosis, requiring a temporary percutaneous nephrostomy tube placement for decompression. A voiding cystourethrogram revealed a small, trabeculated bladder without vesicoureteral reflux. Ultrasound performed 1 month after tube removal found no change to his left hydroureteronephrosis but new right medullary nephrocalcinosis. A Tc-99m MAG3 renogram revealed a split renal function of 30:70 on the left:right, respectively, with poor drainage of the left kidney (Fig. 1A). Serum creatinine remained at 0.2 mg/dL. He was diagnosed with primary obstructive megaureter and has been followed with serial ultrasounds (Fig. 1B).

Genetics—Genetic testing showed an unbalanced chromosome translocation resulting in a duplication of 11p15.5 and deletion of 3p26, confirming a diagnosis of BWS and 3p-syndrome. He had no family history of BWS. Additional clinical features consistent with 3p-syndrome included trigonocephaly, hypotonia, and psychomotor retardation.

Case 2

Clinical Scenario—A 21-month-old male had a prenatal diagnosis of bilateral hydroureteronephrosis and polyhydramnios. He was born at 37 weeks and at birth was large for gestational age, had macroglossia, nevus flammeus, and diastasis recti suggestive of BWS. He also had hypotonia, pancytopenia, thrombocytopenia, dysgenic corpus callosum, hypertelorism, clinodactyly, a flat nasal bridge, narrow palate, and short neck suggestive of Jacobsen syndrome. His urologic history included bilateral cryptorchidism, status postorchipexies; posterior urethral valves, status postablation; and distal hypospadias. A Tc-99m MAG3 renogram at age 4 months showed a split function of 54:46 on the left:right, respectively, but concerning for left primary obstructed megaureter. He subsequently had a left extravesical ureteral reimplantation with excisional ureteral tapering at 10 months. Follow-up ultrasounds revealed stable left nephromegaly and resolving left hydroureteronephrosis.

Genetics—Microarray analysis revealed a duplication of 11p15.5p15.4 and deletion of 11q24.1-q25, consistent with BWS and Jacobsen syndrome. Parental testing showed that the patient's father carried a balanced chromosome inversion with breakpoints at 11p15.4 and 11q24.1.

Case 3

Clinical Scenario—A 3-year-old male born at 36 weeks gestation via cesarean section due to macrosomia had a history of patent ductus arteriosus and prenatally diagnosed bilateral hydroureteronephrosis. BWS features included macroglossia, macrosomia, ear creases, macrocephaly, nephromegaly, and splenomegaly. Genital abnormalities were absent.

Hydroureteronephrosis has remained stable. At age 12 months, a Tc-99m MAG3 renogram showed a split function of 47:53 on the left:right, respectively. He was diagnosed with bilateral primary obstructive megaureter. A repeat renogram at age 21 months showed stable differential kidney function but delayed drainage. He subsequently underwent bilateral cross-trigonal ureteral reimplantation with excisional ureteral tapering at age 2. Serum creatinine has remained at <0.3 mg/dL.

Genetics—Genetic testing showed a paternal duplication of 11p15.5, which includes *IGF2* and *H19*. This genetic change was confirmed in the patient's father, paternal grandfather, and other members of his father's extended family.

DISCUSSION

BWS is a pediatric overgrowth disorder that occurs sporadically in 85% of cases from alteration of growth regulatory genes on chromosome 11, specifically alterations in genomic imprinting from changes in methylation at gene regulatory regions.¹ Imprinting leads to gene expression in a parent-of-origin specific manner, and normal expression requires an equal chromosomal dosage from each parental chromosome.¹ In 1%–3% of all cases, BWS involves chromosomal duplications or rearrangements that lead to additional gain or loss of chromosomal material, such as our patients.¹

Slavotinek et al reviewed single-case reports that linked unbalanced translocations and paternal duplications to BWS on chromosome 11p15.5.² They included a family with balanced chromosome translocation who demonstrated characteristics of BWS, including macroglossia, prenatal overgrowth, and distinctive facial features. These patients had an increased incidence of developmental delay and dysmorphic facial features that persisted after childhood, including a prominent occiput and broad, flat nasal bridge. Nephrourologic findings, however, were not summarized. Table 1 compares the non-nephrourologic clinical features of patients with normal chromosomes and with confirmed paternally derived 11p15.5 duplications.

Interestingly, our first patient has multiple congenital abnormalities including unique facial features and developmental delay, which have been shown to relate not only to BWS but also to 3p- syndrome. This latter syndrome is also associated with atrioventricular septal defects, sacral dimples, and renal anomalies including pelvic kidney.⁵ Conversely, patient 2 has Jacobsen syndrome (11q- syndrome), which can have abnormal facies, low-set ears, intellectual disability, and hypotonia. Cryptorchidism, hypospadias, and renal anomalies like hydronephrosis and duplicated collecting system have also been reported.⁶

Nephrourologic abnormalities of the GU system are a major characteristic of BWS in general. The prevalence of benign renal lesions ranges from 28% to 61%.^{3,7} These anomalies include medullary cysts, calyceal diverticula, hydronephrosis, nephrolithiasis, nephrocalcinosis, and nephromegaly.^{4,8} Nephrocalcinosis may be caused by hyperplastic distal tubules, which mimic findings in medullary sponge kidney disease.⁸ The most common sequelae from these benign renal abnormalities are urinary tract infections (UTI), with incidences between 18% and 25%.³

In paternal duplications of 11p15.5, renal duplication,⁹ nephromegaly,^{10,11} megaureter,^{11,12} hydronephrosis,¹³ and recurrent UTIs^{11,12} have been reported. Table 2 compares the nephrourologic features of patients with normal chromosomes and with confirmed paternally derived 11p15.5 duplications.

BWS children are at 8%–10% risk for embryonal malignancies.¹ The most common tumors are Wilms' tumor and hepatoblastoma,¹ with most occurring before age 8 years. Tumor development is not as well characterized in BWS with chromosomal rearrangements due to the lower frequency of reported cases, but 1 case of nephroblastoma has been reported in a paternal duplication case.¹⁴

Genital manifestations are infrequently described in BWS literature but include cryptorchidism, with 15% incidence accompanying major abdominal wall defects such as omphalocele.³ Other genital anomalies include hypospadias, clitoromegaly, chordee, and enlarged penis. Our second case had multiple genital malformations including bilateral cryptorchidism without omphalocele, hypospadias, and posterior urethral valves, which have been reported in 1 patient with BWS.¹⁵ Although genomic testing was not performed, this reported patient had typical features of BWS and UTIs that led to imaging studies and a diagnosis of posterior valves. Patients with paternal duplications may also develop hypospadias and cryptorchidism.^{12,14} Given the variable urologic findings associated with BWS, careful examination and imaging of the urinary tract should be considered, especially in BWS patients with UTIs.

CONCLUSION

Patients with BWS often present with a spectrum of physical characteristics, reflecting the complexity of genetic alterations that cause this overgrowth disorder. Paternal unbalanced translocations or duplications, as in our patients, account for less than 1–3% of all cases. Given that nephrourological findings can occur in up to 60% of BWS patients and the embryonal tumor risk, it is important for the urologist and geneticist to work closely to clinically diagnose these patients early to provide appropriate management and genetic counseling.

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Figure 1. Select radiologic images from Patient 1 who had Beckwith-Wiedemann syndrome, 3p-syndrome, and left-sided primary obstructed megaureter. (A) Tc-99m MAG3 renogram demonstrating split renal function of 30% on the left and 70% on the right, with poor drainage of the left kidney. (B) Follow-up ultrasound on patient to trend left-sided hydroureteronephrosis. (Color version available online.)

Table 1

Non-nephrourological clinical features of Beckwith-Wiedemann syndrome patients with normal chromosomes compared to those with chromosomal duplications

Features	Normal Chromosomes		Duplications
	Mussa et al ³	Elliott et al ⁴ (review)	Slavotinek et al ²
Macroglossia	87% (58/67)	99%	100% (17/17)
Ear anomalies	36% (24/67)	75%	53% (9/17)
Facial nevus	45% (30/67)	62%	6% (1/17)
Neonatal/Postnatal overgrowth	—	87%	82% (14/17)
Visceromegaly	30% (20/67)		53% (9/17)
Hypoglycemia	33% (22/67)	59%	18% (3/17)
Abdominal wall defects (omphalocele, umbilical hernia)	—	77%	65% (11/17)
Developmental delay	—	4%	92% (11/12)

Nephrourological clinical features of Beckwith-Wiedemann syndrome patients with normal chromosomes compared to those with chromosomal duplications

Table 2

Features	Normal Chromosomes				Chromosome Duplications			
	Mussa et al ³	Goldman et al ⁷	Choyke et al ⁸	Previous cases ⁹⁻¹⁴	Case 1	Case 2	Case 3	
Nephromegaly	36% (23/63)	25% (39/159)	—	2/6	—	+	+	
Collecting system abnormalities	19% (13/63)	11% (17/159)	—	3/6	—	—	—	
Wilms' tumor or nephroblastoma	6% (4/63)	8% (13/159)	—	1/6	—	—	—	
Medullary or cortical cysts	8% (5/63)	11% (17/159)	13% (9/152)	—	—	—	—	
Nephrocalcinosis or nephrolithiasis	6% (4/63)	4% (6/159)	4% (6/152)	—	+	—	—	
Increased cortical echogenicity	—	1% (2/159)	—	—	—	—	—	
Calyceal diverticula	—	3% (4/159)	1% (2/152)	—	—	—	—	
Hydronephrosis	—	6% (10/159)	12% (18/152)	2/6	+	+	+	
Vesicoureteral reflux	—	0.6% (1/159)	—	1/6	—	—	—	