HHS Public Access

Author manuscript

Pediatr Blood Cancer. Author manuscript; available in PMC 2019 October 01.

Published in final edited form as:

Pediatr Blood Cancer. 2018 October ; 65(10): e27296. doi:10.1002/pbc.27296.

Diagnosis of Beckwith-Wiedemann Syndrome in Children Presenting with Wilms Tumor

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Abstract

Beckwith-Wiedemann syndrome (BWS) is a genetic syndrome associated with overgrowth and cancer predisposition, including predisposition to Wilms tumor (WT). Patients with BWS and BWS spectrum (BWSp) are screened from birth to age 7 years for BWS-associated cancers. However, in some cases a BWS-associated cancer may be the first recognized manifestation of the syndrome. We describe 12 patients diagnosed with BWS after presenting with a WT. We discuss the features of BWS in these patients and hypothesize that earlier detection of BWS by attention to its subtler manifestations could lead to earlier detection of children at risk for associated malignancies.

Keywords

Beckwith-Wiedemann syndrome; Beckwith-Wiedemann Spectrum; isolated hemihypertrophy; isolated lateralized overgrowth; cancer predisposition; Wilms tumor; tumor screening

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Conflict of Interest Statement

The authors have no relevant conflicts of interest to disclose.

Introduction

Beckwith-Wiedemann syndrome (BWS, OMIM #130650) is a genetic overgrowth and cancer predisposition syndrome characterized by hemihypertrophy/lateralized overgrowth (LO), macroglossia, macrosomia, organomegaly, hyperinsulinism, omphalocele/umbilical hernia, and distinct facial features.[1–3] The Beckwith-Wiedemann Spectrum (BWSp) includes classic BWS and patients with molecular defects at 11p15, irrespective of the clinical presentation.[3] Patients with BWSp are at risk for embryonal tumors such as Wilms tumor (WT), hepatoblastoma, and neuroblastoma in the first 7 years of life. Wilms tumor is the most common BWSp-associated cancer.[1,4–8] Tumors develop in 5–10% of patients with BWSp, usually early in life, with variation in risk based on genomic subtype.[9–11] Recognizing the clinical manifestations of this genetic syndrome ensures that appropriate screening is initiated to allow for early tumor detection. The nature of this screening currently differs based on the definition of acceptable risk between the United States and Europe.[3,8] In this case series, we describe a subset of patients who presented with WT and were subsequently diagnosed with BWSp.

BWSp is caused by genetic or epigenetic changes on chromosome 11p15, with either specific gene mutations or changes in DNA methylation in imprinting control (IC) regions 1 or 2, leading to a dysregulation in genes affecting growth.[1] The most common aberration found in 50% of BWSp cases is IC2 loss of methylation on the maternal chromosome.[1,2] Alternatively, 5–10% of cases are due to IC1 gain of methylation on the maternal chromosome, and approximately 20% of sporadic cases are caused by paternal uniparental isodisomy of part of chromosome 11 (pUPD11).[1,2] Hereditary causes of BWSp are responsible for 10–15% of cases, usually involving mutations in *CDKN1C* and occasionally microdeletions, duplications, or point mutations in one of the ICs leading to aberrant 11p15 methylation.[3]

Patients with BWSp can be monitored with serial abdominal imaging and serum alpha-fetoprotein levels to screen for BWSp-associated cancers such as WT, hepatoblastoma, and neuroblastoma; as more genotype-phenotype relationships are identified, it may be possible to tailor the monitoring plan based on the genetic subtype of BWSp.[9,10] For example, the risk of WT is higher in patients with IC1 gain of methylation and pUPD11.[9,10] Additionally, over half of patients with BWSp have a renal or genitourinary tract abnormality, including nephromegaly, cryptorchidism, nephrolithiasis, and dysplasia.[12] These renal abnormalities are associated with IC2 hypomethylation, IC1 hypermethylation, or pUPD11.[12]

WT is associated with multiple *WT1* mutations/aberrations, including Wilms-Aniridia-GU anomalies-Retardation (WAGR) syndrome and Denys-Drash syndrome.[13] In one large cohort study of patients with WT with or without indicators of an underlying genetic predisposition, 19% of patients had a germline predisposition to WT, and 8% of those patients had a constitutional 11p15 aberration.[13] Additionally, there can be a range of tissue distribution of 11p15 alterations, as many of the patients with 11p15 aberrations in the kidney affected by WT exhibited constitutional mosacism.[14,15] There are case reports of patients who were diagnosed with BWSp after presenting with WT.[16] However, there has yet

to be a comprehensive evaluation of a cohort of patients presenting with a BWSp-associated cancer that were subsequently diagnosed with BWSp.

Methods

Our institutional database of patients with growth and epigenetic alterations (Children's Hospital of Philadelphia, IRB #13-010658) was reviewed for patients with WT, and further narrowed to those who were referred for BWSp evaluation after WT diagnosis. Testing included genome wide SNP arrays (Illumina), methylation sensitive PCR and copy number analysis of the IC1 and IC2 loci, with reflex sequencing of *CDKN1C* when appropriate.[18,19] Skin biopsies, when indicated, were obtained from the abdomen on the larger side of the body.

Results

Of the 183 patients diagnosed with BWSp/ILO between January 2014 and July 2017, twelve were diagnosed after presenting with WT (Table 1). Age at diagnosis of WT ranged from 2 days to 9 years, stage at diagnosis ranged from 1–5, all patients had favorable histology, and three (25%) had multifocal or bilateral (synchronous or metachronous) tumors. All patients had some degree of ILO, not always with the same laterality as the affected kidney. Six of twelve patients had other findings of BWSp including infraorbital creases (n=2), anterior ear creases (n=2), large for gestational age at birth (n=4), neonatal hypoglycemia (n=1), and umbilical hernia (n=1); the other six patients had isolated ILO without other findings. Eight out of twelve patients met criteria for classical BWSp with or without molecular confirmation given ILO, WT diagnosis, plus additional features; the four that did not met criteria had ILO with unilateral WT, with incomplete molecular findings. All patients either had IC1 gain of methylation or pUPD11 in the WT affected kidney (Table 2). There were a variety of mosaic patterns, some with methylation changes in the affected kidney only (n=7), others with methylation changes in bilateral kidneys (n=4), and one with methylation changes in affected kidney as well as skin (n=1).

Discussion

WT is associated with several genetic predisposition syndromes, including BWSp, WAGR, Denys-Drash, Perlman and other syndromes. Patients with specific physical characteristics that are associated with these predispositions should undergo further genetic evaluation.[8,13] This includes patients who present with multifocal or bilateral WT, who present at an early age, or who present with characteristic syndromic features such as aniridia, genitourinary abnormalities, or ILO. The genetic evaluation should include testing for 11p15 epigenetic modifications and alterations associated with BWSp, which may necessitate testing multiple blood and tissue samples (including tumor, unaffected kidney, and/or skin biopsy from laterality affected by overgrowth). In our cohort, all affected patients had IC1 hypermethylation or pUPD11, which is consistent with previous studies, as these are the two most common genetic findings in BWSp patients with WT.[12] BWSp can affect patients in a mosaic pattern, as shown in this subset of patients. For this reason, multiple blood and tissue

samples may be necessary to detect genetic changes associated with BWSp, and this requires some advance thinking in surgical planning.

The median age at WT presentation for our cohort was 26 months, which is below median age (42 months) for children with sporadic WT, but the age range for our patients with BWSp was broad (2 days to 109 months). Patients with a genetic predisposition to WT tend to be diagnosed earlier (median age 17 months).[20] It is notable that 58% of patients in this cohort presented with stage 3–5 disease, which is similar to sporadic WT.[20,21] Earlier recognition of conditions that predispose to WT is critical in order to initiate screening and early detection tumors, potentially sparing patients the toxicity of anthracycline and radiation exposure. Further, the treatment approach to WT in children with a predisposition differs from that in children with sporadic WT, where upfront nephrectomy is often the standard of care. Because of the risk of developing metachronous tumors, children with BWSp and other WT predisposing syndromes are treated with neoadjuvant chemotherapy followed by nephron-sparing surgery (partial nephrectomy) to preserve renal tissue and function.[22]

The specific mechanism of tumorigenesis in BWSp is unknown, although the genetic and epigenetic changes at 11p15.5 lead to higher expression of growth promoting genes.[23] Previous WT cohorts with chromosome 11 LOH may include BWSp cases that were not recognized due to subtle clinical features. We recommend a high index of suspicion for ILO and other features of tumor predisposition syndromes for patients diagnosed with WT, as well as banking of normal tissue samples (skin from affected side, ipsilateral normal kidney) for additional testing. Ideally, testing affected and unaffected kidney is performed to molecularly diagnose BWSp, accounting for the test's limits of detection for mosaicism; if only skin or blood are available, a clinical determination of BWSp may be required. When an 11p15 alteration is identified in the tumor alone, the change may be present only in the tumor, or the change is present below the detectable limit in the unaffected sample. Long term outcomes are unclear from current data in cases with 11p15 aberration in tumor alone, and further study is warranted to refine BWSp guidelines to address these cases. A clinical genetics or cancer predisposition evaluation is warranted, even with a low index of suspicion for referral, as features may be subtle. Importantly, knowledge of BWSp (as well as other WT predisposing conditions) allows for more appropriate treatment planning, including nephron-sparing surgery.

Patients with BWSp may present with WT before their underlying predisposing condition is recognized. Children presenting with a renal mass should be carefully screened for characteristic BWSp clinical features, such as ILO, macroglossia, hyperinsulinism, umbilical hernia, and organomegaly before upfront nephrectomy is performed, because the treatment approach differs for those with a genetic WT predisposition. Additionally, recognition of a BWSp diagnosis would lead to screening for other BWSp-associated malignancies, including hepatoblastoma.

Conclusion

Given that BWSp can present subtly and that ILO and other features may not be noted before WT diagnosis is made, a careful physical exam and testing for 11p cancer predisposing variants should be considered in any new diagnosis WT patient.

Acknowledgments

This work was made possible by the generous funding support of the Alex's Lemonade Stand Foundation (J.M.K.), the National Institutes of Health (K08 CA193915 J.M.K; K12 CA076931 S.P.M), and St. Baldrick's Foundation (J.M.K.)

Abbreviations key

BWS	Beckwith-Wiedemann syndrome
BWSp	Beckwith-Wiedemann syndrome spectrum
IC1	Imprinting center 1
IC2	Imprinting center 2
pUPD11	Paternal uniparental disomy 11
ILO	Isolated lateralized overgrowth
LOH	Loss of heterozygosity
WT	Wilms Tumor

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Table 1

Clinical characteristics of patients with Beckwith-Wiedemann Syndrome diagnosed in the setting of Wilms Tumor

	Age at WT dx	Age at BWS dx	WT Characterisitics	Kidney Affected	Surgery Performed	Hemihypertrophy Laterality	Other BWS Features	BWSp Clinical Score[3]	Final Clinical Diagnosis
Patient 1	7 m; 20 m	17 m	Stage 1, favorable histology; multifocal metachronous tumor with favorable histology	bilateral (L; R)	L total nephrectomy; R partial nephrectomy	R (face and tongue); L (bicep, forearm, palm, thigh, calf)		4	BWSp
Patient 2	42 m	46 m	Stage 3, favorable histology	L	L total nephrectomy	L (forearm, calf)		3	ILO
Patient 3	45 m	45 m	Stage 4, multifocal, favorable histology, with regional lymph node and pulmonary metastasis	L; L sided para-aortic mass recurrance	L partial nephrectomy; resection L-sided recurrence (mass)	L (biceps, palm, middle finger, calf, foot)		4	BWSp
Patient 4	2 y	10 y	Stage 3, rhabdomyoblastic differentiation, favorable histology	R	R total nephrectomy	L (hand, thigh, calf, foot)		3	ILO
Patient 5	26 m	28 m	Stage 3, favorable histology	L	L total nephrectomy	L (forearm, thigh)	bilateral infraorbital creases; L ear crease	4	BWSp
Patient 6	2 days	2 m	Stage 1, favorable histology	L	L total nephrectomy	R (forearm) L (thigh, calf)		3	ILO
Patient 7	56 m	8 y	Stage 3, favorable histology	R	R total nephrectomy	R (full)	LGA, hypoglycemia	5	BWSp
Patient 8	14 m	39 m	Stage 1, favorable histology	L	L total nephrectomy	L (bicep, forearm, thigh, calf, foot)	infraorbital creases	3	ILO
Patient 9	25 m	32 m	Stage 1, favorable histology	R	R partial nephrectomy	L (full)	bilateral anterior ear creases; LGA; macroglossia; umbilical hernia	6	BWSp
Patient 10	12 m	15 m	Stage 5 - bilateral renal involvement at dx (R and L both local stage 2, favorable histology)	bilateral	Bilateral partial nephrectomy	R (cheek, lower extremity); L (upper etxremity)		4	BWSp
Patient 11	41 m	41 m	Stage 2, favorable histology	L	L total nephrectomy	R (lower extremity)	LGA at birth (>90%)	4	BWSp
Patient 12	109 m	109 m	Stage 4, favorable histology, pulmonary metastases	L	L total nephrectomy	L (full)	LGA at birth (>90%)	5	BWSp

LGA = Large for gestational age; BWSp = Beckwith-Weidemann spectrum; ILO = Isolated Lateralized Overgrowth

Table 2

Beckwith-Wiedemann syndrome genetic type and tissue specific testing

	BWS Genetic Type	Methylation (WT)		Methylation (Ipsilateral Kidney sample)		Methylation (blood)		Methylation (skin bx)		SNP
		IC1	IC2	IC1	IC2	IC1	IC2	IC1	IC2	
Patient 1	IC1 GOM	90%	49%	63%	50%	51%	51%	57%	50%	blood: normal WT (1st): normal WT (2nd): normal ipsilateral kidney: normal skin bx: normal
Patient 2	pUPD11	86%	3%	52%	51%	49%	50%	NP	NP	blood: normal ipsilateral kidney: normal
Patient 3	IC1 GOM	88%	50%	74%	49%	50%	52%	52%	50%	blood: normal WT (1st): no cnLOH 11 ipsilateral kidney: normal skin bx: normal WT (2nd): normal
Patient 4	pUPD11	66%	35%	NP	NP	NP	NP	NP	NP	chromosome 11 cnLOH in WT normal chromosome 11 in Ewings sarcoma
Patient 5	pUPD11	NP	NP	NP	NP	NP	NP	NP	NP	WT: cnLOH 11p15.5p13 ipsilateral kidney: normal
Patient 6	pUPD11	92%	9%	NP	NP	50%	50%	NP	NP	WT: cnLOH in chromosome 11
Patient 7	IC1 GOM	79%	51%	NP	NP	NP	NP	NP	NP	WT: normal
Patient 8	IC1 GOM	61%	50%	NP	NP	NP	NP	NP	NP	NP
Patient 9	IC1 *KCNQ1* duplication	88%	49%	82%	50%	NP	NP	NP	NP	not performed
Patient 10	pUPD11	91% (R) 88% (L)	2% (R) 4% (L)	53%	49%	50%	49%	NP	NP	WT: cnLOH 11p15.5p13 (60% mosaic) ipsilateral kidney margin - normal right side bx - normal
Patient 11	pUPD11	94.42%	0.01%	52%	50%	50%	51%	NP	NP	WT: cnLOH 11p15.5p15.4 (97% mosaic) left skin bx - normal
Patient 12	IC1 GOM	97%	49%	76%	51%	NP	NP	NP	NP	WT: normal for 11p15 region ipsilateral kidney margin - normal left skin bx - normal

NP: not performed, GOM: Gain of Methylation, cnLON: copy neutral loss of heterozygosity