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Nephrological findings and genotype–phenotype correlation in Beckwith–Wiedemann syndrome

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Abstract Beckwith–Wiedemann syndrome (BWS), an overgrowth disorder with several congenital abnormalities, encompasses nephrourological anomalies. The objective of the report is to analyze the latter and related genotype–phenotype correlations. The study was a retrospective review of nephrourological investigations and genotype in 67 BWS patients. Imaging and laboratory studies have been correlated with the molecular anomalies typical of BWS. Thirty-eight (56.7%) patients had a total of 61 nonmalignant nephrourological findings, including nephromegaly (n=24), collecting system abnormalities (n=14), cryptorchidism (n=11), nephrolithiasis (n=5), cysts (n=5), and dysplasia (n=1). Four patients had Wilms' tumor, all associated with renal hyperplasia. Renal findings were almost consistent in the BWS^{IC1} group, with nephromegaly in all patients and collecting system abnormalities in half of them. BWS^{UPD} and negative patients also had frequent anomalies (63.6% and 61.9% respectively), whereas only 36.0% of BWS^{IC2} had renal findings (p=0.003). Cryptorchidism was associated with abdominal wall defects (p<0.001) appearing more frequently in BWS^{IC2} (p=0.028). Urinary tract infections were observed in 17.9% of patients, with two resulting in life-threatening sepsis. Hypercalciuria was present in 10% of cases. 55.5% of BWS patients have renal findings. Although variegate, these anomalies disclose a genotype–phenotype correlation.

Keywords Beckwith–Wiedemann · Kidney · Wilms · Renal anomalies · Nephromegaly · Renal dysplasia

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Abbreviations

BWS   Beckwith–Wiedemann syndrome
GOM   Gain of methylation
IC   Imprinting center
IGF2   Insulin growth factor 2
LOM   Loss of methylation
UPD   Uniparental disomy
WT   Wilms' tumor

Introduction

Beckwith–Wiedemann syndrome (BWS, *OMIM* #130650) is an overgrowth condition characterized by heterogeneous clinical presentation whose cardinal features include macrosomia, abdominal wall defects, macroglossia, renal abnormalities, visceromegaly, body hemihyperplasia, hyperinsulinemic hypoglycemia, facial *nevus flammeus*, auricular anomalies, and facial dysmorphisms [1–3]. The syndrome is characterized by an increased oncological risk, with an overall cancer incidence of 10% in the first decade of life [4, 5]. Nephroblastoma is the most frequent cancer observed in these patients, accounting for approximately 60% of cases. The high incidence of malignancies has prompted clinicians to recommend tumor surveillance programs mainly based on serial screening by abdominal ultrasound, usually scheduled at 3- to 4-month intervals from birth to 8 years of age [2, 5–7].

Genetic and epigenetic anomalies are found in approximately 75% of patients, consisting of the disruption of expression of two imprinted loci on the 11p15.5 chromosomal region: imprinting center 1 (IC1), which regulates the physiological monoallelic expression of the insulin growth factor 2 gene (*IGF2*) and the tumor suppressor gene *H19*, and imprinting center 2 (IC2), which mainly regulates the expression of the cyclin-dependent kinase inhibitor 1C gene (*CDKN1C*). Both imprinting centers are differentially methylated on the paternal and maternal allele in order that only one allele, parent-specific for each imprinted gene, is expressed. The complex regulation may be disrupted by numerous genomic, genetic, and epigenetic mechanisms:

1. Loss of methylation (LOM) of IC2 on the maternal chromosome, the most frequent defect causing approximately 50% of BWS
2. Gain of methylation (GOM) at IC1 on the maternal chromosome, 5–10% of cases
3. Both LOM-IC2 *plus* GOM-IC1 caused by paternal mosaic uniparental disomy for chromosome 11p15 (UPD), accounting for 20% of cases
4. Mutations in *CDKN1C* gene causing inheritable BWS, observed in 10% of patients

5. Rare chromosomal rearrangements including duplications, deletions, inversions, or translocations involving these imprinted regions, accounting for 1–2% of cases overall [1–3]

As molecular analysis can also be negative in clear-cut phenotypes, the diagnosis is currently clinical, relying on specific diagnostic criteria [1, 3, 6–9]. Molecular analysis is primarily employed to confirm the diagnosis and for tumor risk prediction, as an almost unambiguous genotype–phenotype correlation exists in BWS, with BWS[IC1] and BWS[UPD] carrying the highest oncological risk [1–3]. Identification of the molecular lesion is also instrumental in defining the reproductive risk of transmission in a few BWS subgroups [1].

Morphological and structural kidney anomalies have always been recognized as part of the spectrum of the syndrome, and included in the diagnostic criteria for the clinical diagnosis [1, 3, 8]. Actually, most reports on the nephrourological characteristics of BWS are focused on renal neoplasms [5]. However, nonmalignant renal findings require appropriate consideration because of false-positive and misleading results and cancer surveillance imaging procedures being mistaken for malignant or premalignant lesions, potentially leading to unnecessary nephrectomies [10]. Moreover, renal abnormalities can be responsible for impaired renal function, the preservation of which is particularly relevant in respect of the 5% risk of cancer-related nephrectomy [11]. Infections and nephrolithiasis, sometimes associated with hypercalciuria, have also been described, as well as a variety of urological findings [12]. Few valuable reports have examined the issue of nonmalignant renal abnormalities in BWS to date [9, 12–16], and only one partially explored the genotype–phenotype correlation of the renal findings [14].

The aim of this retrospective study is to report the incidence and the spectrum of nephrourological findings in our cohort of BWS patients, review the current literature on the matter, and further characterize genotype–phenotype correlations.

Materials and methods

The medical records of 67 patients with BWS followed up from 1991 to 2010 at the Departments of Pediatrics of the University of Torino and Federico II University of Naples, Italy were reviewed in order to analyze their nephrourological findings. The study group consisted of 39 male and 28 female patients aged 8.0±6.7 years (range 0.9–22.7) who had been diagnosed with BWS at the age of 1.1±2.5 years. All patients were diagnosed according to the criteria by Elliott et al. [8], which are the strictest, including three major features

(anterior abdominal wall defects, macroglossia, and overgrowth), or two major features *plus* three minor (ear anomalies, facial *nevus flammeus*, nephrourological malformations, neonatal hypoglycemia, hemihyperplasia).

Sixty-three (94.0%) of the patients accepted molecular genetic studies by signing the appropriate informed consent and 4 declined DNA analysis. Genomic DNA was extracted from peripheral blood from the probands and their parents. Genotype assessment included standard karyotype and analysis of the methylation pattern of the IC1 and IC2 regions by either COBRA ($n=60$) or MS-MLPA ($n=40$) as described elsewhere [17], 37 were analyzed using both techniques (obtaining consistent results in all cases). UPD has always been confirmed with microsatellite analysis. Patients who tested negative for these analyses were also submitted to CDKN1C sequencing [18] (only familial cases, patients with palatoschisis, or with abdominal wall defects, $n=15$), according to the currently employed diagnostic flow-chart [2, 3, 19].

Anamnestic data and medical records were reviewed to search for previous episodes of urinary tract infections or admissions for nephrolithiasis. Overall, 80 ultrasounds were collected, with all patients having at least one renal ultrasound evaluated for the study. Radiological screening for BWS-associated tumors in these cases typically consisted of abdominal ultrasound every 3–4 months for the first 10 years of life, according to published guidelines [2, 6, 19]. After that age patients were submitted to renal imaging at least once yearly. Imaging studies and kidney ultrasound images were analyzed by an expert nephrologist according to the guidelines for renal ultrasound in children and charts for normal kidney diameters according to age [20]. Findings on renal ultrasound were divided into the following categories: normal, renal hyperplasia (nephromegaly), nephrocalcinosis or nephrolithiasis, medullary or cortical cystic disease, collecting system abnormalities, renal dysplasia, Wilms' tumor (WT), and cryptorchidism. Nephromegaly was defined as the presence of a kidney maximum diameter >2 SD for the age-related standards [20]. Further imaging investigations, including magnetic resonance, computed tomography, and voiding cystourethrography were performed in 11 patients as clinically indicated. All patients were evaluated for renal function by blood creatinine dosage using an enzymatic method (Isotope dilution mass spectrometry, IDMS), by urinalysis once a year, and by estimation of glomerular filtration rate (GFR) using the Schwartz formula (GFR=0.413×height/serum creatinine). Urinary calcium excretion was investigated, when required, in 28 patients on two randomly collected spot urine specimens and expressed as the urinary calcium/creatinine ratio [13]. Urine calcium was measured by the Arsenazo III reflectance spectrophotometry method. Hypercalciuria was defined as a calcium/creatinine ratio

above the +2SD for age, according to our laboratory reference ranges for age.

Data analysis was performed with SPSS 15.0 (Chicago, IL, USA) and GraphPad 5.0 (La Jolla, CA, USA). Proportions among groups were tested by Fisher's exact or Chi-squared tests. Results were considered significant when the p value was less than 0.05.

Results

Among the 67 BWS patients of the cohort, 38 (56.7%) presented one or multiple nephrourological findings accounting for a total of 61 nonmalignant lesions observed. Nephromegaly was the most frequent finding, observed in 24 (35.8%) patients. Other nephrourological abnormalities included renal collecting system anomalies (megaureter, vesicoureteric reflux, ureteropelvic junction stenosis; $n=14$), cryptorchidism ($n=11$), nephrocalcinosis or nephrolithiasis ($n=5$), renal cysts ($n=5$), WT ($n=4$), renal dysplasia ($n=1$), and penile blind fistula ($n=1$). Nephrocalcinosis/lithiasis was diagnosed at the mean age of 4.3±3.2 years, whereas renal cysts were first noted at 6.1±4.7 years of age. Figure 1 depicts some of the findings observed.

Genetic studies were positive in 42 cases (66.7%), revealing LOM at IC2 in 25 patients (BWS^{IC2}, 37.3%), UPD in 11 (BWS^{UPD}, 16.4%), and GOM at IC1 in 6 (BWS^{IC1}, 9.0%), including a familial case with a previously reported microdeletion [21]. None of the patients showed standard karyotype anomalies or CDKN1C mutations. Twenty-one BWS patients tested negative (BWS^{NEG}, 33.3%) in spite of a well-defined and clear-cut BWS phenotype.

Table 1 reports the renal findings in the molecularly defined sub-groups of patients. Nephrological anomalies were almost constant in the BWS^{IC1} patients (6 out of 6) and very frequent in the BWS^{UPD} or BWS^{NEG} ones (63.6% and 61.9% respectively), but were present only in 35.0% of BWS^{IC2} patients ($p=0.003$). Renal hyperplasia was significantly more frequent in BWS^{IC1} (100%, $p<0.001$), was present in 54.5% of BWS^{UPD}, and only in 20.0% of BWS^{IC2} patients. Renal hyperplasia was unilateral in 5 cases (4 with UPD, 1 negative), and bilateral in the remaining 19. Collecting system anomalies were more frequent in the BWS^{IC1} as well, with 50% of patients affected ($p=0.016$). Only BWS^{UPD} or BWS^{NEG} patients had nephrolithiasis.

Table 2 summarizes the additional phenotypic characteristics of the patients and explores their associations with the renal findings observed. No clear-cut associations between nephrourological findings and specific phenotype anomalies were evident, with the notable exception of the frequent finding of cryptorchidism among patients, with major abdominal wall defects being present in 9 out of 20 patients

Fig. 1 Examples of some of the findings encountered in the study. **a** Polar cysts in a 6-year-old Beckwith–Wiedemann syndrome (BWS)[IC2] patient. **b** Nephromegaly in a 2.5 months old BWS[IC1] boy with kidney length of 8.5 and 7.9 cm. **c** Multiple hyperechogenic renal spots in a 9-year-old BWS[UPD] girl with lithiasis and hypercalciuria. **d** Renal dysplasia in an 11-year-old BWS[NEG] patient with an enlarged left kidney plus a double excretory system and agenesis of the right kidney. UPD, uniparental disomy
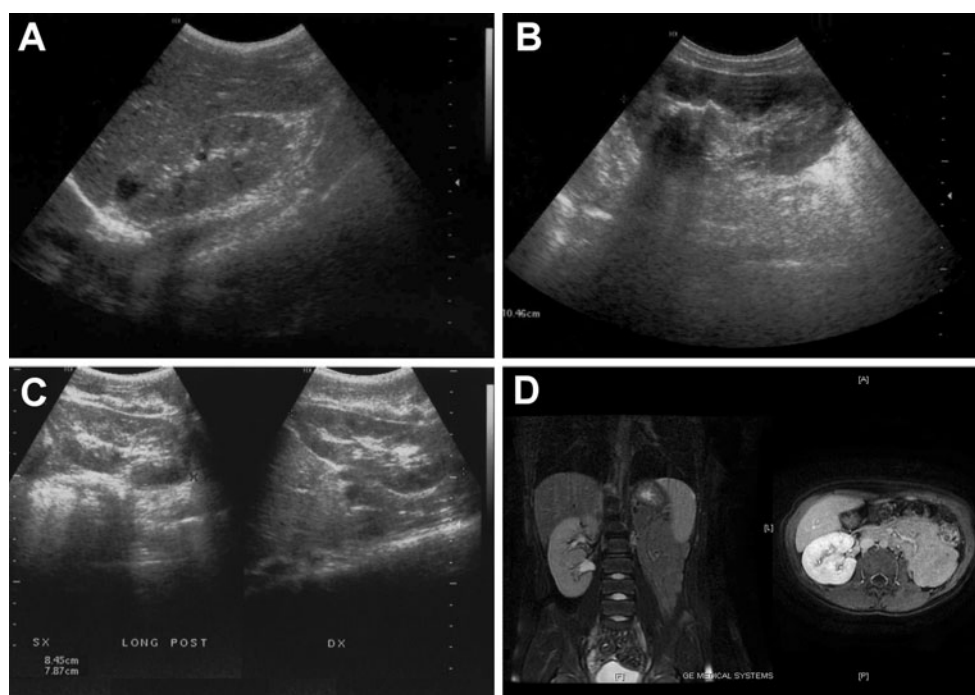
(p<0.001). Cryptorchidism was statistically more frequent in the BWS[IC2] molecular subgroup (p=0.028).

Four (5.9%) patients developed WT (Table 3), associated in 3 out of 4 cases with other renal findings, besides hyperplasia. Two cases had bilateral WT, in 1 of them associated with bilateral nephroblastomatosis, found only in this patient. Interestingly, 1 of these 2 patients was diagnosed with WT at 10 years of age.

Twelve patients (17.9%) reported previous urinary tract infections (7 male and 5 female, mean age at first infection 2.3±4.8 years). Ten occurred in patients with renal anomalies, including 3 cases with nephrolithiasis, 8 with collecting system anomalies, 1 with dysplasia, and 1 with multiple cysts. Only 2 patients had urinary tract infections with no nephrourological anomaly. Two of the 12 patients had severe infections with life-threatening sepsis episodes (both affected by severe enlargement of the ureter and calyceal dilatation) and were submitted to surgery to correct the anomaly.

We collected data of 80 accurate kidney maximum longitudinal diameter measurements obtained in 51 patients by abdominal ultrasound. As various nonmalignant renal findings (renal cysts, hydronephrosis, kidney stones) may affect renal measurement and would be a confounding

Table 1 Renal findings according to the molecular subgroups

	All		LOM at IC2 (BWS[IC2])		UPD (BWS[UPD])		GOM at IC1 (BWS[IC1])		Negative (BWS[NEG])		$p(\chi^2)$
n (%)	63[a]		25	37.3%	11	16.4%	6	9.0%	21	31.3%	
Hyperplasia/nephromegaly	23	36.5%	5	20.0%	6	54.5%	6	100.0%	6	33.3%	0.001*
Nephrocalcinosis/nephrolithiasis	4	6.3%	0	0.0%	2	18.2%	0	0.0%	2	14.3%	0.144
Medullary/cortical cysts	5	7.5%	3	12.0%	1	9.1%	1	16.7%	0	0.0%	0.384
Collecting system abnormalities	13	19.4%	0	0.0%	1	9.1%	3	50.0%	9	42.9%	0.007*
Renal dysplasia	1	1.5%	0	0.0%	0	0.0%	0	0.0%	1	4.8%	0.587
Wilms' tumor	4	6.0%	0	0.0%	1	9.1%	1	16.7%	2	9.5%	0.353
Cryptorchidism (n/males)	9/35	14.9%	7 / 13	53.8%	0/5	0.0%	1/5	20.0%	1/12	8.3%	0.028*
Patients with renal findings	35	55.5%	9	36.0%	7	63.6%	6	100.0%	13	61.9%	0.024*
Overall number of renal findings	59	–	15	–	11	–	12	–	21	–	–

BWS: Beckwith–Wiedemann syndrome; GOM: gain of methylation, IC: imprinting center, LOM: loss of methylation, UPD: uniparental disomy

*Significant values

[a] Four of the 67 patients rejected molecular testing. One had cryptorchidism, one cryptorchidism and renal hyperplasia, one collecting system anomalies with frequent urinary tract infections, and one disclosed no renal anomalies

Table 2 Renal findings in the 67 BWS patients according to phenotype

	n	Hyperplasia	Lithiasis	Renal cysts	Collecting system abnormalities	Renal dysplasia	Cryptorchidism	WT
Neonatal overgrowth	47	20	4	3	11	1	10	4
Postnatal overgrowth	41	18	4	5	10	1	8	4
Neonatal hypoglycemia	22	8	3	1	5	1	6	1
Hemihyperplasia	44	19	3	1	9	1	7	4
Omphalocele	9	2	0	1	0	0	4	0
Umbilical hernia	11	8	1	2	4	0	5	1
Macroglossia	58	22	3	5	13	1	9	3
Organ enlargement	33	11	2	1	5	1	7	4
Ear creases/pits	24	7	0	3	4	0	6	0
Facial nevus flammeus	30	10	2	3	7	1	5	2
Total	67	24	5	5	14	1	10	4

BWS: Beckwith–Wiedemann syndrome; WT: Wilms' tumor

factor for nephromegaly, some of the measurement have been judged unreliable. Measurements of 12 additional patients were excluded as being affected by collecting system anomalies (*n*=7), renal dysplasia (*n*=3), congenital renal cystic lesions (*n*=1), or because of measurement after partial nephrectomy for WT (*n*=1). In one case was the finding of severe nephromegaly autoptic. In 3 patients, the kidney measurement was unavailable. Figure 2 reports the measurements according to the molecular subgroups, and plotted against the nomogram for normal renal growth in children [20].

All patients but two had normal renal function assessed by serum creatinine dosage and estimated GFR: both the patients with mild and stable elevation in serum creatinine (1.7 and 1.9 mg/dl respectively, both with GFR >90 ml/min/1.73 m^2) had major kidney anomalies and underwent treatment for WT (patients 3 and 4 of Table 3). Hypercalciuria was investigated in 28 patients, including all those with nephrolithiasis or nephrocalcinosis. Only 3 of the patients (10.8%) disclosed increased urinary calcium excretion (in all cases confirmed by a second assay): all 3 patients were also affected by nephrocalcinosis, whereas, the fourth patient affected by lithiasis did not show hypercalciuria, in spite of multiple evaluations.

In Table 4 we summarize and compare the nephrourological findings reported in the literature and in this report.

Discussion

Developmental defects of the nephrourological system characterize BWS. The overall prevalence of nephrourological anomalies reported in the literature ranges from 28 to 61% [5, 9, 12–14, 22–26]. These wide differences can be primarily imputed to inclusion criteria, which are neither homogeneous nor unanimously accepted [6]. Moreover, it is possible that patients with overlapping overgrowth conditions have been included in previous series lacking molecular assessment. Finally, age and evaluation timing are important factors as well, since some renal findings, such as cysts or nephrolithiasis, will likely require time to develop and can manifest later in life.

According to our series, nephrourological anomalies are encountered in 56.7% of clinically diagnosed BWS patients, and in 52.0% of those with a diagnosis confirmed at the molecular level.

This study represents the second attempt to establish a correlation between renal findings and molecular defects among patients with BWS. A previous work by Goldman et al. compared the renal phenotype of BWS^{IC2} and BWS^{UPD} patients, which are the two more common genotypes [14]. We present the first description of renal anomalies in a small group of BWS^{IC1} patients, who appear to have a high predisposition to renal hyperplasia. BWS^{IC2} patients seem to have a lower incidence of renal findings among other epigenotypes, as already reported [14]. Anomalies were found in all BWS^{IC1} patients and in approximately two thirds of both the BWS^{UPD} and BWS^{NEG} cases. This similar proportion in the two latter groups could be explained by taking into account that the BWS^{NEG} subgroup likely includes several patients with UPD. Indeed, UPD is a post-zygotic event presenting as a mosaic phenomenon and, therefore, not always detectable on blood leukocyte DNA, but demonstrable at the tissue level in many BWS patients [1–3].

Renal hyperplasia represents the most frequent finding among BWS patients, being present in 36% of the overall cohort, primarily observed in the BWS^{IC1} molecular class in which it seems to be a consistent finding, with the limitation of the small cohort described: almost all the

Table 3 Characteristics of the 4 patients with Wilms' tumor (WT)

Molecular anomaly	Age at WT diagnosis	Sex	Side	Size (mm)	Phenotype	Associated kidney anomalies	Screened	Treatment	Stage
1 UPD	2 years 8 months	Male	Left	25×18×15	Hemihyperplasia, overgrowth, macroglossia, diastasis recti, nevus flammeus	Severe hyperplasia, kidney asymmetry	Yes	Tumorectomy	I
2 Negative	6 months	Female	Right	35×32×27	Hemihyperplasia, overgrowth, organomegaly, hypotonia, ear pits	Extreme hyperplasia, nephroblastomatosis, absent corticomedullary differentiation	Yes[a]	Deceased after chemotherapy	V
3 GOM at IC1	4 years 3 months	Male	Left	45×22×40	Hemihyperplasia, overgrowth, macroglossia, umbilical hernia, hypoglycemia, nevus flammeus, organomegaly	Megaureter, calyceal dilatation, hyperplasia	Yes	Nephrectomy, chemotherapy	II
4 Negative	10 years 4 months	Female	Bilateral	74×87×65 and 65×63×54	Hemihyperplasia, macroglossia, hypoglycemia, organomegaly	Duplicated collecting system, nephrocalcinosis, nephromegaly, kidney asymmetry	No[b]	Radiotherapy, chemotherapy, bilateral tumorectomy	V with lung metastases

UPD: paternal uniparental disomy, WT: Wilms' tumor

[a] Found at first abdominal ultrasound at birth

[b] Screened until the age of 5 years
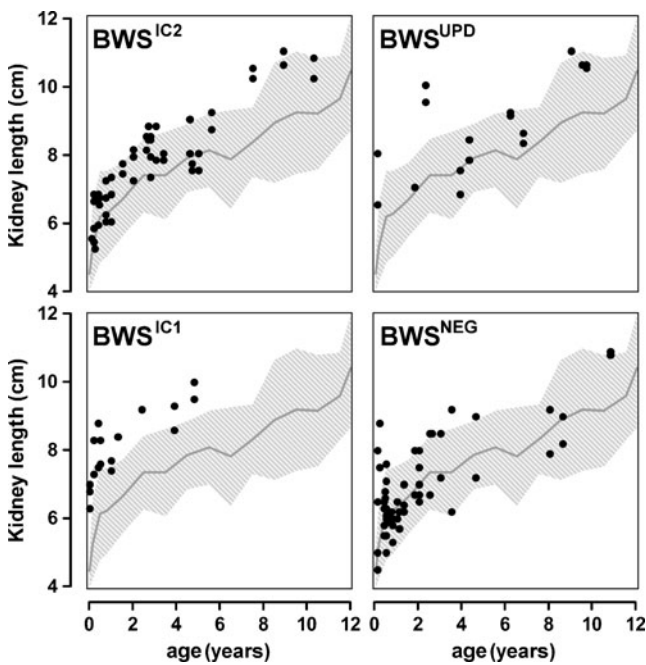
Fig. 2 Kidney maximum diameter measured in 51 patients plotted against the nomogram for normal renal growth (gray area includes normal kidney length mean ± 2 SD) in childhood by Rosenbaum [20] according to the molecular subgroup. A total of 80 measurements were obtained in 19 BWS[IC2], 5 BWS[IC1], 9 BWS[UPD], and 18 BWS[NEG] patients

measurements obtained in the BWS[IC1] patients were well above the +2SD threshold. Renal size in BWS[UPD] varies widely, whereas in BWS[IC2] it is almost constantly at the upper normal limit, with only some of the patients having a measurement >2SD above normal standards. The different prevalence of nephromegaly correlates with the variable WT risk observed among the molecular subclasses. Actually, kidney enlargement has already been reported to be one of the most relevant factors associated with WT development [5, 27], together with the UPD or IC1 molecular anomalies, which are the two classes associated with this tumor. No cases of WT have been described in BWS[IC2] patients to date. Our results confirm what has already been reported in other studies, evidencing the association between renal anomalies and UPD, including a cryptic cytogenetic rearrangement leading to paternal duplication of the 11p15.5 BWS region [28]. We were able to present data on 4 patients who developed WT, disclosing an approximately 5% incidence overlapping that of larger studies. Nephromegaly was present in all cases, and 3 out of 4 of our WT patients also had other relevant kidney anomalies associated. It should be interesting to evaluate whether, besides nephromegaly, other findings could also represent risk factors for WT development. The basis of the serial ultrasound screening program in the first 8 years of age relies on the progressively abating risk of tumors from

birth to this age. The proven advantage of these procedures consists in a downward shift from advanced WT stages to the more localized stages I and II in which nephron-sparing strategies are feasible [11]. With this in mind, the finding of a bilateral WT diagnosed at 10 years of age and after the discontinuation of the screening protocol is of interest. The continuation of yearly ultrasound after the age of 8 can be a subject of debate, since the occurrence of WT beyond this age in BWS is anecdotal. However, these findings and other observations [29] also seem to support a periodic evaluation of renal conditions beyond this age also.

Cryptorchidism is a non-specific feature of BWS. We have observed a 15% prevalence of this anomaly, statistically associated with the IC2 molecular subgroup. This latter finding is not surprising, as the association of cryptorchidism with major abdominal wall defects, which are over-represented in this class of patients, is well known. We also reported the occurrence of renal dysplasia in a patient with obvious BWS phenotype (consisting of macrosomia, macroglossia, hemi-hyperplasia, neonatal hypoglycemia, and typical *nevus flammeus*) and negative molecular testing, representing the first report of renal dysplasia in BWS: her right kidney was severely enlarged and she had a double collecting system, possibly as a result of fusion with the contralateral kidney.

The finding of an 18% occurrence of urinary tract infection matches well that described in a another case series compiled by Elliott and Maher [8] who reported a 25% incidence, observing that it is one of the most frequent problems during childhood in patients with BWS. Elevated urinary calcium excretion has been previously demonstrated in 22% of cases, including half of the patients developing nephrocalcinosis [13]. These data are partially confirmed in our report, although we detected a smaller percentage of hypercalciuric patients.

As with any retrospective study, several limitations of this report have to be discussed. First, longitudinal assessment of renal findings and measurements would be preferable with systematic timing in ultrasounds, including prenatal and neonatal images. The evaluation of patients serially at uniform intervals would have been valuable. Second, ultrasound was performed at a variety of institutions, with unknown inter-operator variability and uninvestigated variation in the equipment and image quality. Moreover, ultrasound reviews over a long time span make safe deductions difficult because of the improvements in ultrasound techniques. However, it should be underlined that we reread each image to ensure that appropriate measurements were obtained. A wide age range should also be considered as some renal findings could require time to develop and become clinically relevant. As a result, this study will likely underestimate the prevalence of renal findings in BWS patients, as it is presumable that some of

Table 4 Review of the renal findings in the literature

Reference	Year	n	Patients with renal anomalies	Percentage	Genotype–Phenotype correlation investigated	Hyperplasia (%)	Calcinosis or lithiasis (%)	Renal cysts (%)	Collecting system anomalies (%)	Renal dysplasia (%)	Cryptorchidism (%)
Shah [22]	1983	10	10	100.0	No	100.0	–	50.0	50.0	–	–
Pettenati [23]	1986	60	58	96.7	No	96.7	–	–	–	–	–
Elliott [24]	1994	74	45	60.8	No	60.8	–	18.9	14.9	–	–
Hunter [25]	1994	13	9	69.2	No	–	–	–	–	–	50.0
Choyke [12]a	1998	152	38	25.0	No	–	4.0	13.0	13.0	–	–
DeBaun [5]a	1998	56	29	51.8	No	28.6	–	–	–	–	–
Borer [10]a	1999	27	10	37.0	No	14.8	4.0	19.0	–	–	–
Moore [26]	2000	12	7	58.3	No	41.7	–	–	–	–	–
Goldman [14]a	2002	159	67	42.1	IC2/UPD	25.0	–	10.5	11.0	–	–
Goldman [13]a	2003	18	7	38.9	No	22.2	16.7	11.1	11.1	–	–
This reporta	2011	67	33	49.3	IC1/IC2/UPD/Neg	34.3	9.0	6.0	17.9	4.5	11.9
Total	–	648	313	48.3	–	–	–	–	–	–	–

IC: imprinting center; UPD: paternal uniparental disomy, WT: Wilms' tumor

a Studies specifically designed to describe renal findings

the conditions could develop later in life, such as renal cysts, infections, nephrolithiasis/nephrocalcinosis. Another potential drawback of the study is the possibility of having included among BWS[NEG] patients some affected by similar overgrowth syndromes, such as Simpson–Golabi–Behemel, Sotos, or Perlman syndromes. However, most of the patients with negative BWS molecular tests and karyotypes have also been tested for the overlapping conditions with known genetic mechanisms, which have been excluded.

In conclusion, we report nephrourological anomalies in approximately 56% of BWS patients: these data confirm a high prevalence of kidney involvement in this syndrome, which deserves systematic and attentive evaluation of the kidney situation over time in all patients. Nephrourological abnormalities are mostly associated with UPD and IC1 molecular subtypes, and hyperplasia is the most frequent finding, and is constant and severe in IC1 patients. A small number of BWS patients may develop complications such as infection, reflux nephropathy, nephrolithiasis or kidney cysts, leading to impaired renal function.

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