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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

The effectiveness of Wilms tumor screening in Beckwith–Wiedemann spectrum

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Abstract

Purpose It is well documented that patients with Beckwith–Wiedemann spectrum (BWS) have a significantly higher risk of developing Wilms tumor (WT) than the general population. There has been little research on the timing of WT diagnosis in BWS in regard to optimizing suggested screening protocols.

Methods A literature search was performed to identify all reports of patients with BWS and WT. These data were combined with unpublished data from patients in the authors' cohorts. Age at WT diagnosis was compared against data collected through the NIH Surveillance, Epidemiology, and End Results Program (SEER) registry.

Results Patients with BWS had a significantly higher incidence of WT diagnoses between age 12 and 84 months compared to patients in the SEER registry. Patients with BWS and WT diagnosed through screening had significantly lower stages at diagnosis compared to patients with BWS that were not screened.

Conclusions Screening until age 7 years is effective in detecting close to 95% of all WT in patients with BWS.

Keywords Beckwith–Wiedemann Syndrome · Wilms tumor · Cancer screening · Cancer predisposition

Introduction

Beckwith–Wiedemann spectrum (BWS) is the most common congenital overgrowth disorder, resulting from genetic or epigenetic changes on chromosome 11p15.5. It is most commonly associated with features of variable severity including macroglossia, lateralized overgrowth, macrosomia, abdominal wall defects, hypoglycemia, and an increased risk for embryonal tumors. Overall tumor risk for patients with BWS is approximately 8%. Wilms tumor (WT) represents the most common cancer to develop, representing 52% of all tumors in BWS (Brioude et al. 2018). Other tumor types include hepatoblastoma, neuroblastoma, adrenal tumors, and rhabdomyosarcoma (Brioude et al. 2018).

Approximately 650 new WT cases are diagnosed each year in the United States, with an incidence of 8 cases per 1,000,000 children less than 15 years of age (Davidoff 2012). Patients within the BWS population have a WT relative risk more than 800 times greater than the unaffected population during the first 4 years of life, and approximately 3.5% of all patients with BWS will develop WT (DeBaun and Tucker 1998; Mussa et al. 2012). Individual WT risk is dependent on the patient's molecular subtype. Risk is highest in patients with H19/IGF2:IG DMR gain of methylation (IC1 GOM) (24%) and paternal uniparental isodisomy of chromosome 11 (pUPD11) (7.9%) and lower in patients with classic BWS features and negative testing (4.1%), *CDKN1C* mutations (1.4%), and KCNQ1OT1:TSS-DMR loss of methylation (IC2 LOM) (0.2%). Nephroblastomatosis and nephrogenic rests are known to be commonly associated with WT development in children with BWS (Beckwith et al. 1990).

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Patients with BWS undergo routine ultrasounds to monitor for WT development. Historically, patients have undergone quarterly ultrasounds until the 8th year of life (Mussa et al. 2016a). A recent national consensus recommended quarterly full abdominal ultrasounds until the 4th year of life and then quarterly renal ultrasounds until the 7th year of life (Kalish et al. 2017) and international screening guidelines suggest differentiating screening based on epigenetic type of BWS.

Despite the recognized increased risk, specific data on the timing of WT development in the BWS population are lacking. Here we provide data on WT epidemiology in BWS, showing differences in age of presentation compared to non-syndromic WT patients, as well as differences in stage of presentation in screened versus unscreened patients.

Methods

A literature search was performed in PubMed from 1972 through 2018 to identify reports of BWS patients with WT (Algar et al. 2007; Andrews and Amparo 1993; Azouz et al. 1990; Bachmann et al. 2017; Beetz et al. 1991; Bilgin et al. 2018; Borer et al. 1999; Brioude et al. 2013; Brzezinski et al. 2017; Cardoso et al. 2012; Carella et al. 2010; Cooper et al. 2005; Darcy et al. 2015; DeBaun and Tucker 1998; Diaz de Bustamante et al. 1990; Gaston et al. 2001; Green et al. 1993; Hedborg et al. 1994; Hilden et al. 1998; Hoban et al. 1995; Jeanes et al. 2002; Kubota et al. 1994; Kulkarni et al. 2002; Lopez et al. 2016; Maas et al. 2016; MacFarland et al. 2018; McManamny and Barnett 1985; McNeil et al. 2001; Mussa et al. 2012, 2016c; Nordenskjold et al. 1995; Nystrom et al. 1992; Olson et al. 1993; Pai 1988; Paterson and Sweeney 2000; Prevot et al. 1977; Reddy et al. 1972; Regalado et al. 1997; Rey et al. 1988; Ritchey et al. 1995; Scalabre et al. 2016; Schneid et al. 1991; Segers et al. 2012; Seshachalam et al. 2011; Sirinelli et al. 1989; Sotelo-Avila et al. 1980; Sotelo-Avila and Gooch 1976; Sparago et al. 2007; Tank and Kay 1980; Van Lierde et al. 2012; White et al. 2018). Given the retrospective nature of this study, patients were included without known molecular test results and clinical features used for diagnosis, as varying criteria and molecular diagnostic methods were available at the time of the reports. Cases included from authors' cohorts were selected according to BWS definition (Brioude et al. 2018), i.e., with either a clinical diagnosis based on the international consensus criteria and/or a specific 11p15.5 anomaly on molecular testing. Cases from the literature with isolated hemihypertrophy/lateralized overgrowth but without molecular confirmation were excluded. Only reports that included the age at WT diagnosis were included. The literature search found 134 cases of BWS with WT. Additional unpublished BWS patients with WT were included from the registries of the authors' institutions ($n=21$). Institutional review board approval and patient consent was obtained for the personal cases included.

Available data concerning WT diagnosis were collected, including age at tumor diagnosis, phenotype, genotype, tumor stage at diagnosis, diagnosis modalities (including information concerning cancer screening), tumor laterality and focality, and treatment performed. Staging was categorized according to SIOP WT 2001 staging criteria for renal tumors of childhood (Vujanic et al. 2002).

The age at WT tumor diagnosis of patients with BWS was compared with that of 3665 patients with WT included in the NIH Surveillance, Epidemiology, and End Results Program (SEER) registry (www.seer.cancer.gov) data entries from 1973 to 2015, this is the largest database available and overlaps with the time frame of our cases. Data were analyzed with GraphPad Prism 7.0 (La Jolla, CA, USA), using ANOVA and Chi-square tests to assess distributions among the different patient groups and log-rank Mantel–Cox test to assess differences in Kaplan–Meier curve plots of age at WT development.

Results

A total of 155 cases with WT were included. Six of the included cases also had nephroblastomatosis, and one also had nephrogenic rests. Data of 10 additional patients with BWS and nephroblastomatosis ($n=8$) or nephrogenic rests ($n=2$), but not WT, were also collected and analyzed separately and will be reported elsewhere.

For patients with BWS, mean age at WT diagnosis was 29.1 ± 30.1 months (median 19.0 months). Molecular test results were available for 99 patients; 46 patients with IC1-GOM, 41 patients with pUPD11, 4 patients with 11p15.5 copy number variants, 4 patients with IC2-LOM, and 4 patients with negative test results. In 56 patients, testing was either not performed or not reported. Characteristics of the patients with BWS included are reported in Table 1.

Age at WT development in patients with BWS was compared with data from a control group of patients with WT from the SEER registry. Only SEER cases diagnosed before the oldest WT reported in a patient with BWS (i.e., up to 156 months of age) were included, corresponding to 3347 cases of those identified in SEER database (91.4% of total WT cases). Age at WT of SEER (mean 43.3 ± 29.9, median 37.0) patients differs with respect to that of the ones with BWS (Mann–Whitney U test $p<0.001$). Kaplan–Meier curves of the age at WT development in BWS and SEER patients are depicted in Fig. 1. From 12 to 84 months, patients with BWS showed a higher percentage of total WT diagnosed than the control patients with WT from the SEER registry. By 12 months, 35.5% of WT in BWS patients had

Table 1 Characteristics of the 155 patients with Wilms' tumor (WT) and Beckwith–Wiedemann spectrum (BWS) according to genotype

Genotype of the patients with BWS and WT	*n*	Age at WT[a]	Mean tumor stage at diagnosis[a]	Screened/not screened (not reported)	Stage at WT diagnosis (screened/not screened)				
					1	2	3	4	5
IC1-GOM	46	28.2 ± 31.4	2.5 ± 1.6 (n = 18)	7/14 (25)	8 (3/5)	1 (1/0)	4 (3/0)	2 (0/2)	3 (1/2)
pUPD11	41	31.4 ± 33.1	2.3 ± 1.3 (n = 14)	6/11 (24)	6 (2/4)	1 (0/1)	5 (0/3)	1 (0/1)	1 (0/1)
IC2-LOM	4	25.8 ± 11.4	2.0 ± 1.4 (n = 2)	2[b]/1 (0)	1 (1/0)	–	1 (0/1)	–	–
11p15 chromosomal rearrangement	4	42.3 ± 75.8	2.5 ± 2.1 (n = 2)	2/1 (1)	1 (1/0)	–	–	1 (0/1)	–
Negative	4	49.0 ± 54.4	5.0 ± 0.0 (n = 2)	1/1 (2)	–	–	–	–	2 (1/1)
Unknown	56	27.1 ± 25.5	1.5 ± 1.5 (n = 12)	24/6 (26)	7 (5/0)	2 (1/1)	2 (0/1)	–	–

BWS Beckwith–Wiedemann spectrum, *IC1-GOM* imprinting center 1 gain of methylation, *IC2-LOM* imprinting center 2 loss of methylation, pUPD11 chromosome 11 paternal uniparental isodisomy, *US* ultrasound, *WT* Wilms tumor

[a]No differences between groups at ANOVA for age (p = 0.817) and tumor stage (p = 0.864)

[b]One case was diagnosed with WT by incidental finding during routine abdominal US due to enlarged kidneys but was not following BWS protocol as BWS not suspected until after WT diagnosis

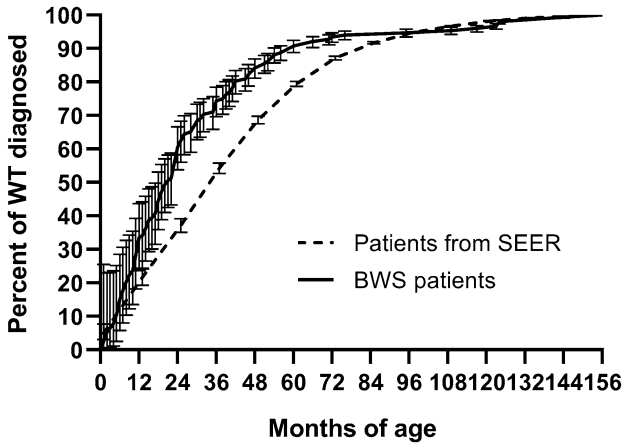

Fig. 1 Kaplan–Meier curves of Wilms tumor (WT) diagnosed by age in the Beckwith–Wiedemann spectrum (BWS) group and in the NIH Surveillance, Epidemiology, and End Results Program (SEER) group (www.seer.cancer.gov) up to 156 months of age. Vertical bars represent 95% CI

been diagnosed compared to only 16.3% of WT in SEER patients. And by 84 months, 94.2% of WT in BWS had been detected whereas WT in SEER patients was 90.5% detected. WT diagnoses in patients with BWS occurred earlier than those of SEER patients in the time period between 12 to 84 months of age (log-rank Mantel–Cox test: Chi square 76.13, $p < 0.0001$), and then reached a plateau. Table 2 details the percentage of WT diagnosed by age in the SEER and BWS groups. Although IC1-GOM patients experienced a higher incidence of WT in the first 2 years of life than pUPD11 patients, there was no significant difference (log-rank Mantel–Cox test: Chi square 0.33, $p = 0.564$). Four IC2-LOM patients developed WT at the ages of 11, 24, 30, and 38 months.

Table 3 summarizes the characteristics of patients with BWS and WT divided based on those diagnosed during typical tumor screening and those not screened. In the unscreened group, all the patients were diagnosed with WT prior to a suspicion of BWS. For an adequate comparison, only patients with age at WT diagnosis ≤ 96 months were included. Six patients were, therefore, excluded: five, diagnosed at 109 (stage 4), 117 (stage 4), 123 (stage not reported), 124 (stage 5), and 156 months of age (stage 4) were never routinely screened and one, diagnosed at 124 months of age (stage 3) after the recommended ultrasound screening period had ended. Patients diagnosed by tumor screening were significantly younger (22.8 ± 18.6 vs 34.7 ± 20.5 months) and had a lower stage tumor (1.5 ± 1.3 vs 2.6 ± 1.6) at the time of diagnosis. Age at WT diagnosis was compared among patients with BWS undergoing tumor screening, patients with BWS not undergoing screening, and patients from the control SEER registry by Kaplan–Meier curves. Screened BWS patients were diagnosed earlier with respect to unscreened BWS patients (Log-rank Mantel–Cox test: Chi square 70.19, $p < 0.0001$), and the unscreened patients had a diagnostic timing that overlapped with that of the SEER patients (Fig. 2).

Discussion

In 1968, the World Health Organization published guidelines related to population-based screening programs (Wilson and Jungner 1968). The guidelines advocated for screening that would optimize early detection, allowing identification of disease at an early stage in which treatment would be more effective (Wilson and Jungner 1968). In regard to WT screening, best practice guidelines advocate that routine

Table 2 Percentage of Wilms tumors (WT) diagnosed by age in the NIH Surveillance, Epidemiology, and End Results Program (SEER) registry control group and in the Beckwith–Wiedemann spectrum (BWS) group, including separately the two most represented genotypes (Imprinting Center 1 Gain of Methylation—IC1-GOM and chromosome 11 paternal uniparental isodisomy—pUPD11)

Age (months)	% of total WT diagnosed			
	SEER ($n=3347$)	BWS ($n=155$)	IC1-GOM ($n=46$)	pUPD11 ($n=41$)
3	4.1	8.4	15.2	4.9
6	5.6	16.8	17.4	7.3
9	8.7	23.9	23.9	17.1
12	16.3	35.5	32.6	29.3
24	32.2	61.3	65.2	56.1
36	49.2	74.8	76.1	80.5
48	64.8	84.5	84.8	90.2
60	76.4	91.0	93.5	90.2
72	85.4	93.5	93.5	92.7
84	90.5	94.2	95.7	92.7
96	94.1	94.8	95.7	92.7
108	96.3	94.8	95.7	92.7
120	97.8	96.1	97.8	95.1
132	98.8	98.1	100.0	95.1
144	99.5	99.4	100.0	100.0
156	100.0	100.0	100.0	100.0

surveillance should cover the age range of at least 90–95% of tumors (Scott et al. 2006), indicating that screening until 7 years of age is sufficient. By 7 years of age, 94.2% of all WT in patients with BWS were detected, whereas by 8 years of age, 94.8% were detected, supporting the recent reduction in screening age (Brioude et al. 2018; Kalish et al. 2017). Furthermore, patients diagnosed with WT through screening experienced lower stages at diagnosis, consistent with criteria for population-based screening programs (Wilson and Jungner 1968).

Although longitudinal studies assessing the long-term outcome of screening and morbidity and mortality are scarce, evidence does suggest that there are benefits to screening for WT in a high-risk population. The benefits of screening include early stage detection (stage 1 or 2) of a small and localized tumor, improved prognosis, and less intensive treatment, such as kidney sparing surgical approaches and the omission of radiation therapy (Beckwith 1998). In this study, patients with BWS who were diagnosed with WT by screening were of a significantly lower age and stage at diagnosis, whereas patients not screened had diagnosis timing overlapping that of nonsyndromic WT. These results are consistent with previous reports comparing the effectiveness of screening. Pritchard-Jones et al (2016) has previously demonstrated that children asymptomatic for WT diagnosed through screening experience a higher proportion of early stage tumors and significantly better outcomes compared to children symptomatic for WT (Pritchard-Jones et al. 2016). These results suggest that those diagnosed with WT after presenting with symptoms are more likely to have advanced-stage WT and require more extensive treatment. Furthermore, Choyke et al (1999) evaluated screening intervals and found that patients screened at intervals of 4 months or less had significantly lower incidence (0/12) of late-stage WT compared to patients screened at intervals greater than 4 months or no screening at all (25/59) (Choyke et al. 1999). Therefore, they concluded that screening at intervals of 4 months or less can significantly reduce the likelihood of late-stage WT.

It has been already observed that IC1-GOM and pUPD11 are associated with WT (Brioude et al. 2013; Maas et al. 2016; Mussa et al. 2016b, c) and that the IC1 region may play a role in WT development (Brioude et al. 2013). The results of this analysis support this hypothesis, as the majority of patients with WT and molecular testing results had IC1 GOM or pUPD11. Patients with IC1 GOM experienced a higher incidence of WT in the first 2 years of life compared to patients with pUPD11, but the difference was not significant.

WT screening in patients with IC2 LOM is debated, due to the relatively low incidence of WT compared to other molecular subtypes. In this series, we have included two previously unreported IC2 LOM patients with WT, bringing the total to nine known patients with IC2 LOM and WT; 5 reported [2 in Maas et al. 2016, 1 in Ibrahim et al. 2014, 1 in Brzezinski et al. 2017, 1 in Bilgin et al. 2018, 2 unreported commented in Brzezinski et al. 2018, and 2 from this present study]. Although there are few cases, the average age at WT diagnosis in patients with IC2 LOM was observed to be lower compared to other molecular groups, although the difference was not significant. These results are consistent with the previous report by Maas et al. (2016). Although WT is

Table 3 Comparison between characteristics of patients with Beckwith–Wiedemann spectrum (BWS) and Wilms' tumor (WT) diagnosed during tumor screening by abdominal ultrasound and those not screened

	Mean age ± SD– median (months)	*n*	Sex F/M (unknown)	Unifocal	Multifocal	Unknown focality	Stage at WT diagnosis						Outcome (in parentheses number of patients with data available)				
							1	2	3	4	5	Mean ± SD	Unknown	Treatment	Recurrence	Deaths	Age at last check (years)
Unscreened	34.7 ± 20.5–40.0	28	13/3 (12)	5	8	15	7	2	7	1	3	2.6 ± 1.6	8	5 PN, 15 TN	4	0 (10)	16.8 ± 13.8 (9)
Screened	22.8 ± 18.6–17.0	41	17/12 (12)	11	9	22	14	2	0	0	2	1.5 ± 1.3	24	12 PN, 20 TN	5	2 (21)	6.0 ± 4.4 (14)
	$p = 0.015$		$p = 0.117$	$p = 0.647$			$p = 0.001$					$p = 0.032$		$p = 0.368$	$p = 0.727$	$p = 0.510$	

PN partial nephrectomy, *TN* total nephrectomy

Fig. 2 Kaplan–Meier curves of Wilms' tumor (WT) diagnosed by age in the Beckwith–Wiedemann spectrum (BWS) group undergoing tumor screening by abdominal ultrasound (continuous black line) and not screened (gray continuous line) compared with the NIH Surveillance, Epidemiology, and End Results Program (SEER) registry control group (www.seer.cancer.gov). Vertical bars represent 95% CI. Screened BWS patients were diagnosed earlier with respect to unscreened BWS patients [log-rank (Mantel–Cox) test: Chi square 70.19, $p < 0.0001$]; the unscreened BWS patients had a diagnosis timing overlapping that of controls in the SEER group

rare in patients with IC2 LOM, the WT may occur earlier than other molecular subtypes. Based on these findings and previous data demonstrating that hepatoblastomas in BWS occur primarily before 30 months, we suggest screening patients with IC2 LOM until 30 months of age, including both AFPs and abdominal ultrasounds (Mussa et al. 2019).

Patients with negative molecular analysis who were not routinely screened had a greater mean age (49 months) at the time of diagnosis. These patients also had a greater mean tumor stage (stage 5). The later stage may be explained by the later age of diagnosis, as the WT had more time to progress. Approximately 1/3 of patients with BWS and WT included in this analysis had negative testing or the testing status was unknown. In some patients with BWS, blood analysis may be negative and additional tissue testing can identify the defect present. A case series of patients first presenting with WT and then subsequently diagnosed with BWS highlights the utility of testing all available tissues which include tumor tissue, adjacent normal tissue, and skin (MacFarland et al. 2018). Additionally, it has recently been suggested that all patients with WT should be tested for 11p15.5 anomalies, regardless of whether other features of BWS are present (Mifsud and Pritchard-Jones 2017). Testing multiple tissues such as tongue, skin, tumor, and adjacent normal tissue can increase the diagnostic yield and help identify children predisposed to WT development, which can also help understand tumor incidence and risk among molecular subtypes.

It has previously been proposed that BWS may provide a favorable biological marker for survival in children with intraabdominal tumors (Vaughan et al. 1995). In a small case series from a single institution, the disease-free survival rate of patients with BWS and WT ($n = 10$) was 100%, with median follow-up of 9 years. Excellent outcomes were observed for both low-stage and advanced-stage WT (Vaughan et al. 1995). It was not reported if these WT were detected by BWS tumor screening protocols.

International guidelines for patients with BWS include tumor screening recommendations targeted at those with the greatest risk, whereas North American guidelines advocate for all patients with BWS to receive tumor screening. The currently accepted screening protocol for WT and hepatoblastoma (HB) includes quarterly abdominal ultrasounds until the 4th birthday followed by quarterly renal ultrasounds until the 7th birthday (Brioude et al. 2018; Kalish et al. 2017). North American guidelines also recommend quarterly alpha-fetoprotein (AFP) measurements until the 4th birthday. We previously reported that all patients with BWS develop HB before the age of 30 months and suggested a possible reduction in AFP screening from 4 to 3 years (Mussa et al. 2019). As HB is the most common tumor to develop in patients with IC2 LOM, we suggest that screening by abdominal ultrasound and AFP until the age of 30 months may be sufficient to detect HB and WT development in these patients. WT risk is higher in those with other molecular subtypes and not understood in *CDKN1C* mutations, and these patients would benefit from screening until their 7th birthday.

It is also important to note that in some cases nephroblastomatosis and nephrogenic rests may be present and do not always necessitate surgical removal, as additional data are needed to determine how many of these progress to WT in patients with BWS.

For 100% detection of WT, screening would need to be performed until 13 years of age. In this analysis, only six patients were diagnosed with WT beyond the age of 7 years. Previous cost–benefit analysis not including genotype data demonstrated a benefit in screening to age 7 years with an even larger benefit in screening only until 4 years (McNeil et al. 2001); however, our data demonstrate that in terms of early detection of cases, screening until the 7th birthday is warranted. Since the McNeil analysis, additional knowledge such as the difference in incidence of WT within the different molecular subtypes of BWS has accumulated. Therefore, further study with larger data sets including genotype and a focus on specific medical practice is needed to reassess the cost–benefit analysis of screening and to determine the optimal length of screening.

Conclusions

In summary, patients with BWS develop WT at an age congruent with that of the general pediatric population, but screening patients with BWS seems to significantly decrease the age at the diagnosis in this population. Screening can also significantly reduce the stage at diagnosis. These data support current recommendations for WT screening every 3 months until the 7th birthday in patients affected by BWS. These data also suggest that WT screening may prove useful in IC2 LOM cases up to 30 months old, consistent with the recommendations for HB screening in this population.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest relevant to this article to disclose.

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