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SCIENTIFIC INVESTIGATIONS

Obstructive Sleep Apnea in Children With Beckwith-Wiedemann Syndrome

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Study Objectives: Beckwith-Wiedemann syndrome (BWS) is a rare pediatric overgrowth disorder that includes a spectrum of clinical findings including macroglossia, especially in those with loss of methylation at the imprinting control region (IC2 LOM) on chromosome 11. Children with BWS can have very severe obstructive sleep apnea (OSA), but the prevalence of OSA in this population is poorly understood, as is the relationship between OSA and the BWS genotype/phenotype. We hypothesized that there would be a high prevalence of OSA in children with BWS, and that OSA would be more severe in children with IC2 LOM.

Methods: Medical records from children evaluated from March 2015 through January 2018 were reviewed for results from polysomnography, genetic testing, and clinical assessment.

Results: A total of 26 children with BWS not previously treated for OSA underwent polysomnography, genetic testing, and clinical assessment. Median (range) age was 5 months (3 days to 33 months). Most children, 20 (76.9%), had an obstructive apnea-hypopnea index (OAHI) > 2 events/h. Median (range) OAHI was 4.4 events/h (0 to 56.1 events/h). OAHI was significantly greater in participants younger than 6 months compared with those older than 6 months (P = .008). Those with IC2 LOM did not have a greater OAHI (P = .61) than those with other genetic causes of BWS, but OAHI had a strong positive correlation with BWS clinical score (Spearman rho = .54, P = .004).

Conclusions: There is a high prevalence of OSA in children with BWS with macroglossia. Younger children with BWS and those with more phenotypic features may be at greatest risk of OSA.

Keywords: Beckwith-Wiedemann syndrome, macroglossia, obstructive sleep apnea

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Infants and children with craniofacial abnormalities are disproportionately affected by obstructive sleep apnea (OSA). Many young children with Beckwith-Wiedemann syndrome (BWS) have macroglossia, but the prevalence and risk factors of OSA in this population is unknown.

Study Impact: OSA is highly prevalent in children with BWS who have macroglossia; infants younger than 6 months are at the greatest risk and those with more clinical BWS features have more severe OSA. Clinicians caring for children with BWS should have a high index of suspicion for OSA, regardless of the specific genetic or epigenetic changes present.

INTRODUCTION

Beckwith-Wiedemann syndrome (BWS) is a rare pediatric overgrowth disorder, affecting approximately 1 in 10,500 live births.[1] The phenotype of children with BWS is highly variable, but typical features include macroglossia, omphalocele, lateralized overgrowth, and hypoglycemia.[1] Children with BWS are at risk for embryonal tumors, most commonly Wilms tumor and hepatoblastoma, and receive routine screening as a result.[1] The syndrome can be caused by multiple genetic and epigenetic changes that affect the chromosome 11p15 region. Despite advancements in genetic testing, approximately 20% of patients with a clinical diagnosis of BWS do not have a molecular defect identified.[1] Among those patients with a molecular diagnosis, approximately 50% of BWS is due to loss of methylation at imprinting control region 2 or KCNQ1OT1:TSS-DMR (IC2 LOM), whereas approximately 20% of BWS is due to paternal uniparental isodisomy for part of chromosome 11 (pUPD11).[2] Less common causes of BWS include gain of methylation at imprinting control region 1 or H19/IGF2:IG-DMR (IC1 GOM), mutations in *CDKN1C*, and chromosome abnormalities and translocations. The constellation of clinical features and molecular causes is now recognized as part of the BWS spectrum.[2] Recent (epi)genotype-phenotype associations have found that the clinical features of patients with BWS may vary by the molecular defect causing the disorder. Macroglossia is the most common finding, affecting approximately 90% of all patients with BWS.[1] The IC2 LOM defect has been most commonly associated with macroglossia[3–6] which is thought to be the main risk factor for obstructive sleep apnea (OSA) in this population.

OSA affects 2% to 5% of children, but disproportionately affects children with craniofacial abnormalities. Children and adults with macroglossia are at increased risk for OSA, presumably by obstruction at the base of the tongue.[7–9] There are multiple small case series describing severe OSA in infants and children with BWS.[10–12] A single case report describes the sudden death of a 2-month-old infant with BWS and macroglossia who had a history of prematurity and had required positive pressure ventilation and supplemental oxygen.[13] Follmar and colleagues reported a 30-year retrospective study of OSA in 118 patients with BWS and estimated the prevalence of sleep-disordered breathing to be 48%.[14] However, few of the participants in this study had polysomnograms, and most were diagnosed with sleep-disordered breathing based on symptoms either as an infant or during childhood.

Because of the small sample size and limitations of previous studies, the relationship between OSA and BWS remains unclear. In the current study, polysomnography was performed on children in whom BWS was diagnosed by genetic testing and standardized clinical evaluation. We hypothesized that there would be a high prevalence of OSA in this cohort and that those with IC2 LOM would have more severe OSA as this group is most associated with macroglossia. We also hypothesized that infants would have more severe OSA due to relatively more severe macroglossia.

METHODS

Study Design and Participants

This was a single-center case series. All participants were children with a clinical or molecular diagnosis of BWS and macroglossia. A BWS research database built specifically for patients referred to Children's Hospital of Philadelphia (CHOP) for evaluation of BWS or suspected BWS from March 2015 through January 2018 was reviewed for potentially eligible patients. Patients who did not meet BWS diagnostic criteria and patients with BWS who did not present with macroglossia at the time of evaluation were excluded. Only patients who underwent a complete evaluation were considered for inclusion. Complete evaluation was defined as comprehensive clinical and molecular evaluations, a diagnostic polysomnogram, and a standardized clinical assessment by a multidisciplinary team that includes human genetics, craniofacial surgery, and the sleep center. Children who had airway surgery such as adenotonsillectomy, tongue reduction, or tracheotomy before the multidisciplinary team evaluation including assessment of OSA was complete were excluded from the final analysis. Clinical data from the included patients were extracted from the BWS research database, which includes a detailed medical and surgical history, clinical information, and extensive medical records from each patient. Informed consent for that database was obtained from parents/guardians of all participants under a protocol approved by the CHOP Institutional Review Board (IRB 13-010658).

BWS clinical score was computed according to the new BWS consensus criteria[2]: two points were assigned for each cardinal feature present (macroglossia; omphalocele; lateralized overgrowth; multifocal and/or bilateral Wilms tumor/nephroblastomatosis; hyperinsulinism; and pathology findings [adrenal cortex cytomegaly, placental mesenchymal dysplasia, or pancreatic adenomatosis]) and one point was assigned for each suggestive feature present (birth weight > 2 standard deviations above the mean; facial nevus simplex; polyhydramnios and/or placentamegaly; ear creases and/or pits; transient hypoglycemia; nephromegaly and/or hepatomegaly; umbilical hernia and/or diastasis recti; and typical BWS tumors [neuroblastoma, rhabdomyosarcoma, unilateral Wilms tumor, hepatoblastoma, adrenocortical carcinoma, or pheochromocytoma]). Total clinical scores of four or less are not consistent with a diagnosis of BWS; patients with scores higher than four are consistent with a clinical diagnosis of BWS regardless of molecular testing results.

Assessments

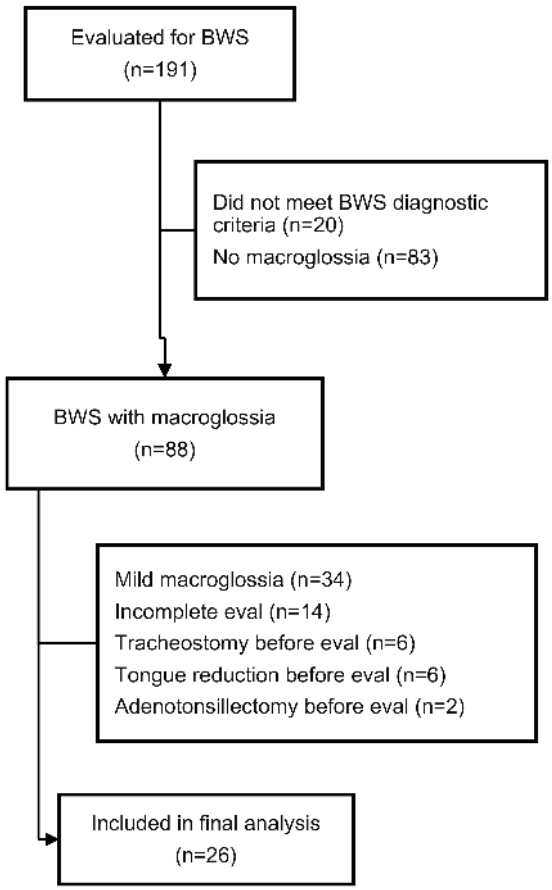
Clinical genetics evaluation was performed by a clinical geneticist and genetic testing included methylation analysis, *CDKN1C* sequencing, and single nucleotide polymorphism microarray analysis. All participants had a standardized history and physical examination that included details about noisy breathing and snoring and a craniofacial assessment with description of tongue size. Macroglossia was documented as part of this evaluation. Significant macroglossia was defined as the resting tongue exceeding the boundaries of the dentoalveolar ridge of the mandible by at least 5 mm. "Mild macroglossia" was identified when the tongue appeared slightly enlarged but did not meet the definition of significant macroglossia. Although patients with significant macroglossia were referred for polysomnography as part of their standard evaluation, those with mild macroglossia generally were not.

Polysomnograms were obtained overnight at an accredited pediatric sleep laboratory and were conducted and scored according to the American Academy of Sleep Medicine pediatric specifications.[15] Data were recorded using a Rembrandt polysomnography system (Embla, Broomfield, Colorado) that included: electroencephalograms (F3-M2, F4-M1, C3-M2, C4-M1, O1-M2, O2-M1), bilateral electrooculograms, chest and abdominal wall motion using respiratory inductance plethysmography, heart rate by electrocardiogram, arterial oxygen saturation (SpO_2) by pulse oximetry (Masimo, Irvine, California); transcutaneous PCO_2 (Radiometer, Brea, California), airflow using a thermistor (Pro-Tech Services, Inc., Mukilteo, Washington), nasal pressure by a pressure transducer (Pro-Tech Services, Inc., Walnut Cove, North Carolina), and bilateral tibialis anterior electromyogram. Patients were continuously observed by a polysomnography technician, and were recorded on video with an infrared video camera. Sleep staging was completed using the criteria outlined by Anders for infants[16] and the American Academy of Sleep Medicine criteria for older children.

Data Analysis

Characteristics of the study sample were summarized using descriptive statistics. The Shapiro-Wilk test was used to test for normality of data. Because most data were not normally distributed, results are presented as median (range). The primary

Figure 1—Consort diagram of patients evaluated and included in the final analysis.



BWS = Beckwith-Wiedemann syndrome, eval = evaluation.

outcome was the obstructive apnea-hypopnea index (OAHI), defined as the number of obstructive and mixed apneas and obstructive hypopneas divided by the total sleep time. Wilcoxon rank-sum test was used to compare OAHI between groups. Spearman rank correlation was used to evaluate the relationship between OAHI and BWS clinical score. Analysis was performed using Stata version 13.1 (College Station, Texas).

RESULTS

A total of 191 children were evaluated clinically for BWS from March 2015 through January 2018. Among these patients, 171 met diagnostic criteria for BWS and 88 presented with macroglossia. Fourteen patients were excluded because of history of airway surgery prior to completion of evaluations. Fourteen patients did not complete the full evaluation, usually because they were traveling from long distances, and only a partial evaluation could be coordinated or polysomnography was inadequate. Twenty-six children were included in the final analysis (**Figure 1**).

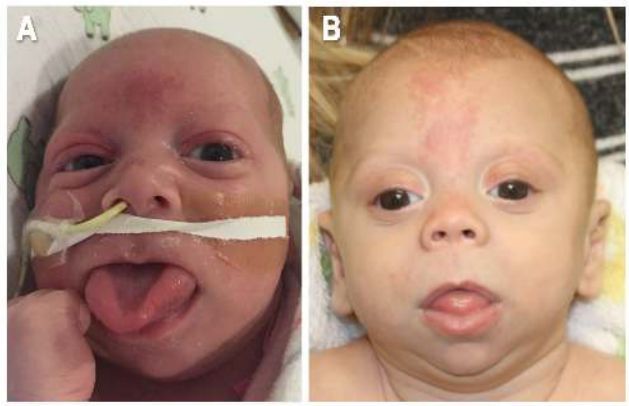
Median age at the time of polysomnography was 5 months (range 0 to 33 months). Seventeen participants (65.4%) had a loss of methylation at the IC2 location on chromosome 11.

Table 1—Characteristics of the 26 participants included in analysis.

Characteristic	Study Group (n = 26)
Age (months), mean (range)	5.0 (0.1–33.0)
Molecular defect	
IC2 loss of methylation	17 (65.4)
Uniparental disomy	2 (7.7)
CDKN1C mutation	2 (7.7)
IC1 gain of methylation	2 (7.7)
No defect identified (clinical diagnosis)	3 (11.1)
Snoring	17 (65.4)
Snoring and/or noisy breathing during sleep reported	22 (84.6)
Polysomnographic findings	
OAHI (events/h), mean (range)	4.4 (0.0–56.1)
OAHI > 2 events/h	20 (76.9)
OAHI > 5 events/h	12 (46.2)

Data are presented as n (%) or median (range) as indicated. OAHI = obstructive apnea-hypopnea index.

Figure 2—Two infants with Beckwith-Wiedemann syndrome, macroglossia, and severe OSA.



(A) 5-week-old girl with OAHI of 38 events/h and saturation nadir of 69%. **(B)** 3-month-old boy with OAHI of 31 events/h and saturation nadir of 82%. Note facial nevus simplex on both patients. OAHI = obstructive apnea-hypopnea index, OSA = obstructive sleep apnea.

Other mutations were less common (**Table 1**). All participants had macroglossia diagnosed clinically (**Figure 2**).

Seventeen infants and children (65.4%) had a history of snoring at the time of polysomnography (**Table 1**). Seventeen (65.4%) had a history of noisy breathing, either during infancy or as older children. Four participants (15.4%) had neither snoring nor noisy breathing; OAHI among these children ranged from 0 to 7.8 events/h. Twenty participants (76.9%) had an OAHI > 2 events/h and 12 (46.2%) had an OAHI > 5 events/h. The median (range) OAHI for the cohort was 4.4 (0 to 56.1) events/h.

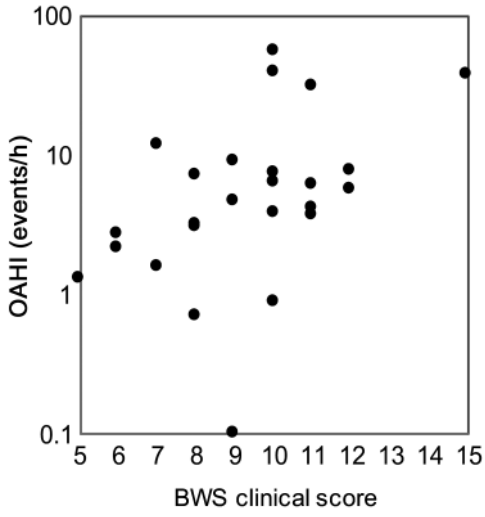
All patients had macroglossia, but there was a spectrum of clinical features of BWS, with clinical scores ranging from 5 to 15 (**Table 2**) based on the international BWS consensus scoring system.[2] There was a significant relationship between OSA severity and BWS phenotype severity (**Figure 3**). OAHI had a

Table 2—Features of Beckwith-Wiedemann syndrome.

ID	Omphaocele	Hyper-insulinism	Birth Weight > 2 SD	Facial Nevus Simplex	Polyhydramnios/ Placentamegaly	Ear Pits/ Creases	Nephromegaly/ Hepatomegaly	Umbilical Hernia/ Diastasis Recti	BWS Clinical Score
1	−	−	+	−	−	+	−	−	6
2	−	−	−	−	−	+	−	+	6
3	−	−	+	+	+	+	+	−	12
4	−	−	−	+	−	+	−	+	7
5	+	+	+	+	+	+	+	−	15
6	−	−	+	+	−	+	−	+	8
7	+	−	+	+	+	+	−	−	11
8	−	−	+	+	−	+	+	+	10
9	+	−	−	−	−	+	+	−	9
10	−	−	−	+	−	+	−	+	8
11	−	+	+	−	−	−	−	+	10
12	+	−	−	+	+	+	+	−	11
13	−	+	+	−	+	+	+	−	10
14	−	−	+	+	−	+	−	+	9
15	+	−	+	−	+	+	+	−	11
16	−	+	−	+	+	+	+	+	12
17	+	−	+	−	+	−	+	−	7
18	−	−	−	+	−	+	−	+	6
19	+	−	−	+	−	+	−	−	8
20	+	−	−	−	+	−	−	−	5
21	+	−	+	+	+	−	−	−	11
22	−	−	+	−	+	+	+	+	9
23	+	−	+	+	−	+	−	−	10
24	−	+	−	+	−	+	+	+	10
25	−	−	+	−	+	+	+	+	10
26	+	+	−	+	−	+	−	−	8

In addition to the features presented, all patients had macroglossia and most patients (except 17, 21, and 26) had lateralized overgrowth. Patients 3 and 5 had placental mesenchymal dysplasia. Patient 21 had a multifocal Wilms tumor and patient 16 had a hepatoblastoma. Patients 3, 7–10, 12, 14, 15, 22, 23, and 25 had transient hypoglycemia. Clinical scores were calculated as described in Brioude et al.[2] BWS = Beckwith-Wiedemann syndrome, SD = standard deviation.

Figure 3—Relationship between BWS clinical score and OSA severity.



There was a strong positive correlation between OAHI and severity of BWS clinical findings. Spearman rho = .54, P = .004. BWS = Beckwith-Wiedemann syndrome, OAHI = obstructive apnea-hypopnea index, OSA = obstructive sleep apnea.

strong positive correlation with BWS clinical score (Spearman rho = .54, P = .004). There was not a significant relationship between BWS clinical score and saturation nadir (Spearman rho = −.38, P = .06).

OSA was significantly worse in younger infants compared with older participants (**Table 3**). OAHI was significantly greater (P = .008) in participants younger than 6 months (median 7.5, range 0.9 to 56.1 events/h) compared to those older than 6 months (2.5, 0 to 7.5 events/h). Saturation nadir was also lower (P = .016) in those younger than 6 months (83%, 63% to 94%) compared to those older than 6 months (90%, 77% to 93%). There were no differences in the number of central apneas or in mean or peak transcutaneous CO_2 based on age group, but patients younger than 6 months had more arousals and a greater percentage of stage R sleep than those older than 6 months. OAHI was not significantly different (P = .61) in those with IC2 LOM (5.6, 0.1 to 56.1 events/h) compared to those with other alterations (3.8, 0 to 39 events/h).

Following evaluation, nine participants (34.6%) underwent tongue reduction surgery. There was persistent OSA following tongue reduction in one patient, who was subsequently successfully treated with continuous positive airway pressure.

Table 3—Summary of polysomnographic factors by age group.

Polysomnographic Finding	Age < 6 Months (n = 14)	Age > 6 Months (n = 12)	*P*
OAHI (events/h)	7.5 (0.9–56.1)	2.5 (0.0–7.5)	.008
Saturation nadir (%)	83 (63–94)	90 (77–93)	.016
Central apnea index (events/h)	0.7 (0.0–3.0)	1.0 (0.0–5.7)	.76
Sleep time with saturation < 90% (%)	0.5 (0.0–29.0)	0.0 (0.0–1.5)	.06
Peak transcutaneous CO_2 (torr)	52 (42–71)	49 (42–58)	.29
Mean transcutaneous CO_2 (torr)	44 (38–56)	42 (37–46)	.16
Arousal index (events/h)	21.4 (9.8–72.6)	10.7 (4.4–17.8)	.0008
Sleep efficiency (%)	86 (50–96)	84 (62–93)	.82
Stage R sleep (% of total sleep time)	41.5 (13.4–54.2)	26.3 (15.0–36.8)	.004

Data are presented as median (range). OAHI = obstructive apnea-hypopnea index.

DISCUSSION

To our knowledge, this is the largest series of children with BWS to be evaluated for OSA using polysomnography. More than three-fourths of children with BWS in our cohort had OSA, and only one participant younger than 6 months had an OAHI < 2 events/h. Surprisingly, in a group where nearly all participants had clinically diagnosed macroglossia, OSA was not worse in those with IC2 LOM than in those with other genetic causes of BWS.

Children included in this study underwent a standardized clinical evaluation by a geneticist, pediatric sleep medicine physician, and craniofacial surgeon. Laboratory testing included methylation and single nucleotide polymorphism array analysis as well as in-laboratory polysomnography. Our data show a greater prevalence of sleep-disordered breathing in children with BWS compared to other studies. The study by Follmar et al.[14] found 48% of children with BWS had sleep-disordered breathing, which may have included snoring, breathing problems immediately after birth, or OSA diagnosed by polysomnography. The greater percentage of children with OSA in the current cohort may be due to the young age of the participants. Our study showed significantly more severe OSA in infants younger than 6 months compared to older participants, with a greater OAHI and more severe desaturation. We chose to group children younger than 6 months together because in younger children with a smaller upper airway, a large tongue may be more likely to obstruct the airway, causing OSA.

All participants in this series had macroglossia, despite the fact that 40% did not have an IC2 LOM defect. As the clinical spectrum of BWS is expanding to include patients with more subtle features, greater numbers of patients with BWS are coming to medical attention.[2] In some cases, macroglossia may be the only presenting feature and current genotype-phenotype correlations are being challenged. Thus, there may be an increase in patients with BWS with causes of BWS other than IC2 LOM that present with macroglossia. Macroglossia may not be the sole risk factor for OSA in children with BWS. In the study by Follmar et al., macroglossia was not associated with sleep-disordered breathing symptoms.[14] Our data show a correlation between the BWS clinical score and severity of OSA. This clinical score, which includes the clinical features consistent with BWS, is currently used in the diagnostic evaluation of BWS and in this study is a proxy for the number of clinical features present in each patient.[2] As patients with greater clinical scores present with more clinical features of BWS, these patients can be considered to have a more severe phenotype than patients who present with lower clinical scores. Given this, it is not surprising that patients with a more severe BWS phenotype presented with more severe OSA.

Interestingly, our data show increased arousals from sleep in the infant group, which had more obstructive apnea, compared to patients older than 6 months. A study comparing infants with an apparent life-threatening event to healthy infants in a control group found that infants with OSA had a greater arousal threshold compared to those without OSA,[17] but that study did not directly compare the absolute number of spontaneous arousals during normal sleep conditions. Although the frequency of arousal responses to obstructive apnea increases according to age, the difference in arousals in the group of infants younger than 6 months is likely due to the threefold increase in obstructive events in that group, because many of the arousals were associated with obstructive events rather than spontaneous events.[18]

Assessing OSA in children can be challenging. Evaluation in a sleep laboratory experienced in studying children and interpreting pediatric polysomnograms is the gold standard, but such facilities are limited.[19] Although screening tools have been shown to be relatively sensitive and specific in research environments for assessing OSA in children,[20] even the best validated such tools are limited to older children[21] and have not been shown to be effective in children with significant underlying medical conditions.[22] In infants and younger children, the task is even more challenging, because they may not present with symptoms typical of OSA in older children.[23]

Despite having a standardized evaluation in a relatively large series of children with a rare disease, this retrospective study had several important limitations. As a retrospective study, the findings are limited by selection bias. Only children with macroglossia were included in this analysis, so it is unclear whether infants and especially older children with BWS who clinically do not have clinically significant macroglossia are also at increased risk of OSA. Because we only included children who had not already had tongue reduction surgery

or other airway surgeries, primarily infants and young children were included in this cohort, making it hard to extrapolate these data to older children with BWS. Infants with the most severe obstructive apnea who had respiratory failure and could not undergo baseline polysomnography were also excluded from this series. Additionally, children with mild macroglossia did not undergo polysomnography as part of their standard evaluation and thus were generally not included in this cohort.

Despite the high prevalence of OSA in children with BWS, this is one of very few studies of sleep apnea in this condition. More research is needed to better understand the relationship between BWS, macroglossia, and OSA. Future studies should not be limited to children with BWS who have macroglossia to try to determine the overall prevalence of OSA in BWS. Imaging studies are needed to determine the role of macroglossia versus other factors in OSA in these patients. Longitudinal studies are needed to better understand the prevalence of OSA throughout childhood and the natural history of OSA in this population. There remains a limited understanding of the benefit of surgical interventions such as tongue reduction on OSA in children with BWS. Surprisingly, most reports of tongue reduction surgery in children with BWS include limited information about its effect on sleep-disordered breathing.[11,12]

It is troubling that there has been a case report related to a death in an infant with BWS with respiratory difficulty, even though that death was not attributed to OSA.[13] Although sudden death is not a common complication of untreated OSA in children, it has been reported in children with Prader-Willi syndrome–initiating growth hormone[24–26] and in infants with Pierre Robin sequence and nasal obstruction.[27] The identification of OSA in high-risk groups, including infants, is important, and more research is needed to determine how to best screen these patients for OSA.

In summary, children with BWS who are identified as having macroglossia have a high prevalence of OSA. Infants younger than 6 months seem to be at particularly increased risk, perhaps because of their relatively large tongue size compared with older children. There is not a clear association between OSA and BWS genotype, but there appears to be a correlation between OSA severity and BWS clinical score. Clinicians caring for children with BWS with macroglossia should have a low threshold for evaluating for OSA, particularly in infants and those with more phenotypic features of BWS.

ABBREVIATIONS

BWS, Beckwith-Wiedemann syndrome
GOM, gain of methylation
IC1, imprinting center 1
IC2, imprinting center 2
LOM, loss of methylation
OAHI, obstructive apnea-hypopnea index
OSA, obstructive sleep apnea
pUPD, paternal uniparental isodisomy

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