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Phenotype evolution and health issues of adults with Beckwith-Wiedemann syndrome

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Abstract

Background: Beckwith-Wiedemann syndrome (BWS) phenotype usually mitigates with age and data on adulthood are limited. Our study aims at reporting phenotype evolution and health issues in adulthood.

Methods: 34 patients (16 males), aged 18–58 years (mean 28.5) with BWS were enrolled.

Results: 26 patients were molecularly confirmed, 5 tested negative, and 3 were not tested. Final tall stature was present in 44%. Four patients developed Wilms' Tumor (2, 3, 5, and 10 years, respectively); one hepatoblastoma (22 years); one acute lymphoblastic leukemia (21 years); one adrenal adenoma and testicular Sertoli cell tumor (22 and 24 years, respectively); and three benign tumors (hepatic haemangioma, uterine myoma, and mammary fibroepithelioma). Surgery for BWS-related features was required in 85%. Despite surgical correction several patients presented morbidity and sequelae of BWS pediatric issues: pronunciation/swallow difficulties (n = 9) due to macroglossia, painful scoliosis (n = 4) consistent with lateralized overgrowth, recurrent urolithiasis (n = 4), azoospermia (n = 4) likely consequent to cryptorchidism, severe intellectual disability (n = 2) likely related to neonatal asphyxia and diabetes mellitus (n = 1) due to subtotal pancreatectomy for intractable hyperinsulinism. Four patients (two males) had healthy children (three physiologically conceived and one through assisted reproductive technology).

Conclusions: Adult health conditions in BWS are mostly consequent to pediatric issues, underlying the preventive role of follow-up strategies in childhood. Malignancy rate observed in early adulthood in this small cohort matches that observed in the first decade of life, cumulatively raising tumor rate in BWS to 20% during the observation period. Further studies are warranted in this direction.

KEYWORDS

adult phenotype, Beckwith-Wiedemann syndrome, cancer risk

Andrea Gazzin, Diana Carli, Giovanni B. Ferrero, and Alessandro Mussa contributed equally to this study.

1 | INTRODUCTION

With a prevalence of approximately 1 in 10,000 overall live births (Mussa et al., 2013) and 1:1,000 in children conceived through assisted reproductive techniques (Mussa et al., 2017), Beckwith–Wiedemann syndrome (BWS, OMIM #130650) is the commonest overgrowth condition and the paradigm of genomic imprinting disorders. Phenotype ranges within a wide spectrum of anomalies including overgrowth, macroglossia, abdominal wall defects, nephrourological malformations, hyperinsulinemic hypoglycemia, lateralized overgrowth, ear lobe creases or helical pits, hemangiomas and facial naevus flammeus, organomegaly (Mussa et al., 2016c; Mussa et al., 2016d; Mussa, Russo, Larizza, Riccio, & Ferrero, 2016; Shuman, Beckwith, & Weksberg, 1993) and increased risk of embryonic tumors in early childhood (Maas et al., 2016; Mussa et al., 2016). The wide range of clinical presentations is partially explained by the complex heterogeneous molecular physiopathology and by the mosaic distribution of the epigenetic anomalies of the 11p15.5 chromosomal region, found in more than 80% of the clinically diagnosed patients (Brioude et al., 2018). The variable clinical presentation and the complex molecular bases have recently been highlighted, consistent with adoption of more appropriate terminology—*BWS spectrum* (BWSp)—and introduction of a new scoring system for the clinical diagnosis (Brioude et al., 2018). Generally, mild presentations do not require treatment, while the severe ones deeply impact patients' health condition and quality of life (Mussa et al., 2016). Some features (e.g., macroglossia, umbilical hernia) frequently mitigate throughout childhood making the syndrome less recognizable and impactful. Conversely, other features (e.g., limb length discrepancy) can persist through adulthood or even worsen (Brioude et al., 2018) potentially easing complications (e.g., scoliosis as a consequence of uncorrected lower limb length discrepancy or anterior open bite consequent to severe macroglossia) (Brioude et al., 2018; Mussa, Di Candia, Russo, et al., 2016).

As tumor risk and overall clinical surveillance are limited to childhood, scientific reports and medical knowledge concerning BWSp is mostly limited to the first decade of life. Very few are currently known on BWSp natural history and presentation in adulthood: information on BWSp impact later in life is limited and rarely reported (Greer, Kirkpatrick, Weksberg, & Pauli, 2008). However, this issue appears to be of paramount importance in clinical practice as parents and young adult patients themselves have a variety of questions about possible medical problems arising in adulthood and later consequences of childhood health issues. Adolescents and adults frequently ask about fertility, pregnancy, tumor risk, and later health status. Anecdotal experiences allow physicians to provide only unsatisfactory information. With these premises and prompted by patients' associations (Italian Association of Patients with BWSp, Associazione Italiana Sindrome di Beckwith-Wiedemann, AIBWS, www.aibws.org); here, we investigated these issues.

2 | METHODS

2.1 | Patients

We recruited patients with BWSp aged ≥18 years with a search conducted through the BWS Registry of the Pediatric Genetics of our Institution and information gathered through AIBWS, data were acquired after obtaining the informed consent. BWSp diagnosis was assessed clinically and/or molecularly according to recent diagnostic criteria (Brioude et al., 2018).

2.2 | Data collection

Data collection was conducted through (a) administration of a standard questionnaire and (b) revision of clinical documentation, including recent medical visits or, when unavailable, conducting a physical exam. Telephone interviews, e-mail communication, contacts with the general practitioners, and personal examination of the available clinical documentation including pictures were used to obtain the data. Data acquisition was divided in the following sections and items: (a) *BWSp diagnosis*. Information about BWSp phenotype and genotype, including ages at diagnosis, molecular tests, specific procedures, and timing of follow-up and tumor surveillance were acquired; (b) *Correction of BWSp related anomalies*. Each BWSp clinical feature was investigated, with the specific medical or surgical strategy adopted, as well as the evolution of the defect, and the impact on the overall health status at the time of the study. Information about macroglossia and associated orthodontic, swallowing and speech anomalies, the need for reductive glossectomy or orthodontic intervention were obtained. Regarding lateralized overgrowth, attention was focused on the affected body part and, in case of lower limb involvement, the orthopedical surgery or orthoses correction needed. For patients affected by abdominal wall defects information about surgery required and aesthetical revision were acquired. In-depth details were also recorded for neonatal hypoglycemia and nephrourological conditions; (c) *Follow-up and cancer surveillance procedures*. Attention was focused on specific procedures and timing of follow-up and medical checks concerning tumoral aspect of BWSp (i.e., abdominal ultrasound, alpha-fetoprotein measurement, etcetera); (d) *Growth*. Current stature, weight, and cranial circumference were acquired. Standard deviation (SD) was calculated for each patient based on local standards (Cacciari et al., 2006) and definitive stature was compared with parental height if known; (e) *Qualification, functioning, and physical activity*. Educational level, current and previous jobs, and sport activities were obtained; (f) *Prenatal findings, pregnancy and delivery data, and psychomotor development*. In this section, we collected information about prenatal findings, pregnancy and delivery complications, as well as data about development milestones, learning difficulties, and eventual intellectual disability (g) *Adult health condition*. Data about current and through-adulthood health status diseases or medical issues arose in adulthood were investigated. To each subject was primarily asked in general terms if since 18 years of age he/she had met relevant health issues requiring a significant medical intervention. (h) *Tumor data* were collected, focusing on histology, age of diagnosis, methods of diagnosis (accidental diagnosis, related symptoms or tumoral screening), and therapeutic strategies. (i) *Reproduction and procreation*. We surveyed data about fertility (attempts to conceive, fertility exams and tests), pregnancy, delivery, and health status of the patients' offspring.

3 | RESULTS

Forty-two patients were contacted and 34 (aged 18 to 58 years, mean age 28.5 ± 9.9, 18 females and 16 males) agreed to participate in the study. Thirty patients had a clinical diagnosis with a BWSp score ≥ 4 and four patients with a clinical score of 3 points had a positive molecular test confirming the diagnosis. Molecular tests were performed in 31 subjects, at mean age of 19.1 ± 15.0 years: 14 patients presented 11p15.5 Imprinting Center 2 Loss of Methylation (IC2-LoM, 41.2%), two *KCNQ1* microduplication (Chiesa et al., 2012) and one microdeletion (Zollino et al., 2010) associated with IC2-LoM, (8,8%), two Imprinting Center 1 Gain of Methylation (IC1-GoM, 5,9%), one microdeletion of the IC1 associated with IC1-GoM (2,9%), five had 11p15.5 Paternal Uniparental Disomy (UPD[11]pat, 14.7%), one *CDKN1C* mutation (2.9%). Five out of the 31 patients analyzed resulted negative at the molecular tests (16.1%), while molecular analysis was not performed in three patients out of 34 (8.8%). Age at diagnosis ranged from birth to 41 years (mean 5.0 ± 9.9 years), in 17 cases (50.0%) diagnosis was formulated at birth due to easily recognizable features, in other three cases (8.8%) in the first year of life.

1. *BWSp features and correction of BWSp-related malformations*—Table 1 shows the clinical features and the related treatment. Figure 1 shows facial characteristics and macroglossia of adult patients. Overall, 52.9% (18/34), 14.7% (5/34), and 17.6% (6/34) patients underwent one, two, or more surgical interventions, respectively, and five patients never underwent surgery. Surgical treatment was required for tongue reduction, cryptorchidism, lower limb length discrepancy correction, mandibular advancement, abdominal wall defects correction (all surgically corrected at birth in case of omphalocele), surgical removal of tumors, penis surgery due to recurvation and labia minora reduction due to asymmetry.
2. *Follow up and cancer surveillance*—Twenty-six patients (76%) underwent cancer surveillance in infancy undergoing quarterly abdominal ultrasound (up to 8 years of age) and, all but three of them, with serum alpha-fetoprotein measurement (up to 4 years of age). Three patients still undergo abdominal ultrasound for nephrourological conditions, while further five by individual initiative. Eight patients never performed cancer surveillance in childhood, seven because of a late diagnosis, made at 8, 11, 15, 16, 23, 28 and 41 years, respectively.
3. *Growth*—Final height was >+2 SDS in 15 patients (44%). Mean height SDS was +1.33 ± 1.50, range from −2.32 to +3.80. In 26 subject parents' anthropometric data were available so it was possible to compare final height to the genetic target: 15 (57.7%) showed height above their genetic target.
4. *Educational level, social inclusion and physical activity*—Educational level in the cohort is quite heterogeneous: four patients achieved university degree and five are successfully performing university studies, while 19 patients obtained or are obtaining a secondary school graduation. Four subjects obtained primary school graduation. Four patients failed and had to repeat the same grade.

TABLE 1 BWSp features in the study group

Feature	Cases/sample[a]
Macroglossia	**31/32 (96.9%)**
Hemi-macroglossia	6/31 (19.4%)
Surgery	14/31 (45.2%)
Surgical tongue reduction	11/31 (35.5%)
Maxillary advancement/mandibular retraction	5/31 (16.1%)
Multiple maxillofacial surgical corrections	3/31 (9.7%)
Orthodontic and speech anomalies	15/31 (48.4%)
Orthodontic therapy	18/29 (62.1%)
Speech therapy	9/29 (31.0%)
Birth weight > +2 SDS	13/23 (56.5%)
Final height > +2 SDS	15/34 (44.1%)
Lateralized overgrowth	**22/33 (66.7%)**
Lower limb length discrepancy	20/33 (60.6%)
Surgically corrected	6/20 (30.0%)
Treated with orthoses only	4/20 (20.0%)
Upper limb overgrowth	8/22 (36.4%)
Facial asymmetry/overgrowth	7/22 (31.8%)
Abdominal wall defects	**24/31 (77.4%)**
Omphalocele	12/24 (50.0%)
Umbilical hernia (one surgically reduced)	7/24 (29.2%)
Inguinal hernia (one surgically reduced)	6/24 (25.0%)
Diastasis recti	3/24 (12,5%)
Neonatal hypoglycemia	**12/31(38.7%)**
Persisting through infancy	5/12 (41.7%)
Treated with diazoxide	3/5 (60.0%)
Pancreatectomy	1/12 (8.3%)
Urinary anomalies	**12/32 (37.5%)**
Cystic kidney	6/12 (50.0%)
Renal agenesis	1/12 (8.3%)
Ureteral malformation	1/12 (8.3%)
Nephrolithiasis	5/12 (41.7%)
Recurrent urinary tract infections	2/12 (16.7%)
Cryptorchidism	**7/16 (43.8%)**
Bilateral cryptorchidism	4/7 (57.1%)
Malignant tumors	**8/34 (23.5%)**
Wilms' tumor	4/34 (11.8%)
Hepatoblastoma	1/34 (2.9%)
Early-T acute lymphoblastic leukemia	1/34 (2.9%)
Intratubular germ cell neoplasia	1/34 (2.9%)
Testicular Sertoli-cell tumor	1/34 (2.9%)
Benign tumors	**4[b]/34 (11.8%)**
Mammary fibroepithelioma	2/34 (5.9%)
Non-functional adrenal adenoma	1/34 (2.9%)
Hepatic angioma	1/34 (2.9%)
Uterine myoma	1/34 (2.9%)

[a]Sample included cases from the whole cohort with information available.
[b]One patient with a malignant tumor had also a benign one (ID #22).

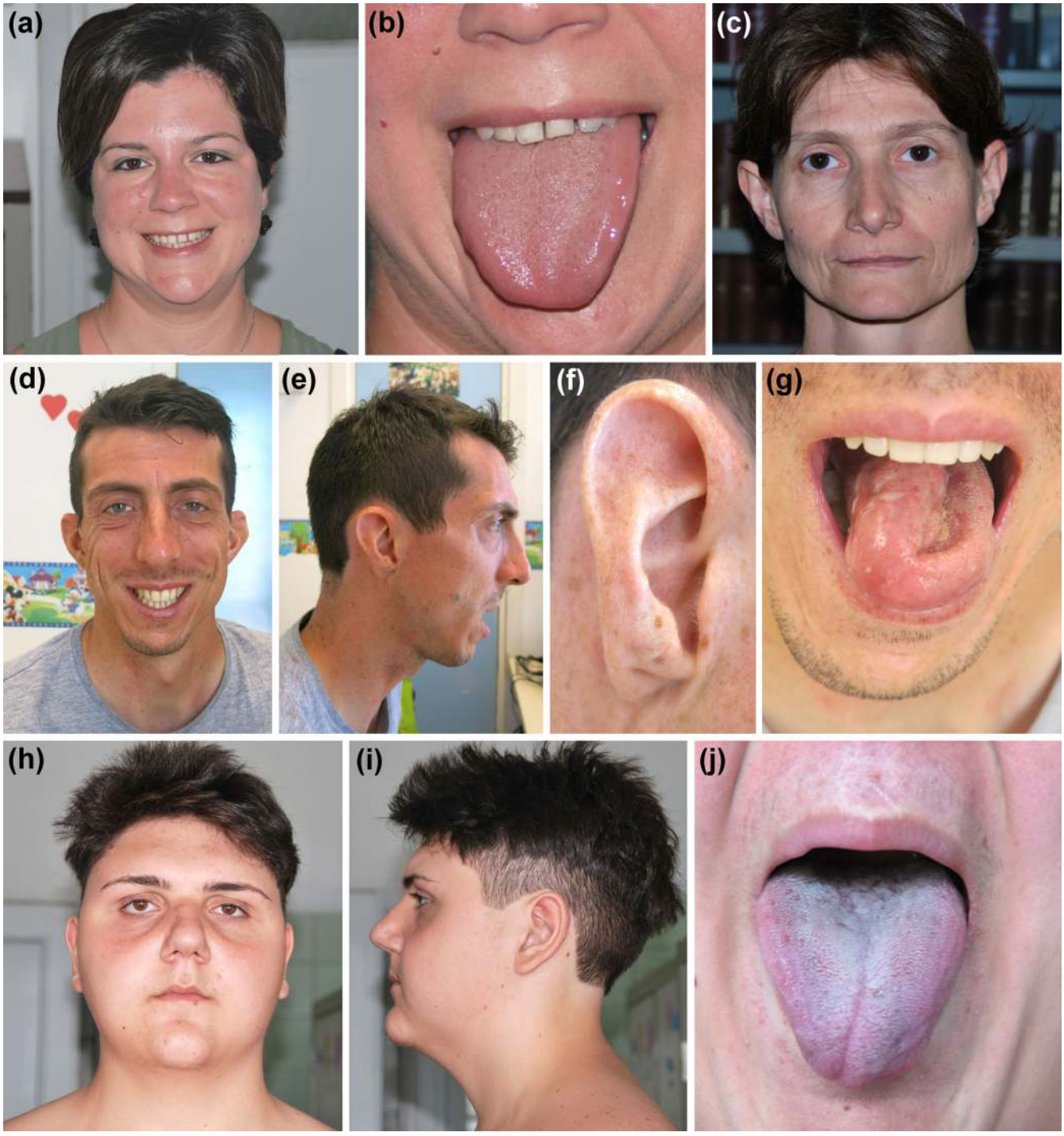

FIGURE 1 Facial characteristics of adult patients with BWSp showing mild (a,c), moderate (h,i) or severe (d,e) prognathism consistent with mild (b) hemimacroglossia or severe one, operated in infancy (g, j), and typical ear creases (f) [Color figure can be viewed at wileyonlinelibrary.com]

Fourteen (66.7%) of the 21 adult patients with available information, were gainfully employed. Regular physical activity was performed by 22 subjects; seven on a competitive level, although lower limb length discrepancy was present in six of them.

5. *Prenatal findings, pregnancy, delivery and developmental milestones*—Prenatal tests detected fetal anomalies consistent with BWSp (such as, macrosomia and/or placentomegaly, increased abdominal circumference, omphalocele, elevated nuchal translucency), or elevated alphafetoprotein levels in mother's serum in 12 patients out of 22 for whom this information was available. In six cases (17.6%) spontaneous delivery was complicate by obstructed labor and in 12 cases (35.3%) caesarean section was necessary because of omphalocele, long/thick umbilical cord with loops, failing of fetal presentation during labor, breech presentation, or suspected

TABLE 2 List of health issues and medical conditions in childhood and adulthood

ID	Age (years)	Genotype	BWSp phenotype	Sex	Relevant[a] health issues	
					In infancy and adolescence	In adulthood
1	30	LoM IC2	MG, UH	F		
2	18	Negative	LO, MG, MS, NTH	M		Scoliosis and recurrent back pain
3	35	LoM IC2	LO, bilateral C, IH, OM, NTH, renal cysts	M		Azoospermia
4	58	Negative	MG, O, NTH	F	Recurrent severe urinary tract infections	Uterine myoma. Maculopathy, two episodes of transitory ischemic attack at 42 years and a third at 45 years resulting in left ear central hypoacusis
5	18	Negative	LO, emi-MG, O, UH, MS, OM, left kidney agenesis, right kidney malformation	F	Brain Chiari malformation (occasional finding at MRI for recurrent lipothymias)	Mammary gland fibroadenoma, scoliosis, atopic dermatitis, labia minora overgrowth with asymmetry (surgical reduction)
6	23	UPD(11)pat	LO, MG, UH, IH NPH, renal cysts	M	Perinatal hypoxic–ischemic encephalopathy, hyperinsulinemic hypoglycemia recurrent through infancy until 9 years, mild intellectual disability	Drug-resistant epilepsy
7	19	GoM IC1	LO, MG, OM, WT	F		
8	45	GoM IC1	LO, MG, IH, NPH, OM, MS, left C, unilateral renal agenesis	M	Perinatal hypoxic–ischemic encephalopathy, hyperinsulinemic hypoglycemia recurrent through infancy, severe intellectual disability	Drug-resistant epilepsy
9	43	LoM IC2	MG, O, NTH, MS	F	Volvulus at 50 days	
10	18	LoM IC2	LO, MG, O	M		
11	25	LoM IC2	LO, MG	F		
12	18	LoM IC2	LO, MG, MS	F	Recurrent syncopal episodes (vasovagal)	
13	20	UPD(11)pat	LO, MG, urolithiasis	F		Recurrent urinary tract infections
14	24	Not tested	LO, MG, UH, NPH, urolithiasis, C	M	Perinatal hypoxic–ischemic encephalopathy, hyperinsulinemic hypoglycemia recurrent through infancy, severe intellectual disability	Nasal polyposis, absence seizure, right ear neurosensorial deafness, psychiatric intermittent explosive disorder requiring involuntary commitment
15	-	LoM IC2, IC2 deletion (Zollino et al., 2010)	MG, MS, UH, OM, NTH	F	Essential Thrombocythemia JAK2 V617F positive, mild psychomotor delay, facial dysmorphisms	Early-T acute lymphoblastic leukemia
16	30	Negative	MG, UH, OM, bilateral C	M		Azoospermia
17	25	LoM IC2	LO, MG, UH, MS	F	Type 1 diabetes mellitus	
18	42	UPD(11)pat	LO, UH, WT, renal cysts	M		Infertility, genital surgery for *recurvatio penis*, recurrent urolithiasis
19	22	LoM IC2		M		Scoliosis, recurrent back pain

(Continues)

TABLE 2 (Continued)

ID	Age (years)	Genotype	BWSp phenotype	Sex	Relevant[a] health issues	
					In infancy and adolescence	In adulthood
			LO, O, UH, OM, renal cysts, severe MG, glabellar nevus flammeus		Corpus callosum dysplasia and congenital abnormalities of the dural venous sinuses, severe macroglossia requiring intubation at birth, bronchiolitis (respiratory support, tracheostomy at 1.5 year of life), left vocal cord paralysis and dysphonia, patent ductus arteriosus surgically corrected (1 year)	
20	18	GoM IC1, IC1 microdeletion (Sparago et al., 2004)	LO, MG, OM, WT, left ureteral malformation, left C, MS	M	Recurrent otitis (myringoplasty)	Mild mitral valve insufficiency, inflammatory bowel disease, obesity (class III), obstructive sleep apnea, primary hypertension
21	41	LoM IC2	LO, MG, MS, sponge kidney, nephrocalcinosis, bilateral C, auricular pits	M		Adrenal adenoma, Sertoli-cell testicular tumor, primary hypertension, atrial fibrillation, azoospermia, recurrent urolithiasis
22	18	Negative	LO, emi-MG, O, NPH, MS	F	Brain Chiari type I malformation, total pancreatectomy for persistent intractable hyperinsulinism	Scheduled abdominal plastic surgery for multiple abdominal laparotomies, iatrogenic diabetes mellitus
23	-	LoM IC2	LO, MG, O, OM, renal cysts, MS	M		Hepatoblastoma
24	19	LoM IC2	LO, MG, O, MS	F		
25	20	LoM IC2	LO, MG, UH	F		Chronic autoimmune thyroiditis
26	29	Not tested	LO, MG	F		
27	30	LoM IC2	MG, O, urolithiasis, MS, NTH	F	Abdominal debridement due to adhesion	Aesthetic abdominal wall surgery for scars
28	41	UPD(11)pat	LO, MG, NTH, OM	F		Scoliosis and recurrent back pain
29	31	*CDKN1C* Mut	MG, O, IH, left C	M		Left testicle IGCNU[b], facial epidermal nevus removal, azoospermia, tibial varism
30	25	Not tested	LO, emi-MG, MS	F		Recurrent migraine, alopecia
31	37	Microdup KCNQ1–LoM IC2 (Valente et al., 2019; Chiesa et al., 2012)	O, MS	F		Long QT syndrome type 1
32	38	Microdup KCNQ1–LoM IC2 (Valente et al., 2019; Chiesa et al., 2012)	MG	M		Long QT syndrome type 1, asthma
33	19	UPD(11)pat	LO, MG, WT	M		
34	28	LoM IC2	LO, MG, O, NPH, OM, auricular pits	M	Recurrent through infancy hyperinsulinemic hypoglycemia	Chronic nonspecific colitis, intestinal resection due to obstruction, asthma

Abbreviations: C, cryptorchidism; MG, macroglossia; MS, macrosomia; LO, lateralized overgrowth; UH, umbilical hernia; IH, inguinal hernia; O, omphalocele; NTH, neonatal transient hyperinsulinism; NPH, neonatal persisting hyperinsulinism; OM, organomegaly; WT, Wilms' Tumor.

[a]BWS features not likely related with adulthood medical status were omitted.

[b]Intratubular germ cell neoplasia, unclassified (IGCNU).

TABLE 3 Incidence of adulthood medical issues and correlation with pediatric BWSp-related features

BWS features		Frequency	Adulthood sequelae allegedly connected	Frequency
Macroglossia		31/32 (96.9%)	Persisting speech, pronunciation, or swallow difficulties	9/31 (29.0%)
Lateralized overgrowth	Presence of lower limb length discrepancy	20/33 (60.6%)	Scoliosis, back pain	3/22 (13.6%)
	Absence of lower limb length discrepancy	2/33 (6.1%)		1/22 (4.5%)
Abdominal surgery		13/33 (39.4%)	Aesthetic surgery for abdominal scars	1/13 (7.7%)
Urinary anomalies[a]		12/32 (37.5%)	Recurrent episodes of urolithiasis	4/12 (33.3%)
			Recurrent urinary tract infections	2/12 (17.7%)
Neonatal macrosomia		13/23 (56.5%)		
	Obstructed labor	6/23 (26.1%)[b]		
	Neonatal hypoxic–ischemic encephalopathy	3/13 (23.1%)	Drug-resistant epilepsy or absence seizure right ear neurosensory deafness, psychiatric intermittent explosive disorder[c]	3/34 (8.8%)
Neonatal hypoglycemia		12/31 (38.7%)	Iatrogenic diabetes mellitus secondary to pancreatectomy	1/12 (8.3%)
Cryptorchidism	Bilateral	4/16 (25.0%)	Azoospermia	3/4[d] (75.0%)
	Monolateral	3/16 (18.9%)	Azoospermia	1/3[d] (33.3%)

[a]Nephrocalcinosis, multicystic kidney, solitary kidney.
[b]Five of the six patients born by obstructed labor were macrosomic fetus.
[c]Of the 12 patients affected by neonatal hyperinsulinism, 2 had drug resistant epilepsy, and 1 had absence seizure, right ear neurosensory deafness, and psychiatric intermittent explosive disorder. These three patients also suffered from perinatal hypoxic–ischemic encephalopathy; therefore, neurological disorders listed above could be consequences either of neonatal hypoglycemia or neonatal hypoxic–ischemic encephalopathy as well.
[d]Three males were never tested for fertility nor tried to conceive.

fetal hypoxia. Developmental delay or mild cognitive impairment was reported in nine (26.4%) out of 34 patients. In most cases the developmental delay was classified as mild, mostly consistent with speech delay, allowing the successfully achievement of secondary instruction, although special school was required in two cases. Neurodevelopmental outcome was more severely impaired in patient #15, probably related to the chromosomal anomaly (Zollino et al., 2010) and patients #8 and #14, likely as a consequence of neonatal hypoxic ischemic encephalopathy or recurrent hyperinsulinemic hypoglycemia. Patient #8, suffered by neonatal asphyxia consistent with prolonged obstructed transvaginal delivery and macrosomia. He suffered from severe neonatal hypoglycemia and recurrent hypoglycemic episodes during infancy up to 12 years of age, requiring diazoxide treatment, complicated by drug resistant epilepsy. He was unable to work, but achieved first level secondary school education. Patient #14 suffered perinatal hypoxia consistent with delivery complication. Neurodevelopmental delay was diagnosed in the first year of age, associated to absence seizure. Speech was delayed (started at 3 years of age), autonomous walking was fully achieved at 7 years and full sphincteric control was only partially achieved. Stuttering and pronunciation deficit improved with speech therapy but were persisting at time of visit. He was able to achieve secondary school diploma with special program.

6. *Adult health condition*—Table 2 shows relevant clinical conditions besides BWSp features. Table 3 lists adult conditions which are allegedly consequent of pediatric phenotype.
7. *Neoplasm* (Figure 2)—Wilms' tumor (WT) has been diagnosed in four patients, at 2, 3, 5, and 10 years of age, respectively: in three cases WT was detected by abdominal ultrasound, either during cancer screening (n = 2) or in the context of an intercurrent illness at 3 years of age, with subsequent diagnosis of BWSp (n = 1). In one case WT was diagnosed at 5 years of age after the finding of hematuria. Adult onset malignancies occurred in four patients. Patient #23 developed hepatoblastoma at the age of 22 years, requiring liver transplantation, duodeno-cephalo-pancreatectomy, multiple cycles of chemotherapy and surgical removal of pulmonary metastasis. In spite of intensive treatment, he died 5 years after diagnosis. Patient #15 developed a T-Acute Lymphoblastic Leukemia (ALL) at 21 years of age. The girl was diagnosed with V617F JAK2 positive essential thrombocythemia at the age of 6 years. She was treated with AEIOP-BFM 2009 protocol and underwent allogenic bone marrow transplantation from HLA identical sibling, with a graft failure

2 months after and deceased after relapse at 23 years of age. Patient #21 developed a non-functional adrenal adenoma at the age of 22 years and testicular Sertoli-cell tumor at 24 years, successfully removed and patient #29 developed testicular *intratubular germ cell neoplasia, unclassified* (IGCNU) at 27 years of age. Figure 3 shows Kaplan–Meier curve of the tumor-free probability in BWS up to 30 years of life. Benign adulthood-onset tumors occurred in further three patients with two mammary gland fibroma, one uterine myoma and one hepatic angioma (Table 4).

8. *Reproduction issues and procreation*—Four patients, two females and two males, successfully procreated, three physiologically and one through artificial reproductive techniques. Patient #9 (female, IC2-LoM) conceived a male at the age of 31 and a female at the age of 33 years, both from uncomplicated pregnancy with normal prenatal screening tests. Delivery was spontaneous for the male and by caesarean section for the female due to transverse fetal position during labor. Both children were in good health, had normal psychomotor development and no BWSp features. Patient #31 (female) and #32 (male) were siblings. In their family segregates an intragenic inverted microduplication of 160-kB within *KCNQ1* exons 10 responsible for both Long QT syndrome type 1 (LQTS1) (Valente et al., 2019) and IC2-LoM (Chiesa et al., 2012). They physiologically conceived and had children with unrelated partners. Patient #31 (female) had a miscarriage and two daughters; the younger was born with omphalocele, macroglossia, facial nevus flammeus, post-axial hexadactyly, and auricular pits consistent with BWSp. Molecular tests showed that she inherited the intragenic inverted microduplication of *KCNQ1* segregating in the family, while her older sister was in good health and did not inherit the molecular anomaly: the mother was diagnosed with BWSp after the daughter. Patient #32 (male) had two children, a female at 34 years of age and a male at 35, both born after uneventful pregnancies and showing normal psychomotor and physical development. The female was affected by absence seizure controlled with valproate and did not carried the intragenic inverted *KCNQ1* microduplication segregating in the family. Conversely, the male was diagnosed with LQTS1 by electrocardiography and by the presence of the intragenic inverted microduplication of *KCNQ1*: he undergoes cardiologic follow-up without any complication. Patient #18 (male) was infertile (oligozoospermia and teratozoospermia) and underwent a cycle of homologous in vitro fertilization (IVF) to conceive a female child. The latter was diagnosed with isolate right renal agenesis during pregnancy. The patient had no cryptorchidism: no specific cause of infertility was detected.

Overall, seven of the 16 males (43.8%) were affected by cryptorchidism, bilateral in four cases. Four of them presented azoospermia or infertility. In three cases fertility tests were not performed. Patient #3 had bilateral orchidopexy at 4 years and had azoospermia. Patient #8 was affected by unilateral cryptorchidism and had his left testicle removed: no further investigation on his fertility status was performed nor he tried to conceive. Patient #14 received bilateral orchidopexy at 5 years of age and never attempted to conceive nor was tested for fertility. Patient #16 received bilateral orchidopexy at 6 years, was diagnosed with azoospermia at 19 years, consistent with left testicle atrophy and hypotrophy of the right one. Patient #20 had left cryptorchidism corrected at the age of 2 years; his subsequent fertility status was undetermined. Patient #21 underwent bilateral orchidopexy at the age of 8 years and showed azoospermia: at 24 years of age he was diagnosed with testicular Sertoli-cell tumor and underwent orchifunicolectomy. Patient #29 had left cryptorchidism surgically treated (age data were not available) and was subsequently diagnosed with azoospermia: he had testicle biopsy

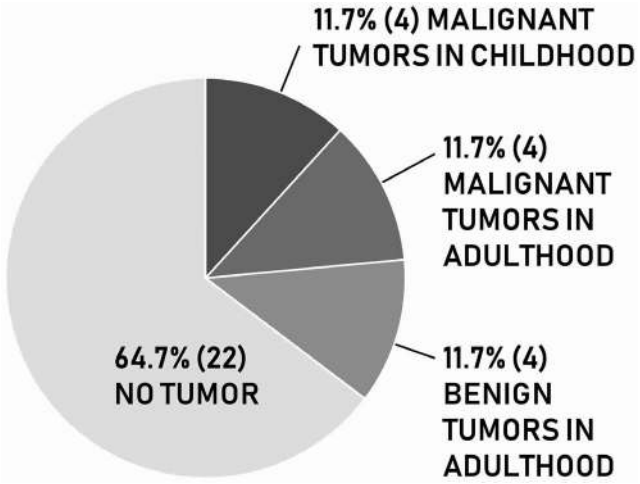

FIGURE 2 Tumor rate in the cohort

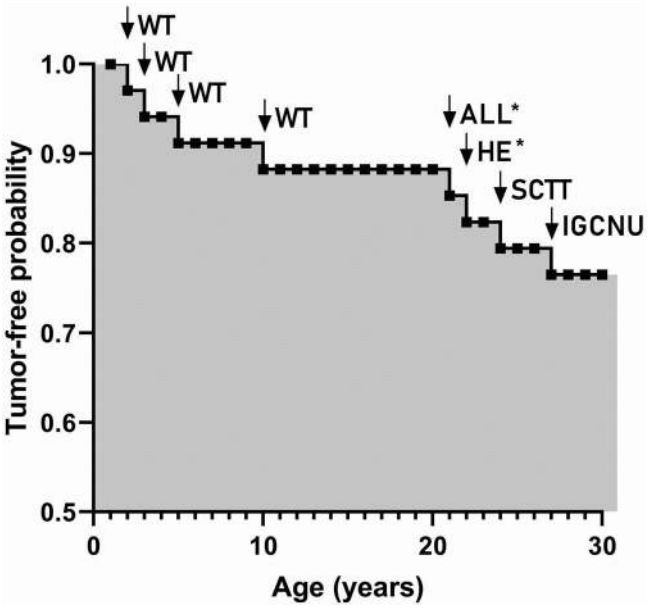

FIGURE 3 Kaplan–Meier curve of the tumor-free probability in BWS up to 30 years of life: Four patients developed Wilms' tumor (WT), one T-acute lymphoblastic leukemia (ALL), one hepatoblastoma (HE), one testicular Sertoli-cell tumor (SCTT), and one Intratubular germ cell neoplasia, unclassified (IGCNU)

TABLE 4 Data of patients with tumors

Patient ID	Tumor type	Malignant (M) or benign (B)	Genotype	Age at tumor diagnosis	Diagnosis modalities	Surgery	Medical therapy	Current age
#7	Wilms' tumor	M	GoM IC1	10 years	Ultrasound abdominal screening	Nephrectomy	-	19 years
#15	Early T- acute lymphoblastic leukemia	M	LoM IC2, IC2 deletion	21 years	Hematological screening in myelodysplasia	Splenectomy due to graft failure	AEIOP- BFM ALL 2009 protocol, allogeneic bone marrow transplantation	Died at 23 years after relapses
#18	Wilms' tumor	M	UPD(11)pat	2 years	Ultrasound abdominal screening	Nephrectomy	-	42 years
#20	Wilms' tumor	M	GoM IC1 (microdeletion) (Sparago et al., 2004)	5 years	Hematuria	Nephrectomy	AIEOP TW 2003 protocol	18 years
#23	Hepatoblastoma, cholangioblastic variant	M	LoM IC2	22 years	Abdominal mass	Orthotopic liver transplant + pancreatic-duodenectomy	Adjuvant chemotherapy	Died at 27 years after relapses
#29	Intratubular germ cell neoplasia, unclassified	M	*CDKN1C* Mut	27 years	Testicular mass	Orchidectomy	-	31 years
#33	Wilms' tumor	M	UPD(11)pat	3 years	Abdominal ultrasound due to intercurrent pathology	Renal lobectomy	Adjuvant chemotherapy	18 years
#21	Testicular Sertoli-cell tumor	M	LoM IC2	24 years	Testicular mass	Orchidectomy	-	41 years
	Non-functional adrenal adenoma	B with uncertain malignant potential		22 years	Incidentaloma at ultrasound	Laparoscopic adrenalectomy	-	
#4	Uterine myoma	B	Negative	40 years	Menorrhagia	Myomectomy	-	58 years
#5	Mammary fibroepithelioma	B	Negative	16 years	Tenderness, self-examination	Tumorectomy	-	18 years
#22	Hepatic angioma	B	Negative	6 years	Ultrasound abdominal screening	-	-	19 years
	Mammary fibroepithelioma	B		18 years	Tenderness, self-examination	-	-	19 years

showing right testicle atrophy and an IGCNU of the left gonad, which was removed.

The eight remaining male patients without cryptorchidism never attempted to conceive and none was ever tested for seminal anomalies. As concerns females, except for patient #9 and #31, none of the 16 remaining women attempted to conceive or referred gynecological or hormonal issues implicated in fertility, with the exception of mild common menstrual disorders and benign tumors showed in Table 4.

4 | DISCUSSION

Despite adulthood health status represents a relevant concern for patients affected by BWSp and their parents, information on these issues are barely mentioned in literature. Greer et al. (2008) described a pedigree with *CDKN1C* mutation responsible for familial BWSp with four adults having fertility issues (azoospermia, low count and motility, abnormal sperm morphology) and hearth anomalies, suggesting echocardiographic follow-up and semen analysis in adulthood. Other authors reported adults with BWSp and renal anomalies with recurrent urinary tract infections and kidney stones (Clouston et al., 1989), severe renal function impairment following diffuse nephroblastomatosis and Wilms' tumor (Kulkarni et al., 2002), hearing deficiency as a consequence of stapedial fixation (Hopsu, Aarnisalo, & Pitkaranta, 2003), genital anomalies (Aleck & Hadro, 1989; Clouston et al., 1989), partial bowel malrotation (Clouston et al., 1989), pituitary adenoma (Brioude et al., 2016), long-QT syndrome (Gurrieri et al., 2013), psoriasis (Romanelli et al., 2010), hypothyroidism, and thyroid adenoma (Cardarelli et al., 2010).

In this study, a consistent number of adults with BWSp are described providing an initial view on the natural history of the condition. Most of medical issues in adulthood are conceivably evolution of BWSp infant features or consequences of their surgical correction. The majority of patients with BWSp undergo at least one surgical intervention. It is interesting to note that, in spite of the surgery performed (overall 50 in 29 patients), only few of them obtained full correction of the defect: indeed, such interventions were rarely judged fully satisfactory by the patients themselves. Although, surgery usually ameliorates the health status, often the features which required intervention persist in adulthood, resulting in compromised function or leading to esthetical concerns. This observation is not trivial, especially from the patients' point of view and underlines the need for specific research and improvement in this setting.

Macroglossia is well known to be the most common feature in patients affected by BWSp. Orthodontic anomalies, speech disturbances, and swallow difficulties persisting in adulthood were reported by nine patients. These findings were present in both patients treated by orthodontic devices and those surgically treated, confirming that patients affected by macroglossia, even after surgical reduction, may not achieve complete normal function (Tomlinson, Morse, Bernard, Greensmith, & Meara, 2007), in spite of the absence of sensory losses after tongue reduction (Matsumoto, Morita, Jinno, & Omura, 2014).

Lateralized overgrowth with or without lower limb length discrepancy was the plausible cause of scoliosis and recurrent back pain described by four patients. Three of them were affected by lower limb length discrepancy (two surgically corrected, one functionally compensated by orthoses). Two of them performed competitive and two of them amateur sport activity.

Pancreatectomy for persistent hyperinsulinism was the cause of iatrogenic diabetes mellitus in one patient. Also nephrourological health issues during adulthood were reported: 70% of patients with nephrourological anomalies had frequent recurrent urolithiasis or urinary tract infections in adulthood (Mussa et al., 2012).

Obstructed labour secondary to fetal macrosomia and the possibly related neonatal hypoxic–ischemic encephalopathy are described in medical literature as a possible cause of intellectual disability in BWSp (Elliott, Bayly, Cole, Temple, & Maher, 1994; Pettenati et al., 1986). Morbidity related to this issue appears to be confirmed in our cohort: the three patients with hypoxic–ischemic encephalopathy showed a mild to severe degree of intellectual disability and seizures. However, all these cases also were affected by persistent hyperinsulinemic hypoglycemia at birth and through infancy, that could have played a role in the neurodevelopmental defect.

Thirty-one percent (5 out of 16) of the male patients in the cohort were infertile and 25% (4 out of 16) showed azoospermia in sperm analysis. Azoospermia was present in four adults: three had bilateral cryptorchidism and one unilateral. Overall, half of the males were affected by cryptorchidism and underwent a not timely surgical correction of cryptorchidism. As an early orchidopexy has been shown to be key for a proper testicular reproductive function (Canavese et al., 2009; Feyles et al., 2014), a late correction was a plausible explanation for the high rate of infertility encountered. This further underlines that, as in nonsyndromic children, a timely orchidopexy is of paramount importance in patients with syndromic presentation (Chan, Wayne, & Nasr, 2014) and surgery should not be postponed during the first years of life although a definite diagnosis has been made or other medical interventions are required. However, the finding of azoospermia in an adult with *CDKN1C* mutation and unilateral cryptorchidism is relevant. Four similar cases have been described by Greer et al. (2008) in a family with the same molecular defect: three had documented severe abnormalities of spermatogenesis (only one with cryptorchidism) and the other had infertility and testicular atrophy by clinical examination. As discussed, a mutation in *CDKN1C* might affect the expression of ZNF215, a zinc-finger protein located within the IC2 domain and important for a regular spermatogenesis (Gianotten et al., 2003). Indeed, male BWSp subfertility appears a potentially relevant issue for BWSp adult patients, either as a consequence of cryptorchidism or a primary dysfunction of the testes, and further studies are therefore warranted to manage and preserve the reproductive function of male BWSp patients. As far as it concerns females, except for two patients, none of the remaining reported attempt to conceive, therefore we are unable to offer further information about female fertility.

The most relevant issue concerning health in adulthood is tumor predisposition. Literature is scattered of anecdotal reports on adult-onset tumors including adrenal adenoma (Hayward, Little, Mortimer, Clouston, & Smith, 1988), bilateral pheochromocytoma (Bémurat et al., 2002), astrocytoma (Aleck & Hadro, 1989), acute myeloid leukemia (Houtenbos & Ossenkoppele, 2002), ACTH-secreting pituitary

adenoma (Brioude et al., 2016), virilizing adrenocortical tumors (Bertoin et al., 2015; Romanelli et al., 2011), thyroid adenoma (Cardarelli et al., 2010), breast cancer (Fleisher, Meltzer, & James, 2000) and fibroadenoma (Bertoin et al., 2015). However, general clinical experience denies specific increase of tumor risk in adults with BWSp and it is a common convincement that it approaches that observed in the general population after the first decade of life, but no study that specifically evaluated this issue on a large cohort has been performed. In this study we have observed a tumor risk of 11.7% during childhood consistent with that reported in literature. Surprisingly, we observed in adults the same number of malignant tumors we documented in childhood. This observation doubles the overall risk previously estimated in BWSp raising tumor rate to 23.5%. Likely, this data is overestimated due to the study design. First, a collection bias is plausible, as more than half of the cohort described has been gathered though a search among the associates of AIBWS, with an over representation of adult with relevant health issues. Second, one of the testicular tumors observed is notably associated with delayed intervention for cryptorchidism. It is anyhow interesting the observation in young adulthood of three tumors usually observed in childhood (ALL, hepatoblastoma and Sertoli-cell testicular tumor), two of them leading to patients' death. Finally, it should be noted that one case of WT was diagnosed at the age of 10 years, beyond the end of the ultrasound screening recommended in infancy.

In conclusion, in this study it is described the first large cohort of adults with BWSp. Although no novel specific aspect of BWSp emerged, adult patients present several medical issues related to complications of developmental defects characterizing the pediatric phenotype. These observations underlie the preventive role of follow-up strategies in childhood and evidence the need for an improvement in treating the medical problems connected with BWSp in the first years of life. With the limitation discussed, our data show that tumor rate in BWSp cumulatively raises 23.5% including young adulthood, but the small number of patients and tumors described do not allow providing a precise estimate of cancer risk in adulthood and mostly do not imply any revision of the proposed tumor screening protocols. However, this issue deserves undoubtedly further investigation.

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