Clinical and Molecular Characteristics of Children with Beckwith-Wiedemann Syndrome and Isolated Hemi Hyperplasia at Sultan Qaboos University Hospital with Their Surveillance Outcomes

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Abstract

Objectives: Beckwith-Wiedemann syndrome (BWS) is a rare genetic and cancer- predisposing disorder characterized by variable clinical and molecular abnormalities. It is considered as a spectrum (BWSp) ranging from classical BWS to isolated hemi hyperplasia (IHH). This study aims to characterize Omani patients with BWS and IHH clinically and molecularly, evaluate their surveillance results, and assess tumor prevalence among the cohort.

Methods: Nine patients with BWS were retrospectively recruited to the study by searching the medical records of Sultan Qaboos University Hospital (SQUH) between January 2012 until December 2022. Demographics, clinical features, molecular findings, and surveillance test results including abdominal ultrasound and alpha-fetoprotein were extracted from hospital information system (HIS) and analyzed systematically.

Results: Nine patients diagnosed with Beckwith-Wiedemann syndrome were studied, comprising four BWS cases and five cases of isolated hemihyperplasia (IHH). The study identified macroglossia as the predominant clinical feature among BWS patients, whereas lateralized overgrowth was consistently observed in IHH patients. Conversely, all BWS patients tested positive for methylation anomalies: two exhibited loss of methylation at IC2 (22.22%), one had paternal uniparental disomy of chromosome 11 (pUPD11) (11.11%), and another showed gain of methylation at IC1 (11.11%). Throughout the surveillance period, none of the patients showed elevated alpha-fetoprotein levels or developed tumors.

Conclusions: The study is the first to examine a cohort of patients with BWSp in Oman. It reveals comparable clinical and molecular characteristics to the previously reported BWS patients, yet no tumors were detected in this cohort.

Keywords: Overgrowth; BWS; IHH; Imprinting; Methylation; Surveillance; AFP.

Introduction

Beckwith-Wiedemann syndrome (BWS, OMIM #130650) is a rare genomic imprinting disorder and the most common overgrowth syndrome characterized by complex of clinical and molecular features.[1,2] It is now considered a spectrum (BWSp) that encompasses both classic form of BWS and lateralized overgrowth (OMIM #235000) initially termed as hemihypertrophy [**Figure 1**].[3]

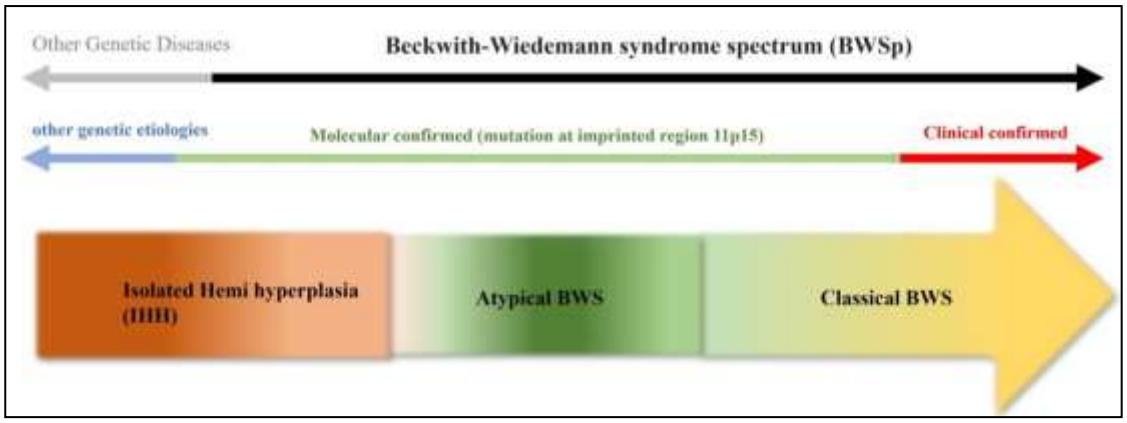

Figure 1: Beckwith–Wiedemann spectrum (BWSp); classical BWS, atypical BWS and isolated lateralized overgrowth.

Clinicians and researchers distinguish between two categories of clinical features observed in BWS patients. Cardinal features are crucial for confirming diagnoses, whereas suggestive features, more prevalent in the general pediatric population, have a lesser impact on the scoring system.

Genetic alternations on chromosome region 11p15.5 are considered to be the main cause of BWS which accounts for 80% of cases, with DNA methylation being the most common molecular abnormalities.[4-6] Gain of methylation at H19/IGF2: IG (DMR; IC1 GOM), loss of methylation at KCNQ1OT1: TSS (DMR; IC2 LOM), paternal uniparental isodisomy (pUPD11), CDKN1C mutation and cytogenetic abnormalities were detected in BWS.[7]

Embryonal tumors are seen in about 8% of BWSp children. Wilms tumor (52%), hepatoblastoma (14%), neuroblastoma (10%), rhabdomyosarcoma (5%), and adrenal carcinoma (3%) are the most prevalent forms of embryonal tumors.[8] Therefore, tumor surveillance strategies play a central role in the management and follow-up of affected patients, which aim to increase survival and reduce mortality rate.[3] It was generally advised that all BWS patients undertake regular tumor surveillance to detect the two most common tumors (Wilms tumor and hepatoblastoma), including serial alpha-fetoprotein tests and abdominal/renal ultrasounds.[9]

The clinical and molecular characteristics of BWS in European and North American patients have been extensively researched in the literature and few in China.[3,10] Few studies have investigated the potential (epi)genotype- phenotype connections.[11,12] Moreover, some highlighted the tumor risk in BWSp population.[3] However, no studies were conducted on Omani patients with BWSp nor their risk of cancer.

Methods

This was a retrospective cohort study conducted to assess the clinical and molecular characteristics of patients with BWS and IHH who attended the genetic clinic at Sultan Qaboos University Hospital (SQUH) in the last decade. It was ethically approved by the medical research ethical committee in Sultan Qaboos university (MREC # 2834).

The study included nine children with clinically confirmed BWS and IHH attended SQUH between January 2012 to December 2022. All patients with BWS who fulfil the scoring criteria and IHH were included in the study. The scoring system is determined by assigning two points for each cardinal feature and one point for each suggestive feature. Based on that, patients with a BWS score of ≥4 meet the clinical diagnostic criteria for classical BWS.[3]

Data were gathered from the electronic records of patients. This encompassed demographic information (age and gender), initial anthropometric measurements (height in cm, weight in kg, and head circumference in cm), as well as subsequent measurements from at least two follow-up visits. The data also included details about consanguinity, positive family history of similar presentation or cancer, as well as clinical findings, and results from methylation tests. **MS-**Multiplex Ligation-Dependent Probe Amplification (MLPA**)** was used in all patients to confirm the molecular pathology. This Methylation-Specific **MLPA** can simultaneously detect the methylation and copy number status **(deletion or duplications)** of the differentially methylated regions related to BWS at 11p15. Moreover, AFP test results (KIU/L), ultrasound imaging (UI) results and other relevant radiological results such as magnetic resonance imaging (MRI), computerized tomography (CT) and X radiation were also compiled.

The study utilized the statistic package for social sciences (SPSS IBM SPSS version 27) for data analysis, including descriptive statistics and Fisher's exact test for association between clinical features and BWS or IHH.

Results

The study included nine patients with BWSp retrospectively studied from 2012 until 2022, four with BWS and five with IHH. Regarding BWS patients, all were males (4/4). While in IHH patients 2/5 were males and 3/5 were females. Consanguinity was noticed in 50% (2/4) of BWS cases and 20% (1/5) of IHH patients. Additionally, there was no family history of BWS nor tumor in both groups.

The most common cardinal feature of clinically diagnosed BWS patients was macroglossia (4/4) followed by hepatosplenomegaly (3/4) then omphalocele and lateralized overgrowth (1/4). Whereas each one of the major suggestive features include hernia, bilateral kidney enlargement, hypoglycemia and nephrological abnormalities was identified in 2/4, followed by macrocephaly, microcephaly, and Mongolian spots (1/4). However, in IHH patients lateralized overgrowth was a constant feature followed by macrocephaly (3/5) then unilateral kidney enlargement (2/5). Other features such as hernia, hepatosplenomegaly, neurological, nephrological abnormalities, cardiac defects, and Mongolian spots were less common (1/5). No tumors were detected in BWS nor IHH patients (0/9).

Table 1 summarizes the clinical and molecular findings of BWS and IHH patients. Further detailed clinical and molecular data are shown in *Appendix 1*.

Table 1: demographic and clinical information of patients with Beckwith Wiedemann (BWS) and isolated hemi hyperplasia (IHH) and their molecular findings.

	BWS n=4	**IHH n=5**
Gender		
Males	4/4	2/5
Female	0/4	3/5
Consanguinity	2/4	1/5
Family history of BWS	0/4	0/5
Family history of tumor	0/4	0/5
Clinical features		
Macroglossia	4/4	0/5

Omphalocele	2/4	0/5
Hernia	2/4	1/5
Lateralized overgrowth	1/4	5/5
Tumor (e.g Wilms, hepatoblastoma)	0/4	0/5
Hyperinsulinism	0/4	0/5
Organomegaly	4/4	3/5
Hepatomegaly	4/4	1/5
Enlarged kidney	2/4 (bilateral)	2/5 (unilateral)
Hypoglycemia	2/4	0/5
Neurological abnormalities	0/4	1/5
Nephrological abnormalities	2/4	1/5
Cardiac defects	0/4	1/5
Macrocephaly	1/4	2/5
Microcephaly	2/4	0/5
Mongolian spots	1/4	1/5

BWS: Beckwith-Wiedemann syndrome, IHH: isolated hemi hyperplasia, n: number of patients.

In regard to the molecular findings, all IHH patients were negative for methylation test. However in our cohort, BWS patients were all positive for the methylation test, two of them had loss of methylation at IC2 (22.22%), one had paternal uniparental isodisomy (pUPD11) (11.11%), and one had gain of methylation at IC1 (11.11%).

Ultrasound results showed enlargement of spleen and liver (hepatosplenomegaly) in 44.44% of the study group, 75% of BWS patients and 20% of IHH patients. Bilateral kidney enlargement was noticed by abdominal US in three BWS patients, one of them showed additional tiny echogenic foci that was further studied by MRI and identified as nephrocalcinosis. The US results also showed that 50% BWS patients had bilateral kidney enlargement and 40% IHH patients had unilateral kidney enlargement.

AFP measurements were normal at base line and in serial follow up tests for all studied patients except for one patient who had transient elevation of AFP in early infancy which declined with consequent follow up. Appendix 2 showed anthropometric measurements, AFP measurements and relevant radiology findings in all BWS and IHH patients included in this study.

Fisher's exact test was conducted to test the significant association between various clinical features and IHH or BWS. It is clearly shown that there is a significant association between macroglossia and organomegaly with BWS ($p= 0.008$ and $p=0.048$ respectively). Also, there is a significant association between lateralized overgrowth and IHH ($p=0.048$). Otherwise, there is no other significant association noted.

Discussion

In this study, we conducted a retrospective cohort study at a single center to analyze the clinical features and molecular abnormalities in patients diagnosed with BWSp who attended the genetic clinic at SQUH over a period of ten years.

The most common clinical features in our cohort of BWS were macroglossia (100%) and hepatomegaly (75%). Other features such as hernia, bilateral kidney enlargement, hypoglycemia at birth and nephrological abnormalities were evident in 50% of cases. Furthermore, omphalocele, lateralized overgrowth, macrocephaly, microcephaly, and Mongolian spots were noted in 25% of cases. Our findings align with a previous study, revealing that among clinical symptoms, macroglossia was the most prevalent, observed in up to 97% of

patients. Other features such as omphalocele and umbilical hernia were present in 80% of BWS patients.[13] Likewise, Wang et al. (2020) found that Macroglossia was the most common clinical features in clinically diagnosed BWS patients (71.4%) followed by umbilical hernia (65.0%).[10] Additionally, a retrospective study conducted across multiple tertiary centers in Hong Kong found that macroglossia (70.4%) and abdominal wall defects (70.4%) were the predominant clinical features.[14]

In our study, lateralized overgrowth was consistently observed in all of our IHH patients (100%) and was present in one patient with BWS. This feature has been noted as predominant, occurring in 51.1% of IHH patients in the West Midlands and in 64% of BWS patients in previous reports.[4,13,15]

Given the high risk of tumor in BWS, it was found that patients with IC1 GOM and pUPD11 have a considerably higher tumor incidence (22.8% - 28.6% and 13.8-17.3%, respectively) than those with IC2 LOM (2.5% - 3.1%).[3,4,8,9,16,17] Moreover, patients without molecular abnormalities have a tumor prevalence around 6.7%.[8,16,17] Additionally, patients with IC1 GOM had a significantly higher incidence of multifocal/bilateral Wilms tumor in comparison to patients with pUPD11.[9] Fortunately, our cohort study did not identify any BWS-related embryonal tumors. This could potentially be attributed to the limited number of patients included in our study. In contrast, another study reported that among 1370 patients diagnosed with BWS, 102 developed tumors (7.4%). Within this group, those with gain of methylation at IC1 (IC1 GOM) had the highest tumor prevalence at 22.8%.[8] Additionally, Maas et al. (2016) found an 8% tumor risk among 1971 BWS patients, with loss of methylation at IC2 (IC2 LOM) showing the highest tumor prevalence at 28%.[18] Similarly, in a retrospective multicenter study conducted in Hong Kong involving 27 molecularly confirmed BWS patients, 7.4% were found to have embryonal tumors, with IC2 LOM being the most prevalent at 41.8%.[10,14]

Molecular testing using Multiplex Ligation-Dependent Probe Amplification (MLPA) revealed that all patients diagnosed with BWS had positive methylation test results. Loss of methylation at IC2 (IC2 LOM) was the most frequent abnormality, occurring in 50% of cases, followed by gain of methylation at IC1 (IC1 GOM) and paternal uniparental isodisomy (pUPD11), each observed in 25% of patients. This was consistent with findings from a study involving BWS patients in North America and Europe, where hypomethylation in the BWS critical region (IC2 LOM) was reported in 50% of cases and other molecular abnormalities noted included hypermethylation in the BWS locus (2-7%), paternal uniparental disomy (pUPD) (20%), mutations in CDKN1C (10%), and 11p15 duplications (1%) and inversions or translocations involving 11p15 (1%).[8,19] On the contrary, In Japanese patients with BWS, no cases were identified with complete hypermethylation, whereas the incidence of chromosomal abnormalities was higher, noted at 13%. These observations indicate that susceptibility to epigenetic and genetic alterations may vary depending on ethnicity.[19] All IHH patients were negative for methylation test. IHH, which can be considered a mosaic form of overgrowth, may be caused by mosaic genetic defects. In particular, pUPD, which is always found in a mosaic form, is associated with enlarged organs that contain a higher proportion of disomic cells. For diagnostic purposes, methylation patterns are typically assessed in blood lymphocytes, not in the hyperplastic tissues themselves. In some unexplained cases of IH, pUPD may only be present in the hyperplastic tissue and not in the blood, thus missed detection by routine diagnostic testing.[20,21]

Several strategies for tumor surveillance in BWSp have been proposed, often involving abdominal US with or without AFP testing at various ages and intervals during infancy.[3] In our study group, AFP levels (in KIU/L) were generally within normal limits, except for one BWS patient who exhibited transiently elevated AFP levels in early infancy that subsequently decreased during follow-up visits. Serial abdominal ultrasound examinations in our cohort did not identify any tumors.

Previous studies found that patients with IC2 LOM had greater rates of omphalocele, macroglossia, ear creases/pits, face nevus simplex, and preterm and lower rates of organomegaly, lateralized overgrowth, and malignancies.[9,20] Our study showed similar findings where patients with LOM had macroglossia, transient hypoglycemia at birth, mild hepatosplenomegaly by US, hernia (umbilical and inguinal) and prematurity. Other reports found that patients with pUPD11 had a considerably higher rate of lateralized overgrowth.[9,20]The only patient among our cohort with pUPD had lateralized overgrowth with body asymmetry and bilateral kidney enlargement.

Based on statistical analysis conducted within our patient cohort, we observed significant associations between macroglossia and organomegaly with Beckwith-Wiedemann syndrome (BWS). Conversely, lateralized overgrowth was significantly associated with isolated hemihyperplasia (IHH). No significant differences were noted in other features between BWS and IHH patients.

Conclusion

Our study represented the first characterization of clinical features and molecular abnormalities in Omani patients with Beckwith-Wiedemann syndrome spectrum. We observed that macroglossia was the predominant feature among BWS patients, while lateralized overgrowth was consistently present in all IHH patients. Methylation abnormalities were exclusively found in BWS patients, with loss of methylation at IC2 (IC2 LOM) being the most prevalent. Crucially, no tumors were detected in our cohort of patients.

Statistical analysis revealed significant associations between Beckwith-Wiedemann syndrome and isolated hemihyperplasia with specific clinical features. To further elucidate genotype-phenotype correlations, understand tumor risks better, and compare findings with other populations and ethnicities, an extended multicenter study is warranted

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Appendix 1: Demographic and clinical information of patients with Beckwith Wiedemann (BWS) and isolated hemi hyperplasia (IHH) and their molecular findings.

Patient Number / **Patient information**	1	2	3	4	5	6	7	8	9
Demographical Information									
Diagnosis	IHH	BWS	IHH	BWS	BWS	IHH	IHH	IHH	BWS
Age	4 years and 7 months	5 years	13 years	10 years	7 years	14 years	9 years	4 years & 7 months	2 years &5 months
gender	Female	Male	Female	Male	Male	Female	Male	Male	Male
consanguinity	No	double 1st cousins	No	Yes (fathers are brothers)	No	2nd cousins	No	No	No
Family history of BWS	No	No	No	No	No	No	No	No	No
Family history of tumor	No	No	No	No	No	No	No	No	No
Additional notes	Born normal and hemi hypertrophy noticed at age of 1 month.	-	Preterm (due to maternal preeclampsia), hemi hyperplasia since birth, IHH noted at birth.	Preterm	Preterm	post term vaginal delivery. Normal at birth	Preterm delivery, came to the hospital with IHH.	Born normal and hemi hypertrophy, noticed by the mother at age of 1 month.	History of sickle cell anemia in father's uncle

Clinical features									
Macroglossia	-	Yes	-	Yes (increasing in size without effect on feeding or speech)	Yes	-	-	-	Yes (mild)
Omphalocele	-	-	-	-	+ corrected	-	-	-	-
Hernia	-	-	-	Umbilical	Rt inguinal	-	Umbilical	-	-
Organomegaly	-	Mild hepatomegaly and enlarged kidneys	-	Mild hepatosplenomegaly.	Mild non-focal enlargement of the liver and spleen.	-	Mild hepatosplenomegaly	-	Enlargement of both kidneys
Lateralized overgrowth	Yes, Lt side smaller than Rt side (includin	-	Yes, asymmetry in limbs (Lt UL and LL hypertrophoid) left limb	-	-	Yes, right sided swelling of the upper body. Face, arms, hands	Yes, mainly in the Lt side UL and LL.	Yes, the limb discrepancy is still present however improving than before.	Yes, right side bigger than left side& mild face asymmetry noticed 1 month after birth.

	g face, UL, and LL)		longer than Rt limb & Asymmetry of the face and body where left side is enlarged			and right buttocks. No swelling noted in the right leg. Without length variation of limbs.		No feet discrepancy in size but UL &LL milder difference Lt side slightly larger.	
Tumor (e.g Wilms, hepatoblastoma)	-	-	-	-	-	-	-	-	-
Hyperinsulinism	-	-	-	-	-	-	-	-	-
Hypoglycemia	-	-	-	Yes, at birth	Yes, at birth	-	-	-	-
Neurological abnormalities	hypotonia	-	-	-	-		-	-	-
Nephrological abnormalities	-	Enlarged both kidneys.	-	-	-	Right kidney larger than left.	Left kidney enlarged with normal renal function.	-	MRI shows a lesion in the upper pole of the left kidney (possible Wilms tumor vs nephrocalcinosis) not changed in size in follow up MRI.

Cardiac defects		-	-	-	-		Hypertension and enlargement of the left ventricle.	-	-
Others	- global developmental delay Macrocephaly - generalized hypotonia with no hydrocephalus - dysmorphic features - hemihypertrophy (bilateral frontal bossing,	-Prominent eyes, retrognathia, mid face hypoplasia, large hand and feet, mongolian spots, full cheeks more on the left side?	• limping to the right side. • Capillary hemangioma at the upper lip. • Bilateral coxa valga and mild hallux valga	-bilateral undescended testicle corrected by orchiopexy. -history of polyhydramnios, and prematurity and neonatal hypoglycemia.	- macrosomina +- micrognathia	Hemihypertrophy more on Rt side involving cheek, Rt arm and Rt leg circumference is larger but no limb length discrepancy in UL and LL	Mongolian spots with eye pigmentation. small swelling in inguinal area, macrocephaly (familial)	No other abnormality, no organomegaly or chest wall deformability, normal development.	no deformability, no organomegaly, no snoring or breathing problems

	- Hypertelorism Hyperpigmentation - WES: -ve								
Molecular findings									
Methylation test	Negative; Methylation studies for BWS	Positive; IC1 gain of methylation confirm BWS	Negative; Methylation studies for BWS - incl deletion duplication of 11p15 region	Positive; loss of methylation of IC2 at maternal chromosome.	Positive; loss of methylation of IC2 on maternal chromosome	Negative; Methylation studies for BWS - incl deletion duplication of 11p15 region	Negative; Methylation studies for BWS - incl deletion duplication of 11p15 region	Negative; Methylation studies for BWS - incl deletion duplication of 11p15 region	Positive; Paternal uniparental disomy of 11p15.5

UL: upper limbs, LL: lower limbs, RT: right, LT: left, MRI: magnetic resonance imaging, WES: whole Exome Sequencing, IC1and 2: imprinting centers 1 and 2 respectively.