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Case report

# A case of unilateral sectoral iris heterochromia in an infant with Beckwith-Wiedemann syndrome

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ABSTRACT

*Purpose:* To report a case of unilateral sectoral iris heterochromia in an infant with Beckwith-Wiedemann syndrome (BWS).

*Observations:* An 8-month-old girl known case of BWS, due to hypomethylation of the DMR2 (KCNQ1OT1) on chromosome 11p15.5, with features of macroglossia, neonatal hypoglycaemia and an unusual finding of partial iris hypopegmentaion in her left eye.

*Conclusions:* This is the first reported case of iris heterochromia in a BWS patient. Further studies are needed to support the association between eye findings and BWS related genetic defects.

## 1. Introduction

Beckwith-Wiedemann syndrome (BWS) is a genetic overgrowth disorder in children that predisposes to childhood cancer.[1] It can present with a variety of clinical features of macrosomia, macroglossia, asymmetric regional overgrowth, outer-ear abnormalities, abdominal wall defects, organomegaly, and neonatal hypoglycemia.[2] Apart from prominent eyes,[3] there are very few reported ophthalmic abnormalities in BWS cases. Congenital cataract was previously described in a case report.[4] Here we report a rare finding of sectoral iris heterochromia occurring in an infant known to have BWS.

## 2. Case

An 8-month-old preterm infant female was born to a heathy 2nd–degree consanguineous couple, delivered via a caesarean section (CS) due to previous multiple CS deliveries, with a history of neonatal intensive care unit (NICU) admission for frequent monitoring of neonatal hypoglycemia. She is a known case of BWS, based on genetic testing, and was referred to our ophthalmology clinic for left bicolored iris noted by her parents since birth. It remained unchanged over this period. She had a low birth weight of 2205 grams. Apgar score was 8 at 1 minute and 9 at 5 minutes with no resuscitation being required.

On general examination, the girl has a slightly protruding tongue, nevus flammeus over her forehead. No lateralized overgrowth was found. She has epicanthic folds and her right iris was dark brown in color and the left one showed an area of hypopigmentation (Fig. 1). Ophthalmic examination revealed visual acuity of central steady maintained both eyes. Both pupils were reactive to light. Intra-ocular pressure was within normal limits (15 mmHg) and symmetric in both eyes. She is following objects and had a full range of ocular movements. There were no other ophthalmic manifestations. The slit lamp examination showed no abnormality in the anterior segment except for a sharply demarcated hypochromic heterochromia occupying almost half of the left lateral iris. Dilated fundus examination revealed normal fundus of both eyes. Cycloplegic refraction showed mild astigmatism without any other significant refractive error.

The most recent abdominal ultrasound showed no visceromegaly, however, it demonstrated left renal pelviectasis. The karyotype of the infant revealed normal female karyotype — 46,XX. Methylation analysis at time of BWS suspicion was carried out using Methylation-Specific Multiplex Ligation-dependent Probe Amplification (MS-MLPA). It showed hypomethylation of the DMR2 (KCNQ1OT1) region and normal methylation of the DMR1 (H16) region, with no deletions or duplications detected on the 11p15 region.

The parents were genetically counselled about the diagnosis and reassured from ophthalmology side.

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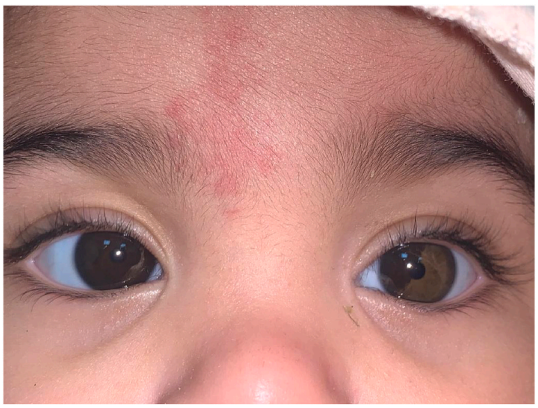

**Fig. 1.** Unilateral Sectoral Iris heterochromia in the left eye.

## 3. Discussion

BWS is the most common genetic disorder that is associated with overgrowth in children, with a prevalence of 1 per 10,340 births.[5] This disease affects both males and females equally.[6] BWS is associated with an increased risk of embryonic tumorigenesis in early life, mainly Wilms tumor and hepatoblastoma.[1,7]

Around 80% of BWS cases have detectable genetic and/or epigenetic defects affecting the genes imprinted on chromosome 11p15.5.[2,8] Imprinted genes follow a monoallelic fashion of expression, in which one of the parenteral alleles is expressed and the other is switched off or weakly expressed.[9] These genes gather in two clusters and are controlled by differentially methylated regions (DMRs) or imprinting centers (ICs). Insulin-like growth factor 2 (IGF2) and H19 form the first cluster and is regulated by H19/IGF2:IG-DMR (IC1). Cyclin-dependent kinase inhibitor 1C (CDKN1C) and KCNQ1-overlapping transcript 1 (KCNQ1OT1) make the second cluster and is regulated by CDKN1C/KCNQ1OT1: TSS-DMR (IC2).[10] The pathogenesis of BWS is largely due to dysregulatory alterations in the controlling mechanisms. Commonly reported alterations were: loss of methylation at KCNQ1OT1:TSS-DMR (~50%), paternal uniparental disomy (UPD) (~20%), gain of methylation at H19: IG-DMR (~5%), and CDKN1C mutations (5–10%). Chromosomal microdeletions, duplications, translocations, and inversions have been less commonly reported.[11] The variety of these defects have been linked to the heterogeneous clinical spectrum of BWS,[1] including macrosomia, macroglossia, abdominal wall defects, nephrourological anomalies, nevus flammeus, pitted earlobes, neonatal hypoglycemia, hemihyperplasia, and organomegaly.[2] Although several genotype-phenotype associations were proposed, the exact relationship remains ambiguous.[12,13] Noncancerous ophthalmic manifestations are poorly described in BWS patients. Prominent eyes are commonly related to the midfacial maxillary hypoplasia in those children.[3] M momtival et al. reported a case of bilateral congenital cataract in a patient with BWS, where it was not claimed to be genetically associated.[4] Iris heterochromia has known to be associated with other genetic syndromes, for example; congenital Horner syndrome, Waardenburg syndrome, Sturge-Weber syndrome, and Fuchs heterochromic iridocyclitis[14,15,16]; however, it has not been reported among BWS cases. Iris heterochromia can be acquired by eye trauma, chronic anterior uveitis, retained metallic intra-ocular foreign body (siderosis bulbi), ocular tumors and the use of topical prostaglandin analogues.[17,18,19,20] These factors were excluded in our case.

We report a case of BWS with unilateral sectoral iris heterochromia. More efforts are demanded to validate this phenotype-genotype association. Characterization of ophthalmic features in BWS patients will improve our understanding of the disease nature.

## Patient consent

Consent to publish this case report has been obtained from the parents in writing.

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## Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

## Declaration of competing interest

The authors have no financial disclosures.

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