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 hypopigmentation 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. It can present with a variety of clinical features of macrosomia, macroglossia, asymmetric regional overgrowth, outer-ear abnormalities, abdominal wall defects, organomegaly, and neonatal hypoglycaemia. Apart from prominent eyes, there are very few reported ophthalmic abnormalities in BWS cases. Congenital cataract was previously described in a case report. 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 healthy 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 hypoglycaemia. 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 pelviectasia. 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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3. Discussion

BWS is the most common genetic disorder that is associated with overgrowth in children, with a prevalence of 1 in 10,340 births. This disease affects both males and females equally. BWS is associated with an increased risk of embryonic tumorigenesis in early life, mainly Wilms tumor and hepatoblastoma.1,11

Around 80% of BWS cases have detectable genetic and/or epigenetic defects affecting the genes imprinted on chromosome 11p15.5,24 Imprinted genes follow a monoallelic fashion of expression, in which one of the parenteral alleles is expressed and the other is switched off or overgrowth in children, with a prevalence of 1 per 10,340 births. midfacial maxillary hypoplasia in those children. described in BWS patients. Prominent eyes are commonly related to the TSS-DMR (IC2).

Imprinted genes are 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). 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. The variety of these defects have been linked to the heterogeneous clinical spectrum of BWS, including macromastia, macroglossia, abdominal wall defects, nephrourological anomalies, nevus flammeus, pitted earlobes, neonatal hypoglycemia, hemihypoplasia, and organomegaly. 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. M mottival et al. reported a case of bilateral congenital cataract in a patient with BWS, where it was not claimed to be genetically associated. 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.2,4,5,15,16 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.

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

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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References

1. Maas SM, Vanfenne F, Kadouch DJ, et al. Phenotype, cancer risk, and surveillance in Beckwith-Wiedemann syndrome depending on molecular genetic subgroups. Am J Med Genet A. 2016;170(9):2248-2260.
2. Bréoude F, Kalish JM, Musa A, et al. Expert consensus document: clinical and molecular diagnosis, screening and management of Beckwith-Wiedemann syndrome: an international consensus statement. Nat Rev Endocrinol. 2018;14(4):229-249.
3. Weksberg R, Shuman C, Beckwith JB. Beckwith-Wiedemann syndrome. Eur J Hum Genet. 2010;18(1):1-14. https://doi.org/10.1038/njgh.2009.106.
4. Mottchilova M, Pelosse B, Laroche L, Vanzuc MP. Cataracte congenitale et syndrome de Wiedemann-Bucke Beckwith [The Wiedemann-Bucke Beckwith syndrome and a congenital cataract]. J Fr Ophtalmol. 2001;24(5):479-481.
5. Musa A, Russo S, De Crescenzo A, et al. Prevalence of Beckwith-Wiedemann syndrome in north west of Italy. Am J Med Genet A. 2013;161A(10):2481-2486.
6. Li M, Squire JA, Weksberg R. Molecular genetics of Beckwith-Wiedemann syndrome. Am J Med Genet. 1998;78A(4):253-259.
7. Bréoude F, Lacoste A, Netchine I, et al. Beckwith-Wiedemann syndrome: growth pattern and tumor risk according to molecular mechanism, and guidelines for tumor surveillance. Horm Res Pediatr. 2013;80(6):457-465.
8. Kalish JM, Boodhastingh KE, Bhatti TR, et al. Congenital hyperinsulinism in children with paternal 11p uniparental isodisomy and Beckwith-Wiedemann syndrome. J Med Genet. 2016;53(1):53-61. https://doi.org/10.1136/jmedgenet-2015-103394.
9. Abramowitz IK, Bartolomel MS. Genomic imprinting: recognition and marking of imprinted loci. Curr Opin Genet Dev. 2012;22(2):72-78.
10. Azzi S, Abi Habib W, Sichert H. Beckwith-Wiedemann and Russell-Silver Syndromes: from new molecular insights to the comprehension of imprinting regulation. Curr Opin Endocrinol Diabetes Obes. 2014;21(1):30-38.
11. Kryzewska IM, Alders M, Maas SM, et al. Genome-wide methylation profiling of Beckwith-Wiedemann syndrome patients without molecular confirmation after routine diagnostics. Clin Epigenet. 2019;11:53. https://doi.org/10.1186/s13148-019-0649-6.
12. Ibrahim A, Kirby G, Hardy C, et al. Methylation analysis and diagnostics of Beckwith-Wiedemann syndrome in 1,000 subjects. Clin Epigenet. 2014;6(1):11. Published 2014 Jan 4.
13. Musa A, Russo S, De Crescenzo A, et al. Epigenotype-phenotype correlations in Beckwith-Wiedemann syndrome. Eur J Hum Genet. 2016;24(2):183-190.
14. Rennie IG. Don’t it make my blue eyes brown: heterochromia and other abnormalities of the iris. Eye. 2012;26(1):29-30.
15. Aggarwal NK, Gandham SB, Weinstein R, Saltzmann R, Walton DS. Heterochromia iridis and pertinent clinical findings in patients with glaucoma associated with Sturge-Weber syndrome. J Pediatr Ophthalmol Strabismus. 2010;47(6):361-365.
16. Kirkwood BJ, Kirkwood RA. Iris Heterochromia. Insight. 2015;40(3):12-16.
17. Inceoglu PD, Wallow IH, Albert DM. The color of the human eye: a review of morphologic correlates and of some conditions that affect iridial pigmentation. Surv Ophthalmol. 1997;41(Suppl 2):S117-S123.
18. Giles CL, Schapert Jr TF. Trauma: inflammation. In: Tasman W, Jaeger EA, eds. Duane’s Ophthalmology on CD-ROM (ch. 62). Philadelphia: Lippincott Williams & Wilkins; 2007.
19. Demirci H, Shields CL, Shields JA, Eagle JR BC, Honavar SG. Diffuse iris melanoma: a report of 25 cases. Ophthalmol. 2002;109(9):1552-1566.
20. Cracknell KP, Grierson I. Prostaglandin analogues in the anterior eye: their pressure lowering action and side effects. Exp Eye Res. 2009;88(4):786-791. https://doi.org/10.1016/j.exer.2008.08.022.