Pediatric Oncall Journal
Volume : 23, Issue 3:124-125
DOI: https://doi.org/10.7199/ped.oncall.2026.75

PEDIATRIC ONCALL
CHILD HEALTH CARE

TEACHING FILES (GRAND ROUNDS)

SUBTLE DYSMORPHIC FEATURES IN A 1-MONTH-OLD INFANT

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ARTICLE HISTORY
Received 21 June 2025
Accepted 7 August 2025

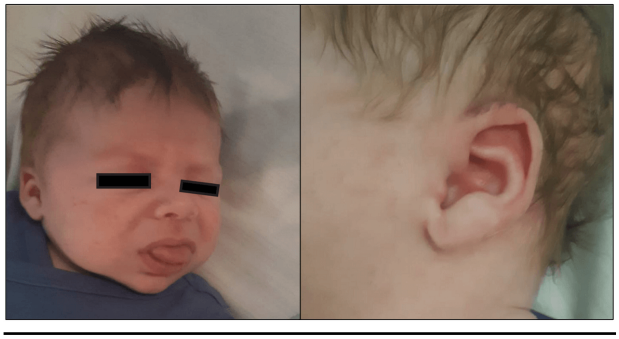
KEYWORDS
Macroglossia, Beckwith-Wiedemann syndrome, Molecular diagnosis, Ear lobe creases.

Clinical Problem:
A previously healthy 1-month-old male infant was admitted to the pediatric ward due to a febrile urinary tract infection caused by *Escherichia coli*. On physical examination macroglossia and bilateral ear lobe creases were noted (Figure 1). No other dysmorphic features were documented to date by other health care professionals during routine well-child visits. The infant appeared well, with appropriate neurodevelopment for age. The clinical course during hospitalization was uneventful. He had been delivered at 39 weeks and 2 days of gestation via cesarean section following a pregnancy complicated with gestational diabetes and maternal hypertension. Maternal serologic and viral screenings were unremarkable, and screening for *Group B Streptococcus* was negative. Prenatal ultrasounds showed no structural abnormalities. Apgar scores at 1 and 5 minutes were 9 and 10, respectively. Birth anthropometric parameters were appropriate for gestational age (weight 3786 g, length 50.0 cm, and head circumference 33.0 cm). Routine neonatal screenings showed no abnormalities. He was discharged on mixed feeding and demonstrated adequate growth and neurodevelopment.

Family medical history was unremarkable.

The infant was referred to pediatrics and medical genetics appointment for further evaluation of the dysmorphic features.

Figure 1. Clinical images of the 1-month-old infant obtained during hospitalization demonstrating macroglossia (left) and ear lobe creases (right), noted during physical examination.



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What is the diagnosis?

Discussion:

At 2 months of age, the diagnosis of Beckwith-Wiedemann syndrome (BWS) was established based on clinical suspicion and positive molecular genetic testing, which revealed a hypermethylation pattern at the DMR1 (H19) region, with a normal methylation profile at DMR2 (KCNQ1OT1). No deletions or duplications were detected at the 11p15 locus, and the karyotype was normal, consistent with an isolated epigenetic alteration. Genetic counselling was provided to the family. At 4 months of age, a mild left-sided body hemihypertrophy was noted on physical examination, sparing the face. At present, the child is 2 years old, demonstrating a normal psychomotor development. He is under multidisciplinary follow-up due to recurrent febrile urinary tract infections, with unremarkable functional (renal scintigraphy) and imaging evaluation of the urinary tract and remains free of other significant clinical complications. He is under regular tumor surveillance with abdominal ultrasound every 3 months. BWS is a rare congenital overgrowth disorder caused by (epi)genetic or epigenetic changes affecting the 11p15.5 chromosomal region. These alterations lead to dysregulation of imprinted genes such as H19, IGF2, KCNQ1OT1, and CDKN1C, which are involved in growth control, cell proliferation, and tumor suppression.[1,2] BWS is clinically heterogeneous, ranging from classic presentations with macrosomia, omphalocele, and evident macroglossia to isolated findings such as lateralized overgrowth or ear creases.[1,3] In this case, the diagnosis was established at 2 months of age based on subtle phenotypic findings (macroglossia and bilateral ear lobe creases), followed by molecular confirmation of isolated H19 hypermethylation (IC1-GOM - gain of methylation at imprinting center 1), with a normal karyotype and DMR2 methylation profile. The development of mild left-sided hemihypertrophy by 4 months further supported the diagnosis and highlighted the progressive nature of some clinical features, often evolving postnatally.[4] Tumor predisposition in BWS is strongly linked to the molecular subtype. Compared to other molecular subtypes, such as IC2 loss of methylation (IC2-LOM), which is typically associated with a lower tumor risk, or paternal uniparental disomy, which carries a higher risk of lateralized overgrowth and embryonal tumors, IC1-GOM presents a distinct clinical profile with an elevated

predisposition to embryonal tumors, particularly Wilms tumor and hepatoblastoma.[1,5] Although this patient did not present with macrosomia or organomegaly, the recognition of minor signs led to early diagnosis and timely implementation of tumor surveillance protocols, which is essential in improving clinical outcomes. Importantly, this case also presented with recurrent febrile urinary tract infections, a manifestation described in association with BWS, even in the absence of detectable genitourinary malformations, underscoring the value of early nephrological evaluation in affected patients.[1] This report reinforces the relevance of recognizing subtle dysmorphic features in infancy and the critical role of epigenetic testing in confirming the diagnosis. Early recognition and multidisciplinary follow-up are central to risk mitigation and long-term prognosis in BWS, particularly in cases with elevated tumor risk based on epigenotype.[5]

Compliance with ethical standards
Funding: None
Conflict of Interest: None

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