

Persistent Hypoglycaemia and Pigmentary Mosaicism: A Case Report of Beckwith-Wiedemann Syndrome

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ABSTRACT

Beckwith-Wiedemann Syndrome (BWS), a rare human genomic imprinting disorder, is characterised by variable phenotypes that include overgrowth, macroglossia, abdominal wall defects, persistent or transient hypoglycaemia, lateralised overgrowth, and predisposition to embryonal tumours. Here, a large-for-gestational-age neonate presented with macrosomia, macroglossia, hemihypertrophy, persistent hypoglycaemia, and structural heart defects. Due to persistent hypoglycaemia, requiring Glucose Infusion Rate (GIR) for more than seven days, the baby was started on oral diazoxide, following which blood glucose levels stabilised. Clinical diagnosis of classic BWS was made, and samples were sent for Methylation-Specific Multiple Ligation-Dependent Probe Amplification (MS-MLPA) analysis, which showed gain of methylation in Imprinting Control (IC) one and loss of methylation in IC2 of the 11p15 locus, suggestive of BWS caused by paternal uniparental disomy. Though the diagnosis is currently based on a clinical scoring system, molecular and genetic testing will confirm the diagnosis and predict the familial recurrence risks and the risk of embryonal tumour. Despite recent advances in knowledge, there is marked heterogeneity in clinical diagnostic criteria and care. This case has been reported to emphasise the wide variations in the clinical presentations and the need for comprehensive protocols for the molecular investigation, care, and management of BWS and also to establish rigorous surveillance protocols for early identification and treatment of various malignancies that these infants are predisposed to.

Keywords: Hemihypertrophy, Hypoglycaemia, Imprinting, Large-for-gestational-age, Macroglossia

CASE REPORT

A large-for-gestational-age boy baby was delivered by caesarean section at 37 weeks of gestation to a 20-year-old primigravida mother from a non-consanguineous marriage. Antenatal scans revealed bilateral renal pelviectasis and progressive left renal pelvis dilatation (11 mm AP diameter) with severe calyceal dilatation suggestive of Pelvi Ureteric Junction (PUJ) obstruction. The baby weighed 3915 grams at birth and had a normal transition with APGAR scores of 7 and 8 at one and five minutes, respectively. Baby was admitted to Neonatal Intensive Care Unit (NICU) in view of Large for Gestational Age (LGA) and respiratory distress in the form of tachypnoea and retractions with a Downes score of 5 [1]. Anthropometry details of the baby include a weight of 3.915 kg (+2.2 SD), a length of 48.1 cm (+0.16 SD), a head circumference of 33.4 cm (+0.31 SD), a chest circumference of 33 cm, and a limb length of 18.8 cm on the left-side and 16.9 cm on the right-side, suggestive of macrosomia and hemihypertrophy [2,3].

A detailed head-to-toe examination revealed macroglossia and left hemihypertrophy [Table/Fig-1], bilateral earlobe creases, and two posterior helical pits in the left ear [Table/Fig-2]. Umbilical cord oedema due to excessive Wharton's jelly was noted. Additionally, ill-defined hyperpigmented macules arranged linearly along Blaschko's lines over the trunk and limbs were observed, suggestive of pigmentary mosaicism type 1 [Table/Fig-3].

Baby was started on Continuous Positive Airway Pressure (CPAP) support in view of respiratory distress. As the first Capillary Blood Glucose (CBG) level done at two hours of life showed hypoglycaemia (20 mg/dL), the baby was started on GIR 6 mg/kg/min, following which the CBG values improved to the acceptable threshold levels. Also, the baby was started on full feeds as per unit protocol. Baby was weaned off from CPAP support after 48 hours. Sepsis screen, urine ketones, urine for reducing substances, serum insulin, serum cortisol and serum free fatty acids were within normal limits. The baby

had asymptomatic polycythemia (PCV 70%), which was managed with additional i.v. fluids of 20 mL/kg/day, and serial haematocrit values came down to 63% [4]. Direct breastfeeding was initiated after the baby was weaned off from CPAP support.



[Table/Fig-1]: Lateralised overgrowth with macroglossia.



[Table/Fig-2]: Helical earpits.



[Table/Fig-3]: Pigmentary mosaicism.

Baby developed hypoglycaemia while GIR was tapered. Due to persistent hypoglycaemia, requiring GIR for more than seven days, the baby was started on oral diazoxide (7 mg/kg/day), following which blood glucose levels stabilised. Sepsis screening was negative. Postnatal USG done at day 3 of life showed left renal enlargement with Anterior Posterior Diameter (APD) 1.5 cm, with dilatation of central and peripheral calyces, without ureteral dilatation and no renal parenchymal thinning which was suggestive of Urinary Tract Dilatation-P1 (UTD-P1) [5]. Echocardiography revealed a big Patent Ductus Arteriosus (PDA) of 2.7 mm bidirectional shunt, mild pulmonary arterial hypertension (36 mmHg), and a 2 mm patent foramen ovale. Otoacoustic Emission (OAE), pulse oximetry screening, thyroid function test, renal function test, and serum electrolytes were normal. MS-MLPA analysis showed an identified gain of methylation in IC1 and loss of methylation in IC2 of the 11p15 locus, thereby confirming the diagnosis of BWS caused by paternal uniparental disomy or imprinting defects resulting in aberrant methylation of the locus causing loss of gene expression [Table/Fig-4] [6].

Parents were advised to do pre-feed CBG monitoring, once a day. Diazoxide was tapered and stopped at five months of age. Serial

Interpretation	: MS-MLPA analysis of the provided clinical sample identified gain of methylation in IC1 and loss of methylation in IC2 of the 11p15 locus. This observation is suggestive of Beckwith - Wiedemann syndrome caused by paternal uniparental disomy - UPD or imprinting defects which may result in aberrant methylation of the locus causing loss of gene expression. No deletion was observed in the 11p15 locus by MLPA testing.
Recommendation	: Correlate the results clinically and genetic counseling is recommended.

[Table/Fig-4]: Multiplex ligation-dependent probe amplification report.

echocardiography done at two month of age showed spontaneous closure of PDA and resolution of pulmonary arterial hypertension. Repeat renal ultrasound was done at six weeks of age showed reduction in APD to 7 mm with no pelvicalyceal dilatation. Hence, Micturating Cystourethrography (MCU) was not done. Baby was advised for serial follow-up ultrasound abdomen every three months to identify malignancies like leukaemia and embryonal tumours like Wilms Tumour (WT), rhabdomyosarcoma, hepatoblastoma, neuroblastoma and adrenal carcinoma. Currently, baby is seven months of age with adequate weight gain, no hypoglycaemic episodes. Ultrasound abdomen including renal ultrasound done at six months of age was within normal limits, without any features of abdominal tumours and complete resolution of pelviectasia.

DISCUSSION

The BWS is a multisystem imprinting disorder characterised by variable clinical features and a complex underlying molecular basis. Although, it can manifest before birth or later in adulthood, BWS is most frequently identified during the neonatal period or early childhood, with an estimated prevalence of approximately 1 in 10,340 live births [6]. BWS was suspected in this neonate, because of macrosomia, macroglossia, and hemihypertrophy. According to the BWS scoring system, a clinical diagnosis of classic BWS was made, and samples were sent for MS-MLPA analysis, which showed gain of methylation in IC1 and loss of methylation in IC2 of the 11p15 locus, suggestive of BWS caused by paternal uniparental disomy [6]. One of the challenges faced in the management of the baby was persistent hypoglycaemia. Though the hypoglycaemia was asymptomatic, it required prolonged GIR for more than seven days to maintain a target blood glucose value of more than 70 mg/dL, for which oral diazoxide therapy was started [7]. Though hypoglycaemia in BWS often resolves within a few days, in up to 20% of neonates it can persist beyond the first week of life and require medical treatments or even pancreatectomy in the most severe cases [8]. Two genes associated with congenital hyperinsulinism, *ABCC8* and *KCNJ11*, are located on chromosome 11p, and some individuals with Beckwith-Wiedemann spectrum (BWSp) may harbour a heterozygous pathogenic variant in one of these genes [9].

Macroglossia is found in 90% of children diagnosed with classical BWS, and BWSp is the most common cause of macroglossia in childhood [10]. Macroglossia regresses spontaneously in half of the cases because of both a decrease in growth velocity and an increase in growth of the mandible. Approximately 40% of the babies have difficulty in feeding, respiration, and articulation and need surgical tongue reduction [11]. This baby initially had a big PDA of size 2.7 mm with a bidirectional shunt, which was followed-up with serial echocardiography and spontaneous resolution was documented at two months of age. Congenital heart disease is more prevalent in BWS than in the general paediatric population and occurs in up to 13-20% of patients with BWS. Though minor anatomical defects like PDA, patent foramen ovale, and interatrial or interventricular defects require echocardiographic monitoring until usual spontaneous resolution occurs [12].

Pavone V et al., in their series of 114 patients with pigmentary mosaicism of Ito, anecdotally found that eight cases had either partial or total body hemi-overgrowth, suggesting that the association between these two conditions is not uncommon [13]. Hailu SS et al., reported a case of BWS in a one-year-old child with multifocal WT and lateralised overgrowth, who presented with abdominal swelling

and limb length discrepancies. A clinical diagnosis of BWS was made based on multifocal WT and hepatomegaly and nephromegaly detected on contrast-enhanced abdominal computed tomography and physical examination findings of lateralised overgrowth and umbilical hernia. Molecular genetic testing was not done in that infant [14]. Elefante P et al., reported a case of a premature twin patient who during her follow-up developed a clinical phenotype compatible with BWS, confirmed genetically. However, the methylation alteration characteristic of the condition was also found in the almost phenotypically normal sibling, making it challenging her management [15]. Joel J et al., reported a case of six-year-old child presented with a visibly enlarged tongue that caused difficulty with speech and eating. The patient had a history of BWS, which was confirmed through genetic testing. The patient underwent a reduction glossectomy, a surgical procedure to reduce its size and improve her ability to speak and eat [16].

Few case reports also mentioned the increased risk of leukaemias in infants with BWS, although the genetic plausibility of such associations need to be explored in detail [17,18]. For most molecular subtypes of BWS, tumour screening includes abdominal ultrasound with visualisation of the liver, adrenal glands, and kidneys every three months until four years of age, followed by renal ultrasound alone every three months from age four through seven years [19].

CONCLUSION(S)

The BWS should be suspected in any LGA baby, particularly with macroglossia, and needs to be confirmed by a molecular genetic test for prognosis and management. Babies with BWS will need aggressive screening and management of hypoglycaemia and also evaluation by a multidisciplinary team comprising a neonatologist, paediatric cardiologist, paediatric surgeon, dermatologist, developmental paediatrician, and genetic specialist and multimodal treatment along with periodical tumour surveillance owing to childhood cancer predisposition.

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