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Case Report

Beckwith–Wiedemann Syndrome Presenting with Transient Features of Congenital Adrenal Hyperplasia in a Nigerian Neonate

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Abstract

Presentation of Beckwith–Wiedemann syndrome (BWS) is widely variable. Congenital adrenal hyperplasia (CAH) is the leading cause of atypical genitalia in the female newborn. Beckwith–Wiedemann syndrome was previously not recognized as a possible cause of a false diagnosis of CAH. A late preterm (gestational age of 36 weeks) female presented at the 3rd hour of life with an anterior abdominal wall defect and swelling. Examination revealed coarse facial features, macroglossia, omphalocele major, prominent labia majora with hyperpigmented and enlarged clitoris. Weight was >97th percentile for age and sex, with length and occipitofrontal circumference at 95th and 50th percentiles, respectively. Initial blood investigations revealed hypoglycaemia, hyponatraemia, hypocortisolaemia, elevated testosterone and 17-hydroxyprogesterone with female internal genitalia suggesting CAH. She was commenced on hydrocortisone. Omphalocele was managed conservatively. Abdominal ultrasound scan showed no enlargement of the adrenal glands or tumours. Genetic analysis showed ***hypomethylation at KCNQ1OT1: TSS-DMR (IC2) within 11p15.5,*** confirming a diagnosis of BWS. Clitoromegaly resolved spontaneously at six months of life without any surgical intervention, with normal pigmentation of the external genitalia. Steroids were tapered off, and repeat adrenal metabolites are normal. BWS may present with transient features suggestive of CAH.

Keywords: Beckwith-Wiedemann syndrome, congenital adrenal hyperplasia, transient, androgens, hypomethylation.

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Quick Response Code:

Introduction

Beckwith-Wiedemann syndrome (BWS) is a rare overgrowth disorder characterized by variable features, including macroglossia, abdominal wall defects, hemihyperplasia, and visceromegaly, with frequent involvement of the adrenal glands in the form of adrenocortical cytomegaly. [1-3] Additional manifestations include renal anomalies, ear creases or pits, and an increased risk of embryonal tumours. [1] Beckwith-Wiedemann syndrome results from genetic or epigenetic alterations involving imprinted genes on chromosome 11p15.5, which regulate foetal growth. [1-4] The estimated prevalence is 1 in 10,340 live births. [2,4-6] Molecular classification is important because tumour risk varies by genetic subtype. [2,3]

Congenital adrenal hyperplasia (CAH), particularly due to 21-hydroxylase deficiency, is the most common cause of atypical genitalia in female newborns and a potentially life-threatening condition if untreated. Elevated 17-hydroxyprogesterone (17-OHP) forms the basis of neonatal CAH screening programs, which are critical for preventing adrenal crisis, salt-wasting, and early neonatal mortality. [7-9]

Beckwith-Wiedemann syndrome has not traditionally been recognized as a cause of false-positive CAH screening results. However, recent reports have described neonates with BWS presenting with transient biochemical and clinical features suggestive of CAH.[10] In settings without routine newborn screening or access to molecular diagnostics, such presentations pose a significant diagnostic challenge and may lead to unnecessary long-term steroid therapy. We report a case of BWS with transient CAH-like features to highlight the diagnostic pitfalls.

Case Report

A late preterm (36 weeks' gestational age) female presented at the third hour of life with an anterior abdominal wall defect and swelling. The pregnancy was spontaneously conceived. There was no history of smoking, drinking alcohol, exposure to radiation or use of herbal preparations by the mother during pregnancy. The antenatal period was relatively uneventful until a few days prior to delivery, when the mother developed preeclampsia and antepartum haemorrhage necessitating delivery via emergency caesarean section.

On examination at presentation, the baby had coarse facial features, macroglossia (Fig 1a) ear pits (Fig 1b) omphalocele major: umbilical defect measuring 7cm, with intact sac and remnant of umbilical cord attached (Fig 1c) and a prominent hyperpigmented labia majora and enlarged clitoris (length of 16mm and width of 8mm) as shown in Fig 1d. The vaginal and urethral openings were distinct, and no gonads were palpable in the labioscrotal folds or in the inguinal region. No hemihypertrophy was noticed. The baby weighed 3600g (> 97th percentile for age and sex), length was 50cm (95th percentile for age and sex), and occipitofrontal circumference was 32cm (50th percentile for age and sex). The initial bedside blood glucose level was 1.7 mmol/L, which was corrected. A “critical sample” was drawn during the hypoglycaemic episode, and serum levels of insulin, cortisol, testosterone and 17-hydroxyprogesterone (17OHP) were determined. Results are shown in Table 1. Insulin was appropriately low. Initial serum cortisol was low, and testosterone and 17-hydroxyprogesterone (17OHP) were elevated. Serum adrenocorticotropic hormone levels could not be measured due to financial constraints. Based on the initial laboratory results and pelvic ultrasound scan (USS) report showing female internal genitalia, a presumptive diagnosis of “Salt-Wasting CAH possibly coexisting with BWS was made. [9] In view of the mortality associated with SWCAH if not promptly treated, the child was commenced on oral hydrocortisone at 10mg/m^2/day. Subsequently, the baby experienced other hypoglycaemic episodes until resolution at 10 days of age.

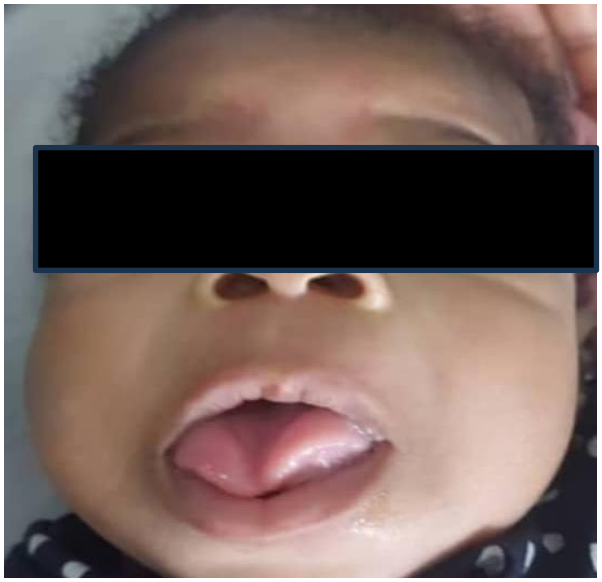

Figure 1a: Macroglossia

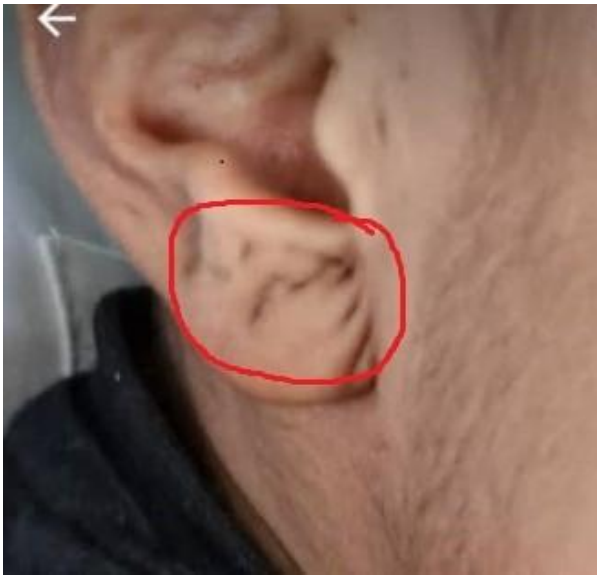

Figure 1b: Ear Pits

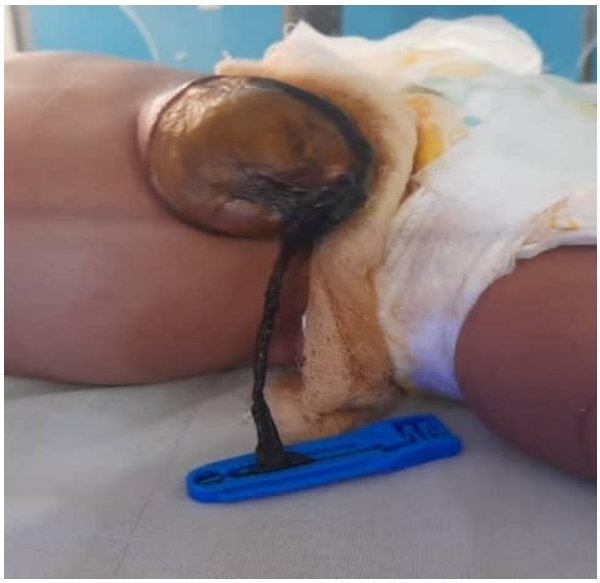

Figure 1c: Omphalocoele

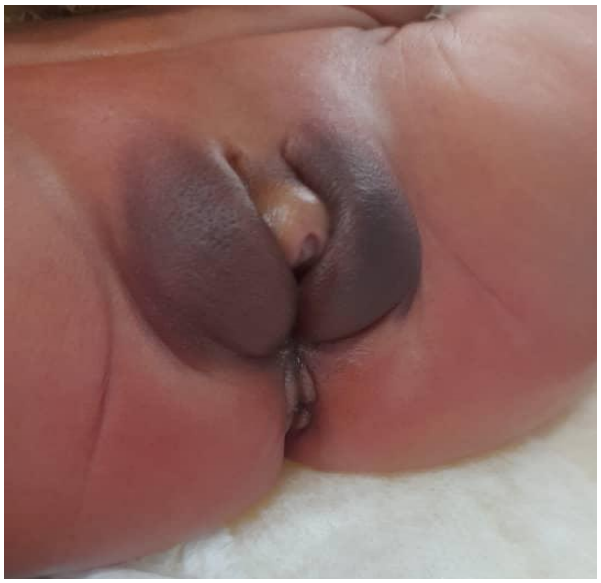

Figure 1d: Clitoromegaly

Figure 1 (a-d): Clinical features at presentation

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Table 1: Serial Results of Laboratory Investigations

Serum analyte	Ref Values	At Presentation	13m*	14m	15m**	19m	20m
Na(mmol/L)	135-145	139	136	134			137
K (mmol/L)	3.5-5.1	4.64	3.68	4.08			3.72
Cortisol (nmol/L)	240-618	77.7					248
Testosterone (nmol/L)	0.03-0.2	2.87			0.04		
17OHProgesterone(nmol/L)	<1.89	32.76			<0.1	0.296	
Insulin (uIU/ml)	2-25	0.8					

*m= months,

**: Hydrocortisone had been discontinued

Methylation-specific multiplex ligation-dependent probe amplification analysis (MRC-Holland kit ME030-C3) showed evidence of hypomethylation at *KCNQ1OT1: TSS-DMR (IC2)* within 11p15.5. as shown in Figure 2. Omphalocoele major was managed conservatively as advised by surgeons and healed. (Fig 3).

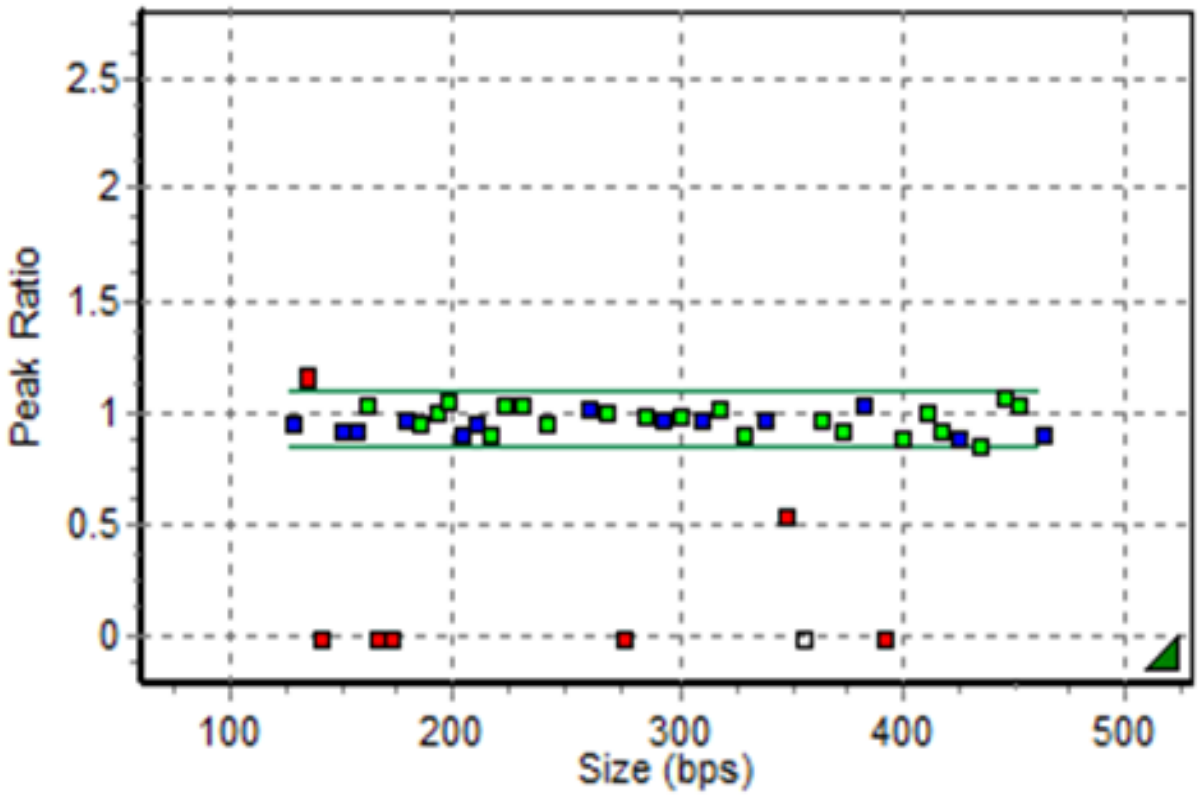

Figure 2: Methylation-specific MLPA (MS-MLPA) results at the Beckwith–Wiedemann syndrome (BWS) locus

Report of the abdominal USS done on the fourth day of life showed no gross enlargement of the adrenal glands nor any tumours. The child was discharged from the hospital at 25days of age and followed up at the outpatient clinic. At six months of age, urogenital examination revealed that clitoromegaly had resolved (length of 5mm and width of 5mm) with normal pigmentation of the external genitalia and the labia minora and clitoris tucked under the labia majora (Fig 3).

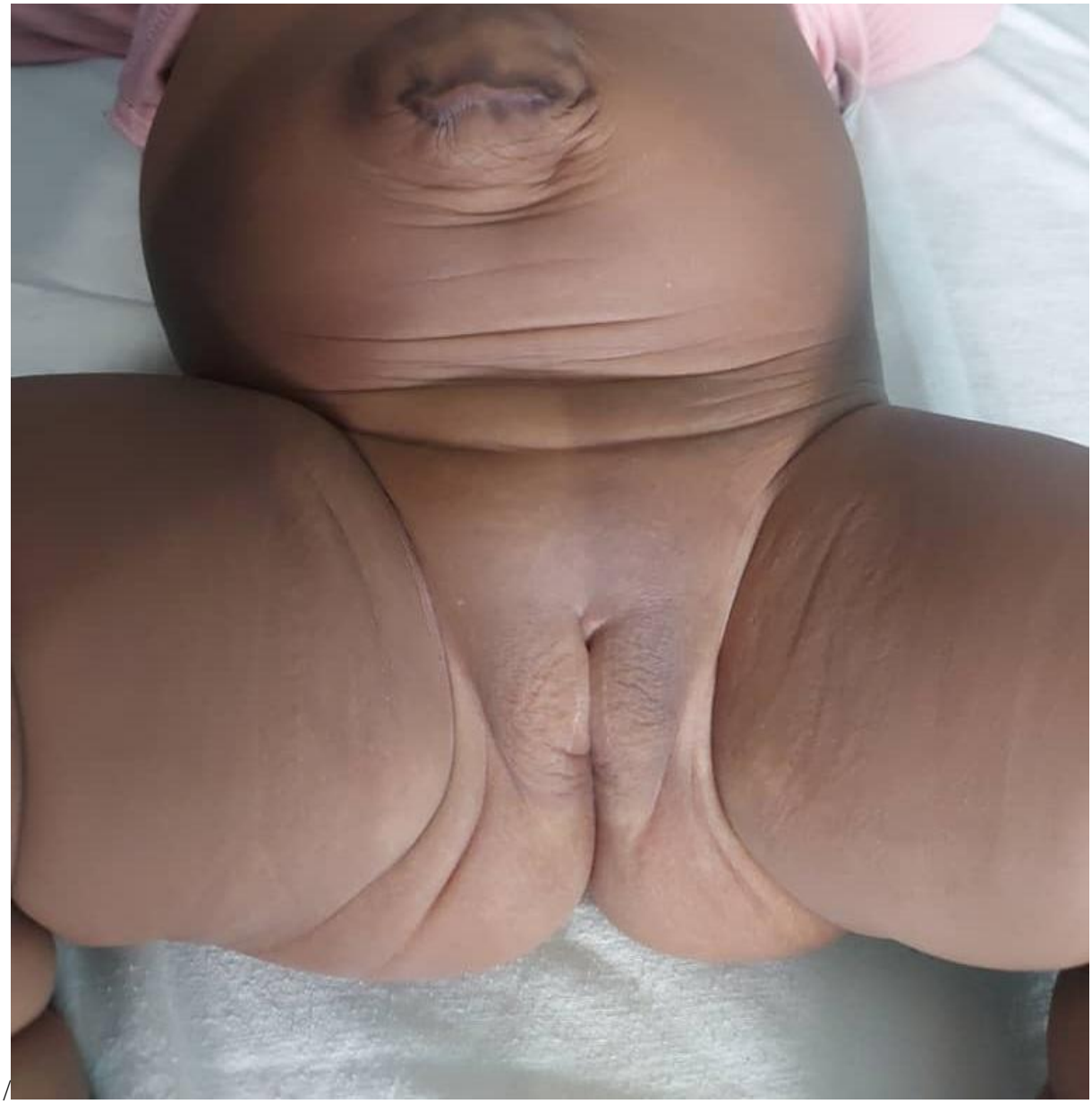

Figure 3: Resolution of clitoromegaly and hyperpigmentation at follow-up at 6 months of age

In view of cases in literature of BWS manifesting with transient clitoromegaly and elevated testosterone and 17OHP, [10] hydrocortisone was subsequently tapered off (5mg/m^2 per day in 2 divided doses for a week, 2.5mg/m^2 per day in 2 divided doses per week and 1.25mg/m^2 daily for another week). Repeat serum cortisol, testosterone and 17OHP have remained normal. The patient is presently three years old and is doing well on follow-up. She is still being monitored, bearing in mind that her genetic subtype (*IC2*) has the least cancer risk.

Discussion

Adrenal abnormalities are well recognized in BWS, with foetal cortical cytomegaly and adrenal hyperplasia frequently reported on histopathology.[3] These changes may result in transient endocrine abnormalities that mimic congenital adrenal hyperplasia.

In our case, the neonate presented with clitoromegaly, hyperpigmented external genitalia, elevated androgens, increased 17-OHP, and hypocortisolaemia; features strongly suggestive of classical CAH. In the absence of newborn screening and with limited access to confirmatory testing, initiation of hydrocortisone was clinically appropriate to prevent potential adrenal crisis.[9] However, spontaneous resolution of virilisation and normalisation of adrenal steroid profiles, which have been maintained for more than 6 months after steroid withdrawal, confirmed a transient CAH-like presentation associated with BWS rather than true enzymatic deficiency.

Similar cases have been documented. Martins *et al* [10] described three neonates with BWS who had false-positive CAH screening results, all of whom demonstrated complete biochemical resolution within the first year of life. Other reports in the literature, including the first series by Beckwith, have documented clitoromegaly in female children with BWS.[11] Some authors have opined that the findings of clinical and laboratory features mimicking CAH may be due to persistence of the transient cortex and/or hyperplasia of the permanent cortex. [10] Other authors suggest that the aetiology of clitoromegaly may be caused by exposure to excess androgen from Leydig cell hyperplasia, which can occur in individuals with BWS irrespective of gender. [11]

In contrast to the current case, other reports of children with BWS did not show low cortisol levels. [10] The cause of the initial hypocortisolaemia in this case is not immediately obvious. It may, however, be related to the gestational age of the patient. Studies have reported a transient adrenocortical insufficiency in premature infants due to immaturity of the hypothalamic-pituitary-adrenal (HPA) axis, though it was described in those with GA less than 30weeks. [12]

Furthermore, in BWS, benign adrenal cytomegaly [3] and androgen-producing adrenocortical carcinoma may be encountered. [13-15] As both lesions are associated with different prognoses, it is imperative to distinguish between them. [3] Imaging of our patient did not show evidence of an adrenal mass. Patients with BWS who have mutations other than *IC2* must have abdominal USS for tumour surveillance every 3 months from diagnosis until the age of 7 years. [2,16] However, in view of the least cancer risk associated with *IC2* mutation, this subset of children should have clinical assessment and USS in response to signs and/or symptoms or parental concern. [2,16]

Limitations

Evaluation was limited by the unavailability of serum ACTH, renin, aldosterone, genetic testing for 21-hydroxylase deficiency, and ACTH stimulation testing due to financial and resource constraints. Despite these limitations, the transient clinical course and biochemical normalisation strongly argue against classical CAH and support a functional, reversible endocrine disturbance associated with BWS.

Conclusion

Beckwith–Wiedemann syndrome is a complex multisystem disorder that can present with transient biochemical and clinical features mimicking classical congenital adrenal hyperplasia. This overlap poses a significant diagnostic dilemma, particularly in resource-constrained settings lacking universal newborn screening and molecular diagnostics. While early hydrocortisone therapy remains essential when CAH is suspected, careful reassessment is crucial to avoid unnecessary lifelong treatment.

Ethical Consideration:
All clinical investigations and genetic testing were performed in accordance with the Declaration of Helsinki guidelines.

Declaration of Patient Consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the mother of the patient has given written consent for her images and other clinical information to be reported in the journal. The mother understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Authors' Contributions
All authors were involved in the management of the case. OEE and EOO drafted the manuscript. All authors read and approved the final manuscript for submission.

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Conflict of Interest
The authors declare no conflicts of interest

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