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Case Report

Prader Willi Syndrome with Maternal Uniparental Disomy Mutation in a 7-year- old Nigerian girl- A Case Report

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Abstract

Prader-Willi Syndrome (PWS) is one of the earliest cases of human genetic imprinting of parental origin involving chromosome 15, with an incidence of 1:10000-30000 per live births. Symptoms of PWS are erratic, beginning early in life with difficulty in feeding and failure to thrive and evolving into new characteristics such as obesity as age advances.

Reported here is a case of a 7-year-old girl who presented at the pediatric endocrinology clinic with a 4-year history of progressive weight gain, voracious appetite, snoring during sleep, and poor academic performance. She had feeding difficulties, growth failure, and delayed developmental milestones in the first year of life. This was managed with a fortified diet till she was 3 years of age, when she started eating voraciously and was gaining weight increasingly.

Medical history, characteristic facial appearance, and anthropometry measurements at presentation were suggestive of Prader-Willi Syndrome, which was confirmed with DNA analysis. She is currently on dietary modification and planned exercises, and she lost 3 kg over a period of eight months. She is also receiving assisted learning both at school and at home.

Prader-Willi syndrome should be considered in a child with initial growth failure that subsequently translates into progressive weight gain following excessive eating and cognitive impairment. Early commencement of lifestyle intervention could help in reducing excessive weight gain. This case confirms limited awareness and insufficient recognition of this rare clinical syndrome. To our knowledge, this is the first genetically confirmed case of PWS in Nigeria.

Key words: Prader Willi syndrome, human genetic imprinting, failure to thrive, obesity.

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Introduction

Prader–Willi syndrome (PWS) is a rare human imprinting disorder resulting from genomic alterations that inactivate imprinted, paternally expressed genes in the human chromosome region 15q11–q13. PWS has a birth incidence of 1:10000-30000 births with no sex or ethnic predilection. [1-3] There are three main classes of chromosomal abnormalities that lead to PWS: deletion on 15q11–q13 (65–75%), maternal uniparental disomy of chromosome 15 (20–30%), or a defect in the imprinting center on 15q11–q13 (2%); gene mutation (< 0.1%) and balanced translocation (0.1%) can also be found.[2] The genetic mutation leads to modified hypothalamic development and function, resulting in impaired satiety, various hormone deficiencies, sleep-related breathing abnormalities, and additional comorbidities.[4]

In the newborn and infantile period, individuals with PWS fail to thrive due to profound hypotonia, poor appetite, and feeding difficulties. This subsequently translates into enhanced feeding and appetite with normal growth, then increased appetite and calorie intake resulting in obesity from age 2 years and above.[3,5] Other characteristics of PWS include characteristic facial appearance, small hands and feet, short stature, hypogonadism, behavioural complications, and cognitive disabilities.[2,3] DNA methylation is essential in the diagnosis of PWS, as it identifies all three molecular groups.[5] There is no cure; however, therapies include growth hormone therapy, puberty hormone replacement, behavioural therapy, physical and occupational therapy, special education, and a well-planned diet. A case reported from North-Central Nigeria in a Caucasian was based on clinical features. [6] To our knowledge, this is the first genetically confirmed case of PWS in Nigeria, and it is reported due to a knowledge gap in local diagnosis, awareness, and access to genetic testing.

Case Presentation

We report a case of a 7-year-old girl who presented at the paediatric endocrinology clinic with a 4-year history of progressive weight gain, voracious appetite, snoring during sleep, and poor academic performance. She is the 1st of a set of twins delivered via emergency cesarean section to a 42-year-old multiparous woman at 36 weeks of gestation following preterm contraction. At birth, she weighed 1.9 kg with microcephaly and profound hypotonia. In the first year of life, she had feeding difficulties and growth failure with delayed developmental milestones. She was managed for recurrent pneumonia in the first two years of life. She started eating voraciously from 3 years of age and was gaining weight, with accompanying snoring at night while sleeping. The mother noticed some other behaviour in her, such as temper tantrums and skin picking, which led to sores in different stages of healing on her legs. Her academic performance was poor based on the grade level classification compared to that of her twin sister. At age 3 years, she was reviewed at the paediatric gastroenterology clinic on account of excessive weight gain, but defaulted from follow-up after a year.

On general examination, she was obese with a narrow forehead, almond-shaped eyes, and a small mouth with downturned corners. (Fig.1) Using the WHO 2007 z-score reference growth standards, her anthropometric measurements were weight: 35 kg (+2.39); height: 109 cm (-1.20); and her body mass index (BMI) was 27.8 kg/m² (+2.91). Musculoskeletal examination revealed scoliosis (as shown in Fig. 2) with multiple healed lesions over the lower limbs. Her hands and feet were small for her age. (Figs. 3 and 4) Other systems examinations were essentially normal.

Figure 1: Front view of the patient showing a narrow forehead, with fat distributed primarily in the breasts, abdomen, hips and thighs.

Figure 2: Backview showing postural deformity.

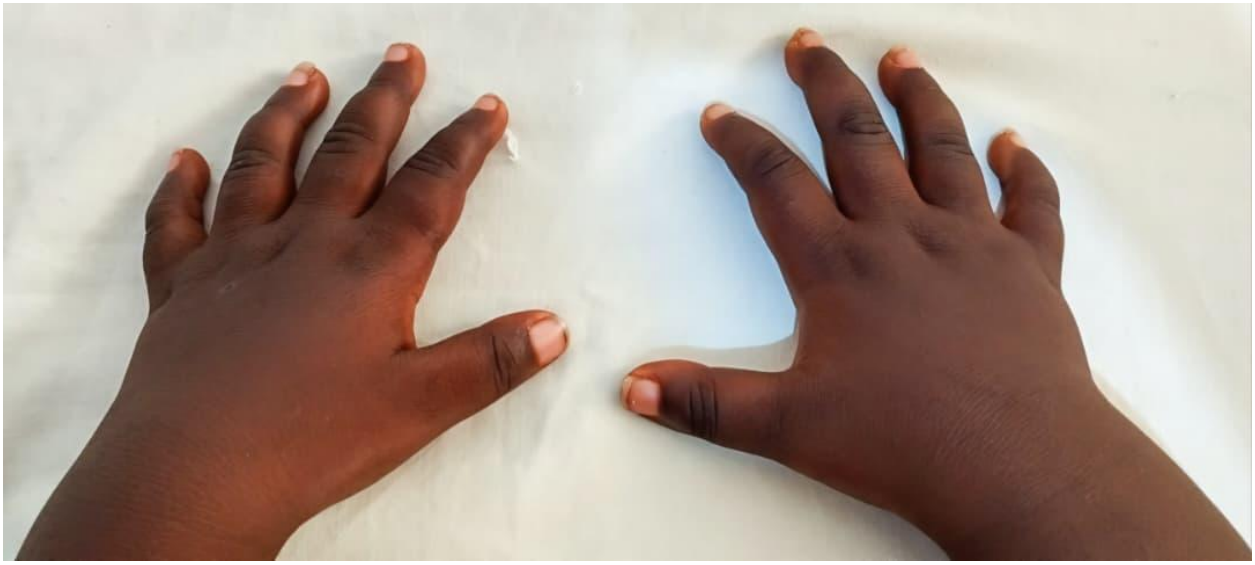

Figure 3: Bilateral small hands and clinodactyly of the index fingers.

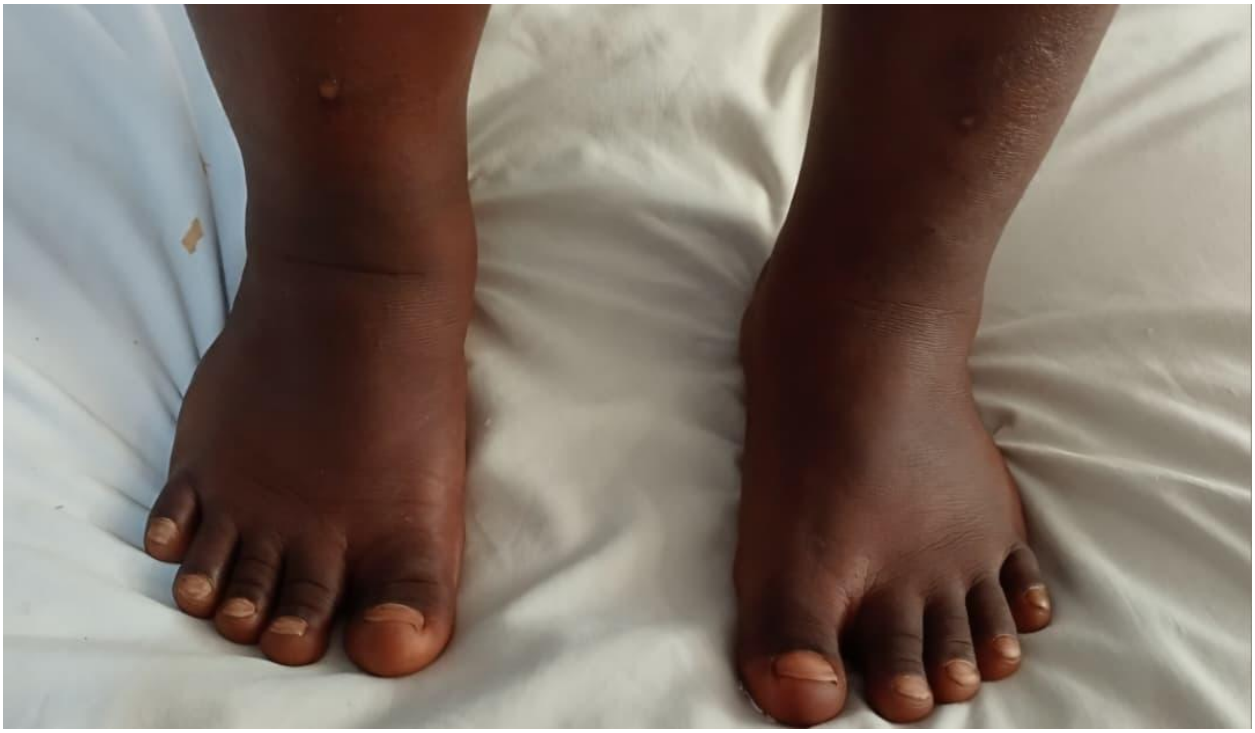

Figure 4: Feet of the patient with short and almost equal digits.

Fasting blood glucose and thyroid function tests were normal. Genetic testing using multiplex ligation-dependent probe amplification analysis (MS-MLPA) detected a maternal methylation profile of both copies of the Prader-Willi Syndrome/Angelman Syndrome (PWS/AS) genetic regions, due to uniparental disomy. A definitive diagnosis of Prader-Willi syndrome and childhood obesity was made. She is on lifestyle modification (balanced diet and portion control) and also undergoing planned exercises, and she lost 3 kilograms over 8 months. She is having assisted learning both in school and at home.

Table 1: Genotype-phenotype correlation in PWS [4,7,8]			
Genetic Mechanism	Description	Approximate frequency	Clinical features
Paternal Deletion	*BPI–BPIII (about 6.2Mb) BPII -BPIII (about 5.3Mb) BPI – BPIV (about 7.4Mb) BPI-BPV (about 9Mb)	60-75%	Young maternal age, higher rates of skin/light hair colour, obesity, hyperphagia, epilepsy, and language delay
Maternal Uniparental Disomy (UPD)	Isodomy Heterodisomy	20-30%	Advanced maternal age, less severe typical facial features, better speech articulation, higher rates of temper tantrums, and autism spectrum disorder.
Imprinting Defect (ID)	Epimutation Imprinting centre deletion	1-3%	Phenotype often overlaps with deletion, with higher rates of psychosis/ASD.
*BP: Breakpoint, *ASD: Autism Spectrum Disorders			

Discussion

The putative diagnosis of PWS was made in this patient when she presented with excessive eating and progressive weight gain after a period of failing to thrive. This pattern has been documented both within and outside Africa. [2,9,10] The features of PWS may be missed earlier in life because of the generic and age-dependent nature of many clinical symptoms, as found in our patient. [11] Experiences differ in various countries, which may be due to a poor knowledge base of the condition and the unavailability of diagnostic resources. [1,2,11,12]

The DNA analysis using MS-MLPA is recommended to diagnose PWS, and it showed that the patient had maternal UPD, the second most common type of PWS. [2] Her mother was advanced in age; she had feeding difficulties, severe skin pricking involving both legs and fair speech articulation. The genetic testing was done through collaborations with the International Prader Willi Syndrome Organization, as the facilities were not available in the institution, signifying the need for global collaborations.

Hypothyroidism was absent in this patient; the mean age of diagnosis of this endocrine condition is 2 years. The case report from Ethiopia had similar findings. [2] PWS is the commonest syndromic cause of obesity, and obesity is the major cause of morbidity and mortality in them. [11] Our patient presented with obesity

at 3 years of age, but other African studies from Cape town, Ethiopia and Tanzania reported earlier development of obesity. [2,9,13] This difference may be a result of early detection and intervention.

Management is multidisciplinary; this was the approach in this case, and as reported in other studies. [2,9,10] She is currently on lifestyle modification and planned exercises, and there has been some improvement in her weight. We are monitoring her for potential comorbidities. The mother is in menopause, and there is no risk of recurrence.

Conclusions

PWS has no cure; it is essential to identify the characteristics of PWS promptly for early referral and intervention due to its potential long-term consequences. Nigeria requires enhanced local diagnostic capabilities regarding personnel and equipment.

Ethics Statement

The authors obtained written informed consent from the parent of the subject mentioned in this article. Institutional ethical clearance was waived.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgement

The authors express their gratitude to the parents of the patient for granting consent to utilize the patient's details and images for this report.

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