

CASE REPORT



Precocious puberty in a 30-month-old Nigerian girl: A case report

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Abstract

The development of secondary sexual characteristics before the expected age and sex is termed precocious puberty. It is usually due to excessive sex steroids production. Cases of precocious puberty are uncommon worldwide with a prevalence of 1/5000–1/10000 per children population and a female to male ratio of 10:1. In Nigeria, the prevalence is unknown with only a few reported cases, probably due to superstitious and religious beliefs. A high proportion of reported cases globally are of the gonadotropin-dependent (central) type. A case is being reported of a 30-month-old female non-identical twin in Cross River State, South-South of Nigeria, who presented with a 6-month history of bleeding per vagina, premature breast development and pubic hair distribution (Tanner stage 3). The patient had appropriate serum concentrations of the pituitary gonadotrophins and gonadal hormones for age. Precocious puberty was not a finding in the family history, and twin and other siblings had normal growth pattern. Radiological and endocrine investigations were diagnostic of precocious puberty. Hence, being proactive with a high index of suspicion is required of clinicians to be able to identify endocrine abnormalities that are increasing in prevalence and are going unnoticed in our environment, among the pediatric age group.

Keywords: Gonadotrophins, hormones, pediatric, precocious, puberty, steroids

Introduction

In normal individuals, secondary sexual characteristics formation is controlled by sex hormones. The development of secondary sexual characteristics before the median age for sex is termed precocious puberty. It is usually due to excessive production of sex steroids. It is a rare endocrine problem. Cases of precocious puberty are uncommon worldwide with a prevalence of 1/5000–1/10000 per children population and a female to male ratio of 10:1. Many cases go undiagnosed because many patients presenting with signs and symptoms do not look for a physician to render health care to them. In Nigeria, prevalence is unknown with only a few reported cases, probably due to superstitious and religious beliefs among parents of affected children.

Case Report

We present a case of 30-month-old female non-identical twin aged 2 years and 6 months brought in by the mother at the metabolic clinic, with a history of bleeding per vaginam of 6 months duration without an associated history of genital trauma or bleeding from other sites. The bleeding was said to

be moderate, occurring at regular monthly cycles of 30 days and lasting for 3 days. There was also the history of premature breast enlargement and pubic hair growth which was observed at about the same period with the bleeding per vaginam. The breasts which were initially bud-like progressively increased in size over the past 6 months before the presentation. The pubic hair which was also initially sparse in distribution had progressively become more widespread and darker. There was no significant past medical or surgical history, and there was no history of chronic medication chronic medication use and patient did not have any chronic disease. Detailed history taken showed she had normal developmental milestones. Pregnancy history of mother and medical history were uneventful. Her twin brother had normal growth and development commensurate with age. Parents and other family members had normal height and body status did not exhibit exaggerated pubertal changes. No history of chronic disease and patient was not on any chronic medication. On examination, the patient appeared bigger for age, with bilateral breast enlargement (Tanner stage 3) and the appearance of pubic hair [Figures 1-3]. Systemic exam yielded no significant findings. She weighed 18kg and was 102 cm tall. Investigations requested for included hormonal profile-prolactin, gonadotropin-

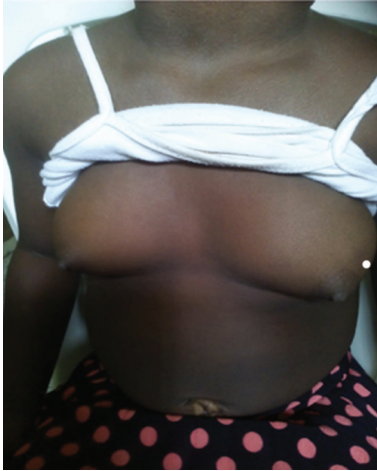


Figure 1: Patient with adult female breast appearance



Figure 2: Patient with adult pubic hair appearance

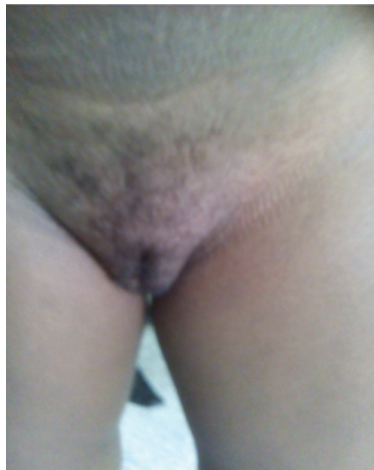


Figure 3: A closer look at adult female hair appearance at the pubic region

releasing hormone (GnRH), luteinising hormone LH, follicle stimulating hormone (FSH), estradiol, complete blood count with peripheral blood film electrolyte, urea, creatinine, liver function test, magnetic resonance imaging (MRI) of the brain, and abdominopelvic ultrasound. X-rays of the wrist and legs to determine bone age were also requested.

Results

Due to financial challenges, the requested investigations were not done until 3 months later, (patient was now 2 years and 9 months), weighed 20 kg, and height was 102 cm. MRI and X-ray were not done. LH was 3.0 IU/L, FSH was 8.6 IU/L, estradiol was 1.77 pg/mol, and prolactin was 18.82 ng/ml. Abdominopelvic scan showed an anteverted uterus, bigger than expected for age and measured 2.4 cm × 4.9 cm with endometrial thickness. The ovaries appeared to be developing follicles.

Discussion

Precocious puberty is a rare medical condition. It is more common in girls than boys. Prevalence is about 1/5000-1/10000 per population of children with a female to male ratio of 10:1. The paucity of data in Africa has accounted for low reported incidences in Nigeria.^[1] Precocious puberty is divided into two main types A. Gonadotropin-dependent (Central, True, Complete). Here, the cause is traceable to hypothalamic or pituitary pathology B. Gonadotropin-independent precocious puberty (Peripheral and precocious pseudopuberty). Etiology of gonadotropin-dependent precocious puberty includes hypothalamic hamartoma or other hypothalamic lesions, central nervous system (CNS) lesions or inflammatory states, Langerhans cell histiocytosis, intracranial tumors, and infections (most especially tuberculosis affecting the CNS, trauma, and hydrocephalus). True (central) precocious puberty is linked to several lesions of the CNS that provoke the precocious activation of the hypothalamic-pituitary-gonadal axis (HPG-A) and leads to premature skeletal maturity.^[2] About 90% of cases of central precocious puberty (CPP) are idiopathic in girls and only 10% in boys.^[1,3,4] Gonadotropin-independent precocious puberty (Peripheral and precocious pseudopuberty) is mainly due to HCG-secreting tumors, congenital adrenal hyperplasia, tumors of the testis, adrenal or ovary that produce sex steroids, accidental or deliberate exogenous sex steroid administration, hypothyroidism, activating mutations of the LH receptor, and GSA subunit.^[5]

Pathophysiology

The cause of precocious puberty is not fully known. The role of MKRN 3 gene, located on human chromosome 15, has since been identified as a cause of premature sexual development or central precocious puberty. MKRN3 is said to act as a “brake” on the central hypothalamic-pituitary axis. Hence, mutations

of the protein allow for early activation of the GnRH pathway and cause phenotypic CPP. Patients with a MKRN3 mutation all display the classic signs of CPP.^[6,7] Mutations in genes such as LIN28 and LEP and LEPR enhance puberty onset. Mutations in kisspeptin, KISS1, and its receptor, KISS1R (GPR54) involved in GnRH secretion and puberty onset, are also thought to be the cause for CPP. These all lead to premature stimulation of GnRH pulse generator that provokes the precocious activation of the HPG-A.^[8] Because pituitary priming has occurred, GnRH elicits LH and FSH responses typical of those seen in puberty characterized by gonadotropin levels that are inappropriately elevated for age. This leads to premature skeletal maturity. Precocious puberty is associated with the advancement of manifestations of sexual secondary characteristics, increased bone age, which leads to early fusion of epiphyses, thus resulting in shortened clinical acumen, laboratory investigations and imaging techniques.

Diagnostic Workup

Clinical assessment

Thorough pubertal history, family history, past medical/surgical, and drug history are important. Physical examination may reveal matured breast, pubic hair, menstrual bleeding, "adult odor," and phallic enlargement in males. There may also be skeletal maturity.

Laboratory

Laboratory tests are done to assess concentrations of gonadotrophins (LH, FSH), sex hormones (estrogen and testosterone). Peak LH/FSH ratio >0.66-1.0 in females is diagnostic of true precocious puberty while basal LH concentration of >0.6 IU/L is diagnostic of precocious puberty in either sex. Response to exogenous GnRH is gold standard for diagnosis of true precocious puberty.

Thyroid function test is useful and may show hypothyroid condition. For patients who have only estrogen effects, the most useful screens for girls include ultrasensitive LH and follicle-stimulating hormone (FSH), and estradiol, and, for boys, LH, FSH, beta-human chorionic gonadotropin, and estradiol. For patients who have mainly androgen effects, the most useful initial tests include measurements of hormones such as total testosterone, dehydroepiandrosterone sulfate, 17-hydroxyprogesterone, and LH; all should be measured using high-sensitivity assays designed for young patients.

Radiological

Imaging is done for bone age determination with X-rays, MRI, and ultrasound scan of the pelvis for any gonadal changes. Plain

X-rays of the left hand and wrist are done to check for increased skeletal maturation as a result of the effect of sex hormone. Pelvic and adrenal ultrasonography may be useful if any of the steroid levels are elevated. MRI scan may be done to rule out intracranial tumors in younger patients or males with central precocious puberty.

Treatment

This involves giving GnRH agonist drugs (for GnRH-dependant precocious puberty); and androgen or estrogen antagonist therapy (for GnRH-independent precocious puberty). Tumor excision may be needed for some tumors. Leuprolide acetate 10 to 20 mcg/kg is given subcutaneously, and LH, FSH, testosterone (in boys), and estradiol (in girls) are measured at 0, 1, and 2 h. Twenty-four hours after leuprolide administration, estradiol and testosterone may be measured to improve sensitivity of the test.

Conclusion

Precocious puberty occurs as a major pediatric endocrine problem in many tropical regions including Nigeria, a high index of suspicion is needed to diagnose such patients.

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