Idiopathic central precocious puberty in a Nigerian boy

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Summary

A case of idiopathic central precocious puberty, a rare condition is reported in a $2^1/_2$ year-old Nigerian boy. He presented with progressive genital growth, a growth spurt, advanced skeletal maturation, and inappropriately high serum concentrations of pituitary and gonadal sex homones for his age. There was no family history of precocious puberty. Physical examination and investigations revealed no identifiable cause for his precocity.

Despite the overwhelming problems of malnutrition and infectious diseases in our environment, clinicians must have a high index of suspicion for endocrine disorders.

Keywords: ***Precocious puberty, Idiopathic, Central, Male, Abakaliki, Nigeria.***

Résumé

Le cas d'une puberté précoce idiopathique centrale, une affection rare est rapportée chez un garçon nigerian âgé de $2,^1/_2$ ans. Il était atteint d'un croissance génitale progressive, une croissance avec des efforts, développement skeletal avancé, et une concentration élevée et inappropriée de la glande pituitaire et gonade hormone du sexe pour son âge. Il n' y avait aucune histoire de la famille sur la puberté précoce. Examen physique et des enquête avaient indiqué aucune cause identifiable pour cette précocité.

En dépit de problème accablants de la sous alimentation et des maladies infectieuses dans notre région, des cliniciens devront avoir un indice élevé de la soupçon pour des troubles endocrines.

Introduction

Precocious puberty comprises a group of disorders that range from variants of normal development (e.g., premature adrenarche) to conditions in which prompt diagnosis and therapy may be lifesaving (e.g. a malignant germ-cell tumor). Normally, pubertal milestones are attained at ages that describe a normal distribution with a standard deviation of approximately one year.[1,2] The dividing line between normal and abnormal onset of puberty is usually drawn such that children entering puberty more than 2.5 to 3 standard deviations earlier than average are considered to have precocious puberty. As a result, most texts define precocious puberty as the onset of secondary sexual development before the age of eight years in girls and before nine years in boys.[3] The diagnosis of precocious puberty requires that a child meet all four of the following criteria.[4]

1. The first physical changes of puberty (usually breast growth in girls and genital growth in boys) should occur at a prepubertal age;
2. A growth spurt should be documented;
3. Skeletal maturity should be documented to be greater than chronological age – and
4. Serum testosterone levels in boys and estradiol in girls should be in the pubertal range (usually > 10ng/dL for testosterone and >5pg/mL for estradiol).

It may not however be possible to readily determine whether the luteinizing hormone (LH) and follicle-stimulating hornones (FSH) levels are above prepubertal range, because of the considerable overlap between the normal prepubertal and pubertal ranges. As a result, the gonadotropin releasing hormone (GnRH) stimulating test is often crucial for the assessment of potentially abnormal pubertal development.[4]

Precocious puberty can be classified according to whether it is true or central puberty (due to early but otherwise normal activation of hypothalamic-pituitary-gonadal function) or pseudo-puberty (due to production of gonadal steroids for other reasons) and whether it is isosexual or heterosexual.[5] Central precocious puberty can occur in association with a wide variety of central nervous system (CNS) lesions (neurogenic central precocious puberty), but most of the children have no identifiable cause (idiopathic central precocious puberty). A striking female predominance, approximately 10:1 in most series, has been noted for the idiopathic category.[6] Less common, GnRH-independent causes of precocious puberty include McCune-Albright syndrome, gonadal or adrenal sex steroid-secreting tumors, familial male gonadotropin-independent precocity, and primary hypothyroidism. The availability of agents that can arrest central precocious puberty and so enable children to avoid premature skeletal maturation and resultant short adult stature gives impetus to promptly diagnose and treat affected patients.

There is paucity of data on endocrine disorders in Africa. Precocious puberty occurs in 1 in 5,000 children in the USA.[4] The incidence of precocious puberty in Nigeria is unknown and the disorder is widely believed to be rare. To the best of our knowledge, this is the first case of idiopathic central precocious puberty to be reported in a Nigerian child. We therefore believe the present case report will be of interest to clinicians. This report describes a case of idiopathic central precocious puberty in a $2^1/_2$ year-old boy seen at the paediatric outpatient clinic of Ebonyi State University Teaching Hospital, Abakaliki, Nigeria.

Case report

NS, a male child was first seen in February 2001 at the age of $2^1/_2$ years, at the paediatric outpatient clinic of Ebonyi State University Teaching Hospital, (EBSUTH) Abakaliki. He presented with gradually progressive testicular and penile enlargement of one-year duration. Appearance of pubic and axillary hair, acne and hoarseness of voice followed six months later. His mother also noticed that the child was taller and more muscular than his age mates. He was the first of two

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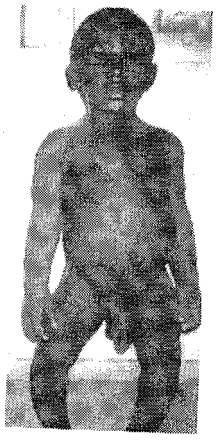
Table 1 Baseline serum hormonal concentrations in the patient

Baseline serum hormone	Finding	Comments
Testosterone (ng/dL)	20.0 (<10)*	Elevated
Luteinising hormone (mIU/mL)	2.0(0.0-1.6)	Elevated
Follicular stimulating hormone (mIU/mL)	5.0 (0.0-2.8)	Elevated
Thyroid stimulating hormone (mIU/mL)	3.5 (0.6-6.3)	Normal
Thyroxine (mcg/dL)	10.5 (7.3-15.0)	Normal
Cortisol (mcg/dL)	11.5 (5.7-16.6)	Normal
Prolactin(mcg/dL)	10.0(7-18)	Normal

**Reference values are in parenthesis.*

children from a non-consanguineous monogamous marriage. He was a product of singleton pregnancy and was delivered to a para 2 + 0 woman at EBSUTH, Abakaliki. Pregnancy was uneventful and his mother, who took routine haematinics and pyrimethamine during pregnancy, received antenatal care at EBSUTH. There was no history of the use of other drugs, herbal medications or exposure to irradiation during pregnancy. Labour was spontaneous, lasted about nine hours and the child was delivered by spontaneous vaginal delivery, vertex presentation. NS had an uneventful neonatal course, had no major childhood illnesses or seizure activity, and completed his immunization. He had been in relatively good health until the onset of the symptoms. The younger sibling, a male, was alive and developing well. His father was a "late bloomer" in terms of pubarche and growth spurt. There was no history of precocious puberty in the family.

Examination revealed a healthy looking child with large muscular upper body and deep hoarse voice. He had papular acne on face and trunk, as well as axillary and public hairs. He had no café-au-lait patches but had obvious genu varus. He had a normal neurological examination and his thyroid gland was not palpable. He weighed 25kg (> 95th percentile for age), his height was 106cm (>95th percentile for age) and body mass index 23.6kg/m^2 (>95th percentile for age) on a growth chart by National Center for Health Statistics.[7] He had Tanner Stage 3 pubic hair and genital development.[2] Penile length was 13cm (measured from the pubic ramus to the tip of glans while traction was applied along length of phallus to point of increased resistance; (normal for 2 - 3year old is 5.0 ± 0.8cm).[8] The long axis of each testis was 3.4cm which corresponds to a testicular volume of 10mL (normal for the prepubertal child is <4mL).[9] (Figures 1 and 2). The cardiovascular, lungs, abdomen and nervous system were normal. After consideration of the clinical presentation, an initial impression of precocious puberty was made.



Figs. 1 & 2 ***Photographs at 2.5 years of age showed accelerated growth, muscular development, penile and testicular development consistent with the degree of secondary sexual maturation.***

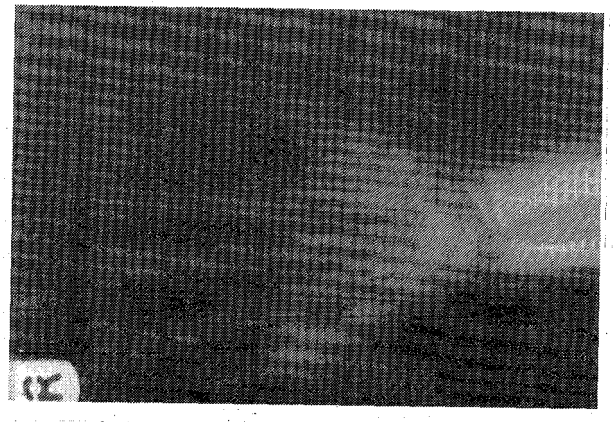


Fig. 3 ***Note ossification of all carpal bones (osseous maturation) except the pisiform that normally ossifies by the age of 11 years.***

Blood samples were drawn for hormonal assay, and the results are shown in Table 1. A full blood count result was normal, as were also the values for serum urea, creatinine, calcium, phosporous and liver function tests. The serum potassium and sodium were within normal limits (4.0mmol/L and 140mmol/L respectively).

Using Greulich and Pyle[10] the bone age of the patient was estimated to be 10 years (Figure 3) when assessed by radiography of the wrist. Note ossification of all carpal bones except the pisiform, which normally ossifies by the age of 11 years. The skull X-ray revealed a normal pituitary fossa, but there was complete ossification of the cranial sutures. These skeletal findings were consistent with an accelerated growth in the patient. The right and left femur had vara deformities and a chest radiograph showed normal heart and lungs. An abdominal and testicular ultrasound examination revealed no abnormalities of the liver, spleen, kidneys, adrenals and testicles. CAT scan of the hypothalamus and pituitary detected no abnormalities. Electrocardiogram done was with normal limits.

The hormonal assay revealed a normal serum cortisol, thyroxine (T4) and thyroid stimulating hormone (TSH) and prolactin levels, marked elevated levels of serum testosterone (T), follicular stimulating hormone (FSH) along with luteinising hormone (LH) levels in adult range. Human chorionic gonadotropin was not detected in the urine. These hormonal abnormalities (comprising high levels of serum T, FSH and LH), when taken together in a child with precocious puberty and no identifiable cause led to the diagnosis of idiopathic central precocious puberty. LH and FSH levels following gonadotropin releasing hormone (GnRH) stimulation were not obtained due to unavailability of GnRH. Facilities for determinations of dehydroepiandrosterone-sulphate, aldosterone and ACTH were also not available.

Six months after presentation, his height increased by 3cm to 109 cm (>95th percentile for age) and weight increased to 27.0kg (>95th percentile for age). The patient continued to grow at the rate of ≥3cm in 6 months. This was consistent with a growth spurt. Sixteen months on, the pubic hair and testicular sizes were of Tanner Stage 4. The patient has not been seen since June 2002 following counseling the parents that the child would benefit from monthly injection of GnRH analog for several years in order to suppress the pituitary hormones. It was estimated that this would cost between twenty-five and thirty thousand naira equivalent to (one hundred and sixty-seven and two hundred US dollars) per month. Parents had since resorted to spiritual form of treatment and all attempts at changing their minds had failed so far.

Discussion

Few cases of precocious puberty have been reported in Nigerian children, but none of these was found to be of idiopathic central precocious puberty. Adadevoh et al[11] in a report on endocrine disorders in African children in 1972 described a case of a 5-year old boy who presented with precocious puberty and was found to have an adrenal cortical carcinoma. Agboola-Abu et al[12] reported two cases of pseudo-precocious puberty due to congenital adrenal hyperplasia in boys aged 4 years 10 months and 3 years 10 months in 1999. Few countries in sub-Saharan Africa had reported sporadically cases of precocious puberty. Mwathe et al[13] in 1991 reported a case of pseudo-precocious puberty in a Kenyan girl due to juvenile granulosa cell tumor while Mouko et al[14] in 2000 reported a similar case in a 3-year old Congolese girl. Unavailability and limited laboratory facilities, as well as the huge burden of infectious and malnutrition disorders in many sub-Saharan African countries may contribute to the apparent low incidence and recognition of this condition.

The sequence and pace of pubertal development in our patient recapitulated normal gonadarche as seen in children with central precocious puberty.[4] He met all the four criteria for the diagnosis of precocious puberty. Genital growth, the first physical change of puberty was present at a prepubertal age.

A growth spurt was documented in this child who grew at the rate of 3cm in 6 months. A clinician's suspicion for possible precocious puberty should be aroused if a prepubertal child gains ≥ 6cm in height in 12 months, or ≥ 3cm in 6 months.[4] Any increase of ≥ 25 percentile points on the growth curve in one year also should be a cause for concern.[4] This child also had an advanced skeletal age of 10 years that was greater than 2 standard deviations above his chronological age. The pace of pubertal development is best assessed by its impact on the skeleton, because the rates of linear growth and skeletal maturation (advancement in bone age) reflect the integrated dose and duration of sex steroid action.[5,15,16] The increases in growth and bone age are more dramatic in children with central precocious puberty in whom serum sex steroid concentrations are higher.[5, 15, 16] These features were present in our patient who had rapid growth, far-advanced bone age and high testosterone levels.

The basal LH and FSH levels of this child were at pubertal range. Children with gonadotropin-dependent (central) precocious puberty can be distinguished from either normal prepubertal children or those with gonadotropin-independent (pseudo) precocious puberty on the basis of serum LH concentration, obtained both basally and after the administration of GnRH, when a sensitive assay is used.[17] In one study,[17] the mean basal serum LH concentration was 0.6mIU/mL (the sensitivity limit of the assay) in 100 normal prepubertal children, 1.6mIU/mL in 58 children with gonadotropin-dependent precocious puberty, and undetectable (<0.6mIU/mL) in 10 children with gonadotropin-independent precocious puberty. The peak serum LH responses to GnRH in the three groups were 3.1mIU/mL, 22mIU/mL and 1.5mIU/mL, respectively. There was a great degree of overlap in the values of serum FSH concentration in the three groups. The specificity and positive predictive value of high basal and GnRH-stimulated serum LH concentrations for the diagnosis of gonadotropin-dependent precocious puberty were 100 percent.[17] The basal serum LH level documented in our patient is in conformity with the basal serum LH level documented in the children with gonadotropin-dependent precocious puberty in this study. However, our inability to obtain GnRH-stimulated serum LH concentration due to unavailability of GnRH limits the interpretation of the LH in our patient.

Central precocious puberty results from the activation of normal hypothalamic GnRH neurons, except in the patients with hamartomas of the tuber cinereum, in whom the tumors are thought to be a source of pulsatile GnRH secretion.[18] While the great majority of patients with central precocious puberty are in the idiopathic category, its association with CNS lesions, especially in boys mandates that a cranial CT or MRI be performed even in absence of any neurological abnormality. NS had a normal cranial CT. MRI, which is superior to computed tomography, especially for the detection of small hypothalamic harmartoma[19] was not done in this patient due to lack of the facility. Since no apparent cause could be identified for this patient, we believe he has idiopathic central precocious puberty.

Some children presenting with early sexual development have a "slowly progressive" variant form of precocious puberty,[15 20] but NS appears to have a "rapid progressive" variant since he was very young at the onset of pubertal development, and grew very rapidly. The patients in this

category have epiphyseal fusion at an early age and attain the smallest adult height.[15, 20] They benefit the most from GnRH agonist therapy. When given, GnRH agonist-induced pituitary-gonadal suppression, with or without the administration of growth hormone when growth is slowed too much, is an effective therapy in children with central precocious puberty.[21,22] Their average height gain drops to 2 - 3 inches per year, which is normal for preadolescent children.[21, 22] Their bone development, the factor that ultimately limits potential height, slows to a rate consistent with their age.

Slowly, the mechanisms underlying precocious puberty are becoming clear. Advances in our understanding of factors that activate the hypothalamic GnRH pulse generator or that activate the gonads themselves should help to clarify the causes of unexplained cases and suggest new therapeutic strategies.[23] Negative feedback by means of gonadal steroids is one inhibitory mechanism, since agonadal infants have heightened gonadotropin secretion as compared with children who have intact gonads. On the other hand, gonadotropin secretion in agonadal children is suppressed during the juvenile pause, which suggests the presence of an intrinsic, hormone-independent inhibitory mechanism in the central nervous system. The subsequent waning of central nervous system suppression leads to the reactivation of the pulse generator for gonadotropin-releasing hormone, which in turn leads to gonadotropin secretion and onset of puberty. The mechanism or mechanisms for this disinhibition remain unknown.[23]

Genetic and environmental factors influence the timing of puberty. The initiation of puberty has been viewed as an energy-dependent process; changes in body fat as well as levels of physical activity can be associated with the onset or delay of puberty in humans. It has been proposed that the hormone leptin, a satiety factor produced in adipocytes, is required but does not initiate puberty.[23]

The tendency to start puberty prematurely can be passed directly from father to son or indirectly from the maternal grandfather through the mother (who does not start puberty early herself) to her son.[24] However, our patient had no known family history of precocious puberty.

Most recently, Seminara and colleagues[25] reported that a G protein-coupled receptor gene, GPR54, is required for pubertal maturation. Their study showed that mutations in GPR54 caused hypogonadotropic hypogonadism, may be corrected with the administration of exogenous gonadotropin-releasing hormone. It is likely but still unproven that GPR54 regulates the processing or secretion of gonadotropin-releasing hormone by the hypothalamus. The biology and role of GPR54 pathway in the regulation of the release or suppression of gonadotropin-releasing hormone has broad implications for the understanding of puberty and disorders of puberty. However, disordered function of the GPR54 gene has not yet been shown to play a role in any form of precocious puberty.

In conclusion, this report demonstrated the characteristic physical, radiological and biochemical features that may be seen in the patients with idiopathic central precocious puberty.

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