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Precocious Puberty in Children - A Review of Eight Cases

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SUMMARY

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Precocious puberty in eight children (one boy and seven girls) have been reviewed. All the patients had complete precocious isosexual puberty of idiopathic origin. They were diagnosed at 5 to $12^1/_2$ years of age range whilst the length of history on presentation varied from 2 to 7 years. Six of them were treated with cyproterone acetate while a girl who was first seen at the age of ten years with prolonged vaginal bleeding was treated with norethisterone and another patients was to follow up before treatment could be initiated. All of them were followed up with measurements of height, weight, bone age, and assessment of rate of sexual development. While on cyproterone acetate, there was no further increase in testicular sizes, bone age remained unchanged, while the height continued to increase. Both the patients and their parents adjusted well pschologically.

Introduction

TRUE sexual precocity is the pathologically accelerated puberty which, without therapy, leads to full maturity. Accelerated puberty, where the reproductive system only partially reaches maturity, is referred to as precocious pseudopuberty.

The diagnosis of precocious puberty is made when sexual maturation begins before the age of eight years in girls or 10 years in boys[1]. Precocious puberty is a problem of great medical and social concern. The onset of precocious puberty may indicate a serious underlying disease or endocrine disorder[2].

However, the study of patients with precocious puberty provides valuable information regarding the mechanisms of puberty. Furthermore, because of its relative rarity, the numerous causes and management approaches, precocious puberty may pose diagnostic and therapeutic difficulties to many clinicians. Socially, precocious puberty is a source of embarrassment and mental stress to the patients and their parents[3 4] while it may also expose the patients to sexual assault[5].

There is little information in the literature

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regarding precocious puberty in Nigeria; Consequently, not much is known of its prevalence in the country. The purpose of this paper therefore, is to report some of our patients with precocious Isosexual puberty that have been fully investigated, in order to highlight the common forms, differential diagnoses and treatment of these forms of precocious puberty.

Materials and Methods

During a three-year period (1983 - 1985), 13 children with complaints of abnormal sexual development were seen in the paediatric endocrine clinic of Lagos University Teaching Hospital. Eight of these (one boy and seven girls) were fully investigated. Their ages at presentation ranged from 5 to $12^1/_2$ years whilst the length of history at presentation varied from 2 to 7 years. The following investigations were carried out on the patients:

Blood samples

Blood samples for haematological and biochemical profiles, liver function tests and estimation follicle - stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), cortisol (T) in the male; dehydroepian drosterone sulfate (DHEAS), thyroid stimulating hormone (TSH), thyroxine (T_4), tri-iodothyronine (T_3), progesterone (P), estradiol (E_2) and human chorionic gonadotropin (HCG) were obtained from the patient between 8 a.m and 11 a.m. After collection, samples for hormonal analyses were allowed to clot at 4^o C for at least 30 minutes before centrifugation also at 4^oC. The sera separate were assayed immediately or stored frozen at -20^oC. Gonadotropins were measured at 30, 15 minutes before and at 0, 15, 45, 50, 90, and 120 minutes after gonadaotropin - releasing - hormone was administered to each patient.

Hormone assay

Serum levels of FSH, LH, PRL, F, T, DHEAS, TSH, T_4, T_3, P, E_2, and HCG were measured by double antibody radioimmunoassay technique on duplicate samples using reagents prepared and standardized by *Radioassay Laboratories, Carson, California,* USA.

Urine examination

Early morning urine specimens were collected from all the patients for microscopy, culture and sensitivity, and serological examination.

Roentgenographic examination

Radiographic examinations of the chest, abdomen, skull, hands and wrists of each patient were undertaken. Other radiological examination of the patients included gonadal ultrasonography.

Results

The summary of clinical and laboratory data of these patients are shown in Table I

Blood levels of electrolytes, haemoglobin, packed cell volume, white blood count and genotype in all, the patients were normal. Urinary studies, X-ray of the skull, chest, abdomen and pelvic ultrasonography also revealed no abnormality. The serum phosphorus and alkaline phosphatase levels in all the patients were well above the normal adult range but were normal for rapidly growing children.

Table One shows the serum levels of the hormones measured in each patient. The basal serum gonadotropin levels were in the pubertal range in all the patients.

There was also increased serum levels of gonadotropins following GnRH stimulation in each patient. In addition, there was pubertal level of serum testosterone in the boy and estradiol in the girls. Serum DHEAS level were at the upper level of the adult range. Serum PRL levels were normal in the patient except Miss S A in whom it was elevated. All other hormones studies were within the normal ranges for the ages of our patients and no abnormality was found in their liver function tests.

TABLE I

Summary of Clinical and Laboratory Data in Eight Children with Sexual Precocity at Presentation

No.	Patients	Age Yr	Sex	Duration of History Yr	Tanner Stage of Sexual Maturation 19	Bone Age Yr	Hormone Levels
1.	B B	6	M	2	III	12 - 121/2	Pubertal range
2.	D H	8	F	5	III	11	. .
3.	S A	10	F	4	V	15	. .
4.	B A	121/2	F	51/2	V	13	.
5.	O S	10.2	F	6	V	12	. .
6.	E A	11	F	4	V	12	. .
7.	L A	111/2	F	5	V	13	. .
8.	W I	12	F	7	V	18	. .

Three of these patients whose clinical features and management were representative of all the eight patients are reported below in detail. The relevant laboratory data in the three are contained in Table II.

Case Reports

Patient 1

B B, a six year-old presented with a history of large penis and scrotum with presence of pubic hair since the age of four years. He was the third of the four children of his patients. Pregnancy, birth and past medical histories were unremarkable.

There was neither history of exposure to steroids and gonadotripins nor that of precocious pubert in the family. Physical examination revealed an excessively developed boy for his age; with a height 140cm and arm span of 149cm. He had a crown to pubic symphysis length and heel to pubic symphysis length ($^{U}/_{L}$) ratio of 1.06. he also had adult size external genitali with a stretched penile length of 15 cm. His testes measured 5 x3 cm each and had Tanner[19] adolescent grade 111 scrotal size and pubic hair growth. X-ray of his left hand and wrist showed a bone age of 12 - $12^{1}/_{2}$ years. There was no axillary or facial hair. His thyroid gland was not enlarged and he was both clinically and biochemically euthyroid. There was no lymphadenopathy. His blood preassure was 95/65mm Hg (12.7/8.7K Pa and no abnormality was detected in his urine.

A diagnosis of precocious isosexual puberty was made and pretreatment laboratory evaluation of his pituitary, testicular, adrenal, and liver functions were undertaken. Other pretreatment investigations included, haematologic and

TABLE II

Initial Endocrine Tests in Three Children with Precocious Isosexual Puberty

Serum Hormone	Master B A	Miss D H	Miss S A
Follicle Stimulating Hormone	4 mIU/ml(2.5)*	6 mIU/ml (2.5)	3 mIU/ml (2.5)
Luteinising Hormone	7 mIU/ml(2.5)	7 mIU/ml (2.5)	10mIU/ml (2.5)
Prolactin	0.5ng/ml(0.1-0.3)	-	18ng/ml (0.10-0.34)
Progesterone	3.ng/ml (0.11-0.26)	-	2 ng/ml (0.10-0.34)
Oestradiol		70pg/ml (25)	100pg/ml (25)
Dehyro-Epiiandosterone sulphate (17 - Ketosteroids)	66 ng/ml(100-600)	-	1200ng/ml (100-600
Thyroid Stimulating Hormone	2u/ml(1.2-6-5)	6u/ml(0.3-6-5)	-
Triiodothyronine	-	1.8ng/dl (0.5-2.1_	-
Thyroxine	90mng/ml (50-138)	-	-
Cortisol	20ng/ml (60-210)	-	-
Chorionic Gonadotropin	-	0.5ng/ml	0.5ng/ml

*Values in parenthesis represent normal prepubertal values
** pg/ml = picogram per ml.
mlu = milli International Unit

biochemical profiles, urine and radiological examination of the skull, chest and abdomen.

He was treated with cyproterone acetate (Androcur), 100mg twice daily and followed-up with constant measurements of his height, weight, bone age and assessment of the rate of his sexual development. Six months later, his stretched penile length reduced to 12cm. His height increased by 4.0cm and his arm span also increased by3.3cm. His testicular sizes remained at 5 x 3 cm each. Bone age was 13 years. No further growth occurred in his scrotum and pubic hair. There was also no acne. He is presently in primary II and gets along very well with his peers. He and his parents responded very well to the psychological support as there were no more feelings of shame and distress that were present prior to treatment.

Patient 2

Miss D.H., eight years old, presented with complaints of gradual increase in the size of her left breast, presence of auxiliary and pubic hairs and excessive growth since the age of 3 years. There was no history of vaginal bleeding. She was the fourth child in a family of five children and there was no history of other cases of precocious puberty in the family. Pregnancy, birth, past medical and social histories were unremarkable. Her growth and development prior to the onset of complaints were normal. Her parents denied history of exposure to

steroids and gonadotropins ante-natally and post-natally. Pertinent findings on physical examination were excessive sexual and somatic growth for age. She had a height of 142cm, arm span of 150cm, weight of 32.4 kilograms, U\L ratio of 1.03 and Tarner's adolescent grade III, breast size and pubic hair growth with few axillary hairs. Her bone age was 11 years. Vaginal and rectal examinations revealed no abnormality.

Pretreatment diagnostic laboratory investigations consisted of haematological and biochemical profiles, liver functions tests, pituitatry, ovarian and adrenal functions evaluation, urine and roentgenographic examinations. She was later lost to follow-up before treatment could be initiated.

Patient 3

Miss S.A. was seen at the age of ten years with a history of breast development at the age of six years appearance of pubic hairs at seven years and vaginal blood spoting at seven and a half years. Menstrual bleeding became well established according to the mother at nine and a half years. There was no history of precocious puberty in her family.

Her mother had her own menarche between the ages of 13 and 14 years. Nothing noteworthy was present in the histories of her pregnancy, birth, social and drug habits, past medical illnesses, growth and development prior to the onset of her problems. There was also no history of exposure to steroids and gonadotropins. Physical examination revealed a well-nourished but pale girl with a female habits who was excessively developed for her age. She had a height of 144 cm, arm span of 156 cm and a weight of 40 kg. She had adult size breasts with milky discharge, adult female quality,quantity and distribution of pubic and axillary hair and vaginal bleeding. Her bone age was 15 years. Pretreatment diagnostic laboratory studies consisted of haematological and biochemical profiles, liver function tests, radiological evaluations of the skull, chest, and pelvis, basal serum gonadotropins, ovarian and adrenal steroid determinations, and GnRH stimulation test

Based on the negative findings of tests for brain, ovarian or adrenal neoplasms and other diseases known to cause sexual precocity, a diagnosis of idiopathic precocious isosexual puberty was made and she was treated with haematinics and primolut - N(Northisterone) 5mg, three times a day for 10 days because of her prolonged (18 days) vaginal bleeding. Her weight, height, bone age, skull X-ray, sizes and functions of the pituitary, adrenals and ovaries were assessed at three-monthly intervals to exclude slowly developing lesions of the brain, ovary and adrenal glands. In addition, both the patient and her parents were reassured.

Discussion

The mean age of onset of puberty in males is eleven and a half years while in girls, it is approximately 2.0to 2 and a half years earlier. The first sign of sexual development in boys is testicular enlargement, breast budding occurs in 85 percent of girls as the first signs of puberty while pubic hair growth is the first sign in 15 percent.

Skeletal maturation (bone age) parallels chronolgic age in normal subjects. The peak growth velocity is usually achieved in boys at 14 years and in girls at 12 years. Careful observation often reveal an acceleration in linear growth velocity preceding the first sign of puberty in girls.

Data from the history, clinical examination and laboratory studies in our patients are consistent with true and complete precocious isosexual puberty.

The appearance of testicular enlargement in a boy of six years and the development of features of puberty at the ages of three years and six years in our female patients are precocious. Skeletal maturation in each of our patients which was more advanced than their chronologic ages but correlated well with their stages of sexual

development supports this diagnosis. Furthermore, the occurence of pubertal levels of gonadotropins, gonadal sex steroids (testosterone and estradiol) and the increased amplitude of pituitary LH release evoked after GnRH administration confirm the premature activation of the hypothalamic - pituitary - gonadal axis in these patients.

In our patients, nearly all the events which characterise normal puberty were present. This contrasts with incomplete sexual precocity where only one of the events that mark puberty occur earlier than the expected age in a child. No aetiological factor of sexual precocity could be identified in any of our patients suggesting that the sexual preccocity in these patients may be of constitutional (idiopathic or cryptogenic) origin. In a previous reports[5] of precocious puberty, no cause of the sexual precocity was identified. Thus idiopathic precocious isosexual puberty appears to be a common form of abnormal sexual development in Nigerians as in other ethnic groups[6].

Epidemic precocious puberty has been known [7 8] to occur following ingestion of food or drugs contaminated by oestrogens. Similarly, uncommon but severe forms of precocious puberty may occur following the use of drugs for convulsion[9]. There may be iatrogenic forms of sexual precocity as a result of the increasing use of chemical substances to improve agricultural yield and the introduction of newer drugs for various medical problems in the country.

Treatment of precocious puberty essentially involves the removal of the cause where possible. In cases, as in our patients, where no cause can be identified, treatment is often symptomatic and directed toward the inhibition of further sexual and exceessive somatic development. Initially, intramusclar medroxyprogesterone acetate was used every two to 4 weeks[10].

The drug caused regression of breast development and bleeding but had no effect on structural bone age. Ultimately, these children had short stature [11]. Apart from these, it also had some adverse effects on the testes. Danazol[12] has similar effects. Cyproterone acetate, a progestational agent with anti- gonadotropins and anti-androgen activity has been advocated and used by a number of workers[13] who have reported regression of the physical signs of puberty and improved prognosis concerning adult height. It however, has corticoid - like activity and is noted for its adrenal suppression and insufficiency [14,15].

Recently, the use of a long-acting gonadotropin - releasing hormone analogue (Buserelin) has been tried by a number of workers[16] and found to be effective and safe for the treatment of various forms of precocious puberty in both sexes. This drug causes a decrease in the breast size, stops pubic hair growth and arrests vaginal bleeding. It is also reported[16] to be free from adrenal suppression.

Buserelin acts by inducing a paradoxical inhibitory effect after initial gonadotropin stimulation by continuous receptor occupancy which leads to desensitization of the gonadotrope and the suppression of the pituitary[17]. Kauli[14] has suggested a combination of cyproterone acetate and buserelin to counteract the initial stimulatory effect of the LHRH analogue alone.

More recently, the use of ketoconazole, an antifugal agent has also been aqdvocated [18] for the treatment of precocious isosextual puberty not responsive to LHRH analogue therapy.

Our patients were seen at ages when their sexual and somatic growths were far more advanced than those of their peers. They therefore, required treatment to avoid the various psychosocial and structural complications.

Our male patient responded well to cyproterone acetate which was the only drug available to us at the time he was seen. The dose had to be reduced following the development of bilateral gynaecomastia. Six out of the twelve female patients that could have benefited from drug treatment were seen at ages 10 - $12^{1}/_{2}$years when it was not more desirable to inhibit their sexual

growth. Patient 3 was therefore, treated for her prolonged vagina bleeding and pallor. In addition to the other forms of treatment, all our patient and their parents received psychotherapy to relieve them of their fears. Most are still being seen in outpatient every three months to assers the efficacy of the medical therapy and to include slowing developing lession of the brain, gonal or adrenal glands.

In conclusion, we make a plea for prompt referral of patients to centres where proper diagnostic work-up can be done and rational treatment instituted. This will ensure prompt and proper management of patients. Publication of studied cases is also suggested to facilitate the epidemiological study of precocious puberty in Nigeria.

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