Case Report

Two year old adults: Clinical Navigation through Precocious Puberty

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ABSTRACT

Precocious puberty is defined as the onset of puberty below the age of eight years in girls and nine years in boys. It is etiologically classified as central and peripheral depending on the source of hormone production. We present a couple of cases of two year old males who presented with increased penile length, pubic hair and height spurt along with testicular volume enlargement. Thus, a clinical diagnosis of isosexual central precocious puberty was made. Central precocious puberty was confirmed by pubertal levels of gonadotropins. MRI brain showed the presence of hypothalamic hamartoma. Both the children were started on Gonadotropin releasing hormone (GnRH) analogs. We use these cases to highlight the paramount importance of a thorough clinical examination including genital examination in all children and emphasize on physical measurement of testicular volume by accurately using an orchidometer as an important step to decide the further line of evaluation and management.

Key words: Precocious Puberty, Hypothalamic Hamartoma, Orchidometry, Epilepsy, Gelastic, Bone Age

Puberty is the developmental stage through which a child becomes a sexually mature young adult capable of reproduction. It comprises of sequential physical changes not only limited to development of secondary sexual characteristics, but also height spurt, osseous maturation, bone mineral accrual, mental as well as behavioural changes [1]. Precocious puberty is defined as children attaining puberty more than 2.5 standard deviation (SD) earlier than the median age, or practically, before the age of eight years in females and nine years in males [2]. It is estimated that precocious puberty occurs in 1:5000 to 1:10,000 children, prevalence being ten times higher in girls [3]. Its incidence has increased in recent times with a secular trend towards earlier onset of puberty, partly being attributed to environmental endocrine disruptors. Clinical diagnosis of precocious puberty in a child depends on four critical questions – Is the milestone of puberty early for this given child, is it isosexual or heterosexual, is it central or peripheral, is the tempo rapid or slow. Aims of management include treatment of the underlying cause, management of associated complications, puberty suppression and achievement of target height potential.

Clinical Description

A two year old male child (Case one) was brought to the OPD with complaints of increased aggressiveness since last one year and gelastic seizures in the form of brief episodes of laughter followed by staring look and tonic clonic movements lasting for 5-10 seconds, occurring almost daily since the last three months. There was no history of developmental delay, neurological deficits, preceding fever, head trauma or surgery. Antenatal and perinatal history was insignificant with no consanguinity in marriage or positive family history. He was immunised upto age with normal nutrition and development. On examination, his vitals were within normal limits with no pallor, icterus, cyanosis, clubbing or lymphadenopathy. His weight was 14.8 kg (at 97th centile), height was 90.2 cm (at 75th centile - above mid parental target height range). The child was found to have pigmented pubic hair at the base of penis. On further examination, his penile length was increased (6x1.5 cm) and testicular volume was 6 ml bilateral (Tanner Stage two). Neurological and rest of the systemic examination was normal. Bone age was 4.5 years which was greater than chronological age (2 years) and height age (2 years 3 months).

Case two, another two year old boy, presented to us with complaints of increased penile length and increased size of testes noticed for his age since the last six months and increase in pubic hair growth since the last two months (Figure 1). Parents also observed that the child is taller than his peers. There was no history of seizures, developmental delay, behavioural changes, neurological deficits, head trauma, surgery, exposure to androgens, hyperpigmentation, salt craving or repeated fractures. Antenatal and perinatal history was insignificant with birth weight of 3.2 kg and no

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consanguinity in marriage. There was no significant past or family history and parents pubertal age was reported to be normal. He was immunised upto age with normal nutrition and development. On examination, his vitals were within normal limits with no pallor, icterus, cyanosis, clubbing or lymphadenopathy. He weighed 19 kg (>97th centile) with a height of 94.5 cm (>97th centile; above mid parental target height range) with weight for height > 99th centile.

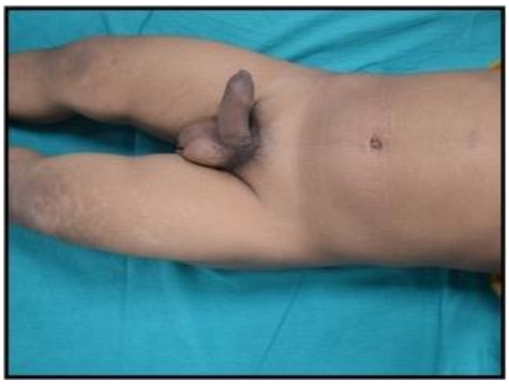

Figure 1: Mature male genitalia in a two year old child

On examination, multiple clusters of hypo pigmented patches were observed over the knees extending to the thighs and back. On genital examination, stretched penile length was 7x2 cm with coarse pubic hair extending to mons pubis and testicular volume measured by orchidometer was 12 ml bilateral (Tanner Stage three). He had no axillary hair and his voice was noted to be heavy. Rest of the systemic examination was normal. X ray left hand with wrist showed an increase in bone age (4.5 years) which was greater than the chronological age (2 years) and height age (2 years 9 months) (Figure 2).

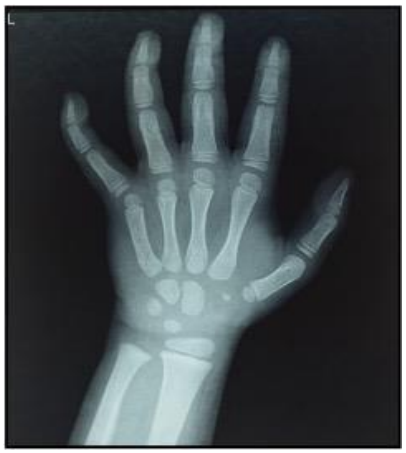

Figure 2: X-ray left hand showing bone age advancement (4.5 years) for a chronological age of 2 years

Investigations and Management

Routine work up which included a complete blood count, liver and renal function tests were normal (Table 1). Endocrinological evaluation for both the children showed a normal thyroid profile. 8 am gonadotropins showed pubertal levels of Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) (LH of 0.7 mIU/ml for case one and 1.34 mIU/ml for case two) with elevated testosterone (284 ng/dl for Case one and 510 ng/dl for Case two). As basal LH was >0.5 mIU/ml with basal testosterone >25 ng/dl, it was suggestive of an active Hypothalamic Pituitary Gonadal (HPG) axis, thus suggesting precocious puberty due to central cause [4] (Table 1).

The clinical picture of concomitant testicular enlargement along with penile enlargement and pubic hair was suggestive of maintenance of the normal sequence of pubertal characteristics thus suggesting central precocity. This was further supported by pubertal values of LH, clearly showing the activation of the hypothalamic-pituitary gonadal axis thus establishing the central etiology and hence, Gonadotropin Releasing Hormone (GnRH) stimulation test was considered unnecessary. As the next step of evaluation, Magnetic Resonance Imaging (MRI) Brain was done in both the children which showed a non enhancing pedunculated mass involving the tuber cinereum of the hypothalamus compatible with tuber cinereum hamartoma (Figure 3 a, b, c). Both the children were put on GnRH analogs to suppress the HPG axis. Currently, these children are on intramuscular Depot Leuprolide preparations every four weeks with no further progression of their pubertal characteristics. Case one has also been planned for Gamma knife radioablation in view of suboptimal seizure control.

Figure 3: MRI brain a) T1 image b) T2 image and c) Post contrast image showing pedunculated mass involving the tuber cinereum of the hypothalamus (arrow)

Table 1: Biochemical and radiological evaluation of index cases

S. No.	Investigations	Case One	Case Two
1.	Complete blood count [Hemoglobin (g/dl)/Total leucocyte count (x 10^3/uL) /Platelet count (x10^3/uL)]	10.8/6.5/250	12.2/6.7/262
2.	Liver Function Test [Total serum bilirubin (mg/dl)/AST/ALT (U/L)/Albumin/Globulin (gm/dl)]	0.32/17/27/4.2/2.2	0.36/22/9/4.5/3.1
3.	Renal Function Test (Urea/Serum Creatinine in mg/dl)	30/0.5	18/0.4
4.	Serum electrolytes (Na/K in mmol/L)	136/4.2	137/4.9
4.	Thyroid Profile (fT3 in pg/ml; fT4 in ng/dl; TSH in uIU/ml)	3.34/1.29/1.54	4.12/1.07/1.97
5.	Serum FSH (mIU/ml)	3.6	4.2
6.	Serum LH (mIU/ml) (>0.5 mIU/ml suggestive of pubertal onset)	0.7	1.34
7.	Serum Testosterone (ng/dl) (>25 ng/dl suggestive of pubertal onset)	284	510
8.	Bone Age (in years)	4.5 years	4.5 years

DISCUSSION

Precocious puberty is defined as the onset of puberty before the age of eight years in females and nine years in males. Precocity can be classified as iso or hetero sexual depending on whether the sexual changes are in consonance with the sex of the child. Classified on the basis of origin of hormone production, precocious puberty is of two types: Central precocious puberty (CPP) or gonadotropin dependent variety occurs due to HPG axis activation or peripheral or gonadotropin independent type which is mediated by peripheral glands such as gonads or adrenal glands [5].

Peripheral precocious puberty (PPP) can be iso or heterosexual while central is always isosexual. CPP is an extension of physiology, hence, the order of true pubertal progression is obeyed i.e. testicular enlargement will always precede penile enlargement and pubic hair development whereas PPP is a disruption of physiology, hence, we can see good penile enlargement and pubic hair development but prepubertal testes. The etiology, investigational approach, treatment and prognosis of these two types is entirely different. Hence, it is imperative to distinguish between these two forms clinically to avoid unnecessary investigations.

Biochemical evaluation in children with precocity includes testing for activation of the HPG axis to differentiate between central and peripheral causes. Pubertal levels of LH (>0.5 mIU/ml) and testosterone (>25 ng/dl) confirms activation of the HPG axis, as in both our patients, suggesting CPP while a low level of LH and raised testosterone suggest PPP[4]. Low LH values need to be confirmed by a GnRH stimulation test wherein a stimulated LH > 5 mIU/ml or LH/FSH ratio > 1 indicates HPG axis activation [6].

Bone age is a cardinal tool in the assessment of growth and pubertal disorders. In children with precocious puberty, as skeletal maturation is an integral part of pubertal development, the bone age is expected to be advanced, hence, it is more than chronological age and height age of the child. A unique scenario of precocious puberty with delayed bone age is seen in patients with hypothyroidism developing precocity. Apart from etiological diagnosis, bone age also helps to monitor progression of puberty (if bone age increment is more than chronological age increment in a specified time period), response to therapy and in prediction of final height [7].

MRI of brain should be done in girls with onset of puberty before 6 years of age, rapid progression and associated neurological features. All boys with CPP should undergo MRI brain as a structural CNS abnormality is found in up to 75% of boys with CPP. Children with prepubertal LH levels should undergo ultrasound of abdomen and pelvis to diagnose follicular cysts and ovarian and adrenal masses in girls. Similarly imaging for adrenals and 17 hydroxy progesterone levels should be done in boys with precocious puberty having prepubertal LH levels.

90% of girls and 25% of boys with CPP are of idiopathic type which is treated with GnRH analogues that are required only for the progressive forms [8]. On the other hand, peripheral precocious puberty is always pathological, evaluation includes a thorough search for gonadal or adrenal disorders including congenital adrenal hyperplasia (CAH) and tumors and always requires specific cause oriented treatment [9].

Case one presented to us with purely neurological complaints of aggressive behaviour and seizures. In a busy OPD, we may miss examining genitalia of the child. But a thorough clinical examination including full undressing and genitals examination made us reach the correct diagnosis. Case two presented with complaints of increased testicular and penile size, hence suggestive of early onset of puberty. In both the patients, a detailed history ruling out any androgen exposure, hyperpigmentation, salt craving or similar family history, followed by Sexual Maturity Rating (SMR) assessment showing increase in testicular volume suggested the maintenance of sequence of normal pubertal progression along with increase in bone age more than chronological age and height age, pointed towards central precocious puberty. This important step of picking up the orchidometer and accurately estimating the testicular volume in children with pubertal disorders is often ignored in a teeming OPD. But this is an imperative step which will save us from advising many unnecessary and costly investigations to the patient.

Hence, in our patients, a diagnosis of central precocious puberty was made clinically which was further supported by biochemical investigations and to search for a central etiology, MRI brain was done which showed hypothalamic hamartoma.

CONCLUSION

We use these cases to highlight the paramount importance of a focused history and thorough clinical examination including genital examination in all children and emphasize on physical measurement of testicular volume by accurately using an orchidometer to decide the further line of management in boys with features of precocious puberty. Accurate plotting of growth chart and bone age assessment are cardinal tools which streamline the diagnostic possibilities and help to plan further focused investigations.

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