Case-Based Literature Review

Central precocious puberty due to hypothalamic hamartoma in a six-month-old infant girl

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ABSTRACT

Precocious puberty defined as an onset of puberty below eight years in girls and nine years in boys, has an incidence of approximately 1 / 5,000 – 1 / 10,000 subjects with a female / male ratio of 20: 1. It is etiologically classified broadly as central and peripheral. We present to you a case of isosexual (central), precocious puberty in a 16-month-old girl, who was symptomatic since the age of six months, and was later, diagnosed to have hypothalamic hamartoma. It is one of the earliest case records ever in the medical literature of menarche, at an extremely early age (six-month-old child) secondary to a central cause.

Key words: Gonadotropins, hypothalamic hamartoma, precocious puberty

Introduction

Precocious puberty in infants is very rare.[1] Precocious puberty is defined as children attaining puberty more than 2.5 to 3 standard deviations (SD) earlier than the median age, or before the age of eight years in girls and nine years in boys;[2] prevalence being 10 times higher in girls. The most common mechanism for progressive precocious puberty is early activation of the pulsatile gonadotropin-releasing hormone (GnRH) secretion (central or gonadotropin-dependent precocious puberty), which results from hypothalamic tumours or lesions; but in most cases (approximately 90%) it remains unexplained.[3] The incidence of hypothalamic hamartomas (HHs) has increased since the introduction of MR imaging. The aetiology of this anomaly and the pathogenesis of its peculiar symptoms remain unclear, but recent electrophysiological, neuroimaging, and clinical studies have yielded important data that will be briefly reviewed in this article. No treatment is necessary in at least half of the cases of precocious puberty, as the gonadotropic axis is not activated and spontaneous regression of pubertal manifestations occur.[4] In cases with progressive precocious puberty, they may present with adverse psychosocial outcomes, early menarche, and short adult stature, because of early epiphyseal fusion.[5] We present a rare case of precocious puberty with clinical, laboratory, and radiological features supporting a central aetiology, presenting at an extremely early age (six months). We also use this case to illustrate an approach to a case of isosexual (central) precocious puberty in girls.

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Case Report

A sixteen-month-old girl was brought by her parents to the Paediatric Endocrinology Outpatient Department with a history of bleeding per vaginum since six months of age, with no previous history of genital trauma. She was the second child of the parents, with no positive history of consanguineous marriage. Initially she had irregular cycles, which evolved into monthly regular cycles of three to four days for the next eight months. The developmental (gross motor, fine motor, language, and social) milestones were achieved normally. Clinically her height and weight were at the eightieth percentile. Head circumference was 50 cm (ninety-fifth percentile). She had bilateral breast enlargement [Figure 1] and normal

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systemic examination. Fresh blood was seen on the genitals, with active vaginal bleeding, and there was edema and erythema of the vaginal introitus, with no local erosions. She had normal haematological and biochemical profiles, however, the hormonal analysis revealed pubertal response of gonadotropins with luteinizing hormone (LH) of 2.20 mI/ mL (N < 0.6 mIU / mL), follicle-stimulating hormone (FSH) of 5.58 mIU / mL (N < 0.6 mIU / mL), and estradiol (E2) of 10.2 pg / mL (N < 5 pg / mL), with normal thyroid functions. X-ray of the left wrist revealed bone age of 24 months [Figure 2]. Tumor markers such as carcinoembryonic antigen (CEA), CA 19.9, alpha-fetoprotein, and human chorionic gonadotropin (HCG) were negative. Uterine volume on pelvic ultrasonography was 2.2 ml, with no evidence of ovarian cyst / tumour. Magnetic resonance imaging (MRI) of the brain (plain [Figure 3a] and contrast [Figure 3b]) revealed a well-defined, sessile hypothalamic mass, isointense to the gray matter on T1-weighted, and hyperintense on T2-weighted sequences, suggestive of hypothalamic hamartoma measuring 1.44 × 1.38 cm. The patient is being managed as a case of isosexual (central) precocious puberty, secondary to hypothalamic hamartoma, with monthly GnRH analogs (Triptorelin). The patient is under regular monthly clinical follow-up for seizures and secondary sexual characters, annual hormonal assays, bone age assessment, and MRI brain, for changes in the hypothalamic hamartoma. The patient has shown good response on the two-year follow-up, with subsidence in size of the hypothalamic hamartoma, reversal of secondary sexual characters, and regression of monthly menstrual cycles.

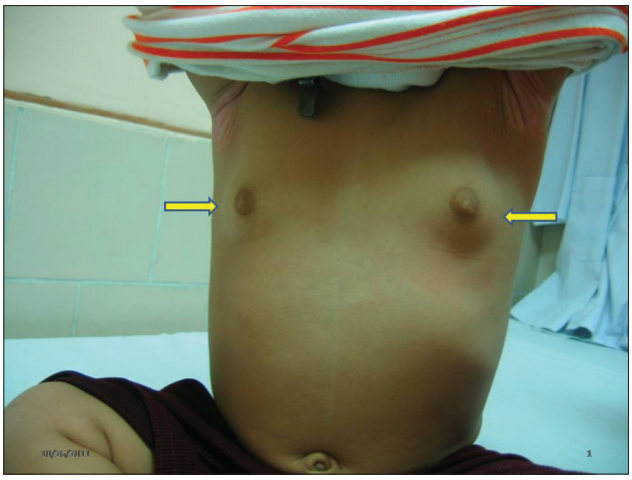

Figure 1: Bilateral breast enlargement (Thelarche - Stage B3)

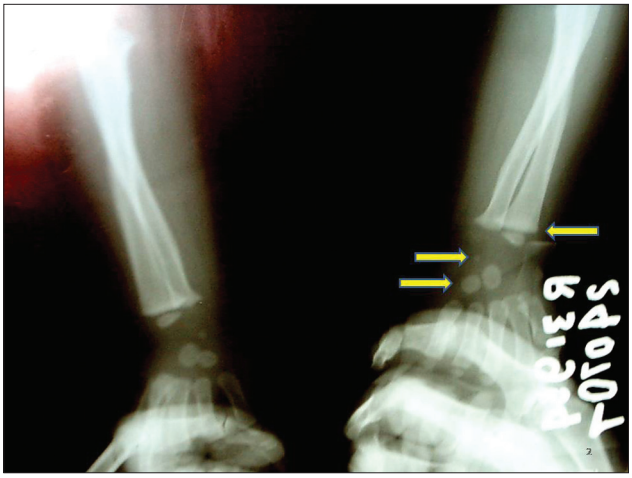

Figure 2: Plain radiograph wrist showing bone age of approximately 24 months

Discussion

Areas of uncertainty in evaluating cases of precocious puberty include, an appropriate age threshold for defining precocious puberty, approach to differentiate progressive from non-progressive forms, and causal mechanisms underlying idiopathic precocious puberty. To evaluate patients with suspected precocious puberty, internists should consider the following questions: Is pubertal development really occurring outside the normal temporal range? What is the etiology, and is there any risk of an intracranial lesion as the underlying mechanism? Is there any impairment in the child's normal physical and psychosocial development secondary to the aberrations in the progression of pubertal development?

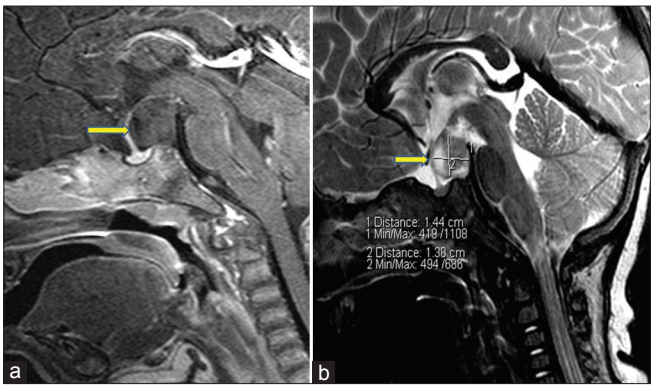

Figure 3: (a) Plain MRI Brain (T1W image) revealing sessile, well-defined hypothalamic mass is intense to gray matter (b) MRI brain, post contrast, revealing a hyper intense mass lesion suggestive of hypothalamic hamartoma, measuring 1.44 × 1.38 cm

Complete family history (age at onset of puberty in first-grade relatives), any signs and symptoms suggesting possible central nervous system (CNS) abnormality, such as, increase in head circumference, seizures (in particular gelastic), visual impairment or headache should be the first step in evaluating the case. Patients should be evaluated for high growth velocity, which may also precede the onset of pubertal manifestations and pubertal development,[6] classified as per Tanner staging. The extremely early age of onset (six

months) of menarche and thelarche (Tanners stage B3), with no positive family history in this patient, directed the diagnosis initially toward peripheral precocious puberty (peripheral tumor or McCune-Albright syndrome) or the existence of an intracranial injury. The examination should comprise consideration for signs such as hyper pigmented skin lesions, suggestive of the McCune–Albright syndrome or neurofibromatosis, which were absent in our case.

Additional tests are recommended in patients with either Tanner stage ≥ 3 or stage 2, with increased growth velocity or symptoms and signs suggestive of CNS dysfunction. On fulfilling the first of these above-mentioned criteria, we subjected this child to additional testing (assessment of the bone age, hormonal analysis, and imaging). In precocious puberty, the bone age is generally greater than the chronological age, which can be assessed using a reference atlas such as by Greulich and Pyle. Our child had a bone age eight months more than the chronological age. Early morning samples are preferred to determine the sex steroid levels. Serum E2 levels in girls have low sensitivity in the diagnosis of precocious puberty due to its high variability. Very high levels of E2 (≥ 100 pg / mL or 367 pmol / L) generally indicate an ovarian cyst or tumour. The gold standard for determining precocious puberty is the gonadotropin assay post stimulation by GnRH or a GnRH-agonist, prior to starting therapy. Peak LH levels of 5 – 8 mIU / L suggest progressive central precocious puberty, with 100% specificity for a cut-off figure of 6 mIU / L.[7] Unless levels of LH are clearly elevated, as in our case (more than four times the ninety-fifth percentile), it is important to be careful while checking the levels of gonadotropin in children less than two to three years (as the levels are generally higher in this age group). As the FSH levels have very little variation throughout pubertal development, its estimation is not very useful.

In girls, ovarian cysts / tumors and uterine changes (with 89% sensitivity and specificity for uterine volume ≤ 2.0 ml)[8] can be noticed on pelvic ultrasonography. This child had increased uterine volume, probably because of increased E2 (twice the normal), but was found to have no evidence of any ovarian pathology. To establish whether a hypothalamic lesion is present, an MRI of the brain should be performed in all cases of progressive central precocious puberty (CPP).[9] The prevalence of these hypothalamic lesions in CPP is lower in girls (8 to 33%) when compared to boys (40 to 90%). The prevalence is much lower (about 2%) if puberty starts after the age of six years. Our patient had a hypothalamic hamartoma measuring 1.44 cm × 1.38 cm, which is the most common causes of CPP at this age.

Hypothalamic hamartomas are non-neoplastic, heterotopic nodules, resembling the normal gray matter of the hypothalamus.[10] HHs occurs due to tissue displacement during the fifth or sixth week of gestation, when the ventral aspect of the neuraxis approaches the anterior tip of the end of the notochord. HH is associated with endocrinological, neurological symptoms, and symptoms due to the accompanying anomaly.[11] Endocrinological symptoms include precocious puberty, obesity, acromegaly, and hypopituitarism. Neurological symptoms include gelastic seizures, 'pressure to laugh', visual impairment, focal seizures with secondary generalization, developmental delay, cognitive impairment, and behavioural disturbance. HHs may sometimes be associated with symptoms of Pallister-Hall syndrome. HH has been classified variably by Arita *et al*.[12] into parahypothalamic / intrathalamic and by Bokyo *et al*.[13] into peduncular / sessile. Various reported modalities include resection surgery, disconnection surgery (disconnection from hypothalamus / corpus callosotomy), stereotactic radiation, radiofrequency thermocoagulation, and vagal nerve stimulation.

Internists evaluating a case of precocious puberty must take the decision on whether to provide treatment for girls, in particular, if onset of puberty is ≤ 8 years of age. The use of GnRH agonists continuously stimulates pituitary gonadotrophs, which further help in decreasing and desensitizing the release of LH, and to a lesser extent, FSH.[14] To determine the desired effect of the therapy, a suppressed response of LH to GnRH or its agonist is ascertained. The mean time to menarche is 16 months after termination of treatment.[15] Discontinuation of treatment at the age of 11 years aids in obtaining an optimal height and reappearance of pubertal manifestations.[16] The European Society for Paediatrics Endocrinology and its American counterpart, the Lawson Wilkins Paediatrics Endocrine Society, are now preparing the consensus statement in relation to the use of GnRH agonists in children. We managed our case with Inj Tryptorelin (GnRH agonist) monthly depot injections, with remittance of pubertal changes (clinical and hormonal). One should remember not to surgically remove a hypothalamic hamartoma to manage precocious puberty. Generally hypothalamic lesions, in association with precocious puberty, may lead to gonadotropin deficiency.

Conclusion

Thorough history taking and careful examination is required to determine the possible causes of precocious puberty, however, it is often vague. Additional evaluation should include hormonal assays and bone age assessment (E2, LH, and TSH). If a randomly measured level of LH is in the pubertal range, an MRI brain should be obtained.

A pelvic ultrasound scan is required to rule out an ovarian tumour or cyst, mainly if the E2 level is elevated. A GnRH or GnRH-agonist stimulation test is the gold standard for diagnosing CPP, and is recommended to assess the activation of the gonadotropic axis, for predicting the progression of puberty. In case of progressive CPP, treatment with a depot GnRH agonist is suggested and is generally continued for 11 years, even though the best duration of therapy is undecided.

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