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Case Report

Hypothalamic hamartoma presenting as central precocious puberty: a rare case report

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ABSTRACT

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. Hypothalamic hamartoma (HH) are rare, non progressive tumor like malformation. Precocious puberty due to HH occurs particularly at early ages, even 2 or 3 years. Treatment options for isolated CPP due to HH include GnRH analogs agonists continuously stimulates pituitary gonadotrophs, which further help in decreasing and desensitizing the release of LH, and to a lesser extent, FSH till the time puberty naturally set in. We present a case of precocious puberty due to hypothalamic hamartoma in 3 years old girl. Treated with GnRH analog lupirode and responded well to treatment with cessation of menstruation and reduction in breast size.

Keywords: Gonadotrophs, Hypothalamic hamartoma, Lupirode, Precocious

INTRODUCTION

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, prevalence being 10 times higher in girls.[1] With a larger number of children entering puberty at an earlier age, it becomes important to distinguish the early normal maturing patient from the one with pathologically precocious puberty.[2] The abnormalities of early pubertal maturation are further subdivided into GnRH-dependent / Central precocious puberty and GnRH-independent / Peripheral precocious puberty. The main concern in cases with progressive precocious puberty particularly before 6 years, are the adverse psychosocial outcomes, early menarche, and short adult stature, because of early epiphyseal fusion.[3] 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] Hypothalamic hamartoma (HH) are rare, non progressive tumor like malformation that 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 during fetal development, the growth of which in due course of time is proportional to the normal brain growth.

Precocious puberty due to HH occurs particularly at early ages, even 2 or 3 years. Treatment options for isolated CPP due to HH include GnRH analogs agonists continuously stimulates pituitary gonadotrophs, which further help in decreasing and desensitizing the release of LH, and to a lesser extent, FSH till the time puberty naturally set in.[5] Discontinuation of treatment at the age of 11 years aids in obtaining an optimal height and reappearance of pubertal manifestations.[6] The mean time to menarche is 16 months after termination of treatment.[7]

CASE REPORT

A 3 year old girl presented to pediatric outpatient department with complaints of enlargement of breast for past six months, which was progressive and symmetrical (Figure 1), followed by menarche, and growth of axillary and pubic hairs since 4 months.

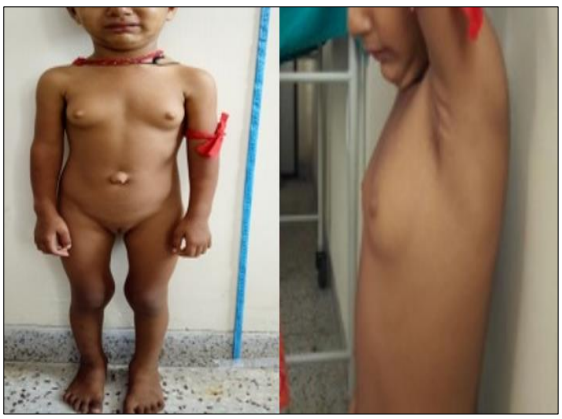

Figure 1: Symmetrical enlargement of breast.

There was no other significant history, anthropometry revealed accelerated growth with US:LS ratio 1.02. Except for SMR stage B4 P2 no other significant abnormality detected on examination. Patient investigated on the lines of precocious puberty, Renal Function Test, Liver Function Test, Thyroid Function Test, lipid profile, serum electrolytes, calcium, Ultrasound abdomen and KUB were unremarkable, complete haemogram was suggestive of moderate microcytic hypochromic anemia, x ray wrist was showing 7 carpel bones and lower end of radius corresponding to bone age of 6-8 years, X ray skull lateral view showed enlarged sella with AP dimensions 18mm and depth of 12mm (Figure 2).

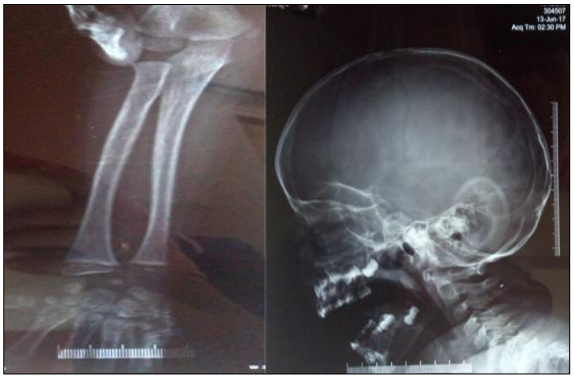

Figure 2: X ray wrist 7 carpel bones with radius corresponding to bone age of 6-8 years and X ray skull lateral view showed enlarged sella.

MRI brain done with a possibility of hypothalamic lesion which revealed hypothalamic hamartoma (Figure 3). Patient was started on GnRH analog lupirode and responded well to treatment with cessation of menstruation and reduction in breast size (Figure 4).

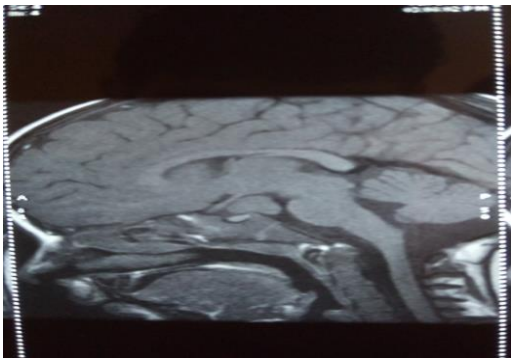

Figure 3: Attachment of the hypothalamic hamartoma lesion in an anterior location in the hypothalamus, in the region of the tuber cinereum or pituitary stalk.

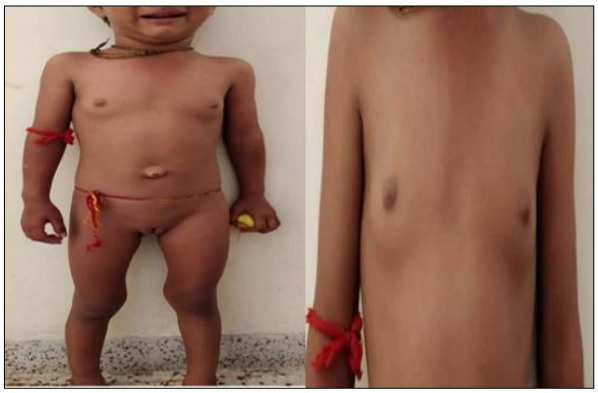

Figure 4: Post-treatment reduction in breast size.

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. 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.[8] Early age of onset of menarche and the larche (tanner stage B4), increased growth velocity, and advanced bone age pointed toward activation of the hypothalamic-pituitary-gonadal axis i.e central precocious puberty. 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, hence the patient was subjected to hormonal analysis and neuroimaging which revealed true precocious puberty with hypothalamic hamartoma, Early morning samples

are preferred to determine the sex steroid levels, 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.[9] Hypothalamic Hamartomas (HH) are a rare developmental benign heterotopic non-neoplastic lesion, located in the region of the hypothalamus, arising from the tuber cinereum and floor of the 3rd ventricle. The incidence is unknown, but depending on the series it has been estimated to be from 1 in 50,000 - 100,000.[10] HH are characterized by intractable seizures, Central Precocious Puberty (CPP), cognitive impairment, emotional and behavioral disturbances. Gelastic Seizures (GS) are the hallmark feature commonly present in early childhood, but patients may also develop other types of seizure.

Epilepsy associated with HH is characteristically refractory to treatment with antiepileptic drugs, being exceptional the achievement of good seizures control despite the administration of high doses of these drugs. The major endocrine abnormality is the CPP, which tends to occur considerably earlier than idiopathic CPP, which has been reported to respond to long-acting Gonadotropin- Releasing Hormone (GnRH) analogue therapy that down-regulate GnRH receptors.[11,12]

Cases were treated with GnRH agonist (leuporide acetate), 7.5 mg monthly intramuscular injection with resultant cessation of menstruation and reduction of breast size. Other modalities of treatment includes surgical approaches, like stereotactic thermoablation, transcallosal interforniceal resection, transventricular endoscopic resection, pterional resection and non invasive gamma knife radiosurgery.

Surgical intervention should not be performed until the degree of clinical severity calls for it like uncontrolled seizures. In case of progressive CPP, treatment with a depot GnRH agonist is suggested and is generally continued for 11 years, withdrawal of which is followed by appearance of normal sequence of pubertal manifestations.

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 confirmation by hormonal assays and bone age assessment (E2, LH, and FSH). 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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