Case Report

Case report: A rare case of central precocious puberty due to hypothalamic hamartoma

Jayashree Satish Rao[1], M Sushmitha[1], M R Savitha[2], Thrupthi Surendra[3]

From [1]Junior Resident, [2]Professor and Head, Department of Paediatrics, Mysore Medical College and Research Institute, [3]Consultant Paediatric Endocrinologist, Department of Paediatrics, Kangaroo Mother Care, Mysuru, Karnataka, India

ABSTRACT

Precocious puberty defined by the onset of secondary sexual characteristics before 8 years in girls and 9 years in boys. It is more common in females than males and is usually sporadic. Depending on the primary source of hormonal production, precocious puberty is classified as central and peripheral. Precocious puberty in infants is very rare. While investigating a case of precocious puberty, it is essential to progress systematically, with an identification of isolated or complete precocious puberty followed by bone age estimation, relevant hormonal assays, including GnRH stimulation, as well as neuroimaging when indicated. We present a case of isosexual (central) precocious puberty in a 1 year, 3-month-old girl, who was symptomatic for 1 year of age and was diagnosed to have hypothalamic hamartoma after methodical evaluation and responded to treatment with GnRH agonists.

Key words: GnRH agonist, Hypothalamic hamartoma, Precocious puberty

Precocious puberty defined by the onset of secondary sexual characteristics before 8 years of age in girls and 9 years in boys. Several genetic, environmental, and nutritional factors play an important role in the onset and progression of puberty [1]. Precocious puberty is classified into central precocious puberty (CPP) (GnRH dependent) and peripheral precocious puberty (GnRH independent). CPP is due to the earlier maturation and activation of the HPG axis [2]. It is 5–10-fold more common in females than in males and is usually sporadic. Its differential diagnosis varies from benign variants to serious conditions such as malignancy [2].

Hypothalamic hamartoma (HH) is the most common brain lesion causing CPP. The ectopic neural cells in the lesion serve as an accessory GnRH pulse generator [3]. HH is a rare, congenital, and benign lesion of the tuber cinereum, presenting with CPP, gelastic seizure, and developmental delay [4].

The decision to treat CPP depends on the age of the child and the progression of puberty. If the child has rapidly progressing symptoms or if bone age is more than the chronological age, treatment is to be considered. The main goals of treatment are to preserve the adult height and to reduce the associated psychosocial stress. GnRH agonists are the standard of care [5].

Access this article online	
Received- 06 July 2022 Initial Review- 11 August 2022 Accepted- 15 August 2022	Quick Response code
DOI: 10.32677/ijch.v9i8.3556	

CASE REPORT

A 1 year, 3-month-old girl first born to a non-consanguineously married couple was brought to the pediatric outpatient department with the complaints of bleeding per vagina for 4 days, 5–6 episodes per day. Similar history was noted 1 month ago. There was no history of genital trauma, infection, headache, visual problems, seizures, behavioral changes, or neurological deficits. She was developmentally appropriate for age. Physical examination showed weight and length between 3rd and 15th percentile and head circumference at 15th percentile as per World Health Organization growth charts. Pallor was present. Breast enlargement corresponding to Tanner Stage 3 (Fig. 1) and pubic hair growth of Tanner Stage 2 noted without any axillary hair growth. On per vaginal examination, pale vagina was seen.

Blood investigations revealed microcytic hypochromic anemia. Thyroid profile was normal. Other hormonal analysis revealed elevated basal Sr. FSH 4.57 mIU/ml (normal <0.6 mIU/ml). Post-GnRH stimulation showed high LH 73.7 mIU/ml and high estradiol of 137.6 pg/ml suggesting CPP. Bone age advancement over chronological age by 1.5 years was recorded as per Greulich and Pyle atlas [6]. Pelvic ultrasound revealed a bulky uterus with a simple ovarian cyst measuring 3.4 × 2.7 cm in the left adnexa (Figs. 2 and 3). Suspecting a central cause of CPP, MRI brain was done which showed a small well-defined lesion in

Correspondence to: Dr. Jayashree Satish Rao, Department of Paediatrics, Mysore Medical College and Research Institute, #38, Kannike, 1st Main, TK Layout, Mysuru - 570 009, Karnataka, India. E-mail: drjayrao95@gmail.com

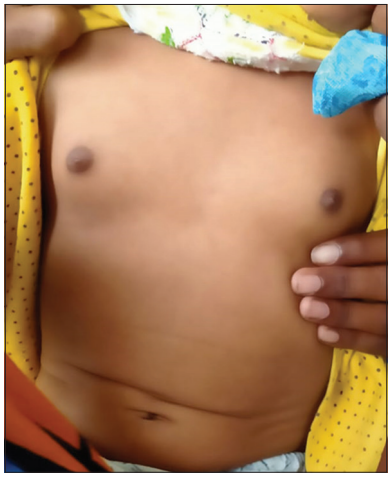

Figure 1: Development of breast Tanner Stage 3

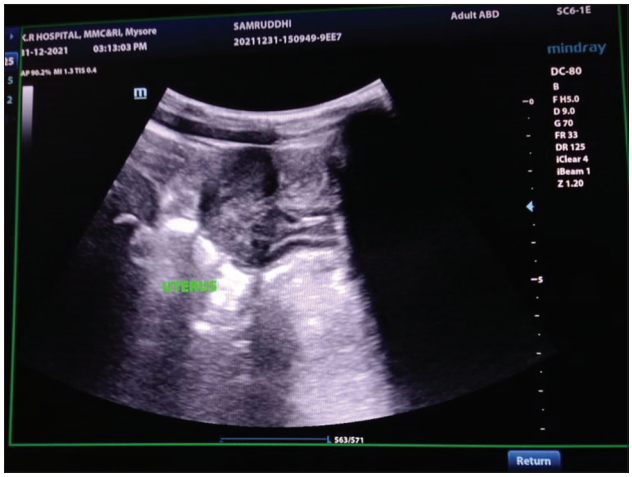

Figure 3: Ultrasonographic image of uterus in patient

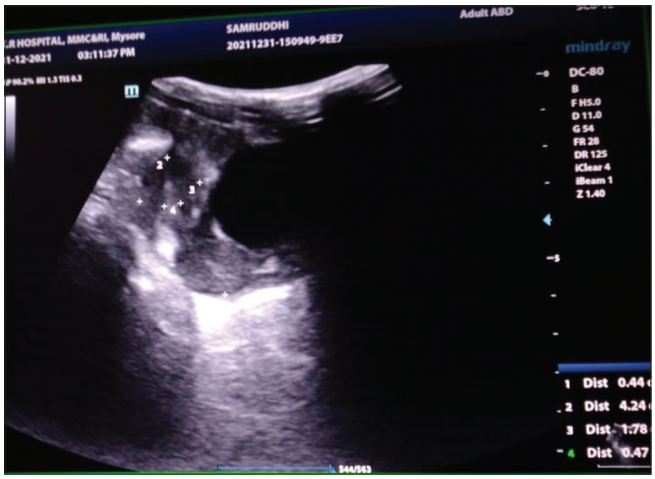

Figure 2: Ultrasonographic image of ovarian cyst

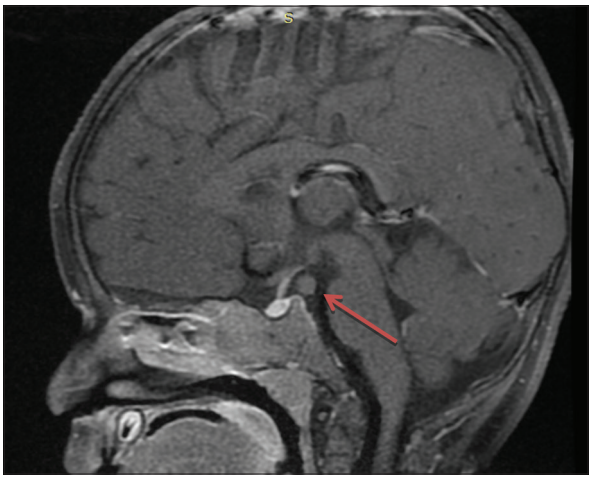

Figure 4: T2-weighted image, post-contrast, and sagittal section showing hypothalamic hamartoma

the hypothalamus, measuring 5 × 5 mm, suggestive of a tuber cinereum hamartoma (Fig. 4 and 5).

The child was started on monthly intramuscular injections of leuprolide acetate 3.75 mg, and on follow-up, Sr. LH (1.01 mIU/mL) (2 h after Inj. leuprolide acetate) after 3 months showed good control (<2 mIU/mL) [7]. Vaginal bleed stopped after 2 months of initiation of treatment. The child is being supplemented with iron 3 mg/kg/day, calcium 600 mg/day, and 600 IU/day Vitamin D. She is on regular monthly follow-up.

DISCUSSION

Precocious puberty is an entity that once had areas of uncertainty regarding the evaluation, treatment modalities, and prognosis. However, with the advent of newer imaging modalities and hormonal assays and availability of GnRH agonists, the treatment of precocious puberty has become more streamlined. The causes of precocious puberty could be central or peripheral and evaluation includes hormonal assays and imaging to investigate the nature of lesion.

HH is a rare, congenital, and benign lesion of the tuber cinereum. It is mainly composed of normal brain tissue, such as neurons, glial cells, and fiber bundles [8]. This congenital

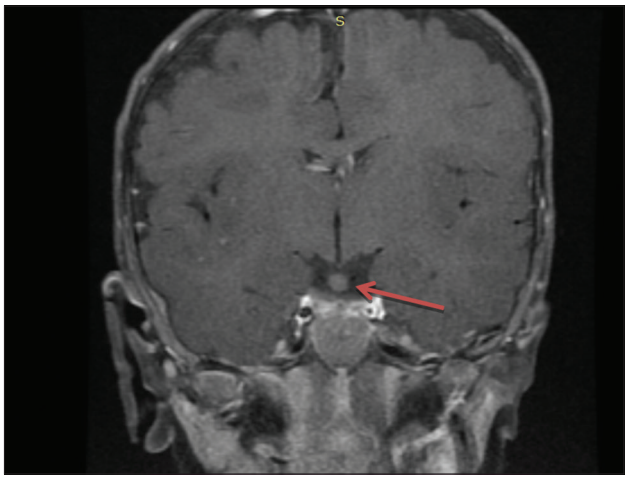

Figure 5: T1-weighted image post-contrast, coronal section showing hypothalamic hamartoma

malformation consists of ectopically located neural tissue, within which glial cells can produce transforming growth factor-alpha, which has the potential to activate the GnRH pulse generator. HHs remain static in size or grow slowly and can be associated with gelastic or psychomotor seizures and developmental delay.

However, more commonly they produce no signs other than precocious puberty.

In our case report, the history was suggestive of precocious puberty and the sexual maturity rating SMR staging confirmed the isosexual discordant nature. In our case, after ruling out hypothyroidism, we opted for hormonal assays including GnRH stimulation test, which were of pubertal range, suggesting a gonadotropin-dependent cause. MRI brain confirmed the presence of a HH.

To establish whether a hypothalamic lesion is present, an MRI of the brain should be performed in all cases of progressive CPP [9]. The prevalence of these hypothalamic lesions in CPP is lower in girls (8–33%) when compared to boys (40–90%). A pelvic ultrasound scan is essential to rule out ovarian tumors or cysts, mainly if the E2 level is elevated.

True precocious puberty involves the activation of the hypothalamic-pituitary-gonadal axis. 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 [10].

Administration of gonadotropin-releasing hormone (GnRH stimulation test, intravenously) or a GnRH agonist (leuprolide stimulation test, subcutaneously) is a helpful diagnostic tool. In females with sexual precocity, however, the nocturnal LH secretion and the LH response to GnRH or GnRH agonist may be quite low at breast Stages II to early III (LH peak, <5 IU/L), and the LH to FSH ratio may be low until mid-advanced puberty. In females with low LH response, the central nature of sexual precocity can be proven by detecting pubertal levels of estradiol (>50 pg/mL) 20–24 h after stimulation with leuprolide.

Standard treatment of CPP involves the suppression of this axis with GnRH agonists [11]. When precocious puberty is not idiopathic, treatment is based first on treating the underlying problem and then may also involve treatment with GnRH agonists [12].

The observation that the pituitary gonadotropic cells require pulsatile, rather than continuous, stimulation by GnRH to maintain the ongoing release of gonadotropins provides the rationale for using GnRH agonists for the treatment of CPP. Long-acting formulations of GnRH agonists, which maintain fairly constant serum concentration of the drug for weeks or months, constitute the preparations of choice for the treatment of CPP. Treatment results in decrease of the growth rate, generally to age appropriate values, and an even greater decrease of the rate of osseous maturation. In females, breast size may regress in those with Tanner Stages II–III development but tends to remain unchanged in females with late Stages III–V development or may even increase slightly because of progressive adipose tissue deposition. Pubic hair usually remains stable in females or may progress slowly during treatment, reflecting the gradual increase in adrenal androgens. Menses, if present, cease. Pelvic sonography demonstrates a decrease of the ovarian and uterine size.

If treatment is effective, the serum sex hormone concentrations decrease to prepubertal levels (testosterone, <10–20 ng/dL in males; estradiol, <5–10 pg/mL in females). The serum LH and FSH concentrations, as measured by sensitive immunometric assays, decrease to less than 1 IU/L in most patients, although rarely does the LH return to truly prepubertal levels (<0.1 IU/L).

Any girl with precocious physical signs of puberty, significantly advanced BA, decreased predicted height, and a pubertal response to gonadotropin testing should be treated with GnRH agonists to suppress pubertal progression and improve adult height. 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 [3].

As treatment guidelines are now being elucidated for the management of precocious puberty, there has been generally a good outcome for patients with HH treated with GnRH agonists.

CONCLUSION

A systematic algorithmic approach to precocious puberty is required, including bone age estimation, pelvic ultrasound, hormonal assays, and neuroimaging when indicated. Administration of gonadotropin-releasing hormone (GnRH stimulation test, intravenously) or a GnRH agonist (leuprolide stimulation test, subcutaneously) is a helpful diagnostic tool. Long-acting formulations of GnRH agonists, which maintain fairly constant serum concentration of the drug for weeks or months, constitute the preparations of choice for the treatment of CPP. Treatment results in decrease of the growth rate, generally to age appropriate values and cessation of menses. It is essential to monitor these patients closely till adolescence, provide dietary supplementation and relevant counseling to parents and the child to ensure adequate growth and development.

REFERENCES

1. Kiess W, Hoppmann J, Gesing J, Penke M, Körner A, Kratzsch J, *et al*. Puberty - genes, environment and clinical issues. J Pediatr Endocrinol Metab 2016;29:1229-31.
2. Kota AS, Ejaz S. Precocious Puberty. Treasure Island, FL: StatPearls Publishing; 2022.
3. Kotwal N, Yanamandra U, Menon AS, Nair V. Central precocious puberty due to hypothalamic hamartoma in a six-month-old infant girl. Indian J Endocrinol Metab 2012;16:627-30.
4. Suh J, Choi Y, Oh JS, Song K, Choi HS, Kwon A, *et al*. Management of central precocious puberty in children with hypothalamic hamartoma. Children 2021;8:711.
5. Aguirre RS, Eugster EA. Central precocious puberty: From genetics to treatment. Best Pract Res Clin Endocrinol Metab 2018;32:343-54.
6. King DG, Steventon DM, O'Sullivan MP, Cook AM, Hornsby VP, Jefferson IG, *et al*. Reproducibility of bone ages when performed by radiology registrars: An audit of Tanner and Whitehouse II versus Greulich and Pyle methods. Br J Radiol 1994;67:848-51.
7. Brito VN, Latronico AC, Arnhold IJ, Mendonca BB. A single luteinizing hormone determination 2 hours after depot leuprolide is useful for therapy monitoring of gonadotropin-dependent precocious puberty in girls. J Clin Endocrinol Metab 2004;89:4338-42.
8. Coons SW, Rekate HL, Prenger EC, Wang N, Drees C, Ng YT, *et al*. The histopathology of hypothalamic hamartomas: Study of 57 cases. J Neuropathol Exp Neurol 2007;66:131-41.
9. Klein KO. Precocious puberty: Who has it? Who should be treated? J Clin Endocrinol Metab 1999;84:411-4.
10. Kim HK, Kee SJ, Seo JY, Yang EM, Chae HJ, Kim CJ. Gonadotropin-releasing hormone stimulation test for precocious puberty. Korean J Lab Med 2011;31:244-9.

11. Comite F, Cassorla F, Barnes KM, Hench KD, Dwyer A, Skerda MC, *et al*. Luteinizing hormone releasing hormone analogue therapy for central precocious puberty: Long-term effect on somatic growth, bone maturation, and predicted height. JAMA 1986;255:2613-6.
12. Stanhope R. Gonadotrophin dependent precocious puberty and occult intra-cranial tumors: Which girls should have neuro-imaging? J Pediatr 2003;143:426-7.

Funding: None; Conflicts of Interest: None Stated.

How to cite this article: Rao JS, Sushmitha M, Savitha MR, Surendra T. Case report: A rare case of central precocious puberty due to hypothalamic hamartoma. Indian J Child Health. 2022;9(8):154-157.