DOI: 10.7860/JCDR/2026/84830.23372

Case Series

Internal Medicine Section

Hypothalamic Hamartoma Presenting with Gelastic Seizure and Precocious Puberty: Successful Management with GnRH Agonists

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ABSTRACT

Precocious Puberty (PP) is defined as an onset of puberty occurring more than 2.5 standard deviations earlier than the population mean age. Central Precocious Puberty (CPP) results from early activation of the hypothalamic-pituitary-gonadal axis. CPP in boys and very young girls is usually due to an organic lesion. Hypothalamic Hamartoma (HH) is the most common organic cause of CPP. HH are rare developmental, non-progressive, non-neoplastic, heterotopic lesions located at the base of the hypothalamus, arising from the tuber cinereum and the floor of the third ventricle, with an estimated prevalence of 1 in 100,000-200,000. HH presents with PP, gelastic seizures, and/or behavioural abnormalities. PP due to HH occurs particularly at age of 2-3 years. CPP can be treated with Gonadotropin Releasing Hormone (GnRH) agonist. Treatment options for seizures include antiepileptic drugs and surgical interventions. We hereby describe a series of four cases of HH from India. All patients presented with CPP and gelastic seizures before the age of three years and Magnetic Resonance Imaging (MRI) revealed HH. Following treatment with GnRH agonist, their pubertal changes regressed and the frequency of gelastic seizures decreased without any antiepileptic drugs and no significant changes in the size of HH. Therefore, GnRH agonist can be effectively used in patients with HH presenting as CPP and gelastic seizure with the regression of pubertal changes and a decrease in the frequency of seizures and surgical interventions are rarely required in case of refractory seizures and compressive symptoms.

Keywords: Hypothalamus, Leuprolide, Seizures

INTRODUCTION

The PP is defined as breast budding before the age of 8 years in girls and enlargement of testes before nine years in boys [1]. The majority of cases of CPP are idiopathic. Organic causes of CPP are HH, developmental malformation of brain, intracranial infections, hydrocephalus, ischemia, irradiation, and head injury [2]. HH is a rare developmental malformation of the hypothalamus and characterised by CPP, various type of seizures, and developmental delay. HH accounts for most organic causes of CPP, with approximately 75% of cases that occur before the age of three attributed to this condition. Seizures commonly begin early in life, often manifesting as gelastic seizures characterised by frequent episodes of inappropriate laughter, and may later develop into other types of refractory seizures [1,3].

The relationship between HH and CPP is not yet fully understood. HH contains ectopic Luteinising Hormone-Releasing Hormone (LHRH) secretory neurons that function, unaccompanied or in coevality with LHRH secretory neurons in arcuate nucleus of hypothalamus. This leads to intermittent pulse of LHRH secretion [1,4]. Differential diagnoses of HH may include optic gliomas, hypothalamic gliomas, craniopharyngioma, and gangliogliomas. All these tumours show post-contrast enhancement, and craniopharyngiomas and optic gliomas show calcification. The close differential is hypothalamic gliomas, which are usually inhomogeneous and often show enhancement [4]. The recommended treatment for isolated CPP due to HH is a long-acting GnRH agonist until natural puberty occurs. Drug-resistant seizures are typically managed through microsurgical resection of the tumour, endoscopic disconnection, or radiosurgery [5].

Case 1

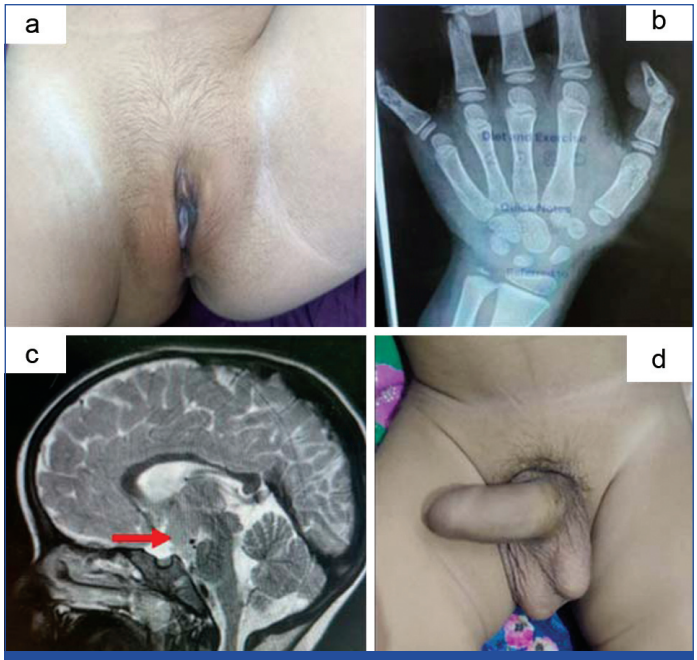
A two-year-old girl presented with premature breast development for the past 18 months and cyclic vaginal bleeding for the last six months. Her parents reported repeated episodes of inappropriate laughter lasting 15-20 seconds, occurring 5-10 times per day. She was a product of non-consanguineous marriage. There was no family history of PP. At presentation, her height was 90.0 cm, and weight was 12.5 kg. Her breast was Tanner stage III and pubic hair Tanner stage II [Table/Fig-1a]. Her Bone Age (BA) was four years [Table/Fig-1b]. Biochemical investigations showed an elevated basal Luteinising Hormone (LH) and estradiol. Ultrasonography revealed a pubertal size uterus and ovaries. MRI of the brain showed a well-defined ~1-1.5 cm T1/T2-isointense, non-enhancing hypothalamic mass consistent with HH [Table/Fig-1c].

Case 2

An 18-month-old boy presented with appearance of pubic hair and increased penile length for last 10 months. His parents also reported uncontrollable bouts of laughter lasting 20-30 seconds, occurring 10-12 times a day. He was a product of non-consanguineous marriage with normal birth weight. His height was 89.0 cm, weight was 12.2 kg, and BA was 3.0 years. Testicular volume was 3 mL bilaterally, pubic hairs Tanner stage II, and Stretched Penile Length (SPL) measured 8 cm [Table/Fig-1d]. Laboratory tests showed an elevated serum testosterone and LH. MRI of the sella revealed oval-round hypothalamic lesion, consistent with HH [Table/Fig-2a].

Case 3

A two-year-and-three-month-old boy presented with the development of pubic hair, penile enlargement, accelerated linear growth, and episodes of uncontrollable laughter lasting 20-30 seconds over the past one year. On examination, his height was 94.0 cm, weight was 14.0 kg, and BA 5.0 years. Testicular volume was

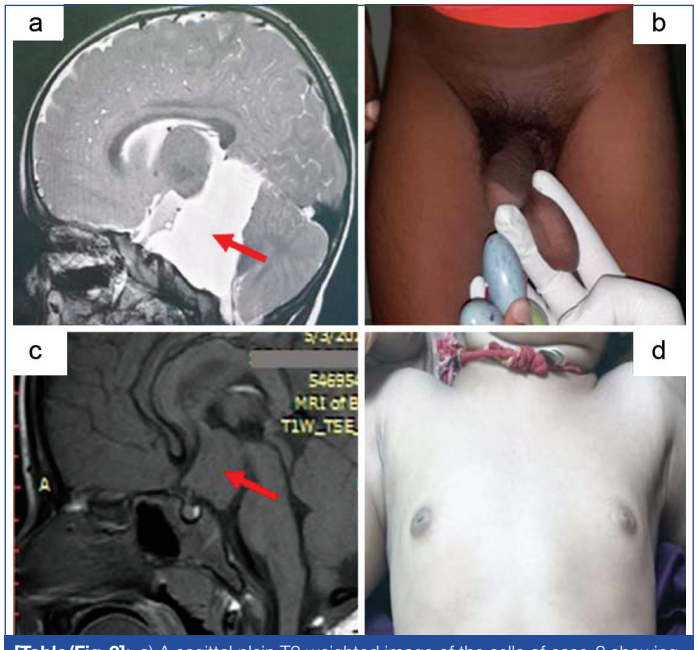


[Table/Fig-1]: a) Pubic hair Tanner stage II of case 1; b) X-ray left hand of case-1 showing Bone Age (BA) of 4 years; c) A sagittal plain T2 weighted image of the sella of case-1 showing well-defined isointense lesion in the hypothalamic region, suggestive of Hypothalamic Hamartoma (HH); d) Pubic hairs Tanner stage II and Stretched Penile Length (SPL) measuring 8 cm of case 2.

8 mL bilaterally with pubic hair Tanner stage III and SPL measuring 7 cm [Table/Fig-2b]. Laboratory tests indicated an elevated serum testosterone and LH. MRI of the sella revealed a well-defined T1 isointense, and T2 and FLAIR hyperintense mass without contrast enhancement, suggestive of a tuber cinereum hamartoma [Table/Fig-2c].

Case 4

A two-year-and-two-month-old girl presented with premature breast development for last 12 months and vaginal bleeding for two months. On further inquiry, her parents reported a history of uncontrollable spontaneous laughter lasting 15-20 seconds. During examination, her height was 96.0 cm, weight 15.8 kg, BA six years, breast Tanner stage III, and pubic hair Tanner stage II [Table/Fig-2d]. Laboratory results showed an elevated basal LH and estradiol.



[Table/Fig-2]: a) A sagittal plain T2 weighted image of the sella of case-2 showing oval to round hyperintense lesion in the hypothalamic region, consistent with Hypothalamic Hamartoma (HH); b) Testicular volume 8 ml bilaterally, pubic hair Tanner stage III and Stretched Penile Length (SPL) measuring 7 cm of case 3; c) A sagittal plain T1 weighted image of the sella of case-3 showing well-defined isointense lesion in hypothalamus; d) Breast Tanner stage III of case 4.

Pelvic ultrasound revealed pubertal size uterus and ovaries. MRI of the brain displayed a well-defined HH (12x13x12 mm).

Management and Follow-Up

Clinical, laboratory and radiological features of cases of HH are shown in [Table/Fig-3]. All patients were treated with intramuscular leuprolide depot injections 11.25 mg every three months to target LH, estradiol, and testosterone of <0.3 IU/L, <5 pg/mL and <20 ng/dL, respectively as per CPP guideline without any adverse effect [6]. Outcomes were assessed by history, clinical examinations, and hormonal analysis every three months. MRI sella was repeated in all patients after two years of initial presentation. At a mean follow-up of 2.68±1.05 years (2.25, 2.0, 2.25 and 4.25 years, respectively), there were remission of clinical and hormonal changes of puberty, decrease in the frequency of gelastic seizures, and no significant change in the size of the HH in all patients. None of the patient required adjunct antiepileptic therapy and surgery.

DISCUSSION

The CPP typically presents with signs and symptoms of PP before the age of three years. In this case series, all patients presented with CPP and gelastic seizures at the age of two to three years [1]. A pathognomonic hallmark of HH is the presence of gelastic seizures, which typically begin in infancy, becoming more prolonged and frequent over time, often accompanied by impaired consciousness [7]. All patients in present case series presented with gelastic seizure without loss of consciousness. On MRI, HH appears as a soft tissue intensity T1 isointense and T2 hyperintense homogeneous lesion, clearly demarcated from the surrounding CSF without contrast enhancement [8]. This classical appearance of soft tissue intensity lesions (1.3 to 2.5 cm) in the hypothalamic region was also observed in our case series.

Patients with progressive CPP can be managed with long-acting GnRH agonist [4]. HH increases in size proportionally to normal brain growth, maintaining the same relative size throughout life and does not expand, spread, or metastasize [9]. Progressive enlargement of the hamartoma has not been reported and surgical intervention may be required in the rare instance of mass effect, progressive neurological deficits, refractory seizures, or hydrocephalus [10]. All patients in this case series were treated with intramuscular leuprolide depot injections, with remission of clinical and hormonal changes of puberty and a decrease in the frequency of gelastic seizures. To the best of our knowledge, this is the first Indian case series where patients with CPP and gelastic seizures due to HH showed excellent response to GnRH agonists alone without antiepileptic drugs or surgery.

Qasim BA et al., reported case of a 10-year-old girl, who presented with CPP, gelastic and generalized seizure at age of one year [3]. Sharma P et al., reported a girl of CPP due to HH at age of three years [5]. Govil-Dalela T et al., reported a case of a four years girl with refractory generalised tonic clonic and complex partial seizure, who developed CPP without any evidence of HH [11]. Zaatreh M et al., reported a case of a girl, who presented with progressive gelastic seizure and CPP at age of five years. Zaatreh M et al., reported another case of a boy who presented with CPP at age two years and developed gelastic seizure at age of eight years [12].

Yoon DY et al., reported an 11-month-old girl with CPP in whom MRI brain showed a well-defined T1/T2-isointense 1-cm-sized nonenhanced mass in the tuber cinereum consistent of HH [1]. Qasim BA et al., reported a case in whom MRI of the brain revealed 1.5 cm HH [3]. Rousso IH et al., reported a seven-month-old girl with CPP in whom MRI brain demonstrated a 9.1 mm non-enhancing HH at the tuber cinereum [4]. Castro C et al., reported a case of a girl who presented with CPP at age of five years and MRI brain evidenced a 5.7×4.8 mm non-enhancing lesion in tuber cinereum,

Age (Years)/ Sex	BA (Years)	Height (SDS) (cm)	Basal LH/FSH (IU/L)		Estradiaol/ Tesosterone		USG Pelvis/ Scrotum	MRI Brain
			Pre-treatment	Post-treatment	Pre-treatment	Post-treatment		
2.0/F	4	90 (+1 SDS)	21.9 /13.05	1.34/2.12	77.4 pg/mL	<5 pg/mL	Uterus 33x16x15 mm ET - 4.3 mm, RO- 2.2 mL, LO- 2.3 mL	12x13x15 mm T1, T2 and FLAIR isointense lesion in hypothalamus
1.6/M	3	88 (+2 SDS)	5.16/2.47	0.33/NA	841 ng/dL	9 ng/dL	RT-2.5 mL, LT-2.6 mL	20x18x23 mm T1, T2 and FLAIR isointense lesion in hypothalamus
2.3/M	5	94 (+1.1 SDS)	4.74/2.29	0.26/1.1	770 ng/dL	13 ng/dL	RT-5.4 mL, LT-6.3 mL	25x17x16 mm T1 isointense, T2 and FLAIR hyperintense lesion in hypothalamus
2.2/F	6	96 (+3 SDS)	2.67/3.9	0.1/NA	65.2 pg/mL	<5 pg/mL	Uterus 36x17x17 mm ET - 5.2 mm, RO-2.8 mL, LO-3.0 mL	12x13x12 mm T1 hypointense, T2 and FLAIR hyperintense lesion in hypothalamus

[Table/Fig-3]: Clinical, laboratory and radiological features of cases of Hypothalamic Hamartoma (HH) with CPP.
F: Female; M: Male; BA: Bone age; SDS: Standard deviation score; LH: Luteinising hormone; FSH: Follicle stimulating hormone; USG: Ultrasonography; ET: Endometrial thickness; RO: Right ovary; LO: Left ovary; RT: Right testis; LT: Left testis; MRI: Magnetic resonance imaging; NA: Not available

characterised by an intermediate signal on T1 and T2, compatible with HH [9]. Zaatreh M et al., reported a case in whom MRI sella showed a 6-mm tuber cinereum hamartoma [12].

Qasim BA et al., treated a girl of CPP and HH with leuprolide and antiepileptic medications, without improvement in seizure. She underwent surgical resection of HH with partial improvement in seizures [3]. Govil-Dalela T et al., reported a girl with CPP and her intractable seizures responded well to GnRH analog, intended for management of CPP [11]. Zaatreh M et al., reported a case in which a girl of CPP and gelastic seizures due to HH was effectively treated with monthly GnRH agonist 15 mg. Her clinical and hormonal changes of puberty remitted and she was seizure free at a 2-month follow-up. She had recurrence of seizures at age of 14 years after stoppage of GnRH agonist, and seizures remitted after six weeks of restarting GnRH agonist [12]. Zaatreh M et al., reported a case in which a boy of CPP and gelastic seizures due to HH was treated with monthly depot GnRH agonist 7.5 mg and carbamazepine, without improvement in seizures. GnRH agonist was increased to 15 mg monthly and his seizures remitted [12].

Previous studies demonstrated that HH itself generates gelastic seizures and intrinsic epileptogenic properties of HH may be attributed to small GABAergic neurons within the HH that fire spontaneously [13,14]. The mechanism of response of GnRH agonists in gelastic seizure is unclear. GnRH agonists suppress oestrogen that is proconvulsant and may modulate an unidentified neurotransmitter that affects epileptic function in patients with HH [12].

CONCLUSION(S)

Gelastic seizure is pathognomonic and CPP is the most usual presenting feature and typically manifest before the age of three years. Relatively, early presentation of CPP necessitates clinical work-up for HH. HH appears as a soft tissue intensity T1 isointense and T2 hyperintense homogeneous lesion without contrast enhancement. GnRH agonists offer effective management for HH-associated CPP and may reduce gelastic seizures, potentially avoiding surgery in select cases.

Acknowledgements

We thank the patients and their family for their participation in this study.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Oct 11, 2025
- Manual Googling: Jan 29, 2026
- iThenticate Software: Jan 31, 2026 (5%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Oct 09, 2025**
Date of Peer Review: **Jan 06, 2026**
Date of Acceptance: **Feb 02, 2026**
Date of Publishing: **May 01, 2026**