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Central Precocious Puberty in a 9-Month-Old Infant Due to Hypothalamic Hamartoma: A Case Report

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ABSTRACT

Central precocious puberty is a rare endocrine disorder characterised by premature activation of the hypothalamic–pituitary–gonadal (HPG) axis, leading to the onset of pubertal development before the defined age criteria. This condition is predominantly seen in girls and is usually sporadic in nature. We report an unusual case of central precocious puberty (CPP) in a 9-month-old female infant who presented with regular menstrual cycles from 5 months of age. The infant was assessed clinically on an outpatient basis and subsequently investigated with neuroimaging and hormonal studies. She was diagnosed with a hypothalamic hamartoma as the underlying cause of CPP and was successfully initiated on a GnRH analogue (leuprolide depot), with subsequent regression of pubertal signs and cessation of menses.

Introduction

Central precocious puberty (CPP) is a result of premature activation of the hypothalamic–pituitary–gonadal (HPG) axis, resulting in the early development of secondary sexual characteristics. It is diagnosed when puberty begins before the age of 8 years in girls or 9 years in boys [1].

In girls, the earliest sign is typically breast budding (Tanner stage II), followed by pubarche, a growth spurt (around Tanner stages II–III), and menarche (usually at Tanner stage IV). In boys, the first sign is testicular enlargement (volume ≥ 4 mL), with the growth spurt occurring later than in girls [2].

The exact mechanism leading to HPG axis activation in CPP remains incompletely understood. However, increased hypothalamic kisspeptin activation is considered an important event leading to gonadotropin-releasing hormone (GnRH) release. This kisspeptin activation may be driven by activating mutations in the KISS1R gene or inactivating mutations in MKRN3, among other genetic factors [3].

In our case, the diagnosis of CPP was established on the basis of a detailed clinical history, physical

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examination demonstrating early pubertal signs, advanced bone age on radiograph, and neuroimaging revealing a hypothalamic hamartoma as the underlying aetiology.

Case Presentation

A 9-month-old female infant presented with a history of vaginal bleeding since 5 months of age. The frequency of cyclical vaginal bleeding was regular, and each episode lasted approximately 2 days. Prior to the onset of vaginal bleeding, the mother had observed breast enlargement at around 4 months of age, which gradually progressed over the following months. Around the same time, the appearance of sparse pubic hair was also noted. On further detailed history, the mother reported that she had noticed an increase in the child's height compared with that of other infants of the same age. There was no history of polydipsia, polyuria, seizures, excessive episodes of laughter or crying, vomiting, or head trauma. There was no prior cranial irradiation or history of central nervous system infection. There was also no history of exposure to exogenous hormones, steroids, or endocrine-disrupting chemicals. There was no significant past medical history.

The birth history was uneventful. The infant was the firstborn child of a non-consanguineous marriage. Developmental milestones were normal and appropriate for age. The family history was significant for type 2 diabetes mellitus in the paternal grandparents.

General examination was unremarkable, with no goitre, skin lesions, or skin tags. There were no dysmorphic features or history of fractures. Pubertal assessment revealed Tanner stage B2–3 for breast development, as shown in Figure 2, and pubic hair stage P2, while facial and axillary hair were absent. Abdominal examination did not reveal any palpable mass.

Neurological examination showed no signs of raised intracranial tension, and fundoscopy was normal. Following the detailed history, the patient underwent a thorough clinical examination, which revealed a

Table 1. Clinical parameters of the case

Parameter	Value
Pulse Rate	122 bpm (regular)
Blood Pressure	76/56 mmHg
SpO_2 (Room Air)	99%
Weight	10.4 kg (90–97th centile)
Length	75 cm (>97th centile)
BMI	18.13 kg/m²
Head Circumference	45 cm (50–97th centile)

Table 2. Biochemical investigations of the case

Test	Patient Value	Normal Reference Range
Random Blood Sugar	89 mg/dL	70–140 mg/dL
Haemoglobin	11.4 g/dL	12–15 g/dL (female)
Serum Creatinine	0.50 mg/dL	0.5–1.0 mg/dL
Total T4	8.2 µg/dL	5.0–12.0 µg/dL
TSH	1.30 mIU/L	0.5–4.5 mIU/L
FSH	5.5 mIU/mL	0–10.1 mIU/mL
LH	2.9 mIU/mL	1.8–13 mIU/mL
Prolactin	18 ng/mL	1–90 ng/mL
Serum β-hCG	<2 IU/L	<1 IU/L
Oestradiol (E2)	27 pg/mL	<10–20 pg/mL

Table 3. Imaging findings of the case

Ultrasonography (USG) Findings	MRI Pituitary — Dynamic Scan	X- ray B/L Hand and wrist
Right ovary: 2.5 mL Left ovary: 2.0 mL Uterus: 3.9 × 1.1 × 1.8 cm Uterocervical ratio: 1.8 Myometrial thickness: 3.6 mm	T1 isointense; T2/FLAIR iso→hyperintense; well-defined, pedunculated lesion Size: 6 × 8.8 × 8.6 mm (AP × CC × TR) Arising from tuber cinereum, projecting into the suprasellar cistern (Fig. 1b)	Bone age - 2 years 6 months (Fig. 1a)



Fig. 1. 1a- Xray Bilateral Hands, 1b- MRI- Brain and Pituitary



Fig. 2. Tanner stage B2–3

weight of 10.4 kg (90th–97th centile); further details of the clinical findings are described in Table 1.

On biochemical examination, the levels of LH, FSH, and estradiol were 2.9 mIU/mL, 5.5 mIU/mL, and 27 pg/mL, respectively, which were consistent with the pubertal range, as described in Table 2. Radiological evaluation at 8 months of age revealed a hypothalamic hamartoma, details of which are described in Table 3 and Figure 1.

Taking into account the above clinical, biochemical, and radiological findings, the infant was diagnosed with central precocious puberty due to a hypothalamic hamartoma.

Following the diagnosis, the patient was started on intramuscular depot injections of leuprolide (11.25 mg) every 3 months. The patient was closely monitored for adverse effects, including any flare-up of clinical signs or symptoms. No adverse events were observed following the injection. The patient is currently under regular follow-up and has demonstrated regression from baseline Tanner stages B2–3/P2 to B1/P1, along with complete cessation of menses within 4 months of treatment.

Discussion

Puberty is a physiological process characterised by concurrent hormonal and physical changes that include breast development in girls, an increase in testicular volume in boys, and pubic hair growth, all of which are staged in clinical practice according to the

criteria defined by Marshall and Tanner [1].

The term "mini-puberty" refers to the transient activity of the hypothalamic–pituitary–gonadal (HPG) axis that occurs after birth. In males, this activity is most prominent at 2 to 3 months of postnatal age and ends at around 6 months. In females, the axis may be active until 2 to 4 years of age [2].

In recent years, precocious puberty has become an increasingly recognised phenomenon, partly attributed to environmental and chemical exposures collectively referred to as endocrine disruptors. Broadly, precocious puberty is classified into peripheral (GnRH-independent) and central (GnRH-dependent) forms. GnRH-dependent precocious puberty is isosexual (true) precocious puberty, whereas GnRH-independent precocious puberty may be either isosexual or heterosexual. The present discussion focuses primarily on GnRH-dependent isosexual (true) precocious puberty [1].

According to Denmark's nationwide registry cohort (1998–2017), the mean annual CPP incidence was 9.2 per 10,000 girls and 0.9 per 10,000 boys (20-year means) [3].

In South Korea, analysis of National Health Insurance Service data from 2008–2014 showed an average incidence of 122.8 per 100,000 children (262.8 per 100,000 girls; 7.0 per 100,000 boys) and a prevalence of 193.2 per 100,000 (410.6 girls; 10.9 boys).[4]

In a large series of girls with CPP (n = 428), 60% had onset between 7.0 and 7.9 years of age, 22% at 6 years, and 18% under 6 years [5]. By comparison, the present patient had a notably earlier onset, with pubertal signs evident from the fifth month of life.

It is also well established that idiopathic CPP accounts for the majority of cases in girls, while boys have a higher likelihood of an underlying organic pathology [6]. However, our patient, a female infant, developed CPP secondary to a hypothalamic hamartoma. According to the published literature, organic CPP was identified in 6.3% of participants (n = 286), with puberty beginning before 6 years of age in 88.9% of girls with organic CPP [7].

Lee J et al. reported that the probability of idiopathic CPP was higher in males when puberty onset occurred after 8 years of age, with no history of cranial radiotherapy or chemotherapy [8].

In a case series of 30 patients, Suh J, Choi Y et al. reported that 16 patients (53.3%) had a pedunculated hypothalamic hamartoma on MRI. They further noted that the pedunculated type was associated with a higher prevalence of both precocious puberty and gelastic seizures compared with the sessile type [9]. This is consistent with our patient's presentation; notably, she has not developed any seizures to date.

In summary, the available epidemiological data suggest that CPP can occur at any age, irrespective of sex or ethnicity. However, further data are needed to better characterise the predominance of organic causes of CPP in infants under 1 year of age, which would help guide more targeted therapeutic strategies.

Suh J, Choi Y et al. also concluded that surgical intervention is reserved primarily for refractory seizures or mass effect, while GnRH agonists are effective in controlling pubertal progression [9]. A meta-analysis by Agrawal M, Samala R et al., encompassing 33 studies and 103 patients, concluded that surgical intervention may be considered for patients with resectable hamartomas for the purpose of tissue diagnosis, in cases of partial response to or failure of medical therapy, and for patients who are unable to afford or wish to avoid long-term GnRH agonist therapy [10].

In the present case, the patient is being treated with intramuscular depot injections of leuprolide (11.25 mg) every 3 months [10].

Several formulations of GnRH analogues are available, including intranasal preparations, subcutaneous implants, and monthly and 3-monthly depot injections. Among these, depot preparations are considered the gold standard. Importantly, the dosing of these preparations is standardised and not weight-based; only standard paediatric CPP doses are used, even in infancy.

Our patient, who remains under regular follow-up, has not developed seizures or cognitive decline and is well oriented to time, place, and person.
Mitrica M, Manole AM et al. noted that patients with intractable seizures may develop cognitive decline over time; such patients therefore require close long-term follow-up and cognitive behavioural therapy [11].

Various neuromodulation techniques are also available, although further studies are required to establish their long-term effectiveness in patients with hypothalamic hamartoma causing CPP, particularly in those with intractable seizures and associated cognitive or memory impairment [12].

Conclusion

Central precocious puberty is not uncommon, and proper aetiological evaluation is essential to identify the pathological cause for appropriate management. At present, there is limited evidence to establish clear medical or surgical treatment protocols for children younger than 1 year of age. This highlights the need for further prospective data to guide optimal management in this vulnerable population.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this article.

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Conflict of Interests

The authors have no conflict of interest to declare.

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