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Hypothalamic Hamartoma Related to Central Precocious Puberty: A Case Report

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Keywords:
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Abstract

Hypothalamic hamartoma is a rare congenital lesion that can cause central precocious puberty, gelastic seizures, and neurobehavioral disturbances. This case report aims to describe the clinical presentation, diagnostic evaluation, multidisciplinary management, and follow-up of a boy with hypothalamic hamartoma associated with central precocious puberty. A descriptive case report was developed based on the patient's clinical history, physical examination findings, hormonal assessments, skeletal maturation evaluation, neuroimaging, electroencephalography (EEG), and treatment records. A 4-year-old boy presented with premature sexual development, accelerated linear growth, obesity, developmental delay, aggressive behavior, and brief episodes of involuntary smiling or laughter accompanied by impaired responsiveness. Physical examination revealed bilateral testicular enlargement, with a testicular volume of 12 mL, while serum testosterone levels reached 362 ng/dL and bone age was advanced to 14 years. Magnetic resonance imaging (MRI) revealed a hypothalamic lesion extending into the suprasellar cistern and third ventricle. Surgical resection was associated with a reduction in seizure frequency; however, residual lesion tissue and persistent seizures were observed. Following six months of gonadotropin-releasing hormone (GnRH) agonist therapy, serum testosterone levels decreased to below 2.5 ng/dL, indicating substantial biochemical suppression of pubertal activity. Continued antiseizure medication and behavioral interventions were required. These findings demonstrate that endocrine suppression and neurological improvement may follow distinct clinical trajectories. Early recognition and coordinated multidisciplinary care involving endocrinology, neurology, and developmental specialists are essential for comprehensive management. Continued follow-up is necessary to evaluate seizure control, pubertal suppression, linear growth, and behavioral outcomes. However, the long-term effects of treatment on final adult height cannot be determined from this single case.

INTRODUCTION

Puberty represents a transitional phase from childhood to adulthood, characterized by a sequential progression of developmental stages regulated by a complex interplay of neuroendocrine factors. Pubertal onset is initiated by the pulsatile secretion of gonadotropin-releasing hormone (GnRH), which stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Puberty typically begins between 8 and 13 years of age in girls and between approximately 9 and 14 years in boys. The development of secondary sexual characteristics before the age of 8 years in girls or 9 years in boys is generally defined as

precocious puberty. Precocious puberty is classified into central precocious puberty (GnRH-dependent) and peripheral precocious puberty (GnRH-independent). Central precocious puberty results from premature activation of the hypothalamic-pituitary-gonadal (HPG) axis, leading to the early development of secondary sexual characteristics (Azhar & Molla, 2022; Idris et al., 2025).

Beyond its underlying neuroendocrine mechanisms, precocious puberty has attracted increasing international attention because of changing diagnostic trends. In a nationwide Danish cohort study, Bräuner et al. (2020) identified 8,596 children diagnosed with central precocious puberty, premature thelarche, or premature adrenarche between 1998 and 2017, of whom 90.4% were girls. The study documented an increasing incidence of diagnosed cases throughout the observation period, highlighting the growing clinical relevance of early pubertal development. Although these nationwide findings cannot be extrapolated to estimate global prevalence, they provide an important epidemiological context for investigating premature sexual maturation. Within this broader clinical context, the relatively uncommon presentation of central precocious puberty in boys warrants particular attention to potential underlying etiologies and associated neurological manifestations (Cho et al., 2026; Jacobs & Hildebrand, 2025; List et al., 1958; Yuhani et al., 2026).

Central precocious puberty (CPP) is more prevalent in girls and occurs less frequently in boys, in whom an identifiable underlying cause, including intracranial lesions or other central nervous system abnormalities, is more likely to be present. One important structural cause is hypothalamic hamartoma, a rare, benign congenital malformation typically located in the region of the tuber cinereum.

Hypothalamic hamartoma (HH) is a rare congenital, heterotopic malformation of the central nervous system composed of disorganized but mature neural tissue. It represents an important organic cause of CPP, particularly in young children, although it does not account for the majority of all CPP cases. Anatomically, hypothalamic hamartomas are commonly classified according to their morphology and attachment to the hypothalamus as sessile (broad-based attachment) or pedunculated (stalk-like attachment). These anatomical characteristics may influence their clinical manifestations and therapeutic management (Delalande & Fohlen, 2003; Dong et al., 2023; Freeman et al., 2004; Harrison et al., 2017; Harvey & Freeman, 2007).

Pedunculated hypothalamic hamartomas are more commonly associated with precocious sexual maturation, whereas sessile lesions, particularly those involving the mammillary region or third ventricular floor, are more frequently associated with gelastic seizures. Nevertheless, both endocrine and epileptic manifestations may coexist, depending on the lesion's anatomical characteristics and extent of hypothalamic involvement. Gelastic seizures associated with hypothalamic hamartomas are epileptic events characterized by brief, stereotyped episodes of involuntary laughter or smiling, often without an accompanying sensation of amusement. In addition to precocious puberty and epilepsy, affected children may develop cognitive impairment, developmental difficulties, and behavioral disturbances, including aggression, emotional dysregulation, and autism spectrum-related features. The severity and progression of these manifestations vary considerably among patients (Cohen et al., 2026; Goel et al., 2024).

The management of pediatric hypothalamic hamartoma has evolved substantially over the past decade, with increasing emphasis on minimally invasive and individualized therapeutic

approaches rather than conventional open surgical procedures. Treatment primarily addresses two major clinical manifestations: central precocious puberty and epilepsy, particularly gelastic seizures. In children presenting predominantly with CPP without severe or drug-resistant seizures, pharmacological treatment is generally the preferred initial approach. Gonadotropin-releasing hormone (GnRH) agonists are the standard medical treatment for suppressing premature activation of the HPG axis, slowing the progression of secondary sexual characteristics, reducing the rate of skeletal maturation, and potentially preserving adult height. For patients with drug-resistant epilepsy, surgical or minimally invasive interventions may be considered to resect, ablate, or disconnect the epileptogenic hamartoma from surrounding hypothalamic networks. Comprehensive multidisciplinary management is essential, including neuropsychological assessment and rehabilitation to address cognitive deficits, memory impairment, developmental delays, and behavioral disturbances associated with the condition. A ketogenic diet may also be considered as an adjunctive treatment for selected patients with drug-resistant seizures, although its effectiveness specifically in hypothalamic hamartoma-associated epilepsy remains uncertain (Jung et al., 2003; Suh et al., 2021).

In this report, we present the case of a 4-year-old boy who was brought to the endocrinology clinic by his parents because of the premature development of secondary sexual characteristics. The clinical history revealed bilateral testicular enlargement, followed by penile enlargement, the appearance of pubic hair, and the development of facial acne. The patient also exhibited delays in speech and motor development. During the clinical evaluation, he demonstrated pronounced restlessness and repeatedly manipulated his external genitalia.

Accordingly, this case report aims to describe the clinical presentation, diagnostic evaluation, multidisciplinary management, and documented follow-up of a 4-year-old boy with hypothalamic hamartoma associated with central precocious puberty. Specifically, it seeks to correlate the clinical manifestations of premature sexual maturation with neuroimaging findings and seizure characteristics, describe the accompanying developmental and behavioral disturbances, and document the hormonal response to treatment alongside the postoperative course of epilepsy. The distinctive contribution of this report lies in its integrated description of markedly advanced skeletal maturation, early androgenization, and persistent neurological manifestations in a preschool-aged child. Furthermore, this case highlights the importance of evaluating endocrine and neurological outcomes independently within a coordinated multidisciplinary care framework. Nevertheless, the findings should be interpreted in the context of a single case report, which cannot establish comparative treatment effectiveness, long-term adult height outcomes, or broadly generalizable therapeutic recommendations.

METHOD

A 4-year-old boy presented to the endocrinology clinic with premature development of secondary sexual characteristics. According to his mother, penile and scrotal enlargement had been present since birth but had initially gone unrecognized as abnormal. Pubic hair had appeared in June 2023, without accompanying axillary hair development. The patient also experienced spontaneous erections, frequently manipulated his genitalia, and reportedly showed interest in girls. These manifestations were accompanied by accelerated linear growth and weight gain compared with his peers. However, he exhibited developmental delays, having achieved independent walking at 17 months of age. Expressive language delay had also been

evident since the age of 2 years, when his speech remained limited to isolated words without sentence formation.

The patient had also experienced recurrent seizure-like episodes characterized by groaning followed by involuntary smiling or laughter and a fixed gaze without ocular deviation. Each episode lasted approximately 5–10 seconds and was associated with impaired responsiveness to verbal and tactile stimuli. No behavioral changes were observed before the episodes. Following each event, the patient reportedly had no recollection of the episode and subsequently fell asleep. These episodes occurred predominantly before sleep onset, approximately 3–4 days per week, with 2–3 episodes per day on symptomatic days. They were not reported during routine activities, meals, or bathing (Arita et al., 2005; Romner et al., 1994; Tariq, 2024; Ventresca et al., 2025).

Since the age of 2 years, the patient had exhibited hyperactivity, aggressive behavior toward peers, and difficulty disengaging from activities. His aggressive behavior included hitting other children, while his hyperactivity often persisted until he became physically exhausted. Episodes of self-injurious behavior, including head banging against walls, were also reported, without apparent emotional distress or crying.

There was no reported history of severe headaches, head trauma, central nervous system infections, encephalitis, diplopia, vomiting, cold intolerance, exogenous hormone exposure, or radiation exposure. The family history was noncontributory.



Figure 1. Gelastic seizures, Tanner stage, and the patient's clinical presentation.
Source: Personal documentation. Image obtained with the consent of the patient's legal guardian.

On admission, the patient appeared moderately ill, with a heart rate of 88 beats/min, a respiratory rate of 22 breaths/min, and a body temperature of 36.7°C. Physical examination revealed tall stature, a deepened voice, facial acne, bilateral testicular enlargement, penile enlargement, and increased pubic hair growth, consistent with advanced pubertal development. Testicular volume was approximately 12 mL, and genital development was classified as Tanner

stage III. Anthropometric measurements revealed a height of 124.5 cm (above the 95th percentile) and a weight of 35.5 kg (above the 95th percentile), with a calculated body mass index of 22.9 kg/m². The patient's midparental target height range was estimated at 162.5–179.5 cm, as illustrated in the Centers for Disease Control and Prevention (CDC) growth chart (Figure 2).

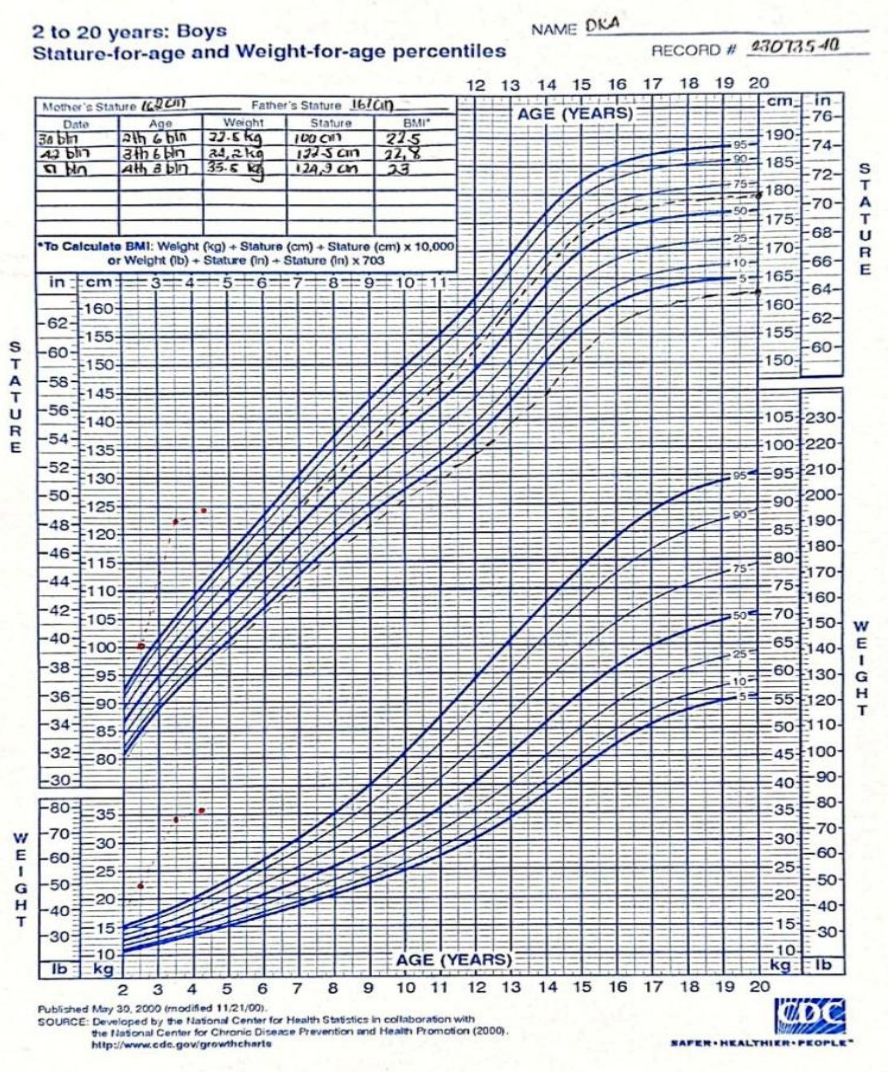


Figure 2. Growth chart of the boy showing height, weight, mid parental height and centiles.

Laboratory investigations revealed normal complete blood count (CBC) and liver function test results. Serum testosterone was markedly elevated at 362 ng/dL, exceeding the prepubertal reference value of 2.5 ng/dL. Serum 17-hydroxyprogesterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) levels were 0.97 ng/mL, 2.17 mIU/mL, and 1.07 mIU/mL, respectively.

Radiographic assessment of the hands and wrists revealed markedly advanced skeletal maturation, corresponding to a bone age of 14 years. Brain magnetic resonance imaging (MRI) demonstrated a well-defined, solid hypothalamic lesion measuring approximately 2.5 × 2.0 × 2.5 cm, extending into the suprasellar cistern posterior to the pituitary stalk. The lesion caused mild displacement of the optic chiasm and extended superiorly into the third ventricle,

producing a mild mass effect. These findings were suggestive of a hypothalamic hamartoma. Contrast-enhanced brain computed tomography (CT) revealed an iso- to hypodense lesion involving both sides of the hypothalamus and extending into the suprasellar cistern, measuring approximately 3.2 × 2.9 × 2.7 cm. The lesion exhibited partially ill-defined margins adjacent to the proximal pituitary stalk and mild heterogeneous contrast enhancement. It displaced the optic chiasm posteriorly, narrowed the third ventricle, and exerted a posterior mass effect on the midbrain. The imaging findings raised suspicion for a hypothalamic hamartoma, with suprasellar germinoma considered in the differential diagnosis. Testicular ultrasonography demonstrated bilateral testicular enlargement relative to age-specific reference values, consistent with precocious pubertal development.

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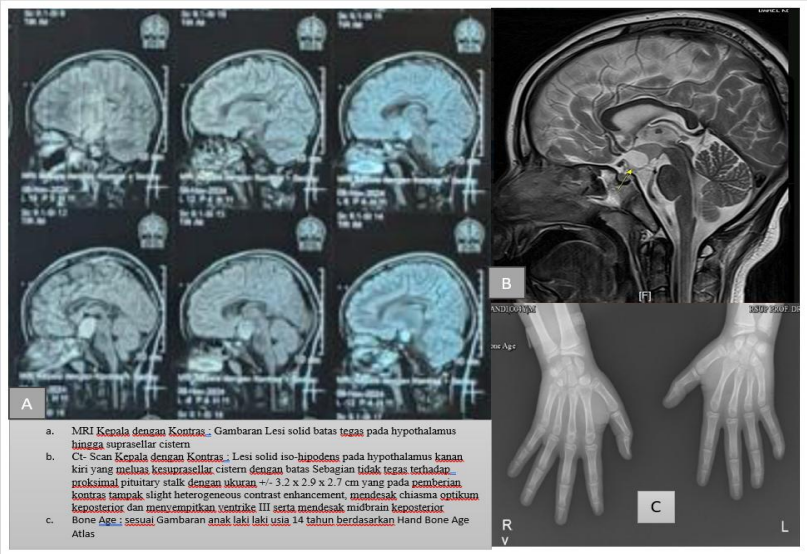


Figure 3. MRI, Ct-Scan dengan kontras, dan bone age patient

Pediatric neurological evaluation revealed neurodevelopmental delay, episodes suggestive of gelastic seizures, and behavioral disturbances. Electroencephalography (EEG) demonstrated a background rhythm of 5–6 Hz interspersed with medium-voltage 3–4 Hz slow waves, without significant asymmetry. Multifocal epileptiform discharges were identified in the right frontal, central, and centroparietal regions. Photic stimulation produced no significant changes. Overall, the EEG findings were abnormal, characterized by multifocal epileptiform activity without evidence of focal background slowing.

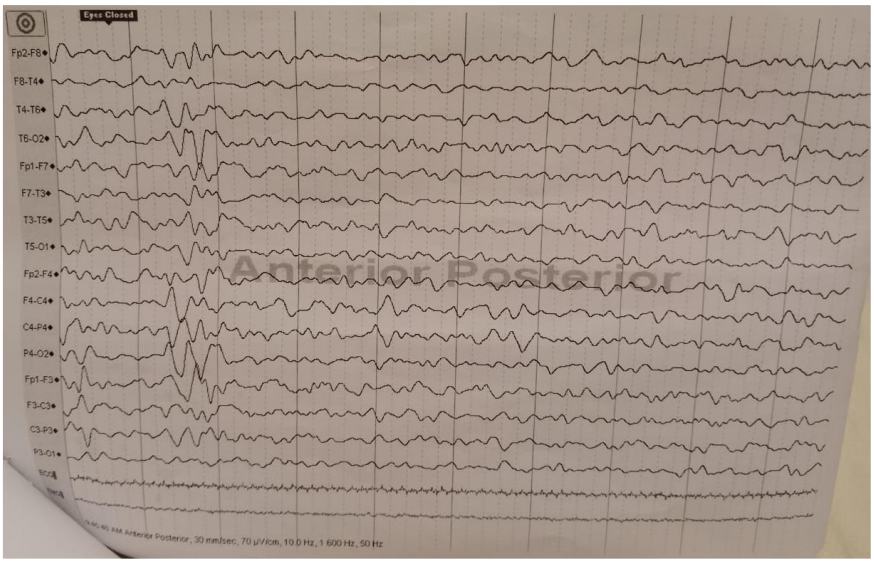


Figure 4. EEG Patient

The patient underwent surgical resection of the hypothalamic lesion in December 2024, followed by a reduction in seizure frequency, with residual episodes occurring predominantly before sleep onset. Brain magnetic resonance imaging (MRI) performed one month postoperatively revealed a well-defined, oval-shaped residual mass with lobulated margins in the suprasellar surgical bed, measuring approximately 1.4 × 0.8 × 1.6 cm and exerting a mass effect on the optic chiasm. Additional findings included postoperative encephalomalacia involving the right caudate nucleus, anterior limb of the right internal capsule, right lentiform nucleus, and part of the right external capsule, along with subdural hygromas in the right frontotemporal and left frontal regions.

Gonadotropin-releasing hormone (GnRH) agonist therapy was initiated at a prescribed dose of 100 µg/kg, with treatment planned until approximately 12 years of age. After six months of therapy, hormonal evaluation demonstrated suppression of pubertal activity, with luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone levels of 0.50 mIU/mL, below 0.10 mIU/mL, and below 2.5 ng/dL, respectively. Seizure management included oral carbamazepine (330 mg twice daily), valproic acid (500 mg twice daily), and diazepam (2.5 mg nightly). Aripiprazole was also prescribed to manage behavioral disturbances. At the most recent follow-up, the patient remained under regular pediatric endocrinology and neurology care and was reported to be adherent to the prescribed treatment regimen.

RESULTS AND DISCUSSION

Hypothalamic hamartoma (HH) is a rare, heterotopic malformation of the central nervous system composed of disorganized neural tissue. The presenting symptoms depend heavily on the size and exact anatomical location of the mass within the hypothalamus, but typically include gelastic seizures, in which patients experience sudden, brief, and uncontrollable episodes of laughter that are inappropriate to the social context or emotional mood. Central precocious puberty (CPP) refers to the development of pubertal changes resulting from the premature activation of pulsatile GnRH secretion. Because the hypothalamus regulates hormonal axes, this mass can trigger the premature release of sex hormones, causing children to undergo puberty at a very young age, which is subsequently accompanied by progressive

cognitive and behavioral impairments. In this case, the suspicion of HH was based on the patient's clinical findings, which included the emergence of secondary sexual characteristics staged at Tanner G4P3, and a testicular volume of 12 mL determined via orchidometer. Additionally, the patient's anthropometric status indicated obesity, with a height of 124.5 cm (>95th percentile) and a weight of 35.5 kg (>95th percentile).

While precocious puberty manifests through endocrine dysfunction, gelastic seizures are characterized by epileptic paroxysms of laughter. These laughter-induced seizures typically begin in early childhood, are brief, and present stereotypically. The laughter is usually involuntary and unprovoked. During the ictus, autonomic signs may be observed, such as pupillary dilation and facial flushing. In patients with lesions located outside the hypothalamic region, these episodes of laughter lack an emotional component and resemble a mechanical act. In children, emotional involvement and expressions of mirth during gelastic seizures strongly correlate with HH; conversely, when the laughter appears mechanical, extra-hypothalamic regions should be considered. The brain structures involved in emotional laughter include the anterior cingulate cortex, amygdala, anterior ventral insula, hypothalamus, and the periaqueductal gray matter. In contrast, mechanical laughter involves the superior temporal sulcus, ventral premotor cortex, pre-supplementary motor area, and the anteroventral sectors. In this case, the patient experienced seizures characterized by a groaning sound accompanied by a smiling or occasionally laughing facial expression, during which both eyes remained fixed without deviation, lasting for approximately 5 to 10 seconds. Prior to the ictus, the child's behavior was unremarkable; postictally, the patient experienced amnesia regarding the event and would subsequently fall into a restful sleep. The seizures typically occurred prior to sleep onset, with a frequency of 3 to 4 days per week, and a daily intensity of 2 to 3 episodes at unpredictable intervals. The episodes never occurred during daily activities, meals, or bathing.

The clinical phenotype of HH is primarily characterized via brain MRI, and HH classification is based on the size and attachment plane of the lesion to the hypothalamus (horizontal, vertical with intrasellar location, intraventricular, combined, or giant HH). Sessile-type HH is typically visualized near the mammillary bodies and can extend into the third ventricle. Conversely, the pedunculated type connects to the tuber cinereum and extends into the suprasellar cistern. In this case, brain MRI evaluation demonstrated a well-defined solid lesion within the hypothalamus extending into the suprasellar cistern (located posterior to the pituitary stalk and attached to its proximal aspect), measuring approximately 2.5 x 2 x 2.5 cm. This lesion caused mild splaying of the optic chiasm and extended superiorly into the third ventricle, exerting a mild mass effect on its inferior aspect, which was highly suggestive of a hypothalamic hamartoma. Furthermore, a contrast-enhanced brain CT scan revealed an iso-to-hypodense solid lesion involving the bilateral hypothalamus and extending into the suprasellar cistern, with partially ill-defined borders against the proximal pituitary stalk, measuring approximately 3.2 x 2.9 x 2.7 cm. Post-contrast administration, it exhibited slight heterogeneous enhancement, posteriorly displacing the optic chiasm, narrowing the third ventricle, and exerting mass effect on the midbrain, raising suspicion for a hypothalamic hamartoma with a differential diagnosis of suprasellar germinoma. Based on these radiological findings, the most appropriate anatomical classification for this lesion is a sessile HH, characterized by a broad-based (solid) attachment to the hypothalamus, extension into the suprasellar cistern, and adherence to the proximal aspect of the pituitary stalk. The lesion also grew superiorly into the

third ventricle, causing a mass effect. In contrast, pedunculated (parahypothalamic) hamartomas typically depend from a thin stalk beneath the hypothalamus and rarely distort the third ventricle or cause significant narrowing of internal structures.

To describe the latest update on the clinical manifestations of HH, reference is made to a journal article entitled "International Consensus on the Evaluation and Management of Hypothalamic Hamartomas" by Nathan T. et al. (2026), providing a Level of Evidence 3 and a Grade of Recommendation C. This study emphasized the primary signs that must immediately prompt medical suspicion of HH, with the consensus stating that gelastic seizures are robustly associated with HH. The journal also noted that parents frequently fail to recognize or misidentify these seizures early on. Case Correlation (Seizures): Patient DKA experienced seizures characterized by groaning and a smiling or laughing expression lasting 5–10 seconds, occurring predominantly prior to sleep onset. This pattern aligns precisely with the characteristics of involuntary gelastic seizures triggered by HH tissue. Central Precocious Puberty & Obesity: The consensus literature highlights the combination of drug-resistant epilepsy (DRE) and endocrine dysfunctions, such as precocious puberty and obesity, as a classic clinical presentation. .Case Correlation (Endocrinology): DKA (4 years old) presented with bilateral penile and scrotal enlargement (testicular volume 12 mL, Tanner stage G4P3), markedly elevated testosterone levels (362 ng/dL), an advanced bone age equivalent to a 14-year-old male, and an anthropometric status indicative of obesity. Diagnostic methodology recommendations from international experts demonstrate several areas of alignment as well as variations in clinical practice compared to this case report: Primary Imaging: A 3T Epilepsy Protocol MRI is considered essential and mandatory. In this case, the brain MRI successfully detected a well-defined solid lesion measuring 2.5 x 2 x 2.5 cm in the hypothalamus extending to the suprasellar cistern, characteristic of a sessile HH. Ancillary Imaging: A brain CT scan is deemed unnecessary and low-yield; however, this patient underwent a contrast-enhanced brain CT to rule out a differential diagnosis of suprasellar germinoma. Electrophysiology: Video EEG is considered crucial. Standard routine scalp EEGs have limitations, as approximately 75% of gelastic seizures do not demonstrate scalp EEG correlates. In this patient, a routine EEG demonstrated multifocal epileptiform discharges in the right frontal, central, and centroparietal regions. Pharmacotherapy: The consensus journal states that there is no absolute agreement regarding first-, second-, or third-line anti-seizure medications (ASMs). However, sodium channel blockers (such as Oxcarbazepine/Carbamazepine) and SV2A receptor modulators (such as Levetiracetam/Brivaracetam) received the highest consensus votes as primary choices. Postoperatively, to control residual seizures, patient DKA was prescribed Carbamazepine (30 mg/kg/day) combined with Valproic acid and Diazepam. The selection of Carbamazepine aligns closely with the expert consensus recommendations. Surgical Management: The consensus reinforces that surgical intervention aims for the disconnection or total/subtotal resection of the epileptogenic hamartoma tissue. In reality, the patient underwent tumor resection in December 2024. A follow-up brain MRI one month postoperatively revealed a residual mass measuring 1.4 x 0.8 x 1.6 cm. This explains why the patient’s seizure frequency decreased but was not completely eliminated (still occurring before sleep), thereby necessitating long-term multi-drug ASM therapy. The consensus journal advocates for an aggressive, multidisciplinary protocol to address non-epileptic comorbidities: Endocrine Therapy: All HH patients with signs of CPP must be referred to pediatric endocrinology. The gold standard therapy involves GnRH

agonists/analogs to suppress the HPG axis. Consistently, the patient was initiated on a GnRH analog at 100 mcg/kg, planned until 12 years of age. This therapy proved highly effective, as evidenced by the suppression of LH, FSH, and testosterone to target prepubertal ranges after 6 months. Neuropsychiatric Comorbidities: The journal notes that 55% of HH patients exhibit psychiatric comorbidities (aggression, temper tantrums, rage attacks) and cognitive decline. Periodic evaluation and pharmacological intervention are strongly recommended. Patient DKA demonstrated speech delay and severe aggressive behavior (striking peers, hyperactivity, and expressionless head-banging). The medical team initiated Aripiprazole, a neuro-psychiatric intervention that aligns with the consensus guidelines for managing behavioral comorbidities.

The prognosis in this case is further analyzed based on the journal article "Early Puberty in Children: Psychological, Social, and Parental Impacts" by Azizah Yuhani (2026), with a Level of Evidence 3 and a Grade of Recommendation C. Psychological and Behavioral Impact: Premature pubertal timing significantly elevates the risk of mental health disorders, diminishes emotional quality of life, and triggers behavioral and emotional issues such as anxiety or aggressiveness. In this case report, patient DKA clearly manifested severe behavioral disturbances. Since the age of 2, he became hyperactive, aggressive, and prone to striking or harming peers during play. He also exhibited atypical head-banging behavior against walls without crying or changing facial expressions. Social Challenges: Children who experience pubertal timing earlier than their peers frequently face social challenges. Asynchronous physical changes make them feel different and isolated, increasing the risk of social rejection or bullying. Due to his aggressive behavior and precocious puberty, DKA's social interactions were highly disrupted. His physical appearance—presenting as a tall, obese child with a hoarse voice and facial acne at just 4 years old—coupled with his aggressive tendencies, severely hindered social adjustment with his age-matched peers. Family Burden: Precocious puberty is not merely a biological issue but a complex social phenomenon that impacts family dynamics. This diagnosis imposes substantial psychological, financial, and routine-based burdens on caregivers (family burden/parental stress). However, active parental social support is crucial in mitigating negative outcomes for the child. DKA's parents demonstrated a highly supportive role, as recommended in the literature. They identified developmental anomalies, sought timely consultation at the endocrinology clinic, consented to the surgical resection in December 2024, and maintained strict compliance with the long-term medical regimen (GnRH analog therapy planned until age 12 and routine multi-clinic follow-ups). This therapeutic commitment reflects the extensive adaptation and pressure faced by the family to optimize the child's quality of life. Asynchronous Development: The journal emphasizes the profound challenges encountered when physical and sexual development accelerates rapidly while emotional and cognitive maturity lags behind. This manifestation was explicitly observed in DKA. At only 4 years of age, he experienced spontaneous erections, frequent manipulation of his external genitalia, and began showing interest in the opposite sex. Conversely, from a cognitive standpoint, he suffered from expressive language and motor delays. The mismatch between adult biological sexual drives and a toddler's mental capacity is what triggers profound psychological confusion in the child.

The prognostic outcome of GnRH therapy is further elaborated in the study "Final adult height in male patients with central precocious puberty after gonadotropin-releasing hormone agonist treatment" (2026) by Kyoung Won Cho. Patient DKA received GnRH analog (agonist) therapy at a dose of 100 mcg/kg, scheduled until age 12. Following 6 months of therapy, highly

effective sex hormone suppression was achieved, with LH levels decreasing to 0.50 mIU/mL and testosterone dropping drastically to <2.5 ng/dL. This study concluded that GnRH agonist (GnRHa) therapy is proven to significantly delay premature bone maturation and improve final adult height (FAH) in boys with CPP. The reduction of sex hormones in patient DKA aligns with the study's findings, where the mean post-treatment peak LH was suppressed to 1.3 mIU/mL and testosterone was suppressed to a mean of 8.5 ng/dL.

The literature notes that children who initiate therapy before the age of 9 experience a significantly greater increase in Predicted Adult Height (PAH), with a mean gain of +4.2 cm. Because patient DKA began therapy at a very young age (4 years), his potential height benefit is maximized. However, the journal also highlights that markedly elevated baseline testosterone levels, obesity (high weight SDS), a severe discrepancy between bone age and chronological age (BA–CA), and large baseline testicular volume correlate with a shorter final adult height (below the initial genetic potential). Regrettably, patient DKA presented with all of these risk factors at initial presentation: extremely high testosterone (362 ng/dL), an obese anthropometric status, a very large testicular volume (12 mL), and an advanced bone age corresponding to a 14-year-old male despite a chronological age of only 4 years. Finally, the study analyzed the performance of two primary GnRHa agents, namely Leuprolide Acetate and Triptorelin Acetate, concluding that there is no significant difference in efficacy regarding height achievement between the two medications. This provides clinical flexibility for the managing physicians in selecting the specific GnRH analog formulation available within the hospital formulary.

A 4-year-old male patient (DKA) presented with the premature emergence of secondary sexual characteristics (central precocious puberty), obesity, aggressive behavioral disturbances, and distinctive seizure semiology. The clinical manifestations included bilateral penile and scrotal enlargement present since birth, the development of pubic hair (Tanner stage G4P3), a testicular volume reaching 12 mL, spontaneous erections, a tendency toward external genitalia manipulation, and an emerging interest in the opposite sex. Physical growth and weight gain were markedly accelerated (above the 95th percentile on the CDC growth charts; height: 124.5 cm, weight: 35.5 kg), accompanied by a hoarse voice and facial acne. Developmental milestones revealed delayed ambulation (achieved at 1 year and 5 months of age) and expressive language delay (speech delay). The patient experienced involuntary seizure episodes lasting 5–10 seconds, characterized by a groaning sound with a smiling or laughing facial expression and fixed gaze; these occurred predominantly prior to sleep onset (3–4 times per week), during which the patient was unresponsive.

Behavioral evaluation revealed marked hyperactivity and aggression, including striking peers and expressionless head-banging against the wall without crying. Ancillary investigations revealed significantly elevated serum testosterone levels, whereas LH and FSH levels remained within normal prepubertal parameters. The radiological bone age was severely advanced, corresponding to a 14-year-old male despite a chronological age of only 4 years. Neuroimaging identified a well-defined solid lesion within the hypothalamus extending into the suprasellar cistern, measuring approximately 2.5 x 2 x 2.5 cm, which exerted mass effect on the optic chiasm and the third ventricle; these features are consistent with a sessile-type hypothalamic hamartoma (HH). Electroencephalography (EEG) demonstrated an Abnormal II pattern, characterized by multifocal epileptiform discharges in the right frontal, central, and centroparietal regions. The patient underwent surgical tumor resection in December 2024. A

follow-up brain MRI performed one month postoperatively revealed a residual mass measuring 1.4 x 0.8 x 1.6 cm. Postoperatively, seizure frequency decreased but occasional episodes persisted before sleep. Hormonal therapy was initiated with a GnRH analog at 100 mcg/kg, planned to continue until the age of 12 years. Following 6 months of therapy, effective suppression of sex hormones was achieved (LH: 0.50 mIU/mL, FSH: <0.10 mIU/mL, testosterone: <2.5 ng/dL). For multi-drug seizure management and behavioral comorbidities, the patient was prescribed a regimen of Carbamazepine (30 mg/kg/day), Valproic acid (40 mg/kg/day), Diazepam (0.1 mg/kg/dose before sleep), and Aripiprazole to manage the cognitive deficits and aggressive behaviors.

The case highlights a profound asynchronous development, wherein physical and biological sexual maturity accelerated rapidly while the patient's mental and emotional capacities remained at a toddler's level. This discrepancy triggered social isolation and substantial parental stress; however, the parents' active support and adherence to long-term treatment are crucial in mitigating these negative impacts. While GnRH agonist therapy is proven effective in optimizing final adult height potential when initiated early (before the age of 9 years), this patient carries multiple risk factors for a shorter final adult height due to his baseline characteristics, which included extremely high testosterone levels, severe obesity, large testicular volume, and a markedly advanced bone age.

EVIDENCE-BASED CRITICAL APPRAISAL (CLINICAL ASPECT)

Are the results of this manifestation study valid?

Table 1. Methodological Validity of the Modified Delphi Consensus on Hypothalamic Hamartoma

1.	Was a defined, representative sample of patients assembled at a common (usually early) point in the course of their disease?	Based on the provided consensus journal article, the answer is **no**. The study did **not** assemble a sample of patients at a common or early point in the course of their disease.
2.	Was patient follow-up sufficiently long and complete?	Because this research was an **international, modified Delphi survey of expert practitioners** rather than a clinical trial or observational cohort study, the concept of tracking longitudinal patient follow-up does not apply to its methodology.
3.	Are clinical outcomes and clinical outcomes measured in the same way in both groups?	Because this study is an **international, modified Delphi survey of medical experts** rather than a comparative clinical trial, there were **no comparative patient groups** (such as a treatment group vs. a control group) assembled by the investigators to measure outcomes.
4.	If subgroups with different prognoses are identified, was there adjustment for important prognostic factors?	Ultimately, because this paper compiles expert consensus rather than statistical clinical trial data, it does not feature multi-variable adjustments for patient subgroups.
5.	Was there validation in an independent group (“test set”) of patients?	Because the study's primary objective was to aggregate the consensus of a panel of 32 multidisciplinary specialists across 17 centers rather than to develop a predictive statistical model, diagnostic algorithm, or clinical tool, the concept of a

		patient "test set" or independent clinical validation cohort does not apply to this study's design.

This study is valid.

Are the valid results of this manifestation study important?

Table 2. Clinical Importance and Precision of Prognostic Evidence for Hypothalamic Hamartoma

1.	How likely are the outcomes over time?	Based on the provided journal article, the explicit likelihood of outcomes over precise timelines is not detailed because the study is a expert consensus survey. However, the paper summarizes historical data and surgical meta-analyses that describe overall seizure and complication
2.	How precise are the prognostic estimates?	Based on the provided journal article, the precision of the prognostic estimates depends on which data you look at, as the paper combines expert qualitative agreement with statistical data from past literature.

This study is important.

Can we apply this valid, important evidence about manifestation in caring for our patient?

Table 3. Applicability of Consensus Recommendations to the Reported Case of Hypothalamic Hamartoma

1.	Were the study patients similar to our own?	Yes, The major caveat noted by the authors is **technological availability**. Some highly precise diagnostic or treatment modalities heavily favored in the consensus (such as **3T epilepsy-protocol MRI** or **MRgLITT/RFTC ablation**) may require specialized regional referrals depending on your hospital's specific infrastructure.
2.	Will this evidence make a clinically important impact on our conclusions about what to offer or tell our patient?	Yes, this evidence will likely make a clinically important impact on what you offer and communicate to your patients, as it shifts the paradigm from historical, highly invasive treatment strategies toward early, minimally invasive, protocol-driven care.

This study is applicable.

CONCLUSION

This case highlighted the complex neuroendocrine manifestations of hypothalamic hamartoma, characterized by central precocious puberty, gelastic seizures, and neurobehavioral disturbances in a 4-year-old boy. The patient presented with markedly elevated serum testosterone levels, advanced skeletal maturation, and a hypothalamic mass extending into the suprasellar cistern and third ventricle. Management involved a multidisciplinary approach combining surgical resection, gonadotropin-releasing hormone (GnRH) agonist therapy, antiseizure medications, and pharmacological treatment for behavioral disturbances. Surgical intervention was followed by a reduction in seizure frequency, while six months of GnRH agonist therapy resulted in biochemical suppression of pubertal activity. However, residual tumor tissue and persistent seizures indicated the need for continued neurological monitoring and individualized treatment.

Despite the early initiation of treatment, the patient's markedly advanced bone age, elevated baseline testosterone levels, obesity, and increased testicular volume raised concerns regarding compromised adult height potential. Nevertheless, the long-term effects on final adult height remained uncertain. Furthermore, the discrepancy between accelerated physical maturation and delayed cognitive and emotional development highlighted the potential psychosocial challenges associated with this condition. These findings emphasized the importance of sustained multidisciplinary follow-up, including endocrine monitoring, seizure management, developmental assessment, behavioral interventions, and family support, to optimize long-term clinical outcomes and quality of life.

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