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Case Report

Rapidly Progressive Precocious Puberty With an Elevated Testosterone Level in a 5-Year-Old Boy With a β -Human Chorionic Gonadotropin-Secreting Intracranial Germ Cell Tumor in the Pineal Gland



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ABSTRACT

Objective: Peripheral precocious puberty (PP) is an infrequent etiology for early sexual development. Intracranial germ cell tumors (GCTs) are rare but can present infrequently with PP with the rate of development affected by the degree of tumor hormone production. Our objective was to describe a young boy with a β -human chorionic gonadotropin (hCG)-secreting intracranial GCT with an extremely elevated testosterone level, who presented with rapidly progressive PP.

Case Report: A 5-year-old boy presented with penile growth plus pubic hair, deepening voice, and body odor for 3 months. Physical examination revealed a height velocity of 16.25 cm/year, Tanner stage 3 pubic hair, and enlarged penis for age. Laboratory results revealed elevated serum and cerebrospinal fluid β -hCG and 17-hydroxyprogesterone progesterone levels. The testosterone level was above the initial detection range at 2700 ng/dL. Follicle-stimulating hormone and luteinizing hormone were prepubertal with normal serum and cerebrospinal fluid alpha-fetoprotein levels. Imaging showed a pineal mass diagnosed as a β -hCG-secreting GCT. During chemotherapy, the physical signs of PP remitted and laboratory values normalized.

Discussion: Intracranial tumors can cause peripheral PP in boys. If the tumor produces high β -hCG levels, this could cause severe hyperandrogenemia resulting in the rapid development of secondary sexual signs. GCTs should be considered in male patients with rapidly progressive PP, even in those lacking other signs of a brain tumor.

Conclusion: When presented with a boy with PP, a GCT should be considered if workup shows an elevated testosterone level in conjunction with an elevated β -hCG level, especially if with rapid development.

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Introduction

Precocious puberty (PP) is a rare condition in childhood, and even rarer in boys. PP is classically defined as the development of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys.¹ It can be classified as gonadotropin-dependent, central PP or peripheral, gonadotropin-independent PP. Peripheral PP is less common and typically associated with exogenous sex hormone

exposure or excess endogenous sex hormone secretion, either adrenal or gonadal but not commonly from intracranial etiologies,² with 1 cause being tumors producing human chorionic gonadotropin (hCG). PP is an uncommon presentation of hormone dysregulation from a brain tumor but most commonly has a peripheral etiology with germ cell tumor (GCT) rather than central PP. Central PP occurs more with other intracranial tumors. PP in boys is more likely to reflect a pathologic etiology rather than idiopathic¹; therefore, urgent workup and referral should be considered.

Intracranial tumors comprise 15% to 20% of all childhood and adolescent malignancies. Presentation occurs in a myriad of ways, often delaying diagnosis, which may allow tumor progression, poorer prognosis, and development of more physical manifestations before diagnosis.³ Intracranial GCTs account for up to 3% of pediatric primary brain tumors in western countries,⁴ disproportionately affecting males at a ratio of 2:1 to 4:1 and typically residing in the

Abbreviations: AFP, alpha-fetoprotein; CSF, cerebrospinal fluid; FSH, follicle-stimulating hormone; GCT, germ cell tumor; hCG, human chorionic gonadotropin; LH, luteinizing hormone; NGGCT, nongerminomatous germ cell tumor; PP, precocious puberty.

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suprasellar or pineal region. Patients with GCT often present with clinical features that may include endocrinopathies related to the tumor’s location and size and age of the patient.⁵ Only limited data regarding the incidence of PP in GCTs are available.

We describe a young boy with a rare β -hCG-secreting intracranial GCT, which led to an elevated testosterone level above the assay detection range, causing a significantly rapid progression of peripheral PP.

Case Report

A 5-year-old boy presented for evaluation of rapid linear growth and penile enlargement, which was noted when a regular-size underwear for boys did not fit him. His mother noted pubic hair, deepening voice, and body odor in the 3 months prior to presentation. He denied neurologic symptoms, including headache, visual changes, or balance difficulties. Examination revealed height and weight above the 99th percentile and a height velocity of 16.25 cm/year corresponding to the 97th percentile for age (Fig. 1 A and B) as well as a muscular body habitus, deep voice, mature male facial bone structures (Fig. 2), enlarged and thinned scrotum, and Tanner stage 3 pubic hair. The penis was markedly enlarged for age with a stretched penile length of 12 cm and diameter of 2.5 cm. The testicular volumes were 2 mL on the left and 5 mL on the right.

Laboratory studies were significant for the following: elevated levels of β -hCG of 695 mIU/mL (0-3 mIU/mL), 17-hydroxyprogesterone progesterone of 633 ng/dL (0-90 ng/dL), estradiol of 81.3 pg/mL (0-20 pg/mL), and total testosterone of >1,500 ng/dL, which after serial dilution was 2700 ng/dL (0-19 ng/dL). He had suppressed luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (FSH, <0.2 mIU/mL; LH, <0.2 mIU/mL) and normal levels of dehydroepiandrosterone of 62.8 mcg/dL (18-194 mcg/dL) and alpha-fetoprotein (AFP) of 6.9 (0.0-9.0 ng/mL). Lumbar puncture revealed an elevated cerebrospinal fluid (CSF) β -hCG level of 851 IU/L (<10 IU/L) and AFP level of <0.5 ng/mL.

Highlights

- Human chorionic gonadotropin-secreting tumors are a rare cause of peripheral precocious puberty in boys.
- Peripheral precocious puberty may raise testosterone above assay detectable range.
- Consider germ cell tumors in rapidly progressing precocious puberty.

Clinical Relevance

A young boy had unusually rapidly progressing precocious puberty and significant elevations in testosterone and β -human chorionic gonadotropin due to pineal tumor. This highlights the importance of high suspicion for extragonadal tumor, prompt work-up in context of precocious puberty and considering special serial dilution of testosterone level if above assay’s detectable range.

Bone age was markedly advanced to 11 years and 6 months at a chronological age of 5 years and 6 months (Fig. 3). Brain magnetic resonance imaging revealed a 1.8 × 1.6-cm heterogeneous cystic pineal mass (Fig. 4). Due to the location of the tumor and significant elevation of β -hCG levels in both serum and CSF, the diagnosis of nongerminomatous GCT (NGGCT) was made without histology confirmation. The patient began chemotherapy with carboplatin, etoposide, and ifosfamide. After 2 months of chemotherapy, biochemical PP resolved with the total testosterone and β -hCG levels decreased to <5 ng/dL and <2 mIU/mL, respectively, with improved clinical virilization, including a decrease in the penile and testicular sizes, higher pitch of voice, and some regression in mature facial features. By completion of chemotherapy, the tumor size had markedly decreased compared with that on initial imaging. Chemotherapy was followed by radiotherapy during which he received 3060 cGy in 17 daily fractions to the ventricles followed by brain primary tumor

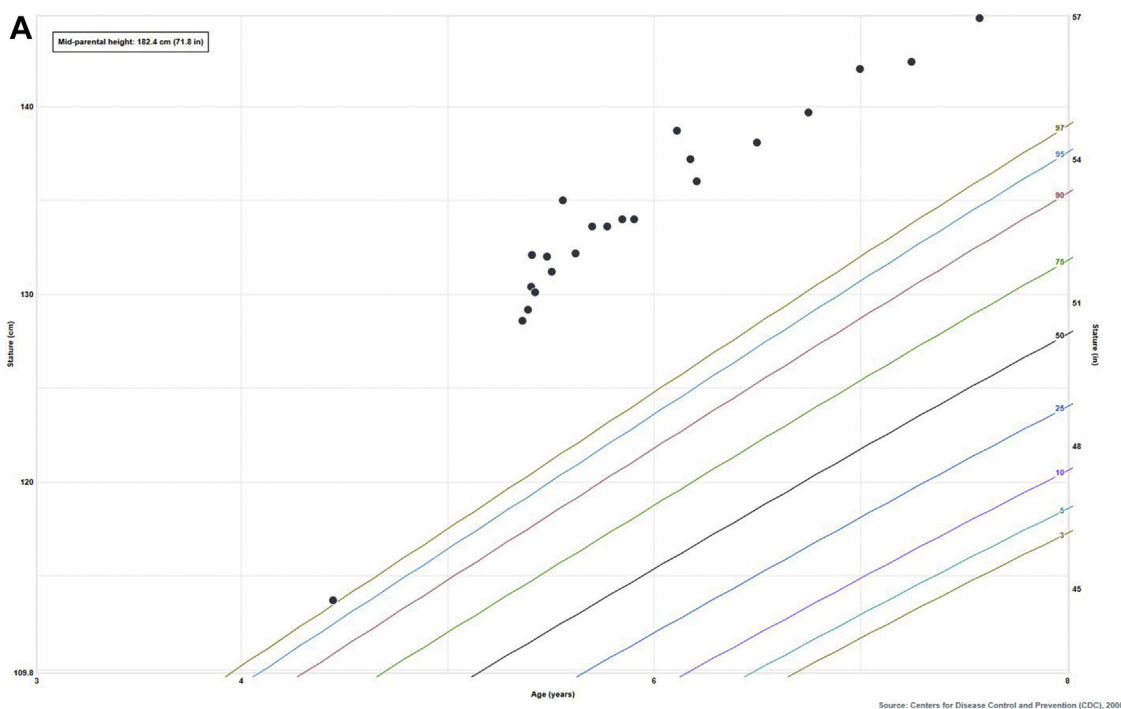


Fig. 1. A, Growth chart demonstrating a marked increase in linear growth from the 97th percentile to >99th percentile within 1 year. B, Height velocity of 16.245 cm/year (>99th percentile) over an 11-month period between documented measurements.

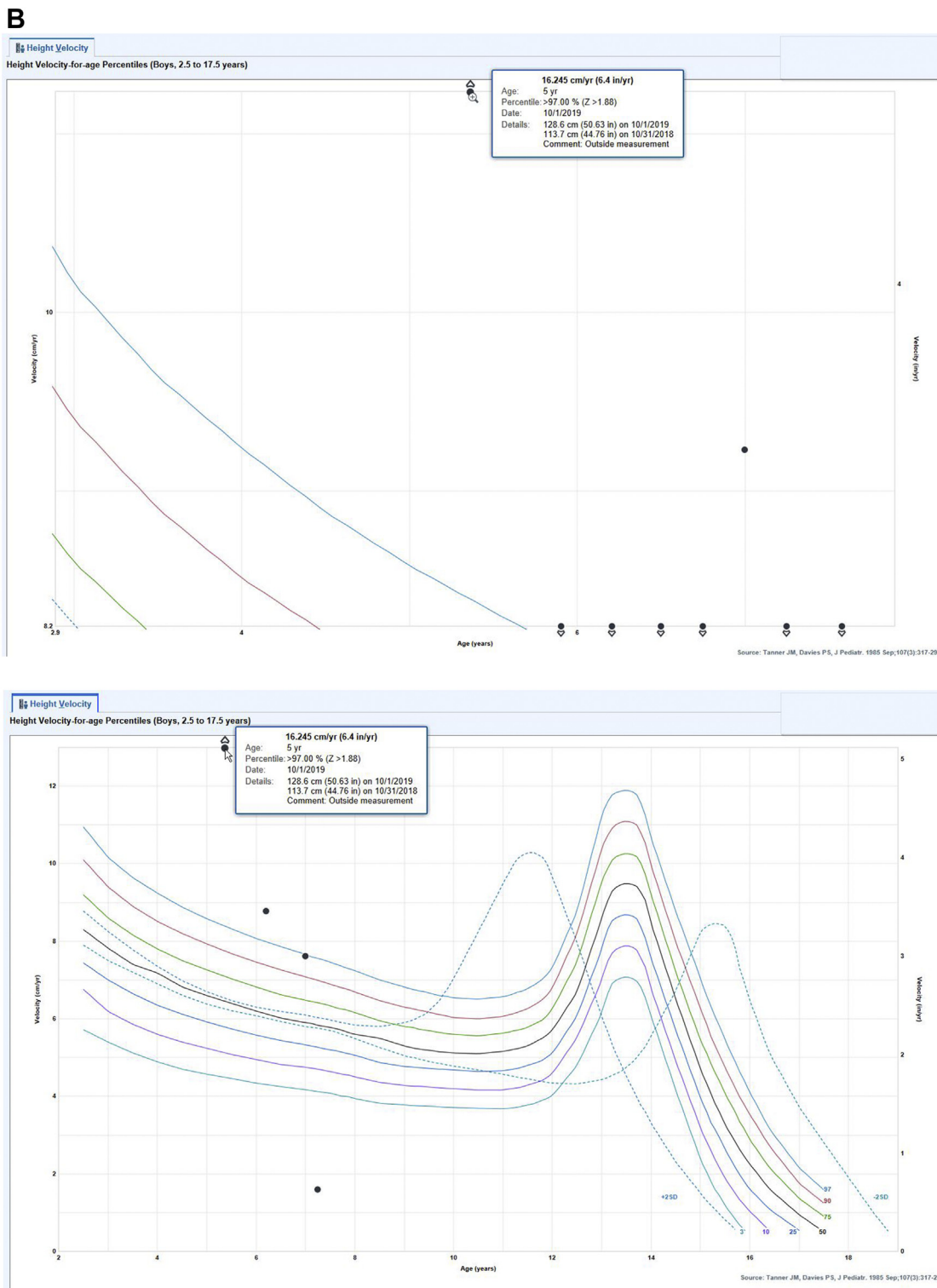


Fig. 1. (continued)

boost, for an additional 2340 cGy in 13 fractions. He did well clinically with persistent regression in his androgenized features, and β -hCG remained undetectable. However, within a year of completion of his oncologic treatment, the patient developed central PP with pubertal gonadotropins, including an LH level of 0.323 mIU/mL. The testosterone level measured via liquid chromatography-mass spectrometry remained low at 6 to 8 ng/dL; therefore, administration of a gonadotropin-releasing hormone agonist was planned.

Informed consent for a case report was obtained.

Discussion

Gonadal and extragonadal hCG-secreting tumors are rare causes of PP in boys with no available data on the prevalence of PP on literature search between the types of intracranial GCT. A thorough, immediate workup of a male with PP is necessary because up to 75% of

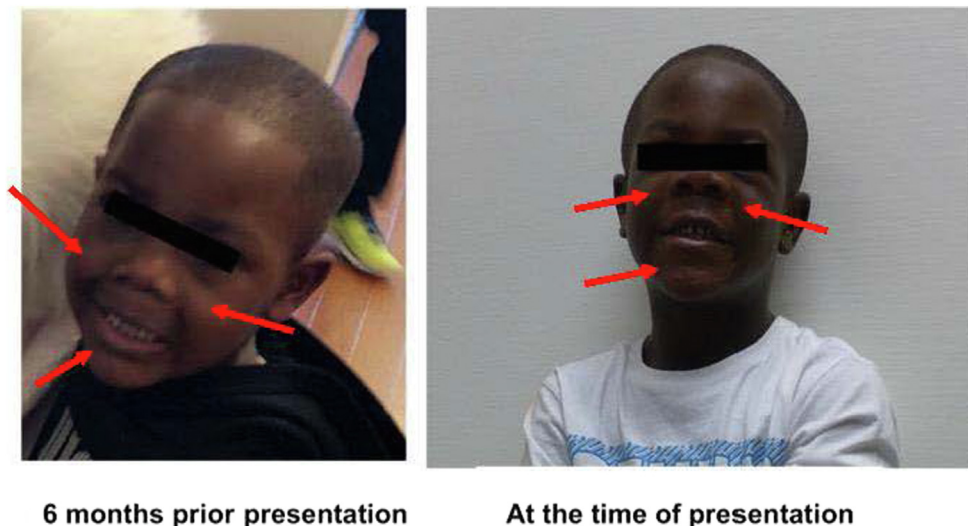


Fig. 2. Dramatic changes of the virilization of the patient's appearance over 6 months, including well-defined, masculine cheek bones, facial elongation, and redistribution of facial adipose tissue.

boys with central PP have a pathologic etiology compared to 10% to 20% of girls.⁶ There is a low frequency of PP presentations similar to our index patient on literature search, although it has been reported. Central PP is more common than peripheral PP, with an estimated incidence of approximately 1 in 5,000 to 10,000 in the general population.⁷ PP caused by a β -hCG-secreting intracranial GCT has been traditionally classified as peripheral. This is because, although the pathophysiology involves a central hormone arising from a central nervous system location, it is independent of the hypothalamic-pituitary axis. hCG-secreting tumors are more often hepatic or mediastinal, specifically in patients with Klinefelter syndrome, but not intracranial, as presented in this case.⁸ Regardless of classification, an important point is that measurement of hCG should be routinely part of the evaluation of rapidly progressive PP.

GCTs are a heterogeneous group of tumors divided into germi-nomas,⁹ encompassing 50% to 70%⁵ of GCTs and presenting between 7 and 30 years, and NGGCTs, comprising approximately one third of

GCTs and occurring commonly from birth to 20 years.¹⁰ NGGCTs include teratomas, embryonal carcinomas, choriocarcinomas, and yolk sac tumors.¹¹ PP can occur rarely with both subtypes, with peripheral PP more common although still rare. Germinomas are generally negative for tumor markers with low levels of serum and CSF β -hCG (<50 mIU/mL), requiring histologic confirmation. Conversely, significant elevated levels of β -hCG (>50 mIU/mL), with or without elevation of the AFP level, are diagnostic for NGGCT.¹² As our case was noted to have a significantly elevated β -HCG level, the histologic features were suggestive of choriocarcinoma, and our oncology team chose the standard of care chemoradiotherapy as in case description.

β -hCG stimulates both testicular and adrenal LH receptors leading to inappropriately elevated testosterone levels as well as elevated levels of adrenal and testicular androgen steroid precursors, in particular 17-hydroxyprogesterone progesterone.¹³ In our index case, serial dilution was required to accurately measure the testosterone level. Serial dilutions of testosterone were requested as a special laboratory order because hyperandrogenemia in this age group warrants further evaluation to narrow differential diagnosis, including central PP, androgen-secreting tumors, and familial male-limited PP. The unregulated synthesis of testosterone resulting from β -hCG stimulation to Leydig cells can lead to the rapid physical changes in males, although sparing testicular growth because of a normal hypothalamic-pituitary-gonadal axis sparing Sertoli cell FSH stimulation. However, a reported risk of PP with GCT varies. In a cohort of 181 patients with intracranial GCT, only 2 patients presented with PP due to elevated β -hCG levels and were diagnosed with NGGCT,¹⁴ which differs from another small study that revealed a 67% incidence of PP in GCT.¹⁵ For these reasons, selection of initial imaging studies can be challenging, especially in the absence of neurologic symptoms, as seen in our case, as the tumor location will be unclear from initial laboratory studies. A swift workup and early diagnosis are critical to minimize progression of PP, both central and peripheral etiologies, in particular nonreversible changes, such as bone age advancement.

Endocrine abnormalities are less frequently identified at the time of diagnosis of these tumors but are common sequelae of their treatments¹⁵. Patients with prior β -hCG stimulation can progress into central PP, as occurred with our patient due to prior hypothalamic-pituitary exposure to testosterone. Suntharesan et al¹⁶ reported the case of an 8-year-old boy with a mediastinal GCT secreting β -hCG. At follow-up after surgical resection, he presented with central PP with an elevated LH level causing bone age advancement requiring



Fig. 3. Bone age was advanced to 11 years and 6 months at a chronological age of 5 years and 6 months.

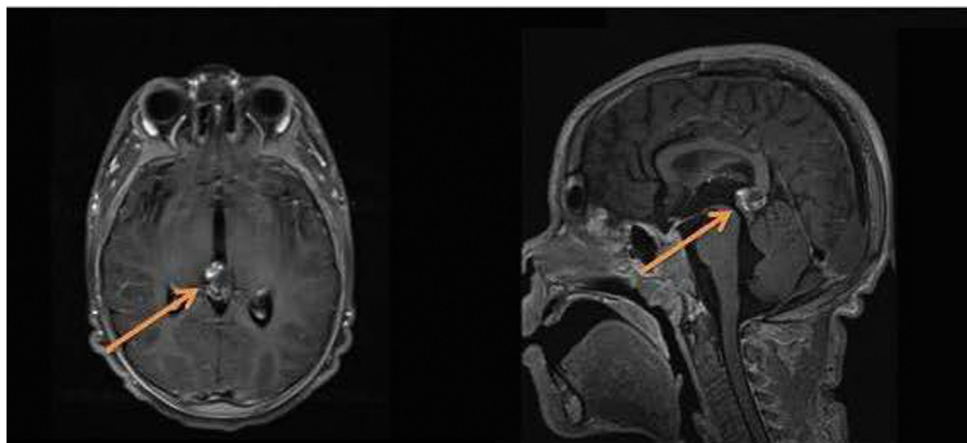


Fig. 4. Brain magnetic resonance imaging with contrast shows a heterogeneous cystic mass at tectal/pineal region with peripheral contrast enhancement. It measures 1.6 (transverse) × 1.8 (anteroposterior) cm. A, Axial plane. B, Sagittal plane.

treatment with gonadotropin-releasing hormone analogs. This is an important consequence of unregulated sex steroid production secondary to β -hCG considering other sequelae of PP, such as short stature from premature epiphyseal fusion.¹⁷

Mature physical appearance has been shown to increase behavior and academic performance expectations¹⁸ and can affect children's self-esteem due to differences compared with peers. Therefore, preservation of adult height, especially when PP presents before the age of 6 years, and prevention of psychosocial difficulties are among the primary goals of PP treatment.¹⁹ There is a paucity of data regarding long-term effects and outcomes related to puberty in cases where PP is due to an intracranial GCT diagnosed at a very young age. Because peripheral PP itself is still a rare side effect of GCT, an extensive literature search failed to encounter recommendations for long-term monitoring or treatment options to prevent recurrence of PP.

Prompt referral is crucial for timely diagnosis and treatment of male PP, both central and peripheral. By the time this patient presented to endocrinology, at least 3 months of clinical symptoms had passed. During that time, he experienced dramatic changes in growth and appearance, only some of which were reversed by the successful treatment of his tumor. Yet, had his workup been further delayed, he could have experienced more physical changes that may not have been reversible, and he still, ultimately, developed central PP.

Conclusion

PP may have deleterious effects on the growth and psychological development of a child as well as compromise final adult height. Pubertal changes can progress extremely rapidly in the context of unregulated testosterone production, which rarely could occur due to intracranial hCG-secreting tumor. Prompt referral in cases of male PP, including investigation for intracranial tumors, is important to prevent delay in diagnosis and treatment.

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this patient's serum to obtain a measurable testosterone level at diagnosis.

Disclosure

The authors have no multiplicity of interest to disclose.

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