CASE REPORT

Peripheral Precocious Puberty Caused by Human Chorionic Gonadotropin Producing Pineal Gland Tumor

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Received: May 22, 2017; Initial review: July 03, 2017; Accepted: December 01, 2017.

Background: Pineal gland lesions usually present with central precocious puberty. **Case characteristics**: A 3½-yr-old boy presented with precocious puberty. Clinically and biochemically, it was gonadotropin releasing hormone (GnRH) independent. Serum and CSF beta-hCG levels were increased. Thin section magnetic resonance imaging of brain revealed a pineal gland tumor. **Outcome**: He received chemotherapy followed by radiotherapy and responded well. **Message**: CSF β-hCG should be measured in all cases of peripheral precocity, and if CSF beta-hCG is elevated, thin section magnetic resonance imaging of brain should be considered.

Keywords: *Cerebrospinal fluid β-hCG, Diagnosis, Magnetic resonance imaging.*

Intracranial germ cell tumors (GCT) are rare accounting for 0.4-3.4% of all pediatric brain tumors in Western countries and upto 11% from Japan and other Asian countries [1,2]. Among all types of GCTs, germinomas are the most common [3]. They are most commonly located in pineal and suprasellar regions of brain. Human chorionic gonadotropin (hCG) secreting GCTs in pediatric age group are extremely rare. Here we describe a case of hCG-secreting pineal tumor which presented with gonadotropin independent precocious puberty, and responded well to chemotherapy and radiotherapy.

Case Report

A 3½-yr-old boy was brought with complaints of progressive penile enlargement, noticed by the mother since the age of two and half years with change in voice and appearance of pubic hair for last 6 months. He had accelerated growth and aggressive behavior. The child did not have headache, vomiting, visual impairment or seizures. There was no evidence of salt wasting crisis, bony pain, fracture or deformity. He was born out of non-consanguineous marriage at full term with an uncomplicated neonatal course. His developmental milestones were appropriate for age. Family history was non-contributory.

He was alert, hyperactive, normotensive with no facial asymmetry, bony deformity or hyperpigmentation. Anthropometry revealed height of 107cm, weight of 22 kg (both >97th centile); mid parental height (MPH) was 163 cm (5th centile) [4]. Testicular volume was 6 mL on both sides, with stretched penile length of 8 cm and Tanner stage 3 pubic hair. There was no hepato-splenomegaly. Fundus examination did not show any abnormality. Rest of the general and systemic examinations were within normal limits.

Investigations revealed normal hemogram, kidney and liver function tests. Bone age was 5.5 years (advanced by two years, according to Greulich and Pyle's atlas). He had normal thyroid function, elevated serum total testosterone (5.09 ng/mL) and suppressed gonadotropins (Leuteinizing hormone [LH] 0.21 mIU/mL; Follicle stimulating hormone [FSH] 0.66 mIU/mL) which did not increase after Gonadotropin releasing hormone (GnRH) agonist stimulation test. A diagnosis of peripheral precocity was made. On further evaluation, serum 17 hydroxy-progesterone (1.37 ng/mL; normal value 0.1-1.39 ng/mL) and dehydro epiandrosterone sulphate (DHEAS) levels (27.8 mcg/dL; normal value <27 mcg/dL) were within normal range for age. However, serum beta-hCG level (31.49 mIU/mL; normal value <5.0 mIU/mL) was increased which was confirmed by three repeated estimations. Hence, a possibility of peripheral precocity caused by beta-hCG producing lesion was considered.

Ultrasound scrotum and contrast enhanced computed tomography (CECT) chest and abdomen were

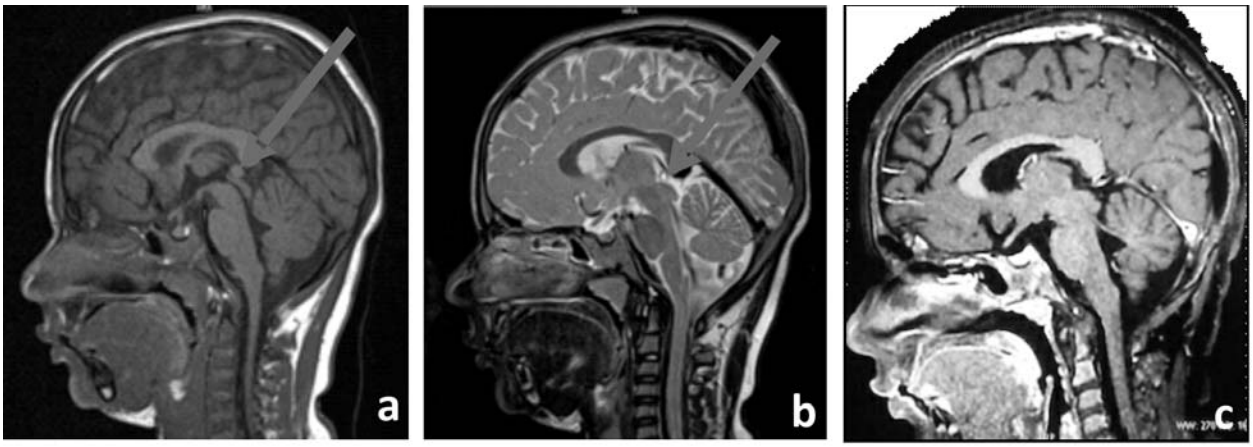

***Fig.* 1** *Thin section MR brain in sagittal section T1 weighted (a) and T2 weighted (b) image showing 8.0 × 6.0 × 5.0 mm pineal gland with necrosis (white dot) within. MR Brain (c) after 4 cycles of chemotherapy revealed disappearance of pineal tumor.*

normal. Magnetic resonance (MR) of sella and brain revealed a subtle abnormality in pineal gland without any definite lesion. ^{18}FDG PET/CT scan and ^{68}Ga-DOTANOC PET/CT scan did not show any abnormal uptake. In view of non-localisation of the source of hCG, cerebrospinal fluid (CSF) analysis was performed which revealed a high CSF beta-hCG level (49.21 mIU/mL, normal value <5.0). Notably, alpha fetoprotein was normal both in the peripheral blood and CSF. To characterise the lesion of pineal gland, thin section MR brain showed a 8.0 x 6.0 x 5.0 mm cystic pineal lesion with blood fluid level within (***Fig.* 1 a** and **b**).

A diagnosis of peripheral precocious puberty caused by beta-hCG secreting pineal tumor was made. He was treated with four cycles of bleomycin, etoposide and cisplatin (BEP) chemotherapy with dramatic response. There was regression of secondary sexual characters. Serum testosterone level and beta-hCG levels both in serum as well as CSF normalised (***Table* I**). Repeat MR sella revealed disappearance of pineal lesion (***Fig.* 1c**). Thereafter he received radiotherapy to the brain. At 12 months of follow up, he was tumor-free and clinically well.

DISCUSSION

Precocious puberty caused by pineal GCT may be gonadotropin-dependent, causing interference with gonadostat or may be gonadotropin-independent caused by secretion of hCG, which acts biologically like LH. In our case, pineal lesion produced hCG causing peripheral precocity, as evidenced by high hCG level in CSF and serum and negative gonadotropin releasing hormone stimulation test. Ectopic hCG secreting tumors are known to cause precocity in boys and occasionally peripheral precocity in girls [5,6]. The postulated mechanisms of precocity in females are: low FSH activity of very high hCG and high aromatase activity of pineal tumor.

The role of tissue biopsy to confirm pineal area tumors and its surgical management remains controversial as the tumors are heterogeneous and the procedure may result in severe complications. Our case responded well with four cycles of cisplatin, etoposide and bleomycin followed by radiotherapy. There are reports of hCG-secreting pineal germ cell tumors which respond well to radiotherapy [7,8] or both radiotherapy and chemotherapy [5,6,9]. Kuo, *et al*. [10] successfully treated a 9-year-old boy with pineal GCT and peripheral precocious puberty without any surgical intervention.

In this case, we first diagnosed peripheral precocity secondary to an hCG secreting tumor. CSF hCG levels

TABLE I BASELINE HORMONAL PARAMETERS AND TUMOR MARKERS IN INDEX PATIENT

	At presentation	*After chemotherapy*		*Age appropriate*
		2 cycles	*4 cycles*	*normal value*
Serum total testosterone (ng/mL)	5.09	1.2	0.29	0.02-0.25
Serum β-hCG (mIU/mL)	31.49	5.09	<1.2	<5.0
CSF β-hCG (mIU/mL)	49.21	9.27	2.45	<5.0

were elevated which indicated central nervous system as the likely tumor site, but initially imaging of brain could not localize any lesion. So, it was a challenge to localize the source of hCG as nuclear imaging like ^{68}Gallium DOTANOC PET/CT and ^{18}FDG PET/CT were normal. Finally, it was the thin section MRI that picked up the lesion.

Present case report suggests measurement of CSF beta-hCG in all cases of peripheral precocious puberty, and if CSF beta-hCG is elevated thin section MR brain is advisable. It also highlights the complete clinical, biochemical and radiological resolution of the tumor with nonsurgical management.

Contributors: SHR, DK: wrote the manuscript; RK, DK, SB: edited the manuscript.
Funding: None; *Competing interests*: None stated.

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