CASE REPORT

Central or Peripheral Precocious Puberty: Diagnostic Difficulties

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Received: August 24, 2015;
Initial review: October 20, 2015;
Accepted: May 27, 2016.

Background: An underlying identifiable organic cause is present in up to 50% cases of central precocious puberty in male patients. **Case characteristics**: A 7-years-8-months-old presented with delayed puberal development. Analytical examinations showed suppressed basal and stimulated levels of testosterone, LH and FSH. Abdominal ultrasound and contrast cranial magnetic resonance results were initially negative. **Outcome**: Germinoma was found on cranial computer tomography. **Conclusion**: There is often a wide time-lapse between symptoms and diagnosis of germinoma, so frequent monitoring is vital.

Keywords: *Central nervous system tumor, Germinoma, Hypopituitarism.*

Central precocious puberty is of idiopathic origin in upto 95% of girls, while in up to 50% of males there is an underlying identifiable organic cause [1]. It is therefore important to take into account that diagnosis of idiopathic central precocious puberty in boys must be a diagnosis of exclusion. One of several organic causes is germinoma, an unusual tumour with variable clinical manifestations. A specific characteristic of these tumours is the considerable length of time that elapses between their onset and their correct diagnosis on MRI scans.

Case-report

A male patient aged 7 years 8 months presented with a 3-month history of facial acne and increase in testicular volume. Upon examination, he had a testicular volume of 6 ml, penis stage IV, pubarche stage I; weight 25 kg (-0.46 SDS), height 124 cm, (-0.62 SDS), body mass index 16.26 kg/m^2 and considerable facial acne, and a bone age of 9 years 3 months (predicted adult height 168.9 cm). The remaining systemic examination showed normal results and the patient did not have any neurological symptoms.

The results of the biochemical analyses showed suppressed levels of LH and FSH (0.11 mUI/mL), androstenedione 0.09 ng/mL (normal 0.3-3.1), DHEA-S 17 mcg/dL (normal 24±22), total testosterone 1.96 ng/mL (normal 1.75-7.81) and free testosterone 2.31 pg/mL (normal 0.04-0.09). In LHRH test, It was administered one single injection of LHRH (100 µg intravenous), with basal blood extraction, and 20, 30 and 60 minutes afterwards: LH 0.11-0.71 mUI/mL and FSH 0.11-0.2 mUI/mL. Serum β-HCG levels were 5 mUI/mL (normal <1.2) and αfetoprotein 1.56 ng/mL (normal 0-15).

A gadolinium-enhanced cranial magnetic resonance imaging (MRI) and abdominal ultrasound scan showed no abnormalities, but following a testicular scan, a 1 cm nodule in the left testicle was detected. Therefore, peripheral precocious puberty was suspected, and a testicular biopsy was taken. However, given that the results of the biopsy were normal, this then indicated a likely case of testotoxicosis. Treatment with Ketoconazole was prescribed, and following three months of treatment, his signs of puberty effectively stabilized (testicles 5-6 mL, improvement in facial acne), height 130.4 cm (0.28 SDS) and weight (-0.3 SDS). However, due to a subsequent onset of polyuria and polydipsia, a computerized tomography scan (CT) and contrast-enhanced cranial MRI scan were taken, both of which presented normal results. Additionally, a blood test was taken, which confirmed that he was suffering from diabetes insipidus. The patient required desmopressin treatment, which controlled the symptomatology. It was thought β-HCG levels were normal, so they were not monitored and repeat CT and MRI, were again normal.

Around 21 months later, following continuous clinical monitoring, the patient began with complaints of headaches and seizures. Another contrast Gadolinium enhanced MRI scan detected a 2.2×2 cm pineal tumour with triventricular hydrocephalus, diagnosed as an hCG secreting tumour (high α-fetoprotein and βhCG in lumbar cerebrospinal fluid and on a ventricular level), which required radiotherapy and chemotherapy. Following this treatment, the tumour was no longer

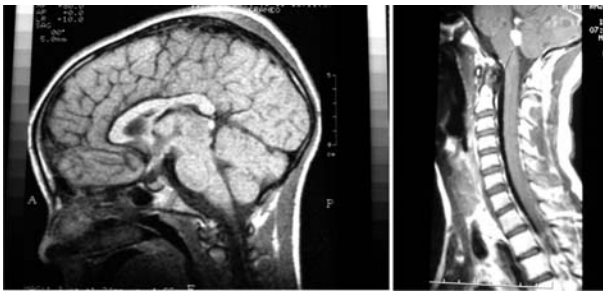
visible on the MRI scan, and tumour markers were negative. At the age of 9 years 9 months, the patient showed a regression in pubertal development (testicular volume 3-4 mL, penis stage IV, no signs of pubarche), with a slow growth rate of 0.3 cm/year, a height of 134.1cm (-1.38 SDS), weight 26.5 kg (-1.07 SDS), and a bone age of 12 years. The clonidine stimulation test confirmed a deficit of GH (maximum GH level: 0.38 ng/mL); however, treatment was not given after a tumour recurrence was detected on the MRI scan 18 months following diagnosis. The patient was administered further radio- and chemo-therapy, but subsequently developed secondary adrenal insufficiency which was treated with hydrocortisone. By the age of 15 years 5 months, the patient's height was 145.3 cm (-3.65 SDS), weight 40.6 kg (-2.02 SDS), testicular volume 10 mL, penis stage IV and pubarche stage IV, but he had no facial or underarm hair. Basal LH and FSH levels were 1.8 and 13.4 mUI/mL respectively, and total testosterone levels were reduced (0.07 ng/mL); GnRH stimulation test could not be done because health state of the patient was seriously affected. So, treatment with intramuscular testosterone was initiated for presence of secondary hypogonadism.

The patient currently continues treatment of chronic replacement therapy with hydrocortisone and testosterone.

DISCUSSION

The diagnostic approach in precocious puberty can be particularly complex. All of the information available initially indicated peripheral precocious puberty, due to the absence of gonadotropins, the negative results of the brain scan and initial normality of the rest of the pituitary axis. However, there were certain symptoms that implied central precocious puberty. Up to 60% of germinomas do not show high âHCG levels, and where present, they tend to be low, with averages values of 7.7 mUI/mL in some studies [2]. Additionally, diabetes insipidus is a symptom that frequently occurs in up to 100% of patients with germinomas. Despite this, in this case, there was no evidence on the serial cranial CT or MRI scans suggesting any type of tumoral pathology. Thus, the most plausible suspected diagnosis was peripheral precocious puberty, and the only viable option was close patient monitoring.

CT and MRI scans are sensitive enough to diagnose suprasellar or pituitary tumours. Neuroimaging was normal initially and it was 2 years after the symptoms began that the pineal germinoma became evident on the MRI brain scan. This is particularly relevant, because there are few cases reported of germinoma in which symptoms actually precede radiographic evidence [3].



(*a*) (*b*)

FIG. 1 *Germinoma MRI imaging. (a) MRI brain sagittal section showing germinoma in pineal region (arrow). (b) Hyperintense mass lesions suggestive of germinoma metastases (arrow) in fourth ventricle.*

Therefore, in the event that any question should arise in diagnosis, it would seem advisable to monitor β-HCG levels rather than depending exclusively on the use of neuroimaging. Although late diagnosis does not appear to affect survival rates in the short-term [4], it does still have an impact on patient morbidity because it increases the risk of disseminated disease and therefore requires a more aggressive therapeutic treatment.

Given that germinoma is a radiosensitive tumour, chemotherapy followed by irradiation enables a smaller dose of RT to be given [5-7], which helps to achieve good long-term survival rates and results in a decrease in side effects. We used a combination of both treatments.

Due to the location of the tumour, the patient developed hydrocephalus with secondary intracranial hypertension. When this occurs, surgery is advised, but there is insufficient evidence to determine whether a ventriculoperitoneal shunt or an endoscopic ventriculostomy [8] is more suitable.

GH-deficiency is the earliest and most frequent complication in patients who have been treated with cranial radiotherapy. In this case, it was not treated due to the complexity of the tumour and its subsequent recurrence. Additionally, both radiotherapy and chemotherapy can cause hypogonadotropic hypogonadism in a considerable percentage of patients [9].

Diagnosis of germinomas is a complex issue. Unfortunately, there is a small percentage of cases in which central nervous system imaging do not reveal any pathological evidence. Consequently, it is advisable to perform an exhaustive and frequent follow-up of the patient, not only analytical or clinically, but also with consecutive radiological brain imaging; this approach will prevent from diagnostic delays and will minimize morbidity and mortality.

Contributors: All the authors have participated in all the aspects of preparation of the manuscript.
Funding: None; *Competing interest*: None stated.

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