CASE REPORTS

HYPOTHALAMIC HAMARTOMA RELATED CENTRAL PRECOCIOUS PUBERTY: REPORT OF A CASE

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ABSTRACT : *Hypothalamic hamartoma (HH) is one of the most important causes of central precocious puberty in children. Hamartomas are malformations composed of ectopic gonadotropin releasing hormone (GnRH) neurons which secrete pulsatile gonadotropin releasing hormone. They are generally observed in children under 3 years. Here we report a $2^{9/12}$ year old male child with complaints of pubic hair growth and growth in his penis starting at the age of one year. Laboratory analysis showed that he had central precocious puberty as a result of a hypothalamic hamartoma. The case was discussed with a review of the literature.*

Key Words: *Hypothalamic Hamartoma, Central Precocious Puberty.*

INTRODUCTION

Hypothalamic hamartoma (HH) is one of the most important causes of central precocious puberty in children. Hamartomas are malformations composed of ectopic GnRH neurons which secrete pulsatile GnRH. They are generally observed in children below 3 years of age. Gelastic (laughing), petit mal, generalized seizures, behavioural disorders and dysmorphic syndromes are rarely seen. Hypothalamic hamartomas which appear to be heterotopic masses that secrete GnRH are not real tumors and they do not grow with time (1). Surgical removal is not recommended; GnRH analogues to stop pubertal findings are preferred (1-3). In this paper, a $2^{9/12}$ year old male child who had central precocious puberty findings that responded to the treatment with GnRH analogues is presented.

CASE REPORT

A $2^{9/12}$ male child was brought to the hospital because he had growth of pubic hair starting from the age of one year. His physical examination revealed the following findings: weight 23.5 kg (>97 p; Standard Deviation Score (SDS) :+2.57), height 105.4 cm (>97p; SDS: +2.65), relative weight 160%, statural age 4, bone age 4, body mass index (BMI) 23.1 (>95), ratio of upper body segment to lower segment : 1.2, heart rate 96 beats/min, and blood pressure: 100/50 mm Hg. There was acne on his forehead. He had a muscular structure (Fig. 1A), his pubic hair was the Tanner III stage and penis length was 6.5 cm (50-90 p) (Fig. 1B). Prader orchiodometers of testis volumes showed 12 ml on the left and 10 ml on the right. Other physical findings on examination were normal. Laboratory findings were as follows, Follicle-

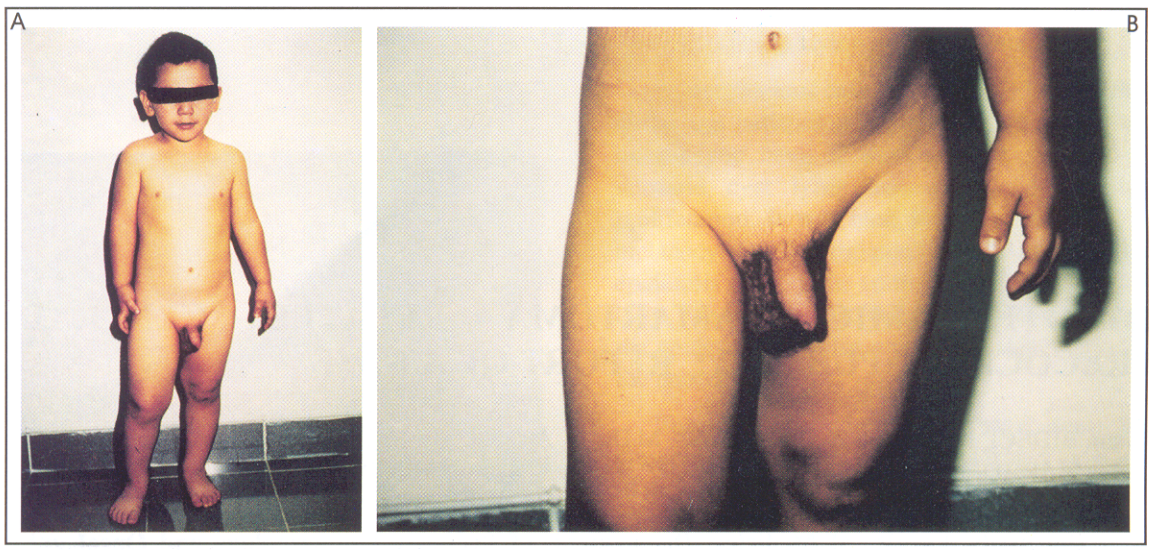

Fig - 1: Patient with a well developed muscular body (A). Patient has an unexpected penile enlargement and testicular development compared to his peers (B).

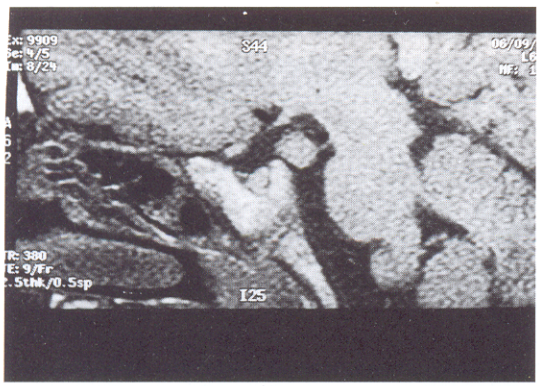

Fig - 2: MRI scan demonstrating a hyopthalamic hamartoma in the case; sagittal T1- weighted image.

stimulating hormone (FSH): 4.37 mIU/ml, Luteinizing hormone (LH): 1.41 mIU/ml, estrodiol (E2) : 17.21 ng/ml (n: 2.5-25ng/ml), free-testosterone: 9.84 pg/ml (adult level; 8.6-54.61), dehydroepianrosterone - sulfate (DHEA-S): 0.27 ug/ml (n: 0.1-0.8 ug/ml), androstenedione : 0.54 ng/ml (n:0.3-2.63 ng/ml), 17-OH progesterone : 0.74 ng/ml (n: 0.74-34.31 ng/ml), prolactine: 5.91 ng/ml (n:2.5-17 ng/ml), adreno - corticotopin - stimulating hormone (ACTH): 30.2 pmol/l (n:0-46 pmol/l), cortisol 11.6 ug/l (n:5-25 ug/l), β HCG: 1.10 mUI/l (n:0-5 mUI/l), alfa-feto protein: 2.81 IU/ml (n:0.5-5.5 IU/ml), Insulin like growth factor-1(IGF-1): 573.22 ng/ml (n:24.3-152 ng/ml), Insulin like growth factor binding protein-3 (IGFBP -3): 3304.5 ng/ml (n:1400-4250 ng/ml). The LH response to the 100 mgr GnRH stimulation test revealed pubertal findings (31.7mIU/ l). Thyroid function tests were normal. The patient showed no adrenal pathology in his ultrasonography and his testicular parenchyma was homogenous with the size of 33x22x15 mm on the right and 33x22x15 mm on the left. Cranial tomogaphy revealed an isodense mass of 20x10 mm in the basal cistern with smooth borders and no significant contrast enhancement. Cranial magnetic resonance imaging (MRI) revealed a 14x11x18 mm lesion in the suprasellar area within the neighbourhood of the posterior infundibulum where the hypothalamus is located (Fig. 2). The lesion had smooth contours, showed no contrast enhancement and was consistent with a hamartoma. Electroencephalography was normal. The bone mineral density was normal for his age. The patient was treated with a long-term effective GnRH analogue leuprolide acetate at a dose of 3.75 mgr (monthly, intramuscular). He was also given oral cyproterone acetate of 75 mg/ m^2 for 4 weeks. During the follow up, his pubertal findings regressed and the level of testosterone (0.32 pg/ml) decreased to the normal level for his age.

DISCUSSION

Precocious puberty is defined as the beginning of puberty before the age of 8 for girls and before the age of 9 for boys and is classified as central (true) and peripheric (pseudo) precocious puberty. Central precocious puberty (CPP) in girls is frequently idiopathic, whereas it is related to pathological causes in boys. Recent findings show that hypothalamic hamartomas are the most frequent causes of CPP in boys (1). Along with hypothalamic hamartomas (4) encephalitis (5), cerebral encephalopathy (6), brain abscess (5), granulomatous lesions of hypothalamus (5), head trauma (7), arachnoid cyst (8), hydrocephaly (8), septo-optic dysplasia (8), empty cella syndrome (8), suprasellar cyst (5), astrocytoma (5), optic glioma (9), pineal ganglioglioma (8) and neurofibromatosis (10) are the other causes of CPP. History, physical examination and imaging techniques are useful in the differential diagnosis of the disorders related to central precocious puberty. For example cafe' au lait lesions together with the findings of precocious puberty should lead the physician to the diagnosis of neurofibromatosis. Many cases which were previously assumed to be idiopathic have been diagnosed as HH after performing cranial tomography or MRI studies. Two diagnoses should be taken into consideration when a male child below 9 years old has secondary sexual characteristics with a testis volume above 4 ml: (true) central precocious puberty and familial testotoxicosis. In familial testotoxicosis , LH does not respond to GnRH and testes are stimulated by G-protein-dependent LH receptors which are activated due to a mutation. If the testis volume is less than 4 ml, then it is false precocious puberty (1-3). Our patient's testis volume was 12 ml on the left and 10 ml on the right and pubic hair was at the Tanner stage III. All these physical examination findings suggested CPP. GnRH test revealed a high peak value of 31.7 mIU/l. Familial testotoxicosis and congenital adrenal hyperplasia diagnosis were ruled out. Cranial CT and MRI studies were performed to establish the causes of true precocious puberty, and in these studies hypothalamic mass lesion consistent with hamartoma was observed.

The CPP caused by a hamartoma leads to pubic hair growth and genital maturation in young children. Along with spontaneous erections, libido and other adolescent behaviour, muscularization is also seen in male children (12,13). During the first examination of our patient, we noticed precocious puberty findings together with a muscular body . In the pathogenesis, it was shown that hypothalamic hamartomas have GnRH neurons and the GnRH secreted by these neurons result in the onset of puberty (1, 14). In the mentioned publications , the patients with HH had mean height SDS values of +1.6 and their body mass indexes were not generally different from those of normal male children. However in some patients obesity was observed (15,16). The values of +2.65 for SDS height, +2.57 for SDS weight and a relative weight of 132.4 % and the measurement of BMI greater than 95 percent in our case were consistent with the values in these publications. It was assumed that the obesity in our patient could be due to stimulation of the appetite center by the hypothalamic hamartoma.

Studies have shown that the level of IGF-1 for the patient's age is higher than the expected level in patients with precocious puberty values compared with those of children with normal puberty. In patients receiving GnRH analogue treatment, the IGF-1 levels are still high for their age, but the levels for their bone age are found to be decreased to the expected normal levels (1). It was found that our patient had a high level of IGF-1 for his age before the treatment.

Uriarte et al. (17) reported that LH peaks stimulated by GnRH were higher in children with HH than patients with idiopathic precocious puberty and showed that there were slight differences in the neuroendocrine regulations that caused those patients to mature rapidly. Also, De Sanctis at al. (14) reported that LH peak values in patients with central precocious puberty related to HH were much higher than those of patients with idiopathic central precocious puberty and that those values showed no correlations with the hamartoma size. Our patient's LH level stimulated by GnRH was 31.7 mIU/L. There are different approaches for the treatment of hypothalamic hamartomas. Today

treatment with GnRH analogues to stop puberty and observing the tumor by means of MRI is accepted. However, in case of intractable seizures or hydrocephaly, surgery is recommended. Stewart et al. (11) compared the patients with hypothalamic hamartoma who were treated by surgical resection to those who received GnRH analogues and observed no differences in growth rate and increased bone maturations (11). They also observed that the growth rate returned to normal and bone maturation rate decreased in the patients who were only treated by GnRH analogues. Therefore they recommended GnRH analogues for the treatment of HH.

We also administered GnRH analogue treatment to our patient together with antiandrogene cyproterone acetate, an for a short period of time (4 weeks). At present he is receiving GnRH analouge every four weeks. The plasma testosterone level is a marker of success of GnRH analogue treatment achieved and values below 0.7 nmol/l indicate that gonadal suppression is sufficient. During the follow up, the testosterone level was 0.32pg/ml in our patient.

In conclusion, central precocious puberty in male children are usually due to intracranial pathologies and hence should be investigated in detail. In hamartomatous cases, medical therapy could be preferred before considering surgical treatment.

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