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Precocious Puberty in a 5-Year-Old Girl with a Giant Hypothalamic Hamartoma Discovered Perinatally: Case Report

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Abstract

Background: Hypothalamic hamartoma is a rare non-neoplastic lesion, typically identified in early childhood during investigations for precocious puberty and/or gelastic seizures. However, cases of diagnosis even earlier or during fetal development have been documented. **Case Presentation:** A newborn girl was diagnosed with hydrocephalus during pregnancy. An MRI revealed a large oval hypothalamic process, which suggested a hypothalamic hamartoma. At the age of 2, she experienced alternating crying and laughing seizures, followed by a decrease in visual acuity. Due to involvement of the optic pathways, surgery was not performed and she underwent antiepileptic medicines and gamma knife radiotherapy. At the age of 5 years and 3 months, she presented with breast development and laboratory tests confirmed central precocious puberty. Quarterly injections of GnRH agonists have since been administered with favorable results. **Conclusion:** Early-diagnosed hypothalamic hamartomas require close monitoring, by an experienced multidisciplinary, to promptly detect and treat potential complications, especially precocious puberty, and prevent any undesirable impact on final height.

Keywords

Perinatally-Hypothalamic Hamartoma-Giant-Precocious Puberty

1. Introduction

Hypothalamic hamartomas, first described by Paillas *et al* in 1969 [1], are rare congenital benign lesions located between the tuber cinereum and the mammil-

lary bodies in the floor of the third ventricle [2] [3]. Their incidence ranges from 1 in 50,000 to 200,000 [4], while giant ones are even rarer, being classified as such when their size exceeds 40 mm in any diameter or their volume exceeds 8 cm^3 [1] [5]. These lesions may remain asymptomatic for a long time or manifest as seizures, mainly gelastic seizures, and/or precocious puberty. The diagnosis of precocious puberty is suspected with the appearance of secondary sexual characteristics before the age of 8 in girls and 9 in boys, confirmed by an increase in serum levels of sex steroids and gonadotropins due to activation of pulsatile secretion of gonadotropin-releasing hormone [6] [7]. The diagnosis of hypothalamic hamartoma is often made by magnetic resonance imaging and the therapeutic modalities are diverse, taking into account the age, symptoms, evolution and exact anatomy of the lesion [8]. Here we describe the case of a 5-year-old girl referred to the paediatric department for precocious puberty due to a giant hypothalamic hamartoma discovered perinatally.

2. Case Presentation

The patient was the second child of non-consanguineous parents. During the pregnancy, hydrocephalus was suspected at 7 months of gestation, and the patient was delivered by caesarean section. On the first day of life, the patient

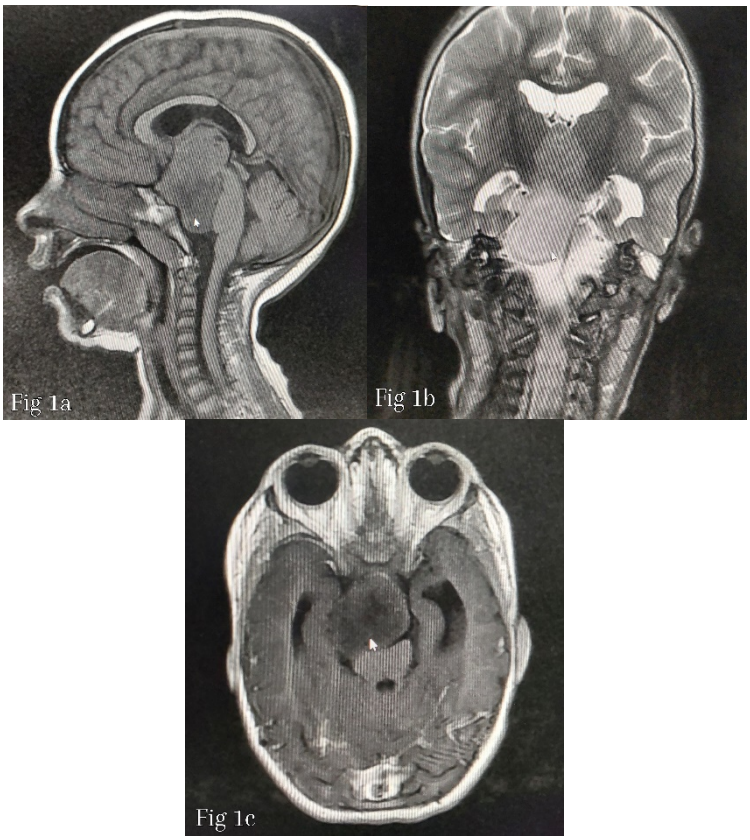

Figure 1. MRI images showing a giant lesion iso hypointense to the gray matter on T1 weighted (a) hyperintense on T2 weighted (b) with no obvious contrast enhancement (c).

was admitted to the neonatal unit. An MRI showed a large oval hypothalamic process with regular contours that was hypo-iso intense in T1 (**Figure 1(a)**) and slightly hyperintense on T2 (**Figure 1(b)**) The lesion did not enhance after contrast (**Figure 1(c)**) and measured 46 × 28 × 28 mm, which suggested a hypothalamic hamartoma. The hamartoma was in contact with the basilar trunk, causing dilatation of the third ventricle. Additionally, it was associated with a cyst of the septum pellucidum. A ventriculoperitoneal shunt was placed, and the patient had a good outcome.

At the age of 2 years, the patient experienced alternating crying and laughing seizures, followed by a decrease in visual acuity. Anticonvulsant medication was administered for medical treatment, and surgical resection was suggested but not carried out due to the involvement of the optic pathways. Subsequently, the patient underwent Gamma Knife radiosurgery with a peripheral reference isodose of 50%, receiving a dose of 12 Gy, taking into account the volume.

The patient was referred to us at the age of 5 years and 3 months for the treatment of precocious puberty. Upon examination, we found the patient to be in good general condition, without any dysmorphic syndrome. The patient's weight was within the average range at 18 kg, and her height measured 116 cm, which is +1 standard deviation. Examination revealed Tanner stage 3 breasts, along with an absence of axillary and pubic hair, and an infantile vertical vulva. Hormonal evaluation revealed an estradiol level of 54.16 pg/ml, LH level of 2.59 IU/L, FSH level of 6.29 IU/L, and normal levels of TSHus (2.55 uUI/ml), free T4 (24.75 pmol/L), prolactin, and morning cortisol (24.7 ug/dL). The patient's bone age was determined to be 11 years. A pelvic ultrasound revealed a uterus measuring 42 mm in length and 13 mm in width and thickness, with a tubular appearance and homogeneous echostructure without visualisation of the empty line. The ovaries were well individualised with a flat shape, measuring 30 mm by 6 mm on the right and 18 mm by 8 mm on the left, with some microfollicles. The patient received quarterly injections of triptorelin 11.25 mg, with no reported adverse effects. After 9 months of treatment, there was a growth rate of 4.7 cm, and the breasts remained at stage 3 of Tanner.

3. Discussion

Hypothalamic hamartomas occur during fetal life and are non-neoplastic, non-progressive lesions that expand with brain growth [1] [9]. Their relative size compared to the brain remains constant, and they can be classified into 4 types based on their insertion plan according to the Delalande and Fohlen classification; Type I is a horizontal implantation (para-hypothalamic), while Type II is a vertical insertion plan and intraventricular location, Type III includes Types I and II, and Type IV includes giant hamartomas [3] [5] [10].

Apart from asymptomatic cases, hypothalamic hamartomas are often diagnosed in early childhood during the investigation of epilepsy (with complex symptoms, often including gelastic seizures-episodes of uncontrollable laughter without joy-or less commonly tonic-clonic seizures, partial seizures, absences,

or dacrystic seizures), central precocious puberty, or developmental delay [3] [5] [8] [11]. Furthermore, some cases of giant hypothalamic hamartomas are identified earlier, sometimes even during fetal life, due to their mass effect [2] [9] [10].

The diagnosis of central precocious puberty is confirmed by an increase in serum levels of sex steroids and gonadotropins, mainly LH which is the most sensitive biomarker, and values > 0.3 IU/L are considered indicative of the onset of puberty [6]. In case of doubt, a second determination through a GnRH stimulation test should be considered; a stimulated LH peak of at least 5 IU/L suggests that puberty is activated, but other thresholds ranging from 4 to 8 IU/L have also been suggested [4] [6] [7] [11]. Bone age is advanced and pelvic ultrasound shows pubertal uterus and ovaries [4] [6] [7]. The exact mechanisms of precocious puberty in the context of hypothalamic hamartomas remain uncertain [5] [12] [13]. Several hypotheses have been proposed, including activation of gonadotropin-releasing hormone (GnRH) by factors derived from astrocytes [5] [12], induction of pubertal hypothalamic neuroendocrine function by secretion of transforming growth factor [5] [8] [12] [13], or the presence of ectopic neurosecretory cells of GnRH located within the hamartoma [4] [5] [8] [13].

MRI allows for the diagnosis of these lesions and differentiates them from tumors in the hypothalamic-pituitary region, which are their main differential diagnosis, including craniopharyngioma, astrocytoma, optic glioma, and meningioma [3] [8] [10] [13]. They are distinguished from normal gray matter by a decrease in intensity on T1-weighted images and an increase in intensity on T2-weighted images [3] [5] [8] [11] [13]. They may also be associated with the presence of cysts, particularly arachnoid cysts. However, it is not known at this time whether these cysts are intrinsic to the lesion or simply an incidental association [9] [14].

The treatment of hypothalamic hamartomas is a real challenge [1] [3] [8]. Remission or at least a decrease in the frequency of epileptic episodes, mainly gelastic seizures, is rarely achieved with anti-epileptic drugs, and radical treatment is often recommended [3] [5] [8]. As for precocious puberty, long-acting GnRH agonists are the preferred treatment. They continuously stimulate the pituitary receptors of GnRH, inducing desensitization and a decrease in gonadotropins. This leads to regression or stabilization of pubertal symptoms, reduction of growth velocity to prepubertal normal values, and slowing down of skeletal age advancement [4] [5] [6] [7]. The radical treatment of hypothalamic hamartomas consists of three components: open surgical resection, which provides the best results in terms of seizure cessation and improvement in neurocognitive, behavioral, and psychiatric symptoms [3] [8]; Gamma knife radiotherapy, which is an excellent tool for treating lesions that are difficult to resect without causing endocrine deficits, despite a late therapeutic effect that can take up to 3 years [1] [13] [15]; and stereotactic thermoablation, where the lesion is heated to about 60℃, thereby impairing its ability to generate seizures [3].

4. Conclusion

Giant hypothalamic hamartomas, diagnosed at an early age, require close monitoring throughout life. A careful approach led by an experienced multidisciplinary team is essential to promptly detect and treat potential complications, especially precocious puberty, and thus prevent any undesirable impact on final height.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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