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Case Report

An Unusual Coexistence of Central Precocious Puberty and Intraventricular Arachnoid Cyst in a Girl

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Abstract: Central precocious puberty (CPP) is a rare disease. In Spain, the annual incidence in girls ranges from 0.13-2.17 new cases per 100,000. CPP in girls is usually idiopathic. Only 7-15% is related to an intracranial lesion. Intracranial arachnoid cysts are usually congenital account for 1% of intracranial masses in newborns. Intraventricular location is rare, account only 0.3-1.4%. Intracranial arachnoid cysts are usually asymptomatic but can present with CPP in 10-33% of patients. We report a case of a 7-year-old-girl presenting the unusual coexistence of CPP and a neurologically asymptomatic intraventricular arachnoid cyst. The etiopathogenesis of this association is not well recognized. Analysis of LH peaks after GnRH testing is the gold standard for the diagnosis of CPP. Although central nervous system disorders account for a higher percentage of cases in boys with CPP, they must also be excluded in girls. In this patient, brain MRI did not show hypothalamic-pituitary axis alterations or the existence of hydrocephalus, so we cannot prove a causal relationship between the intraventricular arachnoid cyst and CPP. Therefore, this coexistence may be only accidental. However, we emphasize that all girls with CPP should undergo brain MRI as part of their evaluation, as clinical characteristics, including age, do not help to predict underlying pathologies. Cyst surgery does no affect the course of pubertal development. There seems to be a consensus that in pediatric patients the indication for surgery is seizure onset, hydrocephalus, ruptured/hemorrhaged, and mass effect or slow-growing clinical course.

Keywords: Central precocious puberty, Brain ventricular tumor, Arachnoid cysts, Magnetic resonance imaging, Child.

INTRODUCTION

Precocious puberty in girls is defined as the development of secondary sex characteristics before the age of 8 years. Central precocious puberty (CPP) is caused by early activation of the hypothalamic-pituitary axis, with gonadotropin-releasing hormone (GnRH)- stimulated gonadotropin secretion causing gonadal maturation (Cantas-Orsdemir, S. *et al.*, 2019). In Spain, the global prevalence of CPP in girls is 0.00037, with an annual incidence ranging from 0.13 and 2.17 new cases per 100,000 and an incidence rate from 1997 to 2009 of 11.23 cases per million girls at risk/year (Soriano-Guillén, L. *et al.*, 2010). CPP in girls is usually idiopathic. Only from 7 % to 15%, depending on the series, is related to a central nervous system (CNS) lesion such as neoplasm, cyst, trauma, infection, midline anomalies, and hydrocephalus (Soriano-Guillén, L. *et al.*, 2019). Therefore, CPP with an intracranial lesion in girls is a rare disease.

Intracranial arachnoid cysts are considered benign developmental anomalies that occur within the arachnoid membrane, which undergoes a splitting and traps cerebrospinal fluid (CSF) inside. Most cases are congenital, and usually do not cause any symptoms throughout an individual's life. In cases in which symptoms occur, headaches, nausea, vomiting, dizziness, and hydrocephalus are common. A variety of additional symptoms occurs in some children depending upon the size and location of the cyst. They include lethargy, seizures, hemiparesis, ataxia, vision abnormalities, hearing abnormalities, developmental delay, behavioral changes, cognitive impairment, and difficulties with balance and walking (Cincu, R. *et al.*, 2007). Intracranial arachnoid cysts can also present with variable endocrine manifestations, although only 10% to 33% of patients have CPP (Soriano-Guillén, L. *et al.*, 2019; & Savas Erdeve, S. *et al.*, 2011). Intracranial arachnoid cysts account for roughly 1% of intracranial masses in newborns. The most frequent location is the middle fossa (30-60%), followed by the sellar and suprasellar region (10-20%), the quadrigeminal cistern (10%), the cerebellopontine angle (10%), and the vermis (9%). The remainder occurs in other regions. Intraventricular location is rare and accounts for 0.3% to 1.4% of the total, depending on the series (Cincu, R. *et al.*, 2007; & Al-Holou, W.N. *et al.*, 2010).

We report a case of a 7-year-old-girl presenting the unusual coexistence of CPP and a neurologically asymptomatic intraventricular arachnoid cyst.

CASE OBSERVATION

A 7-year-old girl who consulted for the development of secondary sexual characteristics over the past year was assessed. There was no relevant personal or family medical history. The father's height was 172 cm, and the mother's height was 169 cm. Signs and symptoms of increased intracranial pressure were not present.

The physical examination showed the following data. Anthropometry: weight, 31 kg; height, 138.5 cm (3.67 SDS); body mass index, 16.1; growth velocity over last year, 10.5 cm. Body odor. Well configured female external genitalia. Tanner stages: breast, stage 3; pubic hair, stage 3. The ophthalmological with ocular fundus examination was normal. The rest of the examination was normal.

With the clinical suspicion of precocious puberty, the following complementary studies were performed:

Laboratory and hormone studies. Hematology, biochemistry, tumor markers, thyroid function, prolactin, progesterone, and testosterone: normal.

Pituitary stimulation test with pulsatile GnRH analogue (GnRHa) (leuprolide acetate): luteinizing hormone (LH), basal = 2.6 / peak = 21.6 UI/L; follicle-stimulating hormone (FSH), basal = 3.3 / peak = 15.4 mU/ml; estradiol (E2), basal = 13 / peak = 44 pg/ml.

Imaging studies. Bone age: 8 years and 10 months. Pelvic ultrasound: signs of estrogenic impregnation; uterus body/neck ratio=1; uterus length >3.5 cm; the endometrial line is observed; ovaries both enlarged with increased follicular endowment and follicles >5 mm. A routine head magnetic resonance imaging (MRI) protocol was performed on a Siemens Verio 3 Tesla System using a 12 channel head coil: a thin-walled cystic formation (size = 4.8 x 2.2 x 3.7 cm) showing CSF-like signal was found in the supratentorial region; it is located inside the left ventricular atrium, which appears widened; it is accompanied by a slight dilation of the left temporal horn, possibly due to segmentary compression (Figure 1). No other brain abnormalities were detected. Findings were compatible with an intraventricular arachnoid cyst.

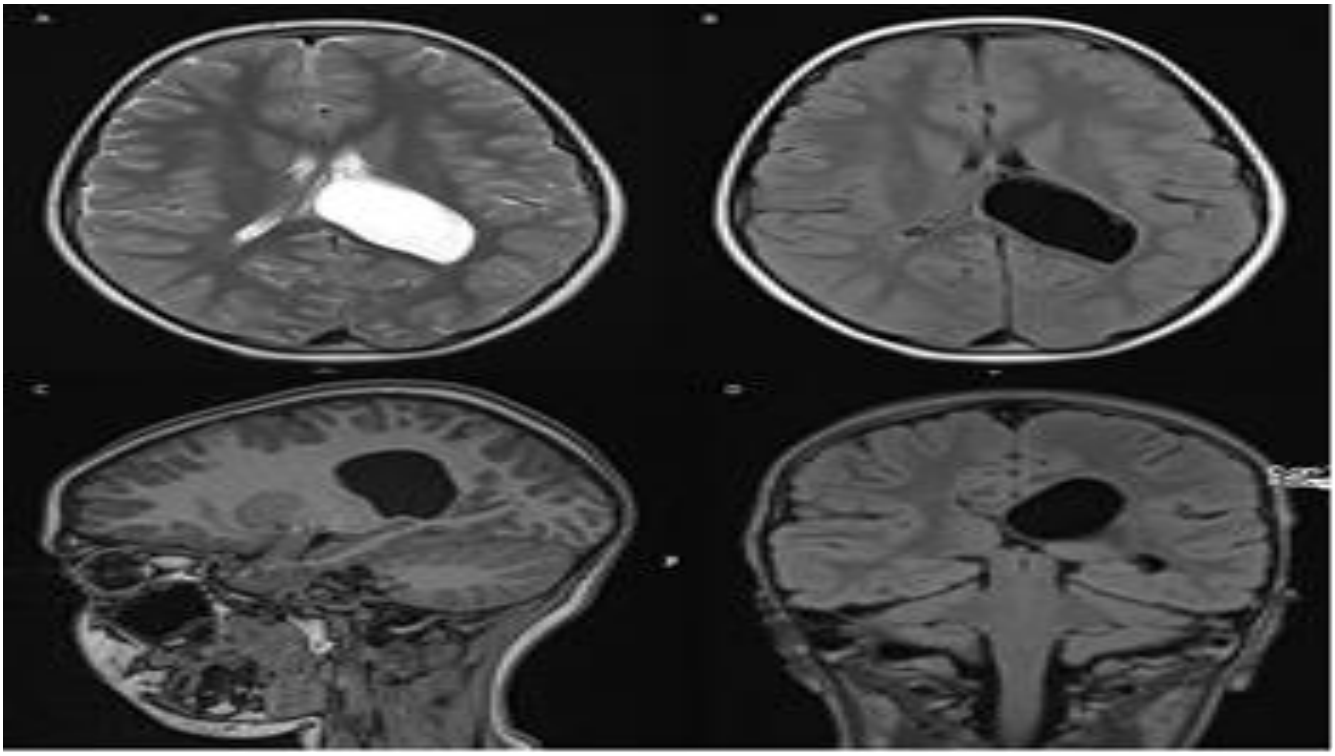

Figure 1. Brain magnetic resonance imaging. A) Axial T2-weighted image. A thin-walled hyperintense CSF-like cyst inside the left ventricle is seen. B) Axial FLAIR image. The intraventricular cyst shows the typical water-like loss of signal, confirming its CSF content. C) Sagittal T1-weighted image. The intraventricular cyst shows a CSF-like signal (hypointensity). The enlargement of the temporal horn can be seen. D) Coronal FLAIR image. The cyst is seen inside the left ventricle. The enlargement of the temporal horn can be seen.

The set of tests confirmed the diagnosis of CPP with organic brain pathology. Treatment with intramuscular GnRHa depot preparation (triptorelin) every 28 days was established. From a neurosurgical point of view, expectant management was recommended.

DISCUSSION

The exact mechanism by which a cyst affects the hypothalamic-pituitary axis is not completely understood. A general concept is the disruption of the normal influence of the hypothalamus on the pituitary gland. One hypothesis is based on the mass effect of the cyst on the hypothalamus. Theories regarding the role of hydrocephalus in CPP include increased ventricular volume and associated mass effect on the hypothalamus, as well as direct compression of various portions of the hypothalamic-pituitary axis (Soriano-Guillén, L. *et al.*, 2019).

For the diagnosis of CPP, hormone studies are needed in addition to the clinical data regarding signs of pubertal onset. Imaging studies, such as bone age, pelvic ultrasound, and brain MRI, are also particularly useful. Furthermore, genetic testing must be incorporated in familial cases. For this purpose, the GnRH test still represents the gold standard. Traditionally, CPP has been characterized by the increase of E2 and an LH peak after stimulation with GnRH or GnRHa (leuprolide acetate) testing. Currently, regardless of the protocol employed, the threshold of LH peak to consider activation of puberty ranges between >5 and 8 IU/L. A basal LH/FSH ratio of ≥0.2 (>0.66 after stimulation) has been recently postulated as an indicator of pubertal activation. Nevertheless, its sensitivity and specificity do not reach that of the GnRH-stimulated LH peak. The bone age is notably greater than their chronological age compared to normal variants of puberty. Notwithstanding, in the early phases of CPP this advance may not be very striking. The main utility of pelvic ultrasound is to detect changes in uterine and ovarian dimensions due to estrogen exposure, and ovarian tumors or cysts that can cause an increase in E2 production (Cantas-Orsdemir, S. *et al.*, 2019; & Soriano-Guillén, L. *et al.*, 2019).

CPP is far more common in girls than in boys. Although CNS disorders account for a higher percentage of cases in boys, they must also be excluded in girls (Soriano-Guillén, L. *et al.*, 2019; Ng, S.M. *et al.*, 2005; & Mogensen, S.S. *et al.*, 2012). In this patient, brain MRI did not show hypothalamic-pituitary axis alterations or the existence of hydrocephalus, so we cannot prove a causal relationship between the intraventricular arachnoid cyst and CPP. Therefore, this coexistence may be only accidental. However, we emphasize that all girls with CPP should undergo brain MRI as part of their evaluation, as clinical characteristics, including age, do not help to predict underlying pathologies. On MRI, regardless of histology, arachnoid cysts are characterized as smooth, well-circumscribed lesions, with an imperceptible wall, displacing adjacent structures, and following the CSF signal pattern (hypodense on CT and hyperintense on T2 with FLAIR suppression). Arachnoid cyst in the lateral ventricle is commonly associated with focal enlargement of the ventricle itself caused by the cyst, with or without partial ventriculomegaly; the shape of the cyst is round or oval, not irregular (Cincu, R. *et al.*, 2007; & Al-Holou, W.N. *et al.*, 2010).

Intraventricular arachnoid cysts represent simple cystic structures. The origin of these lesions is controversial since the ventricles are lined with ependyma and do not contain arachnoid membranes. Researchers have suggested that their origin seems to be secondary to the displacement of arachnoid cells by the vascular mesenchyma, through the choroidal fissure, during the process of choroid plexus development. In some, cases intraventricular arachnoid cysts seem to be secondary to an extension of a subarachnoid arachnoid cyst through the choroidal fissure and into the lateral ventricle (Cincu, R. *et al.*, 2007). Recently Knie *et al.* analyzed follow-up neuroimages after neuroendoscopic cyst fenestration and suggested that the intraventricular arachnoid cysts were originating either from the velum interpositum cistern or from the quadrigeminal cistern. Based on this theory an arachnoid cyst that has its origin laterally may extend through the choroidal fissure to the lateral ventricle when growing. As the lateral ventricle is larger than the velum interpositum cistern, this cyst becomes more prominent. Arachnoid cysts of the quadrigeminal cistern have a close relationship to the posterior midbrain, which causes compression of the aqueduct leading to hydrocephalus, whereas in cysts deriving from the velum interpositum cistern hydrocephalus is a rare finding. A cyst originating from the velum interpositum cistern is usually located parietal at the long axis of the ventricle. A quadrigeminal cyst extends from the midbrain in a parietal direction towards the corpus callosum; during its extension, it can grow laterally into the lateral ventricle, thus mimicking a velum interpositum cyst. Histologically, the cyst wall is of arachnoidal origin but can be covered with the ependymal layer when it protrudes into the lateral ventricle through the choroidal fissure (Knie, B. *et al.*, 2016).

In cases of CPP coexisting with CNS lesions, the etiological treatment, such as surgery, does not affect the course of pubertal development. There seems to be a consensus that in pediatric patients the indication for surgery is seizure onset, hydrocephalus, ruptured/hemorrhaged, and mass effect or slow-growing clinical course (Al-Holou, W.N. *et al.*, 2010; Knie, B. *et al.*, 2016; & Ali, M. *et al.*, 2015). The use of intramuscular GnRHa depot preparations every 28 days is the selected medical treatment for CPP. This product has a decreased enzymatic degradation and in parallel, it has an increased affinity for the GnRH-pituitary receptor resulting in desensitization of the receptor. Consequently, this action produces an inhibition of gonadotropin secretion. On the optimal age to withdraw the GnRHa treatment in girls, with the aim of menarche emerging near to the age of the normal population,

should evaluate whether to discontinue the treatment around 10 years of chronological age or 12 years of bone age. In this regard, spontaneous menses appear around 12 months after GnRHa withdrawal. The available evidence shows that GnRHa is safe and effective, and long-term data suggest that the reproductive function is satisfactory after treatment discontinuation (Cantas-Orsdemir, S. *et al.*, 2019; & Soriano-Guillén, L. *et al.*, 2019).

CONCLUSION

In summary, CPP is a rare disease and in girls, only 7-15% is related to an intracranial lesion. Intracranial arachnoid cysts are infrequent and intraventricular location is very rare. Intracranial arachnoid cysts are usually asymptomatic but can present with CPP in 10-33% of patients. Therefore, the coexistence of CPP and intraventricular arachnoid cyst in a girl is extremely rare. The etiopathogenesis of this association is not well recognized. Analysis of LH peaks after GnRH testing is the gold standard for the diagnosis of CPP. Although CNS disorders account for a higher percentage of cases in boys with CPP, they must also be excluded in girls. In this patient, brain MRI did not show hypothalamic-pituitary axis alterations or the existence of hydrocephalus, so we cannot prove a causal relationship between the intraventricular arachnoid cyst and CPP. However, we emphasize that all girls with CPP should undergo brain MRI as part of their evaluation, as clinical characteristics, including age, do not help to predict underlying pathologies. Cyst surgery does no affect the course of pubertal development. There seems to be a consensus that in pediatric patients the indication for surgery is the onset of neurological symptoms.

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