

Duplication of the Hypophysis Associated With Precocious Puberty: Presentation of Two Cases and Review of Pituitary Embryogenesis

apresentação de casos

ABSTRACT

Pituitary duplication is a rare malformation commonly associated with other major neural/craniofacial anomalies, easily shown by magnetic resonance imaging. The authors describe two girls with duplication of the pituitary gland and thickening of the hypothalamus, facial dysmorphism and precocious pubertal development. The pathogenesis of pituitary duplication and its relationship with precocious pubertal development are discussed. (*Arq Bras Endocrinol Metab* 2005;49/2:323-327)

Keywords: Pituitary duplication; Precocious puberty; Embryogenesis

RESUMO

Duplicação de Hipófise Associada Com Puberdade Precoce: Apresentação de Dois Casos e Revisão da Embriogênese Hipofisária. Duplicação pituitária é uma malformação rara muitas vezes associada a anomalias neurais/craniofaciais, facilmente demonstradas por imagens em ressonância magnética. Os autores descrevem duas crianças do sexo feminino com duplicação da glândula pituitária e espessamento do hipotálamo, dismorfismo facial e desenvolvimento puberal precoce. Discute-se a etiopatogenia da duplicação hipofisária e sua relação com o quadro de puberdade precoce. (*Arq Bras Endocrinol Metab* 2005;49/2:323-327)

Descritores: Duplicação hipofisária; Puberdade precoce; Embriogênese

PITUITARY DUPLICATION IS A rare malformation, reported previously in approximately 23 patients (1-8), three of them presenting with precocious or delayed puberty (2,6,8). Most of the cases are associated with other major neural/craniofacial anomalies which are easily shown by magnetic resonance imaging (MRI) and the majority of patients do not survive beyond infancy. Other pituitary hormone abnormalities are not usually present.

The formation of the hypophysis depends on interaction of the embryonic primordium with normal growth processes in the prechordal region of the head. The prechordal plate and the rostral portion of the notochord are closely related to the development of the pituitary gland. The duplication of the rostral end of the notochord may act as the main factor that leads to duplication of the pituitary primordium, with resultant formation of two morphologically normal glands (8).

The authors describe two girls with duplication of the pituitary gland and thickening of the hypothalamus, facial dysmorphism and precocious pubertal development.

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CASE 1

A 7-year-old white female presented with facial dysmorphism and pubertal development starting at age six. Physical exam revealed hypertelorism, microretrognathia, cleft nose and pubertal development at P3B3 according to Tanner. Laboratory evaluation showed responsive GnRH-stimulated LH levels (7.89UI/L), normal thyroid function, prolactin and IGF-I levels. A pelvic ultrasonography (US) disclosed stimulated uterus (11mL) and ovaries (2.8 and 4.2mL with several follicles greater than 5mm). Bone age was advanced (10 years compared to 7.8 years of chronologic age). Computed tomography (CT) and MRI (figures 1 to 4) showed duplication of the hypophysis with two small and independent glands, each with a stalk, two median eminences, a wide hypothalamus with two infundibular recesses and other malformations. This thickening of the hypothalamus associated with hypophysis duplication has been named pseudohamartoma. This interposed abnormal hypothalamic mass, which consists of arrested cells that normally migrate laterally to form the hypothalamic nuclei, represents the most common associated intracranial abnormality and is probably related to splitting of the end of the notochord (4). The bright posterior pituitary signal was preserved in both glands. Persistence of the cranio-pharyngeal canal, associated with a nasocoanal mass, adherent to the base of the sphenoid was also noted.

The child underwent excision of the nasopharyngeal mass and pathological examination revealed hyperplasia of salivary glands. Treatment with a GnRH agonist was started and 6 months later new laboratory assessment showed non-responsive GnRH-stimulated LH levels, significant improvement of the pelvic US measurements (uterus of 4.2mL, ovaries of 1.2 and 1.6mL with no visible follicles) and no advance in bone age.

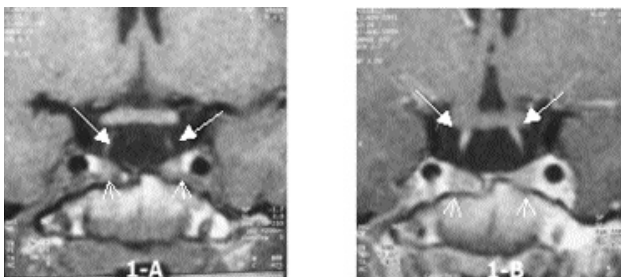


Figure 1. Coronal T1 weighted image before (A) and after (B) contrast, showing pituitary (arrow-heads) and infundibulum duplication (arrows).

CASE 2

A 6.8-year-old white female presented with a history of strabismus, cleft and uvula, dental abnormalities and esophageal fistula, which had been previously treated, and precocious pubertal development. Physical exam revealed right breast development at B2 according to Tanner and growth velocity above the 97th percentile (9cm/year). Laboratory evaluation showed responsive GnRH-stimulated LH levels (7.5UI/L) and a bone age of 6.6 years. Serum measurements of prolactin, thyroid function and IGF-I were within normal limits. MRI (figures 5 to 8) showed duplication of the hypophysis and thickening of the hypothalamus. The patient was reevaluated 6 months later, presenting with no further progression of pubertal development, although persistence of increased growth velocity (8cm/year) was confirmed, associated with advance in bone age (increase of 1.4 years in 6 months), stimulated uterus (6mL) and multiple bilateral ovarian primordial follicles on pelvic US. Treatment with GnRH analog was started and follow-up evaluations showed normalization of growth velocity (6cm/year), uterus volume (3mL) and no progression of Tanner pubertal stage.

DISCUSSION

Hypophysis duplication is a rare phenomenon. Its association with true precocious puberty has been suggested by Burke et al. (6) when they described an 11-year-old female with hypertelorism and pituitary duplication who achieved menarche at 8.5 years of age. The

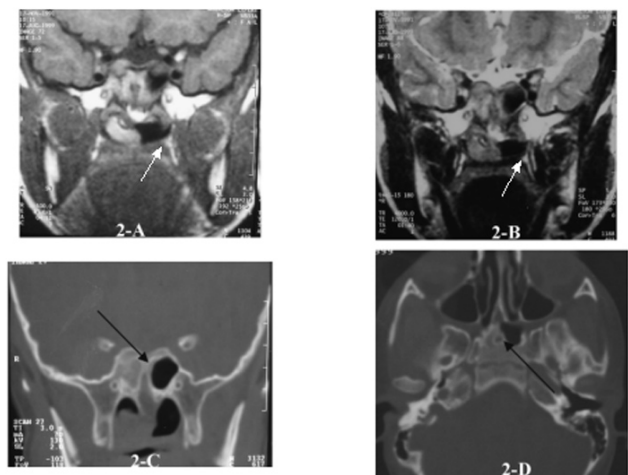


Figure 2. Coronal T1 (A) and T2 weighted (B) images showing nasopharyngeal mass adhered to sphenoid basis (white arrows), with apparent continuity with craniopharyngeal channel (black arrows), better visualized by CT (C and D).

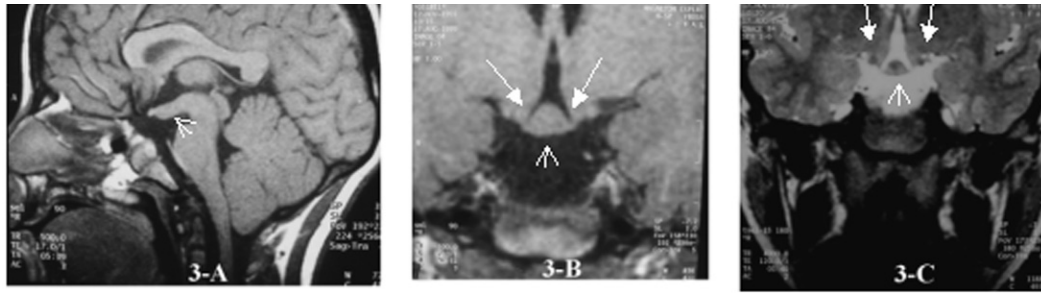


Figure 3. Sagittal (A), and coronal (B) T1 weighted sections, and coronal T2 weighted (C) showing hypothalamic pseudohamartoma (arrow-heads) and duplication of the infundibular recess of the third ventricle (arrows).

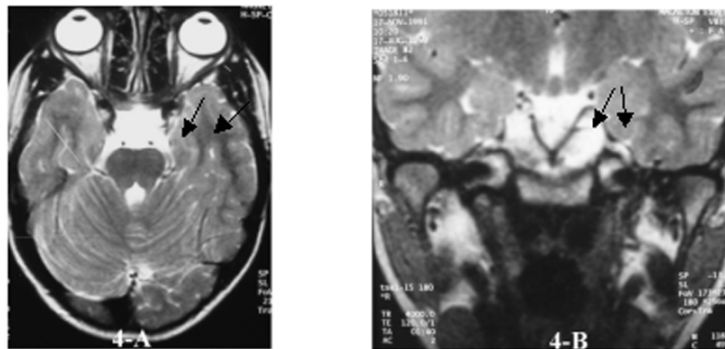


Figure 4. Axial (A) and coronal (B) T2 weighted sections showing cranial duplication of basilar artery (arrows).

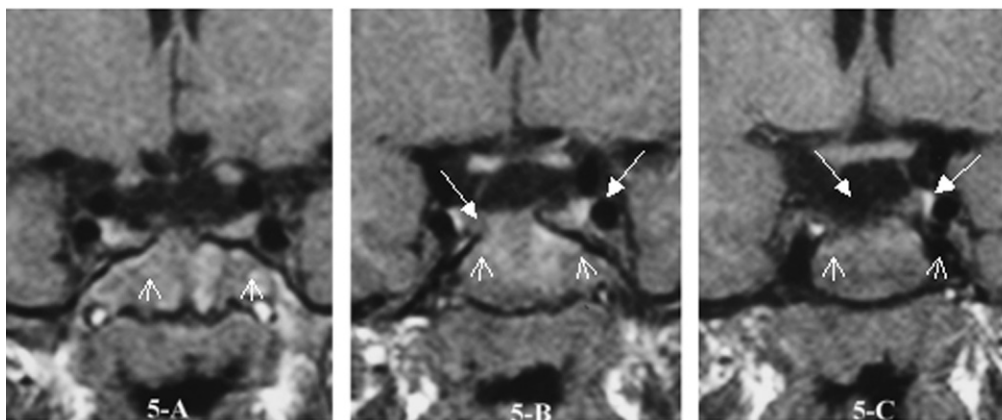


Figure 5. Coronal T1 weighted sections showing pituitary (arrow-heads) and infundibulum (arrows) duplication.

exact mechanism responsible for the early increase in frequency and amplitude of GnRH pulses causing precocious puberty in these patients is still unknown, but may be related to the well-documented association of hypothalamic hamartomas and true precocious puberty. Burke et al (6). proposed that the development disorder leading to duplication may

have caused precocious secretion of LHRH as a consequence of nuclear derangement and failure of regulation. Indeed, delayed puberty has also been described in association with hypophysis duplication (2), emphasizing that the disruption of the hypothalamic hormonal milieu can occur associated with this embryologic abnormality. Taking into consideration

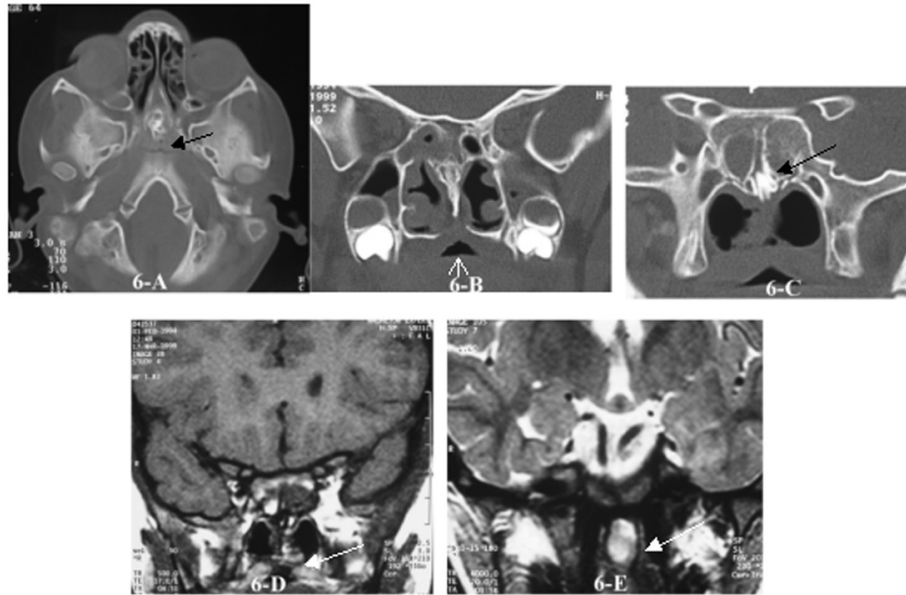


Figure 6. CT – axial (A), coronal (B and C) and MRI coronal T1 (D) and T2 (E) weighted sections showing palate cleft (arrow-head), persistence of nasopharyngeal channel (black arrows) and nasopharyngeal mass (white arrows) in continuity with the sphenoid.

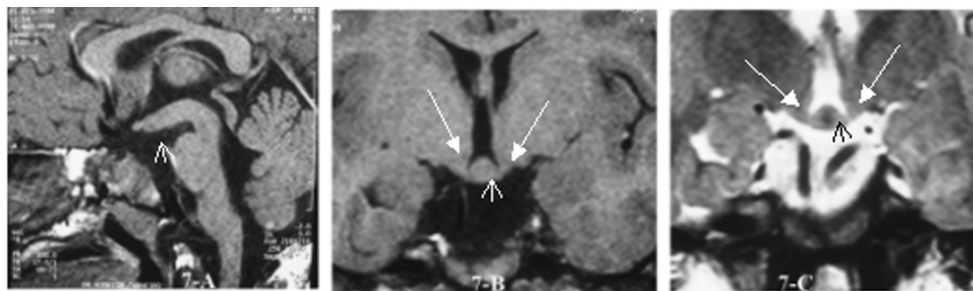


Figure 7. Sagittal (A) and coronal (B) T1 weighted sections; coronal T2 weighted section (C) showing pseudohamartoma (arrow-heads) and duplication of infundibular recess of third ventricle (arrows).

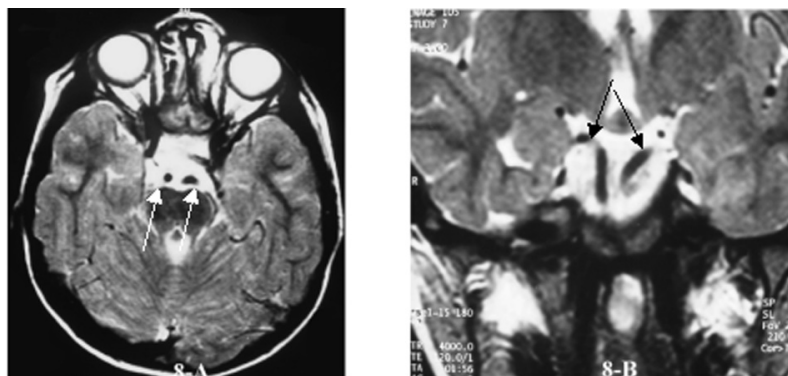


Figure 8. Axial (A) and coronal (B) T2 weighted sections showing duplication of basilar artery (arrows).

that many of the cases of hypophysis duplication reported thus far were diagnosed in very young children, precocious and delayed puberty should probably be far more frequent.

Hypophysis duplication is usually associated with the median cleft face syndrome. Several malformations have been described, including (4): facial dysmorphism, development abnormalities of the tongue, hydrocephalus, abnormalities of the circle of Willis, posterior cranial fossa abnormalities, agenesis of the corpus callosum, spinal abnormalities, thickening of the hypothalamus, cleft palate, nasopharyngeal masses, absence of the anterior commissure, absence of the olfactory bulbs and tracts, and basilar artery duplication.

The embryogenesis of pituitary duplication is still controversial. The rostral end of the notochord and the prechordal plate are closely related to the primordium of the pituitary gland and stalk, which is initially distinguished at about 22 days of gestation. It begins as an adhesion of neural and stomoderm ectoderm. Overgrowth of surrounding mesenchyme leads to elongation and incorporation of the gland to its normal anatomic position. An alternative view to the classic concept is that the anterior lobe may be of neuroectodermal origin (9). In fact, the anterior neural ridge develops into the oral epithelium after head fold turning and delineates the roof of the mouth and all structures derived from this region. The mature pituitary gland originates from a thickening and concurrent invagination or pouching of this oral epithelium.

From these early relationships, it is suggested that splitting of the tip of the rostral end of the notochordal structures may act as the primary factor which leads to duplication of the area of neuroectodermal adherence, with formation of two independent normal glands and the other associated abnormalities.

Burke et al. (6) suggest a different mechanism to explain isolated pituitary duplication: a primary disruption in the area of the neuroectodermal adhesion, independent of the notochord, would result in disjunction of the primordium and, consequently, hypophyseal duplication.

Pituitary duplication should be considered in all patients who present with midline abnormalities and a MRI study should be systematically obtained in these patients. Among the numerous associated anomalies, partial basilar artery duplication or fenestration, which

can be usually demonstrated by routine MRI, may cause altered flow dynamics, leading to a higher incidence of aneurysm (7,8). Periodic supervision for this potential complication may be necessary.

As illustrated by the above case presentations, precocious and delayed puberty can also be associated with hypophysis duplication and clinical surveillance of pubertal development is therefore recommended.

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