

PICTORIAL ESSAY

Head and Neck Imaging

Congenital Abnormalities of the Pituitary Gland

Dimitrios Kourdakis MD, Maria-Michailia Vogiatzi MD, Eleni Makridou MD,
Elena Hadjichristou MD, Maria Malaki MD, Ioannis Tsitouridis PhD
Agios Dimitrios General Hospital, Department of Radiology Thessaloniki, Greece

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ABSTRACT

The pituitary gland, responsible for regulating essential hormones, consists of the anterior and posterior lobes, which develop through a complex interaction of genetic signaling molecules and transcription factors. Disruptions in these processes can lead to congenital conditions such as pituitary aplasia, hypoplasia, and duplication, often associated with midline malformations of the Central Nervous System (CNS). Pituitary stalk interruption syndrome (PSIS), characterized by the absence of the pituitary stalk, anterior pituitary hypoplasia, and ectopic posterior pituitary, is discussed in detail, alongside ectopic neurohypophysis, a condition in which the posterior lobe fails to migrate normally.

These conditions can result in a range of endocrine disorders, from isolated growth hormone deficiencies to combined hormone deficiencies. Imaging, particularly Magnetic Resonance Imaging (MRI), is crucial for diagnosing these disorders, revealing features such as absence or thinning of the pituitary stalk, hypoplasia or aplasia of the anterior lobe and abnormal positioning of the posterior lobe. Other congenital anomalies, including Rathke's Cleft Cyst, Pars Intermedia Cysts, and Persistent Craniopharyngeal Canal are also examined. These conditions, though often benign, may lead to significant endocrine dysfunction and require appropriate medical or surgical management.



KEY WORDS

pituitary gland, adenohypophysis, pituitary development anomalies, craniopharyngeal canal, sellar cystic lesions, MRI imaging



CORRESPONDING AUTHOR, GUARANTOR

Dimitrios Kourdakis, MD, Agios Dimitrios General Hospital, Department of Radiology, Thessaloniki, Greece, Elenis Zografou 2, 54634
E-mail: dimitriskourd1@gmail.com
Tel: +306980385351

Introduction

The pituitary gland, a key regulator of body homeostasis during development, stress, and other physiological processes, serves as an intermediary organ for physiological signal exchanges between the hypothalamus and peripheral organs. It is a bean-shaped gland, situated within the sella turcica, covered partially by a dural fold called the diaphragmatic sella. (**Fig. 1**) It has two anatomically, embryologically and functionally distinct lobes: the anterior lobe or adenohypophysis, which is comprised of the pars distalis, the pars tuberalis, and the pars intermedia, and the posterior lobe or neurohypophysis, which consists of the pars nervosa, the infundibular stalk and the median eminence.

In adenohypophysis, there are five different hormone-secreting cell types: corticotroph cells, secreting adrenocorticotrophic hormone (ACTH), somatotroph cells, secreting growth hormone (GH), thyrotroph cells,

secreting thyroid-stimulating hormone (TSH), gonadotroph cells, expressing follicle stimulating hormone (FSH) and luteinizing hormone (LH), and lactotroph cells, expressing prolactin (PRL); the intermedia lobe contains melanotroph cells that secrete melanocyte-stimulating hormone (MSH). The posterior pituitary lobe does not contain endocrine cells; however, it secretes oxytocin and vasopressin, which are synthesized by the hypothalamic nuclei, and then transported to the neurohypophysis via the hypothalamic-hypophyseal tract.[1],[2]

The development of the pituitary gland is a highly complex procedure, and requires the expression of multiple signaling molecules and transcription factors in overlapping, but distinct spatial and temporal patterns. Defects in this precisely regulated genetic program may lead to congenital pituitary abnormalities and pituitary dysfunction.

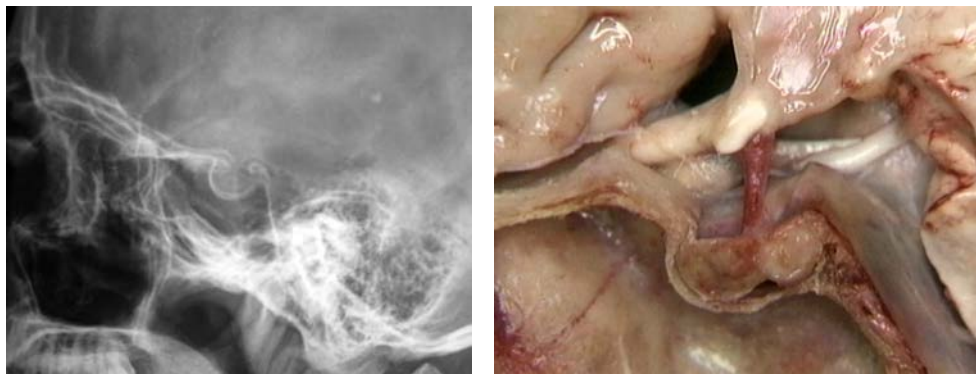


Figure 1 A and B: A) Skull lateral X-ray image showing the sella turcica, B) Sagittal section of a human cadaveric specimen/an anatomical autopsy specimen demonstrating the sella turcica and the pituitary gland.

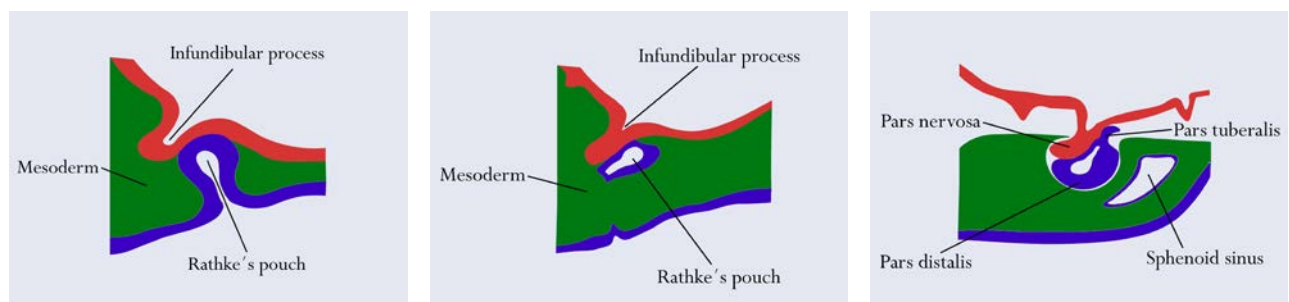


Figure 2 A, B and C: Embryological development of the pituitary gland. **A)** Formation of Rathke's pouch from the oral ectoderm and the infundibular process (infundibulum) from the neural ectoderm. **B)** Progressive expansion of the surrounding mesoderm leads to constriction and eventual separation of the neck of Rathke's pouch from the oral ectoderm, leaving it in close apposition to the infundibular process. **C)** Differentiation of Rathke's pouch and the infundibular process in pituitary development. Rathke's pouch forms the adenohypophysis (pars distalis, pars intermedia, and pars tuberalis), while the infundibular process gives rise to the pars nervosa and the infundibular stalk.

Embryology of the pituitary gland

The pituitary gland develops through a complex interplay between the developing diencephalon and the primitive oral stomodeum. Although it consists of two independent parts, the adenohypophysis and neurohypophysis, it forms as a single structure. It arises from the surface and neural ectoderm, which are closely adherent to each other from the early stages of embryogenesis, before any evagination appears.[3] (**Fig. 2**)

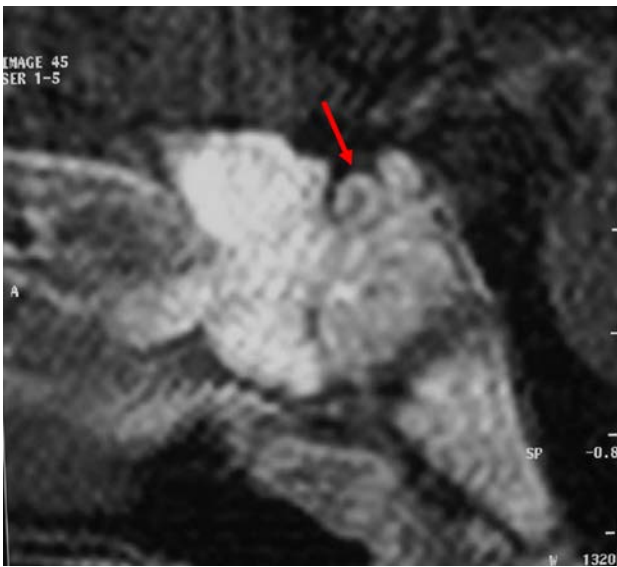


Figure 3: Sagittal T1-weighted post-contrast MRI demonstrating cranial migration of the anterior pituitary lobe (red arrow).

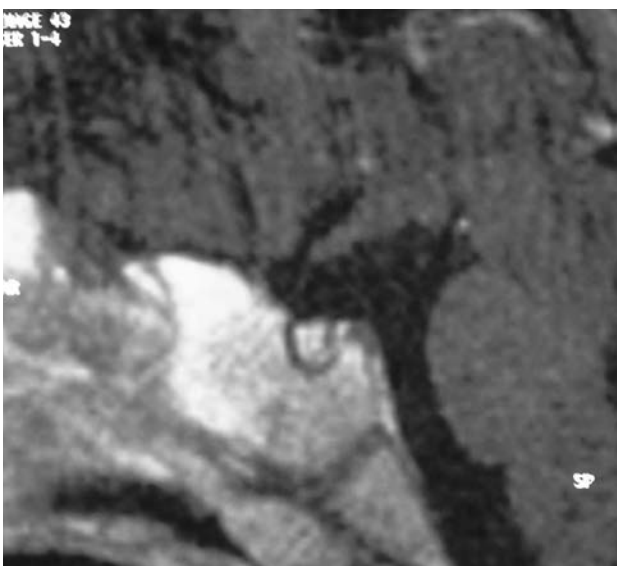


Figure 4: Sagittal T1-weighted post-contrast MRI demonstrating cranial migration of the anterior pituitary lobe.

The primordium of the adenohypophysis is present by the day 22 of gestation at a location just rostral to the oropharyngeal membrane, in close proximity to the overlying neural plate.[3] On the 28th day of gestation, an evagination, the hypophyseal pouch (or Rathke's pouch), arises from the roof of the stomodeum and extends cephalically [in the direction of the craniopharyngeal canal, which we can sometimes see with MRI (**Fig. 3, Fig. 4**)], remaining adherent to the neural tissue of the future neurohypophysis, despite the increasing accumulation of mesenchyme on both sides of the pouch.[3],[4] This overgrowth of mesenchyme, alongside with the rapid growth of the embryonic head in a dorsoventral direction, are the primary factors in the formation of the Rathke's pouch and, consequently, in the development of adenohypophysis.[3]

The neurohypophysis evolves during the sixth week of gestation and is formed by a downgrowth evagination of the floor of diencephalon, called infundibulum, just posterior to the optic chiasm. Between days 37 to 41 of gestation, evidence of the infundibulum becomes apparent, while the adenohypophysis acquires an "open wing" configuration, forming the two lateral lobes, that partially enclose the infundibulum and later differentiate into the pars tuberalis. The mesenchyme that accumulates between the lateral lobes and the floor of the hypothalamus will later differentiate into the blood vessels of the pituitary gland.[3] During the seventh week of gestation, the infundibulum grows and extends progressively toward the adenohypophyseal primordium. Its ventral end folds, forming a diverticulum, that remains attached to the floor of the hypothalamus. Meanwhile, Rathke's pouch becomes constricted at its attachment to the oral epithelium by the pharyngohypophyseal stalk, a process provoked by the development of the primordial sphenoid bone. A remnant of this stalk may persist and give rise to a pharyngeal hypophysis in the pharyngeal roof.[3],[5],[6],[7]

During subsequent development, the cells of the anterior wall of Rathke's pouch proliferate rapidly, giving rise to the pars distalis of the adenohypophysis, while the posterior wall of Rathke's pouch experiences less cell proliferation and develops into the pars intermedia. The remaining space between the pars distalis and the pars intermedia diminishes in size and persists as a cleft (Rathke's cleft). The lateral lobes of the adenohypophysis, that form the pars tuberalis, almost com-

pletely surround the infundibulum, which differentiates into the infundibular stalk and the pars nervosa of the neurohypophysis. The infundibular stalk is initially hollow, but eventually obliterates, except for a small proximal pit, the infundibular recess, which persists in the floor of the third ventricle. The median eminence is the slightly prominent segment of the infundibulum, proximal to the infundibular stem, just below the third ventricle and fuses with the pars tuberalis. Thus, the pituitary stalk contains components of both the anterior and posterior lobe.[3],[6]

The portal system appears at the early stages of pituitary development[7] and derives from mesenchyme entrapped between the evaginations of the floor of the diencephalon and the stomodeum.[8] The hypophyseal portal system begins to form before the seventh week of gestation, and is fully established by 18 to 20 weeks. During the first 12 weeks of gestation, the primitive cells of adenohypophysis undergo rapid proliferation, arranging themselves as cords around the blood sinusoids in a specific bilateral and symmetrical manner, and major differentiation into specialized cell lines, dedicated to producing and secreting specific hormones. By the end of the first trimester all of the major secretory cell compartments of the anterior lobe are structurally and functionally intact.[1],[9] The neurohypophysis undergoes differentiation during the fourth month of gestation, resulting in the emergence of specific neuroglial cells, the pituicytes. It is later colonized by axons, originating from the cells of the paraventricular and supraoptic nuclei of hypothalamus, forming the hypothalamic-hypophyseal tract. Neurosecretory activity of the posterior lobe begins in late fetal life.[6]

Genetic regulation of pituitary gland development

The development of the pituitary gland is closely related to that of the ventral diencephalon and its regulation involves a complex genetic cascade of transcription factors and signaling molecules, that are required for the morphogenesis of Rathke's pouch and the proliferation and differentiation of adenohypophyseal cells.

The initial induction of Rathke's pouch depends on the bone morphogenetic protein (BMP4), which is expressed in the overlying diencephalon.[10] The role of BMP4 signaling in early pituitary development has been investigated in BMP4-gene deleted animals, in which the initial thickening and invagination of Rath-

ke's pouch fail to occur, resulting in fetal lethality.[10],[11] Subsequent proliferation and stratification of Rathke's pouch are determined by the expression of factors, including bone morphogenetic protein (BMP2) in the ventral mesenchyme adjacent to Rathke's pouch and gradually in the pouch itself, three fibroblast growth factors FGF8, FGF10 and FGF18 in the ventral diencephalon, Sonic Hedgehog Protein (Shh) in the ventral diencephalon and in the oral ectoderm apart from Rathke's pouch, and the expression of the Wnt4 and Wnt5a genes, the former in Rathke's pouch and the latter in the ventral diencephalon and the infundibulum. Among these factors, BMP4 and Shh are also essential for the initiation of cell type determination process.[10],[12]

Further formation and maintenance of Rathke's pouch, as well proliferation, lineage commitment and cell fate differentiation, of its progenitor cells, result from a temporally regulated cascade of signaling molecules and transcription factors. The early phases of cellular patterning require the gene expression of multiple transcription factors: i) the paired-like homeodomain proteins; HESX1 functions as a transcriptional repressor and its inactivation results in variable anterior central nervous defects, OTX2 is necessary for HESX1 expression, Ptx1 and Ptx2 act as universal pituitary regulators ii) the LIM homeodomain transcription factors; ISL1 is suggested to be necessary for the proliferation and differentiation of pituitary progenitor cells, LHX3 is required not only for the survival of progenitor cells, but also for the determination of GH-, PRL-, and TSH-cell differentiation and LHX4, iii) the SOX transcription factors; SOX1 and SOX3 iv) the SIX homeodomain proteins, SIX6 and SIX3, v) Notch signaling; Notch2, Notch3, JAG1, Hes1 regulate proliferation, apoptosis, cell fate determination, and morphogenesis.[10],[12],[13],[14] Furthermore, terminal pituitary cell specification is controlled by specific transcription factors, the regulated expression of which, both in time and space is required. The major proximal determinant of pituitary cell lineage is PROP1 expression, which determines the subsequent development of POU1F1-dependent (somatotroph, lactotroph, and thyrotroph lineages), and gonadotroph cell lineages. Corticotroph cell commitment is independent of POU1F1-determined lineages. TPIT protein (encoded by TBX19) is a prerequisite for corticotrophs and melanotrophs expression.[12],[13]

Congenital Disorders Of The Pituitary Gland

Aplasia and Hypoplasia of the pituitary gland

Congenital absence (aplasia) or hypoplasia of the pituitary is an extremely rare occurrence, and may present as an isolated anomaly or as a part of complex syndromes, such as Kallman syndrome, Pallister-Hall syndrome, PHACES syndrome, and Johanson-Blizzard syndrome. Additionally, it is often associated with other central nervous system malformations, such as anencephaly, arrhinencephaly, holoprosencephaly, septo-optic dysplasia, Chiari I malformation, absent septum pellucidum and midline cranio-facial defects. [15],[16],[17]

Hypophyseal aplasia involves absence of both the anterior and posterior lobes and in many cases, absence of the pituitary stalk, resulting in multiple hormone deficiencies.[18] Hypophyseal hypoplasia on the other hand, involves a variety of anatomical variations, including anterior pituitary hypoplasia, ectopic or absent posterior pituitary, thinning or interruption of the pituitary stalk[19], leading to isolated or combined deficiency of the pituitary hormones. Disruption of normal pituitary development, leading to specific patterns of hypopituitarism, is increasingly linked to mutations of genes encoding transcription factors and signaling molecules, including HESX1, LHX3, LHX4, SOX3, SOX4, PIT-1, PROP1, which are critical for cell proliferation and differentiation during early stages of pituitary embryogenesis.[14],[19],[20],[21] Among these, mutations of the homeobox HESX1 gene are implicated in the etiology of septo-optic dysplasia (SOD), also known as de Morsier syndrome. This syndrome is character-

ized by the triad optic nerve hypoplasia, agenesis of midline brain structures - including the corpus callosum and septum pellucidum- and pituitary hypoplasia. [14],[20],[21],[22] Given that mutations in these genes account for very few cases, it is clear that many other genes or environmental factors may also contribute and remain to be identified.[14],[19]

Pituitary aplasia is a life-threatening condition, as clinical manifestations occur during the first hours of neonatal life, with severe symptoms of hypoglycemia, seizures, respiratory distress, cardiovascular collapse, prolonged jaundice and hypotonia, all of which require prompt hormone replacement therapy (HRT). Physical examination may reveal facial abnormalities -cleft lip and palate, deviated nasal septum, hypertelorism / hypotelorism- and in male infants microphallus, a poorly developed scrotum and undescended testes. Most infants with this disorder die in early infancy. On the other hand, pituitary hypoplasia may be asymptomatic and patients with this condition can survive with appropriate HRT.[16],[17],[18],[19]

On MRI, hypophyseal aplasia is characterized by the absence of any identifiable pituitary gland, while the sella turcica is small and shallow. In contrast, in hypophyseal hypoplasia there is detectable pituitary tissue in a well-formed sella. (**Fig. 5**) The other imaging findings are highly variable, reflecting the wide spectrum of anatomical variations/presenting phenotypes encountered in these abnormalities. The differential diagnosis should include the empty sella syndrome, in which the pituitary gland is severely flattened due to the extension of cerebrospinal fluid (CSF) into the sella.[17],[18]

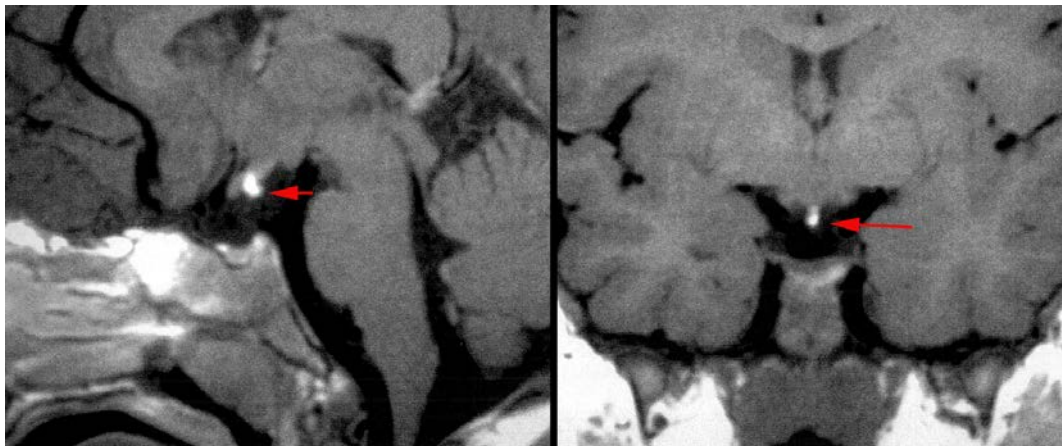


Figure 5: Sagittal and coronal T1-weighted MR images showing ectopic neurohypophysis (red arrow) with hypoplastic configuration of the adenohypophysis.

Duplication of the pituitary gland

Duplication of the pituitary gland (DPG) is an extremely rare developmental anomaly, as fewer than 60 cases have been reported since 1880.[7],[23] It involves the formation of two morphologically normal glands, each with anterior and posterior lobes, lying on either side of the midline. DPG is usually associated with median cleft face syndrome and may be accompanied by a wide spectrum of neural and craniofacial abnormalities. These include agenesis or thickening of hypothalamus, hypoplasia of the corpus callosum, duplication of the anterior third ventricle, widened or duplicated optic chiasm, basilar artery duplication or fenestration, abnormalities of the circle of Willis, absence of the olfactory bulbs and tracts, posterior cranial fossa abnormalities, absence of the anterior commissure, hypertelorism, mouth and tongue dysmorphism, craniofacial clefting, pharyngeal masses attached to the cleft palate, and malformations of the spine, ranging from duplication of the anterior median fissure to diplomyelia and myelomeningocele.[3],[7],[24],[25] Manjila et al. proposed that when DPG is presented throughout the spectrum of other coexisting blastogenesis defects, it should be termed as “DPG-plus syndrome”. [7] Furthermore, Sethi et al. described a sole duplication of the pituitary stalk without any pituitary anomaly, combined with demonstrating tuberomammillary fusion and mega cisterna magna.[26]

Regarding the pathogenesis of pituitary duplication, although several theories have been proposed, the characteristics of DPG and the concomitant craniofacial abnormalities suggest that they may be attributable to a defect early in blastogenesis.[7] As previously mentioned, the pituitary gland forms as a single structure and, during early embryonic period, its primordium, which represents a persistent point of adherence between the surface ectoderm and neuroectoderm, is in close relation with the notochord through the prechordal plate. The latter participates in the formation of the oropharyngeal membrane. These observations of hypophyseal embryogenesis led to the assumption that a splitting of the tip of the rostral end of the notochord may result in duplication of the pituitary primordium, leading to the formation of two pituitary glands and potentially initiating the complex associated abnormalities.[3],[7],[24],[27],[28] The underlying cause of notochordal splitting remains undetermined; however,

maternal exposure to teratogenic factors as well as intrauterine infection and bleeding has been implicated. [3]

DPG-plus syndrome affects female more than male patients, with a 4:1 ratio, but with no yet possible explanation for this discrepancy.[23] Most cases are diagnosed during the neonatal period and are linked to early high mortality rates due to the severity of the co-existing malformations.[29]

The clinical manifestations of this abnormality vary. Interestingly, female patients usually present with precocious puberty, in contrast to male patients who present with hypogonadotropic hypogonadism and delayed sexual development.[23] Other possible symptoms are hypothyroidism, hyperprolactinemia, anosmia and mild chronic nasal obstruction.[30],[31] Very little number of cases are described with incidental discovery of this entity without any prior symptomatology. [29],[31],[32],[33] These cases demonstrate that anatomical duplication can coexist with normal pituitary output.

The anterior pituitary, in order to be functional, should develop an intact portal connection from the median eminence/hypothalamus, in order to receive hypothalamic signals. If duplication includes duplicated portal circulation, intact hypothalamic input and normal pituitary cell lines, both glands can contribute in overall function. If one gland lacks portal system, is hypoplastic, or the hypothalamus is malformed (many cases present with thickening of hypothalamus and cellular dearrangement which could explain the endocrinological manifestation of deficiencies later in life) [29],[34], only one gland (or neither) will be functionally significant, producing either hypopituitarism or axis-specific dysregulation (e.g. disrupted hypothalamic-pituitary-gonadal axis). The posterior pituitary (neurohypophysis) functionality depends on direct hypothalamic axons connection, so an ectopic or duplicated neurohypophysis without axonal connections will not function normally.

MRI imaging demonstrates the duplicated stalk and the duplicated pituitary gland, residing in a broaden or duplicated sella turcica and the midline hypothalamic mass along the floor of the third ventricle, separating the two infundibular recesses. (Fig. 6) It may also reveal a duplicated or fenestrated basilar artery, along with coexisting brain and cranial abnormalities.

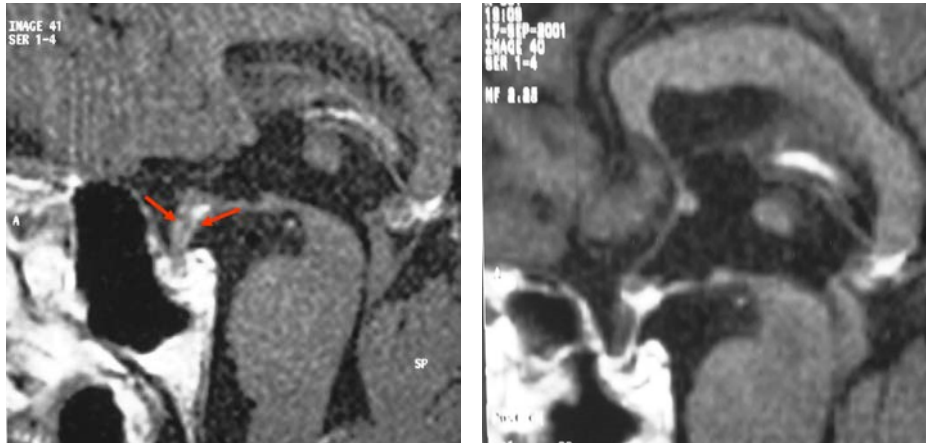


Figure 6 A and B: Duplicated pituitary stalk: Sagittal T1-weighted post-contrast MR images showing two distinct infundibular stalks connecting the hypothalamus to the pituitary gland. (The two distinct infundibular stalks are shown with red arrows)

Pituitary stalk interruption syndrome

The pituitary stalk interruption syndrome (PSIS) was first described in 1987 with the advent of MRI imaging. The estimated incidence of PSIS is approximately 0.5/100,000 births.[35] It is characterized by the presence of a classic triad, which consists of: i) absence or marked thickening of the pituitary stalk, ii) anterior pituitary hypoplasia or aplasia, and iii) ectopic posterior pituitary, which may be found anywhere along the infundibular axis, but it usually is located at the level of the infundibular recess of the third ventricle (60.4%) and at the hypothalamus (18.9%).[35],[36],[37],[38],[39] This entity may be associated with other midline CNS malformations, such as optic nerve hypoplasia, absent septum pellucidum, Chiari malformation, absent left internal carotid artery or median deviation of the carotid arteries[36],[39], and, rarely, with micropenis and cryptorchidism.[36] Clinically, it results in variable endocrine disorders, ranging from isolated growth hormone deficiency (IGHD) to combined anterior pituitary hormone deficiency (CPHD); however, posterior pituitary function is usually maintained.[36],[37],[38]

The pathogenesis of PSIS has yet to be fully understood. Most PSIS cases are sporadic and rarely familial (5%).[38] Previous studies suggested the theory of a traumatic or hypoxic injury of the stalk during delivery being the etiological factor.

However, the more recent hypothesis of defects of genetic origin or environmental factors during early embryogenesis seems to be more likely, as it could explain the extra- pituitary malformations that may

accompany the PSIS. Over the last decade, mutations in genes encoding transcription factors and signaling molecules, including HESX1, LHX4, SOX3, OTX2 have been implicated, showing that PSIS is characterized by a complex genetic heterogeneity which reflects a great phenotypic multiplicity.[36],[37],[38],[39],[40]

MR imaging reveals absence or a thin pituitary stalk, aplasia or hypoplasia of the anterior lobe, and ectopia of the posterior lobe. Posterior dystopia entails the lack of the normal high signal intensity of the posterior lobe in the pituitary fossa on T1-weighted image (T1-WI) (bright spot) and presence of a high signal nodule in the region of the median eminence on T1-WI. (**Fig. 7, Fig. 8**) Pituitary stalk visibility is assessed after intravenous administration of contrast agent, as a very thin stalk may not be identifiable on baseline MRI. Additionally, a small sella may be seen in many cases.[36],[41]

Ectopic Neurohypophysis

Ectopic positioning of the posterior pituitary lobe is a developmental anomaly and, although it is characteristic of the pituitary stalk interruption syndrome[42], it can also occur as a solitary anomaly.

The ectopic neurohypophysis may be located anywhere along the infundibular stalk, but it is characteristically found at the median eminence in the floor of the third ventricle.[43],[44]

Migration arrest of the posterior lobe may be accompanied by various midline brain malformations, such as optic nerve hypoplasia, agenesis of the corpus callosum, Chiari I malformation, septo-optic dysplasia,

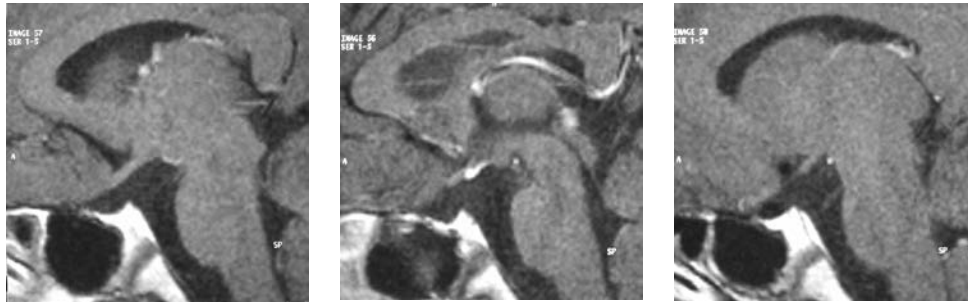


Figure 7 A, B and C: Sagittal T1-weighted post-contrast MR images of a boy with the diagnosis of hypopituitarism demonstrating a hypoplastic empty sella with no identifiable residual anterior pituitary tissue, an ectopic posterior pituitary bright spot at the level of the median eminence and absence of the pituitary stalk [Pituitary Stalk Interruption Syndrome (PSIS)].

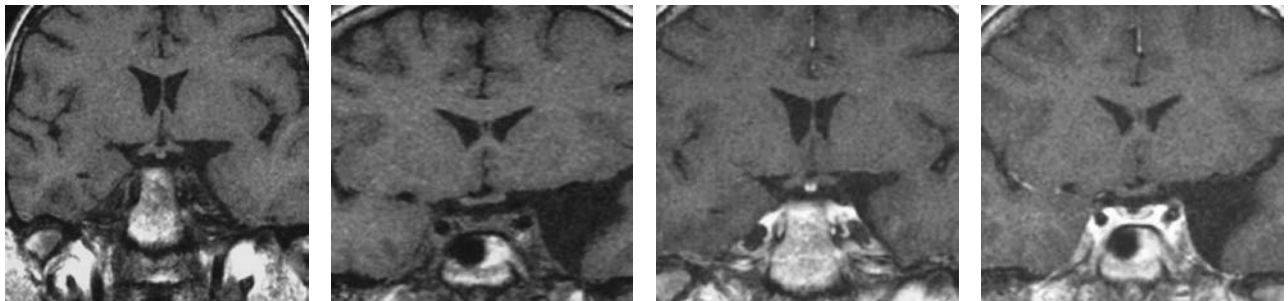


Figure 8 A, B, C and D: Coronal T1-weighted MR images (A, B) demonstrating: A) neurohypophysis lacking an increased number of neurosecretory granules, B) Non-visualization of the pituitary stalk, in keeping with PSIS, and post-contrast coronal T1-weighted images (C, D) demonstrating enhancement of the neurohypophysis and adenohypophysis, without visualization of the pituitary stalk, in keeping with PSIS.

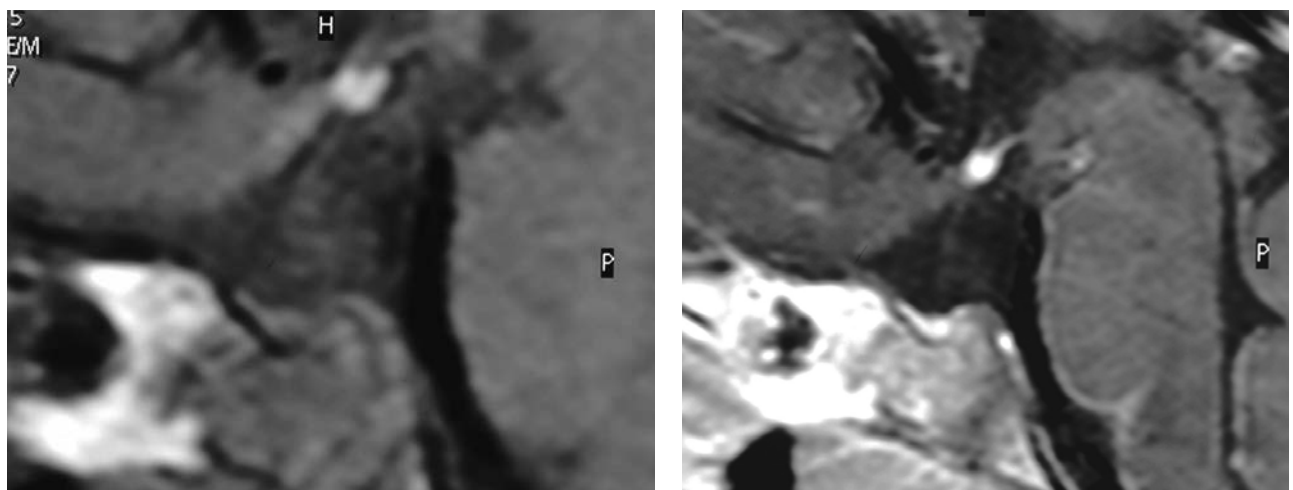


Figure 9 A and B: Sagittal T1-weighted MRI (A: pre-contrast, B: post-contrast), demonstrating the posterior pituitary lobe in ectopic position, located superior to its normal position along the pituitary stalk.

Kallmann syndrome, medial deviation of the carotid arteries, periventricular heterotopias, microcephaly, cerebellar atrophy, vermian dysplasia and persistent craniopharyngeal canal.[43],[45]

Additionally, associated extracranial anomalies, including unilateral renal hypoplasia and ectopia, arthrogryposis multiplex congenital, situs inversus, Fanconi anemia[46], cardiac and musculoskeletal abnormalities have been reported.[43]

Migration arrest of the posterior pituitary lobe has been described in patients with pituitary dwarfism, suffering from isolated growth hormone deficiency or from multiple pituitary hormone deficiency. However, cases of undescended neurohypophysis related to functional preservation of the pituitary hormonal production and release have been reported, indicating that this entity in endocrinologically normal patients may represent an anatomical variant.[44],[47],[48] The pathogenesis of posterior pituitary lobe ectopia is not yet fully understood. Early descriptions of this abnormality postulated a perinatal traumatic cause, potentially resulting in pituitary stalk transection and ectopic posterior lobe formation after axonal reorganization. More recent studies favor a genetic theory, supported by the association of ectopic posterior neurohypophysis with a range of midline abnormalities.[43],[45],[46] Mutations in transcription factors genes, that participate in the complex regulation of pituitary development, such as BMP-4, HESX1, LHX4, SOX3 and GLI2 have been implicated.[43],[46]

On MR images the ectopic neurohypophysis has a distinctive appearance. On T1-WI, the normal posterior lobe appears as a focal spot of hyperintense signal (bright spot) located at the posterior aspect of the sella, immediately anterior to the dorsum sella. This focal hyperintense spot is related to the paramagnetic effect of the vasopressin-neurophysin II-copeptin complex in the posterior lobe, and correlates with normal function.[49]

Consequently, on MR imaging posterior pituitary ectopia is characterized by the absence of the normal bright spot in the sella and by its occurrence along the undersurface of the median eminence. In the case of pituitary stalk interruption syndrome, alongside the ectopic location of the neurohypophysis, there is aplasia or hypoplasia of the anterior pituitary lobe and absence or marked thinning of the pituitary stalk. (Fig. 9)

Rathke's Cleft cyst

Rathke's cleft cysts (RCC) are congenital, benign, cystic lesions of the pituitary gland that derive from failure of regression of the embryonic cleft of Rathke's pouch; thus, they are located between the anterior and the posterior lobes of the pituitary gland. Typically, the cyst's wall consists of cuboidal or columnar epithelium, while the intracystic content can fluctuate between CSF-like transparent fluid and mucinous with varying viscosity. [50]

RCCs are common incidental findings in 4-33% of autopsy cases, most remaining asymptomatic; however, they account for 6-10% of symptomatic sellar and parasellar lesions.[51] In the latter case, the typical clinical manifestations include headache, visual disturbances, hypopituitarism of varying degrees and diabetes insipidus, which are attributed to the compression and mass effect of the cystic lesion to the surrounding structures, such as hypophysis, hypothalamus, optic chiasm[51],[52],[53] or they represent cyst wall infarction, intracystic hemorrhage or leakage of inflammatory cyst content.[51]

On MRI imaging, RCC appear as non-enhancing, non-calcified cystic lesions. (Fig. 10, Fig. 11) Small Rathke's cleft cysts, usually less than 3mm in diameter, are situated between the anterior and the posterior pitui-

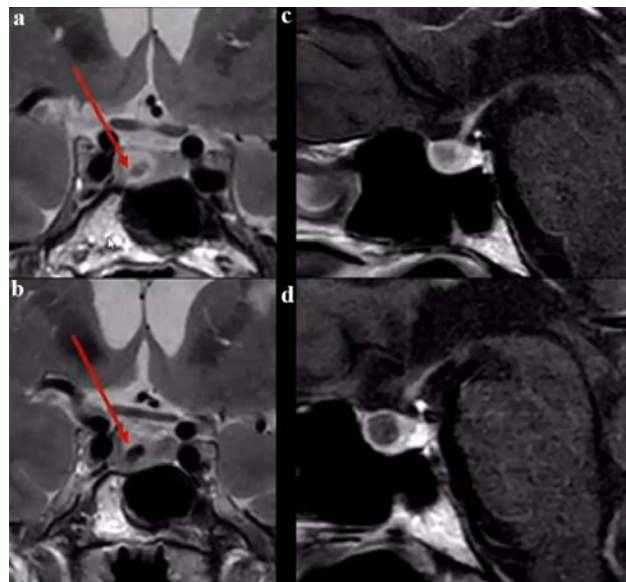


Figure 10 A, B, C and D: A, B) Coronal T2-weighted MR images (A and B) and sagittal T1-weighted post contrast images (C and D) showing Rathke's Cleft cyst containing an intracystic nodule, which is pathognomonic of a Rathke cleft cyst (red arrows).

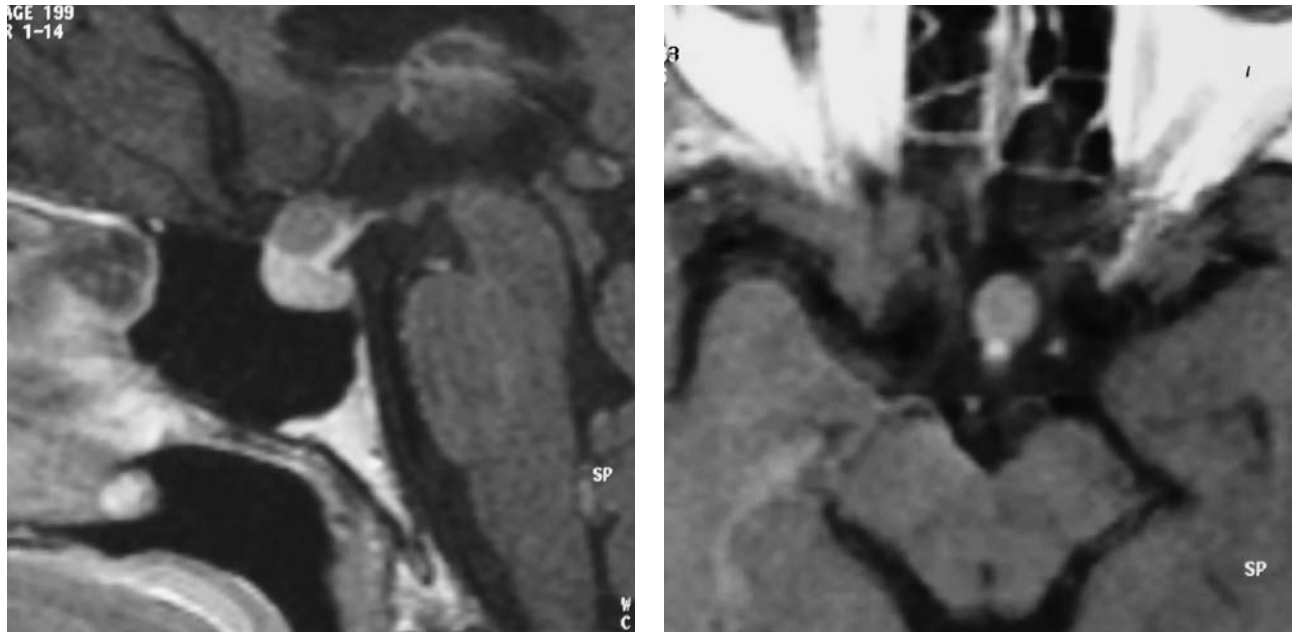


Figure 11 A and B: Sagittal (11 A) and Axial (11 B) T1-weighted post-contrast MR images demonstrating Rathke's Cleft cyst.

tary lobe (sellar RCC) or anterior to the pituitary stalk (suprasellar RCC), while larger cysts involve both the sellar and suprasellar region (sellar RCC with suprasellar extension).[50],[51],[54] On T1-weighted image (T1-WI) and T2-weighted image (T2-WI), the signal intensity of the cyst varies according to the composition of the intracystic fluid. Non-complicated cysts follow the fluid intensity; in other words, they are hypointense in T1-WI and hyperintense in T2-WI. By contrast, a high signal in T1-WI indicates proteinaceous mucinous cyst content, and, rarely, haemorrhage. RCC's wall does not enhance, but a pseudoenhancement may be apparent due

to the enhancement of the surrounding normal pituitary gland.[50],[51],[52],[53],[54] Intracystic nodules have been described in 45-77% of RCC[53]; they appear hyperintense on T1-WI and hypointense on T2-WI and display no enhancement. Histologically, these nodules represent mucinous with mixed cholesterol and protein clumps.

The differential diagnosis of RCCs include mainly craniopharyngioma and cystic pituitary adenomas. Craniopharyngiomas are more commonly suprasellar lesions, have calcifications and solid, enhancing components, while cystic adenomas are situated in the anterior pituitary lobe and exhibit peripheral enhance-

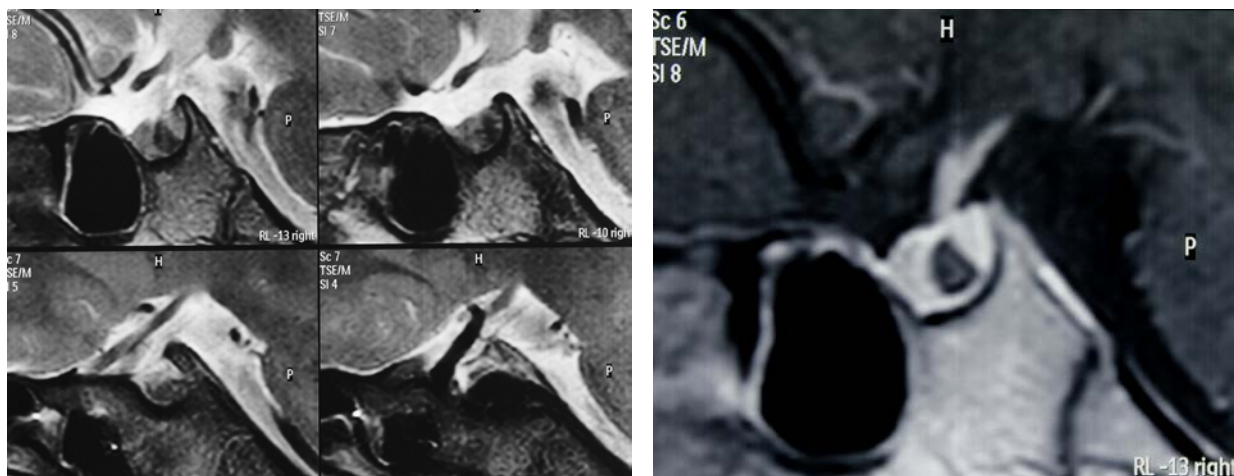


Figure 12 A and B: Sagittal T2-weighted images (12 A) and Sagittal T1-weighted image (12 B) depicting a cystic lesion arising from the pars intermedia, interposed between the anterior and posterior lobes of the pituitary gland.

ment[50]. Diffusion-weighted imaging may contribute to the differential diagnosis of RCCs from other cystic sellar and parasellar lesions, mainly from craniopharyngioma and hemorrhagic pituitary adenoma; the ADC value of RCC is higher in comparison to that of the cystic component of craniopharyngioma and hemorrhagic pituitary adenoma in the subacute phase.[54] In case of ruptured RCCs, Mark et al. described a case series demonstrating enhancement of the basisphenoid bone marrow below the sella as an imaging finding pathognomonic of RCC, which does not present in cystic adenomas. This enhancement is thought to result from mucin leakage from the ruptured RCC, triggering inflammatory changes in the adjacent structures. These findings are better seen/assessed on fat-saturated post-contrast T1WI and T2WI.[55] Asymptomatic RCCs are monitored with serial MRI imaging; on the contrary, symptomatic RCCs are aspirated and resected via transsphenoidal approach. Recurrence after surgical resection is estimated of about 16-18%.[51]

Pars Intermedia cyst

The pars intermedia, a rudimentary part of the human anterior pituitary gland, is located between the

pars distalis and the neurohypophysis and derives from the posterior wall of Rathke's pouch. (**Fig. 12**) Cysts may develop within the pars intermedia, lined with a single layer of cuboidal or columnar epithelium and filled with proteinaceous fluid or cellular debris. These cysts are usually asymptomatic lesions measuring less than 3mm.

Their differential diagnosis from Rathke's cleft cyst, with which share the same location, may be challenging in many cases. However, a flattened cystic cavity in the sagittal plane that broadens in the coronal plane suggests the diagnosis.[50],[56]

Persistent craniopharyngeal canal

The term persistent craniopharyngeal canal is used to describe a midline defect of the skull base, extending between the superior wall of the nasopharynx and the floor of the sella turcica. It is a rare congenital entity, first described by Landzert et al[57], and its incidence in live births and in the asymptomatic population has been reported as 5-10% and up to 0.42% respectively. [58] Currarino et al proposed two subdivisions of this defect according to its size; the hypophyseal channel (or small craniopharyngeal canal) when it measures

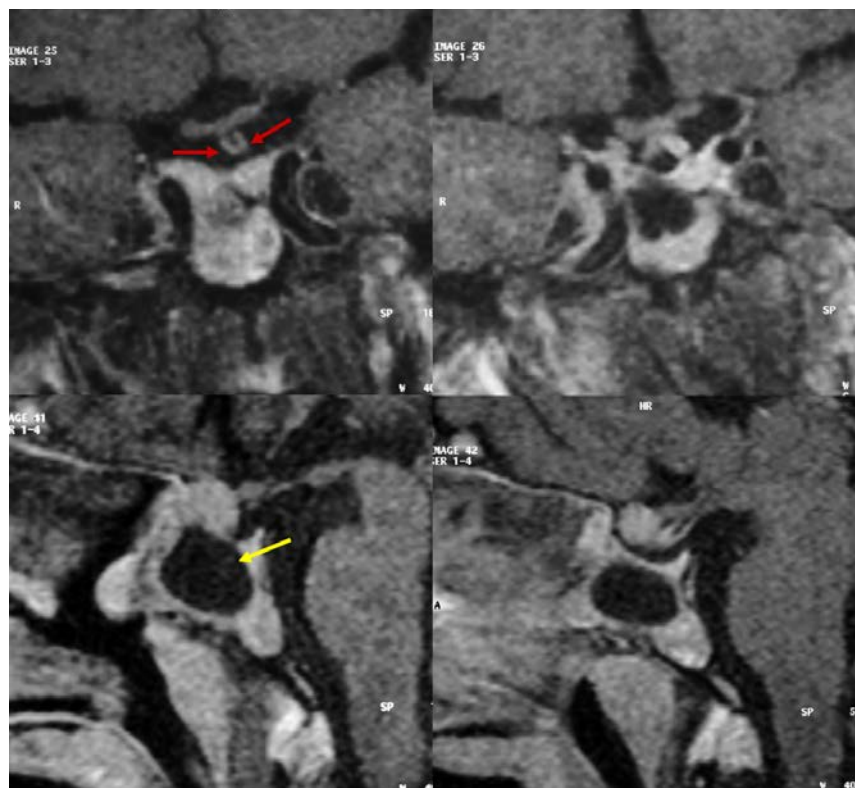
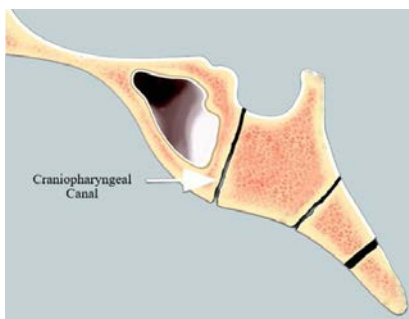


Figure 13 A and B: **A)** Embryological formation of the craniopharyngeal canal. The canal represents a remnant of the migratory pathway of Rathke's pouch and typically corresponds to the boundary between presphenoidal and postsphenoidal ossification of the sphenoid body. **B)** Coronal T1-weighted images (upper row) and sagittal T1-weighted images (lower row) demonstrating an endosphenoidal Rathke's cleft cyst (**yellow arrow**) with concomitant findings of a shallow sella turcica and a duplicated pituitary stalk (**red arrows**).

less than 1.5mm in diameter, and large craniopharyngeal canal (or transsphenoidal channel), when its width is greater than 1.5mm. Moreover, the latter is associated with other skull base malformations and midline facial anomalies, such as hypertelorism, midfacial cleft, cleft lip and palate, abnormal optic tracts, malformed eyes and the absence of corpus callosum.[58],[59],[60]

Little is currently known about the formation of this structure. However, two different theories have been developed in order to explain the etiology of the persistence of the craniopharyngeal canal.[58],[59],[61] The most widely accepted theory supports the hypothesis that the craniopharyngeal canal represents the remnant of the track formed during the dorsal extension of Rathke's pouch through the chondrification centers of the developing presphenoid and postsphenoid. Naturally, during the seventh week of gestation the communication of Rathke's pouch with the oral cavity is restricted to a stalk, and is then interrupted by the development of the cartilage of the primordial sphenoid bone around this stalk. On the other hand, the craniopharyngeal canal is claimed to be a remnant of a vascular channel formed during the osteogenesis of the sphenoid bone.[50],[58],[59],[61] On a molecular basis, recent studies in mice have shown that the presence of the craniopharyngeal canal may arise as a result of modulation in *Shh* signaling.[62]

The persistence of the craniopharyngeal canal may be accompanied by migration arrest of the adenohypophysis, with usually concomitant normal development of the posterior pituitary gland. A portion or all of the anterior pituitary lobe may persist within the canal or within the sphenoid bone, called intrasphenoidal adenohypophysis, or the adenohypophysis may develop in the nasopharyngeal wall.[50],[63] However, larger defects may be associated with nasopharyngeal extension of the third ventricle and the pituitary gland, or with a variety of sphenoidal meningocele, encephalocele, meningoencephalocele or hamartoma.[59],[61]

In most cases, individuals with persistent craniopharyngeal canal are asymptomatic. Possible presentations include cerebrospinal fluid rhinorrhea, intracranial hypotension, recurrent meningitis or precocious puberty[61] or they may be related to pituitary dysfunction due to compression of the gland or unintentional resection of a pharyngeal adenohypophysis during adenoidectomy.[58]

On imaging, the persistent craniopharyngeal canal is located in the midline, oriented vertically, extending from the floor of the pituitary fossa to the posterior wall of the nasopharynx. Its radiological features depend on i) the status of canal obliteration, as may be incomplete without communication with the sella turcica, ii) the existence of communication with the nasopharynx, which may entail air content of the canal and iii) the status of sphenoid sinus aeration.

In cases of excessive sphenoid sinus aeration, the craniopharyngeal channel follows the intersphenoidal septum and it is located within the sinus. On axial Computed Tomography (CT) imaging, it is best appreciated on thin slice bone algorithm images as a sharply circumscribed midline foramen with a sclerotic rim and possible air content, located anterior to the sphenobasilar synchondrosis. On MRI, the canal has a low T1-WI signal intensity compared to that of the clivus. (**Fig. 13**) Furthermore, MRI imaging allows the evaluation of adenohypophysis location, and possible concomitant abnormalities.[50],[63]

The surgical indications and approach of this congenital entity still remain controversial. Anatomic variations, clinical manifestations and coexisting abnormalities determine the individualized management of the persistent craniopharyngeal canal.[58] **R**

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