Review Article

PITUITARY STALK INTERRUPTION SYNDROME: REVIEW OF EMBRYOGENESIS OF PITUITARY GLAND AND IMAGING CORRELATION.

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Abstract

Pituitary stalk interruption syndrome is a rare congenital disorder associated with clinical presentation of small stature and pituitary hypogonadism. The anterior and the posterior pituitary glands are composed of tissues that differ from each other embryologically and histologically. Normal development results in the fusion of the anterior lobe growing cranially from the ectoderm of the stomadaeum (Rathke's pouch) and the posterior pituitary growing caudally from the neuroectoderm of the diencephalon. Ectopic neurohypophysis is commonly associated with structural midline defects. Abnormal posterior pituitary migration such as the ectopic posterior pituitary lobe appearing at the level of median eminence or along the pituitary stalk, absent, small infundibular stalk and or hypoplastic adenohypophysis are the imaging findings. A wide range of gene mutations such as HESX1, LHX4, SOX3 and OTX2 are involved in more complex and heterogeneous phenotypes such as pituitary anomalies, craniofacial and limb malformations in addition to pituitary hormone deficiencies.

Keywords: pituitary, interruption, hormonal deficiencies, imaging

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INTRODUCTION

Pituitary stalk interruption syndrome (PSIS) otherwise called pituitary stalk transection syndrome is a congenital disorder characterized by the triad of an absent or diminutive pituitary stalk, an ectopic or absent posterior pituitary gland and/or absent or hypoplastic adeno-hypophysis.[1] It is a rare condition with an estimated incidence rate of 0.5/1,000,000 births.[2] This condition is said to be associated with midline defects such as septo-optic dysplasia and a wide range of pituitary endocrine deficiencies; from isolated growth hormone deficiency (IGHD) to combined pituitary hormone deficiency (CPHD). However, the posterior pituitary function is usually maintained, but occasionally it may malfunction depending on the location of the posterior pituitary.[3] PSIS is also attributed to a higher-than-normal incidence of breech presentation with resultant difficult delivery. The consequences of adverse perinatal factors such as birth trauma, prolonged labor, or assisted delivery are still not well understood.[4] Later in childhood, patients may present with short stature, growth retardation, seizures, hypotension, intellectual and puberty delay.

EMBRYOGENESIS OF PITUITARY GLAND

In recent years, the molecular mechanisms of anterior pituitary development are now better understood than in the past, but still little is known about the mechanisms regulating posterior pituitary development. The anterior, intermediate and posterior lobes of the pituitary gland develop from separate embryonic cell lineages: the oral ectoderm and neural ectoderm, respectively. At the middle of the 4th week, pituitary organogenesis begins when an area of oral ectoderm at the roof of the

presumptive oral cavity invaginates upwards to form the Rathke's pouch, which eventually becomes the anterior pituitary gland.[5] The ventral wall of Rathke's pouch becomes the anterior lobe, whereas the posterior wall of the pouch develops into the pars intermedia.[6] The posterior pituitary evolves from an infundibulum that develops by downward evagination of the dorsal presumptive diencephalon from the floor of the third ventricle soon after Rathke's pouch begins to extend upward. The two structures maintain close contact while cells migrate from the mesoderm and neural crest into the space between the presumptive brain and oral cavities. It comprises the distal axons of the hypothalamic magnocellular neurones that shape the anterior pituitary gland. After its caudal migration, it is encapsulated together with the ascending ectodermal cells of Rathke's pouch which form the anterior pituitary. By the end of the first trimester, this development is completed and antidiuretic hormone and oxytocin can be found in neurohypophyseal tissue. The cell bodies are located in the paraventricular nucleus (PVN) and supraoptic nucleus (SON) in the hypothalamus and the axons project to the neurohypophysis where the hormones are secreted into the bloodstream.

Structural pituitary abnormalities are mostly seen with anomalies of midline structures of the brain, such as corpus callosum and anterior commissure. Craniofacial anomalies such as cleft lip and palate, septo-optic dysplasia and basal encephalocele are often seen with varying degrees of pituitary dysfunction and hypoplasia.[7] Congenital absence of the pituitary and ectopic anterior pituitary tissue is very rare. Although functional ectopic posterior pituitary (EPP) tissue is sometimes incidentally observed on brain imaging (Fig. 1 A and B). EPP occurs as a result of abnormal pituitary gland development in the growing fetus. In many instances, a cause cannot be identified. In a large number of cases, genetic mutations related to EPP can be explained.

During embryogenesis, neuroepithelial cells from the lining of the third ventricle migrate to the walls where they mature to develop into paraventricular nucleus. Some of these cells migrate laterally towards and superior to the optic chiasm to form the supraoptic nucleus. The unmyelinated axons of the supraoptic nucleus traverse the basal hypothalamus to form the neural stalk and eventually end at the floor of the third ventricle and in the median eminence. Our understanding of the role of transcription factors in hypothalamus development has helped to clarify the early differentiation of this cell lines.[8]

The BRN2, OTP, SIM1 and ARNT2 genes seem to be involved in the cascade of transcription factors associated in the development of the neuroendocrine hypothalamus leading to the completion of posterior pituitary development by the end of the first trimester.[9] Null mutation of UNcx4.1 revealed a phenotype consisting of an ectopic localization that extends vasopressinergic axons from paraventricular and supraoptic nuclei; these axons do not stop at the normal location in the neurohypophysis, but instead grow into the anterior pituitary lobe.[9] A Hes1-null pituitary gland was shown to be reduced in size in a recent study but was otherwise morphologically normal in comparison to the control. In Hes1-Hes5 double-mutant mice, the evagination of the pituitary stalk was affected and the anterior pituitary gland was lost compared to both the wild-type and Hes1-null mice, indicating that both Hes genes transcription factors are essential for the formation of the neurohypophysis.[10]

GENE MUTATIONS ASSOCIATED ECTOPIC NEUROHYPOPHYSIS

Ectopic neurohypophysis associated with adenohypophysis dysfunction has been reported as naturally occurring mutations of transcription factors involved in development of the pituitary gland. Among these are gene mutations taking place in early phase of development such as GLI2, HESX1, FGF8, FGF1, PROK2, PROKR2, OTX2, SOX2, SOX3, PITX2, ARNT2, LHX3, LHX4 which are involved in more complex and heterogeneous phenotypes such as pituitary anomalies, various craniofacial and limb malformations in addition to pituitary hormone deficiencies.[11] On the other hand, mutations of genes playing a role in the late development (PROP1 and POU1F1) are usually associated with multiple pituitary hormone deficiency (MPHD) phenotypes.[11,12] In all these gene mutations, the four most commonly involved in the pituitary stalk transection syndrome are; HESX1, LHX4, SOX3 and OTX2.[13] These mutations of transcription factors have been implicated in abnormal anterior pituitary organogenesis and posterior pituitary migration.[14]

HESX1 which was the first gene mutation described with EPP (a common finding in idiopathic GHD) has been reported to be associated with agenesis of the corpus callosum, hypoplasia of the optic nerves, pituitary hypoplasia and EPP.[15]

Three reports have described patients with LHX4 gene mutations. In the first, a heterozygous mutation in an intron of LHX4 in a consanguineous family with members exhibiting multiple pituitary hormone deficiency (MPHD) characterized by short stature, small sella turcica, hypoplastic anterior pituitary and cerebellar defects presenting with deficiencies in GH, TSH, and ACTH (LH and FSH were not investigated in the study).[16] In the second report, a heterozygous mutation (P366T) affecting a residue in the carboxyl terminus of LHX4 was found to be associated with deficiencies of GH, prolactin, TSH, LH, FSH, ACTH, a hypoplastic anterior lobe, an ectopic posterior pituitary, a poorly developed sella turcica, Arnold-Chiari malformation, and respiratory distress syndrome.[17] In the third study involving 5 patients, three types of heterozygous missense mutations in LHX4 were identified. The patients have GH deficiency and some also display reductions in TSH, LH, FSH, or ACTH. Three patients displayed *in situ* posterior pituitary and two had EPP while the anterior pituitary was hypoplastic in 3 and normal in one; pituitary cysts were found in 2 patients.[18]

SOX3, a single axon gene closely related to SRY is strongly implicated in the etiology of X-linked hypopituitarism in both humans and mice. The phenotype of Sox3 mutant mice is found to be variable and complex, with abnormalities throughout the hypothalamic-pituitary-gonadal axis. In humans, mutations of SOX3 and duplications at Xq26–27 are implicated in a syndrome of X-linked hypopituitarism and mental retardation. Sox3 over expression produces clinical and endocrine hypopituitarism-related disorders linked with EPP, as well as abnormalities of the pituitary stalk, implying that the SOX3 gene is critical for normal diencephalon, infundibulum, and anterior pituitary development.[19]

OTX2, which is not expressed in the hypophysis but important in brain development as a transcription factor, is seen with a large spectrum of syndromes such as with various hypophyseal deficiency findings from isolated growth hormone deficiency to panhypopituitarism, hypoplastic ectopic hypophysis and Chiari syndromes.[12]

IMAGING IN PITUITARY STALK TRANSECTION SYNDROME

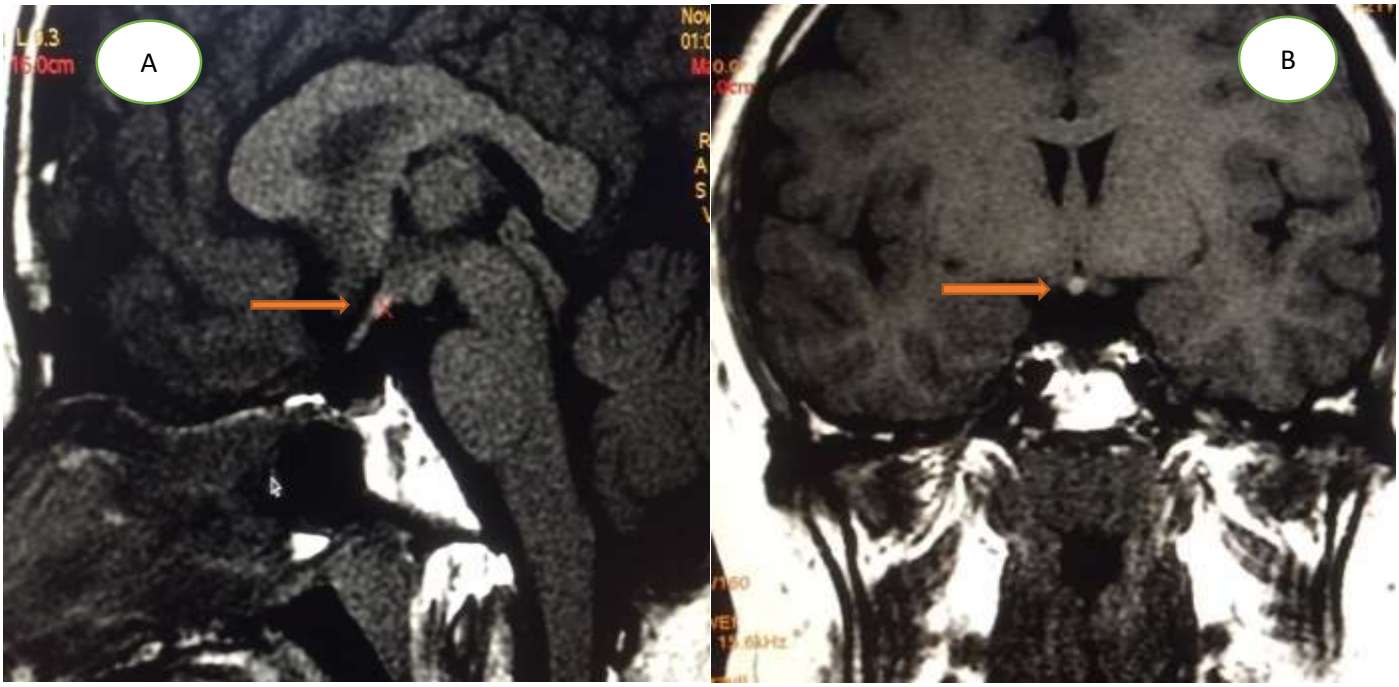
Detection of structural abnormalities accompanying pituitary and hypothalamic deficits really improved with advances in MRI imaging techniques in recent years. Commonly seen pituitary anomalies on imaging include hypoplastic pituitary, complete or partial empty sella turcica, EPP and hypoplastic or absent infundibulum.[20] Imaging of the pituitary gland is very vital not only in confirming the diagnosis of pituitary lesions but also in determining the differential diagnosis of other sella turcica lesions. Plain skull radiographs are not good at delineating soft tissues and are not requested these days for diagnosing pathologies in the sellar and parasellar regions. The radiographic size of sella turcica is not a sensitive indicator of pituitary gland abnormality, as the empty sella turcica may itself lead to enlargement of size.[21] Thus, the plain radiographs have been substituted by cross-sectional imaging techniques such as CT and MRI. CT scan, though not commonly used for evaluating sellar and para-sellar lesions, it is very useful in the detection of soft tissue calcification, bony destruction, and surgically important bony anatomy. CT scan is relevant especially when MRI is contraindicated in patients with pacemakers or metallic implants in the body. However, less optimal soft tissue contrast and radiation exposure are two valuable disadvantages that limit the judicious use of CT scan in pituitary region evaluation.

MRI is the examination of choice for sellar and para-sellar lesions due to its superior soft tissue contrast, multiplanar capability and no risk of ionizing radiation. Besides, MRI also provides useful information about the relationship of the gland with adjacent anatomical structures and helps to plan surgical interventions. MRI techniques in diagnosing pituitary pathologies have witnessed a rapid evolution, ranging from non-contrast MRI in late 1980s, contrast-enhanced MRI in mid-1990s and more recently, dynamic contrast-enhanced MRI. Introduction of dynamic contrast-enhanced MRI has further refined this technique in diagnosing pituitary pathologies such as microadenomas and even vascular component of the infundibulum in pituitary stalk transection syndrome.

On T1-weighted images, the posterior pituitary shows hyperintense signal while the anterior pituitary gland is of intermediate signal intensity. The cause of the hyperintense signal of the posterior pituitary on T1-weighted images is still controversial. The presence of neurosecretory granules in the posterior pituitary has been attributed as to why there is high signal intensity in T1 weighted images by Fujuswa et al.[22] Another report states that the high signal intensity might be associated to lipid in the posterior lobe pituicytes.[23]

Currently, there is a wide range of advanced MR techniques that are particularly helpful in evaluating specific cases. These include 3D volumetric analysis of pituitary volume, high-resolution MR imaging at 3 Tesla (T) for evaluating pituitary stalk.[21] Typical findings are those of small anterior pituitary lobes and pituitary stalks, with hyperintensity at the median eminence corresponding to an ectopic posterior pituitary lobe, which does not suppress on fat-saturated T1-weighted MR images. Other features are that of a thin truncated infundibulum and a small or normal sized sella turcica containing a hypoplastic anterior pituitary lobe (Fig. 1C). The infundibulum is best visualized in the contrast-enhanced images, normally seen angling postero-superiorly toward the median eminence which is identified by its enhancement.

Data available show a varying correlation between anomalies of posterior pituitary development as observed at MRI scan and patient endocrine function. MPHD is particularly associated with EPP and anterior pituitary hypoplasia at a high rate, ranging between 74 and 100% of cases. Isolated GH deficiency, contrarily, is associated with these particular MRI features at a lesser rate, ranging between 2 and 68%.[17] A detailed study of the pituitary stalk should be carried out after the administration of contrast medium injection using gadopentetate dimeglumine (Gd-DTPA). A finding of vascular component of the stalk has a great deal of prognostic significance since patients with agenesis of the pituitary stalk run a greater risk of developing MPHD than those who show the vascular residue of the stalk.[17] Patients in whom the infundibular stalk is not identifiable (Fig. 1 D) after gadolinium administration have a 27 times greater risk of developing additional pituitary hormone deficiencies than those with a residual vascular pituitary stalk.[24] The size and identification of EPP are helpful in the diagnosis and prognosis of patients with GH deficiency and the size of EPP may vary considerably between patients, ranging from small EPP to large EPP and even huge EPP. In particular, the size and the location of EPP are said to be early markers of evolving pituitary hormone deficiencies as reported.[25]



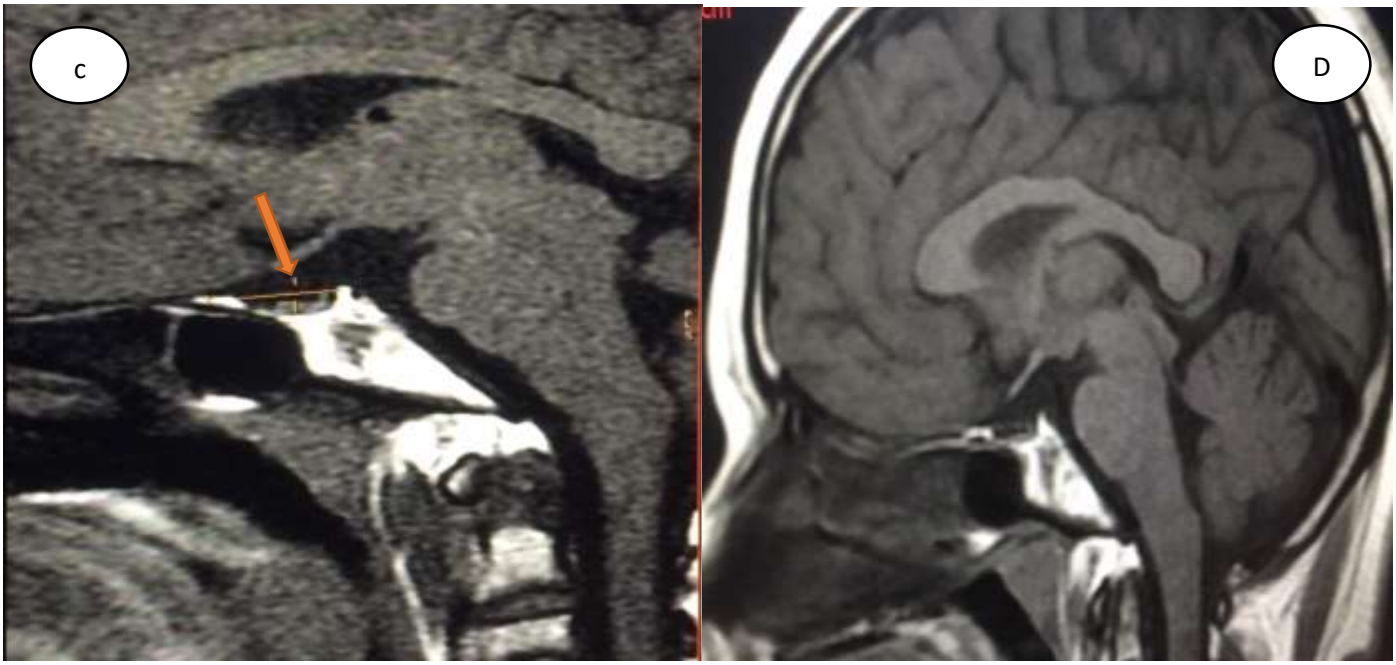


Figure 1A and B: MRI showing Ectopic Posterior Pituitary, Figure 1 C: MRI showing Hypoplastic anterior pituitary, Figure 1 D: MRI of a patient with absent pituitary stalk. From MRI images, by Alloysius Ebi Ligha, 2019.

CONCLUSION

Pituitary stalk interruption syndrome typically has a range of associated clinical and MR imaging abnormalities. The presence of an ectopic posterior pituitary lobe should alert the radiologist to the possibility of associated cerebral malformations, especially in the midline structures. The location of the ectopic lobe can vary, but it is most commonly located along the median eminence in the floor of the third ventricle. The cause of an ectopic posterior pituitary gland is largely defective neuronal migration during embryogenesis. Usually, the anterior pituitary gland is absent, or attenuated and reduced in height, and the infundibular stalk may not be present or diminutive in size. Analysis of this interesting association and potential molecular defects may help to shed more light on the mechanisms of early pituitary development and neuronal cell migration.

CONFLICT OF INTEREST

The authors declared that there are no conflicts of interest

AUTHOR CONTRIBUTIONS

Both authors made substantial contribution to the study and the manuscript.

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