The Missing Link: A Case of Absent Pituitary Infundibulum and Ectopic Neurohypophysis in a Pediatric Patient with Heterotaxy Syndrome

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ABSTRACT

We report a case of absent pituitary infundibulum and ectopic neurohypophysis in a 4-year-old patient presenting clinically with hypopituitarism as well as heterotaxy syndrome complicated by global developmental delay and growth retardation. The clinical and laboratory workup of our patient suggested underlying hypopituitarism related to either congenital or acquired pathology, necessitating MRI to distinguish between them. We explain the various structural causes of hypopituitarism and detail how to predict the MRI findings and treatment, based on a fundamental understanding of the anatomy and pathophysiology of the hypothalamic pituitary axis and distinguishing anterior versus posterior pituitary hormone derangements. We also discuss two important theories widely acknowledged in the literature to explain congenital hypopituitarism: 1. Head trauma typically during birth resulting in a stretch injury to the infundibulum. 2. Congenital fetal maldevelopment of midline structures.

CASE REPORT

CASE REPORT

A 4-year-old male presented to the pediatric endocrinologist with global developmental delay and growth retardation. The patient's prenatal and neonatal records were significant for a maternal history of uncontrolled diabetes mellitus, cesarean section delivery at 40 weeks gestation, and meconium stained amniotic fluid. Following delivery, the patient developed respiratory distress syndrome. Extensive workup during the perinatal period revealed the presence of heterotaxy syndrome with an azygous continuation of the inferior vena cava, functional asplenia, ventricular septal defect, and intestinal malrotation requiring Ladd procedure. The patient's height and weight were 1.8 and 1.4 standard deviations below the mean for age and gender, respectively. Laboratory analysis revealed multiple hormonal deficiencies demonstrated by the following results: insulin growth factor 1 binding protein 16 ng/ml (normal, 30-155 ng/ml), hypoglycemia with inappropriate cortisol response 1.2 ug/dl (normal, 6-21 ug/dl), and low free T4 0.57 ng/dl (normal, 0.9 – 1.9ng/dl) with inappropriate thyroid stimulating hormone response 2.26 uIU/ml (normal, 0.35 – 4.8 uIU/ml), the latter consistent with secondary/tertiary hypothyroidism. Additionally, there was an absence in testosterone surge at 2 to 3 month of age. The constellation of clinical and laboratory findings was highly indicative of a pituitary deficiency disorder. The next step in management was to obtain Magnetic Resonance Imaging (MRI) of the brain and pituitary gland.

The T1-weighted MR images demonstrated a partially empty hypoplastic sella turcica, unidentifiable pituitary stalk, and hypoplastic anterior pituitary gland tissue along the floor of the Sella. In addition, a 2 mm hyperintense round soft tissue nodule at the median eminence, suspected ectopic posterior pituitary tissue. These findings were consistent with congenital

hypopituitarism (Figure 1a and 1b). Treatment began with levothyroxine and hydrocortisone, in addition to, long term prophylactic antibiotics due to the patient's asplenia. Follow up showed significant growth during the first six months of treatment which plateaued thus prompted growth hormone replacement.

DISCUSSION

Introduction:

Congenital pituitary deficiency disorder is usually recognized clinically by failure to thrive and growth retardation in children. It is a rare congenital abnormality associated with structural interruption of the Hypothalamic-Pituitary Axis (H-P axis), whereby the anterior lobe of the pituitary is deprived of the usual hypothalamic stimulating factors [1]. In contrast, the posterior lobe usually remains functional because neurosecretory vesicles typically transported from the hypothalamus to the posterior lobe are arrested above the level of stalk discontinuity where they function as an ectopic neurohypophysis. This ectopic posterior lobe manifests on MRI as a T1 hyperintense nodule at the level of the median eminence [1,2,3,4,5].

Epidemiology:

The overall annual incidence of hypopituitarism is 4.21 cases/100,000 including all causes [6]. Male to female ratio is 1.9:1, with a mean age of 12.8 years for congenital pituitary deficiency disorder [2].

Goals of Magnetic Resonance Imaging:

MRI is an important part of the work up to confirm a structural maldevelopment of the hypothalamic pituitary axis rather than acquired pathology seen in children ranging from neoplastic causes such as craniopharyngioma, germinoma, or adenoma to inflammatory or infectious causes. Anterior lobe dysfunction with preservation of posterior lobe function favors congenital maldevelopment while combined anterior and posterior lobe dysfunction favors other underlying pathology that would disrupt both the hypophyseal portal system as well as the hypothalamohypophyseal tract either due to severe mass effect or direct infiltration (Figure 2) [2].

Imaging findings:

MRI T1-weighted coronal and sagittal images pre and post contrast obtained demonstrates partially empty sella turcica, unidentifiable pituitary stalk, hypoplastic anterior pituitary gland tissue along the floor of the sella, and 2 mm hyperintense round soft tissue nodule at the median eminence on the pre-contrast images. Post contrast T1 images showed an enhancement of the 2 mm nodule at the median eminence. The hyperintensity and enhancement of the 2 mm nodule are typical for an ectopic posterior pituitary gland. These findings were consistent with congenital hypopituitarism (Figure 1a, 1b, 1c and 1d).

Differential Diagnosis:

There is a wide range of acquired pathologies that could interrupt the hypothalamic-pituitary axis, however, for children, there are few possible differentials such as craniopharyngioma, pituitary adenoma, eosinophilic granuloma, germinoma, and hamartoma.

Craniopharyngiomas are neoplasms that arise from epithelial cells of Rathke pouch which usually demonstrate cystic and solid components. On T1 weighted pre-contrast MRI, they could show hyperintense, iso-intense, or hypo-intense cystic component with iso- or hyper-intense solid component. On post-contrast imaging, the solid component enhances and the cystic component may display rim enhancement [7]. Additionally, calcifications are a common finding in craniopharyngiomas neoplasms [8].

Pituitary adenomas are benign tumors of the pituitary gland. On T1 weighted pre-contrast MRI, they typically show signal intensities similar to that of the gray matter and homogeneously enhance after contrast administration. The signal intensities and enhancements may vary if complications such as necrosis, cystic degeneration or hemorrhage had developed [7].

Eosinophilic granuloma belongs to a group of diseases known as Histiocytosis X, they are characterized by reticuloendothelial or histiocytic cells proliferation. They have the affinity to infiltrate the hypothalamus, infundibulum and posterior pituitary gland giving rise to hormonal disturbances. On pre-contrast T1 weighted images, a mass with isointense signal may be present which enhances after contrast administration [9,10].

Germinoma, an intracranial germ cell tumor, shares histopathological characteristics with that of testicular seminoma. On MRI imaging, it appears as an isointense mass on T1 weighted images that enhances post contrast [11]. Furthermore, on T2 sequence suprasellar Germinoma could demonstrate isointense to hyperintense signal [12].

Hypothalamic hamartoma is non-neoplastic hyperplastic tissue which is heterotopic, resembling gray matter. On T1 weighted MRI images it appears as an isointense lesion with sessile attachment to the hypothalamus, however, the lesion does not typically demonstrate enhancement post contrast administration [13].

The Hypothalamus and The Pituitary Gland are connected through the hypophyseal portal system and hypothalamohypophyseal tract. The hypophyseal portal system links the hypothalamus and the anterior pituitary gland. The hypothalamohypophyseal tract links the hypothalamus to the posterior pituitary gland. Both pathways are contained within the infundibulum [14,15,16]. Thus, morphological abnormalities such as absent infundibulum in Congenital Hypopituitarism, compression and obliteration of pituitary by Craniopharyngioma and Pituitary Adenoma, infiltration of (hypothalamus, infundibulum and pituitary gland) by Eosinophilic Granuloma, compression of hypothalamus by Germinoma, and downward extension of Hypothalamic Hamartoma resulting in compression of infundibulum, all of which interrupt the link between the hypothalamus and pituitary hence hormonal disturbances (Figure 2).

Etiology of congenital pituitary deficiency disorder:

Two theories have been proposed to explain the cause of structural failure. One theory proposes that head trauma during birth causes a stretch injury to the pituitary stalk between the mobile brain and the pituitary gland which is fixed to the skull base. This theory relies heavily on the associated high incidence of breech deliveries in children with congenital pituitary deficiency disorders [17,18,19]. Jagtap S, *et al.* (18) study showed an increased incidence of 18% in breech delivery in patients with Growth Hormone Deficiency compared to 3% incidence in general population, additionally, Kikuchi *et al.* and Fujisawa *et al.* (17) study on 21 patients diagnosed with Growth Hormone Deficiency showed that 18 of the 21 patients had prenatal insult most of which were breech deliveries.

The other theory raises the possibility of congenital fetal maldevelopment of midline structures including the hypothalamic pituitary axis. There is a resultant failure of the posterior lobe to descend into the sella turcica to come in contact with the anterior lobe [20,21,22]. The latter theory also provides an explanation for the often found associated midline anomalies of the palate, skull base, optic nerves and septum pellucidum to name a few. Furthermore, multiple genes such as PITI, PROPI, LHX3/LHX4, PROKR2, OTX2, TGIF and HESX1 which are normally responsible for hypothalamic pituitary axis development have been identified as a potential cause of hypothalamic pituitary axis maldevelopment. Upon their failure signaling pathways may malfunction causing pituitary stalk interruption [23].

Interestingly, in addition to maldevelopment of the H-P axis, our patient was found to have other congenital anatomic variants including heterotaxy syndrome with azygos continuation of the IVC and intestinal malrotation requiring Ladd procedure. The presence of additional congenital variants in our patient and lack of breech delivery is more in keeping with the latter maldevelopment theory rather than the traumatic hypothesis [2,24].

Heterotaxy syndrome:

Heterotaxy syndrome has also been thought to be associated with midline central nervous system abnormalities, in addition to other anomalies of major body organs including the spleen, respiratory and cardiovascular system. Therefore, involved organs and systems lead to immune system dysfunction, ciliary dysfunction, venous anomalies, and thromboembolisms [24]. To our knowledge, two cases in the literature described heterotaxy syndrome with associated panhypopituitarism as of yet. First, Tasi *et al.* [25] reported a family (father and daughter) with pan-hypopituitarism, heterotaxy syndrome, and biliary atresia. The genetic defect detected was the deletion of FOXA2. Second, Kevelam *et al.* [26] described a case with a mutation in GLI2 gene which presented with holoprosencephaly, panhypopituitarism, and associated heterotaxy syndrome.

Conclusion:

Absent infundibulum and ectopic posterior pituitary syndrome of clinical relevance, especially in the pediatric population, as a potential cause of failure to thrive and poor growth due to hypopituitarism. Attention to this rare but serious condition is needed, as it can be easily treated, mitigating long term sequelae. The patient medical history of heterotaxy syndrome is important, as it is associated with midline central nervous system abnormalities such as absent corpus callosum, which begs the question of possible association with other anomalies including that of absent infundibulum and ectopic posterior pituitary gland.

TEACHING POINT

Congenital pituitary deficiency is confirmed when MRI demonstrate absent infundibulum, ectopic posterior pituitary gland, and hypoplastic anterior pituitary gland.

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FIGURES

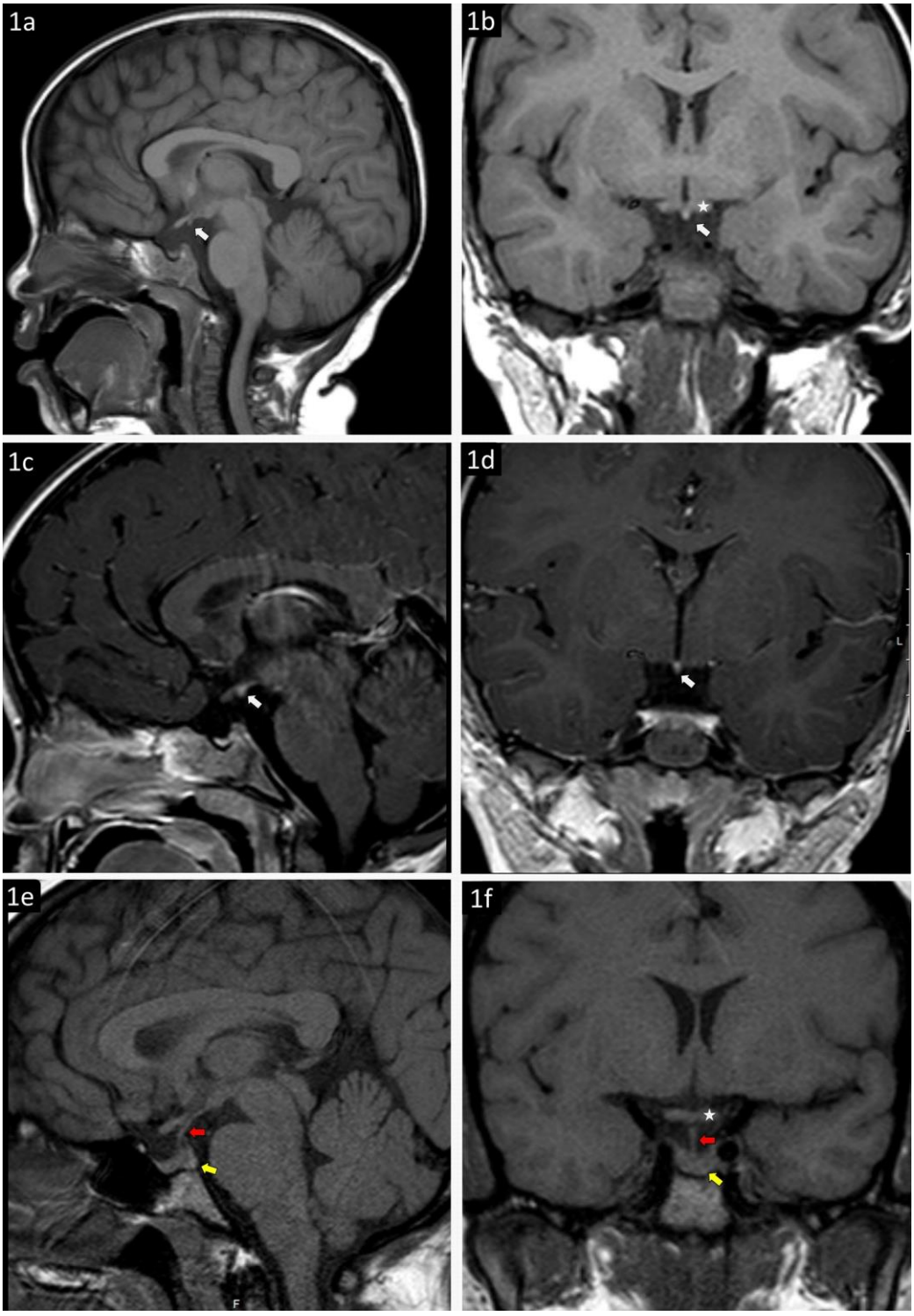

Figure 1: (a), (b), (c), and (d) are images of A 4-year-old male patient with congenital hypopituitarism presented as global developmental delay and growth retardation. Laboratory workup revealed hormonal deficiencies and diagnosis confirmed with MRI. (e) and (f) are images of a normal 30-year female patient provided for comparison.
FINDINGS: MRI scan using Phillips 1.5 Tesla unit, TR 550 and TE 15 with a slice of 3 mm and a distance of 3.3 mm; obtained pre contrast sagittal (a) and coronal (b) T1-weighted images demonstrate a partially empty sella turcica, unidentifiable pituitary stalk, hypoplastic anterior pituitary gland tissue along the floor of the sella, and a 2 mm hyperintense round soft tissue nodule at the median eminence consistent with ectopic posterior pituitary tissue (white arrow). Post contrast sagittal (c) and coronal (d) T1-weighted MR images demonstrate enhancement of the same 2 mm nodule which represents the ectopic posterior pituitary gland (white arrow). Pre contrast sagittal (e) and coronal (f) T1-weighted MR images of a normal 30-year-old patient are provided for comparison. Note the normal infundibulum extending from the hypothalamus to the pituitary gland (red arrow). Also, note the normal well-formed sella turcica containing both the anterior pituitary lobe and T1 hyperintense posterior pituitary lobe (yellow arrow). Finally, superior to both structures the optic chiasm (white star) is normally situated (d).

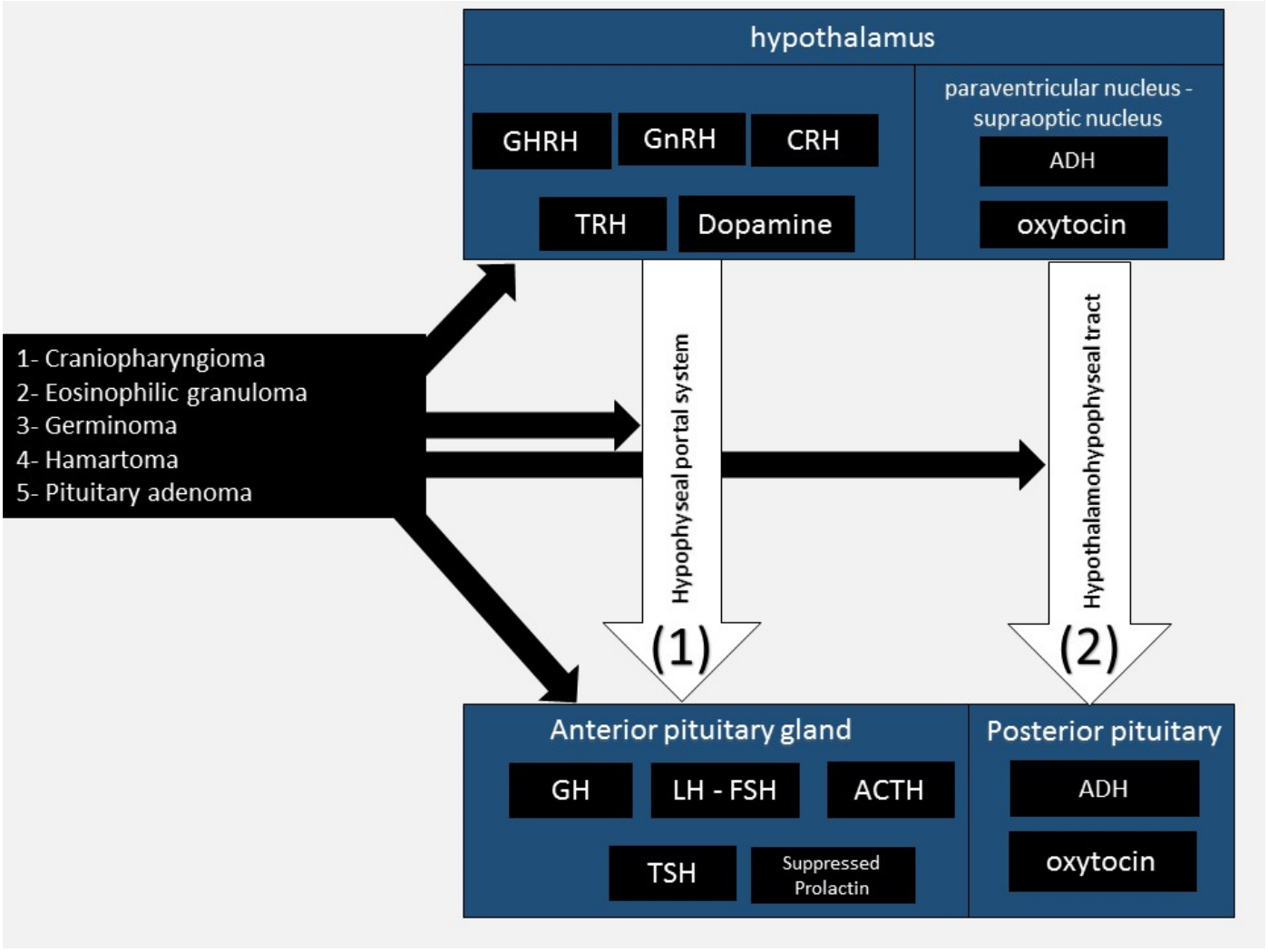

Figure 2: A 4-year-old male patient with congenital hypopituitarism presented as global developmental delay and growth retardation. This illustration shows the normal physiological and morphological relationship between hypothalamus and pituitary, thus, explains the mechanism of hormonal deficiencies caused by congenital hypopituitarism and other differentials.
Arrow (1) represents the hypophyseal portal system, which provides a link between the hypothalamus and the anterior pituitary gland. Arrow (2) represents the hypothalamohypophyseal tract, which links the hypothalamus to the posterior pituitary gland. Both pathways are contained within the infundibulum. To the left a list of etiologies that may interrupt hormonal transportation at the level of hypothalamus, infundibulum, or pituitary gland [14,15,16].

Etiology:	Controversial, with two hypotheses. First is traumatic transection of the infundibulum during birth. Second suggests congenital fetal maldevelopment of midline structures including the hypothalamic pituitary axis [2, 17-21].
Incidence:	Annual incidence rate of all hypopituitarism causes is 4.21 cases/100000 [6].
Gender ratio:	Male to female ratio is 1.9:1 [2].
Age predilection:	Range: 4 months - 43 years, mean age of 12.8 years [2].
Risk factors:	Prenatal insults (hypoglycemia, jaundice, and hypoxia) and breech delivery [2].
Treatment:	Hormonal replacement [2].
Prognosis:	Favorable with timely hormonal replacement therapy of stable patients [27].
Findings on imaging:	MRI: T1-weighted hyperintense nodule at the median eminence which enhances following contrast administration, absence of posterior pituitary hyperintensity at its normal location, and absent infundibulum [2].

Table 1: Summary table for congenital pituitary deficiency.

Entity	T1- weighted MRI pre-contrast	T1-weighted MRI post-contrast	Lesion location / Other features
Congenital hypopituitarism	* Unidentifiable pituitary stalk. * Isointense nodule at the median eminence (ectopic posterior pituitary gland). * Absence of posterior pituitary gland hyperintensity.	* Enhancement of the median eminence nodule with absence of the posterior pituitary gland enhancement at its normal location.	* Children presented with failure to thrive and growth retardation due to hormonal deficiencies.
Pituitary adenoma [7]	* Uncomplicated adenomas usually show signals similar to that of gray matter. * Complicated adenoma may show various signals related to each specific complications (necrosis, cystic degeneration, etc.)	* Uncomplicated adenoma may show homogenous enhancement. * Complicated adenoma may show various enhancing patterns according to complication.	* Mainly arises from Intra-sellar region.
Craniopharyngioma [7,8]	* Hyperintense, iso-intense, or hypo-intense cystic component with iso- or hyper-intense solid component. Calcifications are common finding in pediatric population with craniopharyngioma.	* Mixed lesion with enhanced solid component and rim enhancement of cystic component.	* Mainly arises from the suprasellar region.
Eosinophilic granuloma [9,10]	*Isointense lesion	*Enhances with contrast	* May originate from skull base, mainly involves hypothalamus, infundibulum and posterior pituitary.
Germinomas [11,12]	* Isointense mass	*Mass enhances with contrast. On T2 sequence may show isointense to hyperintense signal.	*Lesion found along the floor of 3rd ventricle (hypothalamus)
Hamartoma [13]	*Isointense lesion with a sessile hypothalamic attachment	* Lesion does not enhance with contrast.	* Lesion does not progress on follow up imaging.

Table 2: Differential diagnosis table for congenital pituitary deficiency.

ABBREVIATIONS

ACTH = adrenocorticotropic hormone
ADH = antidiuretic hormone
CRH = corticotropin releasing hormone
FSH = follicular stimulating hormone
GH = growth hormone
GHRH = growth hormone releasing hormone
GnRH = gonadotropin releasing hormone
H-P AXIS = hypothalamic-pituitary axis
LH = luteinizing hormone
MRI = magnetic resonance imaging
TRH = thyrotropin releasing hormone
TSH = thyroid stimulating hormone

KEYWORDS

MR imaging; absent infundibulum; ectopic posterior pituitary; heterotaxy syndrome; panhypopituitarism; tumors; infections

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