Imaging of pediatric pituitary endocrinopathies

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ABSTRACT

Accurate investigation of the hypothalamic-pituitary area is required in pediatric patients for diagnosis of endocrine-related disorders. These disorders include hypopituitarism, growth failure, diencephalic syndrome, delayed puberty, precocious puberty, diabetes insipidus, syndrome of inappropriate antidiuretic hormone (SIADH) secretion, and hyperpituitarism. Magnetic resonance imaging (MRI) is the modality of choice to visualize hypothalamic-pituitary axis and associated endocrinopathies. Neuroimaging can be normal or disclose abnormalities related to pituitary-hypothalamic axis like (i) congenital and developmental malformations; (ii) tumors; (iii) cystic lesions; and (iv) infectious and inflammatory conditions. Classical midline anomalies like septo-optic dysplasias or corpus callosum agenesis are commonly associated with pituitary endocrinopathies and also need careful evaluation. In this radiological review, we will discuss neuroendocrine disorders related to hypothalamic pituitary-axis.

Key words: Magnetic resonance imaging, neuroimaging, pediatric population, pituitary endocrinopathies, pituitary-hypothalamic axis

INTRODUCTION

Endocrine-related diseases in pediatric population include hypopituitarism, growth failure, diencephalic syndrome, delayed puberty, precocious puberty, diabetes insipidus, syndrome of inappropriate antidiuretic hormone (SIADH) secretion, and hyperpituitarism.1,2 Imaging of pituitary-hypothalamic axis has become essential in diagnosis of these disorders. High quality magnetic resonance imaging (MRI) is the modality of choice in evaluation of pituitary-hypothalamic morphology. Neuroimaging can be normal or can demonstrate pituitary-hypothalamic abnormalities like congenital and developmental malformations such as pituitary hypoplasia or absence, ‘ectopic’ posterior pituitary (translocation of pituitary bright spot to median eminence), absence of pituitary bright-spot (may indicate disruption of normal stalk transport mechanism), duplication of pituitary gland/stalk and empty sella syndrome; tumors, mainly craniopharyngiomas, pituitary adenomas (among hormonally active tumors, adrenocorticotropic hormone-releasing adenomas are most common in the first 11 years of life, while prolactinomas become more common into the teenage years), chiasmatic or hypothalamic glioma, hypothalamic hamartoma, germinoma, and leukemia/lymphoma; cystic lesions such as Rathke’s cleft cysts that are commonly seen in the gland, even in healthy children (they are nonfunctional, however, may cause mass effect on the gland); and infectious/inflammatory conditions such as Langerhans cell histiocytosis, lymphocytic hypophysitis, tuberculosis, and sarcoidosis. One should also pay careful attention to evaluate midline anomalies (like septo-optic dysplasias or corpus callosum agenesis) commonly associated with pituitary endocrinopathies.3,4

NORMAL EMBRYOLOGY, DEVELOPMENT AND PHYSIOLOGY OF PITUITARY-HYPOTHALAMIC STRUCTURES

The pituitary gland forms around sixth to seventh embryonic week. Embryologically, anterior and posterior lobes of the gland develop separately and from different origins. The anterior pituitary (adenohypophysis) develops from Rathke’s pouch or cleft and constitutes ~78% of total gland at term. The posterior pituitary (neurohypophysis) develops from neuroectoderm of diencephalon. The
posterior pituitary is connected to hypothalamus via pituitary stalk and hypothalamo-hypophysal tract. Between anterior and posterior lobes, lies an intermediate lobe, the pars intermedia, which is vestigial. This is a potential site for small nonfunctional Rathke’s cysts.\(^5,6\) Pituitary stalk (infundibulum) can be identified at 6 weeks.\(^7\)

The adenohypophysis contains six different cell types that are characterized by their hormone secretion: corticotrophs secrete adrenocorticotropic hormone or corticotropic (ACTH), somatotrophs secrete growth hormone (GH), thyrotrophs produce thyroid-stimulating hormone or thyrotropin (TSH), gonadotrophs secrete luteinizing hormone (LH), follicle-stimulating hormone (FSH), and lactotrophs produce prolactin (PRL). Posterior pituitary hormones include antidiuretic hormone (ADH) or vasopressin and oxytocin. These hormones are synthesized by supraoptic and paraventricular hypothalamic nuclei, transported through the axon and stored in the axon terminals that lie in the posterior pituitary, from where they are secreted to general circulation. The hypothalamus also secretes trophic factors and releasing hormones (RH) that regulate the function of anterior pituitary.\(^8,9\)

**Radiological Anatomy of Pituitary Gland**

The size and shape of pituitary gland varies with age. At birth it is typically globular in shape, becomes flattened by 6 weeks of age, and again becomes prominent (maximum height of 10–12 mm, globular shape with upward convex margin) during puberty (particularly in girls) and pregnancy. This appearance should not be mistaken for tumor.\(^9,10\) In pubertal boys, it may reach 8 mm in height. Pituitary stalk is normally not more than 2 mm in diameter.\(^7\)

Pituitary gland lies within the sella turcica, a cup shaped depression in sphenoid bone. The surrounding structures include the sphenoid sinus anteriorly and inferiorly, the suprasellar cistern superiorly, the basilar artery and brain stem posteriorly, and the cavernous sinuses bilaterally. The sella turcica is covered by diaphragma sella, which has a defect for passage of the infundibulum. Pituitary gland is connected to hypothalamus via infundibulum.\(^12\)

**Imaging of Pituitary-Hypothalamic Axis**

High resolution MRI using thin sections (2 or 3 mm) coronal and sagittal T1-weighted images through the pituitary-hypothalamic axis before and after intravenous administration of gadolinium are the main-stay of pituitary imaging. Dynamic contrast MRI has been proven to be the best imaging tool in evaluation of pituitary adenomas. Fluid attenuation inversion recovery (FLAIR) and T2-weighted fast spin-echo (FSE) images are also important. MRI of pituitary-hypothalamic morphology has important clinical implication both in terms of diagnostic accuracy and long-term prognosis. CT may be needed to confirm calcification or hemorrhage.\(^13\)

MR signal intensity of the pituitary gland varies with age. At birth it typically shows high signal on T1-weighted images. By approximately 6 weeks, high signal of anterior pituitary tissue diminishes and becomes similar to that of brain tissue. The posterior pituitary tissue, however, retains bright signal on T1-weighted sequence [Figure 1]. This so-called ‘posterior pituitary bright spot’ is due to high neurophysin content.\(^10,14\) During pregnancy and postpartum period, the anterior lobe may appear T1 hyperintense.\(^13\) The pituitary gland, pituitary stalk and cavernous sinuses are vascular structures which are seen to enhance after gadolinium injection; the optic chiasm and hypothalamus, however, do not show enhancement if blood–brain barrier is intact.\(^1,7\)

**Congenital and Developmental Malformations of the Pituitary-Hypothalamic Axis**

Hypoplasia or absence of pituitary gland

Hypoplasia or absence of pituitary gland is extremely rare. There may be absence or hypoplasia of the gland or stalk. Associated congenital abnormalities of midline craniofacial structures may be present. On MRI, the pituitary gland and sella turcica are absent or smaller in size. Midline anomalies like septo-optic dysplasias or corpus callosum agenesis needs careful evaluation. Clinically, the patient presents with pituitary-hypothalamic dysfunction and growth failure.\(^16,17\)

**Figure 1:** Normal pituitary gland. Sagittal T1-weighted image shows normal appearing pituitary gland with posterior pituitary bright spot (arrow)
Ectopic posterior pituitary
Ectopic location of undescended posterior pituitary is visible as a high signal nodule in the region of median eminence on MR imaging. These patients may have associated absence or hypoplasia of pituitary gland or stalk and midline cranio-facial anomalies. An ectopic posterior pituitary may be differentiated from hypothalamic lipoma by lack of fat suppression. Clinically, the patient presents with pituitary dwarfism or idiopathic growth hormone deficiency.\cite{18,19}

Absence of pituitary bright-spot
Absence of posterior pituitary bright spot on MR imaging indicates disruption of the normal stalk transport mechanism (transsection syndrome). It strongly correlates with absent or hypoplastic pituitary gland. Multiple pituitary hormone deficiency (MPHD), isolated GH deficiency (IGHD), and diabetes insipidus (DI) are the abnormalities associated with absent posterior pituitary bright spot.\cite{20,21}

Duplication of the pituitary gland/stalk
Duplication of pituitary including the stalk has been reported. These cases are often associated with midline facial abnormalities. Majority of these patients die in infancy.\cite{19,20}

Empty sella syndrome
The empty sella syndrome results from deficiency of diaphragma sella, which allows suprasellar cistern and its contents to herniate into the sella. On MR imaging, the sella is largely filled-up with cerebrospinal fluid (CSF) and expanded (due to CSF pulsations), the pituitary gland appears flattened along the floor of sella. In children, it may be associated with pituitary-hypothalamic dysfunction (MPHD), visual symptoms, and CSF rhinorrhoea.\cite{22}

Associated syndromes and midline congenital anomalies
Pituitary-hypothalamic dysfunction may be associated with some syndromes such as septo-optic dysplasias, Kallmann’s syndrome, and midline congenital anomalies like corpus callosum agenesis, holoprosencephaly, and basal cephaloceles.

Septo-optic dysplasia (de Morsier’s syndrome), a mild form of holoprosencephaly, is characterized by absence or hypoplasia of septum pellucidum associated with hypoplasia of the optic nerves. Two-third of patients with de Morsier’s syndrome have associated pituitary-hypothalamic dysfunction that ranges from panhypopituitarism to GH deficiency, TSH deficiency, ACTH or ADH deficiency.\cite{23,24}
On MRI, there is absence or hypoplasia of septum pellucidum resulting in a box-like appearance of the frontal horns. Associated optic tract hypoplasia (involving optic nerve, optic tract, or optic chiasma) may be seen in 50% of patients.\cite{25}

Kallmann’s Syndrome is characterized by agenesis of olfactory lobes and bulbs, and isolated gonadotropin deficiency. Clinically, patient presents with anosmia or hyposmia, hypogonadotropic hypogonadism and delayed puberty. On MRI, olfactory sulcus and olfactory apparatus are absent or hypoplastic.\cite{26}

Tumors of the Pituitary-Hypothalamic Axis

Cranioopharyngiomas
Cranioopharyngiomas are commonest tumors to involve the hypothalamic/pituitary region in children aged between 5 and 10 years. In children, it is adamantinomatous histological subtype that is the most common. On MRI [Figure 2], these tumors are characterized by a complex sellar/suprasellar mass containing both cystic and solid components as well as calcification. The calcification is best appreciated on computed tomography (CT) scan. The solid component shows enhancement after contrast injection, while cystic component may show variable signal characteristics from low to high signal on T1-weighted sequences. T1-weighted hyperintense signal within the cyst is due to high content of cholesterol, protein, or desquamated cells. Large lesions may be associated with hydrocephalus. The most common neuroendocrine presentation in cranioopharyngioma is growth hormone deficiency. Panhypopituitarism or diabetes insipidus is rare. Clinically, patient presents with headache, visual field defects, dioplopia, and short stature.\cite{26,27}

Hypothalamic/optic chiasm gliomas
These tumors present as suprasellar mass lesions and are most commonly seen in children. These tumors are often associated with neurofibromatosis type-I (NF-1). On MRI [Figure 3], these tumors appear as well defined suprasellar mass lesions with homogenous postcontrast enhancement. Heterogeneous enhancement may be seen when the tumor is large. Often, it is difficult to differentiate whether the tumor originates from chiasma or hypothalamus as typically both of these structures are involved. In patients with NF-1, there is often involvement of optic nerves, although any portion of optic pathway may be involved. Intratumoral calcification, hemorrhage and cyst are rare. The most common neuroendocrine disorder associated with hypothalamic or chiasmatic gliomas are hypopituitarism, precocious puberty, and diencephalic syndrome (a rare cause of failure to thrive in infancy). Hypothalamic or chiasmatic astrocytomas associated with diencephalic syndrome are often larger in size, are more aggressive and may seed throughout the cerebrospinal fluid pathway.\cite{28,29}
Hypothalamic hamartomas
These are benign developmental masses that arise in tuber cinereum of the hypothalamus. On MRI [Figure 4], these are identified as well-defined, noninvasive rounded suprasellar mass lesions arising from hypothalamus. They are of similar signal to the gray matter and do not show contrast enhancement. Clinically, the presenting symptoms include precocious puberty, gelastic (laughing) seizures and developmental delay.\[17,30\]

Pituitary adenomas
Pituitary adenomas may be functional (hormonally active) or nonfunctional (with no measurable hormonal activity). Among hormonally active tumors, ACTH releasing adenomas are most common in the first 11 years of life, while prolactinomas and GH releasing adenomas become more common into the teenage years.\[31\]

ACTH releasing adenomas or childhood corticotropinomas associated with Cushing’s disease, although rare in familial setting, are common in the context of multiple endocrine neoplasia type 1 (MEN 1).\[32\] Corticotroph adenomas are significantly smaller (usually 3 mm or less) than other types of pituitary tumors. Pituitary microadenomas (< 1 cm size) are identified as an area of low signal on T1-weighted sequences than the normal pituitary gland. Dynamic scanning with gadolinium [Figure 5] improves the sensitivity of pituitary microadenomas, particularly when conventional MR imaging is negative. The microadenomas appear less vascular (hypointense) on initial arterial phase of contrast enhancement but then equilibrate to show similar vascularity to normal gland in next few minutes.\[33\] Remodeling of floor of sella, stalk deviation away from the adenoma or upward convexity of the gland are useful features to identify the presence of microadenoma. Occasionally, patients with Cushing’s syndrome may require petrosal venous sampling for localization of the source of ACTH secretion, particularly when MRI has been equivocal or negative.\[34\] The most characteristic clinical presentation of Cushing’s disease is significant weight gain and severe
failure to gain height. Other common symptoms include headache, hypertension, glucose intolerance, delayed puberty, amenorrhea, virilization and hirsutism.\textsuperscript{[35]} Pro lactinomas are the most common pituitary adenomas in older children and adolescents, with a female preponderance. They may be seen associated with MEN 1 or may occur as familial isolated pituitary adenomas. Prolactinomas can present as a small intrasellar mass lesion measuring <1 cm (microadenoma) or as a large sellar–suprasellar mass measuring > 1 cm (macroadenoma) in size.\textsuperscript{[36,37]} Pituitary macroadenomas with a large sellar-suprasellar component may impinge on optic nerves and/or optic chiasma to produce visual field abnormalities or invade cavernous sinus producing symptoms and signs related to involvement of cranial nerves (3\textsuperscript{rd}, 4\textsuperscript{th} and 6\textsuperscript{th} cranial nerves, as well as 1\textsuperscript{st} and 2\textsuperscript{nd} divisions of the 5\textsuperscript{th} cranial nerve) that run in the cavernous sinus. Macroadenomas may also extend inferiorly into the sphenoid producing remodeling of bone or may be seen invading skull base and infratemporal fossa structures.\textsuperscript{[38]} On MRI [Figure 6], macroadenomas may be homogenous or heterogeneous in signal intensity with areas of hemorrhage, cyst formation or necrosis. A significant hemorrhage with necrosis in an adenoma can produce the syndrome of pituitary apoplexy [Figure 7]. Remodeling and enlargement of sella is usually seen associated with large macroadenomas.\textsuperscript{[38,39]} The symptoms due to a prolactinoma are broadly divided into those that are caused by increased prolactin levels and others that are caused by mass effect. Those that are caused by increased prolactin levels are amenorrhoea/galactorrhea in females, hypogonadism, gynecomastia and erectile dysfunction in males, and loss of axillary/pubic hair; while, those that are caused by mass effect are bitemporal hemianopsia (due to pressure on optic chiasma), vertigo, nausea, and vomiting.\textsuperscript{[40]} Pituitary apoplexy is characterized by clinical findings of sudden onset headache usually associated with visual disturbance.\textsuperscript{[41]}

Somatotropinomas or growth hormone producing adenomas compromise approximately 5–15% of pituitary tumors in children and adolescents. Somatotropinomas are often macroadenomas. Rarely, excess GH production may occur from somatotroph hyperplasia (associated with McCune-Albright syndrome or Carney complex) or due to dysregulation of GHRH signaling as a result of mass effect from a local tumor, for example, with optic glioma in NF-1.\textsuperscript{[42]} Clinical presentation in children and adolescents depends on whether the epiphyseal plate is...
open or fused. Prior to epiphyseal fusion, overproduction of GH causes gigantism in children; while postepiphyseal fusion, overproduction of GH causes acromegaly in adults. Headache and visual disturbances are not infrequent with somatotropinomas.

Germinomas

Germinomas typically present as a suprasellar or pineal region mass in children. Synchronous occurrence of both the suprasellar and pineal region germinoma is not uncommon. Suprasellar germinomas have DI as one of the presenting complaint, reflecting involvement of hypothalamus and pituitary stalk. Characteristic MR imaging appearance of suprasellar germinoma [Figure 8] includes solid, homogenous enhancing mass involving hypothalamic region or isolated pituitary stalk thickening. There is usually no associated cyst or calcification. On CT, these lesions are slightly hyperdense. CSF seeding causing enhancement around ventricular margin is not uncommon. Tumor markers such as human chorionic gonadotropin (HCG) or alpha fetoprotein in serum/CSF, if present, can assist in making the diagnosis and obviate the need for biopsy; however, absence of these markers does not exclude the diagnosis. If biopsy cannot be taken due to location, positron emission tomography (PET) scan, which is positive in germ cell tumors, can be used to assist in making the diagnosis. Germinomas are highly radiosensitive, serial follow up MRI every 3–6 months is recommended for assessment of treatment response.

Leukemias and lymphomas

Pituitary stalk involvement and thickening has been reported with leukemia (chronic myelogenous leukemia and acute myelogenous leukemia) and lymphoma. Clinically these patients have DI.
Rathke’s cleft cysts
These are benign, nonfunctional cysts arising from remnants of squamous epithelium from Rathke’s cleft. These cysts are commonly seen in the gland, even in healthy children. They typically arise close to insertion of the stalk, however, may lie on surface of the gland. They are nonfunctional but may cause mass effect on the gland. On MRI [Figure 9], these lesions may appear hyperintense on T1-weighted sequence due to high proteinaceous content. It is often difficult to distinguish a large Rathke’s cyst from a cystic craniopharyngioma. Minimal cyst wall enhancement, absence of solid enhancing component, and lack of calcification favors Rathke’s cyst over craniopharyngioma. The most common neuroendocrine presentation in Rathke’s cyst is hypopituitarism and delayed puberty.\(^{47}\)

**Inflammatory and Infectious Lesions**

**Langerhans cell histiocytosis**
Patients with systemic LCH may have involvement of the pituitary–hypothalamus axis. The MRI [Figure 10] may demonstrate a granulomatous mass in region of hypothalamus or thickening of pituitary stalk. There is marked enhancement of the lesion after gadolinium administration. In patients with LCH, posterior pituitary bright spot is usually absent. These imaging features correlate with the typical clinical presentation of DI.\(^{48}\)

**Lymphocytic hypophysitis**
LH is an autoimmune condition often found in females during pregnancy and postpartum period. This disorder has also been reported in children and adolescents. There
is lymphocytic infiltration of pituitary gland causing diffuse enlargement of the gland (resembling a mass) and thickening of the infundibulum. Involved gland shows marked heterogeneous enhancement with gadolinium [Figure 11]. There may be associated absence of posterior pituitary bright spot.[49,50] A variant of this condition is the so-called lymphocytic infundibulo-neurohypophysitis (LINH) where the inflammatory process selectively involves the pituitary stalk and the posterior lobe. In LINH, the inflammation is self-limiting; shows regression on follow-up imaging.[51] Anterior pituitary deficiency and DI are the most common presentations in patients with LH; where DI tends to be permanent due to neuronal damage. Granulomatous hypophysitis is an important radiological differential of lymphocytic hypophysitis; both have similar indistinguishable MRI features. However, unlike lymphocytic hypophysitis, granulomatous hypophysitis is less common and has equal incidence in males and females.[50]

**Tuberculosis**

Tuberculosis is a rare cause of neuroendocrine disorder. Tubercular infection can affect the pituitary gland, stalk, or hypothalamus via formation of a tuberculoma or granuloma. Basal meningitis may lead to basal arteritis and subsequent infarction of the gland. CT/MR imaging [Figure 12] may show uniformly thickened pituitary stalk, diffuse enhancement of basal cisterns/diaphragma sellae and ring or nodular enhancing granuloma. Rarely, pituitary abscesses may be seen. Patients may present with DI or anterior pituitary deficiencies.[13,52]

**Sarcoidosis**

A wide spectrum of intracranial imaging appearances have been described with neurosarcoid. Pituitary stalk/hypothalamus involvement may be seen in isolation or as a part of more widespread disease showing leptomeningeal enhancement and periventricular lesions. Measurement of CSF angiotensin converting enzyme (ACE) may help in diagnosis of neurosarcoid. These patients may present with DI, aseptic meningitis, or anterior pituitary deficiencies.[46,53]

**CONCLUSION**

The pituitary gland/hypothalamic–pituitary axis presents a big diagnostic imaging challenge, particularly in pediatric population, because of its small size and versatile disease processes. MRI (with its multiplanar capability) is the modality of choice in evaluation of pituitary–hypothalamic morphology and associated endocrinopathies. In addition to the diagnostic differentiation of these lesions, MRI also provides useful information about relationship of pituitary gland/hypothalamic–pituitary axis with adjacent anatomical structures and helps to plan medical or surgical strategy.
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