Article published online: 2024-06-06

Ectopic Posterior Pituitary and Its Associations with Extrapituitary Intracranial Anomalies

Alamelu Alagappan[1] Manoj Kumar Nayak[1] Biswajit Sahoo[1] Suprava Naik[1] Nerbadyswari Deep (Bag)[1] Sanjeev Bhoi[2]

[1] Department of Radiodiagnosis, All India Institute of Medical Science Bhubaneswar, Bhubaneswar, Odisha, India
[2] Department of Neurology, All India Institute of Medical Sciences Bhubaneswar, Bhubaneswar, Odisha, India

Address for correspondence Manoj Kumar Nayak, MD, Department of Radiodiagnosis, All India Institute of Medical Science Bhubaneswar, Bhubaneswar 751019, Odisha, India (e-mail: tuna.manoj@gmail.com).

Indian J Radiol Imaging 2024;34:740–744.

Abstract

Posterior pituitary ectopia is a very rare entity in the development of the pituitary gland. Several factors and multiple genes are associated with this entity causing both pituitary and extrapituitary abnormalities. Pituitary abnormalities can be various endocrine problems and extrapituitary abnormalities can be optic nerves and cerebellar hypoplasia, heterotopia, and abnormal vessels. This pictorial review represents the imaging manifestations of extrapituitary intracranial anomalies that can be associated with posterior pituitary ectopia.

Keywords

- ectopic posterior pituitary
- interruption of pituitary stalk
- heterotopia
- septo-optic dysplasia

Introduction

Ectopic posterior pituitary (EPP) is defined by the ectopic placement of the neurohypophysis predominantly at the median eminence (base of the 3rd ventricle). EPP is a rare entity with an incidence of 0.5 per 1,000,000 births.[1] The parts of the pituitary gland are adenohypophysis (anterior lobe), neurohypophysis (posterior lobe), pars intermedia, and pituitary stalk. Adenohypophysis is oral ectodermal in origin evolving from Rathke cleft by evagination of the stomodeum. The cells of the posterior wall of the Rathke cleft proliferate to form the vestigial pars intermedia. Neurohypophysis is formed from the neuroectoderm by the downward extension of the diencephalon and infundibulum into the sellar fossa. The pituitary stalk is a funnel-shaped structure connecting the hypothalamus to the posterior pituitary.[2]

Although the exact cause of EPP is unknown, recent research has suggested that 5 out of 93 patients with EPP have *HESX1* gene mutations.[3] Other genes like LHX4 and SOX3 can have a role in abnormal pituitary development with or without extrapituitary abnormalities.[4] Thoughts have been given to traumatic birth damage, breech delivery, and genetic variables as possible etiologies for EPP.[4] More recent theory suggested that neural crest cells help in the development of pituitary vasculature, which can be a contributing factor for abnormal development of both anterior and posterior pituitary as well as abnormal neuronal migration, absent internal carotid arteries due to a shared genetic defect.[5]

Clinical presentation of EPP is highly variable depending on the underlying hormonal deficiency. Most common presentations include growth abnormalities, fatigue, weakness, precocious puberty, obesity, infertility, irregular menstruation, constipation, excessive thirst/urination, etc. Hormonal abnormalities include panhypopituitarism, hyperprolactinemia, antidiuretic hormone deficiency, combined pituitary hormonal deficit, isolated deficiency of adrenocorticotropic hormone, thyroid-stimulating

article published online
June 6, 2024

DOI https://doi.org/10.1055/s-0044-1787160.
ISSN 0971-3026.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

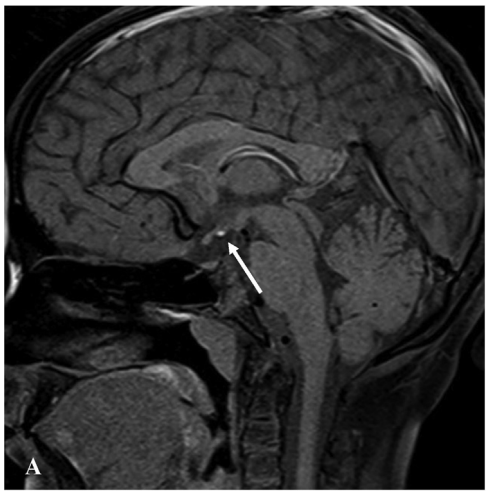

Fig. 1 A 24-year-old female patient presented with hypothyroidism and obesity. Growth hormone and thyroid-stimulating hormone (TSH), T3, and T4 deficiency was identified on hormone analysis. Sagittal magnetic resonance imaging (MRI) image demonstrating ectopic T1-weighted (T1W) bright spot, located at the median eminence with absence of infundibulum.

hormone, gonadotropin-releasing hormone, and growth hormone. EPP can be seen in 87.1% of patients with severe growth hormone deficiency. In combined pituitary hormonal deficit patients, 80% had pituitary stalk abnormalities with accompanied hypocortisolism and/or hypothyroidism, while 18.2% had hypogonadism.[6]

However, in most cases, the function of neurohypophysis is preserved. Pituitary stalk interruption syndrome, like other syndromes, is occasionally linked to various midline intracranial, cerebral, or vascular problems.[7]

Various extrapituitary intracranial abnormalities have been published in literature including septo-optic dysplasia (SOD), optic nerve atrophy, central median maxillary incisor, corpus callosum dysgenesis, migration abnormalities, microcephaly, Kallmann syndrome, Chiari-1 malformation, persistent craniopharyngeal canal, absent internal carotid arteries, medial deviation of the carotid arteries, basilar impression, vermian dysgenesis, and cerebellar hypoplasia.[7,8] This pictorial review presents the imaging manifestations of extrapituitary intracranial anomalies that are associated with posterior pituitary ectopia.

Pituitary Stalk Abnormalities

In the ectopic pituitary, the sella's typical T1-weighted image (T1WI) bright spot is missing on magnetic resonance imaging (MRI), and it is instead present at the median eminence or along the infundibular stalk's interrupted portion. The presence of vasopressin in phospholipids, causing T1W shortening, is the physiology behind the bright spot.[9]

Pituitary interruption syndrome (PSIS) is characterized by a triad of thin or absent pituitary stalk, EPP, and hypoplasia or aplasia of adenohypophysis. The index case of PSIS was documented by Fujisawa et al in 1987.[10] Less than 5% of PSIS instances are thought to be caused by genetic mutations. Most common among them are *HESX1*, *SOX3*, *LHX4*, *OTX2*, and *PROKR2* genes.[11] MRI findings include absent/hypoplastic/thin ($<$ 1 mm) interrupted pituitary stalk with ectopic T1WI bright spot (►**Fig. 1**). In the research by Zheng et al, the pituitary stalk was completely absent in 45% of patients, thin in 37.5%, and interrupted in 17.5%.[12]

Septo-Optic Dysplasia

SOD, an uncommon intracranial anomaly, was first described by de De Morsier in 1956 and is characterized by the optic nerve and chiasm hypoplasia in addition to an absent or rudimentary septum pellucidum.[13] The term "SOD plus syndrome" refers to a group of midline brain abnormalities linked to SOD (►**Fig. 2**). A structural abnormality of the neurohypophysis was present in roughly two-thirds of patients of SOD with clinically diagnosed endocrine dysfunction.[14]

Cerebral Anomalies

Periventricular Heterotopia

The presence of periventricular heterotopia and an EPP point to a shared genetic basis for both conditions, which is caused by neuronal migration abnormalities. The existence of a heterozygous HESX1 mutation in the study by Mitchell et al indicates that this gene is crucial for the formation of both periventricular heterotopia and the EPP, supporting their inclusion in the spectrum of SOD.[8] Other unidentified genes or surrounding environmental factors are likely to play a role in

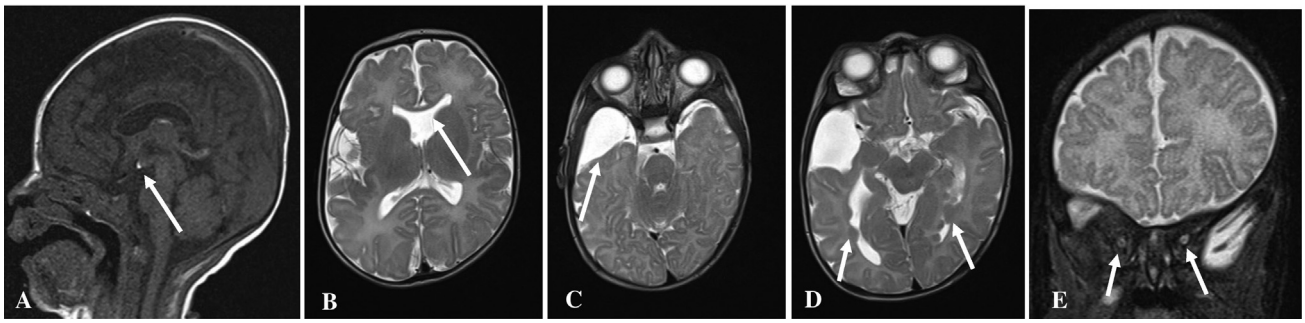

Fig. 2 A 3-year-old male child patient presented with multiple episodes of seizures and developmental delay. Sagittal T1-weighted (T1W) and axial T2W magnetic resonance imaging (MRI) images demonstrating ectopic T1W bright spot, located at the median eminence with associated absent septum pellucidum, right anterior temporal arachnoid cyst, periventricular heterotopia, and bilateral hypoplastic optic nerves. Isolated growth hormone deficiency was elicited on hormone analysis.

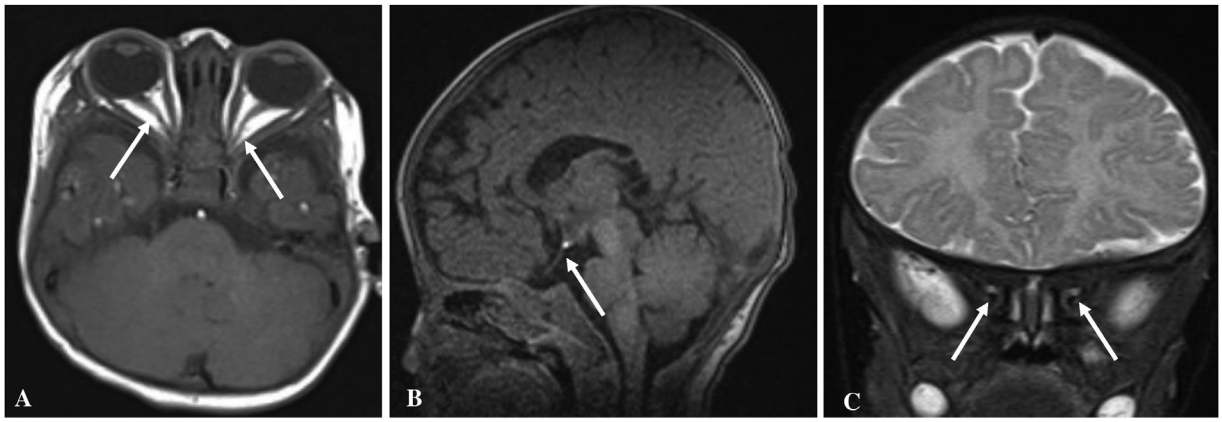

Fig. 3 A 10 months old male infant patient presented with reversal of milestones. On ophthalmoscopy, bilateral small optic discs were seen. Axial, sagittal T1-weighted (T1W), and coronal T2W magnetic resonance imaging (MRI) images demonstrating ectopic T1W bright spot, located at the median eminence with isolated bilateral hypoplastic optic nerves.

the EPP with periventricular heterotopia in addition to known genetic alterations. MRI findings include single/multiple, small, or large heterotopia in the periventricular region (most commonly around the wall of the lateral ventricles), which is isointense to gray matter (►**Fig. 2**). Cases of pachy, poly, and microgyria have been reported in association with ectopic neurohypophysis, supporting the theories of neuronal migration and cleavage disorder, as a possibility.[15]

Arachnoid Cyst

One percent of all intracranial space-occupying lesions are arachnoid cysts, which are benign cystic lesions. The coexistence of the EPP and sellar/suprasellar arachnoid cyst can be explained by the hypothesis, that in the absence of a stalk, the central orifice of the diaphragm sellae may allow cerebrospinal fluid to occupy sella turcica.[16] However, the pathophysiology behind the association of ectopic neurohypophysis and arachnoid cysts at other locations is not clearly understood. On imaging, the cysts appear hypointense on T1WI, fluid-attenuated inversion recovery, and diffusion-weighted imaging sequences and hyperintense on T2WI sequences with no contrast enhancement. These may exert a minor mass effect on nearby brain tissue (►**Fig. 2**).

Isolated Optic Nerve Abnormalities

The majority of childhood cases of reduced visual acuity were brought about by the rare entity known as optic nerve hypoplasia. It was reported that 69% incidence of hypoplasia of optic nerves is related to hypothalamic dysfunction.[17] In 1970, its association with hypopituitarism was identified.[18] The relationship between optic nerve anomalies and ectopic neurohypophysis is well described in the clinical context of its association with anophthalmos and microophthalmos.[19] The invention of MRI was a turning point in the diagnosis of hypoplasia, which is the observation of a nerve smaller than the healthy side, or aplasia and related EPP (►**Fig. 3**).

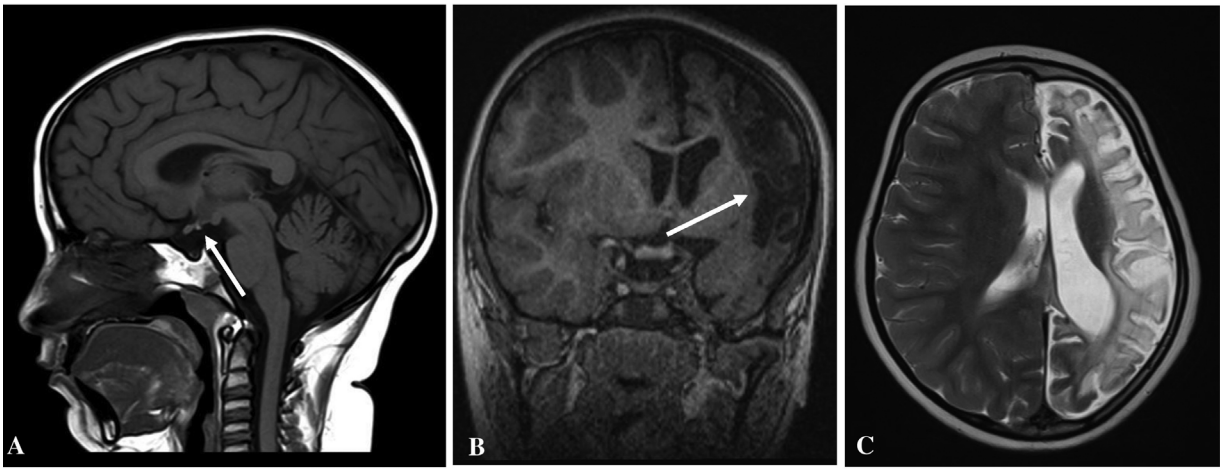

Fig. 4 A 5-year-old female child patient presented with right hemiparesis and developmental delay. On examination, she had height of less than 3 standard deviation (SD) of her age. Growth hormone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) deficiency was seen on hormone analysis. Sagittal, coronal T1-weighted (T1W), and axial T2W magnetic resonance imaging (MRI) images demonstrating ectopic T1W bright spot, located at the median eminence with gliosis and hemiatrophy of left hemisphere, ex vacuo dilatation of left lateral ventricle and compensatory bone hypertrophy seen in Dyke-Davidoff-Masson syndrome.

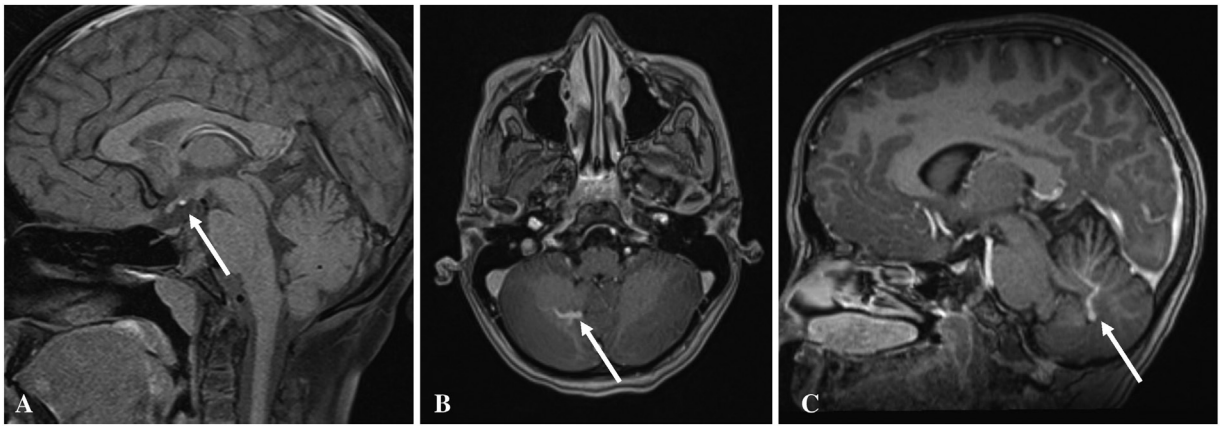

Fig. 5 A 32-year-old female patient presented with infertility. Luteinizing hormone (LH), follicle-stimulating hormone (FSH), and mild growth hormone deficiency was found. Sagittal magnetic resonance imaging (MRI) image demonstrating ectopic T1-weighted (T1W) bright spot, located at the median eminence and postcontrast axial and sagittal T1W images showing developmental venous anomaly.

Cerebral Parenchymal Abnormalities

Zheng et al in their study described a case of Dyke-Davidoff-Masson syndrome associated with posterior ectopic pituitary.[12] It is characterized by contralateral hemiparesis, ipsilateral compensatory osseous enlargement, and hemicerebral atrophy/hypoplasia related to brain insult, typically in the fetal or early childhood period (►**Fig. 4**). The imaging spectrum shows different degrees of ipsilateral hypertrophy of the skull and sinuses along with ipsilateral lateral ventricle enlargement and cerebral hemiatrophy of the affected hemisphere. There may also be ipsilateral falcine displacement and elevation of the petrous ridge. Birth trauma, ischemia, hemorrhagic conditions, and infection are possible etiologies contributing to both of these conditions. Posterior ectopic pituitary can also be associated with corpus callosal dysgenesis with a broad spectrum ranging from hypoplasia to aplasia.[20]

Vascular Anomalies

Posterior ectopic pituitary is associated with vascular abnormalities which can be arterial and/or venous. In a study done by Brener et al, in pediatric endocrine patients, approximately 5.7% of patients had hypothalamo-pituitary-axis structural abnormalities with 1.5% of patients having developmental venous anomalies[21] (►**Fig. 5**). Schulman et al, reported a case of EPP with an absent left internal carotid artery.[22] Rare vascular abnormalities like an infra-optic course of anterior cerebral artery were also reported.[7] The etiology of the association of ectopic neurohypophysis with vascular abnormalities is not well known.

Conclusion

In this pictorial review, the relationship between extrapituitary intracranial abnormalities and ectopic neurohypophysis has been highlighted. During the evaluation of patients with EPP, radiologists and clinicians should be vigilant to search for features of related extrapituitary abnormalities, which are crucial to determining the prognosis of these patients.

Patient Consent
Consent for publication was obtained from the patient.

Availability of Data and Material
DICOM file and consent form would be provided to the editor whenever asked.

Authors' Contributions
A.A. and M.N. primarily drafted the manuscript. S.B. did history taking, clinical diagnosis, and management. Final drafting was done by N.D. CECT and MRI protocol planning and reporting was done by S.N. and B.S.

Funding
None.

Conflict of Interest
None declared.

References

1 Nawaz A, Azeemuddin M, Shahid J. Pituitary stalk interruption syndrome presenting in a euthyroid adult with short stature. Radiol Case Rep 2018;13(02):503–506
2 The Pituitary Gland: Embryology, Physiology, and Pathophysiology. Springer Publishing. Accessed August 7, 2023 at: https://connect.springerpub.com/content/sgrnn/19/2/9
3 Ectopic neurohypophisis in a boy: a case report and review. PubMed. Accessed August 7, 2023 at: https://pubmed.ncbi.nlm.nih.gov/34367394/
4 di Iorgi N, Secco A, Napoli F, Calandra E, Rossi A, Maghnie M. Developmental abnormalities of the posterior pituitary gland. Endocr Dev 2009;14:83–94
5 Davis SW, Mortensen AH, Keisler JL, et al. β-catenin is required in the neural crest and mesencephalon for pituitary gland organogenesis. BMC Dev Biol 2016;16(01):16
6 Jagtap VS, Acharya SV, Sarathi V, et al. Ectopic posterior pituitary and stalk abnormality predicts severity and coexisting hormone deficiencies in patients with congenital growth hormone deficiency. Pituitary 2012;15(02):243–250

7 Boruah DK, Sanyal S, Prakash A, et al. Extra-pituitary cerebral anomalies in pediatric patients of ectopic neurohypophysis: an uncommon association. J Clin Imaging Sci 2017;7:19
8 Mitchell LA, Thomas PQ, Zacharin MR, Scheffer IE. Ectopic posterior pituitary lobe and periventricular heterotopia: cerebral malformations with the same underlying mechanism? Am J Neuroradiol 2002;23(09):1475–1481
9 Côté M, Salzman KL, Sorour M, Couldwell WT. Normal dimensions of the posterior pituitary bright spot on magnetic resonance imaging. J Neurosurg 2014;120(02):357–362
10 Fujisawa I, Kikuchi K, Nishimura K, et al. Transection of the pituitary stalk: development of an ectopic posterior lobe assessed with MR imaging. Radiology 1987;165(02):487–489
11 Brauner R, Bignon-Topalovic J, Bashamboo A, McElreavey K. Pituitary stalk interruption syndrome is characterized by genetic heterogeneity. PLoS One 2020;15(12):e0242358
12 Zheng J, Mao J, Xu H, et al. Pulsatile GnRH therapy may restore hypothalamus-pituitary-testis axis function in patients with congenital combined pituitary hormone deficiency: a prospective, self-controlled trial. J Clin Endocrinol Metab 2017;102(07):2291–2300
13 De Morsier G. Studies on malformation of cranio-encephalic sutures. III. Agenesis of the septum lucidum with malformation of the optic tract [in French]. Schweiz Arch Neurol Psychiatr 1956; 77(1–2):267–292
14 Cerbone M, Güemes M, Wade A, Improda N, Dattani M. Endocrine morbidity in midline brain defects: Differences between septo-optic dysplasia and related disorders. EClinicalMedicine 2020; 19:100224
15 Lyra A, de Faria Guimarães D, Meira AS, et al. Extra-pituitary midline structural abnormalities associated with ectopic posterior pituitary detected on a new rapid MRI protocol (FAST1.2). Arch Endocrinol Metab 2022;66(06):831–836
16 Saylisoy S, Yorulmaz G. Coexistence of ectopic posterior pituitary and sellar/suprasellar arachnoid cyst: a case report. Curr Med Imaging 2020;16(08):1055–1057
17 Garcia-Filion P, Borchert M. . Optic nerve hypoplasia syndrome: a review of the epidemiology and clinical associations. Curr Treat Options Neurol 2013;15(01):78–89
18 Hoyt WF, Kaplan SL, Grumbach MM, Glaser JS. Septo-optic dysplasia and pituitary dwarfism. Lancet 1970;1(7652): 893–894
19 Keppen LD, Brodsky MC, Michael JM, Poindexter AR. Hypogonadotropic hypogonadism in mentally retarded adults with microphthalmia and clinical anophthalmia. Am J Med Genet 1990;36(03): 285–287
20 Ören NC, Cagıltay E, Akay F, Toyran S. Panhypopituitarism with ectopic posterior pituitary lobe, heterotopia, polymicrogyria, corpus callosum dysgenesis, and optic chiasm/nerve hypoplasia: is that an undefined neuronal migration syndrome? AJNR Am J Neuroradiol 2015;36(05):E33–E35
21 Brener A, Kozyrev DA, Shiran SI, et al. Incidental findings on brain magnetic resonance imaging (MRI) in pediatric endocrine patients. Endocr Pract 2020;26(10):1105–1114
22 Shulman DI, Martinez CR. Association of ectopic posterior pituitary and anterior pituitary hypoplasia with absence of the left internal carotid. J Pediatr Endocrinol Metab 1996;9(05):539–542

