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Case Report

Dorsoventral splitting of the infundibulum in a child with pituitary hypoplasia ☆

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ABSTRACT

Pituitary development arises from ectodermal tissue creating Rathke's pouch and ultimately the adenohypophysis anteriorly whereas neuroectodermal tissue arising from the diencephalon creates the neurohypophysis posteriorly. Alterations in pituitary development can lead to hormonal dysregulation and dysfunction. Following clinical suspicion of pituitary endocrinopathy, MRI plays a vital role in identifying and characterizing underlying structural abnormalities of the pituitary gland, as well as any associated extrapituitary findings. Here we report a case of an 18-month-old female presenting with short stature and growth hormone deficiency. MRI was notable for a shallow sella turcica, a hypoplastic adenohypophysis, thin pituitary stalk, and ectopic neurohypophysis. Interestingly, the pituitary stalk was noted to split dorsoventrally with a split pituitary bright spot and T1 hypointense lobe hypothesized to represent separation of the posterior pituitary lobes.

Introduction

Clinical evidence of hypopituitarism in children may raise suspicion for a developmental anomaly of the hypothalamic-pituitary axis. High-resolution MRI is necessary to confirm structural pituitary abnormalities and also to exclude other etiologies such as neoplastic and inflammatory causes [1]. MRI is further useful for identifying any associated extrapituitary malformations including ocular abnormalities, craniofacial dysmorphisms, and other morphology on the holoprosencephaly spectrum [2,3].

Phenotypic variation is broad among congenital pituitary patients. Earlier age at diagnosis is associated with more severe phenotypes [2]. Neonates with hypopituitarism exhibit more severe features including hypoglycemia, hemodynamic instability and cholestasis which are typically apparent soon after birth whereas children with milder presentation such as growth delay present at a median age of 4.1 years [4]. Patients may also present postpubertally or in adulthood [5,6]. The degree of hormonal deficiency is closely linked to the extent of phenotypic abnormality. Additionally, anatomic findings on MRI correlate with extent of hormonal deficiency. Multiple pituitary hormonal deficiency is associated with increased in-

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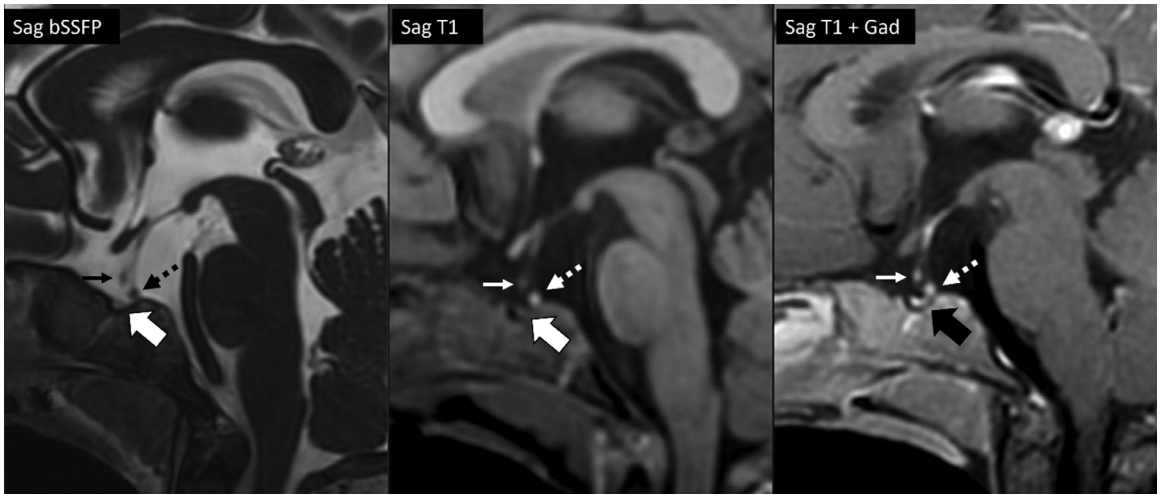

Fig. 1 – Sagittal images of the sella show pituitary hypoplasia within a hypoplastic sella (thick arrow). The pituitary infundibulum is split in the dorsoventral direction and terminates into 2 small nodules (thin and dashed arrows). The dorsal nodule has the characteristic appearance of the posterior pituitary "bright spot" with intrinsic bright signal (dashed arrow) on the pregadolinium T1-weighted image (center). The ventral nodule does not show intrinsic T1 shortening (center) and demonstrates enhancement (right).

cidence of stalk interruption, degree of ectopia, and extent of anterior pituitary hypoplasia as compared to those with isolated growth hormone deficiency [7,8].

Here we present a unique case in a child with multiple pituitary hormone deficiencies in which the pituitary stalk is separated dorsoventrally and the adenohypophysis is hypoplastic.

Case report

An 18-month-old female presented to pediatric endocrinology with chief concern of short stature. She had growth delay with a height z-score of -4.03 and weight -3.55. Weight/length remained around the 50th percentile. Relevant birth history included C-section at 34 weeks gestation secondary to premature rupture of the membranes and fetal distress. Of note, serum screening for congenital disorders of glycosylation and urine screen for lysosomal storage disorders were negative.

Laboratory assessment revealed an undetectable (<10 ng/mL; reference range 28-256) insulin-like growth factor 1 (IGF-1) by LC/MS and an insulin-like growth factor-binding protein 3 (IGFBP-3) 0.8 mcg/mL (ref range 07-3.6). Serum growth hormone measured low at 0.11 ng/mL (ref range 0.01-3.61). AM cortisol was normal at 9.9 mcg/dL (ref range 7-25). Thyroid stimulating hormone (TSH) measured low normal at 3.8 mIU/mL (ref range 0.7-6.0) and subsequent free serum T4 low at 0.8 ng/dL (ref range 1.0-1.8). Additional testing including parathyroid hormone, complete blood and metabolic profile, ferritin, and c-reactive protein (CRP) were within normal limits. Radiographic bone age was delayed with an age of 9 months (SD 3.5 months).

Brain MRI demonstrated a hypoplastic adenohypophysis within a shallow sella turcica with blunting of the dorsum sella (Fig. 1). The pituitary infundibulum was split in a dorsoventral orientation. A nodular focus along the inferior aspect of the dorsal stalk was hyperintense on pre-gadolinium T1-weighted images. A separate nodule along the ventral stalk was isointense to gray matter on T1-weighted images and demonstrated mild enhancement. There were no additional midline CNS anomalies in the brain, face, or spine.

Following work up, patient was subsequently started on subcutaneous growth hormone, levothyroxine, and hydrocortisone to address growth and lab abnormalities. Ongoing endocrinology follow up to assess milestones planned.

Discussion

The pituitary gland arises from ectodermal tissue originating from 2 distinct and separate embryologic locations. The adenohypophysis arises from early dorsal extension of ectodermal tissue from the stomodeum to create Rathke's pouch which further meets the neurohypophysis to create the pars distalis, pars tuberalis, and pars intermedius. Posteriorly, the neurohypophysis descends ventrally from neuroectodermal tissue at the floor of the diencephalon to create the infundibular process and ultimately the pars nervosa. Given its separate ectodermal origins, the anterior pituitary receives signaling uniquely through the neurohypophyseal portal system. As such, hypopituitarism consisting of adenohypophyseal hormones including prolactin, growth hormone, adrenocorticotropic hormone (ACTH), luteinizing hormone (LH), follicle stimulating hormone (FSH), and TSH may arise not only from a hypoplastic adenohypophysis, but also a malformed neurohypophyseal portal system.

In contrast, the posterior pituitary receives direct axonal signaling from the hypothalamus. Specifically, the supraoptic and paraventricular nuclei contain magnocellular neurons

with axons traveling down the hypothalamohypophyseal tract wherein neurosecretory granules are released. The neurosecretory granules containing vasopressin at the terminus of these axons are believed to create the posterior pituitary inherent T1 hyperintense "bright spot" on MRI [9–12]. While both subtypes of magnocellular neurons are found to produce oxytocin and vasopressin, the paraventricular nucleus is closely tied to vasopressin and the supraoptic nucleus to oxytocin [13]. The T1 bright spot is seen in the majority of patients, with approximately 83%-100% of adults exhibiting this finding in different studies [14–17]. In the absence of pituitary pathology, essentially 100% of children have a normal T1 hyperintensity within the neurohypophysis [18,19]. In the presently described case, we note the presence of the intrinsically T1 hyperintense nodule along the dorsal split pituitary stalk in addition to a T1 hypointense nodule along the more ventral split pituitary stalk. Given these differences in signal characteristics, we hypothesize that the posterior pituitary is functionally split into oxytocin and vasopressin containing components.

The spectrum of aberrant pituitary development and associated midline abnormalities including absence or complete stalk interruption are varied. It is important to note that it is unclear whether the present pituitary stalk splitting represents separation of the posterior pituitary or duplication. To our knowledge, only one such similar case has been published. In this case, a 4 1/2 year old female patient with frontal bossing and growth delay was found to have a split pituitary stalk for which dorsoventral duplication was suggested [6]. Notably, lateral duplication of the pituitary is a known rare phenomenon with fewer than 60 cases of pituitary duplication having been reported in the literature [8,20]. Lateral duplication arises embryologically from early separation of the anterior aspect of the notochord and prechordal plate causing phenotypes more commonly associated with hyperpituitarism [1,21]. Future work exploring the functional division and embryologic development in these cases is needed.

MRI is an important for identifying structural anomalies in patients with pituitary hormonal deficiencies. A prior data set of 946 MRI exams performed on pediatric and adult patients with nonacquired constitutional hypopituitarism demonstrated structural pituitary imaging abnormalities in 79.7% of patients [22]. Of these, 61.9% demonstrated adenohypophyseal anomalies, 37.8% had ectopic neurohypophysis and 41.9% had pituitary stalk anomalies. Further, in the same large-scale study, 5.5% exhibited corpus callosal anomalies, 0.2% holoprosencephaly, in addition to other midline abnormalities. Optic pathway abnormalities were common comprising 16.1% of the cohort and include abnormalities such as septooptic dysplasia (5.1%). In the context of pituitary anomalies, MRI plays an important role towards identifying the extent of any additional possible structural abnormalities seen in these patients.

Identifying individual genetic components leading to morphologic sequela is key to understanding pituitary development. Interestingly, Scala et al. in their exploration of the split pituitary case found the patient's father had an ectopic neurohypophysis without similar split. Subsequent microarray implicated ROBO1 deletion as an underlying contributor. ROBO1 has been identified in multiple other cases of split pituitary stalk, but no similar separation of the pituitary stalk has been otherwise described [23–25]. In our above described case, no genetic analysis has been performed. Future work exploring ROBO1, in addition to other implicated genetic factors, for example PROP1, LHX3, LHX4, SOX3, OTX2, GPR161, PROKR2, and HESX1[2], would help expand our understanding of pituitary development.

Conclusion

This case report illustrates a rare example of an anomalously formed pituitary gland revealing insights into embryology of the pituitary gland.

Patient consent

Written parental consent for publication of patient image material and associated medical information was obtained by institutional form.

REFERENCES

[1] Shields R, Mangla R, Almast J, Meyers S. Magnetic resonance imaging of sellar and juxtasellar abnormalities in the pediatric population: an imaging review. Insights Imaging 2015;6(2):241–60. doi:10.1007/s13244-015-0401-5.
[2] Vergier J, Castinetti F, Saveanu A, Girard N, Brue T, Reynaud R. Diagnosis of endocrine disease: pituitary stalk interruption syndrome: etiology and clinical manifestations. Eur J Endocrinol 2019;181(5):R199–209. doi:10.1530/EJE-19-0168.
[3] Reynaud R, Albarel F, Saveanu A, Kaffel N, Castinetti F, Lecomte P, et al. Pituitary stalk interruption syndrome in 83 patients: novel HESX1 mutation and severe hormonal prognosis in malformative forms. Eur J Endocrinol 2011;164(4):457–65. doi:10.1530/EJE-10-0892.
[4] Bar C, Zadro C, Diene G, et al. Pituitary Stalk Interruption Syndrome from Infancy to Adulthood: Clinical, Hormonal, and Radiological Assessment According to the Initial Presentation. PLOS ONE 2015;10(11):e0142354. doi:10.1371/journal.pone.0142354.
[5] Nawaz A, Azeemuddin M, Shahid J. Pituitary stalk interruption syndrome presenting in a euthyroid adult with short stature. Radiol Case Rep 2018;13(2):503–6. doi:10.1016/j.radcr.2017.12.002.
[6] Scala M, Accogli A, Allegri AME, et al. Familial ROBO1 deletion associated with ectopic posterior pituitary, duplication of the pituitary stalk and anterior pituitary hypoplasia. J Pediatr Endocrinol Metab 2019;32(1):95–9. doi:10.1515/jpem-2018-0272.
[7] Hwang J, Jo SW, Kwon EB, Lee SA, Chang SK. Prevalence of brain MRI findings in children with nonacquired growth hormone deficiency: a systematic review and meta-analysis. Neuroradiology 2021;63(7):1121–33. doi:10.1007/s00234-021-02665-3.
[8] Pham LL, Lemaire P, Harroche A, Souberbielle JC, Brauner R. Pituitary stalk interruption syndrome in 53 postpubertal patients: factors influencing the heterogeneity of its presentation. PloS One 2013;8(1):e53189. doi:10.1371/journal.pone.0053189.

[9] Lee MH, Choi HY, Sung YA, Lee JK. High signal intensity of the posterior pituitary gland on T1-weighted MR images. Correlation with plasma vasopressin concentration to water deprivation. Acta Radiol Stockh Swed 1987 2001;42(2):129–34. doi:10.1034/j.1600-0455.2001.042002129.x.
[10] Kucharczyk J, Kucharczyk W, Berry I, et al. Histochemical characterization and functional significance of the hyperintense signal on MR images of the posterior pituitary. Am J Roentgenol 1989;152(1):153–7. doi:10.2214/ajr.152.1.153.
[11] Teshima T, Hara Y, Masuda H, et al. Relationship between arginine vasopressin and high signal intensity in the pituitary posterior lobe on T1-Weighted MR images in dogs. J Vet Med Sci 2008;70(7):693–9. doi:10.1292/jvms.70.693.
[12] Fujisawa I, Asato R, Nishimura K, et al. Anterior and posterior lobes of the pituitary gland: assessment by 1.5 T MR imaging. J Comput Assist Tomogr 1987;11(2):214–20. doi:10.1097/00004728-198703000-00003.
[13] Lechan RM, Toni R Functional anatomy of the hypothalamus and pituitary. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext. South Dartmouth (MA): MDText.com, Inc; 2000. http://www.ncbi.nlm.nih.gov/books/NBK279126/. [Accessed December 11, 2022].
[14] Meyrignac O, Idir IS, Cognard C, Bonneville JF, Bonneville F. 3D TOF MR angiography to depict pituitary bright spot and to detect posterior pituitary lobe cyst: original description at 3T MR imaging. J Neuroradiol 2015;42(6):321–5. doi:10.1016/j.neurad.2015.04.009.
[15] Côté M, Salzman KL, Sorour M, Couldwell WT. Normal dimensions of the posterior pituitary bright spot on magnetic resonance imaging: clinical article. J Neurosurg 2014;120(2):357–62. doi:10.3171/2013.11.JNS131320.
[16] Colombo N, Berry I, Kucharczyk J, et al. Posterior pituitary gland: appearance on MR images in normal and pathologic states. Radiology 1987;165(2):481–5. doi:10.1148/radiology.165.2.3659370.
[17] Brooks B, Gammal T el, Allison J, Hoffman W. Frequency and variation of the posterior pituitary bright signal on MR images. Am J Roentgenol 1989;153(5):1033–8. doi:10.2214/ajr.153.5.1033.
[18] Gudinchet F, Brunelle F, Barth MO, et al. MR imaging of the posterior hypophysis in children. Am J Neuroradiol 1989;10(3):511–14.
[19] Maghnie M, Villa A, Arico M, et al. Correlation between magnetic resonance imaging of posterior pituitary and neurohypophyseal function in children with diabetes insipidus. J Clin Endocrinol Metab 1992;74(4):795–800. doi:10.1210/jcem.74.4.1548343.
[20] Serrallach BL, Rauch R, Lyons SK, Huisman TAGM. Duplication of the pituitary gland: CT, MRI and DTI findings and updated review of the literature. Brain Sci 2022;12(5):574. doi:10.3390/brainsci12050574.
[21] Kollias SS, Ball WS, Prenger EC. Review of the embryologic development of the pituitary gland and report of a case of hypophyseal duplication detected by MRI. Neuroradiology 1995;37(1):3–12. doi:10.1007/BF00588511.
[22] Jullien N, Saveanu A, Vergier J, et al. Clinical lessons learned in constitutional hypopituitarism from two decades of experience in a large international cohort. Clin Endocrinol (Oxf) 2021;94(2):277–89. doi:10.1111/cen.14355.
[23] Liu Z, Chen X. A novel missense mutation in human receptor roundabout-1 (ROBO1) gene associated with pituitary stalk interruption syndrome. J Clin Res Pediatr Endocrinol 2020;12(2):212–17. doi:10.4274/jcrpe.galenos.2019.2018.0309.
[24] Dateki S, Watanabe S, Mishima H, et al. A homozygous splice site ROBO1 mutation in a patient with a novel syndrome with combined pituitary hormone deficiency. J Hum Genet 2019;64(4):341–6.
[25] Bashamboo A, Bignon-Topalovic J, Moussi N, McElreavey K, Brauner R. Mutations in the human ROBO1 gene in pituitary stalk interruption syndrome. J Clin Endocrinol Metab 2017;102(7):2401–6. doi:10.1210/jc.2016-1095.