Pituitary Hypoplasia and Other Midline Developmental Anomalies

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68.1 Epidemiology and Clinical Presentation

- Hypoplasia of the pituitary gland, infundibulum, septum pellucidum, corpus callosum, and optic nerve(s) may be seen in an isolated fashion or in combination with one another. These related midline developmental anomalies are thought to represent a spectrum of congenital and developmental conditions with varying degrees of penetrance, including holoprosencephaly and/or septo-optic dysplasia (SOD) [1].
- Pituitary hypoplasia may occur as an isolated entity (IPH) or in association with various (often overlapping) syndromes [2]:
  - Septo-optic dysplasia (SOD, de Morsier's syndrome)
  - Kallmann syndrome
  - Holoprosencephaly
  - Coffin-Siris syndrome [3]
  - Worster-Drought syndrome (congenital bilateral perisylvian syndrome) [4]
  - Hall-Pallister syndrome [5]
- Although usually sporadic conditions, pituitary hypoplasia and related midline anomaly spectrum disorders have been associated with mutations in a number of genes:
  - *Pit-1* [6, 7]
  - *Sonic Hedgehog* (*SHH*)
  - Growth hormone-releasing hormone (*GHRH*) receptor [8, 9]
  - *HESX1* [10]
  - *SOX2* and *SOX3*
  - Additional genes on the long arm of chromosome 14 [11]
- Isolated pituitary hypoplasia most commonly affects the growth hormone (GH), thyroid, and prolactin axes. Most patients with pituitary hypoplasia present with short stature. Clinically, these syndromes are known as isolated GH deficiency or combined pituitary hormone deficiency [12–14].
- Pituitary hypoplasia may be accompanied by adrenal cortical hypoplasia [15].
- Optic nerve hypoplasia is a leading cause of congenital blindness and is typically diagnosed on funduscopic examination. Additional midline anomalies are often identified with neuroimaging studies [16].
- Septo-optic dysplasia (SOD) and septo-optic-pituitary dysplasia are developmental disorders that involve hypoplasia of one or more midline structures. These conditions have been associated with maternal drug and alcohol use and in rare cases can be congenital.
  - The incidence of SOD is 1 in 10,000 newborns.
  - Affected expression of hypothalamic *Sonic Hedgehog* (*SHH*) has been shown to cause classic SOD [17].
  - The most common finding is optic nerve hypoplasia. Pituitary hypoplasia, agenesis of the septum pellucidum, and cortical developmental malformations can all be seen in combination or as isolated entities. Concurrent pituitary hypoplasia is seen in 64 % of

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patients with optic nerve hypoplasia, and agenesis of the septum pellucidum is seen in 50 % [12, 18].
  - Patients with SOD often present with developmental delay, communication difficulties, visual loss, nystagmus, and hypopituitarism.
  - The presence and degree of endocrinopathy correlate with the absence of multiple midline structures. Patients with absence of the septum pellucidum and hypothalamic-pituitary axis on MRI have the highest degree of endocrinopathy [19].
- Rarely, isolated pituitary stalk hypoplasia, also known as the pituitary stalk interruption syndrome (PSIS), can be seen [20]. This discrete entity has been associated with genes involved in holoprosencephaly (*SHH*, *TGIF*, *SIX3*).

68.2 Imaging Features

- Hypoplasia of the pituitary gland, infundibulum, septum pellucidum, corpus callosum, and/or optic nerve(s) can be seen on MRI (Fig. 68.1) [18, 20].
- The height of a hypoplastic pituitary gland, when present, is typically less than 3 mm; the normal height is more than 5 mm [8].
- An ectopic pituitary gland may be visualized [21].
- In patients with congenital GH deficiency, the triad of an ectopic posterior pituitary (EPP), pituitary aplasia/hypoplasia, and stalk defects is correlated with the presence of other endocrine abnormalities (Fig. 68.2) [22].
- The presence of diabetes insipidus has been shown to correlate with loss of the posterior pituitary bright spot [23, 24].
- Pituitary hypoplasia or ectopia can be associated with agenesis of an internal carotid artery [25, 26].
- On MRI, the cross-sectional area of the optic nerve can be used to support the diagnosis of optic nerve hypoplasia [27].

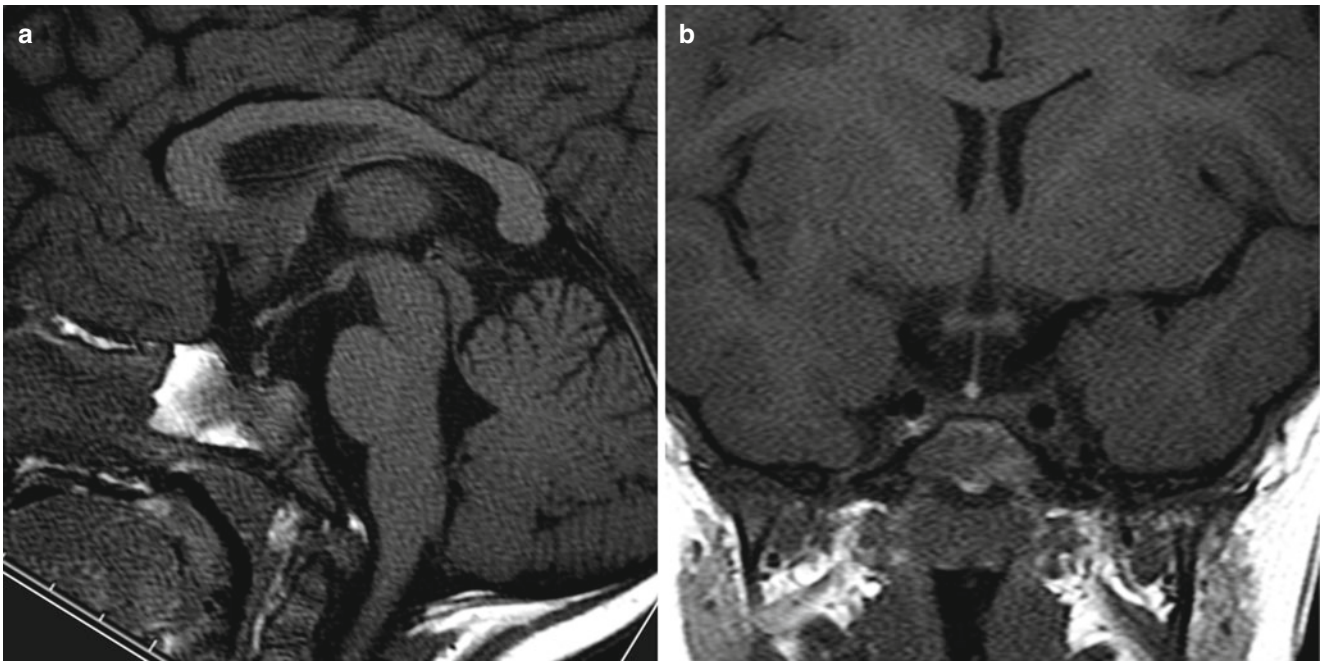

Fig. 68.1 Pituitary hypoplasia. (**a**) Sagittal T1-weighted precontrast MR image. (**b**) Coronal T1-weighted precontrast image. The anterior pituitary gland is hypoplastic and the posterior pituitary T1 shortening is visible in the center of the sella. The stalk is present

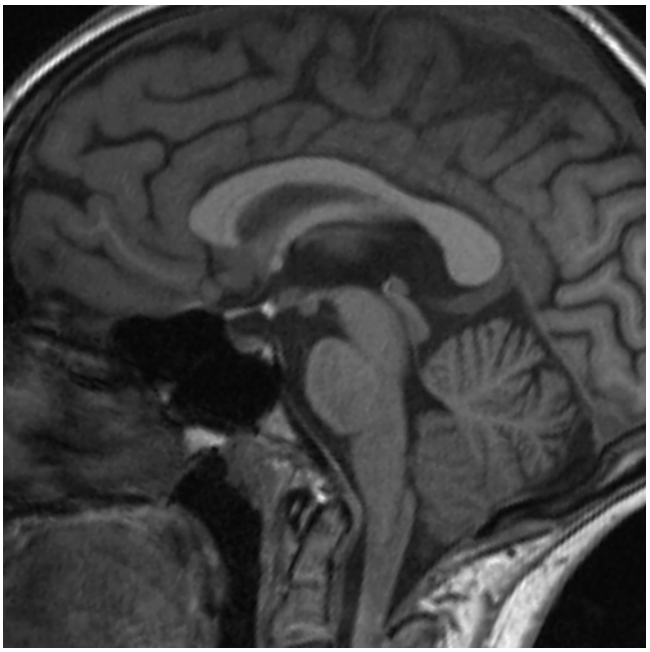

Fig. 68.2 Pituitary hypoplasia. Sagittal T1-weighted precontrast MR image. There is a T1-hyperintense spot in the infundibular recess, indicating ectopic neurohypophysis, and the pituitary stalk is not seen. The anterior pituitary gland is present in the sella

68.3 Clinical Management

- Clinical management is centered on prompt diagnosis and hormone replacement.
- Favorable responses to GH replacement have been shown in many patients [28].
- Multidisciplinary management is recommended for patients with any midline developmental disorders. Among the clinicians required may be endocrinologists, ophthalmologists, psychiatrists, neurologists, neurosurgeons, genetic counselors, and visual and occupational therapists.

References

1. Tatsi C, Sertedaki A, Voutetakis A, Valavani E, Magiakou MA, Kanaka-Gantenbein C, et al. Pituitary stalk interruption syndrome and isolated pituitary hypoplasia may be caused by mutations in holoprosencephaly-related genes. J Clin Endocrinol Metab. 2013; 98:E779–84.
2. Raivio T, Avbelj M, McCabe MJ, Romero CJ, Dwyer AA, Tommiska J, et al. Genetic overlap in Kallmann syndrome, combined pituitary hormone deficiency, and septo-optic dysplasia. J Clin Endocrinol Metab. 2012;97:E694–9.
3. Baban A, Moresco L, Divizia MT, Rossi A, Ravazzolo R, Lerone M, De Toni T. Pituitary hypoplasia and growth hormone deficiency in Coffin-Siris syndrome. Am J Med Genet A. 2008;146A:384–8.
4. Baş F, Darendeliler F, Yapici Z, Gökalp S, Bundak R, Saka N, Günöz H. Worster-Drought syndrome (congenital bilateral perisylvian syndrome) with posterior pituitary ectopia, pituitary hypoplasia, empty sella and panhypopituitarism: a patient report. J Pediatr Endocrinol Metab. 2006;19:535–40.
5. Cianfarani S, Vitale S, Stanhope R, Boscherini B. Imperforate anus, bilateral hydronephrosis, bilateral undescended testes and pituitary hypoplasia: a variant of Hall-Pallister syndrome or a new syndrome. Acta Paediatr. 1995;84:1322–4.
6. Frisch H, Kim C, Häusler G, Pfäffle R. Combined pituitary hormone deficiency and pituitary hypoplasia due to a mutation of the Pit-1 gene. Clin Endocrinol (Oxf). 2000;52:661–5.
7. Pfäffle RW, DiMattia GE, Parks JS, Brown MR, Wit JM, Jansen M, et al. Mutation of the POU-specific domain of Pit-1 and hypopituitarism without pituitary hypoplasia. Science. 1992;257:1118–21.
8. Murray RA, Maheshwari HG, Russell EJ, Baumann G. Pituitary hypoplasia in patients with a mutation in the growth hormone-releasing hormone receptor gene. AJNR Am J Neuroradiol. 2000;21:685–9.
9. Shohreh R, Sherafat-Kazemzadeh R, Jee YH, Blitz A, Salvatori R. A novel frame shift mutation in the GHRH receptor gene in familial isolated GH deficiency: early occurrence of anterior pituitary hypoplasia. J Clin Endocrinol Metab. 2011;96:2982–6.
10. Thomas PQ, Dattani MT, Brickman JM, McNay D, Warne G, Zacharin M, et al. Heterozygous *HESX1* mutations associated with isolated congenital pituitary hypoplasia and septo-optic dysplasia. Hum Mol Genet. 2001;10:39–45.
11. Nolen LD, Amor D, Haywood A, St Heaps L, Willcock C, Mihelec M, et al. Deletion at 14q22–23 indicates a contiguous gene syndrome comprising anophthalmia, pituitary hypoplasia, and ear anomalies. Am J Med Genet A. 2006;140:1711–8.
12. Margalith D, Tze WJ, Jan JE. Congenital optic nerve hypoplasia with hypothalamic-pituitary dysplasia. A review of 16 cases. Am J Dis Child. 1985;139:361–6.
13. Costin G, Murphree AL. Hypothalamic-pituitary function in children with optic nerve hypoplasia. Am J Dis Child. 1985;139:249–54.
14. Lettau M, Laible M. Kallmann's syndrome with pituitary hypoplasia. Rofo. 2011;183:576–8.
15. Mosier HD. Hypoplasia of the pituitary and adrenal cortex; report of occurrence in twin siblings and autopsy findings. J Pediatr. 1956;48:633–9.
16. Garcia-Filion P, Borchert M. Optic nerve hypoplasia syndrome: a review of the epidemiology and clinical associations. Curr Treat Options Neurol. 2013;15:78–89.
17. Zhao L, Zevallos SE, Rizzoti K, Jeong Y, Lovell-Badge R, Epstein DJ. Disruption of SoxB1-dependent Sonic hedgehog expression in the hypothalamus causes septo-optic dysplasia. Dev Cell. 2012; 22:585–96.
18. Acers TE. Optic nerve hypoplasia: septo-optic-pituitary dysplasia syndrome. Trans Am Ophthalmol Soc. 1981;79:425–57.
19. Birkebaek NH, Patel L, Wright NB, Grigg JR, Sinha S, Hall CM, et al. Endocrine status in patients with optic nerve hypoplasia: relationship to midline central nervous system abnormalities and appearance of the hypothalamic-pituitary axis on magnetic resonance imaging. J Clin Endocrinol Metab. 2003;88:5281–6.
20. Kaufman LM, Miller MT, Mafee MF. Magnetic resonance imaging of pituitary stalk hypoplasia. A discrete midline anomaly associated with endocrine abnormalities in septo-optic dysplasia. Arch Ophthalmol. 1989;107:1485–9.
21. Tajima T, Hattori T, Nakajima T, Okuhara K, Tsubaki J, Fujieda K. A novel missense mutation (P366T) of the LHX4 gene causes severe combined pituitary hormone deficiency with pituitary hypoplasia, ectopic posterior lobe and a poorly developed sella turcica. Endocr J. 2007;54:637–41.
22. Deal C, Hasselmann C, Pfäffle RW, Zimmermann AG, Quigley CA, Child CJ, et al. Associations between pituitary imaging abnormalities and clinical and biochemical phenotypes in children with congenital growth hormone deficiency: data from an international observational study. Horm Res Paediatr. 2013;79:283–92.
23. Mark AS, Kolsky M. Optic nerve hypoplasia: absence of posterior pituitary bright signal on magnetic resonance imaging correlates with diabetes insipidus. Am J Ophthalmol. 1997;123(5):715.
24. Sorkin JA, Davis PC, Meacham LR, Parks JS, Drack AV, Lambert SR. Optic nerve hypoplasia: absence of posterior pituitary bright signal on magnetic resonance imaging correlates with diabetes insipidus. Am J Ophthalmol. 1996;122:717–23.
25. 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;9:539–42.
26. Inamo Y, Harada K. Agenesis of the internal carotid artery and congenital pituitary hypoplasia: proposal of a cause of congenital hypopituitarism. Eur J Pediatr. 2003;162:610–2.
27. Birkebaek NH, Patel L, Wright NB, Grigg JR, Sinha S, Hall CM, et al. Optic nerve size evaluated by magnetic resonance imaging in children with optic nerve hypoplasia, multiple pituitary hormone deficiency, isolated growth hormone deficiency, and idiopathic short stature. J Pediatr. 2004;145:536–41.
28. Dattani M, Preece M. Growth hormone deficiency and related disorders: insights into causation, diagnosis, and treatment. Lancet. 2004;363:1977–87.