Congenital Hypopituitarism

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KEYWORDS

• Hypopituitarism • Hypoglycemia • Cholestasis • Growth hormone • MRI
• Pituitary stalk • Guidelines

KEY POINTS

- Congenital hypopituitarism can be life threatening in neonates.
- A combination of prenatal, perinatal, and postnatal findings suggest the diagnosis. These findings include family history, brain or eye abnormalities, breech presentation, micropenis, hypoglycemia, and cholestasis.
- Most neonates with severe combined pituitary hormone deficiency show an ectopic posterior pituitary, abnormal pituitary stalk, and/or anterior pituitary hypoplasia on MRI.
- Characteristic MRI and low growth hormone (GH) levels in infancy establishes a diagnosis of GH deficiency. Recognition of adrenocorticotrophic hormone and/or thyroid-stimulating hormone deficiency establishes a diagnosis of combined pituitary hormone treatment and guides hormone replacement.

INTRODUCTION

Timely recognition of severe, congenital hypopituitarism is challenging. Short stature does not force consideration of the diagnosis, because birth weight and length are typically normal.[1–3] Clinicians must weigh a combination of family history, complications of pregnancy and delivery, physical findings, and postnatal problems such as hypoglycemia and jaundice in deciding whether to pursue the diagnosis. Once suspicion has been aroused, the pathway to diagnosis is fairly clear. It requires neuroimaging and selection of hormone assays to establish deficiency of growth hormone (GH) with or without insufficiency of other pituitary hormones. Early treatment can mitigate the metabolic and developmental consequences of hormone deficiencies, as well as providing the best chance of the infant's achieving a normal adult height.

CRUCIAL QUESTIONS ABOUT HYPOPITUITARISM

There are 3 crucial questions to ask when considering the possibility of congenital hypopituitarism.

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What Hormones Are Missing?

Hypopituitarism involves underproduction of 1 or more of the 6 peptide hormones normally produced by 5 cell types in the anterior pituitary. There may be isolated deficiency of pituitary GH (IGHD) or combined pituitary hormone deficiency (CPHD) with additional deficiencies of thyroid-stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), prolactin (PRL), and the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH). There are also well-defined genetic disorders causing isolated deficiency of TSH,[4] ACTH,[5] and gonadotropins.[6] This article focuses on IGHD and CPHD.

Does MRI Show an Ectopic Posterior Pituitary?

MRI, introduced in the 1980s, provides detailed visualization of the anterior pituitary, the pituitary stalk, and the posterior pituitary bright spot.[7] Many children with congenital hypopituitarism show 1 or more of a triad of findings consisting of an ectopic posterior pituitary (EPP), anterior pituitary hypoplasia, and absence or attenuation of the stalk connecting the hypothalamus and pituitary. This combination is known as pituitary stalk interruption syndrome (PSIS).[8] It is a very common feature of CPHD. The triad is uncommon in IGHD, which is more commonly associated with isolated anterior pituitary hypoplasia or with normal MRI findings. PSIS identifies a subset of patients with IGHD who have a high risk for progression from IGHD to CPHD.[9]

Do Structural Abnormalities Extend Beyond the Pituitary Axis?

The most familiar association of abnormal hypothalamopituitary development with other central nervous system abnormalities is septo-optic dysplasia.[10] In this condition, hypopituitarism is linked to optic nerve hypoplasia and underdevelopment of the septum pellucidum. Other examples include anophthalmia, holoprosencephaly,[11] and Pallister-Hall syndrome,[12] an autosomal dominant disorder in which hypopituitarism is accompanied by hypothalamic hamartoma, polydactyly, imperforate anus, and renal anomalies. There is a risk of overlooking the component of hypopituitarism in infants with these complex conditions.

CATEGORIES OF HYPOPITUITARISM

Genetic Forms of Isolated Growth Hormone Deficiency

Congenital isolated GH deficiency (GHD) has an incidence of 1 in 4000 to 1 in 10,000 live births. There are several well-characterized genetic forms that show autosomal recessive, autosomal dominant, or X-linked patterns of inheritance and these are termed type 1-A, type 1-B, type 2, and type 3 (**Table 1**).[13] Type 1-A shows complete absence of GH and is caused by deletions or complete loss-of-function mutations of the *GH1* gene.[14] It was initially recognized in Swiss children with extremely short stature who developed antibodies that neutralized GH effects when treated with extracted pituitary GH.[15] Subsequent reports indicated that anti-GH antibody formation is a variable feature of this condition.[16] Type 1-B refers to a less severe phenotype. One form is caused by missense mutations or by splice site mutations that eliminate the fourth exon of the *GH1* gene.[17] A similar phenotype is produced by mutations in the *GHRHR* gene encoding the pituitary receptor for the hypothalamic GH-releasing hormone.[18] Type 2 is a dominant form of IGHD. Mutations of the *GH1* gene account for more than 80% of dominant IGHD. Most common are splice donor site mutations that exclude