Magnetic resonance imaging of the hypothalamus-pituitary unit in children suspected of hypopituitarism: Who, how and when to investigate

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ABSTRACT. The magnetic resonance (MR) identification of pituitary hyperintensity in the posterior part of the sella has been the most striking recent finding contributing to the diagnosis of “idiopathic” and permanent GH deficiency (GHD). Moreover, advancements in DNA technology have shed new light on the study of the genetic causes of hypopituitarism. Abnormalities in two genes, the GH-N encoding the GH and the GHRH receptor (GHRH-R), have been identified, while mutations in five other gene-encoding transcription factors such as Pit-1, Prop-1, Hesx-1, Lhx-3 and Lhx-4 involved in anterior pituitary development, have also been described. MR imaging shows marked differences in pituitary morphology indicating different GHD etiologies and different prognoses. Ectopic posterior pituitary is a specific marker of permanent GHD. These patients do not have Pit-1, Prop-1, or Lhx-3 mutations and should be carefully monitored for evolving pituitary hormone defects, though they do not require GH re-evaluation in adulthood; selected cases may have Hesx-1 or Lhx-4 mutations. MR evidence of normal or small anterior pituitary gland, enlarged empty sella, pituitary hyperplasia and/or suprasellar or suprasellar mass when associated with combined pituitary hormone deficiency call for molecular analysis of Pit-1, Prop-1, Hesx-1, or Lhx-3. Limitation of neck rotation and Chiari-I malformation may suggest Lhx-3 or Lhx-4 mutations (exceedingly rare). In “idiopathic” isolated GHD, evidence of normal anterior or small anterior pituitary size with normal location of posterior pituitary and normal connection between the hypothalamus and pituitary gland is suggestive of “transitory” or false positive GHD; patients with such characteristics should be re-evaluated well before reaching adult height. In selected cases, anterior pituitary height that is 2 SD below age-adjusted normal pituitary height could be suggestive of GHRH-R gene defect; it is worth pointing out that normal pituitary MR together with severe GHD has been observed, though rarely, in subjects with a genetic origin of GHD.

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INTRODUCTION
Small progress was made in the field of pituitary imaging until the advent of magnetic resonance (MR), which led to an enormous increase in our detailed understanding of pituitary morphology, thus improving the differential diagnosis of hypopituitarism. Indeed, MR imaging represents the examination method of choice for evaluating hypothalamic-pituitary-related endocrine diseases, thanks to its ability to provide strongly-contrasted high-resolution multi-planar and spatial images. Specifically, MR images allow a detailed and precise anatomical study of the pituitary gland by differentiating between the anterior and posterior pituitary lobes. The MR identification of pituitary hyperintensity in the posterior part of the sella, now considered a marker of neurohypophyseal functional integrity, has been the most striking recent finding contributing to the diagnosis and understanding of some forms of “idiopathic” and permanent GH deficiency (GHD). The definition of GHD in childhood is still difficult and arbitrary, and a considerable amount of attention...
has been devoted to the biochemical assessment of GHD. The advent of molecular biology and MR imaging, however, has greatly improved the etiology of disorders affecting the hypothalamic-pituitary area in patients with apparently "idiopathic" hypopituitarism. Clinical, laboratory and imaging findings have led to a more accurate selection and classification of the possible causes of GHD, while the identification of molecular defects involving the genes expressed along the somatotropic axis, including GH-1 gene and GHRH receptor (GHRH-R) gene, or the pituitary transcription factors such as Pit-1, Prop-1, Hesx-1, Lhx-3 and Lhx-4, have made an important contribution to the understanding of the pathophysiology of these conditions. However, some questions have inevitably been raised. Is there a gold standard for the diagnosis of GHD and what then is the goal of MR imaging? Is MR phenotype imaging informative? Does MR phenotype imaging affect the work-up of patients with GHD? Does MR phenotype imaging predict the outcome of patients with GHD? And what is the contribution of MR results to GHD management? MR imaging may certainly be one important goal, but several questions remain unanswered and others clearly present a challenge. The purpose of this review is to deal with the issue of MR findings in the diagnosis and prognosis of the child presenting short stature.

MR IMAGING OF NORMAL PITUITARY

The morphological evaluation of the pituitary gland calls for the definition of the following: the height and/or volume of the anterior pituitary, the presence and site of the posterior pituitary, and the presence and size of the pituitary stalk. The maximum height of the anterior pituitary is measured (sagittal image) on a plane perpendicular to the sella turcica floor, whereas the volume is calculated using the Di Chiuro formula (2): V = 1/2 length x height x width (underestimated) or, alternatively, V = area x width (overestimated). The changes with age in pituitary shape and size appear mainly due to changes in gland height. Pituitary height, in fact, is used as an indicating parameter for anterior pituitary size, despite the risk of underestimating the size of a pituitary with a concave superior margin or overestimating one with a convex surface (3).

The shape, size and signal of the normal anterior pituitary varies with age and sex. The pituitary gland of the neonate has a convex superior margin which by the age of 2 months flattens out. The gland may have a slightly concave superior margin throughout childhood and is not expected to reach a height of less than 3 mm or greater than 6 mm prior to puberty (4-10). Table 1 summarizes reports from the literature on normal pituitary. The data collected regarding the size of normal pituitary height reported in children, however, remain too scarce to convincingly establish one standard normal pituitary height. At puberty, the pituitary gland increases in size and at this time gender variation has been reported. The gland reaches its maximum height of 8 mm in males, whereas it sometimes become markedly convex in females, reaching 10 mm in height (4). During the first 6 weeks of life, both the anterior and posterior pituitary glands have a homogeneously high signal on T1-weighted pre-contrast MR images, though the signal intensity of the anterior pituitary gradually decreases and the isointense anterior pituitary can be clearly distinguished from the hyperintense posterior pituitary (8).

The posterior pituitary does not undergo variations in either size or signal intensity during childhood; the pituitary stalk diameter is approximately 2 mm (range 1-3 mm) and should never exceed the basilar artery (11). The pituitary stalk is divided into two parts, one is the neuronal component made up of the track of axons extending from the hypothalamic nuclei down to the axon terminals in the posterior pituitary pouch; the other is the vascular component that provides the blood supply to the anterior pituitary gland from the superior hypophyseal arteries through the pituitary portal system.

MR IMAGING IN GHD

"Idiopathic" GHD

"Idiopathic" GHD is a heterogeneous condition whose pathophysiology remains largely unknown. The diagnosis of GHD in childhood can be straightforward when short stature and persistent growth failure are associated with frontal bossing, mid facial hypoplasia, truncal adiposity, small genitalia in the male, and/or hypoglycemia and cholestatic jaundice (12). However, this presentation tends to be the exception rather than the rule and thus the clinical phenotype may not be particularly impressive (Fig. 1). What is the relevance of pituitary MR imaging phenotype and what does pituitary phenotype tell us about genotype? (Fig. 2). Thanks to MR imaging, it has been possible to define some anatomical entities that are associated with isolated GHD or combined pituitary hormone deficits (CPHD). Patients with "idiopathic" GHD can present a variety of pituitary MR features including: 1) normal pituitary gland size; 2) isolated anterior pituitary hypoplasia (congenital) or small pituitary (acquired); 3) empty sella (these 3 conditions present with normal location of the posterior pituitary gland and normal pituitary stalk connecting the hypothalamus to the pituitary gland); and 4) moderate (height of 2-3 mm) to severe (height<2 mm) pituitary hypoplasia and sella turcica associated with ectopic posterior pituitary gland at the level of median eminence or along the stalk pro-