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MR Findings in Hereditary Isolated Growth Hormone Deficiency

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PURPOSE: To describe the MR characteristics by which patients with hereditary isolated growth hormone deficiency (GHD) can be distinguished from patients with other types of GHD. **METHODS:** A total of 51 patients with GHD were examined prospectively with MR imaging. On the basis of familial occurrence of GHD and genetic analysis, 10 patients met the criteria for hereditary deficiency. In each case, the height of the pituitary gland, the presence and location of the posterior neurohypophysis, and the completeness of the stalk were recorded. The findings in the hereditary group were compared with those in the rest of the patients. **RESULTS:** In all 10 patients with hereditary GHD, the adenohypophysis, the neurohypophysis, and the stalk were normal. Of the other 41 patients, the height of the gland was normal in three (7%), the neurohypophysis was abnormal in all, and the stalk was truncated in all but two patients (95%). **CONCLUSIONS:** The subgroup of patients with hereditary GHD exhibited an anatomically normal pituitary-hypothalamic region. This is in contrast to the majority of patients with idiopathic GHD. MR imaging can contribute to the classification of patients with GHD.

Index terms: Hormone deficiency; Pituitary gland, magnetic resonance

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Growth hormone deficiency (GHD) comprises a spectrum of disorders of varying pathogenesis and pathologic characteristics. It may be classified as isolated GHD or as part of a combination of multiple pituitary hormone deficiencies (MPHD) (1).

Until recently, investigators have been unable to relate any particular etiologic factors to GHD. Most cases of GHD, except those that arise consequent to a defined pituitary hypothalamic insult, such as tumor, radiation, or trauma, are still considered as idiopathic, nonorganic GHD. The prevalence of idiopathic GHD is not known; estimates range from one in 5000 to one in 10 000 of the population (1, 2). The advent of magnetic resonance (MR) imaging brought

about a dramatic improvement in the imaging of idiopathic GHD: it became possible to delineate abnormalities in the hypothalamic-pituitary region, including a small hypophysis, a missing neurohypophysis, an ectopic posterior lobe represented by a bright spot in the hypothalamus, and a truncated stalk (3, 4). Subsequent investigators have reported a wide spectrum of findings, ranging from the classical picture described above to a normal appearance (5, 6). Anomalies of the pituitary-hypothalamic region have also been depicted on MR studies in many congenital brain dysplasias associated with midline anomalies and GHD (1).

Genetic studies have identified a distinct subgroup of isolated GHD, in which heredity is a determining etiologic factor. An estimated 5% to 35% of cases of congenital GHD are due to a genetic defect that results in the inability to synthesize GH (1, 2).

The purpose of our prospective study was to characterize the MR findings in the hypothalamic-pituitary region in a subgroup of patients with hereditary isolated GHD and to determine whether these findings can be used to differen-

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Clinical and imaging data of 10 patients with hereditary isolated growth hormone deficiency GHD

| Patient | Age, y/Sex | Category of Hereditary GHD* | Height of Gland, mm† | Neurohypophysis | Stalk | Comments |
|---------|------------|-----------------------------|----------------------|-----------------|-------|---|
| 1 | 19/F | IA | 8 | N | N | Gene deletion |
| 2 | 20/F | IA | 5 | N | N | Gene deletion |
| 3 | 28/M | IA | 5 | N | N | Gene deletion |
| 4 | 13/F | IA | 8 | N | N | Gene deletion |
| 5 | 17/M | IB | 6 | N | N | Sibling of patient 6, cousin of patient 7 |
| 6 | 19/F | IB | 6 | N | N | Sibling of patient 5, cousin of patient 7 |
| 7 | 6/M | IB | 5 | N | N | First cousin of patients 5 and 6 |
| 8 | 16/M | IB | 8 | N | N | Sibling with GHD |
| 9 | 32/F | II | 4 | N | N | Mother of patient 10‡ |
| 10 | 5/M | II | 3 | N | N | Son of patient 9, sibling with GHD |

* IA, deletion of *GH 1* gene; IB, unidentified chromosomal defect; II, autosomal-dominant transmission.

† Normal is greater than 2 mm.

‡ Mother of another son with GHD.

Note.—N indicates normal.

tiating hereditary isolated GHD from other cases of GHD.

Patients and Methods

The study group comprised 51 patients with GHD. The diagnosis was based on clinical findings of short stature (> -2.5 SD) and decreased growth velocity (> -2.5 SD) and on biochemical findings of lack of GH response (GH < 2.5 ng/mL) on at least two stimulation tests (1). Each patient underwent a complete evaluation of hypothalamic-pituitary axis function (1), resulting in a diagnosis of isolated GHD in 23 patients and of MPPHD in 28, seven of whom had associated craniofacial anomalies. Detailed histories of consanguinity and familial occurrence of GHD were obtained. In 10 patients with family histories of isolated GHD, gene analysis was performed. Their clinical data are shown in the Table. The MR findings in this subgroup of 10 patients were compared with those of the other 13 patients with isolated GHD and of the 28 patients with MPPHD.

MR studies were performed on 0.5-T or 2.0-T systems. The imaging protocol included coronal and sagittal T1-weighted images of the pituitary obtained with parameters of 400–500/12–20/3–4 (repetition time/echo time/excitations). In a few cases, a sagittal T1-weighted gradient-echo sequence was used instead of the spin-echo sequence (400/4.7–12/2) with a 70° flip angle. Other imaging parameters included a section thickness of 2.9 to 4.0 mm with a gap of 0.6 to 1.0 mm, a 200 or 256 × 256 matrix, and an 18 × 20-mm field of view. The craniocaudal height of the hypophysis was measured at the site of stalk insertion and graded as normal (> 2 mm) or as hypoplastic or absent. The T1 hyperintense focus of the neurohypophysis was defined as normal or as ectopic or absent. The stalk length was graded as normal or truncated. Contrast material was injected at the discretion of the examining radiol-

ogist to obtain clearer delineation of the anatomic abnormalities of the pituitary and/or stalk.

Results

MR imaging in the 23 patients with isolated GHD revealed that in all 10 patients with hereditary isolated GHD the pituitary gland was of normal height, with a normal neurohypophysis and stalk (Table and Fig 1). Contrast agent was not administered in any of these patients. In the other 13 patients, the gland was normal in only one (8%) and was hypoplastic or absent in 12 (92%). The stalk was truncated and the neurohypophysis was located abnormally in all 13 patients (Fig 2).

Of the 28 patients with MPPHD, the gland was normal in only two (7%) and hypoplastic or absent in 26 (93%). The stalk was normal in only one patient and was truncated in 27 (96%). The posterior hypophysis was located abnormally in all 28 patients. In the subgroup of seven patients with MPPHD and midline anomalies, the anterior hypophysis and stalk could not be recognized in six (86%), and the stalk was normal and the gland small in one (14%). In all seven patients the neurohypophysis was located abnormally: it was ectopic in four patients (57%) and absent in three (43%).

Discussion

GH-related growth failure results from specific alterations in the chain of events from

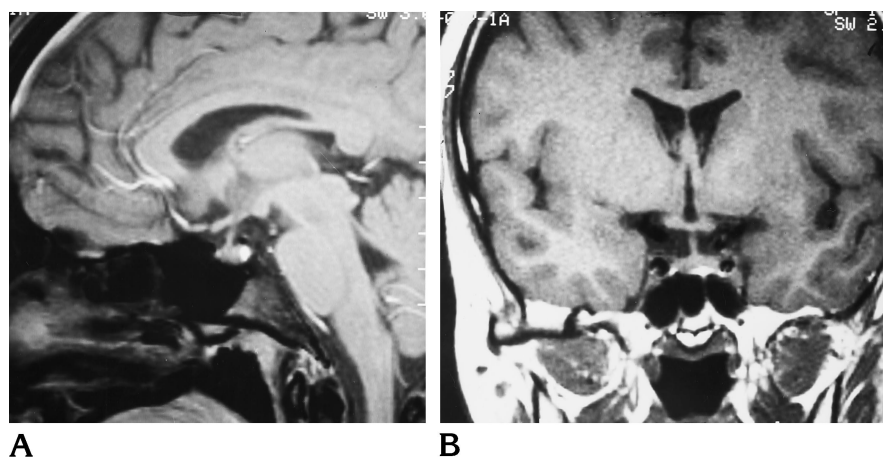


Fig 1. A 19-year-old woman with hereditary GHD. Sagittal gradient-echo T1-weighted MR image (400/4.7/2) with a 70° flip angle (A) and coronal T1-weighted (500/12/2) image (B) show normal appearance of pituitary gland and stalk.

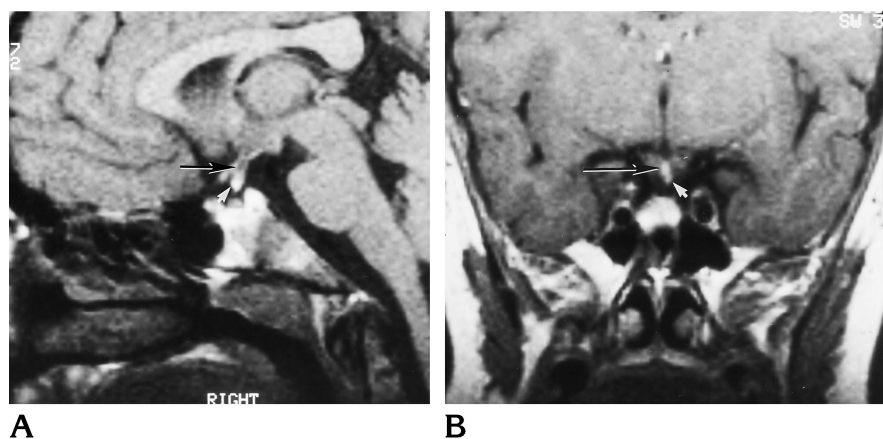


Fig 2. A 13-year-old boy with isolated GHD. Sagittal unenhanced T1-weighted HR image (400/25/4) (A) and coronal contrast-enhanced T1-weighted image (400/25/4) (B) show classical findings of GHD: a truncated stalk (long arrow) and an ectopic bright spot (short arrow). The height of the gland is 3 mm.

synthesis of the hormone to its growth-promoting action (1, 2). GHD can occur either as an isolated entity or in combination with other pituitary hormone deficiencies (MPHD) (1, 2).

The most common form of GHD is the idiopathic type (1). It has been postulated that hypothalamic or pituitary damage could be a result of head trauma at birth (1, 7). Accordingly, the finding of marked hypoplasia or total absence of the stalk in patients with GHD associated with a high prevalence of complicated deliveries led to the hypothesis that idiopathic GHD is probably related to perinatal disruption of the peri-infundibular hypophyseal portal venous system. This impairs anterior pituitary function by interfering with direct delivery of the hypothalamic releasing factors (1, 3, 4, 8).

However, recent studies (9–14) correlating the exact type of endocrine abnormality (isolated GHD versus MPHD) with perinatal history and imaging findings in larger series of patients have shown that isolated GHD does not necessarily exclude the presence of a normal stalk (9,

10, 12–14), and that perinatal abnormalities are not significantly associated with a truncated stalk or an ectopic neurohypophysis (10–14). The notion that perinatal trauma causes idiopathic GHD has therefore fallen out of favor, and the possibility of an earlier intrauterine lesion or developmental defect has been raised instead (11, 15).

In an estimated 5% to 35% of cases, the basis of congenital GHD appears to be genetic (1, 2). The human *GH* gene cluster consists of five similar *GH* and *CS* (chorionic somatotropin) genes, all located in the long arm of chromosome 17 at bands q22–24. One of them is *GHI*, the gene that encodes for the GH peptide synthesized by the somatotrophic cells of the anterior pituitary (1, 2, 7). Based on genetic and clinical characteristics, four distinct types of hereditary isolated GHD have been described. Type IA is characterized by deletion of the *GHI* gene. Its transmission is autosomal-recessive. In the other three types of hereditary isolated GHD, the chromosomal defect has not yet been

identified. Transmission is autosomal-recessive in type IB, autosomal-dominant in type II, and X-linked in type III (1, 2, 7). Of 51 patients examined in this study, the findings in 10 were compatible with hereditary GHD because of a family history of GHD or consanguinity. According to this classification, four of our 10 patients had type IA disease (cases 1–4), and four had type IB, with a normal *GH* gene (cases 5–8). The two remaining patients (cases 9 and 10) had type II (Table).

In a recent review, Rapaport (15) suggested that patients with molecular defects of *GH* have normal pituitary findings. The MR studies in our 10 patients revealed normal anatomy of the pituitary-hypothalamic region. Although post-mortem reports on patients with isolated GHD are rare, our observations are supported by two cases in which autopsy findings were normal. In the first, a 78-year-old man with proved isolated GHD inherited as a recessive trait, the pituitary gland appeared normal in size and shape on gross examination, and no abnormalities of the hypothalamus were observed (7). The second, the brother of one of our patients (case 8), who also had isolated GHD and who died at age 4 years, was found to have a normal pituitary and stalk at autopsy (unpublished data, 1970).

Depending on the population, type IA disease accounts for 0% to 38% of the total number of patients with hereditary isolated GHD. In the large majority of cases, the molecular basis of GHD and the chromosomal locus responsible for it are still unknown (2, 16, 17). Although the patients comprising our subgroup with hereditary isolated GHD had a variety of genetic abnormalities, none of them had any anatomic abnormalities of the pituitary-hypothalamic axis at MR imaging. We cannot, however, exclude the possibility that our “nonhereditary” group may have included patients with *de novo* mutations of genetic GHD. In any case, it is clear that there is a high prevalence of normal anatomy among patients with genetic GHD. Other authors have described familial occurrence of GHD with hypothyroidism (18) or with prolactin deficiency and partial deficiency of thyroid-stimulating hormone (19). The MR findings were normal in these cases as well, suggesting that a genetic multihormonal defect that includes GHD also manifests no anatomic abnormalities of the pituitary-hypothalamic region. On the other hand, GHD can be part of various congenital malformation syndromes as-

sociated with midline facial and central nervous system anomalies, such as cleft lip, cleft palate, septooptic dysplasia, or holoprosencephaly (1, 11). As demonstrated in the present study and in a pathologic study of septooptic dysplasia (11), these patients constitute a nonhomogeneous group exhibiting a wide spectrum of anatomic and endocrinologic abnormalities, including anomalies of the hypothalamus.

In conclusion, we suggest that MR imaging can contribute to the clarification and classification of subgroups of patients with GHD by identifying those in whom the hypothalamic-pituitary anatomy is normal and is therefore compatible with hereditary genetic isolated GHD. Scrutiny of the family history and genetic testing are indicated in such cases.

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