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MAGNETIC RESONANCE IMAGING (MRI) FINDINGS IN ISOLATED GROWTH HORMONE DEFICIENCY*

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SUMMARY: Kandemir N, Cila A, Besim A, Yordam N. (Endocrinology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Magnetic resonance imaging (MRI) findings in isolated growth hormone deficiency. Turk J Pediatr 1998; 40: 385-392.

In this study the presence of pituitary-hypothalamic abnormalities was searched by magnetic resonance (MR) imaging in 30 children (18 males and 12 females, aged 7.4 to 23 years) with isolated growth hormone deficiency (IGHD). Small anterior pituitary was demonstrated in 18 patients and ectopic posterior pituitary (EPP) in four of them. Pituitary stalk was found to be thin in two patients with anterior pituitary hypophasia and EPP and was visible only in post-gadolinium images. In one patient, a hypothalamic mass was found and the bright spot of the posterior pituitary was not observed. In three other patients, the absent bright spot of the posterior pituitary was found without diabetes insipidus, possibly due to a variation in the intensity of the bright signal. Eight patients had normal pituitary imaging suggesting functional damage. In all five patients with familial growth hormone deficiency the anterior pituitary was hypoplastic.

We conclude that a high percentage of patients with IGHD had anomalies of the hypothalamo-pituitary region, which could be demonstrated by MR imaging. Furthermore, the low frequency of perinatal abnormalities in these patients suggested developmental defect as the cause of the morphostructural abnormalities. The presence of the familial cases with the same defect pointed to the genetic origin in some instances. *Key words: growth hormone deficiency, magnetic resonance imaging.*

Magnetic resonance imaging (MRI) offers the advantage of revealing the morphological and structural abnormalities of the hypothalamic-pituitary region in patients with idiopathic growth hormone deficiency (GHD).

The reported abnormalities comprise one of three patterns[1-4].

1. Anterior pituitary hypoplasia, absence of the pituitary stalk and ectopia of the posterior pituitary.
2. Isolated anterior pituitary hypoplasia.
3. Normal morphology of the pituitary gland.

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Anterior pituitary hypoplasia and ectopic posterior pituitary (EPP) with unidentified stalk have been found to be associated with multiple pituitary hormone deficiency, whereas normal and hypoplastic anterior pituitary have been shown in isolated growth hormone deficiency (IGHD)[1-4].

The etiology of the neuroradiological abnormalities found in idiopathic growth hormone deficiency is not clearly understood. Several explanations have been proposed[4-6].

1. Mechanical cut of the stalk during breech and foot delivery.
2. Hypoxia-ischemia during difficult delivery which results in interruption or occlusion of the hypophyseal portal system.
3. Dysgenesis or abnormal embryonic development of both adenohypophysis and neurohypophysis.

The aim of this study was to define the abnormalities of the hypothalamic-pituitary region in IGHD using MRI and to assess the relation between endocrine function and morphological findings. In addition to this, MRI findings were compared with perinatal histories.

Material and Methods

We evaluated 30 patients with IGHD (18 males and 12 females) aged from 7.4 to 23 years who were followed in the Pediatric Endocrinology Unit of Hacettepe University, Ankara. At the time of the evaluation, eight patients were prepubertal and the others reached puberty spontaneously.

The diagnosis of IGHD was based on the following criteria:

1. Short stature (height was below 2 SD for chronological age)[7].
2. Decreased growth velocity (below the 10th percentile for age) evaluated over a period of at least six months[8].
3. Delayed bone age, determined by the Greulich and Pyle method[9].
4. Growth hormone response of less than 10 ng/ml during insulin and L-DOPA stimulation tests.
5. Normal levels of the other pituitary hormones such as thyroxin (T_4), prolactin, cortisol, FSH and LH.

Height was measured by Harpenden stadiometer and converted to standard deviation scores (SDS) to allow comparison of data in children, using reference values at different ages[7]:

$$SDS = \frac{X-\bar{X}}{SD}$$

where X = measurement, $\bar{X}$ and SD = the mean and standard deviation, appropriate for age and sex.

Serum growth hormone (GH), triiodothyronine (T_3), tetraiodothyronine (T_4), TSH, free T_3, free T_4, cortisol, prolactin, FSH, LH and plasma ACTH levels were measured using commercial RIA kits. The diagnosis of isolated growth hormone deficiency was confirmed in all patients with normal levels of the other pituitary hormones.

Perinatal histories were reviewed for breech or cesarean section births and for neonatal asphyxia. A history of breech delivery was recorded in three patients and cesarean section in another three. All other patients were born by normal vaginal delivery at term without any perinatal trauma and/or asphyxia.

Children with an acquired GHD such as that resulting from craniopharyngioma, histiocytosis, a cerebral inflammatory disease, or hydrocephalus and those who received irradiation for tumors were excluded.

Magnetic resonance imaging studies were performed with a 0.5 T Unit (gyroscan T5 II; Philips, The Netherlands). Spin echo T1-weighted sagittal and 3D T1-weighted gradient echo coronal images were obtained in every patient and repeated after gadolinium-DTPA injection. Sella size was evaluated in sagittal plane. Height of the gland was measured on coronal images and the gland was considered hypoplastic if the maximum height was ≤ three mm. Bright spot of the posterior pituitary was located in both coronal and sagittal images. It was considered ectopic if located outside sella turcica. Since all of our patients had received Gd-DTPA injection, stalk continuity was determined in post-contrast images.

Results

The auxological data and MRI findings of 30 children at the time of the diagnosis are shown in Table I.

At the time of the diagnosis, the mean (SD) chronological age was 10.9 (2.8) years and the mean bone age was 7.7 (3.0) years. The height SDS for chronological age was below -2 in all patients and the mean value was -4.07 (1.09). The mean pretreatment growth velocity was 3.3 (0.6) cm/yr. The mean peak GH level was 2.9 (2.3) ng/ml during stimulation test with L-DOPA and 2.3 (2.0) ng/ml with insulin. At the time of the evaluation, the mean chronological age was 13.6 (3.1) years.

Of three patilents who had breech presentation at birth, one boy had pituitary hypoplasia, a thin stalk and EPP. The other two (a girl and boy) had normal pituitary imaging except in one of them the bright spot of the posterior pituitary was not observed. Of three patients born by cesaren section, one had pituitary hypoplasia and two had normal MR imaging.

In 12 patients from 10 families, consanguinity was present between parents (35%) and in five offspring of three families, a familial form of IGHD was diagnosed.

Table I: MR Imaging and Auxological Data of Patients with Growth Hormone Deficiency

Patient No.	Sex	CA (yr)	HSDS-CA	BA (yr)	GV (cm/yr)	Peak GH (ng/ml) L-DOPA	Insulin
Pituitary hypoplasia							
1	M	6.2	-3.26	3	4	2.4	1.7
2	F	10.3	-3.93	5	3	2.1	0.5
3	M	12.5	-5.88	7.5	3	1.1	1.3
4	F	8.7	-4.18	8	2.5	< 0.2	0.9
5	F	8.4	-4.20	6	2.6	1.7	0.7
6	M	15.9	-6.61	14.5	3.5	1.1	0.7
7	M	5.9	-5.76	5	3.5	0.05	0.86
8	M	4.4	-4.31	2.5	3.5	< 1.5	< 0.5
9	M	9.4	-3.75	6	3	6.9	2.7
10	F	7.4	-4.59	2	4	1.7	1.5
11	M	13	-4.53	10	2.8	1.8	1.6
12	F	11.7	-4.72	9	2.5	3.1	0.8
13	F	10.2	-2.60	8	3.5	4.4	2.0
14	M	11	-5.23	5.5	3	0.7	1.3
Pituitary hypoplasia with thin pituitary stalk and EPP							
15	F	8.6	-4.58	4	3.2	2.3	3.2
16	M	9.7	-5.54	4	2.6	2.1	2.1
Pituitary hypoplasia with thick pituitary stalk and EPP							
17	M	12	-2.91	11.5	4	7.2	4.4
Normal pituitary							
18	M	10	-3.14	7	4	7.2	1.8
19	M	13.4	-2.54	10.5	3.5	2.5	2.4
20	M	15.2	-4.26	11	4	1.2	1.7
21	F	12.2	-2.75	9	4	2.2	6.7
22	F	11.5	-3.13	9.5	3.5	6.2	3.4
23	M	13	-4.77	8	2.2	0.8	0.4
24	M	16	-3.80	11	3	3.9	4.2
25	F	12	-3.26	10	4	3.8	1.3
Normal pituitary with absent bright spot of the posterior pituitary							
26	M	15	-5.47	11	4	1.3	1.5
27	F	11	-2.50	8	4	2.4	1.4
EPP with normal anterior pituitary							
28	M	13.4	-2.99	10	4	7.9	5.9
Pituitary hypoplasia with absent bright spot of the posterior pituitary							
29	F	11	-3.51	9	3	1.6	9
Hypothalamic mass							
30	M	9.5	-3.43	6	2.2	7.2	3

The height of the anterior pituitary gland was less than three mm in 18 of 30 children (60%); five patients with a familial form of IGHD were in this group (Fig. 1). In the study group four patients had ectopic posterior pituitary (EPP). In three of them the anterior pituitary gland was hypoplastic and in one of them it was normal. The bright spot indicating posterior pituitary was observed in median eminence (Fig. 2) in two cases, in midstalk (Fig. 3) in one case and in the lower part of the stalk in the other. In the two patients with hypoplastic anterior pituitary and EPP, stalk was found to be thin and was visible only in post-gadolinium images (Fig. 2).

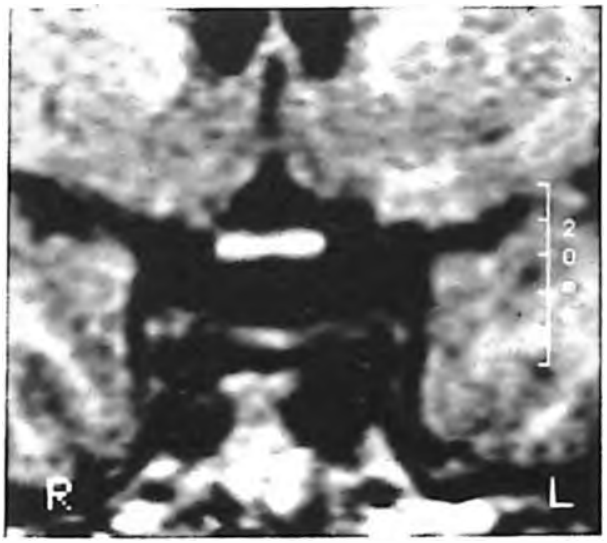


Fig. 1: 15-year-old male. Anterior pituitary gland height of two mm confirming gland hypoplasia.

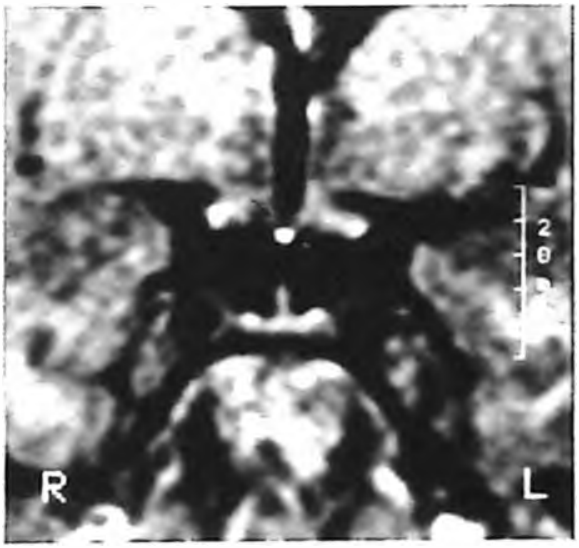
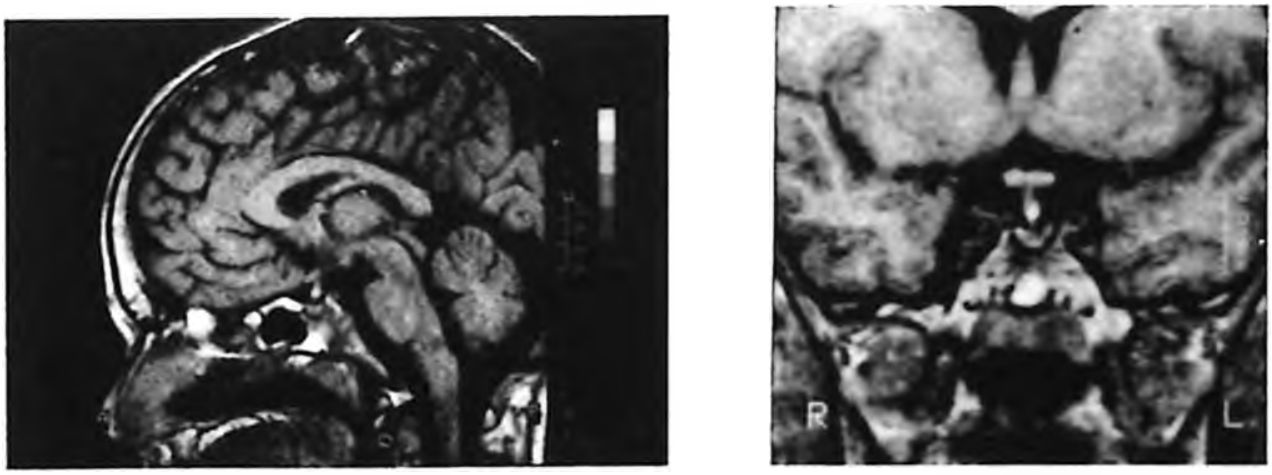


Fig. 2: 14-year-old male. Thickness of the pituitary was less than one mm. The stalk was very thin. Bright spot was located at the median eminence just below hypothalamus (arrow).



(a) (b)

Fig. 3: 13-year-old male. a) Sagittal. b) Coronal. Sella turcica was small and shallow in sagittal image. Thick stalk with bright spot of neurohypophyseal hormones located at the middle of the stalk can be seen in both planes.

In one patient, a hypothalamic mass was found and the bright spot of the posterior pituitary was not observed. In three other patients absent bright spot of the posterior pituitary was found, together with pituitary hypoplasia in one patient and with normal pituitary imaging in two. None of the eight patients with ectopic or absent bright signal of the posterior pituitary had polyuria or polydipsia. Diabetes insipidus was excluded in these patients by water deprivation test results.

Discussion

The most prominent reported MRI finding in IGHD is hypoplasia of the anterior pituitary gland without neuroradiological abnormalities[10, 11]. A small anterior lobe of the pituitary was seen in 60 percent of our cases. The cause of pituitary hypoplasia in growth hormone deficiency is not known. Huot et al.[12] hypothesized that since growth hormone secreting cells are the most abundant cell population in the pituitary gland, reduced pituitary volume can be an expected finding in GHD. However, in many studies no correlation was found between the pituitary size and the hormonal status[1, 13].

High incidence of breech and foot delivery has been reported in patients presenting with pituitary hypoplasia, EPP and stalk transection[1, 4, 14]. Traumatic transection of the stalk results in a newly formed small ectopic posterior lobe at the proximal stump of the transected stalk in both experimental animals and in patients[1-4]. However, the traumatic hypothesis cannot explain the findings in the relatively high percentage of patients with normal delivery[2, 3, 10]. For sample, in our study traumatic delivery history was found in 10 percent of all patients whereas 60 percent had pituitary hypoplasia. Another hypothesis is reduced hypothalamic stimulation or a diminished blood supply consequent to the absence of the hypothalamic and hypophyseal portal system. The association of a transected pituitary stalk with a hypoplastic pituitary gland supported this hypothesis. However, in this study and in others many patients had pituitary hypoplasia without stalk abnormalities. Marwaha et al.[10] reported a thin pituitary stalk with normal-sized pituitary in two patients and suggested that the size of the stalk does not indicate the height of the pituitary. Recently Maghnie et al.[15] showed a collateral arterial system which is easily recognized after gadopentetate dimeglumine (Gd-DTPA) administration both in IGHD or multiple pituitary hormone deficiency (MPHD). Therefore, decreased pituitary perfusion and ischemia are unlikely to cause pituitary dysfunction. In recent studies the association of GHD with congenital facial and central nervous system abnormalities suggested congenital dysembryogenetic anomaly is responsible for the abnormal development of the pituitary gland and stalk[2, 3, 6, 11, 16]. In one of our patients, midstalk localization of the posterior pituitary supported the possibility of defective neuronal migration during embryogenesis as a cause of EPP. In addition, familial occurrence of pituitary hypoplasia suggested a genetic origin.

Ultmann et al.[17] showed that nonvisibility of a stalk was associated with complete lack of anterior pituitary function, while visibility of the stalk was associated with preservation of some anterior pituitary function. In this study, we demonstrated the continuity of the stalk in all cases with IGHD.

A high percentage of normal magnetic resonance images was found in subjects with IGHD, suggesting purely functional damage[18]. Nonvisibility of the posterior lobe in four patients without diabetes insipidus was possibly related to the normal variation of the intensity of the bright signal, as reported previously in some healthy subjects[19, 20].

In conclusion, MR imaging demonstrated a high incidence of morpho-structural abnormalities of the hypothalamic-pituitary area in patients with IGHD. The lack of a significant increase in the frequency of traumatic or hypoxic deliveries in the children with these abnormalities suggested a developmental defect, which in some cases can have a genetic origin.

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