

MR Imaging in Idiopathic Growth Hormone Deficiency

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BACKGROUND AND PURPOSE: MR imaging findings of one or more of the following has been suggested to be a sensitive and specific indicator of hypopituitarism: small anterior pituitary gland, attenuated or absent pituitary stalk, and ectopic posterior pituitary. We hypothesized that these MR findings would be common in our group of patients with idiopathic isolated growth hormone deficiency (GHD) or multiple pituitary hormone deficiencies (MPHD) and would be a good indicator of the severity of the hypopituitarism.

METHODS: MR images were obtained for 35 patients with idiopathic GHD (20 with isolated GHD and 15 with MPHD; age range, 2 to 17 years) and analyzed to define one or more of the following triad of abnormalities: 1) small/absent anterior pituitary, 2) truncated/absent pituitary stalk, and 3) ectopic posterior pituitary, as well as for any other associated anomalies. The findings were correlated with the clinical and biochemical presentation.

RESULTS: Pituitary abnormalities were common in both groups (80% with isolated GHD, 93% with MPHD). We found a high frequency of midline CNS malformations, including optic nerve hypoplasia (9%), Chiari type I malformations (20%), and medial deviation of the carotid arteries (37%). Breech delivery, neonatal hypoglycemia, jaundice, micropenis, or single central incisor occurred equally with both isolated GHD and MPHD. In patients whose peak growth hormone level was less than 3 $\mu\text{g/L}$ ($n = 19$), 90% had the MR triad, compared with 39% of those with growth hormone levels 3 $\mu\text{g/L}$ or greater or less than 8 $\mu\text{g/L}$ ($n = 13$) ($P < .01$). Almost all (92%) of those with ectopic posterior pituitary had anterior pituitary heights less than -2 SD for age.

CONCLUSION: MR abnormalities were common in children with both isolated GHD and MPHD and were closely associated with peak growth hormone levels less than 3 $\mu\text{g/L}$. The presence of other CNS and clinical findings (eg, single central incisor and micropenis) supports the theory of an embryologic defect as the cause of the pituitary abnormalities.

Growth hormone deficiency (GHD) is a common endocrinologic cause of short stature. The rate of occurrence has been estimated at one per 4000 persons (1). It may be idiopathic or associated with organic causes, such as tumor, surgery, or irradiation of the sellar area. Most cases of idiopathic GHD are sporadic, although several familial forms have been described (2).

Idiopathic GHD may occur in isolation or in association with multiple anterior pituitary hormone de-

ficiencies. Clinical features associated with idiopathic GHD include breech position, neonatal or early-onset hypoglycemia, prolonged or severe neonatal jaundice, micropenis, and single central incisor tooth (3-5). Radiologic findings include midline CNS malformations, such as absent septum pellucidum and optic nerve hypoplasia (6, 7).

Normally, the anterior pituitary and stalk are well defined, and the posterior pituitary is easily identifiable as a hyperintense bright spot on unenhanced imaging studies. MR imaging can show characteristic anatomic pituitary abnormalities in patients with idiopathic GHD, including a small to absent anterior pituitary gland, a small or truncated stalk, and an ectopic posterior pituitary (EPP) hyperintensity located at the base of the hypothalamus or at the inferior end of the truncated pituitary stalk.

Studies from Italy, Japan, and the United States have demonstrated a higher frequency of MR abnormalities in children with multiple pituitary hormone deficiencies (MPHD) than in those with isolated

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GHD (7–12). Canada has stringent criteria for the diagnosis of GHD, confirmed by the presence of growth hormone levels not exceeding 8 $\mu\text{g/L}$ on one physiological test and two pharmacologic tests (13). In other reports of MR imaging in subjects with GHD, growth hormone levels of up to 10 to 15 $\mu\text{g/L}$ have been used as the cutoff, with more variability in the number and types of tests needed to confirm the diagnosis (6–8, 10, 11). Because of the strict diagnostic criteria for GHD in Canada, we hypothesized that MR abnormalities would be more common in our patients with both isolated GHD and MPH than previously described in the literature and that the presence of these abnormalities would correlate with the severity of the clinical and biochemical features.

Methods

In 1996, 76 patients with idiopathic GHD received treatment with growth hormone at the Hospital for Sick Children, Toronto. Thirty five (46%) of these patients (27 males and eight females), ranging in age from 5 days to 16 years at the time of diagnosis, underwent MR imaging between 1993 and 1996. These children represent the population treated since MR imaging became available at our institution.

The diagnosis of GHD was determined as follows: 1) short stature (height below the third percentile according to Tanner and Whitehouse standards); 2) growth velocity less than 5 cm per year beyond 3 years of age; 3) retarded skeletal development (ie, bone age more than 2 SD below chronological age, as assessed by the method of Greulich and Pyle); and 4) peak growth hormone response less than 8 $\mu\text{g/L}$ on one physiological test (exercise or hourly blood growth hormone sampling during sleep) and two pharmacologic stimulation tests (arginine, L-dopa-propranolol or clonidine). GHD in the neonate was diagnosed by the presence of suggestive clinical features (eg, hypoglycemia, prolonged jaundice, micropenis) in association with a growth hormone level less than 8 $\mu\text{g/L}$ with spontaneous hypoglycemia and/or in response to a pharmacologic stimulation test (arginine or glucagon). Serum growth hormone was measured using a double antibody radioimmunoassay (Nichols Institute Diagnostics, San Juan Capistrano, CA).

Other anterior pituitary hormones were assessed by initial screening of thyroid-stimulating hormone, free T_4 , and morning cortisol concentrations. Luteinizing hormone and follicle-stimulating hormone levels were measured in children in the pubertal age range. Further stimulation testing (ie, adrenocorticotropic hormone, luteinizing hormone-releasing hormone) was undertaken when indicated clinically or by initial screening. Twenty patients had isolated GHD and 15 patients had MPH.

MR studies were performed with a 1.5-T superconducting unit. Contiguous sagittal and coronal spin-echo T1-weighted images were obtained with parameters of 580/15/3 (TR/TE/excitations) and 3-mm-thick sections, and coronal T2-weighted images were obtained with parameters of 2800/90/1. Sedation, when required, was performed with IV Nembutal at a dose of 5 mg/kg. Patients were followed up with continuous oxygen saturation pulse oximetry, blood pressure, and heart rate monitoring during the imaging procedure. The age of the patients at the time of MR imaging ranged from 2 to 17 years.

The MR studies were evaluated for any CNS malformations, with specific attention to the location and size of the anterior and posterior pituitary. The neuroradiologist was masked to the number of anterior pituitary hormone deficits at the time of imaging interpretation. The stalk was described as normal, thin, interrupted, or absent. Measurements of the height of the

anterior pituitary were obtained using digital calipers at the greatest distance between the base and the top of the gland on the midsagittal T1-weighted image. These were compared with published normal values of anterior pituitary height for age using the same imaging techniques (14). Measurement of the maximum length of the pituitary was performed on the midsagittal section. The transverse diameter of the pituitary gland was determined as the distance between the medial aspects of the internal carotid arteries on the coronal section. Pituitary volume was calculated using the formula for the volume of an ellipsoid ($0.5 \times \text{length} \times \text{width} \times \text{height}$) and compared with published normal values using the same measurement and calculation technique (7).

Other midline malformations seen included Chiari I malformation, optic nerve hypoplasia, and medial deviation of the carotid arteries. The cerebellar tonsils were judged to be low-lying if they were displaced below the foramen magnum, with crowding or pointing of the tonsils and associated loss of surrounding CSF (Chiari I malformation). Medial deviation of the carotid arteries to a dimension less than the transverse diameter of the published normal values of the pituitary gland indicated an abnormal course of the carotid arteries.

Statistical Analysis

Chi-square analysis was performed to compare the frequency of abnormal MR findings in patients with isolated GHD and MPH, and in those with peak growth hormone levels less than 3 $\mu\text{g/L}$ and with levels 3 $\mu\text{g/L}$ or greater or less than 8 $\mu\text{g/L}$. The level of 3 $\mu\text{g/L}$ was chosen because this provided the best discrimination level below which virtually all patients had the full triad of pituitary abnormalities revealed by MR imaging. An unpaired two-tailed *t*-test was used to compare pituitary size (height or volume) in patients with isolated GHD and MPH.

Results

Clinical Findings

Three patients (one with isolated GHD, two with MPH) were initially admitted and their cases diagnosed at a different Canadian hospital, and growth hormone peak levels were not available. Of 20 patients with isolated GHD (16 males, four females), 10 had peak growth hormone levels less than 3 $\mu\text{g/L}$, and nine had peak levels 3 $\mu\text{g/L}$ or greater on the three tests. Of 15 patients with MPH (11 males, four females), 14 had thyroid-stimulating hormone deficiency, eight had adrenocorticotropic hormone deficiency, and four had gonadotropin deficiency. On three tests, nine patients had a growth hormone peak level less than 3 $\mu\text{g/L}$ and four patients had a peak level of 3 $\mu\text{g/L}$ or greater.

Three patients, all with MPH, were born in breech position. The frequency of findings associated with hypopituitarism, including neonatal hypoglycemia, jaundice (defined as hyperbilirubinemia severe enough to require phototherapy), micropenis, and single central incisor, are presented in Table 1. No significant difference in the frequency of abnormalities was found between patients with isolated GHD and MPH. Additional clinical abnormalities included choanal stenosis ($n = 1$), left facial hypoplasia and absent left cochlea ($n = 1$), hypoplastic cochlea associated with sensorineural deafness ($n = 1$), mi-

TABLE 1: Clinical features in patients with isolated growth hormone deficiency and multiple pituitary hormone deficiency

	Isolated GHD (n = 20) (%)	MPHD (n = 15) (%)
Neonatal hypoglycemia	5 (25)	7 (47)
Jaundice	4 (20)	8 (53)
Micropenis	3/16* (19)	6/11* (55)
Single central incisor	2 (10)	0

Note.—GHD indicates growth hormone deficiency; MPHD, multiple pituitary hormone deficiency.

* In male patients.

crophthalmia (n = 2), polydactyly (n = 1), and osteogenesis imperfecta (n = 2).

Radiologic Findings

A spectrum of MR abnormalities was found (Fig 1). MR findings in the patients with isolated GHD and MPHD are presented in Table 2. No significant difference in the frequency of EPP was found between the groups. Five MR studies (14%) showed nothing abnormal, five (14%) showed small anterior pituitary and small/absent stalk with normally placed posterior pituitary, and 25 (72%) showed abnormal location of the posterior pituitary, with small anterior pituitary and stalk.

In addition, other CNS midline abnormalities, including optic nerve hypoplasia (n = 3) and Chiari I malformation (n = 7), were seen in both groups of

TABLE 2: Radiologic findings in patients with isolated growth hormone deficiency and multiple pituitary hormone deficiency

MR Findings	Isolated GHD (n = 20) (%)	MPHD (n = 15) (%)
Normal	4 (20)	1 (7)
Small AP, NPP	2 (10)	3 (20)
Small AP, EPP	14 (70)	11 (73)

Note.—GHD indicates growth hormone deficiency; MPHD, multiple pituitary hormone deficiency; NPP, normal posterior pituitary; EPP, ectopic posterior pituitary; AP, anterior pituitary.

patients (Table 3). Several patients (n = 13) had medial deviation of the carotid arteries, as viewed on the coronal section cut through the sella turcica area (Fig 2). These associated CNS midline abnormalities occurred only in patients with EPP.

The height of the anterior pituitary gland was less than -2 SD at all ages (with the exception of one patient) in those with ectopic posterior pituitary (Fig 3). The anterior pituitary height in patients with a normally located posterior pituitary showed greater variability. A trend toward normal anterior pituitary height was found in the pubertal age range in the group with a normal posterior pituitary.

The pituitary volume could be calculated in 31 patients (the remaining four patients, all with EPP, had at least one view in which the gland was too small to measure). In the group with EPP, the pituitary gland volume was significantly smaller than pub-

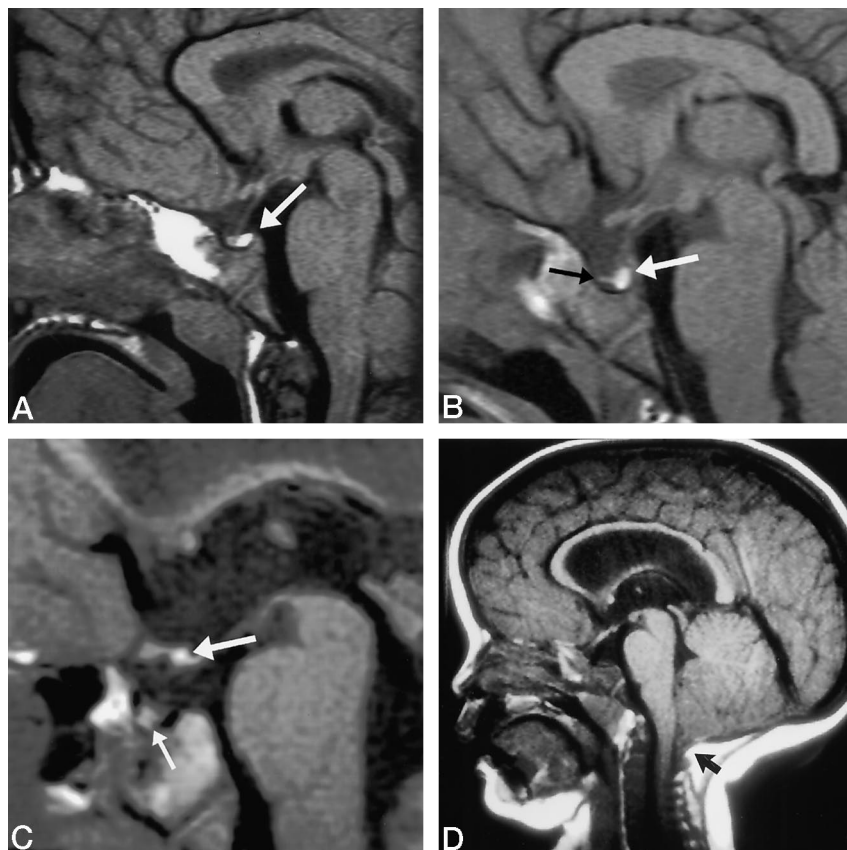


FIG 1. Midsagittal T1-weighted (600/20/3) MR imaging findings.

A, 5-year-old girl with idiopathic GHD (isolated GHD; growth hormone peak level, $5.6 \mu\text{g/L}$) and normal pituitary anatomy: image shows the sella turcica, normal size anterior pituitary and bright spot of the posterior pituitary (arrow), and a well-defined pituitary stalk.

B, 8-year-old boy with idiopathic GHD (MPHD; growth hormone peak level, $4 \mu\text{g/L}$): image shows a small anterior pituitary (black arrow) and the posterior pituitary in a normal position (white arrow).

C, 7-year-old boy with idiopathic GHD (isolated GHD; growth hormone peak level, $3.6 \mu\text{g/L}$): image shows small anterior pituitary (small arrow) and absent stalk and ectopic posterior pituitary at the base of the hypothalamus (large arrow). This patient also had asymptomatic hydrocephalus associated with a compression of the ectopic cerebellar tonsils in a small foramen magnum (not shown).

D, 18-month-old boy with idiopathic GHD (MPHD; growth hormone peak level, $1.2 \mu\text{g/L}$): image shows a small posterior fossa, cerebellar tonsils extending into and obstructing the foramen magnum (arrow), ventricular enlargement, a very small anterior pituitary and absent stalk, and an ectopic posterior pituitary. The posterior pituitary gland is not bright.

TABLE 3: Midline CNS malformations in patients with isolated growth hormone deficiency and multiple pituitary hormone deficiency

	Isolated GHD (n = 20) (%)	MPHD (n = 15) (%)
Optic nerve hypoplasia	2 (10)	1 (7)
Chiari I malformation	4 (20)	3 (20)
Medially deviated carotid artery	9 (45)	4 (27)

Note.—GHD indicates growth hormone deficiency; MPHD, multiple pituitary hormone deficiency.

lished normal values ($30 \pm 45 \text{ mm}^3$ vs $191 \pm 57 \text{ mm}^3$) ($P < .01$). No significant difference in volume was found between the patients with normal posterior pituitary and control subjects ($170 \pm 170 \text{ mm}^3$ vs $191 \pm 57 \text{ mm}^3$).

Clinical-Radiologic Correlates

Peak growth hormone levels and MR imaging results in patients with MPHD and isolated GHD are presented in Table 4. A higher frequency of MR abnormalities was found in those with peak growth hormone levels less than $3 \mu\text{g/L}$, irrespective of the number of anterior pituitary hormone deficits. In total, 17 (90%) of 19 patients with growth hormone peak levels less than $3 \mu\text{g/L}$ had EPP on MR images. Of those with growth hormone peak levels $3 \mu\text{g/L}$ or greater, five (38%) of 13 patients had EPP. By χ^2 test analysis, a significantly greater prevalence of EPP was determined in patients with growth hormone peak levels less than $3 \mu\text{g/L}$ compared with those whose growth hormone peak level was $3 \mu\text{g/L}$ or greater or less than $8 \mu\text{g/L}$ ($P < .01$).

Discussion

A spectrum of findings on MR images was obtained in patients with idiopathic GHD, ranging from normal to the full expression of small or absent anterior pituitary, thin or absent stalk, and EPP. The patho-

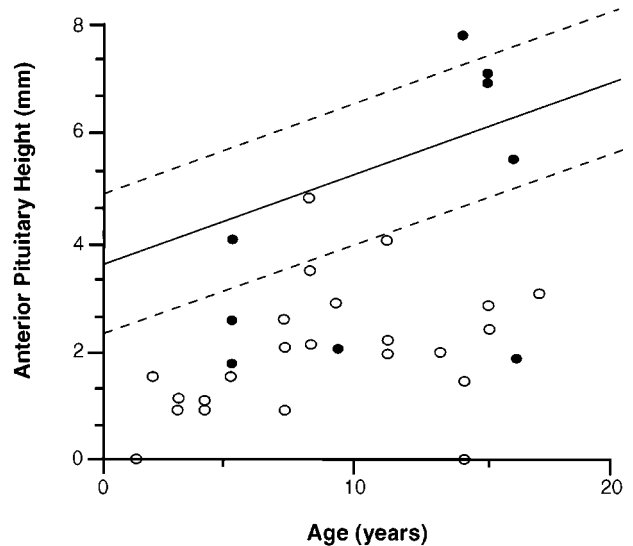


FIG 3. Height of anterior pituitary at different ages in children with GHD and normal posterior pituitary (solid circles) and EPP (open circles). Solid line represents mean and dotted lines ± 2 SD. The anterior pituitary height was frequently below the third percentile; this was more evident in children at a younger age and in those with EPP.

genesis of these abnormalities has been debated, and attempts have been made to correlate the severity of the structural abnormality with the clinical and endocrinologic picture.

In our study, results of MR imaging showed nothing abnormal in one child with MPHD (7%) and in four with isolated GHD (20%). Other reviews have reported that 40% to 90% of patients with isolated GHD have normal pituitary anatomy (7, 9–11, 15, 16). The reasons for these differences are uncertain but may relate in part to different sample sizes, a variation in the characteristics of the growth hormone assays performed, or in the criteria for diagnosing GHD. A general consensus does not exist as to the best diagnostic criteria to use when determining who will benefit from growth hormone therapy. In our population, a diagnosis is made when peak growth

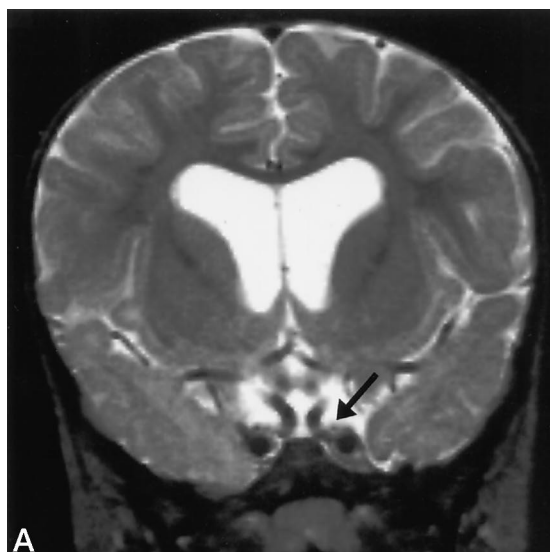


FIG 2. A, Coronal T2-weighted (2800/90/1) MR image in a 7-year-old boy (isolated GHD; growth hormone peak level, $3.6 \mu\text{g/L}$) shows medially deviated carotid arteries (arrow).

B, MR angiogram (3D time-of-flight) in an 18-month-old boy (MPHD; growth hormone peak level, $1.2 \mu\text{g/L}$) shows extreme medial deviation of the carotid arteries (arrow).

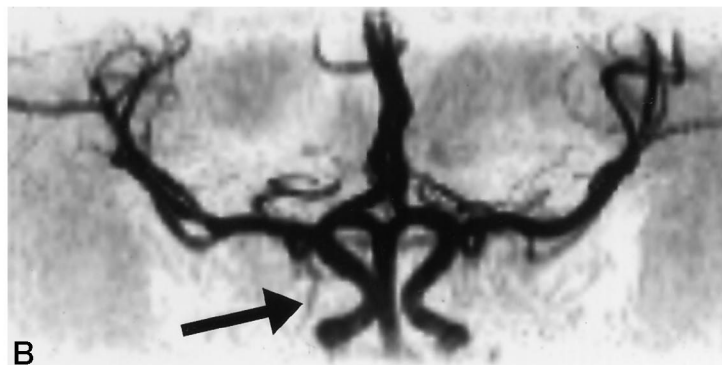


TABLE 4: Growth hormone peak level and MR findings in patients with isolated growth hormone deficiency and multiple pituitary hormone deficiency

MR Findings	Isolated GHD* (n = 10) (%)	MPHD* (n = 9) (%)	Isolated GHD† (n = 9) (%)	MPHD† (n = 4) (%)
Normal	0	1 (11)	4 (45)	0
Small AP, NPP	0	1 (11)	2 (22)	2 (50)
Small AP, EPP	10 (100)	7 (78)	3 (33)	2 (50)

Note.—GHD indicates growth hormone deficiency; MPH, multiple pituitary hormone deficiency; NPP, normal posterior pituitary; EPP, ectopic posterior pituitary; AP, anterior pituitary.

* Growth hormone peak level $<3 \mu\text{g/L}$.

† Growth hormone peak level $\geq 3 <8 \mu\text{g/L}$.

hormone concentration is less than $8 \mu\text{g/L}$ on three tests, one physiological and two pharmacologic. In most other countries, the criteria for diagnosing GHD are less stringent and require two tests with a peak level less than $10 \mu\text{g/L}$ (8, 11). Our series of patients with isolated GHD may represent either a more severely affected group or one that more effectively excludes patients who are not growth hormone deficient.

Unlike several other groups of investigators (7, 10, 11), we were unable to relate the severity of structural pituitary abnormalities with an increased number of hormone deficits. The rate of occurrence of EPP was 70% in children with either isolated GHD or MPH (Table 2). Other published series have shown a lower frequency of EPP associated with isolated GHD than was found in our population. Abrahams et al (10) reviewed 35 patients and found EPP in 13 (87%) of 15 with MPH, but only in two (10%) of 20 patients with isolated GHD. In 24 patients, Ochi et al (11) found that 67% of those with MPH had EPP, compared with 33% with isolated GHD. Truilzi et al (7), reviewing 101 patients, found EPP in 29 (85%) of 34 patients with MPH and in 30 (45%) of 67 with isolated GHD.

We did find an association between the severity of GHD and the likelihood of finding EPP on MR images, irrespective of the number of anterior pituitary hormone deficiencies. Patients with a growth hormone peak level less than $3 \mu\text{g/L}$ were more likely to have EPP than those whose peak level was $3 \mu\text{g/L}$ or greater. Seventeen (90%) of 19 patients with peak growth hormone levels less than $3 \mu\text{g/L}$ had EPP on MR images, whereas only five (38%) of 13 patients with peak growth hormone levels $3 \mu\text{g/L}$ or greater had this abnormality (Table 4). Our data concur with those of Vanelli et al (15), who studied 16 patients with GHD and noted that seven (78%) of nine patients with EPP had growth hormone peak levels less than $3 \mu\text{g/L}$, whereas none of the seven patients with peak growth hormone levels of 3 to $10 \mu\text{g/L}$ had EPP on MR images. Argyropoulou et al (16) reviewed MR imaging results of 46 patients with GHD and found a lower growth hormone peak response in those with interrupted pituitary stalk and EPP than in those with normal pituitary anatomy (3 ± 0.4 vs $5 \pm 0.5 \mu\text{g/L}$).

The pathogenesis of these characteristic MR abnormalities remains uncertain. Fujiwasa et al (17) suggested that trauma occurring at the time of deliv-

ery transects the pituitary stalk. This leads to a hypoplastic anterior pituitary and regeneration of the distal axons of the hypothalamus to form a superiorly located posterior pituitary. A higher than expected frequency of breech delivery (4, 8–10, 18) and adverse neonatal events (3, 5, 9) has been reported in children with idiopathic GHD, and proponents of this theory point to this as a mechanism for stalk ischemia or trauma. Fujita et al (19) reported seven patients with breech delivery, asphyxia, hypopituitarism, small anterior pituitary and stalk, and Chiari type I malformation, and postulated that this constellation of abnormalities might be explained by traction on the brain and spinal cord during delivery. EPP has also been described in a series of patients with sellar tumors, in whom compression or surgery in the area of the pituitary had been performed, suggesting that a functional posterior pituitary developed after the original insult (20). Yamanaka et al (21) reported two previously healthy patients who suffered head injury and subsequently developed anterior pituitary dysfunction associated with the MR picture described above.

In our series, breech presentation occurred in three patients with MPH (20%), all of whom had EPP on MR images. No case of breech delivery was found in the group with isolated GHD. Overall, the frequency of breech presentation was 8.5%, slightly higher than the general population frequency of 3% (22). Truilzi reported the frequency of breech presentation in 101 patients with idiopathic GHD to be 22%, with the majority of these patients having MPH and EPP (7). Other studies with smaller numbers of patients have found the frequency of breech presentation to be between 12% and 60%, with the majority of patients again having MPH and EPP (5, 8, 11, 15, 17, 18). We found no correlation of increased frequency of neonatal asphyxia in the group with EPP; however, it is difficult to quantitate the degree of adverse neonatal events, because they are diverse in nature and of varying severity. Indirect measures, such as cesarean section performed because of concerns of fetal distress or early neonatal hypoglycemia necessitating resuscitation, were found equally in patients with and without EPP. Other series have reported EPP in patients with GHD after normal vertex delivery (6, 12). An alternative theory proposes that a defect in embryogenesis results in the abnormalities seen on MR images and may account for some of the clinical

features, such as breech delivery (23). Other CNS malformations, such as anencephaly, have a high frequency of breech delivery, suggesting that an intact neuromuscular pathway is required for rotation to vertex position in utero (24). In support of this theory are the other associated structural CNS malformations, such as septo-optic dysplasia, which are found in a proportion of patients with GHD. In our group of patients, three had optic nerve hypoplasia and seven had Chiari type I malformations (Table 3). All patients with Chiari type I malformations were delivered in vertex position. Clearly, traction on the spinal cord during breech delivery (as proposed by Fujita et al [19]) could not account for this finding in our seven patients. The abnormal development of the cerebellar tonsils occurs during the fourth to eighth week of gestation, a critical period for formation of the hypothalamo-pituitary region, and this fact lends support to the theory of a defect in embryogenesis as the cause for the abnormalities seen on MR images. Chiari type I malformations have been identified in association with GHD in other studies, also associated with vertex position at delivery (7, 8).

Medial deviation of the carotid arteries was found in a number of the MR images (Fig 2). This finding indicates a narrowing of the central skull base and has not been reported previously in patients with idiopathic GHD. This midline malformation should be added to those already identified in this condition (eg, absent septum pellucidum, optic nerve hypoplasia).

It is difficult to reconcile other clinical associations, such as micropenis and single central incisor, with an insult occurring perinatally. Finally, a familial form of growth hormone deficiency was found in one boy in this series who had EPP on MR images. His mother had received pituitary-derived growth hormone as a child. Results of MR imaging of the mother also showed EPP. This suggests that an embryologic defect is the cause of the structural abnormality in this family.

Recent insights into the developmental biology of the pituitary gland make the defect in pituitary development theory even more intriguing. Specific genes encode for homeodomain proteins, a superfamily of helix-turn-helix proteins that play important roles in cell fate specification during embryogenesis. Pit-1 is a pituitary specific homeodomain protein and has been found to function as a transcription factor in the differentiation of anterior pituitary somatotrophs and lactotrophs. It also plays a role in the control of thyroid-stimulating hormone expression (25–30). Case reports detailing subjects with Pit-1 mutations and growth hormone, prolactin, and thyroid-stimulating hormone deficiencies have also exhibited hypoplastic anterior pituitary at MR imaging (28, 29, 31). In addition, the mouse strains of the Pit-1 mutation show pituitary hypoplasia in conjunction with deficiencies of these three anterior pituitary hormones (32). It is highly probable that other, as yet undiscovered, homeodomain proteins play crucial roles in the initial formation of the hypothalamo-pituitary axis. Ongoing research in developmental biology may

prove that idiopathic GHD may be caused by specific problems in cell induction and differentiation that lead to the spectrum of abnormalities detected by MR imaging.

Conclusion

In our series of well-documented cases of GHD, the triad of MR findings is extremely common, more so than in other series in which less stringent criteria for diagnosis are used. In addition, patients with peak growth hormone secretion less than 3 $\mu\text{g/L}$ were far more likely to have an EPP on MR images. Finally, although some evidence suggests that trauma may play a role in the pathogenesis of certain cases of idiopathic GHD, mounting evidence supports a developmental abnormality as the cause in the majority of cases.

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