SHORT COMMUNICATION

Clinico-Radiological Correlation in Childhood Hypopituitarism

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Non-tumor etiology constitutes a major group of childhood hypopituitarism. Magnetic resonance imaging has enormously complimented hormonal assessment in these patients. We describe clinico-radiological correlates in thirty-one children (23 boys), aged 1-17 years with a peak GH (growth hormone) levels <7 ng/mL after pharmacological stimuli. Hypoplastic pituitary gland was the most frequent abnormality in children with isolated growth hormone deficiency (IGHD) as compared to stalk abnormalities in children with multiple pituitary hormone deficiencies. MRI tetrad (hypoplastic/absent pituitary, hypoplastic stalk, absent/ectopic posterior pituitary bright spot and empty sella) was more prevalent in IGHD. MRI abnormalities correlated with the severity of growth hormone deficiency.

Keywords: *Child, Growth hormone deficiency, Hypopituitarism, MRI, Pituitary hypoplasia.*

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Non-tumoral hypopituitarism is the second major cause of childhood hypopituitarism(1). Genetic defects are being more frequently identified in cases previously labeled as idiopathic growth hormone deficiency(2). Majority of children with non-tumoral hypopituitarism are diagnosed in early infancy because of history of breech delivery, hypoglycemia, prolonged neonatal jaundice, micro-penis, and other midline defects(3-5). The younger the child at the time of presentation, the more likely that the etiology is non-tumoral.

MRI findings are complementary to hormonal assessment in these patients and include the tetrad of hypoplastic/absent pituitary gland, truncated/absent pituitary stalk, absent/ectopic posterior pituitary bright spot (EPPBS) and empty sella(3-5). This study was planned to evaluate the pattern of radiological abnormalities in children with non-tumoral hypopituitarism and to correlate these with the number and severity of hormone deficiencies.

METHODS

Thirty-one consecutive patients (age <18 y) with GH (growth hormone) deficiency were evaluated. Only one child had a family history of GH deficiency. Growth hormone deficiency (GHD) was diagnosed on the basis of short stature (height below 3rd percentile)(6); height velocity less than 4 cm/year beyond 3 years of age; bone age <2 SD of chronological age(7) and peak growth hormone (GH) response <7ng/mL to two pharmacological stimuli (clonidine and insulin induced hypoglycemia) on different days. A value of <3 ng/mL was defined as severe GHD. Patients were assessed for other associated pituitary hormone deficiencies. Respective hormones deficiencies were adequately replaced before subjecting them to GH dynamics. In adolescent subjects, priming with conjugated equine estrogen was done. Two millimeter contiguous sagital and coronal T1 and T2 weighted MR images were obtained using 1.5 Tesla superconducting unit (Magnetom; V_{63} or SP_{63}, Siemens, Germany). The

images were evaluated for any central nervous system malformations with specific attention to the location and size of the anterior pituitary, its stalk and posterior pituitary bright spot by neuroradiologist. Radiological diagnosis of empty sella was a subjective one, with presence of invagination of CSF space into the sella. Hypoplastic pituitary gland was defined as crescentic glandular tissue seen at the floor of the sella, with maximum measurable height of <2 mm. The stalk was reported normal, absent or redundant(8).

Chi-square test was applied to compare proportions. Pearson correlation coefficient (*r*) was calculated. $P<0.05$ was considered statistically significant.

RESULTS

The mean (±SD) age of these children was 10.5 ± 4.2 y (range 1-17 y). Of 31 patients, 8 had isolated growth hormone deficiency (IGHD) (6 boys) and 7 of them had a peak GH response of <3 ng/mL. Of the remaining 23 patients with multiple pituitary hormone deficiency (MPHD) (17 boys), all had GH deficiency and 16 had peak GH response <3 ng/mL. TSH deficiency was observed in 15 subjects and ACTH deficiency in 10 subjects. Seventeen out of 19 adolescent patients had gonadotropin deficiency, 4 had low prolactin and 3 had ADH deficiency. In MPHD group (*n*=23), 14 had vertex and 7 had breech presentation and 2 required lower segment caesarian section, whereas in IGHD group 6 had vertex and 2 had breech presentation. The presenting manifestations included linear growth failure (100%), micropenis (25%), neonatal hypoglycemia (6%) and prolonged severe jaundice (6%). Midline defects were present in one patient.

MR imaging abnormalities are shown in ***Table* I**. Number of imaging abnormalities per patient were comparable in children with IGHD and MPHD groups (2.37 *vs* 2.69, $P=0.06$). ***Table* II** shows the correlation between MRI findings and the severity of GH deficiency. Number of abnormalities per patient was higher in group with GH levels <3 ng/mL (2.9 *vs*

TABLE I MRI ABNORMALITIES IN GROWTH HORMONE DEFICIENCY

MRI abnormality	*N* (%)	IGHD (*n*=8)	MPHD (*n*=23)	*P* value
Empty sella	21 (67.8)	4 (50)	17 (76)	0.45
Absent/hypoplastic anterior pituitary	22 (70.9)	7 (87.5)	15 (65.2)	008
Absent/redundant stalk	22 (71)	3 (37.5)	19 (82.5)	0.01
Posterior pituitary abnormalities	16 (54)	5 (63)	11 (47)	0.64

IGHD-Isolated growth hormone deficiency, MPHD-Multiple pituitary hormone.

TABLE II CORRELATION OF STRUCTURAL ABNORMALITIES ON MRI AND GH LEVELS

Parameters	IGHD (*n*=7) GH<3ng/mL	IGHD (*n*=1) GH ≥3ng/mL	MPHD (*n*=16) GH <3ng/mL	MPHD (*n*=7) GH ≥3ng/mL
Normal imaging	0	1	4	4
Empty sella	4	0	15	2
Absent/hypoplastic pituitary	7	0	12	3
Absent/redundant stalk	2	1	12	7
Absent PPBS	1	0	2	1
Ectopic PPBS	4	0	7	1

PPBS- Posterior pituitary bright spot.

WHAT THIS STUDY ADDS?

- MR imaging abnormalities correlated with presence of severe GH deficiency in children with congenital hypopituitarism.

1.8, *P*= 0.06) irrespective of number of hormone deficiencies. Absent/ectopic posterior pituitary bright spot (EPPBS), the hallmark of transection syndrome, strongly correlated with presence of hypoplastic pituitary (<2mm, *r*=0.54). Sixteen patients had complete MR tetrad, which was more prevalent in IGHD than in MPHD group (75% and 44%, *P* = 0.01), and it correlated with presence of severe GHD (*r*= 0.57, *P*=0.01). All children with breech presentation had structural abnormalities of the pituitary gland compared to those who had vertex (100% *vs* 60%, *P*=0.03) and it correlated with presence of severe GHD *(r*=0.54, *P*=0.04). Hypoplastic anterior pituitary and EPPBS were common in the breech group as compared to vertex (*P*= 0.01 and 0.03, respectively).

DISCUSSION

Though overall imaging abnormalities per patient were comparable in IGHD and MPHD group, complete MR tetrad was more prevalent in IGHD. These imaging abnormalities correlated with presence of severe GHD and breech presentation.

Structural pituitary abnormalities occur in approximately 50-70% of patients with congenital form of GHD(9-14). These abnormalities are more prevalent in patients with MPHD (90%) than in IGHD (20-50%)(14). Contrary to other studies, we observed almost similar prevalence of imaging abnormalities in IGHD and MPHD groups and this is possibly explained by more number of patients with severe GHD (<3 ng/mL) in IGHD group. It has been reported in the literature that patients with severe GHD invariably have structural abnormalities of the pituitary gland and if imaging is normal in them, a hormonal re-evaluation is recommended(15). Four patients in MPHD group with severe GHD had normal imaging and this observation was surprising. This can be explained by Pit-1 and Prop-1 transcription factor mutation in some of these patients, which may be associated with normal imaging(16).

Among the structural abnormalities, absent/ redundant stalk was more frequent in MPHD group as expected, which is in consonance with other studies(8,12,13). The posterior pituitary abnormalities and MR tetrad have been more frequently described in patients with MPHD (90%) than in IGHD (40-50%)(10). However, in our study, the prevalence of posterior pituitary abnormalities was comparable and MR tetrad was more frequent in IGHD group and it correlated with the presence of severe GHD. This is in contrast to the study by Marwaha, *et al*.(17), which could be explained by the fact that some patients with IGHD may manifest with new hormone deficiencies on follow up and may actually be harboring MPHD.

Association between mode of presentation at delivery and MR imaging abnormities is conflicting. The most common abnormality with breech presentation is EPPBS and mostly these patients have MPHD(18). In our study all patients with breech presentation had abnormal imaging and all but one of them had MPHD and severe GH deficiency. The most common imaging abnormality in our patients was absent/redundant stalk followed by hypoplastic pituitary and EPPBS.

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