Eur J Pediatr (1997) 156: 758–763

ENDOCRINOLOGY

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Magnetic resonance images of 91 children with different causes of short stature: pituitary size reflects growth hormone secretion

Received: 1 December 1996 and in revised form: 8 February 1997 / Accepted: 18 February 1997

Abstract In order to validate an association between pituitary size and severity of growth hormone deficiency (GHD) we evaluated the magnetic resonance images (MRI) of 107 children with different causes of short stature. Ninety-one MRIs were evaluable (64 male, 27 female; age: 9.1 ± 3.9 years). The levels of insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3), and tests of GH stimulation and spontaneous secretion, led to the following subgroups: severe isolated GHD (SIGHD) (GH < 7 ng/ml) (n = 21); partial, isolated GHD (GH 7–10 ng/ml) (n = 22); multiple pituitary hormone deficiency (MPHD) (n = 13); neurosecretory dysfunction (n = 10); non-classifiable diagnosis (NC) (n = 13); idiopathic short stature (n = 9); and intra-uterine growth retardation (n = 3). Pituitary height (PHT) was measured and hypoplasia was assumed when PHT was < -2 SDS. An ectopic posterior pituitary with missing stalk and a hypoplastic anterior pituitary was present in 12 (57%) SIGHD cases, 12 (92%) MPHD cases and 1 patient from the NC group. An isolated hypoplastic anterior pituitary was observed in 15%–33% of the other groups. PHT (mm; mean, SD) in MPHD (1.7 ± 0.5) was lower than in SIGHD (2.7 ± 1.0, $P < 0.05$), with PHT of both groups being lower than in all the other groups (3.8 ± 0.9, $P < 0.0001$). PHT SDS correlates with IGF-I SDS (r = 0.48, $P < 0.0001$), IGFBP-3 SDS (r = 0.46, $P < 0.0001$) and the highest peaks in tests of GH stimulation and GH spontaneous secretion (r = 0.36, $P < 0.0001$). In contrast to all the other groups, no correlation with age was observed in MPHD and SIGHD. Breech delivery was recorded in up to 26% of patients in all seven groups. Surprisingly, only 1 out of 23 patients with an ectopic posterior pituitary was born by breech delivery, suggesting that ectopia of the posterior lobe is not necessarily related to breech delivery.

Conclusion PHT is significantly correlated with GH secretion in several types of short stature. Patients with ectopic posterior pituitary, missing stalk and hypoplastic anterior pituitary either suffer from SIGHD or MPHD, and this anatomical defect is not necessarily related to breech delivery.

Key words Magnetic resonance imaging · Pituitary gland · Ectopia of the posterior pituitary · Growth hormone deficiency

Abbreviations *EMH* **E**ctopia of the posterior pituitary, **M**issing stalk and **H**ypoplasia of the anterior pituitary · *GH* growth hormone · *GHD* growth hormone deficiency · *ISS* idiopathic short stature · *IUGR* intra-uterine growth retardation · *MPHD* multiple pituitary hormone deficiency · *NC* not classifiable diagnosis · *NSD* neurosecretory dysfunction · *PHT* pituitary height · *PIGHD* partial, isolated growth hormone deficiency · *SDS* standard deviation score · *SIGHD* severe isolated growth hormone deficiency

Introduction

Since MRI enables good visualization of the hypothalamo-hypophyseal tract, it became possible, 10 years ago, to differentiate for the first time between the anterior and posterior pituitary regions on T1-weighted images [14, 16, 26]. This was followed by reports on the following characteristic anatomical features of children with growth hormone deficiency (GHD) [17–19]: ectopia of the posterior pituitary, observed in the hypothalamic

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region as a hyperintense signal on T1-weighted images; hypoplasia or interruption of the pituitary stalk and hypoplasia of the anterior pituitary gland. Several studies have shown that these features represent a pattern that is common to patients with congenital multiple pituitary hormone deficiency (MPHD) and can also be observed in some patients with severe congenital isolated GHD. Although the cause of "idiopathic" GHD is still unclear, a high incidence of breech deliveries among children with MPHD and severe GHD has been described [5]. There have been no reports to date on the correlation between pituitary size and the extent of GH deficiency in children with different forms of short stature.

Patients and methods

Our study dealt with 107 children with severe short stature who were treated with growth hormone (GH). The diagnostic process included routine MRI of the hypothalamo-hypophyseal region. The MRI investigations in a total of 91 patients (64 male, 27 female) qualified for an in-depth evaluation. In 28 children MRI was done before, and in 63 children after GH therapy was started. At the time of the MRI investigation the mean chronological age of the patients was 9.1 (2.0–19.3) years. Perinatal data were extracted from the hospital records, which were available in 78 cases.

Height of the patients was transformed into standard deviation scores (SDS) according to the following formula: SDS = (a−x):s, in which "a" is the value of the patient, "x" is the mean value of the standard for the corresponding age and "s" is the standard deviation of "x". Standards of Prader et al. were used [28]. Height at the start of therapy in all patients was ≤−2 SDS for chronological age.

Endocrine evaluation

Basal serum (before GH treatment) insulin-like growth factor-1 (IGF-I) and insulin-like growth factor binding protein-3 (IGFBP-3) levels were measured by radioimmunoassay (RIA) [8, 9, 29]. The data were transformed into SDS based on normative data [7]. Concentrations which were below −1.28 SDS, corresponding to the 10th percentile for chronological age, were considered to be subnormal. GH was measured by using an in-house polyclonal RIA and applying the WHO 55/808 standard. All patients underwent either two standard GH stimulatory tests (arginine, clonidine, insulin) or one standard test accompanied by the evaluation of spontaneously-secreted GH (8–12 h, discrete sampling every 30 min). In order to identify MPHD, further pituitary stimulation tests (GnRH, TRH, ACTH) were considered to be necessary.

Based on the hormonal constellation, patients were grouped as follows:

1. Severe isolated GHD (SIGHD): sub-normal levels of IGF-I and/or IGFBP-3, and GH peaks of ≤7 ng/ml in any test.
2. Partial, isolated GHD (PIGHD): sub-normal levels of IGF-1 and/or IGFBP-3 and GH peaks >7 and ≤10 ng/ml in any test.
3. MPHD: sub-normal levels of IGF-1 and/or IGFBP-3 with GH peaks of ≤7 ng/ml in any test, accompanied by other anterior pituitary deficits.
4. Neurosecretory dysfunction (NSD): sub-normal levels of IGF-1 and/or IGFBP-3 and GH peaks of >10 ng/ml in a standard test, accompanied by low spontaneous secretion (peak GH levels ≤10 ng/ml).
5. Idiopathic short stature (ISS): normal size at birth, sub-normal to normal range of IGF-1 and/or IGFBP-3, and GH levels of >10 ng/ml.
6. Intra-uterine growth retardation (IUGR): weight and length at birth ≤3rd percentile for gestational age [21], and no indications of abnormalities on the GH-IGF axis.
7. Not classifiable (NC): the findings of GH tests are contradictory and/or IGF-1/IGFBP-3 levels do not fulfill the criteria for inclusion in one of the other groups.

The characteristics pertaining to the first visit of patients and diagnostic procedures are listed in Table 1.

MRI evaluation

All of the 107 MRI scans of the hypothalamo-hypophyseal tract were carried out in private radiology consultancies, of which 60 were based on the following outline we prepared:

- sagittal and coronal T1-weighted spin echo images (TR 400–600 ms, TE 20–25 ms) with a slice thickness of 3 mm–4 mm;
- coronal T2-weighted spin echo or turbo spin echo images (TR 2000–5000 ms, TE 60–120 ms) with a slice thickness of 4 mm–6 mm. In most cases, axial T1- and T2-weighted images of the whole brain were also available.

Although a different procedure (e.g. gradient echo sequences, different slice thickness) was used in 31 patients, their data were included in our study if sagittal and coronal, non-enhanced T1-weighted images of the hypothalamo-hypophyseal tract were available. We excluded 16 cases for the following reasons: motion artefacts ($n = 3$), incomplete examination ($n = 6$), insufficient image quality due to low signal-to-noise ratio ($n = 5$) and inordinately large slice thickness ($n = 2$). Finally, a total of 91 MRI scans of the hypothalamo-hypophyseal tract were evaluable in our study, in which a magnetic field strength between 0.5 and 1.5 Tesla was used. In all patients, sagittal and coronal T1-weighted images with slice thicknesses between 2 mm–6 mm, and interslice gaps of 0 mm–1.8 mm could be evaluated.

The images were analysed by two experienced neuroradiologists (M.P., D.P.) who were not aware of the diagnosis. The visible cerebral as well as the anatomical structures of the hypothalamo-hypophyseal region and the size of the anterior pituitary were assessed. Anterior PHT was then measured, perpendicular to the sella turcica base, after magnification through an overhead projector using the scaling provided on the films (accuracy of measurement: 0.1 mm). In 6 cases, these measurements could not be done (i.e. pituitary image lacked exact demarcation ($n = 1$), absence of scale ($n = 2$), extremely concave pituitary gland ($n = 3$)).

Since PHT increases with age in normal children, our measurements are expressed in terms of SDS based on the normative data published by Argyropoulou et al. [2]. Pituitary hypoplasia was assumed when its height was < -2SDS.

Statistical analysis

Mean values and standard deviations have been used to express group data which were tested primarily for normal distribution. Comparisons between groups were done by Student's t test. The median and range were calculated in cases of non-normal distribution.

Results

The neuro-anatomical abnormalities that emerged from our findings were grouped as follows: (1) **E**ctopia of the posterior pituitary, **M**issing stalk and **H**ypoplasia of the anterior pituitary (EMH); (2) isolated hypoplasia of the adenohypophysis; (3) other abnormalities. The distribution according to diagnosis is listed in

Table 1 Patient data. Results of age, height SDS, IGF-SDS, IGFBP-3 SDS and PHT [mm; SDS] are given in mean ± SD. (*HAP* isolated hypoplasia of the anterior pituitary, *CBA* other congenital brain anomalies)

Diagnostic group	*n*	At the time of diagnosis					At the time of MRI			Pituitary anatomy [*n*]				Breech deliveries (% of recorded cases)	
		Age [years]	Height [SDS]	GH test peaks [a] [ng/ml]	IGF-I [SDS]	IGFBP-3 [SDS]	Age [years]	PHT [mm]	PHT [SDS]	Normal	EMH	HAP	CBA	All cases	EMH cases
MPHD	13	7.9 ± 5.9	−3.4 ± 2.0	2.5 (1.0–7.0)	−5.0 ± 2.1	−4.0 ± 1.5	10.1 ± 4.2	1.7 ± 0.5*-***	−4.5 ± 1.0***-***	0	12	0	5	0/13	0/12
SIGHD	21	5.0 ± 3.6	−3.8 ± 1.3	2.5 (1.0–6.9)	−3.8 ± 2.2	−3.3 ± 2.4	9.5 ± 3.8	2.7 ± 1.0***	−2.8 ± 1.5***	2	12	6	1	2/14 (14%)	1/10 (10%)
PIGHD	22	4.5 ± 2.1	−3.1 ± 0.8	8.4 (7.1–10.0)	−2.6 ± 1.2	−1.7 ± 1.3	7.3 ± 3.8	3.7 ± 0.8	−0.8 ± 1.1	15	0	5	2	5/19 (26%)	
NSD	10	6.2 ± 3.3	−2.9 ± 0.7	8.1 (5.5–9.7) [b] 18.5 (12.4–28.0) [c]	−3.3 ± 0.9	−1.8 ± 0.8	8.6 ± 2.9	3.8 ± 1.2	−1.1 ± 1.6	6	0	3	1	1/7 (14%)	
NC	13	3.8 ± 2.1	−3.6 ± 1.1	14.8 (5.1–55.4)	−2.8 ± 1.6	−1.5 ± 1.5	9.0 ± 2.4	3.9 ± 0.6	−0.9 ± 1.0	10	1	2	0	1/11 (9%)	0/1
ISS	9	6.6 ± 3.4	−3.1 ± 0.5	17.5 (12.1–57.5)	−2.5 ± 2.0	−0.7 ± 1.3	10.1 ± 2.3	3.8 ± 0.9	−1.1 ± 1.3	6	0	3	0	1/9 (11%)	
IUGR	3	7.4 ± 3.2	−3.2 ± 0.4	55.4 (14.1–79.0)	−1.8 ± 1.0	−1.7 ± 1.3	10.1 ± 2.1	4.5 ± 0.6	−0.2 ± 0.8	3	0	0	0	0/3	

[a] The maximum of all tests done in one patient was taken into account, results are given in median values with minimum and maximum levels
[b] GH peaks of GH spontaneous secretion [c] GH peaks of GH stimulation tests
*compared to SIGHD ($P < 0.05$); **compared to SIGHD ($P < 0.005$)
***compared to the mean values of the other groups ($P < 0.0001$)

Table 1. EMH was observed in 12/13 cases of MPHD, in 12/21 cases of SIGHD and in 1/13 cases of NC. In the group of patients with MPHD, we found 4 cases of EMH which were associated with other cerebral abnormalities. A complex anomaly of the hypothalamo-hypophyseal tract was observed in one case of MPHD, characterized by the protrusion of the hypophysis, optic chiasm as well as the third ventricle into the sphenoidal sinus. Cerebral anomalies were also observed in four patients belonging to the SIGHD, PIGHD and NSD groups (Table 1). There was one patient with septo-optic dysplasia in the SIGHD group with an absent posterior pituitary, which explains the diabetes insipidus he suffered from. An isolated hypoplastic adenohypophysis was noted in 6/21 cases of SIGHD, 5/22 cases of PIGHD, 3/10 cases of NSD, 2/13 cases of NC and 3/9 cases of ISS. The findings in the IUGR cases were normal (Fig. 1). Only 2 patients in the SIGHD group showed a normal anatomy of which one had a splice site mutation in the GH-1 gene [6].

The PHT (mm; mean ± SD) measured in the various diagnostic groups is listed in Table 1. Patients with MPHD proved to have a PHT (1.7 ± 0.5) that was lower than that in SIGHD patients (2.7 ± 1.0, $P < 0.05$), and the dimensions in both these groups were lower than the mean values representing the other groups (3.8 ± 0.9, $P < 0.0001$). The PHT SDS of MPHD patients (−4.5 ± 1.0) was lower than the score computed for SIGHD patients (−2.8 ± 1.5, $P < 0.005$), and SDS in both groups was lower than the mean SDS values of the other groups (−0.9 ± 1.2, $P < 0.0001$) (Fig. 1). Our findings show that the PHT SDS correlates not only with IGF-I SDS ($r = 0.48$, $P < 0.0001$), but also with IGFBP-3 SDS ($r = 0.46$, $P < 0.0001$) as well as with the peak values of the GH stimulation tests and spontaneous GH secretion ($r = 0.36$, $P < 0.0001$) (see Fig. 2). Our study provides evidence that PHT does not gain with age in MPHD and SIGHD patients, while a positive correlation of these variables was characteristic for the remaining groups ($r = 0.42$, $P < 0.001$).

The percentage of documented breech deliveries in the seven diagnostic groups exhibited a range spanning 0%–26% ($n = 78$). Our data revealed only 1 case of breech delivery among the 23 EMH patients, while none of the MPHD patients were born in the breech position (Table 1).

Discussion

Several published reports have described that in patients with MPHD, an ectopic neurohypophysis was observed concomitantly to a disconnected hypophyseal stalk and a hypoplastic adenohypophysis (termed EMH in our study) [1, 3, 10, 17, 19, 20, 23, 27, 31, 32]. The rate of occurrence reportedly ranged between 80% and 100% (Table 2). Our findings correspond with those of other published reports in that 12 out of 13 MPHD patients in our study exhibited EMH.

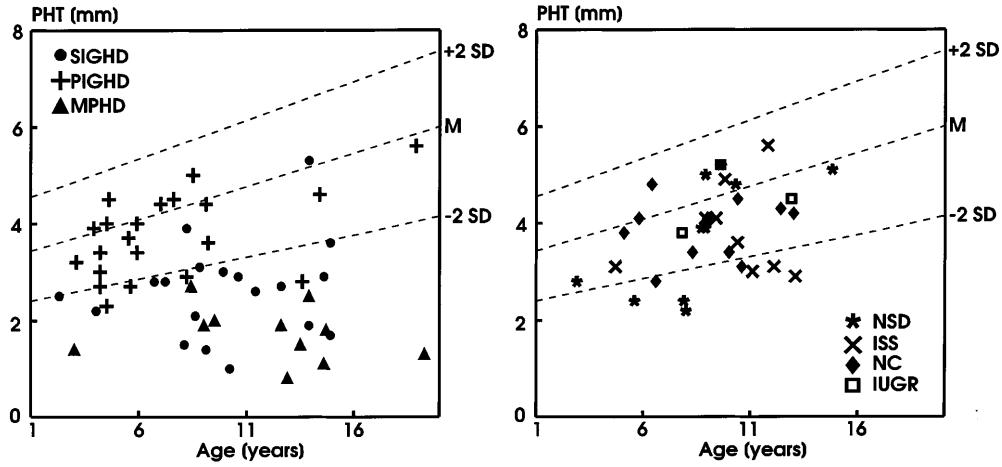

Fig. 1 PHT in patients with SIGHD, PIGHD, MPHD, NSD, ISS, NC and IUGR compared to normal values [2]

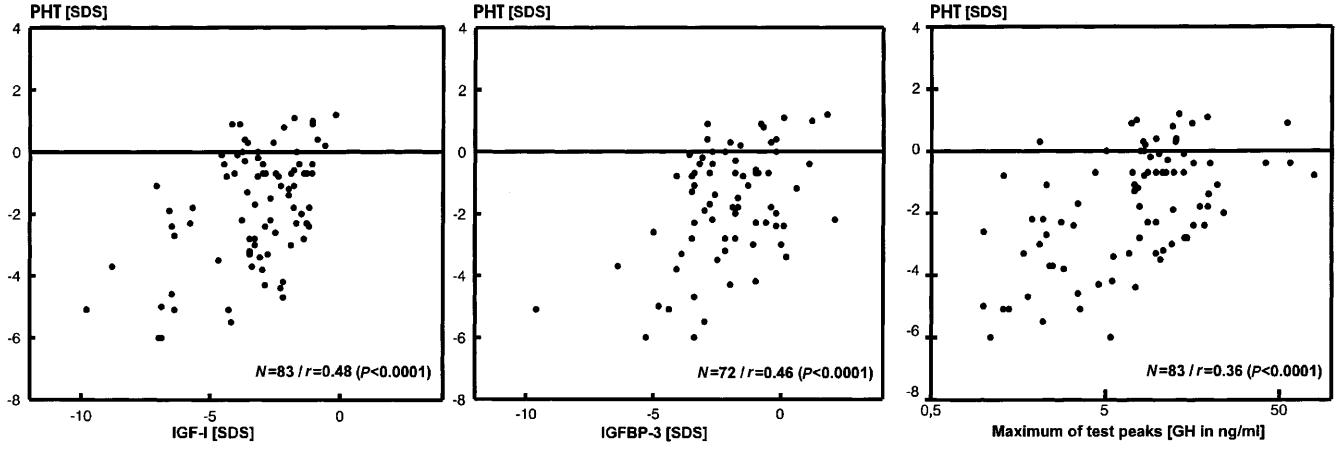

Fig. 2 Correlation between PHT SDS and basal IGF-1 SDS, IGFBP-3 SDS and the highest GH test peaks

In a limited series, Abrahams et al. [1] and Ochi et al. [27] demonstrated that EMH occurred more frequently among patients with severe IGHD than among those with partial IGHD. We encountered 12 instances of EMH among 21 SIGHD patients, a feature that was not discernible in any of the patients with PIGHD, NSD, ISS and IUGR, whereas EMH was, in fact, apparent in a single patient in the NC group. In other studies no signs of ectopic neurohypophysis were found in five patients with NSD [24], neither was this the case in 5 patients with ISS [32]. Only one case of ectopic neurohypophysis was detected by Brooks et al. [11] among a total of 1,500 MRI scans of patients in whom sella and parasellar disease was ruled out. The conclusions of the studies cited here clearly support the view that EMH is a significant predictor of severe GHD whether or not this disorder is accompanied by further pituitary hormone deficiencies.

Measuring PHT provides a single, useful mode for assessing pituitary size because the age-dependent progression in size appears mainly to be related to changes in gland height but not gland length or width [22]. Since the shape of the pituitary varies considerably among healthy children [4, 16, 25], it is not always appropriate to base an assessment of hypophyseal size on PHT. In three cases involving a markedly concave pituitary we, therefore, refrained from measuring its height ($n = 3$).

There is a paucity of data pertaining to the frequency of isolated hypoplastic adenohypophysis among patients with isolated GHD (Table 2). Some studies found evidence of this disorder in 17%–25% of their patients with severe isolated GHD and in 13%–19% of patients with partial, isolated GHD [1, 27]. In our study, 6 out of 21 patients with SIGHD (29%) and 5 out of 22 patients with PIGHD (23%) displayed this anatomical feature. Between 15% and 33% of the patients in the other groups showed the occurrence of a hypoplastic anterior lobe.

The association between the morphological features of the pituitary and its size and function has been a controversial matter. In the series conducted by Abrahams et al. [1] and Cacciari et al. [12] no link could be found between PHT and pituitary function. In children who were exposed to cranial radiation therapy, as part of cancer treatment (mainly acute lymphoblastic leukaemia), a significant correlation was demonstrated between PHT and the peak concentrations of GH during

Table 2 A comparison of results according to authors (*ND* no data, *ectopic pp* ectopic posterior pituitary)

Authors	Endocrine diagnosis	*n*	Normal anatomy	Ectopia of the posterior pituitary	Isolated hypoplastic anterior pituitary	Breech delivery of patients with ectopic pp
Kikuchi et al. [19]	SIGHD	5	0	5 (100%)	0	3 (60%)
	MPHD	4	0	4 (100%)		3 (75%)
Abrahams et al. [1]	PIGHD	16	12 (75%)	1 (6%)	3 (19%)	0
	SIGHD	4	2 (50%)	1 (25%)	1 (25%)	0
	MPHD	15	1 (7%)	13 (87%)	1 (7%)	0
Maghnie et al. [23]	IGHD	33	12	8 (67%)	13 (39%)	3 (38%)
	MPHD	12	0	12 (100%)	0	12 (100%)
Ochi et al. [27]	PIGHD	8	7 (88%)	0	1 (13%)	0
	SIGHD	6	1 (17%)	4 (67%)	1 (17%)	4 (100%)
	MPHD	10	0	8 (80%)	2 (20%)	6 (75%)
Argyropoulou et al. [3]	IGHD	26	16	1 (4%)	10 (38%)	ND
	MPHD	20	1	19 (95%)	0	
Vanelli et al. [32]	IGHD	11	4 (36%)	3 (27%)	3 (27%)	0
	MPHD	7	0	6 (86%)	0	2 (22%)
	ISS	5	4 (80%)	0	1 (25%)	0
Triulzi et al. [31]	IGHD	67	ND	30 (45%)	ND	1 (3%)
	MPHD	34		29 (85%)		18 (62%)
Nagel et al. [this paper]	PIGHD	22	17 (77%)	0	5 (23%)	0
	SIGHD	21	2 (10%)	12 (57%)	6 (29%)	1/10 (10%)
	MPHD	13	0	12 (92%)	0	0
	NSD	10	7 (70%)	0	3 (30%)	0
	ISS	9	6 (67%)	0	3 (33%)	0

tests of spontaneous secretion or arginine stimulation tests, as well as IGF-1 and IGFBP-3 [13, 30]. Our study revealed a significant correlation between PHT SDS and SDS of IGF-1 and IGFBP-3, as well as the highest peaks during the GH test. This is the first investigation which offers evidence for the correlation between PHT and GH secretion in children with variant forms of short stature. A high probability of low GH secretion can thus be assumed in patients with marked hypoplasia of the anterior lobe of the pituitary gland, i.e. those with a PHT of < -2 SDS. Thus, MRI of the hypothalamo-hypophyseal tract is a useful tool in resolving cases of indeterminate hormonal findings, such as in our NC group, and is an asset in scheduling GH therapy.

Our findings also revealed that the PHT of MPHD and SIGHD patients was significantly lower than in all the other groups. Interestingly, it was in these two groups that no positive correlation between chronological age and PHT could be established, whereas – analogous to normal children – this was a characteristic feature in the remaining groups. Thus, in patients with severe GHD, greater impairment in the hypothalamo-hypophyseal circulation or even on the level of hormone-generating cells themselves can be assumed, as compared to other patients.

One of the well-documented characteristics of children with MPHD or SIGHD is the fact that it frequently occurs among breech-delivered babies [5]. The reportedly high prevalence of EMH in children with MPHD and SIGHD raises the question of whether breech deliveries can be associated with EMH in the studied groups. Our present study reveals that only 1 out of 23 patients with EMH was born in this position, and a wide range of breech deliveries (3%–100%) has been reported in this group in the literature (Table 2). Our data lead us to conclude that EMH, in the majority of cases, is not the outcome of damages during breech delivery, but, instead, probably constitutes the underlying factor leading to the breech position. Since the fetal endocrine system is an important trigger in the induction of labour, it is possible that the hypothalamo-hypophyseal abnormalities described above lead to complications during birth, such as the breech position [15].

It can be postulated that either genetic mutations which pertain to the induction of the anterior and posterior lobes, or disturbances affecting migration lead to the hypothalamo-hypophyseal anomalies described above. This could account for the problem of transitional types of GHD which make the differentiation between transient, partial and severe GHD, as well as MPHD difficult. Our findings compare well with those of Triulzi et al. [31], who observed congenital cerebral anomalies in 12% of patients with an ectopic neurohypophysis, as the present study proved this to be the case in 15% of our patients with EMH.

MRI is an indispensable tool in diagnosing GHD. A prerequisite for assessing the functional role of pathomorphology is an exact endocrine diagnosis and high-quality MRI scans, which should routinely entail 3 mm sagittal and coronal sections on T1-weighted images, with a maximum of 10% interslice gaps. EMH patients either suffer from SIGHD or MPHD. PHT serves as an objective parameter, its limitations due to the variability of the pituitary shape should be taken into account. PHT is significantly correlated with the secretion of GH. There are indications that EMH is the result of an anatomical defect occurring during the early fetal stage and is not necessarily related to breech delivery.

Acknowledgement The authors would like to thank Priscilla Herrmann for her assistance in preparing this manuscript.

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