

# Development of additional pituitary hormone deficiencies in pediatric patients originally diagnosed with isolated growth hormone deficiency due to organic causes

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## Abstract

**Objective:** To determine characteristics of children initially diagnosed with isolated growth hormone deficiency (IGHD) of organic aetiology, who later developed multiple pituitary hormone deficiencies (MPHD).

**Design:** Data were analysed for 716 growth hormone-treated children with organic IGHD, who were growth hormone-naïve at baseline in the multinational, observational Genetics and Neuroendocrinology of Short Stature International Study.

**Methods:** Development of MPHD was ascertained from investigator-provided diagnoses, adverse events and concomitant medications. Analyses were performed for all patients and separately for those who developed MPHD within 4.5 years or had >3.5 years follow-up and continued to have IGHD (4-year cohort).

**Results:** MPHD developed in 71/716 (9.9%) children overall, and in 60/290 (20.7%) in the 4-year cohort. The most frequent additional deficiencies were thyroid-stimulating hormone (47 patients) and gonadotropins (23 patients). Compared with those who remained with IGHD, children who developed MPHD had more severe GHD at study entry, significantly lower baseline insulin-like growth factor1, peak stimulated growth hormone, and more frequent diagnosis of intracranial tumour or mutation of gene(s) controlling hypothalamic–pituitary development and/or function. Multivariate logistic regression analyses identified female gender, longer follow-up, higher baseline age and lower peak stimulated growth hormone as predictors of MPHD development.

**Conclusions:** MPHD is more likely to develop in patients with severe organic IGHD, especially those with history of intracranial tumour or mutation of gene(s) controlling hypothalamic–pituitary development and/or function. Older baseline age, female gender and longer follow-up duration were also associated with higher incidence of MPHD. Long-term monitoring of pituitary function is recommended, irrespective of the aetiology of GHD.

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## Introduction

Growth failure is a frequent cause of referral to a pediatric endocrinologist. After excluding causes not associated with the hypothalamic–pituitary axis (such as

chromosomal and genetic anomalies, renal failure, and nutritional/gastrointestinal disorders), anatomical (e.g. computed tomography scan and/or magnetic resonance

imaging (MRI)) and functional assessment of the pituitary gland is usually performed (1).

Causes of childhood growth hormone (GH) deficiency (GHD) include congenital lack of somatotrophs due to abnormal pituitary development and/or genetic defects, or acquired loss of somatotrophs due to causes such as hypothalamic–pituitary trauma, neoplastic disease, surgery, or irradiation. However, the majority of childhood cases of GHD are not due to organic causes but are diagnosed as idiopathic, indicating that the cause remains unknown (2). Irrespective of GHD aetiology, the majority of GH-deficient children initially have isolated GHD (IGHD), without deficiency in other pituitary hormones. Some patients, however, will later manifest other pituitary hormone deficiencies (3, 4), and certain deficiencies, especially adrenocorticotrophic hormone (ACTH) deficiency, may have serious or even fatal consequences (5). Thus, knowledge of the time course and frequency of developing multiple pituitary hormone deficiencies (MPHD), of specific deficiencies and combinations thereof, and of risk factors predicting MPHD, is important to inform patient care.

Previously we reported progression to MPHD for patients with an initial diagnosis of isolated idiopathic GHD (4) who were enrolled in the multinational Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS) observational programme. In the 4-year follow-up cohort (who had at least 3.5 years of follow-up without MPHD or who developed MPHD within 4.5 years), 5.5% developed MPHD, with thyroid-stimulating hormone (TSH) being the most frequent additional deficiency. In this report, also from GeNeSIS, we present information on development of MPHD in a large pediatric cohort with organic causes of GHD who were originally diagnosed with IGHD. As with previously reported patients with idiopathic GHD, we examined the time course and predictive factors for patients who progressed to MPHD while followed in GeNeSIS. These extensive observational data on frequency and temporal progression to specific MPHD deficits in IGHD children with organic causes should help guide physicians in implementing appropriate follow-up testing and therapy.

## Patients and methods

### Patients

Started in 1999, GeNeSIS was a prospective, open-label, multinational (30 countries, >700 study sites), observational research programme of pediatric patients

who received GH treatment to increase growth rate and adult height (Humatrope; Eli Lilly), with GH-untreated patients also followed for certain conditions (ClinicalTrials.gov, NCT01088412). The study collected information on clinical management and treatment outcome of pediatric patients with growth disorders, as documented by the endocrinologist during routine clinical practice. Institutional review board approval was obtained and all applicable regulatory requirements in the participating countries were followed for this post-marketing study, which was conducted according to the ethical principles of the Declaration of Helsinki. Written consent for data collection, electronic processing, and publication were obtained from parents or guardians of enrolled patients, in accordance with national requirements.

The GeNeSIS database includes data from GH-treated children with varied aetiologies of short stature, but for these analyses patients were included only if they had GHD due to organic causes and were GH treatment-naïve at study entry. Because GeNeSIS was an observational study, all information, including diagnosis of GHD, deficiency of other pituitary hormones, and results of MRI or other tests, was as reported by the investigator. Patients were evaluated at baseline and at approximately 6-month intervals according to investigator discretion. Patients reported to have non-GHD causes of growth failure or idiopathic GHD were excluded from the current analysis. Organic GHD included congenital causes such as abnormal hypothalamic–pituitary development (*e.g.* diagnosed by MRI) or genetic anomalies resulting in hypothalamic–pituitary hormone deficiencies and GHD acquired as a result of tumour, radiation or surgery. Both our previous publication, on development of MPHD in patients with idiopathic IGHD (4), and the current analyses for patients with organic GHD, were based on the same GeNeSIS dataset collected through September 2010.

### Methods

All data were collected on study case report forms (CRFs). At baseline, investigators were asked to indicate pituitary hormone status for ACTH, anti-diuretic hormone (ADH), luteinising hormone/follicle-stimulating hormone (LH/FSH), prolactin (PRL) and TSH as abnormally low, normal or abnormally high. When data on more than one stimulation test were available in the database at study start, the higher peak GH value was retained for analysis, providing a conservative assessment of severity of GHD for such patients. At each study visit, investigators

were asked to document occurrence of primary or secondary hypothyroidism and other adverse events, pubertal development, and treatment with concomitant medications, using specific CRFs. Conditions present before GH therapy were classified as pre-existing, whereas those that developed or worsened after starting GH therapy were classified as treatment-emergent adverse events, without implication of causality unless specified by the investigator as being related to GH treatment. Adverse events were categorised according to the Medical Dictionary for Regulatory Activities (version 11.0).

Ascertainment of individual pituitary hormone deficiencies, both pre-existing and emergent, was performed as described previously (4). Any patient with deficiency of ACTH, ADH, LH/FSH, PRL or TSH in addition to GHD was classified as having MPHD. Three categories of MPHD status were defined: MPHD=yes (where data indicated any additional deficiency), MPHD=no (where data indicated absence of such deficiencies) and MPHD=unknown (where data were unclear). Inclusion in this analysis required that patients had IGHD at baseline (MPHD=no) and a defined MPHD status at follow-up (MPHD=yes or no). Thus, the current analysis excluded patients who had MPHD or unclear pituitary status (MPHD=yes or unknown) at baseline, or unclear pituitary status (MPHD=unknown) at follow-up.

### Data and statistics

GH concentrations reported as mIU/L were converted to  $\mu\text{g/L}$  by dividing by 3 (1). Calculation of height standard deviation score (SDS) was based on US general population data (6) for all except Japanese patients, for whom calculation was based on Japanese standards (7). Bone age was determined according to Greulich and Pyle (8) or, if reported according to Tanner and Whitehouse, was converted to Greulich–Pyle as previously described (9). Bone age SDS was calculated as bone age minus chronological age divided by bone age SD from the tables of Greulich and Pyle.

The primary statistical comparison was between patients who continued to have IGHD and those who developed MPHD. Baseline between-group comparisons used ANOVA for continuous variables, with pituitary hormone status (IGHD vs MPHD) as the explanatory variable, and Fisher's exact test for categorical variables. Continuous variables are expressed as mean with s.d., except peak stimulated GH concentrations, which were compared after natural logarithmic (ln) transformation to achieve uniformity of variance, and are presented as

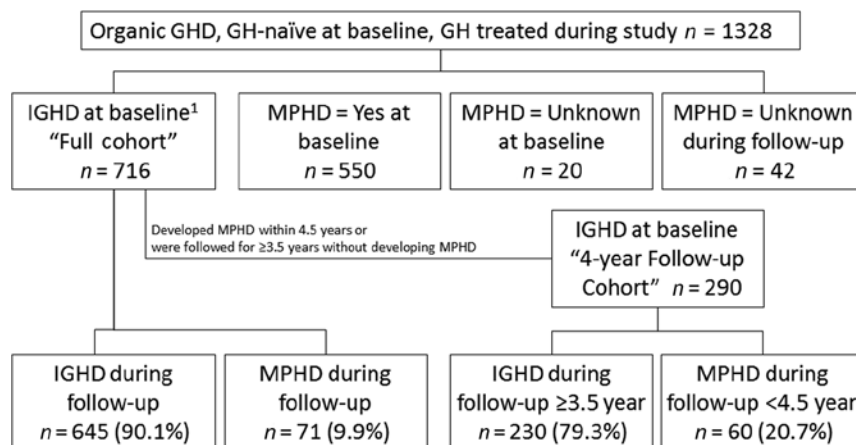
median with first and third quartiles (Q1 and Q3). For patients who developed MPHD, the time course for specific hormone deficiencies was analysed by the Kaplan–Meier method. To identify predictors of developing MPHD, logistic multiple regression analysis was performed, with different sets of explanatory variables; odds ratio (OR) and 95% confidence interval (CI) are presented. Two-sided  $P$  values < 0.05 were considered statistically significant. No adjustment for multiple testing was performed. All analyses were performed using SAS procedures (version 9.1, SAS Institute Inc., Cary, NC, USA).

## Results

### Characteristics of analysis populations

A total of 7500 patients with diagnosis of GHD (both idiopathic and organic) who were GH-treatment naïve at study entry and who received GH treatment during study had been enrolled in GeNeSIS at the time point of these analyses. Of these, initially 1328 patients (63% male, 37% female) were reported to have a diagnosis of organic GHD, and were reviewed for their pituitary hormone status (Fig. 1). Among these 1328 patients, 550 (41.4%) were determined to have MPHD at baseline; MPHD status was unknown for 20 (1.5%) patients at baseline and 42 (3.2%) during follow-up. The majority of patients were enrolled in the following countries: USA (26%), Germany (18%), France (12%), Canada (6%), Japan (6%) and Spain (6%); a full list of participant countries is provided in online [Supplementary table S1](#) (see section on [supplementary data](#) given at the end of this article).

The final study population, with IGHD at baseline and known MPHD status at follow-up, comprised 716 patients (full cohort). IGHD was reported as due to congenital causes for 510 patients (71%), and due to acquired causes for 204 patients (29%); congenital vs acquired status was unknown for two patients. Of the 510 patients with congenital GHD, major diagnostic subcategories were abnormal pituitary development (336 patients), other central nervous system (CNS) malformations including congenital hydrocephalus (64 patients), clinical syndromes including Prader–Willi syndrome (67 patients), or genetic anomalies resulting in hypothalamic–pituitary hormone deficiencies (33 patients). Of the 204 patients with acquired GHD, 151 patients were reported with history of intracranial tumour and/or cranial irradiation. Further detail on numbers of specific aetiologies of GHD is provided in [Supplementary Table S2](#).



**Figure 1**

Study disposition showing numbers of pediatric patients identified as having organic isolated GH deficiency (IGHD) and who developed multiple pituitary hormone deficiencies (MPHD) during follow-up while receiving GH treatment. The full cohort included all patients who were considered to have IGHD at entry to the study; the 4-year follow-up cohort included patients considered to have IGHD at entry and who either developed MPHD within 4.5 years of follow-up or continued to have IGHD and had at least 3.5 years of follow-up in the study. <sup>1</sup>Patients who had IGHD at baseline and known MPHD status during follow-up.

In the 716 patients of the full cohort with mean  $\pm$  s.d. follow-up of  $3.3 \pm 2.9$  years, 71 (9.9%) developed MPHD during follow-up, while 645 (90.1%) continued to have IGHD (Fig. 1 and Table 1, full cohort). Age at diagnosis and start of GH therapy did not differ between patients who developed MPHD and those who continued to have IGHD. Patients who developed MPHD had significantly shorter height SDS ( $P=0.043$ ), and had significantly greater height deficit in relation to target height ( $P<0.001$ ) at start of GH treatment. Baseline insulin-like growth factor I (IGF-I) SDS and peak stimulated GH were significantly lower in patients who developed MPHD ( $P<0.001$ ). However, five patients who developed MPHD had reported peak GH  $>10 \mu\text{g/L}$  (four with acquired GHD due to hepatoblastoma, medulloblastoma, neuroblastoma and CNS infection, respectively, and one with congenital GHD due to ectopic posterior pituitary). Patients who developed MPHD had significantly greater first-year height velocity on GH treatment,  $P<0.001$ ). Mean  $\pm$  s.d. gestational duration did not differ significantly (MPHD  $39.5 \pm 2.1$  weeks and IGHD  $38.9 \pm 2.5$  weeks,  $P=0.083$ ), and length, weight and head circumference measures were similar (data not shown). Likewise, those who developed MPHD and those who continued to have IGHD did not differ in prevalence of complications during pregnancy, delivery or the neonatal period.

Mean  $\pm$  s.d. duration of follow-up was longer for the group who developed MPHD ( $6.2 \pm 3.3$  years) compared with those who continued to have IGHD ( $3.0 \pm 2.6$  years;

$P<0.001$ ). Therefore, to compare features of patients who did or did not develop MPHD over a similar observation period, a subgroup of patients (Fig. 1, 4-year follow-up cohort) was defined who developed MPHD within 4.5 years from baseline or were followed for  $\geq 3.5$  years without developing MPHD. Baseline characteristics of the 4-year follow-up cohort (290 patients (61% male, 38% female, one patient unreported gender)) were similar to those of the full cohort, other than younger age at diagnosis and GH initiation (Supplemental Table S3). As in the full cohort, IGHD aetiology was reported as congenital in 71% and acquired in 29% of patients.

The 4-year follow-up cohort included 60 (20.7%) patients who developed MPHD and 230 (79.3%) who continued to have IGHD. Average follow-up was  $5.5 \pm 2.8$  years for patients who developed MPHD and  $5.9 \pm 2.2$  years for those who continued to have IGHD (compared with  $6.2 \pm 3.3$  years and  $3.0 \pm 2.6$  years, respectively, for the full cohort). Age at GHD diagnosis and start of GH therapy were significantly greater in patients who developed MPHD vs those who continued to have IGHD, but bone age SDS did not differ significantly (Table 1, 4-year follow-up cohort). Baseline height SDS was similar between those who developed MPHD and those who continued to have IGHD, but IGF-I SDS and peak stimulated GH were lower, indicating more severe GHD in the patients who developed MPHD than in those who did not. Of 60 patients who developed MPHD, 7% had a reported peak stimulated GH concentration  $>10 \mu\text{g/L}$  vs 10% of those who continued

**Table 1** Characteristics of patients with isolated GH deficiency (IGHD) at baseline, divided according to those who developed multiple hormone deficiency (MPHD) at any time during study vs those who continued to have IGHD, for all patients (full cohort), and for patients with  $\geq 3.5$  years follow-up without developing MPHD (IGHD) or who developed MPHD in  $\leq 4.5$  years (4-year follow-up cohort). Values are mean  $\pm$  s.d. except for peak GH which shows median (Q1–Q3).

	N	MPHD	N	IGHD	P value
Full cohort					
<i>n</i>		71		65	
Gender, male/female (%)	71	51/49	644	66/34	0.008
Age at diagnosis of GHD (years)	70	7.7 $\pm$ 4.2	636	8.3 $\pm$ 4.3	0.290
Variables at start of GH therapy					
Age (year)	71	8.4 $\pm$ 4.2	644	9.0 $\pm$ 4.3	0.287
Bone age SDS	46	-2.3 $\pm$ 2.4	419	-1.9 $\pm$ 1.8	0.251
Height SDS	70	-2.9 $\pm$ 1.6	636	-2.6 $\pm$ 1.3	0.043
Height SDS – target height SDS	60	-3.0 $\pm$ 1.4	564	-2.3 $\pm$ 1.3	<0.001
BMI SDS	68	-0.2 $\pm$ 2.2	630	-0.5 $\pm$ 2.1	0.265
Peak GH ( $\mu$ g/L)	66	1.7 (0.7–4.0)	645	5.0 (2.7–7.9)	<0.001*
IGF-I SDS	21	-4.3 $\pm$ 2.0	219	-3.0 $\pm$ 2.3	0.014
Variables during GH therapy					
Initial GH dose (mg/kg/week)	69	0.19 $\pm$ 0.06	620	0.23 $\pm$ 0.07	<0.001
First year gain in height SDS	63	0.8 $\pm$ 0.7	508	0.7 $\pm$ 0.7	0.202
First year height velocity (cm/year)	63	9.2 $\pm$ 3.5	511	9.3 $\pm$ 3.4	0.754
First year height velocity SDS	62	4.0 $\pm$ 4.7	505	2.8 $\pm$ 2.7	0.002
Duration of follow-up (year)	71	6.2 $\pm$ 3.3	644	3.0 $\pm$ 2.6	<0.001
4-year follow-up cohort					
<i>n</i>		60		230	
Gender, male/female (%)	60	52/48	229	64/36	0.076
Age at diagnosis of GHD (year)	59	8.2 $\pm$ 4.4	227	6.8 $\pm$ 3.7	0.012
Variables at start of GH therapy					
Age at start of GH (years)	60	9.0 $\pm$ 4.3	230	7.4 $\pm$ 3.6	0.005
Bone age SDS	40	-2.0 $\pm$ 2.4	160	-2.1 $\pm$ 2.0	0.853
Height SDS	59	-2.8 $\pm$ 1.6	226	-2.7 $\pm$ 1.2	0.587
Height SDS – target height SDS	53	-2.9 $\pm$ 1.4	199	-2.5 $\pm$ 1.3	0.120
BMI SDS	58	-0.2 $\pm$ 2.1	223	-0.7 $\pm$ 2.0	0.083
Peak GH ( $\mu$ g/L)	56	1.6 (0.6–3.3)	214	4.9 (2.7–7.9)	<0.001*
IGF-I SDS	19	-4.4 $\pm$ 2.1	84	-2.9 $\pm$ 2.1	0.007
Variables during GH therapy					
Initial GH dose (mg/kg/week)	59	0.18 $\pm$ 0.06	221	0.22 $\pm$ 0.08	<0.001
First year gain in height SDS	54	0.8 $\pm$ 0.7	206	0.8 $\pm$ 0.7	0.739
First year height velocity (cm/year)	54	9.0 $\pm$ 3.9	208	9.6 $\pm$ 3.4	0.219
First year height velocity SDS	53	4.0 $\pm$ 5.0	206	2.9 $\pm$ 2.7	0.078
Duration of follow-up (year)	60	5.5 $\pm$ 2.8	230	5.9 $\pm$ 2.2	0.196

BMI, body mass index; GH, growth hormone; GHD, growth hormone deficiency; IGF 1, insulin-like growth factor 1; SDS, standard deviation score.

\*P value is from analysis of Ln-transformed data.

to have IGHD. It is important to note that report of a GHD diagnosis was as provided by the investigator and may have been independent of the results of stimulation tests reported in the study. There was no statistically significant difference in first-year height SDS gain or first-year height velocity SDS between patients who developed MPHD and those who continued to have IGHD.

### Clinical diagnoses associated with organic GHD

Of 71 patients who developed MPHD in the full cohort, 58% had a congenital aetiology vs 42% acquired. By

comparison, 73% had congenital aetiology vs 27% acquired for the 645 patients who continued to have IGHD. Similarly, of 60 patients who developed MPHD in the 4-year follow-up cohort, 55% had a congenital cause and 45% acquired vs 77 and 23%, respectively, for the 230 patients who continued to have IGHD.

Overall, MPHD developed more often in patients who were GH deficient due to acquired causes than in those with congenital causes ( $P < 0.01$ , Supplemental Table S2, both cohorts). For the 4-year follow-up cohort, MPHD developed in 33.8% of those with acquired GHD vs 15.7% of those with a congenital aetiology. However, the



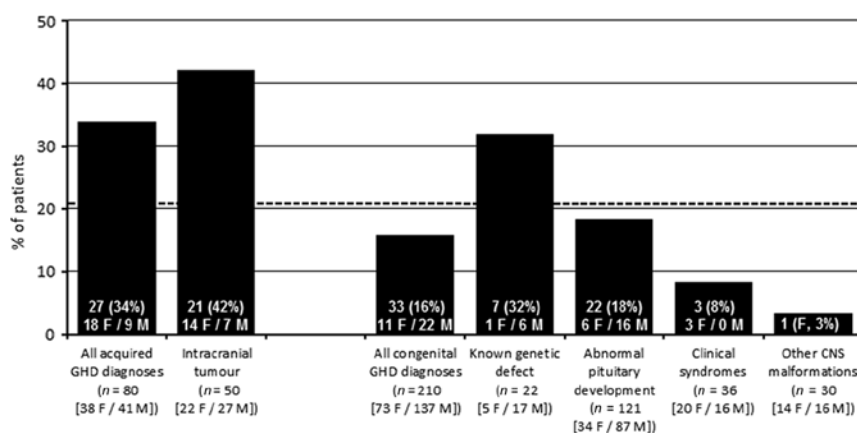
congenital subgroup with genetic anomalies resulting in hypothalamic–pituitary hormone deficiencies (11 *GH1*, four *GHRHR*, five *PROP1*, one *HESX1* and one *POU1F1*) also had a high rate of MPHD progression. Of these 22 patients, seven progressed to MPHD (32%) including four of five patients with *PROP1* mutations (80%), one patient with *HESX1* mutation and two of 11 patients with *GH1* mutation (18%), who developed TSH deficiency (4-year follow-up cohort). Among patients with intracranial tumours, 42.0% developed MPHD (Fig. 2). Among patients with congenital aetiologies of GHD, progression to MPHD occurred more commonly in those with identified genetic anomalies involving hypothalamic–pituitary genes and in those with septo-optic dysplasia (SOD), than in those with other anomalies of the pituitary gland, CNS development or clinical syndromes (Supplemental Table S2).

The proportion of girls who progressed to MPHD was greater than that for boys (35 of 251 (14%) girls vs 36 of 464 (8%) boys in the full cohort, and 29 of 111 (26%) vs 31 of 178 (17%) in the 4-year follow-up cohort). Upon review of impact of clinical diagnosis by gender the higher proportion of girls progressing to MPHD appeared to be most prominent in patients with acquired GHD (Fig. 2), with additional pituitary hormone deficiencies reported for 18 of 38 (47%) girls vs 9/41 (22%) boys in the 4-year follow-up cohort. Furthermore 14/22 (64%) girls vs 7/27 (26%) boys with acquired GHD due to intracranial tumour developed MPHD.

### Additional pituitary hormone deficiencies

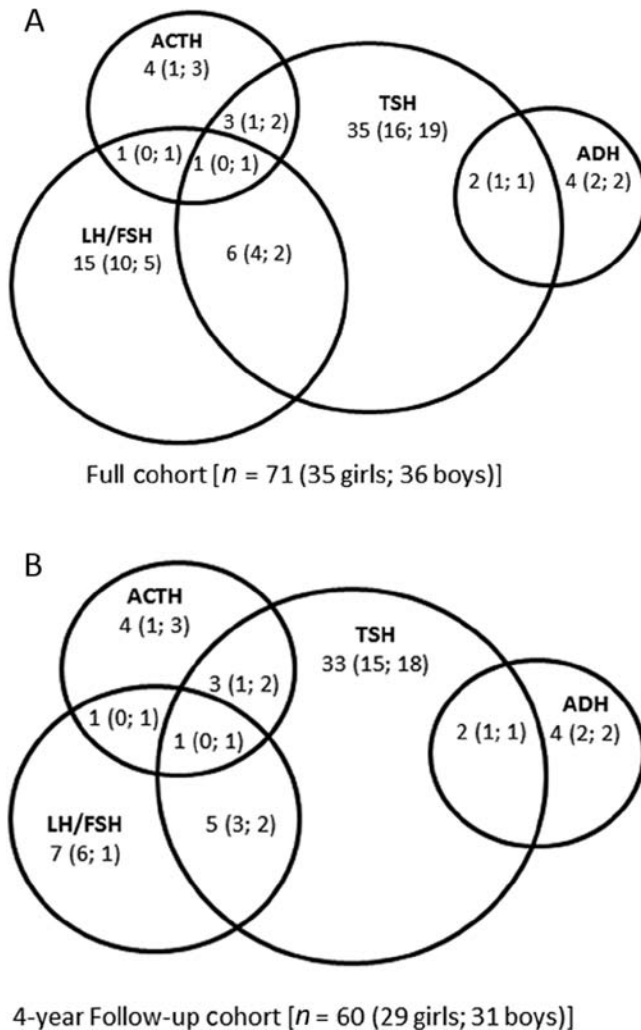
Of the 71 patients who developed MPHD at any time during follow-up (Fig. 3A, full cohort), 58 developed 1 additional deficiency, 12 developed two additional deficiencies and one developed three further deficiencies. The frequency of additional pituitary hormone deficiencies, in descending order, was TSH (47 patients, 66%), gonadotropin (23 patients, 32%), ACTH (nine patients, 13%) and ADH (six patients, 8%). No patient had PRL deficiency reported. In the 4-year follow-up cohort (Fig. 3B), additional pituitary hormone deficiencies developed in 60 patients, of whom 48 (80.0%) had one additional deficiency, 11 (18%) had two additional deficiencies and one patient had three additional deficiencies. The frequency of additional hormone deficiencies was TSH (44 patients (73%)); gonadotropin (14 patients (23%), six with concomitant TSH deficiency); ACTH (nine patients (15%), four with concomitant TSH deficiency); and ADH (six patients (10%), two with concomitant TSH deficiency). Of the patients who developed MPHD, more girls developed gonadotropin deficiency during study than boys, particularly when gonadotropin deficiency presented as the sole additional pituitary hormone deficiency (Fig. 3A and B).

The estimated temporal pattern of development of each additional pituitary hormone deficiency and any additional pituitary hormone deficiency (MPHD), by Kaplan–Meier analysis, is shown in Fig. 4. The median period (Quartile 1, Quartile 3) from diagnosis of GHD to



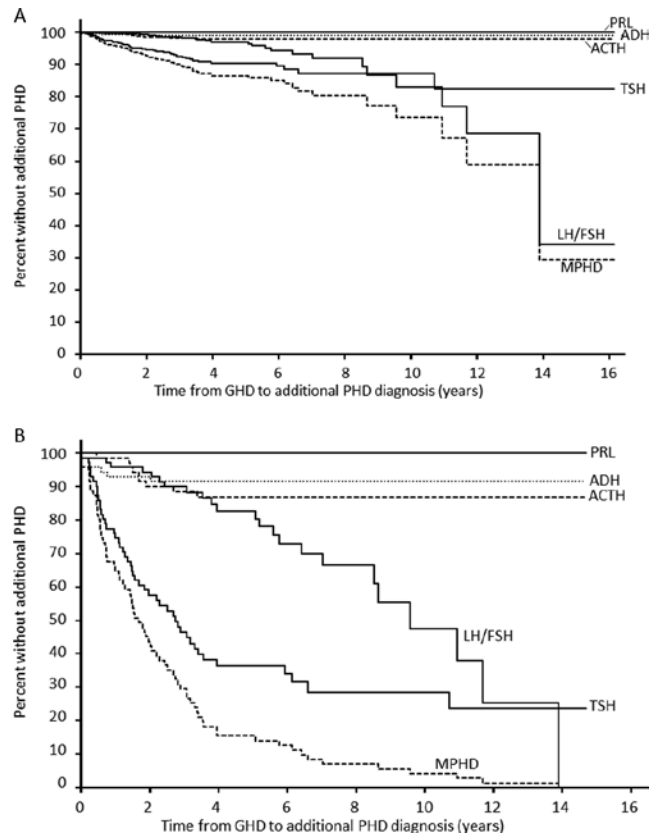
**Figure 2**

Proportion of patients who developed multiple pituitary hormone deficiencies (MPHD) in the 4-year follow-up cohort by selected aetiology of GHD. Intracranial tumour is a subcategory of all acquired GHD diagnoses. Known genetic defect, abnormal pituitary development, clinical syndromes and other CNS malformations are the constituent subcategories of all congenital GHD diagnoses; subcategory unknown for one patient with congenital GHD. The horizontal dashed line represents the proportion of patients progressing to MPHD for all GHD diagnoses at 20.7%. CNS, central nervous system; F, female; GHD, growth hormone deficiency; M, male.

**Figure 3**

Numbers of patients who entered the study with organic isolated GH deficiency (IGHD) and subsequently developed the specified additional pituitary hormone deficiencies at (A) any time in the study (full cohort) or (B) within 4.5 years of entry (4-year follow-up cohort). Note numbers in parentheses are girls first and boys second. Full cohort: ACTH status was unknown for one patient with known TSH deficiency, one with ADH plus TSH deficiency and two with LH/FSH plus TSH deficiency. TSH status was unknown for one patient with ADH deficiency, one with LH/FSH deficiency, two with ACTH deficiency and one with ACTH plus LH/FSH deficiency. 4-year follow-up cohort: Same as the full cohort except TSH status was unknown for four patients with LH/FSH deficiency.

diagnosis of additional deficiency in the full cohort was 1.0 (0.9, 2.3) years for ADH; 1.9 (1.7, 2.8) years for ACTH; 2.4 (1.0, 3.6) years for TSH; and 6.0 (2.5, 7.3) years for LH/FSH. Median age at diagnosis of each additional pituitary

**Figure 4**

Kaplan–Meier analysis for pediatric patients who initially had isolated GH deficiency and developed multiple pituitary hormone deficiencies (MPHD) in the full cohort (Panel A, all patients; Panel B, those who developed MPHD), showing time of development of specified additional pituitary hormone deficiencies and of any pituitary hormone deficiency (MPHD). PRL, prolactin

hormone deficiency was 6.5 (3.1, 9.8) years for ADH; 10.5 (6.9, 13.2) years for TSH; 10.8 (8.9, 12.7) years for ACTH; and 14.8 (13.0, 16.0) years for LH/FSH.

### Factors predicting MPHD development

Multivariate logistic regression analysis, for the 71 patients who developed MPHD and 645 patients who continued to have IGHD (full cohort), indicated the following significant factors for MPHD development: female gender (OR: 2.56, 95% CI: 1.41–4.66); years of follow-up (OR: 1.50, 95% CI: 1.33–1.68); baseline age in years (OR: 1.12, 1.02–1.23); and Ln-transformed peak stimulated GH concentration (OR: 0.52, 0.41–0.66). The ratio of bone age to chronological age, baseline height SDS, and baseline height SDS minus target height SDS had no statistically significant effect.

Except for length of follow-up, the same factors significant for the total study population were significant for the 4-year follow-up cohort (data not shown).

## Discussion

The potential for patients with an initial diagnosis of organic IGHD to develop additional pituitary hormone deficiencies may have far-reaching clinical consequences. In the present study, drawn from routine clinical practice from many countries, we examined the frequency and temporal progression to specific MPHD deficits with the intent to help guide physicians in implementing appropriate follow-up testing and therapy. In this large cohort of children originally diagnosed as having organic IGHD, 9.9% developed MPHD in the full cohort and 20.7% developed MPHD in the 4-year follow-up cohort. By contrast, in our previous analysis of children originally diagnosed as having idiopathic IGHD, progression to MPHD was 2.0% in the full cohort and 5.5% in the 4-year follow-up cohort (4). Even after 4.5 years of observation most patients with organic IGHD had not (yet) developed MPHD, a somewhat unexpected finding given the congenital, genetic or neoplastic aetiology of their GHD. Because development of additional pituitary hormone deficiencies may be delayed, monitoring for additional pituitary deficiencies should continue for an extended period, perhaps indefinitely.

Assessment of the impact of the primary diagnosis that lead to GHD on the progression to MPHD indicated key differences between diagnoses. For instance, more than twice as many patients with history of intracranial tumour in the 4-year follow-up cohort progressed to MPHD, than those in the overall population or those with congenital causes of GHD. Previous studies of children with intracranial tumours have shown a high incidence of progression to MPHD. In a cohort of 88 children treated with irradiation and chemotherapy for embryonal brain tumours, pituitary hormone deficiencies at 4 years after tumour diagnosis were present in 93% for GH, 23% for TSH and 38% for ACTH (10). In a population of 748 adult survivors of childhood cancers treated with cranial irradiation and observed for a mean of 27 years, the point prevalence estimates for pituitary hormone deficiencies were 47% for GHD, 11% for gonadotropins, 8% for TSH and 4% for ACTH (11). In the current study, patients with intracranial tumours had the highest overall rate of progression to MPHD compared to the other groupings of congenital or acquired GHD. The GH axis appears most vulnerable to radiation damage and GHD is usually the

first, and often the only, manifestation of neuroendocrine injury following cranial irradiation for intracranial tumour and leukaemia. However, deficiencies in other pituitary hormones often result, with frequency, combination and temporal pattern of deficiencies dependent to a certain degree on dose and timing of irradiation (5). Consistent data on dose and timing of irradiation is not available in the GeNeSIS database, so while the incidence and temporal pattern of additional pituitary hormone deficits is expected to be influenced by cranial irradiation, the impact cannot be directly assessed in our analyses.

As described in a previous analysis of the GeNeSIS database (12) and other studies, patients with hypothalamic–pituitary genetic defects (13, 14, 15, 16) or anatomical abnormalities of the hypothalamic–pituitary region (17, 18, 19) had more severe GHD and were more frequently diagnosed as MPHD. In our 4-year follow-up cohort seven of 22 patients with hypothalamic–pituitary genetic defects progressed to MPHD (32%), predominantly those with *PROPI* mutations, but also two patients with *GHI* mutation. Development of MPHD in patients with *GHI* mutation was not entirely unexpected as patients with IGHD and autosomal dominant heterozygous *GHI* mutations have been reported to develop additional pituitary hormone deficiencies (20). Patients who developed MPHD during GH therapy were shorter at baseline and had more severe GHD than those who continued to have IGHD, reflecting the high prevalence of patients with history of intracranial tumour and known genetic defects of pituitary development in the MPHD group.

Congenital abnormalities of pituitary development, particularly ectopic posterior pituitary and pituitary stalk anomalies, have been reported as strong predictors of MPHD development in other studies (17, 21, 22, 23). In our cohort, the combined group of abnormal pituitary development diagnoses had a lower rate of progression to MPHD than patients with known genetic defects resulting in central hormone deficiencies (32%), SOD (36%) or acquired conditions (34%). Patients with ectopic posterior pituitary or interrupted pituitary stalk had marginally (non-significantly) elevated progression to MPHD in our cohort, but were present only in small numbers. Of congenital conditions, patients with a primary diagnosis of SOD progressed from IGHD to MPHD at the highest frequency, with two of these patients having concomitant ectopic posterior pituitary and hypoplastic pituitary stalk and 1 with concomitant ectopic posterior pituitary only.

For the full cohort of organic IGHD, multiple logistic regression analysis revealed the following variables as



predictors of progression to MPHD: longer duration of follow-up, greater baseline age, gender and more severe GHD. Except for gender, these are the same predictors as in GeNeSIS patients with idiopathic GHD (4). With organic GHD, girls were more likely than boys to develop MPHD. Otto and colleagues also observed a female predominance for development of MPHD (23).

Slightly more than one-third of our analysed study population was girls. Similar gender proportions have been reported previously in GeNeSIS (12) and in other studies (24, 25). This gender disparity has been attributed to ascertainment or referral bias, as short stature may be socially more detrimental to boys. If so, referred girls might be expected to have more severe GHD, which might confound the effect of gender in our analysis. However, in our cohort boys had marginally lower peak stimulated GH than girls (data not shown), so the finding that female gender is a predictor for development of MPHD appears independent of GHD severity. The relatively higher proportion of girls progressing to MPHD than boys appeared to be most prominent in patients with acquired GHD, particularly those with history of intracranial tumour. As the hypothalamic–pituitary–gonadal axis functions somewhat differently in girls than in boys, it may be more susceptible to irradiation in girls and potentially at least in part driving the higher rate of MPHD development in girls. This hypothesis would appear to be supported by our finding that more girls developed gonadotropin deficiency as the sole additional pituitary hormone deficiency than boys, although the numbers of patients in this report were too small to draw firm conclusions.

The patients with organic GHD and initial IGHD in the current analysis exhibited no differences in history of breech presentation, perinatal asphyxia and neonatal complications between those who developed MPHD and those who continued to have IGHD. In contrast, such perinatal or neonatal conditions have been reported to be more prevalent among children with organic GHD and an initial diagnosis of MPHD (26, 27, 28, 29), and in patients with idiopathic IGHD (4).

TSH was the hormone most frequently deficient in patients who developed MPHD. A similar observation was made in the study reported by Di Iorgi *et al.* (22) in patients with GHD due to structural hypothalamic–pituitary abnormalities. As hypothyroidism may reduce response to GH therapy (30), monitoring of thyroid function is essential during GH treatment.

Although gonadotropins were deficient in about one-third of those who developed MPHD in our study,

the frequency may have been underestimated because of limited follow-up and young age of patients at study entry. Analysis by Kaplan–Meier indicated that, when followed for an extended period of time, deficiency of gonadotropins was estimated in the majority of patients in the full cohort and for all those who progressed to MPHD. In interpreting this estimate it should be noted that the number of patients in GeNeSIS with such extended follow-up is small. Correspondingly, gonadotropins were the most common additional deficiency observed in the single-centre study of Otto *et al.* (23) that followed patients with congenital causes of GHD (thus excluding patients with acquired GHD due to tumour or radiation) for a median of 5.4 (range 1.2–21) years (23). Thus, ongoing surveillance for gonadotropin deficiency is required in all patients with organic GHD.

Incident ACTH deficiency was diagnosed in nine patients, of whom four had concomitant TSH deficiency, consistent with previous observations (31, 32). However, four patients had ACTH deficiency as the sole additional deficiency, emphasising the need to remain alert to potentially life-threatening adrenal insufficiency in patients who present with IGHD due to organic causes.

Limitations of this study include reliance on investigator-provided information, potentially without central laboratory confirmation or auditing of medical records. Because 41% of patients with organic GHD were excluded due to baseline MPHD, this study specifically addresses those organic GHD patients who presented initially with IGHD. To ensure conservative estimation of incident pituitary deficiencies, patients with uncertain MPHD status (5%) at baseline or follow-up were also excluded, which may have caused minor bias in estimates. As the mean follow-up for our cohorts was approximately 3 and 6 years for the full and 4-year cohorts, respectively, and because the incidence of MPHD rose steadily with greater follow-up, the proportion of patients with persistent IGHD (79% of the 4-year follow-up cohort) will likely diminish with further follow-up. The GeNeSIS CRF included checkboxes specific for primary and secondary hypothyroidism, but not for primary or secondary adrenal insufficiency or primary or secondary gonadal failure. A potential underreporting bias for hypoadrenalism and hypogonadism should therefore be acknowledged, although data from multiple CRF modules were used to ascertain additional pituitary hormone deficiencies. Additionally, TSH deficiency within the first year of GH treatment may represent unmasking of pre-existing, latent, central hypothyroidism, as reported in GH-deficient adults

(33, 34) and children (34, 35). However, the median interval from GHD to TSH deficiency diagnosis of 2.4 years, and increasing prevalence of TSH deficiency with extended follow-up, suggest that most TSH deficiency in this study represents new pituitary hormone deficits. Finally, although we could distinguish frequency of progression to MPHD among specific aetiologies of organic IGHD, the number of patients was insufficient to assess predictors of MPHD development, temporal pattern of development or combinations of additional deficiencies for each specific aetiology.

We conclude that patients initially diagnosed with organic IGHD are at significant risk for development of MPHD, particularly those with severe GHD, SOD, genetic defects resulting in central hormone deficiencies or intracranial tumour. Although many patients exhibited characteristics that predict MPHD development, other patients developed MPHD without obvious prognostic factors. In contrast, many patients who appeared at greater risk of developing MPHD, based on GHD severity or diagnosis, did not develop MPHD during this study. ACTH deficiency, the sole additional deficiency in 6% of children with incident MPHD can if undetected cause life-threatening adrenal crisis. As additional pituitary hormone deficiencies can emerge over many years, and as the factors predicting development of MPHD had low sensitivity, long-term monitoring of pituitary function is recommended for all patients, irrespective of the cause of the GHD.

#### Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-15-1203>.

#### Declaration of interest

C J Child and A G Zimmermann are employees of Eli Lilly and Company. C A Quigley is a former employee of Eli Lilly and Company, and G B Cutler Jr and W F Blum are former employees of and have received consultancy fees from Eli Lilly and Company. C Deal, S L S Drop and R G Rosenfeld were members of the GeNeSIS International Advisory Board and have received honoraria and meeting expenses from Eli Lilly and Company.

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#### Author contribution statement

C J Child developed the initial draft of the manuscript and managed all subsequent drafts. All authors were involved in manuscript development and critical revisions, and approved the final version. Additionally all authors were involved in developing the analysis design and implementation.

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