From isolated GH deficiency to multiple pituitary hormone deficiency: an evolving continuum – a KIMS analysis

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Abstract

Objective: To describe baseline clinical presentation, treatment effects and evolution of isolated GH deficiency (IGHD) to multiple pituitary hormone deficiency (MPHD) in adult-onset (AO) GHD.

Design: Observational prospective study.

Methods: Baseline characteristics were recorded in 4110 patients with organic AO-GHD, who were GH naïve prior to entry into the Pfizer International Metabolic Database (KIMS; 283 (7%) IGHD, 3827 MPHD). The effect of GH replacement after 2 years was assessed in those with available follow-up data (133 IGHD, 2207 MPHD), and development of new deficiencies in those with available data on concomitant medication (165 IGHD, 3006 MPHD).

Results: IGHD and MPHD patients had similar baseline clinical presentation, and both groups responded similarly to 2 years of GH therapy, with favourable changes in lipid profile and improved quality of life. New deficiencies were observed in 35% of IGHD patients, which was similar to MPHD patients with one additional deficit other than GH. New deficiencies most often presented within the first year but were observed up to 6 years after GH commencement. Conversion of IGHD into MPHD was not predicted by aetiology, baseline characteristics, surgery or radiotherapy, whereas in MPHD additional deficits were predicted by age (P<0.001) and pituitary disease duration (P<0.01).

Conclusion: Both AO-IGHD and -MPHD patients have similar baseline clinical presentation and respond equally well to 2 years of GH replacement. Hypopituitarism in adults seems to be a dynamic condition where new deficiencies can appear years after the initial diagnosis, and careful endocrine follow-up of all hypopituitary patients, including those with IGHD, is warranted.

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Introduction

Isolated GH deficiency (IGHD) is defined as a condition in which GHD is not associated with other pituitary hormone deficits, as opposed to multiple pituitary hormone deficiency (MPHD). Theoretically, IGHD provides the ideal model to characterise the influence of GHD per se, without the confounding influence from other pituitary hormone deficiencies or their treatment. It thus gives the opportunity to address questions about possible differences in clinical presentation and in responsiveness to GH replacement therapy. The prevalence of IGHD is reported to be between 7 and 9% (1, 2), and large cohorts are therefore required for the assessment of similarities and dissimilarities in IGHD versus MPHD. By virtue of its size, the Pfizer International Metabolic Database (KIMS) permits such subgroup analysis.

In a previous KIMS publication 5 years ago, Abs et al. (2) described a similar clinical presentation at baseline and comparable effects after 1 year of GH replacement in adult-onset (AO) IGHD and MPHD patients. As the number of KIMS patients is still growing, and reached 12 547 by August 2007, the first aim of the present study was to allow a more extensive analysis within a stringently defined cohort of patients with AO-GHD of organic cause, naïve to GH prior to entry in KIMS, and with a longer follow-up.

It is well documented that patients may develop progressive hypopituitarism several years after receiving radiotherapy (3). Non-irradiated IGHD patients are not routinely/regularly evaluated for other pituitary deficiencies in all centres, as the clinical situation is considered stabilised once the diagnosis of IGHD has

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been made. Therefore, the second aim of the present study was to assess the evolution of IGHD, in terms of prevalence of patients who converted from IGHD to MPHD after initiation of GH replacement therapy.

Subjects and methods

Patients

The recruitment of patients to the KIMS database follows good clinical practice guidelines with a quality control system, as described previously (4).

The total number of subjects in KIMS as of August 2007 was 12,547, of which 4,110 were eligible for baseline analysis, meeting the following inclusion criteria: i) GH naive prior to entry in KIMS; ii) an organic cause of hypopituitarism, and iii) severe AO-GHD as defined by a peak GH < 3 μg/l in response to the insulin tolerance test (ITT) or the glucagon test, a peak GH < 0.4 μg/l in response to the arginine test, or below body mass index (BMI) related cut-offs in response to the arginine + GHRH test, defined as a peak GH < 11.5 μg/l with BMI < 25 kg/m², a peak GH < 8 μg/l with BMI 25–30 kg/m² or a peak GH < 4.2 μg/l with BMI > 30 kg/m². Of the 4,110 patients, 3,827 had MPHD and 283 (7%) had IGHD. Two years GH replacement data were available in 2,340 patients, 2,207 with MPHD and 133 with IGHD (6%).

Further analysis was performed to assess the development of other pituitary hormone deficits in both IGHD and MPHD patients, as evidenced by the initiation of glucocorticoid, levothyroxine, sex steroids or desmopressin during follow-up. For this purpose, data on concomitant medication were drawn from patients classified as either IGHD (n = 165) or MPHD (n = 3,006) at baseline, in order to identify those in whom new substitution therapy was added during follow-up. Patients with IGHD at baseline developing MPHD within 2 years of follow-up were classified as MPHD in the analysis of GH treatment effect.

Methods

Background information Data were collected concerning: age at entry to KIMS; estimated duration of pituitary disorder and time since GHD diagnosis; duration of GH therapy and number of additional pituitary hormonal deficiencies (based on recorded deficiencies or recorded use of medications for pituitary deficiencies other than GHD); history of radiotherapy and time from irradiation.

The aetiologic diagnoses responsible for GHD were merged into nine groups with related pathologies: non-functioning pituitary adenomas (NFPA), secreting pituitary adenomas, other sellar tumours, craniopharyngioma, other extra-sellar tumours, malignancy outside the cranium, traumatic brain injury (TBI) and other (the remaining diagnoses (5)).

Associated disorders, recorded as medical history, were obtained with specific reference to: peripheral vascular disease (claudication), cerebrovascular disease (stroke), cardiovascular disease (angina, myocardial infarction), arthrosis, epilepsy, diabetes mellitus, hypertension and bone fractures.

Diagnostic procedures The diagnosis of severe GHD was usually based on a single stimulation test (60.3% in IGHD and 62.9% in MPHD), whereas two or more tests were performed in the remaining patients. The number of tests performed did not differ between IGHD and MPHD. The ITT was performed in 64% of MPHD and in 59% of IGHD patients; the glucagon test in 18% of both MPHD and IGHD patients; and the arginine test in 13% of MPHD and in 21% of IGHD patients, whereas the arginine + GHRH test was performed in 4% of MPHD and in 3% of IGHD patients.

Clinical and metabolic assessment Baseline data at entry into KIMS included age, gender, insulin-like growth factor 1 (IGF1) SDS, BMI, waist circumference (WC), waist-to-hip ratio (WHR), lean body mass (LBM) and fat mass (FM) as assessed by bioelectric impedance analysis, fasting blood glucose (FBG), HbA1c and lipid profile. The percentage of patients exceeding internationally defined target values of increased cardiovascular risk were evaluated and defined as follows: BMI > 30 kg/m²; WHR > 1.0 (men) and > 0.9 (women); WC > 102 cm (men) and > 88 cm (women); total cholesterol > 5.2 mmol/l; high-density lipoprotein (HDL)-cholesterol < 1.04 mmol/l (men) and HDL-cholesterol < 1.3 mmol/l (women); low density lipoprotein (LDL)-cholesterol > 3.38 mmol/l and triglycerides > 1.65 mmol/l (6).

Lipids and IGF1 were measured centrally in a single laboratory. Serum total cholesterol, triglycerides and HDL-cholesterol were measured as previously described (2) and LDL-cholesterol was calculated by the Friedewald formula (7). Serum IGF1 measurements were performed between 1994 and October 1997 at Kabi Pharmacia, Stockholm, Sweden and thereafter at Sahlgrenska University Hospital, Gothenburg, Sweden, until November 2002 using a RIA with acid/ethanol precipitation of IGF-binding proteins (Nichols Institute Diagnostic, San Juan Capistrano, CA, USA), until September 2006 using a chemiluminescence immunoassay (Nichols Advantage System, San Clemente, CA, USA) and since then using Immulite 2500, DPC Siemens. IGF1 values were adjusted for age and gender and expressed as SDS.

Quality of life assessment Quality of life (QoL) was assessed using the QoL-assessment for GHD in adults (QoL-AGHDA) form, which is a disease-orientated questionnaire, measuring the impact of GHD in one overall dimension (8). Each of the 25 items represents a problem and is scored dichotomously, acknowledging or
denying the problem. The sum of recognised problems (number of ‘yes’ answers) constitutes a score, ranging from 0 (no problems) to 25 (all problems recognised), thus a high QoL-AGHDA score denotes poor QoL.

**Assessment of GH treatment effect** All participants received recombinant human GH (Genotropin, Pfizer, Strängnäs, Sweden). The initial GH dosing according to body size was, in the late 1990s, replaced with a more individualised schedule aiming to normalise IGF1 SDS in the upper part of the age-based reference interval.

Treatment effect was evaluated as a change in the baseline parameters after 2 years of GH replacement, and as a difference in the percentage of patients exceeding the predefined target values.

**Ethics** In KIMS, each centre obtains approval from its local ethics committee, and the patients gave informed consent, verbally or in writing, depending on the local legal requirements. The study was performed in accordance with the Declaration of Helsinki (9).

**Statistical methods**

Outcome variables studied were IGF1 SDS, FM, LBM, lipids, blood pressure, BMI, WC, WHR and QoL-AGHDA score. Data are presented as mean ± S.D. Differences between and within groups were studied using parametric statistics (t-tests). In cases where variances were likely to be unequal (Levene’s test) Satterthwaite’s correction of degrees of freedom was applied (10). Non-parametrical analyses were also performed and compared, and produced similar conclusions. Four field tables were analysed with Fisher’s exact tests. Sex- and age-adjusted differences between groups were calculated using linear regression methods. When analysing differences between groups on treatment effects (changes), respective outcome values at baseline were used as predictors. The standard statistical package (SPSS version 15.0) for Windows, V15.0 (SPSS Inc., Chicago, IL, USA) was utilised. Statistical significance was considered if \( P < 0.05 \).

Step-wise forward logistic regression using new pituitary hormone deficiency (no = 0/yes = 1) as dependent variable and baseline characteristics, surgery, radiotherapy and aetiology as independent variables was used to identify predictors of developing new additional pituitary hormone deficits.

**Results**

**Baseline characteristics**

The most common causes of both IGHD and MPHD were non-functioning and secreting pituitary adenomas, which were less frequent in the IGHD group (58%) than in the MPHD group (65%) \( (P < 0.05; \text{Fig. 1}) \). IGHD was more common in patients with other sellar or extrasellar tumours, patients treated for extracranial malignancy and in patients with TBI, whereas MPHD was more frequently observed in patients treated for craniopharyngiomas \( (P < 0.01) \).

A history of irradiation was recorded in 36% of patients with IGHD and in 37% of patients with MPHD \( (\text{ns}) \). Fractures were the most frequently reported condition in both groups, being more frequent in men than in women, although only reaching significance in the MPHD (24 vs 19%; \( P < 0.001 \)) but not in the IGHD (22 vs 18%; \( P = 0.4 \)) group.

There was a higher proportion of women in the IGHD group than in the MPHD group (55 vs 49%; \( P < 0.05 \)). Patients with IGHD were younger at entry in KIMS \( (46.5 \pm 13.20 \text{ vs } 48.6 \pm 12.79 \text{ years, } P < 0.01) \), and had a shorter history of both GHD \( (1.3 \pm 2.61 \text{ vs } 2.0 \pm 3.65 \text{ years, } P < 0.001) \) and pituitary disease \( (5.3 \pm 6.29 \text{ vs } 7.4 \pm 7.60 \text{ years, } P < 0.001) \) compared with the MPHD group.

After adjustment for age and gender, the IGHD group had lower LBM \( (P < 0.01) \) and higher IGF1 SDS \( (P < 0.001) \) as compared with the MPHD group, but did not otherwise differ.

A history of irradiation was recorded in 36% of patients with IGHD and in 37% of patients with MPHD \( (\text{ns}) \), whereas surgery was less frequently reported in IGHD \( (69\%) \) versus MPHD \( (86\%) \), \( P < 0.001 \).

**Influence of 2 years of GH replacement therapy**

Two years of GH treatment caused an increase in mean IGF1 SDS from \(-1.3\) to \(0.6\) in the IGHD group and from \(-1.8\) to \(0.6\) in the MPHD group. In the IGHD group, GH replacement resulted in a significant improvement in terms of a significant decrease in total and LDL-cholesterol, a significant increase in LBM, an improvement in QoL, and an increase in HbA1c, while no other significant changes were observed (Table 1).

Figure 1 Aetiological distribution in 4110 patients with adult-onset GH deficiency, divided into those with multiple pituitary hormone deficiencies (MPHD; dark grey) and those with isolated GH deficiency (IGHD; light grey). A significant difference was observed in the prevalence distribution of all aetiologies except that for secreting pituitary adenomas (PA) and ‘other’, \( P < 0.001 \).

![Figure 1](https://via-free-access.eje-online.org)
In the MPHD group, the treatment resulted in a decreased WC, WHR, body fat, total and LDL-cholesterol, increased LBM, HDL-cholesterol and decreased QoL-AGHDA score, but also caused a slight but significant increase in FBG and HbA1c.

The gender and age adjusted influence of 2 years GH replacement did not differ significantly between the IGHD and the MPHD group.

**Patients exceeding target values**

More than 35% of both IGHD and MPHD patients had a BMI exceeding the target value of 30 kg/m² at baseline, and were thus obese prior to treatment. This percentage was significantly reduced after 2 years of GH therapy where 15% of IGHD and 22% of MPHD patients exceeded the BMI target \((P<0.001)\). Similarly, 41 vs 17% of IGHD, and 42 vs 25% of MPHD patients exceeded the WC target before and after GH treatment; 33 vs 21% of IGHD, and 35 vs 21% of MPHD patients exceeded the cholesterol target, before and after GH treatment; 18 vs 11% of IGHD, and 19 vs 14% of MPHD patients exceeded the HDL-cholesterol target, before and after GH treatment; and 30 vs 18% of IGHD, and 31 vs 21% of MPHD patients exceeded the TG target, before and after GH treatment \((P<0.001)\).

The proportion of patients reaching normalisation after 2 years of GH treatment was not significantly different comparing the IGHD and the MPHD groups, with the exception of WC as a larger percentage of IGHD patients reached normalisation \((P<0.05)\).

**Evolution of pituitary hormone deficits: IGHD versus MPHD**

Out of 283 patients classified as IGHD at baseline, 165 patients had available data on concomitant medication. New deficiencies, as evidenced by commencement of new substitution therapy, were recorded during follow-up in 58 (35%) of these patients (Table 2). New deficiencies were recorded in 24 (41%) of the patients within the first year after start of treatment, but conversion was recorded up to 6 years after GH start (mean \(+2.1\pm0.93\) years from baseline). Secondary hypothyroidism was the most often recorded new deficiency \((n=41; 25\%)\) followed by secondary hypothyroidism.

**Table 1** Longitudinal characteristics of patients with isolated GH deficiency (IGHD) and multiple pituitary hormone deficiencies (MPHD), assessed at baseline and after 2 years of GH replacement therapy.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2 years</th>
<th>Change</th>
<th>P &lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± s.d.</td>
<td>Mean ± s.d.</td>
<td>Delta ± s.d.</td>
<td></td>
</tr>
<tr>
<td>IGF1 SDS</td>
<td>86</td>
<td>1.3 ± 1.2</td>
<td>6.1 ± 1.1</td>
<td>1.9 ± 1.35</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>98</td>
<td>28.5 ± 6.0</td>
<td>28.7 ± 6.5</td>
<td>0.2 ± 2.0</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>91</td>
<td>0.9 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>0.0 ± 0.07</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>91</td>
<td>93.7 ± 13.7</td>
<td>93.3 ± 14.2</td>
<td>0.4 ± 6.8</td>
</tr>
<tr>
<td>Body fat (BIA, kg)</td>
<td>37</td>
<td>30.8 ± 16.3</td>
<td>29.4 ± 15.6</td>
<td>1.4 ± 6.0</td>
</tr>
<tr>
<td>Lean body mass (BIA, kg)</td>
<td>37</td>
<td>49.5 ± 11.9</td>
<td>51.2 ± 11.7</td>
<td>1.8 ± 5.0</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>65</td>
<td>5.9 ± 1.2</td>
<td>5.4 ± 1.0</td>
<td>-0.5 ± 1.0</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>62</td>
<td>3.8 ± 1.1</td>
<td>3.4 ± 0.8</td>
<td>0.5 ± 1.0</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>65</td>
<td>1.2 ± 0.3</td>
<td>1.2 ± 0.3</td>
<td>0.0 ± 0.03</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>65</td>
<td>1.9 ± 1.3</td>
<td>1.8 ± 0.9</td>
<td>-0.1 ± 0.9</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>99</td>
<td>5.1 ± 0.9</td>
<td>5.3 ± 0.9</td>
<td>0.2 ± 0.6</td>
</tr>
<tr>
<td>B-glucose (mmol/l)</td>
<td>53</td>
<td>4.8 ± 0.6</td>
<td>4.9 ± 0.7</td>
<td>0.1 ± 0.7</td>
</tr>
<tr>
<td>QoL-AGHDA-score</td>
<td>70</td>
<td>13.6 ± 6.9</td>
<td>8.1 ± 7.0</td>
<td>-5.5 ± 6.6</td>
</tr>
</tbody>
</table>

Treatment effect was evaluated as the change in the evaluated parameters. Data are given as means ± s.d. and within group changes (2 years baseline) with associated P values. The patients evaluated were identical at baseline and at 2-year evaluation.
hypo-ogonadism (n=21; 13%) and secondary hypoadrenalism (n=20; 12%), whereas ADH deficiency was not recorded. Development of IGHD into MPHD was not predicted by baseline characteristics, surgery, radiotherapy or aetiology. Patients with stable IGHD had higher mean WHR and WC at baseline compared with those who developed MPHD, but did not otherwise differ, and no difference was observed in treatment effect comparing the two groups.

New deficiencies were recorded in 381 (13%) of 3006 patients with MPHD. Patients with a low number of deficient axes at baseline were more likely to develop new deficiencies, illustrated by a 31% risk in patients with one additional pituitary deficit, a 21% risk in patients with two additional deficits, and a 3% risk in patients with three additional deficits (Table 2). New deficiencies occurred within the first year in 34% of the patients, and were recorded up to 11 years from baseline (Fig. 3). As in IGHD, secondary hypothyroidism was the most often recorded new deficiency (n=191; 6.4%), followed by secondary hypoadrenalism (n=121; 4%), secondary hypogonadism (n=93; 3.1%) and ADH deficiency (n=40; 1.3%). In the regression model, only age and duration of pituitary disease were identified as predictors of development of new additional pituitary hormone deficits (P<0.001 and P<0.005 respectively), i.e. the risk of development of new deficits decreased with age and with the duration of pituitary disease.

Table 2 Number (%) of new pituitary deficits in relation to number of additional pituitary deficits at baseline, in multiple pituitary hormone deficiencies (MPHD) and isolated GH deficiency (IGHD) patients.

<table>
<thead>
<tr>
<th>Baseline</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPHD</td>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3 (33)</td>
<td>2 (22)</td>
<td>2 (22)</td>
<td>2 (22)</td>
<td>9 (100)</td>
</tr>
<tr>
<td>1</td>
<td>386 (69)</td>
<td>129 (23)</td>
<td>38 (7)</td>
<td>6 (1)</td>
<td>559 (100)</td>
</tr>
<tr>
<td>2</td>
<td>602 (79)</td>
<td>151 (20)</td>
<td>8 (1)</td>
<td>0 (0)</td>
<td>761 (100)</td>
</tr>
<tr>
<td>3</td>
<td>1563 (97)</td>
<td>43 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1606 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>2625 (87)</td>
<td>325 (11)</td>
<td>48 (2)</td>
<td>8 (0.3)</td>
<td>3006 (100)</td>
</tr>
<tr>
<td>IGHD</td>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>107 (65)</td>
<td>37 (22)</td>
<td>18 (11)</td>
<td>3 (2)</td>
<td>165 (100)</td>
</tr>
</tbody>
</table>

Seventy-one patients with records in concomitant medication had panhypopituitarism.

Discussion

Few data exist on the comparison of IGHD with MPHD with respect to clinical presentation and treatment effect. The main objective of such analysis is to obtain an indirect assessment of the impact of GH by itself upon the clinical syndrome and the biochemical disturbances accompanying hypopituitarism. By virtue of the growing size of the KIMS database, it was possible to assess an even larger, more stringently defined cohort of patients with GH naïve AO-GHD of organic origin, with a prolonged follow-up time compared to the previous study (2). Taking differences in age and gender distribution into consideration, the clinical baseline characteristics were similar in patients with IGHD as compared with patients with MPHD, and both groups responded similarly to 2 years of GH replacement therapy, with favourable changes in lipid profile, improved QoL and a decrease in the observed proportion of patients with increased cardiovascular risk factors, as assessed by the frequency of patients exceeding internationally defined metabolic targets.

Given the size of the study, it also allowed for a separate evaluation on development of additional pituitary hormone deficits in both patients with initial IGHD and MPHD. Our observation that new pituitary hormone deficits occurred not only during the first year of GH treatment but during the entire follow-up period in a substantial proportion of IGHD and MPHD patients suggests that hypopituitarism is a dynamic condition that requires careful endocrine monitoring in IGHD as well as in MPHD.

Since KIMS is a large observational pharmaco-epidemiologic survey, reflecting routine clinical practice and open for all hypopituitary patients treated with Genotropin, a certain level of patient selection bias cannot be excluded. Currently, all patients being considered at risk of hypopituitarism are likely to be assessed for GHD, excluding a small group of patients with such poor clinical condition that treatment is considered irrational. However, in previous years patients with severe symptomatology were more likely to be considered for evaluation of the GH axis and, thus to be included in the database. Further bias could be caused by the approach used in the UK, which is prioritising patients with severely impaired QoL who have a documented treatment effect in terms of improved QoL for prolonged GH replacement. The extent of selection bias was minimised by the inclusion of a stringently defined cohort including only patients with severe GHD. An additional limitation of multicentre, observational studies worth mentioning is the diversity of incorporated laboratory methodologies. Although in KIMS this limitation for IGF1 and lipids is partly overcome by central analyses offered to all investigators, other results, e.g. GH peaks, are measured based on different GH assays. Therefore, variations in
GH assays, i.e. some assays that generate higher and some lower values, should be taken into account and it cannot be ruled out that in clinics where GH assays generating lower results are used, patients are more likely to be diagnosed with GHD. On the other hand, we think that such situations mostly refer to ‘borderline cases’ and believe that by applying very stringent cut-off values, significant inclusion of such ‘false positive’ cases in the studied cohort is prevented.

The prevalence of IGHD in the present study of selected patients was 7% at baseline and 6% at 2 years follow-up, which is in accordance with or even lower than previously reported (1, 2, 11), suggesting that misclassification of MPHD patients as IGHD was minimal. The exact prevalence of IGHD may in the future be influenced by the inclusion of more patients with TBI or subarachnoid haemorrhage as these patients often present with GHD in its isolated form (12, 13).

Nowadays, IGHD is recognised as a clinical entity in patients with organic hypothalamic pituitary disease (14), as GH is often the first hormone to become deficient in the spectrum leading from isolated pituitary hormone deficiency to panhypopituitarism. Two different dynamic tests were previously demanded for the diagnosis of IGHD (15), but the most recent recommendations of the GH Research Society require only a single test, as in MPHD, when using adequate stimulation tests with stringent cut-offs. In the present study, the diagnosis of IGHD was based on a single test in 60% of the patients. The exclusive inclusion of severe GHD was ensured by the use of the stringent cut-offs for GH peak, i.e. < 3 μg/l for ITT and glucagon, and BMI related cut-offs for the arginine + GHRH test, though this test was used infrequently. For patients diagnosed with the arginine test an even lower cut-off value (0.4 μg/l) was introduced following the recommendation of Biller et al. (16). Therefore, we believe that by using appropriate, more stringent cut-off values for this less potent agent (arginine) we ensured inclusion of properly diagnosed patients. Although more than one-fifth of patients with IGHD (versus 13% of MPHD) were diagnosed using the arginine test, overall only 8.5% of patients with IGHD were diagnosed by the arginine test used as a single test (24 out of 283) and in 5.5% of patients with MPHD (212 out of 3827), and it is reassuring that the diagnosis in the majority of these patient was based on two or more tests.

The aetiologic distribution of the present cohort is comparable with that previously reported (2, 17), with more than half of the IGHD and MPHD cases being caused by NFPA or secreting pituitary adenomas, or their treatment, and MPHD being more prevalent in patients with craniopharyngiomas, as compared with IGHD which was more prevalent in extra-sellar tumours, extra-cranial malignancy and TBI, probably reflecting differences of invasiveness and proximity to the hypothalamic pituitary area.

The observed difference in age and gender distribution between IGHD and MPHD was also reported in the first KIMS publication on IGHD (2), and was accounted for in the present analysis. Independent of age and gender, IGHD patients had higher baseline IGF1 SDS, and higher peak GH compared with those with MPHD, which may be explained by the aetiological distribution with MPHD being more prevalent in diseases with a higher degree of invasiveness into and closer proximity to the hypothalamic pituitary area, and thus with a higher theoretical impact on overall pituitary function including GH.

A history of fracture was the most frequently reported associated disorder in the present study: Several studies have reported that patients with hypopituitarism and GHD have an increased incidence of bone fractures (18, 19), with an estimated 2.6 higher incidence rate in hypopituitary men as compared with a control group (19). Osteopenia is a well-established surrogate marker of fracture risk, and reduced bone mineral density (BMD) has been reported in hypopituitary patients (20), a reduction that has been associated with the severity of GHD, rather than the presence of additional hormone defects (21). A history of fracture was reported in up to 24% of male IGHD and MPHD patients. The equal occurrence in the two groups might suggest GHD to be the most important hormonal factor for the increased fracture risk in hypopituitarism. However, conflicting data exist within this field as some studies do not find decreased BMD in AO-GHD patients (22, 23).

Initiation of GH treatment caused a significant rise in mean IGF1 SDS to above mean in both groups, indicating that the IGHD and MPHD patients were equally well substituted. The fact that the two groups
were well matched further strengthens the results from the comparative analysis on treatment effect. Overall, the current study showed a similar responsiveness to 2 years of GH replacement therapy; although fewer significant treatment effects were observed in IGHD, possibly explained by lack of power, rather than true biological difference.

Several studies have shown that adult patients with untreated GHD present with a series of cardiovascular risk factors including increased blood pressure, increased BMI, abnormal body composition and an adverse lipid profile (11, 24–27). Introduction of GH replacement may induce a favourable change in the very same parameters (27–29). An adverse cardiovascular risk profile was confirmed in the present cohort, where 20–40% of all patients exceeded internationally defined metabolic targets, with no difference between the IGHD and MPHD group. This profile improved after 2 years of GH treatment. In the IGHD group, although significant changes were only observed for total and LDL cholesterol, a significant reduction was observed in the percentage of patients exceeding target values within all parameters evaluated, being approximately halved within the treatment period. Again, the similar treatment response observed suggests GH as an important hormonal factor responsible for the observed changes, though the database was not designed to answer these questions in a very precise manner.

It is well documented that GHD has a negative impact on QoL in adults (8, 30, 31), and several studies have reported an improvement following GH treatment (32–35); this has been reported to be paralleled by a reduction in healthcare consumption (34, 35). The present data showed QoL to be equally impaired in the IGHD and the MPHD group at baseline; both groups responded favourably to 2 years of GH treatment. This finding corroborates the previous KIMS study on IGHD (2).

More patients with MPHD than IGHD had available follow-up data concerning treatment effect and concomitant medication, which could reflect an understanding of IGHD as a stable condition with less impact for the patient. The present study demonstrates that IGHD of organic origin is not a stable condition, but may evolve into MPHD in a significant number of patients. In the present cohort, the risk of new pituitary hormone deficits in IGHD patients was similar to that in MPHD patients with only one additional deficit. Some of the new deficiencies in the first year after starting GH replacement could have been precipitated by initiation of GH treatment. It is well documented that GHD can mask central hypothyroidism or central hypoadrenalism in a significant proportion of hypopituitary patients, and that this is exposed upon commencement of GH treatment. The mechanisms seem to be GH-induced enhancement of the peripheral deiodination of $T_4$ to $T_3$, and reduction of cortisone to cortisol conversion (36, 37). However, precipitation by initiation of GH therapy does not entirely explain the observed evolution in pituitary function in either IGHD or MPHD patients since half of the patients developed new deficiencies 3–6 years after commencement of GH therapy. Irradiation per se could explain the gradual impairment of the pituitary function in some patients. Surprisingly, neither irradiation nor duration between radiotherapy and entry into KIMS was identified as a predictor of new deficiencies in either IGHD or MPHD patients, which may be explained by lack of power, as the number of patients with recorded time from radiation and/or surgery was very small. There was an inherent limitation in the way new deficiencies were evaluated because registration of new medication was the only means by which new deficiencies could be assessed within the present design. Definite proof by biochemical data and local reference ranges would have been preferable.

Our data suggest that hypopituitarism in adults seems to be a dynamic condition where new deficiencies can appear years after the initial diagnosis, and the implication of this new and clinically very important observation is that careful long-term endocrine follow-up is indicated in both IGHD and MPHD.

**Declaration of interest**

M Koltowska-Haggstrom is employed by Pfizer Health AB, Sweden; B Sailer is employed by Pfizer Ltd UK; I Kourides is employed by Pfizer Inc., USA; M Klose has received lecture fees from Pfizer and Novartis Health Care; U Feldt-Rasmussen has received research grants and lecture fees from Novo Nordisk and Pfizer; B Jonsson has received consulting fees from Pfizer; V Popovic has received lecture fees from Pfizer and is on the advisory board for the KIMS database; R Abs has received lecture fees from Pfizer. KIMS® is supported by Pfizer Inc. This paper forms part of a European Journal of Endocrinology supplement supported by Pfizer Inc.

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