Etiology, baseline characteristics, and biochemical diagnosis of GH deficiency in the adult: are there regional variations?

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Abstract

Previous work has examined potential links between the etiology of GH deficiency (GHD) and the baseline characteristics of the patients including biochemical and psychometric parameters. Using an update of the KIMS pharmaco-epidemiological database (Pfizer International Metabolic Database), we addressed the question how well such results can be generalized and whether regional differences may play a role. From 30 different countries, 13 167 GH-deficient patients were included in KIMS at the data close in December 2008. In order to explore country-specific differences of baseline characteristics documented in KIMS, separate analyses of baseline characteristics of adult-onset GHD patients (n = 7708) were performed for the six largest contributing European countries and the United States. This analysis revealed striking regional variations in the pathogenesis of the disease, clinical characteristics such as body mass index, and in the classical features of the metabolic syndrome such as blood pressure or lipid status between countries. Moreover, the approach to endocrine function testing was widely different between countries, as well as the distribution of etiologies of GHD. These data suggest that a complex relation between biochemical and clinical signs of GHD exists, and that the spectrum of adult GHD syndrome is influenced by regional diagnostic and clinical particularities.

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Introduction

GH deficiency (GHD) in children predominantly affects their physical development, and as a consequence the main clinical characteristics comprise auxological parameters. However, GH-deficient adults present with a wide spectrum of clinical presentations, commonly called GHD syndrome, which are not pathognomonic and overlap with a variety of other conditions (1, 2). This complicates the diagnosis of GHD, which should ideally be based on the correct identification of baseline characteristics and definite biochemical diagnosis. Still, the detection of GHD is important especially, as successful GH replacement therapy ameliorates many symptoms of the GHD syndrome and is accompanied by a significant increase in quality of life (QoL) in GHD patients (3, 4). Moreover, the untreated condition is associated with an increased morbidity and mortality. In a recent large survey based on National Danish registries, the morbidity of GHD patients was found to be approximately threefold higher than what would be expected in a healthy population. This result was independent of gender and applied to patients with childhood (CO) and adult-onset (AO) GHD (5), with mortality of CO GHD far exceeding AO GHD (6).

To identify and sharpen the pattern of the ‘non-specific’ baseline characteristics of GHD patients, numerous variables have to be analyzed. Therefore, a large database is required for many aspects of the disease, which are potentially lost in the analysis of smaller cohorts.

In the present analysis, we used the KIMS database (Pfizer International Metabolic Database) to examine baseline characteristics and current standard procedures of biochemical testing for AO GHD. As KIMS combines data from a large variety of different countries, we will further compare whether there are country specific approaches discernable to define GHD, and whether patient characteristics are different between the countries.

Patients and methods

The KIMS database is the largest pharmaco-epidemiological follow-up of adult GHD patients under GH treatment, and provides an ever-increasing powerful tool to target questions concerning GHD and the response to GH therapy (7–10). By the end of 2008,
13 167 patients from 30 different countries were included in KIMS with a distribution of 50.4% male (mean age 44.3 ± 15.8 years) and 49.6% female (mean age 44.0 ± 14.6 years) participants. The country-specific sample sizes ranged from 3 patients from Mexico to 2521 from the UK. All patients had been diagnosed as GH deficient by biochemical testing. Of all patients, 76.9% developed GHD in adulthood, whereas 23.1% of patients were reclassified as GHD following the diagnosis of CO GHD.

In order to explore regional differences, separate analyses of baseline characteristics of AO patients, never treated with GH prior to entry into KIMS (GH naïve) patients, were performed for the six largest contributing European countries (Belgium, n = 665; Germany, n = 1453; Spain, n = 595; UK, n = 1427; The Netherlands, n = 539; Sweden, n = 697) and USA (n = 1240). Furthermore, the six European countries were grouped together and compared against the USA. The close of data for this analysis was 10 December 2008.

Analyses were performed using statistical analyses systems (SAS, Cary, NC, USA) software version 8.2. Descriptive statistics of metric data are expressed as mean; median is used if data do not follow normal distribution. For group comparisons, Student’s t-tests (normally distributed data), χ², or Wilcoxon rank-sum tests (not normally distributed data) were used. Significance levels were set to P = 0.05. SAS procedure for general linear models (PROC GLM) was used for cross-sectional analyses of the influence of country on body mass index (BMI), waist-to-hip ratio (w/h), total cholesterol, high-density lipoprotein (HDL)- and low-density lipoprotein (LDL)-cholesterol, and triglycerides. Missing values were treated as missing at random.

The baseline characteristics and biochemical testing of the total KIMS cohort and the six largest European countries and the USA are presented below, with special emphasis on striking regional differences. In order to put previously published data on an evolving database into the context of changing proportions of certain parameters analyzed with comparable methodology, each result section is followed by a short discussion on the relevant topic.

Results and discussion

Patient demographics: total KIMS cohort (n = 13 167)

A large number of different etiologies form the basis of GHD in these patients, but the great majority of the patients suffered from a pituitary adenoma (44%) and another 11% of a craniopharyngioma. Idiopathic GHD (iGHD) was the reason for hGH replacement in 16.4% and brain tumor/irradiation in 7.0%, whereas traumatic brain injury (TBI: 3.1%), post partum pituitary necrosis (2.9%), and lymphocytic hypophysitis (0.9%) belong to the rarer diagnoses for hGH replacement in KIMS. Compared with previous studies, these findings mark a shift in the relative frequency of the etiologies of the patients included in KIMS, since an evaluation published in 2005 (7) reported a higher incidence of hypothalamic/ pituitary tumors and less patients with TBI, malignant diseases, or radiation to the brain for other than hypothalamic/pituitary tumors. The decrease in proportion of patients with pituitary adenomas, craniopharyngioma, and pituitary hemorrhage when compared with an increasing proportion of patients with iGHD or less common diagnoses fits with a recently published report of another global surveillance database (8). Following the initial therapeutic intervention, pituitary function (excluding the somatotropic axis) is preserved in only 15.9% of patients, whereas the majority of patients included in the database suffered from single or multiple additional pituitary hormone deficiencies. These include 69.8% with gonadotropin deficiency, 68.0% with TSH, and 61.4% with ACTH deficiency or combinations of these. Expectedly, the percentage of patients suffering from posterior pituitary deficiency was small (22.1%).

Baseline characteristics of GHD in KIMS: total cohort

Previous reports have indicated an increased morbidity and mortality in GHD patients (1, 2, 5–7, 9–13), most likely explained by an increased cardiovascular risk. Obesity, particularly visceral obesity with an increased w/h ratio, is found to be the most prominent feature (13). In our present evaluation, 35.2% of all patients fulfilled the criteria of obesity with a BMI of > 30 kg/m² and a further 35.5% were overweight. The overall w/h ratio averaged at 0.95 in males and 0.87 in females, indicating a moderately increased metabolic risk in males (cut-off: 1.0) and a high risk in females (cut-off: 0.85).

Treatment modalities appear to impact on body composition. A previous evaluation of the KIMS database published in 2005 (7), comparing patients with isolated GHD to those with multiple pituitary hormone deficiencies, was unable to reveal significant differences between these groups. However, predominantly, male patients with craniopharyngioma were significantly more obese, had a higher w/h ratio combined with a lower level of HDL-cholesterol and higher concentrations of triglycerides than the controls with a pituitary adenoma (14, 15). Similarly, patients treated with radiotherapy to the brain had a higher fat mass and a more unfavorable lipid distribution (16). Interestingly, their body composition was not related to all classical features of the metabolic syndrome, as the mean blood pressure was normal with 126/78 mmHg. This fits with the analysis of hypertension within our KIMS cohort, where only 15% of all patients were recorded to suffer from hypertension. Thus, blood
pressure control in GHD is better than expected from population studies (17), a finding at variance to a recent study from The Netherlands that described a higher frequency of hypertension in GHD patients than in controls (18).

Mean total cholesterol levels of 5.7 mmol/l were clearly raised in this KIMS cohort including semi- and true naïve patients, and exceeded in 45.7% the desired threshold of 5.2 mmol/l. Similarly, threshold levels for HDL-cholesterol (>1.04 mmol/l in males and >1.30 mmol/l in females) were met in only 45.7% (mean of all patients: 1.27 mmol/l), for LDL-cholesterol (<3.88 mmol/l) in 47.4% (mean: 3.53 mmol/l), and for triglycerides (<1.65 mmol/l) in 46.8% of patients (mean: 2.16 mmol/l). It is important to note that this analysis does not include the US, which is not participating in the centralized measurements of lipids. The proportion of patients diagnosed with diabetes mellitus was 5.9%. This suggests a similar relation for triglycerides (mean of all patients: 1.27 mmol/l), for LDL-cholesterol (<1.65 mmol/l) in 46.8% of patients (mean: 2.16 mmol/l). It is important to note that this analysis does not include the US, which is not participating in the centralized measurements of lipids.

The proportion of patients diagnosed with diabetes mellitus was 5.9%. This suggests a similar relation between insulin-like growth factor 1 (IGF1) and lipid parameters as previously described for a subset of KIMS between insulin-like growth factor 1 (IGF1) and lipid parameters as previously described for a subset of KIMS (19), and suggested by Maison et al. (20) who also could not relate the function of the somatotropic axis to blood pressure. These unfavorable relations to lipid parameters most likely explain the well-recognized increased risk of arteriosclerosis, which may be successfully reversed by GH replacement, as recently shown in a 5-year-longitudinal study measuring intima-media thickness (21). However, the low rate of claudication (0.6%), and the low proportion of coronary artery disease and stroke reported in medical history in this population (3.6 and 1.8% respectively) contrast to this and was a surprising finding.

Further exploration of the patient cohort revealed that arthrosis (reported in 5.6% of the patients) was expectedly linked with obesity ($\chi^2$-test, P<0.0001). The proportion of fractures, however, was exceedingly high with 19.8% suggesting direct GH-related effects on the bone, but also indirect reasons for bone fractures due to accompanying health problems (7) such as visual problems or epilepsy. Of the patients documented in KIMS, 6.0% were reported to be ophthalmoplegic and 33.6% reported visual field defects, whereas epilepsy was found in 3.5%. Again, the etiology of GHD may play a role as patients previously irradiated have a lower bone mineral density (16).

### Regional differences: AO, GH-naïve cohort (n = 7708)

Interestingly, when data were analyzed region specifically, we found prominent differences between countries.

Table 1 provides a comparison of baseline characteristics in KIMS in the European countries, the USA, and worldwide. Note that there are statistically significant differences in almost all the baseline criteria between European countries and the US, except for the QoL assessment of GH deficiency in adults (QoL-AGHDA) scores in males.

Furthermore, it is interesting to note that etiologies of GHD vary largely between European countries and the US. In the six largest European countries, the percentage of AO patients with iGHD ranges between 2.6 (NL) and 9.1% (Spain), whereas a pituitary adenoma was diagnosed in 44.4 (Spain) to 64.5% (UK). This contrasts to the US where the fraction of patients diagnosed with iGHD was dominant (56.6%), and only 20.7% were diagnosed with a pituitary adenoma (Fig. 1).

The high proportion of iGHD in the US prompted us to check whether this different distribution in comparison with European countries was due to a limited number of US centers prescribing recombinant...
GH for this diagnosis. However, this was not the case. Patients with iGHD came from many US centers. However, the majority of patients with this diagnosis stem from old days, when diagnostic procedures and knowledge about other etiologies of GHD such as TBI and radiotherapy were not clearly established. This is particularly highlighted in the data from US patients where 31% of all patients currently treated with GH are classified as iGHD, but only 20% of new patients are labelled with this diagnosis.

Similarly, there is a wide variation between countries in the approach to treatment of pituitary adenomas. Whereas surgery is the dominant form of treatment (67.9% of patients) in all countries, the use of radiotherapy (overall 27.1% of patients) varies considerably. In Germany, only 17.0% of patients received radiotherapy for a pituitary adenoma, in contrast to 58.7% in UK, or 46.7% and 49.4% in Sweden and The Netherlands respectively.

Interestingly, the GLM analysis revealed that the BMI of US KIMS patients (mean 33.3) was significantly higher ($P < 0.0001$) than the BMI of patients in any other European country included in the analysis. Of the six largest European countries, UK patients exhibited the highest BMI (mean 30.0 kg/m²), which again was significantly higher than the BMI of patients in Spain (mean 29.3), Germany (mean 29.0), Belgium (mean 28.5), The Netherlands (mean 28.4), and Sweden (mean 28.2; all $P$ values $< 0.0001$). Interestingly, despite exhibiting the highest BMI US patients had in comparison to Europeans a quite favorable w/h ratio. In this parameter, the GLM revealed Belgian patients to have the most favorable w/h ratio (mean 0.91), followed by patients from the US, UK, Germany, The Netherlands, Sweden, and Spain. This parameter was significantly different to any other European country included in the GLM (all $P$ values $\leq 0.0054$), except the US ($P = 0.1867$). GLM analysis of total cholesterol, HDL- and LDL-cholesterol, and triglycerides in European patients revealed only few country-specific differences: UK patients exhibited significantly lower mean LDL-cholesterol levels than patients from Sweden (mean 3.50 vs 3.66 mmol/l; $P = 0.006$) and patients from The Netherlands (3.70, $P = 0.015$), whereas Spanish patients had the lowest and British patients the highest triglyceride levels (1.81 vs 2.47 mmol/l; NS). In Spain and the UK, HDL levels were significantly lower than in the other European countries (all $P$ values $\leq 0.0026$). These findings were, however, not related to all features of the metabolic syndrome. Systolic blood pressure was significantly lower not higher in the US when compared with the European patients ($P = 0.0001$). Consistent with these results, US patients in KIMS are significantly less frequently diagnosed with hypertension ($P = 0.0055$) and coronary artery disease ($P = 0.0052$, $\chi^2$-tests respectively). Potentially, these differences may be explained by the differences in the etiologies of the US versus European patients with the higher prevalence of pituitary and hypothalamic tumors in the European group.

There are large differences in QoL between the countries. In the UK, an impaired QoL (defined as a score above 11 in the QoL-AGHDA) is a prerequisite to start GH replacement in deficient patients, whereas in countries like Germany or Belgium biochemical diagnosis of GHD is sufficient for GH replacement. Not surprisingly, UK patients exhibited the highest mean QoL-AGHDA score at baseline (16.2 points, scale ranges from 0 to 25 with a higher score denoting a worse QoL). This was significantly higher than the scores of any other European country or the US ($P < 0.0001$ for all investigated countries). In terms of poor QoL, the UK was followed by the US (mean QoL-AGHDA score 12.6), Belgium (mean 12.0), and Spain (mean 11.9), whereas German (mean 9.8) and Swedish patients had the best QoL of the investigated countries. When analyzing male and female patients separately in this sample, female patients exhibited a significantly worse QoL than male patients (mean QoL-AGHDA score 12.6 vs 10.6; $P < 0.0001$). This observed difference between male and female patients fits well into a recent comparison of

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**Figure 1** Proportion of GHD primary etiologies in Belgium, Germany, Spain, United Kingdom, Netherlands, Sweden and the United States (according to the KIMS classification list). Abs R, Feldt-Rasmussen U (eds) 2004 Growth Hormone Deficiency in Adults: 10 Years of KIMS, Oxford PharmaGenesis pp. 346–348.

**Figure 2** Proportion of tests used in KIMS in the six largest European countries and the US.
patients entered into the German KIMS database and a large cross-sectional cohort of 2734 controls (22).

Despite these country-specific differences, it is of interest that a recent survey clearly supports a country-independent reduction in morbidity under GH substitution therapy, supporting a beneficial effect ofGH replacement despite country-specific differences in baseline conditions (23).

**Biochemical testing for GHD**

Due to the pulsatile nature of GH secretion, only multiple sampling will allow evaluation of the GH status from basal levels (3). IGF1 and IGF-binding protein-3 as non-pulsatile targets of GH do correlate with the mean 24 h GH secretion, but the discriminative power of both factors is too low to preclude GHD (24). Confounding factors including age, nutritional status, and genetic factors influence absolute levels. Only when three or four other pituitary axes are deficient, a low IGF1 predicts GHD with high accuracy (25). Therefore, the current diagnostic approach rests on provocative tests for GH (3). None of them is optimal and fulfills the requirements of an ideal test defined by Casanueva as being convenient, economical, with a high discriminatory power between health and disease, reproducible, devoid of unwanted effects, not dependent on assay specificity, or on physiological factors such as the status of other pituitary axes, gender, and age (26).

The variability of used procedures is very high and the KIMS database is a particularly telling example for the enormous variety in diagnostic procedures used.

Figure 2 depicts the most frequently used tests in KIMS in the six largest European contributing countries and the US (data of CO and AO patients). Most strikingly, the insulin tolerance test (ITT), as the most popular test used in 44.3% of all countries, was unpopular (13.3%) in the US. Similarly, the glucagon test ranking third (10.9%) was very popular in the UK (29.9%), but virtually not used in Germany or The Netherlands (0.1%).

Unfortunately, most of these procedures are not validated sufficiently regarding cut-offs, reproducibility, and dependence on confounding factors. Even for the ITT, generally regarded as the ‘gold standard’ (27), reproducibility is a major problem (28, 29), and a number of other confounders such as gender, age, and BMI are known (30). This and the known risks, as well as the demanding surveillance during the ITT, stimulated the search for other, more practical procedures. But only the GHRH–arginine (ARG) and the GHRH–GH-releasing peptide-6 tests were evaluated in large series of patients and controls, as yet (31). They contrast to the ITT predominantly by the marked influence of adiposity, which particularly in the GHRH–ARG test led to the proposition of a BMI-adapted threshold level to define GHD (32). Within KIMS, the GHRH–ARG test only recently captured a larger share, but due to the orphan drug status of GHRH, this test was stopped in several countries including the US. In contrast to that, the other tests used in KIMS are based much on less well-characterized procedures. The rationale behind their choice as the large variety between countries remains obscure may be related to different health care systems and clinical settings, specific personal experience, and availability of drugs like GHRH (Fig. 2).

So far, a systematic comparison of the various tests in the same set of patients and controls was only performed in cross-sectional studies or in small series of patients with pituitary deficiency. Biller et al. (33) compared various test approaches under highly standardized conditions within the same individuals. As expected from larger but cross-sectional studies, the ITT as the GHRH–ARG test had higher discriminatory power than the clonidine, the L-DOPA test, or combination tests of ARG and L-DOPA.

It will be an important future task to better develop a reliable test procedure that will allow relation of clinical signs of the GHD syndrome to biochemical test results to clearly define patients at risk and patients who will benefit the most of GH replacement therapy.

**Summary**

This analysis combined a new evaluation of the etiologies, therapeutic approaches, baseline characteristics, and biochemical diagnosis of GHD within the KIMS database with an emphasis on regional differences. The distribution of etiologies is substantially changing with an increasing number of patients included who developed GHD following TBI and after treatment for tumors outside the hypothalamus and pituitary. Whether the marked regional differences in the underlying diagnosis for GHD represent a true difference between countries – prompted for example by differences in the health care systems and the availability of different GH stimulation tests – or rather, a wider diagnostic spectrum beyond the classical etiologies for GHD, is currently open. Differences in body composition, however, suggest that non-classical obesity-related indications are included in some regions that link up to the substantial differences in biochemical testing.

**Declaration of interest**

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