GH deficiency after traumatic brain injury: improvement in quality of life with GH therapy: analysis of the KIMS database

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Abstract

Objective: Prevalence of GH deficiency (GHD) caused by traumatic brain injury (TBI) is highly variable. Short-term studies show improvement in quality of life (QoL) during GH replacement (GHR), but long-term data are lacking. The aim of this study was to analyse the clinical characteristics of post-traumatic hypopituitarism and the QoL effects of long-term GHR. **Design/methods:** Pfizer International Metabolic Database patients with GHD caused by TBI and by non-functioning pituitary adenoma (NFPA) were compared regarding: clinical characteristics at baseline and 1-year of GHR, and QoL response up to 8-years of GHR (QoL-AGHDA total scores and dimensions) in relationship with country-specific norms. **Results:** TBI patients compared with NFPA patients were younger, diagnosed with GHD 2.4 years later after primary disease onset ($P < 0.0001$), had a higher incidence of isolated GHD, higher GH peak, a more favourable metabolic profile and worse QoL, were shorter by 0.9 cm (1.8 cm when corrected for age and gender; $P = 0.004$) and received higher GH dose (mean difference: 0.04 mg/day $P = 0.006$). In TBI patients, 1-year improvement in QoL was greater than in NFPA (change in QoL-AGHDA score 5.0 vs 3.5, respectively, $P = 0.04$) and was sustained over 8 years. In TBI patients, socialisation normalised after 1 year of GHR, self-confidence and tenseness after 6 years and no normalisation of tiredness and memory was observed. **Conclusion:** Compared with NFPA, TBI patients presented biochemically with less severe hypopituitarism and worse QoL scores. GHR achieved clinically relevant, long-term benefit in QoL.

European Journal of
Endocrinology
(2015) 172, 371–381

Introduction

There is evidence to demonstrate that following a traumatic brain injury (TBI), patients are at significant risk of developing post-traumatic hypopituitarism (PTHP) (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14). Following TBI, patients have significantly reduced quality of life (QoL) and cognitive indices (15, 16). Symptoms of fatigue are further exacerbated in the presence of growth hormone (GH) deficiency (GHD) compared with patients with normal GH reserve (17). These functional outcomes, together with PTHP, have been associated with abnormal neuroimaging findings in

TBI patients (18). Cognition and mood can be improved with GH replacement (GHR), with benefits shown after 1 year of therapy (19, 20). However, little is known about long-term changes in QoL following GHR in this population, with only one study reporting improvements in QoL (21). Furthermore, data are lacking about the impact of GHR on body composition and metabolic profiles, both of which are known to improve in other patient groups following GHR.

Studies that address how common this problem is have revealed widely differing estimates of the prevalence

rates of PTHP, partly because of variation in the definitions of GHD, the use of different provocation tests to diagnose GHD and different time points for assessing pituitary function post-TBI (12, 22). Furthermore, results of several dynamic function tests are dependent on the BMI of the patient (23), therefore confounding the data.

Despite the high prevalence of PTHP reported in some studies, a review of the Pfizer International Metabolic (KIMS) database by Casanueva *et al.* (24) in 2005 highlighted only 51 KIMS patients with adult-onset PTHP compared with 688 KIMS patients with GHD following non-functioning pituitary adenoma (NFPA). Subsequent to this, a further interrogation of the German KIMS database in October 2006 found 69 cases of GHR for this indication (25). These data may suggest deficiencies in the neuroendocrine evaluation of patients after TBI and potentially a very high prevalence of undiagnosed and symptomatic TBI-related GHD and hypopituitarism. It should be highlighted that only patients receiving GHR are followed in the KIMS database, and therefore alternative explanations could account for the lack of patients: either these TBI patients do not receive GH therapy or they have not been registered on the KIMS database.

The aim of the current study was to utilise the KIMS database to examine: i) the secular trends in numbers of new KIMS patients with PTHP; ii) the metabolic profile and associated defects of patients with PTHP; and iii) the effect of GHR on QoL measures over an extended period to assess the degree of long-term response. We used patients treated for NFPA as a comparator group.

Patients and methods

Patient groups

In August 2012, the KIMS database (a pharmaco-epidemiological survey of adult hypopituitary patients with GHD; total number of KIMS patients=16 266) (26) was interrogated for all patients with a diagnosis of TBI (Fig. 1). Diagnosis was recorded based on the clinical history taken by the registering physician. In this study, three different groups were analysed: i) all patients with TBI for the assessment of trends in the registrations of PTHP (Group 1, $n=479$); ii) patients with TBI, diagnosed with adult-onset GHD, never treated with GH before entry into KIMS and who had baseline and a minimum of 12-month follow-up data for the 1-year analysis of changes in metabolic profile and QoL (Group 2, $n=161$); and iii) patients with TBI, diagnosed with adult-onset GHD, never treated with GH

Figure 1

Investigation algorithm demonstrating inclusion criteria and analyses performed.

before entry into KIMS, with reported QoL-AGHDA up to 8-year follow-up for the cross-sectional internal reference analysis of QoL (Group 3, $n=154$). For the external reference analyses comparing the normal population, a subgroup of 126 patients was selected due to availability of reference data from Belgium, France, Germany, The Netherlands, Spain, Sweden and the UK. Patients with more than one pituitary diagnosis were excluded. Patients diagnosed with GHD in adulthood due to a TBI sustained in childhood were included.

Data from all patients with a diagnosis of adult-onset GHD caused by NFPA and no reports of cranial irradiation, who had baseline and a minimum of 12-month follow-up data, were used as a reference group. There were 1268 eligible NFPA patients for 1-year longitudinal analysis and a maximum number of 1143 NFPA patients from the same countries as TBI patients with QoL data at entry into KIMS for cross-sectional QoL analysis. All patients commencing GHR were required to be on complete replacement of other pituitary hormones and on stable doses before commencement of GHR.

Assessments

Three separate analyses were performed:

In the first analysis, in order to ascertain whether the number of KIMS patients with TBI were increasing, the database was interrogated for all registrations from inception in 1994–2009 (Fig. 1). In order to ascertain relative proportions, this number was expressed as

percentage of the total number of registrations. Additionally, in patients with an injury date/onset of pituitary disease, the age at onset was compared with age at diagnosis of GHD to ascertain the lag time from injury to diagnosis in both TBI and NFPA (Group 1).

In the second analysis, patients with TBI and NFPA were compared at baseline and 1-year follow-up (Group 2). Data analysed included demographic characteristics, number of associated pituitary deficiencies, stimulation test used, GH peak, insulin-like growth factor 1 (IGF1)-SDS, height, weight, BMI, cholesterol, HDL-cholesterol (HDL), LDL-cholesterol (LDL), triglycerides, lean body mass (bioimpedance (BIA)), fat mass (BIA), systolic and diastolic blood pressure, fasting glucose, HbA1c and total QoL-AGHDA score. This analysis was carried out on the database not only as a whole, but also on a subgroup of patients with 'severe' GHD defined as:

- i) GH peak $<3 \mu\text{g/l}$ during insulin tolerance test or glucagon stimulation, or
- ii) suboptimal BMI-dependent GH peak during GHRH-Arginine stimulation according to international guidelines, BMI <25 and GH peak $<11.5 \text{ ng/ml}$, BMI $25\text{--}30$ and GH peak $<8 \text{ ng/ml}$, BMI >30 and GH peak $<4.2 \text{ ng/ml}$ (27), or
- iii) IGF1-SDS <-2 in combination with three or more additional pituitary hormone deficiencies.

In the third analysis, QoL-AGHDA scores in patients with TBI and NFPA were analysed cross-sectionally in relationship with country-specific normative values up to 8 years of KIMS follow-up (Group 3).

The QoL-AGHDA, a disease-specific instrument, consists of 25 items that evoke yes/no answers, acknowledging or denying certain problems (28). QoL-AGHDA score is scored from 0 (best QoL) to 25 (worst QoL). A numerical decrease in the QoL-AGHDA score indicates an improvement in QoL. The instrument is reliable and valid with a high level of internal consistency (29). The normative reference values for the QoL-AGHDA were derived from general population samples from seven European countries (30, 31, 32, 33).

The analysis was also performed for the following QoL-AGHDA dimensions: problems with memory and concentration (six items), tiredness (seven items), tenseness (three items), social isolation (five items) and problems with self-confidence (four items), and the results presented as proportion of items with impairment within each dimension (33).

Serum IGF1 and lipids were centrally analysed at Kabi Pharmacia (Stockholm, Sweden) (1994–1997), and

thereafter at Sahlgrenska University Hospital, Gothenburg, Sweden. The following assay methods were used: until November 2002, RIA after acid/ethanol precipitation of IGF-binding proteins (Nichols Institute Diagnostic, San Juan Capistrano, CA, USA); until September 2006, chemiluminiscence immunoassay (Nichols Advantage System); and after September 2006, Immulite 2500 (DPC Siemens, Munich, Germany) (34). Intra-assay, inter-assay, and total coefficients of variation were $<9\%$ in the concentration range of $125\text{--}1046 \mu\text{g/l}$. The assay detection limit was $13.5 \mu\text{g/l}$. Age and gender-specific reference ranges were used to determine an IGF1-SDS for each patient (35). Serum total cholesterol, HDL-cholesterol and triglycerides were measured by standardised methods and serum LDL-cholesterol was calculated according to the Friedewald formula (36). Waist and hip measurements were conducted according to KIMS Guidelines (36), and BMI was calculated as body weight (kg)/(height)² (m²).

Statistical analysis

Descriptive statistics were presented and analysed with means and s.d., or proportions, depending on the type of variable. Regression analysis on time between TBI date or date of diagnosis of NFPA and diagnosis of GHD was adjusted for age (numerical), gender, calendar-year (numerical) and were performed by PROC REG, SAS version 9.2.

The statistical analyses for baseline outcome variables and 1-year change outcome variables were performed by covariance analyses for unbalanced designs (PROC GLM, SAS version 9.2). Group comparisons, using mean values, were adjusted, in general, for age at measurement and gender, except for the analysis of GH peak, which additionally were adjusted for type of stimulation test. As these adjusted means are assumed to vary with age and gender, we chose to present them for both study groups at a typical (KIMS entry) age of 45 years with equal gender distribution. For the analyses of dimensions of QoL-AGHDA, mixed-linear regression was used as the within-patient dimension scores are expected to correlate. The number of items differed by dimension, so standardisation was necessary and this was achieved by computing the percentage of items within a dimension that a patient expressed problems with. The covariance structure was estimated with an unstructured variance-covariance matrix. Adjustments were made for age and gender. Analyses were performed at yearly visits (cross-sectionally). CIs were Wald based. Statistical significance was set to $P<0.05$.

Results

Analysis 1 (Group 1)

See [supplementary data](#) section.

Analysis 2 (Group 2)

Differences in baseline profiles ► For the analysis of metabolic profile and QoL baseline characteristics in Group 2 – adult-onset GHD patients (161 TBI and 1268 NFPA patients) are given in [Table 1](#). TBI patients were younger; however, there was no difference in gender distribution with a male preponderance in both groups. TBI patients were shorter than NFPA patients by 0.9 cm (1.8 cm when corrected for age and gender; 95% CI: –3.0 to –0.6 cm; $P=0.004$).

Body composition was similar in both groups, with the exception of a reduction in lean mass in the TBI group. Metabolic indices were more favourable in the TBI group even after correction for age and gender with lower systolic and diastolic blood pressure, and total cholesterol and LDL ([Table 2](#)).

Despite similar IGF1-SDS in both groups, peak GH was greater in the TBI patients after adjustment for age, BMI, gender and stimulation test ($P=0.02$) when the group was considered as a whole. Proportions of GH stimulation tests by group are shown in [Fig. 2](#).

TBI patients had fewer associated pituitary deficiencies (1.6; 95% CI: 1.4–1.8 for TBI vs 2.4; 95% CI: 2.3–2.5 for NFPA) and a higher prevalence of isolated GHD (24.9% TBI vs 6.4% NFPA). The most frequent additional deficiency was adrenocorticotrophin deficiency in both groups, followed by TSH, LH/FSH and ADH in TBI patients, and LH/FSH, TSH and ADH in NFPA. QoL-AGHDA score was statistically significantly worse in TBI patients compared with NFPA patients. This was consistent across all QoL-AGHDA subdomains of memory, tiredness, tenseness, socialising and self-confidence (data not shown).

One year follow-up data ► Follow-up data for both TBI and NFPA patients are given in [Table 1](#). Improvements were seen in IGF1-SDS and waist-to-hip ratio in both groups; however, improvements were also seen in body composition in the NFPA group with an increase in lean mass, which was not seen in the TBI group. Likewise, NFPA patients saw marginal increases in fasting glucose and HbA1c with reductions in total cholesterol, LDL and triglycerides. There were no statistically significant between group changes in any of these variables. Mean GH

dose over the 12-month period was somewhat higher in the TBI group (0.37 mg/day vs 0.33 mg/day for NFPA patients (mean difference: 0.04 mg/day 95% CI: 0.01–0.07; $P=0.006$; adjusted for age and gender).

Assessment of QoL: total QoL-AGHDA ► At baseline TBI patients had significantly worse QoL-AGHDA scores compared with NFPA patients (13.8 vs 9.7). There was no association between time from injury and baseline QoL in the 51 patients in whom an injury date was recorded ($P=0.7$). When reassessed 12 months after treatment commenced, QoL-AGHDA score had improved significantly in both groups, with the improvement being greater in the TBI patients (5.0 vs 3.5 points; $P=0.04$); however, the overall score remained worse in TBI patients ([Fig. 3A](#)).

Assessment of QoL: QoL-AGHDA dimensions ► Data on dimensions at baseline are given in [Table 1](#). At baseline, both TBI and NFPA patients showed impairment in all QoL-AGHDA dimensions. TBI patients had greater impairment in all areas compared with NFPA. TBI patients showed greatest impairment in tiredness, followed by tenseness, memory, self-confidence and lastly socialising. At 1 year, both groups of patients improved significantly in all areas. Self-confidence was the only dimension where patients with TBI improved to a significantly greater extent than patients with NFPA ([Table 1](#)).

The analysis was repeated in patients documented with ‘severe’ GHD. A total of 89 patients and 896 NFPA patients were eligible for inclusion in this analysis. In this group, there was no significant difference in peak GH after correction for age, gender, BMI and type of stimulation test. Although power was reduced due to smaller numbers, our key findings were unchanged.

Analysis 3 (Group 3)

QoL-AGHDA scores for 8 years post GH start were available in both sets of patients. These are shown in [Fig. 3](#). In the TBI patients, the initial improvement in QoL observed after 12 months was sustained over the 8-year period; however, it remained significantly worse than that in the NFPA group ([Fig. 3A](#)). When compared with data from the general population, TBI patients had a significantly worse QoL score up until year 8 when this difference became non-significant ([Fig. 3B](#)).

Analysis of QoL-AGHDA dimensions showed that TBI patients demonstrated normalisation of socialisation compared with the normal population after 1 year.

Table 1 12-month data for 161 TBI patients and 1268 NFPA patients demonstrating age- and gender-adjusted change within groups between baseline and 1 year, together with significant changes between groups at 1 year.

Variable	TBI (mean, 95% CI)		NFPA (mean, 95% CI)		Between groups					
	Whole cohort	Severe GHD	Whole cohort	Severe GHD	Whole cohort	Severe GHD				
BMI (kg/m ²)	-0.19	-0.46, 0.08	-0.09	-0.45, 0.28	-0.04	-0.16, 0.08	0.0	-0.14, 0.14	NS	NS
Waist hip ratio	-0.01	-0.02, 0.0	-0.02	-0.03, 0.0	-0.01	-0.01, 0.0	-0.01	-0.01, 0.0	NS	NS
IGF1-SDS	1.59 ^a	1.19, 1.98	1.85 ^a	1.30, 2.39	1.90 ^a	1.76, 2.04	2.02 ^a	1.85, 2.19	NS	NS
Lean mass (kg) BIA	0.12	-1.56, 1.80	0.64	-1.93, 3.21	0.96 ^a	1.17, 1.75	0.73	-0.35, 1.80	NS	NS
Fat mass (kg) BIA	-1.91	-3.88, 0.06	-1.30	-4.23, 1.64	-0.87	-1.8, 0.05	-1.01	-2.24, 0.21	NS	NS
Fasting glucose (mmol/l)	0.17	-0.12, 0.46	0.03	-0.31, 0.36	0.17 ^a	0.06, 0.28	0.20 ^a	0.07, 0.33	NS	NS
HbA1c (%)	0.1	-0.04, 0.24	0.06	-0.11, 0.23	0.1 ^a	0.05, 0.15	0.10 ^a	0.04, 0.16	NS	NS
Diastolic BP (mmHg)	0.15	-1.71, 2.02	1.06	-1.38, 3.50	-0.32	-1.12, 0.48	-0.32	-1.25, 0.60	NS	NS
Systolic BP (mmHg)	1.71	-1.33, 4.75	3.47	-0.46, 7.40	-1.07	-2.38, 0.23	-0.98	-2.47, 0.51	NS	0.04
Cholesterol (mmol/l)	-0.06	-0.34, 0.21	0.03	-0.30, 0.36	-0.20 ^a	-0.31, -0.10	-0.20 ^a	-0.31, -0.10	NS	NS
LDL (mmol/l)	-0.12	-0.32, 0.09	-0.05	-0.33, 0.22	-0.16 ^a	-0.24, -0.08	-0.18 ^a	-0.27, -0.09	NS	NS
HDL (mmol/l)	-0.03	-0.10, 0.05	-0.04	-0.13, 0.06	0.02	-0.01, 0.04	0.01	-0.02, 0.04	NS	NS
Triglycerides (mmol/l)	0.08	-0.30, 0.46	0.10	-0.31, 0.51	-0.15 ^a	-0.29, -0.01	-0.09	-0.22, 0.04	NS	NS
GH dose (mg/day)	0.37	0.35, 0.40	0.38	0.34, 0.42	0.33	0.32, 0.34	0.34	0.33, 0.36	0.006	0.06
QoL-AGHDA score	-5.0 ^a	-3.7, -6.4	-4.3 ^a	-6.0, -2.7	-3.3 ^a	-3.0, -4.0	-3.3 ^a	-3.9, -2.8	0.04	NS
QOL-AGHDA dimensions:										
Memory	-0.17 ^a	-0.23, -0.1	-0.13 ^a	-0.22, -0.05	-0.13 ^a	-0.15, -0.10	-0.12 ^a	-0.15, -0.09	NS	NS
Tiredness	-0.22 ^a	-0.3, -0.15	-0.19 ^a	-0.28, -0.09	-0.21 ^a	-0.23, -0.18	-0.19 ^a	-0.22, -0.16	NS	NS
Tenseness	-0.21 ^a	-0.3, -0.13	-0.19 ^a	-0.30, -0.09	-0.14 ^a	-0.17, -0.11	-0.14 ^a	-0.17, -0.10	NS	NS
Socialising	-0.14 ^a	-0.2, -0.08	-0.11 ^a	-0.18, -0.03	-0.09 ^a	-0.12, -0.07	-0.09 ^a	-0.11, -0.06	NS	NS
Self confidence	-0.2 ^a	-0.27, -0.14	-0.17 ^a	-0.25, -0.09	-0.08 ^a	-0.11, -0.06	-0.08 ^a	-0.11, -0.06	0.0008	0.04

^aSignificant difference within group between baseline and 1 year.

Table 2 Baseline data for 161 TBI patients and 1268 NFPA patients demonstrating age- and gender-adjusted mean and 95% CIs with between-group differences.

Variable	TBI (mean, 95% CI)		NFPA (mean, 95% CI)		P value					
	Whole cohort	Severe GHD	Whole cohort	Severe GHD	Whole cohort	Severe GHD				
Age (years)	42.6	40.8, 44.5	40.9	38.4, 43.4	53.2	52.5, 53.8	52.4	51.5, 53.2	<0.0001	<0.0001
Gender (% male)	58		61		62		64		NS	NS
BMI (kg/m ²)	29.0	28.2, 29.8	28.3	27.3, 29.4	28.9	28.6, 29.3	28.7	28.3, 29.1	NS	NS
Height (cm)	169.9	168.8, 171.0	169.8	168.3, 171.3	171.7	171.2, 172.2	171.7	171.1, 172.3	0.02	NS
Waist-to-hip ratio	0.93	0.91, 0.94	0.93	0.92, 0.95	0.92	0.92, 0.93	0.92	0.92, 0.93	NS	NS
Lean mass (kg) BIA	54.7	52.0, 57.5	54.0	50.3, 57.8	58.1	56.9, 59.3	57.6	56.1, 59.2	0.02	NS
Fat mass (kg) BIA	25.7	22.7, 28.7	25.0	21.2, 28.8	26.9	25.6, 28.3	25.8	24.2, 27.4	NS	NS
Fasting glucose (mmol/l)	5.0	4.8, 5.3	4.9	4.7, 5.2	4.9	4.8, 5.0	4.9	4.8, 5.0	NS	NS
HbA1c (%)	5.3	5.2, 5.5	5.2	5.0, 5.5	5.2	5.2, 5.3	5.2	5.1, 5.2	NS	NS
Diastolic BP (mmHg)	79	77, 80	79	77, 81	81	80, 81	81	80, 81	0.02	NS
Systolic BP (mmHg)	125	122, 128	124	121, 128	128	127, 129	127	126, 129	0.03	NS
Cholesterol (mmol/l)	5.37	5.06, 5.68	5.30	4.91, 5.69	5.76	5.64, 5.88	5.79	5.66, 5.92	0.02	0.02
LDL (mmol/l)	3.25	2.99, 3.51	3.26	2.93, 3.60	3.55	3.45, 3.65	3.61	3.49, 3.72	0.03	0.06
HDL (mmol/l)	1.27	1.18, 1.36	1.21	1.10, 1.33	1.27	1.23, 1.30	1.28	1.24, 1.32	NS	NS
Triglycerides (mmol/l)	1.81	1.41, 2.20	1.83	1.42, 2.24	2.19	2.04, 2.34	2.08	1.95, 2.22	NS	NS
Peak GH (µg/l) ^a	3.22	1.55, 4.89	1.04	0.55, 1.52	1.79	1.08, 2.49	0.82	0.63, 1.00	NS (0.12)	NS
IGF1-SDS	-1.27	-1.63, -0.90	-1.94	-2.42, -1.45	-1.52	-1.66, -1.38	-1.74	-1.90, -1.58	NS	NS
Additional deficiencies (no.)	1.6	1.4, 1.8	1.9	1.7, 2.2	2.4	2.3, 2.5	2.4	2.4, 2.5	<0.0001	<0.0001
QoL-AGHDA score	13.9	12.5, 15.4	12.8	10.9, 14.7	10.4	9.8, 10.9	9.9	9.2, 10.5	<0.0001	0.004
QoL-AGHDA dimensions										
Memory	0.63	0.56, 0.70	0.55	0.45, 0.65	0.46	0.43, 0.49	0.44	0.41, 0.48	<0.0001	0.04
Tiredness	0.66	0.59, 0.73	0.60	0.51, 0.69	0.50	0.47, 0.53	0.47	0.44, 0.50	<0.0001	0.01
Tenseness	0.65	0.57, 0.72	0.62	0.52, 0.72	0.50	0.47, 0.53	0.49	0.46, 0.52	0.0004	0.02
Socialising	0.38	0.32, 0.45	0.36	0.28, 0.44	0.30	0.28, 0.33	0.30	0.27, 0.33	0.02	NS
Self confidence	0.42	0.35, 0.48	0.39	0.31, 0.48	0.27	0.25, 0.30	0.25	0.23, 0.28	<0.0001	0.002

^aPeak GH adjusted for age, gender and type of stimulation test. QoL-AGHDA dimensions are shown as age- and gender-adjusted mean proportion of items that patients have problems with.

Figure 2

Growth hormone stimulation tests used for diagnosis of GHD in 161 TBI patients and 1268 NFPA patients.

Self-confidence returned to within the range of the normal population by year 6 as did tenseness, although small numbers led to wider CIs by this point. Impairment in tiredness and memory never returned to the level of the normal population (Fig. 4).

Discussion

In this analysis, we have examined the largest cohort of patients following TBI with 1-year follow-up data on a range of variables. We have additionally presented QoL data for 8 years post GHR and compared this with other patients with hypopituitarism due to another cause (NFPA), and with a reference population.

We have shown that the proportion of registrations for PTHP is increasing, but remains low (Supplementary Analysis, see section on supplementary data given at the end of this article). We had speculated that after the recent interest in PTHP, registrations for this cause of GHD would have increased. The incidence of hospitalised TBI patients is 235 per 100 000 population (37). Considering a pooled prevalence of PTHP of 27.4% (95% CI: 22.8–28.9%) found by Schneider *et al.* (6), this could suggest that a large number of undiagnosed patients with GHD exist, although the meta-analysis does include data from highly selected cohorts, so prevalence may be overestimated.

Our second hypothesis, that with increased awareness, the lag time from injury to GHD diagnosis would have reduced, was not confirmed. We demonstrated once again a significant lag time between injury date and

diagnosis of GHD, with patients with TBI diagnosed over 2 years later than NFPA patients. This lag was observed in the two previous KIMS studies (24, 25). It may be that a reduction in the lag time is observed in future studies.

We have shown that TBI patients with PTHP have a different hormonal and metabolic profile in comparison with hypopituitary patients with NFPA. Our analysis of the metabolic profile and nature of PTHP in this population has reconfirmed that the TBI population is younger, and of similar BMI to NFPA patients. Our analysis shows that the nature and risk of PTHP differ from that seen with NFPA. There is a higher incidence of isolated GHD, and a consequent reduction in the number of associated pituitary deficiencies, which could be considered suggestive of less severe hypopituitarism than in NFPA. This is also supported by the finding of a trend to higher peak

Figure 3

Changes in QoL-AGHDA score over time in patients given GHR. (A) 154 TBI patients and 1143 NFPA patients at baseline and (B) 126 TBI patients in whom country-specific normative data were available. Dotted line indicates level of normal population, *n* equals number of TBI patients available for follow-up at each point.

Figure 4

Percentage difference in AGHDA dimensions in comparison with general population (GP) in TBI patients (126 at baseline) in whom country-specific normative data were available. Higher percentage equals worse QoL for each specific dimension.

GH to stimulation in GHD patients, although this can partially be explained by differences in stimulation testing, with no significant difference in peak GH observed after correction for type of stimulation test. It could be postulated that healthy patients could have been misclassified as GHD which has been a concern in recent studies (38); however, we also observed similar pre-treatment IGF1-SDS between the groups which would refute this. We have also demonstrated similar findings when the analysis has been repeated on patients with documented severe GHD as defined before (39), including taking account of BMI in the GHRH/Arginine test, the only test currently where BMI-specific cut-offs are available. The body composition and metabolic data of PTHP suggest a lower cardiovascular risk than in patients with NFPA, with lower cholesterol and LDL concentrations, and lower systolic and diastolic blood pressures even after correction for age and gender. The only marker of adverse body composition in the TBI group is the finding of lower lean muscle mass, which may represent disuse atrophy.

We have shown that similar to previous KIMS data (24, 25), patients post TBI were shorter than counterparts with NFPA. Subgroup analysis has shown that this difference can be accounted for by patients whose injury date was before 19 years of age (data not shown). This suggests that head injury in childhood when incurred before attainment of final height, may in some cases account for reductions in growth, although the numbers involved are small. However, Bellone *et al.* (40)

demonstrated an association between reduced height velocity in children post TBI and PTHP in this group.

This study has provided initial evidence on the beneficial and sustained effect of GHR on QoL in this cohort over 8 years. It has been shown in many studies that TBI patients have reduced QoL, and that TBI patients with PTHP have a worse QoL and greater fatigue than compatriots without PTHP (17, 20, 41, 42), although this is not universally agreed (43). GHR is known to improve QoL in patients with GHD (33), and this is reconfirmed by the improvements in QoL seen in the NFPA patients in our study. Short-term studies and case reports have shown GHR to improve QoL and cognition in TBI patients with GHD up to 12 months (44, 45). Kozłowski *et al.* (21) demonstrated improvements in cognition, particularly verbal memory and in QoL after 12 months treatment, whilst Maric *et al.* (20) demonstrated improved cognitive abilities particularly in verbal and non-verbal memory, and improvements in psychiatric functioning with subsequent worsening in three patients who discontinued treatment for 12 months. Our data show significant improvement in QoL-AGHDA score after 12 months; however, additionally we have demonstrated sustained improvement over a number of years. There was no association between length of time since injury and baseline QoL which suggests that improvements in QoL were not simply due to increasing length of time since the injury rather than GHR.

Similar to previous data on changes in QoL-AGHDA dimensions in GHD patients treated with GHR (33), we have shown a more rapid improvement in problems with socialising, and a much slower improvement in problems with memory and tiredness. As would be expected QoL scores remain significantly lower than both NFPA patients and the reference population, most likely reflecting other consequences of injury in these patients. Recently it has been shown by Tanriverdi *et al.* (5) that hypopituitarism improves in a proportion of patients when pituitary function is rechecked 5 years post injury. This factor as well as overall physical recovery may be responsible for the continued gradual improvement in QoL after the initial 12-month period.

This study has several weaknesses. Our data cover only patients with GHD rather than the full spectrum of pituitary deficiencies without GHD. However, given that GHD is usually the first deficiency to occur due to the location of the somatotrophs within the pituitary, it would be expected that most patients with other pituitary hormone deficiencies would also have GHD. This study only includes patients commencing GH, which would

indicate that patients, particularly in the UK would need to be symptomatic – this could lead to over-reporting of poor QoL scores compared with the overall population of patients with PTHP. The cross-sectional nature of such a registry-based study also means that there could be a bias to more positive outcomes, as patients who fail to improve may simply have dropped out. Furthermore, although concomitant medication was part of a standard KIMS data collection, the quality of information on other medication than pituitary hormone replacement does not allow for a meaningful analysis. Therefore, we could not correct our analyses for the impact of medications such as antidepressants. It must also be acknowledged that there are limitations when studying QoL as an outcome measure for TBI including poor definitions, lack of sensitivity and poor differentiation of the effect of comorbidities.

In conclusion, we have shown that registrations for PTHP are increasing, however remain proportionately lower than may be expected suggesting either under-diagnosis or failure to register patients. We have also demonstrated that compared with NFPA patients there remains a lag time between injury and diagnosis in TBI patients. Finally, our findings suggest that whilst PTHP may be biochemically less severe than hypopituitarism secondary to NFPA, there are significant and clinically relevant improvements in QoL, which are sustained in the long term in this population. These important findings provide an evidence base for treating affected patients with PTHP.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-14-0654>.

Declaration of interest

M Korbonits received honoraria from Pfizer as member of the KIMS Strategic Advisory Board, A F Mattsson is permanent employee of Pfizer, M Koltowska-Haggstrom was a full-time employee at Pfizer, Inc. when the work was done but now is an affiliate at the Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden. C Daousi and D J Cuthbertson have both received unrestricted research grants from Pfizer. The authors were not paid for their contribution to this manuscript.

Funding

KIMS is sponsored by Pfizer, Inc.

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Received 4 August 2014

Revised version received 1 December 2014

Accepted 23 December 2014