Hypopituitarism : clinical assessment in different conditions

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Chapter 3

Low prevalence of hypopituitarism after traumatic brain injury – a multi-center study

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Abstract

Objective: Hypopituitarism after traumatic brain injury (TBI) is considered to be a prevalent condition. However, prevalence rates differ considerably among reported studies, due to differences in definitions, endocrine assessments of hypopituitarism, and confounding factors, like timing of evaluation and the severity of the trauma.

Aim: To evaluate the prevalence of hypopituitarism in a large cohort of TBI patients after long-term follow-up using a standardized endocrine evaluation.

Study design: Cross-sectional study

Patients and Methods: We included 112 patients with TBI, hospitalized for at least 3 days and a duration of follow-up > 1 yr after TBI from 5 (neurosurgical) referral centers. Evaluation of pituitary function included fasting morning hormone measurements and insulin tolerance test (ITT n=90) or, when contraindicated, ACTH-stimulation and/or CRH-stimulation test and a GHRH-arginine test (n=22). Clinical evaluation included quality of life questionnaires.

Results: We studied 112 patients (75 males), with median age 48 yr, and mean BMI 26.7±4.8 kg/m^2. Mean duration of hospitalization was 11 days (3–105) and 33% had a severe trauma (Glasgow Coma Scale < 9) after TBI. The mean duration of follow-up was 4 (1–12) years. Hypopituitarism was diagnosed in 5.4% (6/112) of patients: severe GH deficiency (n=4), hypogonadism (n=1), adrenal insufficiency (n=2). Patients diagnosed with pituitary insufficiency had significantly higher BMI (P =0.002).

Conclusion: In this study, the prevalence of hypopituitarism during long-term follow-up after TBI was low. Prospective studies are urgently needed to find reliable predictive tools for the identification of patients with a significant pre-test likelihood for hypopituitarism after TBI.

Introduction

Traumatic brain injury (TBI) is common and an important cause of death, especially among adolescents in developed countries. The last decade, pituitary insufficiency has emerged as an important sequel following TBI, potentially influencing short- and long-term morbidity. After TBI, many patients experience persistent, invalidating complaints that resemble those observed in patients with hypopituitarism, such as impaired cognition, depression, fatigue and impaired quality of life (QoL) (1–4). Consequently, pituitary insufficiency following TBI may contribute to the problems reported by these patients (4). This condition is important to identify since it can be treated by hormone replacement therapy resulting in improved QoL (3;5).

However, the actual prevalence of hypopituitarism after TBI in an unselected population is subject for debate. The available cohort studies studying the prevalence of pituitary insufficiency report percentages ranging from 15 to 90% (6–18). There are several explanations for this remarkably wide range in reported prevalences, including differences in inclusion criteria, differences in duration of follow-up since TBI (short *vs* long term follow-up) and the use of different tests, different assays and different cut-off values (19).

Therefore, the aim of our study was to evaluate the prevalence of hypopituitarism in a large cohort of TBI-patients after long-term follow-up, using standardized endocrine evaluation including golden standard tests. The secondary aim was to assess QoL and the contribution of hypopituitarism on QoL.

Patients and methods

Study protocol

We performed a multicenter study in 5 hospitals across the Netherlands (Leiden University Medical Center; Academic Medical Center, Amsterdam, St. Elisabeth Hospital, Tilburg; Isala Clinics, Zwolle; Medical Spectrum Twente, Enschede). Eligible patients were selected from electronic registries of the departments of neurology using the following inclusion criteria: confirmed diagnosis of TBI and hospitalization for at least three days for head injury at least one year prior to endocrine evaluation (to exclude possible hormone alterations mimicking pituitary insufficiency in the early post trauma period), age 18–70 yrs. Exclusion criteria were: medical or psychological problems (not related to TBI) that could disturb interpretation of results, including drug- or alcohol abuse, previously known hypothalamic- or pituitary dysfunction or history of cranial irradiation or pregnancy. Details on trauma severity were derived from the medical records. The Glasgow Coma Scale (GCS) at hospitalisation defined trauma severity. A GCS 13–15 indicates mild trauma, between 9–12 moderate trauma, and < 9 severe trauma (20;21). Ethical approval was obtained by the Medical Ethics Committees of all centers and all patients gave written informed consent.

Patients

A total of 2350 potential patients were retrieved from the electronic databases that had been diagnosed with TBI. The electronic patient records of these patients were retrieved in the departments of neurology of all participating hospitals. However, 1960 patients did not meet the abovementioned inclusion criteria and were excluded. The remaining 390 patients were invited to participate, of whom 278 patients could not be included for various reasons: not willing to participate without giving any reason, not meeting the inclusion criteria (either 2 days of hospitalization, drug or alcohol abuse, or medication that could not be stopped) or were loss to follow-up. Ultimately, we included a total of 112 patients in the study (Figure 1).

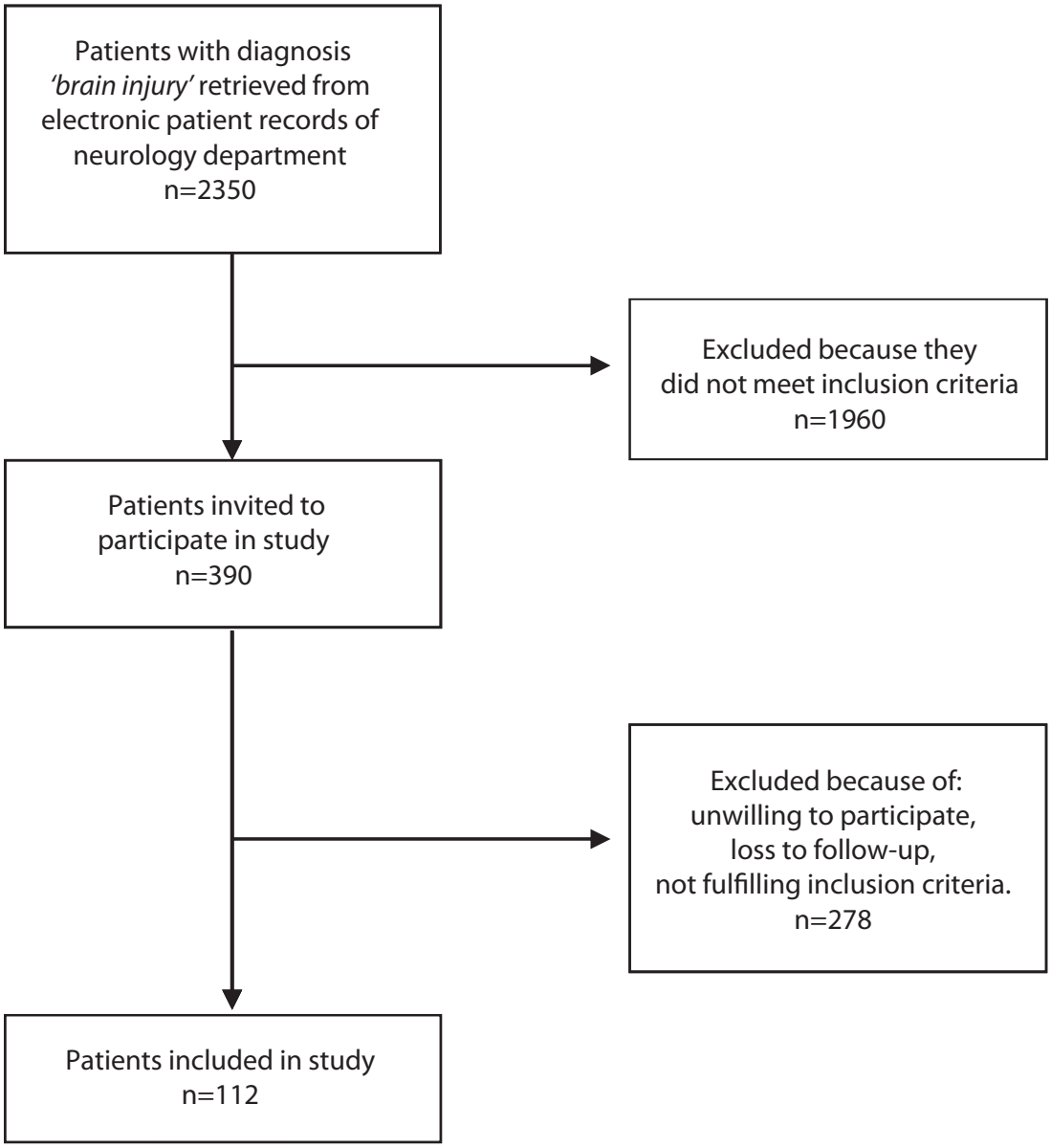

Figure 1. Flow chart of inclusion of patients

Endocrine evaluation

Blood was sampled for assessment of basal and stimulated hormone concentrations between 08.00 and 09.00h A.M. after an overnight fast. All patients rested 30 min prior to testing after insertion of an indwelling catheter in a large forearm vein. Baseline samples were drawn for analyses of cortisol, free thyroxine (fT_4), TSH, testosterone (men) estradiol (E_2; women), LH, FSH, prolactin (PRL), GH and IGF-I. Oral contraceptives were discontinued for at least 6 weeks before testing.

The hypothalamic-pitutiary adrenal (HPA) and GH-IGF-I axes were evaluated with an insulin tolerance test (ITT), unless contraindicated, or alternatively by ACTH/CRH and GHRH-stimulation tests. An ACTH-test (1 or 250μg Synacthen iv, Novartis Pharma BV, Arnhem, the Netherlands), with measurement of cortisol at T= -5, 30 and 60 min, was performed routinely in all patients prior to the ITT to ensure sufficient adrenal function. ITT was performed by administering soluble insulin intravenously (0.10 U/kg, Actrapid, Novo, Alphen aan den Rijn, The Netherlands) to induce hypoglycaemia (glucose < 2.2 mmol/L). Cortisol, ACTH, GH and glucose levels were measured at T = -15, 0, 15, 30, 45, 60 and 90 min. Peak values of GH of 3 μg/L and cortisol of >500 nmol/L were considered to reflect sufficient pituitary GH and ACTH function. If ITT was contraindicated, a GHRH-arginine test was conducted to evaluate GH secretory reserve. Patients received 1 μg/kg GHRH (Ferring BV, Hoofddorp, the Netherlands) and 500 mg/kg arginine with a maximum of 30 gr. GH levels were measured at T = –15, 0, 30, 45, 60, 75 and 90 min. BMI adjusted cut-off values of 11.5 μg/L (< 25 kg/m^2), 8.0 μg/L (25-30 kg/m^2), and 4.2 μg/L (> 30 kg/m^2) were used (22). For the evaluation of the HPA axis when ITT was contraindicated, the response to ACTH-stimulation was considered and an additional CRH-stimulation test was performed in selected cases (Table 2).

Assays

GH was measured in participating centers using in-house assays. The measurement of GH has been harmonized in the Netherlands (23) and in all centers, GH was calibrated against the WHO-IRP 98/574 (1 μg/L = 3.0 mU/L). IGF-I measurement was centralized at the Department of Clinical Chemistry, Sahlgrenska University Hospital, Göteborg, Sweden using a chemiluminescence immunoassay (DPC, Immulite 2500 system, Siemens Healthcare Diagnostics, Deerfield, IL, USA). The intra- and inter-assay coefficients of variation (CVs) were 4 and 11%. Reference values based on Brabant *et al.* (24) were used. With these IGF-I values IGF-I SD scores were calculated.

The participating centers used the following in house assays and cut-off values:

Leiden University Medical Center, Leiden: Cortisol, fT_4, TSH, LH, FSH and prolactine blood levels were measured by electrochemoluminescent

immunoassay (ECLIA), using a Modular E170, (Roche Diagnostics, Mannheim, Germany). The maximal inter-assay coefficient of variation was 5.0%. ACTH, GH and IGF-I were determined by immunolimunimetric assay using an Immulite 2500 (Siemens Healthcare Diagnostics, Deerfield, IL, USA). The maximal inter-assay coefficient of variation was between 5.0 and 10.0%. Glucose levels were measured using a Modular P800 (Roche Diagnostics Mannheim, Germany) (CV is 3%). For measurement of estradiol levels a radioimmunoassay (RIA, Orion Diagnostica, Espoo, Finland) was used (CV is 6% at 70 pmol/L). The estradiol detection limit was 20 pmol/L. Testosterone was measured using a RIA (Siemens Healthcare Diagnostics, Deerfield IL, USA). (CV is 20% at 1.0 nmol/L and 12% at 14 nmol/L) The detection limit was 0.2 nmol/L.

Academic Medical Center, Amsterdam: Plasma LH, TSH and FSH were analysed by an automated assay on the E170 of Roche (Roche, Mannheim, Germany). The maximal intra- and inter-assay variations were < 5%. Plasma fT_4, PRL and GH were analyzed by fluoroimmunoassay (Delfia, Perkin Elmer, Waltham, MA, USA) using the Delfia 1232 Fluorometer (Perkin Elmer). The maximal intra- and inter-assay CVs were 5.1 and 6.8% for fT4, 3.4 and 5.3% for PRL, and 3.8 and 6.2% for GH, respectively. Testosteron was analysed by an in-house RIA. The maximal intra- and inter-assay CVs were 11.8 and 12.8% respectively. Cortisol was analysed by chemoluminiscence assay using the Immulite 2000 (Siemens, Healthcare Diagnostics). The maximal intra- and inter-assay CVs were 5.5 and 8.3% respectively. E_2 was measured by RIA (Siemens Healthcare Diagnostics). The intra- and inter-assay CVs were < 20% (low level) and maximal at 8.6% (medium level).

St. Elisabeth Hospital, Tilburg and Isala Clinics, Zwolle: Plasma TSH, fT_4, PRL, LH, FSH, testosterone and E_2 were analyzed by ECLIA (Modular Analytics E170, Roche, GmbH). The maximal intra- and inter-assay CVs as specified by the manufacturer were as follows: TSH, 3.0 and 7.2%; fT_4, 2.0 and 4.8%; PRL, 1.7 and 2.0%; LH, 1.2 and 2.2%; FSH, 2.8 and 4.5%; testosterone, 2.8 and 3.2%; and E_2, 3.6 and 3.9%. GH was analyzed by a solid-phase, two-site chemiluminescent immunometric assay (Immulite 2000, Siemens Healthcare Diagnostics). Intra- and inter-assay CVs given by the manufacturer were 4.2 and 6.6% respectively.

Medical Spectrum Twente, Enschede: Plasma GH, LH, FSH, PRL, testosterone, and E_2 levels were analyzed by solid-phase, two-site

chemiluminescent immunoassays (Immulite 2000, Siemens Healthcare Diagnostics). The maximal intra- and inter-assay CVs were as follows: GH, 4.2 and 6.6%; LH, 3.6 and 6.7%; FSH, 2.9 and 4.1%; PRL, 3.6 and 7.4%; testosterone, 10.0 and 10.3%, and E_2, 7.8 and 11.0%. Cortisol was analyzed by a solid-phase, competitive chemiluminescent immunoassay (Immulite 2000, Siemens). Intra- and inter-assay CVs were 7.4 and 9.4% respectively. Plasma TSH and fT_4 were analysed by ECLIA (Modular Analytics E170, Roche, GmbH). Intra- and inter-assay CVs were: 3.0 and 7.2% for TSH and 2.0 and 3.6% for fT_4.

Quality of life assessment

To assess QoL the following questionnaires were used:

Hospital Anxiety and Depression Scale (HADS) – The HADS questionnaire consists of 14 items pertaining to anxiety and depression, measured on a four-point scale. The scores for the two subscales anxiety and depression range from 0–21 and the total score from 0–42. A high score indicates more severe anxiety or depression (25).

Nottingham Health Profile (NHP) – The NHP questionnaire features 38 yes/no questions subdivided in six subscales, *i.e.* energy, pain, emotional reaction, sleep, physical ability and social isolation. Scores of the subscales are valued in a range from 0–100. The total score is the mean of all subscales. A high score indicates a worse QoL (26;27).

Multidimensional fatigue index (MFI-20) – The MFI-20 questionnaire contains 20 statements to assess fatigue, measured on a five-point scale. The scores of the five subscales general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue vary from 0 to 20. A high score indicates more fatigue experienced (28).

Short Form-36 (SF-36) – The SF-36 consists of 36 statements or questions evaluating general well-being during the previous 30 days. Scores of the nine subscales physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, vitality, pain, general health perception and health change are expressed in a 0–100 scale. Higher scores indicate a better QoL (29;30).

Statistics

Data were analyzed using PASW Statistics version 17.0.2 (SPSS Inc.,Chicago, IL, USA). All data were presented as mean±SD,

unless mentioned otherwise. The analysis comprised the comparison of the results between patients with and without pituitary insufficiency.

Groups were compared using an independent-samples t-test. A χ^2-test was used in case of categorical data. To analyse QoL the groups were compared using univariate analysis of variance (ANOVA) with gender and GCS as fixed factors and age as covariate when appropriate. Factors influencing QoL were explored using a Pearson correlation. A P-value of <0.05 was considered to be statistically significant.

Results

Patient demographics

We included 112 patients (75 males) with a median age of 48 (range 19–69) years (Table 1). Patients were evaluated 1–12 years after trauma (median 3 years). The median duration of hospitalization after TBI had been 11 (3–105) days. BMI was 25 (18–43) kg/m^2. The causes of TBI had been traffic accidents (51%), fall (38%), violence (5%), and sport- or work related accidents (6%), respectively. A total of 36 patients (32%) had been diagnosed with a severe trauma and 56% of the patients (n=60) had a mild trauma, in 4 patients the GCS was not clear from the medical records.

Table 1. Baseline characteristics

	TBI Patients (n=112)
Gender (M/F)	75/37
Age (years)	48 (19–69)
BMI (kg/m^2)	26.7 ± 4.8
GCS:	
Mild (%)	57%
Moderate – Severe (%)	43%
Time since TBI (years)	4.2 ± 3.3
Duration of hospitalization (days)	11 (3–105)

BMI, body mass index; F, female; M, male; TBI, traumatic brain injury
Data are presented as mean±SD or median (range).

Endocrine evaluation

Any pituitary insufficiency was diagnosed in only 6/112 patients, resulting in a prevalence rate of 5.4%. Patients with and without pituitary insufficiency were comparable in age and gender, but in patients diagnosed with pituitary insufficiency BMI was significantly higher (P = 0.02). Trauma severity, the duration of follow-up, and duration of hospitalization were not different between the two groups.

GH-IGF-I axis: The ITT was used in 80% of the patients (90/112) for the evaluation of GH secretory reserve (Figure 2). Because of contra-indications (epilepsy (n=6), ischemic heart disease or rhythm disorders (n=3), other (n=13)), the remaining patients were tested using combined GHRH-arginine stimulation. Severe growth hormone deficiency (GHD) was diagnosed in 3.6% of the patients (2M/2F, Table 2).

HPA axis: At baseline, all patients initially were screened with basal morning cortisol levels and a 1 or 250μg ACTH-test to evaluate adrenal function. Subsequently, 90 patients were tested by ITT (Figure 2). In the remaining 22 patients the HPA axis was assessed by the results of basal cortisol and the ACTH-test. In addition, 2 patients (diagnosed with other pituitary insufficiencies) were tested also by a 100 μg CRH test.

ACTH deficiency was diagnosed in 1.8% of patients (2/112) by insufficient cortisol responses during ITT (Table 2).

Gonadal axis: Hypogonadism was diagnosed only in one male patient (0.9%).

Thyroid axis: We did not diagnose any patient with thyroid insufficiency.

Quality of life

There were differences in QoL between patients diagnosed with and without pituitary insufficiency. Patients with pituitary insufficiency scored worse on almost all subscales of the QoL questionnaires. More specifically, they scored significantly worse on the subscale 'Depression' of the HADS ($P = 0.05$), on the subscale 'Social isolation' of the NHP ($P = 0.02$), on the subscale 'Reduced activity' of the MFI-20 ($P = 0.027$) and on the subscale 'General health perception' of the SF-36 ($P = 0.016$) (data not shown).

Table 2. Characteristics of patients diagnosed with any pituitary insufficiency

Patient no.	Sex	Age (years)	BMI (kg/m²)	GCS score	Time since TBI (years)	Dynamic test		IGF-I SDS	Peak GH (µg /L)	Peak cortisol (nmol/L)	Deficiency
						GH axis	*HPA axis*				
1	M	65	32.2	3	3	ITT	ITT	-1.0	4.0	425	Cortisol
2	M	64	29.7	7	9	GHRH-arg	ACTH,CRH	-2.4	2.8	508	GH
3	M	41	32.8	3	4	GHRH-arg	ACTH	-0.2	9.9	590	Testosterone
4	M	27	23.5	3	10	GHRH-arg	ACTH, CRH	-0.7	9.4	757	GH
5	F	28	29	15	1	ITT	ITT	1.2	1.9	790	GH
6	F	23	32.3	14	3	ITT	ITT	-0.6	2.4	395	GH, Cortisol

BMI, body mass index; CRH, corticotropin releasing hormone; F, female; GCS, Glasgow Coma Scale; GH, growth hormone; GHRH, growth hormone releasing hormone; HPA, hypothalamic pituitary adrenal axis; ITT, insulin tolerance test; M male

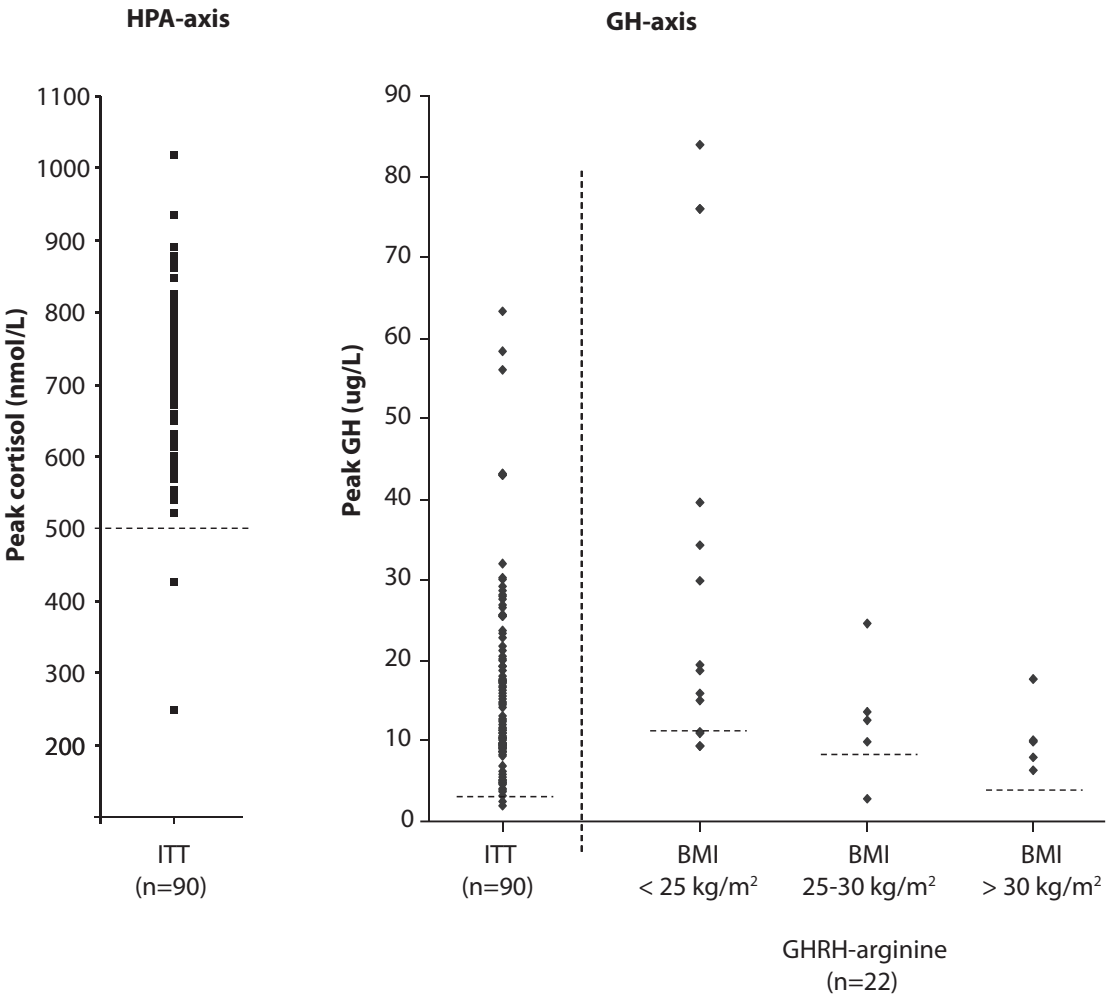

Figure 2. Test results of the stimulation of GH and cortisol secretory reserves during ITT or combined GHRH-arginine test. The dotted horizontal line represents the cut-off value used to define an insufficient response.

Discussion

This study demonstrates that the prevalence of hypopituitarism after TBI in a large patient cohort after long-term follow-up is low. Using a standardized evaluation that included the gold standard test for the evaluation of GH and cortisol secretory reserves in the majority of the patients, we found a prevalence of only 5.4% of any pituitary insufficiency.

This prevalence of hypopituitarism is much lower compared with the prevalence rates reported in the majority of the previous studies (15–90%) (6–18). This might be explained by the use of different endocrine tests and cut-off values (19). For example, comparable low prevalences of hypopituitarism was found in another study that also used the ITT for screening (15). In addition, when using the combined GHRH-arginine test without BMI-adjusted cut-off values the prevalence of severe GHD varied between 8 and 20%(19). A higher BMI is associated with a decreased GH response to GH stimulation tests (22). If BMI-adjusted cut-off values are not used, a higher proportion of patients will be classified as GHD. In addition, age adjusted cut-off values have recently been reported for the GHRH-arginine test (31).

Differences in the duration of follow-up between TBI and endocrine assessment may also play an important role. Hormone alterations mimicking pituitary insufficiency can be present in the acute phase after trauma. In general, these transient effects are almost exclusively reported only within the first six months after TBI (15;32). Therefore, assessment of the function of pituitary axes within this timeframe may result in higher prevalence rates of hypopituitarism. To avoid this bias we decided to assess patients at least one year after the trauma, as suggested in the consensus guidelines for the evaluation and diagnosis of patients with possible GHD (33). In addition to the time interval between TBI and endocrine assessment, the severity of trauma may affect the prevalence rate of pituitary insufficiency (15;34). As shown by Klose *et al.* (34), increased trauma severity increases the risk of pituitary insufficiency. This may result in higher prevalence rates when patients with a more

severe degree of trauma are included. Conversely, prevalence rates of hypopituitarism may decrease when patients with only minor traumas are included (35).

It is important to note that in our study, only a minority of the screened patients fulfilled our inclusion criteria, of which 28.7% participated. Therefore, by definition, we investigated a pre-selected cohort, which may have affected the results, and, therefore, our conclusions cannot simply be extrapolated to all TBI patients. However, we were able to evaluate the most important clinical characteristics in the majority of the patients (79%) who did not participate and found no differences in age during TBI, gender, trauma severity and duration of hospitalization when compared to those that finally did participate (data not shown). This makes a possible bias as a result of pre-selection less likely.

Thus, according to our results, pituitary insufficiency may be a rare complication of TBI in patients evaluated at least one year after TBI. Intriguingly, comparable low prevalence rates were found in another study that also used the ITT to evaluate cortisol and GH secretory reserve (32). However, it should be taken into account that there is a high incidence of TBI in the population probably translating in still a high prevalence of posttraumatic hypopituitarism on a population-based level. Besides pre-selections of patients, the use of different tests with different cut-off values has contributed to the differences and large variations in the prevalence rates found in previous studies (19). Our results accentuate that we urgently need consensus for a more uniform and protocol endocrine evaluation after TBI. More importantly, we urgently need prospective studies to find reliable predictors that enable the identification of patients with a significant pre-test likelihood for hypopituitarism. This is of paramount importance, because the presence of pituitary failure, even in a small proportion of patients, is potentially treatable, may be lifesaving, and is likely to significantly ameliorate quality of life (3;5).

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