Prevalence of anterior pituitary insufficiency 3 and 12 months after traumatic brain injury

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Abstract

Objective: Cross-sectional studies report a high prevalence of hypopituitarism after traumatic brain injury (TBI); however, no longitudinal studies on time of manifestation and reversibility exist. This study was conducted to assess hypopituitarism 3 and 12 months after TBI.

Design: This was a prospective, longitudinal, diagnostic study.

Methods: Seventy-eight patients (52 men, 26 women, mean age 36.0 years) with TBI grades I–III and 38 healthy subjects (25 men, 13 women, mean age 36.4 years) as a control group for the GHRH + arginine test were studied. The prevalence of hypopituitarism was assessed 3 and 12 months after TBI by GHRH + arginine test, short adrenocorticotropic hormone (ACTH) test, and basal hormone measurements in patients.

Results: After 3 months, 56% of all patients had impairments of at least one pituitary axis with axes being affected as follows: gonadotropic 32%, corticotropic 19%, somatotropic 9% and thyrotropic 8%. After 12 months, fewer patients were affected, but in some cases new impairments occurred; 36% still had impairments. The axes were affected as follows after 12 months: gonadotropic 21%, somatotropic 10%, corticotropic 9% and thyrotropic 3%.

Conclusions: Hypopituitarism occurs often in the post-acute phase after TBI and may normalize later, but may also develop after the post-acute phase of TBI.

Introduction

The incidence of traumatic brain injury (TBI) is 200/100 000/year (1), and 100/100 000 US residents are hospitalized for non-fatal TBI each year (2). Hypopituitarism following head injury was first described in 1918 (3), but, until recently, hypopituitarism as a consequence of brain trauma was reported only anecdotally (4), and hormonal assessment after TBI is still not part of routine diagnostics. Typical clinical consequences of TBI are disorders of consciousness, attention deficits, impulsion impairment, depression and sleep. Some of these symptoms might also be a consequence of anterior pituitary insufficiency (5, 6). Therefore, it is possible that post-traumatic hypopituitarism often remains unrecognized due to masking by TBI sequelae, and that symptoms of TBI might be aggravated by hypopituitarism. Moreover, undiagnosed hypopituitarism might lead to life-threatening hormonal crisis, and until now it has not clear whether hormonal replacement might lead to additional benefit in post-traumatic rehabilitation due to positive effects on cognition and body composition.

In their review in 2000, Benvenga et al. counted 367 cases of non-traumatic hypopituitarism since the 1950s (7). Recent cross-sectional studies show that anterior pituitary dysfunction after traumatic brain injury is more common than expected (8–13), with a prevalence of 30–70% of hormonal abnormalities present after TBI. However, the patient populations examined in most of these studies were inhomogeneous, with intervals between trauma and hormone assessment of 3 months to 23 years (8), 49±8 months (9), 12–64 months (10) and 6–36 months (11), and differing methods and cutoffs for endocrine testing. In a recent study, hormonal assessments in a very early phase after TBI (mean 12 days after trauma) indicated a substantial prevalence of pituitary deficiencies (14). However, in this early phase, it is not clear whether these hormonal changes are specifically due to brain...
trauma or are an unspecific reaction to critical illness (15). To date, only one longitudinal study on clinical course of post-traumatic hypopituitarism has been published (13).

To avoid the possibly nonspecific hormonal disturbances of the acute phase and to assess the prevalence of pituitary dysfunction in an early stage and in the chronic phase after TBI, we conducted a prospective, longitudinal diagnostic study with pituitary testing and clinical evaluation at 3 and 12 months after TBI.

Subjects and methods

Subjects

Seventy-eight consecutive patients (52 men, 26 women, mean age 36 years) from the Rehabilitation Unit of the Neurologic Clinic Bad Aibling, Germany, were included in the study. The patients gave written, informed consent to participate in the study. For patients who were not able to understand the significance and character of the study, consent was provided by a legally accepted representative.

The study was approved by the ethics committee of the Bavarian physicians’ chamber in Munich. Inclusion criteria were TBI grades I – III (assessed by initial Glasgow Coma Scale (GCS)), age 18– 65 years, and body-mass index (BMI) 17– 30 kg/m². Exclusion criteria were glucocorticoid treatment within 3 weeks or growth hormone (GH) treatment within 12 months before the visits; a history of cranial irradiation; pre-existing pituitary diseases; severe cardiac, renal or hepatic diseases; sepsis; or substance abuse. In a control group of 38 healthy subjects (25 men, 13 women, mean age 36.4 years), matched for sex, BMI and age, a growth hormone-releasing hormone (GHRH) + arginine test was performed to test for appropriateness of the cutoff. Table 1 shows the subject characteristics.

Hormonal and clinical assessments

All assessments were done 3 months ± 2 weeks after TBI at visit 1 (V1) and repeated at 12 months ± 4 weeks after trauma (V2). If patients were on hormone substitution before V2, substitution was stopped before testing as follows: hydrocortisone 24 h, sex hormones 4 weeks and thyroid hormones 2 weeks. Stimulation tests were done at V1 in all patients and at V2 in those patients who had pathological basal or stimulated hormonal values at V1 or pathological basal hormone levels at V2. In all patients, basal fasting measurements of insulin-like growth factor (IGF)-I (age-dependent standard deviation scores calculated according to Brabant et al. (19)), thyroid-stimulating hormone (TSH), free thyroxine (FT₄), total triiodothyronine (T₃), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL) and testosterone (in men) or estradiol (in women), a combined GHRH + arginine test and a short adrenocorticotropic hormone (ACTH) test were performed. All hormonal assessments were done between 0800 and 1000 h. For the GHRH + arginine test, 50 μg GHRH were given i.v. as a bolus, 30 g L-arginine in 250 ml physiological salt solution were administered as a 30-min infusion, and GH was measured at 0, 30, 45, 60, 90 and 120 min. As two different abnormal stimulatory tests in the presence of hypothalamo-pituitary disease are recommended for the diagnosis of isolated GH deficiency (16), we refrained from using the term ‘GH deficiency’ and considered a GH response of ≥ 9 ng/ml as indicative of impaired GH secretion. For the ACTH test, 250 μg synacthen were given i.v. as a bolus, and cortisol was measured at 0 and 30 min. A cortisol response under 18.1 μg/dl was considered hypocortisolemic. If basal or stimulated cortisol was ≥ 18.1 μg/dl, corticotropic deficiency was ruled out. Secondary hypogonadism was defined as testosterone under 3.5 μg/dl without elevated gonadotropins in men and lack of menses bleeding since trauma in premenopausal women, or inappropriately low gonadotropins in postmenopausal women. Secondary hypothyroidism was diagnosed if FT₄ was below 0.93 ng/dl and TSH was not elevated (reference range 0.27–4.4 μIU/ml). The diagnosis of hyperprolactinemia was based on PRL levels above 25 ng/ml.

Severity of TBI was assessed by initial GCS (17), a GCS of 3–8 indicating severe (grade III), 9–12 moderate (grade II) and 13–15 mild TBI (grade I). Clinical status at V1 and V2 was assessed by the modified Rankin scale (18), including the following grades: 0, no symptoms; 1, no substantial disability despite symptoms (able to carry out all usual duties and activities); 2, slight disability (unable to carry out all previous activities but able to look after own affairs without assistance); 3, moderate disability (requiring some help, but able to walk without assistance); 4, moderately severe disability (unable to walk without assistance and unable to attend to own bodily needs without assistance); 5, severe disability (bedridden, incontinent and requiring constant nursing care and attention); and 6, vegetative state. Transient clinical diabetes insipidus in the acute phase was documented as far as apparent from patient records.

### Table 1 Subject characteristics: means (s.d.) NS: not significant vs patients at visit 1.

<table>
<thead>
<tr>
<th></th>
<th>Patients visit 1</th>
<th>Patients visit 2</th>
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<tr>
<td><strong>n</strong></td>
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<td>70</td>
<td>38</td>
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<tr>
<td><strong>Sex</strong></td>
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<td></td>
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<td>47 M, 23 F</td>
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<td>36.4 (14.7), NS</td>
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<td>23.8 (3.2)</td>
<td>22.7 (2.9), NS</td>
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<td>2.1 (1.8)</td>
<td>–</td>
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<tr>
<td><strong>Initial GCS</strong></td>
<td>7.4 (4.5)</td>
<td>7.5 (4.6)</td>
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Hormone measurements

Blood was drawn by venipuncture and centrifuged at 3000 g for 10 min. and the serum was stored at −20°C until further processing. GH and IGF-1 were measured by chemiluminescence with the Nichols Advantage System (Nichols Institute Diagnostics, San Clemente, CA, USA). The other hormones were measured by electrochemiluminescence with the Elecsys 2010 analyzer (Roche Diagnostics, Basel, Switzerland). The maximal intra- and interassay coefficients of variation at different hormone concentrations were as follows: GH: 8% and 12%; IGF-I: 5% and 7%; TSH: 9% and 9%; T3: 5% and 5%, FT4: 3% and 7%; LH: 2% and 5%; FSH: 2% and 5%; estradiol 6% and 6%; testosterone: 5% and 7%; PRL 3% and 4%; and cortisol 3% and 5% respectively.

Statistical analyses

Data are displayed as mean ± standard deviation. To test for significance between groups, the unpaired two-tailed Student’s t-test was used; for changes within groups, the paired Student’s t-test. Correlations were measured with Spearman’s correlations coefficient. Differences of proportions between patients and controls were assessed by Fisher’s exact test (SPSS 12.0). Receiver-operating characteristics (ROC) analysis was performed to test predictive values of stimulated and basal hormone assessments.

Results

3 months after trauma

At V1, in one patient, only basal hormone levels were available due to refusal of stimulation testing. Therefore, the corticotropic and somatotropic axis could be evaluated in only 77 patients. The thyrotrropic axis could not be evaluated in another patient due to continued treatment with levothyroxine. Forty-four patients (56%) showed impairments of at least one pituitary axis. Secondary hypogonadism was present in 24/74 patients. One man with a traumatic scrotal hematoa had primary hypogonadism with elevated gonadotropins. In four premenopausal women, information on menses bleeding was not available. Fifteen of 77 patients had hypocortisolism. Stimulated GH was ≤ 9 ng/ml in 7/77 patients and in 1/38 control subjects (one-sided P = 0.19, Fisher’s exact test). In 6/77 patients, secondary hypothyroidism was found. Eight patients had combined impairments of two axes (four corticotropic plus gonadotrophic, three gonadotrophic plus somatotrophic, and one thyrotrropic plus somatotrophic); in the other cases, only single axes were affected. PRL levels were elevated in nine patients not taking known hyperprolactinemic drugs and in another seven patients taking such drugs.

Among patients with or without hypopituitarism, there were no differences among initial GCS, modified Rankin scale, age, BMI or prevalence of hyperprolactinemia (data not shown). However, patients with hypogonadism had lower initial GCS (5.1 ± 3.2 vs 8.4 ± 4.5; P = 0.005) and higher modified Rankin scale (3.9 ± 1.7 vs 2.4 ± 1.6; P < 0.001) than eugonadal subjects. Patients with impaired GH secretion were older (54.0 ± 5.5, range 46.7–62.3 vs 34.2 ± 14.4 years; P < 0.001), and had higher BMI (25.2 ± 3.9, range 17.2–30.4 vs 21.7 ± 2.8; P = 0.004) and lower IGF-I levels (132 ± 47 vs 212 ± 97 ng/ml; P = 0.045) than patients with normal GH stimulation, even though age-dependent standard deviation scores (IGF-I SDS), calculated with a formula derived from Brabant et al. (19), were not different (-0.1 ± 0.9 vs 0.0 ± 1.3; P = 0.8). Stimulated GH levels correlated negatively with age and BMI in both patients (age: r = −0.52; P < 0.001; BMI: r = −0.40; P < 0.001) and control subjects (age: r = −0.45; P = 0.004; BMI: r = −0.58; P < 0.001). Fig. 1 shows the prevalences of hormonal deficiencies at 3 and 12 months.

Clinical signs of diabetes insipidus in the acute phase after TBI were reported in nine patients with no case of persistent diabetes insipidus at V1 or V2.

12 months after trauma

Seventy patients participated in V2. Eight patients refused retesting. In these 70 patients, there was an increase in mean BMI of 25.00 ± 0.98 (P < 0.001) and a decrease of modified Rankin scale of −0.69 ± 1.03 (P < 0.001), compared with V1. Stimulation tests were done in 32 patients. In those patients in whom the 3-month results were normal and in those, who were incapable or unwilling of repeating stimulation testing, only basal hormone evaluation was performed. The patients with normal basal levels and no stimulation tests were regarded as normal. Thus, the true prevalence of hormonal disturbances requiring stimulation testing (corticotropic and somatotropic axes) might be underestimated. As shown by Fig. 2, there were good correlations of stimulated GH levels, and basal FT4 and testosterone levels (the latter in men only) between 3 and 12 months. Stimulated cortisol levels of V1 and V2 did not correlate significantly.

Of all patients, 36% still had hormonal disturbances. In all axes apart from the somatotropic axis, the prevalences of impairment were lower than at V1. Two axes were impaired in only three patients. Two patients with previous deficiencies of the gonadotropic and somatotropic axis remained deficient in both axes, and an additional patient with low stimulated GH at V1 additionally became hypocortisolemic at V2. Hyperprolactinemia was still present in 10 patients (four of them taking hyperprolactinemia-inducing drugs).

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Patients with hypopituitarism at 12 months were older than those without (41.7±14.6 vs 36.9±14.0 years; \(P = 0.01\)) but still showed no differences in initial GCS, modified Rankin scale, BMI, prevalence of hyperprolactinemia, or changes of BMI or modified Rankin scale at 12 vs 3 months (data not shown). Hypogonadal patients still had a higher modified Rankin scale (3.8±2.0 vs 1.7±1.5; \(P = 0.0001\)) but no difference in initial GCS.

Figure 1 Percentage of patients with pituitary impairments. Please note that in patients in whom a stimulation tests was not done and basal values were not discriminative, no impairment was assumed.

Figure 2 Hormone levels at 3 vs 12 months.

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Changes of BMI and modified Rankin scale were also not different for patients with or without hypogonadism. However, men with decreased testosterone levels had a significantly lower decrease of modified Rankin scale at 3–12 months (−0.3 vs −1.2; P = 0.036). In patients with GH of ≤ 9 ng/ml, BMI (27.5 ± 2.4, range 25.0–32.2 vs 23.3 ± 3.0; P = 0.001) and age (52.5 ± 8.9, range 40.1–60.1 vs 33.9 ± 14.2 years; P = 0.001) were higher, and IGF-I was lower (126 ± 43 vs 202 ± 86 ng/ml; P = 0.026). Again, there was no significant difference between age-dependent IGF-I SDS (−0.4 ± 0.8 vs 0.0 ± 1.2; P = 0.4) as well as no difference in modified Rankin scale, BMI, prevalence of hyperprolactinemia, or changes of BMI or modified Rankin scale at 12 vs 3 months (data not shown).

**Prediction of hypopituitarism by measurement of basal hormone levels**

Measurement of basal hormone levels as a screening test for hormonal abnormalities could be of high practical value in the diagnostic workup of patients after TBI. Therefore, the predictive value of basal hormone measurements to detect or exclude pituitary deficiencies was evaluated.

Overall, neither basal morning cortisol nor IGF-I could well predict stimulated cortisol or GH values (Fig. 3). At 3 months, ROC analysis for measurement of basal morning cortisol to predict insufficient cortisol stimulation in the ACTH test revealed a sensitivity of 90% at a cutoff point of 15.4 μg/dl and a specificity of 90% at a cutoff point of 9.3 μg/dl. For IGF-I, a sensitivity of 90% could be reached at a cutoff point of 0.6 SDS, and a specificity of 90% at a cutoff point of −1.6 SDS.

At least one abnormality (basal morning cortisol of < 9.3 μg/dl, FT₄ of < 0.93 ng/dl, testosterone of < 3.5 μg/l (in men)/amenorrhea (in women) or IGF-I of < −1.6 SDS) was found 3 months after TBI in 43/78 patients (55.1%). Out of these 43 patients, 36 had isolated or combined pituitary insufficiency in the complete workup including stimulation tests (positive predictive value 83.7%). Of the 35 patients with normal basal values, 27 proved to have also normal endocrine function tests (negative predictive value 77.1%). This corresponds to an overall sensitivity and specificity of this approach to predict hypopituitarism of 81.8% and 79.4% respectively. However, by this approach, 5/15 (33.3%) patients with insufficient response of cortisol to ACTH stimulation, and 3/7 (42.9%) of patients with insufficient GH response to GHRH + arginine would have not been transferred to stimulation testing due to normal basal hormone values.

**Discussion**

We have found more than one-half and one-third of the patients showing hormonal disturbances at 3 and 12 months after trauma respectively. These results are comparable to previous results of other groups (8–13). Until now, however, reportings on affected axes were inhomogeneous and the time course of post-traumatic hypopituitarism was not clear. We found a high prevalence of hypogonadism and hypocortisolism at 3 months that normalized during follow-up in many but not all cases, and impairment of stimulated GH secretion in about 10% that remained stable after 12 months. The thyrotropic axis was least affected.

Hypogonadism at three months was closely related to severity of disease as assessed by modified Rankin scale and severity of trauma assessed by initial GCS. It is known that reproductive function is downregulated in episodes of severe illness (15, 20). Moreover, in studies of the early phase after TBI, a reversible, severity-dependent decline of testosterone has been described (21, 22).
This would explain the correlation of disease severity with hypogonadism as well as the fact that hypogonadism was normalizing in a substantial portion of patients but was still present in the more severely affected ones after 12 months. Hypogonadism in male patients was associated with significantly less clinical improvement at 12 months assessed by change of modified Rankin scale. Possibly, this is due to the fact that a lack of testosterone prevented further clinical improvement in these patients. It is also possible, on the other hand, that the greater severity of disease that had caused hypogonadism is also the reason for less clinical improvement. Further studies are needed to address this question and the possible beneficial effects of androgen replacement in this phase.

The assessment of somatotropic function still remains controversial. The insulin-tolerance test (ITT) still is the reference standard (16); however, since seizures are a common complication in brain trauma patients, we refrained from using this test in our study. As an alternative, the GHRH + arginine test with a cutoff of 9 ng/ml has been proposed (23, 24). This cutoff represents the first percentile in a lean population comparable to our study population, and is now generally accepted (23, 24). It has been shown that this test might be BMI dependent, and a cutoff of 4.3 ng/ml has been suggested, derived from a sample of subjects with a mean BMI of > 30 (25). To avoid the problem of GH impairment due to obesity, we have excluded patients with BMI of > 30. Yet, there still was a negative correlation of BMI and age with peak GH, and, strikingly, all patients with impaired GH secretion were older than 40 years and overweight at V2. Therefore, it is not clear whether impairment of GH secretion is really due to brain injury or merely an effect of being overweight and of higher age. On the other hand, advanced age and higher BMI might also promote risk factors that lead to increased vulnerability of somatotropic cells, putting patients at higher risk of GH deficiency. To address this question, we have performed GHRH + arginine tests in a healthy, BMI- and age-matched control group. In this group, only one out of 38 persons (2.6%) had a GH response of ≤ 9 ng/ml, supporting the use of this cutoff value in our sample and suggesting an increased prevalence of impaired GH secretion in TBI patients. Nevertheless, the difference between patient and the control population was not statistically significant, possibly due to the small sample size. It is clear from these findings that future studies aiming to establish age- and BMI-dependent cutoffs for the GHRH + arginine test are advisable. In the most recent study in a similar collective, Aimaretti et al. (13) found a higher prevalence of GH impairment. Possibly, a slightly higher BMI and age in their population might have contributed to this difference.

It is of particular clinical significance that a high percentage of patients had hypocortisolism, as this might lead to potentially life-threatening complications. The ITT is also the reference standard for assessment of the corticotrophic axis; however, the short ACTH test has been shown to be a reliable alternative (26). Although hypocortisolism resolved in most cases at 3–12 months after trauma, there were three new cases of hypocortisolism at the 12-month visit. Therefore, retesting even of those patients that formerly had a normal cortisol response appears advisable.

In attempting to establish a practicable approach to endocrine testing based on our 3-month data, we have found satisfying positive and negative predictive values for presence of pathological test results when basal morning cortisol of < 9.3 µg/dl or IGF-I of <-1.6 SDS or other subnormal basal hormone levels would lead to complete endocrine testing. It has to be taken into account, however, that with this approach a substantial amount of pathological cortisol and GH responses to stimulation would not be detected. Regarding the time of testing, our data show that initial impairments of the gonadotropic, corticotropic and thyrotropic axes often resolve after 12 months, whereas impairments of the somatotropic axes remain rather stable. However, as shown by Fig. 2, it is also possible that new impairments, particularly of the gonadotropic and corticotropic axes, might occur later, supporting retesting of these axes even if they were formerly normal.

It is still not clear what factors predispose to development of post-traumatic hypopituitarism. Severity of TBI as assessed by initial GCS does not seem to be associated with the presence of hypopituitarism in general, yet a more severe clinical status seems to predict a higher risk of secondary hypogonadism. A possible explanation might be that the initial GCS is not discriminative enough to assess reliably the severity of injury. In many patients with a high initial GCS, secondary worsening through bleeding or brain edema might render TBI more severe than indicated by initial GCS. Possibly, further studies evaluating clinical conditions and severity in more detail might help to clarify the predictors of post-traumatic hypopituitarism. At present, our findings suggest that pituitary function after TBI should be assessed in all patients, regardless of the severity of the trauma.

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