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Hypopituitarism following Severe Traumatic Brain Injury

Abstract

Although hypopituitarism is a known complication of traumatic head injury, it may be under-recognized due to its subtle clinical manifestations. To address this issue, we determine the prevalence of neuroendocrine abnormalities in patients rehabilitating from severe traumatic brain injury (Glasgow Coma Scale ≤ 8). 76 patients (mean age 39 ± 14 yr; range 18 – 65; 53 males and 23 females; BMI 25.8 ± 4.2 kg/m^2; mean ± SD) with a severe traumatic brain injury, an average of 22 ± 10 months before this study (median, 20 months), underwent a series of standard endocrine tests, including TSH, free T4, T4, T3, prolactin, testosterone (males), estradiol (females), cortisol, ACTH, GH, and IGF-I. All subjects also underwent GH response to GHRH + arginine. Growth hormone deficiency (GHD) was defined as a GH response < 9 µg/L to GHRH + arginine and was confirmed by ITT (< 3 µg/L). Pituitary deficiency was shown in 24% of the patients (18/76). 8% (n = 6) had GHD (GH-peak range [GHRH + arginine]: 2.8 – 6.3 µg/L; GH-peak range [ITT]: 1.5 – 2.2 µg/L; IGF-I range: 62 – 174 µg/L). 17% (n = 13) had hypogonadism (total testosterone < 9.5 nmol/L and low gonadotropins in 12 males; low estradiol, and low gonadotropins in 1 female). Total testosterone levels did not correlate with BMI or age. 2 males with hypogonadism also showed a mild hyperprolactinemia (33 and 41 ng/ml). 3% (n = 2) patients had partial ACTH-deficiency (cortisol-peak [ITT] 392 and 417 nmol/L) and 3% (n = 2) had TSH-deficiency. In summary, we have found hypopituitarism in one-fourth of patients with predominantly secondary hypogonadism and GHD. These findings strongly suggest that patients who suffer head trauma must routinely include neuroendocrine evaluations.

Key words
Severe traumatic brain injury · hypopituitarism

Introduction

Pituitary and hypothalamaic tissue damage is commonly diagnosed in young and otherwise healthy road accident victims and is commonly accompained by skull fractures and coma (Edwards and Clark, 1986). Hypopituitarism of these patients after traumatic brain injury (TBI) is under-recognized (Benvenga et al., 2000), because subtle and nonspecific symptoms of pituitary deficiencies are covered from physical and cognitive sequelae, psychological dysfunction and social isolation (Breed et al.,

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2004; Masel, 2004; Agha et al., 2005). Case reports and recent studies of TBI patients in the chronic recovery phase have evaluated the prevalence of deficits of the hypothalamo-pituitary axis (Benvenga et al., 2000; Rees, 2001; Valenta and de Feo, 1980; Benvenga et al., 1997; Lieberman et al., 2001; Kelly et al., 2000; Richard et al., 2001). The frequencies of chronic neuroendocrine deficits among these patients have received only some systemic studies (Agha et al., 2004a; Agha et al., 2004b; Bondanelli et al., 2004). This may be due to the heterogenous profile of patients (mild, moderate and severe TBI), the lag-time between injury and hormone testing, and the different tests and cutoff levels defining pituitary deficiency.

We undertook the present study to determine the prevalence of hypopituitarism in patients after severe TBI (Glasgow Coma Scale ≤ 8). All patients underwent hormone and pituitary function testing after the acute phase of physical, cognitive and vocational rehabilitation (minimum 5 months).

Subjects and Methods

Study group

Patients, who were already discharged from the departments of neurosurgery of the University Hospital of Essen, the Alfried-Krupp-Hospital of the University of Duisburg-Essen and of the Clinic of Neurosurgical Rehabilitation, University of Witten/Herdecke in Germany, were evaluated between July 2003 to May 2004. None of the patients were hospitalized at the time of endocrine evaluation. Participation was solicited from all patients admitted to these departments without preselection and informed consent was obtained from all subjects. The date of head injury could be determined in all patients and the Glasgow Coma Scale (GCS) at the time of presentation with injury were recorded when available (n = 40). All patients without documented GCS were unconscious for at least 1 day. The GCS represents the summary of the patient's level of consciousness as indicated by scores on eye opening (1 – 4), motor responses (1 – 5), and verbal responses (1 – 6). Severity of brain injury is indicated by the total score: 3 – 8 = severe, 9 – 13 = moderate, and 14 – 15 = mild (Clifton et al., 1980).

76 patients (mean age 39 ± 14 yr; range 18 – 65; 53 males and 23 females; BMI 25.8 ± 4.2 kg/m^2) with a severe traumatic brain injury (GCS score < 8, mean 4.4 ± 2.8), an average of 22 ± 10 months before this study (range 5 – 47 months), were included. The patients were tested once only. The duration of coma was 12 ± 24 days (range 0 – 180). Exclusion criteria were patients with persistent alcohol abuse, apallic syndrome or too ill to undergo dynamic testing, known pituitary deficiencies or other pituitary diseases or pregnant women. Patients receiving glucocorticoid therapy during the last 3 months before study entry, or patients for whom informed consent was refused or could not be obtained, were not included in the study. In all females, menstrual history was obtained. The type of head injury was characterized by computerized tomography and MRI according to Marshall's classification (Marshall et al., 1992).

Methods

Testing started between 8:00 and 8:30 a.m. after an overnight fast. Patients initially underwent a series of standard endocrine tests, including TSH, free T4, T4, T3, prolactin, testosterone (males), estradiol (females), SHBG, cortisol, ACTH, GH, and IGF-I. All subjects also underwent GH response to GHRH + arginine (1 µg GHRH/kg BW was administered by an iv bolus, followed by a 30-min infusion of 30 g arginine with measurement of GH at – 15, 0, 15, 30, 45, 60, 75, 90, 105, and 120 min).

In terms of current medication of antiepileptic drugs (n = 23), additional stimulation tests were not performed.

Assays

Serum GH levels were determined by a chemiluminescence immunometric assay (Nichols Institute Diagnostics, Bad Nauheim, Germany), serum IGF-I concentrations were measured by an immunoradiometric assay (Nichols Institute Diagnostics, Bad Nauheim, Germany). In our laboratory, the normal IGF-I ranges were 182 – 780 µg/L for adults aged 16 – 24, 114 – 492 µg/L for adults aged 25 – 39 yr, 90 – 360 µg/L for adults aged 40 – 54 yr, and 71 – 290 µg/L for adults aged ≥ 55 yr.

Free T4 (reference range: 10 – 25 pmol/L), T4 (reference range: 58 – 154 nmol/L), T3 (reference range: 1.23 – 3.08 nmol/L), and TSH (0.3 – 3.0 mU/L), total testosterone (male reference range: 9.5 – 30.0 nmol/L), estradiol, prolactin (male reference range: < 20 ng/ml; female reference range: < 25 ng/ml), LH (male basal reference range: 2 – 10; female, postmenopausal reference range: > 20), FSH (male basal reference range: 1 – 7; female, postmenopausal reference range: > 20), cortisol (morning reference range: 180 – 640 nmol/L) were measured by immunoassay (ADVIA Centaur, Bayer Diagnostics, Fernwald, Germany). ACTH (reference range, 17 – 52 pg/ml), SHBG (male reference range, 13 – 71 nmol/L; female reference range, 18 – 114 nmol/L) were measured by chemiluminescence-assay (Immunlite 2000, DPC Biermann, Bad Nauheim, Germany).

Data analysis and definition of abnormalities

The data represent the mean ± standard deviation (SD). The standard reference ranges for TSH, free T4, T4, T3, prolactin, LH, FSH, testosterone (males), estradiol (females), ACTH, and cortisol were used to discriminate abnormal from normal results. Age-specific normal ranges were used for interpreting IGF-I levels. The normal cortisol response was defined by an increase of at least 500 nmol/L after insulin-induced hypoglycemia (ITT). Growth hormone deficiency was defined by a GH-peak less than 9 µg/L after GHRH + arginine in combination with low or decreased age-related IGF-I levels and was affirmed by a GH-peak less than 3 µg/L during ITT (Growth Hormone Research Society, 1998). TSH deficiency was defined by low serum free T4 level (after excluding artifactual causes) without appropriate elevation in serum TSH. In males, secondary hypogonadism was defined by low serum testosterone with inappropriately low gonadotropin level, in premenopausal females by amenorrhea in the presence of a low serum estradiol level without a rise in gonadotropin level, and in postmenopausal females by serum gonadotropin concentration in the premenopausal range.

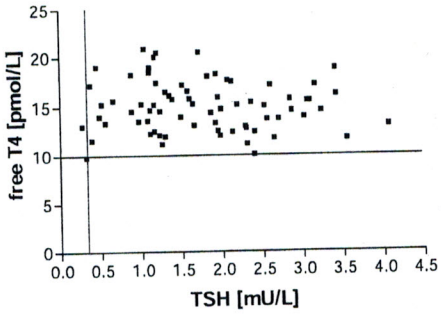

Fig. **3** Correlation between free T4 and TSH in 76 patients with severe traumatic brain injuy.

TSH-deficiency

TSH, free T4, T4, and T3 were available in all patients. One patient with a decreased free T4 level (9.6 pmolL) had an inadequate low basal TSH (0.32 mU/L). Another patient had low free T4 levels (13.0 pmol/L) with decreased or low TSH levels (0.27 mU/L). These 2 patients (3%) had a normal ultrasound of the thyroid and were defined as TSH-deficient subjects (Fig. **3**). Three other patients receiving 150 µg iodine + 75 µg levothyroxine, 75 and 100 µg levothyroxine due to goiter had no other pituitary deficiencies and were considered TSH-sufficient.

Discussion

In the present prospective study, we have examined pituitary function in 76 patients after severe TBI after a minimum of 5 months after injury. We found pituitary deficits in one-fourth of the patients with deficiencies predominantly of the gonadal and somatotropic axis. Furthermore, patients with an abnormal axis had a longer time of coma.

GH response < 9 µg/L to GHRH + arginine was seen in 12/76 patients and we tried to affirm the GHD by ITT (< 3 µg/L) to conform with the recommendations of the Growth Hormone Research Society (1998). Although insulin-induced hypoglycemicia is the preferred test for diagnosing GHD in adults, it was contradicted in 3 patients after severe TBI receiving antiepileptic drugs or was refused in 2 patients. The discrepancies of the prevalence of GHD in different studies (18% from Kelly et al. [2000] and Agha et al. [2004a]; 15% from Lieberman et al. [2001]; 37% from Aimaretti et al. [2004]) are explained by the different numbers of included cases, the different tests and cutoff levels of the tests which were used (ITT [Kelly et al., 2000], glucagon [Lieberman et al., 2001; Agha et al., 2004c], and GHRH + arginine [Aimaretti et al., 2004]). GHD after TBI can be due to hypothalamic-pituitary damage or may result from acetycholine deficiency (Muller, 1987; Goni et al., 1997). Consequently, somatostatin secretion may be increased after TBI, because the inhibitory effect of acetylcholine is missing.

In the present study, GHD was seen in 6 patients (8%) and was accompanied with other deficits in 4 patients. IGF-I levels were lower in patients with GHD than those with normal GH response in accordance with the study of Lieberman et al. (2001). However, IGF-I concentrations may not be a reliable reflection of GH secretion, because IGF-I levels are influenced by factors other than GH secretion and action (Abs, 2003). Moreover, there is often an overlap in IGF-I levels between patients with and without GHD (Abs, 2003). However, 50% of our patients with GHD had IGF-I levels below the normal age-related range in comparison to 7% in the GH-sufficient group.

The interrelationship between GHD and obesity is complex, because obesity is associated with blunted GH secretion on the one hand, and patients with GHD are more obese than those with normal GH secretion on the other hand (Bengtsson et al., 1990). Moreover, GH replacement therapy in patients with GHD, as well as treatment with GH in patients with metabolic syndrome, can reduce total body fat (Johannsson et al., 1997, Herrmann et al., 2004). In the present study, patients with GHD had a trend of a higher BMI than those without GHD and waist circumference was significantly higher than in non-GHD. This may be due to the observation of increased visceral/abdominal fat, which correlates with waist circumference (Seidell and Visscher, 2000).

Similar to the psychological consequences after TBI, several studies in GHD adults reported psychological changes, including emotional lability, social isolation and deminished quality of life (Mazaux and Richer, 1998; Jean-Bay, 2000). Whether these changes can be sufficiently treated with GH replacement therapy, has to be evaluated in further treatment studies of patients with TBI. But this evaluation is limited by the fact that patients after TBI are often severely injured and need, e.g., a wheelchair.

After GH, gonadal axis is traditionally held to be the most suspectable to all varieties of pituitary damage and was reported in 22% from Kelly et al. (2000) and in only 2% from Lieberman et al. (2001). These discrepancies may be due to the different normal ranges of testosterone levels and the different lag-times after injury (3 versus 13 months). In the present study, twelve males and one female had secondary hypogonadism. The female was 57 years old, postmenopausal and had low gonadotropins. All males had total testosterone levels below 9.5 nmol/L and two of them had mild hyperprolactinemia. The hyperprolactinemia could be explained by the dopamin-antagonistic effect of the concomitant medication in one patient. The hyperprolactinemia in the other patient remains speculative and could be explained by psychological stress or by affection of the pituitary stalk. As it has been shown in the study of Benvenga et al. (2000), we have seen hypoprolactinemia in 3% of patients. In contrast to previous studies, we could not confirm a correlation between severity of TBI and prolactin levels (Agha et al., 2004a).

The diagnosis of glucocorticoid deficiency in the acute phase of TBI is challenging, because relative adrenal insufficiency exists in acutely ill patients and brain edema is treated with high doses of glucocorticoids, which may interfere with hormonal testing (Kelly et al., 2000; Webster and Bell, 1997). In the present study, two patients had (partial) ACTH-deficiency, verified by a decreased morning cortisol level and insufficient increase after insulin-induced hypoglycemia.

Central hypothyroidsm was seen in two patients (3%) consistent with the prevalence of the study from Kelly et al. (2000). The loss of TSH secretion may be due to the acquired hypothalamo-pituitary damage or may be due to hypotheses of the increased somatostatin secretion similar to the explaination of the GHD. Soma-

tostatin is known to suppress TRH-stimulated TSH secretion (Radetti et al., 2000; Coiro et al., 2000).

The prevalence of predominant secondary hypogonadism and GHD after traumatic brain injury reflects the traditional sequence of all varieties of pituitary damage (Benvenga et al., 2000; Benvenga et al., 1997; Lieberman et al., 2001). The fact that the pituitary deficiencies did not correlate with the score of the Glasgow Coma Scale is obvious, because we have included only patients suffering from severe and not from mild or moderate TBI. Beside the low score of the GCS, these patients often had diffuse brain swelling in the acute phase of the injury and had a long duration of coma. These are the three risk factors for hypopituitarism after TBI (Kelly et al., 2000). In the present study, patients with an abnormal axis had a significant longer time of coma.

In summary, we have found hypopituitarism with predominantly hypogonadism and GHD in one-fourth of patients after rehabilitation from severe traumatic brain injury. Based on these findings, basal and pituitary function testing is warranted in patients after severe traumatic brain injury.

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ow Doses of Dexamethasone ffect Immune Parameters in the Absence f Immunological Stimulation

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bstract

ecent findings suggest an important role of subtle changes in ne plasma levels of inflammatory cytokines within the brain-mmune interplay. It is unclear how such changes are regulated n the absence of acute inflammatory or infectious stimuli. Endo-rine systems are a good candidate, because innate immunity nd the hypothalamo-pituitary-adrenal (HPA)-system are losely related: glucocorticoids have immunosuppressive prop-rties and modulate cytokine release from stimulated mononu-lear blood cells *in vitro* and the immune response *in vivo*, but it till remains unclear, whether they also modulate circulating cy-okine levels in the absence of immunological stimuli. We mea-ured the influence of 1.5 or 3.0 mg dexamethasone (DEX) per os t 09:00 or 21:00 hours on body temperature, cortisol plasma lev-els, differential white blood cell counts, and cytokine plasma lev-els in 40 healthy male volunteers using a double-blind, placebo-controlled study design. In addition to significant morning-eve-ning differences in tympanic temperature and several immune parameters, we found that DEX-intake significantly increased tympanic temperature, decreased cortisol plasma levels, altered differential white blood cell counts and induced changes in un-stimulated plasma cytokine levels. Whereas the levels of TNF-α and sTNF-R p75 were reduced, the levels of sTNF-R p55 increased after a transient decrease.

Key words
Hypothalamo-pituitary-adrenal-system · glucocorticoids · tu-mor-necrosis-factor

ntroduction

uring recent years there is growing evidence that subtle changes n circulating cytokine levels play an important role with respect o immune-brain interaction and in the pathophysiology of cen-ral nervous system diseases (Pollmächer et al., 2002): slight hanges in the levels of inflammatory cytokines were found to e correlated with the actual vigilance state in healthy subjects Vgontzas et al., 1999) and in obese people with and without leep apnea (Vgontzas et al., 1998). Additionally, changes in the irculating plasma levels of tumor-necrosis-factor (TNF)-α and s soluble receptors have been reported in patients with psychi-atric diseases compared to healthy controls (Haack et al., 1999; Maes, 1999). In addition, there is experimental evidence pointing to an influence of circulating cytokines on central nervous func-tion in humans from a series of studies using experimental im-mune stimulation induced by the injection of bacterial endotox-in or cytokines to healthy volunteers. In these experiments the modulation of the biological activity of the TNF-α cytokine-sys-tems in the circulation was correlated with alterations in appe-tite, mood, cognition, and sleep-wake behavior (Schuld et al., 1999; Mullington et al., 2000; Reichenberg et al., 2001). Finally it has been suggested that psychotropic drugs may exert their ef-fects on the brain not only via pharmacological interaction with

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