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Psychiatric and neuropsychological changes in growth hormone-deficient patients after traumatic brain injury in response to growth hormone therapy

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ABSTRACT. ***Objective:*** **Traumatic brain injury (TBI) has been recently recognized as a risk factor for cognitive impairment and hypopituitarism, presented most frequently with GH deficiency (GHD). GHD is associated not only with changes in body composition, but also with impaired quality of life, cognitive dysfunctions and some psychiatric sequelae, usually classified as "depression" or "atypical depression". The impact of GH therapy on mental status in TBI patients is still unknown.** ***Design:*** **Psychiatric and cognitive functions were tested in 6 GHD patients at baseline (minimum 3 yr after TBI), reassessed after 6 months of GH therapy as well as 12 months after discontinuation of GH therapy. Psychiatric and cognitive examinations included semi-structured interviews and 3 instruments: Symptom-checklist (SCL-90-R), Zung Depression Inventory, and standard composite neuropsychological battery.** ***Results:*** **Six months of GH therapy in GHD TBI patients improved cognitive abilities (particularly verbal and non-verbal memory) and significantly improved psychiatric functioning. Severity of depression decreased, as well as intensity of interpersonal sensitivity, hostility, paranoid ideation, anxiety, and psychoticism. Somatization, obsessive-compulsive symptoms and phobic anxiety decreased in all except in one patient. In 3 GHD patients who stopped GH therapy for 12 months we registered worsening of the verbal and non-verbal memory, as well symptoms in 3 SCL dimensions: inter-personal sensitivity, anxiety, and paranoid ideation.** ***Conclusion:*** **GH-deficient TBI patients are depressed and have cognitive impairment. GH therapy induced reduction of depression, social dysfunction, and certain cognitive domains. Our preliminary data support the necessity of conducting randomized placebo-controlled trials on the effects of GH therapy on neuropsychological and psychiatric status in GHD TBI patients.**

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INTRODUCTION

Deficiency of one or more anterior pituitary hormones is present in nearly 35% of patients with traumatic brain injury (TBI) (1, 2). GH deficiency (GHD) is the most frequent and recent studies showed that 8-15% of the adult patients with TBI have severe GHD (1, 3). TBI patients, like patients with GHD due to hypothalamic-pituitary disease, are known to experience reduced quality of life and neuropsychological dysfunction. The possibility that untreated TBI-induced hypopituitarism contributes to chronic neurobehavioral problems diagnosed as post-traumatic dementia warrants consideration. The main question is whether GHD affects cognitive functioning in adults with TBI and, if it does, whether replacement with GH will improve it as well as mental functioning. GHD in adults with hypothalamic-pituitary disease is associated not only with changes in body composition (decrease in lean body mass, increase in percentage of body fat *etc.*), but also with impaired quality of life (QoL) and some psychiatric *sequelae*, usually referred to as "depression" or "atypical depression" (4-6). These patients feel less energetic, are emotionally more labile, experience disturbances in sex life and feelings of social isolation at a significantly higher frequency than controls (7). A meta-analysis from The Netherlands provided no evidence that GH improved patient-reported outcomes and QoL in GHD patients (7).

In the few case reports described, hormone replacement therapy in hormone-deficient head-injured patients resulted in neurobehavioral improvements. A good example is a case report on a 47-yr-old male who sustained head injury in a motor vehicle accident and was diagnosed as post-traumatic dementia (8). Hypopituitarism was diagnosed 2 yr later, the patient was replaced with conventional hormone replacement therapy and his cognitive abilities improved. Thus in view of the magnitude of the prevalence of TBI-related disability, endocrine evaluation and hormone replacement need additional research. Psychiatric and neuropsychological examinations of TBI patients are necessary to define mental domains potentially affected by GH and other hormonal deficiencies in order to monitor treatment effects. Moreover, individual responses to GH therapy are highly variable and there are attempts to understand what predicts individual responsiveness to GH.

The aim of the present case-study was to examine psychiatric and neuropsychological changes in adult GHD patients treated with GH for 6 months and reassessed 12 months after discontinuation of GH therapy and compared to GHD TBI patients not treated with GH therapy.

Key-words: Traumatic brain injury, GH deficiency, GH therapy, psychiatric symptoms, depression.

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SUBJECTS AND METHOD

Subjects

This case-study included 6 adult TBI patients with either isolated GHD or multiple pituitary hormone deficiencies (MHPD). Patients were identified from the study of occurrence of anterior pituitary dysfunction in survivors of TBI conducted by a multidisciplinary team (neurosurgeon, endocrinologist, neurologist and psychiatrist) at the University Clinical Center in Belgrade (2).

We included patients: 1) with moderate and severe TBI defined by Glasgow Coma Scale (GCS) score <13; 2) confirmed GHD according to the Consensus Guidelines (9); 3) age of <55 yr; 4) time elapsed from the TBI >3 yr. Exclusion criteria for the study were neurological, psychiatric and medical conditions known to influence cognitive performance prior to TBI.

The study was approved by the Ethics Committee of the University Clinical Center, Belgrade, Serbia and informed consent was obtained from all patients for the endocrine, neurological and neuropsychological testing.

Six TBI patients (one female) who fulfilled inclusion and exclusion criteria were enrolled in the study (Table 1). None of the patients had been treated with glucocorticoids during their stay at Intensive Care Unit. Patients with MPHD were replaced with conventional hormone replacement therapy (hydrocortisone, L-thyroxine and sex steroid hormones) at least 6 months before study entry.

Hormonal testing

The somatotropic axis was evaluated by the combined GHRH (GEREF, Serono,Madrid, 1 μg/kg iv at 0 min) plus GH releasing peptide-6 test (GHRP-6; Clinalfa, Laufelingen, Switzerland, 1 μg/kg iv at 0 min). Samples for GH were taken at 0, 15, 30 and 45 min after bolus GHRH+GHRP-6 injection. GH was assayed with immunofluorimetric assay (Wallac-Turku, Finland) with a GH sensitivity of 0.01 μg/l, inter-assay coefficient of variation (CV) of 6.3% and intra-assay CV of 4.2%. Severe GHD was defined by a peak GH response of <10 μg/l during the combined GHRH+GHRP-6 test (10). IGF-I level was measured at baseline (prior to GH therapy), during GH therapy and after 6 months of discontinuation of GH therapy. IGF-I level was assayed by enzyme-labeled chemiluminescent immunometric assay (Immulite 2000; Siemens, Camberley, UK).

Methods (psychiatric and neuropsychological examination)

All 6 TBI patients were examined prior to GH therapy (Visit 0). Two patients declined GH therapy and they served as "controls" (C1-2). Four patients (T1-4) were treated 6 months with GH therapy and then reassed (Visit 1). After 12 months of discontinuation of GH therapy all patients were re-examined (Visit 2). One patient (T3) was treated continuously for 18 months with GH. Two patients who declined GH replacement therapy were re6-examined after 6 months (Visit 1) and 12 months of follow-up (only C1).

Psychiatric assessment

The psychiatric evaluation included psychiatric interview, personal and family history of emotional, behavioral or developmental disorders and two psychometric instruments: Scale for depression (Zung Depression Inventory) and Symptom-checklist (SCL-90-R).

Zung Depression Scale (11) is a self-rating scale, as opposed to observer-based scales, consisting of 20 items, four grades each (maximum score 80 and the cut-off score for depression 40). Zung scale has questions relating to mood, anxiety, motor, cognitive, social, and vegetative symptoms of depression. It is useful to validate symptoms, as well as the extent of the problem and, if necessary, it provides with additional motivation to seek help.

The SCL-90-R instrument (12) is a brief, multidimensional self-report inventory designed to screen for a broad range of psychological problems and symptoms of psychopathology. The SCL-90-R instrument is also useful as a progress or outcomes measurement instrument. It measures nine primary psychiatric symptom dimensions (somatization, obsessive-compulsive, interpersonal sensitivity, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism and depression) on a five-point rating scale (scores in the range 0-4 are reflecting symptom severity). All SCL-90-R dimensions were used for the present study, except Depression, because the assesment of depression was performed by Zung scale. The SCL-90-R instrument is a well-researched instrument and many studies demonstrated its reliability, validity, and utility. Recently, the instrument was reccomended to measure emotional distress among persons with brain injuries (13). It can be useful in both the initial evaluation of patients and for measuring patient progress during monitoring.

Neuropsychological examination

Each TBI patient was assessed with standard neuropsychological procedure (about 2 h) with standard neuropsychological battery sensitive for subtle brain dysfunction, covering a wide array of functional domains. Testing was conducted between 10:00 and 12:00 h and patients were allowed to have a light meal before. All patients were tested and retested by the same investigator and in the same conditions, in a quiet room. The battery comprised the following tests:

- Mini Mental State Examination (MMSE) as a general cognitive screening;
- Rey Auditory-Verbal Learning Test (RAVLT) for verbal memory assessment;
- Rey-Osterrieth Complex Figure Test (RCF) for visuo-spatial and non-verbal memory assessment;
- Trail Making Test (TMT) A and B for visual conceptual and visuomotor tracking examination, and the assessment of simple and divided attention;
- Boston Naming Test (BNT) to assess nomination impairment;
- Wisconsin Card Sorting Test (WCST) for executive functions (14-18).

One patient could not adequately perform TMT and BNT due to a visual impairment – strabismus with diplopia (subject T1).

GH therapy

Three GHD TBI patients were treated with recombinant human GH in a standard adult dose (0.3 mg for males and 0.4 mg for female sc) in the evening (20:00 h). The IGF-I levels during the therapy normalized and remained stable during the treatment period (data not shown).

RESULTS

Clinical characteristics and hormonal evaluation of six TBI patients

Clinical and endocrinological parameters for all patients are shown in Table 1. Three TBI patients had isolated GHD, while 3 had MPHD (GHD, hypogonadism, hypocor-

Table 1 - *The clinical characteristics of six traumatic brain injury (TBI) patients treated (T1-T4) and not treated (C1-C2) with GH.*

Patient	Age (yr)	Gender	BMI (kg/m^2)	Time since TBI (yr)	Age at TBI (yr)	GCS	GHD	MPHD	GH Th (months)
T1	42	M	24.9	27	15	10	Yes	Yes	6
T2	35	M	32.9	3	32	Unknown	Yes	Yes	6
T3	27	F	18.6	7	20	10	Yes	Yes	18
T4	53	M	28.1	27	26	8	Yes	No	6
C1	35	M	22.6	4	31	13	Yes	No	Not treated
C2	40	M	24.7	12	28	6	Yes	No	Not treated

M: male; F: female; BMI: body mass index; GCS: Glasgow Coma Scale; GHD: GD deficiency; MPHD: multiple pituitary hormone deficiency; GH Th: duration of GH therapy

ticism and hypothyroidism). Out of 4 patients who were treated with GH (T1-4), 3 (T1-3) had MPHD, while one (T4) had isolated GHD. Two patients who declined GH therapy (C1-2) had isolated GHD.

Psychiatric assessment

TBI patients presented with a variety of personality traits, attitudes and values, and came from different backgrounds with diverse sociodemographic characteristics. Psychiatric interview at baseline was uneventful except for patient T4. Patient T4 had positive family history of depression and alcohol abuse (father) and positive personal history of major depression, diagnosed for the first time at age 43 (17 yr after TBI). Life after TBI was complicated with stressful events which led to depression and occasional alcohol abuse. This patient was treated with antidepressants (selective serotonin reuptake inhibitor) 2 yr before Visit 0, but compliance was poor. Between Visits 0 and 1, he was treated with GH and antidepressant venlafaxine (serotonin-norepinephrine reuptake inhibitor; daily dose 150 mg). Between Visits 1 and 2, he stopped GH but continued therapy with the same antidepressant in the same dose, with compliance scored as low. This patient was included in the study despite positive personal history of major depression because depression started after TBI and we expected that GH therapy could have beneficial effects in his condition. The results of patient T4 were evaluated separately and compared with results of other GHD patients.

In 4 TBI patients (T1-T4), Zung depression score on Visit 0 was above the cut-off score (score range 40-62) indicating clinically significant intensity of mood, anxiety, motor, cognitive, social and vegetative symptoms of depression at baseline. After 6 months of GH therapy (Visit 1), all subjects except T4 improved according to Zung scale (for subjects T1-3 the score range was 31-36; score for T4 was 61).

Similarly, the majority of SCL-90-R dimensions yielded symptom-reduction after 6 months of GH therapy, although in patient T4 the improvement was not found in somatization, obsessive-compulsive dimension and phobic anxiety. On Visit 2, only patient T3, who was on continual GH therapy, had sustained improvement, while other 3 patients (T1, T2 and T4) had variations in symptom intensity, mostly evident as a symptom progression. SCL-90-R symptom worsening after stopping GH therapy was the most prominent in three dimensions: interpersonal sensitivity, anxiety and paranoid ideation (Fig. 1). This pattern of changes separated T1, T2 and T4 from either T3

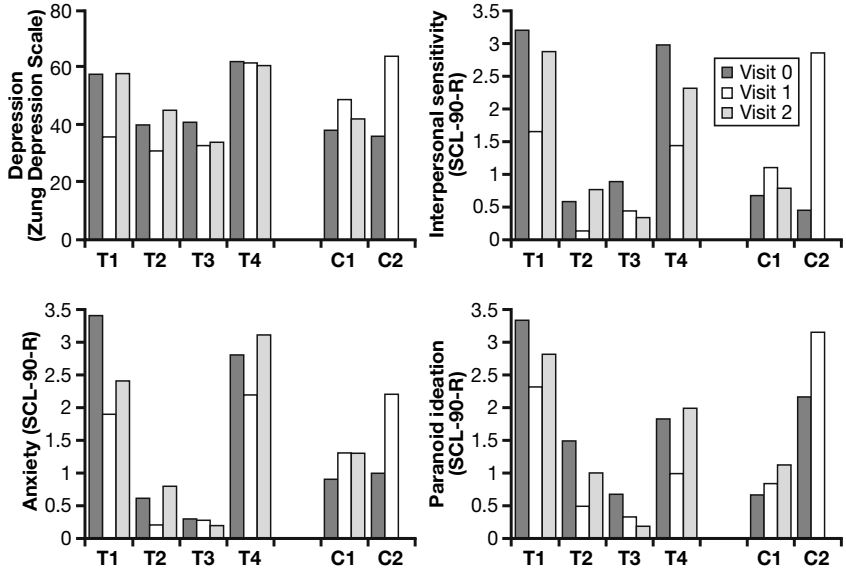

Fig. 1 - *Psychiatric parameters (depression, interpersonal sensitivity, anxiety, paranoid ideation) in traumatic brain injury patients (T1-T4 and C1) at baseline (Visit 0) and during follow-up period [T1-T4: 6 months of GH therapy (Visit 1) and 12 months after discontinuation of GH therapy (Visit 2, except T3 who was treated continuously with GH for 18 months); C1-2: without GH therapy after 6 (Visit 1) and 12 months of follow-up (Visit 2)]. SCL-90-R: Symptom-checklist-90.*

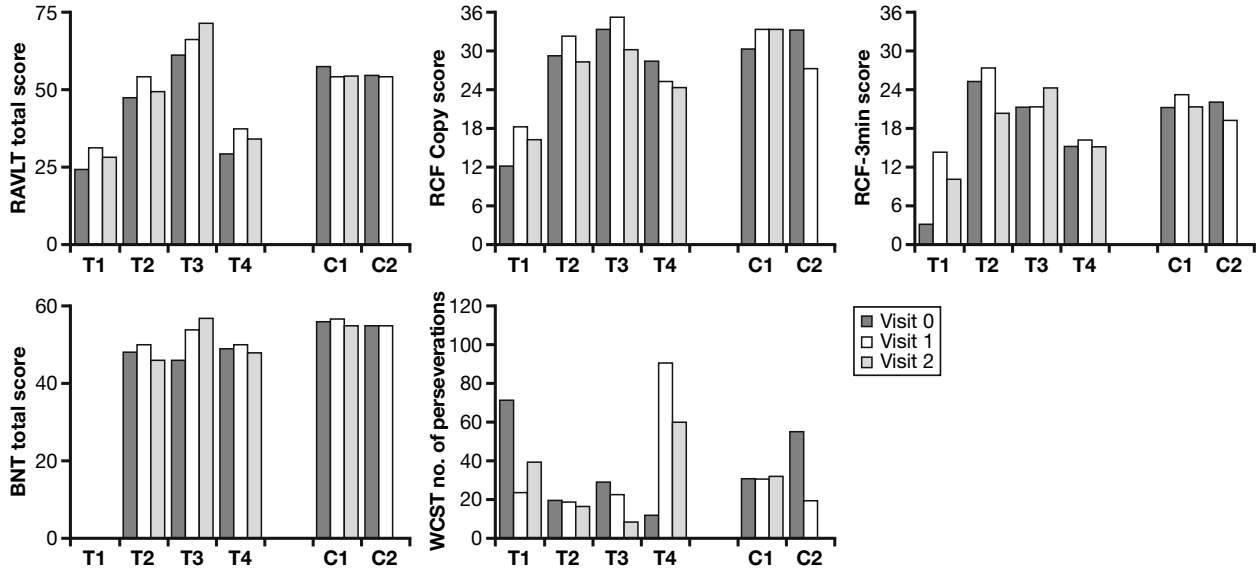

Fig. 2 - *Neuropsychological parameters (RAVLT total score, RCF Copy score, RCF-3min score, BNT total score and WCST number of perseverations) in traumatic brain injury patients at baseline (Visit 0) and during follow-up period [T1-T4: 6 months of GH therapy (Visit 1) and 12 months after discontinuation of GH therapy (Visit 2, except T3 who was treated continuously with GH for 18 months); C1-2: without GH therapy after 6 (Visit 1) and 12 months of follow-up (Visit 2)]. See text for acronyms of tests.*

(with sustained improvement) or C1 (with different patten of symptom changes). Almost similar pattern of changes in symptom intensity was shown regarding depression except in T4. The nature of depression in T4 was different in comparison to patients with no psychiatric or family history of depression, therefore major depression in T4 should be considered as a comorbid diagnosis to GHD-induced psychiatric and neuropsychologic changes.

Two GHD patients without GH therapy had no clinically significant intensity of depressive symptoms on inclusion. On Visit 1 (without GH therapy) symptoms of depression increased (Zung score). In addition, a broad range of SCL-90-R symptoms were intensified. On Visit 2, no further substantial changes were evident on psychometric testing.

Neuropsychological examination

Mean education level of subjects was 11.3±0.3 yr. Global cognitive ability (MMSE scores) was within normal limits in all GHD TBI patients and did not change during GH therapy or after stopping the GH therapy (data not shown). Verbal memory (RAVLT) had the tendency to improve after 6 months of GH therapy (Visit 1) in all treated patients, with a return to pre-treatment values after discontinuation of GH therapy (T1, T2, T4) or with a further improvement after 18 months of GH therapy (T3) (Fig. 2 – RAVLT total score shown). Visuoconstructional ability (RCF Copy score) demonstrated a tendency of initial improvement on GH therapy which was not sustained on a prolonged GH therapy (T3) and showed a regression to lower performances in patients in which GH therapy was discontinued. The exception was patient T4 whose TBI was complicated with stressful events in the meantime that lead to secondary depression and alcohol abuse (Fig. 2).

Short-term non-verbal memory (RCF-3min score) demonstrated a trend of improvement on GH-therapy with a return to pre-treatment values after GH-therapy discontinuation (Fig. 2). Performance on TMT A and B tests did not change after 6 months of GH therapy or after stopping of GH therapy (data not shown). Nomination (BNT) had the tendency to improve during GH therapy and return to lower values after discontinuation of GH therapy or improve further in T3 on Visit 2 (Fig. 2 – BNT total score shown). A trend of improvement in executive functions (WCST) was observed on GH therapy, and even sustained in one patient after the GH-therapy discontinuation. The exception was patient T4 (Fig. 2 – WCST number of perseverations shown).

DISCUSSION

In the present case-study, we have studied the effects of GH therapy on cognitive and psychiatic functioning in adult TBI patients with GHD. We have shown that 6 months of GH therapy improved psychiatric status in several domains: severity of depression decreased, as well as intensity of interpersonal sensitivity, hostility, paranoid ideation, anxiety and psychoticism, paralleled by a certain improvement in cognitive abilities (verbal and non-verbal memory, nomination and executive functions). Adult TBI patients with GHD but without GH therapy scored highly on depression and showed more distress in several domains of mental dysfunctioning during the follow-up period. However, in patients who stopped GH therapy, we noticed symptom worsening, particularly in terms of anxiety, interpersonal sensitivity, paranoid ideation and depression. Only one patient, who continued GH therapy for 18 months, had sus-

tained improvement in psychiatric and some neuropsychologic domains.

All patients were examined minimum 3 yr after TBI, when the neuronal repair mechanisms were completed and GHD was confirmed by provocative testings. All patients included in the study were younger than 55 yr, as the intention was to minimize the influence of an age-related cognitive decline. Patients with MPHD were on stable conventional hormone replacement therapy for 6 months prior to psychiatric and neuropsychological examinations, as the possible influence of other hormonal replacement therapy on the examined functions was considered and avoided.

The rationale for studying the interrelation of GH and brain-function in TBI is GH and IGF-I receptors located in cerebral regions vulnerable to traumatic injury (19, 20). GH receptors are present in the choroid plexus, thalamus, hypothalamus, pituitary, putamen, and hippocampus, while IGF-I receptors in the hippocampus, parahippocampal areas, cerebellum, frontal and other neocortical areas and caudate nucleus (19, 20). Hippocampus is involved in cognition, memory and spatial functions and is associated with storage, processing, and retrieval of spatiotemporal memories, central to the protective function of fear conditioning (21). Abnormality in the hippocampus may lead to the exaggerated conditioned fear response (22). Hippocampus is also a part of neural networks that putatively modulate aspects of emotional behavior. GH therapy has been shown to induce some changes in the levels of neurotransmitters in the cerebrospinal fluid (CSF), which may influence neurocognitive and psychiatric functions (23). Hypopituitary patients on GH therapy have a decrease in CSF concentrations of the dopamine metabolite homovanillic acid (HVA), similarily to depressed patients after successful treatment (24). The second important finding is that the level of aspartate (the ligand for N-methyl-D-aspartate, NMDA receptor) which is increased in CSF during GH therapy. NMDA receptor is involved in memory function and attentional performance (25).

Many, but not all studies in patients with GHD due to hypothalamic-pituitary disease, report an improved quality of life, mood, incidental learning and psychomotor speed after IGF-I level normalization on GH therapy (26-29). Our case-study, inspite of a variety of personal and sociodemographic characteristics of the subjects included, showed a relationship between GH therapy and anxiety, inter-personal sensitivity and paranoid ideation in GHD TBI patients. Althogh a small number of TBI patients included in this study is its limitation, the strenght of this study lies in the complexity of psychiatric and neuropsychological evaluation.

In conclusion, this study shows that TBI patients with GHD are more depressed and may have cognitive impairment. GH therapy reduced depression and improved affect and some cognitive abilities. These preliminary data show that GH therapy in patients with TBI clearly warrants additional research.

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