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Lasting Pituitary Hormone Deficiency after Traumatic Brain Injury

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Abstract

Pituitary deficiencies have been reported after traumatic brain injury (TBI) and may contribute to lasting cognitive disorders in this context. In a population of TBI patients with persistent cognitive and/or behavioral disorders, we sought to determine the prevalence of lasting pituitary deficiency and relationships with TBI severity, cognitive disorders, and impairments in activities of daily living (ADL). Fifty-five patients were included (mean age 36.1 years; 46 men) at least 1 year after TBI. They underwent a comprehensive evaluation of pituitary function (basic tests and stimulation), initial TBI severity, and long-term outcomes (cognitive performance, Glasgow Outcome Scale score, impact on ADL, and quality of life [QoL]). We used chi-squared and Mann-Whitney tests to probe for significant ($p \leq 0.05$) relationships between pituitary disorders and other parameters. Thirty-eight (69%) patients had at least one pituitary hormone deficiency. Growth hormone deficiency was more prevalent (severe: 40.0%; partial: 23.6%) than corticotropin (27.3%) or thyrotropin (21.8%) deficiencies. Other deficiencies were rare. Growth hormone deficiency was associated with attention and verbal memory disorders and reduced involvement in ADL. We did not find any relationship between pituitary deficiency and the TBI's initial severity. In a multivariate analysis, the TBI severity was introduced as a first factor, and pituitary deficits as a secondary factor for explaining the late outcome (ADL and QoL). In conclusion, TBI patients with cognitive sequelae must undergo pituitary screening because growth hormone, corticotropin, and thyrotropin deficits are particularly common and can adversely affect ADL and reduce QoL.

Key words: activities of daily living; cognitive disorders; pituitary deficiency; sequelae; traumatic brain injury

Introduction

Traumatic brain injury (TBI) has both physical and predominantly cognitive sequelae (such as attention, memory, and executive function disorders, slowing, and anosognosia; Azouvi et al., 2009; Russell, 1971; Van der Naalt et al., 1999). Patients may also suffer from behavioral disorders (particularly fatigability and irritability; Thomsen et al., 1992). These difficulties lead to loss of independence (Mathé et al., 2005), and cause social, family-related, and work-related problems (Mazaux et al., 1997) that degrade their quality of life (QoL).

Asthenia, cognitive impairment, and psychic disorders can also be due to anterior pituitary gland disorders. Associations between low growth hormone (GH) levels and attention, memory (visual and verbal), and executive function disorders have been reported (Falleti et al., 2006; Popovic et al., 2004; Stabler et al., 1992; van Dam and Aleman, 2004). The ability to concentrate may also be altered (van Dam et al., 2000). Moreover, patients with GH deficiency (GHD) are less self-confident and more socially isolated than control patients. QoL is still altered when all pituitary hormone deficiencies other than GHD are treated.

Pituitary deficiencies can occur after TBI and several studies have evaluated the prevalence of these conditions (Agha et al., 2004a,2004b,2005a,2005b; Bondanelli et al., 2004; Kelly et al., 2000). The somatotropic axis is most frequently altered (in between 7% and 32% of patients), and this deficiency is usually isolated (in between 25% and 76% of cases; Agha et al., 2004a; Aimaretti et al., 2004a,2005; Kelly et al., 2000; Schneider et al., 2003,2006; Tandon et al., 2009; Tanriverdi et al., 2006). Other hormones may also be deficient, such as corticotropin (0–19% of patients), thyrotropin (1–11%; Aimaretti et al., 2004a,2005; Bondanelli et al., 2004; Tanriverdi et al., 2006) and gonadotropin (7.7–14%; Bondanelli et al., 2004), more than 1 year after TBI. Hyperprolactinemia is found in between 4.5% and 14% of cases (Agha et al., 2004a; Popovic et al., 2004; Schneider et al., 2006), and the prevalence

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of diabetes insipidus 1 year after injury stands at between 3% and 7%. The relationship with initial TBI severity remains debatable, but some authors (Bondanelli et al., 2004) have reported that TBI patients without pituitary deficiency had better Glasgow Coma Scale (GCS) scores. In addition, several studies have suggested a link between pituitary deficiency and the presence of brain edema (Bondanelli et al., 2004; Kelly et al., 2000) and diffuse axonal injury, especially in the corpus callosum, basal ganglia, and thalamus, and gray-white matter junction (Jeong et al., 2010) and with brain infarct (Tandon et al., 2009).

Studies in patient populations have suggested that TBI patients with GHD have more severe attention, executive function, memory, and emotional disorders (Bondanelli et al., 2007; Leon Carrion et al., 2007), depressive symptoms, fatigue, physical impairments, dependence, and lower QoL (Kelly et al., 2006; Park et al., 2010) than patients without GHD. However, the impact of GHD on fatigue and on cognitive disorders in TBI patients is subject to debate (Belmont et al., 2006; Bushnik et al., 2007; Pavlovic et al., 2010).

These studies are important in terms of understanding the mechanisms that underlie cognitive, behavioral, and mood disorders and reduced QoL in TBI patients. However, many aspects have yet to be resolved, notably those concerning the putative links between hormone deficiency and the severity and types of brain damage and cognitive and behavioral disorders.

The objectives of the present study were to (1) evaluate the prevalence of pituitary hormone deficiency in a relatively large sample of TBI patients complaining of long-term difficulties in activities of daily living (ADL), (2) evaluate potential relationships with the severity of injury, and (3) analyze the links between hormone deficiency, cognitive, and behavioral disorders and QoL. Our main hypothesis was that significant links would be detected (notably for memory, attention, and QoL), but that they would be moderate, given that these disorders result primarily from TBI and not from hormone deficiency.

Methods

Patients

Brain-damaged patients were recruited during follow-up consultations at the Neurological Rehabilitation Department at Lille University Medical Centre and by community-based healthcare services.

The inclusion criteria were as follows: age between 18 and 60 years, at least 1 year post-TBI, and the presence of cognitive and/or behavioral disorders (memory, attention, or concentration disorders, slowing, fatigability, lack of initiative, and emotional lability) reported by the patient or their caregivers or revealed during consultations. We excluded pregnant women, subjects on corticosteroids, and patients with a history of drug abuse, neurological disease, hypothalamus or pituitary disorders, or severe kidney, liver, or heart disease. The patient or his or her legal representative provided written informed consent prior to participation. The study was performed in accordance with the Declaration of Helsinki and institutional guidelines.

During a medical consultation with a specialist, the patient's baseline parameters were recorded, including the age, education level, cause of the TBI (road accident, domestic accident, sports accident, assault, or attempted suicide), initial severity factors (the lowest GCS score during the first 24 h post-injury, and the length of stay in a rehabilitation ward), and the time elapsed from TBI. The computer tomographic (CT) scan data recorded immediately after the TBI (brain edema, meningeal hemorrhage, extradural hematoma, subdural hematoma, and focal or diffuse parenchymal lesions: present [1)] or absent [0]), and the magnetic resonance imaging (MRI) data more than 3 months thereafter (focal or multifocal parenchymal lesions, diffuse axonal injury, and brain atrophy).

If the patient or his or her caregivers reported the presence of cognitive difficulties, the attending physician suggested a consultation with an endocrinologist, followed by a hormone profile investigation. A cognitive evaluation was performed during the same period.

Hormone profiling

Hormone profiling was preceded by a consultation with an endocrinologist, during which the assay methods were explained. The patient or his or her legal representative provided written informed consent prior to participation. A general clinical examination was performed and the body mass index (BMI) was measured. The main complaints of the patients were recorded, including the presence of asthenia and fatigue, cold intolerance, decreased libido, and amenorrhea.

An analysis of posterior pituitary function included a screen for the syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH, excessive ADH secretion leading to hyponatremia (<135 mmol/L), and plasmatic hypo-osmolality (<275 mOsm/kg of water), natriuresis >40 mmol/L with urinary osmolality >100 mOsm/kg of water, absence of any edema or hypovolemia, and normal renal, adrenal, and thyroid functions (Ellison and Berl, 2007) and, in cases of polyuria and polydipsia, diabetes insipidus. Hyperprolactinemia was defined by a blood prolactin level >22 ng/mL; in cases of hyperprolactinemia, a metoclopramide test was performed to determine its origin or to reveal a lactotroph deficiency by an absence of elevation of the prolactin range during the test. A deficiency in the gonadotropin axis (GD) was defined for women as secondary amenorrhea or a menstrual cycle disorder with a blood estradiol level below 20 pg/mL and normal or low gonadotropin levels, or for men as a blood testosterone level below 1 ng/mL and normal or low gonadotropin levels. Thyrotropin deficiency (TD) was defined as a low free thyroxine (FT_4) level with normal or low thyroid-stimulating hormone (TSH) levels. Corticotropin deficiency (CD) was defined as (1) complete if the blood cortisol level was below 3 μg/dL in the absence of elevated adrenocorticotropic hormone (ACTH), and (2) partial if the blood cortisol level fell below 20 μg/dL during an insulin tolerance test (ITT), or if the plasma 11-deoxycortisol level fell below 70 ng/mL during a short metyrapone test. GHD was detected by a reference test, an ITT, and/or an arginine-GHRH (growth hormone-releasing hormone) test (Ghigo et al., 2008; Growth Hormone Research Society, 1998). Severe GHD was defined by a GH peak lower than 3 ng/mL during ITT. When the arginine-GHRH test was used, severe GHD was defined by a peak of GH lower than 4.0–15.6, depending on the age and BMI (see Colao et al., 2009 for

threshold values). When the assay result was abnormal, a second assay was performed, and we considered the GHD as severe if both results were abnormal, or if one abnormal result was associated with another pituitary deficiency. Somatotrophic function was considered to be unaffected if the response to the reference test was normal (>10 ng/mL for the ITT, and greater threshold values of Colao et al. [2009] percentile 1, for the arginine-GHRH test). In an intermediate situation, the GHD was classified as partial. We also measured the blood insulin-like growth factor (IGF-1) level. MRI of the hypothalamus and pituitary gland was performed for all patients presenting at with least one anterior pituitary deficiency with an indication for hormone replacement therapy. The MRI protocol featured T1-weighted 3-mm-thick coronal and sagittal slices before and after injection of gadolinium, as well as T2-weighted coronal slices for visualizing hemosiderin deposits.

The cognitive battery

Cognitive function was comprehensively evaluated at the time of the hormone screen (±2 months). Attentional function was evaluated using the phasic alertness (simple visual reaction time [RT], and RT following a warning signal), selective attention RT, and divided attention RT subtests of Zimmerman's computerized TAP test (Zimmermann and Fimm, 1994). A 2-minute verbal semantic and phonemic fluency test and a flexibility test from the TAP battery were used to evaluate executive function. For logical visual reasoning and conceptualization, we administered the matrices subtest from the Wechsler Adult Intelligence Scale III-R (WAIS-R; Wechsler, 1989). Memory and orientation in space and time were measured by asking the patient to state the exact date (score/5; day of the week, date, month, year, and season), and to give his or her current location (score/3; building, town, and county). Short-term verbal memory and working memory were evaluated with the digit span forward test and the digit span backward test, respectively. Verbal episodic memory was evaluated with free recall (R-3) and recognition of a 16-word test (score/16; Van der Linden et al., 2004) that highlighted information encoding, storage, and retrieval. The visuospatial component of episodic memory was evaluated with the Rey Osterrieth Complex Figure Test (score/36; Rey, 1941). Cognitive and behavioral disorders were assessed with the Neurobehavioural Rating Scale-Revised (NRS-R; Vanier et al., 1997; McCauley et al., 2001). A structured interview with the patient served as the basis for scoring 29 items on a scale ranging from 1 (the absence of alteration) to 4 (severe alteration). This scale evaluates memory disorders (score/32), motivated behavior, and emotional hypoactivation (depressive mood and withdrawal; score/12), anxiety, emotional, and behavioral hyperactivation (irritability, disinhibition, excitement, and lability of mood; score/32), reduced alertness (motor slowing and fatigability; score/16), and language disorders (expression, articulation, and understanding; score/12).

Activities of daily living and quality of life

The general outcome was evaluated with the Glasgow Outcome Scale (GOS; Jennett and Bond, 1975), as published by the European Brain Injury Society (Brooks and Truelle, 1994): good recovery (0 = upper level, 1 = lower level), moderate disability (2 = upper level, 3 = lower level), severe disability (4 = upper level, 5 = lower level), and a persistent vegetative state (6). Independence in personal and instrumental activities of daily living (pADL and iADL, respectively) were analyzed according to the EBIS guidelines (each score from 0, full participation, to 18, no participation; Brooks and Truelle, 1994). We also analyzed (on a yes/no basis: 1/0) the patient's requirement for a caregiver and their return to work (with or without special arrangements, and on a full-time or part-time basis) after TBI.

QoL was assessed on the Quality of Life after Brain Injury (QOLIBRI) scale (Truelle et al., 2008). The scale's sub-items concern the physical, intellectual, psychological, functional, social, and personal domains, and each is scored from 1 (not at all satisfied) to 10 (fully satisfied). The QOLIBRI questionnaire was administered to the patient.

Statistical analyses

All statistical analyses were performed with SPSS (SPSS Inc., Chicago, IL) software (version 16.0). We used the Pearson chi-squared and Mann-Whitney tests to probe putative relationships between the presence of endocrine deficiency and categorical or quantitative variables, and the Spearman test to test relationships between quantitative variables. The threshold for statistical significance was set at $p \leq 0.05$.

Results

The study population

We invited 117 patients to undergo hormone profiling and 9 refused (mostly due to fear of blood sampling). Hence, 108 patients underwent pituitary hormone screening. Of these, 55 (46 men and 9 women) also underwent cognitive evaluation and were thus included in the study. The mean ± standard deviation (SD) age was 36.1 ± 11.3 years, and the mean number of years in full-time education was 10.9 ± 3.4.

The causes of TBI were as follows: road accidents (n = 41), domestic accidents (n = 9), sporting accidents ($n = 1$), assault ($n = 3$), and attempted suicide ($n = 1$). On average, the lowest GCS score in the first 24 h was 8.2. The mean duration of coma was 17.7 days. The mean length of stay in the intensive care unit was 29.0 days, and the mean length of stay in a rehabilitation ward was 124.3 days. The initial MRI data (analyzed in 47 cases) revealed 13 cases of meningeal hemorrhage, 8 cases of extradural hematoma, 8 cases of subdural hematoma, 24 focal contusions, and 17 cases of diffuse edema.

The brain MRI performed at least 3 months after the TBI ($n = 40$) revealed 16 focal contusions, 14 multifocal contusions, 10 cases of diffuse axonal injury, and 5 cases of brain atrophy. The imaging data were normal in 14 cases.

The mean time interval between the TBI and the endocrine and neuropsychological evaluations was 79.2 ± 72.8 months. In physical terms, 14 patients were hemiplegic, 8 had cerebellar syndrome, 17 had gait disorders, and 11 were being treated for epilepsy.

According to the GOS, there were 9 level 1 patients, 32 level 2 patients, 14 level 3 patients, and no level 4, 5, or 6 patients. According to the EBIS guideline document, the mean levels of independence in pADL and iADL were 1.5 ± 3.2 and 7.0 ± 6.3, respectively; the higher the score, the greater the dependence. Fourteen patients had returned to work (11 with no special arrangements and 3 with special arrangements).

Hormone status

At clinical examination, 22 patients complained of asthenia and fatigue, 11 of decreased libido, and 4 of cold intolerance. However, those symptoms, except cold intolerance, are not specific for pituitary deficiency in a TBI context.

Forty-two patients (76.4%) presented with at least one pituitary deficiency (Table 1). The most frequent deficiency ($n=35$, 63.6%) was GHD, and it was more frequently severe ($n=22$) than partial ($n=13$). The mean ± SD IGF-1 level was 139.08 ± 80.62 ng/mL. Corticotropin deficiency was relatively frequent ($n=15$, 27.3%), but always partial (cortisol level $>3\,\mu g/dL$), and was diagnosed using dynamic tests. Thyrotropin deficiency was found in 12 cases (21.8%). Other screened-for deficiencies were rarer. We did not find any cases of diabetes insipidus, but we did have a case of SIADH in a patient with lasting hyponatremia (<130 mEq/L) and increased urinary sodium (>105 mEq/L). He received gabapentin (800 mg/d) and clobazam (10 mg/d), which are not recognized as classical sources of SIADH. He had no evidence of cancer and his body CT scan was normal. Furthermore, severe GHD was significantly associated with corticotropin deficiency ($p=0.013$), but not with any of the other endocrine deficiencies.

Association between demographic variables and initial trauma severity, and cognitive disorders, participation in ADL, and QoL

Greater age, lower education level, lower GCS score, longer rehabilitation period, and longer time since TBI were partially associated with lower performance on cognitive and QoL estimations (Table 2). The initial GCS score was the factor most frequently correlated with the late period variables, especially participation in iADL and most components of the QoL QOLIBRI scale.

In addition, we found relationships between multifocal lesions and diffuse axonal lesions on MRI and several cognitive and social measures. Multifocal lesions were associated with the selective attention RT, Rey complex figure recall, NRS-R emotional hypoactivation, and psychological and social components of the QoL QOLIBRI questionnaire. We also found tendencies toward significance ($0.05<p\leq 0.07$) for participation in iADL and the intellectual component of the QoL QOLIBRI questionnaire. Diffuse axonal lesions were associated with selective attention RT, divided attention RT, Rey complex figure recall, and participation in pADL and iADL.

Table 1. Frequency of Pituitary Deficiencies (Either Isolated or Combined)

	Isolated		*Associated*		*Total*	
	n	%	n	%	n	%
One deficit at least	22	40.0	20	36.4	42	76.4
Global GHD	16	27.3	19	34.5	35	63.6
Partial GHD	7	12.7	6	10.9	13	23.6
Severe GHD	9	16.4	13	23.6	22	40.0
Corticotropic deficit	1	1.8	14	25.4	15	27.3
Thyreotropic deficit	3	5,4	9	16.4	12	21.8
Gonadotropic deficit	0	0.0	1	1.8	1	3.6
Hyperprolactinemia	1	1.8	3	5,4	4	7.3
SIADH	0	0.0	1	1.8	1	1.8

GHD, growth hormone deficiency; SIADH, the syndrome of inappropriate antidiuretic hormone hypersecretion.

Associations between endocrine deficiency, demographic variables, and the initial trauma

Given the relatively low proportions of patients with gonadotropin hormone deficiencies or hyperprolactinemia, we did not analyze the links between these parameters and other variables.

There were no statistically significant relationships between severe GHD, CD, TD, and GD, and the age, clinical severity of the initial trauma, and presence of specific brain lesions on the initial CT scan and MRI performed 3 months later. The time since TBI was longer in GHD- than in non-GHD patients (Table 3).

Associations between endocrine deficiency, cognitive disorders, and participation in activities of daily living

Severe GHD was associated (Table 3) with a tendency toward longer visual reaction time in the presence of a warning signal, a longer reaction time on the TAP battery flexibility test, and a tendency toward less orientation in time and space and poor performance in free recall and retrieval on the word memory test. Corticotropin deficiency was also associated with poor retrieval in the latter test ($p=0.009$). There was a non-significant trend toward an association between thyrotropin deficiency and poor performance on the digit span forward test ($p=0.061$), and digit span backward test ($p=0.052$).

There were also trends towards associations between GHD and the overall severity of the outcome (GOS), and involvement in iADL. The IGF-1 level did not correlate with cognitive performance, participation in ADL, and QoL. Corticotropin deficiency was associated with poor physical QoL on the QOLIBRI scale ($p=0.022$).

In addition, the actual degree of depressive mood and withdrawal, as quantified by the NRS-R hypoactivity subscore, correlated with the digit spans forward and backward ($p=0.020$ and $p=0.022$, respectively), but not with the degree of other cognitive difficulties, participation in ADL, and QoL measurement.

Multivariate analysis

We performed regression analyses (stepwise variable selection), to identify the variables that best explained performance on cognitive tests, GOS scale, participation in ADL, and QoL. For each regression, we introduced factors best correlated with the different performance measures in the monovariate analyses, especially age, education level, initial GCS score, presence of multifocal and diffuse axonal lesions on MRI (0/1), and presence (0/1) of severe GHD, CD, and TD. The probability of the F-to-enter value was $p=0.10$, and of the F-to-exclude was $p=0.15$.

As shown in Table 4, the GCS score and the presence of multifocal and diffuse axonal lesions were the main factors of late patient difficulties. But pituitary deficits, especially CD and GHD, also contributed to explain these late disorders.

Discussion

In the present study we examined a relatively large number of TBI patients presenting with lasting cognitive disorders

Table 2. Presentation of the Relationships between Cognitive Testing, GOS Score, Participation in ADL, and QoL Questionnaire (QOLIBRI), and the Age, Education Level, Initial GCS Score, Time Since TBI, and Presence of Multifocal Lesions (MFL) or Diffuse Axonal Lesions (DAL) on MRI

	Correlation analysis (r values)					*Mann-Whitney (Z values)*	
	Age	*Education*	*GCS*	*Period rehabilitation*	*Time / TBI*	*MFL*	*DAL*
Simple visual RT	0.48***	0.02	0.05	−0.17	0.16	−0.70	−0.91
Phasic alertness RT	0.48***	−0.14	0.04	−0.09	0.18	−0.28	−1.28
Selective attention RT	0.16	−0.10	−0.30*	0.08	0.11	−2.21*	−2.12*
Divided attention RT	0.32*	0.06	−0.11	0.03	0.34*	−1.39	−2.27*
Flexibility RT	0.31	−0.40**	−0.14	−0.03	0.06	−0.42	−1.05
Semantic fluency	−0.09	0.27*	0.12	0.06	−0.05	−1.76	−1.22
Phonemic fluency	−0.01	0.33*	0.18	0.04	0.01	−1.12	−1.17
Matrices, WAIS-R	0.02	0.32*	0.03	0.20	−0.03	−1.67	−1.00
Orientation in time / 5	0.03	0.04	−0.07	0.04	0.02	−1.31	−0.55
Orientation in space / 4	−0.07	−0.03	−0.19	0.06	0.08	−1.73	−0.13
Digit span forward	−0.13	0.25	0.02	0.40**	0.01	−1.15	−0.45
Digit span backward	−0.16	0.34*	0.05	0.31*	0.03	−0.59	−0.19
Verbal memory free recall / 16	−0.13	0.04	0.07	−0.11	−0.28*	−1.40	−0.68
Verbal memory recognition / 16	−0.12	0.08	0.11	0.05	0.12	−1.18	−0.00
Rey complex figure score / 36	−0.06	0.17	0.41**	−0.29	−0.31*	−2.13*	−2.36*
NRS-R memory disorders / 32	0.01	−0.21	0.03	−0.18	0.08	−0.48	−0.72
NRS-R emotional hypoactivation / 12	0.16	0.03	0.46**	−0.47**	0.03	−2.32*	−1.51
NRS-R emotional hyperactivation / 32	−0.12	−0.11	0.13	−0.08	−0.08	−0.766	−0.27
NRS-R reduced alertness / 16	0.22	−0.08	0.20	−0.23	0.05	−1.78	−0.08
NRS-R language disorders / 12	−0.14	−0.09	0.01	0.12	0.22	−0.09	−0.82
Glasgow Outcome Scale / 6	−0.34*	−0.08	0.07	0.43**	0.15	0.00	−1.15
pADL / 18	0.10	−0.15	−0.28	0.30*	0.09	−0.63	−2.34*
iADL / 18	0.05	−0.35*	−0.45**	0.47***	0.22	−1.83	−2.96**
QOLIBRI physical /10	−0.17	0.13	−0.24	0.35*	−0.07	−1.49	−0.85
QOLIBRI intellectual /10	−0.09	−0.03	−0.39**	0.19	−0.05	−1.86	−1.79
QOLIBRI psychological /10	−0.12	0.03	−0.56***	0.24	−0.03	−2.35*	−1.65
QOLIBRI functional /10	−0.26	−0.14	−0.18	0.16	0.01	−0.41	−0.55
QOLIBRI social /10	−0.18	0.03	−0.38*	0.22	0.02	−1.99*	−0.89
QOLIBRI personal /10	−0.04	−0.07	−0.49***	0.34*	0.05	−1.68	−1.62

*$0.01 < p < 0.05$.
**$0.001 < p < 0.01$.
***$p < 0.001$.
GOS, Glasgow Outcome Scale; GCS, Glasgow Coma Scale; ADL, activities of daily living; QoL, quality of life; QOLIBRI, Quality of Life after Brain Injury; iADL, instrumental activities of daily living; pADL, personal instrumental activities of daily living; NRS-R, Neurobehavioural Rating Scale-Revised; WAIS-R, Wechsler Adult Intelligence Scale III-R; TBI, traumatic brain injury; MRI, magnetic resonance imaging; RT, reaction time.

more than a year after the initial accident. It highlighted (1) the high prevalence of pituitary deficiencies (above all GHD deficiency) in this population, and (2) the relationships between GHD and CD on one hand and certain long-term cognitive difficulties (above all affecting attention and memory) and the overall post-trauma outcome on the other. However, we did not identify any associations between pituitary deficiencies and initial TBI severity scores.

The study population was representative of TBI, with predominantly young, male patients having suffered a road accident. Most (but not all) of the cases of TBI were severe. Although the brain lesions observed on CT and MRI scans were those typically reported in the literature, a significant proportion of patients did not have any abnormal morphological imaging results. Most of the patients were autonomous in terms of pADL, but dependent for iADL (most often due to cognitive disorders and fatigability). Work activity tended to be part-time, with special arrangements in the workplace. The mean time since trauma in the present study (over 5 years) was much longer than in previous studies. This leads us to believe that the patients' hormonal status had stabilized, and that the observed pituitary deficiencies were lasting aftereffects of TBI.

Pituitary deficiency was very frequent in this population because 76% of the patients presented with at least one pituitary deficiency. GHD was the most frequent, since the somatotropic axis is typically the most fragile. The prevalence of severe GHD was higher (40.0%) than in previous studies, in which it ranged from 8–32% (Agha et al., 2004a,2005a; Berg et al., 2010; Kelly et al., 2000; Leal-Cerro et al., 2005; Lieberman et al., 2001; Popovic et al., 2004; Schneider et al., 2006; Tandon et al., 2009; Tanriverdi et al., 2006). The investigation of this axis is debatable because a variety of diagnostic methods are used, and there are confounding factors such as body weight and BMI (Kokshoorn et al., 2010). The ITT has good sensitivity and specificity but poor

Table 3. Performance Level (Median Value, 5th–95th Percentiles) in Cognitive Testing, GOS Score, Participation in ADL, and QoL Questionnaire (QUOLIBRI), in the Entire Group of 55 Patients and in Patients without and with Severe GHD

	All patients	*No-GHD patients*	*GHD patients*	p
Age	34.3 (22.1–56.7)	31.7 (21.2–57.8)	37.3 (23.3–56.5)	0.151
Education level	11.0 (7.0–7.3)	10.0 (7.0–16.0)	12.0 (7.0–16.9)	0.432
Gender (M / F)	46 / 9	26 / 7	20 / 2	0.234
Glasgow Coma Scale Score	7.0 (3.0–15.0)	7.0 (3.0–15.0)	6.0 (3.0–15.0)	0.320
Rehabilitation period	60.0 (0.0–435.7)	20.5 (0.0–240.0)	90.0 (0.0–666.7)	0.148
Time / TBI	58.9 (16.0–243.1)	53.8 (13.7–249.6)	65.7 (31.4–215.0)	0.032*
BMI	25.2 (18.0–35.5)	24.2 (17.4–32.4)	26.6 (20.4–38.5)	0.131
Phasic alertness visual RT	301.5 (219.9–701.5)	279.0 (226.7–535.5)	357.0 (216.1–741.2)	0.087
Divided attention RT	732.5 (629.0–980.0)	710.0 (631.4–894.0)	809.0 (629.0–980.0)	0.044*
Verbal memory free recall / 16	11.0 (0.6–15.0)	11.0 (6.2–15.0)	9.0 (0.0–15.0)	0.031*
Verbal memory recognition / 16	16.0 (4.8–16.0)	16.0 (14.1–16.0)	16.0 (0.0–16.0)	0.008**
Glasgow Outcome Scale / 6	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.087
pADL / 18	0.0 (0.0–6.3)	0.0 (0.0–4.2)	0.0 (0.0–13.6)	0.119
iADL / 18	6.5 (0.0–18.0)	3.0 (0.0–15.4)	9.0 (0.0–18.0)	0.021*

*$0.01 < p < 0.05$.
**$0.001 < p < 0.01$.
***$p < 0.001$.
p Values indicate significance of between-group differences.
GOS, Glasgow Outcome Scale; ADL, activities of daily living; QoL, quality of life; QOLIBRI, Quality of Life after Brain Injury; iADL, instrumental activities of daily living; pADL, personal instrumental activities of daily living; RT, reaction time; BMI, body mass index; GHD, growth hormone deficiency; TBI, traumatic brain injury.

reproducibility (Hoeck et al., 1995). The arginine-GHRH stimulation test is a well-tolerated "gold standard" test and was used in the present study. It has good reproducibility and the same sensitivity as the ITT (Aimaretti et al., 1998). Disparities between our findings and previous reports may also be due to the nature of our study population. In fact, some studies recruited patients from a neurosurgery department soon after the initial injury; these participants were not necessarily suffering from cognitive disorders (Agha et al., 2004b,2005b; Aimaretti et al., 2004b,2005; Leal-Cerro et al., 2005; Tanriverdi et al., 2006). Other studies have examined patients hospitalized in rehabilitation departments; again, the time since the initial trauma was relatively short (Lieberman et al., 2001; Schneider et al., 2006). If one hypothesizes that a proportion of the cognitive disorders seen after TBI are linked to pituitary deficiency, the frequency of deficiency should be greater in a population with cognitive disorders and/or slowing and fatigue. We also found that the severe GHD was frequently associated with CD, even if there was no relationship of pituitary deficiencies with the initial TBI severity.

Although other deficiencies were less prevalent than GHD, significant proportions of our patients had corticotropin and/or thyrotropin deficiencies (27.3% and 21.8%, respectively). These values are higher than the literature values (from 0–19% for corticotropin and from 0–19.2% for thyrotropin; Agha et al., 2004b, 2005a; Aimaretti et al., 2004b,2005; Bondanelli et al., 2004; Leal-Cerro et al., 2005; Lieberman et al., 2001; Popovic et al., 2004; Schneider et al., 2006; Tanriverdi et al., 2006). These disparities may also be related to the types of assay used and the populations studied. The rarity of gonadotropin deficiency, hyperprolactinemia, diabetes insipidus, and SIADH in our series is probably explained by the fact that these conditions are often transient and occur soon after TBI (Aimaretti et al., 2005; Schneider et al., 2006; Tanriverdi et al., 2006).

Several mechanistic explanations for hormone deficiency in TBI have been proposed. Pituitary necrosis is possible; the pituitary gland is poorly vascularized and its vascular system is fragile, notably after fracture of the sella turcica (Daniel et al., 1959; Kawai et al., 1995; Massol et al., 1987), or during hypotension or prolonged hypoxia (as in Sheehan's syndrome; Sheehan and Stanfield, 1961). Other mechanisms of late-onset pituitary hormone deficiency are possible, but remain speculative. Excessive, acute-phase release of stored hormones may result in the detection of normal or even abnormally high release of hormones soon after the TBI; in this context deficiency would only reveal itself some time after injury (Agha et al., 2005a).

As with most other studies, we did not find a clear relationship between the presence of a pituitary disorder and the initial TBI severity indicators. Only one study has described a link with the GCS score (Bondanelli et al., 2004). We did not find any significant association between pituitary dysfunction, especially severe GHD, and the presence of specific brain lesions on the initial CT scan and MRI performed more than 3 months after the TBI. Therefore, we did not confirm the association with brain edema (Bondanelli et al., 2004; Kelly et al., 2000; Tandon et al., 2009) and diffuse axonal injury (Jeong et al., 2010) reported in other series.

GHD, CD, and TD were associated with cognitive disorders (notably attention and memory disorders) in monovariate and multivariate analyses. GHD was also associated with the patients' overall outcome, especially participation in iADL in the monovariate analysis and the GOS score, participation in pADL, and QOLIBRI social subscore in the multivariate analysis. Associations between GHD, cognitive disorders, and QoL have already been described in the literature (Bondanelli et al., 2007; Kelly et al., 2006; Leon Carrion et al., 2007). In our series, other pituitary deficits, especially CD and TD, also contributed to explain the late cognitive and

Table 4. Presentation of Multivariate Analyses Explaining Performance Level in Cognitive Testing, Glasgow Outcome Scale (GOS) Score, Participation in ADL, and QoL Questionnaire (QOLIBRI)

	Factor 1	*Factor 2*	*Factor 3*	*R2 value*
Simple visual RT	Age			0.126
Phasic alertness RT	Age			0.178
Selective attention RT	MFL			0.120
Divided attention RT	GHD			0.147
Flexibility RT	TD			0.144
Semantic fluency	Time / TBI			0.124
Phonemic fluency	Education			0.115
Matrices, WAIS-R				
Orientation in time / 5	CD	GHD	DAL	0.346
Orientation in space / 4	GHD	MFL		0.332
Digit span forward	TD			0.127
Digit span backward	TD			0.111
Verbal memory free recall / 16	Time / TBI			0.126
Verbal memory recognition / 16	CD			0.162
Rey complex figure score / 36	GCS			0.172
NRS-R memory disorders / 32				
NRS-R emotional hypoactivation / 12	GCS			0.366
NRS-R reduced alertness / 16	MFL			0.203
NRS-R language disorders / 12	Time / TBI			0.108
Glasgow Outcome Scale / 6	GHD			0.118
pADL / 18	DAL			0.127
iADL / 18	DAL	GHD	Education	0.411
QOLIBRI physical /10	GCS	CD		0.282
QOLIBRI intellectual /10	GCS	CD		0.343
QOLIBRI psychological /10	GCS			0.379
QOLIBRI functional /10	CD			0.136
QOLIBRI social /10	MFL	GHD		0.407
QOLIBRI personal /10	GCS	CD		0.282

MFL, multifocal lesions on MRI; DAL, diffuse axonal lesions; GCS, Glasgow Coma Scale; TBI, traumatic brain injury; GHD, growth hormone deficiency; RT, reaction time; CD, corticotrophin deficiency; TD, thyrotropin deficiency; QOLIBRI, Quality of Life after Brain Injury; ADL, activities of daily living; QoL, quality of life; MRI, magnetic resonance imaging; NRS-R, Neurobehavioural Rating Scale-Revised.

QoL evaluations. The global outcome of patients as determined by the ADL and QoL evaluations was also related to the initial TBI severity (GCS score), and the presence of multifocal contusion and diffuse axonal lesions. In the multivariate analysis, these factors were selected first to explain the late outcome. But the presence of GHD and CD was selected in a second step, confirming that pituitary deficiencies are aggravating factors of the late condition (Bondanelli et al., 2007). The mechanism underlying the development of cognitive disorders and reduced involvement in ADL is still subject to debate. There are GH receptors in the thalamus, pituitary gland, hypothalamus, hippocampus (Schneider et al., 2003), and prefrontal cortex (van Dam and Aleman, 2004). Areas of the temporal lobe and the prefrontal cortex also contain high concentrations of IGF-1 receptors. Reduced activation in these areas can contribute to attention and memory disorders.

In conclusion, pituitary deficiency is common late after TBI, and can contribute to the late ADL and QoL status of patients. Accordingly, it would make sense to perform a pituitary hormone screen in all TBI patients with this type of difficulty. This type of screening raises a health-cost problem because patients found to have deficiencies would then have to be treated. Even though the value of treating corticotropin, thyrotropin, and gonadotropin deficiencies is universally accepted, the treatment of GHD remains controversial, especially when the deficiency is only partial. But recent studies have suggested that treating post-traumatic GHD can be beneficial for speed of information processing, memory, and executive functions (High et al., 2010).

Author Disclosure Statement

No competing financial interests exist.

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