

INVITED REVIEW

Hypopituitarism after traumatic brain injury

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Abstract

Traumatic brain injury (TBI) is one of the main causes of death and disability in young adults, with consequences ranging from physical disabilities to long-term cognitive, behavioural, psychological and social defects. Post-traumatic hypopituitarism (PTHP) was recognized more than 80 years ago, but it was thought to be a rare occurrence. Recently, clinical evidence has demonstrated that TBI may frequently cause hypothalamic–pituitary dysfunction, probably contributing to a delayed or hampered recovery from TBI. Changes in pituitary hormone secretion may be observed during the acute phase post-TBI, representing part of the acute adaptive response to the injury. Moreover, diminished pituitary hormone secretion, caused by damage to the pituitary and/or hypothalamus, may occur at any time after TBI. PTHP is observed in about 40% of patients with a history of TBI, presenting as an isolated deficiency in most cases, and more rarely as complete pituitary failure. The most common alterations appear to be gonadotropin and somatotropin deficiency, followed by corticotropin and thyrotropin deficiency. Hyper- or hypoprolactinemia may also be present. Diabetes insipidus may be frequent in the early, acute phase post-TBI, but it is rarely permanent. Severity of TBI seems to be an important risk factor for developing PTHP; however, PTHP can also manifest after mild TBI. Accurate evaluation and long-term follow-up of all TBI patients are necessary in order to detect the occurrence of PTHP, regardless of clinical evidence for pituitary dysfunction. In order to improve outcome and quality of life of TBI patients, an adequate replacement therapy is of paramount importance.

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Introduction

Traumatic brain injury (TBI) is one of the main causes of death and disability in young adults, with consequences ranging from physical disabilities to long-term cognitive, behavioural, psychological and social defects (1, 2); these long-term consequences make TBI a public health problem (3).

Post-traumatic hypopituitarism (PTHP) was recognized more than 80 years ago (4), but it was thought to be a rare occurrence. Recently, TBI has been demonstrated to be a frequent cause of hypothalamic–pituitary function impairment, contributing to a delayed or hampered recovery in many TBI patients (5–10).

The purpose of this review is to update the epidemiological and clinical data on the occurrence of PTHP, in order to identify the possible specific risk factors, and to assess the functional consequences of PTHP on TBI outcome. The present review of the current literature aims to promote diagnostic and therapeutic strategies which could improve the quality of life of these patients.

Definition, epidemiology and classifications of TBI

TBI is a non-degenerative, non-congenital insult to the brain from an external mechanical force causing temporary or permanent neurological dysfunction, which may result in impairment of cognitive, physical and psychosocial functions. Head injury is a non-specific and antiquated term indicating clinically evident external injuries to the face, scalp and calvarium that may or may not be associated with TBI (2, 11).

The overall incidence of TBI in developed countries is about 200/100 000 population per year (11). Population-based studies show that the incidence of TBI is between 180 and 250/100 000 population per year in the United States (11–14). Incidence is higher in Europe (ranging from 91/100 000 in Spain to 546/100 000 in Sweden) (15–19), in Southern Australia (322/100 000) (20) and in South Africa (316/100 000) (21), and lower in China (22) (Table 1).

These numbers probably underestimate the true incidence of TBI, because they typically refer to the TBI patients admitted to hospital. Many patients with

Table 1 Incidence of traumatic brain injury and mortality rate in different populations.

Reference	Locality	Dates	Incidence/100 000	M:F	Fatal TBI incidence/100 000
Kraus <i>et al.</i> (12)	San Diego, California	1980	180	2.2	30
Cooper <i>et al.</i> (13)	Bronx, New York	1980–1981	249	2.8	27.9
Durkin <i>et al.</i> (14)	Northern Manhattan, New York	1983–1989	155	1.2	16.7
Wang <i>et al.</i> (22)	China	1983	56	1.3	
Nell & Brown (21)	Johannesburg, South Africa	1991	316	4.4	80
Hillier <i>et al.</i> (20)	Southern Australia	1987	322		7
Tiret <i>et al.</i> (15)	Aquitaine, France	1986	281	2.1	22
Vazquez-Barquero <i>et al.</i> (16)	Cantabria, Spain	1988	91	2.7	20
Ingebrigtsen <i>et al.</i> (17)	Northern Norway	1993	229	1.7	NR
Andersson <i>et al.</i> (18)	Western Sweden	1992–1993	546	1.5	(0.7%)
Servadei <i>et al.</i> (19)	Italy		314	1.6	
	Romagna	1998	297		7.7
	Trentino		332		2.1

mild TBI (not presenting to the hospital) or with severe TBI (associated with death at the scene of the accident or during transport to a hospital) may not, in fact, be accounted for in the epidemiological reports (11). The highest incidence of TBI is among subjects aged 15–24 years or 75 years and older, with an additional incidence peak in children aged 5 years and younger (3, 11). Incidence rate for males is almost twice that for females, with the highest male:female (M:F) ratio occurring in adolescence and young adulthood, and ranging from 1.2:1 to 4.4:1 in different populations (13–15, 18–21). M:F ratio approaches parity with ageing owing to the increased likelihood of TBI caused by falls, for which members of both sexes have similar risks in later life (11).

Approximately 50% of TBIs are the result of motor vehicle, bicycle or pedestrian–vehicle accidents. Falls are the second-commonest cause of TBI (20–30% of all TBI), being more frequent among the elderly and the very young population. Violence-related incidents account for approximately 20% of TBI, almost equally divided into firearm and non-firearm assaults (3).

Several classifications for TBI severity are reported in the literature. The post-resuscitation Glasgow Coma Scale (GCS; Table 2) is the most widely used clinical classification of TBI severity. GCS is based on the patient's response (eye opening, verbal and motor function) to various stimuli. A score of 13–15 is considered mild, 9–12 moderate and ≤ 8 severe TBI (23). Clinical severity of TBI is also defined by duration of loss of consciousness (LOC), loss of memory for events immediately before or after the accident (post-traumatic amnesia) and identified intracranial lesion (11, 24). Radiological findings by computed tomography (CT) may be helpful in TBI severity evaluation, and the most used radiological scale is the Marshall's classification (25).

Functional outcome after TBI is usually evaluated by the Glasgow Outcome Scale (GOS), a descriptive and easy to use scale, describing five outcome categories (death, vegetative, severely disabled, moderately disabled, good recovery) (26).

Pathophysiology of TBI

Cerebral damage resulting from trauma can be divided into primary and secondary brain injury. Primary injury is due to mechanical disruption of brain tissue occurring at the time of the initial trauma. Secondary injury develops in the hours or days following the initial insult and may lead to further damage and a worse neurological outcome. In fact, as a result of the primary injury brain edema and circulatory disturbance occur, and hypoxia due to increased intracranial pressure results in secondary brain injury (24, 27). Inflammatory mediators (cytokines, free radicals, amino acids and nitric oxide) and excitatory amino acids (such as *N*-methyl-D-aspartate) appear to be implicated in secondary brain injury development (24, 27, 28). Cytokines – in particular interleukin-6 – which stimulate vasopressin secretion, may also be involved in the pathogenesis of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) after TBI (29). As the

Table 2 Glasgow Coma Scale (GCS) (23).

Verbal response
Oriented to person, place and date = 5
Converses but is disoriented = 4
Says inappropriate words = 3
Says incomprehensible sounds = 2
No response = 1
Motor response
Follows commands = 6
Makes localizing movements to pain = 5
Makes withdrawal movements to pain = 4
Flexor (decorticate) posturing to pain = 3
Extensor (decerebrate) posturing to pain = 2
No response = 1
Eye opening
Spontaneous = 4
To speech = 3
To painful stimulation = 2

GCS score defines severity of TBI within 48 h of injury: GCS 13–15, mild TBI; GCS 12 to 9, moderate TBI; GCS ≤ 8 , severe TBI.

primary injury is not preventable, medical management should be directed at the mechanisms of secondary injury in order to improve outcome. Both primary and secondary injury can be focal or diffuse (28) (Table 3). Focal injury tends to be caused by contact forces, whereas diffuse injury is more likely to be caused by non-contact, acceleration–deceleration and rotational forces. Rotational acceleration–deceleration (e.g. in motor vehicle collisions) can induce shearing injury of the axons, with disruption of the white matter and widespread damage, most likely vasogenic. Shearing injury is most often seen in midline structures of the brain and may represent a possible mechanism of hypothalamic–pituitary dysfunction in TBI (24). Skull fractures observed in TBI may be associated with hematoma, cranial nerve damage and severe brain injury (28). Basal skull fractures may cause direct mechanical injury to pituitary gland, stalk or hypothalamus (30, 31).

Consequences of TBI

TBI may impair cognition (concentration, memory, judgment and mood), movement abilities (strength, coordination and balance), sensation (tactile sensation and special senses, such as vision) and sexual function, leading to important behavioural changes and consequences on daily living activities (2, 3, 8, 28). TBI may also result in seizure disorders, with an overall risk of 2–5%. In patients with cortical injuries and neurologic sequelae the risk ranges from 7 to 39%, reaching levels of up to 57% in patients with dural penetration (32). It has been estimated that permanent disability is present in 10% of mild TBI patients, in 66% of moderate TBI and in 100% of severe TBI (33, 34). About 1% of subjects with severe TBI survive in a state of persisting unconsciousness (35).

The complications of TBI are not restricted to neurological consequences (8). Gastrointestinal complications occur in about 50% of patients; these patients develop hepatic dysfunction, bowel incontinence, dysphagia and gastroparesis, with consequent nutrition problems (36). Loss of neurological control may frequently cause chronic genitourinary problems. Cardiovascular complications are seen in over 30% of TBI patients, hypertension being the most frequent (10–15%) (8, 36). Deep venous thromboses and pulmonary emboli are frequent after severe TBI. Musculoskeletal problems are also

common, with an incidence of fractures of approximately 30% (8). Neuroendocrine dysfunction occurs in approximately 40% of patients with TBI (5, 6, 30). Medical complications occur not only in the immediate post-injury period with implications for early rehabilitation, but may persist for many months or become chronic.

It is not possible to estimate the human costs of TBI and only a few analyses of the monetary cost of TBI are available. These studies estimate that the lifetime medical cost for an individual TBI patient ranges from 0.6 to 1.9 million US dollars (3). The overall annual cost of acute care and rehabilitation in the United States is estimated to be 10 to 48 billion dollars (3, 37).

Since a large number of people experience TBI each year, often with severe consequences, TBI has become a public health problem that requires more effective strategies to improve outcomes and minimize disability.

Pituitary dysfunction during the acute phase post-TBI

Pituitary dysfunction following traumatic events can be divided into: (a) functional alterations during the acute phase post-TBI, which result in a temporary increase or decrease in blood pituitary hormone concentrations; (b) alterations in pituitary hormone secretion that may occur at any time after TBI, resulting in permanent hypopituitarism caused by damage at pituitary and/or hypothalamic level.

The pituitary gland responds to acute traumatic events with two secretory patterns: adrenocorticotropin (ACTH), prolactin (PRL) and growth hormone (GH) levels increase, while luteinizing hormone (LH), follicle-stimulating hormone (FSH) and thyrotropin (TSH) levels may either decrease or remain unchanged, associated with a decreased activity of their target organ. Changes in the circulating hormone levels become apparent during the first hours or days after trauma, and may persist for the duration of the acute critical illness (38). These alterations represent part of the acute adaptive response to the injury, and may be influenced by the type of injury and pharmacological therapy used to treat the critical illness (glucocorticoids, narcotic analgesics or dopaminergic agents) (38).

In the acute phase of TBI, low (39, 40) or high (41–43) basal circulating GH levels associated with low insulin growth factor (IGF)-I concentrations have been reported. Peripheral GH resistance, manifested by elevated GH levels with low IGF-I concentrations, has been observed in patients with acute critical illness (44). A decrease in GH bursts frequency has been detected 24–48 h after severe trauma, indicating a relative hyposomatotropinism (45). A blunted GH response to arginine (ARG) stimulation has been found in patients with severe TBI and very poor outcome (41). Gottardis *et al.* (46) reported that a GH-releasing hormone (GHRH) test elicited a significant

Table 3 Brain injuries following head trauma.

Focal injuries	Diffuse brain injuries
Epidural hematoma	Mild concussion
Subdural hematoma	Classical cerebral concussion
Contusion	Prolonged coma
Intracerebral hematoma	Mild diffuse axonal injury
	Moderate diffuse axonal injury
	Severe diffuse axonal injury

GH rise in the patients who survived after severe TBI, whereas GH response was blunted in the patients who died. By contrast, Dalla Corte *et al.* (47) reported a normal GH response to GHRH in the severely head-injured patients, with a progressive increase in this response from day 2 to day 15 after injury in the patients with poor outcome. Other authors have demonstrated that i.v. glucose administration results in a paradoxical increase in GH levels, which is greater in patients with worse neurological function (43). These data indicate an imbalance of the complex neuroendocrine system controlling GH secretion during the acute phase post-TBI, but they do not draw reliable conclusions. In one of our recent studies, patients receiving rehabilitation after leaving the intensive care unit for severe TBI did not show significant changes in GH secretion, as assessed by GHRH, GHRH plus ARG, and somatostatin administration, in comparison with healthy controls, indicating a normal function of the GH axis in the post-acute phase of TBI. Only one patient had subnormal GH response to GHRH plus ARG, indicative of severe GH deficiency (GHD), even if IGF-I levels were in the age- and sex matched normal range (48). A reduced GH response to glucagon stimulation, suggestive of GHD, has recently been demonstrated in 18% of patients during the early phase (7–20 days) following TBI, regardless of patient age, body mass index or initial GCS. However, IGF-I levels did not differ between GHD and non-GHD patients (49).

Elevated serum cortisol concentrations are generally present during the initial phase after trauma, and are associated with increased ACTH release, presumably driven by corticotropin-releasing factor (CRF), cytokines and noradrenergic system activation (50–52). In some cases, abnormalities in cortisol secretory dynamics (fasting hypercortisolemia, abolition of the normal diurnal rhythm and inadequate suppression after dexamethasone) may persist for many months after TBI (53). A positive correlation between cortisol concentrations and injury severity has been demonstrated in patients with mild or moderate TBI, but not in those with severe injury (51). On the contrary, adrenal insufficiency has been found in 16% of patients during the early phase post-TBI, suggesting post-traumatic damage at the hypothalamic–pituitary level (49). Primary or secondary adrenal insufficiency has been shown in 15% of patients with moderate to severe TBI, 7–60 days after injury, by using the low-dose ACTH test and corticotropin-releasing hormone (CRH) test (54). These data highlight the importance of an early recognition of adrenal insufficiency that may lead to a worse outcome. However, the diagnosis of glucocorticoid deficiency is challenging during the acute phase, due to the difficulty in selecting a reliable test for assessing cortisol secretion. In fact, the insulin tolerance test (ITT) is regarded as potentially dangerous in these patients owing to the risk of seizures in the acute phase post-TBI. Moreover, the low-dose ACTH test may evoke false-normal cortisol responses,

as the time elapsed since TBI might be insufficient for the development of adrenal failure. Recently, Agha *et al.* (49) proposed the glucagon stimulation test as a reliable alternative to the ITT in the early phase after TBI.

A high incidence of sex-steroid deficiency has been reported in the immediate post-TBI period. In this phase, testosterone concentration has been shown to negatively correlate with the severity of injury (55, 56). Testosterone levels in men and estrogen levels in women significantly fall within 24 h following brain injury and remain lowered for 7–10 days. Testosterone levels may return to normal after 3–6 months or remain low (56–58). Gonadotropin levels also decrease, but their response to gonadotropin-releasing hormone (GnRH) administration may be normal (57) or increased (55), indicating a hypothalamic mechanism. In the early recovery period post-TBI or during rehabilitation hypogonadism has been demonstrated in 25–67% of cases (48, 54, 59). A more recent study performed in 50 patients in the early, acute phase of moderate-to-severe TBI has detected central hypogonadism in 80% of cases, including 18 patients with hyperprolactinemia (49).

Hyperprolactinemia is present in more than 50% of patients in the early, acute phase post-TBI and may persist in 31% of cases during rehabilitation (48, 49). A blunted PRL response to TRH has also been reported (60). The demonstration of a paradoxical response of PRL to GHRH in comatose patients with a good outcome (47) and of a negative correlation between PRL concentrations and severity of TBI (49, 61) may suggest a good prognostic role for PRL responses during the acute phase post-TBI.

Acute illness or trauma induce alterations in thyroid hormone equilibrium within hours. Although TSH usually remains normal, circulating thyroxine (T₄) levels may be reduced or normal, while tri-iodothyronine (T₃) rapidly drops, partly due to decreased T₄ conversion to T₃ and/or increased thyroid hormone turnover. These changes are consistent with the occurrence of low-T₃ syndrome. As the patients recover, thyroid hormones return slowly to normal over weeks (62, 63). In head-injured patients, lower TSH levels may be present in the early phase after injury, suggesting that the reduced production of thyroid hormones may have a central cause (62). A recent evaluation of 50 patients in the acute phase post-TBI showed central hypothyroidism in 1 case (5%) (49). Central hypothyroidism was also demonstrated in 15% of critical care patients with moderate to severe TBI (54).

The association between TBI and diabetes insipidus has been recognized for many years (64, 65). However, diabetes insipidus has been considered as a rare complication (<1%), generally observed within 5–10 days after severe TBI and/or craniofacial fractures, although delayed onset has been reported (65–67). A recent retrospective review confirmed the low prevalence (2.9%) of diabetes insipidus in TBI patients admitted

to the intensive care unit, and underlined that patients who developed the disease within the first 3 days after injury had a high mortality rate (68). By contrast, other authors demonstrated a high prevalence of diabetes insipidus during the acute phase post-TBI in patients admitted to a neurosurgical center (22–26%) (49, 69) and in patients with head injury damaging the chiasm (37%) (70). However, diabetes insipidus is frequently transient and can spontaneously disappear within a few days or up to 1 month (66, 70, 71) after the acute event, as confirmed by its low prevalence (0–6.9%) in patients evaluated after months or years following TBI (5, 6, 69).

SIADH can manifest during the immediate post-TBI period, as a result of damage to the pituitary stalk or the posterior pituitary. Studies on SIADH post-TBI have yielded conflicting results, showing a prevalence ranging from 2.3 to 36.6% (69, 72–76).

Post-traumatic hypopituitarism (PTHP)

In 1918 Cyran (4) described the first case of PTHP, and the first prevalence data concerning PTHP were provided in 1942 by Escamilla and Lisser (77) who observed brain injury as a cause of hypopituitarism in 4 out of 595 cases (0.7%). Up to 1986, 52 cases of PTHP were reported in the literature (78). In 2000, Benvenega *et al.* (79) carried out an overview of 357 cases of PTHP published between 1942 and 1998, underlining important aspects of this emerging problem (79). Over the last few years, 5 major studies on PTHP have been published, on a total of 344 patients (258 males, 86 females, M:F = 3) who had suffered TBI at some time between 1 month and 23 years preceding the studies. The prevalence of hypopituitarism was 42.7%, ranging from 28 to 68.5% in the different series evaluating patients who recovered from the acute phase post-TBI (5–7, 9, 30) (Table 4). Recently, extrapolating data from KIMS (Pharmacia International Metabolic Database), containing information on more than 8500 patients with GHD, TBI was identified as a cause of GHD in 168 cases, indicating TBI as a relevant cause of GHD in adults (80).

The prevalence of PTHP appears to be similar in males and in females (5, 9, 30), although Benvenega *et al.* (79) reported a greater prevalence of PTHP in males (84% vs 16% in females). In the Benvenega series, the occurrence of PTHP was about 60% in the patients aged 11–29 years, with the third decade most at risk, and progressively declined with advancing age, suggesting young age as a possible risk factor for developing PTHP (79). However, more recent studies have not confirmed this hypothesis. In fact, no correlation (7) or, by contrast, a positive relationship between age and occurrence of post-traumatic hypogonadism (9) or GHD (5) has been documented. Concerning the causes of TBI in patients who developed

Table 4 Prevalence of pituitary dysfunction in patients with previous TBI.

Reference	No. of cases	M:F	Age (years)	GCS	Time since TBI	Prevalence of PD (%)	LH/FSH deficit (%)	GH deficit (%)	TSH deficit (%)	ACTH deficit (%)	Low PRL (%)	High PRL (%)	Permanent DI (%)
Kelly <i>et al.</i> (30)	22	4.5:1	20–52	3–15	3 months–23 years	36.4	22.7	18.2	4.5	4.5†	0	0	0
Lieberman <i>et al.</i> (7)	70	1.5:1	18–58	3–15	1 month–23 years	68.5	1	14.6	21.7	45.7§	0	10	0
Bondanelli <i>et al.</i> (5)	50	4.0:1	20–87	3–15	1–5 years	54	14	28*	10	0§	8	8	0
Aimaretti <i>et al.</i> (6)	100	1.7:1	37±2	3–15	3 months	35	17	37**	5	8§	NR	10	4
Agha <i>et al.</i> (9)	102	5.7:1	15–65	3–12	6–36 months	28.4	11.8	17.6***	1	22.5†	NR	11.8	NR
Total	344					42.7				12.7‡			

PD, pituitary dysfunction; DI, diabetes insipidus; NR, not reported. GH deficiency: *, severe GHD = 8% and partial = 20%; **, severe GHD = 21% and partial = 16%; ***, severe GHD = 7.8%. ACTH deficiency: §, diagnosed by basal morning cortisol levels; †, ‡, diagnosed after one or two standard cortisol stimulation tests respectively.

PTHP, available data show that the majority (74%) of patients had a traffic accident, which is also the major cause of TBI in young adults. Falls, the major cause of TBI in the elderly, represent only 9% of the causes of PTHP. Less frequent causes are firearm accidents, work accidents, sport accidents and child abuse (79). These data suggest that patients with TBI following traffic accidents are at high risk for PTHP. In a study on post-traumatic central hypothyroidism, domestic and vehicle accidents represented the main causes of TBI (81).

Severity of TBI and secondary cerebral damage have been suggested as risk factors for the development of PTHP (30, 41, 79). In the past, the risk of developing pituitary dysfunction was considered as strictly dependent on the severity of TBI, particularly when associated with skull and facial fractures, cranial nerve injury and a prolonged period of unconsciousness (64, 76, 78). It has also been reported that traumatic chiasmal syndrome is associated with impairment of anterior pituitary function in 10% of cases and permanent diabetes insipidus in 16% (70). The recent review by Benvenega *et al.* (79) reported that 93% of patients with PTHP had suffered coma or unconsciousness following TBI. Kelly *et al.* (30) identified GCS scores of <10 and diffuse brain swelling on initial computed tomography (CT) scan/magnetic resonance imaging (MRI) as significant predictors of PTHP. We recently demonstrated that the occurrence of pituitary dysfunction was 59% in patients with severe TBI and 37.5% in those with mild TBI (according to GCS). However in our series, the initial neuroradiological findings and/or the presence of cranial fractures did not predict the development of PTHP (5). By contrast, Agha *et al.* (9) did not observe any relationship between hormone abnormalities and TBI severity, as measured by either GCS score or CT scan findings in patients who survived severe or moderate TBI. Patients with mild TBI, however, were not included in this study. The high prevalence of anatomical damage at the hypothalamic–pituitary level, found in the autopsy series from patients dying after acute TBI, may further support the hypothesis that TBI severity is an important risk factor for developing PTHP. However, mild TBI cannot be excluded as a cause of hypopituitarism. In fact, some degree of pituitary dysfunction has been found in a significant portion of patients with mild TBI (5).

To date, few systematic studies provide useful information in order to define the temporal relationship between traumatic event and occurrence of PTHP. It is well known that functional alteration of pituitary hormone secretion may become evident in the early phase post-TBI (38). However, because of metabolic derangement, functional alterations and use of drugs, a condition of permanent hypopituitarism is difficult to assess during the acute phase of a critical illness such as TBI. On this subject, recovery of pituitary function in patients with well-established PTHP has been

documented (82). In 1986 Eiholzer *et al.* (83) reported a boy with PTHP who recovered completely after 12 years. Similarly, in a 32-year-old man with complete PTHP assessed 3 months after severe TBI, a spontaneous recovery of the gonadal, thyroid and adrenal function was demonstrated 6 months after the acute event (58). Therefore, hormonal abnormalities identified early in the post-TBI period may not always persist and do not require a long-term treatment.

In the studies performed after the acute phase of TBI, the time of PTHP diagnosis varies markedly. A very wide time interval has been reported between TBI occurrence and PTHP diagnosis: from 5 months to 15 years (30), and from 1 month to 23 years (7). In a recent review (79), PTHP occurred within 1 year in 71% of cases. Our study (5) did not find statistically significant correlation between the occurrence of PTHP and the time elapsed since TBI over 5 years.

In a recent series (6), PTHP occurred in one-third (35%) of 100 cases studied 3 months after TBI and in 28% of a subgroup of 47 cases studied 12 months after the acute event, with occurrence of new hormonal deficiencies in two cases (4%) (84). The frequency of diabetes insipidus was similar both at 3 and 12 months (4 and 6% respectively).

The present data do not allow us to define the precise time course of PTHP development. Although in most cases hypopituitarism may occur early after TBI, a delayed PTHP development cannot be excluded, as well as a possible recovery of pituitary function after a long time. Signs and symptoms of PTHP can remain unrecognized, escaping detection for months or years, unless a careful evaluation of pituitary function is performed.

Pathophysiology of PTHP

The infundibular hypothalamic pituitary structure is particularly fragile due to its peculiar anatomical and vascular structure. Vascular damage may be a common cause of PTHP. Anatomical data from 496 autopsies of patients dying after acute TBI (85–88) indicate that hemorrhage or necrosis occurred in approximately 21% of cases at the anterior pituitary level, in 16% in the stalk and in 22% in the posterior pituitary. Peripituitary vascular damage was also common, occurring in one-third of these patients (85–87); hypothalamic hemorrhage or infarction was found in 22 of 53 cases (42%) (88). Moreover, neuroradiological (CT scan and/or MRI) evidence of vascular lesions (hemorrhage or infarction) at the hypothalamic–pituitary level has been described in 79% of 76 patients with some degree of PTHP (79). The vascular damage pattern corresponds with the blood supply of the long hypophyseal portal system, which goes through the sellar diaphragm. This site is highly vulnerable to mechanical compression from both brain and pituitary gland swelling. By contrast,

anatomical integrity of the hypothalamic–pituitary region has been found in 14–74% in the different autopsy series of patients dying after acute TBI (85–88). In the clinical series, no radiological alteration has been found in 6.6% up to 92.7% of patients with PTHP (79, 5). In patients without radiological alteration the functional damage at hypothalamic and/or pituitary level could be due to a secondary hypoxic insult. Shearing axonal injury, most often involving the midline structures, might also induce hypothalamic–pituitary axis dysfunction. These alterations might not be detectable by means of CT scan and MRI in the initial phase, thus explaining the lack of radiological findings in some patients with PTHP (24). Kelly *et al.* (30) reported diffuse swelling, extending into the hypothalamic region, without any evidence of hemorrhagic hypothalamic injury in all of the 8 patients with PTHP. A further mechanism for PTHP refers to direct mechanical insult to the pituitary gland, the stalk or the hypothalamus, since stalk resection has been radiologically demonstrated in 3.9% of 76 cases (79). Although penetrating injury to the sella is rare, cases of PTHP after sellar fractures have also been reported (30, 31, 66).

Types of deficit

In a collection of literature data, over 95% of the hypopituitary patients were diagnosed with hypogonadism, followed by hypothyroidism (90%), adrenal insufficiency (58%), hyperprolactinemia (45%), diabetes insipidus (32%) and GHD (23%) (79) (Table 5). Moreover, TBI was identified as the cause of central hypothyroidism in 15 patients: resulting as isolated in 3 cases, as associated with other deficits in 11 and as part of panhypopituitarism in one case (81).

Summarizing recently published papers (Table 6), however, the prevalence of specific pituitary deficits observed in TBI patients with pituitary dysfunction is as follows: GHD in 30.1% (ranging from 14.6 to 60%), gonadotropin deficiency in 28.8% (ranging from 2.1 to 62.5%), corticotropin deficiency in 18.5% (ranging from 0 to 44.8%) and thyrotropin deficiency in 18.5% (ranging from 3.6 to 31%) of patients. Nearly 75% of patients had an isolated hormonal deficiency, 21.9% had multiple deficits and only 3.4%

Table 5 Types of hormonal deficiencies in 357 patients with PTHP studied at various times after TBI.

Hypogonadism	> 95%
Hypothyroidism	90%
Hypoadrenalism	58%
GH deficiency	23%
Hyperprolactinemia	45%
Diabetes insipidus	31%

Table 6 Types of hormonal deficiencies in 146 patients with PTHP studied after the acute phase of TBI (5–7, 9, 30).

	Kelly <i>et al.</i> (30)	Lieberman <i>et al.</i> (7)	Aimaretti <i>et al.</i> (6)	Bondanelli <i>et al.</i> (5)	Agha <i>et al.</i> (9)	Total
No. of PTHP patients	8	48	35	26	29	146
LH/FSH deficiency	62.5% (5)	2.1% (1)	48.6% (17)	26.9% (7)	41.4% (12)	28.8% (42)
Severe GHD	50% (4)	14.6% (7)	60% (21)	15.4% (4)	27.6% (8)	30.1% (44)
ACTH deficiency	12.5% (1)	10.4% (5)	22.8% (8)	0	44.8% (13)	18.5% (27)
TSH deficiency	12.5% (1)	31% (15)	14.3% (5)	19.2% (5)	3.4% (1)	18.5% (27)
Isolated deficiency	62.5% (5)	75% (36)	71.4% (25)	76.9% (20)	79.3% (23)	74.7% (109)
Multiple deficiencies	37.5% (3)	25% (12)	17.1% (6)	23.1% (6)	17.2% (5)	21.9% (32)
Complete anterior pituitary deficiency	0	0	11.4% (4)	0	3.4% (1)	3.4% (5)
Permanent DI	0	0	11.4% (4)	0	0	2.7% (4)

DI, diabetes insipidus. Number of cases is shown in parentheses.

of patients had panhypopituitarism. Diabetes insipidus was present in 2.7% of patients with PTHP (Table 6).

In a recent series of 85 patients who had suffered severe or moderate TBI, studied by the water deprivation test, permanent diabetes insipidus was detected in 6.9% of patients (69). The higher frequency of permanent diabetes insipidus as compared with other studies (5, 6, 9, 30) could be explained by the presence, in five out of seven patients, of a partial defect discovered through the water deprivation test.

Hyperprolactinemia has been reported in 0–12% of patients with previous TBI, and a reduced prolactin secretion has also been demonstrated in a few cases (Table 4).

The prevalence of specific pituitary deficit observed by Benvenega *et al.* (79) is therefore different from that reported in Table 6. These discrepancies may be due to differences in severity and type of TBI in the populations examined, in the clinical management of patients, in the time elapsed since TBI, in the tests applied for endocrine evaluation and in the definition of normal or impaired hormone secretion.

GHD and gonadotropin deficit appear to be the most common deficiencies, in accordance with the anatomical site of gonadotrope and somatotrope cells in the vascular territory of the long hypophyseal portal system, which can be easily affected by TBI.

The diagnosis of GHD is performed by clinical and biochemical criteria. The current consensus is that patients with appropriate clinical history should have the diagnosis of GHD confirmed by a provocative test of GH secretion (89, 90). In TBI patients GHD has been diagnosed by means of classical provocative tests (glucagon, ITT or GHRH plus ARG), but the suspected GHD in these patients was not supported by an appropriate clinical context, except for TBI history. Among the provocative tests, ITT is widely considered as the gold standard for diagnosis of adult GHD. To select the patients with severe GHD, the arbitrary cut-off has been established as $<3 \mu\text{g/l}$ (89, 90). By means of this test, Kelly *et al.* (30) diagnosed GHD in four TBI patients out of 22 (18.2%). However, ITT is potentially dangerous in patients with TBI who have high risk of developing post-traumatic seizures. The combined GHRH plus ARG infusion provides an excellent alternative test to assess somatotroph function, with well-defined cut-off levels. A GH response peak higher than $16.5 \mu\text{g/l}$ is considered normal; a response $<9 \mu\text{g/l}$ is considered as diagnostic for severe GHD; a response between 16.5 and $9 \mu\text{g/l}$ is indicative of partial GHD. This test has good intra-individual reproducibility, good sensitivity and high specificity for the diagnosis of GHD, and has no contra-indications (91–93). This test allowed the diagnosis of severe GHD in 8–21% of TBI patients and of partial GHD in 16–20% (5, 6). Agha *et al.* (9) considered TBI patients as having GHD if they failed both the glucagon stimulation test and a second provocative test. Eighteen

TBI patients (17.6%) had a low GH response to glucagon ($<5 \mu\text{g/l}$), with 11 patients (10.7%) failing the second provocative test (ITT or the GHRH plus ARG); among these, only eight (8.8%) were considered as having severe GHD.

Low IGF-I levels have been suggested as diagnostic of GHD when multiple pituitary deficits are present (89). However, this parameter has low diagnostic sensitivity and is not applicable to TBI patients, who frequently display isolated pituitary defects. Moreover, in TBI, IGF-I levels of patients with GHD may be either lower (7) or similar (30) to those of patients without GHD. In addition, IGF-I levels may be in the normal range in up to 50% of patients with GHD and below the normal range in up to 12% of patients without GHD (5, 7).

Gonadotropin secretion in males is tested by measuring the morning serum total testosterone concentration on two or more occasions. A low testosterone in the absence of elevated LH levels indicates central hypogonadism. Gonadotropin secretion in premenopausal females with amenorrhea is tested by measuring estradiol concentrations. A low estradiol level in the absence of elevated FSH indicates central hypogonadism (94). The GnRH stimulation test has been used in the diagnosis of central hypogonadism. However, this test lacks both sensitivity and specificity, and rarely adds helpful additional information to basal endocrine evaluation (95). In TBI patients, basal plasma sex steroid and gonadotropin levels, together with an appropriate clinical context, are sufficient for diagnosis of central hypogonadism, which is disclosed in 1–17% of cases (5–7, 9). However, the GnRH stimulation test may provide further useful information in patients with normal sex steroid hormone levels and reduced LH/FSH response, since they may be at risk of future hypogonadism and need close follow-up (30). In addition, hypogonadism in some cases has been found in association with hyperprolactinemia, most probably due to hypothalamic/pituitary stalk lesions or to drug interference (7, 9).

Corticotrope function is generally tested by measuring serum cortisol concentration from 0800 to 0900 h on two or more occasions. A serum cortisol level $<3 \mu\text{g/dl}$ is characteristic of adrenal insufficiency, while a serum cortisol $>18 \mu\text{g/dl}$ defines normal cortisol secretion. When the morning cortisol value is persistently in the lower limit of the normal range, a test of ACTH reserve should be performed, in order to demonstrate the presence of a subclinical corticotrope deficiency (96). In TBI patients, corticotrope hypothalamic–pituitary axis function has been studied by measuring basal ACTH and cortisol values (5, 6) or by performing stimulation tests (ITT or ACTH) (7, 30) with different results. Basal evaluation detected corticotrope deficiency in $<10\%$ of the cases in three series (5, 6, 30). On the other hand, in a series of 70 patients, basal morning cortisol levels were below normal in 45.7% of subjects, whereas ACTH-stimulated levels

were low in 7.1% (7). Other authors have diagnosed corticotropin deficiency by failure of two provocative tests to evoke a normal cortisol response (9). In 23 patients (22.5%) with a low cortisol response to glucagon, 13 (12.7%) also failed to respond to ITT or ACTH test, and were defined as corticotropin deficient (9). In conclusion, despite the different tests applied for the assessment of the function of the hypothalamic–pituitary axis, corticotropin deficiency has been demonstrated in less than 10% of TBI patients. However, endocrine evaluation and definition of normal or impaired corticotropin secretion in TBI patients is still a matter of debate.

A low T4 in the absence of elevated TSH indicates secondary hypothyroidism (94, 96). TSH deficiency has been found in TBI patients evaluated by assessing either basal hormone levels (1–22%) (5, 7, 9) or response to TRH stimulation (4.5%) (30). A previous series demonstrated a very high occurrence of thyrotropin deficiency among TBI patients with hypopituitarism, suggesting TBI as an important cause of otherwise unexplained central hypothyroidism (79, 81).

Consequences and treatment of PTHP

Pituitary insufficiency may have serious consequences, possibly aggravating the physical and neuropsychiatric morbidity observed after TBI. Acute glucocorticoid deficiency can be life threatening, while mild chronic deficiency may impair recovery and rehabilitation after TBI since it causes fatigue, weakness and inability to respond to stress. Hypothyroidism causes apathy, muscle weakness and cognitive dysfunction. GHD is associated with reduced lean body mass, reduced bone mineral density, decreased exercise capacity, impaired cardiac function, social isolation and reduced psychophysical well-being, which may hamper recovery in TBI patients. Besides the effect on libido and fertility, estrogen deficiency in females promotes osteoporosis, and testosterone deficiency in males leads to reduced lean body mass and bone mineral density (94, 96). Diabetes insipidus causes a volume-depleted state with subsequent hypernatremia that can predispose to seizures and to severe dehydration (97).

PTHP may develop during the recovery phase, which lasts at least 2–5 years (2, 98). Therefore, an early diagnosis is crucial, since an adequate replacement therapy may result in an improvement in the outcome. In this regard, only a few authors have evaluated the relationship between outcome from TBI and the presence of pituitary dysfunction. As mentioned above, either positive or negative relationships between pituitary dysfunction and outcome from TBI have been observed in the early, acute phase post-TBI (41, 46, 47, 61). We did not find any statistical correlation between outcome measures and presence of pituitary

dysfunction, both in patients examined over a 5-year period after TBI (5) and in patients evaluated during the early rehabilitation period (48). An association between poor outcome and pituitary dysfunction cannot be excluded, because patients with more severe TBI might escape endocrine assessment. Indeed, pituitary function evaluation cannot be performed in TBI patients who either suffer from severe disabilities that preclude participation in the studies or die early after the event. Autopsy studies demonstrated a high incidence (14–74%) of anatomical lesions in the hypothalamic–pituitary region; this suggests, therefore, that hypopituitarism might contribute to the poor prognosis of the latter TBI patients (85–88).

Many symptoms of pituitary dysfunction are similar to other consequences of TBI (Table 7), and this explains the frequent delay in PTHP diagnosis. In particular, TBI causes life-long impairment in cognitive, behavioural and social function, which is more disabling than the residual physical deficits and can disguise PTHP (2, 3, 10, 99).

On the basis of these considerations, all patients hospitalized for TBI should undergo an adequate evaluation of anterior and posterior pituitary function.

Table 7 Consequences of traumatic brain injury.

Neurological impairment (motor, sensory and autonomic)

- Motor function impairment: paralysis (hemiplegia, quadriplegia, triplegia, pseudobulbar palsy), involuntary movements (chorea, athetosis, ballism, Parkinsonism, tremor, etc.), ataxia
- Spasticity
- Visual disturbance: visual loss, visual-field defects
- Sensory loss: taste, touch, hearing, smell
- Speech disturbance: aphasia, disarthria, etc.
- Sleep disturbance: insomnia, fatigue
- Medical complications: post-traumatic epilepsy, hydrocephalus
- Sexual dysfunction

Cognitive impairment

- Memory impairment: difficulty with new learning, attention and concentration; reduced speed and flexibility of thought processing; impaired problem-solving skills
- Problems in planning, organizing and making decisions
- Language problems: dysphasia, problems finding words, and impaired reading and writing skills
- Impairments in communication
- Impaired judgement and safety awareness

Behavioural abnormalities

- Impaired social and coping skills, reduced self-esteem
- Emotional disturbance, emotional lability
- Self-control disturbance: reduced insight, disinhibition, impulsivity, hyperirritability
- Psychiatric disorders: anxiety, depression, post-traumatic stress disorder, psychosis
- Apathy

Consequences on activities of daily living

- Loss of pre-injury roles, loss of independence
- Unemployment and financial hardship
- Inadequate academic achievement
- Lack of transportation alternatives
- Difficulties in maintaining interpersonal relationships

Patients with severe injury or basilar skull fractures are at major risk for developing PTHP and/or posterior pituitary dysfunction. Assessment of fluid and electrolyte balance is useful for the diagnosis of diabetes insipidus or SIADH, in order to correct these syndromes and avoid their complications.

PTHP should be considered in TBI patients with unexplained symptoms (hypotension, weight loss, fatigue, loss of libido, depression) or suspicious biochemical alterations (hyponatremia, hypoglycemia, reduced blood cell count, etc.), and in those who do not achieve the expected recovery. Despite the challenges of diagnosis of corticotropin deficiency in the acute phase of critical illness, patients with suspected glucocorticoid deficiency require prompt and adequate replacement therapy. Then, hypothyroidism should be treated. On the other hand, no consensus exists about the treatment of hypogonadism and GHD in the acute phase post-TBI. Recent studies have investigated the use of recombinant human GH (rhGH) and IGF-I (rhIGF-I) to reduce protein loss in catabolic states (100–102), which resemble the acute phase of TBI. In patients undergoing major abdominal surgery, rhGH treatment has preserved limb lean tissue mass, increased postoperative muscular strength and reduced long-term postoperative fatigue (103). Moreover, perioperative rhGH administration has improved cardiac performance during aortic surgery (104). It has been demonstrated that, in patients with HIV-associated wasting syndrome, high-dose rhGH treatment increases body weight, lean body mass and treadmill work output (101, 102). However, it is not clear whether rhGH treatment can improve the metabolic state of patients with critical diseases, characterized by a temporary GH-deficient state. Indeed, a multicenter trial has shown an association between rhGH treatment and increased mortality in intensive care unit patients (105), thus discouraging the application of such therapy in acute TBI.

All patients who overcome the critical phase should perform a complete re-evaluation of pituitary function, in order to exclude late occurrence of hormonal deficiencies and to assess possible regression of existing dysfunctions (e.g. hypogonadism). A long-term follow-up of these patients, as well as an evaluation of those with a previous history of TBI who escaped initial assessment, are then necessary to avoid the possibility that PTHP remains undiagnosed for months or years, hampering recovery and rehabilitation. In the post-acute phase, an adequate hormonal replacement should also include sex steroids, in order to restore sexual function, as well as ameliorate body composition and bone mass. The International Consensus Conference on rhGH replacement therapy (90) suggests that severe GHD should be treated. Therefore, since severe GHD is quite frequently detected in TBI, GH therapy should be offered to many TBI patients. The benefits of GH replacement in TBI patients are similar to those observed in patients with GHD caused by other diseases,

as recorded in the KIMS database (80). GH replacement in GHD has largely been demonstrated to increase muscle mass, reduce body fat and have positive effects on cardiac profiles, exercise capacity, mood and quality of life; all of which may have a positive influence on recovery from TBI (96, 106). In this respect, growing evidence indicates that GH plays an important role in promoting recovery after experimental brain injury (107, 108), offering a possible additive advantage for TBI patients with GHD receiving GH replacement.

Conclusions

TBI is a public health problem that requires more effective strategies to improve the outcome and minimize disability of the affected patients. Changes in pituitary hormone secretion may be observed during the acute phase post-TBI, representing part of the acute adaptive response to the injury. PTHP, caused by damage to the pituitary and/or hypothalamus, is a frequent complication of TBI and may occur at any time after the acute event. In most cases, PTHP is diagnosed within the first year after TBI; however, the time interval between TBI and occurrence of permanent hypopituitarism remains to be defined. Severity of TBI seems to be an important risk factor for developing PTHP; however, some degree of hypopituitarism can also manifest after a mild TBI.

Pituitary dysfunction presents more frequently as an isolated, and more rarely as a complete, deficiency. Gonadotropin and GH defects appear to be the most common, although some reports indicate a high occurrence of central hypothyroidism. Diabetes insipidus may be frequent in the early, acute phase post-TBI, but it is rarely permanent.

Accurate evaluation and long-term follow-up of all TBI patients are necessary in order to detect the occurrence of PTHP, regardless of clinical evidence for pituitary dysfunction. It is therefore necessary that medical professionals involved in the management of TBI patients are aware of the PTHP issue, in order to diagnose promptly any pituitary dysfunction. An adequate replacement therapy is indeed indicated in the attempt to improve outcome and quality of life of TBI patients. Therefore, further studies should be encouraged in order to better define the risk factors for PTHP, adequate screening tests for TBI patients and the specific benefits of hormonal replacement on TBI outcome.

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