Clinical picture and the treatment of TBI-induced hypopituitarism

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Abstract

Traumatic brain injury (TBI) is an important public health problem with an increasing incidence in the last years. Relatively few cases are fatal; most individuals will survive and, in the long-term, the sequalae of TBI will include neuroendocrine dysfunctions with a much higher frequency than previously suspected. Patients who develop hypopituitarism after TBI present manifestations due to the number of deficient hormones, severity of hormonal deficiency, and the duration of hypopituitarism without diagnosis and treatment. The clinical spectrum of hypopituitarism is very large and many signs and symptoms of TBI survivors such as fatigue, concentration difficulties, depressive symptoms are nonspecific and overlap with symptoms of post-traumatic stress disorder and variably severe hypopituitarism related to brain damage remaining undiagnosed. This can explain why the diagnosis of hypopituitarism is often missed or delayed after this condition with potentially serious and hazardous consequences for the affected patients. Moreover, clinical experience cumulatively suggests that TBI-associated hypopituitarism is associated with poor recovery and worse outcome, since post-traumatic hypopituitarism is independently associated with cognitive impairment, poor quality of life, abnormal body composition, and adverse metabolic profile. In the present review, the current data related to clinical consequences of pituitary dysfunction after TBI in adult patients and therapeutic approaches are reported.

Keywords Traumatic brain injury · Hypopituitarism · Replacement therapy

Introduction

Traumatic brain injury (TBI) is defined as an alteration in brain function caused by an external force. TBI is a leading cause of death and disability, being a major public health problem nowadays [1]. A recent meta-analysis suggested that the incidence is increasing and affects 134–618 persons per 100,000 per year with the highest incidence appearing in adult men [2]. Relatively few cases are fatal, and most individuals will survive beyond the event such

that neuroendocrine dysfunctions may occur with a much higher frequency than previously suspected [1]. The reported prevalence of chronic anterior pituitary hormone deficiency following TBI reportedly exceeds 25%, and accounts for approximately 5% of all causes of hypopituitarism [3]. Neuroendocrine dysfunction due to TBI was described for the first time in 1918 [4], though the syndrome did not garner significant attention until the turn of this century. Since then, a large body of research has demonstrated the importance of post traumatic hypopituitarism [3, 5–19] and, over the past 15 years, numerous studies have documented a high rate of pituitary gland dysfunction following moderate or severe TBI with the evidence that hypopituitarism contributes significantly to the morbidity and possibly mortality in TBI patients [20]. Direct mechanical trauma and vascular/hypoxic insult to the hypothalamus, pituitary stalk or pituitary gland, compression from hemorrhage, edema or increased intracranial pressure are among the factors proposed to explain the pathophysiology of TBI-induced pituitary dysfunction. Genetic and immunologic studies have given new insight into the pathophysiology of TBI-induced pituitary dysfunction, since the Apolipoprotein E3/E3

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genotype decreases the risk of TBI-induced hypopituitarism and anti-pituitary antibodies and anti-hypothalamic antibodies may have a role in the development and/or worsening of hypopituitarism in patients with TBI [21–23]. In spite of the large literature on this topic [24], pituitary disorders are a frequently overlooked complication of TBI. A group of experts reviewed the evidences on TBI-induced hypopituitarism and concluded that it is often underdiagnosed, and that medical community is not adequately informed about the importance of this problem [25]. In fact, many symptoms of TBI survivors such as fatigue, concentration difficulties, and depressive symptoms are nonspecific and overlap with symptoms commonly attributed to post-traumatic stress disorder (PTSD), leaving a consistent of cases of hypopituitarism related to brain damage undiagnosed [25, 26]. This would explain why the diagnosis of hypopituitarism is often missed or delayed after these conditions with potentially serious and sometimes life-threatening consequences for the affected patients. Moreover, recent findings suggest that hypopituitarism after TBI is associated with poor recovery and worse outcome, since post-traumatic hypopituitarism is independently associated with poor quality of life, abnormal body composition, and adverse metabolic profile [27–29].

The aim of the present review is to update the current data regarding the clinical consequences of pituitary hormone deficiencies after TBI and the treatment of TBI-induced hypopituitarism in adulthood.

Clinical features

Patients who develop hypopituitarism after TBI present manifestations due to the number of deficient hormones, severity of hormonal deficiency, and the duration of hypopituitarism without diagnosis and treatment. Independent of the underlying cause, the clinical spectrum of hypopituitarism is very large and varies from some nonspecific complaints including fatigue, anorexia, arthralgia, and headache, to life-threatening conditions which necessitate emergency admission such as adrenal crisis, water and salt imbalance, and severe hypoglycemia [30]. Overall, the most frequent abnormalities reported are growth hormone deficiency (GHD), adrenocorticotropic hormone (ACTH) insufficiency, and gonadotropin deficiency [1, 3, 8, 31]. Because of the mild and nonspecific manifestations recorded in the majority of patients with hypopituitarism due to different causes including TBI, hypopituitarism remains undiagnosed in most TBI patients and thereby untreated [23]. The symptoms of hypopituitarism are summarized in Table 1 [30, 32].

In TBI, we can distinguish an acute phase, that is day 1–14 post event, and the chronic phase, that is 3–6 months post TBI. Hormonal patterns occurring during the acute phase have been investigated in order to understand whether the changes are related to critical illness or are TBI-specific, and it seems that most of the hormonal alterations in the acute phase reflect the acute adaptive response to the traumatic event and are, therefore, transient [15, 19]. The most clinically significant abnormalities in the acute phase of TBI are ACTH- cortisol deficiency and salt and water imbalance [11, 33, 34]. Acute-phase hypocortisolism is potentially life threatening. In fact, a number of studies have shown an association between increased morbidity or mortality and acute post-traumatic hypoadrenalism [33–35]. However, some of these early abnormalities are only transient: recovery of hypoadrenalism can be achieved in 50% of cases, while diabetes insipidus dissipates in up to 90% of cases [11, 15]. The full recovery may thus happen within days or weeks after TBI, while new pituitary hormone deficiency may become apparent in the post-acute phase [10, 36].

Table 1 Clinical features and investigative findings of hypopituitarism

Hormones deficiency	Clinical features	Findings
ACTH	Fatigue, pallor, anorexia, weight loss Life-threatening adrenal crises: weakness, dizziness, nausea, vomiting, circulatory collapse, fever, shock	Hypoglycaemia, hypotension, anaemia, lymphocytosis, eosino-philia, hyponatraemia
TSH	Tiredness, cold intolerance, constipation, hair loss, dry skin, hoarseness, cognitive slowing	Weight gain, bradycardia, hypotension
FSH/LH	Men: loss of libido, impaired sexual function, mood impairment, loss of facial, scrotal, and trunk hair, weight changes Women: oligoamenorrhea, loss of libido, dispareunya, infertility, weight changes	Decreased muscle mass, osteoporosis, anaemia Osteoporosis
GH	Decreased muscle strength, visceral obesity, fatigue, decreased quality of life, impairment of attention and memory	Dyslipidemia, premature atherosclerosis, decreased muscle mass
ADH	Polyuria, polydipsia	Decreased urine osmolality, hypernatraemia, polyuria

ACTH adrenocorticotropic hormone, *TSH* thyrotropic hormone, *FSH* follicle-stimulating hormone, *LH* luteinising Hormone, *GH* growth hormone, *ADH* antidiuretic hormone

Gonadotropin and growth-hormone deficiencies, instead, cause chronic morbidity.

Among the pituitary hormone deficiencies, GH deficiency appears to be the commonest deficiency in those who were tested 6 months or more following the event [9, 32, 37, 38]. Long-term adult GH deficiency is associated with clinical and biochemical findings compatible with GHD syndrome, comprehending reduced lean body mass, reduced bone mineral density, impaired cardiac function and decreased quality of life (QoL) [30, 39].

In addition to the classic symptoms of hypopituitarism described, there is a rapidly growing body of literature suggesting that hypopituitarism following TBI has a negative impact on cognition, and recent data seem to confirm that anterior pituitary hormone deficiency has a negative impact on functional outcome at 6 months post TBI, as assessed by mini-mental state exam and functional independence measure scores [20]. Other studies have found a correlation between post-TBI hypopituitarism and unfavorable metabolic and body composition profiles with associated lower QoL scores [27, 39] as well as decreased exercise capacity [12] and then neuropsychiatric complications [13]. Intuitively, these complications could lead to a vicious circle and be thus coexistent.

Cognitive impairment

Neuropsychiatric symptoms after TBI are common and impair QoL of survivors. Hypotheses concerning the pathological roots of these sequelae have pointed to a number of causes, of which post traumatic hypopituitarism, and particularly post-TBI GHD, is likely particularly important.

Cognitive impairment after TBI ranges from attention, memory, information processing speed and executive functions to even more robust functions, such as language and visuospatial constructional skills. Such deficits can severely impact an individual's ability to return to an active, independent role in society. In this scenario, the cognitive manifestations of hormone deficiencies can be quite obvious, or incredibly subtle. The consequences of these deficiencies may be minor, or they may keep the individual from functioning independently in society, and these deficiencies may be masked by what has been previously attributed to the intrinsic signs and symptoms of the TBI itself. Moreover, symptoms associated with pituitary dysfunction overlap considerably with those of PTSD, as cognitive deficiencies, mood and anxiety disorders, sleep problems, diminished QoL, deleterious changes in metabolism and body composition, and increased cardiovascular mortality [40]. The differential diagnosis is very important since, when such symptoms are due to hypopituitarism, they may be alleviated by hormone replacement. The diagnosis and treatment of

post-traumatic hypopituitarism may, therefore, play a significant role in the cognitive recovery from a brain injury [29, 39].

So, the disruption of anterior pituitary post TBI is related to cognitive impairment and each deficient hormone can contribute to this symptomatology.

Regarding HPA axis, given its role in response to stress, a relationship between cortisol levels and psychiatric symptoms (particularly symptoms of anxiety) seems reasonable. In fact, a complex relationship among post-injury cortisol levels, injury severity, and the development of anxiety is reported in literature. In particular, the results of the studies by Tanriverdi et al. [41] and by Flesher et al. [42] suggest that injury severity is antagonistic to an elevated cortisol response. It is possible that cortisol response is related to stressful recollections of the incident that caused the injury. Factors such as loss of consciousness and post- traumatic amnesia may prevent awareness of the injury and its potential tragic consequences, thus precluding an associated stress response.

Concerning thyroid hormone, hypothyroidism is associated with both disturbed neuropsychologic well-being and neurocognitive functioning [43]; in fact, hypothyroid patients typically demonstrate the types of deficits so commonly seen following TBI, such as executive functioning, speed of information processing, and aspects of memory, predominantly short-term memory [44]. Evidence from animal models suggests a possible mechanism linking thyroid function to cognition as well as the positive effects of thyroid hormone replacement on cognition following brain injury. The data suggest that thyroid hormone regulates neurogenesis in the rat hippocampus, providing a logical role for the thyroid hormone in learning and memory [45].

Hypogonadism is also associated with cognitive dysfunction [46]. The results of testosterone supplementation in hypogonadal males have shown improvement in some domains of memory [46, 47]. Moreover, of the individuals who have sustained TBI, those with lower testosterone levels also appear to have an increased risk for Alzheimer's disease [48]. However, studies on cognitive improvement following estrogen supplementation in females have yielded conflicting results [49, 50]. So, presently, the issue of cognitive changes with sex hormone supplementation remains unresolved [51].

According with these evidences, it seems that the cognitive dysfunctions following TBI are not only the result of brain injury itself but also of hypopituitarism and, in particular, GHD may result in cognitive abnormalities. In patients with chronic hypopituitarism not secondary to head trauma, similar complaints of fatigue, depression, anxiety, and loss of emotional well-being also arise. GHD in particular is associated with diminished psychological health and decreased QoL in adults, and since about 30 years ago has been designated as its own specific clinical syndrome

[52]. Research has revealed significant decreases in energy and emotional lability, heightened sense of social isolation, greater difficulties with sexual relationships, decreased QoL, and greater psychological distress in untreated versus treated GHD [39, 53]. Furthermore, it has been repeatedly demonstrated that post-TBI GHD is similarly associated with impaired motivation, depression, and decreased QoL, with no convincing role of trauma severity [54, 55]. Therefore, it comes as no surprise that these same symptoms after head trauma that were once regarded simply under the umbrella of post-concussive syndrome are being reconsidered in the context of post traumatic hypopituitarism and specifically post-TBI GHD. Moreover, many symptoms of PTSD overlap with those of TBI, and questions whether neuroendocrine pathologies may contribute to PTSD in the setting of head trauma have arisen [40].

The mechanism by which GH may affect cognition is not well-understood but greater cognitive dysfunction has been reported in patients with TBI who have GH deficiency compared to those with normal GH levels [54]. In particular, three recent studies evaluated neurobehavioral and QoL, demonstrating that those patients with GH deficiency had higher rates of depression, impaired cognitive performance, greater deficits in simple attention, more intrusions and repetitions on a memory task, increased reaction time, and greater emotional disruption [54–56]. In particular, patients with GHD after TBI showed lower QoL in the domains of general health, physical health, and emotional health when compared to subjects with normal pituitary function [54]: Health-related quality of life (HRQL) and Quality of Life Assessment of GHD in Adults (QoL-AGHDA) in TBI survivors are worsened, independent of pituitary functions, when compared with healthy controls. In the study by Popovic et al., GH peak was significantly correlated with short- and long-term memory deficits in the patients with GHD due to TBI and also a correlation between lower IGF-I levels and visual memory was reported [12]. Moreover, has been recently reported that decreased IGF-I levels seem to indicate an increased risk of developing Alzheimer's disease [57]. In an experimental study, serum IGF-I levels were found to be decreased in both the early and late periods of TBI and low levels of serum IGF-I were correlated with hippocampal neuron loss and spatial memory deficits [58].

Metabolic alterations

Hypopituitarism, in general, and GHD, in particular, are associated with a number of metabolic alterations [59]. Consequently, it is feasible that TBI patients with neuroendocrine dysfunction may have metabolic alterations; however, few studies have evaluated these issues, including changes in body composition and BMI, lipid profile, glucose metabolism, and hypertension [27, 28, 60].

The study by Klose et al. demonstrated that patients with hypopituitarism after TBI (due to acute road accident) have higher BMI and abnormal lipid profile characterized by increased LDL-cholesterol and total cholesterol when compared to patients who have normal pituitary function [27]. Moreover, Tanriverdi et al. investigated anthropometric and body composition variables in a population of amateur boxers compared to healthy controls. The authors found that waist circumference, fat mass and abdominal fat mass, as well as serum leptin level were significantly higher and IGF-I level was significantly lower in retired boxers as compared to healthy non-boxing controls, with high risk for cardiovascular complications [61]. Prodam et al. in a cross-sectional retrospective study in a tertiary care endocrinology center, confirmed that TBI patients who developed hypopituitarism had a worse metabolic profile than TBI patients who did not, particularly in terms of altered glucose levels, insulin resistance and dyslipidemia, independent of the BMI of the patients [28]. The authors confirmed previous data on a tendency towards an altered lipid profile in TBI subjects with hypopituitarism with elevated triglycerides, but similar HDL-, LDL- and total cholesterol in both populations. The second finding was the high prevalence of fasting or postchallenge glucose alterations. This is in line with other reports on "classical" hypopituitarism [62, 63], a condition marked by higher insulin resistance. The pathophysiological mechanism of diabetes and insulin resistance in patients with hypopituitarism is not completely understood; however, available evidence suggests GH as the principal player due to its interaction with many other hormonal and/or peptidic systems [59]; in fact, in the study by Prodam et al. GHD was the most common anterior hormone deficiency [28]. This evidence is confirmed more recently by Giuliano et al. who found that in mild TBI patients, increased visceral adiposity and BMI, higher basal glucose, altered lipid profile and hypertension were significantly more common in GHD as compared to no-GHD patients; moreover VAI, an index of insulin resistance and cardiovascular risk was also significantly increased in the GHD group [64].

Weight gain is another overlooked event following TBI. A longitudinal observational study of Z-score curves in children with TBI of mixed severity revealed early weight loss followed by a rapid increase in body weight, with 15% of children becoming overweight by the time of final assessment [65]. In a study on adult TBI patients presenting with sleep-related complaints, 45% exceeded a BMI of 30 kg/m^2 and most complained of having gained weight in the time period following TBI [66]. In a longitudinal follow-up of adults with TBI, patients could be categorized in three weight groups showing stable (30%), loss (28%) and gain (42%), with factors related to weight gain being hyperphagia

and presence of a dysexecutive syndrome [67]. While mechanisms for weight gain after TBI could involve injury to hypothalamic centres controlling feeding-satiety and energy homeostasis that warrant investigation, other potential factors could intervene such as loss of circadian rhythms, inactivity secondary to pain or neurological handicap, feature of posttraumatic mood disorder, use of corticosteroids to treat acute post-traumatic syndrome or use of antiepileptic drugs, antidepressants, and psychotropic drugs to treat long-term post-traumatic complications.

Treatment

The treatment of TBI-induced hypopituitarism depends on the appropriate replacement of the deficient hormones and is not different from the treatment of hypopituitarism due to other causes [30]. Reversibility of pituitary dysfunction in TBI victims should be kept in mind before treatment is started, so we can distinguish the treatment in acute and chronic phase.

Acute phase

Based on the prospective studies evaluating pituitary function, most pituitary hormonal changes (especially follicle-stimulating hormone (FSH)/luteinising hormone (LH), GH and thyrotropic hormone (TSH) deficiencies) are transient and recover after 3–12 months of injury [15, 17, 19]. Currently, there is no clear evidence that the replacement of GH, FHS/LH and TSH deficiencies in critically ill TBI patients during the acute phase is beneficial [3, 68]. However, in the acute phase of TBI, the diagnosis of glucocorticoid deficiency should not be missed because it is life-threatening [3, 33, 35].

ACTH deficiency

Current evidences suggest that hypothalamus pituitary adrenal (HPA) axis insufficiency during the acute phase after head trauma is associated with a poor neurological outcome, a greater need for vasoactive drug therapy, hyponatremia, relative or absolute hypoglycemia, hemodynamic instability, and rapidly progressive hypotension, all of which may increase the risk of morbidity and mortality [33–35]. Therefore, the focus during the acute phase of brain injury should be on detecting adrenal insufficiency.

On the other hand, the CRASH trial, a large-scale clinical study including 10,000 patients with head trauma, and other literature reviews have clearly shown that routine administration of corticosteroids at high doses or pharmacological doses

to all TBI patients is not indicated or may be harmful [69]. It is generally agreed, however, that therapy should be provided for patients with confirmed hypoadrenalism in whom clinical circumstances, such as hypotension, hyponatremia, a need for higher dose of vasopressors and hypoglycemia, warrant intervention [1].

A stress dose of glucocorticoid replacement is mandatory in critically ill TBI patients who have ACTH deficiencies. The dose of glucocorticoid replacement should be titrated based on the clinical status and the requirements of the critically ill patient. If the patient has adrenal insufficiency and is stable, replacement with a physiological dose of hydrocortisone (30 mg/d) could be sufficient initially. When severe stress is present and the patient is not stable, 50–100 mg of hydrocortisone intravenously (IV) every 8 h (150–300 mg/d; stress dose hydrocortisone) or an intravenous (IV) infusion of approximately 15 mg/h is recommended [70, 71]. Dexamethasone or methylprednisolone could be used alternatively at equivalent hydrocortisone doses. The optimal duration of corticosteroid supplementation is still not known, but it should be continued until the patient's clinical situation has improved and when there is no need for vasopressor therapy. When the patient is stable, re-evaluation of the ACTH axis is suggested before discharge and a physiological dose of glucocorticoid therapy is recommended until the second follow-up to establish persistent ACTH deficiency [1, 32].

TSH deficiency

The effects of thyroid hormone replacement therapy during the acute phase of TBI have not been studied systematically in clinical studies. Prospective studies demonstrated that TSH deficiency generally recovers during or after the acute phase [3, 72]. In critically ill burn or medical patients, acute thyroid hormone replacement therapy was not shown to produce short-term improvement [73]. Therefore, based on current evidence, thyroid hormone replacement in the acute phase of TBI is not recommended [1, 32].

FSH/LH deficiency

Changes in the gonadotropic axis in the acute phase of TBI are mainly an adaptive response and most of the hormone deficiencies are transient [3, 17]. Therefore, gonadotropin replacement is not recommended in the acute phase [1].

GH deficiency

To date, there has been no clinical study investigating the effects of GH replacement therapy in the acute phase of TBI in patients with GH deficiency. In a previous randomized,

prospective, double-blind, placebo-controlled study by Hatton et al. IGF-I and GH therapy within 72 h of TBI produced sustained improvement in metabolic and nutritional endpoints [74], but GH status of TBI patients in this particular study was not defined. A large multicenter study by Takala et al. showed that the administration of high doses of GH in critically ill patients (but TBI patients were not included), instead of improving outcome, doubled mortality [75]. Experimental studies revealed that GH and IGF-I may play a crucial role in brain repair mechanisms or neuronal recovery after trauma by regulating the factors including neuronal plasticity, myelin formation and vascular tone [76]. Moreover, some authors proposed that GH treatment may be indicated in every TBI patient in combination with rehabilitation, independent of the presence of GH deficiency [77, 78]. Thus, GH screening or supplementation is not currently recommended in the acute phase and during the first 12 months of TBI [1, 32].
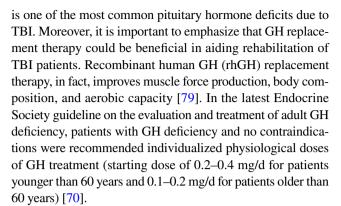
Chronic phase

TSH, FSH/LH and ACTH deficiencies

Patients with hypopituitarism, independent of the etiology, require the replacement of deficient hormones as part of their standard clinical care. Adequate replacement with glucocorticoids, L-thyroxine and sex steroids generally reverses the symptoms and signs of relevant pituitary hormone deficiencies and normalizes the risks associated [3]. Hormone-replace regimens are the same used for the other causes of hypopituitarism [30]. In fact, to date no systematic study has been published comparing patients with TBI-induced hypopituitarism and patients with other causes of hypopituitarism regarding the effects of the treatment of TSH, FSH/LH and/or ACTH deficiencies.

In patients with moderate and severe TBI, if there is any pituitary hormonal deficiency at the 12th month, appropriate replacement of the deficient hormones is suggested, and because the recovery of pituitary dysfunction is extremely rare, routine follow-up for the titration of replacement therapy is recommended [1]. If there is no pituitary hormone deficiency at the 12th month in patients with moderate/severe TBI, no further investigation is recommended. However, it is important to inform these patients regarding the symptoms and signs of hypopituitarism, and if they develop suspicious signs and symptoms of hypopituitarism they can be screened at any time after TBI.

GH deficiency

GH deficiency deserves special attention in TBI patients because GH deficiency, isolated GH deficiency in particular,

is one of the most common pituitary hormone deficits due to TBI. Moreover, it is important to emphasize that GH replacement therapy could be beneficial in aiding rehabilitation of TBI patients. Recombinant human GH (rhGH) replacement therapy, in fact, improves muscle force production, body composition, and aerobic capacity [79]. In the latest Endocrine Society guideline on the evaluation and treatment of adult GH deficiency, patients with GH deficiency and no contraindications were recommended individualized physiological doses of GH treatment (starting dose of 0.2–0.4 mg/d for patients younger than 60 years and 0.1–0.2 mg/d for patients older than 60 years) [70].

The beneficial effects of GH replacement therapy on QoL have been investigated in a retrospective German KIMS study including patients with TBI and patients with nonfunctioning pituitary adenoma (NFPA); it was shown that QoL was significantly improved in both groups after GH replacement therapy [80]. In addition to the previously mentioned nation-based KIMS study, recently Gardner et al. retrospectively assessed the clinical characteristics of hypopituitarism due to TBI and the QoL measured by QoL-AGHDA scores and the effects of long- term GH replacement therapy in a large number of TBI patients involved in the KIMS database. When compared to NFPA (used as the control group), hypopituitarism in TBI victims was biochemically less severe but QoL was worse and GH replacement therapy not only significantly improved QoL but sustained the relevant improvement in the long-term period in patients with TBI [81]. Moreover, a beneficial effect on memory and information processing speed [79, 80, 82] and an improvement also in verbal processing [83, 84] has been recently demonstrated.

In conclusion, current data show that GH replacement therapy seems to have beneficial effects in TBI patients as in those with other causes of GH deficiency in adults. Therefore, at least 12 months after head trauma, an individualized physiological dose of GH replacement therapy in TBI patients with severe and sustained GH deficiency is recommend [1, 32]. If GH replacement therapy is commenced in GH-deficient patients with mild TBI, it is important to keep in mind that GH deficiency may recover over a 5 year period after TBI and a yearly evaluation of the GH status is necessary. However, further placebo-controlled studies with a larger number of patients to assess the benefits of treatment with recombinant GH in terms of rehabilitation, functional recovery, metabolic and cardiovascular risk factor improvement, and neurocognitive/neuropsychological functions in TBI patients are needed.

Conclusion

In conclusion, TBI is a common cause of hypopituitarism. An increased level of awareness of TBI-induced hypopituitarism in the medical community should lead to early

diagnosis and, therefore, timely treatment of hypopituitarism, that is a serious but treatable complication of the traumatic event. Therefore, close collaboration between neurosurgery, endocrinology, rehabilitation medicine is essential to ensure optimal delivery of care. Each specialist of interested disciplines should keep in mind the clinical picture of TBI induced hypopituitarism for a prompt diagnosis and adequate treatment. In fact, replacement therapy has the potential to improve recovery, rehabilitation, and QoL for those patients.

Compliance with ethical standards

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