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High Risk of Hypogonadism After Traumatic Brain Injury: Clinical Implications

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Abstract. **Several recent studies have convincingly documented a close association between traumatic brain injury (TBI) and pituitary dysfunction. Post-traumatic hypogonadism is very common in the acute post-TBI phase, though most cases recover within six to twelve months following trauma. The functional significance of early hypogonadism, which may reflect adaptation to acute illness, is not known. Hypogonadism persists, however, in 10–17% of long-term survivors. Sex steroid deficiency has implications beyond psychosexual function and fertility for survivors of TBI. Muscle weakness may impair functional recovery from trauma and osteoporosis may be exacerbated by immobility secondary to trauma. Identification and appropriate and timely management of post-traumatic hypogonadism is important in order to optimise patient recovery from head trauma, improve quality of life and avoid the long-term adverse consequences of untreated sex steroid deficiency.**

Key Words. **traumatic brain injury, hypogonadism, hypopituitarism**

Abbreviations. **TBI: traumatic brain injury, LH: luteinizing hormone, FSH: follicle-stimulating hormone, GnRH: gonadotropin-releasing hormone**

Introduction

Traumatic brain injury (TBI) is the leading cause of death and disability among young adults [1,2]. Young adult males under the age of 35 years are at particular risk, although it appears that the number of females sustaining TBI is rising steadily [3]. In the United States, it is estimated that five million persons are living with the sequelae of TBI at a lifetime cost of $ 600,000 to $1.9 million per person [3]. Over the last few years there has been an increasing recognition that hypopituitarism of varying severity is a frequent complication of TBI, but it remains undiagnosed in most patients [4–12]. This raises legitimate and serious concerns about the potential contribution of undiagnosed post-traumatic hypopituitarism to the high morbidity seen in many patients after head injury.

Hypogonadism secondary to gonadotropin deficiency has been shown to be particularly common in the acute phase of TBI while its prevalence among long-term survivors varies considerably from study to study. This article will review the reported frequency of post-traumatic hypogonadism and discuss the potential clinical implications and recommendations for patients' assessment and follow-up

Hypogonadism in the acute phase of TBI

Suppression of the hypothalamic-pituitary-gonadal axis, resulting in low sex-steroid concentration and both immunoreactive and biologically active serum gonadotropin levels, has been reported in patients with acute critical illness [13,14]. It has been hypothesized that the inhibition of secretion of anabolic androgens is appropriate in critical illness, in order to reduce energy expenditure and preserve metabolic substrates for the more vital organs such as the brain at the expense of the less vital ones such as muscles [15]. Suppression of the gonadal axis has also been reported to occur acutely in most patients following head trauma [16–21]. A correlation between the degree of hypogonadism and the severity of head trauma has been reported in some [16,20] but not all studies [21].

We have assessed gonadal function prospectively in 50 unselected adult TBI patients (30 males), studied prospectively at a median of 12 days post-trauma [6]. Eighty percent of patients had biochemical evidence of secondary hypogonadism, diagnosed by low serum gonadal sex-steroid concentration with inappropriately low gonadotropin levels. There was a significant positive correlation (r=0.32) between acute serum testosterone levels and admission Glasgow Coma Scale (GCS) scores, which were used to assess the severity of TBI [22], indicating a relationship between the severity of trauma and the extent of hypogonadism Acute phase serum testosterone concentration also correlated significantly (r=0.55) with the 12-months Glasgow Outcome Scale scores, which measure functional recovery [23]. Prospective longitudinal follow-up of this TBI cohort showed that 73% of subjects who were hypogonadal in the acute phase had recovered by 6 months and 85% recovered by 12 months [24]. Among the hypogonadal patients, hyperprolactinemia was present in 48% in the acute phase, 28% at six

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months and 33% at 12 months [24]. Therefore, suppression of the gonadal axis is very common in the early period after TBI and the degree of this suppression relates to the severity of injury and has prognostic implications.

Hypogonadism in long-term survivors of TBI

Hypogonadism has been a common presenting feature of case reports of post-traumatic hypopituitarism. In a series of 53 TBI cases compiled by Edwards & Clark [25], the typical patient was a young male with significant head trauma, presenting with symptoms of hypogonadism (loss of libido, impotence, and loss of secondary sexual characteristics). More recently, Benvenga et al. [26] reviewed 367 case reports of post-traumatic hypopituitarism. In their patients with anterior hypopituitarism, they found gonadotropin deficiency to be invariable with a reported prevalence of almost 100%. They concluded that the gonadotrophs are the most vulnerable cell type of the anterior pituitary to traumatic injury. However, since this was a case-series report, there was an inherent bias in the relative frequency of anterior pituitary hormone deficiencies as hypogonadism (especially in the typical young adult head injury victim) gives rise to specific symptoms prompting the patient to seek medical help.

Several recent studies have examined the frequency of hypogonadism in cross-sections of TBI patients who were tested several months to many years after the event. The reported prevalence ranged from 1% to 23% although the more recent studies had reported less variation with a rate of between 9–17% [7–10]. A summary of the results from the various studies is shown in Table 1. The variation in the reported frequency of hypogonadism may be explained by differences in patient selection, the timing of the evaluation, method of diagnosis (whether basal hormone measurement or GnRH-stimulated gonadotropin response was used to define normality) and the frequency of hyperprolactinemia which ranged from 3%–12% in the reported series. Because interpreting the gonadotropin response to GnRH is difficult and arbitrary cut-offs are often used (see below), studies that used this test may have over or underestimated the frequency of true hypogonadism. Using basal early morning serum samples and clinical history, we found gonadotropin deficiency to occur in 12 of 102 severe or moderate TBI cases (admission GCS scores 3/15 to 13/15) that we studied at a median of 17 months post-trauma. Gonadotropin deficiency was isolated in 9 patients, was associated with other pituitary hormone deficiency in 3 patients and with hyperprolactinemia in 3 patients [7]. The only patient with hypogonadism in the Lieberman series [5] had mild hyperprolactinemia but other studies did not report the association between hypogonadism and hyperprolactinemia.

The association between gonadotropin deficiency and the severity of TBI was not reported by most studies, perhaps because the small numbers did not allow for reliable statistical comparisons. However, we were unable to show a significant association between gonadotropin deficiency and the initial admission GCS scores or computerized tomography (CT) findings of TBI patients [7]. Therefore, unlike acute hypogonadism, chronic gonadotropin deficiency is not associated with more severe head injury.

Mechanisms of Post-Traumatic Hypogonadism

Several factors may cause or contribute to gonadal suppression after TBI. Damage to the hypothalamic-pituitary region may be caused by vascular injury, particularly affecting the long hypophysial vessels, which supply most of the anterior pituitary. The vascular hypothesis is supported by evidence from post-mortem studies showing hemorrhage and ischemic necrosis affecting the pituitary gland and its stalk in patients who died shortly after TBI [26]. Hypothalamic-pituitary injury can also result from

Table 1. *Summary of cross-sectional studies reporting the frequency of hypogonadism in the chronic phase of traumatic brain injury*

Authors	Sample Size	Time from injury (month)	GCS scores	Hypopituitarism (% of total)	Hypogonadism (% of total)	Method of diagnosis of hypogonadism
Kelly et al. [4]	22	Median 26	3–15	36.4	22.7	GnRH test
Lieberman et al. [5]	70	Median 13	N/A	68.5	1.4	Basal samples & GnRH test
Agha et al. [7]	102	Median 17	3–13	28	11.8	Basal samples
Bondanelli et al. [8]	50	Range 12–64	3–15	54	14	Basal samples
Aimaretti et al. [9]	100	3	3–15	35	17	Basal samples
Popovic et al. [10]	67	Mean 45	9–13	34	9	Basal samples
Leal-Cerro et al. [12]	Total =170* Tested = 99*	>12	3–8	24.7	Of total =17* Of those tested = 29*	GnRH test

Abbreviations: GCS, Glasgow Coma Scale; GnRH, gonadotropin-releasing hormone.

*Total sample was 170 patients but 71 were excluded due to lack of symptoms or refusal to have biochemical testing.

compression secondary to edema, skull fracture, or increased intracranial pressure; hypoxic insult or by direct mechanical injury [26,27].

Hyperprolactinemia is well recognized to cause suppression of the hypothalamic-pituitary-gonadal axis [28], and has been reported both in the acute [6,29,30] and chronic phases of TBI [5,7–10,12] including in patients with documented gonadotropin deficiency [5–7]. Post-traumatic hyperprolactinemia can be mediated by physical stress (acute TBI), damage to the hypothalamus or the pituitary stalk or caused by anti-dopaminergic medications.

As mentioned previously, gonadal dysfunction often occurs transiently following acute or critical illness as an adaptive response with subsequent recovery in the post-acute phase.

In males, there is a natural decline in serum testosterone levels with age [31]. In one study, men with post-traumatic hypogonadism were significantly older than men with normal gonadal function [7]. This characteristic contrasted with other pituitary hormone deficiencies where a significant association with age was not observed. However, age-related decline in testicular function is usually associated with increased serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels [32], whereas the hypogonadism we observed in our TBI patients was characterised by low or low-normal LH and FSH values. A mixed pattern, however, may exist in some older TBI patients leading to further compromise in testicular function..

Assessment of gonadal function following TBI (Table 2)

The diagnosis of hypogonadism relies on the presence of clinical features and supported by biochemical evidence of gonadal sex-steroid deficiency.

Timing of assessment

Because hypogonadism presenting in the acute phase of TBI is transient in most cases and its clinical significance is unclear, it is more clinically appropriate to carry out the assessment in the post-acute phase (3 to 6 months post-TBI) as part of an overall evaluation of pituitary function. Recovery of gonadal function may occasionally occur later than 6 months, therefore, in patients with documented hypogonadism at the 3–6 months assessment phase, re-evaluation of the gonadal axis is recommended at one year [24].

History and physical examination

Medical history and physical examination may reveal symptoms and signs of sex-steroids deficiency and these features are summarized in Table 2. Establishing a temporal relationship between the head injury and the onset of hypogonadal symptoms is useful. Physical examination may be entirely normal, particularly if hypogonadism is mild or of recent onset but typically loss of secondary sexual characteristics and in males gynecomastia and reduced testicular size may be found [33].

Table 2. *Assessment of gonadal function after traumatic brain injury (TBI)*

Timing
3–6 months post-TBI. If hypogonadism diagnosed, reassess at 1 year for recovery

Men	Premenopausal women
Clinical features	
Loss of libido and erectile dysfunction reduced energy and vigour infertility	A-oligomenorrhea Loss of libido Vaginal dryness, dyspareunia
Loss of secondary sexual characteristics	Excessive sweating
Gynecomastia	Galactorrhea
Testicular atrophy	Breast atrophy
Biochemical evaluation	
Total testosterone, if low check free testosterone or testosterone/SHBG ratio	Estradiol LH and FSH
LH and FSH	Prolactin
Prolactin	Progesterone challenge

Abbreviations: SHBG, sex-hormone binding globulin; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

Laboratory assessment

The biochemical diagnosis of hypogonadism depends on the finding of testosterone deficiency in men and estradiol deficiency in women. Most clinical laboratories measure total (protein bound) serum testosterone concentration but the diagnostic accuracy can be improved by having an estimate of free or bioavailable testosterone either by direct measurement or indirectly by measuring sex-hormone binding globulin (SHBG) level and calculating the free testosterone index (total testosterone-to-SHBG ratio) [34,35]. In addition to serum estradiol measurement, the diagnosis of estrogen deficiency can be further supported by the absence of a withdrawal bleed following progesterone challenge [36].

The diagnosis of central or hypogonadotropic hypogonadism is made by the finding of inappropriately low (ie, not increased) circulating levels of LH and FSH in the presence of gonadal sex-steroid deficiency [37,38]. The use of the GnRH test in the diagnosis of gonadotropin deficiency is outdated. The response to this test is heterogeneous among hypogonadal patients with hypothalamic and pituitary disease and overlaps with responses observed in normal subjects [35,37,38]. Therefore, the utility of this test in diagnosing gonadotropin deficiency and in distinguishing hypothalamic from pituitary lesions is uncertain. Serum prolactin levels should also be measured in all cases.

Implications and Management of Post-Traumatic Hypogonadism

In addition to the adverse effects of hypogonadism on fertility, psychosexual function and general well-being,

undiagnosed hypogonadism has important and specifically relevant consequences for TBI subjects. Testosterone deficiency in males is associated with muscle weakness, reduced lean body mass and impaired exercise tolerance [40]. In both males and females, hypogonadism is associated with reduced bone mineral density and the development of osteoporosis [41,42]. These adverse consequences are further exacerbated by the long durations of immobility seen after TBI. Gonadotropin deficiency in TBI patients may have added adverse consequences for muscle function and bone mass because of co-existing other anterior pituitary hormone deficiencies in particular growth hormone. In our series, 7 of 40 patients with hypogonadism in the acute phase of TBI had co-existing GH deficiency [6] while among long-term survivors, 2 of 12 patients with gonadotropin deficiency showed evidence of severe GH deficiency also [7]. Among the 44 patients who had both the GH and gonadal axes assessed using dynamic stimuli in the series recent reported by Leal-Cerro et al. [12], 6 of 19 patients with the diagnosis of gonadotropin deficiency also had definite or possible GH deficiency.

As the result, recovery and rehabilitation may be delayed and suboptimal, and the chance of return to normality and employment after TBI may be further compromised. In addition, a recent large epidemiological study has shown that untreated hypogonadism in hypopituitary patients to be associated with premature mortality mainly secondary to cardiovascular disease [43]. For these reasons, identification and treatment of post-traumatic hypogonadism is essential and should become part of routine clinical care after TBI.

In hypogonadism due to various aetiologies, beneficial effects of sex-steroids replacement are well-documented [40,42]. These benefits include increased self-esteem, vigour and libido and reduced fatigue and irritability in addition to improvement in muscle strength and bone mineral density [40]. Although the benefit from sex-steroid replacement in the particular case of post-TBI hypogonadism remains unclear and needs to be investigated in properly designed randomised controlled studies, it is likely that similar benefits will be observed with the potential to optimise physical and psychological recovery and rehabilitation after head injury.

In our practice, replacement sex-steroid therapy is commenced if the diagnosis of hypogonadism is made in the post-acute phase (3–6 months after TBI) because of the potential benefit for physical recovery while the patient is undergoing intensive rehabilitation during the first year after injury. Treatment is continued until the patient is reevaluated at one year to determine whether they have persistent deficiency (see above). If hyperprolactinemia is present, it should be corrected first to see if normalisation of prolactin level restores normal gonadal function. Different preparations and routes of administration are available for both testosterone and estrogen therapy and this topic has been comprehensively reviewed elsewhere [42,44]. Androgen deficiency may also be present in hypogonadal females, particularly if there is a co-existing adrenal insufficiency, and replacement with dihydroepiandrosterone may be considered in those women [44].

Conclusion

Traumatic brain injury is a high risk condition for hypogonadism which may have important implications for recovery and rehabilitation after injury. It is essential that hypogonadal patients are identified and treated in an appropriate and timely fashion in order to optimise their recovery and avoid long-term adverse consequences of sex-steroids deficiency.

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