Pituitary 8: 233–237, 2005

DOI: 10.1007/s11102-006-6046-0

Hypopituitarism and Growth Hormone Deficiency in Adult Subjects after Traumatic Brain Injury: Who and When to Test

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Published online: 27 February 2006

Abstract. **Traumatic brain injury (TBI) was traditionally considered an infrequent cause of hypopituitarism. However recent reports strongly suggest that TBI-mediated pituitary hormones deficiency may well be more frequent than previously thought. As the prevalence of hypopituitarism is not dependent on the severity of the trauma and considering the high number of TBI events in all industrialized countries a screening procedure for detecting hormone deficiencies in all TBI patients is not possible. In the present work a suggestion for screening a subgroup of TBI patients is discussed in order to increase the effectiveness of the whole procedure.**

Key Words: **Traumatic brain injury, severe head trauma, GH deficiency, pituitary hormone deficiency**

Introduction

Traumatic brain injury (TBI) was recognized as a cause of neuroendocrine dysfunction more than 60 years ago [1–4]. Over the last few years, several case reports and original articles have documented that in adult patients, head traumas may induce a variety of pituitary hormone deficiencies and in particular growth hormone (GH) deficiency [5–9]. However, over the last decades TBI has been considered an exceptional cause of hypopituitarism, and in several endocrine textbooks it has been omitted when listing the causes of pituitary dysfunction [10–13]. In some series dealing with hypopituitarism, TBI is either no listed as a potential cause or it appears but with an exceedingly low number of cases reported. Interestingly enough, in that type of lists the low numbers attributed to TBI paralleled the high number of patients in whom the etiology is "idiopathic" [11–13].

The situation changed dramatically in the year 2000 when several publications showed that TBI-mediated hypopituitarism might be more frequent than had previously been believed [14–16]. Spurred on by such reports in the last few years several groups have revisited the topic and changed previously admitted dogmas, showing that TBI-mediated hypopituitarism is reasonably frequent, not necessarily associated with diabetes insipidus, and not necessarily associated with hyperprolactinemia [17–24]. Some reviews and consensus statements have confirmed the rising interest and the social impact of this medical problem, as well as the need of conducting controlled studies in order to understand whether the hormonal deficiency post TBI can be partially responsible for the poor quality of life and general outcome of these patients [25–27]. In fact, the post concussion syndrome, very common in 30% of patients in the short period after TBI, presents with headache, irritability, loss of memory and attention deficit, depression, fatigue and low working capability, symptoms also associated with pituitary hormones deficiency and in particular with growth hormone (GH) deficiency.

In summary we are facing a very relevant clinical and social problem, on the one hand the hormonal deficits of patients who suffered TBI may be partially responsible for their poor recovery, then patients need to be tested and diagnosed, and on the other hand potential subjects to check out are too numerous. This made it necessary to decide what subgroup of the subjects that suffered TBI must be tested, and how long after trauma they should be evaluated.

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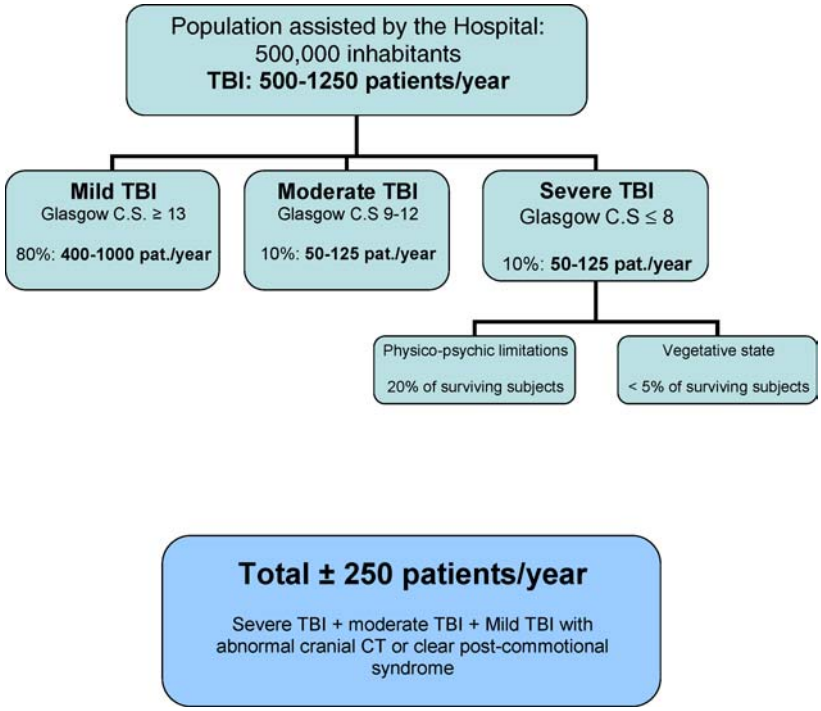

Fig. 1. *Scheme of the number of TBI cases expected for a hospital covering a population of half a million inhabitants.*

Who Should be Tested for Pituitary Function After TBI?

Considering the high number of pituitary deficiencies after TBI the spontaneous approach would be to test any patient with a relevant head trauma. Obviously this is not suitable due to the tremendous amount of head traumas world-wide. In fact, TBI is a major public health problem with an incidence rate around 200 cases per 100,000 inhabitants and year [25], of which almost 10% are fatal and 20–40% have a moderate to severe outcome [28]. Considering such high incidence, if anyone calculates the prevalence in his own country or city it is soon evident that testing them all would exhaust the health resources of a community. The arbitrarily decided strategy has been to cut the number of patients at both extremes, not testing those patients with severe damage after TBI, or those with an irrelevant or mild trauma (Fig. 1).

Following that reasoning, most of the groups active in the field are not studying patients with severe disability after TBI, i.e., those who are in a vegetative state or who are not to any extent autonomous. The rationale for avoiding this group is that not data are available showing that diagnosis and replacement of pituitary hormones can be of any benefit for patients in such extreme conditions. Obviously this policy may change in the future when more information becomes available. More controversial is the decision of not to test subjects who have suffered minor head trauma, as it has been reported that head directed traumatic events, of minor relevance with no loss of consciousness, no inwardly follow up, and without subsequent neurological deficiencies may be also be associated with severe hypopituitarism. In fact, severe hypopituitarism after irrelevant TBI has been reported both in children [29], and in adults [14]. Occasionally, the traumas were so minor that patients lost recollection of them, even after direct questioning about them, and only the family was able to remember the event [14]. It is actually a common belief that mild head traumas account for a substantial part of those patients with a previous diagnosis of idiopathic hypopituitarism, and may explain why TBI is associated with a later diagnosis and treatment when compared with any other cause of hypopituitarism [30]

Although head traumas of minor intensity may be associated with hypopituitarism, on a population basis, greater is the trauma higher is the likelihood that hypopituitarism may be present [24]. That seems reasonable despite the fact that several reports were unable to correlate hypopituitarism with the Glasgow Coma Score or the Glasgow Outcome Score [15]. From a cost-effective approach it is then better to focus on patients with moderate to severe head traumas based on the following facts: (a) the chance of finding a hormone deficiency is higher, (b) the possibility of changing the outcome after hormone replacement therapy is likely

Table 1. *Which patients with TBI should be tested for hypopituitarism?*

Those patients with an initial Glasgow Coma Score (GCS) of 13 or lower, or with a GCS between 13–15 with abnormalities in the brain imaging techniques. Patients who need inward surveillance for at least 24 h
Those with intracranial hemorrhagic lesions
Those who develop acute hypopituitarism manifestations during the immediate post TBI period
Those with current signs or symptoms of hypopituitarism
Children with loss of consciousness or who needed inward surveillance for at least 24 h after TBI
Exclusion criteria: patients severely disabled or in a vegetative state, until more studies be performed

greater, and (c) most of the data and current knowledge about TBI-hypopituitarism was generated precisely in that group of patients (Table 1).

When Should a Patient with TBI be Assessed in Order to Detect Hypopituitarism?

The time factor is particularly important in the problem of hypopituitarism following TBI due to the evolving nature of the lesion. In fact, pituitary hormonal sequelae after a traumatic event can either disappear with time or appear after a given time. Why a given hypopituitarism may disappear after several months is easily explainable as the damaged tissues may become repaired to some extent spontaneously. For example, the fact that diabetes insipidus may be transient after a head trauma is very well known [31], and based on experimental animal studies it has been shown that the stumps of experimentally disconnected pituitary stalks may reunite with further reinnervation after a given time [32]. In most series the prevalence of clinically evident diabetes insipidus after TBI is very low when patients are assessed more than one year after insult, in contrast with the high prevalence of this disorder in the days following TBI. However, a high incidence of subclinical vasopressin deficiency has been recently reported [33]. A case of GH, gonadotropins and TSH deficiency after a car accident and deep trauma at 7.2 yr has been documented with fully hormonal recovery at 19 yr [17]. A case of selective GH deficit with ulterior recovery may well be due to a reabsortion of the hematoma [34]. Just as some forms of hypopituitarism may vanish time after TBI, in other cases they may also appear some time after injury. The explanation for this fact is not available, but most probably the trauma induces an inflammatory response in the neural tissues that may progress generating further damaging and retrograde axonal degeneration leading to neuronal soma death [35]. Due to the time factor in the events unfolding after TBI, patients who undergo pituitary function testing short time after the head injury have yielded inconsistent and confusing results [15,20,36,37]. For that reason, and considering the tremendous amount of potential subjects to be tested for hypopituitarism in all countries it seems reasonable that for population analysis and when considering screening methods that patients should be tested at least one year after TBI, and not before.

TBI-mediated hypopituitarism in children is worth special consideration. Despite the fact that several case reports relating TBI with GH deficiency and hypopituitarism have been published [29, 38], no systematically assessed series are available. It is more than evident that if a child were to suffer from severe TBI with the ensuing hormonal deficiency and in particular with GH deficiency, he would soon be diagnosed, and the deficiencies corrected. The great problem arises in those traumas occurring at pre-puberty when somatic growth has occurred but has not yet been completed. In that situation, a GH deficiency will be overlooked because the already grown child is not severely short compared with his counterparts, although a deficit in his full growing potential have occurred. Endorsing this hypothetical scenario, came the comparison of adult patients with GH deficiency, in which those with TBI as a cause were 4 cm shorter than those with other causes for example due to non functioning pituitary adenomas [30]. As patients with GH deficiency due to TBI are diagnosed with a considerable delay due to the general unawareness on the problem, the explanation provided to such a finding was that these patients undergo the GH deficiency at a time in their lives later to be clinically evident, but when they were still growing [30]. In children to wait for one year before testing may be detrimental for the pubertal development, then it seems more adequate to test them six months after trauma.

Is there a place for pituitary hormonal evaluation soon after TBI? Studies of pituitary function at early stages are currently ongoing. In particular, the studies performed 3 months after TBI have changed the well accepted view about the problem, pointing to the fact that hypopituitarism at that stage was very frequent and undiagnosed [22]. The authors raise the crucial question of how severe the burden is that the hormonal deficiency posses on the outcome of these patients as well as on their ability to recover. A logical conclusion of this study was that in the early post TBI period a close liaison between endocrinologists with other specialists was mandatory to assure that no deficiency was interfering with the full recovery of the patient, as well as to ensure that after discharge patients will not be lost at follow up (Table 2).

Conclusions and Further Works

In order to gain more insight on the problem of hypopituitarism due to TBI, new models need to be addressed, either experimentally or in particular clinical situations. Of particular relevance is the work of TBI

Table 2. *TBI patients should be tested for hypopituitarism?*

Based on evidence
(1) Adults, one year after TBI
(2) Children, 6 months after TBI
Under current experimental evaluation
(3) At the peri-trauma period (before the patient leaves the hospital)
(4) Three months after trauma
(5) Long time after trauma (5 of more years)

caused by sport boxing [39]. This is a fine and elegant model as brain trauma in boxing is not extremely intense when comparing with a car crash, but is highly repetitive along the years of activity and is suffered by boxers both in matches and in training. The high prevalence of pituitary deficiency and in particular of isolated GH deficiency in boxing [39], may help to clarify the mechanisms underlying this kind of hypopituitarism in TBI.

In conclusion, patients with TBI should be evaluated when reporting moderate to severe trauma one year after the trauma, earlier in children. Other groups and other timing need more confirmatory data at present, but the results generated in those studies may change the present recommendations in the future.

Acknowledgments

Supported by research grants from the Fundación Mutua Madrileña-Investigación Médica and from a research grant of Pfizer Spain.

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