Hypopituitarism After Traumatic Brain Injury

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KEYWORDS

• Traumatic brain injury • Hypopituitarism • Growth hormone deficiency
• Hormone replacement therapy

KEY POINTS

- The prevalence of hypopituitarism after traumatic brain injury (TBI) is widely variable in the literature; a meta-analysis that included more than 1,000 patients determined a pooled prevalence of anterior hypopituitarism of 27.5%.
- Growth hormone (GH) deficiency is the most prevalent hormone insufficiency after TBI; however, the prevalence of each type of pituitary deficiency is influenced by the assays used for diagnosis, severity of head trauma, and time of evaluation.
- It is not recommended to evaluate pituitary deficiencies in early acute phases because of the high proportion of pituitary function recovery with the exception of corticotropin deficiency, which should be evaluated within the first several days after TBI.
- Vascular damage and the presence of antipituitary antibodies have been proposed as factors involved in the development of hypopituitarism after TBI.
- Recent studies have demonstrated improvement in cognitive function and cognitive quality of life with substitution therapy in GH-deficient patients after TBI.

INTRODUCTION

TBI is one of the primary causes of death in young people in industrialized countries, and patients who survive suffer important clinical consequences, such as long-term cognitive, behavioral, and social defects.[1,2] TBI represents a significant public health problem worldwide, with a described overall annual incidence in Western countries of 200 to 235 cases per 100,000 individuals.[3]

The authors have nothing to declare.

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Endocrinol Metab Clin N Am 44 (2015) 151–159
http://dx.doi.org/10.1016/j.ecl.2014.10.012 **endo.theclinics.com**
0889-8529/15/$ – see front matter

In the past decade, several studies have highlighted the existing relationship between TBI and pituitary dysfunction.[4–15] Hypopituitarism is believed to contribute to TBI-associated morbidity[16] and to functional and cognitive final outcome,[17] neurobehavioral outcome, and quality-of-life impairment.[16] Evaluations have also indicated a specific association between GH deficiency and certain cognitive disorders, such as depression and memory affection.[18] It is also expected that hypopituitarism significantly impedes recovery and rehabilitation after TBI.[19]

PATHOPHYSIOLOGY

The pathophysiology of hypopituitarism after TBI is not completely understood, and several factors implicated in its development have been suggested.[20] One of the main theories involved in pituitary impairment involves vascular damage to the pituitary gland,[21] which is a theory supported by the high prevalence of hypopituitarism in patients who have suffered an ischemic stroke.[22] Vascular damage to the pituitary gland can also be caused by several mechanisms. (1) Traumatic damage to the long hypophyseal portal vessels and subsequent venous infarction are believed to be the main underlying vascular mechanisms.[23,24] The long hypophyseal vessels supply the anterior lobe, which are more susceptible to damage and could explain the higher prevalence of anterior hypopituitarism in cases of TBI. Conversely, the short hypophyseal vessels supply the posterior lobe, which is preserved in most cases and is associated with a lower prevalence of hypopituitarism. (2) Postmortem studies have revealed a high prevalence of necrosis or hemorrhage into the pituitary gland, which suggests a direct traumatic injury to the pituitary gland as another possible mechanism.[25] (3) Multiple secondary insults from hypotension, hypoxia, anemia, and brain swelling could also lead to an ischemic pituitary gland.[26] (4) Another mechanism described as responsible for hypopituitarism due to vascular damage is the transection of the pituitary stalk, which potentially causes hypopituitarism because of infarction of the pituitary tissue.[21,23]

In addition to the vascular damage, recent research has indicated a possible interaction between autoimmunity and the development of hypopituitarism after TBI. It has been demonstrated that antipituitary and antihypothalamic antibodies are present in patients with TBI-induced pituitary dysfunction and persist even 5 years after diagnosis.[27,28] Moreover, in patients with higher titers of pituitary antibodies, the development of pituitary deficiencies is more frequent,[22,29] with increasing importance with a longer duration after trauma.[28] In addition, the recovery of pituitary function is related to negative antibodies titers.[28]

The dynamic condition of hormonal function suggests that head trauma may trigger an ongoing process, such as autoimmunity or neuroinflammation.[30] More studies are still needed, but these findings may support a proposal of the detection of pituitary antibodies as predictive markers of persistent hypopituitarism after TBI.

EPIDEMIOLOGY OF HYPOPITUITARISM AFTER TRAUMATIC BRAIN INJURY

The prevalence of any grade of hypopituitarism after TBI described in published studies thus far is highly variable, ranging from 5.4% to 90%.[4–15,31] In 2007, a meta-analysis, including 1015 patients with TBI, reported a pooled prevalence of hypopituitarism of 27.5%. The prevalence of anterior pituitary dysfunction in the studies included in this meta-analysis ranged from 15% to 68%.[32]

There are no differences in the epidemiology of hypopituitarism in children and adults, with the exception of early childhood. In these cases, the prevalence of pituitary abnormalities is lower and comparable to the prevalence expected for the general population.[33]

The degree and subtype of pituitary deficiencies also varied among the studies published. GH deficiency has been reported as the most prevalent type of pituitary deficiency, particularly as an isolated deficiency,[6,9,10,28] with a prevalence ranging from 2% to 66% and of 28% when the evaluation was performed 5 years after TBI.[28] The prevalence of the other pituitary hormone deficiencies is also widely variable, ranging from 0% to 60% for secondary adrenal insufficiency, 0% to 29% for secondary hypothyroidism, 0% to 29% for central hypogonadism, and 0% to 48% for abnormal hyperprolactinemia.[4–7,9–15,34] Diabetes insipidus tends to improve in long-term survivors, with a reported prevalence of 7% in large series.[35]

There are several explanations for this remarkable variability in the prevalence reported among these studies. The severity of brain damage of the patients, timing of pituitary evaluation, and diagnostic methods used are not homogeneous among the published reports.[34,36]

Severity of Traumatic Brain Injury

TBI severity is graded using the Glasgow Coma Scale (GCS) score[37] according to consciousness level and ocular and motor movements. This scale classifies the head trauma in 3 groups: severe if the score is less than or equal to 8, moderate if the score is from 9 to 12, and mild if the score is greater than or equal to 13.

Pituitary deficiencies have been detected more frequently in cases of moderate and severe trauma (GCS <13),[4,7,12,13,29] although other investigators did not find any association between injury severity and prevalence of hypopituitarism.[5,10,11] The pooled prevalence of hypopituitarism in cases of severe, moderate, and mild TBI reported by Schneider and colleagues in 2007[32] was 35.3, 10.9, and 16.8%, respectively. Several situations, such as the presence of anatomic abnormalities on initial CT scan (diffuse axonal injury or skull fractures),[38] diffuse brain swelling, hypoxia, hypotension,[4] duration of coma,[14] increased intracranial pressure, longer intubation and hospitalization,[32] and advanced age, have been associated with a worse prognosis and predict a higher incidence of hypopituitarism.[39–41] Overall, there is no cost/benefit indication for global screening of all cases of mild TBI.[42] In recent years, however, it has also been reported that sports associated with low-intensity repetitive head trauma may be related to pituitary insufficiency,[43] most likely related to a decrease in pituitary volume,[44] and should be taken in consideration. In these cases, GH deficiency followed by corticotropin deficiency are the most common findings.[44,45]

Timing for Evaluation

Another factor that influences the prevalence of hypopituitarism is the time interval between TBI and pituitary hormone assessment. The design and time of pituitary evaluation in the literature were also variable, ranging from 24 hours up to 23 years after the head trauma. Only a few studies have been designed to evaluate the incidence of hypopituitarism after TBI with specific criteria and evaluation at a particular time,[8,10,13,46] and most of the published studies are retrospective or cross-sectional.[4–7,9,11,15]

The detection of pituitary dysfunction in early acute phases (first 24 h) or acute phases (up to 2–3 weeks) after TBI has not been associated with hypopituitarism after 12 months.[13,46] In 1 study, the prevalence of hypopituitarism was 56% at 3 months but dropped to 36% at 12 months after TBI.[12] This improvement in pituitary function throughout the first year after TBI has been observed particularly in patients with mild and moderate TBI. Conversely, in patients with severe head trauma, pituitary deficiencies may persist even 5 years after the traumatic event.[28] Hypopituitarism has been described as a dynamic condition associated with the development and recovery of hormone deficiencies,[10,13,46] with recovery in pituitary function even 12 years

after TBI.[47] Possible pituitary revascularization and cellular pituicyte repopulation may explain these findings.[14]

Moreover, physiologic hormonal changes that can mimic pituitary dysfunction are often observed in the early posttraumatic period.[48] The physiologic response to acute and critical illness comprises hormonal changes similar to GH deficiency, central hypogonadism, and hypothyroidism.[49] Moreover, the metabolism of the protein-binding hormones can be altered by acute illness or drugs frequently used in severe diseases, resulting in increased circulating levels and, consequently, false deficiencies.[50] Conversely, cortisol, prolactin, and vasopressin are stress hormones that are increased in acute phases of severe disease.[51,52] Low or low-normal baseline free cortisol can still be proposed as a potential early marker for the development of chronic corticotropin deficiency in head trauma patients.[48] Acute corticotropin deficiency may be life threatening, and, therefore, the focus during the acute phase should be in detecting glucocorticoid deficiency, with the monitoring of early morning cortisol within the 7 days after TBI in hospitalized patients.[53]

The overestimation of hypopituitarism in the acute phase after TBI makes it reasonable to propose the evaluation of pituitary function at least 1 year after the head trauma and not at an earlier time point, particularly for hormones that do not necessarily need to be replaced urgently, such as the gonadal and somatotropic axes.[54]

Methods for Endocrine Assessment

Another factor that potentially influences the variability in the results reported is the heterogeneity in the methods used for pituitary function evaluation.

The GH axis has been assessed using a dynamic test in addition to basal GH and insulinlike growth factor 1 values. The dynamic tests used, however, have differed among the studies and include the insulin tolerance,[4,15,31,48] glucagon stimulation,[5,11,55] GH-releasing hormone (GHRH)–arginine,[6,10,15] and GHRH–GH-releasing peptide (GHRP)-6[9,13] tests. The vagaries of the GH provocation test are well known.[56] Studies that have used the insulin tolerance test have detected lower prevalence of hypopituitarism.[15,31,57] The optimal diagnostic is the one that identifies the patients who will benefit from treatment with GH and excludes those who will not.[19] The GHRH–GHRP6 test, which is a rigorous and reliable test not affected by known factors that modify GH secretion, such as obesity,[58] has demonstrated its utility in the diagnosis of GH deficiency specifically after TBI,[9,13] even in a single assay after a 30-minute test.[59]

The stimulation tests used when there is a need to evaluate the adrenal axis are the corticotropin stimulation test[7,13] and insulin tolerance test.[4,11,15,60] The corticotropin stimulation test is performed with either 250 μg of cosyntropin[7] or 1 μg of tetracosactrin.[13]

For the thyroid, gonadal, and prolactin axes, basal levels are sufficient for a diagnosis to be made.[7,9,10,15,16,46]

The proposed algorithm for the diagnosis of hypopituitarism after TBI is represented in **Fig. 1**. The recommended tests for diagnosis of hypopituitarism after TBI are the same as for other causes of pituitary dysfunction and have been previously described.[61]

HORMONE REPLACEMENT THERAPY

The Pfizer International Metabolic Database (KIMS) reported a significant improvement in quality of life, as assessed by the Assessment of Growth Hormone Deficiency in Adults score, in patients with posttraumatic hypopituitarism and GH treatment.[62] Recent data also suggest that certain cognitive impairments observed in patients

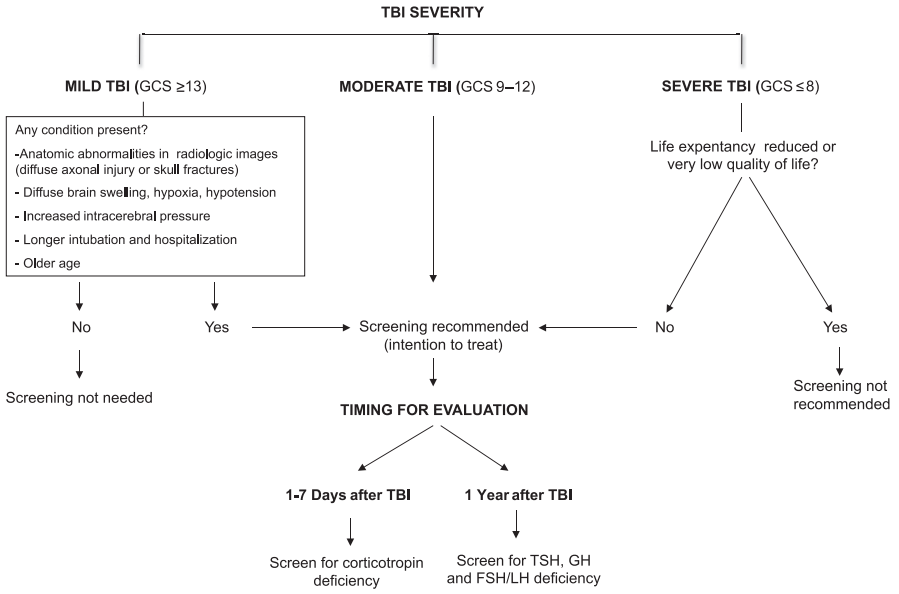

Fig. 1. Proposed algorithm for the diagnosis of hypopituitarism after TBI.

with GH deficiency after TBI and quality of life can improve with GH replacement.[63–65] Serious and life-threatening adrenal crises due to corticotropin deficiency after TBI have significantly improved with glucocorticoid replacement.[60] Long-term follow-up studies are still needed, however, to evaluate the outcome and the necessity and benefits of hormone replacement with GH and gonadal steroids in these patients.

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