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REVIEW

Traumatic brain injury: endocrine consequences in children and adults

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Abstract Traumatic brain injury (TBI) is a common cause of death and disability in young adults with consequences ranging from physical disabilities to long-term cognitive, behavioral, psychological and social defects. Recent data suggest that pituitary hormone deficiency is not infrequent among TBI survivors; the prevalence of reported hypopituitarism following TBI varies widely among published studies. The most common cause of TBI is motor vehicle accidents, including pedestrian-car and bicycle car encounters, falls, child abuse, violence and sports injuries. Prevalence of hypopituitarism, from total to isolated pituitary deficiency, ranges from 5 to 90 %. The time interval between TBI and pituitary function evaluation is one of the major factors responsible for variations in the prevalence of hypopituitarism reported. Endocrine dysfunction after TBI in children and adolescents is common. Adolescence is a time of growth, freedom and adjustment, consequently TBI is also common in this group. Sports-related TBI is an important public health concern, but many cases are unrecognized and unreported. Sports that are associated with an increased risk of TBI include those involving contact and/or collisions such as boxing, football, soccer, ice hockey, rugby, and the martial arts, as well as high velocity sports such as cycling, motor racing, equestrian sports, skiing and roller skating. The aim of this paper is to summarize the best evidence of TBI as a cause of pituitary deficiency in children and adults.

Keywords Traumatic brain injury · Concussion · Hypopituitarism · Adolescents · Athletes

Introduction

Traumatic brain injury (TBI) is a common cause of death and disability in young adults with consequences ranging from physical disabilities to long-term cognitive, behavioral, psychological and social defects [1, 2]. It is considered a significant public health problem worldwide. Hypopituitarism post-traumatic brain injury was described almost one century ago; it was thought to be a rare condition [3]. The last 10 years, have brought increased awareness that pituitary dysfunction is common after TBI in children and adults. The most common cause of TBI is motor vehicle accidents, falls, child abuse, violence and sports injuries.

Recent data suggest that pituitary hormone deficiency is not infrequent among TBI survivors; the prevalence of reported hypopituitarism following TBI varies widely among published studies [4, 5]. Prevalence of hyopituitarism, from total to isolated pituitary deficiency, ranges from 5 to 90 %. The reported prevalence of hypopituitarism after TBI in children and adolescents is similar to the prevalence in adults, but in early childhood, the reported prevalence is lower when compared with adult data.

The pathophysiology of TBI involves not only the primary mechanical event but also secondary insults such as hypotension, hypoxia, increased intracranial pressure, and changes in cerebral blood flow and metabolism. Pituitary

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function after TBI undergoes remarkable variation over time, endocrine surveillance is recommended to ensure early intervention and diminish sequelae.

The aim of this paper is to summarize the best evidence of TBI as a cause of pituitary deficiency in children and adults.

Epidemiology

TBI is increasingly common and the leading cause of death in industrialized countries for individuals between the ages of 1 and 45 [1]. Rates of TBI are highest in early childhood (0–4 years), young adults (15–24 years) and the elderly (>65 years). The most common cause of TBI is motor vehicle accidents, including pedestrian-car and bicycle-car encounters, falls, child abuse, violence and sports injuries. Younger kids are more likely to have TBI due to falls while teenagers have more TBI than any other population from motor vehicle accidents. Many survivors live with significant physical and psychological sequelae [2]. Despite the high prevalence of TBI in the general population, post-traumatic hypopituitarism remains largely under-diagnosed. Until recently, evidence for pituitary insufficiency secondary to TBI was limited to anecdotal case reports. The first report of a patient with hypopituitarism after TBI was published in 1918, subsequent to this, autopsy series showed high rates of pituitary damage following fatal TBI [3]. Recent data suggest that pituitary hormone deficiency is not infrequent among TBI survivors. The prevalence of reported hypopituitarism following TBI varies widely among published studies. A meta-analysis including more than 1,000 patients with TBI reported a pooled prevalence of hypopituitarism of 27.5 %; pituitary evaluation was performed in a range of 3 months to 7 years after the head trauma [4].

Pathophysiology

The pathophysiology of TBI is not completely understood, involves not only the primary mechanical event but also secondary insults such as hypotension, hypoxia, increased intracranial pressure, and changes in cerebral blood flow and metabolism. Skull fracture, edema, and acute hemorrhage can lead to increased intracranial pressure [5]. Direct mechanical damage through axonal shearing injury can also lead to hypothalamic-pituitary injury [6].

Anterior pituitary dysfunction in survivors of TBI is more common than posterior lobe dysfunction because the blood supply to the posterior lobe is derived from the short hypophyseal vessels in contrast with the more susceptible to damage blood supply of the anterior lobe which derives from the long hypophyseal vessels and the portal capillaries in the pituitary stalk [7].

Located in the lateral regions of the anterior pituitary gland, somatotrophic and gonadotrophic cells are more vulnerable due to their location and blood supply. Distributed more centrally, corticotrophic and thyrotrophic cells may be somewhat less vulnerable.

Recent research suggests a possible role of autoimmunity in the development of hypopituitarism following TBI. Antipituitary antibodies are present in patients with TBI-induced pituitary dysfunction and persist even 3 years after diagnosis [8].

Clinical presentation of hypopituitarism

Hypopituitarism after TBI remains largely under-diagnosed, mostly due to lack of awareness among physicians who take care of patients with TBI. Some patients present with nonspecific symptoms such as fatigue, weakness, cold intolerance, decreased appetite, weight loss, headaches, abdominal pain, low blood pressure, visual disturbances, menstrual irregularities and decreased libido.

In childhood and adolescence, impairment in growth and development is a common finding and represents the hallmark of potential damage to the hypothalamus-pituitary function after TBI [9–13].

The clinical manifestations depend on the degree of the specific hormonal deficiency. In secondary hormone deficiencies, for example thyrotropin deficiency, some basal hormone secretion can be preserved, resulting in a less severe clinical phenotype compared with primary hypothyroidism [13]. Corticotropin deficiency is less evident than primary adrenal deficiency, since most mineralocorticoid secretion remains intact. In men with recent onset hypogonadism, physical examination is usually normal, but gynecomastia, diminished facial and body hair, and small and soft testicles are common findings in longstanding hypogonadism. Patients with growth hormone deficiency frequently report diminished exercise tolerance, develop central body fat distribution, dyslipidemia and complain of tiredness. Hyperprolactinemia is common in patients with hypopituitarism, galactorrhea may occur, but more frequently hypogonadism is observed, due to the effect of raised prolactin levels on normal pulsatile gonadotropin secretion.

Variations in pituitary function over time

The time interval between TBI and pituitary function evaluation is one of the major factors responsible for variations in the prevalence of hypopituitarism reported. The presence of pituitary dysfunction in the acute phase

following TBI is not related to hypopituitarism after 12 months, in fact, hypopituitarism is often transient [10]. An Italian prospective study evaluated the pituitary function 3 and 12 months after TBI in 100 patients. The 3 months evaluation showed some degree of hypopituitarism in 35 % of the TBI patients. The follow up at 12 months after TBI demonstrated some degree of hypopituitarism in 22.7 %. Interestingly in this study, total hypopituitarism was always confirmed in the 12 months evaluation. The authors suggest that patients who suffer TBI may experience improvement in pituitary function over time and transient hypopituitarism would reflect effective repair of the hypothalamus-pituitary damages induced by the brain injury [14, 15].

Diagnosis of hypopituitarism

Corticotropin deficiency

The most clinically important axis to be disrupted in acute TBI is the pituitary-adrenal axis. Corticotropin insufficiency can lead to adrenal insufficiency, leading to life threatening hyponatremia and hypotension. The excellent clinical response to glucocorticoid replacement therapy makes rapid and appropriate diagnosis and treatment a priority in patients with moderate and severe TBI.

Serum cortisol and ACTH concentrations vary with time after TBI. Serum cortisol concentrations increase immediately after TBI with a subsequent gradual decline toward normality [16]. Some authors have found plasma cortisol concentrations to correlate with severity in mild or moderate TBI and that normalization of serum cortisol predicted good outcome. A recent study demonstrated that acute hypocortisolemia and central diabetes insipidus are predictive of mortality and long-term pituitary deficits in TBI [17]. Several studies in the early phase after TBI have reported that the incidence of ACTH-cortisol deficiency varies between 4 and 53 % [18, 19].

Growth hormone deficiency

Growth hormone deficiency is the most common hormonal deficiency reported after TBI, with a prevalence between 2 and 66 % [20, 21]. This variability could be explained by several factors, including a different time interval between TBI and the assessment of growth hormone secretion, the type and severity of brain injury, and the different criteria and methods used to define growth hormone deficiency. For the somatotropic axis evaluation after TBI, determination of IGF-1 levels, plus dynamic testing with either GHRH + arginine, GHRH + GHRP-6, glucagon is indicated. Insulin induced hypoglycemia (ITT) testing can be used when not contraindicated and experienced personnel performing this test is available. The choice of a test instead of another one depends on the preference and familiarity with it of the endocrinological team [22].

All patients with documented severe growth hormone deficiency are candidates for growth hormone replacement.

Thyrotropin deficiency

Low serum levels of free T4 with normal or low serum TSH levels allow diagnosis of central hypothyroidism to be made. Serial determinations of free T4 and TSH levels are helpful in order to make the diagnosis. The modern assays have significantly reduced the need for dynamic testing the hypothalamic-pituitary thyroid axis.

When appropriately prescribed, thyroxine replacement therapy is highly effective and safe. Corticotropin deficiency should be excluded before thyroxine therapy is started, in order not to provoke an adrenal insufficiency crisis due to increased cortisol clearance.

The prevalence of hypothyroidism after TBI varies between a 0 and 19 % in different studies. In a study of 70 patients who suffered TBI, the prevalence of hypothyroidism 12 months after the event, defined as a low free T4 concentration with normal or low TSH levels, was 5.7 % [23].

Gonadotropin deficiency

The hypothalamic-pituitary gonadal axis deficiency following TBI ranges between 0 and 29 %. Although suppression of gonadotrophins with secondary gonadal failure present in most patients within the first days following TBI, follow up studies have demonstrated that complete recovery of the pituitary-gonadal axis occurs in 76 % of patients by 6 months and in 85 % by 1 year.

It is important to measure prolactin levels since hyperprolactinemia also produces hypogonadism [24]. Testosterone and estrogen deficiency require replacement for the relief of symptoms and for the prevention of osteoporosis and cardiovascular disease.

Diabetes insipidus

Diabetes insipidus is a well recognized complication in patients who suffer TBI, with a reported incidence between 3 and 26 % [25, 26]. Acute phase diabetes insipidus is associated with more severe head injury and the presence of cerebral edema, and a higher mortality rate [27]. Follow-up evaluation at 12 months after TBI using water deprivation tests has shown that only 12 % of patients with acute diabetes insipidus had persistent diabetes insipidus [28]. Rapid and appropriate diagnosis and treatment of diabetes insipidus following TBI is important because there

is a strong association between hypernatremia and mortality in this scenario.

Caution is required for the occasional development of the syndrome of inappropriate anti-diuretic hormone release (SIADH) that may also occur as a result of TBI. As a rule SIADH secondary to TBI is transient but if undiagnosed it may result in profound hyponatremia.

TBI in children and adolescents and pituitary dysfunction

Adolescence is a time of growth, freedom and adjustment, consequently TBI is also common in this group. TBI is one of the first causes of death and disability in children. The most common cause of TBI is motor vehicle accidents, falls, child abuse, violence and sports injuries. Endocrine dysfunction after TBI in children and adolescents is common. Many case reports series after TBI in children and adolescents have documented pituitary dysfunction, including a particularly high frequency of precocious puberty. However, few studies have systematically evaluated the prevalence of hypopituitarism in the pediatric population, and there is no consensus if the real prevalence of precocious puberty is increased or not in patients after TBI compared to the general population. Permanent hypopituitarism is rarely reported in early childhood. In a study of 198 survivors of structural TBI sustained in early childhood (age at injury 1.7 + −1.5 years) found no cases of permanent hypopituitarism, 0.5 % of the patients developed precocious puberty, 8 % had subnormal peak stimulated growth hormone levels in the context of normal growth and normal IGF-1 levels. 8 % had initial low stimulated peak cortisol levels but normal cortisol and ACTH levels on follow-up [10]. A very recent research in the pediatric population, evaluated 37 children, in the >6 years-old group, 47.8 % had a subnormal growth hormone peak 3 months after TBI that persisted in 34 % of the patients after 12 months. A sub-optimal cortisol was found in 43.5 % of the patients at 3 months and persisted in 13.0 % 12 months after TBI. No clinical or hormonal abnormalities were found in the <6 years-old group [11]. Among retrospective studies there is a 16–61 % prevalence of hypopituitarism at 1–5 years after TBI. Diabetes insipidus is rarely reported after TBI in children. A recent prospective study, evaluated the pituitary function after TBI in 31 children. The incidence of endocrine dysfunction was 15 % at 1 month, 75 % at 6 months and 29 % at 12 months. At 1 year after TBI, 14 % had precocious puberty, 9 % had hypothyroidism, and 5 % had growth hormone deficiency [29]. A study of 23 patients in the transition period (ages 16–25 years), showed a 34.6 % of hypopituitarism 3 months after TBI and at 12 months, hypopituitarism was present in 30.3 % of the patients [30]. Hypopituitarism may develop in patients who are submitted to neurosurgery for primary brain tumors, even far from the hypothalamic-pituitary region [31].

TBI-induced hypopituitarism has important clinical endocrine consequences in childhood and adolescence given the implications in growth and development. The onset of TBI induced endocrine dysfunction requires an appropriate evaluation and treatment in order to prevent possible adult health consequences.

Sports-related TBI and pituitary dysfunction

Sports-related TBI is an important public health concern, but many cases are unrecognized and unreported. There is a worldwide increase of athletes participating in a wide variety of amateur and professional sports. Sports that are associated with an increased risk of TBI include those involving contact and/or collisions such as boxing, football, soccer, ice hockey, rugby, and the martial arts, as well as high velocity sports such as cycling, motor racing, equestrian sports, skiing and roller skating [32].

Although sports are a well-known cause of concussion, trauma due to sports is generally not considered to be a cause of TBI in most epidemiological studies. Thus, the association between sports-related head trauma and pituitary dysfunction is not fully understood. Recent studies have demonstrated that sports related repetitive head trauma might induce pituitary dysfunction, and in particular, isolated GH deficiency [33].

A recent study evaluated the pituitary function in 61 boxers and found that 15 % had growth hormone deficiency and 8 % had ACTH deficiency, findings similar to previous studies in boxers [34]. An investigation in 22 amateur kickboxers demonstrated that 22.7 % had growth hormone deficiency and 9.1 % had ACTH deficiency [35]. Soccer is also related with TBI and pituitary dysfunction, although only case reports have being published. A 14-year old soccer player developed growth hormone, ACTH and TSH deficiency after a series of head traumas in a short period of time [36]. Another case report described a 27 year-old professional soccer player who was diagnosed with isolated gonadotropic deficiency after multiple concussions [37]. Diabetes insipidus was demonstrated in a 24 year-old swimmer who experienced TBI against the edge of the pool, although did not result in loss of consciousness, did require hospitalization for several days [38].

Effects of rhGH therapy in GH-deficient subjects following TBI

Growth hormone has several targets in the central nervous system (CNS) including the limbic structures related to well-being and hypothalamic centers associated with pituitary hormone regulation [39]. Growth hormone deficiency, whether caused by TBI or other mechanism may lead to a syndrome of mental health-related problems including a decreased sense of well-being and loss of memory and cognitive capabilities [40]. In fact it is the diminished sense of well-being that became a major factor in the approval process for GH therapy in GH-deficient adults in the US.

Beyond the reversal of some of the metabolic abnormalities GH-treatment of GH-deficient adults enhances energy, motivation and sense well-being. There are objective findings for improved memory and cognitive capabilities [40, 41].

GH is permeable to the brain and there are receptors for both GH and IGF-I in areas associated with cognitive function and behavior (reviewed in [40]). Some patients with GH deficiency following TBI, experience improvements in motor and/or cognitive affectations in response to therapy with rhGH [42, 43]. Whether the salutary effects of rhGH work through the GH or the IGF-I receptor is at present unknown; however, research is being actively pursued to determine this issue (F. Nyberg, personal communication to ADR May, 2013).

Conclusion

Recent data confirm that pituitary hormone deficiency after TBI is common in children and adults. The prevalence of hypopituitarism varies among published studies, but is often transient. The pathophysiology of TBI is not completely understood, anterior pituitary dysfunction in survivors of TBI is more common than posterior lobe dysfunction because the blood supply to the posterior lobe is derived from the short hypophyseal vessels in contrast with the more susceptible to damage blood supply of the anterior lobe which derives from the long hypophyseal vessels and the portal capillaries in the pituitary stalk. Somatotrophic and gonadotrophic cells are more vulnerable due to their location and blood supply. Distributed more centrally, corticotrophic and thyrotrophic cells may be somewhat less vulnerable.

In children, impairment in growth and development is a common finding and represents the hallmark of potential damage to the hypothalamus-pituitary function after TBI. Recent studies have demonstrated that sports-related repetitive head trauma might induce pituitary dysfunction, and in particular, isolated GH deficiency. Some patients with GH deficiency following TBI experience improvements in motor and/or cognitive functions in response to therapy with rhGH.

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