In today’s realm of competitive sports environments worldwide, a large number of athletes participate in a wide variety of amateur or professional sports. Closed head injury is an occupational hazard of many sports, such as boxing, kickboxing, ice hockey, football, and many others. Participants in these sports are at risk for concussion, which is considered a type of mild TBI. During the past decade, numerous studies have shown that TBI is often responsible for pituitary dysfunction such as hypopituitarism, which seems to be readily present even after mild TBI. 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 link between sports-related head trauma and pituitary dysfunction is not well understood, even now. Recent studies have demonstrated that sports-related repetitive head trauma might induce pituitary dysfunction, and in particular, isolated GH deficiency.

The aim of this paper was to summarize the best evidence for understanding the pathophysiological mechanisms and to discuss the current data and recommendations on sports-related head trauma as a cause of hypopituitarism.

Sports-Related Concussion

Concussion is considered a clinical syndrome characterized by immediate and transient posttraumatic impairment of neural function, such as alteration of consciousness or disturbance of vision or equilibrium, and other signs due to the involvement of brainstem. Mild TBI (or concussion) may lead to postconcussion syndrome (secondary symptoms), including additional cognitive problems, headaches, anxiety, fatigue, and psychosocial problems.

Concussion is a type of injury that can occur in any sports activity, and is the most frequent type of acute TBI in sports. It is most often associated with boxing, football, ice hockey, and martial arts. The nature of the risk depends on the nature of the game and its specific activities. Individual variables might predispose an athlete to concussion, such as previous concussions, position played, and the sex of the athlete.
Although sport is a well-known cause of TBI, it was only in the 1980s that the medical community started to direct research toward the risk of sports-related concussion. In the early 1980s, thanks to the work of Barth et al.8 and Rimel et al.,27 a discussion was started among members of the medical community regarding the description, classification, and management of sports-related concussion.40

**Hypopituitarism and Mild TBI**

Traumatic brain injury has been recognized for almost a century as a cause of neuroendocrine dysfunction.19 However, it was thought to be a rare occurrence,27 despite the results of autopsy studies that showed pituitary gland necrosis in up to one-third of patients who suffered fatal TBI.10

In the past decade, studies reported that 5.4%—69% of hypopituitarism was associated with TBI.1,4,13,32,39,41,43,45,51,52,62 The severity of hormonal disturbance is generally related to the severity of TBI. However, mild TBI can contribute to pituitary dysfunction.10 Bondanelli et al.12 noticed hypopituitarism in 37.5% of patients with mild TBI versus 59.3% of patients with severe TBI. Pituitary dysfunction can be partial or complete. Gonadotropin and GH deficiencies appear to be the most common.3,12

Recent studies have reported that pituitary function can improve over time in a considerable number of patients. However, it may also worsen over the 1- and 3-year period after TBI.4,64 Traumatic brain injury may also cause hypothalamic dysfunction and diabetes insipidus.14,33,37

**Hypopituitarism and Sports**

As mentioned earlier, sports-related concussion could be considered as a subgroup of mild TBI. Also, TBI is one of the most important public health problems,70 and may be associated with pituitary secretion dysfunction, which may contribute to long-term physical, cognitive, and psychological disability.

Almost all of the studies regarding the relationship between TBI and sports published so far in the literature are based on neuropsychological or radiological assessment, and no neuroendocrine changes are investigated. There is a paucity of data regarding the association between sports and hypopituitarism. To our knowledge, only 3 studies and 1 case report investigated the link between pituitary dysfunction and sports-related concussion.35,38,45,67 Three of these studies were conducted by the same medical team.35,38,45 The studies only concern 3 sports—boxing,45 kickboxing,35 and soccer35—that are obviously associated with chronic mild TBI.

The first report of pituitary function in boxers was published in 2004 by Kelestimur et al.38 In this preliminary study, the authors included 11 actively competing or retired male amateur boxers and investigated their GH status compared to a control group. A GH deficiency was found in 45% of these amateur boxers. The mean IGF-I levels in boxers (237 ± 23.3 ng/ml) were significantly lower than in the control group (367 ± 18.2 ng/ml). There was a significant negative correlation both between peak GH levels and boxing duration and between peak GH levels and number of bouts.

In 2007, Tanriverdi et al.65 investigated the GH status of 22 amateur kickboxers compared with a control group. The serum IGF-I level was significantly lower in kickboxers (276.5 ± 25.9 ng/ml) than in the control group (346.9 ± 20.9 ng/ml). Of the 22 amateur kickboxers, 22.7% had a GH deficiency and 9.1% had an ACTH deficiency. There were negative correlations between serum IGF-I level and age, length of time the athlete had participated in sports, and number of bouts.

Ives et al.35 reported a case of a 16-year-old high-level junior soccer player who had experienced 4 episodes of mild TBI at different time points over a 4-month period. The first 3 traumas were considered by the athlete to be minor, and thus were not reported to medical personnel. The fourth trauma was a medically diagnosed concussion. Over the next year, the patient presented with failure of physical growth, stagnation of soccer abilities and physical skills, and lower energy levels. After a full battery of endocrine tests, the diagnosis was compatible with hypopituitarism (GH, ACTH, and thyroid-stimulating hormone [TSH] deficiencies).

In 2008, Tanriverdi et al.66 investigated the pituitary function in 61 retired or active amateur boxers. The findings were similar to those in previous studies, with 15% and 8% of GH and ACTH deficiency, respectively, among boxers. An interesting fact is the lower rate of hypopituitarism in active boxers (18%) than in retired boxers (47%).

All of these findings suggest that sports-related repetitive TBI has a cumulative effect on the development of pituitary dysfunction.

**Pathophysiological Mechanisms of Hypopituitarism**

Hypopituitarism was first described in 1914 by Simmonds.57 It is defined as an inability of the pituitary gland to provide sufficient hormones adapted to the needs of the human body. The classic cause of hypopituitarism is pituitary tumor (in 61% of cases).55

**Anatomical Vulnerability of the Pituitary Gland**

The pituitary gland is located in the sella turcica in the skull base. It measures 8 × 10 mm and weighs less than 1 g. It is tethered to the hypothalamus by the pituitary stalk (infundibulum), which inserts on its superior surface. It is separated from the suprasellar cistern by the diaphragma sellae. The ICAs are the primary blood supply for the adenohypophysis and neurohypophysis. Blood reaches the anterior pituitary by means of long hypophysial portal vessels (branches of the ICA and anterior circle of Willis) and short hypophysial portal vessels (branches of the intracavernous ICA and the inferior hypophysial artery) via the pituitary stalk. The long portal vessels provide 70%—90% of its blood supply, whereas the short portal vessels provide less than 30%.

The confined location within the bony sella, the delicate infundibular hypothalamic structures, and the vulnerable blood supply of the pituitary gland may be responsible for the vulnerability of the pituitary to mechanical trauma.

J. Dubourg and M. Messerer
Hypopituitarism and sports

The Most Common Theories

The pathophysiological mechanisms of hypopituitarism after TBI remain incompletely understood. However, several mechanisms have been evoked to explain pituitary dysfunction, such as hypoxic insult or direct mechanical injury to the hypothalamus, pituitary stalk, or pituitary gland; compression from hemorrhage, edema, or increased intracranial pressure; and vascular injury to the hypothalamus or the pituitary gland.

In the 1960s, Ceballos and Kornblum and Fisher provided descriptions of pituitary lesions after fatal head injury. In a total of 202 patients from these 2 reports, 26% of the specimens were normal, 59% had capsular hemorrhage, 31% posterior lobe hemorrhage, 22% anterior lobe necrosis, 17% stalk hemorrhage, and 3% stalk necrosis.

Ischemic injury of the pituitary gland, due to secondary insults from hypotension, hypoxia, anemia, and brain swelling, can occur and compromise the integrity of the gland. Necrosis processes seem to be due to the vulnerability of the long hypophysial portal vessels when they pass through the diaphragm sellae, where they are particularly vulnerable to mechanical compression from both brain and pituitary swelling and direct stalk injury.

Direct injury of the pituitary gland, pituitary stalk, and/or hypothalamus can be caused by the following mechanisms: rotational and shearing injuries of the brainstem and hypothalamic-pituitary axis, and fractures through the skull base and sella turcica. This direct injury also can be reinforced by subsequent hemorrhage into the sella turcica or into the pituitary gland.

Antibodies Theory

Goudie and Pinkerton first suggested that autoimmunity could play a role in affecting the pituitary gland, by describing the first case of lymphocytic hypophysitis in 1962. Some studies have shown the presence of antibodies in patients with selective idiopathic hypopituitarism and in patients with autoimmune endocrine diseases. Also, animal studies have shown a possible role of autoimmunity involving the hypothalamic-pituitary region and triggered by head trauma.

In a preliminary study, in 2008, Tanriverdi et al. investigated the presence of APAs in 29 patients with TBI 3 years after head trauma, and in 60 age- and sex-matched normal controls. The APAs were detected in 44.8% of TBI patients but in none of the controls. Furthermore, the hypopituitarism ratio was significantly higher in APA-positive patients (46.2%) than in APA-negative patients (12.5%) (p = 0.04). There was also a significant positive correlation (r = 0.74) between high APA titer ratio and low peak GH response to the GH-releasing hormone plus GH-releasing peptide—6 test.

Subsequently, the same team investigated the presence of APAs and AHAs in active or retired amateur boxers who were exposed to sports-related repetitive head trauma. The patient population contains the same participants as in one of their previous studies (61 active or retired boxers), plus 60 normal controls of similar age and sex. In boxers, AHAs and APAs were found in 21.3% and 22.9% of cases, respectively. Antibodies were found in none of the control patients. The hypopituitarism ratio was significantly higher in AHA-positive boxers (46.2%) than in AHA-negative boxers (10.4%) (p = 0.003). However, in contrast to findings in the study on TBI and APAs, there was no significant difference between APA-positive and APA-negative boxers with regard to hypopituitarism.

Involvement of Genetic Polymorphisms

Genetic polymorphisms have been recognized as playing a role in CNS disorders. Apolipoprotein E is one of the most abundant proteins in the hypothalamic-pituitary region. Tanriverdi et al., in a preliminary study, investigated the relationship between ApoE polymorphism and TBI-induced hypopituitarism. This study included 93 patients with TBI (61 with sports-related head trauma and 32 in road traffic accidents) and 27 healthy controls. The ratio of hypopituitarism after TBI was significantly lower in patients with ApoE-ε3/ε3 (17.7%) than in those without ApoE-ε3/ε3 (41.9%; p = 0.01). Thus, the ApoE-ε3/ε3 genotype may decrease the risk of hypopituitarism after TBI.

Issues, Prevention, and Recommendations

Issues of Mild TBI-Related Hypopituitarism

On the one hand, symptoms of pituitary dysfunction can be masked by identical postconcussion symptoms or overshadowed by other symptoms. Thus, symptoms of hypopituitarism may not show up until several years after trauma. Furthermore, at the time of concussion, only approximately 10% of athletes are rendered unconscious. That is why this complication may be undiagnosed in many patients with mild TBI. Because most sports participants are young adults with near-normal life expectancy, the implications of undiagnosed postconcussion pituitary dysfunction can be dramatic. Although reports have increased, concussions are not recognized as serious injuries or are not consistently identified by athletic training staff.

On the other hand, many questions persist, especially regarding the exact pathophysiological mechanisms of hypopituitarism in sports-related head trauma. The curr
rent hypotheses seem synergistic, and seem to play a different role in the function of the mechanism and severity of the TBI. Indeed, sella turcica fractures and brain swelling might be related to severe TBI and cause immediate pituitary dysfunction. Severe brain injuries can occur in sports, such as the “knockout” in boxing, but mild TBI is more frequent. Autoimmunity might play more of a role in the long term. Time and repeated trauma seem also to play an important role, because pituitary dysfunction is more frequent in retired boxers than in active ones.

Thus, further multidisciplinary and multicenter studies are warranted to clarify all these possible mechanisms and their role in each type of TBI, and to produce clear recommendations.

Prevention and Recommendations

The potential long-term consequences of repetitive head trauma sustained in high-contact sports have been known for years. Although clearly criticized by the medical community, because of the possible damage to health that can be induced, certain sports such as boxing remain authorized and very common worldwide. This increasing problem has led to the release of several consensus guidelines on concussion management in sports. For instance, the American Collegiate Athletic Association and the American Academy of Neurology have established clear guidelines and management plans for concussion. However, several fundamental issues remain, as follows: the difficulty of the recognition of a concussive event by medical staff, the recognition and understanding of short- and long-term sequelae; the management of each stage; and the establishment of proper action to mitigate effects of the injury. Therefore, sponsors of sports programs should be fully involved and should design and maintain an injury-prevention program. Furthermore, regulatory controls, educating participants, designing specialized protective products, and monitoring injury frequency are evidently necessary.

As mentioned, many means of prevention exist. However, there are no specific recommendations on hypopituitarism in sports-related head trauma; thus, further research is necessary.

Pending these recommendations based on evidence, Tanriverdi et al. recommend the routine investigation of pituitary function in retired athletes who had participated in contact sports, and also in athletes who have a history of concussion or who have clinical findings suggesting pituitary hormone deficiencies.

Conclusions

Current knowledge clearly supports the proposition that sports, especially combat sports, are a cause of hypopituitarism, particularly isolated GH deficiency. Therefore, the medical community should be aware of this, and participants in sports who were exposed to chronic repetitive TBI should be screened. However, further multicenter and multidisciplinary studies are required to explore the details of pathophysiological mechanisms and to produce accurate prevention recommendations and guidelines on hypopituitarism in sports-related head trauma.
27. Escamilla RF, Liesser H: Simmonds disease. A clinical study with review of the literature; differentiation of anorexia nervosa by statistical analysis of 595 cases, 101 of which were proved pathologically. *J Clin Endocrinol Metab* 2:65–96, 1942
50. Nishida Y, Yoshioka M, St-Amant J: The top 10 most abundant transcripts are sufficient to characterize the organs functional specificity: evidence from the cortex, hypothalamus and pituitary gland. *Gene* 344:133–141, 2005


---

Manuscript submitted July 14, 2011. Accepted August 22, 2011. Address correspondence to: Mahmoud Messerer, M.D., Département des Neurosciences Cliniques, Service de Neurochirurgie, Centre Hospitalier Universitaire Vaudois, Rue du Bugnon, 21, 1011 Lausanne, Switzerland. email: m.messerer@laposte.net.