Research Progress on Effects of Craniocerebral Trauma on Pituitary Function

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DOI: 10.32629/jcmr.v5i4.3316

Abstract: Traumatic brain injury presents a significant public health challenge, with far-reaching implications for the well-being of those. In recent years, there has been increasing attention to the decline in pituitary function following traumatic brain injury, which has gradually emerged as a major contributing factor to mortality and disability among young individuals experiencing such injuries. Concurrently, hypopituitarism, characterized by inadequate secretion of pituitary hormones, is a common complication following traumatic brain injury. However, the clinical manifestations of hypopituitarism have been shown to be a major contributing factor to mortality and disability among young individuals experiencing such injuries. However, the clinical manifestations of hypopituitarism lack specificity and can easily be confused with other potential post-traumatic complications. However, the clinical manifestations of hypopituitarism lack specificity and can easily be confused with other potential post-traumatic complications. Consequently, hypopituitarism following traumatic brain injury is prone to misdiagnosis or underdiagnosis. This article provides a comprehensive review of the current clinical diagnosis and research progress regarding post-traumatic pituitary function and associated hormone changes.
***Keywords*:** Craniocerebral injury; Pituitary; Pituitary function changes.

1. Introduction

Craniocerebral injury (CBI) is common in neurosurgery and termed the "silent epidemic" due to high disability and death risks[1-4]. Post-traumatic hypopituitarism is a major cause of death/disability in young TBI patients, a global issue. ~62% of TBI deaths are from complications; ~55% of CBI patients have internal imbalance from neuroendocrine dysfunction in acute/recovery phases[5-6]. Severe neuroendocrine disorders can delay CBI recovery or cause death. After moderate-severe TBI, patients have physical changes and neuropsychiatric symptoms (once "postconcussive syndrome"). Endocrine and internal environment need attention in CBI diagnosis/management. Pituitary glands respond variably to acute trauma, altering hormone levels and target organ activity. Blood glucose fluctuates; neuroendocrine regulation stabilizes the internal environment and ensures normal organ function[7-8].

2. Mechanisms of altered pituitary function following craniocerebral trauma (specific)

The mechanism of altered pituitary function after craniocerebral trauma is not well understood, and the following hypotheses have been proposed.

2.1 Vascular theory

Because of its anatomic location, brain swelling, increased intracranial pressure, skull base fractures, and shear forces are more likely to affect the long portal vessels supplying the anterior pituitary gland, resulting in direct injury to the pituitary gland. When the injury involves the pituitary stalk, the blood supply to the pituitary portal vessels may be interrupted, leading to necrosis of the pituitary tissue, which in turn may lead to alterations in the normal function of the pituitary gland[9].

2.2 Ischemic/hypoxic hypothesis

Following traumatic brain injury, the body may experience a variety of physiological responses, such as a decrease in blood pressure (hypotension), a decrease in oxygen content of the blood (hypoxemia) and an increase in intracranial pressure (intracranial pressure). In addition, changes in intracerebral blood flow and metabolic disturbances may occur. These complex pathophysiological changes may lead to ischemic or hypoxic injury to the pituitary gland [10], which is the result of inadequate blood or oxygen supply to the pituitary tissue. In addition, the release of blood metabolites and inflammatory substances following traumatic brain injury can lead to vascular stenosis (vasospasm), which can exacerbate

pituitary ischemia and hypoxia. This cascade of events ultimately leads to significant changes in pituitary function, affecting its ability to regulate hormone production and other important functions.

2.3 The doctrine of genetic susceptibility

The hypothalamic-pituitary region is rich in ApoE, a key protein in the nervous system that enhances lipid transport and metabolism and plays a critical role in neuronal membrane repair mechanisms. In patients with craniocerebral trauma, ApoE expression is upregulated and accelerates the onset and progression of neuroinflammation. ApoE polymorphisms are associated with pituitary dysfunction after traumatic brain injury. Also, Karaca et al. found that the E2/E3 genotypes of ApoE were associated with altered pituitary function, suggesting an association between ApoE polymorphisms and pituitary dysfunction in patients with craniocerebral trauma.11 In addition, Karaca et al. found that the E2/E3 genotypes of ApoE were associated with pituitary function in patients with craniocerebral trauma.

2.4 Autoimmune theory

A study by Guaraldi et al.[12] found that elevated titers of anti-pituitary (APA) and anti-hypothalamic (AHA) antibodies were associated with persistent pituitary dysfunction in patients with craniocerebral trauma during both the acute and chronic phases of the disease. In particular, there is an increased risk of growth hormone and gonadotropin deficiency. Therefore, it can be hypothesized that when patients with craniocerebral trauma undergo autoimmune changes, this may lead to altered pituitary function [13].

2.5 Inflammatory response doctrine

Neuroinflammatory response is one of the important secondary injury mechanisms after craniocerebral trauma, and its persistence and spread may lead to persistent nerve degeneration and injury. After craniocerebral trauma, the blood-brain barrier is disrupted, leading to a significant increase in circulating neutrophils, macrophages, and lymphocytes, and immune cells are recruited to the site of injury, activating neurons, microglia, and neuroglial cells, inducing the release of a variety of deleterious cytotoxic substances including proinflammatory factors and metabolites, and exacerbating neuronal damage.

In this case, the brain tissue may be necrotic or apoptotic. At the same time, undamaged brain tissue may also release cytotoxic substances, causing peripituitary vascular spasm, which can aggravate pituitary ischemia and lead to changes in pituitary function[13-14].

3. Factors causing changes in pituitary function after craniocerebral trauma

In clinical practice, the Glasgow Coma Scale (GCS) is commonly used to assess the severity of traumatic brain injury. In the acute phase of traumatic brain injury, prolactin levels are inversely related to the GCS, whereas cortisol and male testosterone levels are positively related to the GCS.[15] A meta-analysis conducted by Schneider et al. showed that the prevalence of pituitary alterations in patients with mild, moderate, and severe traumatic brain injury was 16.8%, 10.9%, and 35.3%, respectively.[16] Therefore, in patients with severe traumatic brain injury, pituitary alterations are more common than those with severe traumatic brain injury. Therefore, patients with severe traumatic brain injury are more likely to have altered pituitary function.

(1) Liang Guanqin et al[16]. found that in the mid-to-late stages of the disease, subarachnoid hemorrhage (causing CSF circulation impairment, increased ICP, hydrocephalus, pituitary gland compression, vasospasm, and ischemia-hypoxia), cerebral herniation, skull base fracture (directly or indirectly damaging the pituitary gland and its vessels), and a GCS score > 5 are significant risk factors for pituitary hormone dysfunction.

(2) Pituitary hormone, a protein hormone crucial for bodily function regulation, can have its binding protein metabolism altered by drugs like hormones, tranquilizers, and certain painkillers (e.g., fentanyl, pethidine, sufentanil, eplerenone, diazepam), causing pseudopituitary dysfunction[17]. In traumatic brain injury, drugs like Advil used to reduce agitation may disrupt neuroendocrine function. Oltmanns et al noted secondary epinephrine related to opioid use and potential adenohypopituitary insufficiency risk, but tapering fentanyl doses improved the hypothalamic-pituitary-adrenal axis, indicating opioids' inhibitory effect on the body's response to noxious stimuli[18]. Considering these drug effects on neuroendocrine function, especially in TBI, is vital for minimizing adverse impacts on hormone regulation and physiological homeostasis[19].

4. Detection and diagnosis of hypopituitarism after craniocerebral trauma

The methods for detecting hypopituitarism and the thresholds for abnormality are not clearly defined, but in general the following methods can be considered.

(1) With respect to the growth hormone-insulin-like growth factor-1 (GH-IGF-1) axis, a certain diagnosis can be made

by means of stimulation tests. The insulin tolerance test is the main diagnostic criterion for GH in the absence of GH and has a high degree of specificity. The diagnosis can be made with a post-stimulation GH peak of <3 ng/ml (but is not suitable for those with severe cardiovascular disease or history of epilepsy)[19]. The growth hormone-releasing hormone + arginine test is commonly used in the clinic and has fewer complications, but is less specific. The GRH+GRP-6 test is more rigorous and reliable, and is less susceptible to the effects of GH hormone secretion. For example, in obese patients, a GH peak <10 g/L is diagnostic, >20 g/L can be ruled out, and an additional stimulation test is needed if it is between 10 and 20 g/L.

(2) Detection of the adrenal axis can be diagnosed by testing basal cortisol levels. When the basal cortisol level is below At 50 nmol/L, hypopituitarism can be diagnosed. If the basal cortisol level is higher than this value, a stimulation test, such as the ACTH stimulation test or the insulin tolerance test, is required. Hypopituitarism can be diagnosed when the post-stimulation cortisol concentration is less than 550 nmol/L[20].

(3) For the diagnosis of the thyroid axis,in addition to basal hormone levels, thyroid antibody levels and thyroid ultrasonography can be considered as adjunctive tests, and a comprehensive analysis of these indicators can provide a more comprehensive assessment of the patient's thyroid function. Hypopituitarism is diagnosed when the serum free thyroxine level is less than 12 pmol/L and the serum thyrotropin hormone (TSH) level is normal or low. In addition, the patient's clinical symptoms and history of disease should be taken into account to fully assess pituitary function[21].

(4) The diagnosis of hypopituitarism can be made by measuring the levels of testosterone (in males) or estradiol (in females), as well as the levels of gonadotropins (FSH) and luteinizing hormone (LH)[22]. Testosterone levels below 9.9 nmol/L in men and amenorrhea or luteinizing hormone below 1.7 U/L in women. Follicular spiking hormone is below 1.5 U/L in the premenopausal stage and below 1.5 U/L in the postmenopausal stage.

These indicators can be used as part of the diagnostic criteria for hypopituitarism and hypogonadotropic hypogonadism, as well as LH below 15 U/L.

(5) In the PRL axis, hyperprolactinemia may present with symptoms such as menstrual disorders, breast enlargement, and sexual dysfunction[23]. Therefore, when the PRL is higher than normal, further investigations may be considered to determine whether abnormalities of the pituitary-prolactin axis are present[24].

5. Analysis of risk factors associated with altered pituitary function following craniocerebral trauma

5.1 Effect of brain herniation on hypopituitarism after craniocerebral trauma

Brain herniation seriously affects patients after craniocerebral trauma, resulting in severe displacement of brain tissue and a series of life-threatening signs and symptoms such as impaired consciousness, dilated pupils, and hemiparesis[25]. Emergency treatment is required, otherwise the patient's life will be jeopardized[26].

5.2 The effect of diffuse brain swelling on hypopituitarism after craniocerebral injury

Clinical studies have found that diffuse cerebral swelling can be caused by a variety of reasons, including acute cerebral vasodilatation in the pontine nucleus accumbens, midbrain reticular formation, hypothalamus, hypoxia, and shock due to rotational force. All of these conditions can affect pituitary function in patients after craniocerebral trauma[27]. Meanwhile, GCS<10 or diffuse brain swelling on CT/MRI in the first patients are important predictors of pituitary hypopituitarism[28].

5.3 Effects of midline structural displacement on hypopituitarism after craniocerebral trauma

In cranial anatomy, the cranial cavity is divided by the falx and the cerebellar vermis into left, right, and infratentorial cavities, which communicate with each other by means of the infratentorial foramen and the cerebellar vermis fissure. Cranial CT shows that subfalciform and even axial displacement of the brainstem can occur when intracranial pressure is unevenly increased, demonstrating possible displacement of the hypothalamus/pituitary gland, which can lead to mechanical damage [29].

5.4 Impact of Skull Base Fractures on Hypopituitarism after Craniocerebral Trauma

The anatomy of the pyriform region is complex, and in addition to the many cerebral nerves and blood vessels that pass through it, it also houses the pituitary gland and pituitary stalk, and the pituitary hilar system is connected to the pituitary gland through the saddle diaphragm[30]. When a fracture extends into the saddle region, mechanical damage to the pituitary stalk and pituitary gland can occur, resulting in compromised pituitary function[31-32].

6. Treatment of hypopituitarism following craniocerebral trauma

After receiving hormone replacement therapy, patients with hypopituitarism showed a significant improvement in

disability scores compared to pre-treatment.

This improvement emphasizes the beneficial effect of hormone replacement therapy on the rehabilitation of hypopituitarism patients[33]. This improvement emphasizes the beneficial effects of hormone replacement therapy on the recovery of patients with hypopituitarism.33 It is important to note that hypopituitarism can occur as a consequence of craniocerebral trauma, and the clinical symptoms are often very similar to the complications associated with such trauma. Unfortunately, this similarity can lead to misdiagnosis and prevent patients from receiving appropriate alternative treatments [34]. After traumatic brain injury, hypopituitarism is a key factor in the sequelae of the patient, affecting neurobehavioral deficits and recovery of quality of life[35].

Hormone replacement therapy is the standard for hypopituitarism post-cranial trauma, usually effective in reversing it and improving outcomes. Some patients may have temporary, mild hypopituitarism after trauma. Early prediction and diagnosis of chronic pituitary hypothyroidism are vital for effective treatment and better prognosis[36]. Craniocerebral trauma complexly affects the pituitary system; the hypothalamic-pituitary axis is crucial. Pituitary insufficiency from such injury harms patients. Definitive diagnosis and timely treatment are key to minimizing complications[37].

7. Summary and outlook

The study of pituitary function after craniocerebral trauma still has many aspects that need to be further investigated, including further exploring the association between the theories of mechanism and other possible mechanisms (e.g., neurological injury and inflammation), strengthening large-sample epidemiological studies to clarify the specific roles of various factors on pituitary function, improving the sensitivity and specificity of the existing methods of diagnosis and testing (especially for the different axes), studying the mechanisms of the related risk factors in depth to better In the future, we will focus on exploring mechanisms, individualized treatment, diagnostic tests, and comprehensive treatment, in order to provide patients with better strategies to improve their quality of life and recovery.

Acknowledgments

This paper was supported by the following fund project: 2023 Development and Regeneration Key Laboratory of Sichuan Province Open Project (23LHNBZYB17).

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