INTERNATIONAL JOURNAL OF INTEGRATIVE AND MODERN MEDICINE

Pathophysiology of TBI-Associated Hypopituitarism

Rakhimova Gulnoz Shamsievna
Assistant of the Department of Pathological Physiology of the Bukhara State Medical Institute

Abstract: Hypopituitarism associated with traumatic brain injury (TBI) has been considered a clinical condition for more than a century, since the first case was reported in 1918. Since 2000, several studies have convincingly proven that TBI-mediated pituitary hormone deficiency may be more common than previously thought. As a result of several studies, it has been seriously suggested that pituitary hormone deficiency mediated by TBI may be more common than previously thought. Gonadal hormone deficiency is the most common condition, followed by growth hormone deficiency, hypothyroidism, cortical hypofunction, and diabetes insipidus. Elucidating the pathophysiology of hypopituitarism, especially hypogonadism, is a real challenge for medicine.

Keywords: traumatic brain injury, hypopituitarism, hypogonadism, pathophysiology.

Traumatic brain injury is a heterogeneous disease. There are many ways to classify patients based on both the clinical severity and the pathophysiological mechanism of injury.

The pathophysiological mechanisms underlying pituitary injury in patients with TBI include primary damage leading to direct damage to the hypothalamus or pituitary gland, while secondary damage is mainly due to the interaction of a complex, ongoing cascade of specific molecular/biochemical events. The severity of a clinical condition is usually assessed using special severity scores; The Glasgow Coma Scale (GCS) is most commonly used, which evaluates three neurological areas (eye opening, best verbal response, best motor response) and evaluates TBI as mild (GCS 13-15), moderate (GCS 9-12) or severe (GCS $\leq$ 8).

The pathophysiology of traumatic brain injury is usually divided into two categories: primary brain damage and secondary brain damage.

Primary traumatic brain injuries occur as a result of the impact of mechanical external forces transmitted to the intracranial contents at the time of injury. Pathological consequences of primary traumatic brain injury include rupture of white matter tracts (also known as diffuse axonal injury), focal bruises/cerebral hemorrhages and focal extraaxial hematomas/hemorrhages (epidural hematoma, subdural hematoma, subarachnoid hemorrhage, intraventricular hemorrhage).

Primary damage is followed by a complex and continuous chain of events called secondary brain damage, which leads to extensive and persistent damage. Pathology is caused by complex interacting mechanisms, including, in particular, neurotransmitter excitotoxicity, secondary ischemia (due to secondary vascular damage, for example, vasospasm or local microvascular obstruction) and inflammatory reactions. Ultimately, these damage mechanisms lead to the death of neurons, swelling of the brain and increased intracranial pressure, which further exacerbates brain injury.

From a general point of view, the pathophysiological mechanisms underlying pituitary injury in patients with traumatic brain injury are similar to those described for traumatic brain injury as such.

Primary injuries occur as a result of direct trauma to the hypothalamus or pituitary gland or the compressive effects of surrounding structures; in addition, primary injuries can lead to severing of the pituitary pedicle, especially in cases of fractures of the base of the skull.

Secondary injuries, on the other hand, are mainly caused by the interaction of a complex and continuous cascade of specific molecular/biochemical events.

As already mentioned, one of the three main mechanisms of secondary brain damage after head injury is excitotoxicity. Excitotoxicity is caused by abnormal levels of excitatory neurotransmitters (mainly

glutamate), which are released uncontrollably in patients with traumatic brain injury. In high concentrations, these neurotransmitters act as excitotoxins and affect ion channels, which leads to disruption of electrolyte shifts between intracellular and extracellular spaces and changes in the permeability of the cell wall. Another mechanism of secondary brain damage after traumatic brain injury is ischemia. In general, pituitary-specific ischemic stroke is likely to be based on the same pathophysiological events as in the brain. However, some features related to the specific vascularization of the hypothalamic-pituitary region still deserve discussion. It is known that the anterior pituitary receives blood supply from the hypothalamic-pituitary portal circulation, which probably exposes the pituitary gland to a greater risk of ischemic damage. In particular, the long portal vein of the pituitary gland is, in fact, the only vascular source for the lateral and nodular parts (where the cells secreting mainly GH, PRL and FSH/LH are located). Instead, the anterolateral part and the central wedge (where mainly TTH and ACTH-secreting cells are located) are supplied with a mixture of both long and short pituitary portal veins. Thus, the hypothesis of susceptibility to ischemia is probably one of the most plausible explanations for the differential frequency of damage to the pituitary axis after TBI. Indeed, the most vulnerable axes (GH and FSH/LH) are those whose blood supply depends solely on the long portal vein of the pituitary gland, and they themselves are susceptible to vascular damage; on the contrary, the most stable axes (ACTH and TTH) are those whose blood supply is carried out from both the long and short portal veins the pituitary gland.

The third and last major mechanism underlying the pathophysiology of secondary pituitary injury after injury is inflammation. Some mechanisms of inflammation affecting the pituitary gland after traumatic brain injury are likely similar to the general mechanisms of inflammation, which are known to affect the entire parenchyma of the brain, with uncontrolled and self-sustaining release of inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α). The mechanism is similar to that in the pituitary gland.

In addition, pituitary-specific inflammatory mechanisms may be associated with autoimmunity and, in particular, with the presence of antihypothalamic antibodies (ANA) and/or antihypothalamic antibodies (ARA). It has been shown that in patients with a history of traumatic brain injury, the positive level of these antibodies is higher (from 44 to 60%, depending on the study) than in healthy people (0%). In the cohort of subjects who suffered chronic repetitive head injury during amateur boxing, higher rates of positive antibodies to AHA (21%) and APA (23%) were also found compared with the control group (0%). In addition, various authors have demonstrated a statistically significant correlation between AHA and/or APA positivity and post-traumatic hypopituitarism in trauma patients, with the odds ratio (OR) varying from 2.2 to 8.5 depending on the study. Thus, given these results, it can be assumed that autoimmunity is involved in the etiology of hypopituitarism caused by TBI: the occurrence of AGA and/or APA production is probably associated with exposure to the hypothalamus and/or pituitary gland and the release of antigens that would otherwise not be exposed is associated with the release of antigens that otherwise the case would not have been exposed. Despite the above association, the available data are insufficient to establish whether AHA/APA positivity actually plays an active pathophysiological role in the spread/maintenance of pituitary disorders associated with TBI, or whether it is simply a concomitant phenomenon of exposure to hypothalamic-pituitary antigens due to necrotic changes in these areas after TBI is clearly insufficient to establish is that so.

Finally, another potential mechanism of pituitary-specific regulation of inflammation may be related to a person's genetic predisposition. In the general context of traumatic brain injury, it has been widely shown that ApoE polymorphisms are associated with various clinical outcomes after traumatic brain injury, such as the onset of seizures, duration of coma, and subsequent neurobehavioral recovery. Indeed, ApoE is an important protein that promotes the transport and metabolism of lipids in the nervous system and plays a role in the repair and maintenance of neurons. In the specific context of post-traumatic hypopituitarism, a study by Tanriverdi et al. confirmed the possible role of ApoE polymorphism in neuroendocrine outcomes; in particular, in this study, the ApoE3/E3 genotype with an estimated OR of 0.29 protects against the development of posttraumatic pituitary dysfunction. A possible protective role is indicated.

References:

1. Gasco V, Cambria V, Bioletto F, Ghigo E, Grottoli S. Traumatic Brain Injury as Frequent Cause of Hypopituitarism and Growth Hormone Deficiency: Epidemiology, Diagnosis, and Treatment. Front Endocrinol (Lausanne). 2021;12:634415.
2. Tanriverdi F, De Bellis A, Bizzarro A, Sinisi AA, Bellastella G, Pane E, et al. Antipituitary antibodies after traumatic brain injury: Is head traumainduced pituitary dysfunction associated with autoimmunity? Eur J Endocrinol (2008) 159(1):7–13.
3. Mele C, Pingue V, Caputo M, Zavattaro M, Pagano L, Prodam F, Nardone A, Aimaretti G, Marzullo P. Neuroinflammation and Hypothalamo-Pituitary Dysfunction: Focus of Traumatic Brain Injury. Int J Mol Sci. 2021 Mar 7;22(5):2686.
4. Shamsievna R. G. Modern Aspects of Studying the Features of Morphofunctional Characteristics of Testes under Various Factor Influences //Eurasian Scientific Herald. – 2022. – Т. 7. – С. 279-286
5. Sh R. G. Experimental modelling of traumatic brain injury in white rats //Тиббиётда янги кун. – 2021. – Т. 2. – №. 34. – С. 197-200.
6. Rakhimova G. Sh. The Importance of Proteinuria as a Predictor of Diagnosis Risk Factor for Chronic Kidney Disease// The Pharmaceutical and Chemical Journal. – 2021. – Т. 8. - №. 1. – С. 79-81.
7. Rakhimova G. MODELING OF ACUTE TRAUMATIC BRAIN INJURY IN WHITE MONGREL RATS //Академические исследования в современной науке. – 2022. – Т. 1. – №. 19. – С. 206-208.
8. Shamsievna, R. G. (2023). The Leading Mechanisms of the Pathophysiology of Traumatic Brain Injuries. *Scholastic: Journal of Natural and Medical Education*, *2*(3), 115–119.
9. Shamsievna R. G. Secondary Tissue Damage in Acute Traumatic Brain Injury //Web of Synergy: International Interdisciplinary Research Journal. – 2023. – Т. 2. – №. 5. – С. 469-473.
10. Shamsiyevna, Raximova Gulnoz. "O'tkir Bosh Miya Shikastlanishidan Keyingi Gipopituitarizmda Skrining Mezonlari." *AMALIY VA TIBBIYOT FANLARI ILMIY JURNALI* 2.5 (2023): 239-242.
11. G. Sh., R. (2023). Morphometric Studies of the Testes of White Mongrel Rats in the Acute Stage of Traumatic Brain Injury. *International Journal of Integrative and Modern Medicine*, *1*(2), 57–60.
12. Sh R. G. Assessment of the Mechanisms of Vertebrogenic Lumbar Chronic Pain Syndrome //International Journal of Formal Education. – 2023. – Т. 2. – №. 12. – С. 541-545.
13. Рахимова Г. Ш. ВКЛАД ТРУДОВ ИБН СИНЫ В РАЗВИТИЕ МЕДИЦИНЫ И В ЧАСТНОСТИ КАРДИОЛОГИИ //AMALIY VA TIBBIYOT FANLARI ILMIY JURNALI. – 2024. – Т. 3. – №. 4. – С. 1-5.
14. Shamsievna R. G. The Contribution of Ibn Sina's Works to the Development of Medicine and in Particular Cardiology //Best Journal of Innovation in Science, Research and Development. – 2024. – Т. 3. – №. 4. – С. 19-22.
15. Hohl A, Mazzuco TL, Coral MH, Schwarzbold M, Walz R. Hypogonadism after traumatic brain injury. *Arq Bras Endocrinol Metabol*. 2009;53(8):908-914.