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Mini Review

Hypopituitarism Post-Traumatic Brain Injury

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Hypopituitarism Post-Traumatic Brain Injury

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Abstract
Traumatic brain injury often causes disability and death among adults and children. The injury may have a significant long-lasting effect to the neuroendocrine system. One of the most common effects is hypopituitarism. It can affect the quality of life and increase healthcare burden. This review is made to understand the hypopituitarism post-traumatic brain injury. The review was done by searching journal literature published in the last 10 years. Hypopituitarism can be found in the acute or chronic phase. Sometimes patients come with specific symptoms such as amenorrhea, infertility, precocious puberty, or even diabetes insipidus. A severe case of Addisonian crisis patient may end in an intensive care unit. Hypopituitarism post-traumatic brain injury will impair rehabilitation. Therefore, traumatic brain injury patient should be assessed for pituitary function examination in 6-12 months post injury to prevent further deterioration and improve the quality of life.

Keywords: Traumatic brain injury; Neuroendocrine; Hypopituitarism.

1. INTRODUCTION

Traumatic brain injury (TBI) is caused by direct blow or inertial forces during relative head–brain movement. It is usually related to sports accident, physical abuse, motor vehicle accident, military conflict, or terrorist activity [1]. High-risk sports are boxing, football, martial arts, motor racing, roller skating, and cycling [2]. Approximately, 52,000 TBI patients died in the United States [1].

Neuroendocrine dysfunction following TBI was approximately 23-60% in adults and 15-21% in children [3]. Hypopituitarism occurs in 35-40% of the TBI cases [4,5]. Integrity and functioning impairment of hypothalamic–pituitary structures might cause temporary and permanent neuroendocrine impacts and morbidities [3].

World Health Organization (WHO) predicted that TBI will become the third leading cause of death and disability in the world by 2020. Pathophysiological mechanisms in the post TBI can be divided into primary and secondary damage cascades. Primary injury happens in the initial phase. It is refractory to most treatments. Meanwhile, secondary cascade happens due to neuronal apoptosis, neuroinflammation, necrosis, and massive gliosis. It is more treatable and sometimes preventable [4].

2. NEUROENDOCRINE DYSFUNCTION

Inertial forces due to rapid acceleration–deceleration and rotation of the brain may cause diffuse axonal injury, axonal swelling, and disconnection [1]. Diffuse TBI is often unseen through CT or MRI [6]. Approximately, 70-75% of the TBI cases were diffuse lesion; meanwhile, the remaining cases were local and diffuse TBI. Sometimes, there might be a retraction ball formed by severing axon in severe TBI cases. The most common form of TBI is secondary axotomy. It is the secondary swelling and disconnection in the axon, due to intracellular protein and organelles accumulation along the axon. In microscopic examination, it is identified as diffuse axonal injury. Thus, downstream axonal segments will have Wallerian degeneration, about 1-3 h post trauma, up to several months after [1].

Perifocal brain edema will decrease cerebral perfusion pressure. A deficit in cerebral perfusion leads to further ischemic lesion. Neuroglial cells will also be damaged. Thus, the contusion will get worsened [7].

Oxidative stress in the early post injury stages can cause synaptic malfunction and alter plasticity. Those pathologies continue over months and include the development of inappropriate new synaptic connections. These mechanisms are considered as etiology of functional morbidities and secondary injuries [8,9].

TBI cases cause immediate and short-term neuronal excitation in the upper to middle cortical layer. This might happen due to stress wave phenomena and alteration in ionic balance. A wave of cortical spreading depression might cause hyperpolarization and long-term presynaptic depression [10]. Some cognitive disorders evolved in TBI are attention deficit, learning and memory, and higher order executive functions. These conditions will lead to the development of neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, chronic traumatic encephalopathy, depression, accelerated cognitive decline,

and amyotrophic lateral sclerosis [9,11]. Verbal fluency score has persistent deterioration in chronic phase TBI.[10] At the end, TBI will cause secondary brain damage [12].

Hippocampus and neocortex are susceptible to TBI. They undergo synaptic reorganization consistent with changes between excitation and inhibition. Reduction in interneuron activity could deteriorate excitation/inhibition balance and thus sensory cortical deficit occurs. Functional or inhibitory cell diminish might compromise cortical information processing [1].

Glutamate excitotoxicity as a TBI secondary injury mechanism can alter dendritic outgrowth in the cortical neuron. Dendritic regression will induce abnormalities in the neurotransmitter system [1]. Increased extracellular glutamate level induces intracellular calcium overload. Excessive intracellular calcium level results in programmed cell death. This may happen through many special pathways such as calcineurin, protease, transcription factor, and DNA degrading endonuclease. Overproduction of those molecules leads to oxidative stress and proapoptotic gene activation [9]. Thinning of the right temporal lobe and left insular cortex was shown in recurrent TBI patients. The temporal lobe is associated with verbal fluency, and insular cortex is important is emotional processing [11].

3. HYPOPITUITARISM POST-TRAUMATIC BRAIN INJURY

Neurology and endocrine dysfunction in TBI patients were usually related to hypothalamic–pituitary structures. Hypopituitarism following TBI might happen due to a lesion of the pituitary gland, pituitary stalk lesion, or secondary effect of hypothalamus damage [13]. Hypophyseal portal vessels are susceptible to injury, such as from direct shearing forces, brain swelling and hemorrhage, vasospasm, and increased intracranial pressure [14]. A possible role of autoimmunity in post-traumatic hypopituitarism has been studied recently [15]. Apolipoprotein E haplotypes might also increase the risk of hypopituitarism [14]. Post-traumatic hypopituitarism in adult patients was approximately 3-254 months from the time of injury, and it was 1-115 months in children. The prevalence of hormonal dysfunction was 10.8-68.5% in adults and 16.67-61% in children [3]. The prevalence of hypopituitarism after TBI ranges from 5 to 90% [2].

Adrenal axis and posterior pituitary function should be assessed in the first two weeks post injury. The entire anterior and posterior pituitary function need to be focused in the subsequent months afterward. Growth hormone deficiency is the most common deficiency in hypopituitarism patients following TBI. Meanwhile, ACTH cortisol deficiency and salt and water imbalance are the most apparent conditions in the early phase [16]. Diabetes insipidus and central hypoadrenalism may be found in the acute-phase moderate and severe TBI. Chronic hypopituitarism can occur in 3 months or later after TBI. Those patients may develop typical hypothyroid symptoms such as weight gain, irregular menses, constipation, cold intolerance, depression, and neurocognitive dysfunction. Nevertheless, they usually do not have a goiter, which is in contrast to Hashimoto diseases patient. Hyperprolactinemia may occur in 11.8% of TBI patients [14].

Krahulik *et al.* [3] did retrospective studies of 58 patients after brain injury. They found that frequent complication of neurohypophysis disorder was diabetes insipidus (DI) and syndrome of inappropriate antidiuretic hormone (SIADH). In 45% of study patients, there was central hypothyreosis. Hypogonadotropic hypogonadism was revealed in 25% adolescence. The level of prolactin is increased in 35% of patients. Cortisol and ACTH level increased in 10% of patients [3]. Acute electrolyte disturbances might happen in severe cases and it was life threatening. These hormone disturbances showed normal findings in 3 months after injury in 56 of 58 patients [14].

The contributing factors in the accurate diagnosis of neuroendocrine dysfunction in TBI patients are the patients' age, medication taken (e.g., hormonal contraception, thyroid medication), and adaptation to hormonal level. Acute finding hormonal changes are usually transient and do not require specific treatment. Late unidentified hormonal changes (hypopituitarism) could significantly deteriorate the recovery phase [14].

Somatotropic and gonadotrophic hormones are affected in most cases. They are related to body growth and maturation. Menstrual cycle or pubertal development detainment might be a sign of post-traumatic dysfunction. However, precocious puberty could arise due to craniocerebral injury [18]. Amenorrhea in women and erectile dysfunction in men may urge patient to seek for medical evaluation. Hypogonadism and testosterone deficiency in males often accompanied by decreased energy, muscle weakness, and reduced lean body mass [13]. Growth hormone deficiency usually occurs in 15-21% of patients [16]. Patient with growth hormone deficiency may develop dyslipidemia, insulin resistance, poor stamina, central adiposity, and low bone mass [14]. Transient hormonal changes usually do not need any treatment, and they are merely an expression of adaptive changes [17].

Anabolic hormones such as thyroid-stimulating hormone (TSH), follicle-stimulating hormone, luteinizing hormone, and growth hormone often decline, thus primary organs metabolic resources are impaired. Brain, cardiovascular system, and kidney will have poor nutrition and circulation. Increasing stress hormone levels (prolactin and ACTH) will further deteriorate TBI and reduce the quality of life [13,16]. Persistent fear and depression may decrease the quality of life [18].

Adrenal insufficiency has some nonspecific symptoms such as fatigue (73%), weight loss, loss of axillary and pubic hair, myalgia, cramps, joint stiffness, and flexion contracture. Delayed diagnosis is common in this case. Sometimes, adrenal insufficiency cases are often diagnosed incorrectly as psychiatric, gastrointestinal disorders, rheumatic diseases, and neuromuscular diseases [19]. However, severe posterior pituitary damage may cause an Addisonian crisis that ends up in the intensive care unit [13].

4. SCREENING FOR HYPOPITUITARISM POST-TRAUMATIC BRAIN INJURY

Factors predisposition for hypopituitarism in TBI are severe brain injury (with Glasgow Coma Scale 3-8), brain imaging pathological finding (diffuse axonal injury and basal skull fracture), younger age, elderly, prolonged admission in ICU, water and mineral disturbance (SIADH, diabetes insipidus) during the early phase, and hypothalamus and pituitary gland pathological result for 12-24 months post brain injury [3,16]. Patients who develop post-traumatic seizures and brain hemorrhages have a higher risk for severe pituitary dysfunction [20]. The presence of antihypothalamus antibodies and antipituitary antibodies is associated with a higher incidence of pituitary dysfunction [21]. The patients with these conditions need to undergo screening for hypopituitarism post TBI.

Acute-phase cortisol deficiency post TBI is life threatening. Serial morning cortisol levels can be done to reveal this condition. A result below 300 nmol/l shows adrenal insufficiency. In the chronic phase assessment, patients should be assessed for their adrenal, thyroid, and gonadal axes at 3-6 months post TBI. Corticotrophin test (Synacthen test), thyroid function tests (free T4 and TSH), and sex steroids with anamnesis of menstrual history should be carried out. Adult patients and children need to be reevaluated at 2-6 months, and 1 year after TBI [14]. A further multidisciplinary prospective study is needed to characterize the onset and detail symptoms of hypopituitarism in TBI patients. Identifying the whole risk factors and deciding the best management for each TBI patient are crucial to improving the quality of life.

5. CONCLUSION

In conclusion, long-term hypopituitarism post TBI is difficult to deal with if it is found in the late phase. Post TBI patients should be monitored for every physical and physiological disturbance that might be related to hypopituitarism. A thorough examination should be carried out within 6-12 months post injury. Younger patients, the incidence of SIADH, diabetes insipidus, and pathological finding of brain structures are some red flag factors that need to be concerned in the possibility of hypopituitarism post TBI.

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