Pituitary dysfunction following a traumatic brain injury (TBI) at the desk of a General Practitioner

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Abstract

Traumatic brain injuries are among the serious causes that affect the health of many people around the world. There are many causes for traumatic brain injuries such as road traffic accidents, work-related accidents, sports activities, falls, and assaults. The injuries could cause transient or permanent pituitary dysfunction which affects a lot of body activities and may decrease significantly the quality of life of such victims. Diagnosis of pituitary dysfunction associated with brain injuries constitutes a real challenge for physicians. This review aims to discuss the current knowledge about this condition and simplify current recommendations to the busy general practitioner at his/her clinic.

Key words: Pituitary dysfunction, traumatic brain injury (TBI), general practitioners

Abbreviations

GH	Growth Hormone
TSH	Thyroid Stimulating Hormone
ACTH	Adreno-Cortico-Trophic Hormone
LH	Luteinising Hormone
FSH	Follicle-Stimulating Hormone
ADH	Anti-Diuretic Hormone
SIADH	Syndrome of Inappropriate Diuretic Hormone
CDI	Central Diabetes Insipidus
TBI	Traumatic Brain Injuries
PTHP	Post Traumatic Hypo-Pituitarism
APA	Anti-pituitary antibodies
AHA	Anti-Hypothalamic antibodies

Introduction

Traumatic brain injuries are the commonest cause of morbidity and mortality among adolescents in developed countries (1). Traumatic brain injuries have consequences that vary from acute physical disability to long-term cognitive, behavioural, social, and psychological defects (2). Hypopituitarism is not common but an important consequence of traumatic brain injuries (3). This condition was long time reported. It was reported 80 years ago in literature (1) but considered as a rare consequence. Recently studies have shown that traumatic brain injuries could cause hypothalamic-pituitary axis dysfunction and delayed recovery from brain injuries (4). Patients who faced moderate to severe head trauma are at increased risk of developing post-traumatic hypopituitarism (3). Studies showed that even mild trauma could cause post-traumatic hypopituitarism (1). Precise assessment and follow-up are necessary to detect post-traumatic hypopituitarism (1). Hormonal replacement therapy is important to improve the outcome and the quality of life (1). This review will discuss the epidemiology, causes, clinical presentation, investigations, and management of post-traumatic brain injury hypopituitarism.

Epidemiology

Post Traumatic Hypopituitarism is generally considered to be a medical problem for young people. Benvenga et al (5) studied 218 cases of hypopituitarism post head trauma and they observed that the majority of the cases were seen under the ages of 40 years. Out of 218 cases, the highest number of cases were seen in the third decade of life between the ages of 20-29 years. After the third decade of life, the incidence of hypopituitarism decreases progressively. In 2007 a meta-analysis of about 700 adult patients (6) was carried out and this showed that about 35% had acquired some degree of pituitary dysfunction post major head trauma in the first five months. There are little data on the pituitary outcomes of TBI in children. A prospective French study of 87 children, mean age of 6.7 years, reported a prevalence of 7% for GHD, 2% for thyroid, and 1% for adrenal insufficiency evaluated 5 months after head trauma (6). Most patients who have PTHP (Post Traumatic Hypopituitarism) are men (Male: Female ratio is 5:1) (6). Schneider et al (6) studied about 357 cases of hypopituitarism post-TBI and they observed that the majority of the cases were male patients (frequency around 84%). Post-traumatic hypopituitarism may develop any time after the initial trauma and many patients go on to develop pituitary dysfunction many years later after the initial trauma (about 15% of patients went on to develop pituitary dysfunction about 5 years after the initial traumatic brain injury) (6). Most cases of hypopituitarism happen within the 1st year; however, cases have been reported up to 20 years after the initial trauma. In terms of the type of trauma responsible for pituitary dysfunction, in about three-quarters of the cases, they are represented by road accidents. (There is more on this in the causes section) (6). In one study (5) that included 147 cases of hypopituitarism, the investigators found that more than 70% of cases were because of road traffic accidents.

Etiology

There are many causes for TBI. These causes can be categorized into:

i) Closed head injury – such as falls, motor vehicle accident, violence, injuries due to sports, shaken baby syndrome (4). In this case, the brain is left intact, with no breaks or fractures in the skull. It is caused as a result of the sudden movement of the brain (forward, backward, shaking) within the enclosed dura and the skull. The result is damage and tearing of brain tissue and blood vessels (7).

ii) Penetrating brain injury – is the opposite of closed head injury, where here there is a break in the skull, with penetrating blows directly to the brain. Common causes include gunshots, and exploding material (7).

iii) Falls - Falls can occur in patients of all ages and all settings. As toddlers attempt to start walking, they can fall from their height. Later on, in adolescence, falls can occur because of alcohol intoxication and drugs (8). Falls can occur at the place of work or even at home whilst on a ladder, in the bathroom, or tripping on objects that are on the floor such as carpets (9). Falls however are particularly more common in the elderly due to multiple factors:

- Weaker muscles and bones because of osteoporosis resulting in balance problems and consequently greater risk of fall (4).
- Vision problems leading to inability to see clearly and therefore trip on objects easily (4).
- Polypharmacy – as we age, the number of drugs increases, leading to increased chances of blood pressure dropping leading to episodes of fainting and dizziness. Studies conducted to assess the effect of stress related to sickness and effects of medication on pituitary dysfunction found that almost 50% of TBI patient suffered pituitary dysfunction and this could be attributed to the excessive use of certain medications. Opioids, phenobarbitones, high dose heparins cause adverse effects on the endocrine gland and thus caution should be used when administering such medications (9).
- Moreover, older people are at increased risk of suffering from vascular conditions such as strokes, MI and atrial fibrillation leading to episodes of loss of consciousness and falls with risk of resulting in TBI (NHS, 2018) (9).

iv) Violence can involve anything ranging from domestic violence, child abuse, as well as a shaken baby syndrome. In this case, it involves pushing someone against a wall or down the stairs, striking someone with an object, or shaking the individual very vigorously. Strangulation is another form of TBI, resulting in hypoxic brain damage. Gunshot wounds, explosives leading to debris, and objects penetrating the skull are other forms of violence that can result in TBI (10) and (Washington State Department of Social and Health Services).

v) Motor vehicle accidents are another extremely common cause of TBI. They include cars, motorbikes, or even pedestrians. Studies have shown that the most vulnerable individuals to suffer the most severe injuries are pedestrians and motorcyclists (11, 12). Moreover, it was found that pedestrians and motorcyclists suffered significantly more frequently head and neck injuries compared to car occupants (13).

vi) Sports-related activities. The majority of injuries are relatively mild, with many of them going unrecognized and undiagnosed. They most commonly occur in contact sports such as boxing, football, rugby, and martial arts (14).
vii) Intentional self-harm though not so common, is becoming increasingly more frequent (Centre for Disease Control and Prevention 2019). It can involve choking or carbon monoxide poisoning resulting in brain tissue hypoxia and consequent traumatic brain injury (15).
viii) Autoimmunity and genetic predisposition: Recent studies have shown that pituitary dysfunction was prominent in TBI patients who tested positive for Anti-pituitary antibodies (APA) and Anti-hypothalamic antibodies (AHA) (16).
ix) Apolipoprotein E (ApoE) is an essential protein found to play a vital role in membrane repair; studies showed that TBI patients who tested positive to ApoE3 had a better outcome after pituitary injury than those who tested positive to ApoE4 (17).

Pathophysiology of post-TBI hypopituitarism

No single mechanism is responsible for causing TBI hypopituitarism. Additional insults from hypoxia, hypotension, anaemia, raised intracranial pressure, and reduced cerebral perfusion pressure (18) are involved in causing hypopituitarism.

Direct mechanical impact on the pituitary gland. The location of the pituitary gland in the Sella turcica makes it susceptible to injuries that result in basal skull fracture (19). A recent study in fatal TBI revealed a high prevalence of stalk rupture and pituitary gland haemorrhage (43.3%) and this was associated with subdural haemorrhage (20).

Clinical Presentation

Traumatic brain injury is a serious problem with a serious consequence to health. It can cause permanent or transient pituitary dysfunction. The part that secretes GH (somatostatin) is the most vulnerable part followed by gonadotropin, thyrotropin, corticotropin, and lastly the secretion of ADH. These disturbances can cause abnormalities in the somatotropic axis, hypogonadism, hypothyroidism, hypocortisolism, and diabetes insipidus. The exact mechanism of pituitary dysfunction after trauma is not yet clear but different hypotheses have been stated (21). Shearing forces during head trauma could lead to the destruction of blood vessels supplying the pituitary gland, and as a consequence gland necrosis occurs (22). Another hypothesis blamed the increased intracranial pressure as a cause of pituitary gland dysfunction (22). Many extracranial causes have been suggested to be the causes of pituitary dysfunction following trauma (23) but, all remain hypotheses till now. The vascular insufficiency hypothesis correlates well with the pattern of hormonal insufficiency. Somatotrophs and gonadotrophs are located laterally in the anterior pituitary gland and pars tuberalis which are areas exposed to ischemia due to portal blood vessel supply (21). The central part of the gland is occupied by cortico- and thyrotrophs which make them less susceptible to ischemia (24).

Traumatic brain injury is a complex disease, and increases over time. It is not a single episode in time (25). Pituitary Trauma Brain Injury (PTBI) can lead to high morbidity and mortality (26). It can lead to a decrease in quality of life, change in body composition, abnormal metabolic tests, and a decrease in bone density (27) (28). Some studies reported memory deficit, attention deficit, worse reaction-time, and emotional problems in patients with GH deficiency post-trauma (29). Increased body weight, total cholesterol, and LDL cholesterol are also reported (26).

Acute phase:
This is the period after traumatic brain injury. It is about two weeks from the trauma date. In this period, the deficit of GH and gonadotropin are the most common changes. At this phase, care should be given to the occurrence of secondary hypoadrenalism (30)(31). Hyperprolactinemia was found to be due to either stress process or pituitary stalk compression. Hypothyroidism and central diabetes insipidus, are temporary consequences in this phase and can be resolved within 3 -12 months (32). Early detection of central diabetes insipidus and SIADH is essential as the hydro – electrolytes balance is a life-threatening condition (33).

Chronic phase:
It is defined as a period starting 3 months after the traumatic brain injury. As in the acute stage, growth hormone deficiency and hypogonadism are the common hormonal abnormalities. Long-term ACTH and TSH deficiency are not common (34). Tanirverdi et al (32) reported that GH, ACTH, and LH/FSH deficiencies were found in 28%, 4%, and 4% respectively of their study participants (20 male, 5 female) after 5 years from the initial trauma. Central diabetes insipidus is found to persist in 7% of patients in some observational studies (35).

Investigations

Pituitary dysfunction is a well-known complication of traumatic brain injuries, but it is underestimated. CT sac can predict post-traumatic hypopituitarism (PTHP) (36) (6). Bondanelli et al (1) did not find a CT scan of benefit to detect PTHP. Agha et al (2) shared the same finding that CT scan was not of benefit to detect PTHP. Screening for pituitary function in all patients with TBI is carrying a great load on health systems.

At admission to hospital (34):
Screening for anterior pituitary function:
Some studies recommended screening of all patients with a clinical picture of (hypotension, hypoglycemia, hyponatremia)/or risk factors for acute hypoadrenalism (37). The authors did not recommend routine screening for serum cortisol in non-suspected cases in the acute phase of post-traumatic brain injury (34). Also, the authors recommended no testing for pituitary function early (acute phase) (34).

Screening for posterior pituitary function:
Cranial diabetes insipidus is associated with poor long-term outcomes (38). Early screening for CDI is important in the context of hypernatremia and hypotonic polyuria. If CDI is suspected, check serum creatinine, electrolytes, plasma glucose, and paired serum/plasma and urine osmolalities (34). SIADH should be considered if hyponatremia found (34).

After hospital discharge (34):
For patients who were admitted for more than 48 hours post-trauma, pituitary function screening should be done after 3-6 months. Those with abnormal results should be referred to an endocrinologist for further assessment. It is important to do a 9 am serum cortisol test to determine the need for glucocorticoid treatment. For patients who did not admit or were admitted for less than 48 hours, if they have symptoms suggesting pituitary dysfunction, they need to undergo pituitary function assessment. Screening for depression is also recommended. If they did not have symptoms, screening at 12 months, if no symptoms, no further action is required. If they have symptoms after 12 months, then refer to an endocrinologist for GH and other pituitary deficiencies' assessment (Table 1).

Management (34)

Most TBI hypopituitarism causes functional, cognitive morbidity, and mortality. GH deficiency has the most effect, with an association with dyslipidemia, hypertriglyceridemia, insulin resistance, and increased CVS risk.

There is a role of GH replacement which improves functional and cognitive impairment. Adrenal crisis after TBI treated with glucocorticoids. Testosterone replacement in hypogonadal men is associated with decreased irritability and increased libido and energy and estrogen replacement in postmenopausal women improves verbal memory and vigilance.

Patients with post-TBI pituitary dysfunction may receive suboptimal rehabilitation unless the underlying hormone deficiency is identified and treated. Also, replacement is important in patients who may require surgery and patients at risk of adrenal insufficiency postoperatively. Once the patient with TBI pituitary dysfunction is identified, TSH, ADH, and ACTH deficiencies should be replaced but GH replacement remains controversial, therefore referral to an endocrinologist is recommended.

Patients with TBI who require hospitalization for at least 24 hours, those with abnormalities on initial CT, and those with symptoms and signs of pituitary failure after TBI, should be screened at 3 months and 12 months post-injury and even further out if symptomatic.

All symptomatic patients should be screened immediately with endocrinologist consultation and hormonal replacement therapy if needed.

Clinicians involved in the treatment of TBI patients should consider hypopituitarism and its impact on health, ongoing evaluation of pituitary, endocrinologist, and psychiatrist for specialized testing and long term follow up is recommended for all TBI patients who were hospitalized with or without symptoms. Hormonal replacement is essential for optimal rehabilitation for TBI patients with a positive screen.

Conclusion

Although TBI is a common incident particularly among adolescents, PTHP remains an under-diagnosed complication. Lack of proper algorithms leads to underestimating the post traumatic hypopituitarism, which may have a great impact on patient's health and their quality of life. Early clinical suspicion is needed to start the cascades of investigation. Early treatment of hypopituitarism can improve the long-term outcome and mortality of traumatic brain injuries.

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Table 1: Screening for pituitary dysfunction post-traumatic brain injury (post-TBI)

For males	For females
Urea, creatinine and electrolytes Free T4 and Thyroid-Stimulating Hormone (TSH) Cortisol Luteinising Hormone (LH), follicle-stimulating hormone (FSH), testosterone, sex hormone-binding globulin, albumin	Urea, creatinine and electrolytes Free T4 and TSH Cortisol In premenopausal women, if menstrual cycle has become abnormal post-TBI, check LH, FSH, oestradiol

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