Endocrine consequences of traumatic brain injury. Literature review

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Abstract: Traumatic brain injury (TBI) is associated with increased mortality and morbidity, as well as high rates of longterm disability in survivors. TBI-related deficiencies of both anterior pituitary (posttraumatic hypopituitarism, PTHP) and posterior pituitary (diabetes insipidus PTDI or syndrome of inappropriate antidiuretic secretion, SIADH) are much more frequent than previously known and associated with an unfavourable outcome.

The pathophysiology of pituitary dysfunction after TBI is not entirely clear. The traumatic event can induce skull base fractures, hemorrhages or infarction affecting the hypothalamic and pituitary region with consequent endocrine dysfunction. In addition, metabolic and vascular brain changes, frequent in a critically ill patient also aggravate the neuroendocrine dysfunction. In the first days after trauma, the deficiency of adrenocorticotropic hormone and PTDI or SIADH are the main concern because if undiagnosed and untreated are associated with severe dyselectrolitemia and hypotension with increased mortality rate.

Posterior pituitary dysfunction occurs in the first days after injury; SIADH usually resolves completely, PTDI can persist in a minority of cases. In contrast, PTHP can occur after a long time interval after TBI. Some degree of PTHP is present in 30-40% of TBI survivors.

Early recognition and endocrinological treatment are essential to optimize the outcome of the intensive care management and of the rehabilitation process.

Key Words: trauma, brain injury, hypopituitarism, diabetes insipidus.

Traumatic brain injury (TBI) is a major cause of death and acute as well as chronic morbidity in both children and adults and an important public health problem with an ever increasing prevalence worldwide [1-3]. In the USA 1.5 million persons suffer a TBI each year; nationwide surveillance data for TBI indicate that males and certain age groups (15-19 years or >65 years-old) are at increased risk. Motor-vehicle accidents (MVA), falls and assaults are most frequent causes of TBI [4].

TBI is defined “as an alteration in the brain function, or other evidence of brain pathology caused by an external force” [5]. The common mechanism of brain injuries is due to direct physical insult to the head resulting in penetration of the skull and largely focal damage, compression and shearing of adjacent tissues [6]. Diffuse brain injuries (as concussion or diffuse axonal injuries) may be caused by rotational and acceleration - deceleration forces, such lesions being frequently seen in motor vehicle accidents. Traumatic injuries of the pituitary gland can occur in typical basilar skull fractures, hinge fractures due to massive side to side compression, or longitudinal fractures of the skull base as a result of the impact to the back or
the forehead (common in falls, both type of fractures crossing pituitary fossa) [7].

Among the numerous complications of TBI, hypothalamic-pituitary dysfunction is increasingly being recognized to occur much more frequently than previously thought [8, 9]. Anterior pituitary insufficiency (posttraumatic hypopituitarism, PTHP) can be represented by ACTH deficiency (central adrenal insufficiency, CAI), TSH deficiency (central hypothyroidism), LH/FSH deficiency (central hypogonadism), GH deficiency (GHD). Posterior pituitary dysfunction is most frequently represented by decreased antidiuretic hormone (ADH) secretion -posttraumatic diabetes insipidus (PTDI); in rarer cases the ADH secretion is inadequately increased- syndrome of inappropriate antidiuretic hormone secretion, (SIADH).

In the first days after the event, CAI and PTDI/ SIADH are the major concern since these conditions are associated with increased TBI mortality and are predictive of longterm pituitary insufficiency [10, 11].

Overall 30-40% of TBI cases are diagnosed with some degree of PTHP either in the acute setting or after a time interval from the traumatic event [11, 12]. PTHP can be transient in many cases but it persists in 25-40% of TBI cases (especially those with moderate to severe traumatic event) [13]. In the long term GHD is the most frequent deficiency but over a half of all PTHP cases have global pituitary insufficiency (panhypopituitarism) [14], associated with unfavourable functional outcome, increased risk of morbidity and mortality [15].

PTDI is typically diagnosed during the acute phase [16]; in most series the prevalence of this complication is around 20% [17] but only about 6% of the cases have persistent chronic DI [18].

Etiopathogeny of the endocrine complications

The major cause of TBI is represented by motor vehicle accidents (MVA) [19]. MVA and assaults are the major traumatic mechanism in younger adults while at the extremes of age (infants and elderly) falls are an important etiological category [20].

The neuroendocrine dysfunction results significantly more frequently from severe TBI although it can also occur following mild TBI [21].

The exact mechanism of the hypothalamo-pituitary dysfunction in TBI is not known but there are several plausible hypothesis. The insult is viewed as multifactorial, with not only the brain trauma itself but secondary metabolic and vascular brain changes, stress response associated with critical state and secondary drug effects also play a role [13].

The traumatic event (especially in moderate-severe injuries) frequently results in lesions of the hypothalamus or pituitary. In one autopsic study including 66 victims of closed TBI, 40% of the cases had pituitary lesions (77% posterior lobe hemorrhage, 37% anterior lobe hemorrhage, 26% anterior lobe infarction –evident only in cases surviving at least 14 hours after the event). In another study similar results were reported: pituitary infarction of variable extent was only found in cases surviving hours to days (in 43% of these cases) and in none of the cases deceased at the scene of the accident [22]. Hemorrhage or infarction of the hypothalamo-pituitary stalk, hemorrhages in the hypothalamic nuclei or the infundibular region are also frequent findings in such cases, explaining the dysfunction of the posterior pituitary [23]. The lesions can be caused directly by the traumatic agent but can also be the consequence of skull base fractures, present in around 17% of cases with moderate to severe TBI [24]. External transversal forces applied to the skull (as part of the acceleration/deceleration mechanism underlying most TBI cases) can result in fractures of the skull base [25], with secondary shearing injuries of the pituitary or hypothalamic vessels [26].

The need for neurosurgical intervention in the acute post-traumatic phase is also an independent predictive factor for the development of PTHP also contributes to an increased risk of PTHP increases the risk of PTHP [24].

During intensive care, the effects of the initial trauma are frequently augmented by cerebral edema, increased intracranial pressure, secondary ischemia and tissue hypoxia [27].

Frequent endocrine abnormalities in TBI patients

Strong epidemiological data are relatively scarce because of the heterogeneity in diagnostic criteria, patient population, timing of evaluation among the published series.

In the acute setting CAI affect around 15% of cases [19] and increases the risk of severe hypotension, hypoglycemia or hyponatremia [28]. Cases with severe TBI, skull base fractures or hemorrhage and edema in the hypothalamic/pituitary region are at particularly increased risk [28].

Gonadotropin deficiency occurs in 25-80% of cases in the acute phase (but the immediate impact on the outcome is negligible) and central hypothyroidism is diagnosed in about 15% [19]. The interpretation of thyroid function tests is unreliable in the acute phase of TBI so repeated measurements are frequently needed and a definite diagnosis and treatment is frequently offered in the recovery phase.

Acute PTHP is not predictive of longterm PTHP [21]. During follow-up, the initially established endocrine status changes in almost a third of cases, with recovery (total or partial) or aggravation being equally frequent [24]. Prospective, longitudinal studies evaluating the dynamics of the pituitary function after TBI are scarce.
After 3 months 56% of cases still have some degree of PTHP [29], and PTHP recover in over half of cases after one year [30]. However, new pituitary deficits also occur such that 36-51% have PTHP after 1 year (most frequently, GHD, gonadotropin deficiency or CAI) [30, 31].

Chronic PTHP affects 30-40% of cases with 10-15% of cases having more than one pituitary axes affected. (9) GHD and gonadotropin deficiency are most frequent, affecting 18% and 13% of cases, respectively. (32) Cases with early-diagnosed panhypopituitarism are typically confirmed at further retesting during follow-up while milder cases can recover with time [33].

Posterior pituitary dysfunction is most significant in the acute posttraumatic phase. Severe PTDI with hyponatremia occurs in about 3% of cases [32] while up to 50% of cases develop less severe PTDI [19]. Most cases recover completely; the frequency of persistent longterm PTDI is around 6% [18]. The recovery is presumably the result of the slow involution of the edema and possibly vessel regeneration in the affected areas [17] SIADH can affect 14% of acute cases, and full recovery is the rule in survivors [32].

Assessment
All patients who suffer a TBI (especially moderate or severe trauma) should routinely undergo a complete investigation of the hypothalamic-pituitary axis [34], with a particular attention to CAI and ADH abnormalities.

In the acute post-traumatic phase any endocrine deficit is usually very difficult to diagnose clinically, because of the severe general condition of most TBI cases (frequent neurological deficits or altered consciousness). Intensive care unit protocols are essential for raising the diagnostic suspicion if abnormalities are noted during constant monitoring of the hydration status, blood pressure, heart rate, Glasgow coma scale (GCS) score, fluid and electrolyte homeostasy. PTDI results in polyuria (sometimes massive) and consequently severe dehydration and hyponatremia can occur with a significant adverse impact on the outcome [17]. Acute CAI is by itself life-threatening as it most leads to severe hypotension, vomiting, possibly hyponatremia (especially in cases associating SIADH) [15].

Laboratory testing in intensive care are sometimes difficult to interpret. Initial mild abnormalities can reflect a non-specific response to critical illness and careful monitoring is mandatory [26]. Cerebral imaging (CT or MRI) is routinely obtained in TBI patients and frequently reveal intracranial hemorrhage (intracerebral, subarachnoid, subdural), cerebral edema, skull fractures [35].

Focal injury of the hypothalamic-pituitary region (hemorrhage, infarction, stalk transection) can be demonstrated on regional MRI images in 30% of all TBI cases [36], but no direct correlation with a specific endocrine complication can be established and laboratory data are essential for a positive diagnosis. Confirmatory laboratory tests are usually not possible in the acute phase, therefore the initial diagnosis usually relies on basal hormonal determinations.

During follow-up of TBI survivors regular endocrine assessment is recommended. While PTDI is an early posttraumatic complication, PTHP can be a late complication (sometimes occurring months or even years afterwards [19]) so longterm monitoring is needed. Initial post-acute assessments are performed at 3,6 an 12 months after the traumatic event [37].

Predictive factors for endocrine deficits
The severity of trauma [11, 37], the presence of skull fractures [11], increased intracranial pressure, low Glasgow Outcome Scale [37], hypothalamic edema, prolonged unresponsiveness, hyponatremia, and/or hypotension [9], post-traumatic seizures, intracranial hemorrhage, petechial brain hemorrhages [38] are associated with a higher occurrence of endocrinopathy. Older patients are at particular risk [11].

The risk factors for PTDI development are the presence of a low Glasgow coma scale (GCS) score, cerebral edema, severe injury [16]. Although acute DI is generally associated with a more severe traumatism, PTDI can also rarely occur in victims of mild TBI [39].

Medicolegal issues
Medicolegal examination is mandatory for all victims with traumatic injuries due to vehicle accidents or physical assault. Medico-legal reports are the main type of evidence describing the reality of the physical damage and its severity. As mentioned, chronic endocrine deficiencies are certified in more than 40 % cases [9] but the link between the long term outcome and primary traumatic injury is not entirely clear [40].

The existence of a free interval, more or less symptomatic, between TBI and late clinical endocrine states requires a careful determination of the etiological causes.

Systematic screening of the pituitary function following moderate to severe TBI, an early diagnosis and a correct assessment of the potential impact of the post-traumatic endocrine deficit may have an important contribution in the medico-legal practice in order to determine causal effects and prejudice status.

The medicolegal expertise in neuroendocrine disruptions secondary to TBI has numerous goals. The assessment of the endocrine deficiencies, of possible severe or definitive secondary disabilities is mandatory, together with the evaluation for other possible complications: post-traumatic cerebral syndromes, post-traumatic, chronic fatigue [41], postural orthostatic tachycardia syndrome and the risk for cardiac arrhythmia [42]. Aspects related to psychosocial rehabilitation [43], rehabilitation in the
standard of care and objective assessment of recovery, functional independence and quality of life [44] are also essential in the medicolegal expertise of TBI victims.

**Prognosis**

PTDI is a marker of the severity of trauma and it is associated with a higher mortality rate [45, 46]. TBI patients developing PTDI have a fatal outcome in about 2/3 of cases, reaching almost 90% in those with early posttraumatic onset [17]. Among pituitary deficiencies, early-onset CAI is also associated with an increased mortality rate [10].

**References**


**CONCLUSION**

Neuroendocrine abnormalities are frequent after TBI and have significant prognostic implications. The adequate and timely diagnosis and management is of paramount importance especially for CAI and PTDI/SIADH – conditions most clearly associated with increased morbidity and mortality. A follow-up strategy with periodic neuroendocrine evaluation is essential for the optimal care of TBI patients.

Conflict of interest. The authors declare that they have no conflict of interest concerning this article.


