

Neuroendocrine Dysfunction in Traumatic Brain Injury: Does Evaluation Improve Outcome in Acute Setting?

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Abstract: Traumatic brain injury is one of the most common causes of mortality in young adults, with significant long term physical disability, behavioural and psychological deficits. Pituitary dysfunction is unrecognised in most traumatic brain injuries. Earlier it was considered to be a rare cause of hypopituitarism. In recent times, the surge in the incidence of pituitary dysfunction due to TBI is because of increased number of road traffic accidents and increased awareness on the same. The main aim of this study was to know the incidence of pituitary dysfunction due to traumatic brain injury and factors influencing the incidence and severity of dysfunction, and to correlate the pituitary dysfunction with overall outcome. We have evaluated 60 patients of traumatic brain injury who met the criteria. Hormonal evaluation was done, first-within 24 hours of hospital admission and after 1 month, 6 months and 1 year of follow up. Hypopituitarism was observed in 45% of patients of traumatic brain injury in acute phase, and the deficiency was attributed to adaptive response to the injury or as a pathological hormonal deficit. In majority of cases the dysfunction could be long lasting leads to various neuro-hormonal and psychological manifestations. Most common dysfunction appears to be gonadotropin and somatotropin deficiency, followed by cortisol and thyrotropin deficiency. Assessment of cortisol is of vital importance in acute phase, as cortisol deficiency is undetected, and can be lifesaving if supplemented.

Keywords: traumatic brain injury, hypopituitarism, hypogonadism, cognitive dysfunction.

INTRODUCTION

Traumatic brain injury is one of the most common causes of mortality in young adults, with significant long term physical disability, behavioural and psychological deficits [1]. It is unrecognised in most traumatic brain injuries. Earlier it was considered to be a rare cause of hypopituitarism. Now it has become well recognised public health problem worldwide. In recent times, the surge in the incidence of pituitary dysfunction due to traumatic brain injury is because of increased number of road traffic accidents and increased awareness on the same [2].

The most common causes of traumatic brain injury are road traffic accidents, accounts for more than 50% of all cases, followed by fall, violence and sports related injuries. Although traumatic brain injury was previously considered to be a rare cause of

hypopituitarism, the prevalence of neuroendocrine dysfunction in patients with traumatic brain injury has been reported during the last 15 years.³ Evaluation of pituitary function in the acute phase (10-14 days) can be difficult in critically ill traumatic brain injury patients. Performing dynamic hormonal tests particularly ACTH and growth hormones in acute phase is impractical. Moreover, there are no clear or internationally accepted diagnostic cut-off values for the diagnosis of hypopituitarism during the acute phase.

Currently, there is no clear evidence that replacement of TSH, FSH/LH, or Growth hormone deficiency in critically ill TBI patients is beneficial during the acute phase [4, 5]. However, in acute phase of TBI, diagnosis of glucocorticoid deficiency should not be missed because it is life threatening [4, 6]. The current evidence implies that insufficiency in the

hypothalamo-pituitary-adrenal axis during the acute phase after head injury is associated with worse neurological outcome. Increased need for vasoactive drug therapy is due to hemodynamic instability, relative or absolute hypoglycemia, hyponatremia, and rapidly progressive hypotension all of which may increase the risk of morbidity and mortality [6, 7]. The emphasis during the acute phase of brain injury should be on detecting adrenal insufficiency.

OBJECTIVE

The main aim of this study was to know the incidence of pituitary dysfunction due to traumatic brain injury and factors influencing the incidence and severity of dysfunction. To know the incidence of adrenal insufficiency in acute phase and its impact on

outcome. And to correlate the pituitary dysfunction with overall outcome.

MATERIALS AND METHODS

In present study 60 patients of traumatic brain injury who met the criteria were evaluated. Hormonal evaluation was done in all patients, first within 24 hours of hospital admission and after 6 months and 12 months of follow up. We analyzed the patients based on demographics, imaging, GCS, GOS, and cognitive and neuropsychological evaluation. CT & MRI brain was done. Both anterior & posterior Pituitary hormonal evaluation done. Hormonal replacement given based on deficits. Follow up hormonal evaluation done at 6 months and 12 months post injury.

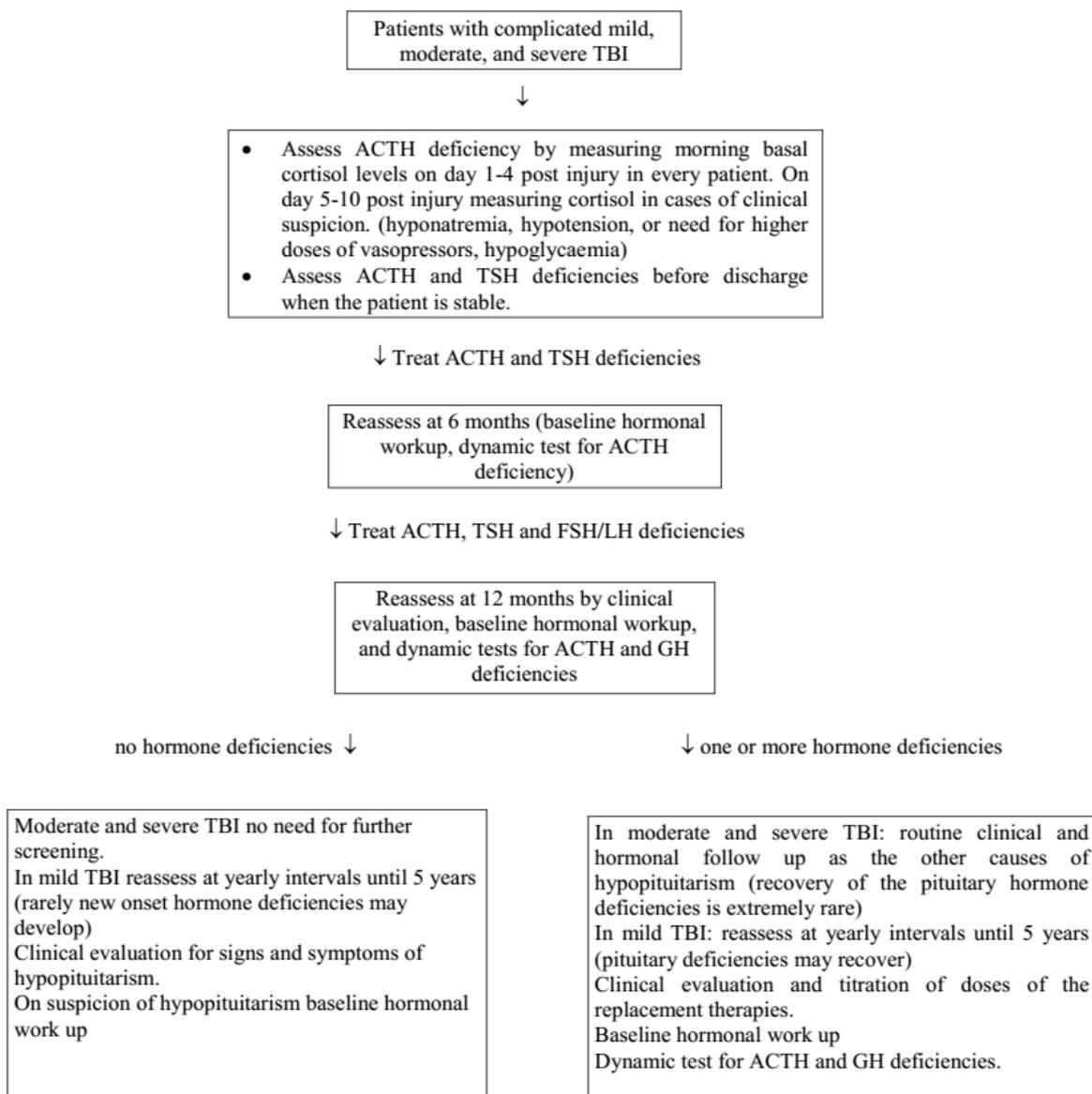


Fig-1: Pituitary hormones screening protocol

value for ACTH deficiency during the acute phase is morning serum cortisol level $< 11\mu\text{g/dL}$ (300 nmol/L). Stress dose glucocorticoid replacement is warranted in critically TBI patients who have ACTH deficiency. Dynamic test need to be performed before discharge in patients who is stable and the critically ill phase is resolved, if the basal cortisol level is between $3.5\ \mu\text{g/dL}$ (98 nmol/L) and $18\ \mu\text{g/dL}$ (500 nmol/L) and clinical findings suggestive of ACTH deficiency. TSH deficiency could be evaluated by measuring basal FT4, FT3 and TSH levels when the patient is stable before discharge. Physiological doses of steroid and/or thyroid replacement therapy are recommended in patients with ACTH and/or TSH deficiency until the second reassessment at 6 months after TBI.

Inclusion Criteria [8, 9]

- All TBI patients who need hospitalization in Neurosurgery units and ICU monitoring in particular, regardless of severity are included.
- Those with a history of complicated mild TBI, moderate or severe TBI, who experience clinical signs and/or symptoms associated with hypopituitarism should be included.
- Complicated mild TBI is defined by the presence of at least one of the following conditions:
 - Need for hospitalization for more than 24 hours
 - Need for ICU monitoring and/or need for any neurosurgical intervention.
 - Presence of acute pituitary hormone changes during the first 2 weeks after TBI (ACTH deficiency and/or Central DI)
 - Any anatomical changes on initial CT or MRI

Exclusion criteria

- Mild TBI patients who are discharged from emergency units

- Who have no loss of consciousness and/or post traumatic amnesia of less than 30 minutes
- TBI patients in a chronic vegetative state with low life expectancy
- Who have pre-existing dys-hormonogenesis
- Who died or lost follow up within 6 months of TBI

RESULTS

We have evaluated 60 patients of traumatic brain injury who met the criteria. Males were 48 and females were 12. Most common mode of injury was RTA with the incidence of 87 %, followed by fall (8%), assault (3%) and sports related injuries (2%). Among 60 patients the incidence of severe TBI is 28%, moderate TBI is 47%, and complicated mild TBI is 25%. Hormonal evaluation was done, first within 24 hours of hospital admission and after 1 month, 6 months and 1 year of follow up. Hypopituitarism was observed in 45% of patients of traumatic brain injury in acute phase, and the deficiency was attributed to adaptive response to the injury or as a pathological hormonal deficit. In majority of cases the dysfunction could be long lasting leads to various neuro-hormonal and psychological manifestations. Most common dysfunction appears to be gonadotropin and somatotropin deficiency, followed by cortisol and thyrotropin deficiency. Clinically these patients presented with hypotension, hyponatremia & apathy (15%), hypothyroidism (8.3%), loss of libido and infertility (11.6%), diabetes insipidus (11.6%), cognitive and behavioral abnormalities (16.6%). Glucocorticoids, thyroid hormones and Vasopressin supplementation given in ACTH deficiency, hypothyroidism, and diabetes Insipidus respectively. In growth hormone deficiency, no supplementation is required up to 1 year. Psychosocial rehabilitation is given in patients with cognitive and behavioral abnormalities.



Fig-2: CT imaging showing basifrontal contusion with obliteration of cistern spaces

Table-3: Incidence of hormonal deficiencies in TBI

Type of deficiency	Complicated Mild TBI (n=15)	Moderate TBI (n=28)	Severe TBI (n=17)
ACTH deficiency (15%) n = 9	2	4	3
FSH/LH deficiency (11.6%) n = 7	1	3	3
TSH deficiency (8.3%) n = 5	2	1	2
ADH deficiency (11.6%) n = 7	2	2	3
Growth hormone def (10%) n = 6	2	2	2
Cognitive & Behavioral abnormalities (16.6%) n = 10	3	4	3

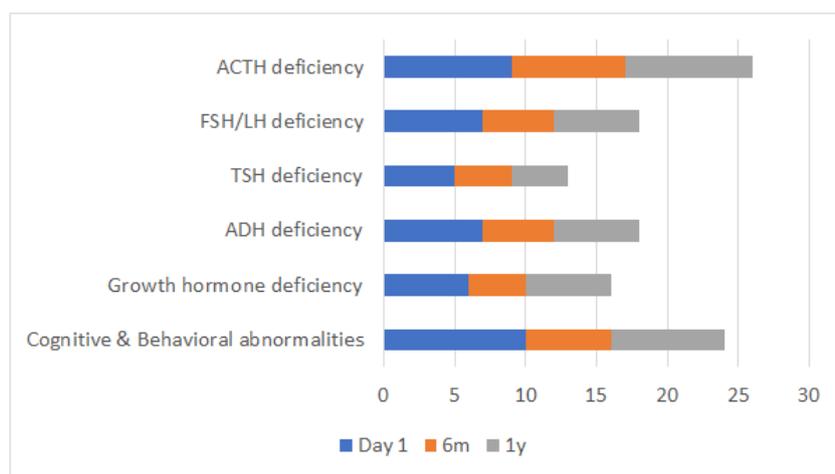


Fig-4: Comparative hormonal analysis during follow up

DISCUSSION

TBI in acute phase can lead to pituitary dysfunction, results in temporary increase or decrease in pituitary hormonal levels. Most pituitary hormonal changes are transient, and recover within 3-12 months of injury. However, in some patients the hypopituitarism is so severe, may leads to significant clinical manifestations. The severity of dysfunction is directly proportional to the severity of brain injury. Most common dysfunction appears to be gonadotropin and somatotropin deficiency, followed by cortisol and thyrotropin deficiency. Gonadotroph and somatotroph cells are located in the vascular territory of the long hypophyseal system which can be easily affected by TBI, which explains most common involvement of these axes [10].

Although mild TBI is the most common type of head trauma, screening of all mild TBI patients is not practical or cost effective[11]. Therefore, selection of mild TBI patients who have a significant risk for pituitary dysfunction is a strategic clinical challenge. It is documented that approximately 40% of mild TBI patients may not have clinical manifestations [12]. However, previous studies have shown that nearly 10%-39% of patients with mild TBI have significant intracranial abnormalities on routine imaging [13, 14]. Tanriverdi *et al.* studied 77 patients, among which 72% were uncomplicated mild TBI patients, 53% did not have loss of consciousness and 90% had post traumatic

amnesia of less than 30 minutes. Half of the patients with mild TBI were discharged directly from the emergency service without hospitalization; only 14% of these mild TBI patients needed monitoring in intensive care and none had any neurosurgical intervention. Finally, in their study they concluded that, global pituitary screening of all mild TBI patients admitted to emergency services is not necessary due to the low risk of hypopituitarism [15]. In present study, patients with uncomplicated mild TBI were excluded.

The term complicated mild TBI was initially used by Williams *et al*, defined by the presence of skull fractures or intracranial abnormalities on initial imaging in addition to clearly demonstrable neuropsychological dysfunction¹⁶. Based on data in the literature and current predictive factors for TBI, majority of researchers recommended routine screening for hypopituitarism in patients with complicated mild TBI in addition to moderate and severe TBI patients. In present study 25% of patients were diagnosed as complicated mild TBI, out of which 80% suffered with pituitary dysfunction. Moderate TBI patients were 47%, among which 54% effected. Among 28% of severe TBI patients, 94% were affected. Good recovery has been observed in patients with hypothyroidism, cortisol deficiency and diabetes insipidus after hormonal supplementation. Growth hormone deficiency has been resolved without any supplementation.

As described in various studies, cortisol levels were raised immediately following TBI and it was concordant with ACTH level suggestive of activation of hypothalamic-pituitary-adrenal axis due to stress response [17, 18]. Cortisol levels were correlated positively with the severity of brain injury. But during recovery phase sustained low levels of cortisol and unresponsive hypotension suggestive of posttraumatic damage at the hypothalamic pituitary level. Primary or secondary adrenal insufficiency has been shown in around 15% of patients with TBI during 7-60 days post injury, diagnosed by using the low dose ACTH test and corticotropin releasing hormone (CRH) test [19]. In present study adrenal insufficiency observed in 15% of the patients, manifested as unresponsive hypotension. Low dose glucocorticoid supplementation has shown improved outcome in all patients in immediate post injury period.

Acute TBI induces alterations in thyroid hormone equilibrium within hours. Although TSH usually remains normal, fT4 levels may be reduced or normal, while fT3 levels rapidly falls. Thyroid hormone levels returns to normal slowly over weeks, as the patient recovers [20] Agha *et al.* in their evaluation of 50 patients in the acute phase of post TBI showed central hypothyroidism in 5% of cases [21]. Dimopoulou *et al.* also demonstrated central hypothyroidism in 15% of cases in moderate to severe TBI [19]. We found that fT3, fT4 were low in 8.3% of patients. Previous studies have shown that low thyroid hormones correlated with worse prognosis [22]. In present study, hypothyroidism was considered a risk marker for increased mortality.

In acute phase of TBI, low or high basal circulating GH levels associated with low insulin growth factor (IGF)-1 concentrations have been reported [23, 24]. Peripheral GH resistance, manifested by elevated GH levels with low IGF-1 concentrations has been observed in patients with acute illness [25]. A decrease in GH bursts has been detected in 24-48 hours after severe trauma, indicating a relative hyposomatotropinism [26]. Gottardis *et al.* reported that a GH releasing hormone (GHRH) test elicited a significant GH rise in the patients who survived after severe TBI, whereas GH response was blunted in the patients who died [27]. By contrast, Dalla Corte *et al.* reported a normal GH response to GHRH in the severely head injured patients, with a progressive increase in this response from day 2 to day 15 after injury in the patients with poor outcome [28]. Other authors have demonstrated that i.v glucose administration results in paradoxical increase in GH levels, which is greater in patients with worse neurological function [24]. These data indicate an imbalance of the complex neuroendocrine system controlling GH secretion during the acute phase of post TBI, but they do not draw reliable conclusions. In present study, GH deficiency has been observed in 10%

of patients, no supplementation has given and the deficiency resolved completely after 1 year of follow up.

Hyperprolactinemia is present in more than 50% of patients in the acute phase of post TBI and may persist in 31% of cases during rehabilitation [21]. A blunted prolactin (PRL) response to TRH has also been reported. The demonstration of a paradoxical response of PRL to GHRH in comatose patients with a good outcome and of a negative correlation between PRL concentrations and severity of TBI may suggest a good prognostic role for PRL responses during the acute phase of post TBI [28]. In present study; prolactin dysfunction has not been reported.

A high incidence of sex steroid hormone deficiency has been reported in the immediate post TBI period. In this phase, testosterone concentration has been shown to negatively correlate with the severity of injury [29]. Testosterone levels in men and oestrogen levels in women significantly fall within 24 hours following TBI and remain lowered for 7 to 10 days. Testosterone levels may return to normal after 3 to 6 months or remain low [30]. Gonadotropin levels also decrease, but their response to gonadotropin releasing hormone (GnRH) administration may be normal or increased, indicating a hypothalamic mechanism [31]. In the early recovery period or during rehabilitation, hypogonadism has been demonstrated in 25-67% of cases [31]. Agha *et al.* detected central hypogonadism in 80% of cases, including 18 patients with hyperprolactinemia [21]. In present study, hypogonadism has been observed in 11.6% of patients. Fertility has been restored after hormonal supplementation. Testosterone deficiency has not been reported in this study.

The association between TBI and diabetes insipidus has been recognised for many years [32]. However, diabetes insipidus has been considered as a rare complication, generally observed within 5-10 days of post injury. The incidence of diabetes insipidus is frequently transient and can spontaneously disappear within a few days or up to 1 month [33]. In present study, diabetes insipidus observed in 11.6% of patients, out of which 28.5% of patients required vasopressin.

In TBI patients with persistent cognitive disorders, fatigability or mood disorder, the risk of anterior pituitary deficiency is high and justifies a systematic pituitary assessment with specific reference tests [34]. In present study, Cognitive & Behavioral abnormalities were observed in 16.6% of patients. The relationship between pituitary dysfunction and cognitive dysfunction, need to be established by large number of randomize studies.

CONCLUSION

Alterations in pituitary hormones may be observed in post injury in acute phase, most common dysfunction appears to be gonadotropin and somatotropin deficiency, followed by cortisol and thyrotropin deficiency. Assessment of cortisol is of vital importance in acute phase, as cortisol deficiency is undetected, and can be lifesaving if supplemented. The FT3 could be one of the predictors of an adverse outcome.

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