

## Traumatic brain injuries- How can Endocrinologists help?

There has been a significant increase in vehicle ownership in India. As of 2017, there were 253 million vehicles on the roads in India.<sup>[1]</sup> Driving in India is extremely risky; at least 400 people are killed in road traffic accidents every day, according to a survey. At 18.9 deaths per hundred thousand populations, the estimated mortality from road traffic accidents (RTA) is also among the highest in the world in our country.<sup>[2]</sup> For every death on the road, there is 20 times the number of patients who survive with significant head injuries. This is one of the reasons traumatic brain injuries (TBI) and their aftermaths have become a public health issue. Globally, it is estimated about 69 million patients suffer TBI every year and because it affects younger individuals with long life in front of them, it has significant implications on health-related budgets and resources.<sup>[3]</sup> A recent meta-analysis estimated that the pooled annual global rate of TBI was 349/100,000 patient-years. Among them, 224/100,000 had mild TBI [defined as Glasgow coma scale (GCS) at presentation between 13 and 15], 23/100,000 had moderate TBI (GCS between 9 and 12), and 13/100,000 had severe TBI (GCS below 8).<sup>[4]</sup>

Post-traumatic hypopituitarism (PTHP) was first recognized as early as the beginning of the twentieth century.<sup>[5]</sup> PTHP then gained visibility as a complication from contact sports such as boxing, horse-riding, American soccer, and kick-boxing which are associated with mild but repeated episodes of TBI.<sup>[6,7]</sup> Accurate estimates of PTHP are not available because of the differing severity cohorts, the differing definition of PTHP, and different time periods of pituitary function assessments followed in different studies. The estimated prevalence of PTHP among patients who suffered TBI is anywhere between 15% and 68%.<sup>[8-10]</sup> The severity of the TBI is correlated with the chances of development of PTHP. Patients who have mild TBI have a 16% chance of developing PTHP. Meanwhile, patients with moderate and severe TBI have 11% and 35% chances of being diagnosed with PTHP, respectively.<sup>[11]</sup>

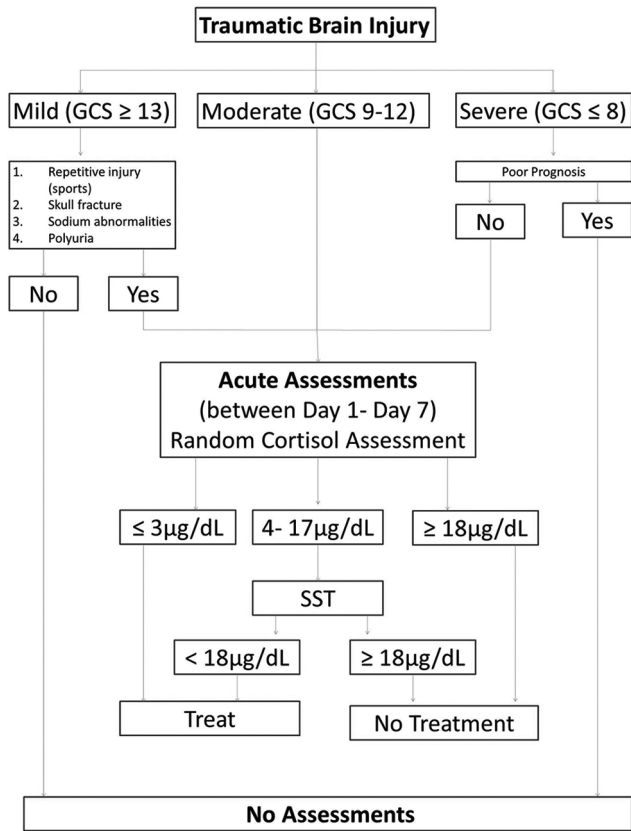
The sequence of the loss of pituitary hormones is different from that seen with pituitary adenomas. The sequence can be remembered as GFTA with the earliest axis affected being the growth hormone axis, followed by the hypothalamic-pituitary-gonadal axis, which is then followed by the pituitary thyroid axis, and the last anterior pituitary axis to be disrupted is the hypothalamic-pituitary-adrenal axis.<sup>[12]</sup> Diabetes insipidus is usually the last pituitary dysfunction seen in most cases with TBI except those involving seatbelt-related stalk injuries that accompany whip lash trauma.<sup>[13]</sup> A significant number of PTHP is transient with gradual restoration of hormonal secretion and feedback loops over a period of 1 to 3 years. Though in some cases, the sequence of hormonal deficiency might progressively worsen over a period of time.<sup>[14]</sup>

The most likely cause of PTHP after trauma is vascular insult due to the shearing forces that accompany TBI disrupting the blood supply to the anterior pituitary in turn leading to infarction of the gland. This explains why the laterally situated somatotropes and gonadotropes are more susceptible in comparison to the centrally located thyrotropes and corticotropes. The centrally located pituitary cells are supplied by short hypophyseal vessels which are less susceptible to shearing forces.<sup>[15]</sup> A second explanation for PTHP could be direct harm to the gland and especially the vulnerable stalk of the gland.<sup>[16]</sup> The third postulated mechanism is the potential exposure of pituitary-specific antigens to the immune system following disruption of the blood-brain barrier as a consequence of TBI. Anti-pituitary antibodies (APA) were found in 44% of patients 3 years after TBI.<sup>[17]</sup> Patients with higher titers of APA had more permanent PTPH, and those with no autoantibodies were more likely to recover.<sup>[18]</sup>

In the context of TBI, the first 14 days are considered the acute phase of the disease. The physiological changes in the hypothalamo-pituitary axes that accompany acute critical illness and the difficulties in performing dynamic hormonal tests among patients with TBI in the first 14 days makes an assessment of pituitary functions in the acute phase difficult. However, the assessment of the hypothalamo-pituitary-adrenal (HPA) axis remains critical in the first 14 days. In a study among 200 patients with TBI, around 2.8% had significant adrenal insufficiency with a random cortisol level  $>3 \mu\text{g/dL}$ . These patients would definitely benefit from steroid replacements. In the same study, 21% and 37% of the patients presented with cortisol levels below 10 and 15  $\mu\text{g/dL}$ , respectively. The benefits of steroid replacement among them are still a matter of debate.<sup>[19,20]</sup>

The assessments of pituitary functions are best done 3 months after a TBI. Only the HPA axis should be assessed in the acute phase and a proposed protocol for HPA axis evaluation is summarized in Figure 1. Among the patients who undergo acute phase assessment for HPA axis or those who have diabetes insipidus or syndrome of inappropriate diuresis (SIAD) in the first 14 days should have a complete examination of pituitary functions at 3 months, 6 months, and again at 12 months. In some cases, long-term annual evaluations are also warranted.

In this issue of the journal, Vishwakumar and colleagues from Hyderabad look at the acute assessment of pituitary functions among 54 patients with severe TBI at two-time points during the acute phase of TBI. The first assessment was done within 24 h of the TBI and the second assessment on the Day 4. The sampling of cortisol,  $T_3$ ,  $T_4$ , TSH, and prolactin were timed between 8 am and 10 am on Day 1 and Day 4 after the occurrence of TBI. However, despite the



**Figure 1:** A proposed protocol for assessment of hypothalamo-pituitary-adrenal (HPA) axis in the acute phase of traumatic brain injury (TBI). [GCS: Glasgow coma scale, SST: short synacthen test]

occurrence of a small number of patients with significant adrenal insufficiency (random cortisol  $\leq 3$   $\mu\text{g/dL}$ ), none of the patients were treated with steroid replacements as steroid therapy was not followed by the neurosurgeons in the institute based on the Brain Trauma Foundation guidelines.<sup>[21]</sup> However, a careful reading of the guidelines will reveal that the guidance is essentially avoidance of steroids in nonselected patients with TBI for reducing intracranial pressures, and the guidance document makes no mention of neuroendocrine assessments or steroid replacement in contrast to therapy in patients with documented adrenal insufficiency.

The primary objective of the study was to assess the prevalence of hormonal dysfunction and to assess its role in the prognosis of mortality and overall outcomes at 3 months. The authors used a cut-off of morning cortisol  $< 10$   $\mu\text{g/dL}$  to classify 15/34 patients with TBI (prevalence of 28%) on day 1 as having adrenal insufficiency and using the same cut-offs, this prevalence reduced to half (7/54) (14%) by day 4. None of the patients received steroid replacements. The number of patients with unequivocal adrenal insufficiency ( $\leq 3$   $\mu\text{g/dL}$ ) is not clear from the paper, but there appears to be at least one patient as noted from the range of cortisol values at Day 1. A more accurate prevalence would have been possible with a more robust definition of adrenal insufficiency in the acute

phase of TBI and the use of simulation tests to help classify the borderline cases.

However, the second objective of the paper appears to give more clinically useful information with the Day 4 random cortisol levels being the most statistically useful predictor of mortality at 3 months ( $P$  value  $< 0.001$ ). All 7 patients with Day 4 random cortisol  $< 10$   $\mu\text{g/dL}$  succumbed to the TBI. The addition of thyroid function tests at Day 4 additionally contributed to the prognosis but not to the same extent as the morning cortisol values. Assessment of prolactin levels which the authors assumed would reflect as an early sign of stalk interruption did not contribute to the clinical picture or prognosis of the patients with TBI.

This and previous information about PTHP should encourage physicians/neurosurgeons caring for patients with TBI to assess the HPA axis in all patients with moderate and severe TBI preferably 72 h after injury. As endocrinologists, we should encourage our neurosurgery colleagues to appropriately interpret cortisol values in the acute phase of TBI and help perform dynamic testing when values are in the grey zone. It is also important to educate about the differences between steroid therapy for patients with TBI and steroid replacement among patients with unequivocal adrenal insufficiency.

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