**Functional disorders of the hypothalamic-pituitary-adrenal axis in patients with severe brain injury**

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**ABSTRACT**

**Objectives:** Determination of the role of the hypothalamic-pituitary-adrenocortical system (HPAS) after brain injury. Investigations of the relationships between adrenocorticotrophic hormone (ACTH), cortisol levels, and clinical condition of the patients.

**Materials and Methods:** Patients with traumatic brain injury (TBI, n=19), subarachnoid haemorrhage (SAH, n=8), intracerebral haemorrhage (ICH, n=5), cerebral hypoxia (Hypoxia, n=5), other neurological diseases (Others, n=5). Measurement of ACTH and Cortisol values basal and after stimulation with CRH (100 µg i.v.): -15, 0, 15, 30, 45, 60, 90, 120 min. Areas under the curve (AUC) were calculated and ANOVA test was performed for statistical evaluations. P values less than 0.05 were considered as significant.

**Results:** The evaluation of the measurements of ACTH and Cortisol values basal and after stimulation with CRH has mainly depended on the clinical conditions of the patients. The calculations of the statistical results have been considered, whereas it was ensured, that the patients have passed the eventually complication of brain oedema.

**Conclusion:** Brain injuries mainly exercise influence over the above-mentioned hypothalamic-pituitary-adrenocortical system (HPAS) depending on the severity of the trauma. The results of this study indicate that investigation of HPAS hormones might be useful as an additional method in the common complex of ordinary examinations in establishing an early prognosis and improving the treatment of patients with brain injury.

**Key word:** head-brain-injury, hypopituitarism, HPAS, pituitary gland

**INTRODUCTION**

After many decades of being considered simply a clinical endocrinology “curiosity”, the long-term endocrine consequences of traumatic brain injury (TBI) have been in the past few years the subject of resurgent interest. First reported almost 100 years ago, chronic pituitary dysfunction following a head injury was originally thought to be a rare occurrence¹⁻⁵. Pituitary dysfunction has a recognized association with traumatic brain injury, including subarachnoid hemorrhage. However, the magnitude and nature of the association had not been thoroughly investigated.
of severe brain injury, which variously report the prevalence of pituitary hormone deficiencies to be between 23% and 69%1-5. It is clear from recent studies that one or any number of hypothalamic-pituitary hormone axes may be impaired in the chronic phase following head injury, with the growth hormone (GH; 10–33%), adrenal (5–23%) and gonadal axes (8–30%) apparently the most vulnerable to problems. Further clinical complexity is also evident from prospective, longitudinal observations, which suggest that in many head-injury survivors pituitary hormone dysfunction may not develop until at least 6 to 12 months after TBI, whereas, others deficiencies can be transient and resolve spontaneously during the year after the trauma6-14. Morbidity following moderate-to-severe head injury is high, and many of the chronic problems and symptoms (eg, fatigue, poor concentration and depression) reported in this group of patients are common to the clinical phenotype associated with hypopituitarism7,15-19. Moderate to severe brain trauma increases the risk of pituitary abnormalities that warrant investigation before they become symptomatic, according to many investigators6,8,20-22. A third of prospectively studied patients and 45% of a retrospectively identified group had endocrine abnormalities consistent with pituitary dysfunction, Gerard Raverot, MD, of Hospices Civils de Lyon in France, reported at the Endocrine Society meetings 2005 and 2006. While growth hormone deficiency accounted for the largest proportion of cases, 10 to 20% of patients had evidence of multiple hormonal disorders. These results are preliminary, but they confirm the high risk for pituitary disorders after moderate to severe neurologic events, including traumatic brain injury and subarachnoid hemorrhage and the results support a recommendation for evaluation of pituitary function in patients with subarachnoid hemorrhage or moderate to severe traumatic brain injury. Ischemic strokes probably disturb pituitary function, but the ability to study any association is complicated especially by an older patient population that might already be

Figure 2: Functions of the pituitary gland in man and woman
predisposed to endocrine disorders. Seeking a better understanding of brain trauma's impact on pituitary function, investigators in a multicenter French study prospectively evaluated 64 patients with moderate to severe traumatic brain injuries or subarachnoid hemorrhage. They also reviewed records of another 64 patients with a history of brain trauma.

In addition to neurologic and general medical examination, the prospectively studied patients had an extensive endocrinologic workup that included determination of free thyrotropin, prolactin, thyrotropin-stimulating hormone, insulin-like growth factor, testosterone, follicle-stimulating hormone, luteinizing hormone, and evaluation for cortisol and growth hormone deficiencies.

It was reported that 36% of prospectively studied patients (23 of 64) had endocrine abnormalities, including growth hormone deficiency in 14 (21%), gonadotrope deficiency in eight (12.5%), and corticotrope deficiency in five (3.1%). Six patients (9.3%) had combined deficiencies.

The retrospectively identified patients had a 45.3% prevalence of endocrine disorders (29 of 64), including growth hormone deficiency in 21 (32.8%), gonadotrope deficiency in 11 (17.1%), cortisol deficiency in 6 (9.3%) and combined deficiencies in 11 (17.1%).

In the present study the functional disorders of the hypothalamic-pituitary-adrenal axis in patients with severe brain injury are be demonstrated.

Adrenal insufficiency is a common and under diagnosed disorder that develops in critically ill patients. A deficiency of one or more of the hormones regulated by the pituitary gland may have physical and/or psychological effects such as reduced muscle mass, hypotension, weakness, decreased exercise capacity, fatigue, irritability, depression, impaired memory, reduced sex drive. To determine the role of the hypothalamic-pituitary-adrenocortical system (HPAS) after brain injuries, the relationship between adrenocorticotropic hormone (ACTH), cortisol levels, and clinical condition has been investigated.

MATERIALS AND METHODS
Examination in 42 patients with different types of brain injuries. Brain-injured patients with cerebro-cranial traumatic brain injury (TBI, n=19), subarachnoid hemorrhage (SAH, n=8), intracerebral hemorrhage (ICH, n=5), cerebral hypoxia (HYP, n=5), and other neurological diseases: Guellain-Barre, Parkinson disease, Alzmeimerdementia (OTH, n=5). Basal and CRH (100 µg i.v.)- stimulated ACTH and cortisol values were measured at -15, 0, 15, 30, 45, 60, 90 and 120 minutes respectively. Areas under the curve (AUC) were calculated and Anovatest was performed, p<0.05 has been considered as significant (Figures 4-9).

RESULTS
Following measurements of ACTH were obtained (mean+SEM): TBI 5567+557, SAH 4071+564, ICH 6009+1353, HYP 4551+786, OTH 3878+1290pg/ml x min (not significant, n.s.). The cortisol measurements (mean+SEM) have been:
Figure 4. Traumatic brain injury

Figure 5. Subarachnoid haemorrhage

Figure 6. Intracerebral haemorrhage
Figure 7. Cerebral hypoxia

Figure 8. Other neurological disorders

Figure 9. Area under the Curve (AUC)
TBI 2046+182, SAH 1975+152, ICH 2704+320, HYP 2439+228, OTH 2305+588 μg/dl x min (n.s.). The p-values for the group with other neurologic diseases was not significant. But all other groups of study had p values less than 0.05, which was considered as significant.

Patients with hypocortisolism have been substituted, whereas their clinical outcome could be improved throughout the subacute period and most of them have recovered very slowly. Complications in this constellation haven’t been observed.

**DISCUSSION**

Pituitary hormone deficiency may result from head trauma subarachnoid hemorrhage. Symptoms of hormone deficiency can mimic other effects of a traumatic brain injury, which can prevent suspicion of this disorder. A deficiency of one or more of the hormones regulated by the pituitary gland may have physical and/or psychological effects such as: reduced muscle mass, hypotension, weakness, decreased exercise capacity, fatigue, irritability, depression, impaired memory and reduced sex drive.

Most patients do not even realize that they have the hormone deficiency until specific laboratory tests for this disorder are performed. However, individuals with a history of a moderate to severe brain injury are more likely to have a pituitary deficiency than those with a mild brain injury.

The likelihood of pituitary damage exists even if the injury occurred years ago and a good rehabilitative outcome has been achieved. The pituitary gland, hypothalamus, and surrounding structures, including their blood supply, may have been injured.

Damage to the pituitary gland causes a condition called hypopituitarism: a loss or reduction in the normal activity of the pituitary gland. Hypopituitarism means that any pituitary hormone can be deficient. The pituitary is a pea-sized gland at the base of the brain. Pituitary hormones are important because they regulate other hormones from the thyroid, gonads (ovaries and testes), and adrenals (cortisone). Prolactin, oxytocin, and ADH (antidiuretic hormone) may also be affected by brain injury, but the incidence is less common. These hormones are chemical messengers that target vital organs that control vital functions. In our study we could show that some pituitary hormone axes (HPAS) are significantly affected after severe brain injuries and the patient had a good clinical benefit after substitution.

**CONCLUSION**

These observations suggest that brain injuries cause mainly influence and activation of the above-mentioned system depending on the severity of trauma. Close follow-up and screening using appropriate endocrine-testing protocols have recently been proposed for patients who survived moderate-to-severe brain injury, not least because the early detection and treatment of partial or complete hormone deficiencies can lead to successful recovery and rehabilitation. The results of this study indicate that investigations of HPAS hormones might be useful as an additional method in the complex of ordinary examinations in establishing early prognosis and improving the treatment in patients with brain injury.

**REFERENCES**


