Review Article

# Endocrinological disorders affecting neurosurgical patients: An intensivists perspective

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## ABSTRACT

Management of critically ill neurosurgical patients is often complicated by the presence or development of endocrinological ailments which complicate the clinical scenario and adversely affect the prognosis of these patients. The anatomical proximity to the vital centers regulating the endocrinological physiology and alteration in the neurotransmitter release causes disturbances in the hormonal homeostasis. This paves the way for development of diverse disorders where single or multiple hormones may be involved which can have deleterious effect on the different organ system. Understanding and awareness of these disorders is important for the treating intensivist to recognize these changes early in their course, so that appropriate and timely therapeutic measures can be initiated along with the treatment of the primary malady.

**Key words:** Cerebral salt wasting syndrome, diabetes insipidus, endocrinological disorder, neurosurgery, syndrome of inappropriate antidiuretic hormone secretion

## Introduction

Neurosurgical patients can present with myriad pathologies notably amongst which are traumatic brain injury (TBI), subarachnoid hemmorhage (SAH), intracranial tumors, cervical spine injuries, or pituitary disorders.[1-3] A common factor in this subset of patients is a high susceptibility to develop endocrinological aberrations, especially those affecting the sodium and water homeostasis of the body. These complications are commonly anticipated or encountered due to the underlying neurological lesion, subsequent surgical intervention, or postoperative treatment (steroids, diuretics, radiotherapy) and can occur anytime in the perioperative period.[4,5] Disturbances in the hypothalamic hypophyseal axis can also occur following TBI, craniopharyngiomas or skull base tumors.[6] The development of these endocrinological disorders in critically ill neurosurgical patients have an adverse effect by exacerbating the mortality and morbidity of these patients and cause unnecessary diversion of the attention of the treating physicians or intensivists and resources from the primary neurosurgical affliction. This review aims to discuss the commonly encountered endocrinological disorders in neurosurgical patients and evaluate the relevant literature in this context.

For the purpose of this review, endocrinological disorders in neurosurgical patients have been broadly classified into those affecting the sodium and water balance and those affecting the other endocrinological elements. Moreover, the treatment pattern highlights the importance of adopting the concept of logical empiricism in these clinical challenging scenarios.[7]

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## Neuro-Endocrinological Disorders Affecting Sodium and Water Regulation

Disorder in sodium regulation represents failure of several mechanisms in the central nervous system (CNS) which tightly regulate the levels of sodium. They are particularly common after brain injury when changes in sodium and water levels may have intense effects on the injured brain.[8]

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Also the therapeutic measures for injured brain like use of diuretics or mannitol may be responsible for disturbing water and sodium balance. Cause of sodium disorders vary and the associated morbidity is also diverse. Sodium disorders can be further differentiated into hyponatremia and hypernatremia with varying etiopathologies and management strategies.

## Hyponatremia

Hyponatremia (serum sodium concentration <135 meq/L) is more common in critically ill brain injured patients.[9] It develops 2-7 days after head injury and can increase mortality by 60%.[8,10] Hyponatremia occurs in 29% of the patients with SAH and in 35% of the patients following pituitary surgeries. Though commonly associated with hypotonicity, it can occasionally be associated with isotonicity or hypertonicity.[11] Assessment of the volume status of the patient is vital in formulating the diagnosis and treatment strategies. Usually the volume status of hyponatremic patients can be determined clinically aided by weight, jugular venous pressure, and orthostatic changes in blood pressure, skin turgor and moistness of mucous membranes. Invasive monitoring by using a central venous catheter can also assist in determining volume status.

Hyponatremia is predominantly manifested as neurological dysfunction and it may be exacerbated by other disease processes or underlying conditions especially when the pathological process is located intracranially. Disturbance in plasma sodium levels demands close monitoring in neurosurgical patients to ensure timely and appropriate therapeutic measures so that the complications do not magnify. Two distinct syndromes are associated with hyponatremia namely Syndrome of Inappropriate Anti Diuretic Hormone secretion (SIADH) and Cerebral Salt Wasting Syndrome (CSWS).

The SIADH can occur following TBI, SAH, brain tumor, meningitis or encephalitis, or use of Carbamazepine. In SIADH, deranged release of vasopressin leads to dilutional hyponatremia. Plasma anti diuretic hormone (ADH) concentration is unaffected by continued fluid administration/intake or by osmotic stimulus. In intracranial hemmorhage and hyponatremia, vasopressin levels have been found to be elevated in proportion to serum osmolarity.[12] Thus in SIADH, ADH levels are inappropriately high in context to the production of small volumes of concentrated urine. It is associated with elevated volume status and hence requires fluid restriction as therapy. SIADH is self-limiting and treatment is indicated when the patient is symptomatic or the levels of sodium are very low or falling rapidly. Electrolyte free water restriction (800-1000 ml/day) is the cornerstone of management, however, fluid restriction is unpleasant, can cause hemodynamic instability or increase ischemia in the injured brain. Hypertonic saline is indicated in severe cases especially those coexisting with SAH, where fluid restriction is contraindicated. Hypertonic saline infusion should be stopped when serum sodium reaches 120-125 meq/L and further management is done using fluid restriction. Pharmacological therapies include the following classes of drugs:-

- Frusemide and other diuretics by increasing excretion of water. However saline or salt supplementation should be done to replace sodium losses
- Demeclocycline and Lithium reduce the renal response to ADH
- ADH antagonists like conivaptan and lixivaptan inhibit binding of ADH to renal receptors and promote aquaresis (electrolyte sparing excretion of free water).

Conversely, in CSWS, primary renal loss of sodium leads to hyponatremia, polyuria, natriuresis, and extracellular fluid depletion (hypovolemia) as a consequence of a centrally mediated pathology. Principally associated with SAH and TBI, it also occurs due to intracranial tumors, ischemic strokes and tubercular meningitis. It usually occurs in the first week of brain injury and resolves spontaneously after 3-4 weeks.[13] Natriuretic peptides secreted as a result of intracranial disorders causes the loss of sodium and extracellular fluids depleting the total circulating volume (characteristic feature of CSWS). This activates the rennin_angiotensin-aldosterone mechanism, sympathetic system and vasopressin hormone. Consequently, volume regulation predominates osmoregulation giving rise to hyponatremia in CSWS. Volume depletion thus, is the important diagnostic criteria in CSWS. Treatment involves fluid and sodium replenishment using isotonic or hypertonic saline.

The peptide which deserve mention in this context is Brain Natriuretic Peptide (BNP) secreted by thalamus exerts an action similar to atrial natriuretic peptide (ANP) secreted by cardiocytes,[14] causing diuresis, natriuresis, vasodilatation, and inhibits the secretion of aldosterone, renin and vasopressin. Increased levels of BNP are found in patients with SAH or hemmorhage at the base of the brain or third ventricle.[15,16]

Treatment of hyponatremia is supportive and involves the management of underlying condition. Volume and sodium resuscitation forms the mainstay of treatment. Generally 0.9% saline is used initially, though in severe cases hypertonic saline along with frusemide to reduce volume overload is indicated. In refractory cases fludrocortisone (0.1-0.4 mg daily) may be used to

increase the sodium reabsorption from renal tubules. Hyperkalemia may occur with this therapy and hence serum potassium should be closely monitored.[13] Myelinolysis of pontine and extrapontine structures can occur following rapid elevation of serum sodium levels. The condition is characterized by mutism, dysarthria, lethargy, spastic quadriparesis, and pseudobulbar palsy. Accordingly, correction of sodium levels should not exceed more than 10 mmol/L/24 hrs.[17] If overcorrection is suspected, then reversal using desmopressin and water may be adviced.[18]

The natural course of hyponatremia shows that 15% of patients recovering from TBI develop hyponatremia of which 80% of the patients develop SIADH.[19] Following SAH; development of hyponatremia is unrelated to the anatomical location of the bleed but, its incidence rises after interventions which may be through craniotomy and clipping or neuro-radiological coiling.[20]

### Hypernatremia

Hypernatremia is defined as serum sodium levels above 145 meq/L. It is less common than hyponatremia and is a paraphenomenon, indicating the severity of underlying disease process. Mortality in head injured patients with associated hypernatremia is higher as compared to those with normal sodium levels.[21] Serum sodium elevation gives rise to increase in brain swelling. Excessive losses of free water can give rise to hypernatremic dehydration. This in turn decreases the renal plasma flow and filtration rates aggravating the hypernatremia.[21] It occurs when access to water or thirst is impaired as seen in altered mental status, decreased consciousness, sedation for airway management or fraility. Other important causes are central diabetes insipidus (CDI), fever, dehydration and osmotic diuresis.[22]

CDI occurs due to disturbance of homeostatic release of ADH from hypothalamic pituitary axis. CDI disturbs the urinary concentrating ability leading to inappropriately dilute urine. Progressive dehydration along with consequent rise in serum osmolarity occurs due to excessive loss of water. This condition is frequently encountered following pituitary surgery, TBI and anterior communicating artery aneurismal rupture causing SAH or intracerebral hemmorhage, brain abscess, or subdural hemmorhage.[23-25] CDI is associated with high volume urine often exceeding 6 L/day. Other causes of high urine output must be excluded before DI is diagnosed like fluid resuscitation, osmotic diuretics, hypertonic saline, and application of Triple H Therapy (Hypervolemia, Hemodilution, and Hypertension) to treat cerebral vasospasm. Diagnosis of CDI is based on the laboratory findings of abnormally high serum osmolality (>305 mmol/kg) and serum sodium (>145 mmol/L) in combination with an abnormally low urine osmolality revealing the defect in urine concentrating abilities of kidneys. A urine specific gravity of less than 1.005 in presence of high serum sodium is a useful adjunct which points towards CDI.[8]

CDI also assumes importance in the management of brain dead organ donors as it is often associated with severe pre terminal brain edema and is a common finding following brain stem death.[26] Anatomically, damage to the hypothalamus above the median eminence leads to permanent CDI. However damage below this level or disturbances in the posterior lobe of pituitary leads to transient CDI as ADH can subsequently be released from the nerve endings of the median eminence.[13]

Management of hypernatremia involves water replacement. Water intake can be increased in concious patients and if this fails or if the output is greater than 250 ml/hr, vasopressin may be administered either intravenously (0.4 μg) or intranasally (100-200 μg). Rapid correction can however lead to pulmonary or cerebral edema. A reduction of 10 mmol/L per day has been suggested with a more rapid correction indicated in those who have developed hypernatremia over a period of hours.[27]

The risk of development of DI initially closely correlates with the severity of TBI (based on Glasgow Coma Scale) and presence of oedema in imaging studies, however cross sectional studies of long term survivors of TBI have shown low rates of chronic DI ranging from 3% to 7%.[24,28] In survivors of SAH, DI can persist for 3 months in 8% of patients.[29] The risk is higher in patients with anterior communicating artery (ACom) aneurysm as blood supply of hypothalamus may be compromised.

Adipsic DI is another entity whereby impaired thirst mechanism confounds the deranged water balance. It is closely associated with clipping of ACom aneurysms with dramatic rise in the plasma ADH levels occurring during nonosmotic stimuli like hypotension and apomorphine.[30] This indicates the intactness of supraoptic and paraventricular nuclei and the posterior pituitary whereas the osmoreceptors of anterior pituitary are affected. Vascular supply to this zone is through small arterioles supplied by ACom artery. Disruption of blood supply causes infarction of these nuclei due to which secretion of ADH in response to thirst or hyperosmolarity is impaired but the response to other stimulations like hypotension is maintained.[30] Patients who had undergone surgery for craniopharyngioma and had suffered more extensive injuries to hypothalamus demonstrate other abnormalities along with adipsic DI like loss of baroregulated ADH release, polyphagia, obesity and sleep apnoea (hypothalamic dysfunction).[30]

## Hypothalamic Pituitary Axis Dysfunction

TBI and SAH are associated with neuroendocrine dysfunctions affecting the pituitary disorders.[29,31] Hormonal deficiencies can develop acutely or long after (months to years) after TBI or SAH which necessitates endocrinological follow up to guide hormone supplementation.[32] Tumors in the vicinity of pituitary gland like craniopharyngiomas are notorious for development of endocrine disturbances.[6] Pituitary aberrations can also develop following intracranial surgeries not related to the pituitary gland.[33,34] Pituitary dysfunction can exists preoperatively and should be suspected in cases of unexplained fatigue, weakness, altered mental status, and decreased exercise tolerance and treated with adequate supplementation. In the critical care settings where intravenous sedatives are commonly used, it has been observed that those patients who receive drugs like etomidate, propofol, and barbiturates, have higher incidence of HPA dysfunction.[35,36] Commonly encountered pituitary dysfunction in neurosurgical population includes the following:

### Growth hormone deficiency

Diagnosed with the aid of Insulin Tolerance Test (ITT) or growth hormone releasing hormone (GHRH) or arginine test.[37,38] Patients with severe are eligible for growth hormone (GH) replacement for normalization of disturbances.[39] Tumors of the hypothalamic –pituitary regions and their subsequent treatment are an important caused of adult GHD. More than 60% of patients with these tumors have GHD before surgery and more than 80% of them demonstrate severe impairment of somatotroph functions following neurosurgery. Thus, patients bearing hypothalamic pituitary tumors should be evaluated for their somaotrophic functions before and after neurosurgery.[40] Amongst the endocrinopathies affecting critically ill neurosurgical patients, GH function is more fragile than the other hormonal axes.[41] However, administration of growth hormone in long standing critically ill patients has been shown to double mortality.[42]

### Corticotrophic deficiency

It is diagnosed on the basis of low baseline cortisol levels and/or low levels of cortisol following ITT or adrenocorticotropic hormone (ACTH) tests. A high rate of isolated ACTH deficiency is observed in patients with history of seizure disorders. The explanation of this phenomenon remains unclear and it may be due to seizure itself or the effect of antiseizure medications.[34] 15% of patients with TBI suffer from ACTH deficiency, though the clinical manifestation of this phenomenon in form of hyponatremia is attributed to glucocorticoid deficiency.[24] However acute severe hyponatremia caused by ACTH deficiency should also be kept in mind while formulating the diagnosis.[43] Presence of hypoglycaemia or hypotension in presence of SIADH like biochemical findings should raise the suspicion of ACTH deficiency. A subset of TBI patients demonstrate reversible adrenal failure as seen in critically ill patients which is probably mediated by cytokines and/or other inflammatory circulating mediators.[44] This dysregulation necessitated higher levels of vasopressor support during the initial posttraumatic period. Additionally it may demand replacement therapy with low dose hydrocortisone (200-300 mg/day) in the intensive care unit (ICU) phase.[45]

### Thyrotrophic deficiency

It is diagnosed with a low levels of free thyroxine (fT4)[31,46] associated with inappropriately normal or low normal Thyroid Stimulating Hormone (TSH). Therapy for TSH is similar for primary hypothyroidism.[47] The dosage of levothyroxine should be adjusted according to the patient's clinical status and levels of fT4 and free tri-iodothyroxine (fT3) levels. Primary hypoparathyroidism also need to be managed meticulously in such patients.[48] Repeated administration of Thyroid Releasing Hormone (TRH) appears to increase thyroid hormone levels in critically ill patients. In addition if dopamine infusion is withdrawn before TRH administration (dopamine causes non iatrogenic TSH suppression), values of TSH and T3 can be normalized. T4 levels show a minor increase whereas reverse T3 values are not augmented. In this manner, the so called sick euthyroid syndrome or low T3 levels can be near normalized in 8 hours.[49,50]

### Hypogonadism

Diagnosed with the help of low testosterone concentration with inadequately low gonadotropin levels i.e., Luteinizing Hormone (LH) and Follicular Stimulating Hormone (FSH).[51] Most of the clinically non-functioning pituitary tumors are gonadotropin releasing tumors. Gonadotroph pituitary adenomas are inefficient producers and secretors of gonadotroph hormones: LH, FSH and the $\alpha$ subunit of pituitary glycoprotein hormone.[52] Functional FSH secreting tumors can cause spontaneous ovarian hyperstimulation syndrome[53] and testicular enlargement.[54] Gonadotrophins along with GH are the most vulnerable pituitary hormones and they seem to be affected even with mild TBI.[55-57]

### Nutritional aspects

The nutritional deficiencies in such population can exaggerate endocrinological symptoms. The nutritional supplementation should aim to provide not only requisite alimentation and calories but should also provide adequate

micronutrients which are highly essential for early recovery and better outcome in neurosurgical patients.[57-59]

It is postulated that the anatomical location of the hormone secreting cells is the reason for observing the dysfunction along the axis. The somatotrophic cells are located in the lateral wings of the anterior lobe and gonadotrophic cells are situated in the pars distalis and tuberalis which is susceptible to vascular alterations in the long hypophyseal portal system passing through the diaphragma sella. As against this the corticotrophic and thyrotrophic cells are located more antero-medially, which lies in a relatively safe zone in the short hypophyseal system.[29] Thus hypoperfusion of the pituitary gland specially following surgeries is responsible for these endocrinological disturbances.[29] Furthermore, it is hypothesized that secondary hypothalamic dysfunction occurring following radiation in children is due to the altered neurotransmitter release from other brain centers.[60]

## Conclusion

Considering the diverse range of endocrinological dysfunctions affecting neurosurgical patients, it becomes imperative for the treating physicians or intensivists to have a thorough understanding of the different disorders that these patients may be susceptible to. Moreover the time of occurrence of these disorders is inconsistent and hence manifestations can occur anytime during the course of the primary disease. This calls for a high degree of clinical vigilance and suspicion regarding the impending endocrinological derangements and urgent actions in form of replacement (wherever indicated) and other supportive therapies which is required for an overall favorable outcome.

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