Clinical challenges of endocrinological origin in neurocritical care practice

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Received: January 26, 2015
Published online: February 15, 2015

Certain endocrinological disorders are a frequent finding in neurosurgical patients admitted in the neurocritical care units and these disorders have a deleterious bearing in the overall course of the illness and the final outcome. Alteration of neurotransmitters release responsible for maintaining the hormonal homeostasis is the presumable explanation of these disorders. The anatomical nearness of vital centers controlling the release of neurotransmitters and the site of lesion alters the normal pattern of the release and affecting the normal homeostasis thereby leading to adverse consequences on the other organ systems. The anatomical proximity to the vital centres regulating the endocrinological physiology and alteration in the neurotransmitter release causes disturbances in the hormonal homeostasis. Thus, an indepth understanding and early recognition of the clinical changes is necessary so as to arrest the further progress of the endocrine abnormality and to commence early remedial measures.

Keywords: Neurosurgery; Endocrinological Disorder; Syndrome of Inappropriate Antidiuretic Hormone Secretion; Cerebral Salt Wasting Syndrome; Diabetes Insipidus


Introduction

Neurosurgical patients are an exclusive subset of patients who may have varied presentations, amongst which traumatic brain injury (TBI), subarachnoid haemorrhage (SAH), intracranial tumours or pituitary disorders are just to name a few. A common denominator uniting this class of patients is their propensity to develop coexisting endocrinological disorders in addition to their primary pathology, once they are admitted in the neurocritical care units. Disturbances in the hypothalamic hypophyseal axis is often seen following traumatic brain injury TBI, craniopharyngiomas or skull base tumours. Majority of times, the sodium and water homeostasis of the body is influenced, however this is always not the rule. Therapeutic interventions like surgery, medications (steroids, diuretics) and radiotherapy can influence the development of these endocrinological alterations. Once the endocrinological disorders set in, they increase the patient’s morbidity and mortality and escalate the duration of their hospital admission thereby leading to an overall soaring of the treatment related expenditures. Through this review we attempt to highlight the common endocrinological disorders affecting neurosurgical patients and appraise the relevant literature on this topic.

Disorders affecting sodium and water regulation

Disorder in sodium regulation is the commonest endocrinological manifestation of neurosurgical patients and symbolizes the malfunction of different control mechanisms
of the central nervous system (CNS) which control the sodium levels in the body. Sodium disorders are often encountered following brain injury especially when the brain is vulnerable to changes in water and electrolyte levels [1]. Moreover, therapeutic measures like diuretics or mannitol may themselves disturb the water and sodium balance. Etiology of sodium disorders can be varied and these disorders are further classified into hypernatremia and hyponatremia. As with the etiologies, the management strategies of these two conditions also differ.

**Hypernatremia**

This clinical condition is characterized by elevated serum sodium levels (> 145meq/L). Basically this condition is a paradox phenomenon, which reveals the severity of underlying disease process. Patients suffering from head injury associated with hypernatremia have increased mortality rates as compared to those with normal sodium levels [2]. Elevated sodium levels lead to swelling of brain. Hypernatremic dehydration results from disproportionate loss of free water. This further reduces the renal plasma flow and filtration rates aggravating the hypernatremia [2]. Common scenarios where this condition is encountered comprises of altered mental status, decreased consciousness, sedation for airway where this condition is encountered comprises of altered mental status, decreased consciousness, sedation for airway management or frailty. Other important reasons include central diabetes insipidus, fever, dehydration and osmotic diuresis.

Central diabetes insipidus (CDI) is a clinical entity characterized by disturbed homeostatic release of Anti Diuretic Hormone (ADH) from hypothalamic pituitary axis. CDI upsets the normal urinary concentration resulting production of dilute urine. Consequently dehydration and rise in serum osmolarity occurs. This circumstance is often associated with pituitary surgeries, traumatic brain injuries and anterior communicating artery aneurysmal rupture causing subarachnoid haemmorhage (SAH) or intracerebral haemmorhage, brain abscess or subdural haemmorhage [3,4,5]. Very high volume (>6L/day) is seen with this condition, however other differential reasons (aggressive fluid resuscitation, diuretics, hypertonic saline, Triple H Therapy) should be ruled out before DI is confirmed. Lab values characteristically shows unusually raised serum osmolality (>305mmol/kg) and serum sodium (>145 mmol/L) associated with an unusually decreased urine osmolality signifying defect in the renal urine concentrating abilities. Urinary specific gravity of less than 1.005 associated with raised sodium levels is an useful indicator of CDI [1].

CDI is a common association of brain stem death and hence its management is important for brain dead patients posted for organ harvesting [6]. Based on anatomical level of damage (above or below the median eminence), CDI can either be permanent or transient [7].

Treatment of hypernatremia consists of water replacement. Increasing water (in conscious patients) or vasopressin (0.4µg i.v or i100-200µg intranasally) in severe cases are the treatment measures. Rapid correction can however lead to pulmonary or cerebral oedema.

Correlation exists between the initial severity of TBI and presence of oedema and the development of DI. The risk of development of DI initially closely matches with the severity of TBI. In patients with anterior communicating artery (ACom) aneurysm blood supply of hypothalamus may be affected leading to DI. Following SAH, DI can continue up to 3 months in certain patients [8].

Thirst mechanism may be deranged in Adipsic DI which might accompany clipping of ACom aneurysms. Plasma ADH levels are augmented with nonosmotic stimuli like hypotension and apomorphine [9]. Herein, the supraoptic and paraventricular nuclei of the posterior pituitary remain unaffected whereas the osmoreceptors located in the anterior pituitary are affected. Since blood supply to this zone is maintained through small arterioles supplied by ACom artery, disruption of blood supply leads to infarction of these nuclei. Subsequently secretion of ADH in response to thirst or hyperosmolarity is impaired but the response to other stimulations like hypotension is maintained [9]. Extensive surgery for craniopharyngioma or severe injuries to hypothalamus can also produce abnormalities like adipsic DI, loss of baroregulated ADH release, polyphagia, obesity and sleep apnoea which suggest hypothalamic dysfunction [9].

**Hyponatremia**

This clinical situation is described by reduced serum sodium concentration (< 135 meq/L). It is usually observed in critically ill brain injured patients [10]. 29% of the patients affected with subarachnoid haemmorhage and 35% of the patients following pituitary surgeries exhibit features of hyponatremia. Following TBI, it can develop after 2-7 days after head injury and can dramatically increase the mortality (upto 60%) [1,11]. Though commonly associated with hypotonicity it can occasionally be associated with isotonicity or hypertonicity [4]. Volume status estimation of the patient is important as hyponatremia can be hypotonic, isotonic or hypertonic. Clinical aids to assess volume status of hyponatremic patients are weight, jugular venous pressure, orthostatic changes in blood pressure, skin turgor and moistness of mucous membranes. Monitoring the central venous pressure can provide a rough estimation of volume status.
Two diverse entities associated with hyponatremia exist:

1) Syndrome of Inappropriate Anti Diuretic Hormone secretion (SIADH)

2) Cerebral Salt Wasting Syndrome (CWS).

1) The Syndrome of Inappropriate Anti diuretic Hormone secretion (SIADH) can result from TBI, SAH, brain tumour, meningitis/encephalitis or carbemazepine administration. Here inappropriate release of vasopressin causes dilutional hyponatremia. There is failure of plasma ADH concentrations to change following fluid administration/intake or through osmotic trigger. Thus in SIADH, ADH levels remain high inspite of generation of small amounts of concentrated urine. Fluid restriction is the treatment of choice as it is an hypervolemic state. SIADH per se is self limiting however treatment must be initiated when hyponatremia becomes symptomatic or the levels of sodium are very low or falling rapidly. Upto 800-1000ml/day electrolyte free water restriction may be indicated as management. Hypertonic saline is reserved for severe cases especially those with coexisting SAH, where fluid restriction may be contraindicated. Infusion of hypertonic saline should cease when serum sodium reaches 120-125 meq/L .Further management is done using fluid restriction.

Certain drugs which might be added include:-

a) Frusemide:- increases water excretion . Loss of sodium should however be replaced with saline or salts supplementation

b) Demeclocycline and Lithium: -Renal sensitivity to ADH is reduced.

c) Conivaptan and Lixivaptan:-Being ADH antagonists, they inhibit attachment of ADH to renal receptors and promote aquaresis (electrolyte sparing excretion of free water)

2) Cerebral Salt Wasting Syndrome (CSWS) is associated with primary renal losses of sodium causing natriuresis, hyponatremia, polyuria and finally extracellular fluid depletion (hypovolemia) due to central cause. Though its occurrence is common following SAH and TBI, it can be associated with intracranial tumours, ischaemic strokes and tubercular meningitis. It evolves usually during the first week of brain trauma and subsides automatically after 3-4 weeks [12]. Brain derived natriuretic peptides (secreted following intracranial disorders) are responsible for the loss of sodium and extracellular fluids leading to hypovolemia. As a result, the rennin-angiotensin –aldosterone mechanism, sympathetic system and vasopressin hormone are activated for volume regulation. Hence volume depletion is an important diagnostic criteria for CSWS. Treatment involves fluid and sodium replenishment using isotonic or hypertonic saline.

Brain derived Natriuretic Peptide (BNP) is an important mediator of this disorder. It is secreted by thalamus causing diuresis, natriuresis, vasodilatation and inhibits the release of aldosterone, renin and vasopressin. Elevated levels of BNP are present in patients with subarachnoid haemorrhage or haemorrhage at the base of the brain or third ventricle [13,14].

Treatment of hyponatremia requires volume and sodium resuscitation. Initial resuscitation with 0.9% saline is done. Severe cases may require hypertonic saline along with frusemide to reduce volume overload. Refractory cases may necessitate fludrocoritisone (0.1-0.4 mg/day) to increase the sodium reabsorption .This therapy may be complicated by hyperkalemia, so serum potassium levels need to be monitored vigilantly. Pontine and extrapontine myelinolysis is a dreaded complication of rapid rectification of serum sodium. Thus correction of sodium levels should be gradual and not exceed more than 10mmol/L/24 hrs. [15] In suspected rapid or over correction, reversal using desmopressin and water may be advised [16].

A substantial number of patients recovering from TBI develop hyponatremia and majority of them develop SIADH [17]. Following interventions for SAH (craniotomy, clipping or coiling) incidence of hyponatremia also [18].

Hypothalamic pituitary axis dysfunction

TBI and SAH affect the pituitary gland causing endocrinial disorders [19,20]. Tumours like craniopharyngiomas which are in close proximity to pituitary gland can lead to development of endocrine disturbances. Changes in pituitary endocrinology can however also follow intracranial surgeries unrelated to the pituitary gland [21,22]. Common pituitary disorders in neurosurgical population are as follows:

1) Growth Hormone Deficiency (GHD): Tumours of the hypothalamic –pituitary regions and their subsequent treatment can often result in adult GHD. Since about 60% of these patients have preoperative GHD and 80% of them develop somatotrophic dysfunction following surgery, these patients should be evaluated for their somatotrophic functions before and after neurosurgery [23] and require GH replacement [24]. Diagnosis of GHD is done using Insulin Tolerance Test (ITT) or GHRH/arginine tests [25,26].

2) Corticotrophic deficiency (CD): Diagnosed of CD is formulated based on low baseline cortisol levels and/or low levels of cortisol following ITT or ACTH tests. 15% of TBI
patients suffer from ACTH deficiency, although often the resultant hyponatremia is assumed to be due to glucocorticoid deficiency [27]. Hence ACTH deficiency causing hyponatremia should not be overlooked. Hypoglycaemia or hypotension in presence of SIADH like biochemical findings should raise the suspicion of ACTH deficiency. Isolated ACTH deficiency can be a finding in seizure disorder which may be due to the primary pathology or as an effect of anti seizure drugs.

3) Thyrotrophic Deficiency (TD): Diagnosis is based on a low levels of fT4 [23, 28] accompanied by inappropriately normal or low normal Thyroid Stimulating Hormone (TSH). Treatment for TD involves levothyroxine whose dosage should be adjusted according to the patient’s clinical condition and levels of free T4 and free T3

4) Hypogonadism: Indicated by low testosterone concentration with inadequately low Luteinizing Hormone (LH) and Follicular Stimulating Hormone (FSH) levels [29]. Majority of the clinically non functioning pituitary tumours release gonadotropins. Gonadotroph pituitary adenomas are inefficient producers and secretors of gonadotroph hormones: LH, FSH and the α subunit of pituitary glycoprotein hormone [30].

The anatomical position of the hormone secreting cells is the accepted explanation of observing the endocrine alterations along the axis. Since the somatotrophic cells are placed on the lateral wings of the anterior lobe and gonadotrophic cells are situated in the pars distalis and tuberalis, the region which is prone to blood flow changes inside the long hypophyseal portal system. Conversely, corticotrophic and thyrotrophic cells being located more anteromedially in the short hypophyseal system, are in a relatively safer region [19]. Hence pituitary gland hypoperfusion after surgeries causes these region specific disturbances and effects particular hormones. Secondary hypothalamic dysfunction can also occur following radiation in children resulting from altered neurotransmitter release from other brain centres [31].

Since a myriad of endocrinological dysfunctions can be observed in neurocritical care units, the treating physician should be well versed with the diverse etiologies and pathophysiologicals of these disorders. Vigilance over impending endocrinological disturbances and timely and appropriate measures (replacement, corrections etc) can aid in achieving a better patient outcome.

References