Triple Phase Response of Transient Hyponatremia or Secondary Adrenal Insufficiency? A Case Report

Keywords: Hyponatremia; Secondary; adrenal insufficiency; Pituitary gland

Abstract

Hyponatremia is common in neurosurgical patients especially after pituitary surgery. It is the most common electrolyte abnormality encountered in general hospital admissions. Diagnosis of the underlying cause can be challenging. It has serious clinical sequelae if not diagnosed promptly, and can be fatal. Hyponatremia can result from severe hypothyroidism and secondary adrenal insufficiency. In this report, we describe a case of fluctuating sodium level in a middle aged male resembling triple phase response of transient hyponatremia. However, we suggest another diagnosis of hyponatremia due to secondary adrenal insufficiency followed by unmasking of underlying CDI by glucocorticoid replacement after resection of a large non-functioning pituitary macroadenoma.

Case Report

A 42-year-old male presented with bi-temporal hemianopia associated with a large non-functioning pituitary macroadenoma. Pre-operative pituitary hormonal assessment is shown in Table 1. Post PEG recovery index of prolactin was 79%. Other laboratory tests are shown in Table 1. He underwent trans-sphenoidal resection. Intravenous hydrocortisone was commenced peri-operatively. His surgery was complicated by hematoma (Figure 1). He underwent evacuation of haematoma. Second MRI shown in Figure 2. Histopathology confirmed the diagnosis of pituitary adenoma expressing FSH. He initially developed Central Diabetes Insipidus (CDI) with urine output more than 300 ml/hour, hypernatremia (147 mmol/L), serum hyper-osmolarity (307 mOsm/kg) and urine hypo-osmolality of 144 mOsm/kg. He was managed with intermittent 1 µg I.V desmopressin injections (7 times over 4 days). Serum sodium fell to 129mmol/L with desmopressin administrations. His fluid intake was then restricted to 1.5 L/day. Over the next few days,
hyponatremia. We are going to discuss the approach of hyponatremia pattern of hypernatremia followed by hyponatremia and finally shortly after pituitary surgery. The serum sodium showed a triphasic

**Discussion**

The authors presented a case of hyponatremia in a young adult shortly after pituitary surgery. The serum sodium showed a triphasic pattern of hypernatremia followed by hyponatremia and finally hypernatremia. We are going to discuss the approach of hyponatremia first and then how to differentiate triple phase response of transient hyponatremia from SIADH like syndrome due to secondary adrenal insufficiency and unmasking of CDI by steroid replacement.

In approaching hyponatremia, pseudohyponatremia (due to hypertriglyceridemia or hyperparaproteinemia) should be excluded first [2]. Although the index case showed elevated level of lipids as shown in Table 1, pseudohyponatremia was excluded for 3 reasons: first, there was clear serum hypotoncity. Second, the TG was not extremely elevated (less than 9 mmole/L). Third, the osmolar gap (the difference between measured and calculated serum osmolarity) was less than 14 mOsm/kg [2]. Upon clarification, the patient admitted a history of familial hyperlipidemia and he deliberately stopped hypolipidemic agent shortly prior to surgery.

Then we excluded primary polydipsia and reset osmostat syndrome, which is characterised by downward resetting of serum osmolality level to stimulate ADH secretion [2], by the presence of impaired water excretion reflected by urine osmolality ≥ 100 mOsm/kg which indicates complete and appropriate suppression of ADH [2]. Effective arterial blood volume depletion states were excluded by the urine sodium > 20 mmol/L [2]. Ultimately, our provisional diagnosis was limited to SIADH, CSWS, hypothyroidism and hypoadrenalism. CSWS was excluded by the lack of sign and symptoms of hypovolemia such as postural change in pulse rate, laboratory evidence of haemoconcentration, urine osmolality of more than 450 mOsm/kg and urine sodium concentration lower than 20 mmol/L. Furthermore, the low TSH and early morning serum cortisol confirmed the diagnosis of hypopituitarism which was the culprit of hyponatremia in this case. Also, normal potassium level supports the diagnosis of secondary rather than primary adrenal insufficiency. As expected, hyponatremia was dramatically improved after steroid replacement [3]. Interestingly, the glucocorticoid replacement corrected hyponatremia in the index case before thyroxine replacement was initiated which is similar to another case report [10]. This indicates that the hyponatremia was mainly due to adrenal insufficiency rather than hypothyroidism. Hyponatremia can be the only presenting feature of patients with secondary adrenal insufficiency and requires high index of suspicion. Hyponatremia was present in 80% of patients with secondary adrenal insufficiency in a study [1]. Several case reports support this conclusion [1,5,11,12]. Two case reports described hyponatremia secondary to Sheehan’s syndrome [13,14] despite the fact that the latter has classically been associated with CDI. Another case report described hyponatremia in primary empty sella syndrome [10]. Pekic et al. described a case of hyponatremia in familial hypopituitarism due to PROP1 mutation [8]. However, the cases in these reports were mainly elderly [1,5,11,12,15] in contrasts to the index case which is a middle aged patient. similarity Jahangiri et al. study found that age is not a risk factor to develop postoperative hyponatremia [16]. Preoperative hypopituitarism is the single most predictive factor of postoperative hyponatremia [16]. This contrasts the index case whom preoperative pituitary assessment was normal.

Triple phase response which is characterized by hypernatremia due to CDI followed by a transient hyponatremia as result of the rapid release of pre stored ADH in the adenohypophysis due to surgical trauma to the stalk and finally hypernatremia secondary to permanent CDI [3,12]. Our patient’s pituitary stalk seemed relatively

| Table 1: Preoperative hormonal assessment and lipid profile. |
|----------------------|------------------|----------------------|
| Test               | Result           | Reference range      |
| Prolactin          | 522 mIU/L        | 85-500 mIU/L         |
| Testosterone       | 8.9 nmol/L       | 9.5-28 nmol/L        |
| FSH                | 16.7 IU/L        | 1-12 IU/L            |
| TG                 | 4.7 mmol/L       | 0.5-1.7 mmol/L       |
| Cholesterol        | 7 mmol/L         | 3.9-5.5 mmol/L       |

FSH: Follicular stimulating hormone; TG: Triglyceride
intact, as seen in the postoperative MRI scan (Figure 2). Cortisol deficiency can cause hyponatremia by five mechanisms. Firstly, hypocortisolemia will stimulate CRH release from the hypothalamus which is associated with the co-secretion of ADH [1,3]. Secondly, cortisol deficiency stimulates the up-regulation of aquaporin-2 on which ADH exerts its action at the collecting tubules [7]. Thirdly, hyptension which results from cortisol deficiency stimulates the production of ADH via baroreceptors [1,3,8]. Fourthly, cortisol deficiency increases water permeability at the collecting tubules [2]. Fifthly, cortisol has an important role in the maintenance of the normal inhibition of vasopressin in response to hypotonicity and cortisol is a physiological tonic inhibitor of ADH [7,14]. Therefore, steroid replacement can unmask CDI and this is what occurred in the index case. The patient developed DI as a result of hypophysectomy which was treated effectively by desmopressin. Then when he developed secondary hypoadrenalism, the CDI state changed to a SIADH like syndrome which was corrected by steroid replacement. The later resulted in unmasking of a pre-existent and permanent CDI. This scenario is highly similar to triphasic CDI and it is hard to differentiate between the two conditions. However, the prompt response to steroid replacement and the lack of evidence of stalk trauma during surgery can help to differentiate.

In summary, hyponatremia may be the sole presenting feature of secondary adrenal insufficiency. Hypothyroidism should be excluded as well. Prompt replacement with corticosteroids followed by thyroxine is essential and lifesaving. Unmasking of permanent CDI can lead to rapid and over correction of hyponatremia, and this should be differentiated from “triple phase response” of transient hyponatremia.

References