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A Peripheral Marker for a Central Cause – Hyponatremia

E SUMANRAJ*, A NANJIL KUMARAN†, R UMARANI‡, P MUTHIAH‡

ABSTRACT

Hyponatremia is among the commonest electrolyte abnormalities, with an incidence ranging from 10% to 30%. The condition is associated with increased morbidity and mortality. Although endocrine disorders, including adrenal insufficiency and hypothyroidism, are uncommon causes of hyponatremia, yet testing for pituitary-adrenal-gonadal hormone profiles should be part of the hyponatremia workup. Presented here is the report of an uncommon cause of hyponatremia.

Keywords: Hyponatremia, hypothyroidism, adrenal insufficiency, SIADH

Hyponatremia is the most common electrolyte disorder, with an incidence ranging from 10% to 30%. Acute (<48 hours) and chronic hyponatremia are both associated with increased morbidity and mortality. Endocrine disorders, including adrenal insufficiency and hypothyroidism, are uncommon causes of hyponatremia. The appropriate diagnosis of the causative factor is of paramount importance for the proper management and avoidance of treatment pitfalls. Herein, we report an uncommon cause of hyponatremia.

CASE REPORT

A 50-year-old male presented to the outpatient department with complaints of giddiness and easy fatigability of 1 month duration, which was not associated with nausea or vomiting and associated with loss of weight and loss of appetite for the past 3 months. There was no preceding history of fever, headache, abdominal pain, loose stools or vomiting. The patient also did not have any visual disturbances, polyuria, polydipsia, polyphagia, yellowish discoloration of urine or syncopal attacks. Patient consumes alcohol and denied intake of drugs, including steroids and diuretics, in the past.

General physical examination was unremarkable. His height was 161 cm and weight was 58 kg. His vitals were normal except repeated low blood pressure readings of around 100/60 mmHg without any postural change, which responded to fluid challenge. Pulse rate was 78/min which was regular in rhythm. There were no hyper- or hypopigmented patches. Cardiovascular and respiratory systems examinations were normal. Neurological examination revealed no abnormalities, with no localizing cerebellar findings. Ophthalmological examination revealed no visual field defects and normal fundus.

The initial laboratory results were as follows: random blood sugar - 56 mg/dL, hemoglobin - 14.3 g/dL, white cell count - 4.8 × 10^9/L, platelet - 178 × 10^9/L, serum creatinine - 0.9 mg/dL, serum sodium - 116 mmol/L, serum potassium - 4.3 mmol/L and normal liver function tests. Urine osmolality was 223 mOsm/kg and serum triglyceride levels were within normal limits. Electrocardiogram (ECG) and chest X-ray were normal. In the absence of cardiac, renal, liver failure and with no preceding history of vomiting and diarrhea, diagnosis of euvolemic hyponatremia was made. As there were features of fatigability with low blood pressure values and documented hypoglycemia and the absence of pigmentation, secondary adrenal insufficiency was suspected. Pituitary hormone profile was then carried out and the results were as follows: free tetraiodothyronine (fT_4) - 0.52 ng/dL (N = 0.8-2.0), thyroid-stimulating

*Postgraduate
†Lecturer
‡Professor
Dept. of General Medicine and Radiodiagnosis
Rajah Muthiah Medical College, Chidambaram (RMMCH), Tamil Nadu
Address for correspondence
Dr E Sumanraj
Postgraduate
Dept. of General Medicine, RMMCH, Chidambaram, Tamil Nadu

hormone (TSH) - 4.17 μIU/mL (N = 0.35-5.5), luteinizing hormone (LH) - 2.15 mIU/mL (N = 1.7-8.6), follicle-stimulating hormone (FSH) - 3.57 mIU/mL (N = 1.5-12.4) and prolactin - 39.17 ng/mL (N = 4.79-23.3). His morning (6 am) serum cortisol level was 0.17 μg/dL (N = 6.02-18.4). The absence of clinical features of primary adrenal failure together with low cortisol levels, presence of euvolemic hyponatremia and ultrasonically normal adrenals, pointed the finger towards a central cause for hyponatremia. Magnetic resonance imaging (MRI) brain revealed T2 hyperintense mass lesion (20 × 17 mm) in sella with suprasellar extension displacing optic chiasma superiorly, raising the possibility of a pituitary macroadenoma (Fig. 1).

On contrast administration, there was patchy enhancement of lesion, suggestive of pituitary macroadenoma (Fig. 2).

The diagnosis of a nonfunctioning pituitary macroadenoma with secondary hypoadrenalism was made. However, his prolactin level was slightly high, probably due to hormone release from local pressure effect on pituitary stalk. Patient was started on hormone replacement with prednisolone and was referred to neurosurgery department for surgical resection of pituitary adenoma. Adrenocorticotropic hormone (ACTH) stimulation and other hormonal assays were not done as neuroimaging studies were diagnostic.

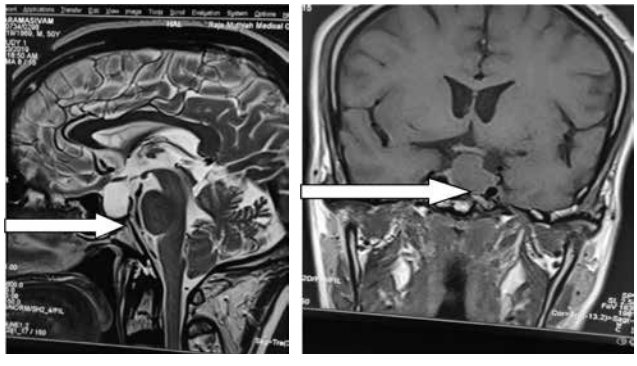

Figure 1. MRI brain revealed T2 hyperintense mass lesion (20 × 17 mm) in sella with suprasellar extension displacing optic chiasma superiorly.

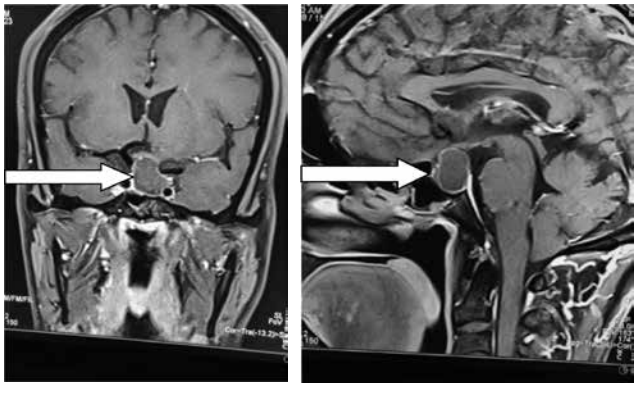

Figure 2. Patchy enhancement of lesion, suggestive of pituitary macroadenoma, on contrast administration.

DISCUSSION

Hyponatremia (serum sodium <135 mmol/L) is generally attributed either to water retention or to loss of effective solutes in excess of water. Hyponatremia can be hypovolemic hyponatremia (diarrhea, vomiting, diuretics, cerebral salt wasting syndrome, mineralocorticoid deficiency), euvolemic hyponatremia (syndrome of inappropriate antidiuretic hormone secretion [SIADH], hypothyroidism, ACTH deficiency) and hypervolemic hyponatremia (congestive cardiac failure [CCF], hepatic cirrhosis, renal failure). Even though endocrine disorders are uncommon causes of hyponatremia, testing for adrenal insufficiency and hypothyroidism should be part of hyponatremia work-up, as the disorder responds promptly to hormone replacement.

Endocrine causes of hyponatremia are as follows:

Adrenal insufficiency

- Primary
  - Addison's disease
  - Autoimmune adrenalitis
  - Infections (tuberculosis, acquired immunodeficiency syndrome [AIDS])
  - Metastatic carcinoma
- Secondary
  - Pituitary or hypothalamic tumors
  - Infections (tuberculosis, histoplasmosis)
  - Craniopharyngioma
  - Empty sella syndrome
  - Lymphocytic hypophysitis

Primary adrenal insufficiency (Addison's disease) is characterized by both aldosterone and cortisol deficiency which contributes to hyponatremia by causing sodium wasting and hypovolemia resulting in hypovolemic hyponatremia, in contrast to euvolemic hyponatremia in secondary adrenal insufficiency. Cortisol is a physiological inhibitor of antidiuretic hormone (ADH) secretion. Hyponatremia in patients with adrenal insufficiency should be ascribed to inappropriate secretion of ADH. The hypersecretion

of ADH by cortisol deficiency may be in part due to the reduction of systolic blood pressure and cardiac output.

Pituitary adenomas are considered the third most frequent intracranial neoplastic lesion (15%), after meningioma and gliomas. The nonfunctioning pituitary adenomas are considered the second most common pituitary adenoma, exceeded only by prolactinoma. Usually, these tumors are manifested by the effect of mass compression, such as headache, blurred vision and seizures. Histopathologically, most nonfunctioning pituitary adenomas have positive immunohistochemistry staining for FSH/LH. Hypopituitarism, especially due to space-occupying lesions, is usually accompanied by more than one pituitary hormone deficiency. Hypopituitarism with secondary adrenal insufficiency is another overlooked cause of hyponatremia, often presenting with a 'SIADH-like picture' (euvolemic hyponatremia, low serum uric acid and urea levels, high urine sodium and osmolality).

Hypothyroidism

Hypothyroidism can result from a defect anywhere in the hypothalamic-pituitary-thyroid axis. In the vast majority of cases, it is caused by thyroid disease (primary hypothyroidism). Much less often, it is caused by decreased secretion of thyrotropin (TSH) from anterior pituitary gland or by decreased secretion of thyrotropin-releasing hormone (TRH) from the hypothalamus (secondary or tertiary hypothyroidism).

Hyponatremia has been reported in patients with moderate-to-severe hypothyroidism. For every 10 mIU/L rise in TSH, serum sodium has been shown to be decreased by 0.14 mmol/L. Mechanism by which hypothyroidism induces hyponatremia involve the inability to maximally suppress ADH. This is due in part to a reduced cardiac output, which can lead to the release of ADH via the carotid sinus baroreceptors. On the other hand, the glomerular filtration rate has been reported to be decreased in hypothyroidism, which leads to diminished water delivery to the diluting segments and subsequently diminished free water excretion. The net effect of impaired water excretion is retention of ingested water and dilutional hyponatremia.

Diagnostic Clues of Hyponatremia due to Endocrine Causes

The diagnosis of acute adrenocortical insufficiency (adrenal crisis) is relatively straightforward in a patient presenting with weakness, abdominal pain, confusion, nausea, vomiting, diarrhea, fever and hypotension combined with hyponatremia, hyperkalemia and raised blood urea. The co-existence of hypoglycemia, hypercalcemia, hypotension is also helpful, if present.

Addison's disease can be recognized by the presence of hyperpigmentation, salt craving, hypotension and hyperkalemia. Hyperkalemia may be absent in approximately 30-50% of patients with Addison's disease. Secondary adrenal insufficiency due to pituitary adenoma can be diagnosed by the presence of mass effect like headache, nausea, vomiting and visual disturbances.

The SIADH is the most common cause of hyponatremia. It is suggested that hypopituitarism should be thought of in all patients with an SIADH-like clinical picture without an obvious cause and even in patients who appear to be mildly dehydrated. The diagnosis of SIADH is suspected in patients with hyponatremia and hypo-osmolality, increased urine osmolality, inappropriate natriuresis, normovolemia, normal renal, pituitary, adrenal and thyroid function and normal acid-base and potassium balance. The diagnosis of SIADH is also supported by the presence of hypouricemia, as well as by low serum urea and phosphate levels.

The differential diagnosis of hyponatremia with a high urine sodium osmolality includes diuretic use, primary and secondary adrenal insufficiency, cerebral salt-wasting, salt-wasting neuropathy and SIADH. Uric acid serves as a valuable index to assess the extracellular fluid volume expansion (SIADH, hypocortisolism), as uric acid reabsorption in the renal proximal tube is inhibited, producing a low serum concentration and a high fractional excretion.

A tendency towards metabolic alkalosis suggests SIADH or diuretic use, whereas metabolic acidosis suggests primary adrenal insufficiency. It has been proposed that secondary adrenal insufficiency might be differentiated from SIADH by the presence of low plasma bicarbonate level and low carbon dioxide levels. Hypokalemia may accompany hyponatremia in diuretic use, whereas hyperkalemia is more typical for primary adrenal insufficiency.

CONCLUSION

Endocrine disorders, including adrenal insufficiency and hypothyroidism, are uncommon causes of hyponatremia. Testing for pituitary-adrenal-gonadal hormone profiles should be part of the hyponatremia workup, as this disorder responds promptly to hormone replacement, while the consequences can be grave when the diagnosis is missed.

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FDA Oks New Therapy for Patients with Previously Treated Multiple Myeloma

The US FDA has given approval for isatuximab-irfc, combined with pomalidomide and dexamethasone, for the treatment of adults with multiple myeloma who have received at least two previous therapies including lenalidomide and a proteasome inhibitor.

Isatuximab-irfc is a CD38-directed cytolytic antibody that assists certain cells in the immune system attack multiple myeloma cancer cells. The drug is administered through intravenous (IV) infusion… (*FDA*)

Variation in Nightly Bedtime, Sleep Duration Tied to CVD Risk

People who frequently change the amount of sleep and the time they go to bed each night have double the odds of developing cardiovascular disease, independent of traditional CVD risk factors, suggests new research published in the *Journal of the American College of Cardiology*. Investigators used data of 1,992 Multi-Ethnic Study of Atherosclerosis (MESA) participants, aged 45 to 84 years, who were free of CVD and were followed for a median of 4.9 years. About 39.5% had sleep duration standard deviation (SD) >90 minutes and 25.6% had sleep-onset timing SD >90 minutes. In comparison with people who had <1 hour of variation in sleep duration, the risk for incident CVD was 9% higher for those whose sleep duration varied 61 to 90 minutes, even after controlling for several cardiovascular and sleep-related risk factors including BMI, systolic blood pressure, smoking status, total cholesterol, average sleep duration, insomnia symptoms, and sleep apnea.