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Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH) Associated with Cerebellar Stroke: Case Report and Literature Review

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Authors' contributions

This work was carried out in collaboration among all authors. Author KI designed the report, wrote the protocol, done literature searches and wrote first draft of the manuscript. Authors RMAS and GV were involved in the design of report, proofread the first draft, done the literature searches and assisted in finalizing the manuscript. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

11-34 % of acute ischemic stroke patients will develop hyponatremia. Hyponatremia in stroke is usually of the hypoosmolar type caused either due to the Syndrome of Inappropriate Secretion of Anti Diuretic Hormone (SIADH) or Cerebral Salt Wasting Syndrome (CSWS). In Ischemic strokes hyponatremia secondary to SIADH is mostly seen in strokes involving anterior circulation where the hypothalamic-pituitary axis is directly involved. In this report, we present SIADH in a patient with cerebellar stroke and discuss the possible mechanisms of development of SIADH in cerebellar stroke.

Keywords: Inappropriate secretion syndrome; Antidiuretic Hormone (SIADH); cerebellar stroke.

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1. INTRODUCTION

Acute ischemic stroke is the fourth leading cause of death and most common cause of long-term disability worldwide. Studies have shown that about 11-34 % of acute ischemic stroke patients will develop hyponatremia [1]. A study by Rodrigues B et al. [2] has shown that patients with hyponatremia have worse National institute of health stroke scale (NIHSS) scores on admission and their NIHSS Score worsens during hospitalization. Also low sodium levels on admission are associated with increased 30-day mortality after an acute ischemic stroke and significantly longer hospital stay [3]. A study by Nelson M et al. [4] had shown that patients with hyponatremia on admission to an in-patient cancer rehabilitation unit, had a prolonged rehabilitation length of stay, but Functional Independence Measure (FIM) change and survival was not significantly different from those with normal sodium level.

Saleem S et al. in their study on hyponatremia in stroke showed a 35% incidence of hyponatremia (Serum Sodium <130 meq/L) among which 67% were having Syndrome of Inappropriate Secretion of Anti Diuretic Hormone (SIADH) and 33% were having Cerebral Salt Wasting Syndrome(CSWS) [5]. Incidence of hyponatremia was more in haemorrhagic compared to ischemic strokes, and most of the cases were associated with middle cerebral artery strokes. Hyponatremia in stroke is usually of the hypoosmolar type caused either due to the SIADH or CSWS. It is important to distinguish between these two disorders, as the treatment of the two differs to a large extent.

In a report by Jeong-Min Kim et al. they presented a lateral medullary syndrome patient with CSWS and suggested that CSWS could have been caused by the descending sympathetic tract injury which disrupted the sympathetic stimulus to the kidney [6]. Another report by Hiroro Nakano et al presented an association with lateral medullary syndrome and SIADH and speculated that the ischemic damage of the ascending neural pathway from the nucleus of solitary tract to the paraventricular nucleus in the hypothalamus could be related to the pathogenesis of SIADH in lateral medullary syndrome [7].

1.1 Aim

In this report, we present SIADH in a patient with cerebellar stroke and discuss the possible mechanisms of development of SIADH in our patient. Literature search failed to yield a similar report showing association of SIADH in cerebellar stroke.

2. CASE PRESENTATION

A 62 year old man, with history of systemic hypertension and diabetes mellitus, presented to the emergency room of a tertiary health care institution in Qatar in December 2019, with acute onset dizziness and unsteadiness. CT scan ruled out stroke and he was discharged with medications to control hypertension and dizziness. 4 days later he presented again with worsening dizziness, unsteadiness, nausea and vomiting. His blood pressures were in the range of 180/100 mm Hg. He was admitted for observation and detailed work up. On admission, muscle tonus was normal without obvious paralysis in all four limbs. His right upper extremity demonstrated slight tremors, dysmetria and dysdiadochokinesia. His gait was ataxic with poor scores in SARA (Scale for assessment and rating of ataxia), BBS (Berg balance score) and Trunk impairment scale. His was functionally dependent because of his co-ordination and gait disturbances with FIM of 59 and Rankin score of 3 (Moderate disability).

Brain magnetic resonance imaging (MRI) demonstrated an acute infarct in right superior cerebellar hemisphere, middle cerebellar peduncle and tiny part of right posterior midbrain in keeping with right acute superior cerebellar artery infarct. Right superior cerebellar artery was occluded. Rest of the brain was normal except for mild cerebral cortical atrophy. (Fig. 1)

His blood pressure was controlled with four antihypertensives (Amlodipine, Carvedilol, Perindopril and Hydralazine) and he was started on Insulin for glycemic control. Hematological examination showed normal serum sodium levels of 135 mEq/L (Normal range 135-145 mEq/L) on admission to acute care. However, the serum sodium levels decreased gradually, and on admission to rehab hospital (8 days after stroke), his sodium levels dropped to 126 mEq/L. But he was asymptomatic and there were no signs of volume expansion or fluid loss. Investigations revealed a decreased serum osmolality of 254 mOs mol/kg (Normal range 285-295 mOs mol/kg). Urine osmolarity was 472 mOsmol/kg (<100 mOsmol/kg, appropriate suppression of ADH), and random urine sodium was 70 mmol/L (Normal >20 mmol/L). Thyroid, renal, and adrenal functions were normal. He was not

diabetic (HbA1C 5.4% (<6% normal; >6.5% diabetic). Chest X ray didn't reveal any abnormalities and abdominal ultrasound was also normal except for increased echogenicity of both kidneys.

He was diagnosed as having SIADH based on the diagnostic criteria of Bartter and Schwartz. He was treated with free water restriction to less than 800 ml and increased solute intake in the form of oral salt tablets. He didn't require diuretics or vasopressin receptor antagonists as his sodium levels normalised with above therapy. Laboratory examination after 10 days (18 days post stroke) showed normal serum sodium levels (140 mEq/L). His admission and discharge key laboratory values are summarized in Table 1. His neurological symptoms, such as dizziness, dysarthria and ataxia, also gradually resolved, and thereafter, hyponatremia was not observed till discharge from rehabilitation. His functions also improved well with a discharge FIM of 125 as compared to 59 on admission.

3. DISCUSSION

Cerebellar infarcts are relatively uncommon and represent ≈2% of all ischemic strokes. Potential pathogeneses include cardiac emboli, large-vessel atherosclerosis, vertebral artery dissection, local arterial disease, and less commonly hypercoagulable conditions, vasculitis, venous sinus thrombosis, and drug use [8].

Hyponatraemia is the most common electrolyte disorder encountered in clinical practice and s seen in a wide variety of conditions and is defined as a serum sodium < 135 mmol/L. It may be classified according to severity as mild: 130-134 mmol/L, moderate: 125-129 mmol/L and Severe: < 125 mmol/L, and depending on the time of onset as, acute: < 48 hours duration and

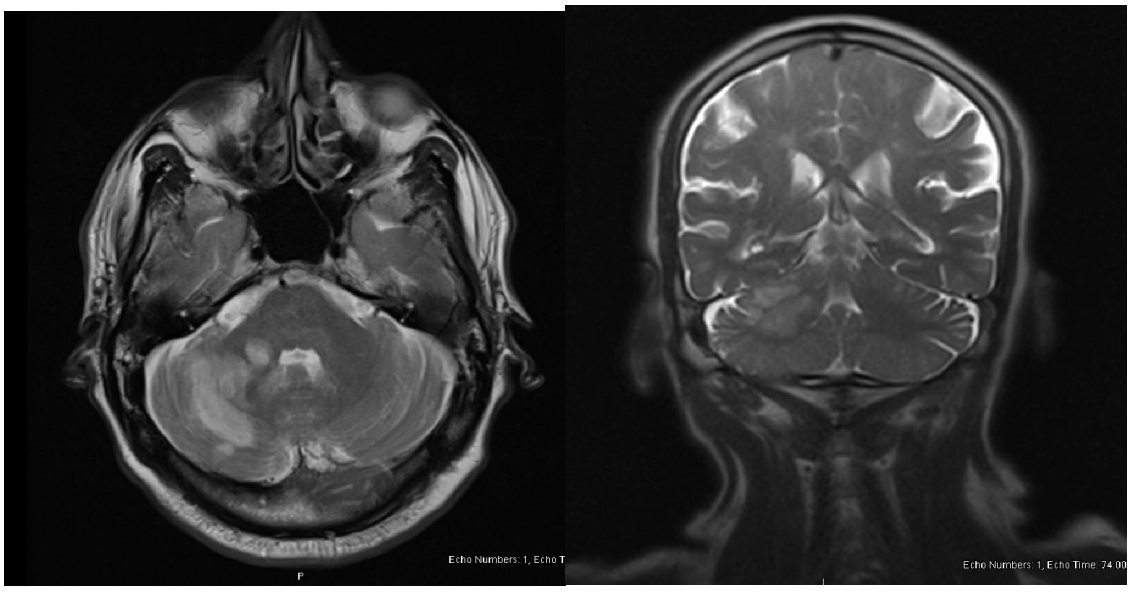

Fig. 1. Brain magnetic resonance imaging

Table 1. Admission and discharge laboratory values

Lab parameter	Admission	Discharge/Post hyponatremia correction	Reference range
Serum Sodium	126 mEq/L	138 mEq/L	135-145 mEq/L
Serum Potassium	4.8 mEq/L	4.8 mEq/L	3.5- 5.5 mEq/L
Serum creatinine	82 umol/L	-	74-107 umol/L
Serum Osmolality	254 mOsmol/kg	285 mOsmol/kg	285-295 mOsmol/kg
Urine Osmolality	472 mOsmol/kg	80 mOsmol/kg	<100 mOsmol/kg
Random serum sodium	70 mmol/L	28 mmol/L	>20 mmol/L
TSH	2.8 mU/L	-	0.4-4 mU/L
Serum Cortisol	16 ug/dl	-	10-20 ug/dl (AM)

chronic: > 48 hours duration. Mild hyponatraemia is not life threatening and the management should be that of the underlying disorder, whereas, severe hyponatraemia, particularly when of rapid onset, may be associated with acute fluid shifts which can cause life-threatening cerebral edema.

The extracellular and intracellular compartments are in osmotic equilibrium, and water moves freely across the cell membrane in response to changes in serum osmolality. Sodium is the most abundant solute in ECF, and is thus the largest contributor to serum osmolality. The main hormone that regulates extracellular water is antidiuretic hormone (ADH), which is secreted by the posterior pituitary gland in response to high serum osmolality acting through osmoreceptors in hypothalamus. It acts on the V2 receptors in the distal convoluted tubule and collecting duct of the kidney. This causes aquaporin 2 proteins to be inserted into the cell membrane, which increases its permeability to water. This makes the urine more concentrated and decreases the serum osmolality and serum sodium concentration. ADH secretion is also a potent stimulator of thirst, which also brings more water into the ECF via fluid ingestion [9].

The cerebellum and hypothalamus are interconnected through a multitude of direct (monosynaptic) and indirect (polysynaptic) pathways. Direct hypothalamocerebellar fibres are mainly uncrossed and reach all parts of the cerebellar cortex and nuclei. Indirect hypothalamocerebellar connections may be relayed through various brain stem nuclei. The hypothalamo-ponto-cerebellar pathway, which has a contralateral predominance, appears to be the quantitatively most important of these. The direct cerebellohypothalamic projection originates from the cerebellar nuclei and terminates in the posterior hypothalamus, in the same regions where the direct hypo-thalamocerebellar pathway has its main origin. Indirect cerebellohypothalamic connections with brain stem relays have also been demonstrated. The functions of hypothalamocerebellar circuits are so far unknown. However, these pathways are probably involved in the coordination and integration of somatic as well as non-somatic responses to a given set of inputs [10]. We assume that the reason behind the development of SIADH in our patient is likely due the involvement of these cerebello-hypothalamic circuits.

SIADH is essentially a diagnosis of exclusion [11]. SIADH occurs in a wide range of pulmonary, CNS and malignant conditions, as well as frequently being implicated in drug-induced hyponatraemia. A number of drugs can enhance ADH release or action. However our patient was not receiving any of the commonly implicated drugs that can precipitate SIADH. Lung tumors, especially small cell carcinoma, produce ADH ectopically. Other tumors like cancers of pancreas, duodenum, head and neck may also produce ADH occasionally. Several lung disorders including pneumonia can cause SIADH by unknown mechanisms. Other pulmonary diseases causing SIADH are bronchial asthma, atelectasis, acute respiratory failure and pneumothorax. Major surgical procedures, which include abdominal and thoracic surgeries, can cause hypersecretion of ADH, probably mediated by pain afferents. Pituitary surgery is also associated with inappropriate ADH release [12]. We have ruled out all possible causes of SIADH in our patient with appropriate investigations. SIADH is diagnosed using the Bartter and Schwartz criteria [13] (Table 2).

Table 2. Bartter and Schwartz criteria Criteria for diagnosing the syndrome of inappropriate antidiuretic hormone secretion (SIADH)

1.	Hyponatraemia with corresponding hypoosmolality of the serum and ECF (<275 mosm/kg)
2.	Continued renal excretion of sodium (>20 mEq/L)
3.	Absence of clinical evidence of fluid volume depletion or overload, that is, normal skin turgor and blood pressure, or absence of oedema
4.	Osmolality of the urine greater than that appropriate for the concomitant tonicity (effective osmolality) of the plasma, that is, urine not maximally dilute (>100 mosm/kg)
5.	Normal renal function
6.	Normal adrenal function
7.	Normal thyroid function

Fluid restriction is the main stay of treatment in SIADH. Usual recommended fluid intake is less than 800 ml/day. Oral salt tablets are also recommended to be provided along with a loop diuretic like furosemide which interferes with the counter current concentrating mechanism by decreasing sodium chloride reabsorption in the thick ascending limb of loop of Henle. Vasopressin receptor antagonists produce a selective water diuresis without interfering with sodium and potassium excretion. Tolvaptan, satavaptan and lixivaptan are selective V2 receptor antagonists, while conivaptan blocks both V1 and V1a receptors. Demeclocycline is a tetracycline derivative which induces drug-induced diabetes insipidus by acting on the collecting tubule cell to diminish its responsiveness to ADH. The role is limited in emergency care due to the slow onset of action [14].

4. CONCLUSION

SIADH is a common cause of hyponatremia in stroke patients, which can lead to adverse outcomes if not diagnosed and treated early. However, association of SIADH with posterior circulation strokes are not frequently reported. Our case demonstrates such an association of SIADH with cerebellar stroke. We postulate that the involvement of cerebello-hypothalamic circuits could be the pathology behind SIADH in our patient.

CONSENT AND ETHICAL APPROVAL

As per institutional medical research committee guideline, informed and written participant consent and ethical approval have been collected and preserved by the author

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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