

Salt wasting syndrome; a review on current findings and new concepts

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Abstract

Cerebral/renal salt wasting is a disease category that has evolved as a medical entity by differentiation of syndrome of inappropriate ADH (SIADH) secretion. It is characterized by depletion of extracellular volume and thereby negative sodium balance. While there is a great overlap in the clinical and laboratory characteristics of SIADH and salt wasting; the therapeutic interventions are contradictory and they include limiting water intake in SIADH and providing for free water and salt intake in salt wasting to overcome the tendency to develop hypernatremia.

Introduction

Cerebral/renal salt wasting is a disease category that has evolved as a medical entity by differentiation of syndrome of inappropriate anti-diuretic hormone (SIADH) secretion. It is characterized by depletion of extracellular volume and thereby negative sodium balance (1,2).

While SIADH was first described in Schwartz et al in 1957 (3); the medical entity of "salt wasting" was first reported by Peters et al in 1957 as case reports of patients of cerebral disease presenting with renal sodium loss resulting in hyponatremia (4). In 1981, Nelson et al once again highlighted in their paper that hyponatremia in intracranial disease was perhaps not the SIADH and rekindled the interest in cerebral/renal salt wasting (5). Maesaka et al showed in the literature published that salt wasting could occur in patients without cerebral disease and hence in recent times the syndrome is referred to as renal salt wasting syndrome (1,6).

Materials and Methods

For this review, we used a variety of sources by searching through Web of Science, PubMed, EMBASE, Scopus and directory of open access journals (DOAJ). The search was performed using combinations of the following key words and or their equivalents such as; salt wasting, syndrome of inappropriate ADH secretion (SIADH), cerebral/renal salt wasting, Alzheimer's

Core tip

Cerebral/renal salt wasting is a disease category that is characterized by depletion of extracellular volume and thereby negative sodium balance.

disease, hyponatremia and hypernatremia.

Pathophysiology of salt wasting syndrome

There are controversies around the pathophysiology of salt wasting due to the overlap with SIADH. However, there is consensus that in salt wasting; in spite of a normal hypothalamic-pituitary-adrenal axis there is renal inability of varying degrees to retain salt resulting in decreased extracellular volume and hyponatremia (4).

Recently Oh et al described two hypothesis for the development of this syndrome. The first hypothesis is reduced sympathetic tone which should result in decreased renin and aldosterone in salt wasting. But contrary to this renin and aldosterone levels have been noted to be high in salt wasting (1). This may be because after the initial sodium loss which results in decreased extracellular volume; the patient reaches a steady state level where sodium loss matches sodium intake due to compensatory hemodynamic and neurohumoral changes (7). Aldosterone production is stimulated by the decreased extracellular volume. When sodium intake is sufficient; the defect in proximal sodium transport ensures salt supply to distal



nephron to maintain renin production (8).

Another hypothesis is increased circulation of natriuretic peptides like brain natriuretic peptide. The natriuretic peptides cause increase sodium loss through increased glomerular filtration rate and prevent sodium reabsorption in the collecting duct (7).

Thus the initial pathology in salt wasting is a defect in sodium transport in the kidneys. The extracellular volume in the end depends on the extent of this defect and sodium intake by the patient. The decreased extracellular volume acts as stimulus for the baroreceptors to cause an increased release of anti-diuretic hormone (ADH) (6). In patients of salt wasting the stimulus for increased ADH secretion due to hypovolemia is more powerful than the ADH inhibition which is caused by decreased plasma osmolality (8).

Renal salt wasting may be observed in patients with impaired physiological thirst for example geriatric patients or Alzheimer's disease. Such patients may present with hypo- or hypernatremia (9).

Distinguishing SIADH from salt wasting

There are considerable similarities in symptomatology and investigation results of salt wasting and SIADH. While hyponatremia is the common symptom between these two conditions; hypovolemia is characteristic of salt wasting where in SIADH the patient is euvolemic or hypervolemic. Since the fluid of hypervolemia accumulates in extracellular space; it has no routine clinical manifestations like edema; increase in blood pressure or engorgement of neck veins (10,11). The circulating blood volume can be measured; however there may be false estimations in case of concomitant cardiac or pulmonary disorders (10). Radio-isotope dilution method is the gold standard for determining ECF volume (12). Another differentiating factor is an increase in fractional excretion of phosphate which is seen in salt wasting but absent in SIADH (2).

Plasma renin and aldosterone levels which are increased in salt wasting and generally depressed in SIADH should be interpreted carefully as they may be normal in patients of salt wasting who have adequate intake of salt (1,2).

Maesaka et al tabulated the differences between SIADH and renal salt wasting, which is given in Table 1 (6).

The main pathophysiology in SIADH is excess secretion of ADH in spite of euvolemia.

In SIADH, a certain amount of volume expansion may be noted with free water intake due to increased ADH and atrial natriuretic peptide levels and decreased renin and aldosterone levels. Also, the volume expansion may cause hyponatremia and plasma hypoosmolarity (13). In SIADH; after the initial Salt Wasting and excess retention of water; there is a phenomenon of vasopressin escape where sodium and water intake measures the output (2,13).

Hyponatremia is accompanied by hypouricemia and increased fractional excretion of urate. Fractional excretion of urate returns to normal after correction of hyponatremia but ADH levels do not correct themselves with correction of hyponatremia. Therefore the hypouricemia and

Table 1. Differences between SIADH and renal salt wasting syndrome

	Salt wasting	SIADH
Extracellular volume	↓	Normal/↑
Urinary sodium concentration	Normal/↑	Normal/↑
Renin	± ↑	± ↓
Aldosterone	↑	± ↓
Serum Urate	↓↓	↓/ Normal
Fractional excretion of urate	↑↑	↑/ Normal
Fractional excretion of phosphate	± ↑	Normal

Abbreviation: SIADH, syndrome of Inappropriate secretion of antidiuretic hormone.

increased fractional excretion of urate cannot be attributed to V1 activity of ADH. Also, when SIADH is induced by administration of desmopressin which is devoid of V1 activity; an increase in fractional excretion of urate is observed along with hyponatremia (14).

In patients of moderate to severe Alzheimer's disease; there is elevated fractional excretion of urate and decreased serum urate in the absence of hyponatremia (9).

Treatment

While there is a great overlap in the clinical and laboratory characteristics of SIADH and salt wasting; the therapeutic interventions are contradictory and they include limiting water intake in SIADH and providing for free water and salt intake in salt wasting to overcome the tendency to develop hypernatremia. Oral salt supplementation with loop diuretics can be considered as a treatment of hyponatremia caused by SIADH (15). Euvolemia and hypervolemic hyponatremia may merit the use of vasopressin receptor antagonists in cases of SIADH in adults (16); however caution should be exerted in use of these drugs in children (17,18).

Hyponatremia can be dangerous in patients of salt wasting due to the phenomenon of vasogenic cerebral edema (19). Vasogenic cerebral edema can be catastrophic and it involves the accumulation of high protein rich contents in the extracellular space which can penetrate the blood brain barrier secondary to increased vascular permeability (20-23). The treatment of acute symptomatic hyponatremia is administering three percent NaCl. However, caution must be exerted as an excessive correction in chronic cases as can lead to osmotic demyelination in rare cases which can result in severe neurologic complications like seizures, paralysis, coma or death (24,25). NaCl or normal saline; initially hypertonic and then later isotonic is used in Salt Wasting to bring the sodium levels and intravascular volume back to normal (7). Hypertonic saline is also used when large amounts of fluids are necessary to obtain euvolemia or when serum sodium levels are extremely low i.e. <125 mEq/L (26). Once the patient becomes euvolemic; hyponatremia also resolves quickly. Therefore a critical step is to evaluate sodium levels post achievement of euvolemia as at times mineralocorticoids (27-30) may be necessary to elevate the serum sodium concentration and intravascular volume. For stable patients; oral salt

supplementation can be done (7).

Conclusion

Cerebral/renal salt wasting is a disease category that has evolved as a medical entity by differentiation of SIADH secretion. It is characterized by depletion of extracellular volume and thereby negative sodium balance. While there is a great overlap in the clinical and laboratory characteristics of SIADH and salt wasting; the therapeutic interventions are contradictory and they include limiting water intake in SIADH and providing for free water and salt intake in salt wasting to overcome the tendency to develop hyponatremia.

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Authors' contribution

CJG and SSW searched and gathered the related articles. CJG prepared the draft. GSR edited the final manuscript. All authors read and signed the final paper.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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