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INVITED REVIEW

Clinical salt deficits

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Abstract Salt retention or salt deficit has a bearing on the body fluid volume. Both states are clinically difficult to recognize and quantitate. Salt deficit is particularly cumbersome in that regard since orthostatic blood pressure, heart rate changes, and simple physical inspection are inaccurate and unreliable. Salt deficit can be acute such as after hemorrhage or massive diarrhea, or more chronic as observed in Addison's disease, failure of renal sodium chloride transporters, drug-related effects, or distal nephron disease. Molecular genetics has given us important new insights into salt deficit syndromes. Recent recognition of a novel sodium storage compartment involving sodium binding to proteoglycans adds to the overall complexity of these syndromes.

Keywords Sodium wasting · Salt losses · Sodium reabsorption · Cerebral salt wasting · Volume deficit · Hypotension

Introduction

Assessing salt deficit or volume depletion, despite common belief, in patients is not trivial [12]. After a careful history, physicians generally (or should) measure blood pressure and heart rate with and without orthostatic stress, assess atrial filling pressures, inspect skin and mucous membranes, and if necessary, resort to laboratory tests and invasive measurements. Supine hypotension and tachycardia are frequently absent, even after up to >1000 mL of blood loss. Surgeons have known since World War I that patients in hemorrhagic shock not uncommonly have bradycardia rather than tachycardia. The finding of mild postural dizziness has no proven value. In patients with vomiting, diarrhea, or decreased oral intake, the presence of a dry axilla supports the diagnosis of hypovolemia, and moist mucous membranes and a tongue without furrows argue against it. In adults, the capillary refill time and poor skin turgor have no proven diagnostic value. As a matter of fact, large postural pulse change (≥30 beats/min) or severe postural dizziness is required to clinically diagnose hypovolemia due to blood loss, although these findings are often absent after moderate amounts of blood loss. In patients with vomiting, diarrhea, or decreased oral intake, few findings have proven utility, and clinicians should measure serum electrolytes, serum blood urea nitrogen, and creatinine levels when diagnostic certainty is required. In persons with a more chronic salt and volume deficit extending over days, weeks, or indefinitely, no clinical tests are helpful. For animal models of disease from worms, flies, fish, rodents, and larger mammals, the state-of-affairs regarding volume assessment is surely worse.

A clinical scenario with accepted volume (or salt) deficit at least in the circulating fluid space is septic shock. In such patients, an early goal-directed therapy involving intensive monitoring of blood pressure, filling pressures, and central venous oxygen saturation was introduced over a decade ago [14]. Here, "almost everything" was directly measured, and surely any volume deficit present was detected. Nevertheless, a recent multicenter trial of this strategy has called even goal-directed therapy into question [13]. Thus, the entire topic of salt deficit, either acute or chronic, should be approached with respective humility.

Salt is ingested through the mouth and is distributed in the extracellular space with some salt being deposited into reservoirs. The kidneys regulate salt excretion as the final common pathway to maintain the internal environment life compatible and to maintain circulating fluid volume at an appropriate

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level. In the kidney, numerous salt re-absorptive mechanisms have been described at the finest molecular level and physical effects, including pressure natriuresis being worked out in detail. A recently induced confounder (Fig. 1) involves a third space for sodium, bound to proteoglycans predominantly in the skin. Immune cells, mostly monocyte phagocytic system (MPS) cells harboring tonicity-responsive enhancer binding protein (TonEBP/NFAT5), regulate this space. The local micro-environmental signals involve MPS-cell release of vascular endothelial growth factor-C (VEGF-C) that controls lymph-capillary density and regulates local sodium clearance from stores. Bone indeed stores sodium, albeit not in a very exchangeable form. The sodium "third space" indeed appears to involve primarily the skin and other glycosamino-glycan-rich areas [18].

Genetics

Mendelian syndromes causing hypertension or hypotension have been the richest source of delineating salt excess (expansion) or salt deficit (contraction), the mirror image. Interestingly, the mirror-image syndromes have helped us perhaps the most. Gitelman described related persons with hypokalemic alkalosis and hypotension. The patients were indeed volume depleted according to the best tests of the time. Gitelman's syndrome represents the predominant subset of Bartter's patients having hypomagnesemia and hypocalciuria. The Lifton laboratory demonstrated complete linkage of Gitelman's syndrome to the locus encoding the renal thiazide-sensitive Na-Cl cotransporter and identified a wide variety of non-conservative mutations, consistent with loss of function alleles, in affected subjects [17]. The Lifton group followed up on this major finding in collaboration with Rossier et al. [3] The collaborators identified a critically important mutation in the epithelial sodium channel (ENaC) was that produced the mirror image of Liddle's syndrome, a Mendelian form of hypertension. Autosomal recessive pseudohypoaldosteronism type I is a rare life-threatening disease characterized by severe neonatal salt wasting, hyperkalaemia, metabolic acidosis, and unresponsiveness to mineralocorticoid hormones. Mutations in either the alpha or beta subunits of the amiloride-sensitive epithelial sodium channel in five kindreds demonstrated the molecular basis and explained the pathophysiology of this disease. That report was quickly followed by a subsequent study involving a mechanism that gates ENaC [6]. Geller et al. from the Lifton laboratory reported that heterozygous mineralocorticoid receptor mutations also can cause pseudohypoaldosteronism type I, which underscores the important role of mineralocorticoid receptor function in regulation of salt and blood pressure homeostasis in humans and motivate further study of this gene for a potential role in blood pressure variation [5].

Finally, the Bartter syndromes have been investigated in detail [15]. There are numerous types. Patients with Bartter syndrome types 1, 2, and 4 present at a younger age than classical Bartter syndrome type 3 patients. The severe, steady-state hypokalemia in Bartter syndrome and Gitelman syndrome may abruptly become life threatening under certain aggravating conditions. The sodium chloride cotransporter, NCCT; the chloride channel, ClC-Kb, in distal convoluted tubule dysfunction; the sodium–potassium–chloride cotransporter, NKCC2; the renal outer medullary potassium channel, ROMK; and the chloride channels ClC-Ka and ClC-Kb, and their beta-subunit, Barttin, are all involved here. Clinicians need to be cognizant of such renal tubular disorders and promptly treat at-risk patients. Furthermore, mutations in the K^+ channel gene, KCNJ10 (Kir4.1), cause the autosomal

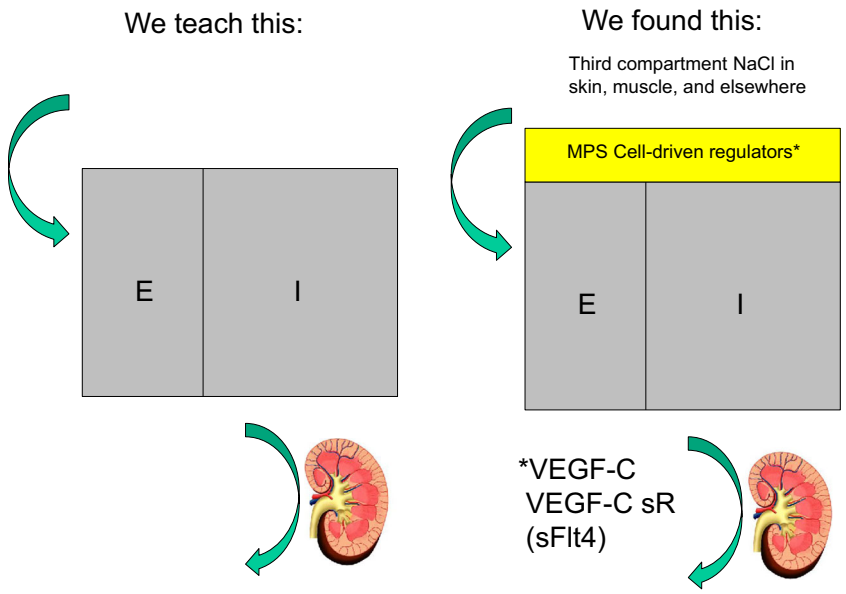

Fig. 1 Conventional salt balance perceives a two-compartment model with the mouth and the kidneys offering input and output. Recent evidence draws attention to a third compartment regulated by immune cells that could account for the clinical confusion accompanying these syndromes

recessive EAST syndrome, which is characterized by epilepsy, ataxia, sensorineural deafness, and a salt-wasting tubulopathy [1].

In addition, there are various adrenal syndromes. Congenital adrenal hyperplasia caused by steroid 21-hydroxylase deficiency occurs in 1 of 16,000 births and can cause death in early infancy from shock, hyponatremia, and hyperkalemia [19]. Affected girls usually have ambiguous genitalia but boys appear normal. Diagnosis is based on elevated levels of 17-hydroxyprogesterone, the preferred substrate for steroid 21-hydroxylase. Moreover, congenital adrenal hyperplasia diagnosis rests upon the measurement of levels of steroid precursors after stimulation with cosyntropin. A diagnostic second tier relies on DNA-based methods or liquid chromatography followed by tandem mass spectrometry.

Genetic distal tubular disease can also cause salt deficit. Most of the hereditary tubulointerstitial nephropathy involves cyst formation in the kidney [8]. Among these syndromes are juvenile nephronophthisis and medullary sponge kidney, which primarily involve the tubule structures of the renal medulla. The conditions are associated with variable enlargement of the distal tubules and collecting ducts with interstitial fibrosis and inflammation to a variable extent. Juvenile nephronophthisis features sodium wasting, anemia, and renal failure.

Do these genetic syndromes play a role in the blood pressure (salt surfeit–deficit) in the general population? Interestingly, the salt deficit syndromes are relevant to research on essential hypertension. Studies from the Framingham cohort would suggest that this is indeed the case [9]. Heterozygosity for these mutations in the general population can lower blood pressure and confound hypertension-producing mechanisms. As a result, genome-wide association studies of hypertension could be similarly confounded.

Acquired salt wasting

Thomas Addison first described a clinical syndrome characterized by salt-wasting and skin hyperpigmentation, associated with a destruction of the adrenal gland. Primary adrenal insufficiency can present as a life-threatening condition, since it frequently goes unrecognized in its early stages. Autoimmune Addison's disease is currently the most common cause of primary adrenal insufficiency. Rdo et al. recently illustrated the prevalence of different etiologies, clinical manifestations, and laboratorial findings, including the adrenal cortex autoantibody and 21-hydroxylase antibodies, in a Brazilian series of patients with primary adrenal insufficiency [16]. We recently described a typical patient who entered an emergency room with abdominal discomfort, hyponatremia, hypoglycemia, and metabolic acidosis. Half of Addison's patients do not exhibit hyperkalemia. The diagnoses made by the admitting clinicians were metabolic acidosis through vomiting (faulty thinking) and acute appendicitis (Addison's disease commonly is accompanied by abdominal discomfort). The hyponatremia and hypoglycemia were ignored, and any tests of volume deficit (despite their inaccuracies) were not performed [10]. The patient survived, thanked her surgeons for saving her life, and left the hospital (albeit with hormonal replacement) as oblivious as she had come.

Acquired distal tubular disease can result in total-body salt deficit. Renal impairment with a decline in glomerular filtration has been the classical nephrotoxicity of cisplatin. Renal salt wasting syndrome is another complication of cisplatin, albeit not common [7]. Cisplatin nephrotoxicity may exhibit decreased renal function, polyuria, hyponatremia, hypokalemia, hypomagnesemia, and other disturbances, although volume depletion is not commonly recognized. Because of similarities in clinical settings and laboratory values, the condition may be misdiagnosed as a syndrome of inappropriate antidiuretic hormone (SIADH). Other causes of polyuria and hyponatremia should be excluded. Treatment aims at restoring the lost water and salt. Substituting cisplatin with carboplatin depends on individual clinical settings. The long-term prognosis is quite good, as recovery was the rule in most reported cases.

The sodium-glucose transport protein-2 (SGLT2) is responsible for at least 90 % of glucose reabsorption in the kidney. Blocking this transporter causes blood glucose to be eliminated in the urine. Compounds such as dapagliflozin inhibit SGLT2, lower HbA1C by about 0.9 percentage points, and could be of utility for treating type 2 diabetes mellitus. The resultant glycosuria acts as an osmotic diuretic. Furthermore, SGLT2 resorbs not only glucose, but also sodium. Because glomerular hyperfiltration currently is recognized as a risk factor for progression of kidney disease in diabetic patients, limiting proximal tubular reabsorption of both glucose and sodium constitutes a potential target to reduce hyperfiltration [4]. Detailed evaluations of SGLT2 inhibitors and total-body sodium homeostasis have not been performed, although clinicians are warned about volume depletion. These warnings would appear to be disingenuous without underlying detailed data on the effects of these drugs and sodium homeostasis.

Cerebral salt wasting is a recognized salt volume deficit. Distinguishing cerebral from renal salt wasting is not easy [11]. Hyponatremia and increased antidiuretic hormone release are confounders within these syndromes. The difficulty in differentiating renal salt wasting or cerebral salt wasting from SIADH lies in the clinical and laboratory similarities between the syndromes and the conundrum of accurately assessing extracellular volume status (see "Introduction"). Furthermore, few clinicians measure cardiac filling pressures directly. Radioisotopic determinations of extracellular volume

in neurosurgical patients suggested that renal salt wasting could be even more common than SIADH. The presence of hypouricemia as a marker of SIADH and increased fractional excretion of urate in renal salt wasting, compared to correction of both in SIADH, the appropriateness of ADH secretion in renal salt wasting, and the importance of differentiating renal salt wasting from SIADH because of disparate treatment goals, hardly clarified the cloudy situation. Fluid volume repletion in renal salt wasting and fluid restriction in SIADH are diametrically opposed strategies. Patients with renal salt wasting or cerebral salt wasting could be incorrectly treated by fluid restriction, with clinical consequences. As a result, what is the difference between renal salt wasting and cerebral salt wasting?

Perhaps the most convincing paper on cerebral salt wasting was the report by Berendes et al. [2]. These authors measured the plasma concentrations of digoxin-like immunoreactive substances and natriuretic peptides, aldosterone, renin, and antidiuretic hormone in patients with aneurysmal subarachnoid hemorrhage, 10 patients undergoing elective craniotomy for cerebral tumors and 40 healthy controls of similar age and sex distribution. They found that all patients with subarachnoid hemorrhage, but none of the tumor patients, showed increased urine output and urinary excretion of sodium. The patients with subarachnoid hemorrhage had much higher plasma concentrations of brain natriuretic peptide than controls, accompanied by lower than normal aldosterone concentrations and normal plasma concentrations of atrial and C-type natriuretic peptides. The patients with tumors had similar plasma concentrations of natriuretic peptides compared to the controls. No digoxin-like immunoreactive substances were detected in either group of patients. Thus, salt wasting of central origin may induce hyponatremia in patients with aneurysmal subarachnoid hemorrhage, possibly as a result of increased secretion of natriuretic peptides with subsequent suppression of aldosterone synthesis.

Perspectives

Similar to policemen, “the clinician’s lot is not a happy one.” Salt deficit (volume depletion) syndromes are largely a matter of clinical judgment (policy) and arbitrary definitions. In chronic volume depletion cases, genetic analyses may help in finally classifying patients. Better tests are desperately needed to assess sodium stores and volumes. Careful history, clinical assessment, and even monitoring of cardiac filling pressures, cardiac output, oxygen delivery, oxygen demand, and oxygen extraction do not always seem to “fit the bill.” Possibly, sodium magnetic resonance imaging of third-space sodium stores could fulfill a substantial clinical and experimental deficit [18].

Disclosures None.

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