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Differentiating between SIADH and CSW Using Fractional Excretion of Uric Acid and Phosphate: A Narrative Review

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Abstract

Background: Sodium imbalances are among the most common electrolyte abnormalities encountered in the acute care setting. The syndrome of inappropriate anti-diuretic hormone (SIADH) and cerebral salt wasting (CSW) are characterized by hyponatremia and can be difficult to differentiate. Failure to accurately diagnose these conditions and implement the correct treatment results in an increased mortality risk, a longer length of stay in the hospital, and an increase in the cost of hospitalization. **Objective:** The purpose of this review is to summarize the key diagnostic findings in each disorder and to review the use of the fractional excretion of uric acid (FeUA) and the fractional excretion of phosphate as additional diagnostic measures to differentiate between SIADH and CSW. **Observation:** Publications from MEDLINE, CINAHL, and Google Scholar from 2009 through 2017 were reviewed. Articles were included if original data was presented and diagnosed either SIADH or CSW. Articles were excluded if they did not discuss diagnostic measures or were review articles. **Results:** Thirteen out of 51 publications met the inclusion criteria; four (31%) were clinical trials, seven (54%) were case reports, one (7.5%) was a prospective study and one (7.5%) was a retrospective-observational study. The populations studied, the etiologies causing hyponatremia, and diagnostic criteria used to distinguish between SIADH and CSW varied. **Conclusion and Relevance:** There is a need for consistent diagnostic criteria for SIADH and CSW. Based on current evidence, the use of FeUA and the fractional excretion of phosphate have consistently and accurately differentiated between SIADH and CSW.

Keywords

Hyponatremia, Syndrome of Inappropriate Anti-Diuretic Hormone, Cerebral

*These authors contributed equally to the manuscript.

Salt Wasting, Fractional Excretion of Uric Acid, Fractional Excretion of Phosphate

1. Introduction

Hyponatremia is one of the most frequently encountered electrolyte imbalances observed in both neurosurgical patients as well as patients in the acute care setting. It is commonly associated with traumatic brain injuries (TBI) or other neurological insults such as subarachnoid hemorrhage (SAH), subdural hematoma (SDH), epidural hematoma (EDH), aneurysmal clipping or coiling, tumors, or infections. It has a prevalence rate of 15% - 30% [1].

It is often difficult to diagnose these conditions because they are diagnoses of exclusion. SIADH and CSW can be even more difficult to diagnose correctly because they share many of the same characteristics. Determination of fluid volume status has been the mainstay key indicator in differentiating between the two, however, unless CVP monitoring is implemented (which can only be done in the ICU), it can be difficult to correctly determine FVS.

Prompt recognition is imperative so that the appropriate treatment can be implemented. SIADH and CSW appear very similar clinically, however the treatments for both are not only different, but implementing the wrong treatment has been shown to increase the risk of mortality, increase the length of stay in the intensive care unit (ICU) and the hospital, and result in an increased cost of hospitalization [2] [3].

One approach that has been used recently includes the determination of the fractional excretion of uric acid and the fractional excretion of phosphate. These lab results are not only easy to obtain and trend, but also consistently and accurately differentiate between SIADH and CSW.

The purpose of this review is to summarize the key diagnostic findings in each disorder and to review the use of the fractional excretion of uric acid (FeUA) and the fractional excretion of phosphate as additional diagnostic measures to differentiate between SIADH and CSW.

2. Methods

A literature search of the MEDLINE and CINAHL databases and Google Scholar from 2009 through 2017 was performed. Initial search criteria included phrases such as “hyponatremia” AND “syndrome of inappropriate anti-diuretic hormone”, “hyponatremia” AND “cerebral salt wasting”, “syndrome of inappropriate anti-diuretic hormone” AND “fractional excretion of uric acid”, “cerebral salt wasting” AND “fractional excretion of uric acid”, “syndrome of inappropriate anti-diuretic hormone” AND “fractional excretion of phosphate”, “cerebral salt wasting” AND “fractional excretion of phosphate”. A manual search using the references of select articles was also performed. The search was limited

to English publications only.

Studies were included if original data was presented in the forms of clinical trials, case studies, and prospective or retrospective observational studies and if the diagnosis of either SIADH or CSW was made. Studies were excluded if they were review articles or if they discussed only the pathophysiology of SIADH or CSW, or if they successfully differentiated between SIADH and CSW but did not include the treatments implemented.

Information was collected and analyzed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement checklist (**Figure 1**) [4]. Information included the year and source of publication, the type and size of the study, the inclusion and exclusion criteria, and the etiologies of SIADH and CSW. Glasgow Coma Scale (GCS) scores were also recorded upon admission and discharge. Intake and output was recorded as well as levels of urine specific gravity, plasma and urine osmolality, serum sodium, serum uric acid, blood urea nitrogen (BUN), creatinine, plasma vasopressin, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), fractional excretion of sodium, fractional excretion of uric acid, and fractional excretion of phosphate.

3. Results

A total of 51 articles were selected for review. Forty-two were identified through

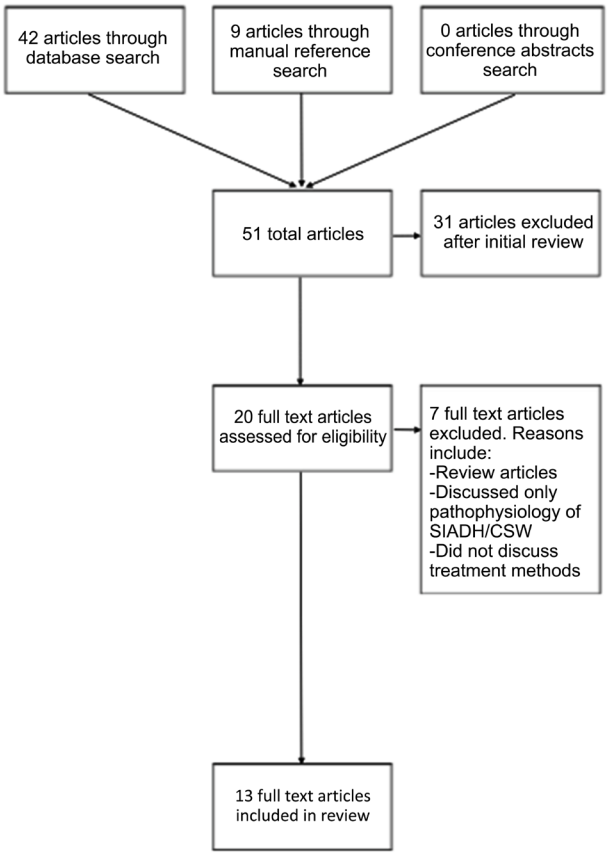

Figure 1. PRISMA flow diagram demonstrating article selection process.

a Google scholar and electronic database search. Nine articles were hand selected through searching references. After a preliminary review, 31 articles were eliminated based on the exclusion criteria. A final review excluded 7 articles for not meeting the inclusion criteria.

Thirteen out of 51 total publications met the inclusion criteria; four (31%) were clinical trials, seven (54%) were case reports, one (7.5%) was a prospective study and one (7.5%) was a retrospective-observational study. Three out of 13 articles (23%) were from a neurology or neurosurgical journal [2] [5] [6]. Six out of 13 articles (46%) were published in a nephrology journal [7]-[12], and 4 out of 13 articles (31%) were found within journals of different specialties [13] [14] [15] [16].

4. Discussion

4.1. Pathophysiology

The anti-diuretic hormone, arginine vasopressin (AVP) is synthesized by the supraoptic and paraventricular nuclei in the hypothalamus in response to osmotic and non-osmotic stimuli. Once synthesized, it is released into the bloodstream where it can bind to the V2 receptors in the distal convoluted and collecting tubules in the kidneys [17] [18]. Binding and activation of the V2 receptors allow for water reabsorption and sodium excretion by the kidneys in an effort to regulate blood volume and serum osmolality [18].

Osmotic triggers for AVP release include changes in the plasma osmolality. If the plasma osmolality is low (less than 275), secretion of AVP is stopped, resulting in excretion of free water to prevent decreases in plasma osmolality. If greater than 284, the osmoreceptors signal to the hypothalamus to release AVP. Another trigger for AVP release is through non-osmotic stimuli, such as with changes in extracellular fluid (ECF) as recognized by baroreceptors in the aorta, carotid sinuses, atria, and pulmonary veins. A decreased ECF and low FVS trigger the secretion of vasopressin, epinephrine, and angiotensin II, and the subsequent secretion of AVP [17].

Disruptions of AVP are often caused by a direct or indirect insult to the hypothalamus or pituitary gland. Indirect causes include medications such as lithium or demeclocycline. Direct causes include TBI, SAH, pituitary surgery, SAH, diffuse axonal injury, or clipping of anterior communicating artery aneurysms [13].

4.2. SIADH

SIADH is a dysfunction of AVP secretion due to an insult of the hypothalamus or pituitary gland. Normally, there are negative feedback mechanisms regulating the release of AVP, however in SIADH, there is a failure to suppress ADH even at low plasma osmolalities. This results in the retention of water and a dilutional hyponatremia [17].

4.3. Cerebral Salt Wasting

CSW is a disorder characterized by ECF depletion and hyponatremia. It is a true hyponatremia, first described by Peters et al as a cerebral disease causing natriuresis and diuresis [19]. The pathophysiology is still not yet understood, however there are two proposed mechanisms. The first theory is that a direct injury to the central nervous system (CNS) may cause a disruption in the stimulation of the proximal tubules, causing abnormal natriuresis and diuresis [20] [21]. The second theory is an increased secretion of human atrial natriuretic peptide (hANP) and brain natriuretic peptide (BNP) in response to brain injury, resulting in an increased natriuresis and diuresis [14].

5. Clinical Presentation

SIADH and CSW

Patients with SIADH and CSW share almost identical clinical presentations, making early recognition extremely difficult. Symptoms do not usually appear unless the serum sodium is less than 120 and are non-specific. Initial symptoms may include headache, lethargy, inattention, nausea, muscle cramps and weakness and may progress to confusion, hallucinations, psychosis, and dysarthria with worsening hyponatremia. Patients that have "grave" hyponatremia may present with seizures, respiratory insufficiency, hemiplegia, coma, and death [22].

The one difference in clinical presentation is the patient's fluid volume status. Patients with SIADH are typically euvolemic whereas patients with CSW are hypovolemic and may appear dehydrated. Determination of the patient's FVS has been the gold standard in identifying one condition over the other, as clinically diagnosing a patient based upon presentation can be almost impossible.

6. Assessment and Diagnosis

Patients presenting with Neurogenic DI, SIADH, or CSW require a thorough history and physical examination with relevant diagnostic scans (CT/CTA, MRI), laboratory testing (including but not limited to blood levels of electrolytes, plasma, and urine osmolalities), and accurate determination of FVS [23].

SIADH and CSW

Correct diagnosis of SIADH and CSW can be very difficult to determine and it is essential that a careful and thorough workup has been conducted before making a diagnosis. According to a study by Zomp & Alexander, 62% of neurosurgical patients with hyponatremia have SIADH and 4.8% - 31.5% of patients with hyponatremia have CSW [24]. They appear very similar clinically, as both syndromes are often associated with neurological insults, have relatively normal renal, adrenal, and thyroid functions, have similar diagnostic laboratory results, yet have very different treatment options [25].

Laboratory findings associated with both SIADH and CSW include a serum

sodium level less than 135 mEq/L, a serum osmolality less than 275 mOsm/kg, a normal or elevated urinary sodium level (greater than or equal to 30 mEq/L), an elevated urinary osmolality level (>100 mOsm/kg), a urinary specific gravity of >1.010, decreased urine output, and an initially elevated fractional excretion of uric acid (**Table 1**) [25] [26].

Current practices rely upon the FVS as the key indicator in differentiating between the two syndromes, however obtaining accurate FVS is not always easy. Hypovolemia, as seen in CSW, is diagnosed most reliably when CVP monitoring is available [13]. CSW is marked by a low CVP (<6), whereas SIADH has a normal or increased CVP (6 - 10) [20] [27]. The problem with CVP monitoring is that it is limited to patients in the ICU setting and is not available to patients on the medical-surgical or telemetry floors. In cases where accurate FVS is difficult to obtain, there is promising new research regarding the fractional excretion of uric acid (FeUA) and the fractional excretion of phosphate that is demonstrating a potentially easier, safer, and more reliable method of differentiating between the two.

In both SIADH and CSW, there is an increased level of FeUA (>10). The key difference is that in SIADH, FeUA is initially elevated but as the hyponatremia is corrected and returns to baseline, there is a return of the FeUA to baseline (<10). In CSW, there is an increase is FeUA (>10) but as the hyponatremia is corrected, the FeUA continues to stay elevated (>10) [10] [14] [15] [16].

The fractional excretion of phosphate is another diagnostic lab that is promising, but has limited research. Initial studies have consistently demonstrated that the fractional excretion of phosphate is elevated in CSW (>20%) and normal in SIADH (**Table 1**) [28] [29].

7. Treatment

7.1. SIADH

The initial treatment of SIADH depends on the severity of the hyponatremia. Current US guidelines classify the severity of hyponatremia based upon serum sodium levels and formulate a treatment plan based upon serum sodium levels and symptoms.

Recommendations for the treatment of moderate to profound hyponatremia suggest the restriction of fluid intake as initial therapy. For hyponatremia with severe symptoms, they recommend the intravenous (IV) administration of hypertonic saline and subsequent checking of serum sodium levels every 6 hours. The goal for therapy is an increase in serum sodium levels to a maximum of 10mmol/L in the first 24 hours and a maximum of 8mmol/L for every 24-hour period afterwards until a serum sodium level of 130mmol/L is reached [26].

Other medications used in the treatment of SIADH include the use of vasopressin receptor antagonists, loop diuretics, urea, and sodium chloride tablets. Lithium and demeclocycline has been previously used in the management of

Table 1. Clinical and diagnostic characteristics of SIADH and CSW.

Diagnostic Values	SIADH	CSW
Serum Na level, mEq/L [11]	Hyponatremia (<135)	Hyponatremia (<135)
Serum Osmolality, mOsm/kg [26]	<275 (low)	<275 (low)
Urinary Na level, mEq/L [26]	Normal or elevated (>30)	Elevated (>30)
Urinary Osmolality, mOsm/kg [26]	Elevated (>100)	Elevated (>100)
Urinary Specific Gravity [18]	>1.010 (concentrated)	>1.010 (concentrated)
Urine Output [18]	Decreased (500 mL/24 h)	Decreased
Fluid Volume Status [13]	Euvolemic	Hypovolemic
Central Venous Pressure [2] [26]	Normal, or increased (>6 cm water)	Decreased (<6 cm water)
Fractional Excretion Of Uric Acid [14] [26]	>12%, then decreases as Na returns to baseline	>12%, and stays elevated as Na returns to baseline
Fractional Excretion of Phosphate [32]	Normal (<10%)	Elevated (>20%)

SIADH, however their use is controversial as they can lead to the development of DI [30].

7.2. CSW

Current guidelines recommend the use of hypertonic saline in the initial management of severe hyponatremia. Once the serum sodium level has been corrected, they recommend converting to 0.9% normal saline in an effort to restore FVS [28]. Other medications such as fludrocortisone have been used in the treatment of CSW. Fludrocortisone acts on the distal tubules in kidney to promote reabsorption of water and sodium, successfully restoring fluid volume status [31].

8. Prognosis

The prognosis for patients with SIADH and CSW varies and is dependent upon multiple variables: the etiology of the underlying disease, the severity of hypo-/hypernatremia, if diagnosis was prompt and accurate, and if appropriate treatment was administered. If treatment was delayed, if sodium levels were corrected too quickly (resulting in osmotic demyelination), or if the incorrect treatment was implemented (as in the restriction of fluids for a patient with CSW rather than SIADH), then the risk of mortality due to sequelae significantly increases. Failure to accurately diagnose these conditions and implement the correct treatment results in an increased mortality risk, a longer length of stay in the hospital, and an increase in the cost of hospitalization [2] [3].

9. Conclusion

The incidence of SIADH and CSW in patients with TBI or other neurosurgical

insults is common and requires accurate diagnosis and prompt treatment; current practices use the determination of fluid volume status as the key to differentiating between SIADH and CSW, although it is not always easy to obtain. Implementing the wrong treatment in these patients has been shown to increase mortality risk as well as other sequelae, thus prompting the need for additional diagnostic criteria that is safe, reliable, and consistent. Current evidence has demonstrated that the use of FeUA and the fractional excretion of phosphate is not only safe, but accurately and consistently differentiates between SIADH and CSW

Ethical Standards

The manuscript does not contain clinical studies or patient data.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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