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Cerebral Salt-Wasting Syndrome

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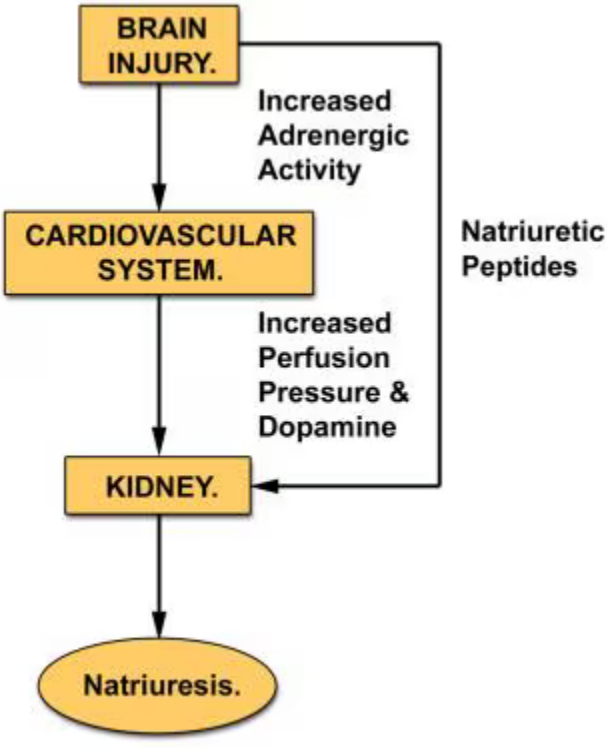
Overview

Practice Essentials

First described by Peters et al in 1950, cerebral salt-wasting syndrome is defined by the development of extracellular volume depletion due to a renal sodium transport abnormality in patients with intracranial disease and normal adrenal and thyroid function.[1, 2] As such, it may be more appropriately termed renal salt wasting. Complications of cerebral salt-wasting syndrome include symptomatic hyponatremia and dehydration. (See Pathophysiology, Etiology, and Presentation.) Management of cerebral salt-wasting syndrome centers on correction of intravascular volume depletion and hyponatremia, as well as on replacement of ongoing urinary sodium loss, usually with intravenous (IV) hypertonic saline solutions.[3]

Differentiation of this disorder from the syndrome of inappropriate antidiuretic hormone secretion (SIADH), a common cause of hyponatremia, can be difficult because both can present with hyponatremia and concentrated urine with natriuresis. However, distinguishing between the two disorders is important because treatment options differ. Attention to the volume status of the patient is important in making the distinction. Failure to distinguish cerebral salt-wasting syndrome from SIADH in a patient with hyponatremia who has brain injury could lead to inappropriate therapy with fluid restriction. (See Presentation and Workup.)

Although the diagnosis of cerebral salt-wasting syndrome is thought to be controversial by some,[4] it should be considered a discrete clinical entity and may be more common than perceived.[5] It should also be considered in patients without cerebral disease.[4, 6] Possible mechanisms for cerebral salt-wasting syndrome are shown in the chart below.



Possible mechanisms for cerebral salt-wasting syndrome. The injured brain may release natriuretic proteins that act directly on the kidney. In addition, cerebral injury may increase sympathetic nervous system activity, elevating renal perfusion pressure and releasing dopamine.

Signs and symptoms of cerebral salt-wasting syndrome

Physical signs of cerebral salt-wasting syndrome (renal salt wasting) include those associated with severe hyponatremia or intravascular volume depletion.

Hyponatremia can be indicated by acute central nervous system (CNS) dysfunction, such as altered mental status, seizures, and coma.

The differentiation of SIADH from cerebral salt-wasting syndrome depends on an accurate estimation of extracellular volume. Unfortunately, no single physical finding can accurately and reproducibly measure effective circulating volume. Commonly used signs of hypovolemia include the following:

- Orthostatic tachycardia or hypotension
- Increased capillary refill time
- Increased skin turgor
- Dry mucous membranes
- A sunken anterior fontanelle

These signs usually appear only when the degree of dehydration is moderate to severe. Central venous pressure may be an unreliable determinant of extracellular volume.

Workup in cerebral salt-wasting syndrome

The following lab studies may be indicated in patients with cerebral salt-wasting syndrome:

- Serum sodium concentration - Patients with untreated cerebral salt-wasting syndrome are often hyponatremic
- Serum osmolality - If measured serum osmolality exceeds twice the serum sodium concentration and azotemia is not present, suspect hyperglycemia or mannitol as the cause of hyponatremia
- Urinary output - Urine flow rate is often high in cerebral salt-wasting syndrome; urine flow rate is low in SIADH

Management

Evaluation and treatment of cerebral salt-wasting syndrome, or renal salt wasting, typically occurs in the inpatient setting because most patients are seriously ill with acute CNS disease.

Management centers on correction of intravascular volume depletion and hyponatremia, as well as on replacement of ongoing urinary sodium loss, usually with intravenous (IV) hypertonic saline solutions.[3] Some clinicians have reported a favorable response to mineralocorticoid therapy in cerebral salt-wasting syndrome. Once the patient is stabilized, enteral salt supplementation can be considered.

Pathophysiology

Cerebral salt-wasting syndrome, or renal salt wasting, may be more common than SIADH and may even occur in the absence of cerebral disease.[4, 5, 7] Although the exact mechanism that underlies the development of cerebral salt-wasting syndrome is unclear, it is known that the initiating defect in renal sodium transport leads to extracellular volume depletion and that a cascade of compensatory changes occurs.

Abnormalities in the proximal tubule result in excessive sodium losses, which lead to decreased effective circulating volume. This activates baroreceptors, which increase antidiuretic hormone (ADH) secretion. This results in water conservation and a return to an equilibrated state. In contrast, SIADH primarily occurs due to an inappropriate euvolemic rise in ADH secretion.

The relationship among serum urate, fractional excretion of urate, and hyponatremia in cerebral salt-wasting syndrome is unclear. Fractional excretion of urate may remain elevated even after correction of hyponatremia in patients with cerebral salt-wasting syndrome. This is distinct from SIADH, in which the fractional excretion of urate returns to the reference range once the hyponatremia is corrected.[6] The physiologic basis for this in cerebral salt-wasting syndrome may be related to the

receptor-mediated processing of sodium and urate in the proximal tubule, which may be defective in this syndrome. The physiologic basis for hypouricemia in SIADH remains unclear.

The abnormalities in proximal tubular transport may be secondary to a plasma natriuretic factor that reduces proximal and, possibly, distal sodium transport in cerebral salt-wasting syndrome. It may also inhibit the tubular transport of urate, phosphate, and urea in addition to sodium.[8]

A retrospective study by Musch and Decaux indicated that the existence of transient cerebral salt-wasting syndrome (renal salt wasting) in normonatremic hospital patients is not rare, especially in individuals with neurologic or cardiac disorders. The investigators found that out of 200 normonatremic patients with normal kidney function who were admitted to the internal medicine department of a Belgian hospital, 11 had transient renal salt wasting, none of it associated with diuretic intake. The majority of these patients presented with neurologic or cardiac disease or hypertension.[9]

Research by Maesaka et al suggested that the natriuretic factor haptoglobin-related protein without signal peptide (HPRWSP) can serve as a biomarker for cerebral salt-wasting syndrome (renal salt wasting). The investigators also indicated that in patients with Alzheimer disease, HPRWSP progressively rises as the Mini-Mental State Examination (MMSE) score decreases, with volume depletion in most or all patients with Alzheimer disease worsening as their dementia becomes more severe. Moreover, while upregulation of HPRWSP was found in various research patients to be transient, with the protein's level dropping with treatment of the comorbid disorder, in Alzheimer disease, the increase seemed to be permanent.[10]

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Etiology

Cerebral salt-wasting syndrome, or renal salt wasting, occurs in the setting of acute central nervous system (CNS) disease. Conditions leading to cerebral salt-wasting syndrome include the following:

- Head injury
- Brain tumor
- Intracranial surgery
- Stroke
- Intracerebral hemorrhage[11]
- Tuberculous meningitis
- Craniosynostosis repair

Cerebral salt-wasting syndrome can also occur in the absence of cerebral disease.[7]

The exact mechanism underlying cerebral salt-wasting syndrome remains unclear. In the setting of cerebral injury, one hypothesis is that an exaggerated renal pressure–natriuresis response caused by increased activity of the sympathetic nervous system and dopamine release is responsible for urinary sodium loss.

Another hypothesis involves the release of natriuretic factors, possibly including brain natriuretic peptide (C-type natriuretic peptide) or urodilatin by the injured brain. Kojima et al have described an animal model of cerebral salt-wasting syndrome that may allow better clarification of the condition's etiology.[12]

A study by Léveillé et al indicated that in persons with traumatic brain injury, risk factors for subsequent significant hyponatremia include a diffuse injury pattern on computed tomography (CT) scan, the presence of multiple lesions on CT scan, and intracerebral hemorrhage.[13]

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Epidemiology

Occurrence in the United States

Exact incidence data for this disorder are not available. Approximately 60% of children with brain injuries or tumors develop hyponatremia during their hospital course. Some experts suggest that cerebral salt-wasting syndrome (renal salt wasting) is responsible for hyponatremia at least as often as SIADH is, particularly in neurosurgical patients. Other studies indicate that this syndrome explains the development of hyponatremia in no more than 6% of patients with acute brain injuries.[14] A literature review by Leonard et al found the incidence of cerebral salt-wasting syndrome reported in traumatic brain injury to vary between 0.8-34.6%, with the studies determining these incidences differing with respect to the populations evaluated and the definitions used for hyponatremia and cerebral salt wasting.[15] The exact incidence of renal salt-wasting syndrome without cerebral disease is also unknown.

Age-related demographics

Cerebral salt-wasting syndrome can occur at any age. Published reports include patients aged 6 months to 65 years.

Mortality/morbidity

A study by Kalita et al suggested that cerebral salt wasting is the most frequent cause of stroke-related hyponatremia. The study, of 100 patients with stroke, including 47% with ischemic stroke and 53% with intracerebral hemorrhage, found that 43% of the stroke patients had hyponatremia. Of these, 19 (44.2%) had cerebral salt wasting, while 3 (7.0%) had SIADH, 14 (32.6%) had miscellaneous causes of hyponatremia, and 7 (16.3%) had indeterminate causes of the condition. The investigators also found that length of hospital stay independently predicted the development of cerebral salt wasting and hyponatremia.[16]

A study by Misra et al suggested that in patients with tuberculous meningitis, hypovolemia associated with cerebral salt wasting may play a role in the occurrence of stroke. The report included 81 individuals with tuberculous meningitis, 39.5% of whom suffered ischemic stroke; 50% of these stroke patients had cerebral salt wasting.[17]

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Prognosis

Cerebral salt-wasting syndrome usually develops in the first week following a brain insult. Its duration is usually brief (spontaneously resolves in 2-4 wk), although it can last for several months. Death and complication rates for this syndrome are not available. (See Treatment and Medication.)

Presentation

History

Hyponatremia and cerebral salt-wasting syndrome

As the decline in serum sodium concentration reduces serum osmolality, a tonicity gradient develops across the blood-brain barrier that causes cerebral edema. Symptoms include lethargy, agitation, headache, altered consciousness, seizures, and coma.[18]

The severity of symptoms typically reflects the magnitude and rapidity of the decrease in serum sodium concentration.

Intravascular volume depletion

Historical features suggesting hypovolemia include thirst, abrupt weight loss, decreasing urinary frequency, and negative fluid balance.

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Physical Examination

Physical signs of cerebral salt-wasting syndrome (renal salt wasting) include those associated with severe hyponatremia or

intravascular volume depletion.

Hyponatremia can be indicated by acute CNS dysfunction, such as altered mental status, seizures, and coma.

The differentiation of SIADH from cerebral salt-wasting syndrome depends on an accurate estimation of extracellular volume. Unfortunately, no single physical finding can accurately and reproducibly measure effective circulating volume. Commonly used signs of hypovolemia include orthostatic tachycardia or hypotension, increased capillary refill time, increased skin turgor, dry mucous membranes, and a sunken anterior fontanelle. These signs usually appear only when the degree of dehydration is moderate to severe. Central venous pressure may be an unreliable determinant of extracellular volume.

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Workup

Approach Considerations

Failure to distinguish cerebral salt-wasting syndrome (renal salt wasting) from SIADH as the cause of hyponatremia may lead to improper therapy (ie, fluid restriction), thereby exacerbating intravascular volume depletion and potentially jeopardizing cerebral perfusion.

The following lab studies may be indicated in patients with cerebral salt-wasting syndrome:

- Serum sodium concentration - Patients with untreated cerebral salt-wasting syndrome are often hyponatremic
- Serum osmolality - If measured serum osmolality exceeds twice the serum sodium concentration and azotemia is not present, suspect hyperglycemia or mannitol as the cause of hyponatremia
- Urinary output - Urine flow rate is often high in cerebral salt-wasting syndrome; urine flow rate is low in SIADH

Urinary sodium concentrations

Urinary sodium concentrations are typically elevated in SIADH and in cerebral salt-wasting syndrome (>40 mEq/L). However, urinary sodium excretion (urinary sodium concentration [mEq/L] x urinary volume [L/24 h]) is substantially higher than sodium intake in cerebral salt-wasting syndrome but generally equals sodium intake in SIADH. Therefore, net sodium balance (intake minus output) is negative in cerebral salt-wasting syndrome.

Urinary sodium excretion and urinary volume

A retrospective study by Arieff et al indicated that in patients with cerebral lesions who exhibit hyponatremia, urinary sodium excretion and urinary volume can be used to differentiate cerebral salt-wasting syndrome from SIADH. In patients with cerebral salt-wasting syndrome, these values were 394 ± 369 mmol/24 h and 2603 ± 996 mL/24 h, respectively. In comparison, the values were significantly lower—51 ± 25 mmol/24 h and 745 ± 298 mL/24 h, respectively—in patients with SIADH.[19]

Cerebral salt-wasting syndrome and central diabetes insipidus

A retrospective study by Wu et al found that distinctive features of combined central diabetes insipidus and cerebral salt-wasting syndrome following traumatic brain injury include massive polyuria (the most typical presentation) that responds to vasopressin plus cortisone acetate but not to vasopressin alone, low central venous pressure, a high level of brain natriuretic peptide precursor in the absence of cardiac dysfunction, high 24-hour urine sodium excretion and hypovolemia, and a much greater osmolarity for urine than for serum.[20]

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Fractional Excretion of Uric Acid and Phosphate

Uric acid

Fractional excretion of uric acid (FEUA) is defined as the percentage of urate filtered by glomeruli that is excreted in urine. It is calculated by dividing the product of (urinary uric acid [mg/mL] x serum creatinine [mg/mL]) by the product of (serum uric acid [mg/mL] x urinary creatinine [mg/mL]) and multiplying the result by 100%. Normal values are less than 10%.

Patients with either cerebral salt-wasting syndrome or SIADH can have hypouricemia and elevated FEUA. However, after correction of hyponatremia, hypouricemia and elevated FEUA may normalize in SIADH but persist in cerebral salt-wasting syndrome (renal salt wasting).[5, 6]

A report by Bardanzellu et al indicated that, while the continued elevation of FEUA following correction of hyponatremia has been used diagnostically for cerebral salt-wasting syndrome in adults, it would also be valid to employ in the diagnosis of children over age 1 year.[21]

Phosphate

Fractional excretion of phosphate (FEP) should be determined when evaluating patients with hyponatremia and hypouricemia. Elevated FEP suggests cerebral salt-wasting syndrome as opposed to SIADH.[6]

Treatment

Approach Considerations

Evaluation and treatment of cerebral salt-wasting syndrome, or renal salt wasting, typically occurs in the inpatient setting because most patients are seriously ill with acute CNS disease.

Management centers on correction of intravascular volume depletion and hyponatremia, as well as on replacement of ongoing urinary sodium loss, usually with intravenous (IV) hypertonic saline solutions.[3] Some clinicians have reported a favorable response to mineralocorticoid therapy in cerebral salt-wasting syndrome. Once the patient is stabilized, enteral salt supplementation can be considered.

Ongoing monitoring of body weight, fluid balance, and serum sodium concentration is essential during the hospital course.

A retrospective, single-center study by Sigmon et al found an increased risk of hyperchloremia and acute kidney injury in patients with neurologic injury who undergo hypertonic sodium therapy with a large chloride load. The 142 patients in the study received high volumes of intravenous hypertonic sodium chloride, with acute kidney injury and hyperchloremia developing in 13% and 38% of them, respectively.[22]

Long-Term Monitoring

Patients whose neurologic insult has improved and who demonstrate normal intravascular volume and serum sodium concentrations on enteral salt supplements, fludrocortisone, or both can be closely observed on an outpatient basis until cerebral salt-wasting syndrome resolves.

Medication

Medication Summary

IV hypertonic saline solutions are employed to correct intravascular volume depletion and hyponatremia and to replace ongoing urinary sodium loss.[3]

As previously mentioned, some clinicians have reported a favorable response to mineralocorticoid therapy in cerebral salt-wasting syndrome (renal salt wasting). Mineralocorticoids, such as fludrocortisone, promote increased sodium reabsorption, as well as potassium loss, from the renal distal tubules.

Mineralocorticoids

Class Summary

Mineralocorticoids enhance sodium reabsorption in the kidney by direct action on distal tubule cells, resulting in expanded extracellular fluid volume. They increase renal excretion of potassium and hydrogen ion.

Fludrocortisone

Fludrocortisone promotes the increased reabsorption of sodium and the loss of potassium by the renal distal tubules.

Questions & Answers

Overview

What is cerebral salt-wasting syndrome (CSWS) (renal salt wasting)?

What is the pathophysiology of cerebral salt-wasting syndrome (CSWS) (renal salt wasting)?

What causes cerebral salt-wasting syndrome (CSWS) (renal salt wasting)?

What is the incidence of cerebral salt-wasting syndrome (CSWS) (renal salt wasting)?

What age group is at highest risk for cerebral salt-wasting syndrome (CSWS) (renal salt wasting)?

What is the mortality and morbidity of cerebral salt-wasting syndrome (CSWS) (renal salt wasting)?

What is the prognosis of cerebral salt-wasting syndrome (CSWS) (renal salt wasting)?

Presentation

What are the signs and symptoms of cerebral salt-wasting syndrome (CSWS) (renal salt wasting)?

Which physical findings are characteristic of cerebral salt-wasting syndrome (CSWS) (renal salt wasting)?

Workup

What is the role of lab studies in the workup of cerebral salt- cerebral salt-wasting syndrome (CSWS) (renal salt wasting)?

How are urine studies used to differentiate SIADH from cerebral salt-wasting syndrome (CSWS) (renal salt wasting)?

What are the signs and symptoms of combined central diabetes insipidus and cerebral salt- cerebral salt-wasting syndrome (CSWS) (renal salt wasting)?

What is the role of the fractional excretion of uric acid (FEUA) and of phosphate (FEP) in the workup of cerebral salt-wasting syndrome (CSWS) (renal salt wasting)?

Treatment

How is cerebral salt-wasting syndrome (CSWS) (renal salt wasting) treated?

What is included in the long-term monitoring of cerebral salt-wasting syndrome (CSWS) (renal salt wasting)?

Medications

What is the role of medications in the treatment of cerebral salt-wasting syndrome (CSWS) (renal salt wasting)?

Which medications in the drug class Mineralocorticoids are used in the treatment of Cerebral Salt-Wasting Syndrome?

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