An Integrative Review of Cerebral Salt Wasting Syndrome

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CE

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ABSTRACT

BACKGROUND: Although cerebral salt wasting syndrome (CSWS) is widely recognized, its clinical characteristics, diagnostic criteria, and management have not been clearly defined. This study was undertaken to comprehensively review current literature and provide a more complete picture of CSWS. This review also aimed to provide information for nurses on how to differentiate cerebral salt wasting syndrome from syndrome of inappropriate antidiuretic hormone secretion. **METHODS:** An integrative review was performed. Searches were conducted between May and July 2018. The primary information sources were CINAHL, Google Scholar, MEDLINE, PubMed, Scopus, and Web of Science. Included articles were published from 1954 to July 2018. **RESULTS:** The essential features of CSWS are hyponatremia, hypovolemia, and increased urine output. Treatment regimens may be determined based on the acuity and severity of hyponatremia and hypovolemia as well as evident symptoms and signs. **CONCLUSION:** This review may help neuroscience nurses become knowledgeable about CSWS for the drafting of appropriate nursing care plans and also be able to differentiate CSWS from syndrome of inappropriate antidiuretic hormone secretion as early as possible for timely and proper management.

Keywords: cerebral disorder, hyponatremia, hypovolemia, literature review, neuroscience nursing

Hyponatremia is the most frequently observed type of electrolyte imbalance among neurological patients.[1] The normal range for serum sodium levels is 135 to 145 mEq/L, and hyponatremia is generally defined as a serum sodium level of less than 135 mEq/L. Two major causes of hyponatremia in patients with disorders of the central nervous system (CNS) are cerebral salt wasting syndrome (CSWS) and syndrome of inappropriate antidiuretic hormone secretion (SIADH).[1,2] CSWS and SIADH have similarities in clinical features and laboratory signs. It is critical to differentiate CSWS from SIADH because of disparate treatment: fluid replacement in CSWS and fluid restriction in SIADH.[1,2] An understanding of CSWS is important for proper diagnosis and successful management. This study was undertaken to review literature and provide a more comprehensive picture of CSWS. This review also aimed to provide information for nurses on how to differentiate CSWS from SIADH.

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Background

Cerebral salt wasting syndrome was first introduced by Peters et al[3] in 1950 in a report describing 3 patients with an intracranial disorder who exhibited hypovolemic hyponatremia with clinical evidence of diuresis, natriuresis, and dehydration. However, the justification of classifying CSWS as a separate clinical entity was questioned. As a result, CSWS was considered an element of SIADH. It was then largely ignored for more than 20 years, but it was reintroduced in the early 1980s and is now well recognized as a different condition.

CSWS is characterized by excessive natriuresis, extracellular fluid (ECF) volume depletion, and hyponatremia.[2] Because sodium is the predominant determinant of serum osmolality, hyponatremia is associated with low serum osmolality and causes water to move from the intravascular into the interstitial space in brain tissue, leading to brain edema, which is a potentially life-threatening complication if not promptly treated.[4] It has been suggested that "CSWS" be replaced by "renal salt wasting syndrome" because salt wasting can occur in the absence of a CNS disorder.[5] However, the term CSWS is used in this study

because it places focus on the association between CSWS and CNS disorders.

Methods

Searches were conducted between May and July 2018. The primary patient population of interest was CNS disorder patients with hyponatremia. The main topics reviewed were issues regarding the definition, prevalence, pathophysiology, clinical characteristics, diagnosis, and management of CSWS. The primary information sources were CINAHL, Google Scholar, MEDLINE, PubMed, Scopus, and Web of Science. The search terms used were "cerebral salt wasting," "CSW," "renal salt wasting," "RSW," "central hyponatremia," "nephrogenic salt wasting," and "salt losing cerebral syndrome." These search terms were decided upon after several trials of manual search and by continuous discussion among authors until consensus was reached.

The search encompassed entire databases and yielded 1467 studies (published from 1954 to July 2018) in CINAHL (55), Google Scholar (60), MEDLINE (275), PubMed (310), Scopus (477), and Web of Science (290). Inspections of these studies resulted in the identification of 907 duplicates. Thus, 560 studies were initially identified, and their abstracts were reviewed. However, 139 of the 560 were excluded because they were animal studies (n = 9), not written in English (n = 84), or irrelevant (n = 46). Finally, 421 studies were reviewed (Fig 1). There was no limit on date of publication and study design to obtain the maximum number of eligible primary sources about the topics of review.[6]

Results

Cerebral salt wasting syndrome is a condition of extracellular volume depletion due to a renal sodium transport abnormality with or without high urinary sodium concentration, presence of hyponatremia with serum sodium less than 135 mEq/L, or cerebral disease with normal adrenal and thyroid functions.[5] More recently, CSWS has been described as renal loss of sodium associated with intracranial disorder leading to hyponatremia and a reduction in extracellular volume.[7]

Most signs and symptoms of CSWS are associated with hyponatremia. Mild to moderate hyponatremia (120-134 mEq/L) may be associated with nausea, vomiting, anorexia, headache, irritability, and muscle weakness.[8] Large or rapid reductions in serum sodium levels to less than 120 mEq/L cause more severe symptoms such as delirium, hallucinations, lethargy, seizures, cerebral herniation, respiratory arrest, and, potentially, death.[8,9] Signs and symptoms of volume depletion such as dehydration, dry mucous membranes, decreased skin turgor, tachycardia, hypotension, and elevated hematocrit or urea levels may also occur.[8]

Incidence

Several intracranial disorders including brain tumor, ischemic or hemorrhagic stroke, traumatic brain injury (TBI), tuberculous meningitis, encephalitis, intracranial surgery, status epilepticus, and craniosynostosis repair have been reported to be associated with CSWS.[10] As shown in Table 1, reported incidence rates of CSWS vary widely, with the highest in tuberculous meningitis (47.8%) followed by TBI (34.6%), aneurysmal subarachnoid hemorrhage (23%), and stroke (19%).[2,11–13]

A small number of studies have addressed the nature of associations between CSWS occurrence and sex; age; Glasgow Coma Scale (GCS) score, which is an indicator of level of consciousness; or injury severity. According to Shapiro and colleagues,[14] age was not significantly associated with the occurrence of hyponatremia. On the other hand, the prevalence of CSWS was shown to be higher among elderly patients or children younger than 7 years in other studies.[15]

FIGURE 1 A Schematic of Study Selection Process

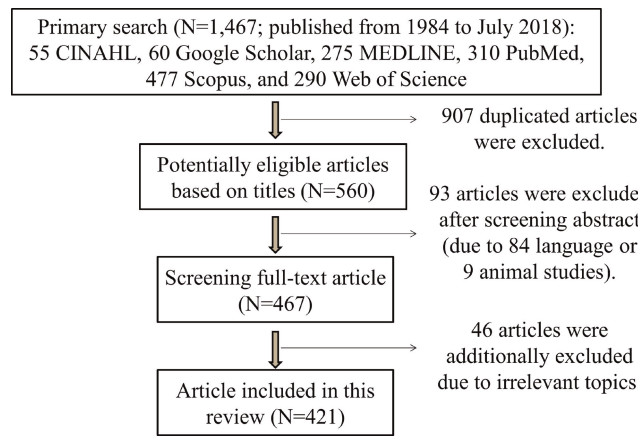

TABLE 1. Incidence of Cerebral Salt Wasting Syndrome (CSWS)

Author (Year)	Sample Size	No. Subjects With CSWS (%)	Age, Mean or Range	Diagnosis
Hoffman (2018)	114	14 (12%)	55.1 y	Aneurysmal subarachnoid hemorrhage
Misra (2018)	67	32 (47.76%)	9–75 y	Tuberculous meningitis
	77	9 (11.69%)	18–85 y	Acute encephalitis
Kalita (2017)	100	19 (19%)	18–90 y	Stroke
Inamdar (2016)	75	10 (13.3%)	3 mo to 2 y	Tuberculous meningitis
Misra (2016)	76	17 (22.4%)	7–80 y	Tuberculous meningitis
Murthy (2015)	133	24 (18.05%)	48 y	Aneurysmal subarachnoid hemorrhage
Meng (2015)	45	13 (28.89%)	—	Acute cervical cord trauma
Barber (2014)	344	15 (4.4%)	48 y	Transsphenoidal resection
Hannon (2014)	100	0 (0%)	16–82 y	Aneurysmal subarachnoid hemorrhage
Saleem (2014)	1000	115 (11.5%)	—	Stroke
Sorkhi (2013)	102	4 (3.9%)	2.5–144 mo	Acute central nervous system diseases
Hardesty (2012)	282	15 (5%)	0.71–13.75 y	Craniotomy
Lohani (2011)	31	3 (9.1%)	19–70 y	Traumatic brain injury
Zhang (2010)	68	20 (29.4%)	4–60 y	Traumatic brain injury
Costa (2009)	26	9 (34.6%)	29.1 y	Traumatic brain injury
Kao (2009)	—	— (23%)	55.5/59.6 y	Aneurysmal subarachnoid hemorrhage
Moro (2007)	298	13 (4.4%)	59.5/67.3 y	Traumatic brain injury
Einaudi (2006)	30	3 (10%)	>18 y	Traumatic brain injury
Bussmann (2001)	195	9 (4.6%)	0.1–16 y	Central nervous system diseases
Vingerhoets (1988)	256	2 (0.8%)	—	Traumatic brain injury

Note. Refer to Supplemental Digital Content 3, http://links.lww.com/JNN/A299, for references that are not cited in the main text but used in this table.

Lohani and Devkota[16] demonstrated that the incidence of CSWS was not correlated with GCS scores but was correlated with brain injury severity (as assessed by computed tomography) in TBI. Leonard et al[17] reported that the incidence of CSWS was highest in TBI patients with a GCS score less than 9, and Misra et al[18] indicated a significant association between hyponatremia and disease severity and GCS scores in patients with tuberculous meningitis.

Pathophysiology

The pathogenic mechanism of CSWS is considered to involve 2 major hypothetical pathways. First, release of natriuretic peptides contributes to the development of CSWS. Five natriuretic peptides have been identified to be associated with CSWS: atrial natriuretic peptide, brain natriuretic peptide, C-type natriuretic peptide, dendroaspis natriuretic peptide, and ouabainlike peptide.[19] All five have similar effects on sodium and water homeostasis by directly increasing glomerular filtration rate, inhibiting sodium reabsorption in renal tubules, and suppressing the renin-angiotensin-aldosterone system.[19,20] Second, disruption of efferent sympathetic input to kidneys is another postulated mechanism. Reduced sympathetic stimulation increases glomerular filtration and inhibits sodium reabsorption by proximal tubules, leading to a reduction in ECF volume.[9] In addition, renal sympathetic inhibition also suppresses renin-angiotensin-aldosterone activity, which further inhibits sodium retention.[9] This explains why CSWS is sometimes called *renal salt wasting syndrome*.

Diagnostic Criteria

Diagnostic criteria used in studies are summarized in Supplemental Digital Content 1 (http://links.lww.com/JNN/A297). Studies have emphasized that the need to differentiate CSWS and SIADH is critical because therapy for one may be detrimental to patients with the other.[2,19] Both present hypoosmolar hyponatremia, and therefore, it is difficult to differentiate these 2 syndromes by evaluating serum and urine sodium and osmolality. Accordingly, meticulous clinical evaluations and laboratory tests are needed (Supplemental Digital Content 2, http://links.lww.com/JNN/A298). The most important difference between the two is volume status; urine output is high in CSWS and normal or low in SIADH, and therefore, ECF volume is always hypovolemic in CSWS, whereas SIADH patients are euvolemic or hypervolemic.[20,21] When ECF volume needs to be

directly estimated, a central catheter or Pulmonary Artery catheter can be used.[20,21] Second, serum biochemistry findings such as blood urea nitrogen, serum uric acid, and hematocrit may aid the differentiation.[22] In particular, serum uric acid and fractional excretion of uric acid (FEUa) are useful for differentiating CSWS and SIADH. There are initially hypouricemia and high FEUa in both, but after correction of hyponatremia, hypouricemia and high FEUa may normalize in SIADH but persist in CSWS.[22] In less severe cases, response to fluid therapy or diuretics also differentiates SIADH and CSWS. Isotonic saline solution improves hyponatremia in CSWS but exacerbates the condition in SIADH. Loop diuretics exacerbate hyponatremia in patients with CSWS but improve hyponatremia in patients with SIADH.[20]

CSWS Management

The goals of CSWS management are replacement of extracellular volume and sodium, hormonal replacement therapy, and treatment of underlying CNS causes. To correct volume depletion, isotonic solutions (0.9% sodium chloride) are administered intravenously. The duration of isotonic solution treatment varies from a few days to 4 weeks.[23] In addition, hypertonic solutions (1.5% or 3% sodium chloride) can be administered to patients with profound volume depletion and hyponatremia.[23] Oral sodium supplements can be combined with intravenous fluids to replace sodium loss and correct serum sodium levels in patients with severe hyponatremia less than 120 mEq/L.[8] The target serum sodium level during the treatment of hyponatremia should be 130 to 135 mEq/L.[8] Hyponatremia must be corrected slowly, at the rate of approximately 0.5 mEq/L per hour, because rapid correction may result in osmotic demyelination syndrome (ODS), an irreversible neurologic state caused by severe damage of myelin sheath.[24]

Because natriuretic peptides inhibit mineralocorticoid secretion, fludrocortisone has also been used in patients with CSWS. Fludrocortisone is a synthetic mineralocorticoid that directly increases sodium reabsorption and expands ECF volume.[25] The dose of fludrocortisone used in studies varied, but mostly daily doses of 0.2 to 0.6 mg via the oral route.[26,27] Yee et al[9] reported fludrocortisone was administrated from the beginning of the diagnosis of CSWS and continued until serum sodium concentration and intravascular volume remain stably normal, typically 3 to 5 days later. Misra et al[26] reported that serum sodium levels improved within 10 days of fludrocortisone administration. Prolonged or high doses of fludrocortisone can lead to hypokalemia, hypertension, sodium and water retention, and hyperglycemia.[9,26,27] In particular, the administration of fludrocortisone requires close monitoring of serum potassium level. [26,27]

Discussion

On the basis of this literature review, CSWS can be defined as excessive urinary sodium losses in individuals with intracranial lesion that result in hyponatremia, extracellular volume depletion, and high urinary volume. Reported incidence rates of CSWS varied widely, probably because of small study sizes, the populations studied, and the study inclusion and diagnostic criteria used.[17] It was noted that the cutoff values for some diagnostic criteria differed: for example, in some studies, the definition of low serum sodium was "a serum sodium level of ≤135 mEq/L," whereas in others, a serum sodium level of 125 mEq/L or lower was used.[13,14] Furthermore, single and multiple (within a 24-hour period) measurements of serum sodium level often yield significantly different results.[9]

There has been a higher prevalence of CSWS among elderly patients, probably because of smaller total body water levels, decreased renal function, impaired responsiveness to sodium changes, and reduced osmoreceptor sensitivity.[28] Because renal and brain tissues of children are relatively immature, the prevalence of CSWS was also shown to be higher among children.[15] However, results regarding the relationship between CSWS and age are still contradictory. Further studies are needed on this issue.

Most of the studies emphasized that the diagnosis of CSWS requires measurement of ECF volume. Although invasive monitoring of central venous pressure or pulmonary wedge pressure or radioisotope-dilution–based methods may provide more accurate estimates of ECF volume status,[9] these techniques are not always available or practical in a clinical setting.[15] Many clinical and biochemical parameters are more routinely used to evaluate ECF volume, including physical signs such as skin turgor, tachycardia, and hypotension, and laboratory markers such as hematocrit, blood urea nitrogen, and FEUa.[29] Therefore, nurses need to be knowledgeable of noninvasive parameters to assess hypovolemia and hyponatremia.

CSWS and SIADH have similarities in clinical features such as hyponatremia, low serum osmolality, and high urine osmolality. If CSWS is misdiagnosed as SIADH and treated by fluid restriction, hypovolemia can worsen and serious sequelae may result. These include hypotension, cerebral vasospasm, ischemia, or infarction of brain tissue.[25] When symptoms of volume depletion are not apparent, the persistence of hypouricemia and increased FEUa after the correction of hyponatremia can be a provocative means of distinguishing the two.[30] It has not been determined why initial uric acid clearances are high in

SIADH and CSWS but differ after correction of hyponatremia.

Because hyponatremia is poorly tolerated and even a small fall in serum sodium aggravates vasogenic cerebral edema in patients with CNS disorders,[24] hyponatremia needs to be treated promptly.[25] Hyponatremia should not be corrected rapidly to avoid ODS.[24] The mechanism by which ODS induces myelin destruction involves osmotic force of the water movement from cells to extracellular space, yielding intracellular dehydration. This places myelin-forming oligodendrocyte in pons (central pontine myelinolysis) or other parts of the brain (extrapontine myelinolysis).[8,24]

CSWS treatment consists of volume replacement and the correction of hyponatremia with isotonic and/or hypertonic saline. In addition, fludrocortisone has also been administered as a therapeutic option.[8] Nakagawa et al[27] recommended that early administration of fludrocortisone is probably needed to prevent hyponatremia. However, fludrocortisone should be cautiously administered because there is a risk of serious adverse effects such as hypokalemia, hypertension, and pulmonary edema.[25]

Nursing Implications

Because delayed diagnosis and improper management of CSWS can aggravate secondary brain injury, nurses should be knowledgeable of this syndrome to ensure it is promptly recognized and managed. It is usually difficult to assess electrolyte imbalance by using simple bedside physical examination unless changes are quite marked. Therefore, nurses should closely monitor laboratory data such as serum and urine electrolytes and uric acid.

It is believed that a significant proportion of patients with CSWS have been incorrectly given a diagnosis of SIADH.[1] Extracellular fluid volume status can crucially distinguish the two; patients with CSWS are hypovolemic, whereas patients with SIADH are either euvolemic or hypervolemic. Accordingly, particular attention should be paid to skin turgor and mucous membranes. In addition, the presence of hypervolemia or hypovolemia can be differentiated by examining jugular venous distension and by observing orthostatic variations in blood pressure and pulse. Daily weight measurements may also provide helpful additional information. Proper documentation of fluid intake and output is important. However, nurses should bear in mind that signs and symptoms of volume depletion may become less apparent and obscured by other neurological symptoms or treatments.

Conclusions

The most characteristic clinical features of CSWS are hyponatremia, hypovolemia, and increased urine output. Treatment regimens may be determined based on the acuity and severities of hyponatremia and hypovolemia as well as evident symptoms and signs. This review may help neuroscience nurses become knowledgeable about CSWS for the drafting of appropriate nursing care plans and also be able to differentiate CSWS from SIADH as early as possible for timely and proper management. Nurses must recognize that close bedside and laboratory data monitoring is an essential part of nursing care for patients with CSWS.

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