Review Article

Cerebral salt wasting syndrome

Harshal Dholke, Ann Campos, C Naresh K. Reddy, Manas K. Panigrahi[1]

Abstract

Traumatic brain injury (TBI) is on the rise, especially in today's fast-paced world. TBI requires not only neurosurgical expertise but also neurointensivist involvement for a better outcome. Disturbances of sodium balance are common in patients with brain injury, as the central nervous system plays a major role in sodium regulation. Hyponatraemia, defined as serum sodium <135 meq/L is commonly seen and is especially deleterious as it can contribute to cerebral oedema in these patients. Syndrome of inappropriate antidiuretic hormone secretion (SIADH), is the most well-known cause of hyponatraemia in this subset of patients. Cerebral Salt Wasting Syndrome (CSWS), leading to renal sodium loss is an important cause of hyponatraemia in patients with TBI. Although incompletely studied, decreased renal sympathetic responses and cerebral natriuretic factors play a role in the pathogenesis of CSWS. Maintaining a positive sodium balance and adequate hydration can help in the treatment. It is important to differentiate between SIADH and CSWS when trying to ascertain a case for patients with acute brain injury, as the treatment of the two are diametrically opposite.

Key words: Brain natriuretic peptide, cerebral salt wasting, conivaptan, fludrocortisone, hypertonic saline, hyponatraemia

INTRODUCTION

Sodium is the most important osmotically active solute in the extracellular fluid. It is the major determinant of serum osmolality, which in turn plays a major role in the regulation of body water. Increased serum osmolality, triggers the release of anti-diuretic hormone (ADH) from the posterior pituitary. Hypovolaemia and hypotension results in baroreceptor stimulation which reflexly causes ADH release.[1,2]

Sodium balance in the body is maintained via regulation of its renal excretion which is affected by:

Departments of Neuroanaesthesia and Critical Care and [1]Neurosurgery, Krishna Institute of Medical Sciences, Secunderabad, Telangana, India

Address for correspondence:
Dr. Harshal Dholke, Department of Neuroanaesthesia and Critical Care, Krishna Institute of Medical Sciences, Secunderabad, Telangana, India.
E-mail: haarshal_21@yahoo.co.in

Access this article online	
Quick Response Code:	Website: www.jnaccjournal.org
	DOI: 10.4103/2348-0548.190065

Glomerular filtration rate

About 70% of filtered sodium is reabsorbed in the proximal tubules with <5% being excreted. Any fall in glomerular filtration rate (GFR) would, therefore, mean less filtration and excretion of sodium and vice versa.

Renin-angiotensin-aldosterone system

Sympathetic stimulation decreases in mean arterial pressure or decreases in distal tubular sodium levels, all activate renin-angiotensin-aldosterone system (RAAS) which results in sodium reabsorption secondary to aldosterone release.[1]

Natriuretic peptides (atrial natriuretic peptide and brain natriuretic peptide)

These are produced in the atria and brain and cause reduction of sympathetic outflow from the brainstem as well as induce natriuresis by increasing the GFR, and by inhibiting renin and aldosterone release.[2]

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Dholke H, Campos A, Reddy CN, Panigrahi MK. Cerebral salt wasting syndrome. J Neuroanaesthesiol Crit Care 2016;3:205-10.

In traumatic brain injury (TBI), hyponatraemia can occur due to a variety of causes, such as syndrome of inappropriate antidiuretic hormone secretion (SIADH), CSWS, Anterior hypopituitarism, and drugs such as oxcarbazepine used for seizure prophylaxis. The incidence of hyponatraemia in head injury patients commonly linked to CSWS and SIADH is 5–10%.[3,4] While SIADH is the cause of hyponatraemia in the majority of cases, in a small subset of patients, the diagnosis of CSWS is often missed as it appears to be very similar to SIADH and is therefore often confused with it. This can have disastrous consequences as the treatment of the two conditions is diametrically opposite. In SIADH, despite a low serum osmolality, there is an inappropriate secretion of ADH in response to hyponatraemia, leading to water retention and hypervolaemia.[3] CSWS mimics SIADH except for the fact that salt wasting is the primary defect causing volume depletion.[4,5]

First described by Peters *et al*. in 1950, cerebral salt wasting (CSW) is a clinical condition characterised by renal loss of sodium causing dehydration and hyponatraemia in patients with intracranial neurological disorders.[6] In 1953, Leaf *et al*.[7] demonstrated that exogenous administration of the ADH (vasopressin) resulted in hyponatraemia, water retention and weight gain. The increase in the intravascular volume resulted in a decrease in sodium and chloride levels. This was not 'salt wasting'; but was a physiologic response to an expanded intravascular volume. Four years later, Schwartz *et al*.[8] published their landmark paper on SIADH. A subsequent paper from the group at Yale attributed hyponatraemia in neurologic disease to SIADH.[7] For over 20 years, the term CSWS virtually vanished from literature. In 1981, Nelson *et al*.[9] studied hyponatraemia in neurosurgical patients, primarily subarachnoid haemorrhage, and found that isotopically measured blood volumes were contracted; he attributed this finding to CSWS [Figures 1 and 2].

PATHOPHYSIOLOGY OF CEREBRAL SALT WASTING SYNDROME

In TBI, there can be disruption of hypothalamo-renal pathways,[2] imbalance of sympathetic output with decreased renal sympathetic activity,[10] and also possibly direct injury to the anterior and posterior pituitary, all of which can play a role in the pathogenesis of hyponatraemia in these patients. This can disrupt the cerebral influence on renal salt and water balance, and therefore, disturb the kidneys ability to handle sodium properly.[6]

It is now believed that natriuretic factors such as an atrial natriuretic peptide, brain natriuretic peptide (BNP), C-type natriuretic peptide, and possibly dendroaspis natriuretic peptide are secreted by the injured brain and may play a role in CSWS. Of all these factors BNP might be the main factor in CSWS.[5] These peptides have potent effects on cardiovascular homeostasis by dampening the sympathetic response thereby altering the vascular tone and causing dilatation of arteries and veins.[11] Natriuretic peptides also induce sodium loss (natriuresis) by inhibiting renin release from the renal juxtaglomerular cells and preventing aldosterone release from the adrenals thus antagonising the RAAS.[1] This effect on the afferent tubules of nephrons leads to, dilatation of the afferent arteriole resulting in increased filtration of water and sodium through the glomerulus. These molecules also have renal natriuretic and diuretic effect by inhibiting the angiotensin-induced sodium reabsorption from collecting ducts and antagonising the action of vasopressin at the collecting duct, respectively.[12]

Local production of natriuretic peptides within the adrenal medulla has been demonstrated, which, might have paracrine inhibitory effects on mineralocorticoid synthesis.[13] This paracrine mechanism might explain why, in patients with CSWS, aldosterone and renin levels fail to rise despite the presence of hypovolaemia.

Other mechanisms suggest that downregulation of renal sodium transporters due to extracellular volume expansion and the adrenergic surge that occurs in the early phase of brain injury might cause pressure natriuresis.[14,15]

CLINICAL FEATURES AND DIAGNOSIS

In clinical practice, it is important to distinguish CSWS from SIADH as they share several diagnostic criteria. The following laboratory studies may be indicated in patients with cerebral salt-wasting syndrome:[15]

Serum sodium concentration

Patients with untreated CSWS are often hyponatremic and signs and symptoms may vary according to the severity as shown in Table 1.[16] As the decline in serum sodium concentration reduces serum osmolality, a tonicity gradient develops across the blood-brain barrier that causes cerebral oedema. Symptoms include lethargy, agitation, headache, altered consciousness, seizures and coma.[17,18]

Serum osmolality

Normal serum osmolality is 285–295 mosmosm/L. This is found to be decreased in SIADH but is either normal or decreased in CSWS. If the measured serum osmolality exceeds twice the serum sodium concentration and azotaemia is not present, hyperglycaemia or mannitol should be suspected as the cause of hyponatraemia.[15,18]

Urinary output

Urine appears relatively dilute and the flow rate is often high in CSWS. It is concentrated with a low flow rate in SIADH. However, in CSWS, despite its apparently diluted appearance, urine osmolality is high due to increased sodium loss.

Fluid balance

The differentiation of SIADH from CSWS depends on an accurate estimation of intravascular volume. Unfortunately, no single physical finding can accurately and reproducibly measure effective circulating volume. Commonly used signs of hypovolaemia include orthostatic tachycardia or hypotension, increased capillary refill time, increased skin turgor, dry mucous membranes and a sunken anterior fontanel. 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.[15]

In SIADH, there is generally euvolaemia or hypervolaemia. As opposed to this the important finding in CSWS is volume depletion. The daily sodium excretion is also more than the intake, and the overall sodium balance is negative in CSWS. Therefore, a daily clinical examination for signs of hypovolaemia as well as a daily intake and output charting should be done, which will reveal an overall negative balance.[2] Sometimes, hypovolaemia has been identified in patients who fulfill all other diagnostic criteria for SIADH. This occurs because the volume depletion of CSWS causes a secondary rise in ADH. However, under such conditions, the correct diagnosis is CSWS rather than SIADH.[19]

Fractional excretion of uric acid

This 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] × serum creatinine [mg/mL]) by the product of (serum uric acid [mg/mL] × urinary creatinine [mg/mL]) and multiplying the result by 100. Normal values are <10%.[20]

Patients with either CSWS or SIADH can have hypouricaemia and elevated fractional excretion of uric acid (FEUA). However, after correction of hyponatraemia, the hypouricaemia and elevated FEUA may normalise in SIADH but persist in CSWS (renal salt wasting).[15]

Fractional excretion of phosphate

This should be determined when evaluating patients with hyponatraemia and hypouricaemia. Elevated fractional excretion of phosphate >20% suggests cerebral salt-wasting syndrome as opposed to SIADH where it is <10% [Table 2].[20,21]

Table 1: Clinical presentation of hyponatraemia

Plasma concentration of Na in (mmol/L)	Signs/symptoms
>125	Asymptomatic
120-125	Nausea, malaise, vomiting
120-110	Muscle cramps, weakness, confusion, agitation, delirium, lethargy and seizures
<110	Seizures, coma, permanent brain damage, respiratory arrest

Table 2: Clinical and biochemical features of the syndrome of inappropriate antidiuretic hormone secretion and the cerebral salt wasting syndrome

Biochemical marker	SIADH	CSWS
Intravascular volume	Normal to high	Low
Serum sodium	Low	Low
Urinary sodium level	High	Very high
Vasopressin level	High	Low
Urine output	Normal to low	High
Serum uric acid level	Low	Low
Initial fractional excretion of urate	High	High
Fractional excretion of urate after correction of hyponatraemia	Normal	High
Urinary osmolality	High	High
Serum osmolality	Low	Low
BUN/creatinine level	Low to normal	High
Serum potassium level	Normal	Normal to high
Central venous pressure	Normal to high	Low
Pulmonary capillary wedge pressure	Normal to high	Low
Brain natriuretic peptide level	Normal	High
Fractional phosphate excretion (%)	<10	>20

BUN=Blood urea nitrogen, SIADH=Syndrome of inappropriate antidiuretic hormone secretion, CSWS=Cerebral salt wasting syndrome

TREATMENT

The main-stay of management of CSWS is the replacement of water and sodium which is lost due to diuresis and natriuresis, whereas, in SIADH, free water has to be restricted.[22]

Once a diagnosis of CSWS is made, efforts should be made to address hypovolaemia first. This can be done with the use of crystalloids like 0.9% normal saline. This treatment holds true for those patients with mild hyponatraemia. By doing this, both hypovolaemia and hyponatraemia can be addressed.[23,24] When the patient is severely hyponatraemic and hypovolemic he will require aggressive resuscitation to first become euvolemic, followed by the correction of hyponatraemia, with the use of 3% saline which should be administered via a central line. With the use of 3% saline, the sodium correction should not exceed 12 meq/L for every 24 h. This is necessary, to avoid complications such as central pontine myelinolysis, metabolic acidosis, volume overload and pulmonary oedema.[25,26]

Some clinicians have found it useful to the use of mineralocorticoids in CSWS. Fludrocortisone is one such drug, which promotes the increased reabsorption of sodium and the loss of potassium by the renal distal tubules. Secondary effects such as hypokalaemia, pulmonary oedema and hypertension may occur with prolonged use. Apart from this, the steroid base can cause hyperglycaemia warranting the periodic monitoring of serum potassium and blood sugars. Hence, it's use is only indicated when salt and fluid replacement are unable to correct the hyponatraemia.[27,28]

Diuretics and fluid restriction are the main-stays of treatment in SIADH. However, one of the newer drugs recently approved by the United States-Food and Drug Administration is worth a mention, Conivaptan, is a non-selective antagonist at V1 and V2 vasopressin receptors. It antagonises the action of vasopressin at the collecting ducts causing electrolyte-free water excretion, thereby raising serum sodium in patients with SIADH.[29,30] Most recently, Ghali *et al*. published results from their randomised, double-blind, placebo-controlled trial conducted across 21 cities in the United States, Canada and Israel, involving the efficacy of oral conivaptan in the treatment of patients with euvolemic and hypervolaemic hyponatraemia.[31] Based on currently available studies, conivaptan appears to be effective in inducing aquaresis to correct hyponatraemia in both euvolemic and hypervolemic hyponatremic patients. Although conivaptan has been shown to be an effective aquaretic with short-term use, this is not without limitations. Adverse effects reported with short-term use are typically minimal, but may include serious effects such as hypokalaemia, orthostatic hypotension, and unexpectedly rapid serum sodium correction. Careful patient selection, avoidance of combined use with conventional diuretics, and close monitoring may reduce complication rates with the use of conivaptan.[31,32] When used in CSWS, conivaptan can cause a negative fluid balance and further worsen the situation. This novel treatment for SIADH also backs the need for accurate differentiation between CSWS and SIADH before the start of hyponatraemia correction in cerebral injuries.[33,34] Conivaptan should not be administered to patients in whom CSWS or a high likelihood of cerebral vasospasm is suspected.[34,35]

PREVENTION OF HYPONATRAEMIA IN TRAUMATIC BRAIN INJURY

In TBI, the maintenance of intracranial pressure (ICP) is pivotal and we need to strongly address the changes in serum osmolality and serum sodium levels. There are ample data which suggests that maintenance of slight hypernatraemia is associated with a reduced increase in ICP.[6] This can be very well achieved with the continuous infusion of hypertonic saline (3% NaCl) and is found to be well tolerated in these patients.[26]

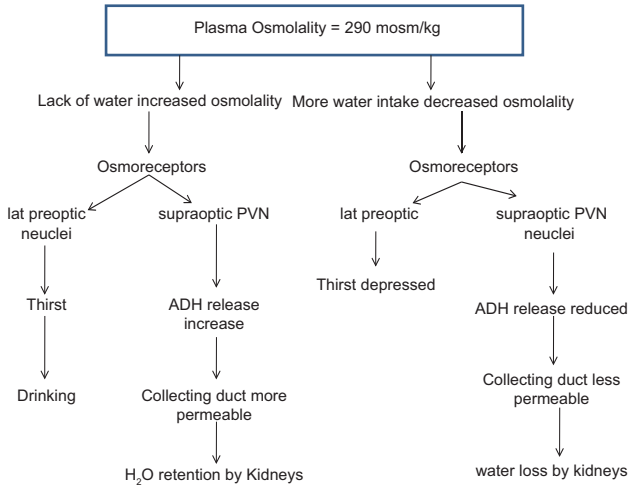

Figure 1: Sodium regulation in the body

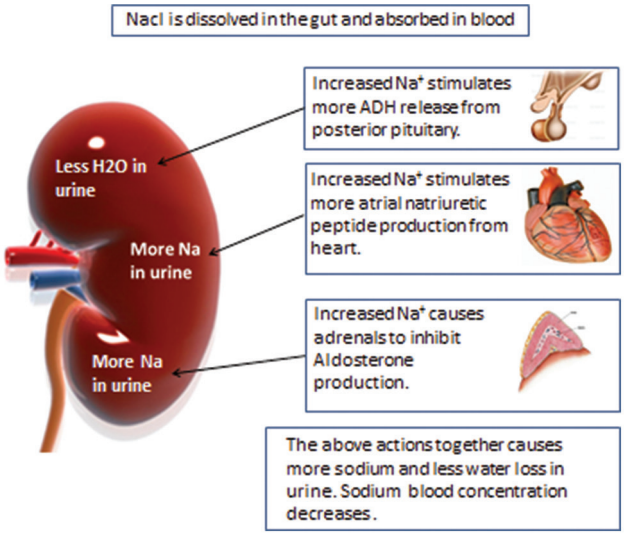

Figure 2: Effect of hormones on sodium regulation

A recent study at the University of California, Los Angeles used an aggressive sodium correction treatment regimen as a component of their TBI protocol. The mean target goal was a serum sodium level of 138 mmol/L or higher if ICP was 15–20 mm Hg. This was achieved with the use of 3% NaCl to control serum sodium levels and prevent hyponatraemia. Using this protocol, there was a 12% incidence of serum sodium levels of <137 mmol/L and a 1% incidence rate of serum sodium levels of <132 mmol/L. There were no documented cases of central pontine myelinolysis using this protocol.[5]

Treatment protocol suggested for sodium regulation in TBI[5]

- Measure serum sodium level twice daily for initial 96 h after TBI
- Establish serum sodium goal of ≥138 mmol/L
- Start continuous infusion of 3% NaCl at 25 mL/h for Na of ≤138 mmol/L
- Maintain 3% NaCl at 15–25 mL/h if ICP is 15–20 mm Hg
- Add fludrocortisone 0.1 mg bid (oral) if Na is ≤138 mmol/L
- Increase 3% NaCl to around 50 mL/h to achieve Na of >145–155 mmol/L if ICP is >20 mm Hg despite the use cerebrospinal fluid drainage using ventriculostomy.

CONCLUSION

Hyponatraemia can complicate the clinical outcome in TBI. CSWS is a syndrome of hypovolemic hyponatraemia caused by renal natriuresis and diuresis. Brain natriuretic peptide, secreted by the injured brain plays a crucial role in the pathogenesis of CSW. Making a distinction between SIADH and CSWS is important due to different treatment required for the two conditions. The maintenance of high normal levels of serum sodium in patient with TBI may help limit increases in ICP as well as avoid the detrimental effects of hyponatraemia due to CSWS or SIADH in these patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Levin ER, Gardner DG, Samson WK. Natriuretic peptides. N Engl J Med 1998;339:321-8.
2. Bradshaw K, Smith M. Disorders of sodium balance after brain injury. Continuing Education in Anaesthesia, Critical Care & Pain. Vol. 8. 2008.
3. Powell KR, Sugarman LI, Eskenazi AE, Woodin KA, Kays MA, McCormick KL, *et al.* Normalization of plasma arginine vasopressin concentrations when children with meningitis are given maintenance plus replacement fluid therapy. J Pediatr 1990;117:515-22.
4. Weidmann P, Hasler L, Gnädinger MP, Lang RE, Uehlinger DE, Shaw S, *et al.* Blood levels and renal effects of atrial natriuretic peptide in normal man. J Clin Invest 1986;77:734-42.
5. Vespa P. Cerebral salt wasting after traumatic brain injury: An important critical care treatment issue. J Surneu 2007;69:230-2.
6. Peters JP, Welt LG, Sims EA, Orloff J, Needham J. A salt-wasting syndrome associated with cerebral disease. Trans Assoc Am Physicians 1950;63:57-64.
7. Leaf A, Bartter FC, Santos RF, Wrong O. Evidence in man that urinary electrolyte loss induced by pitressin is a function of water retention. J Clin Invest 1953;32:868-78.
8. Schwartz WB, Bennett W, Curelop S, Bartter FC. A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. Am J Med 1957;23:529-42.
9. Nelson PB, Seif SM, Maroon JC, Robinson AG. Hyponatremia in intracranial disease: Perhaps not the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). J Neurosurg 1981;55:938-41.
10. Samuels MA. The brain-heart connection. Circulation 2007;116:77-84.
11. Harris PJ, Thomas D, Morgan TO. Atrial natriuretic peptide inhibits angiotensin-stimulated proximal tubular sodium and water reabsorption. Nature 1987;326:697-8.
12. Dillingham MA, Anderson RJ. Inhibition of vasopressin action by atrial natriuretic factor. Science 1986;231:1572-3.
13. Lee YJ, Lin SR, Shin SJ, Lai YH, Lin YT, Tsai JH. Brain natriuretic peptide is synthesized in the human adrenal medulla and its messenger ribonucleic acid expression along with that of atrial natriuretic peptide are enhanced in patients with primary aldosteronism. J Clin Endocrinol Metab 1994;79:1476-82.
14. Cerdà-Esteve M, Cuadrado-Godia E, Chillaron JJ, Pont-Sunyer C, Cucurella G, Fernández M, *et al.* Cerebral salt wasting syndrome: Review. Eur J Intern Med 2008;19:249-54.
15. DiBona GF. Neural control of the kidney: Functionally specific renal sympathetic nerve fibers. Am J Physiol Regul Integr Comp Physiol 2000;279:R1517-24.
16. Duggal AK, Yadav P, Agarwal AK, Rewari BB. Clinical approach to altered serum sodium levels. JIACM 2006;7:91-103.
17. Sahay M, Sahay R. Hyponatremia: A practical approach. Indian J Endocrinol Metab 2014;18:760-71.
18. Sherlock M, O'Sullivan E, Agha A, Behan LA, Owens D, Finucane F, *et al.* Incidence and pathophysiology of severe hyponatraemia in neurosurgical patients. Postgrad Med J 2009;85:171-5.
19. Tisdall M, Crocker M, Watkiss J, Smith M. Disturbances of sodium in critically ill adult neurologic patients: A clinical review. J Neurosurg Anesthesiol 2006;18:57-63.
20. Moritz ML. Syndrome of inappropriate antidiuresis and cerebral salt wasting syndrome: Are they different and does it matter? Pediatr Nephrol 2012;27:689-93.
21. Maesaka JK, Miyawaki N, Palaia T, Fishbane S, Durham JH. Renal salt wasting without cerebral disease: Diagnostic value of urate determinations in hyponatremia. Kidney Int 2007;71:822-6.
22. Carlotti AP, Bohn D, Rutka JT, Singh S, Berry WA, Sharman A, *et al.* A method to estimate urinary electrolyte excretion in patients at risk for developing cerebral salt wasting. J Neurosurg 2001;95:420-4.
23. Wijdicks EF, Vermeulen M, Hijdra A, van Gijn J. Hyponatremia and cerebral infarction in patients with ruptured intracranial aneurysms: Is fluid restriction harmful? Ann Neurol 1985;17:137-40.
24. Isotani E, Suzuki R, Tomita K, Hokari M, Monma S, Marumo F,

et al. Alterations in plasma concentrations of natriuretic peptides and antidiuretic hormone after subarachnoid hemorrhage. Stroke 1994;25:2198-203.
25. Adrogué HJ, Madias NE. Hyponatremia. N Engl J Med 2000;342:1581-9.
26. Khanna S, Davis D, Peterson B, Fisher B, Tung H, O'Quigley J, Deutsch R. Use of hypertonic saline in the treatment of severe refractory posttraumatic intracranial hypertension in pediatric traumatic brain injury. Crit Care Med 2000;28:1144-51.
27. Taplin CE, Cowell CT, Silink M, Ambler GR. Fludrocortisone therapy in cerebral salt wasting. Pediatrics 2006;118:e1904-8.
28. Singh S, Bohn D, Carlotti AP, Cusimano M, Rutka JT, Halperin ML. Cerebral salt wasting: Truths, fallacies, theories, and challenges. Crit Care Med 2002;30:2575-9.
29. Decaux G, Soupart A, Vassart G. Non-peptide arginine-vasopressin antagonists: The vaptans. Lancet 2008;371:1624-32.
30. Murphy T, Dhar R, Diringer M. Conivaptan bolus dosing for the correction of hyponatremia in the neurointensive care unit. Neurocrit Care 2009;11:14-9.
31. Ghali JK, Koren MJ, Taylor JR, Brooks-Asplund E, Fan K, Long WA, *et al.* Efficacy and safety of oral conivaptan: A V1A/V2 vasopressin receptor antagonist, assessed in a randomized, placebo-controlled trial in patients with euvolemic or hypervolemic hyponatremia. J Clin Endocrinol Metab 2006;91:2145-52.
32. Hline SS, Pham PT, Pham PT, Aung MH, Pham PM, Pham PC. Conivaptan: A step forward in the treatment of hyponatremia? Ther Clin Risk Manag 2008;4:315-26.
33. Annane D, Decaux G, Smith N; Conivaptan Study Group. Efficacy and safety of oral conivaptan, a vasopressin-receptor antagonist, evaluated in a randomized, controlled trial in patients with euvolemic or hypervolemic hyponatremia. Am J Med Sci 2009;337:28-36.
34. Yee AH, Burns JD, Wijdicks EF. Cerebral salt wasting syndrome: Pathophysiology, diagnosis, and treatment. Neurosurg Clin N Am 2010;21:339-52.
35. Sterns RH, Silver SM. Cerebral salt wasting versus SIADH: What difference? J Am Soc Nephrol 2008;19:194-6.