Electrolyte imbalance in neurologic patients

Electrolyte imbalance is known to be the most frequent systemic complication in patients with neurologic diseases. Most electrolyte imbalances in neurologic patients, except dysnatremia, show comparable frequency with patients from other diseases and mainly influenced by medical conditions or co-morbidities. For instance, hypokalemia is commonly manifested as a mild form combined with hypochloremic alkalosis and mostly associated with medical treatment such as diuretics, intravenous fluid, and iatrogenic hyperventilation. Meanwhile, hyperkalemia is almost always related to deterioration of renal function.

Hyponatremia is the most common and important electrolyte disorder affecting patients with critical neurologic diseases. In these patients, the maladaptation to hyponatremia by impaired osmoregulation in pathologic lesions of brain may cause more aggressive cerebral edema and increased intracranial pressure due to hypoosmolality induced by hyponatremia. Furthermore, hyponatremia accompanied by CNS disorders has shown to increase delayed cerebral ischemia and mortality rates. Two main pathophysiologies of hyponatremia, excluding iatrogenic causes, are inappropriate secretion of antidiuretic hormone (SIADH) and cerebral salt wasting (CSW) syndrome. Differential diagnosis between these two entities can be difficult due to considerable overlap in the laboratory findings and clinical situations. SIADH is in a volume expanded status due to inappropriately secreted arginine vasopressin (AVP) and requires water restriction. However, CSW syndrome is characterized by renal sodium wasting mainly due to increased natriuretic peptides resulting in volume depletion and follows appropriate secretion of AVP. Therefore, maintenance of volume status and sodium replacement is the mainstay of treatment in CSW syndrome. In this review, we aimed to describe the regulation of sodium and water balance, and pathophysiology, diagnosis and treatment of hyponatremia in neurologic patients, especially focusing on SIADH and CSW syndrome.

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mone (SIADH) and cerebral salt wasting (CSW) syndrome in neurologic patients will be described.

**Physiologic regulation of water and sodium balance**

The kidney and the brain, with organ cross talk and interaction, play an important role in maintaining sodium and water balance\(^4\). AVP, also known as antidiuretic hormone (ADH), is a peptide hormone which is synthesized as a precursor prohormone in the supraoptic and paraventricular nuclei of the hypothalamic magnocellular neurons\(^5\). AVP is carried by its unique neurophysin from the hypothalamus to its storage site of axon terminals in the posterior pituitary gland. During the axonal transport, it is cleaved from the neurophysin and stored as a free form\(^6\).

The secretion of AVP is tightly regulated mainly by extracellular osmolality detected by osmoreceptors which are thought to be located in the anteromedial hypothalamus near the neurohypophyseal cell bodies in the supraoptic nucleus\(^7\). The secretion of AVP in response to plasma osmolality is extremely sensitive, and only 1% increase in osmolality above 280 mOsm/Kg can cause significant rise in plasma AVP levels, which can activate regulatory systems for antidiuresis and restore the plasma osmolality to normal\(^8\). At a plasma osmolality of 295 mOsm/kg, the plasma AVP level reaches approximately 5 pg/mL and maximum antidiuresis occurs, reflected by a urine osmolality greater than 800 mOsm/kg\(^8\). In addition to osmotic regulation, the secretion of AVP is also influenced by blood pressure and volume status detected by baroreceptors. Although the response of AVP to hypovolemia is less sensitive and does not occur without concomitant decrease in blood pressure, excess amount of AVP is secreted and acts as a potent vasoconstrictor on the vascular smooth muscle cells during the hypovolemic or vasodilatory shock\(^9\). Angiotensin II also have shown to induce AVP release in some animal studies via angiotensin II type 1 receptors in the lamina terminalis, located in the anterior wall of the third ventricle\(^10\). Nausea is another potent non-osmotic factor triggering the secretion of AVP to increase the plasma level by 20 to 500 fold even if the nausea is short-lived and unaccompanied by vomiting or changes in blood pressure\(^7\). After secretion, AVP circulates as a free form peptide, diffuses readily into the extracellular fluid space, and is metabolized within minutes by vasopressinase in the kidney and liver\(^11\).

AVP is an effective agonist to all vasopressin receptor isoforms: V1a, V1b, and V2 receptor (V2R). The antidiuretic effect of AVP is mediated by V2R expressed on the basolateral membrane of principal cells in the collecting tubule and epithelial cells of the thick ascending loop of Henle\(^12\). Binding of AVP to V2R in these cells activates adenylate cyclase, which in turn increases cytosolic cyclic adenosine monophosphate (cAMP) and cAMP mediated activation of protein kinase A (PKA). Subsequently, activation of PKA results in phosphorylation of aquaporin 2 (AQP2) and its translocation from intracellular vesicle to the apical membrane of the principal cells of the collecting tubule\(^13\). As a result, urine flow rate is reduced by increased transepithelial solute free-water reabsorption from the tubular lumen by this apical localized AQP2 which increases hydro-osmotic permeability of the tubular cells (Fig. 1).

**Hyponatremia in patients with neurologic disorders**

Hyponatremia defined as serum sodium level less than 135 mEq/L is known to occur in up to 20% of hospitalized patients\(^14\) and is associated with 1.5 fold higher in-hospital mortality rate than patients without hyponatremia\(^15\). Hyponatremia is more common in patients with neurologic dis-

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**Fig. 1.** Role of arginine vasopressin in the regulation of water balance. AVP, arginine vasopressin; SON, supraoptic nucleus; PVN, paraventricular nucleus; V2R, V2 receptor; cAMP, cyclic adenosine monophosphate; AQP2, aquaporin 2.
orders than in the general in-hospital population and the incidence is reported to be 34% of patients with aneurysmal subarachnoid hemorrhage (SAH) and more than 70% in tuberculous meningitis. The prevalence of hyponatremia developed after transphenoidal pituitary surgery for tumor resection may range between 25% and 35%.

In the presence of hypoosmolality by hyponatremia, water gain causes cerebral edema. Soon after this osmotic insult, the restoration of brain volume occurs through the adaptation mechanisms of brain cell, also known as ‘osmoregulation’, by losing the electrolytes and organic osmolytes. However, patients with neurologic diseases may be more vulnerable to cerebral edema due to impaired osmoregulation in pathologic lesions of the brain. Thus, these patients can exhibit more aggressive cerebral edema with deterioration of both clinical status and intracranial pressure than hyponatremic patients without brain lesions. Furthermore, hyponatremia accompanied by central nervous system (CNS) disorders actually has shown to increase delayed cerebral ischemia and mortality rates.

Although many etiologies such as diuretics, gastrointestinal salt loss, hypotonic solutions, and various co-morbid conditions may cause hyponatremia, two main mechanisms of hyponatremia, SIADH and CSW syndrome, account for most of the hyponatremia in patients with neurologic diseases and is directly related to disruption of organ interaction between the brain and kidney. Differential diagnosis between these two disease entities can be difficult due to considerable overlap in the laboratory findings and clinical situation.

**SIADH in patients with neurologic diseases**

SIADH is volume expanded status due to increased renal water reabsorption by excessive and inappropriate AVP secretion in the absence of hyperosmolality or volume depletion. In addition, downward resetting of the osmotic threshold for thirst in these patients is known to be implicated in the development of volume expansion. However, these patients do not show overt hypervolemic signs, because only one-third of the fluid remains in extracellular space. Nevertheless, increased glomerular filtration rate induced by this modest intravascular volume expansion lead to decreased proximal sodium reabsorption and increase urinary sodium excretion. This sodium wasting accompanied with water retention often lead to an equilibrated state of sodium and water balance due to the vasopressin escape phenomenon. Such normal renal sodium handling despite hyponatremia is a characteristic feature of SIADH. Serum levels of uric acid and urea nitrogen which co-transported with sodium in the proximal tubule are also decreased with increased sodium excretion, and return to normal value with correction of hyponatremia in patients with SIADH.

The diagnosis of SIADH is usually made from history, physical examination, and suitable laboratory tests. The diagnostic criteria for SIADH is summarized in Table 1.

**Table 1. Diagnostic Criteria for SIADH**

| Essential feature                                      |
|--------------------------------------------------------|
| Decreased effective osmolality (<275 mOsm/kg of water) |
| Urinary osmolality >100 mOsm/kg of water during hypotonicity |
| Clinical euvolemia                                      |
| No clinical signs of volume depletion of extracellular fluid |
| No orthostasis, tachycardia, decreased skin turgor, or dry mucous membranes |
| No clinical signs of excessive volume of extracellular fluid |
| No edema or ascites                                     |
| Urinary sodium >40 mEq/L with normal dietary salt intake |
| Normal thyroid and adrenal function                     |
| No recent use of diuretic agents                        |

| Supplemental feature                                   |
|--------------------------------------------------------|
| Plasma uric acid <4 mg/dL                              |
| Blood urea nitrogen <10 mg/dL                          |
| Fractional sodium excretion >1%; fractional urea excretion >55% |
| Failure to correct hyponatremia after 0.9% saline infusion |
| Correction of hyponatremia through fluid restriction    |
| Abnormal result on test of water load (<80% excretion of 20 mL of water per kilogram of body weight over a period of 4 hours), or inadequate urinary dilution (<100 mOsm/kg of water) |
| Elevated plasma AVP levels, despite the presence of hypotonicity and clinical euvolemia |

SIADH, syndrome of inappropriate secretion of antidiuretic hormone; AVP, arginine vasopressin.
The stimulation of AVP release from the neurohypophysis in these diseases may be the possible mechanism for SIADH except some neuroendocrine tumors with ectopic AVP secretion. The treatment of hyponatremia in patients with SIADH should be guided by the severity of the disorder, onset and symptoms of hyponatremia. Fluid restriction is the mainstay of therapy in patients with asymptomatic hyponatremia. Although patients with severe neurologic symptoms due to acute reductions in serum sodium, require rapid initial correction with hypertonic saline, excessively rapid correction should be avoided because it can lead to late onset of neurologic complications from osmotic demyelination. The AVP receptor antagonist represents more targeted therapy to the treatment of hyponatremia in SIADH, and may be potentially beneficial for the treatment of hyponatremia in patients with SIADH secondary to neurologic diseases. However, the exclusion of CSW syndrome through careful assessment of volume status and strict monitoring of serum sodium during treatment will be needed to avoid complications.

### CSW syndrome in patients with neurologic diseases

Many neurosurgical patients with hyponatremia, who meet the diagnostic criteria for SIADH, have a volume status incompatible with that diagnosis. The evidence of volume depletion and negative sodium balance estimated by mass balance for urinary electrolytes in these patients is more consistent with the diagnosis of CSW syndrome. CSW syndrome, which is frequently followed by SAH, is characterized by excess renal sodium wasting with resulting volume depression. Although, the mechanism of CSW syndrome is not fully understood, the most possible hypothesis is central amplification of natriuretic peptides, especially brain natriuretic peptide (BNP), combined with decreased sympathetic outflow due to various neurologic diseases.

### Table 2. Neurologic Diseases Commonly Associated with SIADH

| Neurologic Diseases                                      | SIADH, syndrome of inappropriate secretion of antidiuretic hormone. |
|----------------------------------------------------------|--------------------------------------------------------------------|
| Encephalitis (viral or bacterial)                        |                                                                   |
| Meningitis (viral, bacterial, tuberculosis, fungal)      |                                                                   |
| Traumatic brain injury                                   |                                                                   |
| Brain abscess                                            |                                                                   |
| Brain tumors                                            |                                                                   |
| Guillain-Barré syndrome                                  |                                                                   |
| Acute intermittent porphyria                             |                                                                   |
| Subarachnoid hemorrhage                                  |                                                                   |
| Subdural hematoma                                        |                                                                   |
| Cerebellar and cerebral atrophy                          |                                                                   |
| Cavernous sinus thrombosis                               |                                                                   |
| Neonatal hypoxia                                         |                                                                   |
| Hydrocephalus                                            |                                                                   |
| Delirium tremens                                         |                                                                   |
| Cerebrovascular accident                                 |                                                                   |
| Acute psychosis                                          |                                                                   |
| Peripheral neuropathy                                    |                                                                   |
| Multiple sclerosis                                       |                                                                   |
| Any kind of surgery, most notably transsphenoidal pituitary surgery |                                                                   |

### Fig. 2. Pathophysiology of cerebral salt wasting syndrome

Brain

- Sympathetic outflow ↓
- Natriuretic peptides ↑ (especially BNP)
- Proximal Sodium reabsorption ↓
- RAS inactivation

Kidney

- • Natriuresis
- • Volume depletion
- • Appropriate AVP secretion
- Vasorelaxant: GFR ↑
- IMCT Sodium reabsorption ↓
- AVP antagonism: water reabsorption ↓

- RAS, rennin angiotensin system; AVP, Arginine vasopressin; GFR, glomerular filtration rate; IMCT, inner medullary collecting tubule.
diseases\textsuperscript{36, 37} (Fig. 2). Since the sympathetic tone in the kidney plays an important role in proximal sodium and water handling and the control of renin release in juxtaglomerular epithelioid cells\textsuperscript{38}, decreased sympathetic input into the kidney induces urinary sodium wasting and volume depletion. In addition, natriuretic peptides stimulate dilatation of afferent renal arterioles and constriction of efferent arterioles, leading to an increased glomerular filtration rate\textsuperscript{39}. These peptides can also act on renal tubules, suppressing angiotensin II stimulated sodium and water transport, inhibiting sodium transporter in the inner medullary collecting tubules, antagonizing the renal effects of AVP and reducing sympathetic tone\textsuperscript{24, 40}. Once volume depletion occurs due to renal sodium wasting, it activates baroreceptors that increase AVP release appropriately, resulting in increased water conservation. Therefore, most patients with CSW syndrome show elevated AVP levels and meet the criteria of SIADH. Nevertheless, distinguishing between CSW syndrome and SIADH should be emphasized since the adequate treatment regimen is quite different from each other\textsuperscript{23}. Although, these disorders are commonly associated with neurologic diseases and there may be overlapping laboratory findings, volume status tends to be normal or slightly increased in SIADH, whereas decreased in CSW syndrome. Thus, the evidences of volume depletion such as weight loss, negative fluid balance, orthostatic hypotension and tachycardia in a hyponatremic patient with neurologic disease are strongly suggestive of CSW syndrome\textsuperscript{27}. In addition, laboratory findings reflecting hemococoncentration such as elevated hematocrit, albumin, bicarbonate and urea nitrogen levels can provide further support for that diagnosis\textsuperscript{36}. However, uric acid, which is usually elevated in patients with volume depletion, tends to be unexpectedly low in these patients\textsuperscript{41}. As noted above, hypo-uricemia due to increased urate excretion also existed in patients with SIADH. But, the correction of serum sodium concentration usually leads to normalization of uric acid levels in patients with SIADH. On the other hand, hypouricemia persists after the correction of hyponatremia in patients with CSW syndrome, possibly due to prolonged proximal tubule dysfunction\textsuperscript{28, 42}. Table 3 shows differential clinical features and diagnosis of CSW syndrome and SIADH.

In patients with CSW syndrome, the cornerstone of treatment is achieving euvoilema through vigorous volume resuscitation with intravenous saline and correcting hypotonicity with sodium replacement\textsuperscript{14, 27}. Administration of mineralocorticoid agents which increases sodium re-absorption in renal tubules can also be considered in cases refractory to salt and fluid therapy\textsuperscript{43}. As noted above, volume restriction following erroneous diagnosis of SIADH in patients with CSW syndrome can potentially aggravate hyponatremia. Thus, careful assessment of volume status in patients is needed to differentiate these diseases.

### Table 3. Differential Diagnosis of CSW Syndrome and SIADH

|                      | CSW syndrome | SIADH   |
|----------------------|--------------|---------|
| Extracellular volume | ↓            | ↔/↑     |
| Sodium balance       | Negative     | Neutral |
| Hematocrit           | ↑↑           | ↔       |
| Albumin              | ↑↑           | ↔       |
| Urea nitrogen        | ↑↑           | ↓/↔     |
| Bicarbonate          | ↑↑           | ↔/↔     |
| Potassium            | ↔/↔↑        | ↔       |
| Uric acid            | ↓/↔        | ↓       |

CSW, cerebral salt wasting; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

### Summary

Hyponatremia is the most common electrolyte imbalance in patients with neurologic disease. SIADH and CSW syndrome are two main mechanisms of hyponatremia in these patients, excluding iatrogenic causes. Distinction between the diseases may be difficult due to overlapping laboratory findings and clinical presentations, but have critical importance since the adequate therapy is quite different each other and erroneous diagnosis can lead to grave prognosis as well as aggravation of hyponatremia. The fundamental differences between the diseases are the appropriateness of increased AVP release and presence of dysfunctional renal sodium handling. SIADH is in a volume expanded status due to inappropriately secreted AVP and water restriction is the treatment of choice. However, CSW syndrome is in a volume depleted status characterized by
renal sodium wasting and appropriate secretion of AVP, requiring volume resuscitation combined with sodium replacement. Thus, physicians should focus on the volume status of hyponatremic patients with neurologic disease to differentiate between these two diseases.

References

1) Piek J: Medical complications in severe head injury. New Horiz 3:534-538, 1995
2) Arango MF, Andrews PJ: Systemic complications of neurologic diseases. Curr Opin Crit Care 7:61-67, 2001
3) Tisdall M, Crocker M, Watkiss J, Smith M: Disturbances of sodium in critically ill adult neurologic patients: a clinical review. J Neurosurg Anesthesiol 18:57-63, 2006
4) Davenport A: The brain and the kidney--organ cross talk and interactions. Blood Purif 26:526-536, 2008
5) Swaab DF, Nijveldt F, Pool CW: Distribution of oxytocin and vasopressin in the rat supraoptic and paraventricular nucleus. J Endocrinol 67:461-462, 1975
6) Sachs H, Poryanova R, Haller EW, Share L: Cellular processes concerned with vasopressin biosynthesis, storage and release. In: Neurosecretion. 1st ed., Berlin, Springer-Verlag, 1967, p146-154
7) Robertson GL: Antidiuretic hormone. Normal and disordered function. Endocrinol Metab Clin North Am 30:671-694, 2001
8) Robertson GL, Aycinena P, Zerbe RL: Vasopressin secretion: osmotic and hormonal regulation by the lamina terminalis. J Neuroendocrinol 16:340-347, 2004
9) Landry DW, Oliver JA: The pathogenesis of vasodilatory shock. N Engl J Med 345:588-595, 2001
10) McKinley MJ, Mathai ML, McAllen RM, et al.: Vasopressin secretion: osmotic and hormonal regulation by the lamina terminalis. J Neuroendocrinol 16:340-347, 2004
11) Baumann G, Dingman JF: Distribution, blood transport, and degradation of antidiuretic hormone in man. J Clin Invest 57:1109-1116, 1976
12) Verbalis JG: Vasopressin V2 receptor antagonists. J Mol Endocrinol 29:1-9, 2002
13) Nielsen S: Renal aquaporins: an overview. BJU Int 90(Suppl 3):1-6, 2002
14) Flear CT, Gill GV, Burn J: Hyponatraemia: mechanisms and management. Lancet 2:26-31, 1981
15) Waikar SS, Mount DB, Curhan GC: Mortality after hospitalization with mild, moderate, and severe hyponatremia. Am J Med 122:857-865, 2009
16) Reeder RF, Harbaugh RE: Administration of intravenous urea and normal saline for the treatment of hyponatremia in neurosurgical patients. J Neurosurg 70:201-206, 1989
17) Hasan D, Wijdicks EF, Vermeulen M: Hyponatremia is associated with cerebral ischemia in patients with aneurysmal subarachnoid hemorrhage. Ann Neurol 27:106-108, 1990
18) Karandatis D, Shulman JA: Recent survey of infectious meningitis in adults: review of laboratory findings in bacterial, tuberculous, and aseptic meningitis. South Med J 69: 449-457, 1976
19) Sane T, Rantakari K, Poranen A, Tahtela R, Valimaki M, Pelkonen R: Hyponatremia after transsphenoidal surgery for pituitary tumors. J Clin Endocrinol Metab 79:1395-1398, 1994
20) Olson BR, Gumowski J, Rubino D, Oldfield EH: Pathophysiology of hyponatremia after transsphenoidal pituitary surgery. J Neurosurg 87:499-507, 1997
21) Adrogue HJ, Madias NE: Hyponatremia. N Engl J Med 342:1581-1589, 2000
22) Boulard G, Marguinard E, Sesay M: Osmotic cerebral oedema: the role of plasma osmolarity and blood brain barrier. Ann Fr Anesth Reanim 22:215-219, 2003
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 17:137-140, 1985
24) Rabinstein AA, Wijdicks EF: Hyponatremia in critically ill neurological patients. Neurologist 9:290-300, 2003
25) Robertson GL: Regulation of arginine vasopressin in the syndrome of inappropriate antidiuresis. Am J Med 119: S36-42, 2006
26) Smith D, Moore K, Tormey W, Baylis PH, Thompson CJ: Downward resetting of the osmotic threshold for thirst in patients with SIADH. Am J Physiol Endocrinol Metab 287: E1019-1023, 2004
27) Palmer BF: Hyponatremia in patients with central nervous system disease: SIADH versus CSW. Trends Endocrinol Metab 14:182-187, 2003
28) Maesaka JK, Imbriano L, Ali NM, Ilamathi E: Is it cerebral or renal salt wasting? Kidney Int 76:934-938, 2009
29) Ellison DH, Berl T: Clinical practice. The syndrome of inappropriate antidiuresis. N Engl J Med 356:2064-2072, 2007
30) Bhardwaj A: Neurological impact of vasopressin dysregulation and hyponatremia. Ann Neurol 59:229-236, 2006
31) Casulari LA, Costa KN, Albuquerque RC, Naves LA, Suzuki K, Domingues L: Differential diagnosis and treatment of hyponatremia following pituitary surgery. J Neurosurg Sci 48:11-18, 2004
32) Palmer BF, Gates JR, Lader M: Causes and management of hyponatremia. Ann Pharmacother 37:1694-1702, 2003
33) Laurenzo R, Karp BI: Myelolysis after correction of hyponatremia. Ann Intern Med 126:57-62, 1997
34) Rabinstein AA: Vasopressin antagonism: potential impact on neurologic disease. Clin Neuropharmacol 29:87-93, 2006
35) Sherlock M, O'Sullivan E, Agha A, et al.: The incidence and pathophysiology of hyponatraemia after subarachnoid haemorrhage. Clin Endocrinol (Oxf) 64:250-254, 2006
36) Palmer BF: Hyponatremia in a neurosurgical patient: syndrome of inappropriate antidiuretic hormone secretion versus cerebral salt wasting. Nephrol Dial Transplant 15:262-268, 2000
37) Berendes E, Walter M, Cullen P, et al.: Secretion of brain
natriuretic peptide in patients with aneurysmal subarachnoid haemorrhage. Lancet 349:245-249, 1997
38) Schweda F, Friis U, Wagner C, Skott O, Kurtz A: Renin release. Physiology (Bethesda) 22:310-319, 2007
39) Marin-Grez M, Fleming JT, Steinhausen M: Atrial natriuretic peptide causes pre-glomerular vasodilatation and post-glomerular vasoconstriction in rat kidney. Nature 324:473-476, 1986
40) Levin ER, Gardner DG, Samson WK: Natriuretic peptides. N Engl J Med 339:321-328, 1998
41) Maesaka JK, Gupta S, Fishbane S: Cerebral salt-wasting syndrome: does it exist? Nephron 82:100-109, 1999
42) Bitew S, Imbriano L, Miyawaki N, Fishbane S, Maesaka JK: More on renal salt wasting without cerebral disease: response to saline infusion. Clin J Am Soc Nephrol 4:309-315, 2009
43) Hasan D, Lindsay KW, Wijdicks EF, et al.: Effect of fludrocortisone acetate in patients with subarachnoid hemorrhage. Stroke 20:1156-1161, 1989