Hyponatremia in Acute Stroke Patients: Pathophysiology, Clinical Significance, and Management Options

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Keywords

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Abstract

Background: Hyponatremia is frequent in acute stroke patients, and it is associated with worse outcomes and increased mortality. **Summary:** Nonstroke-related causes of hyponatremia include patients' comorbidities and concomitant medications, such as diabetes mellitus, chronic kidney disease, heart failure, and thiazides. During hospitalization, "inappropriate" administration of hypotonic solutions, poor solute intake, infections, and other drugs, such as mannitol, could also lower sodium levels in patients with acute stroke. On the other hand, secondary adrenal insufficiency due to pituitary ischemia or hemorrhage, syndrome of inappropriate antidiuretic hormone secretion, and cerebral salt wasting are additional stroke-related causes of hyponatremia. Although it is yet unclear whether the appropriate restoration of sodium level improves outcomes in patients with acute stroke, the restoration of the volume depletion remains the cornerstone of treatment in hypovolemic hyponatremia. In case of hyper- and euvolemic hyponatremia, apart from the correction of the underlying cause (e.g., withdrawal of an of-

fending drug), fluid restriction, administration of hypertonic solution, loop diuretics, and vasopressin-receptor antagonists (vaptans) are among the therapeutic options. **Key Messages:** Hyponatremia is frequent in patients with acute stroke. The plethora of underlying etiologies warrants a careful differential diagnosis which should take into consideration comorbidities, concurrent medication, findings from the clinical examination, and laboratory measurements, which in turn will guide management decisions. However, it is yet unclear whether the appropriate restoration of sodium level improves outcomes in patients with acute stroke.

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Introduction

Hyponatremia (commonly defined as serum sodium levels <135 mmol/L) is the most common electrolyte disorder both in the in-hospital and the community setting with a reported incidence up to 30 and 8%, respectively [1, 2]. Even mild hyponatremia has been associated with increased morbidity, including gait disturbances, cognitive impairment, osteoporosis, falls and fractures, and mortality [1].

This review focuses on hyponatremia in acute stroke patients and provides an overview of the pathophysiology, incidence, clinical sequelae, and management strategies.

Pathogenesis of Hyponatremia

Antidiuretic hormone (ADH) is synthesized in the hypothalamus and stored in posterior pituitary secretory granules until its release is prompted by either osmotic or nonosmotic stimuli [3]. Serum hyperosmolality and effective circulating volume depletion represent the major stimuli to ADH secretion; its release can also be influenced by a variety of other factors including nausea, stress (e.g., pain), or drugs (e.g., oxcarbazepine, carbamazepine, selective serotonin reuptake inhibitors) [3]. ADH promotes water reabsorption at the cortical and medullary collecting tubules and plays a pivotal role in the pathogenesis of hyponatremia [3].

Water retention or (less often) loss of effective solutes (sodium and potassium) in excess of water could lead to hyponatremia [3]. Retention of water causing hyponatremia occurs only in the presence of conditions impairing renal excretion of water; this does not happen in patients with primary polydipsia in which the excessive water intake (10–15 L per day) can overwhelm the normal renal excretory capacity [3]. Considering the fact that the suppression of ADH secretion is essential for the excretion of any water load, the presence of inappropriately high serum concentrations of ADH in relation to low plasma osmolality should be considered as the prerequisite for the development and maintenance of hyponatremia [3]. Apart from renal failure, primary polydipsia, beer potomania, and low dietary solute intake, the majority of causes of hyponatremia are associated with an absolute or relative excess of ADH (despite the presence of hypotonicity) mostly due to the syndrome of inappropriate ADH secretion (SIAD) or the depletion of effective circulating volume [3].

Incidence and Etiology of Hyponatremia in Stroke Patients

Hyponatremia is frequently observed in patients with stroke either on admission (3.9–45.3%; Table 1) [4–13] or during their hospitalization (40–45%) [14–17].

Nonstroke-Related Causes of Hyponatremia

The causes of hyponatremia in patients with stroke are shown in Table 2. Briefly, “baseline” hyponatremia, that is, identified upon admission, is mainly attributed to the presence of comorbidities such as diabetes mellitus, chronic renal failure, and heart failure [5, 6, 18]. Besides, stroke patients, the elderly in particular, are frequently treated with medications that can induce hyponatremia, including antihypertensive agents, antidepressants, and nonsteroidal anti-inflammatory drugs [19, 20]. As far as antihypertensive therapy is concerned, thiazides and potassium-sparing diuretics (i.e., spironolactone and amiloride) can induce hyponatremia [19, 20]. On the other hand, loop diuretics and angiotensin-converting enzyme inhibitors are only occasionally associated with hyponatremia [19, 20]. Loop diuretics prevent the generation of a concentration gradient in the renal medulla causing thus renal salt and water loss [19, 20]. If this water loss is replaced insufficiently (not infrequently in stroke patients), hyponatremia may ensue [21]. Of note, loop diuretics are recommended for the treatment of euvolemic and hypervolemic hyponatremia since they lead to hypotonic renal losses [22, 23].

During hospitalization, the emergence or the aggravation of hyponatremia may be due to a variety of causes: “inappropriate” administration of intravenous fluids (e.g., hypotonic solutions), poor solute intake, infections (e.g., aspiration pneumonia), or stroke-related therapies.

Indeed, several drugs could be required for the early management of patients with acute stroke [24]. First, treatment with antihypertensive agents could be needed in the following groups: (a) patients with acute ischemic stroke being candidates for acute reperfusion therapy and having blood pressure $\geq 185/110$ mm Hg; (b) patients with concomitant acute coronary event, acute heart failure, aortic dissection, post thrombolysis, intracerebral hemorrhage, or preeclampsia/eclampsia; and (c) patients with BP $\geq 220/120$ mm Hg, no comorbid conditions and not being candidates for reperfusion therapy [24]. In this context, the available therapeutic options include intravenous treatment with labetalol, nicardipine, clevidipine, hydralazine, and sodium nitroprusside, which have not been associated with the development of hyponatremia [24]. Likewise, reperfusion therapies (i.e., intravenous treatment with alteplase, endovascular treatment, or mechanical thrombectomy) have not been described to cause directly hyponatremia. However, their potential adverse events, such as intracerebral hemorrhage as well as periprocedural stimuli of ADH secretion (i.e., pain and anxiety), could lower sodium levels by

Table 1. Characteristics of hyponatremia on admission in patients with stroke

Study	Design	Sample	Definition of hyponatremia	Prevalence of hyponatremia, %	Associations of hyponatremia
<i>Ischemic stroke</i>					
Fofi et al. [4], 2012	Prospective	<i>n</i> = 475; 53.9% male; mean age 67.0 years	Na <136 mmol/L	6.3	Increased in-hospital mortality
Huang et al. [5], 2012	Prospective	<i>n</i> = 925; 52.5% male; mean age 69.5 years	Na <135 mmol/L	11.6	Higher 3-year mortality (but not short-term mortality within 3 months)
Rodrigues et al. [6], 2014	Retrospective	<i>n</i> = 3,585; 49.6% male; mean age 71.0 years	Na <135 mmol/L	16.0	Higher admission NIHSS values, lower admission mBI values, worse disposition at discharge from hospital, and higher 3- and 12-month mortality
Lasek-Bal et al. [7], 2014	Prospective	<i>n</i> = 464; 46.1% male; mean age 70.4 years	Na <136 mmol/L	18.9	Higher mortality within 1 month, more severe neurological patients' state in both the acute and subacute phases of stroke
Bei et al. [8], 2017	Prospective	<i>n</i> = 3,314; 57.7% male; mean age 68.6 years	Na <135 mmol/L	3.9	Higher admission mRS and NIHSS scores No association with in-hospital mortality
Gao et al. [9], 2018	Retrospective	<i>n</i> = 718; 21.4% male; median age 73 years	Na <135 mmol/L	15.2	Association with 1-month mortality only in univariate analysis
<i>Acute ischemic or hemorrhagic stroke</i>					
Soiza et al [10], 2015	Retrospective	<i>n</i> = 8,540; 47.4% male; mean age 77.3 years	Na <135 mmol/L	13.8	Higher mortality (within 1 week – 11 years) in patients <75 years
<i>Hemorrhagic stroke</i>					
Kuramatsu et al. [11], 2014	Retrospective	<i>n</i> = 464; 45.0% male; mean age 69.6 years	Na <135 mmol/L	15.6	Increased in-hospital mortality and within 90 days of index stroke; higher admission NIHSS values; lower Glasgow Coma Scale
Gray et al. [12], 2014	Retrospective	<i>n</i> = 99; 61.6% males; mean age 58 years	Na <135 mmol/L	24	Increased in-hospital complications (fever, infection and a longer hospitalization); no association with in-hospital mortality
Carcel et al. [13], 2016	Retrospective analysis of a randomized trial	<i>n</i> = 3,002; 62.8% males; 64±13 years	Na <135 mmol/L	12	Increased mortality within 3 months; larger baseline intracerebral hemorrhage volume

NIHSS, National Institutes of Health Stroke Scale; mBI, modified Barthel Index; mRS, modified Rankin Scale.

causing SIAD. On the other hand, mannitol, which might be used in the setting of acute ischemic stroke and cerebral edema, is associated with hyponatremia [20]. It creates a transcellular osmotic gradient by increasing plasma osmolality, which leads to water movement out of the cells and reduction of serum sodium concentration by means of dilution (dilutional or translocational

hyponatremia) [20]. In this setting, hyponatremia is accompanied by normal or increased serum osmolality [20]. Furthermore, mannitol could lower sodium levels by causing acute renal failure [25, 26]. Nevertheless, the administration of mannitol constitutes also a significant contributing factor for in-hospital hypernatremia [27]. The inability of patients with stroke to drink water along

Table 2. Etiology of hyponatremia in stroke patients*Stroke-related causes*

- SIAD: increased hypothalamic production of ADH
- CSW syndrome: inappropriate renal sodium wasting possibly due to impaired sympathetic neural input and increased release of brain natriuretic peptide from the damaged brain
- Secondary adrenal insufficiency: pituitary ischemia or hemorrhage

Nonstroke-related causes

Other causes and/or superimposed factors

- Comorbidities: diabetes mellitus, chronic renal failure, and heart failure
- Inappropriate administration of intravenous fluids (e.g., hypotonic solutions)
- Poor solute intake
- Infections (e.g., aspiration pneumonia)

Drug-induced hyponatremia

–Mannitol

- Diuretics* (thiazides, indapamide, loop and potassium sparing diuretics)
- Antidepressants* (tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors)
- Anxiolytics* (benzodiazepines)
- Antipsychotics* (phenothiazines, butyrophenones)
- Anticonvulsants drugs* (oxcarbazepine, carbamazepine, eslicarbazepine, sodium valproate, lamotrigine, levetiracetam, gabapentin, phenytoin, topiramate)
- Others*: non-steroidal anti-inflammatory drugs, proton pump inhibitors, antibiotics (ciprofloxacin, co-trimoxazole), angiotensin-converting enzyme inhibitors, antiarrhythmics (amiodarone, lorcinide, propafenone), opioids

SIAD, syndrome of inappropriate antidiuresis; ADH, antidiuretic hormone; CSW, cerebral salt wasting.

with the mannitol-induced renal hypotonic losses coupled with the administration of isotonic or hypertonic solutions could eventually increase sodium plasma concentration [21].

Stroke-Related Causes of Hyponatremia

Conditions related to stroke per se such as secondary adrenal insufficiency due to pituitary ischemia or hemorrhage, SIAD, and cerebral salt wasting (CSW) could also lead to hyponatremia. In a study of 100 stroke patients, CSW was the most common cause of hyponatremia (44.2%), whereas only 7% of hyponatremia cases were attributed to SIAD [15]. On the contrary, in another series of 100 patients with mild/moderate subarachnoid hemorrhage (corresponding to a median Hunt and Hess scale of 2/5 and a median Fisher grade of 3/4), SIAD (71.4%) and acute glucocorticoid insufficiency (8.2%) were found to be the leading causes of hyponatremia. Of note, no cases of CSW were identified in this study [28, 29]. In clinical practice, it is a diagnostic challenge to differentiate between CSW and SIAD considering the fact that both syndromes share a similar laboratory testing profile consisting of: normal renal, adrenal and thyroid function, hyponatremia, hypouricemia, high urine sodium levels

(higher than 40 mmol/L), concentrated urine (urine osmolality >100 mOsmol/kg and usually >300 mOsmol/kg), and a high fractional excretion of uric acid (FEUA) > 11%. The diagnosis should be based on the assessment of extracellular volume (normovolemia in cases of SIAD versus hypovolemia in cases of CSW) which, not infrequently, is unreliable on clinical grounds. Thus, in a nonedematous patient with hyponatremia associated with “intracranial disease” only the presence of clear evidence of volume depletion (e.g., hypotension, decreased skin turgor, elevated hematocrit, increased blood urea nitrogen to creatinine ratio) strongly suggests CSW rather than SIAD as the underlying cause of hyponatremia.

FEUA is calculated by the formula: $100 \times (\text{serum creatinine} \times \text{urine uric acid}) / (\text{serum uric acid} \times \text{urine creatinine})$ and is very useful in the diagnostic approach of hyponatremia. In fact, a normal FEUA (4–11%) is observed in hyponatremic patients with a reset osmostat and psychogenic polydipsia, while a low FEUA (<4%) is a common feature in effective circulating volume depletion (true hypovolemia or edematous states such as congestive heart failure and cirrhosis) [30]. Maesaka et al. [31] have proposed the estimation of FEUA after the correction of hyponatremia as a reliable “tool” to differenti-

Table 3. Proposed steps in the evaluation and treatment of hyponatremia in stroke patients

Diagnostic approach pearls

- In the presence of marked hyperproteinemia or hyperlipidemia (i.e., hypertriglyceridemia), “pseudohyponatremia” should be excluded. (“Spurious” hyponatremia refers to nonhypotonic hyponatremia with normal values of plasma osmolality [Posm 275–290 mOsmol/kg])
 - When osmotically active substances (e.g., mannitol, glucose) are present, serum osmolality is normal or increased. In hyperglycemic states, the corrected serum sodium should be calculated by increasing the measured serum sodium level by 1.4–2.4 mmol/L for every 100 mg/dL (5.55 mmol/L) of blood glucose increase above normal
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Step-by-step management

- Discontinuation of the offending drugs or hypotonic solutions
 - Treatment of underlying conditions associated with hyponatremia (e.g., infections, hyperglycemia, adrenal insufficiency)
 - Acute hyponatremia (established in a period of <48 h) and hyponatremia with severe or moderate symptoms: 100–150 mL over 10–20 min for 2–3 times as needed or continuous infusion (0.25–0.5 mL/kg per hour) 3% NaCl
 - Euvolemic hyponatremia: hypertonic saline (0.25–0.5 mL/kg per hour) or urea (second line)
 - Hypervolemic hyponatremia: hypertonic saline (0.25 mL/kg per hour) plus furosemide (20–40 mg intravenously)
 - Hypovolemic hyponatremia: normal saline
-

Note

- In acute or symptomatic hyponatremia serum sodium levels should increase by 4–6 mEq/L within the first 4–6 h. In all cases (acute, symptomatic or asymptomatic hyponatremia) the elevation in serum sodium levels should not exceed 10–12 mmol/L/day. The correction rates must be even lower in patients with risk factors (hypokalemia, malnutrition, advanced liver disease, alcoholism, and serum sodium ≤ 105 mmol/L) of developing the ODS.
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ODS, osmotic demyelination syndrome.

ate between CSW and SIAD. Specifically, FEUA normalizes in SIAD patients with corresponding values of <11%, whereas FEUA remains persistently elevated in patients with CSW (corresponding values higher than 11%).

Copeptin, the C-terminal part of the ADH precursor peptide, is secreted in an equimolar ratio to ADH and is a sensitive surrogate marker for its release. Copeptin, being more stable, could be measured more easily compared to ADH. Increased copeptin levels may be useful for the prediction of the functional outcome and all-cause mortality within 3 months or 1 year after an acute ischemic stroke, as well as for early risk stratification in patients with transient ischemic attack [32]. However, serum copeptin levels, being elevated in the majority of hyponatremic patients, are of limited usefulness in the differential diagnosis of the underlying cause of hyponatremia. In 2 relevant studies, copeptin measurement reliably identified only patients with primary polydipsia wherein copeptin concentrations were low, as anticipated [33, 34].

Hyponatremia and Mortality in Patients with Stroke

It has been reported that either hyponatremia or even low normal serum sodium levels are independent predictors of mortality and organ dysfunction due to hypo-

tonicity-mediated cellular edema plays a significant role [35–38]. Specifically, acute hyponatraemia (defined as hyponatremia of <24–48 h of duration) produces brain edema, which might potentially lead to neuropathological consequences or death [38]. On the other hand, rapid correction of chronic hyponatremia is associated with increased risk of developing central pontine myelinolysis or osmotic demyelination, which results in major disability or even fatal outcome. It is also possible that hyponatremia indirectly contributes to mortality by causing organ dysfunction [38]. Nonetheless, it is not entirely clear whether causality between serum sodium concentrations and elevated mortality really exists or that a decrease in serum sodium is just an index of the severity of the underlying disease process, which leads independently to hyponatremia and to adverse outcomes.

There is no experimental evidence regarding the effects of hyponatremia on the brain after an ischemic or hemorrhagic stroke. On the other hand, a plethora of observational studies have evaluated the association of hyponatremia (upon admission [4–13] or during hospitalization [14–17]) with mortality in patients with ischemic or hemorrhagic stroke. More interestingly, a recently published meta-analysis including $n = 21,973$ patients with stroke demonstrated that hyponatremia was associ-

ated with a higher risk of all-cause mortality in short-term (hazard ratio 1.78; 95% CI 1.19–2.75) and long-term follow-up (hazard ratio 2.23; 95% CI 1.30–3.82) [39]. Therefore, it could be assumed that the aforementioned complications of hyponatremia (i.e., brain edema) or the comorbidities of patients with stroke further worsen an already injured brain. It has to be noticed though that the discrepancies regarding the prognostic value of hyponatremia in stroke patients observed in the aforementioned studies may, partly at least, be attributed to differences in the inclusion criteria, the demographic characteristics, and the sample size. Of note, potential important parameters such as the etiology of hyponatremia, the deterioration of serum sodium levels during hospitalization, and serum sodium levels at discharge were not investigated. Noteworthy, a recent registry analysis from 225 sites showed that appropriate laboratory tests to assess the underlying causes of hyponatremia were performed in <50% of patients, whereas 78% of patients continued to be hyponatremic (serum sodium <135 mmol/L) at discharge [40]. Consequently, taking in to account that hyponatremia is related to a plethora of underlying disease conditions with different and often multiple pathophysiologic mechanisms further studies are required to illustrate the precise association between hyponatremia and stroke. Furthermore, it will be of paramount importance to know whether the appropriate restoration of sodium level improves the outcome in patients with acute stroke.

Treatment of Hyponatremia in Stroke Patients

Treatment of hyponatremia differs significantly in accordance with the patient's volume status (i.e., hypovolemia, normovolemia, or hypervolemia; Table 3) [22, 23, 41–43]. The restoration of the volume depletion is the cornerstone of treatment in hypovolemic hyponatremia. On the other hand, treatment of hyper- and euvolemic hyponatremia is more complex. In addition to the correction of the underlying cause (e.g., withdrawal of an offending drug), fluid restriction, administration of hypertonic solution, loop diuretics, urea, and vasopressin-receptor antagonists (vaptans) are among the therapeutic options.

Of note, in the 2 sets of current guidelines for the treatment of hyponatremia, there is no specific mention to stroke patients [22, 23]. However, some crucial points deserve special attention. Fluid restriction (the first-line therapy of SIAD in both guidelines) may be inappropriate in stroke patients due to increased risk for deteriorating

an already impaired cerebral circulation. Fluid restriction is also contraindicated in hypovolemic states such as CSW, which is difficult to differentiate from SIAD in the majority of cases. It has been proposed that hyponatremia ascribed to intracranial diseases should be treated with hypertonic saline [44]. This therapeutic strategy has also another potential advantage. Taking into consideration that there are no established pretreatment predictive factors in differentiating SIADH from CSW, the computation of FEUA after correcting hyponatremia by careful administration of hypertonic saline might be a valuable way to determine the correct diagnosis. Isotonic saline, often used as maintenance therapy in stroke patients, should be avoided in patients with hyponatremia due to SIAD since it can aggravate hyponatremia if the urine osmolality is higher than serum osmolality (especially in cases with urine osmolality above 530 mOsm/kg) [45]. It has been proposed that urea may be an attractive option in treating stroke patients with hyponatremia due to SIAD [46, 47]. Urea exerts beneficial effects on brain swelling regardless of changes in sodium levels leading to a considerable decrease in intracranial pressure [48]. It has been also suggested that urea may exhibit neuroprotective effects, possibly including astrocytes, known to play an important role in the pathogenesis of osmotic demyelination syndrome in the setting of rapid correction of chronic hyponatremia. In fact, it has been reported that urea is associated with a lower risk of osmotic demyelination syndrome as compared to vasopressin antagonist or hypertonic saline [49]. It should be emphasized, however, that the clinical experience with reference to urea administration is limited worldwide, especially in stroke patients [46–48]. Moreover, urea should be avoided in hypovolemic hyponatremia since it induces increased renal water excretion leading to a deterioration of volume depletion [46–49].

Tolvaptan (an oral V₂ receptor antagonist) has been approved in the United States for the treatment of euvolemic and hypervolemic hyponatremia and in the European Union only for the treatment of hyponatremia secondary to SIAD [50]. The FDA has approved intravenous conivaptan (a dual V_{1a}/V₂ receptor antagonist) for short-term use (≤4 days) in hospitalized patients with nonhypovolemic hyponatremia [51]. There is also evidence that conivaptan diminishes the cerebral edema and blood-brain barrier disruption following an experimental stroke in mice possibly through osmotic and anti-inflammatory mechanisms [51, 52]. However, studies conducted to evaluate the role of vaptans in treating exclusively hyponatremic patients with stroke are lacking. Moreover,

both approved vaptans were related to overcorrection of hyponatremia [50, 53]. Recently, high rate of sodium overcorrection (up to 19%) even with a single oral dose of tolvaptan was observed in a small study including 36 “neuro”-critically ill patients. Although, no cases of overcorrection due to conivaptan were identified in this study, the number of patients received conivaptan was low ($n = 5$) [54]. It should be noticed that the use of vaptans is contraindicated in severe symptomatic hyponatremia (serum sodium <120 mmol/L), in hypovolemic hyponatremia, as well as in patients with impaired thirst mechanisms. Consequently, in view of the limited clinical data and the risk of rapid increase of serum sodium levels, it is prudent that the use of vaptans in stroke might be restricted in selected patients with nonhypovolemic hyponatremia refractory to other treatment modalities including hypertonic saline.

To sum up, physicians treating patients with stroke and hyponatremia should bear in mind that serum sodium concentration should be determined frequently in order to avoid inappropriate increase in serum sodium levels (i.e., >10 – 12 mmol/L/day). Close monitoring is of vital importance. Administration of large amounts of isotonic fluids or hypertonic fluids to patients with congestive heart failure or chronic renal failure, which are common comorbidities in stroke patients, may lead to cardiac decompensation and pulmonary edema. Special attention should be paid to hypovolemic hyponatremic patients for the possibility of an overly rapid increase in serum sodium levels when volume depletion is restored; an abrupt decrease in ADH secretion and subsequently a rapid increase in diuresis may occur. In this context, a large-volume polyuria is considered an alarming sign that indicates an inappropriate correction of hypovolemia-related hyponatremia.

Conclusions

Hyponatremia in acute stroke patients is frequent. It is associated with worse stroke outcomes and increased mortality; however, the quality of evidence is low to conclude whether this is a direct effect of hyponatremia. The plethora of underlying etiologies warrants a careful differential diagnosis, which should take into consideration comorbidities, concurrent medication, findings from the clinical examination and laboratory measurements, which in turn will guide management decisions. It is yet unclear whether the appropriate restoration of sodium level improves outcomes in patients with acute stroke.

Randomized studies scheduled to compare the available therapeutic options in treating hyponatremic stroke patients are required.

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Statement of Ethics

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References

- 1 Liamis G, Rodenburg EM, Hofman A, Zietse R, Stricker BH, Hoorn EJ. Electrolyte disorders in community subjects: prevalence and risk factors. *Am J Med*. 2013 Mar;126(3):256–63.
- 2 Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. *Am J Med*. 2006 Jul;119(7 Suppl 1):S30–5.

- 3 Liamis G, Milionis HJ, Elisaf M. Hyponatremia in patients with infectious diseases. *J Infect.* 2011 Nov;63(5):327–35.
- 4 Fofi L, Dall'armi V, Durastanti L, Valenza A, Lorenzano S, Prencipe M, et al. An observational study on electrolyte disorders in the acute phase of ischemic stroke and their prognostic value. *J Clin Neurosci.* 2012 Apr;19(4):513–6.
- 5 Huang WY, Weng WC, Peng TI, Chien YY, Wu CL, Lee M, et al. Association of hyponatremia in acute stroke stage with three-year mortality in patients with first-ever ischemic stroke. *Cerebrovasc Dis.* 2012;34(1):55–62.
- 6 Rodrigues B, Staff I, Fortunato G, McCullough LD. Hyponatremia in the prognosis of acute ischemic stroke. *J Stroke Cerebrovasc Dis.* 2014 May–Jun;23(5):850–4.
- 7 Lasek-Bal A, Holecki M, Kret B, Hawrot-Kawecka A, Dulawa J. Evaluation of influence of chronic kidney disease and sodium disturbances on clinical course of acute and subacute stage first-ever ischemic stroke. *Med Sci Monit.* 2014 Aug;20:1389–94.
- 8 Bei HZ, You SJ, Zheng D, Zhong CK, Du HP, Zhang Y, et al. Prognostic role of hyponatremia in acute ischemic stroke patients. *Acta Neurol Scand.* 2017 Dec;136(6):672–9.
- 9 Gao H, Sun X, Li W, Gao Q, Zhang J, Zhang Y, et al. Development and validation of a risk score to predict 30-day mortality in patients with atrial fibrillation-related stroke: GPS-GF score. *Neurol Res.* 2018 Jul;40(7):532–40.
- 10 Soiza RL, Cumming K, Clark AB, Bettencourt-Silva JH, Metcalf AK, Bowles KM, et al. Hyponatremia predicts mortality after stroke. *Int J Stroke.* 2015 Oct;10 Suppl A100:50–5.
- 11 Kuramatsu JB, Bobinger T, Volbers B, Staykov D, Lücking H, Kloska SP, et al. Hyponatremia is an independent predictor of in-hospital mortality in spontaneous intracerebral hemorrhage. *Stroke.* 2014 May;45(5):1285–91.
- 12 Gray JR, Morbitzer KA, Liu-DeRyke X, Parker D Jr, Zimmerman LH, Rhoney DH. Hyponatremia in Patients with Spontaneous Intracerebral Hemorrhage. *J Clin Med.* 2014 Nov;3(4):1322–32.
- 13 Carcel C, Sato S, Zheng D, Heeley E, Arima H, Yang J, et al. Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2 Investigators. Prognostic Significance of Hyponatremia in Acute Intracerebral Hemorrhage: Pooled Analysis of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial Studies. *Crit Care Med.* 2016 Jul;44(7):1388–94.
- 14 Alam MN, Uddin MJ, Rahman KM, Ahmed S, Akhter M, Nahar N, et al. Electrolyte changes in stroke. *Mymensingh Med J.* 2012 Oct;21(4):594–9.
- 15 Kalita J, Singh RK, Misra UK. Cerebral Salt Wasting Is the Most Common Cause of Hyponatremia in Stroke. *J Stroke Cerebrovasc Dis.* 2017 May;26(5):1026–32.
- 16 Saleem S, Yousuf I, Gul A, Gupta S, Verma S. Hyponatremia in stroke. *Ann Indian Acad Neurol.* 2014 Jan;17(1):55–7.
- 17 Shah A, Sabir S, Artani M, Salam O, Khan S, Rizwan A. Significance of Hyponatremia as an Independent Factor in Predicting Short-term Mortality in Patients with Hemorrhagic Stroke. *Cureus.* 2019 Apr;11(4):e4549.
- 18 Kesarwani M, Perez A, Lopez VA, Wong ND, Franklin SS. Cardiovascular comorbidities and blood pressure control in stroke survivors. *J Hypertens.* 2009 May;27(5):1056–63.
- 19 Liamis G, Milionis H, Elisaf M. Blood pressure drug therapy and electrolyte disturbances. *Int J Clin Pract.* 2008 Oct;62(10):1572–80.
- 20 Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. *Am J Kidney Dis.* 2008 Jul;52(1):144–53.
- 21 Liamis G, Milionis HJ, Elisaf M. A review of drug-induced hyponatraemia. *NDT Plus.* 2009 Oct;2(5):339–46.
- 22 Spasovski G, Vanholder R, Alolio B, Annane D, Ball S, Bichet D, et al. Hyponatraemia Guideline Development Group. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Eur J Endocrinol.* 2014 Feb;170(3):G1–47.
- 23 Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med.* 2013 Oct;126(10 Suppl 1):S1–42.
- 24 Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al.; American Heart Association Stroke Council. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke.* 2018 Mar;49(3):e46–110.
- 25 Tsai SF, Shu KH. Mannitol-induced acute renal failure. *Clin Nephrol.* 2010 Jul;74(1):70–3.
- 26 Shi J, Qian J, Li H, Luo H, Luo W, Lin Z. Renal tubular epithelial cells injury induced by mannitol and its potential mechanism. *Ren Fail.* 2018 Nov;40(1):85–91.
- 27 Liamis G, Tsimihodimos V, Doumas M, Spyrou A, Bairaktari E, Elisaf M. Clinical and laboratory characteristics of hyponatraemia in an internal medicine clinic. *Nephrol Dial Transplant.* 2008 Jan;23(1):136–43.
- 28 Hannon MJ, Behan LA, O'Brien MM, Tormey W, Ball SG, Javadpour M, et al. Hyponatremia following mild/moderate subarachnoid hemorrhage is due to SIAD and glucocorticoid deficiency and not cerebral salt wasting. *J Clin Endocrinol Metab.* 2014 Jan;99(1):291–8.
- 29 Verbalis JG. Hyponatremia with intracranial disease: not often cerebral salt wasting. *J Clin Endocrinol Metab.* 2014 Jan;99(1):59–62.
- 30 Maesaka JK, Imbriano LJ, Miyawaki N. Determining Fractional Urate Excretion Rates in Hyponatremic Conditions and Improved Methods to Distinguish Cerebral/Renal Salt Wasting From the Syndrome of Inappropriate Secretion of Antidiuretic Hormone. *Front Med (Lausanne).* 2018 Nov;5:319.
- 31 Maesaka JK, Imbriano L, Mattana J, Gallagher D, Bade N, Sharif S. Differentiating SIADH from Cerebral/Renal Salt Wasting: Failure of the Volume Approach and Need for a New Approach to Hyponatremia. *J Clin Med.* 2014 Dec;3(4):1373–85.
- 32 Xu Q, Tian Y, Peng H, Li H. Copeptin as a biomarker for prediction of prognosis of acute ischemic stroke and transient ischemic attack: a meta-analysis. *Hypertens Res.* 2017 May;40(5):465–71.
- 33 Fenske W, Störk S, Blechschmidt A, Maier SG, Morgenthaler NG, Alolio B. Copeptin in the differential diagnosis of hyponatremia. *J Clin Endocrinol Metab.* 2009 Jan;94(1):123–9.
- 34 Nigro N, Winzeler B, Suter-Widmer I, Schuetz P, Arici B, Bally M, et al. Evaluation of copeptin and commonly used laboratory parameters for the differential diagnosis of profound hyponatraemia in hospitalized patients: 'The Co-MED Study'. *Clin Endocrinol (Oxf).* 2017 Mar;86(3):456–62.
- 35 Mazza A, Pessina AC, Pavei A, Scarpa R, Tikhonoff V, Casiglia E. Predictors of stroke mortality in elderly people from the general population. The Cardiovascular Study in the Elderly. *Eur J Epidemiol.* 2001;17(12):1097–104.
- 36 Sajadieh A, Binici Z, Mouridsen MR, Nielsen OW, Hansen JF, Haugaard SB. Mild hyponatremia carries a poor prognosis in community subjects. *Am J Med.* 2009 Jul;122(7):679–86.
- 37 Wannamethee G, Whincup PH, Shaper AG, Lever AF. Serum sodium concentration and risk of stroke in middle-aged males. *J Hypertens.* 1994 Aug;12(8):971–9.
- 38 Hoorn EJ, Zietse R. Hyponatremia and mortality: how innocent is the bystander? *Clin J Am Soc Nephrol.* 2011 May;6(5):951–3.
- 39 Chen Z, Jia Q, Liu C. Association of Hyponatremia and Risk of Short- and Long-Term Mortality in Patients with Stroke: A Systematic Review and Meta-Analysis. *J Stroke Cerebrovasc Dis.* 2019 Jun;28(6):1674–83.
- 40 Greenberg A, Verbalis JG, Amin AN, Burst VR, Chiodo JA 3rd, Chiong JR, et al. Current treatment practice and outcomes. Report of the hyponatremia registry. *Kidney Int.* 2015 Jul;88(1):167–77.
- 41 Filippatos TD, Liamis G, Christopoulou F, Elisaf M. Ten common pitfalls in the evaluation of patients with hyponatremia. *Eur J Intern Med.* 2016 Apr;29:22–5.
- 42 Liamis G, Liberopoulos E, Barkas F, Elisaf M. Spurious electrolyte disorders: a diagnostic challenge for clinicians. *Am J Nephrol.* 2013;38(1):50–7.
- 43 Filippatos T, Elisaf M, Liamis G. Pharmacological management of hyponatremia. *Expert Opin Pharmacother.* 2018 Aug;19(12):1337–44.
- 44 Sterns RH, Silver SM. Cerebral salt wasting versus SIADH: what difference? *J Am Soc Nephrol.* 2008 Feb;19(2):194–6.
- 45 Musch W, Decaux G. Treating the syndrome of inappropriate ADH secretion with isotonic saline. *QJM* 1998;91:749–53.

- 46 Decaux G, Andres C, Gankam Kengne F, Soupart A. Treatment of euvolemic hyponatremia in the intensive care unit by urea. *Crit Care*. 2010;14(5):R184.
- 47 Pierrakos C, Taccone FS, Decaux G, Vincent JL, Brimioulle S. Urea for treatment of acute SIADH in patients with subarachnoid hemorrhage: a single-center experience. *Ann Intensive Care*. 2012 May;2(1):13.
- 48 Annoni F, Fontana V, Brimioulle S, Creteur J, Vincent JL, Taccone FS. Early Effects of Enteral Urea on Intracranial Pressure in Patients With Acute Brain Injury and Hyponatremia. *J Neurosurg Anesthesiol*. 2017 Oct;29(4):400–5.
- 49 Gankam Kengne F, Couturier BS, Soupart A, Decaux G. Urea minimizes brain complications following rapid correction of chronic hyponatremia compared with vasopressin antagonist or hypertonic saline. *Kidney Int*. 2015 Feb;87(2):323–31.
- 50 Schrier RW, Gross P, Gheorghiadu M, Berl T, Verbalis JG, Czerwiec FS, et al.; SALT Investigators. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med*. 2006 Nov;355(20):2099–112.
- 51 Zeynalov E, Jones SM, Seo JW, Snell LD, Elliott JP. Arginine-Vasopressin Receptor Blocker Conivaptan Reduces Brain Edema and Blood-Brain Barrier Disruption after Experimental Stroke in Mice. *PLoS One*. 2015 Aug;10(8):e0136121.
- 52 Decker D, Collier L, Lau T, Olivera R, Roma G, Leonardo C, et al. The Effects of Clinically Relevant Hypertonic Saline and Conivaptan Administration on Ischemic Stroke. *Acta Neurochir Suppl (Wien)*. 2016; 121:243–50.
- 53 Li-Ng M, Verbalis JG. Conivaptan: evidence supporting its therapeutic use in hyponatremia. *Core Evid*. 2010 Jun;4:83–92.
- 54 Der-Nigoghossian C, Lesch C, Berger K. Effectiveness and Tolerability of Conivaptan and Tolvaptan for the Treatment of Hyponatremia in Neurocritically Ill Patients. *Pharmacotherapy*. 2017 May;37(5):528–34.