Neurology Asia 2024; 29(2) : 321 – 328

Predictive factors of hyponatremia in subarachnoid hemorrhage and outcomes

[1]Chokchai Chaovarin, [1]Pungjai Keandoungchun, [1]Ampai Phinthusophon, [2]Korrapak Wangtanaphat, [3]Srikul Veerasarn

[1]Department of internal medicine, Neurological Institute of Thailand; [2]Department of neurosurgery, Neurological Institute of Thailand; [3]Department of neurology, Neurological Institute of Thailand

Abstract

Background & Objective: The prevalence of hyponatremia in subarachnoid hemorrhage (SAH) was 30-55%. There was lack of evidence about predictive factors and clinical outcomes of hyponatremia in SAH patients. This study aimed to evaluate factors associated with hyponatremia following SAH and to review the clinical outcomes and treatment of hyponatremia in SAH patients. *Method:* This is a retrospective cohort study. SAH patients presented during January 2013 to January 2019 were reviewed. They were divided into 2 groups: SAH with normonatremia and SAH with hyponatremia. Clinical data, laboratory profile, aneurysm characteristics and clinical outcomes were recorded and analyzed. *Result:* A total number of 278 patients with SAH were included, 139 patients in each group. The populations were female 66% with mean age of 56 years old and mean serum sodium (Na) level 132 mmol/L. Aneurysm location associated with hyponatremia; anterior cerebral artery (ACA) (OR 4.2, 95%CI 1.4-13.0, p-value 0.009) and posterior cerebral artery (PCA) (OR 3.7, 95%CI 1.2-11.5, p-value 0.017). Aneurysms clipping procedure was also associated with hyponatremia (OR 4.0, 95%CI 1.8-8.8, p-value < 0.001).
Conclusion: ACA and PCA aneurysms and aneurysms clipping procedure were risk factors for hyponatremia following SAH. Mild hyponatremia was not associated with morbidity and mortality in SAH patients.

Keywords: Hyponatremia, subarachnoid hemorrhage, cerebral salt wasting syndrome (CSW), Syndrome of in appropriate antidiuretic hormone (SIADH)

INTRODUCTION

The prevalence of hyponatremia following subarachnoid hemorrhage (SAH) was 30-55%.[1-3] Hyponatremia is associated with increased mortality and morbidity due to cerebral vasospasm, cerebral edema, seizure, osmotic demyelination syndrome, and prolonged hospital stay. After a ruptured brain aneurysm, hyponatremia can occur during the first to ninth day. SAH with hyponatremia patients had prolonged intensive care unit (ICU) stay up to 7 days and increased length of hospitalization up to 11 days.[4] Pathogenesis of hyponatremia after SAH has two general mechanisms: cerebral salt wasting syndrome (CSWS) and syndrome of inappropriate antidiuretic hormone secretion (SIADH). However, they were difficult to distinguish because of their identical laboratory results.

Pathophysiology of CSWS has two current theories[5,6], the first theory is sympathetic nervous system dysfunction with decrease outflow tract resulting in decrease sodium (Na) reabsorption at proximal tubule. The second theory is the releasing of brain natriuretic peptide (BNP) after brain injury. BNP acts on the collecting duct of renal tubular cells to inhibit Na reabsorption resulting in Na loss in urine and decrease intravascular volume. This hypovolemic state activates renin angiotensin aldosterone system (RAAS). Then antidiuretic hormone (ADH) is secreted from hypothalamus resulting in free water reabsorption and cause hyponatremia. Pathophysiology of CSWS was demonstrated in Figure 1.

On the other hand, patients with SIADH are in euvolemic to hypervolemic state. Non-osmotic stimuli induce inappropriate ADH secretion, which impaired water excretion at the collecting duct and cause hypotonic hyponatremia.[7]

Address correspondence to: Dr Chokchai Chaovarin, Division of Nephrology, Department of Internal Medicine, Neurological institute of Thailand. 312 Ratchawithi Rd, Khwaeng Thung Phaya Thai, Khet Ratchathewi, Ratchatewi, Bangkok 10400, Thailand. Tel: (66) 2 306 9899, Email: Dchvr@nit.go.th

Date of Submission: Date of Submission: 23 January 2024, Date of Acceptance: 25 January 2024

https://doi.org/10.54029/2024wfc

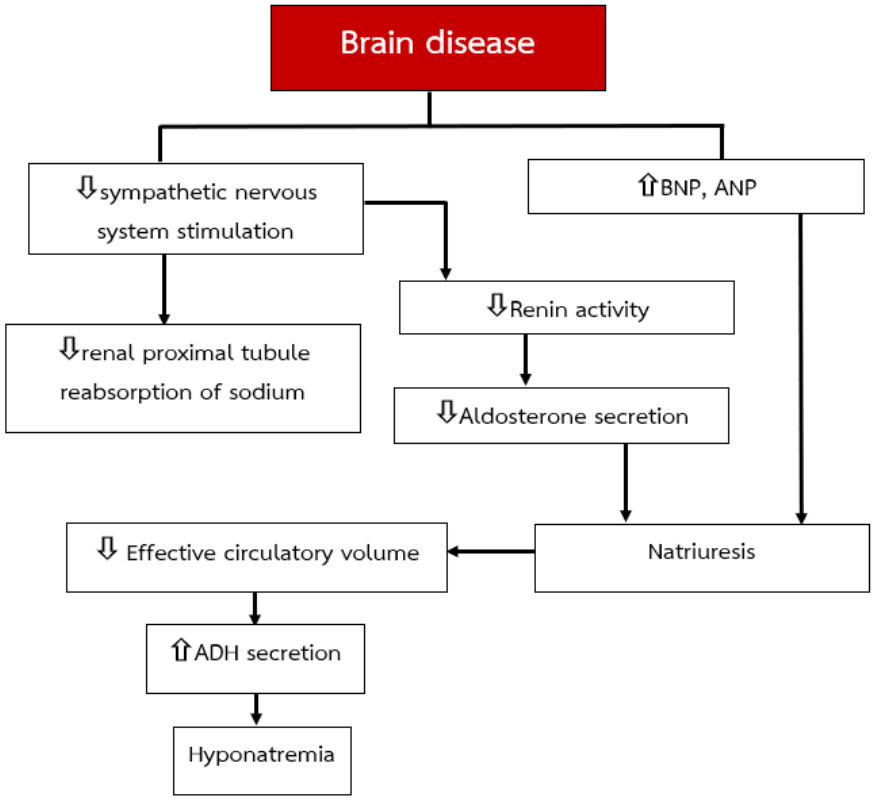

Figure 1. Pathophysiology of CSWS
BNP, brain natriuretic peptide; ANP, atrial natriuretic peptide; ADH, antidiuretic hormone

The primary objective of this study aims to analyze factors associated with hyponatremia following SAH and the second objective aims to review the clinical outcomes and management of hyponatremia.

METHODS

Trial design

This retrospective cohort study was conducted at Neurological Institute of Thailand (NIT). The patients with SAH were divided into two groups: SAH with hyponatremia and SAH with normonatremia. This study was approved on September 2nd, 2021, by the ethics committees of Institutional Review Board of Neurological Institute of Thailand (code: 061/2563). An independent data and safety monitoring committee reviewed pertinent safety data. Data were collected and analyzed by investigators. The authors interpreted the data, collaborated in the manuscript preparation, and aimed for the accuracy and completeness of the data and for the adherence of the trial based on the protocol. The first and last authors wrote the first draft of the manuscript and made final decisions regarding the content of the submitted manuscript. All the authors had access to the data, critically reviewed the manuscript, and approved it for submission. The authors and their institutions were required to maintain data confidentiality during the trial.

Trial participants

According to medical record, patients with spontaneous SAH who were admitted at NIT during January 2013 to January 2019 were enrolled to the study. Key eligibility criteria included spontaneous SAH, age more than 18 years old, and hospitalization within 7 days of onset. The patients who had following conditions were excluded from our study; traumatic SAH, central nervous system vascular malformations, chronic kidney disease, glucocorticoid insufficiency, and hypothyroidism. Full list of inclusion and exclusion criteria were provided in the Supplementary Appendix. After the enrollment, clinical data, laboratory data, aneurysm characteristics, treatment procedures, and clinical outcomes were collected and analyzed.

Statistical analysis

The data was analyzed by SPSS 18.0 software (version 18.0, SPSS Inc, Chicago, IL). Normally distributed data were reported as mean and standard deviation, while non-normally distributed data were reported as median and interquartile ranges. Categorical variables were described as percentages. Univariate logistic model was used to examine the individual relationship between each variable and hyponatremia. The independent sample t test, chi-square test (χ 2 test), Mann-Whitney U test, and Fisher's exact test were also used. Odds ratio (OR) and 95% confidence intervals (CI) were used to illustrate the association between potential risk factors and hyponatremia. All probability values were two sided and level of significance was set at p-value < 0.05.

RESULT

Population characteristics

We identified 507 patients with SAH during 2013 to 2019. However, 229 patients were excluded by exclusion criteria. The total number of 278 patients remained in this study: 139 patients with hyponatremia and 139 patients with normonatremia. Flow chart sheet was demonstrated in Figure 2.

There were similarities of patient characteristics between both groups. Half of the patients in each group had hypertension with the mean blood pressure of 150/86 mmHg. The median Glasglow Coma Scale (GCS) was 15. Intraparenchymal hemorrhage (IPH) was reported to be 12.2% in hyponatremia and 17.3% in normonatremia, while intraventricular hemorrhage (IVH) was equal in both groups at 18.7%. The aneurysm size was insignificantly different between hyponatremia and normonatremia, 5.4 mm and 5.0 mm, respectively. According to the classification of hyponatremia[8], the degree of hyponatremia was mild, the average serum Na concentration was 132 mmol/L. (Table 1)

Locations of aneurysm and hyponatremia

Locations of aneurysm were risk factors of hyponatremia as shown in Table 2. Anterior

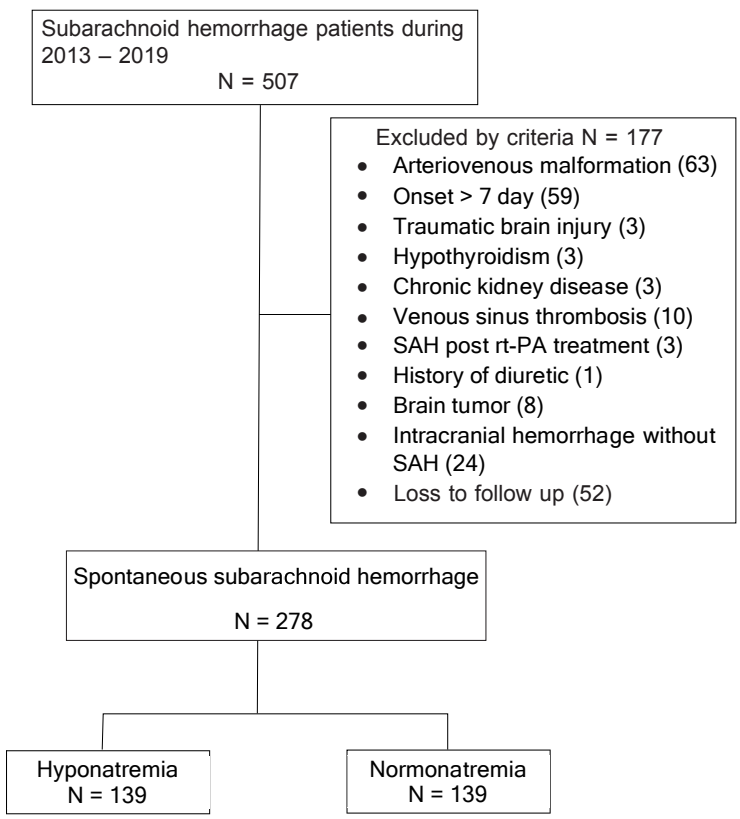

Figure 2. Flow chart sheet
SAH, subarachnoid hemorrhage; rt-PA, recombinant tissue plasminogen activator

Table 1: Population characteristics

	SAH with normonatremia (N= 139)	SAH with hyponatremia (N= 139)	p-value
Age*, years	54.7 (47.8-64.0)	56.1 (47.5-64.3)	0.342
Sex			0.899
– Male†	45 (32)	47 (34)	
– Female†	94 (68)	92 (66)	
Hypertension†	74 (53)	74 (53)	1.00
Smoking †	30 (21)	23, (17)	0.360
DM †	13 (9.4)	8 (5.8)	0.364
DLP †	28 (20)	19 (14)	0.2
Stroke†	4 (2.9)	8 (5.8)	0.377
Initial BP			
SBP ‡	150 (20)	151 (20)	0.891
DBP ‡	86 (14)	87 (12)	0.386
MAP ‡	107 (14)	108 (13)	0.531
BMI*	23.2 (21.1-27.6)	22.9 (20.4-26.9)	0.445
Initial GCS*	15 (9-15)	15 (10-15)	0.325
IPH †	24 (17.3)	17 (12.2)	0.236
IVH †	26 (18.7)	26 (18.7)	1.000
Aneurysm size*, mm	5.0 (3.5-8.5)	5.4 (4.0-8.0)	0.505
Serum Na concentration*, mmol/L	137 (135-138)	132 (129-133)	< 0.001
Hematocrit‡, %	38.0 (5.18)	38.6 (5.51)	0.391
Creatinine*, mg/dL	0.66 (0.56-0.84)	0.59 (0.49-0.77)	0.003
Glucose*, mg/dL	127 (104-148)	124 (104-144)	0.361

*Median (Interquartile range; 25th–75th percentile)
†n (%)
‡Mean (SD)
DM, diabetes mellitus; DLP, dyslipidemia; BP, blood pressure; BMI, body mass index; GCS, Glasgow Coma Scale; IPH intraparenchymal hemorrhage; IVH, intraventricular hemorrhage

cerebral artery (ACA) aneurysm and posterior cerebral artery (PCA) aneurysm were common and significantly associated with hyponatremia (OR 4.2, 95%CI 1.4 to 13.0, p-value 0.009 and OR 3.7, 95%CI 1.2 to 11.5, p-value 0.017, respectively). However, other sites of aneurysm were not associated with hyponatremia.

Treatment procedures and hyponatremia

Aneurysm clipping was most performed in this study, 92.1% in hyponatremia group and 74.1% in normonatremia group. Whereas conservative treatment was the second most option. Aneurysm clipping was associated with hyponatremia

Table 2: Locations of aneurysm and hyponatremia

	SAH with normonatremia	SAH with hyponatremia	p-value	OR, 95% CI
Location of Aneurysm†				
Anterior cerebral artery (ACA)	28 (66.7)	42 (89.4)	0.009	4.2 (1.4-13.0)
Middle cerebral artery (MCA)	17 (54.8)	19 (79.2)	0.060	3.1 (0.9-10.5)
Posterior cerebral artery (PCA)	40 (88.9)	30 (68.2)	0.017	3.7 (1.2-11.5)
Basilar artery	15 (51.7)	6 (54.5)	0.873	1.1 (0.3-4.5)
Vertebral artery	6 (30)	6 (54.55)	0.255	2.8 (0.6-12.9)
Internal carotid artery (ICA)	17 (54.8)	17 (77.3)	0.093	2.8 (0.8-9.5)
Multiple Sites	12 (46.2)	4 (44.4)	1.000	0.9 (0.2-4.3)

†n (%)

Table 3: Treatment procedures and hyponatremia

Treatment procedures†	SAH with normonatremia (N= 139)	SAH with hyponatremia (N= 139)	p-value	OR, 95% CI
			<0.001	
Conservative treatment	29 (20.9)	9 (6.5)		
Clipping	103 (74.1)	128 (92.1)		4.0, (1.81-8.83)
Coiling	4 (2.9)	1 (0.7)		0.8, (0.08-8.16)
Craniectomy	3 (2.2)	1 (0.7)		-
Craniotomy	1 (0.7)	0 (0)		-

†n (%)

(OR 4.0, 95%CI 1.81 to 8.83, p-value <0.001). However, other surgical procedures could not be analyzed due to very small sample size. (Table 3)

Clinical outcomes

Clinical outcomes after spontaneous SAH were similar in both groups. In-hospital complications occurred in about one-third of all patients. Quarter of each group developed pneumonia. Length of hospitalization was insignificantly longer in patients with hyponatremia (IQR of 10 to 24 days vs. 8 to 20 days). In addition, duration of ICU stays, and mechanical ventilation were indifferent between both groups. However, in-hospital death occurred in 11 patients and 5 patients, upon hyponatremia and normonatremia group. Most patients achieved complete recovery at their hospital discharge. (Table 4)

DISCUSSION

Hyponatremia was a common electrolyte imbalance following SAH, which usually occurs during second to seventh day after the onset. This condition required early detection and aggressive treatment. In our study, prevalence of new hyponatremia following SAH was 50%, after excluding hyponatremia secondary to adrenal insufficiency, hypothyroidism, and chronic kidney disease. The mean serum Na concentration was 132 mmol/L. The degree of hyponatremia related with clinical symptoms. Mild hyponatremia were usually asymptomatic.[8] The moderate to severe hyponatremia (Na < 130 mmol/L) is associated with neurological manifestation such as nausea,

Table 4: Clinical outcomes

Clinical outcomes	SAH with normonatremia (N= 139)	SAH with hyponatremia (N= 139)	p-value
Pneumonia†	36 (25)	41 (29.5)	0.592
Gastrointestinal hemorrhage†	3 (2.2)	3 (2.2)	1.000
Seizure†	13 (9.4)	6 (4.3)	0.152
Length of hospitalization*, days	14 (8-20)	14 (10-24)	0.094
Length of ICU stay*, days	3 (1-6)	4 (1-7)	0.328
Mechanical ventilation*, days	0 (0-5)	0 (0-6)	0.724
Clinical status at discharge			0.261
Full recovery†	86 (61.9)	85 (61.2)	
Disability†	42 (30.2)	49 (35.3)	
Death†	11 (7.9)	5 (3.6)	
Clinical status at 3 months			0.119
Full recovery†	79 (66.4)	71 (61.2)	
Disability†	8 (6.7)	16 (13.8)	
Death†	7 (5.9)	2 (1.7)	

*Median (interquartile range; 25th–75th percentile)
†Mean (SD).

confusion, headache, convulsion and coma.[9] An interesting finding of this study is an association between aneurysm location and hyponatremia; the mechanism of this association is unclear. A proposed mechanism for anterior circulation aneurysm related hyponatremia was that the aneurysm located adjacent to pituitary gland and hypothalamus. When aneurysm ruptured, it could affect hypothalamo-pituitary-adrenal axis and increase antidiuretic hormone secretion.[10] From previous studies, ruptured aneurysm in either anterior or posterior circulation are associated with hyponatremia.[11,12]

Majority of patients with aneurysm ruptured was female (66%) with the mean age of 56-years old, as correlated with previous study.[1] Age of onset older than 55 years old are associated with poor clinical outcomes.[2,3] According to literature review, hyponatremia is associated with increase length of hospital stay and ICU stay. The average length of hospitalization was 22 to 24 days.[4,11,13,14] Moreover, hyponatremia could worsen the cerebral edema, increase intracranial pressure and induce cerebral vasospasm.[15] In contrast, our study demonstrated that mild hyponatremia had no impact on neurological outcomes. The key success of treatment was close monitoring and early detection of hyponatremia. In our study, the mean duration of hospital stay was 14 days. This shorter period of hospitalization was owing to early detection and closed monitoring of electrolyte on the first few days after admission. When hyponatremia was recognized, aggressive treatment began, and electrolyte was closely followed until serum Na returned to normal. We suggested that in clinical practice, electrolyte panel should be measured on the day of SAH onset. For patients with normonatremia, close monitoring of electrolyte panel should be done on an alternate day. (Figure 3)

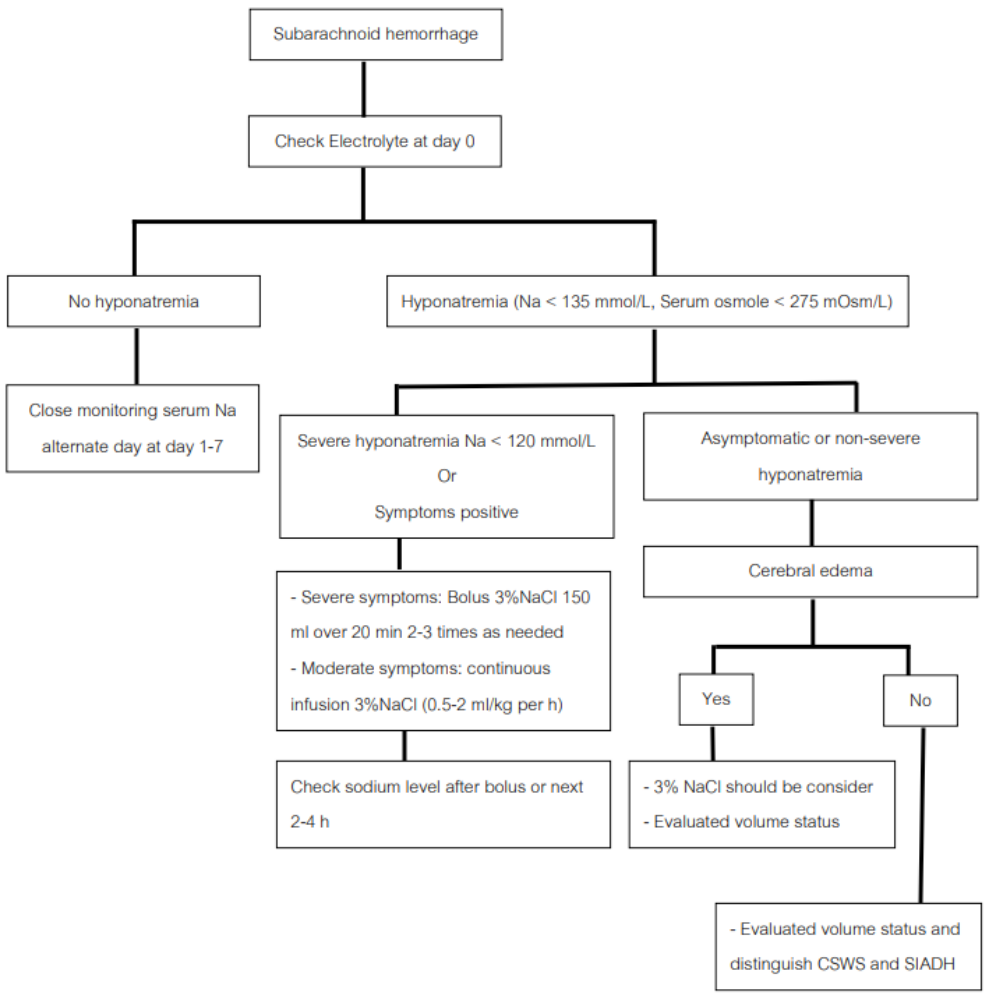

Figure 3. Treatment protocol of hyponatremia in SAH patients

Table 5: Clinical and laboratory data to distinguish SIADH and CSWS

	SIADH	CSWS
Volume status	Euvolemia	Hypovolemia
Blood pressure	Normal	Normal or low
Central venous pressure	Normal	Low
Hematocrit	⇔⇧	⇧
Urine volume	⇩	⇧
Serum uric	⇩	⇔,⇧
Serum bicarbonate	⇔, ⇩	⇧
Blood urea nitrogen	⇔, ⇩	⇧
Urine sodium	> 30 mmol/L	>>30 mmol/L
Na-Cl different	⇩	⇔
Cl/Na ratio	⇔	⇩

Current treatment strategies for intracranial aneurysm were aneurysm clipping, endovascular coiling, craniectomy, and conservative treatment. According to previous study, there was no difference in the incidence of hyponatremia between aneurysm clipping and conservative treatment, but the limitation was small sample size.[16] In our study, we found that aneurysm clipping was a risk factor for hyponatremia (OR 4.0, 95%CI 1.81-8.83, p-value <0.001). However, the mechanism was unknown. Further study should focus on the cause of hyponatremia following aneurysm clipping.

The strength of this study was a relatively large cohort of 278 patients which was more than previous studies. The secondary causes of hyponatremia had been excluded. Moreover, neurological outcomes at 3 months after SAH were collected. Limitation of this study was a retrospective study design and the indetermination of hyponatremia cause, CSWS or SIADH. Future study should distinguish cause of hyponatremia in SAH patients.

Hyponatremia approach in SAH patients

SIADH is the most common cause of hyponatremia in SAH patients.[4] As SIADH and CSWS are difficult to distinguish according to their identical laboratory profile, volume status is the key to differentiate between these two conditions (Table 5). However, it is difficult to differentiate between euvolemia and hypovolemia. CSWS characterizes by hypovolemia, polyuria and response to crystalloid treatment. In contrast, SIADH usually has water retention and euvolemia due to inappropriate secretion of antidiuretic hormone.

Dynamic treatment response of hyponatremia is the key for diagnosis. If serum Na rises along with normal saline intravenous treatment, it is salt wasting hyponatremia. On the other hand, if serum Na falls after positive volume intake with normal saline, it could be SIADH.

Treatment of SIADH is fluid restriction but it may lead to hypovolemia and cerebral vasospasm. Therefore, volume status should be correctly evaluated and water restriction as necessary. In general, aneurysm ruptured causes cerebral edema. Treatment with normal saline solution should be carefully used because isotonic and hypotonic solution can worsen cerebral edema. Hypertonic saline solution should be considered in this situation.

In conclusion, aneurysm located in ACA and PCA and treatment with aneurysm clipping have strong association with hyponatremia following SAH. Morbidity and mortality are not different in mild hyponatremia and normonatremia. Comprehensive monitoring of serum Na and aggressive treatment should be done. To distinguish SIADH and CSWS, volume status and treatment response are the keys.

REFERENCES

1. Tam CW, Shum HP, Yan WW. Impact of dysnatremia and dyskalemia on prognosis in patients with aneurysmal subarachnoid hemorrhage: A retrospective study. *Indian J Crit Care Med* 2019;23(12):562-7. DOI: 10.5005/jp-journals-10071-23292
2. Rosengart AJ, Schultheiss KE, Tolentino J, Macdonald RL. Prognostic factors for outcome in patients with aneurysmal subarachnoid hemorrhage. *Stroke* 2007;38(8):2315-21. DOI: 10.1161/STROKEAHA.107.484360
3. Lanzino G, Kassell NF, Germanson TP, *et al*. Age and outcome after aneurysmal subarachnoid hemorrhage: why do older patients fare worse? *J Neurosurg*

1996;85(3):410-8. DOI: 10.3171/jns.1996.85.3.0410
4. Sherlock M, O'Sullivan E, Agha A, *et al*. The incidence and pathophysiology of hyponatraemia after subarachnoid haemorrhage. *Clin Endocrinol* (Oxf) 2006;64(3):250-4. DOI: 10.1111/j.1365-2265.2006.02432.x
5. Yee AH, Burns JD, Wijdicks EF. Cerebral salt wasting: pathophysiology, diagnosis, and treatment. *Neurosurg Clin N Am* 2010;21(2):339-52. DOI: 10.1016/j.nec.2009.10.011
6. Tenny S, Thorell W. Cerebral salt wasting syndrome. StatPearls. Treasure Island (FL): StatPearls Publishing LLC. 2024.
7. Mentrasti G, Scortichini L, Torniai M, *et al*. Syndrome of inappropriate antidiuretic hormone secretion (SIADH): Optimal management. *Ther Clin Risk Manag* 2020;16:663-72. DOI: 10.2147/TCRM.S206066
8. Spasovski G, Vanholder R, Allolio B, *et al*. Clinical practice guideline on diagnosis and treatment of hyponatraemiaThe guidelines were peer reviewed by the owner societies and by external referees prior to publication. *Eur J Endocrinol* 2014;170(3):G1-G47. DOI: 10.1530/EJE-13-1020
9. Krogulska A, Nowicka D, Nowicki Z, Parzęcka M, Sakson-Słomińska A, Kuczyńska R. A loss of consciousness in a teenage girl with anorexia nervosa, due to polydipsia: case report and a minireview. *Eat Weight Disord* 2019;24(5):969-74. DOI: 10.1007/s40519-018-00636-x
10. Karaca Z, Hacioglu A, Kelestimur F. Neuroendocrine changes after aneurysmal subarachnoid haemorrhage. *Pituitary* 2019;22(3):305-21. DOI: 10.1007/s11102-018-00932-w
11. Hoffman H, Ziechmann R, Gould G, Chin LS. The impact of aneurysm location on incidence and etiology of hyponatremia following subarachnoid hemorrhage. *World Neurosurg* 2018;110:e621-e6. DOI: 10.1016/j.wneu.2017.11.058
12. Ridwan S, Zur B, Kurscheid J, *et al*. Hyponatremia after spontaneous aneurysmal subarachnoid hemorrhage—A prospective observational study. *World Neurosurg* 2019;129:e538-e44. DOI: 10.1016/j.wneu.2019.05.210
13. Kao L, Al-Lawati Z, Vavao J, Steinberg GK, Katznelson L. Prevalence and clinical demographics of cerebral salt wasting in patients with aneurysmal subarachnoid hemorrhage. *Pituitary* 2009;12(4):347-51. DOI: 10.1007/s11102-009-0188-9
14. Benvenga S. What is the pathogenesis of hyponatremia after subarachnoid hemorrhage? *Nat Clin Pract Endocrinol Metab* 2006;2(11):608-9. DOI: 10.1038/ncpendmet0302
15. Marupudi NI, Mittal S. Diagnosis and management of hyponatremia in patients with aneurysmal subarachnoid hemorrhage. *J Clin Med* 2015;4(4):756-67. DOI: 10.3390/jcm4040756
16. Hannon MJ, Behan LA, O'Brien MM, *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;99(1):291-8. DOI: 10.1210/jc.2013-3032