

The productions of atrial natriuretic peptide and arginine vasopressin in small cell lung cancer with brain metastases and their associations with hyponatremia

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Abstract. – **OBJECTIVE:** Hyponatremia is one of the most frequently encountered electrolyte disorder in small cell lung cancer (SCLC) patients. It was shown that some SCLC cell lines could produce atrial natriuretic peptide (ANP) and arginine vasopressin (AVP). The aim of the study was to assess the secretion of ANP, AVP and their relative contributions to hyponatremia in SCLC patients, especially in patients with brain metastases.

PATIENTS AND METHODS: In total, 194 SCLC patients including 51 patients with brain metastases were collected. The levels of ANP and AVP were measured with radioimmunoassay kits. And then their associations with serum sodium were investigated. The progression-free survival (PFS) was compared between the hyponatremia group and the normal serum sodium group.

RESULTS: Serum sodium was negatively correlated with the plasma levels of ANP ($r=-0.171$, $p=0.017$) and AVP ($r=-0.244$, $p=0.001$) in all SCLC patients. In the brain metastatic subgroup, there was also a negative correlation between serum sodium and ANP ($r=-0.399$, $p=0.004$), while there was no correlation between serum sodium and AVP ($r=-0.232$, $p=0.101$). The occurrence rate of hyponatremia (serum sodium values below 135 mmol/l) in patients with brain metastases (21/51, 41.18%) was higher than that in patients without brain metastases (37/143, 25.87%) ($p=0.040$). The progression-free survival (PFS) in the hyponatremia group was significantly shorter than that in patients of the group without hyponatremia ($p=0.010$). Moreover, compared with patients which regained normal serum sodium after the treatment, the PFS of patients still with hyponatremia after the treatment was significantly shorter ($p=0.049$).

CONCLUSIONS: ANP might play a leading role in the formation of hyponatremia of SCLC patients with brain metastases. Correcting hyponatremia timely and appropriately could improve SCLC patients' prognosis.

Key Words:

Atrial natriuretic peptide, Arginine vasopressin, Hyponatremia, Small cell lung cancer.

Introduction

Lung cancer is the leading cause of tumor-related mortality throughout the world, of which approximately 15-20% is the small cell lung cancer (SCLC)^{1,2}.

SCLC is characterized by rapid doubling time, high growth fraction, and early development of metastatic diseases³.

Approximately 60-70% of cases with SCLC are metastatic at the time of the initial diagnosis, of which about 20-30% are brain metastases⁴⁻⁶. Patients with SCLC, especially those with brain metastases, have a poor prognosis. Many clinical indicators are related to the prognosis of SCLC, such as disease stage, clinical performance status (PS), and lactate dehydrogenase (LDH)^{7,8}. Hyponatremia has also been proved to be an independent risk factor⁹⁻¹¹. Hyponatremia, could cause a series of clinical symptoms, reduce the response to the treatment of tumor chemotherapy or radiotherapy in SCLC patients, and increase their

side reactions. All of the above could shorten the patients' survival time. Correcting hyponatremia timely and appropriately may be beneficial to improve the prognosis of SCLC patients.

It was reported in different studies that the occurrence rate of hyponatremia in SCLC patients was 16.5%-44%^{9,12,13}. Most cases of hyponatremia were caused by the paraneoplastic syndrome of inadequate arginine vasopressin secretion (SIADH). As early as 1957, Schwartz et al¹⁴ described this syndrome. However, other paraendocrine hormones, such as the atrial natriuretic peptide (ANP), have also been found to play a role in the formation of hyponatremia. ANP is mainly produced in atrial and ventricular myocytes. ANP regulates salt-water balance and blood pressure by promoting renal sodium and water excretion and stimulating vasodilation. Under pathological situations, such as congestive heart failure, ANP is highly up-regulated and decreases the retention of water and sodium¹⁵. Recent studies have shown that ANP can be secreted ectopically by SCLC cells¹⁶ and appears to be related to the formation of hyponatremia. At present, there are few reports investigating the relationship between ANP and hyponatremia of SCLC patients, especially of patients with brain metastases. This study is focusing on this aspect.

Patients and Methods

This prospective study enrolled 194 patients with newly diagnosed SCLC from January 2006 to October 2012 at Yantai Yuhuangding Hospital. The investigation was approved by the Ethics Committee of the Yantai Yuhuangding Hospital. SCLC was diagnosed by histology or cytology in all cases. All the patients underwent clinical examinations, computed tomography (CT) scans of the chest and the brain, CT or ultrasonography scans of the upper abdomen, bone scanning, and so on. Metastases of the brain were confirmed by CT or nuclear magnetic resonance imaging (MRI). Patients with brain metastases who needed urgent therapy were excluded in the study. SCLC was classified into limited or extensive stage disease. The limited stage disease was defined as stage I to III from American Joint Committee on Cancer (AJCC). These stages could be safely treated by definitive radiation therapy¹⁷. In addition, patients taking any medications that were known to alter sodium homeostasis, such as diuretics, antihypertensive agents, demeclocycline,

and corticosteroids were excluded. Patients with other active cancers, congestive heart failure and renal failure were not eligible.

At the time of diagnosis, Eastern Cooperative Oncology Group-performance status (ECOG-PS) was measured. The serum sodium values were measured regularly by the clinical chemistry laboratory; hyponatremia was defined as serum sodium values below 135 mmol/l. For hyponatremia patients, other biochemical indicators such as plasma osmotic pressure, urine osmotic pressure, urine specific gravity and natriuresis were measured. Those indicators could give indications to choose appropriate ways to correct hyponatremia, such as limiting fluid intake, taking sodium supplementation, or both.

Blood samples were obtained early in the morning, following an overnight fast. After centrifuging, the samples were stored at -80 °C until the time of analysis. The plasma ANP and AVP concentrations were measured with radioimmunoassay kits (Beijing North Institute of Biological Technology, Fengtai, Beijing, China).

Patients included in this study were treated and followed according to the standard clinical practices in use at the time. 49 patients were treated with surgical procedures including wedge resection, lobectomy or pneumonectomy with ipsilateral hilar and mediastinal lymphadenectomy. After the surgery or from the beginning, all patients received the first-line systemic therapy with platinum-based chemotherapy. Cisplatin was dosed at 80 mg/m² IV day 1 or carboplatin at Calvert AUC 5 IV day 1 followed by etoposide at 100 mg/m² IV for 3 days. All chemotherapy cycles were repeated every 3 weeks. The maximum cycle number was 6. The radiotherapy was implemented if necessary for the local lesion, the brain metastatic or other localized metastatic lesions. The second-line chemotherapy was given when the condition of patients worsened or the first-line failed. Irinotecan was dosed at 65 mg/m² IV at day 1 and 8. About 8% of all patients were treated within the clinical trial. All patients were followed up for at least 3 years. The progression-free survival (PFS) was calculated as the period from the date of surgery to the first observation of the tumor recurrence (metastatic recurrence and/or local relapse) or the last follow-up. The overall survival (OS) was calculated as the period from the date of surgery to death caused by SCLC or the last follow-up. The work was conducted in accordance with the Declaration of Helsinki. The informed consents were obtained from all the patients in this study.

Table I. Correlation between hyponatremia and clinical characteristics.

Characteristics	All patients No. (%)	Hyponatremia (No. = 58), No. (%)	Normal sodium (No. = 136), No. (%)	χ^2	<i>p</i> -value
Sex					
Male	135	41 (30.37)	94 (69.63)	0.047	0.828
Female	59	17 (28.81)	42 (71.19)		
Age					
≤60 years	62	22 (35.48)	40 (64.52)	1.357	0.244
>60 years	132	36 (27.27)	96 (72.73)		
Stage					
LD	71	15 (21.13)	56 (78.87)	4.110	0.043
ED	123	43 (34.96)	80 (65.04)		
ECOG PS score					
0-1	161	45 (27.95)	116 (72.05)	1.711	0.191
2-3	33	13 (39.39)	20 (60.61)		
Brain metastases					
Yes	51	21 (41.18)	30 (58.82)	4.200	0.040
No	143	37 (25.87)	106 (74.13)		

ECOG-PS, Eastern Cooperative Oncology Group-performance status; LD, limited stage disease; ED, extensive stage disease.

Statistical Analysis

Statistical analyses were performed by PASW 18.0 software (SPSS, IBM Company, Quarry Bay, Hong Kong). All continuous data was expressed as the mean \pm standard deviation. The comparisons between two independent variables were performed by the independent sample *t*-test. The comparisons of rate were assessed by χ^2 -test. The correlations between the plasma ANP or AVP levels and serum sodium were analyzed with the Pearson rank correlation method. PFS and OS analyses were evaluated by the Kaplan-Meier method, and the differences in survival curves were analyzed with the log rank test. $p < 0.05$ was considered to indicate a statistically significant difference.

Results

Correlation Between Hyponatremia and Clinical Characteristics

58 out of 194 patients (58/194, 29.90%) had serum sodium values below 135 mmol/l before the treatment. Brain metastases occurred at the time of initial diagnosis in 51 out of 194 patients (51/194, 26.29%). The mean level of serum sodium with brain metastases was 134.77 \pm 4.72 mmol/l, while the mean level of serum sodium without brain metastases was 137.00 \pm 4.92 mmol/l. The difference was statistically significant ($p = 0.006$). Hyponatremia was present in 21 out of 51 patients (21/51, 41.18%) with brain metastases and 37 out of 143 patients (37/143, 25.87%) without brain me-

tastases ($p = 0.040$). The clinical characteristics of patients with hyponatremia and those without are shown in Table I. There was no association between hyponatremia and age, sex, ECOG performance score. The occurrence rate of hyponatremia in patients with ED Stage SCLC was higher than those with LD Stage SCLC ($p = 0.043$). After the treatment, 32 out of 194 (32/194, 16.49%) patients gained the normal levels of serum sodium, and the sodium levels of 26 (26/194, 13.40%) patients failed to be corrected, or decreased again after a temporary normal state.

Relationship Between Plasma Levels of ANP or AVP and Serum Sodium

For all 194 patients in our study, the plasma concentrations of both ANP ($p = 0.029$) and AVP ($p = 0.002$) in the hyponatremia group were significantly higher than those in the normal sodium group. For the brain metastatic subgroup, the plasma levels of ANP in the hyponatremia subgroup were statistically different from the normal sodium subgroup ($p = 0.013$), but there was no statistical significance of the plasma levels of AVP ($p = 0.099$) in these two subgroups (Table II). Pearson rank correlation showed that there was a negative correlation between serum sodium and plasma ANP levels in both the whole group ($r = -0.171$, $p = 0.017$) (Figure 1A) and the brain metastatic subgroup ($r = -0.399$, $p = 0.004$) (Figure 1B). There was also a negative correlation between serum sodium and plasma AVP levels in the whole group ($r = -0.244$, $p = 0.001$) (Fi-

Table II. Comparison of plasma ANP and AVP in different groups.

	Group	ANP (ng/L)	p-value	AVP (ng/L)	p-value
Whole group, (No.=194)	hyponatremia	478.75±115.56	0.029	61.98±24.79	0.002
	normal sodium	436.09±126.59		51.00±21.40	
Brain metastatic subgroup, (No.=51)	hyponatremia	540.0±109.18	0.013	64.07±24.90	0.099
	normal sodium	450.10±131.72		52.92±22.16	

ANP, atrial natriuretic peptide; AVP, arginine vasopressin.

gure 1C), while there was no correlation between serum sodium and plasma AVP levels in the brain metastatic subgroup ($r=-0.232, p=0.101$).

Correlation Between Hyponatremia and The Survival Time

The deadline for follow-up was October 2015. The PFS of the hyponatremia group was significantly

shorter than that in the group without hyponatremia (7.3 vs. 8.7 months, $p=0.010$) (Figure 2A). The OS of the hyponatremia group was shorter than that in the group without hyponatremia (12.0 vs. 14.7 months, $p=0.098$), while there was no statistical significance (Figure 2B). Compared with patients who regained normal serum sodium after the treatment, the PFS of patients still with hyponatremia after the treat-

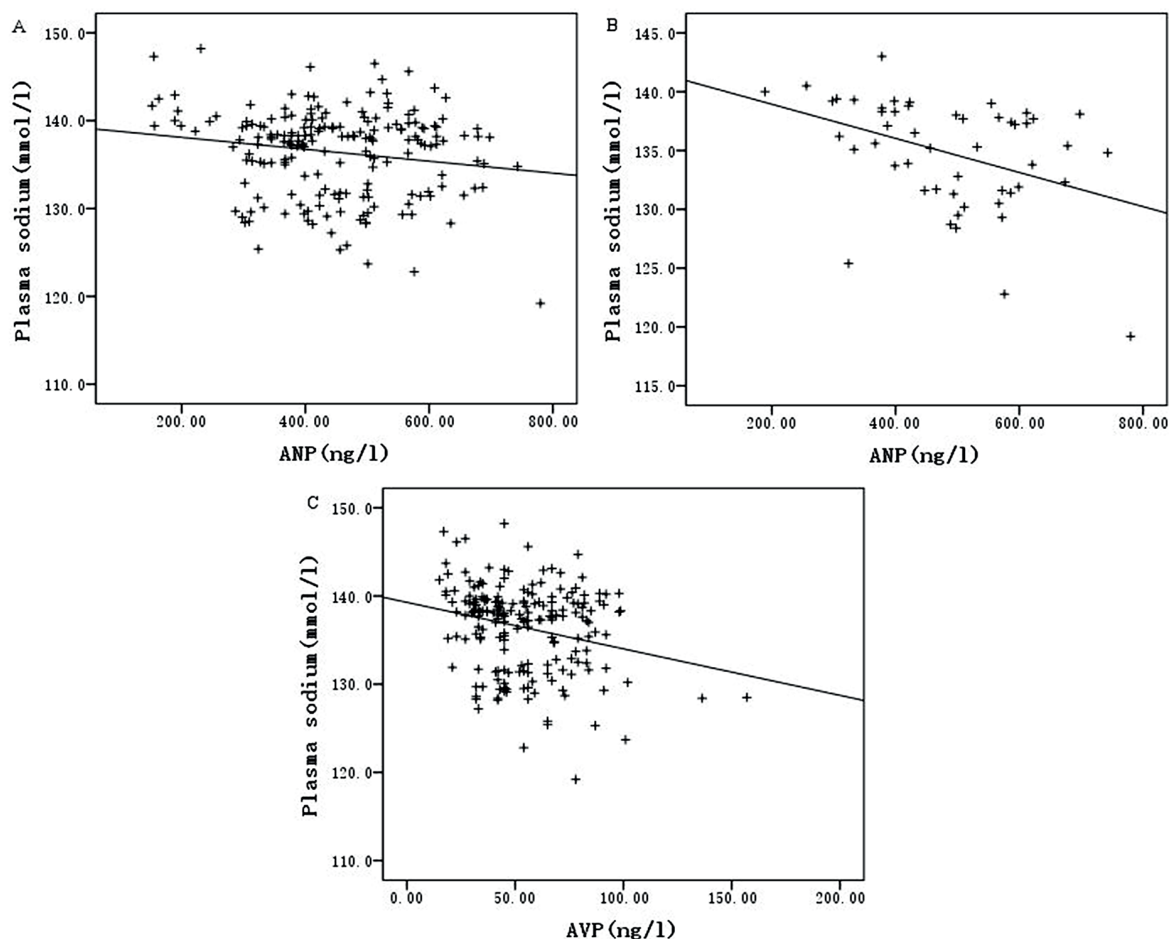


Figure 1. Correlations between serum sodium and the plasma ANP and AVP levels. (A) Correlation between serum sodium and the plasma ANP levels of the whole group ($r=-0.171, p=0.017$). (B) Correlation between serum sodium and the plasma ANP levels of the brain metastatic subgroup ($r=-0.399, p=0.004$). (C) Correlation between serum sodium and the plasma AVP levels of the whole group ($r=-0.244, p=0.001$). ANP, atrial natriuretic peptide; AVP, arginine vasopressin.

ment was significantly shorter (6.3 vs. 8.4 months, $p=0.049$) (Figure 2C). Also, there was no statistical significance of the OS between the two groups (11.4 vs. 13.2 months, $p=0.062$) (Figure 2D).

Discussion

Hyponatremia is a common electrolyte disturbance in SCLC patients. In smaller cohort stu-

dies, the occurrence rates of hyponatremia were 16.5%-44%^{9, 12, 13}. In our study, hyponatremia accounted for 29.90% in the whole SCLC group. In the brain metastatic subgroup, the rate was significantly higher, approximately 41.18%. Hyponatremia could occur at any time of the disease process, and could occur repeatedly.

There are several conditions that could cause hyponatremia in SCLC patients, including diarrhea and vomiting, some medications such as

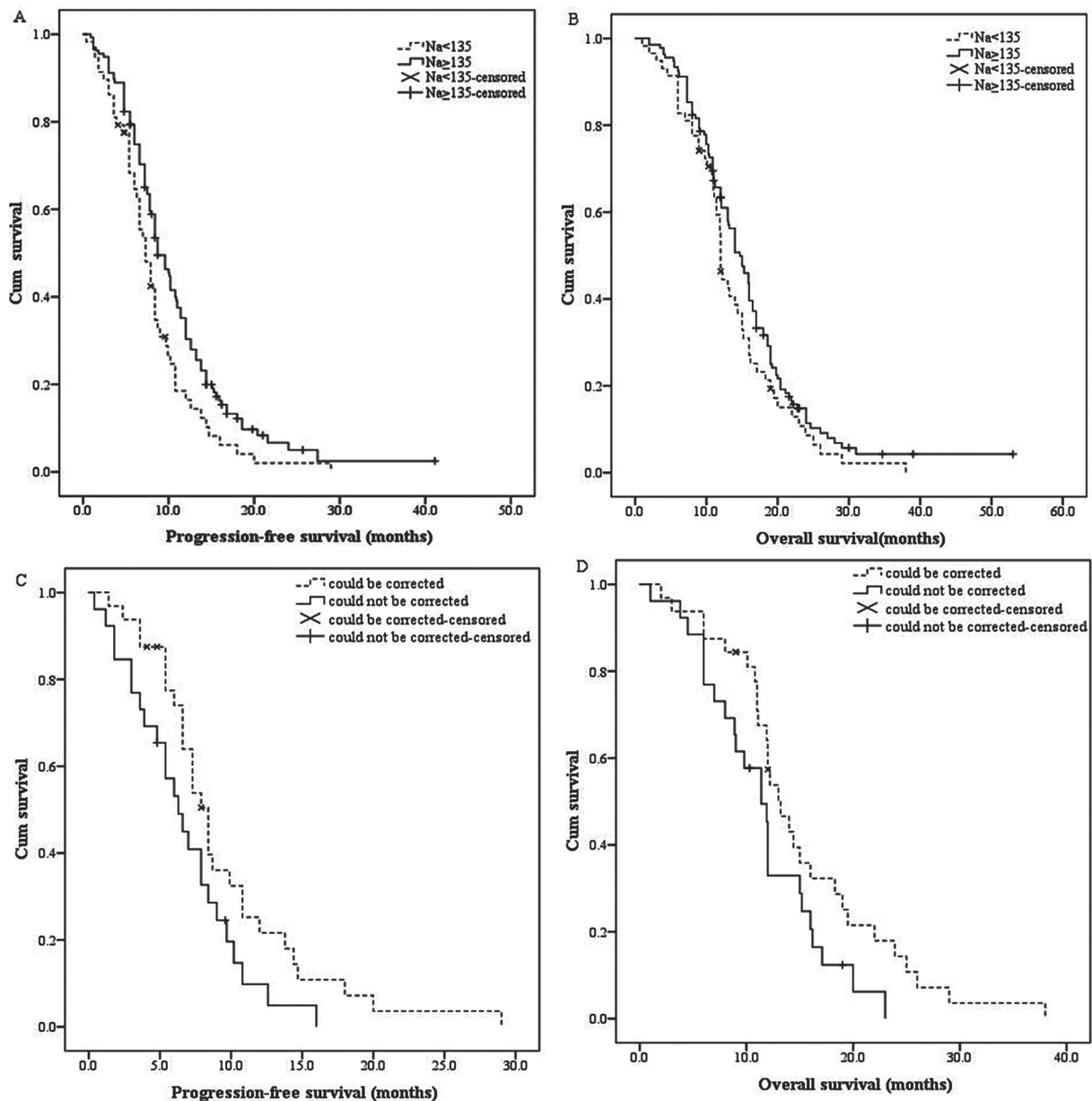


Figure 2. Comparisons of PFS and OS. (A) Comparison of PFS between the hyponatremia group and the normal serum sodium group ($p=0.010$). (B) The comparison of OS between the hyponatremia group and the normal serum sodium group ($p=0.098$). (C) Comparison of PFS between patients regained normal serum sodium after the treatment and patients still with hyponatremia after the treatment ($p=0.049$). (D) Comparison of OS between patients regained normal serum sodium after the treatment and patients still with hyponatremia after the treatment ($p=0.062$). PFS, progression-free survival; OS, overall survival.

diuretics, angiotensin-converting-enzyme (ACE) inhibitors and so on¹⁰. Among them, the syndrome of SIADH was more frequently and earlier described¹⁸⁻²⁰. The paraneoplastic secretion of AVP could activate AVP receptor 2 (V2) located in the renal collecting duct cells and promote water reabsorption and then result in dilutional hyponatremia²¹. Our results indicated that the plasma concentration of AVP in the hyponatremia group was significantly higher ($p=0.002$) than that of the normal sodium group and there was a negative correlation between the serum sodium and AVP ($r=-0.244$, $p=0.001$). Our results were consistent with the above viewpoint. To correct hyponatremia caused by SIADH, fluid restriction (up to <800 ml/d) must be prescribed. Most patients with mild or moderate hyponatremia could gain normal levels of serum sodium. Those with severe hyponatremia may need to be given an infusion of saline or AVP receptor antagonist tolvaptan in addition²². However, we observed that some of the hyponatremia worsened after the fluid restriction. This kind of phenomenon appeared more frequently in hyponatremia patients with brain metastases.

After the review of literature, we found that some SCLC patients with hyponatremia had no elevated AVP in their tumors²³, tumor cell lines²⁴, or plasma^{12, 25}. ANP might participate in the process of hyponatremia formation. The presence of ANP peptide in the SCLC tumor cell lines and tumor tissues was tested by the radioimmunoassay or gel chromatography²⁵⁻²⁷. Our studies indicated that ANP was a kind of ectopic hormone secreted by SCLC patients. The results showed that the levels of serum sodium were negatively correlated with ANP ($r=-0.171$, $p=0.017$) in all SCLC patients. Several studies indicated that SCLC patients with hyponatremia had elevated ANP levels at presentation with or without elevation of AVP^{12, 27-31}. However, the relation between ANP and brain metastases was rarely mentioned. We observed that ANP was negatively correlated with hyponatremia ($r=-0.399$, $p=0.004$) in patients with brain metastases. In addition, to the secretion of ANP by tumor tissues, the brain metastatic lesions may also cause the increased secretion of ANP. ANP, not AVP, might play a leading role in the formation of hyponatremia for SCLC patients with brain metastases. Hyponatremia caused by ANP was also reported in other endocranial diseases such as subarachnoid hemorrhage, post-operative neurosurgery, brain injury and

so on³²⁻³⁴. This syndrome was named cerebral salt-wasting syndrome (CSWS). CSWS is a disorder of sodium and water and occurs as a result of cerebral diseases in the setting of normal kidney function. The elevated ANP increased the renal excretion of sodium and water mediated by the ANP receptors in the kidney and resulted in hypovolaemic hyponatremia^{35, 36}.

To distinguish SIADH from CSWS is important, because their treatments are entirely different. For the dilutional hyponatremia caused by SIADH, limiting fluid intake is the first choice. For the hypovolaemic hyponatremia caused by CSWS, fluid restriction may aggravate hyponatremia. A supplement of liquid with sodium is the correct method. However, to distinguish the two syndromes is difficult, because both are characterized by low serum sodium, high urine sodium concentration, and higher urine than plasma osmolality³⁷. For this reason, the accurate determination of the patients' volume status is the key to distinguish the two syndromes. Unfortunately, the volume status is also difficult to be accurately measured in the routine clinical practice. The measurement of CVP can be useful, but its injury to patients limits its application. Our study may offer a new way to differentiate the two syndromes by the measurement of plasma ANP and AVP. Hyponatremia with high levels of ANP, especially those with brain metastases, should be first considered as hypovolaemic hyponatremia. Restoring intravascular volume and supplementary a supplement of sodium is the appropriate treatment. The isotonic (0.9%) saline is typically administered until the volume deficits are corrected. For those patients with serious hypovolaemia, colloid fluid such as plasma may be considered. The hypertonic solution should be avoided, because it may increase the loss of water. After the patients return to a euvolemic state or nearly euvolemic state, the attention should be directed to the correction of hyponatremia. For those with serious hypovolaemia and hyponatremia, mineralocorticoid may be useful. Mineralocorticoid is a kind of drug, which is helpful for the correction of both hyponatremia and hypovolemia^{38, 39}.

Correction of hyponatremia is really important for patients with SCLC, because hyponatremia has a close relationship with their prognosis. Hermes et al¹⁰ found that hyponatremia was an independent predictor of mortality in patients with ED and LD SCLC after adjustment for age, gender,

LDH and performance status. Hyponatremia was also proved to be correlated with the tumor activity and the proportion increase of metastatic disease^{9,40}. In our study, we found that hyponatremia was correlated with ED and LD stage ($p=0.043$). Some researches^{11,40,41} revealed that SCLC patients with hyponatremia had a shorter survival time. In our study, although there was no statistical difference in the OS between the hyponatremia group and the normal serum sodium group ($p=0.098$), the PFS of hyponatremia was significantly shorter ($p=0.010$).

Relapsed hyponatremia after the treatment might accelerate tumor recurrence⁴². Also, the studies of Hansen et al⁹ and Ma et al⁴³ found that both initial hyponatremia and an inability to normalize sodium levels during chemotherapy were significant prognostic factors associated with poor prognosis. Our study gained the similar conclusion: SCLC patients with hyponatremia who failed to gain the normal sodium levels had shorter PFS ($p=0.049$). Correction of hyponatremia timely and appropriately may extend the lifetime.

Certainly, CSWS and SIADH may occur overlapped in the clinical practice. A series of factors should be taken into account to distinguish hyponatremia, such as the measurements of plasma osmolality, urine osmolality, urine sodium, and the clinical assessments of extracellular volume status. In order to improve the prognosis of SCLC, hyponatremia must be corrected appropriately and timely.

Nonetheless, several fundamental questions have yet to be answered, such as how brain metastases lead to the release of excessive amounts of ANP, why this only occurs in a subgroup of brain metastases of SCLC, and which subgroup is easy to have an excessive release of ANP. We will continue to investigate in this field.

Conclusions

The occurrence rate of hyponatremia in SCLC is high, especially for those with brain metastases. Patients with hyponatremia who cannot regain normal serum sodium after the treatment had a poor prognosis. Hyponatremia caused by different origins should be corrected by different ways. ANP might play a leading role in the formation of hyponatremia for SCLC patients with brain metastases. For hypovolaemic hyponatremia caused by ANP, a supplement of liquid with sodium is the correct method.

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Conflict of interest

The authors declare no conflicts of interest.

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