Hyponatremia and Cognitive Impairment in Patients Treated with Peritoneal Dialysis

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Abstract

Background and objectives Hyponatremia has been identified as a relevant factor for cognitive impairment but has not been investigated in patients receiving peritoneal dialysis (PD). This study investigated the relationship between hyponatremia and cognitive functions in PD patients.

Design, setting, participants, & measurements A total of 476 clinically stable patients from five PD units who were older than 18 years of age and had undergone PD for at least 3 months between March 2013 and March 2014 were enrolled in this multicenter cross-sectional study. Global cognitive function was measured using the Modified Mini-Mental State Examination (3MS); executive function, by trail making tests A (trails A) and B (trails B); and immediate memory, delayed memory, and language ability, by subtests of Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Hyponatremia was defined as serum sodium level ≤135 mmol/L, which was calculated as the mean of measurements taken over the preceding 3 months.

Results Fifty patients (10.5%) had hyponatremia; these patients tended to be older and less educated, to have less inflammation, and to have the higher prevalence of cognitive impairment. They also had lower scores on RBANS subtests. After adjustment for demographic and clinical confounders, hyponatremia was independently associated with lower 3MS score (coefficient, −5.28; 95% confidence interval [CI], −8.44 to –2.13) and longer completion time of trials A (coefficient, 22.68; 95% CI, 3.44 to 41.92) and B (coefficient, 45.56; 95% CI, 1.30 to 89.81). After additional adjustment for laboratory measures, hyponatremia was still associated with 3MS score and completion time of trails A. Hyponatremia was independently associated with CI (odds ratio, 2.17; 95% CI, 1.02 to 4.94) and executive dysfunction (odds ratio, 2.43; 95% CI, 1.01 to 5.87) using multivariate logistic regression analysis. Sensitivity analyses with multivariable models that included propensity score still supported the association between hyponatremia and cognitive impairment.

Conclusions Hyponatremia was associated with global and specific cognitive impairment in PD patients.

Clin J Am Soc Nephrol 10: 1806–1813, 2015. doi: 10.2215/CJN.02240215

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Introduction

Peritoneal dialysis (PD) as a home-care therapy requires patients to be able to self-monitor and self-manage their treatment (1). This ability partly depends on normal cognitive function (2). Unfortunately, the prevalence of cognitive impairment is high: 27%–67% among patients with ESRD (3–5). Cognitive impairment is an independent predictor of mortality (3) and technical survival (6) in dialysis patients. Exploring the relevant factors for cognitive impairment is therefore critical in this population.

It is well known that cognitive impairment onset in the general population and patients with CKD is associated with many factors, such as age, sex, level of education, cardiovascular disease (CVD), GFR, dialysis adequacy, hemoglobin, and inflammation (4,5,7–9). The few interventional studies of improvement in cognitive impairment in dialysis patients showed controversial results (10,11). Therefore, more investigations are needed to explore potentially relevant factors of cognitive impairment in dialysis patients in searching for potential interventions.

Hyponatremia in dialysis patients has received increased attention in recent years because of its higher prevalence compared with the rates in the general and nondialysis populations (12,13) and its deleterious effect on patient outcome (14,15). Several studies identified risk factors of hyponatremia in general and dialysis populations, such as malnutrition, residual renal function, and comorbidities (15–17). The association between acute hyponatremia and cognitive impairment has long been well understood; the neurologic problems are thought to be due to cerebral edema and hyponatremic encephalopathy (18). Until recently, chronic hyponatremia was identified as an independent risk factor for cognitive impairment in the general population (19) and patients with chronic diseases (20,21). Among dialysis patients, limited data on this association have been published. Only two single-center studies with small

sample sizes indicated the intriguing link between hyponatremia and cognitive impairment in hemodialysis patients (22,23). However, the association of hyponatremia and cognitive impairment cannot be extended to PD patients, who have a higher prevalence of cognitive impairment (24) and different serum sodium profile (25) compared with hemodialysis patients. This multicenter cross-sectional study aimed to investigate this association in patients undergoing PD.

Materials and Methods

Study Design and Participants

Five PD centers from five provinces in China (Beijing, Heilongjiang, Hebei, Anhui, and Guangdong) located in four geographic regions (North, Northwest, East, and South) participated this multicenter cross-sectional study. Each participating center is the largest center in the province in which it is located. The centers have professional PD doctors and nurses and well developed databases recording baseline characteristics and follow-up data for patients every 1–3 months. As do most of the PD centers in China, all these centers follow similar clinical practice guidelines (guidelines from International Society for Peritoneal Dialysis and Chinese Society of Nephrology) in timing of dialysis initiation, patient training, follow-up, and treatment. Data from each center were collected within a strict quality control framework and were further inspected and optimized to ensure the integrity and accuracy of the database. All study investigators and staff members completed a training program that taught them the study methods and processes. A manual of detailed instructions for data collection was distributed. The ethics committee of Peking University First Hospital approved the study. Patients gave written consent for their information to be stored on the hospital database and for it to be used in research.

Inclusion criteria for participants were as follows: patients who had undergone PD between March 2013 and March 2014; were age ≥18 years; had been undergoing PD for ≥3 months and were clinically stable; and were able to undergo all measurements and questionnaires as required. Patients were excluded if they had a systemic infection, acute cardiovascular events, active hepatitis, or cancer; had undergone surgery or experienced trauma in the month before the study; or had any study-obstructive

Table 1. Differences in clinical characteristics between PD patients without and with hyponatremia

Variable	Total	Patients without Hyponatremia	Patients with Hyponatremia	*P* Value
Patients, *n* (%)	476	426 (89.5)	50 (10.5)	–
Serum sodium (mmol/L)	139.1±3.1	139.8±2.4	133.1±1.9	<0.001
Age (yr)	51.9±14.3	51.4±14.3	55.9±13.2	0.04
Men (%)	244 (51.4)	221(51.9)	23 (46.0)	0.42
PD duration (mo)	26.3 (12.2–49.9)	26.3 (12.0–49.2)	29.7 (13.0–54.0)	0.36
Primary kidney disease, *n* (%)				0.36
Diabetic nephropathy	99 (20.8)	86 (20.4)	13 (26.0)	
Hypertensive nephropathy	77 (16.1)	66 (15.6)	11 (22.0)	
Chronic GN	207 (43.6)	187 (44.5)	20 (40.0)	
Other	93 (19.5)	87 (19.5)	6 (12.0)	
Diabetes mellitus, *n* (%)	113 (23.7)	97 (22.7)	16 (32.7)	0.12
Cardiovascular disease, *n* (%)	95 (20.1)	86 (20.4)	9 (18.0)	0.69
Charlson index	5 (3–8)	5 (3–8)	5 (2–8)	0.93
Level of education, *n* (%)				0.02
Elementary school or lower	92 (19.3)	74 (17.3)	18 (36)	
Middle school	145 (30.4)	133 (31.1)	12 (24)	
High school	141 (29.6)	130 (30.4)	11 (22)	
Above high school	98 (20.7)	89 (21.1)	9 (18)	
Body mass index (kg/m^2)	23.0±3.5	23.0±3.5	22.9±3.5	0.97
Systolic BP (mmHg)	135.9±18.7	135.3±18.8	141.9±17.2	0.02
Diastolic BP (mmHg)	82.4±12.3	82.5±12.6	82.1±9.4	0.84
Mean arterial pressure (mmHg)	100.3±13.0	100.1±13.3	102.0±10.3	0.34
Hemoglobin (g/L)	103.3±18.1	105.0±17.9	98.2±19.1	0.01
Serum albumin (g/L)	36.1±5.6	36.5±5.4	32.5±5.7	<0.001
hsCRP (mg/L)	2.96 (0.99–8.70)	2.82 (0.91–8.36)	5.90 (1.67–12.1)	0.03
RRF (ml/min)	1.39 (0.00–3.77)	1.43 (0.00–3.89)	0.63 (0.00–2.93)	0.15
Total Kt/V	1.91±0.55	1.88±0.41	1.92±0.46	0.51
Total Ccr (ml/min per 1.73 m^2 per week)	57.9±19.6	57.8±16.9	56.5±23.6	0.64

Values are expressed as mean±SD, median (interquartile range), or number (percentage). PD, peritoneal dialysis; hsCRP, high-sensitivity C-reactive protein; RRF, residual renal function; Ccr, creatinine clearance.

conditions (severe eyesight loss, language incompatibility, illiteracy, mental disturbance, or upper limb disability). All the participants received conventional glucose-based, lactate-buffered PD solutions (Ultrabag, Baxter Healthcare, Guangzhou, China).

Clinical Characteristics

Demographic characteristics and comorbidities were recorded, including age, sex, education level, duration of PD, body mass index (BMI), systolic and diastolic BP (SBP and DBP), primary kidney disease, the presence of diabetes mellitus, and history of CVD. Level of education was recorded as the highest school level at which a diploma was received: elementary school or lower, middle school, high school, or greater than high school. Information on cardiovascular morbidities was collected from chart review, and CVD was recorded if one of the following conditions was present: angina, class III or IV congestive heart failure (per New York Heart Association classification), transient ischemic attack, history of myocardial infarction or cerebrovascular accident, and peripheral arterial disease (26).

Laboratory Methods

After overnight fasting while continuing PD therapy, participants had their venous blood sampled for routine and biochemical measurements. Biochemical data, including serum sodium, serum albumin, triglycerides, total cholesterol, high-sensitivity C-reactive protein (hsCRP), and hemoglobin, were calculated as the mean of measurements taken over the preceding 3 months. Biochemical profiles were investigated using an automatic Hitachi chemistry analyzer. In all PD centers, serum sodium was investigated by using the ion selective electrode method. Hyponatremia was defined as the mean of serum sodium level $\leq$135 mmol/L. Residual renal function (RRF) was defined as the mean of residual creatinine and urea clearance from collection of 24-hour urine. Dialysis adequacy was defined as weekly Kt/V from dialysis and RRF.

Psychologic Status

The full battery consisted of the Modified Mini-Mental State Examination (3MS) (27) to test global cognitive function and trailmaking tests A (trails A) and B (trails B) (28) to test executive function, including decision-making and processing speed. The 3MS is a brief test of global cognitive function with components for orientation, attention, language, and memory. The 3MS has a maximum score of 100 (scores range from 0 to 100) and is considered to be more sensitive for mild cognitive impairment compared with the traditional 30-point Mini-Mental Status Examination (27). Global cognitive impairment was defined as a score of less than 80 on the 3MS (29). Executive dysfunction was defined as a trails A score of $>$75 seconds and trails B score of $>$180 seconds (30). In addition, the index scores derived from raw scores of subtests of RBANS, using tables in stimulus booklet appendix, was adopted to assess immediate memory, delayed memory, and language ability (31).

Assessment of cognitive function was performed in a separate room with one medical staff for one patient. Four medical staff members participated in this study as observers; they all completed a training program that taught them the methods and processes to ensure the integrity and accuracy of the assessment.

Statistical Analyses

Continuous data are presented as mean$\pm$SD except for duration of PD, RRF, and hsCRP, which are presented as the median with interquartile range because of high skew. Categorical variables are presented as proportions. Demographic data, biometric profiles, and measures of cognitive functions were compared between patients with hyponatremia and those without.

The primary analysis explored the association between hyponatremia and cognitive function. First, correlations of serum sodium or other clinical factors and measures of cognitive functions were examined by using univariate correlation analysis. All variables with a significance level of 0.10 in univariate test would be included into further multivariate analysis. Second, two kinds of linear regression models were built to explore the role of hyponatremia in predicting the cognitive functions. Model 1 consisted of basic models including hyponatremia and recognized demographic and clinical confounders as covariables. Model

Table 2. Differences in cognitive function measures between PD patients without and with hyponatremia

Variable	Total	Patients without Hyponatremia	Patients with Hyponatremia	*P* Value
Patients, *n* (%)	476	426 (89.5)	50 (10.5)	–
3MS score	84.0$\pm$12.8	84.7$\pm$12.3	76.7$\pm$15.9	$<$0.001
Cognitive impairment, *n* (%)	132 (28.4)	108 (25.8)	24 (52.2)	$<$0.001
Trails A (s)	66 (47–95)	65 (46–92)	86 (64–120)	0.002
Trails B (s)	148 (106–235)	144 (105–229)	198 (132–415)	0.004
Executive dysfunction, *n* (%)	134 (30)	114 (28.1)	20 (48.8)	0.006
Immediate memory score	73.1$\pm$17.9	73.7$\pm$17.9	67.3$\pm$17.8	0.02
Delayed memory score	88.2$\pm$17.2	88.9$\pm$16.7	81.5$\pm$20.7	0.03
Language ability score	92.5$\pm$13.8	93.0$\pm$13.7	87.8$\pm$13.4	0.02

Values are expressed as mean$\pm$SD or number (percentage). 3MS, Modified Mini-Mental State Examination; Trails A, trail making test A; Trails B, trail making test B.

Table 3. Correlation between demographic, clinical, and laboratory measures and cognitive function measures by univariable correlation analysis

Variable	3MS		Trails A		Trails B		Immediate Memory		Delayed Memory		Language Ability	
	r Value	*P* Value	*r* Value	*P* Value	*r* Value	*P* Value	*r* Value	*P* Value	*r* Value	*P* Value	*r* Value	*P* Value
Age	−0.33	<0.001	0.36	<0.001	0.37	<0.001	−0.23	<0.001	−0.08	0.10	−0.11	0.02
Female sex	−0.14	0.002	0.21	<0.001	0.17	<0.001	−0.06	0.21	−0.06	0.20	−0.06	0.19
PD duration	0.01	0.84	−0.01	0.81	0.02	0.67	0.01	0.76	0.09	0.06	0.03	0.56
Primary kidney disease	0.01	0.79	−0.01	0.89	−0.03	0.50	0.01	0.77	−0.05	0.28	0.02	0.73
Diabetes mellitus	−0.15	0.001	0.16	0.001	0.19	<0.001	−0.15	<0.001	−0.03	0.48	−0.10	0.03
Cardiovascular disease	−0.10	0.02	0.09	0.05	0.10	0.03	−0.12	0.01	−0.03	0.56	−0.08	0.07
Level of education	0.51	<0.001	−0.37	<0.001	−0.36	<0.001	0.44	<0.001	0.48	<0.001	0.34	<0.001
Body mass index	−0.16	0.001	0.09	0.07	0.14	0.003	−0.15	<0.001	−0.11	0.02	−0.06	0.17
Mean arterial pressure	0.01	0.91	−0.09	0.06	−0.11	0.03	0.03	0.52	−0.12	0.01	−0.07	0.15
Serum sodium	0.13	0.005	−0.09	0.06	−0.12	0.01	0.12	0.01	0.07	0.14	0.05	0.25
Hyponatremia	−0.19	<0.001	0.14	0.003	0.13	0.005	−0.11	0.02	−0.13	0.01	−0.11	0.02
Hemoglobin	0.11	0.01	−0.08	0.09	−0.002	0.96	0.00	0.93	0.18	<0.001	0.08	0.07
Serum albumin	0.33	<0.001	−0.25	<0.001	−0.22	<0.001	0.17	<0.001	0.30	<0.001	0.19	<0.001
hsCRP	−0.10	0.04	0.11	0.03	0.11	0.03	−0.13	0.01	−0.13	0.01	−0.07	0.13
RRF	0.04	0.43	−0.05	0.28	−0.07	0.17	0.00	0.93	0.00	0.96	−0.03	0.52
Total Kt/V	0.04	0.46	−0.01	0.91	−0.03	0.60	0.05	0.28	0.07	0.12	−0.02	0.63
Total Ccr	0.01	0.80	−0.03	0.59	−0.05	0.30	−0.01	0.86	−0.02	0.64	−0.07	0.13

3MS, Modified Mini-Mental State Examination; Trails A, trail making test A; Trails B, trail making test B; PD, peritoneal dialysis; hsCRP, high-sensitivity C-reactive protein; RRF, residual renal function; Ccr: creatinine clearance.

2 had further adjustment for laboratory measures. Third, multivariate logistic regression analyses were performed to investigate the influence of hyponatremia on cognitive impairment and executive dysfunction, respectively.

To reduce the effect of possible selection bias and the influence of small number of hyponatremic patients and relative large number of associations on the reliability of multivariable model, and also to adjust the influence of other potential confounders (*e.g.*, generalized comorbidities, albumin, and RRF), but not to decrease the events per variable ratio, we further performed a sensitivity analysis by using propensity score matching for having hyponatremia. The following variables were used for propensity score matching: age, sex, Charlson index (as a measurement of generalized comorbidities), RRF, hsCRP, and albumin. All these factors were identified as risk factors of hyponatremia (15,16,32–34). The maximum difference in the propensity score allowed for a match was 0.02. We calculated the area under the receiver-operating characteristic (ROC) curve to quantify overall model predictability (35). Then, the propensity score (as a continuous variable) was entered into the former mentioned multivariable models.

All probabilities were two tailed, and the level of significance was set at 0.05. Statistical analysis was performed using SPSS for Windows, version 19.0 (IBM, Armonk, NY). The propensity score matching process was automatically performed by an add-on R extender for SPSS software (version 2.10.1).

Results

Basic Characteristics

A total of 667 patients were eligible for the study and 495 (74.2%) gave consent; 476 (96.2%) completed laboratory and cognitive testing. Of 476 enrolled patients, 212 had three sets of biochemical measurements, 211 had two sets of biochemical measurement, and 53 had one set of biochemical measurement. These enrolled patients had a mean age of 51.9±14.3 years, durations of PD of 25.3 (interquartile range, 12.2–49.9) months, BMI of 23.0±3.5 kg/m^2, hemoglobin of 104.3±18.1 g/L, serum albumin of 36.1±5.6 g/L, and serum sodium of 139.1±3.1 mmol/L. Of these patients, 51.4% were men, 23.7% were patients with diabetes, 20.1% had a history of CVD, 50.4% had a high school diploma or higher, 28.4% had cognitive impairment, 30.0% had executive dysfunction, and 10.5% had hyponatremia (Table 1). Age, sex proportion, duration of PD, comorbidities, serum sodium, and other laboratory measures did not significantly differ between enrolled patients and those not enrolled (data no shown).

Hyponatremia, Clinical Characteristics, and Cognitive Impairment

Patients with hyponatremia had lower 3MS scores, longer completion time on trails A and B, lower scores for each RBANS subtest, and higher prevalence of cognitive impairment and executive dysfunction (Table 2). They also were older and had a lower level of education. In addition, hyponatremia was associated with

Table 4. Association between hyponatremia and cognitive function measures by multivariable linear regression analysis

Variable	Model 1			Model 2			Model 3		
	Patients (*n*)	Coefficient (95% CI)	*P* Value	Patients (*n*)	Coefficient (95% CI)	*P* Value	Patients (*n*)	Coefficient (95% CI)	*P* Value
3MS	469	−5.28 (−8.44 to −-2.13)	0.001	447	−4.56 (−7.87 to −1.25)	0.007	423	−4.54 (−8.83 to −-0.26)	0.03
Trails A	457	22.68 (3.44 to 41.92)	0.02	435	23.43 (3.2 to 43.65)	0.02	411	20.24 (0.12 to 40.35)	0.04
Trails B	453	45.56 (1.30 to 89.81)	0.04	431	39.45 (−6.9 to 85.81)	0.09	407	28.59 (−2.58 to 59.75)	0.10
Immediate memory	467	−3.51 (−8.52 to 1.49)	0.17	445	−2.86 (−8.06 to 2.35)	0.28	421	−2.82 (−8.20 to 2.56)	0.30
Delayed memory	463	−4.41 (−9.26 to −0.45)	0.08	442	−2.85 (−7.83 to 2.14)	0.26	418	−1.01 (−6.12 to 3.99)	0.66
Language ability	467	−3.64 (−7.99 to −0.71)	0.10	445	−3.06 (−7.21 to 1.09)	0.15	421	−3.62 (−8.05 to 0.81)	0.10

Values in parentheses are 95% confidence intervals. Model 1: adjusted for demographic and clinical measures (including age, sex, level of education, body mass index, diabetes mellitus, cardiovascular disease, and mean arterial pressure). Model 2: model 1 plus laboratory measures (including hemoglobin and high-sensitivity C-reactive protein). Model 3: adjusted for level of education, body mass index, mean arterial pressure, and propensity score. Propensity scores were generated using logistic regression models with hyponatremia as dependent variable. The following variables were used for propensity score matching: age, sex, Charlson index, residual renal function, high-sensitivity C-reactive protein, and serum albumin. 95% CI, 95% confidence interval; 3MS, Modified Mini-Mental State Examination; Trails A, trail making test A; Trails B, trail making test B.

higher SBP, lower hemoglobin, lower serum albumin, and higher hsCRP values. There were 108 and 18 anuric patients in the nonhyponatremic and hyponatremic group, respectively. Sex, durations of PD, primary kidney disease, history of diabetes mellitus, baseline CVD, BMI, DBP, mean arterial pressure, RRF, and dialysis adequacy did not differ between these two groups (Table 1).

Association between Hyponatremia and Cognitive Function

Correlation analysis showed that serum sodium, age, sex, DM, CVD history, level of education, BMI, hsCRP, hemoglobin, and serum albumin were all significantly correlated with almost all cognitive function measures. Mean arterial pressure was correlated with completion time of trails A and B (Table 3). Of note, age and level of education were the only two variables that almost uniformly showed r values $>\pm 0.3$. The r value for serum sodium was only 0.05–0.13. When serum sodium was analyzed as a continuous variable in multivariable linear regression model, a marginal association was found for global cognitive function and executive function (P=0.05 and 0.07, respectively). When serum sodium was analyzed as a discrete variable, after adjustment for confounders, hyponatremia was independently associated with global cognitive function and executive function. This result implied that the relationship between serum sodium and cognitive function was more possibly nonlinear; thus, it is more appropriate to analyze serum sodium as a discrete variable. After further adjustment for laboratory measures, hyponatremia was still independently associated with 3MS score and completion time of trails A (P=0.007 and 0.02, respectively) (Table 4). Logistic regression analysis showed that hyponatremia was associated with cognitive impairment (odds ratio, 3.14; 95% confidence interval [CI], 1.69 to 5.83; $P<0.001$) and executive dysfunction (odds ratio, 2.44; 95% CI, 1.27 to 4.67; P=0.007). After adjustment for demographic, clinical, and laboratory variables, hyponatremia was still associated with global cognitive impairment (odds ratio, 2.17; 95% CI, 1.02 to 4.94) (Table 5).

Sensitivity Analysis

Our propensity score model performed moderately well in distinguishing between patients with hyponatremia and those without (area under the receiver-operating characteristic curve, 0.73). Multivariable regression analyses containing propensity score as a covariable revealed that hyponatremia was associated with lower 3MS score, longer trails A completion time, and higher risk of cognitive impairment (see Tables 4 and 5).

Discussion

To our knowledge, this is the first study to examine prevalence and relevant factors for cognitive impairment in an Asian PD population from a multicenter cross-sectional data set. We found that in addition to recognized risk factors, such as age and level of education, hyponatremia was a new potential relevant factor for cognitive impairment for PD patients. Further studies are needed to verify this finding and to investigate whether correcting hyponatremia would lead to the improvement in cognitive function.

The prevalence of cognitive impairment in this PD population was 28.4%, which is significantly lower than that in a previous study from a western PD population (74.5%) (5). The main reason is that the two studies adopted different diagnosis criteria of cognitive impairment (5). Other possible explanations for this might be that participants included in this study were younger (51.9 years versus 57.5 years) and had lower prevalence of diabetes mellitus (23.7% versus 41.2%). Further studies are needed to clarify other mechanisms for the differences in prevalence of cognitive impairment.

We found that age and level of education were the most prominent influence factors, whereas other variables had relatively weak association with cognitive function. In addition, hyponatremic patients were prone to have a lower level of education. In our former study (37), patients with a lower level of education had smaller individual income, less frequent doctor visits, and heavier burden of medical expenses. All these factors constituted barriers for low-education patients to obtain and understand instruction from clinician about nutrition intake and dialysis scheme adjustment; as a result these patients are vulnerable to hyponatremia. Of note, age and level of education cannot be changed for specific patient. Therefore, it is

Table 5. Association of hyponatremia with cognitive impairment and executive dysfunction by univariable and multivariable logistic regression analysis

Variable	cognitive Impairment			Executive Dysfunction		
	Patients (n)	OR (95% CI)	P Value	Patients (n)	OR (95% CI)	P Value
Univariable	472	3.14 (1.69 to 5.83)	<0.001	465	2.44 (1.27 to 4.67)	0.007
Multivariable model 1	469	2.43 (1.12 to 5.29)	0.03	452	2.27 (0.97 to 5.31)	0.06
Multivariable model 2	447	2.17 (1.02 to 4.94)	0.048	430	2.43 (1.01 to 5.87)	0.048
Multivariable model 3	423	2.08 (1.00 to 4.84)	0.05	407	1.95 (0.94 to 4.49)	0.09

Model 1: adjusted for demographic and clinical measures (including age, sex, level of education, body mass index, diabetes mellitus, cardiovascular disease, and mean arterial pressure). Model 2: model 1 plus laboratory measures (including hemoglobin and high-sensitivity C-reactive protein). Model 3: adjusted for level of education, body mass index, mean arterial pressure, and propensity score. Propensity scores were generated using logistic regression models with hyponatremia as dependent variable. The following variables were used for propensity score matching: age, sex, Charlson index, residual renal function, high-sensitivity C-reactive protein, and serum albumin. OR, odds ratio; 95% CI, 95% confidence interval.

meaningful for clinicians to explore other modifiable factors, such as bioclinical factors. This exploratory study revealed that hyponatremia was an independent relevant factor, which provides a potential therapeutic direction for improvement of cognitive impairment in PD patients.

This study revealed that hyponatremia was associated with not only global but also specific cognitive functions by univariable correlation analysis. After adjustment for confounders, hyponatremia was still an independent predictor of global cognitive function. It is possibly related to the effect of hyponatremia on brain physiologic function (38–40) and brain anatomic alterations (41,42). Previous studies demonstrated that correction of chronic hyponatremia could resulted in complete recovery of attention abnormalities (43). Therefore, it is reasonable to speculate that cognitive impairment in hyponatremic dialysis patients could also be improved by correcting plasma sodium concentration. Further interventional studies are needed to clarify this issue. For executive dysfunction, hyponatremia was a statistically significantly relevant factor only in multivariable model 2, not in multivariable models 1 and 3. It was possibly due to the difference in observation number of these multivariable models (which resulted from the difference in data integrity level of covariables, such as hemoglobin and hsCRP). In addition, we think adjusting for the effect of metabolic measures as in model 2 and 3 presents a dilemma. It is necessary to distinguish the effect of metabolic measures from unmodifiable factors, such as demographic characteristics and comorbidities. Not controlling for these measures may bias the results because they are risk factors for cognitive impairment. However, hyponatremia as a modifiable metabolic measure had a significant interrelationship with other metabolic measures. Therefore, controlling for these metabolic measures may also bias the estimated effect of serum sodium.

The extent to which these measures are confounders is unknown. We believe that through the presentation of the results from multivariable regression models with and without metabolic measures, readers can better understand the relationship between hyponatremia and cognitive function. Of note, the association between hyponatremia and other specific cognitive function disappeared after adjustment for hemoglobin, hsCRP, and other confounders. Former studies revealed that cognitive function could be improved by correction of anemia and inflammation in dialysis patients (44) and general population (45). Therefore, it is reasonable to speculate that correction of anemia and inflammation might also help improve specific cognitive functions in PD patients with hyponatremia.

Compared with former studies, the assessment of cognitive function in our study was more comprehensive, including both global and four types of specific cognitive functions. The method for defining hyponatremia in this study was more accurate than that in previous studies because it was based on the mean of serum sodium over 3 months rather than a single-point measurement.

This study had some limitation. First, because of the nature of a cross-sectional study, it could not determine whether hyponatremia is a pathogenic factor or just a risk biomarker. A randomized controlled study to explore whether cognitive function would be improved by correction of hyponatremia would help clarify this issue. A longitudinal assessment of cognitive function and serum sodium would possibly provide more information. Second, as in other similar studies, we did not investigate the pathogenesis behind hyponatremia, such as intake insufficiency, water retention, and loss of sodium *via* the gastrointestinal tract, urine, or dialysate. Further study is needed to explore the potential confounding effect of different pathogenesis. Third, because of the differences in demographic, socioeconomic, and bioclinical characteristics, our findings cannot be generalized to other PD populations. Further studies should be conducted to clarify this issue widely and deeply.

In conclusion, this is the first multicenter study with a large sample size to investigate the cognitive impairment prevalence and comprehensively assess cognitive function in an Asian PD population. Our findings support the hypothesis that hyponatremia is associated with cognitive impairment in dialysis patients. This novel finding encourages us to determine this issue through large-scale longitudinal cohort studies. Potential mechanisms for the link between chronic hyponatremia and cognitive impairment are intriguing topics for future study. Further interventional studies are needed to observe the effect of correcting hyponatremia on the improvement of cognitive impairment and patient survival.

Acknowledgments

The authors would like to express their appreciation to the patients, doctors, and nursing staff of the Peritoneal Dialysis Centers of Peking University First Hospital, Peking University Shenzhen Hospital, Second Hospital of Anhui Medical University, Second Affiliated Hospital of Harbin Medical University, and Handan Central Hospital who participated in this study.

This study was in part supported by the New Century Excellent Talents from Education Department of China and an ISN Research Award from ISN GO R&P Committee. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosures

None.

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Received: February 26, 2015 **Accepted:** July 11, 2015

Published online ahead of print. Publication date available at www.cjasn.org.