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In addition to malnutrition and renal function impairment, anemia is associated with hyponatremia in the elderly

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ABSTRACT

Hyponatremia is the most common electrolyte abnormality among the elderly living in long-term care facilities. In this study, we investigate the associated factors of hyponatremia, and its association with anemia in the institutionalized elderly in Taiwan. A total of 414 participants aged 65 years and above were recruited from eight long-term care facilities in 2002–2003. Baseline characteristics, medical records, and biomarkers were obtained. Hyponatremia was defined as a serum Na-concentration < 135 mmol/l. Relationships between hyponatremia and the demographic and laboratory characteristics were tested using multiple logistic and linear regression analyses. The prevalence of hyponatremia and anemia was 14.7% and 56.0%, respectively. Anemia, hypouricemia, and the placement of tubes (including nasogastric tube, tracheostomy tube, and Foley catheter) were significantly associated with hyponatremia after adjustment for potential confounders using multiple logistic regression analysis. The adjusted odds ratios (OR) and 95% confidence interval (95%CI) for these three factors were 3.28 (1.40–7.69), 4.98 (2.18–11.36), 9.15 (3.33–25.12), respectively. Multiple linear regression analyses also showed that serum Na concentration was significantly associated with hemoglobin, uric acid, and number of tubes. In conclusion, it was found that anemia, the placement of tubes, and hypouricemia were associated with hyponatremia in the institutionalized elderly. In those with the above conditions, serum Na concentration should be monitored.

1. Introduction

Population aging is a global phenomenon which progresses more rapidly and significantly in East and Southeast Asian countries, including Taiwan (Kinsella et al., 2001). It is estimated that the percentage of population aged 65 and over in Taiwan is 10.8% in 2010, which will reach 20% in 2025 (Council for Economic Planning and Development, 2010). The rapid population aging have caused expanding burden of care and demand for long-term care facilities. According to the survey among Taiwanese in 2000, nearly 10% of the elderly needs long-term care (Directorate-General of Budget Accounting and Statistics, 2000). As a result, issues regarding elderly in long-term care facilities are increasingly important.

Hyponatremia has been reported as the most common electrolyte abnormality in the elderly, and the prevalence of hyponatremia is higher among those indwelling in long-term care facilities than those living in community (Oh et al., 2005; Chua et al., 2007). Elderly patients are more prone to hyponatremia as a result of co-morbidities such as heart failure, chronic liver disease, renal insufficiency, gastrointestinal losses, chest infection, polypharmacy, and poor nutritional status (Chen et al., 2006; Chua et al., 2007; Yawar et al., 2008). Although being usually asymptomatic, hyponatremia is associated with poor long-term prognosis, in both institutionalized elderly and community-dwelling subjects (Chua et al., 2007; Sajadieh et al., 2009). Besides, hyponatremia is found to be associated with increased mortality in hospitalized individuals, and resolution of hyponatremia can

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attenuate the increased mortality risk conferred by hyponatremia (Waikar et al., 2009). Therefore, it is important to identify potential risk factors of hyponatremia.

Anemia is also frequent in the elderly, especially those who lived in long-term care facilities (Artz et al., 2004). In the anemic elderly, the possible etiologies include malnutrition, renal insufficiency, chronic inflammation, primary disorders of hematopoiesis, undiscovered blood loss, or age-associated reduction in bone marrow cellularity (Mitrache et al., 2001; Steensma and Tefferi, 2007). The clinical importance of anemia is highly related to the poor outcomes such as prolonged hospitalization or higher mortality rate (Endres et al., 2009; Riva et al., 2009).

Since previous studies evaluating hyponatremia and anemia in the elderly are little (Chen et al., 2006), the purpose of this study was to investigate the associating factors of hyponatremia in the institutionalized elderly, and the possible relationship between hyponatremia and anemia.

2. Subjects and methods

2.1. Study subjects

We conducted a cross-sectional study of institutionalized elderly in 2002–2003. The target population was residents living in eight long-term care facilities in Taichung City, Taiwan, as in the previous report (Lin et al., 2010). Subjects aged 65 years and older (age range: 65–101 years) were recruited. Thus, a total of 414 participants were enrolled (men = 180, mean age = 77.0 ± 6.7 years; women = 234, mean age = 79.8 ± 7.1 years). Ethics approval for patient recruitment and data analyses was obtained from the Institutional Review Board of the China Medical University Hospital. All participants gave their written informed consent.

2.2. Anthropometric measurements

All of the demographic information and health care records were collected by trained staffs as previous study. In brief, they measured body weight (to the nearest 0.1 kg), body height and waist circumference (WC) (to the nearest 0.1 cm). WC was taken at the midway point between the inferior margin of the rib cage and the iliac crest in a horizontal plane. Body mass index (BMI) was calculated as body weight (kg) divided by height squared (m^2). The presence of pressure ulcer was evaluated by registered nurse using the National Pressure Ulcer Advisory Panel (NPUAP) staging system (NPUAP, 1997). The placement of any tubes (nasogastric tube, tracheostomy tube, or Foley catheter) was also recorded by the same staff.

2.3. Laboratory examinations and performance status

A venous blood sample was taken after a 12-h fast for the determination of hemoglobin, albumin, total cholesterol (TC), triglyceride (TG), serum creatinine, uric acid, and electrolytes (Na, K, and Cl) concentration. The laboratory data was obtained using a biochemical autoanalyzer (Beckman Coulter, Fullerton, CA, USA) at the Clinical Laboratory Department, China Medical University Hospital, Taichung, Taiwan. The performance status was assessed according to the definition of the Eastern Cooperative Oncology Group (ECOG) (Oken et al., 1982) in terms of five categories, from 0 (fully active) to 4 (completely disabled).

In this study, hyponatremia was defined with the serum Na concentration < 135 mmol/l. Following the definition of the World Health Organization (WHO) criteria, anemia was set as serum hemoglobin concentration < 13 g/dl in men or <12 g/dl in women. Central obesity was defined as WC ≥ 90 cm in men and/or WC ≥ 80 cm in women. Characteristics indicating malnutrition were judged as follows: hypoalbuminemia (albumin < 3.5 g/dl), hypocholesterolemia TC < 160 mg/dl), under-weight (BMI < 18.5 kg/m^2). Hypouricemia was defined as serum uric acid concentration < 4 mg/dl (Musch and Decaux, 2001). The estimated glomerular filtration rate (eGFR) was calculated by using the modified Modification of Diet in Renal Disease Study (MDRD) equation for Chinese people, as follows: 186 × serum creatinine [mg/dl]$^{-1.154}$ × age[years]$^{-0.203}$ × (0.742 if female) × (1.227 if Chinese) (Ma et al., 2006). Renal function impairment was determined by the eGFR < 60 ml/min/1.73 m^2. Poor performance status was defined as ECOG score ≥ 3.

2.4. Statistical analysis

Data are presented as means ± S.D. for continuous variables. Student's *t*-test was used to compare mean values between two groups. Proportions and categorical variables are presented as percentages; they were tested for statistical significance by using the χ^2-test and the two-tailed Fisher's exact test. The variables with statistical significance were further tested with multiple logistic and linear regression. All statistical tests were two-sided at the $p < 0.05$ significance level. These statistical analyses were performed by using the PC version of the SPSS statistical software (version 13.0, SPSS Inc., Chicago, IL, USA).

3. Results

The age of the participants was 78.6 ± 7.1 years. The prevalence of hyponatremia was 14.7% (men: 16.7%; women: 13.2%). Table 1 shows comparisons for the anthropometric indices and biomedical markers between subjects with hyponatremia and non-hyponatremia. Subjects with hyponatremia had lower body weight, BMI, WC, hemoglobin, albumin, uric acid, and higher prevalence of underweight, anemia, hypoalbuminemia, hypocholesterolemia,

Table 1
Baseline characteristics according to hyponatremic status, *n*, %, mean ± S.D.

Subjects	With hyponatremia	Without hyponatremia	*p*
Number	61	353	
Male gender	49.2	42.5	0.331
Age (years)	80.0 ± 7.1	78.4 ± 7.1	0.107
Body height (cm)	152.3 ± 8.5	153.1 ± 7.7	0.436
Body weight (kg)	46.3 ± 9.3	51.1 ± 10.8	0.001
BMI (kg/m^2)	20.1 ± 4.0	21.8 ± 4.1	0.003
WC (cm)	78.6 ± 10.6	82.5 ± 10.6	0.010
Hemoglobin (g/dl)	11.2 ± 1.8	12.0 ± 1.9	0.002
Albumin (g/dl)	2.96 ± 0.49	3.21 ± 0.44	<0.001
TC (mg/dl)	170.1 ± 63.4	176.4 ± 43.8	0.348
TG (mg/dl)	77.3 ± 43.7	115.1 ± 180.1	0.115
BUN (mg/dl)	19.0 ± 14.9	18.5 ± 11.8	0.781
Creatinine (mg/dl)	1.34 ± 1.61	1.22 ± 0.96	0.567
eGFR (ml/min/1.73 m^2)	97.4 ± 52.7	84.5 ± 36.1	0.069
Uric acid (mg/dl)	4.70 ± 1.97	5.60 ± 1.69	<0.001
K (mmol/l)	4.76 ± 1.03	4.23 ± 0.72	<0.001
Cl (mmol/l)	97.6 ± 4.7	106.6 ± 3.7	<0.001
Underweight	34.4	19.4	0.008
Anemia	75.4	52.7	0.001
Central obesity	28.6	42.0	0.057
Hypoalbuminemia	86.9	69.4	0.005
Hypocholesterolemia	50.9	36.8	0.042
Renal function impairment	24.6	24.4	0.970
Hypouricemia	40.4	14.0	<0.001
ECOG	3.44 ± 0.98	2.46 ± 1.27	<0.001
Poor performance status	83.6	57.2	<0.001
Placement of any tubes	80.3	36.5	<0.001
With nasogastric tube	76.8	27.9	<0.001
With tracheostomy tube	19.6	6.1	0.001
With Foley catheter	32.1	15.8	0.003
Presence of pressure ulcer	10.9	3.1	0.007

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Table 2
Demographic characteristics according to anemic status, *n*, %, mean ± S.D.

Subjects	With anemia	Without anemia	*p*
Number	232	182	
Male gender	49.1	36.3	0.009
Age (years)	79.2 ± 7.0	77.9 ± 7.1	0.074
Body height (cm)	153.5 ± 7.7	152.3 ± 7.9	0.110
Body weight (kg)	48.9 ± 10.1	52.3 ± 11.1	0.001
BMI (kg/m^2)	20.8 ± 4.1	22.5 ± 4.1	<0.001
WC (cm)	79.6 ± 9.8	84.9 ± 10.9	<0.001
Albumin (g/dl)	3.03 ± 0.46	3.36 ± 0.37	<0.001
Total cholesterol (mg/dl)	166.1 ± 42.6	187.6 ± 49.7	<0.001
Triglyceride (mg/dl)	107.0 ± 215.5	113.6 ± 72.6	0.694
BUN (mg/dl)	21.3 ± 14.6	15.1 ± 6.9	<0.001
Creatinine (mg/dl)	1.41 ± 1.27	1.02 ± 0.74	<0.001
eGFR (ml/min/1.73 m^2)	81.6 ± 42.3	92.5 ± 34.0	0.004
Uric acid (mg/dl)	5.40 ± 1.78	5.56 ± 1.73	0.366
Na (mmol/l)	138.1 ± 5.2	140.1 ± 3.7	<0.001
K (mmol/l)	4.36 ± 0.78	4.24 ± 0.81	0.123
Cl (mmol/l)	105.0 ± 5.4	105.6 ± 4.3	0.198
Underweight	26.3	15.6	0.009
Central obesity	29.8	53.2	<0.001
Hypoalbuminemia	82.8	58.2	<0.001
Hypocholesterolemia	47.6	27.4	<0.001
Renal function impairment	29.7	17.6	0.004
Hypouricemia	18.8	16.2	0.498
Hyponatremia	19.8	8.2	0.001
ECOG	2.78 ± 1.21	2.37 ± 1.32	0.002
Poor performance status	66.5	54.1	0.014
Placement of any tubes	47.0	37.9	0.064
With nasogastric tube	39.1	29.8	0.058
With tracheostomy tube	7.0	9.4	0.393
With Foley catheter	21.4	14.0	0.062
Presence of pressure ulcer	6.1	1.8	0.035

hypouricemia, poor performance status, placement of any tubes, and presence of pressure ulcer than subjects without hyponatremia.

Table 2 shows comparisons according to the anemic status. The prevalence of anemia was 56.0% (men: 63.3%; women: 50.4%). Subjects with anemia had lower body weight, BMI, WC, albumin, TC, eGFR, Na, percentage of central obesity, and higher prevalence of underweight, hypoalbuminemia, hypocholesterolemia, renal function impairment, poor performance status, and presence of pressure ulcer than participants without anemia.

In Table 3, after adjustment for age, gender, underweight, central obesity, hypoalbuminemia, hypocholesterolemia, renal function impairment, poor performance status, and presence of pressure ulcer using multiple logistic regression analysis, subjects with hyponatremia were significantly associated with anemia, hypouricemia, and placement of any tubes. The adjusted OR and 95%CI for these three factors were 3.28 (1.40–7.69), 4.98 (2.18–11.36), and 9.15 (3.33–25.12), respectively.

Table 4 shows that serum Na concentration was significantly associated with hemoglobin level, uric acid level, and number of tubes using multiple linear regression analysis after adjustment for age, gender, BMI, WC, albumin, TC, eGFR, and ECOG.

4. Discussion

4.1. Impact and interpretation

In the present study, we have demonstrated that anemia, hypouricemia, and placement of any tubes are significantly associated with hyponatremia among Taiwanese elderly living in the long-term care facilities. Furthermore, we also found that hemoglobin and uric acid were positively associated with serum Na level, and number of tubes was negatively associated with serum Na level. Because the prevalence of hyponatremia was high among the institutionalized elderly, it is important to identify the potential risk factors of hyponatremia. Therefore, our findings are important to the health care of elderly in the long-term care facilities.

Both anemia and hyponatremia were common health problems in the elderly. Chen et al. (2006) found that the prevalence of hyponatremia in the institutionalized elderly in Taiwan was as high as 30% during a 6-month follow-up period. Anemia, using the WHO definition, was found in 10.6% of the elderly aged 65 years and older in the National Health and Nutrition Examination Survey (NHANES) in the United States (National Center for Health Statistics, 1994), but it increased up to 40% of the elder residents in long-term care facilities (Kalchthaler and Tan, 1980). The prevalence of anemia was even higher (56.0%) in our study, and it might be related to the relatively older age of our study population. Besides, only few studies had investigated the association between hyponatremia and anemia. For example, Chen et al. (2006) found no significant difference on the hemoglobin level between hyponatremic and normonatremic groups. But in this study, we have demonstrated different findings that anemia was significantly associated with hyponatremia.

Although the mechanism linking hyponatremia and anemia is not well understood, two possible underlying mechanisms had been mentioned: undernutrition and chronic systemic diseases. First, undernutrition is potentially related to hyponatremia. Previous studies showed that hyponatremia was related to underweight and low serum total cholesterol level (Chen et al., 2006), which were both frequently used as malnutrition markers (Rudman et al., 1988; WHO, 2000). Other common malnutrition markers include hypoalbuminemia (Seiler, 2001) and low hemoglobin concentration. In our study, underweight, hypocholesterolemia, and hypoalbuminemia were all found to be associated with both hyponatremia and anemia. Even though we further adjusted

Table 3
The OR and 95%CI of having hyponatremia after adjustment for potential confounders using multiple logistic regression analysis.

	Model 1	Model 2	Model 3	Model 4
Anemia	2.96 (1.46–6.00)$^{\mp}$	2.62 (1.27–5.39)$^{\mp}$	3.23 (1.41–7.40)$^{\mp}$	3.28 (1.40–7.69)$^{\mp}$
Hypouricemia	4.24 (2.15–8.35)$^{\#}$	4.52 (2.26–9.03)$^{\#}$	5.23 (2.39–11.44)$^{\#}$	4.98 (2.18–11.36)$^{\#}$
Placement of any tubes	7.75 (3.70–16.24)$^{\#}$	7.92 (3.75–16.75)$^{\#}$	7.94 (3.53–17.85)$^{\#}$	9.15 (3.33–25.12)$^{\#}$
Underweight			1.12 (0.50–2.52)	1.18 (0.50–2.79)
Central obesity			0.95 (0.37–2.40)	0.87 (0.33–2.29)
Hypoalbuminemia			0.83 (0.29–2.39)	0.75 (0.25–2.27)
Hypocholesterolemia			1.17 (0.58–2.39)	1.08 (0.51–2.29)
Renal function impairment				1.34 (0.54–3.30)
Poor performance status				0.94 (0.31–2.90)
Presence of pressure ulcer				0.99 (0.24–3.99)

Notes: Model 1: unadjusted; Model 2: adjusted for age and gender; Model 3: adjusted for age, gender, underweight, central obesity, hypoalbuminemia, and hypocholesterolemia; Model 4: adjusted for age, gender, underweight, central obesity, hypoalbuminemia, hypocholesterolemia, renal function impairment, poor performance status, and presence of pressure ulcer. $^{\mp}p < 0.01$; $^{\#}p < 0.001$.

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Table 4
The coefficients (±S.E.M.) of hemoglobin, uric acid, and number of tubes to serum Na concentration after adjustment for potential confounders using multiple linear regression analysis.

	Model 1	Model 2	Model 3	Model 4
R square value	0.191	0.213	0.223	0.235
Hemoglobin	0.43 (±0.11)$^{\#}$	0.44 (±0.11)$^{\#}$	0.38 (±0.13)$^{\mp}$	0.48 (±0.14)$^{\mp}$
Uric acid	0.44 (±0.12)$^{\#}$	0.50 (±0.13)$^{\#}$	0.44 (±0.13)$^{\mp}$	0.33 (±0.14)$^{¥}$
Number of tubes	−1.62 (±0.24)$^{\#}$	−1.51 (±0.24)$^{\#}$	−1.43 (±0.27)$^{\#}$	−0.99 (±0.32)$^{\mp}$
BMI			0.09 (±0.09)	0.05 (±0.09)
WC			0.01 (±0.03)	0.01 (±0.04)
Albumin			0.35 (±0.65)	0.15 (±0.66)
Total cholesterol			−0.00 (±0.01)	−0.00 (±0.01)
eGFR[2]				−0.01 (±0.01)
ECOG[2]				−0.41 (±0.22)

Notes: Model definitions in Table 3. $^{¥}p < 0.05$; $^{\mp}p < 0.01$; $^{\#}p < 0.001$.

for these characteristics of malnutrition, anemia remained significantly associated with hyponatremia. These findings suggested that undernutrition may be insufficient to explain the relationship between anemia and hyponatremia.

Another possible mechanism is chronic systemic diseases. There are some common cormorbid diseases relating to both hyponatremia and anemia, such as chronic renal failure. Hyponatremia is common in patients with end stage renal disease (Malangone et al., 1989), and renal failure could result in hyponatremia (Alcazar Arroyo, 2008). Researches also found that chronic renal failure is an important cause of anemia (Matzner et al., 1979; Chassagne et al., 2004). These findings suggested that hyponatremia and anemia may be linked via chronic renal failure. In our study, however, there was no significant correlation between hyponatremia and renal function impairment. The association between hyponatremia and anemia remained significant even after adjustment for renal function impairment. There should be other mechanisms linking hyponatremia and anemia.

Similar hypothesis among cardiac failure could be made according to previous studies. For instance, it is assumed that hyponatremia may be caused by dilutional disorders such as congestive heart failure (Siragy, 2006; Haskal, 2007; Rotolo et al., 2008; Yawar et al., 2008). As for anemia, it is found to be common in patients with congestive heart failure (Silva et al., 2007), and the prevalence of anemia increased with severity of the functional class of heart failure (Silverberg et al., 2000). Anemia may induce heart failure through the pathophysiologic pathway of increased cardiac output and development of left ventricular hypertrophy (Metivier et al., 2000). Therefore, hyponatremia and anemia may be linked via congestive heart failure. Although our study could not offer detail information regarding heart failure, the above findings suggested that hyponatremia and anemia may be connected through the chronic systemic diseases of the elderly. Further investigation is necessary for advanced understanding of the mechanisms linking hyponatremia and anemia.

This study also revealed that the placement of any tubes (including nasogastric tube, tracheostomy tube, and Foley catheter) is correlated to hyponatremia after being adjusted for age, gender, underweight, central obesity, hypoalbuminemia, hypocholesterolemia, poor performance status, and presence of pressure ulcer. Besides, the number of tubes is negatively associated with serum Na concentration. Among these commonly used tubes in long-term care facilities, the placement of nasogastric tube and tracheostomy tube were found to be individually associated with hyponatremia using multiple logistic regression analysis in this study (data not shown). Though other information such as feeding formula or systemic disease resulting in the placement of tubes was not obtained, it is a rational recommendation that the serum Na level should be monitored in the institutionalized elderly with a nasogastric tube or a tracheostomy tube.

An additional finding is the association between hypouricemia and hyponatremia. In this study, hypouricemia was found in 40.4% of the hyponatremic elderly, and remained significantly associated with hyponatremia using multiple logistic regression analysis. Previous studies found that hypouricemia and hyponatremia often co-existed in the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in the elderly (Musch and Decaux, 2001; Decaux and Musch, 2008). However, we did not have the information of SIADH, and it merits further study.

4.2. Limitations

Although we have identified the correlation between anemia, hypouricemia, placement of tubes and hyponatremia, our study had some limitations. First, due to the cross-sectional nature of our study design, we could not tell the causal relationship between anemia, hypouricemia, placement of tubes and hyponatremia. Further longitudinal cohort study is necessary. Second, the underlying chronic systemic diseases, medicine prescription, laboratory tests such as serum osmolarity, urine Na excretion profile and osmolarity were not obtained in our study. These might aid in further assessment of hyponatremia. Third, our study subjects were Taiwanese elderly living in long-term care facilities. The generalization to the community-dwelling elderly or other adult population should be alert. Further investigation is required.

5. Conclusion

In conclusion, we have demonstrated that anemia, placement of tubes, and hypouricemia are strongly associated with hyponatremia among elderly living in long-term care facilities. The results of the present study suggested the importance of monitoring serum Na level in the institutionalized elderly. Future studies should aim to further clarify the relationship and causality among these factors, and possible benefits of intervention.

Conflict of interest statement

None.

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