HYPONATREMIA IN HOSPITALIZED OLDER ADULTS IS ASSOCIATED WITH POLYPHARMACY, LONGER HOSPITAL STAY, AND HIGHER MORTALITY

Hiponatremia em idosos internados está associada à polifarmácia, maior permanência hospitalar e maior mortalidade

Lívia Auriemma[a], Genolívia Viana Quarto[a], Guilherme Azevedo Fracalossi[b], Brenda Costa Buzatto[b], Thaís Petri Felix[b], Alessandra Tieppo[a,b], Renato Lírio Morelato[a,b]

ABSTRACT

OBJECTIVE: To evaluate hyponatremia in older patients during hospital stay and determine its association with polypharmacy, length of hospital stay, and mortality. **METHOD:** This was an observational, analytical, cross-sectional study of patients aged 65 years and older during hospitalization. The first sodium sample requested by the physician was considered for analysis. Hyponatremia was classified according to severity as mild (130–135 mEq/L), moderate (125–129 mEq/L), or severe (< 125 mEq/L) and according to osmolarity as isotonic (275–295 mOsm/L), hypotonic (< 275 mOsm/L), or hypertonic (> 295 mOsm/L). The χ^2 test and one-way analysis of variance followed by Tukey's *post hoc* test were used to analyze length of hospital stay between the groups (normonatremia and mild, moderate, and severe hyponatremia). The χ^2 test was also used to compare mortality between the groups. **RESULTS:** We included 174 patients, with a mean age of 74 (SD, 7; range, 65–95) years; 52.3% were men. Overall, 44.8% had normonatremia, 37.8% had mild hyponatremia, 9.2% had moderate hyponatremia, and 8.0% had severe hyponatremia. Increased hospital stay was observed in patients with hyponatremia, being longer in those with severe hyponatremia. Polypharmacy occurred in 39.3% of patients. Of patients with severe hyponatremia, 71.4% had polypharmacy (p = 0.01). **CONCLUSIONS:** Hospitalized older adults showed a high rate of hyponatremia and an important association with polypharmacy and prolonged hospital stay.
KEYWORDS: hyponatremia; length of stay; health of the elderly.

RESUMO

OBJETIVO: Avaliar a hiponatremia em pacientes idosos durante o período de internação e sua associação com polifarmácia, permanência hospitalar e mortalidade. **MÉTODO:** Estudo observacional, transversal e analítico, de pacientes com mais de 65 anos de idade durante o período de internação. A primeira amostra de sódio solicitada pelo médico foi considerada para análise. A hiponatremia foi classificada quanto à gravidade em: leve (130 – 135 mEq/L), moderada (125 – 129 mEq/L) e grave (< 125 mEq/L); quanto à osmolaridade em: isotônica (275 – 295 mOsm/L), hipotônica (< 275 mOsm/L) e hipertônica (> 295 mOsm/L). Empregamos o teste do χ^2 e a análise de variância (ANOVA a uma via), com teste *post hoc* de Tukey, para analisar o período de permanência entre os grupos (normonatremia, hiponatremia leve/moderada e grave), e o teste do χ^2, para comparar a mortalidade entre os grupos. **RESULTADOS:** Cento e setenta e quatro pacientes com idade média de 74 ± 7 anos (65 – 95 anos), sendo 52,3% do sexo masculino, foram avaliados. Do total, 44,8% apresentaram normonatremia; 37,8%, hiponatremia leve; 9,2%, hiponatremia moderada; e 8%, hiponatremia grave. Houve aumento do período de permanência hospitalar nos pacientes com hiponatremia, sendo mais acentuado em portadores de hiponatremia grave. Polifarmácia esteve presente em 39,3% dos pacientes. Entre aqueles com hiponatremia grave, 71,4% apresentavam polifarmácia (p = 0,01). **CONCLUSÕES:** Idosos hospitalizados apresentam alta frequência de hiponatremia e associação importante com polifarmácia e prolongamento da permanência hospitalar.
PALAVRAS-CHAVE: hiponatremia; tempo de internação; saúde do idoso.

[a]Geriatrics Residency, Hospital Santa Casa de Misericórdia de Vitória – Vitória (ES), Brazil.
[b]Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória (EMESCAM) – Vitória (ES), Brazil.

Correspondence data
Renato Lírio Morelato – Hospital Santa Casa de Misericórdia de Vitória – Rua Doutor João dos Santos Neves, 143 – Vila Rubim – CEP: 29025-023 – Vitória (ES), Brazil. E-mail: renato.morelato@emescam.br
Received on: 12/04/2018. Accepted on: 12/21/2018
DOI: 10.5327/Z2447-211520181800061

INTRODUCTION

Normal serum sodium concentration ranges from 135 to 145 mEq/L, defined as normonatremia. Hyponatremia, characterized by serum sodium concentration less than 135 mEq/L, is one of the most common electrolyte abnormalities.[1,2] The severity of hyponatremia is graded into three categories according to sodium levels:

- mild: between 130 and 135 mEq/L;
- moderate: between 125 and 129 mEq/L;
- severe: less than 125 mEq/L.

Mild hyponatremia is often asymptomatic, but the risk increases when it is associated with cognitive decline. In these circumstances, symptoms such as confusion, gait disturbance, and altered consciousness may arise. Seizures may occur with increasing severity of hyponatremia, with acute symptomatic hyponatremia signaling a medical emergency. In severe symptomatic hyponatremia, intravenous infusion of hypertonic saline is used to slowly increase sodium concentration.[3]

There is still no clear evidence whether hyponatremia is reflective of a causal relationship or only a marker of clinical severity. However, a prospective study demonstrated a 2.7-fold higher risk of death in patients with hyponatremia,[3] while other studies, in addition to mortality, have associated hyponatremia with increased length of hospital stay and readmissions in the general population.[4] Regardless of age, hyponatremia occurs in up to 30% of hospitalized patients, with the severe form of the disorder affecting 2 to 3% of these patients during hospital stay.[5,6] In the older population, the mortality rate is higher in patients with hyponatremia than in those with normonatremia.[7]

The purpose of this study was to evaluate hyponatremia in older patients during hospital stay and determine its association with polypharmacy, length of hospital stay, and mortality.

METHOD

This was an observational, analytical, cross-sectional study of patients aged 65 years and older during their stay in the wards of Hospital Geral Santa Casa de Misericórdia in Vitória, state of Espírito Santo, Brazil, over a 10-month period (August 2016 to May 2017). Hospitalized patients who agreed to participate and provided written informed consent were included. Because this was an observational study, the first sodium sample requested by the attending physician was considered for analysis.

Hyponatremia was classified into three levels of severity according to serum sodium concentration:

- mild: between 130 and 135 mEq/L;
- moderate: between 125 and 129 mEq/L;
- severe: less than 125 mEq/L.[3]

Serum osmolarity was calculated using the following formula: 2 × Na + glucose/18 + urea/16. In relation to osmolarity, hyponatremia was classified as isotonic (275–295 mOsm/L), hypotonic (< 275 mOsm/L), or hypertonic (> 295 mOsm/L).[8] Hypotonic hyponatremia was classified according to extravascular fluid as hypovolemic, hypervolemic, or euvolemic.[9] Polypharmacy was considered to occur when patients had more than 5 medications prescribed in their medical records.

Continuous variables were expressed as mean (SD), and categorical variables as counts and percentages. Independent variables were collected as dichotomous variables (presence or absence) in relation to the disorders analyzed (neoplasms, diabetes mellitus, heart failure, cirrhosis, and hypothyroidism under treatment).

The χ^2 test and analysis of variance followed by Tukey's *post hoc* test with polynomial contrasts and linear trend were used to analyze length of hospital stay between the groups (normonatremia and mild, moderate, and severe hyponatremia). The χ^2 test was also used to compare mortality between the groups. Statistical analysis was performed using SPSS, version 25.0. A p-value ≤ 0.05 was considered significant. The study was approved by the research ethics committee of the institution (approval number CAAE 50772615.6.0000.5065 of February 23, 2016).

RESULTS

A total of 174 patients, with a mean age of 74 (SD, 7; range, 65–95) years, were included in the study. Of these, 52.3% (n = 91) were men and 47.7% (n = 83) were women. Ninety-six patients (52.2%) had altered serum sodium concentrations. Of these, 37.8% (n = 66) had mild hyponatremia, 9.2% (n = 16) had moderate hyponatremia, and 8.0% (n = 14) had severe hyponatremia.

Forty-one patients (23.6%) died, with the following distribution among the groups: normonatremia, 10.3% (n = 8); mild hyponatremia, 31.3% (n = 21); moderate hyponatremia, 45.5% (n = 5); and severe hyponatremia, 38.7% (n = 7) (p < 0.002); with post hoc difference between the groups: normonatremia × mild hyponatremia (p = 0.01), normonatremia × moderate hyponatremia (p = 0.01), and normonatremia × severe hyponatremia (p = 0.01). There was no significant difference between the groups with hyponatremia.

Overall, in 36.8% (n = 64) of patients, neoplasia was the reason for hospitalization, with urogenital and gastrointestinal tract neoplasms as the most common causes. Of these,

35.93% (n = 23) died of the neoplasia (p = 0.04), with *post hoc* difference only between the normonatremia × moderate hyponatremia groups (p = 0.04).

Among patients with mild hyponatremia, 59.1% had low osmolarity and 40.9% had normal osmolarity; among those with moderate hyponatremia, the rates were 81.2 and 18.8%, respectively. All patients with severe hyponatremia had hypotonic osmolarity (Table 1). Plasma osmolarity was not associated with length of hospital stay (F = 2.025; p = 0.35).

One hundred and twenty-six patients (72.4%) were normovolemic: 46.0% in the normonatremia group and 40.5, 4.0, and 9.5%, respectively, in the mild, moderate, and severe hyponatremia groups. Forty-six patients (26.4%) were hypovolemic: 43.6% in the normonatremia group and 32.6, 13.0, and 10.5% in the mild, moderate, and severe hyponatremia groups, respectively. Only two patients were hypervolemic, one with mild and one with severe hyponatremia (c^2 = 9.220; p = 0.16).

Severe hyponatremia was associated with longer hospital stay, with patients spending a mean of 24 days in the hospital *vs.* 12 days for those with normonatremia (p = 0.03) (Table 2).

Polypharmacy occurred in 39.3% (n = 68) of patients, and 58.0% (n = 101) used at least one medication known to increase the risk of hyponatremia. Of these, diuretics and proton pump inhibitors were the most commonly used during hospitalization (51.7% and 27.0%, respectively). Of patients with severe hyponatremia, 71.4% (n = 10) had polypharmacy (p = 0.01).

Neoplasia was not associated with hyponatremia (p = 0.08).

DISCUSSION

The present study, conducted in a nonprofit general hospital, identified hyponatremia in 55.2% of patients during hospital stay, an increased prevalence compared with that reported in a meta-analysis, in which hyponatremia was observed in up to 20% of hospitalized patients.[10]

In the older population evaluated in our study, hyponatremia was associated with longer hospital stay and higher mortality, results similar to those reported in previous studies.[11-13] Studies have demonstrated that older patients are more prone to hyponatremia because of associated comorbid

Table 1 Distribution of the sample (n = 174) in relation to plasma osmolarity in patients hospitalized at Hospital Santa Casa de Misericórdia in Vitória, ES, Brazil.

Natremia	Hypotonic osmolarity (< 275 mOsm/L)	Isotonic osmolarity (275–295 mOsm/L)	Hypertonic osmolarity (> 295 mOsm/L)	Total*
Normonatremia (> 135 mEq/L)	1 (1.3%)	65 (83.3%)	12 (15.4%)	78 (100%)
Mild hyponatremia (130–135 mEq/L)	39 (59.1%)	27 (40.9%)	–	66 (100%)
Moderate hyponatremia (125–129 mEq/L)	13 (81.2%)	3 (18.8%)	–	16 (100%)
Severe hyponatremia (124 mEq/L)	14 (100%)	–	–	14 (100%)

*χ^2 test = 98.937 (p < 0.001).

Table 2 Length of hospital stay in patients with normonatremia (n = 78) vs. hyponatremia (n = 96) hospitalized at Hospital Santa Casa de Misericórdia in Vitória, ES, Brazil.

	Normal (n = 78)	Mild hyponatremia (n = 66)	Moderate hyponatremia (n = 16)	Severe hyponatremia (n = 14)	p-value	Total (n = 174)
Age (years)	76 ± 8	74 ± 7	74 ± 5	74 ± 7	0.58	74 ± 7
Glucose (mEq/L)	92 ± 38	86 ± 16	93 ± 36	87 ± 15	0.65	
Urea (mEq/L)	50 ± 33	32 ± 32	48 ± 16	60 ± 56	0.70	
Creatinine (mEq/L)	1.3 ± 0.84	1.4 ± 0.94	1.4 ± 0.87	1.42 ± 0.80	0.98	
Length of hospital stay (days)	12 ± 12*	16 ± 12	22 ± 19	24 ± 25*	0.02	02 a 120

*One-way ANOVA with Tukey's *post hoc* difference in relation to length of hospital stay between the normonatremia vs severe hyponatremia groups (p = 0.02).

conditions, such as chronic diseases (*e.g.*, renal, cardiac, and hepatic failure, among others), polypharmacy, and age-related physiological changes, such as decreased glomerular filtration rate and total body water.[11]

The signs and symptoms of hyponatremia vary in severity, often being more prominent in older patients because of the failure of homeostatic mechanisms.[11] Hyponatremia was observed in 15 to 30% of patients hospitalized for acute or chronic diseases,[2] and in geriatric units the rate was 22.2% for mild and 4.5% for severe hyponatremia.[14] In our study, investigating the presence of hyponatremia during hospital stay, we found a higher rate than that reported in previous studies.[5,6]

The occurrence of polypharmacy was higher in patients with severe hyponatremia (71.4%), but no individual association was found with medications with a risk of causing hyponatremia. Other studies have demonstrated an important relationship between polypharmacy and hyponatremia.[15-17]

The limitations of this study include difficulty in evaluating readmissions associated with hyponatremia, in monitoring patients after hospital discharge, and in controlling for other covariates, such as central nervous system disorders, heart failure, renal failure, chronic lung disease, diabetes mellitus, and neoplasms, among others. In addition, a cohort design would be more appropriate to demonstrate the relative risks associated with the study variables.

Given the importance and high frequency of this fluid and electrolyte disorder, we highlight that there is a need for further understanding of the severity and recognition of the symptoms of hyponatremia by medical professionals because of the risk of serious consequences for patients if not managed properly.

CONCLUSION

The population of older patients investigated here showed a high rate of hyponatremia and an important association with polypharmacy and prolonged hospital stay.

ACKNOWLEDGEMENTS

The study was funded by an undergraduate research grant received from the Research Support Foundation of the State of Espírito Santo (Fundação de Amparo à Pesquisa e Inovação do Espírito Santo, FAPES).

REFERENCES

1. Adrogué HJ, Madias NE. Hyponatremia. New Eng J Med. 2000;342:1581-15. http://doi.org/10.1056/NEJM200005253422107
2. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. Am J Med. 2006;119(7 Suppl. 1):S30-5. https://doi.org/10.1016/j.amjmed.2006.05.005
3. Chawla A, Sterns RH, Nigwekar SU, Cappuccio JD. Mortality and serum sodium: do patients die from or with hyponatremia? Clin J Am Soc Nephrol. 2011;6(5):960-5. https://doi.org/10.2215/CJN.10101110
4. Waikar SS, Mount DB, Curhan GC. Mortality after hospitalization with mild, moderate, and severe hyponatremia. Am J Med. 2009;122(9):857-65. https://doi.org/10.1016/j.amjmed.2009.01.027
5. Upadhyay A, Jaber BL, Madias NE. Epidemiology of hyponatremia. Semin Nephrol. 2009;29(3):227-38. https://doi.org/10.1016/j.semnephrol.2009.03.004
6. Hoorn EJ, Rivadeneira F, van Meurs JB, Ziere G, Stricker BH, Hofman A, et al. Mild hyponatremia as a risk factor for fractures; the Rotterdam Study. J Bone Mineral Res. 2011;26(8):1822-8. https://doi.org/10.1002/jbmr.380
7. Mannesse CK, Vondeling AM, van Marum RJ, van Solinge WW, Egberts TC, Jansen PA. Prevalence of hyponatremia on geriatric wards compared to other settings over four decades: a systematic review. Ageing Res Rev. 2013;12(1):165-73. https://doi.org/10.1016/j.arr.2012.04.006
8. Rocha P. Hyponatremia: basic concepts and practical approach. J Bras Nefrol. 2011;33(2):248-60.
9. Rondon-Berrios H, Agaba E, Tzamaloukas A. Hyponatremia: pathophysiology, classification, manifestations and management. Int Urol Nephrol. 2014;46(11):2153-65. https://doi.org/10.1007/s11255-014-0839-2
10. Corona G, Giuliani C, Parenti G, Colombo GL, Sforza A, Maggi M, et al. The Economic Burden of Hyponatremia: Systematic Review and Meta-Analysis. Am J Med. 2016;129(8):823-35. https://doi.org/10.1016/j.amjmed.2016.03.007
11. Chua M, Hoyle G, Soiza R. Prognostic implications of hyponatremia in elderly hospitalized patients. Arch Gerontol Geriatr. 2007;45(3):253-8. https://doi.org/10.1016/j.archger.2006.11.002
12. Hansen O, Sørensen P, Hansen KH. The occurrence of hyponatremia in SCLC and the influence on prognosis: a retrospective study of 453 patients treated in a single institution in a 10-year period. Lung Cancer. 2010;68(1):111-4. https://doi.org/10.1016/j.lungcan.2009.05.015
13. Berardi R, Caramanti M, Castagnani M, Guglielmi S, Marcucci F, Savini A, et al. Hyponatremia is a predictor of hospital length and cost of stay and outcome in cancer patients. Support Care Cancer. 2015;23(10):3095-101. https://doi.org/10.1007/s00520-0152683-z
14. Anpalahan M. Chronic idiopathic hyponatremia in older people due to syndrome of inappropriate antidiuretic hormone secretion (SIADH) possibly related to aging. J Am Geriatr Soc. 2001;49(6):788-92.
15. Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. Am J Kidney Dis. 2008;52(1):144-53. https://doi.org/10.1053/j.ajkd.2008.03.004
16. Sørensen JB, Andersen MK, Hansen HH. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in malignant disease. J Intern Med. 1995;238(2):97-110.
17. Berghmans T, Paesmans M, Body JJ. A prospective study on hyponatraemia in medical cancer patients: epidemiology, aetiology and differential diagnosis. Support Care Cancer. 2000;8(3):192-7.