Q J Med 2008; **101**:583–588
doi:10.1093/qjmed/hcn061 Advance Access published on 13 May 2008

Mild hyponatremia and risk of fracture in the ambulatory elderly

F. GANKAM KENGNE[1], C. ANDRES[1], L. SATTAR[1], C. MELOT[2] and G. DECAUX[1]

From the [1]Department of General Internal Medecine, Hopital Erasme, Université Libre de Bruxelles, and [2]Department of Intensive Care Hopital Erasme and European Centre for Advanced Research in Economics and Statistics (ECARES), Université Libre de Bruxelles, Bruxelles, Belgique

Received 30 January 2008 and in revised form 4 April 2008

Summary

Background: Mild hyponatremia is the commonest electrolyte imbalance in the older population and has been shown to be associated with gait and attention deficits resulting in higher frequency of falls. The association of mild hyponatremia and bone fracture is still unknown.
Objective: To determine if mild hyponatremia is associated with increased risk of bone fracture in ambulatory elderly.
Design, setting and participants: Case control study of 513 cases of bone fracture after incidental fall in ambulatory patients aged 65 or more in general university hospital. Controls were age and sex matched randomly selected ambulatory patients without history of bone fracture.
Main exposure measures: Odds ratio (OR) of bone fracture after incidental fall associated with presence of hyponatremia.
Results: Prevalence of hyponatremia (serum sodium <135 mEq/l,) in patients with bone fracture and in controls patient was, respectively, 13.06% and 3.90%. Hyponatremia was mild and asymptomatic in all patients (mean serum sodium 131 mEq/l) and was found to be associated with bone fracture after incidental fall in ambulatory elderly (unadjusted OR: 3.47, 95% CI: 2.09–5.79, and adjusted OR: 4.16 95% CI: 2.24–7.71). Hyponatremia was either drug induced (36% diuretics, 17% selective serotonin reuptake inhibitors) or resulted from idiopathic syndrome of inappropriate antidiuretic hormone secretion (37%). Hyponatremia was associated with 9.20% of all bone fractures.
Conclusions: Mild asymptomatic hyponatremia is associated with bone fracture in ambulatory elderly and avoiding iatrogenic hyponatremia or treating hyponatremia may decrease the number of bone fractures in this population.

Introduction

Hyponatremia is a common electrolyte imbalance in the elderly.[1,2] Hyponatremia in this population results from many mechanisms, the most common being iatrogenic hyponatremia (from diuretics) and inappropriate antidiuretic hormone secretion.[3–6] In contrast to the hospitalized elderly patient, hyponatremia is less prevalent in the community and is usually milder.[2,4] Cognitive impairment and various neurological disturbances are associated with hyponatremia, mostly when severe.[7,8] The clinical significance of hyponatremia in the ambulatory elderly is not clear and the term asymptomatic hyponatremia is usually devoted to that usually milder form, since it is believed to be without consequences.[5,6,9] Very few studies however addressed the consequences of the milder and chronic form of hyponatremia among ambulatory seniors. Recently, mild hyponatremia has been shown to influence

Address correspondence to F. Gankam Kengne, Service de Médecine Interne Générale, Hôpital Erasme, 808, Route de Lennik, 1070 Bruxelles, Belgium. email: fgankamk@ulb.ac.be

gait and attention in the elderly, resulting in high incidence of falls.[10] Falls are a major socioeconomic problem in the elderly: ~30% of people over 65 will fall every year.[11–13] Fall-related injury in the elderly is associated with numerous psychological and physical consequences and is a leading cause of death and disability. Falls are associated with bone fracture in 4–6% of cases and death occurs from complication of fall in around 2% of cases mostly in patients with hip fracture;[14,15] the reported proportion of elderly people seeking care after incidental fall is around 8% and almost 5.3% of all hospitalizations in people aged 65 years or older are due to fall related injuries.[15,16] Falls have also been found to be a risk factor for admission to a nursing home facility.[17] Falls and fractures in the elderly are generally due to a complex interaction between intrinsic and extrinsic factors and some of those have been successfully modified, resulting in a decrease of fall incidence.[18]

To date, no study has addressed the possible association of bone fracture and clinically asymptomatic hyponatremia. This work investigated the association between bone fracture after incidental fall and hyponatremia in the ambulatory elderly.

Patients and methods

We used a computer-assisted search in our hospital database to track all ambulatory patients older than 65 years, who arrived in our institution from January 2003 to December 2006 with a complaint of recent fall and who had at time of discharge, a diagnosis of bone fracture recorded in the database as one of the diagnoses established by first line physician in emergency department. Recent fall was defined as fall which occurred less than 2 h before medical attention was sought. The complaint of fall was confirmed by the analysis of patient note in all patients and the accuracy of the diagnosis of bone fracture was confirmed by checking the orthopaedic surgeon's and radiologist's reports. Patients were considered eligible for the study if their fall was incidental (not due to a road traffic accident etc.) and if they had a pre-treatment serum sodium (SNa) value available (pre-treatment SNa was defined as SNa in blood sample taken day of fall, before any fluid or drug administration). Controls were sex- and age- (within 4 years) matched ambulatory patients with no history of bone fractures, randomly selected among all patients who attended the outpatient clinic at least once between January 2004 and December 2006. Only patients who had current blood sample with SNa, updated medical diagnoses and treatment at the time they attended out patient clinic, were included in the control group. Hospitalized patients or patients attending the 1 day clinic or dialysis clinic were not eligible for the study. Patients with unavailable past medical history, or unavailable current medical diagnoses and treatment were excluded from the study. In both groups, patients with blood glucose value over 150 mg/dl were excluded.

Definition and identification of hyponatremia

For both groups, hyponatremia was defined as SNa lower than 135 mEq/l. Pre-treatment blood chemistry was used for evaluation of hyponatremia in cases and similarly, in controls only blood sample taken at time of consultation was considered. All blood chemistry tests were done in the same institution. Causes of hyponatremia were further identified by review of medical history, current medications, blood chemistry and urine chemistry when available.

Identification of risk factors for fall

Risk factors we included in our analysis are shown in Table 1. Risks factors for cases and controls were identified after analysis of standardized physician note mentioning current medical diagnoses, past medical history and current medical treatment. All relevant medical information was confirmed by analysis of a standardized computer medical file of each patient and control.

Statistical analysis

The prevalence of the selected risks factors for a fall (including hyponatremia) were compared in cases and controls subjects using univariate conditional logistic regression. Adjusted odds ratio for hyponatremia was obtained after a multivariable conditional logistic-regression. Covariates for multivariable model were identified if the $P < 0.05$ on the basis of the univariate analysis. Age was also included in the multivariable analysis. All analyses used a two-sided significance level of 5% and were performed with the use of Statistix software for Windows (version 8). Prevalence of hyponatremia in the 513 randomly selected controls was compared to the prevalence of hyponatremia in all ($n = 27\,908$) ambulatory patients by chi square test. Association measurements in population and patients with hyponatremia (risk of bone fracture attributable to hyponatremia in all patients with bone fracture and in patients with bone fractures and hyponatremia) were calculated by Levin's modified formula for

Table 1 Distribution of all covariates analysed in patients and controls subjects

Variables	Cases (%) $n=513$	Controls (%) $n=513$	P value
Age	80 ± 8	81 ± 7	0.001*
Male	133 (25.93)	133 (25.93)	1
Hyponatremia (Na < 135 mEq/l)	67 (13.06)	20 (3.90)	<0.0001*
Benzodiazepine	198 (38.60)	157 (30.60)	0.007*
SSRI	110 (21.44)	76 (14.81)	0.006*
Antiepileptic drug	30 (5.85)	20 (3.90)	0.135
Any CNS acting drug	305 (59.45)	249 (48.53)	0.0004*
Multiple medications	310 (60.42)	355 (69.20)	0.0027*
Vasodilators	209 (40.74)	246 (47.95)	0.019*
Diuretics	125 (22.41)	143 (27.87)	0.28
COPD	64 (12.47)	61 (11.89)	0.78
Hypotension	33 (6.43)	12 (2.34)	0.0027*
Acute illness	24 (4.68)	34 (6.62)	0.1914
Multiple chronic conditions	109 (21.28)	178 (34.69)	<0.001*
Walking problems	144 (29.24)	194 (37.82)	0.0038*
Inactivity	30 (5.84)	14 (2.72)	0.0162*
History of stroke	57 (11.11)	41 (7.99)	0.0934*
Alcohol consumption	31 (6.04)	9 (1.75)	0.0009*
Cognitive impairment	90 (17.24)	36 (7.01)	<0.0001*
Parkinson disease	33 (6.43)	12 (2.34)	0.0027*
Dizziness	14 (2.73)	30 (5.85)	0.0162*
Visual Problems	37 (7.21)	78 (15.20)	<0.0001*
Nursing home residency	71 (13.84)	16 (3.11)	<0.001*

COPD, chronic obstructive pulmonary disease; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; Multiple medications, more than four drugs taken; Hypotension, systolic blood pressure was lower than 100 mmHg; Multiple chronic conditions, more than three of the followings: diabetes, chronic lung disease, heart failure, renal failure, neoplasia and liver cirrhosis. Walking problems included peripheral neuropathy, arthritis or severe arthrosis of lower limb and use of any walking aid device.
*Included in multivariable analysis.

matched-pairs cases-controls data.[19] Results are presented by mean and SD.

Results

From January 2003 to December 2006, 24 337 patients of 65 years or over visited our 900-bed university hospital fall. Of patients, 2507 consulted for recent fall; all patients had acute fall and were taken care in the surgical ward of emergency department (150 015 overall visits in the same department); 923 patients were diagnosed bone fracture. Among patients with bone fractures, 386 had non incidental fall or had no blood sample drawn and 537 patients had incidental fracture with SNa mostly in the setting of preoperative evaluation. From the 537 patients with SNa available, 24 patients were excluded from the study (13 patients with unavailable medical information and 11 patients with glycaemia over 150 mg/dl) and 513 patients were finally included in the study (Figure 1), 380 were females whereas 133 were males. Mean age for patients with bone fracture was 81 ± 8 years.

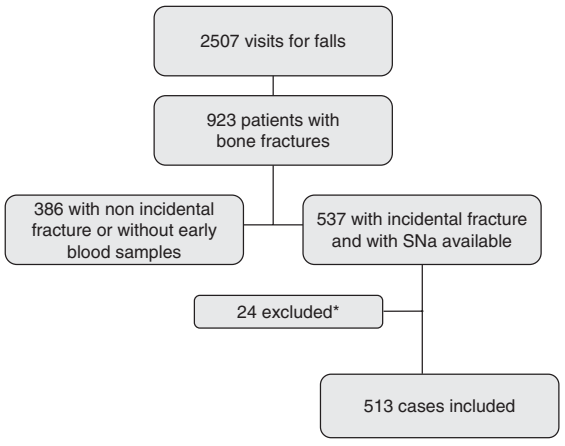

Figure 1. Selection of patients included in the study (all patients are 65 years or older).

From January 2004 to October 2006, 27 908 patients visited our ambulatory consultation unit and had blood chemistry including SNa drawn the day of the consultation. Among them, we selected

Table 2 Baseline characteristics of patients and controls and site of bone fracture in patients

	Cases			Controls		
	SNa < 135 $n = 67$	SNa > 135 $n = 446$	Overall $n = 513$	SNa < 135 $n = 20$	SNa > 135 $n = 493$	Overall $n = 513$
Mean age (years)	81 ± 9	81 ± 8	80 ± 8	85 ± 6	81 ± 7	81 ± 7
Male/female	16/51	117/329	133/380	9/11	126/367	133/380
Mean SNa (mEq/l)	**131 ± 3**	140 ± 3.2	139 ± 4	**131 ± 3**	141 ± 3	140 ± 3
Hip and femoral fractures	40	242	282			
Upper limb fractures	16	139	155		NA	
Fracture of other sites	11	65	76			

NA, Non applicable.

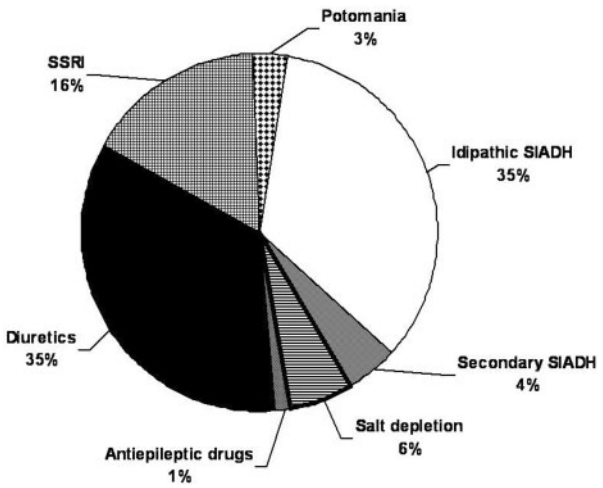

Figure 2. Distribution of hyponatremia according to aetiology.

513 age- and sex-matched controls. Mean age for selected controls was 81 ± 7 years.

Anatomic distribution of fracture site and baseline demographic characteristic of cases are given in Table 2.

Of the 513 patients included in the study, 67 (13.06%) had SNa value <135 mEq/l (SNa: 131 ± 3 mEq/l). Of patients, 22 were discharged without SNa measurement at the end of hospital stay,18 were still hyponatremic at discharge and four of them had recurrent falls and bone fracture. Attribution of causes of hyponatremia is given in Figure 2. In the 513 control subjects, the prevalence of hyponatremia was 3.90% ($n = 20$, SNa: 131 ± 3 mEq/l) see Tables 2 and 3. This was similar to patients attending the ambulatory consultation unit of whom 1198 (4.26%) of 27 908 were hyponatremic ($P = 0.66$).

Unadjusted odds ratio for bone fracture associated with presence of hyponatremia was 3.47 (95% CI: 2.09–5.79); after adjustment for potential confounders, odds ratio for bone fracture associated with hyponatremia was 4.16 (95% CI: 2.2–47.71). The risk of bone fracture attributable to hyponatremia was 9.20% (95% CI: 5.54–12.86) in all patients with bone fractures and in hyponatremic patients, bone fracture was attributed to hyponatremia alone in as much as 72.52% of cases (95%CI: 57.82–87.21).

Discussion

Our results identified hyponatremia as a major single risk factor for bone fracture from incidental fall in elderly ambulatory patients. Hyponatremia was associated with 9.20% of all cases of bone fractures. Almost 55% of all bone fractures were hip and femoral fractures.

Our study confirmed previous findings about causes of hyponatremia in the ambulatory geriatric population[3,4] and particularly the high prevalence of idiopathic syndrome of inappropriate antidiuretic hormone secretion (SIADH)[4,20] which was found in more than 30% of hyponatremic patients.

In our study population, hyponatremia was clinically not symptomatic and hence more likely to go unnoticed. Only 56% of patients with bone fracture had SNa measurement done; blood samples were drawn in all cases only for preoperative assessment. In fact of the 67 hyponatremic elderly with bone fractures, only one had hyponatremia mentioned in his discharge summary as one of the final diagnoses in emergency room or orthopaedic ward; many were discharged without correction of hyponatremia and 25% had no SNa measurement at discharge. Four hyponatremic patients had recurrent bone fractures.

The selective serotonin reuptake inhibitors (SSRI) antidepressants and diuretics are a commonly prescribed drug in the elderly, the use these drugs is associated with a high incidence

Table 3 Prevalence of hyponatremia in patients and controls and ORs for bone fracture associated with hyponatremia

	Patients (%) $n = 513$	Controls (%) $n = 513$	Unadjusted OR (CI)	Adjusted OR (CI)
Hyponatremia	67 (13.06)	20 (3.90)	3.47 (2.09–5.79)*	4.16 (2.24–7.71)*

OR, Odds ratio; CI, 95% confidence interval; *$P < 0.001$.

of hyponatremia.[22,23] As seen in Figure 2, a significant proportion of hyponatremia in patients with bone fractures was drug induced; for all those patients, the treatment at discharge was similar to treatment on admission and most of them remained hyponatremic.

The SSRI and antiepileptic drugs (AED) were incriminated in an increase risk of fall and bone fracture by their sedative and hypotensive properties;[24–26] our results identified hyponatremia as another possible mechanism accounting for high incidence of fall and bone fractures in elderly patients taking these drugs.

In the present study, the cut off value for hyponatremia was SNa < 134 mEq/l. Other workers have previously reported hip fracture as a complication of hyponatremic encephalopathy;[21] in that study, hyponatremia was severe (SNa 117 mEq/l) and symptomatic and bone fractures resulted from seizures. However, a recent experimental study tested gait and attention in hyponatremic elderly and it was shown that the threshold for attention and gait deficits induced by hyponatremia were 132 mEq/l and 134 mEq/l, respectively.[27] In the present study, hyponatremia in patients with bone fractures was mild (mean SNa 131 mEq/l) and asymptomatic and no patients had seizures or signs of hyponatremic encephalopathy.

The relationship between hyponatremia and bone fracture could be explained by gait instability and attention deficits observed in hyponatremic elderly.[10,27]

Like other retrospective studies, our study has some important limitations. First, some factors might have not been correctly reported in cases or controls or were unavailable. We cannot therefore exclude the possibility that misreported risk factor like inactivity or unassesed risk factor like muscle strength or palmomental reflex influenced the result of our study. Similarly, bone mass density and body mass index were not available in most of the patients. This could have possibly also influenced our results but, the trigger for bone fracture in our case was incidental fall and fracture was unlikely to occur without a fall even in patients at high risk. Besides, all shared risk factors for fall and bone fracture were included in the multivariable analysis and the fact that our control population had overall more comorbidities than our patient with bone fractures suggest that unassesed risk factors were not likely to induce an overestimated odd ratio. Second, in this study, only 56% of patients with bone fracture had their SNa measured. This limited electrolyte evaluation could have overestimated the prevalence of hyponatremia. However, that possibility is weak since sodium was measured as part of electrolyte preoperative check up and no patient showed signs of metabolic abnormalities, in addition, the SNa measurement in a ambulatory patient with bone fracture for which surgery is not planned is not a part of routine management in many institutions probably due to the lack of evidence of hyponatremia associated morbidity on absence of overt clinical signs of metabolic encephalopathy. Third, the prevalence of hyponatremia in our control sample was lower than the previously reported prevalence of hyponatremia in elderly ranging from 8 to 11%.[2,4,5] Nevertheless, the possibility that an underestimation of hyponatremia in our controls has lead to an inaccurate estimation of risk of bone fracture in hyponatremic patients is not likely: previous papers reporting higher prevalence of hyponatremia in the elderly included hospitalized patients or patients living in a nursing home where hyponatremia is more frequently found; in addition the cut off value for definition of hyponatremia varies widely. Moreover, hyponatremia was no less frequent in our randomly selected controls than in a larger elderly population attending our ambulatory consultations unit over 3 years (more than 27 000 patients).

The association between hyponatremia and bone fractures in the ambulatory elderly is of a particular interest in clinical practice since bone fracture carries a major socioeconomic burden and hyponatremia in the elderly is mostly drug induced (SSRI and diuretics) and thus preventable.

Our results also suggest that all ambulatory geriatric patients with a bone fracture secondary to incidental fall should have their SNa checked to exclude possible hyponatremia even without obvious neurologic symptoms.

In conclusion, mild hyponatremia is risk factor for bone fracture due to incidental fall and a non

negligible proportion of fall and subsequent fractures in the ambulatory seniors could possibly be prevented by avoidance of iatrogenic hyponatremia and treatment of idiopathic SIADH.

Acknowledgements

We are grateful to Mrs Luc Moest and Dr Decuyper Jean for their helpful contribution in data extraction and processing.

Conflict of interest: None declared.

References

1. Miller M. Hyponatremia and arginine vasopressin dysregulation: mechanisms, clinical consequences, and management. *J Am Geriatr Soc* 2006; **54**:345–53.
2. Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. *Clin Chim Acta* 2003; **337**:169–72.
3. Musch W, Decaux G. Utility and limitations of biochemical parameters in the evaluation of hyponatremia in the elderly. *Int Urol Nephrol* 2001; **32**:475–93.
4. Miller M, Hecker MS, Friedlander DA, *et al*. Apparent idiopathic hyponatremia in an ambulatory geriatric population. *J Am Geriatr Soc* 1996; **44**:406–8.
5. Miller M, Morley JF, Rubinstein LZ. Hyponatremia in a nursing home population. *J Am Geriatr Soc* 1995; **43**:1410–3.
6. Adrogué HJ, Madias NE. Hyponatremia. *N Engl J Med* 2000; **342**:1581–9.
7. Kumar S, Berl T. Sodium. *Lancet* 1998; **352**:220–8.
8. Fraser CL, Arieff AI. Epidemiology, Pathophysiology, and Management of hyponatremic encephalopathy. *Am J Med* 1997; **102**:67–77.
9. Singer GG, Brenner BM. Fluid and electrolytes disturbances. In: Braunwald E, *et al*., eds. *Harrison's Principles of Internal Medecine*. 15th edn. McGraw-Hill, New York, 2001:181–8.
10. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med* 2006; **119**:71.e1–8.
11. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med* 1988; **319**:1701–7.
12. O'Loughlin JL, Robitaille Y, Boivin JF, Suissa SF. Incidence of and risk factor for fall and injurious falls among the community dwelling elderly. *Am J Epidemiol* 1993; **137**:342–54.
13. Graafmans WC, Ooms ME, Hofstee HM, Bezemer PD, Bouter LM, Lips P. Falls in the elderly: a prospective study of risk factors and risk profiles. *Am J Epidemiol* 1996; **143**:1129–36.
14. Sattin RW. Falls among older persons: A public health perspective. *Annu Rev Public Health* 1992; **13**:489–508.
15. Sattin RW, Lambert DA, DeVito CA, Rodriguez JG, Ros A, Bacchelli S, *et al*. The incidence of fall injury events among the elderly in a defined population. *Am J Epidemiol* 1990; **131**:1028–37.
16. Alexander BH, Rivara FP, Wolf ME. The cost and frequency of hospitalization for fall-related injuries in older adults. *Am J Public Health* 1992; **82**:1020–23.
17. Tinetti ME, Williams CS. Falls, injuries due to falls, and the risk of admission to a nursing home. *N Engl J Med* 1997; **337**:1279–84.
18. Campbell AJ, Robertson MC, Gardner MM, Norton EN, Buchner DM. Psychotropic medication withdrawal and a home based exercise program to prevent falls: a randomized controlled trial. *J Am Geriatr Soc* 1999; **47**:850–3.
19. Kuritz SJ, Landis JR. Attributable risk ratio estimation from matched-pairs Case-control data. *Am J Epidemiol* 1987; **125**:324–8.
20. 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**:788–92. Erratum in: *J Am Geriatr Soc* 2002; **50**:204.
21. Ayus JC, Arieff AI. Chronic hyponatremic encephalopathy in postmenopausal women: association of therapies with morbidity and mortality. *JAMA* 1999; **281**:2299–304.
22. Wilkinson TJ, Begg EJ, Winter AC, Sainsbury R. Incidence and risk factors for hyponatremia following treatment with fluoxetine or paroxetine in elderly people. *Br J Clin Pharmacol* 1999; **47**:211–7.
23. Spital A. Diuretic-induced hyponatremia. *Am J Nephrol* 1999; **19**:447–52.
24. Thapa PB, Gideon P, Cost TW, Milam AB, Ray WA. Antidepressants and the risk of falls among nursing home residents. *N Engl J Med* 1998; **339**:875–82.
25. Ensrud KE, Blackwell TL, Mangione CM, Bowman PJ, Whooley MA, Bauer DC, *et al*. Central nervous system-active medications and risk for falls in older women. *J Am Geriatr Soc* 2002; **50**:1629–37.
26. Liu B, Anderson G, Mittmann N, To T, Axcell T, Shear NL. Use of selective serotonin-reuptake inhibitors or tricyclic antidepressants and risk of hip fractures in elderly people. *Lancet* 1998; **351**:1303–7.
27. Renneboog B, Sattar Loubna, Decaux G. Determination of threshold for attention and gait deficits encountered in chronic hyponatremia. Abstract. *JASN* 2006; **17**:37A.