Hyponatremia associated with long-term medication use in the elderly: an analysis in general practice

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ABSTRACT

INTRODUCTION: The aim of this study is to determine the prevalence of hyponatremia, its association with long-term medication use and underlying chronic conditions, the rate of hospitalisation and death within 3 months from its discovery and its management in community-dwelling older people.

METHODS: One year of data for ~5635 patients aged >65 years was extracted from the databases of 19 general practitioners (GPs); 2569 (45.6%) were checked for hyponatremia.

RESULTS: Hyponatremia occurred in 205 (8.0%) of 2569 checked individuals: 78.5% (161/205) had hypertension, 31.2% (64/205) diabetes, 23.9% (49/205) chronic renal failure; 38.0% (78/205) received diuretics, 36.6% (75/205) renin-angiotensin system antagonists (ACE-I/ARB) and 9.8% (20/205) serotonin reuptake inhibitors. Drug consumption was higher in hyponatremic patients, although only diuretics, ACE-I/ARB, anti-arrhythmics and opioids were significantly associated with hyponatremia. The likelihood of hyponatremia trebled when four drugs were taken, and it was seven-fold higher with the use of six drugs. Hyponatremia was associated with a higher prevalence of chronic illnesses and higher rate of hospitalisation (13.7% vs 7.7%, $P = 0.005$) and death (3.9% vs 1.8%, $P < 0.035$). The use of at least one long-term medication was associated with hospitalisation or death in hyponatremic patients (10% vs 6.3%, $P = 0.010$). Less than 20% of hyponatremic patients had their sodium level checked again after 1 month.

DISCUSSION: Hyponatremia is not uncommon among community-living older patients, especially in patients taking medications potentially causing hyponatremia. Hyponatremic patients are likely to encounter more serious events, including hospitalisation and death. Targeted training of GPs is desirable to improve their practice.

KEYWORDS: Arterial hypertension; diabetes; elderly; general practice; hyponatremia

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Introduction

Hyponatremia is defined as a fall in serum sodium concentration below 135 mEq/L and is the most common electrolyte alteration, especially in elderly people. A recent systematic review including 53 studies found evidence of mild hyponatremia in 22% of geriatric hospital patients and in 6% and 17% of people admitted to general hospitals and intensive care units respectively.[1] In other studies, its prevalence is 4–7% in outpatients and 19% in nursing home residents.[1–5] Although it is not clear whether hyponatremia may represent an unfavourable prognostic factor itself or simply reflects the severity of underlying conditions, it is known to be associated with poor outcomes in elderly patients, as suggested by increased rates of morbidity and mortality.[6–9] Its clinical importance relies on the crucial role of sodium in maintaining the osmolarity of body fluids. Even mild changes in sodium concentration determine important variations in plasma osmolarity as a consequence of water movement from intra- to extra-cellular spaces. Establishing volaemic status represents the main guide for treatment choices.[3] The central nervous system is greatly affected by this sodium shift, with cerebral oedema as a complication. Symptoms accompanying hyponatremia may be non-specific (headache, fatigue, mood alterations) when its onset is slowly progressive over a period of weeks and the serum sodium level remains slightly below the normal range. By contrast, when serum sodium falls quickly to very low levels (<125 mEq/L), clinical manifestations are dramatic, with appearance of lethargy, confusion, disorientation, tonic-clonic spasms and coma.[9]

Without stratifying patients by age, the most frequent causes of hyponatremia are the syndrome of inappropriate antidiuresis (35%), which includes the inappropriate antidiuretic hormone (ADH) secretion (SIADH), hypovolaemia (30%), hypervolaemia (20%), diuretics (8%), primary polydipsia (5%) and adrenal insufficiency (2%).[10,11] While the latter prevails in adults, the underlying cause in older people is difficult to identify because it is often multifactorial.[12] Diagnostic investigations include taking a history with special attention to medications and laboratory tests. Management is based on contrasting precipitating factors including suspension or replacement of the drug potentially causing the condition, restoring electrolyte deficiency and establishing volaemia, and hospitalisation in the case of severe acute symptomatic forms.

Usually, general practitioners (GPs) observe mild and asymptomatic chronic forms of hyponatremia which are, however, at high risk of switching to severe symptomatic forms when a concomitant major illness occurs.[3,13] Beyond diuretics and among drugs with a high rate of prescription in general practice, attention should be paid to drug classes such as selective serotonin re-uptake inhibitors (SSRIs), which are reported to be associated to hyponatremia in over 30% of cases.[14] The prolonged use in older patients of some antihypertensive medications may be involved too, in particular the renin-angiotensin system antagonists (ACE-I/ARBs), anti-epileptics, anti-arrhythmics and proton pump inhibitors (PPIs).[15–17]

Although drug-induced hyponatremia represents an important issue for elderly and in frail patients, little is known about its clinical relevance and management in community-dwelling people. This study retrospectively investigated the prevalence of hyponatremia in general practice and its prognosis in terms of hospitalisation and death in people aged >65 years, its association with long-term use of some drugs and the concomitant presence of chronic illnesses. The management of hyponatremia by GPs was also evaluated.

Methods

General practice databases were retrospectively searched from January to December 2015. Data were extracted for all patients aged >65 years who were tested for serum sodium levels and showed hyponatremia (<35 mEq/L) on at least one occasion. The long-term use of drugs known to potentially cause hyponatremia (diuretics, ACE-I/ARBs, SSRI, PPIs, opioids, anti-arrhythmics) was checked. Patients receiving at least two prescriptions for one class of drug in the study year were considered to be treated with that drug class.

The presence of underlying chronic conditions (arterial hypertension, type 2 diabetes mellitus, chronic renal failure, chronic heart failure, ischaemic heart disease, chronic cerebrovascular disease) was evaluated. We calculated the rate of hospitalisation and death during 3 months following the first finding of hyponatremia.

Finally, the GP management of hyponatremia was evaluated. The GPs' approach was checked by determining if sodium and creatinine levels in serum, and sodium concentration in urine were tested in the month following the diagnosis of hyponatremia and whether care was reassessed (plasma osmolarity check, change in medications, fluid and nutritional advice).

The study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol was approved by the local Ethics Committee.

Analytic approach

Data are expressed as mean ± standard deviation (s.d.) or as percentages, and we used the Student's *t*-test to compare the absolute values of two different groups and the chi-square test to compare percentages. In all instances, $P < 0.05$ indicates significant differences. Linear regression analysis was performed to measure the relationship between hyponatremia, chronic conditions and use of medications. The relative risk of developing hyponatremia as a consequence of the number of long-term medicine classes taken by the patients was calculated and expressed as odds ratios (ORs) against patients receiving no medications.

Multivariate logistic regression was used to measure the effects of age, sex, hyponatremia, chronic conditions and use of medications (absent vs present) as independent factors on the occurrence of major events (hospitalisation, death). Positive and negative predictive values were calculated to differentiate patients with and without hyponatremia. All statistical analyses were performed by using SigmaStat 4.0 (Systat Sofware Inc., Chicago, IL, USA).

Results

Nineteen GPs working in Southern Italy participated in the study (two women and 17 men; mean age 57 years [s.d. 4 years]; all with >20 years of practice experience). In total, these GPs managed the health care of 24,559 patients, with 5635 (22.9%) patients aged >65 years (mean age 76 years [s.d. 7 years]; females 56.9%).

During the study year, the serum sodium level was checked at least on one occasion for 2569 of 5635 (45.6%) patients aged >65 years old; this is the study group and their demographic and clinical characteristics are shown in Table 1. Their most common chronic conditions were arterial hypertension and diabetes, followed by chronic renal failure, atherosclerosis and coronary heart disease. Of all prescribed tests for this elderly participant population, the proportion of sodium testing from blood samples was 84.5%. Hyponatremia was found in 205 of 2569 patients (8.0%). Patients with chronic conditions were more likely to have hyponatremia; there was an average of 2.2 long-term conditions in the group of 205 patients with hyponatremia and 1.8 long-term conditions in the group of 2364 patients whose sodium was checked and who were not found to have hyponatremia ($P < 0.001$). Arterial hypertension, diabetes, chronic heart failure and cerebrovascular disease were significantly more common in hyponatremic patients, whereas coronary heart disease, atherosclerosis and chronic renal failure, although more prevalent, were not statistically dissimilar (Table 2).

Prolonged use of medications potentially causing hyponatremia (diuretics, ACE-I/ARBs, SSRI, opioids, PPIs, anti-arrhythmics) in both normo- and hyponatremic patient groups are reported in Table 3. In particular, while the use of all drug classes was higher in hyponatremic patients, only the prolonged use of diuretics, ACE-I/ARBs, opioids and anti-arrhythmics, individually, were significantly associated with hyponatremia (Table 4). When two or more drugs were taken long-term by patients, the risk of developing hyponatremia increased. Relative risk of developing hyponatremia trebled with the use of four drugs and was seven-fold higher with the use of six drugs (Table 4). Hyponatremia was significantly more common in patients taking an ACE-I/ARB in combination therapy with a diuretic than in patients taking diuretics alone (37.8% vs 11.4%, $P < 0.001$). By contrast, there was no difference in the percentage of patients with hyponatremia when an SSRI was taken with an ACE-I/ARB (8.8% vs 7.6%, $P = 0.09$) or with a diuretic (6.3% vs 4.9%, $P = 0.067$) compared with when a SSRI, ACE-I/ARB or diuretic was taken alone.

Table 1. Demographic and clinical characteristics of the study group (n = 2569 patients aged >65 years)

Age (years, standard deviation)	76.4 (7.5)
Sex	1108 (43.1) males; 1461 (56.9) females
Arterial hypertension	2029 (79.0)
Type 2 diabetes mellitus	807 (31.4)
Chronic heart failure	194 (7.6)
Coronary heart disease	365 (14.2)
Atherosclerosis	532 (20.7)
Chronic cerebrovascular disease	126 (4.9)
Chronic renal failure	620 (24.1)

Data are presented as percentages unless stated otherwise.

Hyponatremia was associated with a higher rate of hospitalisation (19.5% vs 7.7%, $P = 0.005$) and death (13.7% vs 1.8%, $P < 0.035$) during the 3 months following its first finding. The long-term use of at least one drug class in hyponatremic patients was significantly associated with hospitalisation or death (10% vs 6.3%, $P = 0.010$). The multivariate analysis identified the use of opioids (coefficient 0.546, $P < 0.003$) and of anti-arrhythmics (coefficient 0.704, $P < 0.035$) among drugs, and age (coefficient 0.021, $P < 0.03$), congestive heart failure (coefficient 0.582, $P < 0.007$), coronary heart disease (coefficient 0.534, $P < 0.002$) and cerebrovascular disease (coefficient 0.547, $P < 0.03$) among chronic conditions, as factors significantly associated with hospitalisation and death in hyponatremic patients.

During the first month following the diagnosis of hyponatremia, only 18.5% of patients had their serum sodium levels tested again by their GPs and 18% had serum creatinine levels checked. The concentration of sodium in urine was investigated in 2.4% of patients. A new check for serum sodium levels in the 3 months following the initial diagnosis was performed in 28.3% of patients, creatinine was checked in 32.6% of patients and urine sodium was checked in 4.4% of patients. We did not have sufficient data to comment on medications change.

Discussion

Our study addresses an issue that is important to patients and under-researched. We report on the

Table 2. Prevalence of the most common chronic illnesses in the study group (n = 2569 patients aged >65 years)

	AH** *N* (%)	Diabetes* *N* (%)	CHF** *N* (%)	CHD *N* (%)	ATS *N* (%)	CVD** *N* (%)	CRF *N* (%)
Normonatremic patients (*n* = 2364)	1851 (78.3)	727 (30.7)	156 (6.6)	334 (14.1)	484 (20.5)	107 (4.5)	561 (23.7)
Hyponatremic patients (*n* = 205)	178 (86.8)	80 (39.0)	38 (18.5)	31 (15.1)	48 (23.4)	19 (9.3)	59 (28.8)
Statistical difference (*P*)	0.004	0.014	< 0.001	0.073	0.067	0.003	0.082

AH (arterial hypertension); ATS (atherosclerosis); CHF (chronic heart failure); CHD (coronary heart disease); CVD (chronic cerebrovascular disease); CRF (chronic renal failure).
*$P < 0.05$; **$P < 0.01$.

Table 3. Prolonged use of medications potentially causing hyponatremia in the study group (n = 2569 patients aged >65 years)

	Diuretics** *N* (%)	ACE-I/ ARBs* *N* (%)	SSRIs *N* (%)	Opioids* *N* (%)	PPIs *N* (%)	Anti-AR* *N* (%)
Normonatremic patients (*n* = 2364)	560 (23.7)	1507 (63.7)	152 (6.4)	295 (12.5)	1196 (50.6)	104 (4.4)
Hyponatremic patients (*n* = 205)	78 (38.0)	148 (72.2)	20 (9.8)	38 (18.6)	116 (56.6)	18 (8.8)
Statistical difference (*P*)	< 0.001	0.015	0.068	0.013	0.100	0.048

ACE-I/ARBs (renin-angiotensin system antagonists); anti-AR (anti-arrhythmics); SSRI (selective serotonin reuptake inhibitors); PPIs (proton pump inhibitors).
*$P < 0.05$; **$P < 0.01$.

Table 4. Relative risk of developing hyponatremia by the number of long-term medicine classes prescribed

	No. of concurrent long-term drugs (classes) being used						
	0	1	2	3	4	5	6
Normonatremic patients (*n* = 2364)	464 (19.6)	654 (27.7)	685 (29.0)	393 (16.6)	131 (5.5)	30 (1.3)	7 (0.3)
Hyponatremic patients (*n* = 205)	29 (14.1)	41 (20.0)	58 (28.3)	43 (21.0)	24 (11.7)	7 (3.4)	3 (1.5)
Risk of hyponatremia (OR)	–	1.003	1.355	1.751	2.931	3.733	6.857
Statistical difference (*P*)		< 0.001	0.075	< 0.001	< 0.001	< 0.001	< 0.001

OR (odds ratio). –, no risk.

prevalence of hyponatremia in a large cohort of patients attending general practice, its association with commonly used drugs and chronic illnesses. The present study shows that higher prevalence of hyponatremia occurs in older patients receiving medications that potentially cause electrolyte disturbances. This study also shows that hyponatremia is not uncommon among community-living older patients, especially in patients taking drugs known to cause sodium alterations which is associated with poor clinical outcomes.

In line with other studies,[18] we found that hyponatremic patients had significantly more comorbidities than normonatremic individuals. This difference does not exclude the hypothesis that electrolyte levels were preferentially checked by GPs in patients carrying a higher risk of electrolyte disturbance because of chronic comorbidities and polypharmacy; the consequent results may overestimate the true prevalence in the community.

An important finding from our study results is the relationship between long-term use of drugs and the occurrence of hyponatremia, suggesting the existence of a cause–effect relationship, although it is also plausible that hyponatremia could simply be a marker of frailty. It is noteworthy that the use of all the considered drugs was higher in patients with hyponatremia than in patients with normonatremic levels. In particular, with the exception of opioids, ACE-I/ARBs, anti-arrhythmics and diuretics, the other drug classes when considered alone do not appear to induce serum sodium alterations, although the prolonged use of opioid drugs is often associated with more severe forms of illness and worse general health status. Concerning diuretics, it is known that their prolonged use, for thiazides in particular, is associated with hyponatremia.[19] Although diuretics have well-documented metabolic side-effects, including hyponatremia and hypokalemia, they are still recommended as first or second line agents in the pharmacological treatment of arterial hypertension.

Regarding the other investigated drugs, although statistical significance was not reached for the association with hyponatremia, we cannot exclude some effects on sodium homeostasis. Possibly, another study with more patients may show a statistically significant association. In contrast, the main purpose of our study was not to show that some drug classes can induce hyponatremia, which is already known, but to investigate the effect of hyponatremia on the general population who are checked by GPs. Therefore, and as a consequence, demographic and clinical characteristics of patients with and without hyponatremia were not the same.

Other studies[20] have shown that hyponatremia is prevalent in patients hospitalised with severe and more advanced conditions, such as heart failure, and that it is associated with increased in-hospital mortality and longer hospital stays. Although it is questionable whether hyponatremia merely represents a marker of disease progression or is itself detrimental,[21] our study suggests that hyponatremia is an independent predictor of mortality in the outpatient population.

Previous studies of geriatric inpatients suggest that hyponatremia is a frequent side-effect in patients who were taking a diuretic on admission, and that hyponatremia may be as common as 11–33% in such patients.[22,23] These studies concluded that inpatients frequently have comorbidity and that the risk of hyponatremia in primary care, where diuretics are most frequently prescribed, is unknown. We provide new data supporting the potential hyponatremic effect of some drug classes. In more detail, the association between disturbances of serum sodium levels and ACE-I consumption has been demonstrated by personal interviews from a large population study of the very elderly.[24] Also, case reports support the association between anti-arrhythmic drugs (amiodarone and propafenone, in particular) and hyponatremia as a consequence of drug-induced SIADH.[25]

Our results have important implications for research and practice. Hyponatremia is the most common electrolyte abnormality encountered in clinical practice. Its prevalence is known to change according to the nature of the patient population and healthcare setting.[26–29] It frequently appears during hospital stays either as a feature of the underlying cause or as the consequence of therapeutic interventions, and is associated with increased morbidity and mortality.[7,30] However, mortality also increases with raised serum sodium levels, and even mild hypernatremia is associated with significant mortality.[31] Older people are predisposed to alteration in electrolytes because of age-related physiologic changes and due to underlying chronic conditions impairing sodium homeostasis, including urinary concentrating ability and altered total body water distribution. Medications may exacerbate this predisposition.

We found that hyponatremia is an underestimated and poorly managed problem in general practice patients. The reasons could be attributed to more attention being focused on the alteration of other electrolytes, such as potassium and calcium, or to more attention paid to other conditions such as hypernatremia, as GPs reported in a telephone survey.[32] Older patients are predisposed to alteration of circulating electrolytes, as sodium and water balance is regulated by several factors including thirst, the arginine vasopressin pathway and the renin–angiotensin–aldosterone system.[33]

This study underscores the need for improved understanding and management of sodium disturbance by GPs, because we discovered that after first finding hyponatremia, sodium levels in blood and urine and serum creatinine levels were tested again in less than 20% of patients. This suboptimal management could expose patients to much more important sequelae of hyponatremia and, at least in some cases, negative outcomes such as hospitalisation. We recommend a periodical revision of long-term treatment, in particular in older patients under multi-drug therapy. This is a crucial point because older people may rapidly change their general health status by altering the biochemical and physical adaptation systems according to the underlying conditions, their sodium and water homeostasis and their capacity for drug metabolism. GPs are the most appropriate health professionals to help patients maintain metabolic balance.

In conclusion, hyponatremia is common among community-dwelling elderly people and is associated with significant morbidity and mortality. The geriatric population is particularly prone to develop hyponatremia as a result of physiologic changes and of medication side-effects, and they are likely to experience poor outcomes in the short time following hyponatremia diagnosis, including hospitalisation and death. Although we do not have to act on every hyponatremic result and many patients may be asymptomatic, it is particularly important to carefully consider hyponatremia in elderly patients affected by polypharmacy. Regular sodium monitoring is advised to reduce the risk of harm and increase the detection and treatment of this metabolic abnormality. Finally, targeted training of GPs is desirable to improve their practise on managing hyponatremic patients.

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COMPETING INTERESTS
None.