Title: Severe hyponatremia in older patients at admission in an internal medicine department

Author: Lurdes Correia Rogério Ferreira Inês Correia Ana Lebre José Carda Rita Monteiro Adélia Simão Armando Carvalho Nascimento Costa

PII: S0167-4943(14)00140-X
DOI: http://dx.doi.org/doi:10.1016/j.archger.2014.08.002
Reference: AGG 3042

To appear in: *Archives of Gerontology and Geriatrics*

Received date: 2-1-2013
Revised date: 31-7-2014
Accepted date: 3-8-2014

Please cite this article as: Correia, L., Ferreira, R., Correia, I., Lebre, A., Carda, J., Monteiro, R., Simão, A., Carvalho, A., Costa, N.,Severe hyponatremia in older patients at admission in an internal medicine department, *Archives of Gerontology and Geriatrics* (2014), http://dx.doi.org/10.1016/j.archger.2014.08.002

SEVERE HYPONATREMIA IN OLDER PATIENTS AT ADMISSION IN AN INTERNAL MEDICINE DEPARTMENT

Lurdes Correia[1], Rogério Ferreira[2], Inês Correia[3], Ana Lebre[4], José Carda[5], Rita Monteiro[1], Adélia Simão[6], Armando Carvalho[7], Nascimento Costa[8]

Centro Hospitalar e Universitário de Coimbra – Hospitais da Universidade de Coimbra e Faculdade de Medicina da Universidade de Coimbra

[1] Assistant of Internal Medicine

[2]Internal Medicine Resident

[3] Neurology Resident

[4]Infeccious Diseases Resident

[5] Assistant of Hemathology

[6]Consultant of Internal Medicine

[7]Associate Professor of Medicine and Head of Department of Internal Medicine

[8]Full Professor of Medicine

Corresponding Author:

Name: Maria de Lurdes Martins Malva Correia

E-mail address: lurdescorreia@portugalmail.pt

Full postal address: Rua 15 de Agosto, nº 80, Ribeira de Frades, 3045-423 Coimbra - Portugal

Telephone: +351966720243

All authors disclose any actual or potential conflict of interest.

Highlights

- 72.26% of the patients admitted to Hospital were 65 years old or higher
- Hyponatremia incidence was 27.55% at admission
- The incidence of severe hyponatremia was 5.94%
- Hyponatremia was associated with a higher mortality
- HCTZ, ARBs, PPIs and spironolactone were the most relevant risk factors

Abstract

Hyponatremia is common in older people, most often of multifactorial origin, and can be associated with poor clinical outcomes. The aim was to analyze the frequency of severe hyponatremia (sodium concentration below 125 mmol/L), risk factors and mortality association in hospitalized older patients. A retrospective study was performed in older patients (over 65 years) with hyponatremia, diagnosed at admission in an Internal Medicine Department during one year. A control group of 127 older patients without hyponatremia was considered. Statistical analysis of the data gathered was made with SPSS Statistics 20. The main results were: a group of 1060 patients with age superior to 65 years was identified (representing 72.26% of total admissions); incidence of hyponatremia in those patients was 27.55% and severe hyponatremia was 5.94%; diagnosis of hyponatremia was mentioned in the discharge note in 66.67% of cases; mortality was 27.0%, against 16.0% in the control group ($p=0.057$, OR=1.940); drugs were a significant risk factor ($p<0.001$), specially thiazide diuretics ($p=0.029$,OR=2.774), angiotensin receptor blockers ($p=0.001$, OR=4.097), proton pump inhibitors ($p=0.007$, OR=2.561) and spironolactone ($p=0.011$, OR=4.473); other relevant risk factors were: increased water intake ($p=0.004$), tube feeding

(p<0.001), vomiting (p=0.032, OR=2.492), cirrhosis (p=0.008, OR=10.862) and hyperhidrosis (p=0.017, OR=2.542). We conclude that, although this group of patients had a high mortality, hyponatremia is often not investigated and not always mentioned as a diagnosis. Clinicians should have a clear appreciation of the roles that iatrogenic interventions and lapses in nutrition frequently play in upsetting the homeostatic balance in older patients.

Keywords: Hyponatremia, geriatrics, older patients, Syndrome of Inappropriate Antidiuretic Hormone Secretion, Drugs accompanied by hyponatremia, iatrogeny.

1. INTRODUCTION

Hyponatremia is defined as a serum sodium concentration below 135 mmol/L and may be associated with low, normal (275 to 290 mosmol/Kg) or high osmolality. [1,2]

Clinical severity is dependent both on the magnitude of the hyponatremia and the rate at which the serum sodium level has declined. When the decrease in serum sodium is marked (≤125mmol/l) or acute (occurring over <48h), serious neurological complications can ensue as a result of cerebral oedema. Headache, nausea, vomiting, muscle cramps, lethargy, restlessness, disorientation, and depressed reflexes can be observed. Complications of severe and rapidly evolving hyponatremia include seizures, coma, permanent brain damage, respiratory arrest, brain-stem herniation, and death.[1,2,3,4,5]

Diagnosis is based on a detailed clinical history and physical examination, serum and urinary sodium and plasma osmolality.[6]

Hyponatremia with normal serum osmolality is a laboratory phenomenon, usually caused by extreme hyperlipidemia or hyperproteinemia.[2,3,4] Hyperosmolar hyponatremia is caused by the accumulation of osmotically active non-electrolyte solutes, with hyperglycemia being the most common cause.[1,3,4] The two most common causes of hyponatremia with a low serum osmolality are effective arterial blood

volume depletion and the Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), but it is most often multifactorial.[1] Other causes of hyponatremia described in the literature are central nervous system disorders (stroke, hemorrhage or tumor), malignancy with ectopic ADH production (bladder, prostate or rectal carcinoma), pneumonia, hypothyroidism, drugs (thiazide diuretics, furosemide, spironolactone, indapamide, chlortalidone, metolazone, proton-pump inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitor antidepressants, antipsychotics, carbamazepine anticonvulsant, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, amiodarone, nonsteroidal anti-inflammatory agents, ciprofloxacin), increased water intake, tube feeding, advanced renal failure, vomiting, diarrhea, age superior to 80 years, heart failure, cirrhosis, hipersudoresis.[1,3,7,8,9,10,11,12]

Hyponatremia is a common clinical problem in older people.[1,3] The aging process is usually accompanied by various maladaptations to stress in different organs and physiologic functions. The mechanisms associated with water metabolism are vulnerable to age-related maladaptations and to the various disease processes and medical interventions that frequently occur in older people.[3] The physiologic changes in water regulatory systems that occur as part of normal aging, including the decreased sensation of thirst, decreased total body water, decreased renal sodium-conserving ability (altered renal tubular function, increased atrial natriuretic hormone secretion, decreased renin-angiotensin-aldosterone secretion), decreased renal water excretion ability (decreased renal blood flow and glomerular filtration rate, decreased distal renal tubular diluting capacity, increased renal passive reabsorption of water and increased antidiuretic hormone secretion), and the reduced distal solute delivery due to poor nutrition limiting free water excretion, make older person more susceptible to the development of hyponatremia.[3,7]

Therefore, it is absolutely essential for clinicians to be aware of the pathophysiology of hyponatremia in this group of patients.[3] The authors made a retrospective study of the hyponatremia cases in older patients, diagnosed at admission in an Internal Medicine Department in a one year period. The objectives of this study were to determine the

frequency of severe hyponatremia in these patients and to identify the associated risk factors and mortality.

2. MATERIALS AND METHODS

A retrospective analysis of all clinical files from patients admitted in two Internal Medicine wards in the University Hospitals of Coimbra from the 1st December 2007 to the 30th November 2008 was conducted. From that data, a selection of older people (age equal or superior to 65 years old), and older people with hyponatremia (sodium plasma concentration lower than 135 mmol/L) in the first analytic control at the admission was made. From this group, those with severe hyponatremia (sodium plasma concentration lower or equal to 125 mmol/L) were identified. Data was presented by age bands 65-74, 75-84 and superior to 85 years old. The group of older patients with severe hypoosmolar hyponatremia (normal plasma osmolality was defined between 275 and 290 mosmol/Kg) was analyzed and compared with a control group of 127 patients with the same age and sex distribution, but without hyponatremia in the first analysis at admission to hospital (Table 1). The following parameters were assessed: incidence of hyponatremia, sodium plasma concentration, plasma osmolality, risk factors for hyponatremia (mentioned above), symptoms, etiologic evaluation performed, reference to hyponatremia in the discharge letter and mortality. The risk factors were all mentioned in the discharge note.

The analysis of the data gathered was made with SPSS Statistics 20 and Mann-Whitney U-Test and X^2 Test were applied to determine p-value (significant if < 0.05).

3. RESULTS

Among the 1467 patients (798 men and 669 women) admitted between December 1st 2007 and November 30th 2008, a group of 1060 older patients was identified (72.26%), composed by 546 men (51.5%) and 514 women (48.5%); age ranged between 65 and 98years old, with a mean age of 78 in men and 82 in women. Considering basal

laboratory results on admission, hyponatremia was diagnosed in 292 older patients (27.55%), 152 men (27.84%) and 140 women (27.24%). Mean age of men and women was 78 and 88 years, respectively, being equal in patients with or without hyponatremia.

As far as plasma osmolality is concerned, 62% (55% male, 64% on female), had osmolality lower than 275 mosmol/Kg, 29% (33% on male, 29% on female) had a normal value and 9% (12% on male, 7% on female) had osmolality higher than 290 mosmol/Kg.

Sodium values ranged between 103 mmol/L and 134 mmol/L (Figure 1), with severe hypoosmolar hyponatremia in 63 cases, which means a global incidence of 5.94%, 7.39% in females (n=38), 4.58% in males (n=25). Characteristics of study group and control group are described in table 1. Patients with severe hypoosmolar hyponatremia were aged between 68 and 97 years old. The most frequent symptom was lethargy (Figure 2). Risk factors for hyponatremia were analyzed, according to those reported in literature and data was compared with a control group of 127 patients without hyponatremia, with the same sex and age distribution (Tables 2 and 3). The number of drugs took and the percentage of severe hyponatremia is showed in Table 4. The diagnosis of hyponatremia was mentioned in the discharge letter of 43 patients (68.25%). If the incidence of hyponatremia had been calculated based only on the final diagnosis written in the discharge letter, it would be only 3.96%. An etiology for hyponatremia was identified in 9 patients (drug iatrogeny in 5 patients; SIADH in 3 patients; increased water intake in 1 patient). Mortality was 27% (53% women and 47% men, with ages between 70 and 97 years old, mean age 83.65 years); mortality in the control group was 16% (p=0.057), with an Odds Ratio (OR) of 1.940 (95% confidence interval of 0.932 to 4.041).

4. DISCUSSION

Old population has increased in Portugal in the last decades, and a similar tendency is being expected in the future. In our study, 72.26% of patients admitted to Hospital have an age equal or above 65 years old. Clinicians involved in the care of older

patients recognize that hyponatremia is a common finding in this age group. In our analysis, hyponatremia incidence in older patients at admission was 27.55%, similar to that described by others, who found 22.5% of cases of hyponatremia in older patients (mean age of 72 years) institutionalized in a chronic disease hospital.[7] Severe hyponatremia incidence was 5.94%, more frequently found in women than in men (7.39% vs 4.58%). Future studies with larger groups of patients would be necessary to enlighten the reasons for this difference. More than half of the cases occurred after 75 years old.

Hyponatremia was considered a final diagnosis in only 3.96% of the patients, which may reflect a sub valorization of this condition by the clinicians. However, severe hyponatremia is associated with a 1.94 times higher mortality than in patients without hyponatremia (p=0.057), demonstrating its importance, and should not be underestimated.

In our study, like in others, hyponatremia is most commonly associated with low serum osmolality.[3,4] The group of older patients with severe hypoosmolar hyponatremia was analyzed and compared with a control group. The authors chose to study only patients with severe hyponatremia because severe hyponatremia has a high mortality and associated symptoms while mild hyponatremia is generally asymptomatic.

In our study, the most relevant risk factor related with severe hypoosmolar hyponatremia was iatrogeny ($p<0.001$). Hyponatremic patients have more prescribed drugs than those without (mean of 2 drugs vs one, respectively; p=0.022). Certain drugs taken by older people can affect water balance by direct action on the kidney or by enhancing antidiuretic hormone (ADH) release or effect. [7,8] The exact incidence is unknown, but patients above age 65 may be more susceptible to drug adverse events.[4] In Yawar study medicines accounted for 30% of the cases of hyponatremia, of which diuretics, the angiotensin converting enzyme inhibitors (ACEI) and the angiotensin receptor blockers (ARB) were on the top of the list.[11] Although initial reports indicated that the risk was greater when ACEI were used in combination with thiazide diuretics, ACEI alone can precipitate hyponatremia.[7] Together, ACEI and ARB represent the most

common drugs taken by patients in our study. The ACEI were not a significant risk factor (p=0.342) in our patients, however the ARB were associated with a risk for hyponatremia of 4.097 (p=0.001).

Diuretics are one of the most common causes of severe hyponatremia.[13] The most commonly involved are thiazyde or thiazide-like agents.[13] In our patients, thiazide diuretic hydrochlorothiazide (HCTZ) increased the risk of hyponatremia in 2.774 times (p= 0.029). Blijderveen J et al study has shown an increased risk of hyponatremia with chlorthalidone, a thiazide-like diuretic, relative to hydrochlorothiazide at equal milligram-to-milligram dose per day.[14] However, in our study chlorthalidone has not been shown to be associated with severe hyponatremia. There is no particular reason why the use of chlorthalidone in Portuguese older patients should be causing less or no hyponatremia and these different results may be a consequence of a focus only in severe hyponatremia in our study. Usually hyponatremia develops within the first one to two weeks of therapy if diuretic dose and dietary intake remain relatively constant.[7,9] After this period, the patient has a new steady state in which further sodium and water losses do not occur.[9] However, in the patients of our study and as described in the literature [9], the disorder first appears after many months of therapy. In these patients, perturbation of the steady state, such as an acute gastrointestinal or respiratory illness, an increase in diuretic dose, or the development of heart failure, may explain the occurrence of hyponatremia.[9]

Furosemide shows a tendency to hyponatremia, although non-significant (p=0.074),

increasing the risk 1.776 times. Furosemide on its own does not cause hyponatremia as it increases free water clearance, and indeed can be a very useful treatment for some forms of hyponatremia. When hyponatremia occurs in the presence of furosemide, this generally reflects the indication for furosemide (heart failure, oedema, renal failure, etc), or less commonly increased, unbalanced free water intake to replenish circulating volume.[9] However, loop diuretics appear to have a greater natriuretic effect in older than in younger persons and cases of severe hyponatremia secondary to loop diuretics have been described.[7, 13]

Hyponatremia is described as a rare side-effect of proton pump inhibitors (PPI), but

this type of drugs originated a risk of 2.561 to develop severe hyponatremia (p=0.007). The mechanism is not fully established but excessive urinary sodium loss has been postulated, due to PPI effects on renal tubular ion exchange. An alternative hypothesis is fluid retention possibly related to SIADH secretion or action.[12] In this case, it is also possible that stressful triggers, like infection or concomitant use of other medication, may precipitate hyponatremia. It has been argued that PPIs are overprescribed and there is suboptimal review of the need to continue regular use of these medications. It is important for clinicians to be aware of this possible side-effect to PPIs and that hyponatremia may be reversible upon cessation of this drugs.[1]

Spironolactone causes increased amounts of sodium and water to be excreted, inducing or aggravating hyponatremia.[15] In our study the risk of severe hyponatremia was 4.473 higher (p=0.011).

Hyponatremia with the characteristics of SIADH is recognized as a side effect of all antipsychotic drugs[10], carbamazepine, selective serotonin reuptake inhibitors (SSRI), selective serotonin and noradrenalin reuptake inhibitors, tricyclic antidepressants, opiates, nonsteroidal anti-inflammatory agents, sodium valproate and amiodarone.[4,7] The onset of hyponatremia typically occurs within 2 weeks after initiation of drug therapy. None of these drugs constituted a significant risk factor in our patients.

There is evidence that the SSRI antidepressants (most commonly fluoxetine), can also induce SIADH, with a reported incidence of 3.5-6.3 per 1000 people treated per year.[7] Individuals at highest risk for SSRI-induced hyponatremia are those older than age 65 years.[7] The lack of association between selective serotonin reuptake inhibitors and tricyclic antidepressants and hyponatremia might result from the fact that only severe hyponatremia was analyzed and those drug classes tend to cause more mild to moderate hyponatremia.

Loss of sodium and water by vomiting was a risk factor in our patients over 85 years old (p=0.036), and probably in a larger sample diarrhea would also be a risk factor (p=0.077).

Heart failure was not considered a risk factor (p=0.844), but cirrhosis was important (p=0.008) in our patients.

In our study, advanced renal failure was not a significant risk factor (p=0.611).

Over time, low sodium intake, coupled with age-associated impaired renal sodium conserving ability, can lead to sodium depletion with hyponatremia.[7] Many patients whose nutritional support is primarily or entirely provided by tube feeding (a frequent situation in Portugal), develop either intermittent or persistent hyponatremia[7]; indeed, tube feeding was a relevant risk factor for hyponatremia in our study (p<0.001).The underlying cause appears to be sodium depletion, because of the low sodium content of most tube-feeding diets.[7] The hyponatremia usually resolves in response to increasing the dietary sodium intake.

A major risk factor for the development or worsening of hyponatremia in older patients is the administration of hypotonic fluid, either as an increase in oral intake, or as intravenous 0.45% saline solution or 5% glucose in water, which is found in 78% of nursing home residents with hyponatremia.[7] In our patients, increased water intake, described in the discharge note, was considered an important risk factor (p=0.004).

Advanced age itself may be a risk factor for hyponatremia.[7] Age superior to 80 years was common in our patients (58.7%) and probably was a significant risk factor for hyponatremia. However, since the control group was constituted by patients with the same demographic characteristic, the impact of this risk factor could not be assessed.

Many diseases that are common in older patients can cause SIADH.[7] Pneumonia can lead to the SIADH, although the mechanism by which this occurs is not clear.[4,7] However, pneumonia, although a frequent diagnosis, was not a risk factor for hyponatremia in our study.

Any central nervous system disorder can lead to dysfunction of the hypothalamic system and enhance ADH release.[7,8] However, in our study they were not a significant risk factor (p=0.254).

In our patients, the cancers found were bladder, prostate and rectal carcinoma. However malignancy with ectopic ADH production only appears to be a risk factor for hyponatremia over 85 years old (p=0.014).

The mechanism by which hypothyroidism can induce hyponatremia is incompletely understood.[4] In our study it was not associated with hyponatremia (p=0.850).

SIADH is characterized by the continued release of ADH and it is a diagnosis of exclusion.[2] A probable cause for the low frequency of SIADH in our study (only diagnosed in 3 patients) was an insufficient study of the hyponatremia, in part due to the difficulty in performing urinary sodium determinations in our Emergency Department if the patient was admitted at night or weekend and also because most of them start treatment with a saline solution before an urine sample had been collected, making the results of dubious interpretation.

SIADH is involved in the pathogeny of several risk factors presented therefore its incidence in this cohort should be higher.

The most common symptom found in our patients was lethargy. Manifestations of hypotonic hyponatremia are largely related to dysfunction of the central nervous system. The severity of clinical symptoms is dependent on both the magnitude of the hyponatremia and the rate at which the serum sodium level has declined, and they are more conspicuous when the decrease in the serum sodium concentration is large or rapid (occurring within a period of hours).[1,2,5,7] There is often a poor correlation between serum sodium concentration and the severity of symptoms.[7] Patients with a serum sodium concentration lower than 125 mmol/L may present with nausea, headache, lethargy, confusion, muscle cramps, irritability, seizures, coma, permanent brain damage, respiratory arrest, brainstem herniation and death, especially if the disorder has developed rapidly.[1,3] Patients with mild and moderate hyponatremia constitute the vast majority of hyponatremic patients in our cohort. As far as mild hyponatremia is concerned, the authors were not able to perform neither mortality nor risk factors analysis, since it was not the major endpoint of this article. However, several community-based studies have shown that mild hyponatremia carries specific morbidity as it has been independently associated with gait and attention deficit, and

with an increased risk of falls, bone fractures and possibly osteoporosis.[16] F Gankam-Kengne et al study has shown that serum sodium lower than 135 mEq/l was relatively common and associated with a nearly twofold increased risk of death.[16] Mohan S et al large cohort study has shown that mild hyponatremia is a predictor of mortality in the general population independently of age, gender, and comorbid conditions.[17]

In conclusion, although severe hypoosmolar hyponatremia is associated with higher mortality, quite often it is not completely investigated, nor always mentioned as a diagnosis in the discharge note. Clinicians should have a clear appreciation of the roles that iatrogeny and nutrition fails frequently play in upsetting the homeostatic balance in older patients.

5. CONCLUSIONS

- 72.26% of the patients admitted to Hospital were 65 years old or higher.
- Hyponatremia is a common finding in this group, with a incidence of 27.55% at admission.
- Incidence of severe hyponatremia is 5.94%, and is frequently underestimated by clinicians, even though it is associated with a higher mortality.
- The most relevant risk factor for hyponatremia is medication. Clinicians must be aware of the number of drugs taken by the patients. Special care should be taken when thiazide diuretics, angiotensin receptor blockers, proton pump inhibitors and spironolactone are given.
- Tube feeding associated with a low sodium intake is a relevant risk factor and hyponatremia usually resolves in response to increasing the dietary sodium intake.

6. APPENDICES

A. TABLES

Table 1 – Characteristics of the study group and control group			
Characteristics	**Study Group**	**Control**	
Number of patients	63	127	
65-74 years old	12 (19.0%)	24 (18.9%)	
75-84 years old	27 (42.9%)	56 (44.1%)	
≥85 years old	24 (38.1%)	47 (37.0%)	
Age (mean ± SD)	81.57 ± 7.04	81.56 ± 7.15	p=0.980
Female (number of cases, %)	38 (60.32%)	75 (59.05%)	p=0.497
Female age (mean ± SD)	82.58 ± 7.10	82.39 ± 6.96	p=0.876
Male (number of cases, %)	25 (39.68%)	52 (40.94%)	p=0.497
Male age (mean ± SD)	80.04 ± 6.94	80.37 ± 7.43	p=0.855
SD: Standard deviation			

Table 2 – Factors which were significantly and independently associated with severe hypoosmolar hyponatremia in Aging			
Risk Factors	**Study Group**	**Control**	**P**
Drugs accompanied by hyponatremia	82.6%	64.5%	p<0.001
• **65-74**	61.1%	38.9%	p=0.042
• **75-84**	72.3%	27.7%	p=0.002
• **>85**	70.4%	29.6%	p=0.008
- Thiazide diuretics	17.5%	7.1%	p=0.029 OR=2.774 (1.084 to 7.096)
- Spironolactone	12.7%	3.1%	p=0.011 OR=4.473 (1.292 to 15.481)
- Proton-pump inhibitors	34.9%	17.3%	p=0.007 OR=2.561 (1.281 to 5.118)
• **65-74**	25%	16.7%	0.429
• **75-84**	44.4%	17.9%	0.012

• **>85**	29.2%	17%	0.189
- Angiotensin receptor blockers	23.8%	7.1%	p=0.001 OR=4.097 (1.679 to 9.996)
• **65-74**	41.7%	8.3%	p=0.029
• **75-84**	25.9%	5.4%	p=0.012
• **>85**	12.5%	8.5%	p=0.682
Increased water intake	6.3%	0.0%	p=0.004
Tube feeding	22.2%	0%	p<0.001
Vomiting	20.6%	9.4%	p=0.032 OR=2.492 (1.063 to 5.841)
• **65-74**	16.7%	12.5%	p=1.00
• **75-84**	14.8%	8.9%	p=0.463
• **>85**	29.2%	8.5%	p=0.036
Cirrhosis	7.9%	0.8%	p=0.008 OR=10.862 (1.241 to 95.080)
Hyperhidrosis	25.4%	11.8%	p=0.017 OR=2.542 (1.162 to 5.559)

ADH = antidiuretic hormone, OR= Odds Ratio, SIADH = Syndrome of Inappropriate Antidiuretic Hormone Secretion

Table 3 – Risk Factors for hyponatremia in aging described in the literature that were not significantly associated with severe hypoosmolar hyponatremia in the study

Risk Factors	Study Group	Control	
Central Nervous System Disorders (stroke, hemorrhage,tumor)	7.9%	4.0%	p=0.254
Malignancy with Ectopic ADH Production (bladder, prostate or rectal carcinoma)	12.7%	6.3%	p=0.136
• **65-74**	0%	4.2%	p=0.48
• **75-84**	18.5%	12.5%	p=0.468
• **>85**	12.5%	0%	p=0.014
Hypothyroidism	6.3%	7.1%	p=0.850
• **65-74**	8.3%	8.3%	p=1
• **75-84**	3.7%	8.9%	p=0.392
• **>85**	8.3%	4.3%	p=0.484
- **Furosemide**	41.3%	28.3%	p=0.074 OR=1.776

			(0.943 to 3.345)
• **65-74**	33.3%	20.8%	p=0.429
• **75-84**	40.7%	28.6%	p=0.273
• **>85**	45.8%	31.9%	p=0.256
- Indapamide	3.2%	3.1%	p=0.993
- Clorotalidone	1.6%	0.8%	p=0.612
- Metolazone	1.6%	0.0%	p=0.156
- Tricyclic antidepressants	3.2%	7.1%	p=0.278
- Selective serotonin reuptake inhibitor antidepressants	1.6%	3.9%	p=0.385
- Haloperidol	1.6%	0.8%	p=0.612
- Melperone	1.6%	2.4%	p=0.727
- Ciamemazine	1.6%	3.9%	p=0.385
- Risperidone	1.6%	3.9%	p=0.385
- Carbamazepine anticonvulsant	3.2%	0.8%	p=0.215
- Angiotensin-converting enzyme inhibitors	31.7%	25.2%	p=0.342
• **65-74**	8.3%	29.2%	p=0.162
• **75-84**	37%	25%	p=0.190
• **>85**	37.5%	23.4%	p=0.166
- Amiodarone	4.8%	3.9%	p=0.790
- Nonsteroidal anti-inflammatory agentes	4.8%	7.9%	p=0.420
Pneumonia	46.0%	65.4%	p=0.011 OR=0.452 (0.244 to 0.837)
• **65-74**	41.7%	54.2%	p=0.486
• **75-84**	37%	62.5%	p=0.030
• **>85**	58.3%	74.5%	p=0.167
Diarrhea	6.3%	1.6%	p=0.077
Heart failure	27.0%	28.3%	p=0.844
Advanced renal failure	12.7%	10.2%	p=0.611

ADH = antidiuretic hormone, OR= Odds Ratio, SIADH = Syndrome of Inappropriate Antidiuretic Hormone Secretion

Table 4 – Number of drugs in different groups			
Number of drugs	**Study Group (%)**	**Control (%)**	
0	17.5%	35.4%	p=0.022
1	12.7%	22.8%	
2	30.2%	22.8%	
3	27.0%	12.6%	
4	9.5%	4.7%	
5	1.6%	0.8%	
6	1.6%	0.8%	
Mean of drugs	2.1	1.3	p<0.001

FIGURES

Figure 1 – Distributions oh hyponatremia cases by serum sodium concentration

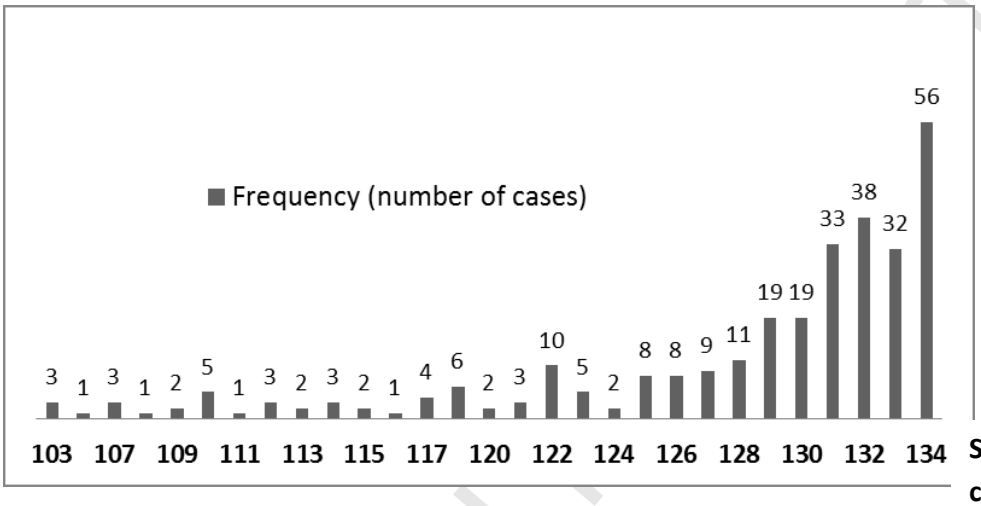
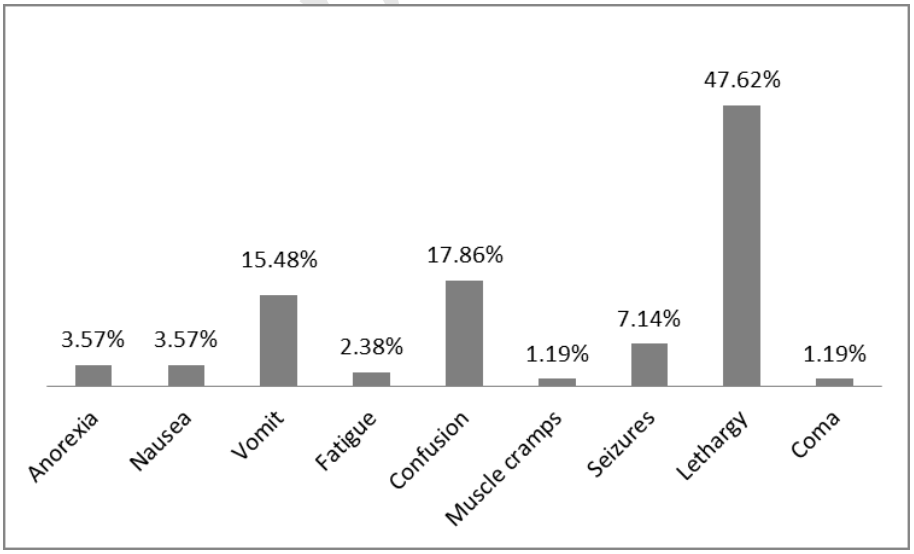


Figure 2 – Clinical manifestations of patients with severe hyponatremia



ACKNOWLEDGEMENTS

We are indebted to Margarida Marques from the Technology and Information System Department of Centro Hospitalar e Universitário de Coimbra – Hospitais da Universidade de Coimbra, for assistance in the statistic preparation of the manuscript.

REFERENCES:

[1] Adrogué H, Madias N. Hyponatremia. N Engl J Med, 2000;342:1581-1590.

[2] Singer GG, Brenner BM, Robertson GL: Hyponatremia. In Harrison's Principles of Internal Medicine,18th edition, edited by Kasper DL, Fauci AS, Brauwald et al, McGraw-Hill,2012, 45:731-736.

[3] Kugler P, Hustead T. Hyponatremia and Hypernatremia in the Elderly. Am Fam Physician 2000;61:3623-30

[4] Sterns RH. Causes of hyponatremia. UpTodate 2012.

[5] Manifestations of hyponatremia. UpTodate 2012.

[6] Sterns RH. Evaluation of the patient with hyponatremia. UpTodate 2012.

[7] Miller Myron. Hyponatremia in the Elderly: risk factors, clinical consequences, and management. Clinical Geriatrics 2009; Vol 17 (9);34:39.

[8] Burton R. Pathophysiology and etiology of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). UpTodate 2012.

[9] Sterns RH. Diuretic – induced hyponatremia. UpTodate 2012.

[10] Taylor D, Paton C, Kapur S. The Maudsley Prescribing Guidelines in Psychiatry. Wiley-Blackwell Eleventh Edition. 148-149.

[11] Yawar A, Jabbar A, Haque NU, et al. Hyponatraemia: etiology, management and outcome. J Coll Physicians Surg Pak. 2008 Aug;18(8):467-71.

[12] Ogundipe OA. Hyponatremia associated with the use of a proton pump inhibitor. Scottish Medical Journal 2009 54(1): 58

[13] Spital A. Diuretic-Induced Hyponatremia. Am J Nephrol 1999;19:447-452.

[14] Blijderveen J, Straus S, Rodenburg E, Zietse R, et al. Risk of hyponatremia with diuretics: chlorthalidone versus hydrochlorothiazide. Am J Med. Published Online: May 05, 2014.

[15] Spironolactone Side Effects. www.drugs.com

[16] Gankam-Kengne F, Ayers C, Khera A, Lemos J, Maalouf N. Mild hyponatremia is associated with an increased risk of death in an ambulatory setting. Kidney International 2013, 83:700-706.

[17] Mohan S, Gu S, Parikh A, Radhakrishnan J. Prevalence of hyponatremia and association with mortality: results from NHANES. Am J Med. 2013 Dec;126(12):1127-37

FIGURES

Figure 1 – Distributions oh hyponatremia cases by serum sodium concentration

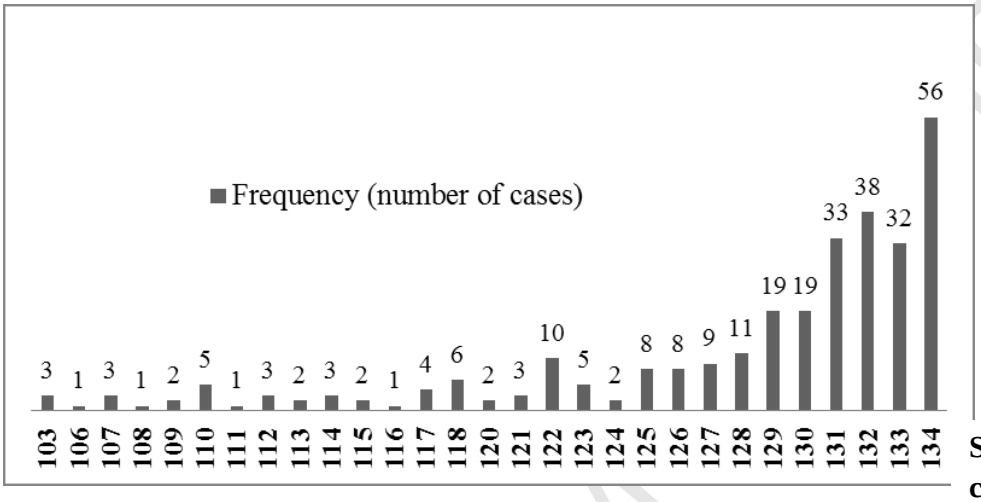


Figure 2 – Clinical manifestations of patients with severe hyponatremia