Proceeding S.Z.P.G.M.I. Vol: 4 (1990), pp. 16-20.

Hospital Associated Hyponatremia

Tahir Shafi, Riaz Ahmad, and Shahid Ahmad.
Department of Nephrology and National Health Research Complex,
Shaikh Zayed Postgraduate Medical Institute Lahore

SUMMARY

Out of 7843 hospitalized patients 342 (4. 36%) have serum electrolytes abnormalities. Hyponatremia was the most common which was seen in 3.45% of al patients and 79.2% of 342 patients with serum electrolyte abnormalities. 73.4% had mild hyponatremia (serum sodium concentration 121-130 mEq/L) 53 patients (9.6%) had moderate hyponatremia , (serum sodium concentration 111-120 mEq/L) and 19 patients (7%) had severe hyponatremia (serum sodium 110 mEq/L or less). Advanced renal failure was the most common cause while gastrointestinal problems with vomiting diarrhoea, congestive heart failure, liver disease, post-operative states, and i.v. fluid administration were other frequent causes. Mildly hyponatremic patients were usually asymptomatic but progressive symptomatology appeared with further decline of serum sodium concentration. Cerebral symptoms were seen in 8% of patients with mild hyponatremia 53% of cases with moderate and 84% of cases with severe hyponatremia. 9 patients with hyponatremia died, mortality being 3.3%.

INTRODUCTION

Sodium is the major cation in the extra-cellular fluid. Under normal circumstances sodium with accompanying anions make up majority of plasma osmolality. Changes in the serum and extra-cellular fluid sodium level will result in changes in serum and extra cellular fluid osmolality which in turn will cause shift of water across the cell membrane. If there is increase in serum sodium and serum osmolality water would shift out of cells into extra-cellular fluid compartment and if there is decrease in serum sodium and osmolality the water will move into the cell causing cell swelling. The effects of this cell swelling are best appreciated in the brain. Since brain is encased in a rigid structure, cell swelling will result in increased intracranial pressure and its consequences.

Hyponatremia is probably the most commonly reported electrolyte disorder seen in hospitalized patients[1]. It is not only a frequent occurrence but it is also associated with substantial morbidity and mortality [1-6].

This prospective study was done to find incidence, causes of hyponatremia in our hospitalized patient and to see if there is any correlation between symptoms and serum sodium level.

PATIENTS AND METHODS

This study includes the patients who were admitted at Shaikh Zayed Hospital, during 5 months from April, 1988 till August 1988. Most of these patients had serum electrolytes done at admission or during hospital stay. Daily laboratory reports were reviewed. The new patients who were found to have serum sodium of 130 mEq/L or less were seen. History was taken with special emphasis on previous medical illness, drug intake, dietary habits, and also present symptoms particularly related to hyponatremia like lethargy, confusion, obtundation, coma and seizures. Physical examination was done with special emphasis on their volume status and neurological manifestations. These patients were followed up with serial serum electrolyte determinations.

Blood urea, creatinine, blood sugar, complete urine analysis, urine electrolytes were done. Chest x-ray, electrocardiogram and liver function tests were performed. In addition to these, other investigations were requested as indicated. Normal serum sodium concentration was taken as 131 to 150 mEq/L. Levels below or above that range were considered hyponatremic and hypernatremic respectively.

The patients with hyponatremia were divided into 3 groups, mild, moderate and severe hyponatremia. In mild hyponateremia group patients had serum sodium between 121 to 130 mEq/L, in moderate hyponatremia group serum sodium was 111 to 120 mEq/L and in severe hyponatremia serum sodium was 110 mEq/L or less than that. Symptoms of these patients in each group were noted. Normal serum potassium values were taken

3.5mEq/L to 5 mEq/L. Hyperkalemia was diagnosed when serum potassium level was above 5.0 mEq/L.

RESULTS

During five months period 7843 patients were admitted at Shaikh Zayed Hospital. Out of these 342 patients had or developed serum electrolyte abnormalities during hospital stay. The frequency of different electrolytes abnormalities is shown in Table 1.

Table 1: Frequency of Different Serum Electrolyte Abnormalities

Hyponatremia only	162	2.06%
Hyponatremia and hypokalemia	94	1.20%
Hyponatremia and hyperkalemia	15	0.19%
Hypokalemia only	51	.65%
Hyperkalemia only	18	0.23%
Hypernatremia only	3	0.04%
All hyponatremia	271	3.45%
All hypokalemia	145	1.85%
All hyperkalemia	33	0.42%

Hyponatremia was seen in 271 patients i.e 3.45% of all patients and 79% of the patients with serum electrolyte abnormalities. Table 2 shows age and sex distribution of the patients with hyponatremia. 56 patients were in fifth and 84 patients were in sixth decade. Thus 52% of these patients belonged to age group between 41 and 60 years. 170 patients were male and 101 patients were female. Frequency of hyponatremia according to severity is shown in Table 3 73.4% of the patients had mild hyponatremia. 19.6% had moderate hyponatremia and 7.0% had Severe hyponatremia.

Table 2: Age And Sex Distribution Of Patients With Hyponatremia

Age group	Male	Female	Total
0-10 years	5	5	10
11-20	11	9	20
21-30	30	11	41
31-40	10	10	20
41-50	38	18	56
51-60	52	32	84
61-70	17	13	30
>70	7	3	10
Total	170	101	271

Different causes of hyponatremia seen in these patients are shown in Table 4. Most frequent clinical setting associated with hyponatremia was advanced renal failure. 89 patients had moderate to severe renal insufficiency. Next most common cause was gastrointestinal problems associated with vomiting and or diarrhoea which was seen in 43 patients. 34 patients with congestive heart failure 22 patients with liver diseases mainly cirrhosis with ascites and hepatitis with liver failure had hyponatremia. 21 patients with surgical conditions like intestinal obstruction, trauma or during post operative period developed hyponatremia. In 18 patients hyponatremia occurred due to intravenous fluid administration which were given due to lack of oral intake for different reasons. 14 patients had malignant disease. 6 of these had high urine specific gravity and high urine sodium. 4 patients had hyperglycemia, two of them were getting chlorpropamide. Two patients with pulmonary tuberculosis also had hyponatremia with high urine specific gravity and high urine sodium. One patient with hyponatremia had hypothyroidisim. In one patient hyponatremia developed following mannitol administration. Table 5 shows the volume status of these patients. 141 patients (Renal failure 89, CCF 34, Liver disease 22) presented with edema or fluid overload. 66 patients had evidence of volume depletion (vomiting, diarrhoea 43, lack of oral intake 18, diuretics 5) 64 patients were euvolemic.

Table 3: Frequency Of Hyponatremia According To Severity

Mild hyponatremia (serum sodium 121-130 mEq/L)	199	73.4%
Moderate hyponatremia (serum sodium 111-120 mEq/L)	53	19.6%
Severe hyponatremia (serum sodium 110 mEq/L or less)	19	7.0%

Table 4: Causes Of Hyponatremia

Renal failure	89
Gastrointestinal problems with diarrhoea & vomiting	43
CCF	34
Liver disease (cirrhosis and other)	22
Post-operative	21
I.V fluids	18
Malignant disease	14
Diuretics	5
Hyperglycemia	4
Pulmonary tuberculosis	2
Hypothyroidism	1
Mannitol	1
Undetermined	17
Total	271

Table 5: Volume status

Hypervolemic or edematous	141	52%
Hypovolemic	66	23.6%
Euvolemic	64	22.4%

Table 6: Symptoms Associated With Different Groups Of Hyponatremia

	Mild	Moderate	Severe
	199	53	19
Alert	112	11	1
Lethargy, Weakness	71	14	2
Confusion	12	12	4
Stupor	3	12	6
Coma	1	3	5
Fits	-	1	1

Table 6 shows symptoms seen in these patients. 84% of patients with severe hyponatremia, 53% of patients with moderate hyponatremia and 8% of patients with mild hyponatremia had CNS symptoms. 3 patients out of 53 with moderate hyponatremia, 3 patients out of 19 with severe hyponatremia and one out of 199 with mild hyponatremia died. In most of these cases hyponatremia was responsible for death directly or indirectly.

DISCUSSION

Hyponatremia is a common occurrence in hospitalized patients. It is probably the most common of all electrolyte abnormalities [1-6]. Owen and Campbell in 1968 reported that mean plasma sodium concentrations are 5 to 6 mEq/L lower in hospitalized patients, than in healthy out-patient control subjects [7]. In an other study daily incidence and prevalence rates of hyponatremia were reported to be 1% and 2.5% respectively in hospitalized patients in general medical/ surgical wards [1]. Devita reported 27% incidence of hyponatremia in 196 patients admitted in intensive care unit.[8]. We found incidence of hyponatrema 3.45% in the hospitalized patients. It was most frequently encountered electrolyte abnormality. Hyponatremia was present in 3.45% of cases, hypokalemia in 1.75%, hyperkalemia in 0.42% and hypernatremia in 0.04% cases. Out of 342 patients with electrolyte abnormalities hyponatremia was present in 271 i.e. 79%.

Serum sodium concentration is determined by the external balance of water which is maintained by a precise interplay between water intake and water excretion. Water intake is controlled by variation in the thirst mechanism and both the availability and ability of individual to ingest water. The excretion of water is controlled by regulation of antidiuretic hormone (ADH) released by hypothalmo-hypophyseal system, adequate response of renal tubule to the hormone and intact renal mechanisms to concentrate and dilute the urine. Thirst is controlled by osmoreceptors and by intravascular volume [9-10]. Baroreceptor input may modulate the osmoreceptor regulation of thirst in the same manner as they do the osmoreceptor regulation of ADH. It appears now that the rennin angiotensin system is the primary pathway regulating volume mediated thirst responses.[11].

Hyponatremia and hypo-osmolality will lead to suppression of thirst. The patient will reduce the intake of water which will prevent worsening of hyponatremia. But when patients have continued water intake orally or as I.V. hypotonic fluids this protective mechanism is bypassed. I.V. fluid administration was responsible for hyponatremia in approximately 7% of the cases in the present study.

Appropriate elimination of excess of ingested water requires suppression of ADH in response to hypo-osmolality. Continued secretion of ADH even in the presence of hypoosmolality will lead to retention of water and persistence of hyponatremia [12]. Various nonosmotic stimuli such as status of extracellular fluid and blood volume, emotional status, pain and B-adrenergic stimulation, nicotine use, and decreased cardiac output, may increase ADH release [13-16]. Clinical conditions associated with such stimuli include cardiovascular instability, volume depleted states, nephrotic syndrome, liver disease like cirrhosis, other hypoprotenemic states, post operative states, glucocorticoid deficiencies, hypothyroidism and certain malignancies [17-19]. In this study in 48 cases with volume depletion (43 due to gastrointestinal losses and 5 due to diuretics), 56 edematous cases, (34 congestive heart failure and 22 liver disease) 14 cases with malignancies, 2 with pulmonary tuberculosis and with hypothyroidsm, these non osmolar stimuli for ADH release would have contributed to the development of hyponatremia.

A variety of drugs stimulate ADH release. These include narcotics, chlorpropamide, vincristine, clofibrate and anticonvulasants. 2 of our patients were receiving cholorpropamide which probably was responsible for hyponatremia in these cases [20].

The intrarenal mechanisms which determine the ability of kidney to excrete free water and to form dilute urine in response to changing levels of ADH are important to prevent hyponatremia. The ability to excrete free water in the absence of ADH is dependent upon three factors:-

1. Adequate delivery of tubular fluid to the distal nephron and thus into the urine. Distal delivery in turn depends on (a) normal glomerular filtration rate. (b) normal proximal tubular fluid reabsorption. If the glomerular filtration rate is reduced or proximal tubular reabsorption of sodium is increased distal delivery of filtrate would be diminished and hence the ability to excrete adequate amounts of dilute urine is decreased.
2. Adequate function of the ascending limb of loop of Henle. In this segment of nephron chloride and sodium is reabsorbed and water is not and thus dilute urine is formed. Patients who are receiving loop diuretics have impairment of this function.
3. Hypotonic fluid thus formed must escape water reabsorption while it passes through the hypertonic meddulla. This requires little or no circulating ADH activity. Thus as is well known, excessive water intake in the presence of renal failure leads to water retention, positive water balance and hyponatremia. 89 patients i.e. 33% had hyponatremia in this study associated with renal failure. Patients with chronic renal failure are able to dilute the urine if ADH is adequately suppressed, but the free water excretion is impaired due to marked decrease in the number of functioning nephrons.

In normovolemic patient hyponatremia can occur due to syndrome of inappropriate secretion of ADH (SIADH). This syndrome has been characterized by the presence of hyponatremia with hyposmolality, urine that is less than maximally dilute and continued sodium excretion in the presence of hyponatremia, absence of edema and normal renal adrenal and cardiovascular function. SIADH has been recognized in number of diseases like malignant tumors, disorders of central nervous system, and pulmonary infections, [21]. 6 patients with different malignancies and two patients with pulmonary tuberculosis in this study probably had SIADH.

Hyponatremia is also associated with hypertonic states. Where an impermeant solute (effective osmale) other than sodium is circulating in the plasma in high concentration. It will draw water from intracellular fluid which is low in sodium, into extracellular fluid to maintain osmotic equilibrium across cell membranes. This will dilute the sodium concentration in extracellular fluid. Glucose and mannitol are most often responsible for such hyponatremia, [22,23]. Two patients with hyperglycemia and one patient after mannitol administration developed hyponatremia in this study. For each one hundred milligram per deciliter rise in blood glucose or mannitol level serum sodium has been reported to drop by 1.6 mEq/L.[22].

The clinical features of hyponatremia are due to decline in plasma osmolality resulting in water movement into the brain. The usual symptoms are nausea, malaise, lethargy, coma and seizures. Hyponatremia related seizures are almost always generalized and decrease in frequency as serum sodium rises. Patient with primary seizure disorders manifest increased frequency if hyponatremia is induced [6].

Confusion lethargy stupor and rarely coma usually preceede the onset of seizures. Onset of seizures is usually associated with further decline in level of consciousness. 49% (out of 23) with acute hyponatremia hard seizures. Their mean serum sodium was 107 mmol/L vs 112 mmol/L [6].

The occurrence of neurological manifestation associated with hyponatremia correlates with high mortality when compared to asymptomatic patients. Neurological manifestations of seizures, stupor and coma within symptomatic group have not been found to predict out come of treatment [6]. The presence and severity of these clinical manifestations depend upon the level of serum sodium and rapidity of development of hyponatremia. Cerebral manifestations are usually absent when the concentration of serum sodium is higher than 125 mEq/L, while progressive symptomatology may appear when the level of sodium falls below 115 mEq/L. Arrieff et.al found a gross correlation between the decrease in serum sodium concentration and the presence of cerebral manifestations. We found that 84% of the patients with serum sodium less than 110 meq/L and 53% of cases with serum sodium 111-120 mEq/L have cerebral symptoms. Thus although there is some overlap but still a gross correlation between the decrease in serum sodium concentration and the presence of cerebral manifestations is present as reported by others [4,24-27]. Mild hyponatremia is usually asymptomatic with little increase in morbidity and mortality. Many patients with hyponatremia are extremely sick with advanced heart, liver, renal , lung disease or advanced cancer. The consistently higher mortality in hyponatremic than in

normonatremic likely reflects the nature and severity of the underlying disease process [1,2,28]. In this study we found mortality 3.3% while mortality as high as 50% has been reported in patients who had a rapid fall of serum sodium concentration below 113 mEq/L by Arrief et al [4]. The nature and severity of underlying disease state, the magnitude and the rate of decline of serum sodium concentration appears to be major determinations of outcome in hyponatremia patients.

ACKNOWLEDGEMENT

The authors are thankfull to Prof. Alvi, DR. Naseem R. Khan and other members of department of Biochemistry for their help.

REFRENCES

1. Anderson RF, Chung HM, Kluge R, Schrier Rw. Hyponatremia a prospective analysis of its epidemilogy and the pathogenetic role of vasiopression.Ann Inter Med. 1985; 10: 164-8.
2. Ayus JC, Krothapalli RK, Arieff AC. Changing concepts in the treatment of severe symptomatic hyponatremia. Rapid correction and the possible relationship to central pontine mylinosis. Am J Med 1983; 78: 897-902.
3. Ashraf H, Locksley R, Arieff Al: Thiazide induced hyponatremia associated with death or neurological damaghe in outpatients. Am J Med 1981; 70:1163-8.
4. Arieff AL, Liack F, Massry SG: Neurological manifestations and morbidity of hyponatremia. Correlation with brain water and electrolytes. Medicine 1976; 55:121-9.
5. Defornzo RA, their SO: Pathophysilogic approach to hyponatemia. Arch Intrn Med 1980; 141:897-902.
6. Arieff AL: Effects of water, electrolyte and acid base disorders on the central nervous system. In: Arrief AL, DeFronzo RA, eds. Fluid electrolyte and acid base disorders. New York: Churchill Living Stone, 1985; 969-1040.
7. Dwen JA, Campbell DG: A comparison of plasma electrolyte and urea values in healthy persons and in hospital patients. Clin Chim Acta 1968; 22:611-8.
8. Devita MV, Konecky A, et al: Pathophysiologic machanisims of hyponatremia in critically ill patients. Kidney Intrn. abstract 1989; 35:216.
9. Anderson B: Regulation of water intake. Physiol Rev 58:1978: 582-3.
10. Fitzsimmons JI: The physiological basis of thirst. Kidney Intrn 1970: 10:3-8.
11. Epstein AN: The phsiology of thirst. Can J Physiol Pharmacol 1976; 54:639.
12. Schrier RW, Berl T, Anderson RF: Osmotic and nonosmotic control of vasopressin release. Am J Physiol 1979; 236:F321-32.
13. Berl T, Harbottle JA, Schrier RW: Effects of alpha and beta adrenergic stimulation of renal water excretion in normal subjects and patients with diabetes insipdis. Kidney Int 1974:6:247.
14. Schrier RW.Berl T, Anderson RJ, McDonald KM: Humoral. neural and hemodynamic influences on renal water excretion. In:Moses AM, Share L, eds. Neuro-hypophysis. Basel: Karger. 1977.
15. Candnapaphronchai P. Boykin JL, Berl, Mcdonald KM. Schrier RW: Mechanism of effect of nicotine on renal water excretion Am J Physiol 1974; 227:1216.
16. Anderson RJ. Cadnapaphornchai P. Harbottle JA. Mcdonald KM, Schrier RW: Mechanism of effect of thoracic inferior vena cava construction on renal water excretion. J Clin Invest 1974; 54:1473-9.
17. Bichet D, Schrier RW: Water metabolism in edematous disorders. Semin Nephrol 1984; 4:325-33.
18. Bichet DG, Van Putten VJ, Schrier RW: Potential role of increased sympathetic activity in impaired sodium and water excretiuon in cirrhosis. N Eng J Med 1982; 307:1152-7.
19. Rose CE JR, DIXON BS, Anderson RJ: Water metabolism in respiratory disorders. Semin Nephrol 1984; 4:295-300.
20. Miller M, Moses AM: Drug induced states of impaired wate excretion. Kidney Int 1976; 10:96.
21. Martine-MalDonado M. Nephrology forum: Inappropriate antidiuretic hormone secretion of unknown origin. Kidney Int 1980; 17:554-67.
22. Katz M. Hyperglycemia-induced hyponatremia-calculation of expected serum sodium depression. N Eng J med 1973; 289:843
23. Aviram A, Pfau A, Czaczkes JW, Ullmann TD: Hyperosmolality with hyponatremia caused by inappropriate administration of mannitol. Am J Med 1967; 42:648.
24. Anderson RJ: Nephrology forum: Hospital associated hyponatremia. Kidney Int 1986; 29:1239-47.
25. Swanson Ag, Iseri OA: Acute encephalopathy due to water intoxication. N Engl J Med 1958; 258:831-4.
26. Wynn V.Water intoxication and serum hypotonicity. Metabolism 1956; 5:490-9.
27. Logothetis J: Neurological effects of water and sodium disturbances. Postgrad Med J 1966; 42:621-9.
28. Baran D, Hutchinson TA. The outcome of hyponatremia in a general hospital population. Clin Nephrology 1984; 22:72-6.

The Authors:

Prof. Tahir Shafi
Department of Nephrology,
Shaikh Zayed Postgraduate Medical Institute,
Lahore.

Riaz Ahmad.
Department of Nephrology.
Shaikh Zayed Postgraduate Medical Institute,
Lahore.

Shahid Ahmad.
National Health Research Complex.
Shaikh Zayed Postgraduate Medical Institute
Lahore.

Author's Address:

Prof. Tahir Shafi
Department of Nephrology,
Shaikh Zayed Postgraduate Medical Institute,
Lahore.