Clinical Study

American Journal of Nephrology

Am J Nephrol 2000;20:37–41

Received: February 10, 1999
Accepted: July 22, 1999

Hyponatremia in Acute-Phase Response Syndrome Patients in General Surgical Wards

Daniel Ferreira da Cunha Jacqueline Pontes Monteiro
Vitorino Modesto dos Santos Frederico Araújo Oliveira
Selma Freire de Carvalho da Cunha

Nutrition Division, Department of Internal Medicine, Medical School of Uberaba, Brazil

Key Words

Acute-phase response syndrome · Hyponatremia · Hypoalbuminemia · Surgical patients

Abstract

Background: In surgical patients, hypoalbuminemia may occur as a component of acute-phase response (APR) syndrome, which we hypothesized could decrease serum sodium levels. ***Aim:*** To compare the frequency of hyponatremia in adult surgical inpatients with or without APR syndrome. ***Methods:*** All the simultaneous plasma sodium and albumin results (n = 168), obtained from adults in surgical wards and corresponding to a 6-month period, were searched in the hospital mainframe. Other relevant laboratory and clinical data were also registered. APR was ascertained by the presence of major physical trauma, surgery or infection, plus hypoalbuminemia (serum albumin <3.5 g/dl) and neutrophil left shift (≥7% of band count) associated with peripheral leukopenia (white blood cells <4,000/mm^3) or leukocytosis (WBC >9,000/mm^3). Hyponatremia was defined by serum sodium concentration <135 mEq/l. ***Results:*** APR-positive patients (n = 113) had lower blood hemoglobin (10.92 ± 2.18 vs. 13.53 ± 2.30 g/dl), and serum albumin levels (median, range: 2.8, 1.9–3.4 vs. 3.7, 3.5–4.2 g/dl) than APR-negative (n = 55) ones, the same occurring in relation to antibiotics (54.8 vs. 10.9%) and intravenous 5% dextrose in water (55.7 vs. 20.0%) or isotonic saline (46.0 vs. 9.1%) infusion. The hyponatremia frequency was higher among APR-positive patients (31.0 vs. 10.9%). ***Conclusion:*** The higher percentage of hyponatremia among APR-positive patients could be attributed to decreased serum albumin levels associated with APR.

Introduction

Surgical patients often have hyponatremia, a condition characterized by high levels of circulating antidiuretic hormone (ADH) and attributed to stress and concomitant infusion of excessive amounts of 5% dextrose in water (D5W) or hypotonic saline [1]. However, euvolemic hyponatremia may also develop in surgical patients after infusion of isotonic saline, a situation associated with increases in ADH, which promote sodium excretion despite low sodium serum levels [2]. Third spacing of fluids and volume contraction can also cause hyponatremia in surgical patients; nonetheless, isotonic saline administration, which can enhance extracellular fluid volume, often fails to increase serum sodium levels [2, 3].

Acute-phase response (APR) syndrome is a complex, nonspecific, systemic adaptive response commonly seen

KARGER

Fax + 41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0250–8095/00/0201–0037$17.50/0

Accessible online at:
www.karger.com/journals/ajn

Daniel Ferreira da Cunha, MD
Nutrition Division, Department of Internal Medicine
Medical School of Uberaba, Getúlio Guaritá s/n. 38025-180
Uberaba, MG (Brazil)
Tel. +55 (034) 318 5335, Fax +55 (034) 318 5335, E-Mail dfcnutro@mednet.com.br

in surgical and trauma patients, mainly when associated with infection [4]. APR is a cytokine-driven process that can be clinically characterized by anorexia, fever, blood neutrophilia, hyperglycemia, anemia and hypoferremia, besides increased hepatic production of acute-phase proteins, including C-reactive protein, ferritin and fibrinogen [4–6]. At the same time, patients with APR often have a decrease in serum albumin concentration, which is primarily caused by reduced albumin liver synthesis and enhanced endothelial permeability, with albumin passage from the vascular into extravascular space [5, 7].

As occurs in nephrotic syndrome or cirrhosis, APR-associated hypoalbuminemia may be connected with decreased colloid oncotic pressure, which causes interstitial sodium and water retention, relative hypovolemia and increases in aldosterone and ADH secretion and/or activities [8]. In addition to poor intravascular retention of administered fluids, these hormonal changes lead to a positive body water balance, besides progressive dilution of cells and other solid components of plasma, including erythrocytes, albumin and sodium, the main intravascular cation [8]. Therefore, because most surgical APR-positive patients would have a decrease in albumin serum levels, we hypothesized that those patients could show a higher frequency of hyponatremia than APR-negative ones. The aim of this study was to compare the frequency of hyponatremia in adult surgical hospitalized patients with or without APR syndrome.

Patients and Methods

The study was conducted at a 400-bed teaching hospital of the Medical School of Uberaba (Brazil), after official approbation by the institutional Ethic Committee board. All the simultaneous plasma sodium and albumin biochemical determinations (n = 288), obtained from adults in surgical wards and corresponding to a 6-month period, were searched in the hospital mainframe.

When a patient had more than one sodium and albumin determination, only the first biochemical results were analyzed. In order to better describe other laboratory parameters, cases without concomitant total proteins, glucose, urea, creatinine, potassium, calcium, phosphorus, magnesium and blood cell count determinations were not included. Other exclusion criteria were patients with clinical or laboratory findings suggestive of hepatic cirrhosis or nephrotic syndrome, as well as those receiving diuretics, total parenteral nutrition or intravenous albumin supplementation.

Charts of the remaining 168 patients were perused to obtain relevant clinical details and the diagnoses registered when the blood samples to determine albumin and sodium were taken. Age, gender, color and the presence of edema, fever, vomiting or diarrhea were also registered. Other parameters added to the database were the concomitance of intravenous glucose (D5W) or isotonic saline infusions, length of hospital stay and mortality rate.

APR syndrome was ascertained by the presence of major physical trauma, surgery or infection plus hypoalbuminemia (serum albumin <3.5 g/dl) and peripheral leukopenia (white blood cells $<4{,}000/mm^3$) or leukocytosis (WBC $>9{,}000/mm^3$) with neutrophil left shift ($>7\%$ of band count). Diabetes mellitus was ascertained by previous diagnosis or by the finding of two or more fasting glucose serum levels of 126 mg/dl (7.0 mmol/l) or higher [9]. Renal insufficiency was established by previous diagnosis or serum creatinine values higher than 1.5 mg/dl. Hyponatremia was defined by serum sodium concentrations <135 mEq/l.

All serum measurements were made using an ion-selective electrode Automatic Chemical Analyzer, model Cobas Mira Plus® (Roche Diagnostic Systems Inc., Branchburg, N.J., USA). The laboratory reference ranges were 135–148 mEq/l for sodium, 2.0–4.8 mg/dl for phosphorus, 1.9–2.5 mg/dl for magnesium, 8.5–10.4 mg/dl for calcium, 3.5–5.5 mEq/l for potassium, 70–115 mg/dl for glucose and 3.5–5.0 g/dl for albumin.

Numerical variables with normal distribution were expressed as means ± standard deviation; differences among patients with APR and without APR were compared by the nonpaired t test. The Mann-Whitney test was applied to compare nonhomogeneous numerical data that were expressed as median, minimum and maximum values (range). The χ^2 or Fisher's exact tests were performed to compare frequencies. Pearson's correlation coefficients were determined for serum albumin and sodium. Probabilities (p) less than 0.05 were considered significant.

Results

Most of the 55 APR-negative patients were in preoperative preparation for elective surgery. A hundred thirteen (67.3%) APR-positive patients did not differ, respectively, from those classified as APR-negative in relation to age (54.0 ± 16.6 vs. 55.4 ± 15.6 years) and white color predominance (68.1 vs. 78.2%). There was a male predominance in both groups, but there were only 54% of males in the APR-positive group, in contrast to 70.9% of males in APR-negative patients (p = 0.04). APR-positive patients had a longer (median, range) hospital stay (25, 2–99 days) than APR-negative ones (14, 4–58 days), but mortality was statistically similar (8.0 vs. 3.6%).

Diabetes mellitus was diagnosed in 14.5% of APR-negative and 20.3% of APR-positive patients (p = 0.45). APR-positive patients had a higher frequency of peritonitis, appendicitis, acute suppurative cholecystitis, acute pancreatitis and other inflammations/infections (34.5 vs. 5.4%), the same occurring with wound infection and abdominal wall dehiscence (15 cases, all in the APR-positive group).

There were no statistical differences between APR-positive and APR-negative patients in relation to diagnosis of malignant neoplasms (15.9 vs. 16.4%), cholelithiasis (16.4 vs. 8.8%), peripheral atherothrombotic vascular dis-

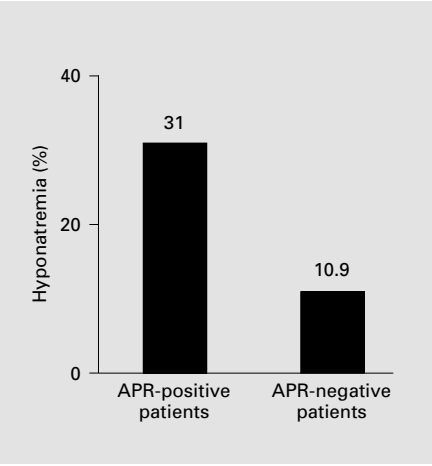

Fig. 1. Frequency (%) of hyponatremia in APR-positive (n = 113) and APR-negative (n = 55) patients in general surgical wards ($\chi^2 = 8.1$; $p < 0.01$).

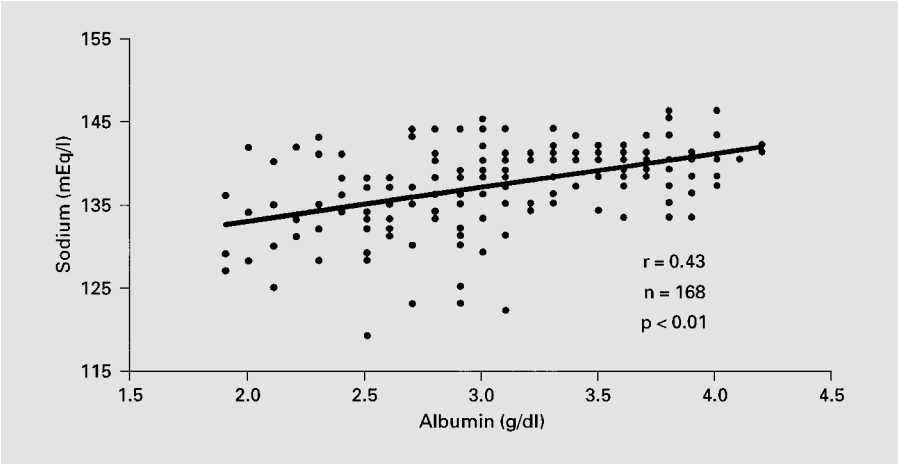

Fig. 2. Pearson's correlation between serum albumin and sodium levels of 168 adults hospitalized in general surgical wards.

Table 1. Peripheral leukocyte and band counts, hemoglobin, total protein, albumin and sodium serum levels of APR-positive and APR-negative patients in general surgical wards

Parameter	APR-positive (n = 113)	APR-negative (n = 55)
Leukocytes, cells/mm^3	10,700 (1,700–43,200)	8,400 (3,100–19,500)
Total bands, cells/mm^3	194 (17–5,184)	97 (31–890)
Hemoglobin, g/dl	10.92 ± 2.18	13.53 ± 2.30
Total protein, g/dl	6.0 (3.5–8.1)	6.9 (5.4–8.2)
Albumin, g/dl	2.8 (1.9–3.4)	3.7 (3.5–4.2)
Sodium, mEq/l	135.97 ± 5.28	139.73 ± 4.32

All differences between groups are significant, $p < 0.01$.

orders (12.7 vs. 9.7%), chagasic megacolon (5.4 vs. 10.6%), megaesophagus (10.9 vs. 5.3%) or renal insufficiency (16.8 vs. 9.1%).

The percentage of patients receiving one or more antibiotics was greater among APR-positive (58.4%) than APR-negative (10.9%) ones, the same occurring in relation to intravenous D5W (55.7 vs. 20.0%) and isotonic saline (46.0 vs. 9.1%) infusion. APR-positive patients had a higher frequency of edema than APR-negative patients (9.7 vs. 1.8%).

There were no significant differences between APR-positive and APR-negative patients in relation to serum (mg/dl) glucose (median, range: 99.0, 43–475 vs. 99.0, 78–275), urea (30.0, 5–335 vs. 30.0, 7–865), creatinine (mean ± SD: 1.34 ± 1.5 vs. 1.30 ± 1.71 mg/dl), phosphorus (3.45 ± 1.20 vs. 3.65 ± 1.00 mg/dl) and potassium (4.2, 2.4–6.2 vs. 4.3, 2.8–5.8 mEq/l).

Serum calcium (8.69 ± 1.13 vs. 9.45 ± 1.05 mg/dl) and magnesium (1.62 ± 0.44 vs. 1.86 ± 0.34 mg/dl) were statistically lower among APR-positive patients. Laboratory data suggestive of APR syndrome were commoner in the APR-positive group, including lower hemoglobin values (10.92 ± 2.18 vs. 13.53 ± 2.30 g/dl), higher leukocytes (median, range: 10,700, 1,700–43,200 vs. 8,400, 3,100–19,500 cells/mm^3) and total band counts (194, 17–5,184 vs. 97, 31–890 cells/mm^3).

Hyponatremia occurred in 41 cases (24.4% of total), with a higher frequency in APR-positive (31.0%) than in APR-negative (10.9%) patients (fig. 1) and a relative risk of 2.84 (95% confidence interval 1.27–6.34, $p < 0.01$).

The correlation of serum albumin and sodium levels was positive and significant ($r = 0.43$; $p < 0.01$; fig. 2). Hyponatremic (n = 24) and nonhyponatremic (n = 127) patients showed similar (median, range) urea (30, 8–302 vs. 30, 5–335 mg/dl) and creatinine (1.0, 0.4–6.7 vs. 0.9, 0.2–4.9 mg/dl) serum levels, respectively. All cases (n = 6) with serum sodium levels ≤ 125 mEq/l were in the APR-positive group.

Discussion

This study showed a high percentage of hyponatremia (24.4%) among general surgical ward patients, with a higher risk of hyponatremia for those displaying the APR syndrome. APR-positive patients received more antibiotics and D5W or isotonic saline infusion, had lower blood hemoglobin and albumin and total protein serum levels than APR-negative ones. These findings, together with the longer hospital stay suggest that APR-positive patients had worse clinical conditions, in accordance with the increased morbidity and mortality in hyponatremic patients [1, 10, 11].

Hyponatremia occurs when the kidneys are unable to excrete free water excess or the urinary loss of sodium exceeds the intake [1, 10]. Inappropriate secretion of ADH is thought to be the cause of decreased serum sodium levels in surgically stressed patients receiving isotonic saline or D5W [2, 12], and decreased sodium serum levels have been associated with vomiting and diarrhea [1], transsphenoidal surgery [13], transurethral resection of the prostate [14] and transcervical endometrial resection [15].

In general clinical wards, hyponatremia has been registered in conditions often associated with hypoalbuminemia, including nephrotic syndrome, cirrhosis, protein-losing gastrointestinal diseases and congestive heart failure [1, 16, 17]. Except for some APR-positive patients under gastric aspiration, however, these conditions did not occur and do not explain our findings. Rather, the APR syndrome concept is able to justify most of our findings, including decreased albumin and sodium serum levels. Decreased serum albumin levels were registered in all APR-positive patients and are probably due to diminished liver synthesis [7], besides functional changes in vascular permeability [18], with enhanced albumin endothelial passage into the interstitial space [6, 7, 18].

In APR syndrome, immune-derived cytokines may cause nitric-oxide-mediated vasodilation, with an increase in ADH and renin-angiotensin activities and serum levels, which reduce glomerular filtration rate, enhance tubular sodium reabsorption and diminish electrolyte-free water excretion, causing hyponatremia [1]. Another possible associated mechanism would be the APR-induced increase in serum glucose levels, which promotes cellular water efflux, hemodilution and a decrease in serum sodium concentration [19].

Clinical manifestations of hyponatremia in surgical patients are often null or quite mild and depend on the rate of decline in plasma sodium and the hyponatremia degree [10]. However, many hyponatremia signs and symptoms overlap those manifestations commonly seen in APR syndrome, including anorexia, fever, somnolence, headache, nausea, emesis, weakness, impaired response to verbal stimuli or severer expression of metabolic encephalopathy [10, 11]. Since hyponatremia is best treated by water restriction, another problem in the postoperative care of APR-positive hyponatremic patients is volume expansion, because often there is capillar leak, a condition associated with sodium passage into the interstitial space and hypooncotic edema formation [20]. Another problem in this setting is hypoalbuminemia treatment in critically ill patients, because of increased mortality associated with intravenous human albumin administration [21].

Magnesium serum levels were below normal limits in most patients; nevertheless they were lower in APR-positive ones. As the laboratory method determines total instead of ionized serum magnesium levels, besides possible magnesium dilution, one must consider a possible role of hypoalbuminemia in decreasing serum magnesium levels of APR syndrome [22], the same occurring with decreased calcium serum levels.

Limitations of this retrospective study include lack of information about creatinine clearance, urine osmolality or sodium excretion rate, in addition to total body water assessment and determination of some serum hormone levels, including ADH and aldosterone. Another possible concern is the APR criteria, lacking positive acute-reactant indicators, such as C-reactive protein or erythrocyte sedimentation rate. However, as obvious causes of hypoalbuminemia as hepatic cirrhosis or nephrotic syndrome were excluded from this study, the presence of decreased serum levels of albumin in stressed patients [7] strengthens the presence of a systemic response to surgical trauma or infection and its associated hyponatremia.

Acknowledgement

This study was supported by FUNEPU.

References

1 Kumar S, Berl T: Sodium. Lancet 1998;352:220–228.
2 Steele A, Gowrishankar M, Abrahamson S, Mazer D, Feldman RD, Halperin ML: Postoperative hyponatremia despite near-isotonic saline infusion: A phenomenon of desalination. Ann Intern Med 1997;126:20–25.
3 McDonald GA, Dubose TD Jr: Hyponatremia in the cancer patient. Oncology 1993;7:55–64.
4 Cunha DF, Santos VM, Monteiro JP, Cunha SFC: Hypophosphatemia in acute-phase response syndrome patients: Preliminary data. Miner Electrolyte Metab 1998;24:337–340.
5 Kaysen GA: Biological basis of hypoalbuminemia in ESRD. J Am Soc Nephrol 1998;9:2368–2376.
6 McMahon MM, Bistrian BR: The physiology of nutritional assessment and therapy in protein-calorie malnutrition. Dis Mon 1990;36:373–417.
7 Margarson MP, Soni N: Serum albumin: Touchstone or totem? Anaesthesia 1998;53:789–803.
8 Garcia-Tsao G: Cirrhotic ascites: Pathogenesis and management. Gastroenterologist 1995;3:41–54.
9 Wareham NJ, O'Rahilly S: The changing classification and diagnosis of diabetes. Br Med J 1998;317:359–360.
10 Fraser CL, Arieff AI: Epidemiology, pathophysiology, and management of hyponatremic encephalopathy. Am J Med 1997;102:67–77.
11 Soupart A, Decaux G: Therapeutic recommendations for management of severe hyponatremia: Current concepts on pathogenesis and prevention of neurologic complications. Clin Nephrol 1996;46:149–169.
12 Chung HM, Kluge R, Schrier RW, Anderson RJ: Postoperative hyponatremia: A prospective study. Arch Intern Med 1986;146:333–336.
13 Olson BR, Gumowski J, Rubino D, Oldfield EH: Pathophysiology of hyponatremia after transphenoidal pituitary surgery. J Neurosurg 1997;87:499–507.
14 Hahn RG: Trapping of electrolytes during fluid absorption in transurethral resection of the prostate. Scand J Urol Nephrol 1997;31:259–263.
15 Istre O, Bjoennes J, Naess R, Hornbaek K, Forman A: Postoperative cerebral oedema after an uterine irrigation with 1.5% glycine. Lancet 1994;344:1187–1189.
16 Cunha DF, Barbosa AAS, Manfrin A, Tiveron FS, Cunha SFC: Sodium serum levels in hypoalbuminemic adults at general medical wards. Rev HC-FMUSP 1999;54:39–42.
17 Gross PA, Pehrisch H, Rascher W, Schomig A, Hackenthal E, Ritz E: Pathogenesis of clinical hyponatremia: Observations of vasopressin and fluid intake in 100 hyponatremic medical patients. Eur J Clin Invest 1987;17:123–129.
18 Hennig B, Honchel R, Goldblum SE, McClain CJ: Tumor necrosis factor-mediated hypoalbuminemia in rabbits. J Nutr 1988;118:1586–1590.
19 Roscoe JM, Halperin ML, Rolleston FS, Goldstein MB: Hyperglycemia-induced hyponatremia: Metabolic considerations in calculation of serum sodium depression. Can Med Assoc J 1975;112:452–453.
20 Gaudio AR: Therapeutic use of albumin. Int J Artif Organs 1995;18:216–224.
21 Offringa M: Excess mortality after human albumin administration in critically ill patients: Clinical and pathophysiological evidence suggests albumin is harmful. Br Med J 1998;317:223–224.
22 Saha H, Harmoinen A, Karvonen AL, Mustonen J, Pasternack A: Serum ionized versus total magnesium in patients with intestinal or liver disease. Clin Chem Lab Med 1998;36:715–718.