Frequency of Hyponatremia and Nonosmolar Vasopressin Release in the Acquired Immunodeficiency Syndrome

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The frequency and pathophysiology of hyponatremia were studied in the acquired immunodeficiency syndrome. Of 71 hospitalized patients surveyed retrospectively, hyponatremia was observed in 37 (52%). Of 48 patients studied prospectively, 27 (56%) were hyponatremic. In 16 hyponatremic patients, volume status; serum and urine osmolalities; renal, adrenal, and thyroid function; and plasma vasopressin levels were assessed. Urine osmolalities were inappropriately elevated (mean, 377 mmol/kg of water) relative to serum osmolalities (mean, 268 mmol/kg of water). Four patients had moderate renal insufficiency. Plasma vasopressin levels were elevated in 15 patients, with the highest levels seen in patients who died (median, 7.08 pmol/L). Hyponatremia of multiple etiologies occurred in a majority of inpatients with the acquired immunodeficiency syndrome, often following the administration of hypotonic fluids, and was associated with a 30% (8/27) short-term mortality.

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HYPONATREMIA in hospitalized patients is a relatively common electrolyte disorder.[1-3] It tends to occur in the setting of serious disease and is associated with increased mortality.[4-6] Patients with renal, cardiac, hepatic, pulmonary, intracranial, and endocrine diseases may develop hyponatremia when urinary free-water excretion is impaired by renal tubular dysfunction, decreased distal tubular delivery of filtrate, or nonosmolar vasopressin release.

Impairment of one or several organ systems is common in the acquired immunodeficiency syndrome (AIDS). Hyponatremia has been reported in several patients with AIDS,[7-9] but this association has not been studied systematically. We undertook to describe the prevalence of hyponatremia in hospitalized patients with AIDS and to characterize the disorders of water excretion in this setting.

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PATIENTS AND METHODS

Clinical Protocol

The study included a retrospective survey and a prospective analysis.

For the retrospective survey, the charts of 71 patients with AIDS were reviewed consecutively. They had all been admitted to Lenox Hill Hospital in New York, NY, in the first 5 months of 1986 and fulfilled the criteria for the diagnosis of AIDS established by the Centers for Disease Control. Hyponatremia was defined as a serum sodium level less than 133 mmol/L on at least one routine automated chemical profile during hospitalization.

To examine the pathophysiology of hyponatremia in AIDS, a prospective study was undertaken. Forty-eight consecutive patients with AIDS were identified between June 5 and August 21, 1986. All clinical diagnoses, medications, and routine chemical profiles were recorded on admission and reassessed three times weekly. If hyponatremia was noted, the patient underwent further study.

After informed consent was obtained, extracellular fluid volume status was assessed clinically. Fluid depletion was inferred from the findings of decreased skin turgor, dry mucous membranes, or orthostatic hypotension. Fluid overload was suggested by the presence of jugular venous distention, dependent pulmonary rales, a third heart sound, evident pleural effusion or ascites, or dependent edema. Serum samples were obtained for a chemical profile, osmolality, and random cortisol determination. When hypothyroidism was considered on clinical grounds, serum triiodothyronine resin uptake and thyroxine levels were also determined. Plasma was obtained for determination of renin activity, aldosterone, and arginine vasopressin (AVP) levels. Simultaneous specimens of urine were analyzed for sodium concentration and osmolality. A

24-hour collection of urine was used to determine the clearance of creatinine and the excretion of sodium, chloride, potassium, and free water. If the random serum cortisol level was less than 1100 nmol/L, a standard stimulation test was performed. After a baseline serum cortisol specimen was obtained, a 250-μg bolus of 1-24 corticotropin was injected intravenously, followed by measurement of serum cortisol levels at 30 to 60 minutes.

The experimental protocol was approved by the Ethics and Experimentation Committee of Lenox Hill Hospital.

Laboratory Procedures

Serum chemical profiles were run on a multichannel autoanalyzer (SMAC, Technicon Inc, Tarrytown, NY); urine chemistries were determined by an ion-selective analyzer (ASTRA, Beckman Instruments, Brea, Calif). Osmolality was measured by determination of freezing-point depression. Triiodothyronine resin uptake was measured by a standard adsorbent assay; thyroxine was determined by radioimmune assay; free thyroxine index was computed by multiplying the serum thyroxine by the quotient of the patient's triiodothyronine resin uptake and the mean normal triiodothyronine resin uptake. Cortisol and aldosterone were determined by radioimmunoassay. Plasma renin activity was assessed by determination of the generation of angiotensin I by radioimmunoassay. Arginine vasopressin was measured with a specific radioimmunoassay,[10] which was performed by Alan G. Robinson, MD, at the Endocrinology Laboratory, Department of Medicine, University of Pittsburgh (Pa).

Statistical Methods

When the data were normally distributed, values were expressed as the mean ± SE, and a nonpaired t test was applied to check for differences between groups. Nonparametric data were analyzed with the Wilcoxon Rank-Sum Test and dichotomous data by χ^2. The null hypothesis was rejected at $P < .05$ in all cases.

RESULTS

Incidence of Hyponatremia

In the retrospective survey of 71 patients with AIDS, 37 (52%) were found to exhibit hyponatremia during their hospital course.

In the subsequent prospective study, 48 patients were identified with AIDS. The initial presenting disease was *Pneumocystis carinii* pneumonia in 34 patients, cytomegalovirus (CMV) infection in 5, and Kaposi's sarcoma in 4; the remaining 5 patients had presented with various other illnesses. The mean age of these patients was 39.8 years; there were 47 men and 1 woman. In this series, 27 patients (56%) were noted to have hyponatremia, with the lowest serum sodium concentrations during hospitalization ranging from 117 to 132 mmol/L (mean, 126 ± 4 mmol/L). Thirteen patients (27%) were hyponatremic on admission; the remaining 14 (29%) had normal serum sodium concentrations on admission and later developed hyponatremia during their hospital course.

The organ system involvement of AIDS patients with and without hyponatremia is outlined in Table 1. While hyponatremia occurred in 65% of patients with pulmonary disease and 63% of patients with intracranial disease, the distribution of organ involvement was not found to be different from that of normonatremic AIDS patients.

Factors Contributing to Hyponatremia

Of the 27 patients with hyponatremia, 16 were studied fully as described in the "Patients and Methods" section; the results of these studies are summarized in Table 2. Fifteen patients had

Table 1.—Clinical Characteristics of 48 Patients With the Acquired Immunodeficiency Syndrome

Organ System Involvement	Hyponatremic Patients (n=27)	Normonatremic Patients (n=21)	All Patients (n=48)
Pulmonary	17	9	**26**
Central nervous system	5	3	**8**
Intestinal	3	5	**8**

Table 2.—Clinical Data of 16 Patients With the Acquired Immunodeficiency Syndrome Who Were Studied During Hyponatremia*

Patient No.	Admitting Diagnosis	Fluid Status	Medications			Values Determined on Study Day					
			Barbiturates	Narcotics	Hypotonic Solutions	SNa, mmol/L	Sosm, mmol/kg	Uosm, mmol/kg	UNa, mmol/L	AVP, pmol/L	Ccr, mL/s
1	PCP†	Decreased	–	–	–	128	263	394	29	7.08	0.82
2	*Cryptococcus* meningitis†	Decreased	–	–	+	122	243	442	161	7.08	1.55
3	*Salmonella* bacteremia†	Decreased	–	+	–	128	289	300	40	17.03	1.17
4	Lung abscess†	Decreased	–	+	–	131	261	381	70	0.84	0.62
5	Anemia	Decreased	+	–	–	127	264	421	150	0.57	0.80
6	Pneumonitis	Normal	–	+	+	131	276	335	56	1.11	1.38
7	CMV pneumonitis,† CMV meningitis	Normal	+	+	+	131	267	690	192	2.44	0.77
8	*Candida* esophagitis	Decreased	–	–	–	130	265	457	3	0.37	1.27
9	CMV retinitis/colitis	Decreased	–	–	+	129	264	514	51	0.88	1.27
10	PCP	Normal	–	–	+	126	263	246	55	0.71	1.10
11	PCP	Normal	–	–	+	131	273	341	29	1.02	1.43
12	PCP	Normal	–	+	+	131	269	443	132	0.81	1.63
13	PCP	Decreased	–	–	+	130	265	215	30	0.71	1.08
14	CMV retinitis, CMV pneumonitis	Normal	+	–	+	130	259	436	106	1.21	1.63
15	PCP	Decreased	–	+	+	132	278	156	25	0.70	0.38
16	Lymphoma	Decreased	–	+	+	128	281	259	105	1.31	0.25

*SNa indicates serum sodium; Sosm, serum osmolality; Uosm, urine osmolality; UNa, urine sodium; AVP, arginine vasopressin; Ccr, creatinine clearance; PCP, *Pneumocystis carinii* pneumonia; and CMV, cytomegalovirus.
†Died in hospital.

decreased serum osmolality (mean, 266 ± 2 mmol/kg of water); the remaining patient had a normal serum osmolality with concomitant azotemia (Fig 1).

The urine osmolality was inappropriately elevated (mean, 377 mmol/kg of water) in all 15 patients with serum hypotonicity. Four patients had a creatinine clearance of less than 0.67 mL/s. Of the remaining 12 patients, all but 1 had urinary sodium concentrations greater than 20 mmol/L. None of the patients had evident cardiac or hepatic disease or fluid overload.

Adrenal function was evaluated in the 16 patients (Tables 3 and 4 and Fig 2). In no instance was there evidence of overt hypoadrenalism. While the renin and aldosterone levels varied between subjects, a correlation of aldosterone and renin revealed a linear relationship between these two hormones ($r = .76$, $P < .005$). In 4 patients (Nos. 1, 2, 5, and 8) in whom there was a relatively flat response to cosyntropin stimulation, aldosterone levels were significantly suppressed ($P < .005$), despite clinical evidence of hypovolemia, and serum sodium levels were significantly lower ($P < .05$) than in patients with a cosyntropin-stimulated cortisol increment. While a possible reason for the low aldosterone levels in these patients might have been their apparent hyporeninemia (0.34 ± 0.16 ng·L^{-1}·s^{-1} vs 3.84 ± 2.22 ng·L^{-1}·s^{-1}), we found no significant difference between the renin levels of the two groups by the Mann-Whitney U Test ($P = .07$). In 1 patient with a cortisol response of less than 190 nmol/L, hyponatremia was rapidly corrected with no therapy other than physiological doses of hydrocortisone.

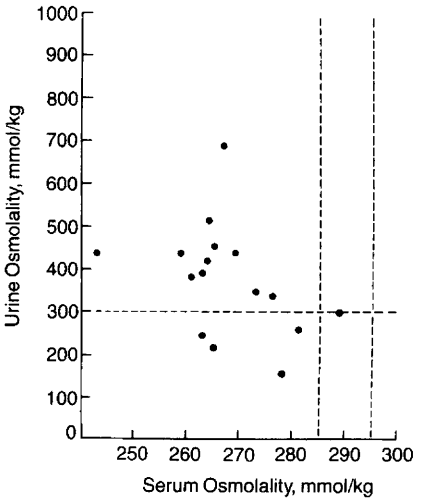

Fig 1.—Simultaneous serum and urine osmolalities in 16 patients with the acquired immunodeficiency syndrome. Normal range of serum osmolality is between the vertical dashed lines.

Nine of the 16 patients were clinically euthyroid; the remaining 7 had nonspecific signs consistent with hypothyroidism and underwent thyroid function testing. Of these 7 patients, 5 had normal free thyroxine indexes. The 2 remaining patients had slightly depressed free thyroxine indexes of 60 and 62 nmol/L, respectively (normal range, 64 to 154 nmol/L). One of these patients was shown to be euthyroid with a normal thyroid-stimulating hormone level of 2.2 mU/L (normal range, 0 to 7 mU/L).

Fourteen of the 15 patients with serum hypotonicity had plasma AVP levels greater than 0.5 pmol/L, representing a lack of suppression of vasopressin release despite serum hypoosmolality (Fig 3). Four of these patients lacked significant impairment of renal, adrenal, and thyroid function and were clinically normovolemic. The sole basis of their free-water retention appeared to be non–volume-mediated, nonosmolar vasopressin release.

Agents Contributing to Hyponatremia

Patients in the study were commonly treated with narcotics and other drugs known to stimulate vasopressin release (Table 5), and 79% received hypotonic saline infusions. There were no significant differences between hyponatremic and normonatremic patients with respect to drugs or hypotonic saline infusions. No patients received hypoglycemic agents that might affect water metabolism.

Mortality

Ten (21%) of 48 patients died in the hospital during the prospective study; 8 of those who died had been hyponatremic. Although the mortality rate in hyponatremic patients of 30% compared with a 10% mortality rate in normonatremic patients, the difference was not significant by χ^2 analysis. Patients who died had had a lower nadir serum sodium level than survivors (128 ± 2 mmol/L vs 133 ± 1 mmol/L, $P < .04$).

Plasma AVP levels were significantly elevated in 5 patients who died compared with 11 patients who survived (median, 7.08 pmol/L vs 0.81 pmol/L, $P < .01$).

Autopsy Findings

Among the 71 patients surveyed retrospectively and the 48 patients enrolled prospectively, 8 patients who were hyponatremic were examined postmortem. These consisted of 6 patients from the retrospective group and 2 from the prospective group. All 8 patients had active pulmonary infiltrates associated with *Pneumocystis carinii* pneumonia (5 patients), CMV infection (4 patients), bacterial pneumonia (3 patients), or unclassified pneumonia (1 patient). Central nervous system lesions included CMV encephalitis (2 patients) and cryptococcal meningitis (1 patient). Five patients had enterocolitis, most commonly associated with CMV (4 patients).

In all eight patients adrenal abnormalities were seen. Extensive cortical necrosis, often hemorrhagic, was observed in six patients. In five of these, intracellular inclusion bodies characteristic of CMV adrenalitis were seen; the sixth patient had disseminated *Myco-*

Table 3.—Status of Adrenal Function and Renin-Aldosterone System in 16 Hyponatremic Patients

Patient No.	Serum Cortisol, nmol/L, After Corticotropin			Adrenal Function	
	Baseline	30 min	60 min	Plasma Aldosterone, pmol/L	Plasma Renin Activity, ng·L^{-1}·s^{-1}
1	760	...	810	140	0.14
2	540	660	700	70	0.06
3	1630	...	...	430	4.64
4	650	1220	1180	120	0.12
5	750	820	880	80	0.36
6	250	470	610	360	2.56
7	360	820	840	200	0.26
8	630	630	740	40	0.78
9	980	1240	1660	360	2.50
10	750	...	...	720	2.48
11	480	740	830	710	3.02
12	310	630	730	60	0.20
13	350	710	790	330	0.76
14	530	780	950	150	0.48
15	240	630	740	120	1.30
16	>1660	...	...	470	27.76

Table 4.—Clinical Correlates of Adrenal Status in 15 Hyponatremic Patients

	Patients With <190 nmol/L Cortisol Response to Corticotropin (n=4)	Patients With >190 nmol/L Cortisol Response to Corticotropin or Baseline Cortisol >1100 nmol/L (n=11)
Mean arterial pressure, mm Hg (mean ± SE)	88 ± 7	84 ± 2
Fluid status		
Hypovolemic	4	6
Normovolemic	0	5
Hypervolemic	0	0
Laboratory values		
Serum sodium, mmol/L	127 ± 1*	130 ± 1
Serum potassium, mmol/L	3.9 ± 0.2	4.4 ± 0.2
Serum bicarbonate, mmol/L	21 ± 2	22 ± 1
Plasma aldosterone, pmol/L	80 ± 20†	310 ± 10

*$P<.05$ compared with hyponatremic patients with a greater than 190-nmol/L corticotropin–induced cortisol response.
†$P<.005$ compared with hyponatremic patients with a greater than 190-nmol/L corticotropin–induced cortisol response.

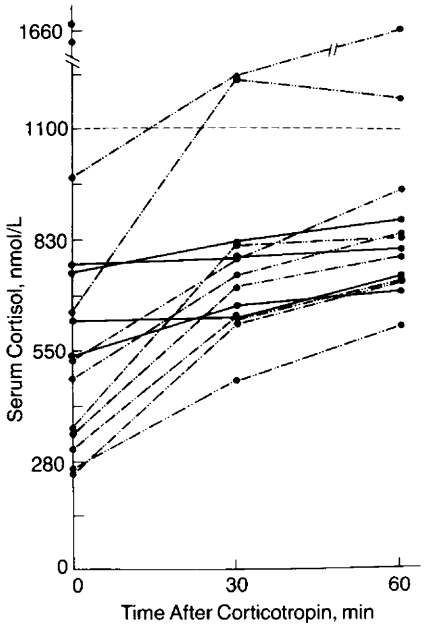

Fig 2.—Serum cortisol response to corticotropin stimulation test in 13 patients with the acquired immunodeficiency syndrome. Results in patients with cortisol increments of less than 190 nmol/L are shown by solid lines; those with cortisol increments of greater than 190 nmol/L are shown by dotted lines.

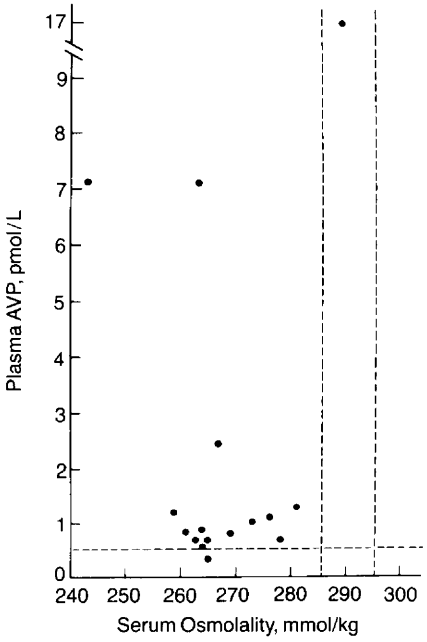

Fig 3.—Plasma arginine vasopressin (AVP) and serum osmolality in 16 patients with the acquired immunodeficiency syndrome. Normal range of serum osmolality is between the vertical dashed lines. Range of maximally suppressed AVP levels is below the horizontal dashed line.

Table 5.—Medications Given to 48 Patients With the Acquired Immunodeficiency Syndrome

	Hyponatremic Patients (n=27)	Normonatremic Patients (n=21)
Central nervous system drugs		
Opiates	13	8
Barbiturates	4	1
Acetaminophen	25	16
Hypotonic saline		
0.45% Sodium chloride	15	6
0.20% Sodium chloride	5	2
0.00% Sodium chloride	18	9

bacterium avium-intracellulare infection. In the two patients without adrenal necrosis, the only adrenal abnormality noted was cortical lipid depletion. One of the above patients with CMV adrenalitis was found to exhibit a subnormal adrenocorticotropic hormone response during the prospective analysis (patient 1, Table 3).

COMMENT

We found hyponatremia to occur in 56% of hospitalized patients with AIDS. This frequency was higher than in other series of hospitalized patients. Flear et al[3,5] noted hyponatremia in 15% of 2852 routine specimens from general hospitalized patients and in 45% of 190 patients with acute myocardial infarction. Samadi and colleagues[4] reported an incidence of 21% in 1320 children with severe diarrhea. Anderson et al[1] observed a daily prevalence of hyponatremia of 2% in a general hospital population, but the total incidence was not reported. Thus, hospitalized patients with AIDS are at higher risk of developing hyponatremia than any previously described patient subgroup. This hyponatremia results not from any mechanism that is new or pathophysiologically distinct, but rather from the accumulated multiorgan morbidity that is unique to patients with AIDS.

In the 16 patients with hyponatremia who were further studied to elucidate the pathophysiology of hyponatremia, a number of factors were found to contribute to the development of hyponatremia. Pseudohyponatremia caused by hyperlipidemia, hyperproteinemia, or hyperglycemia was not observed. No patients in our series had cardiac or hepatic disease or evident fluid overload, in contrast to other series of hospitalized patients.[1,2,6]

Ten of the 16 patients were clinically dehydrated, in part because of poor nutritional intake and abnormal gastrointestinal losses. Among these 10 patients were 4 patients with moderate renal insufficiency (creatinine clearance <0.67 mL/s) and 4 patients with possibly diminished adrenal reserve. In only 1 hypovolemic patient was tubular sodium avidity demonstrated by a random urine sodium concentration less than 20 mmol/L. This is in keeping with the abnormal urinary sodium conservation often seen with altered renal or adrenal function.

Renal insufficiency per se has been shown to result in impaired urinary diluting ability.[11] Previous reports on hospitalized patients[1,6] have found renal failure to contribute to hyponatremia in 9% and 23% of cases, respectively. Our finding of moderate renal functional im-

pairment in 4 (25%) of 16 patients is consistent with this prior experience.

Hypothyroidism and hypoadrenalism, two endocrinopathies known to contribute to hyponatremia, were not reported in the previous series.[1,6] We noted two patients to have mildly decreased thyroxine levels; one patient had a normal thyroid-stimulating hormone level and was likely truly euthyroid. Hyponatremia caused by hypothyroidism has been reported predominantly in the setting of frank myxedema,[12] and we consider it unlikely that the mild degree of hypothyroidism in the second patient contributed significantly to the development of hyponatremia.

Adrenal function in our patients was assessed with random determinations of serum cortisol levels. Two patients had a random cortisol level greater than 1100 nmol/L and were presumed to be normoadrenal; the remaining 14 patients underwent a standard rapid corticotropin stimulation test.[13] Although none of these 14 patients had random cortisol levels below the commonly cited normal ranges, 4 of them responded to a short cosyntropin stimulation test with a cortisol increment of less than 190 nmol/L. Although their cortisol increment is difficult to assess because of their baseline cortisol elevation, these 4 patients were clinically dehydrated and had significantly lower serum sodium levels compared with the 12 hyponatremic patients with cortisol increments of greater than 190 nmol/L. Hyperkalemia was not seen, perhaps as a result of depletion from diminished intake and increased gastrointestinal losses. The 1 patient (No. 1, Table 3) with a subnormal response to corticotropin who was examined postmortem was found to have adrenal cortical necrosis caused by CMV adrenalitis, in a pattern described in a number of autopsy series of patients with AIDS.[14-17] Another patient was receiving ketoconazole, a known inhibitor of adrenal steroidogenesis.[18] In comparison, 2 of the 12 patients with a cortisol response greater than 190 nmol/L were treated with ketoconazole.

The rapid-bolus corticotropin stimulation test was utilized to screen for the adequacy of adrenal reserve in this patient population, known to be at risk for adrenal infection and hemorrhagic necrosis.[14-17] This test has been employed widely in the evaluation of adrenal reserve[19,20] and has been utilized in the adrenal evaluation of patients with AIDS.[21,22] Despite the widespread acceptance of this convenient rapid-bolus test, however, the criteria for a normal response have not been standardized and remain unclear.[19] In addition, a retrospective review of the rapid corticotropin test, when compared with a continuous corticotropin infusion as a reference test, showed the results of the rapid-bolus test to be falsely abnormal in some patients.[19] The authors thus support the use of the rapid corticotropin test as a screening test but recommend the use of the 48-hour corticotropin infusion test to establish a diagnosis of adrenocortical failure. Similarly, Membreno et al[22] propose a 3-day corticotropin infusion test in AIDS patients before administering replacement steroid therapy. Patients with AIDS are known to exhibit a variety of morphologic and functional adrenal abnormalities,[14-17] findings corroborated by this study. Although the rapid-bolus corticotropin test has potential limitations, the occurrence of a flat cortisol response in this setting of hyponatremia, decreased aldosterone levels, and increased risk of anatomic adrenal abnormalities may identify patients for whom more definitive adrenal evaluation is warranted.

Plasma AVP levels have been found to be useful in evaluating hyponatremia. During hypo-osmolar states, plasma AVP levels are normally suppressed to less than 0.5 pmol/L. In 15 (94%) of 16 patients with documented serum hypoosmolality (Table 2), AVP levels were not suppressed, demonstrating nonosmolar vasopressin release. This phenomenon was observed in other groups of hospitalized hyponatremic patients,[1,23] in 97% and 81% of cases, respectively. In 8 patients in our series the levels were pathologically elevated to greater than 1.0 pmol/L. Four of these patients appeared clinically normovolemic; hence, the release of vasopressin was not volume mediated. Furthermore, they lacked evidence of renal, thyroid, or adrenal failure. This pattern is consistent with the so-called syndrome of inappropriate antidiuretic hormone secretion. All 4 patients had active pulmonary disease, and 3 were receiving opiates or barbiturates, agents previously reported to be associated with the syndrome.[24,25]

Although the above mechanisms may impair free-water clearance in inpatients with AIDS, most of our patients did not actually become hyponatremic until they received hypotonic fluids. These were often administered as a diluent with antibiotics such as sulfamethoxazole-trimethoprim, as parenteral nutrition, or as a precaution against sodium overload. Although the official packaging information for sulfamethoxazole-trimethoprim recommends that only dextrose in water be used as the diluent,[26] the drug has been shown to be stable in a maximally concentrated solution with normal saline for up to 2 hours.[27] Isotonic formulations for parenteral nutrition are also available. Problems with cardiac or hepatic failure and fluid overload were not encountered in our patients. Hence, it should not be difficult to avoid hypotonic infusions in most patients with AIDS who are predisposed to free-water retention or who are already overtly hyponatremic.

It is difficult to assess the morbidity from hyponatremia per se in a group of patients with many nonspecific and constitutional symptoms and frequent central nervous system disease with its attendant symptomatology. Of the 27 patients who developed hyponatremia, 5 patients had concomitant obtundation, but none were observed to have seizures or coma. In 3 of these, the lowest serum sodium levels ranged from 117 to 122 mmol/L, and the mental status improved somewhat after correction of hyponatremia. The other 2 patients had ongoing central nervous system disease and remained obtunded despite correction of hyponatremia. The association of AIDS-related central nervous system disease and vasopressin-mediated hyponatremia is likely to become an increasingly common problem in view of the vastly enlarging incidence and spectrum of central nervous system lesions caused by human immunodeficiency virus, which is neurotropic.[28]

The hyponatremic patients in our study had a 30% short-term mortality rate compared with a 10% mortality in the normonatremic patients. Although this difference did not achieve statistical significance, the lack of significance may have been influenced by the sample size. We did note that plasma AVP levels were significantly greater in hyponatremic patients who died compared with those who survived. To our knowledge, this association has not been reported previously. It may reflect the generally poor prognosis associated with serious disease, the stress of which may result in markedly increased vasopressin release.

In summary, hyponatremia occurs commonly in hospitalized patients with AIDS, and it may predict a more immediately fatal outcome. Its etiology is multifactorial, and contributing factors might include hypovolemia; renal, thyroid, and adrenal insufficiency; and other states of nonosmolar vasopressin release. Diminished adrenal reserve in patients with AIDS may not necessarily be associated with overt hypotension, azotemia, hyperkalemia, or depressed cortisol levels, and a prolonged corticotropin stimulation test may be required

for its diagnosis. Arginine vasopressin levels are frequently increased, especially in patients who have active pulmonary disease or who are receiving drugs previously associated with hyponatremia. In this study, elevated AVP levels were also associated with increased mortality. Since hospitalized patients with AIDS may be at risk for free-water retention and hyponatremia, the serum sodium concentration should be monitored frequently, and hypotonic fluids should be administered with appropriate caution.

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