

Chronic Hyponatremic Encephalopathy in Postmenopausal Women

Association of Therapies With Morbidity and Mortality

J. Carlos Ayus, MD

Allen I. Arieff, MD

CHRONIC HYPONATREMIA IS A common clinical problem in the elderly, particularly among women.¹ Although the mortality among such patients is substantial,²⁻⁵ it is unclear if these patients die of hyponatremia, the effects of therapy, or associated medical conditions. It is now well accepted that acute symptomatic hyponatremia (hyponatremic encephalopathy) in menstruant women can result in death or permanent brain damage.⁶⁻⁹ While failure to institute active therapy (intravenous [IV] sodium chloride) in such patients may lead to increased morbidity, IV hypertonic sodium chloride therapy is both safe and effective in preventing hyponatremic brain damage.¹⁰⁻¹³ However, for the past decade it has been suggested that there are important clinical distinctions between acute and chronic hyponatremia in regard to indications for active therapy and propensity for permanent brain damage.^{2,7,14} Furthermore, it has been suggested that much of the brain damage associated with chronic hyponatremia may be a consequence of improper therapy rather than hyponatremic encephalopathy.^{2,3,15} In general, studies of patients with chronic hyponatremia usually have not included information on whether the patients were symptomatic.¹⁻⁵ In the vast

For editorial comment see p 2342.

Context Chronic hyponatremia in postmenopausal women is a common clinical problem often viewed as benign. Fluid restriction is usually the recommended therapy, largely because the extent of morbidity is unknown and because it has been postulated that intravenous (IV) sodium chloride may cause brain damage.

Objective To compare IV sodium chloride with fluid restriction in the treatment of postmenopausal women with chronic symptomatic hyponatremia.

Design Nonrandomized prospective study.

Setting Two university medical centers and affiliated community hospitals.

Patients A total of 53 postmenopausal women with chronic symptomatic hyponatremia (chronic plasma sodium <130 mmol/L in the presence of central nervous system manifestations) treated consecutively from 1988-1997 and followed up for 1 year. The mean (SD) age of the patients was 62 (11) years.

Interventions The therapeutic interventions were IV sodium chloride before respiratory insufficiency (n = 17), IV sodium chloride after respiratory insufficiency (n = 22), and fluid restriction only (n = 14).

Main Outcome Measures Morbidity and neurological outcome at 4 months or longer as assessed by cerebral performance category (CPC) in relation to the therapy, initial plasma sodium level, and rate of correction.

Results Chronic symptomatic hyponatremia (mean [SD] sodium level 111 [12] mmol/L) was present for 5.2 [4.5] days. Death or major morbidity occurred in 44 (83%) of 53 patients, including 10 with orthopedic injury. Twelve patients had hypoxemia (PO₂ = 63 [25] mm Hg) and cerebral edema. Among patients who received IV sodium chloride before respiratory insufficiency, plasma sodium levels were increased by 22 (10) mmol/L in 35 hours and patients had a CPC of 1.0 (normal or slight disability). Among patients who received IV sodium chloride after respiratory insufficiency, plasma sodium levels were increased by 30 (6) mmol/L in 41 hours and patients had a CPC of 3.0 (1.2) (severe disability). Among patients who had fluid restriction only, plasma sodium levels were increased by 3 (2) mmol/L in 41 hours and patients had a CPC of 4.6 (0.7) (4 = persistent vegetative state; 5 = death). The outcomes did not correlate with either the initial plasma sodium level ($r = 0.05$, $P > .12$) or the rate of correction ($r = 0.31$, $P > .10$).

Conclusions Chronic symptomatic hyponatremia in postmenopausal women can be associated with major morbidity and mortality. Therapy with IV sodium chloride was associated with significantly better outcomes than fluid restriction.

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majority of instances, chronic hyponatremia occurs in postmenopausal women, often in association with thiazide therapy or the syndrome of inappropriate secretion of antidiuretic hor-

Author Affiliations: Department of Medicine, Baylor College of Medicine, Houston, Tex (Dr Ayus); and Department of Medicine, University of California School of Medicine, San Francisco (Dr Arieff).

Corresponding Author and Reprints: Allen I. Arieff, MD, 299 South St, Sausalito, CA 94965 (e-mail: aarief@itsa.ucsf.edu).

Table 1. Demographics and Laboratory Values*

Demographics (n = 53)	
Age, y	62 (11)
Weight, kg	62 (11)
Duration of hyponatremia, d	5.2 (4.2)
Arterial parameters (n = 12)	
pH	7.42 (0.13)
Arterial PO ₂ , mm Hg	63 (25)
Arterial PCO ₂ , mm Hg	31 (7)
Arterial bicarbonate, mmol/L	25.1 (3.1)
Plasma parameters (n = 53)	
Sodium, mmol/L	111 (12)
Potassium, mmol/L	3.2 (0.9)
Glucose	
mmol/L	9.1 (5.4)
mg/dL	164 (97)
Urea nitrogen	
mmol/L	3.9 (1.2)
mg/dL	11 (3)
Creatinine	
μmol/L	71 (26)
mg/dL	0.8 (0.3)
Urine parameters (n = 9)	
Sodium, mmol/L	78 (36)
Potassium, mmol/L	38 (29)
Osmolality, mmol/kg H ₂ O	426 (41)

*All data are mean (SD) unless otherwise noted.

As a result, it is widely believed that postmenopausal women are in little danger of morbidity associated with chronic hyponatremia, and that initiation of therapy with IV sodium chloride is potentially hazardous.^{2,3}

Recent studies have demonstrated that the major criterion for use of IV sodium chloride therapy in patients with acute symptomatic hyponatremia is the presence of central nervous system symptoms, regardless of the level of plasma sodium.^{9,10,12} It has been suggested that therapy with sodium chloride might be appropriate in patients with chronic symptomatic hyponatremia.^{7,14} However, little if any actual data are available to support this contention, and fluid restriction is frequently suggested as the appropriate therapy.^{3-5,15,17} We have found no studies in which therapy with IV sodium chloride was compared with fluid restriction in patients with chronic symptomatic hyponatremia.

METHODS

We performed a prospective study of the outcomes and effects of interventional therapy in postmenopausal women with chronic symptomatic hyponatremia. The study group consisted of 53 consecutive patients about

whom 1 of the authors was consulted during the interval 1988-1997. No patients were omitted from the study. Other aspects of 5 of the 53 patients have been published in another context.¹⁸ Symptomatic hyponatremia (hyponatremic encephalopathy) was defined as a plasma sodium level below 130 mmol/L in the presence of central nervous system manifestations.^{7,19} Chronic hyponatremia was documented by 2 different modalities: (1) a documented duration of at least 48 hours,⁷ and (2) a rate of decrease in plasma sodium levels of less than 0.5 mmol/L per hour over at least 48 hours.²⁰ Fifty of 53 patients had a decrease in plasma sodium level of 0.5 mmol/L or less for at least 48 hours. In all 53 patients there were at least 2 values for plasma sodium levels below 130 mmol/L separated by 48 or more hours, while in 44 patients there were more than 2 such values. The hyponatremic values were obtained either following surgery or during initial and subsequent visits to an emergency department or physician's office. None of the 53 patients had either edematous disorders (eg, heart failure, hepatic cirrhosis, or nephrotic syndrome) or acquired immunodeficiency syndrome.

The 53 postmenopausal women were divided into 3 groups based on the therapeutic regimen as follows: (1) 17 patients who were treated with IV sodium chloride before the onset of respiratory insufficiency; (2) 22 patients who had not been treated with sodium chloride prior to the onset of respiratory insufficiency, but received IV sodium chloride after respiratory insufficiency, as well as intubation and assisted ventilation; (3) 14 patients who were treated with fluid restriction only. The authors were directly involved in the therapy of the patients in group 1. The authors were consulted about the patients in group 2 only after the patients had experienced respiratory insufficiency and were intubated and receiving assisted ventilation. The authors were consulted about patients in group 3 only after the patients had experi-

enced respiratory insufficiency. For all patients in group 3, the managing physician(s) had made the decision to treat the hyponatremia with fluid restriction rather than IV sodium chloride. The major reason given by the managing physicians for therapy with fluid restriction was the fear of iatrogenic illness related to sodium chloride infusion, particularly cerebral demyelinating lesions.^{2,3} Respiratory insufficiency was defined as a state characterized by impaired respiration such that there was either respiratory arrest or arterial PO₂ below 50 mm Hg.

Cerebral edema was assessed by standard neuroradiological criteria.²¹ The functional outcome was assessed by cerebral performance category (CPC) based on the Glasgow outcome performance categories.^{22,23} Based on functional outcome after 4 months or longer, patients were classified in 1 of the 5 following groups: (1) normal function or only slight disability; (2) conscious and alert with moderate disability but able to care for self and live independently; (3) severe disability such that the subject was unable to care for self and usually required institutional care; (4) persistent vegetative state; and (5) death. In all patients, therapy with sodium chloride was considered to be complete after 48 hours, or earlier when any of the 3 following conditions were met¹³: (1) the patient became asymptomatic; (2) plasma sodium level increased by 25 mmol/L; (3) plasma sodium level increased to 132 mmol/L.

All values are presented as mean (SD). Significance was determined using analysis of variance or coefficient of correlation (*r*) using regression analysis.

RESULTS

Demographics

The mean (SD) age of the 53 women was 62 (11) years (range, 45-89 years) and all were postmenopausal (5 had surgically induced menopause). The duration of the hyponatremia was 5.2 (4.5) days. The laboratory values for all patients at the time hyponatremia was diagnosed are shown in TABLE 1. The

etiologies for the hyponatremia were similar among the 3 groups and included polydipsia (n = 21), use of thiazide diuretics (n = 17), postoperative complications (n = 15), and syndrome of inappropriate secretion of antidiuretic hormone (n = 5). Ten of the 53 patients were taking hormone replacement therapy (estrogens).

Clinical Presentation

Orthopedic injury was a prominent presenting feature in this series. The orthopedic injury was the initial clinical manifestation that led to the discovery of hyponatremia in 10 patients (FIGURE 1). The orthopedic injuries were hip fracture (n = 3), fractured vertebral processes (n = 1), tibia fracture (n = 1), shoulder dislocation (n = 1), knee dislocation (n = 2), and skull fracture (n = 2). The mean plasma sodium level when the orthopedic injury was discovered was 117 (11) mmol/L. All 10 orthopedic injuries followed seizures that were a consequence of the hyponatremia. In addition to orthopedic injury, the most common presenting clinical manifestations were headache (n = 16), nausea (n = 14), emesis (n = 15), generalized weakness (n = 24), and grand mal seizures (n = 12). The 12 patients (groups 1 and 2) whose blood gases were measured before initiation of therapy had severe hypoxemia, with arterial PO₂ = 63 (25) mm Hg.

Associated Medical and Surgical Conditions

Associated comorbid conditions included 10 patients with psychiatric disorders (schizophrenia [n = 2], bipolar disorder [n = 3], depressive illness [n = 3], posttraumatic stress disorder [n = 1], and beer potomania [n = 1]). There were 36 patients with the following medical conditions: coronary artery disease (n = 1), pneumonia (n = 1), survivable malignancy (n = 4), hypertension treated with thiazides (n = 17), irritable bowel syndrome (n = 1), military tuberculosis (n = 1), alcoholism (n = 2), febrile illness with polydipsia (n = 5), diabetes mellitus (n = 3), and cholecystitis (n = 1). There were 26 pa-

tients with associated surgical conditions, of whom 16 were postoperative: orthopedic (n = 6), plastic (n = 1), gynecological (n = 4), vascular (n = 2), neurosurgical (n = 1), gastrointestinal (n = 2), and primary orthopedic injury (n = 10).

Effects of Therapy

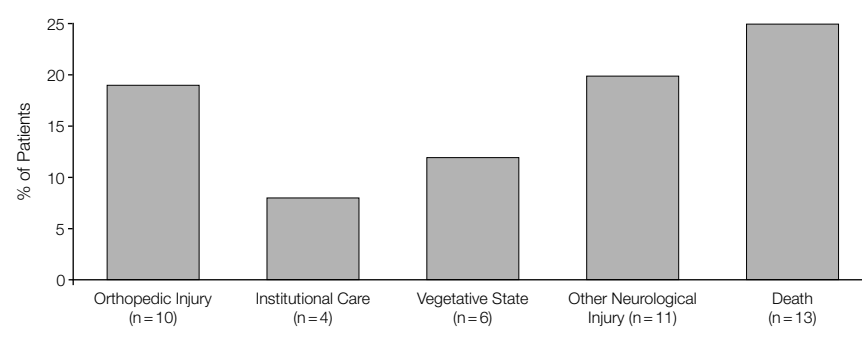
A summary of the effects of therapy for all 3 groups of patients is shown in TABLE 2. Prior to the episode of hyponatremia, all 53 patients were living independently (CPC = 1).

Group 1

The rate of decrease in plasma sodium levels for the group 1 patients was 0.27 (0.14) mmol/L per hour. All 17 group

1 patients were treated with IV sodium chloride (12 with 514 mmol/L and 2 with 154 mmol/L), 7 also received furosemide. The absolute change in plasma sodium levels after 12, 24, and 35 hours, the rate of correction (mmol/L per hour) and the initial plasma sodium level are shown relative to the outcome (CPC = 1 to 5) in Table 2 and FIGURE 2. All 17 recovered without neurological impairment or other complications (CPC = 1). Follow-up examination was done after at least 1 year for 9 of the 17 group 1 patients. All 9 were leading lives comparable to that before the episode of hyponatremic encephalopathy, without evidence of disability (CPC = 1). The other 8 were lost to follow-up.

Figure 1. Sequelae of Chronic Hyponatremic Encephalopathy in 53 Postmenopausal Women



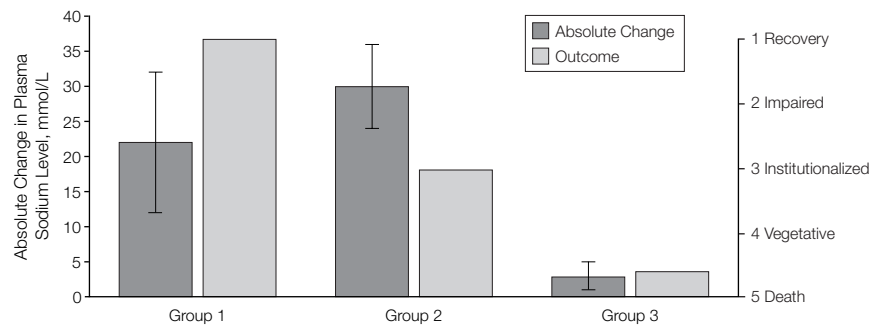
Forty-four of the 53 experienced neurological or orthopedic injury or died.

Table 2. Effects of 3 Different Therapies on Outcome in Elderly Women With Chronic Hyponatremic Encephalopathy*

	Group 1† (n = 17)	Group 2† (n = 22)	Group 3† (n = 14)
Age, y	71 (12)	55 (7)	64 (8)
Initial plasma sodium, mmol/L	111 (10)	103 (7)	109 (12)
Plasma sodium at 12 h, mmol/L	119 (4)	113 (9)	111 (10)
Plasma sodium at 24 h, mmol/L	125 (4)	125 (10)	112 (11)
Final plasma sodium, mmol/L	133 (5)	132 (4)	112 (11)
Absolute change in plasma sodium, mmol/L	22 (10)	30 (6)	3 (2)
Time of correction, h	35 (11)	41 (13)	10 Patients died within 24 h; 3 patients institutionalized or vegetative; 1 patient died after 70 d
Rate of correction, mmol/L per h	0.7 (0.3)	0.8 (7.0)	0.1 (0.1)
Outcome, CPC‡	1 (0)	3.0 (1.2)	4.6 (0.7)

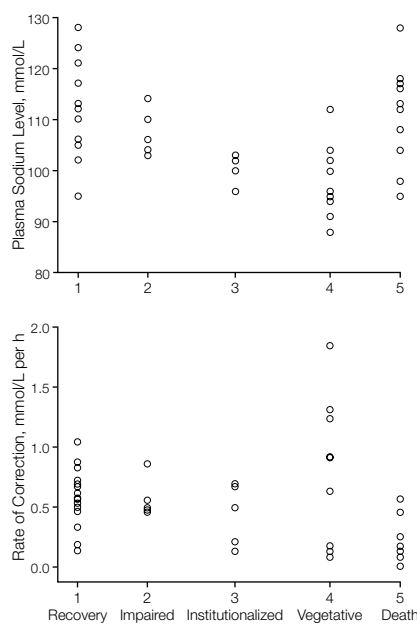
*All data are mean (SD) unless otherwise noted.
 †Group 1 was given intravenous sodium chloride before respiratory insufficiency, group 2 was given sodium chloride after respiratory insufficiency, and group 3 was treated with fluid restriction only.
 ‡CPC indicates cerebral performance category: (1) normal function or only slight disability; (2) conscious and alert with moderate disability but able to care for self and live independently; (3) severe disability such that subject is unable to care for self; (4) persistent vegetative state; and (5) death.

Figure 2. Effects of Therapy on Outcome (Cerebral Performance Category) in 53 Postmenopausal Women With Chronic Hyponatremic Encephalopathy



The absolute change in plasma sodium level over the initial 2 days of therapy was significantly less in group 3 patients than in either group 1 or 2 patients ($P < .01$). The absolute change in group 2 patients was significantly larger than the absolute change in group 1 patients ($P < .05$). The outcome in both group 1 and 2 patients, who were treated with intravenous sodium chloride therapy, was significantly better ($P < .01$) than that in group 3 patients, who were treated with fluid restriction. Error bars represent SD. Group 1 outcomes 1 in all cases.

Figure 3. Relationship Between Patient Outcome (Cerebral Performance Category) and Initial Plasma Sodium Level Before Therapy and Rate of Correction of Plasma Sodium



There is no significant correlation between the outcome and either the initial plasma sodium level ($r = 0.05$; $P = .10$) (top) or the rate of correction ($r = 0.31$; $P = .12$) (bottom).

Group 2

The rate of decrease in plasma sodium levels for the group 2 patients was 0.33 (0.15) mmol/L per hour. All 22 patients experienced respiratory insuffi-

ciency and were intubated with assisted ventilation before therapy with sodium chloride was initiated. The absolute change in plasma sodium levels after 12, 24, and 41 hours, the rate of correction, and the initial plasma sodium levels are shown relative to the outcome in Figure 2 and Table 2. Two patients recovered completely and another 6 recovered so that they were able to live independently (CPC = 2). The remaining 14 either died or developed neurological impairment such that institutionalization was necessary (CPC = 3 to 5) (Figure 1). None of these 14 patients had any other associated medical condition that could have accounted for their morbidity. Follow-up examination was performed after at least 1 year in the 6 group 2 patients who were able to live independently. All 6 continued to live independently.

Group 3

The rate of decrease in plasma sodium levels for the group 3 patients was 0.26 (0.12) mmol/L per hour. The 14 patients were treated with fluid restriction only, and all 14 experienced respiratory insufficiency within 24 hours of the diagnosis of hyponatremia. Therapy with sodium chloride was never provided. The plasma sodium levels after 12 and 24 hours, the rate of correction, and the initial plasma sodium level are shown relative to the out-

come (CPC 1-5) in Figure 2 and Table 2. All 14 patients were eventually intubated and received assisted ventilation, but not until at least 15 minutes after respiratory insufficiency was diagnosed. Despite eventual intubation and ventilation, all 14 patients died or experienced permanent brain damage. None of these 14 patients had other associated medical conditions that accounted for their morbidity. Eleven patients died, 10 within the initial 24 hours, and 1 after 70 days. Three survived in an institutionalized or vegetative state for more than 6 months (CPC = 3 to 5).

Effects of Initial Plasma Sodium Level, Rate of Correction, and Absolute Correction on Patient Outcome

There was not a significant correlation between either the rate of correction of plasma sodium ($r = 0.31$, $P = .10$) or the initial plasma sodium level ($r = 0.05$, $P = .12$) for any of the 53 patients (FIGURE 3). The absolute change in plasma sodium level during correction for group 1 patients was 22 (10) mmol/L; for group 2 patients, 30 (6) mmol/L; and for group 3 patients, 3 (2) mmol/L. The absolute change for both group 1 and group 2 was significantly greater than that for group 3 patients ($P < .01$ by analysis of variance) and group 1 patients had significantly less than group 2 patients ($P < .05$). The outcome in group 1 patients was 1.0 (all recovered), while it was 3.0 (1.2) in group 2 patients and 4.6 (0.7) in group 3 patients (Figure 2).

Autopsy Findings

Postmortem examination was performed for 5 patients. Three patients from group 3, who had died within 24 hours of respiratory arrest, had generalized cerebral edema, with evidence of tentorial herniation (uncal notching) in 1. In 4 of the 5 patients, the pons was normal. In 2 patients from group 2, there were focal infarctions of the basal ganglia, thalamus, hypothalamus, cortical gray matter, subcortical white mat-

ter, putamen, lateral pons, and corpus striatum. There was no evidence of central pontine myelinolysis in any of the 5 patients.

Neuroradiological Evaluation

Eleven patients (2 in group 2, 9 in group 1) had neuroradiological evaluation of the brain (either computed tomographic scan or magnetic resonance imaging) before the initiation of therapy with sodium chloride. In 6 of these 11 patients, the neuroradiological evaluation revealed evidence of cerebral edema. Follow-up magnetic resonance imaging of the brain was done at least 4 months after recovery from hyponatremic encephalopathy in the 10 patients in group 1 and the 8 patients in group 2 who recovered to the point where they could live independently. All 18 patients evaluated had no evidence of central pontine myelinolysis; 1 patient in group 2 had a lateral pontine lesion.

COMMENT

This study demonstrates that chronic symptomatic hyponatremia (hyponatremic encephalopathy) in postmenopausal women is not a benign condition, as has been previously suggested.^{2,3} There is substantial morbidity and mortality among such patients, with sequelae ranging from primary orthopedic injury to neurologic impairment and death (Figure 1). The morbidity and mortality associated with chronic symptomatic hyponatremia were caused primarily by consequences of the hyponatremia itself, in conjunction with failure to initiate therapy with IV sodium chloride in a timely manner. None of the patients who were treated with sodium chloride¹³ before the onset of respiratory insufficiency (group 1) showed any evidence of brain damage after 1 year of follow-up. The 2 patients in group 2 who were treated with IV sodium chloride after respiratory insufficiency and recovered also showed no evidence of brain damage after 1 year of follow-up. The 22 group 2 patients had a maximum correction of 30 (6) mmol/L over the initial 48 hours, and

this probably contributed to the brain damage, particularly in the 14 whose absolute correction exceeded 25 mmol/L in the initial 48 hours.¹³ Thus, central nervous system symptoms would appear to be an indicator of the need for initiation of therapy with hypertonic sodium chloride.

There are at least 2 distinct mechanisms that can induce brain injury in hyponatremic patients.²⁴ The first is hyponatremic encephalopathy, which is the result of brain edema and increased intracranial pressure. In group 1 patients, who had brain edema before therapy was initiated, this was most likely the mechanism of the neurological dysfunction. When therapy is begun before respiratory insufficiency, patient outcome is generally favorable, both in the current study (Figure 2) and among patients with acute hyponatremia.^{9,10,12,24} The second mechanism is improper therapy for hyponatremia (defined as an increase of more than 25 mmol/L in the initial 48 hours), which can be associated with brain damage.^{2,13,25,26}

Among 158 patients with hyponatremic encephalopathy, less than 4% of the brain damage was associated with improper therapy.²⁴ Among our group 2 patients, 14 had an outcome of CPC of 3 or higher (ie, disabled, vegetative, or dead) and in these, the absolute change in plasma sodium levels following respiratory insufficiency was 30 (6) mmol/L in the initial 48 hours. A change in plasma sodium in excess of 25 mmol/L in 48 hours has been associated with brain damage in hyponatremic patients,^{13,25} and these conditions in our group 2 patients probably contributed to their brain damage. Data from the current study strongly suggest that, in addition, fluid restriction, resulting in only a small change in plasma sodium (3 [2] mmol/L per day) in symptomatic patients, is often associated with respiratory insufficiency, leading to death or permanent brain damage (Figure 2). While our study was not designed to determine the appropriate therapy for chronic hyponatremic encephalopathy, it suggests that either overcorrection¹³ or undercorrec-

tion (Figure 2) can lead to an adverse outcome. The use of normal (154 mmol/L of sodium chloride) vs hypertonic (514 mmol/L of sodium chloride) sodium chloride solution deserves comment. If the patient has seizures and/or respiratory distress, it is prudent to increase plasma sodium levels by about 8 mmol/L within the initial hour,¹⁰ and this can only be accomplished with IV hypertonic sodium chloride or sodium bicarbonate. If the patient has volume contraction, plasma sodium levels can be best increased with IV isotonic (normal) sodium chloride.

In addition to overcorrection or undercorrection of hyponatremia, hypoxia has been found to play a major role in the genesis of hyponatremic brain damage in both humans¹⁸ and laboratory animals.²⁷ Twelve group 1 and 2 patients in whom blood gases were evaluated prior to therapy were found to have arterial PO₂ of 63 (25) mm Hg when they had chronic hyponatremic encephalopathy. This level of hypoxia has also been reported in animals with chronic hyponatremia.²⁸ It has been suggested that chronic hyponatremia is usually not accompanied by cerebral edema because the brain has had time to adapt.^{26,29} In the current study, 6 of the 11 group 1 patients with chronic hyponatremic encephalopathy had evidence of cerebral edema on neuroradiological evaluation, which indicates that the adaptive process was impaired. Hypoxia impairs brain adaptation to hyponatremia,²⁷ and it is quite possible that in our patients with hypoxia, the failure to adapt to hyponatremia, despite a duration of more than 48 hours, was in part the result of associated hypoxemia. Our study also indicates that in postmenopausal women with hyponatremic encephalopathy who have seizures, orthopedic injury, such as hip fracture, can be the initial clinical manifestation, as well as a major cause of morbidity (Figure 1). Similar orthopedic injuries have been reported following hyponatremia with convulsive activity.³⁰ Patients with chronic hyponatremia may also have brain atrophy of the temporal lobe.³¹

The plasma potassium level was low (3.2 [0.9] mmol/L) in these 53 hyponatremic patients. This hypokalemia may have contributed to the hyponatremia by a number of mechanisms, including stimulation of thirst, polydipsia, and impaired urinary concentrating ability.³²

There are several limitations to the present study. Men and younger women were not evaluated, and these data apply only to postmenopausal women. There was no attempt at epidemiological evaluation, and we have provided no information on the incidence or prevalence of any of the conditions associated with hyponatremia, which include orthopedic injury, respiratory insufficiency, and brain dam-

age. Furthermore, our findings only apply to patients with chronic hyponatremia and central nervous system symptoms. Unlike patients with hyponatremic encephalopathy, elderly patients with asymptomatic hyponatremia often will do well when treated with fluid restriction.⁵ Elderly patients with chronic hyponatremia have a very high mortality rate: among 295 such patients, the mortality rate was 25%.²⁻⁵ Of these, neither the percentage with encephalopathy or that died of hyponatremia can be ascertained, but at least part of this total appears to be associated with reluctance to treat chronic hyponatremic patients with IV sodium chloride.²⁻⁵ Among postmenopausal women with chronic hyponatremic en-

cephalopathy, neither the initial plasma sodium level nor the rate of correction are correlated with patient outcome (Figure 3).

In conclusion, chronic hyponatremic encephalopathy in postmenopausal women is associated with substantial morbidity and mortality (Figure 1). Active therapy with IV sodium chloride is both safe and effective. Fluid restriction, on the other hand, is inadequate therapy for such patients (Figure 2).

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