Neurologic Sequelae After Treatment of Severe Hyponatremia: A Multicenter Perspective[1]

Richard H. Sterns,[2] Joseph D. Cappuccio, Stephen M. Silver, and Eric P. Cohen

R.H. Sterns, J.D. Cappuccio, S.M. Silver, University of Rochester School of Medicine, Rochester General Hospital, Department of Medicine, Rochester, NY

E.P. Cohen, Medical College of Wisconsin, Froedtert Memorial Lutheran Hospital, Department of Medicine, Milwaukee, WI

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ABSTRACT

Severe, symptomatic hyponatremia is often treated urgently to increase the serum sodium to 120 to 130 mmol/L. Recently, this approach has been challenged by evidence linking "rapid correction" (>12 mmol/L per day) to demyelinating brain lesions. However, the relative risks of persistent, severe hyponatremia and iatrogenic injury have not been well quantified. Data were sought on patients with serum sodium levels ≤105 mmol/L from the membership of the American Society of Nephrology. Respondents were given a report form asking specific questions regarding the cause of hyponatremia, presenting symptoms, rate of correction, and neurologic sequelae. Data on 56 patients were analyzed. Fourteen developed posttherapeutic complications (10 permanent, 4 transient) after correction to a serum sodium >120 mmol/L. Eleven of these 14 patients (including 3 with documented central pontine myelinolysis) had a biphasic course in which neurologic findings initially improved and then worsened on the second to sixth day. Posttherapeutic complications were not explained by age, sex, alcoholism, presenting symptoms, or hypoxic episodes. Increased chronicity of hyponatremia and a high rate of correction in the first 48 h of treatment were significantly associated with complications. No neurologic complications were observed among patients corrected by <12 mmol/L per 24 h or by <18 mmol/L per 48 h or in whom the average rate of correction to a serum sodium of 120 mmol/L was ≤0.55 mmol/L per hour. It was concluded that patients with severe chronic hyponatremia are most likely to avoid neurologic complications when their electrolyte disturbance is corrected slowly.

Key Words: *Osmolality, brain, demyelinating diseases, central pontine myelinolysis, water intoxication*

Clinicians treating severe, symptomatic hyponatremia face a dilemma. Should the serum sodium be urgently restored to a "safe" level (120 to 130 mmol/L), to rescue the patient from the perils of cerebral edema (1)? Or, should the serum sodium be prevented from increasing "too much" (>12 mmol/L per day) to avoid demyelinating brain lesions caused by "rapid correction" (2)?

The lower the serum sodium, the more serious the dilemma. At extremely low concentrations, it becomes impossible to both raise the sodium level into a "safe" range and avoid excessive correction; a choice must be made between the risks of persistent severe hyponatremia and the risks of iatrogenic injury. Unfortunately, the limited data available do not allow these risks to be quantified. Thus, controversy continues to reign over what treatment strategy is best. A recent article (3) concluded: "Judiciously rapid correction of severe hyponatremia . . . until levels are mildly hyponatremic (120–132 mmol/L) is not harmful, is not associated with clinical or radiologic neurologic damage, and is definitely indicated in symptomatic patients." By contrast, another survey of severely hyponatremic patients (4), concluded: "there is no evidence that such therapy improves the prognosis of severe chronic hyponatremia; on the contrary, it may well be responsible for the few neurologic complications that occur."

Three months after these two conflicting articles appeared, we began to seek data from the membership of the American Society of Nephrology (ASN) on patients with serum sodium concentrations of 105 mmol/L or less. This serum sodium concentration was chosen for two reasons. First, several investiga-

[1] Received June 30, 1993. Accepted August 31, 1993.
[2] Correspondence to Dr. R. H. Sterns, Rochester General Hospital, Nephrology Unit, 1425 Portland Avenue, Rochester, NY 14621.

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tors had identified this level as one with a high incidence of neurologic morbidity (4 to 7). Second, when the serum sodium concentration is below 106 mmol/L, a clear distinction can be drawn between the two conflicting recommendations: raising the serum sodium concentration to at least 120 mmol/L in 24 h versus maintaining the rate of correction below 12 mmol/L per day.

METHODS

Survey of All ASN Members

In February 1988, we sent a letter to all 4,100 members of the ASN requesting data on patients with serum sodium concentrations of 105 mmol/L or less. The letter expressed interest in all recently treated patients with sodium concentrations in this range, including those with and without neurologic complications, but excluding cases in which hyponatremia could be explained by laboratory error, pseudohyponatremia, hyperglycemia, or infusions of mannitol or glycine.

Respondents to the letter completed a report form that asked for the patient's age and sex, date of the hyponatremic episode, preexisting conditions, etiologic factors that may have contributed to hyponatremia, and the patient's neurologic symptoms before, during, and after treatment (Table 1). The form asked whether the patient had become hypoxic or had suffered a respiratory arrest before or during treatment, whether a diagnosis of central pontine myelinolysis had been made, whether the patient died, and if so, whether the death was due at least in part to neurologic complications.

Respondents noted the use or nonuse of hypertonic saline and reported several measures of the rate of correction of hyponatremia, including the time required to raise the serum sodium concentration above 120 mmol/L, the most rapid increase in millimoles per liter per hour during any period of 4 h or more, the increase in serum sodium during the first 12, 24, and 48 h, and the highest serum sodium during the first week of therapy. All patients with serum sodium levels ≤105 mmol/L who were seen and treated by the authors or their associates during the past 5 yr were included in the survey.

Definitions

As previously described (4), "acute hyponatremia" included psychotic patients with severe polydipsia and patients who had become hyponatremic in the hospital. Patients who had become hyponatremic at home drinking conventional volumes of water defined the "chronic hyponatremia" group.

Data Analysis

The presence or absence of neurologic complications of any duration after the correction of the serum sodium to 120 mmol/L divided patients into two groups. The *t* test compared all continuous variables between the groups of patients with complications and patients without them. χ^2 techniques were used to compare dichotomous variables. Data are expressed as means ± SE.

RESULTS

Sixty-four response forms met the selection criteria for the study. Ten of these cases were identified prospectively at the authors' institutions, and an additional four had been encountered during the course of a 3-yr prospective study of hyponatremic patients admitted to a French hospital. The remaining 50 cases originated from 38 different medical centers located in the United States, Canada, France, Chile, and Taiwan, of which 5 contributed multiple cases: three centers, $N = 2$; one center, $N = 4$; and one center, $N = 7$. Of these 50 patients, 34 had been encountered within 6 months before or after the receipt of the letter (23 had been seen within 3 months of the letter); 2 had been seen between 11

TABLE 1. Presenting symptoms in the total patient group and in those with posttherapeutic neurologic sequelae[a]

Symptoms	No. of Patients	No. With Sequelae
(a) Evidence of Brain Death Before Treatment	None	None
(b) Ongoing Seizures	8	3
(c) Unarousable	5	3
(d) Obtunded but Arousable	7	1
(e) Less Than Fully Awake but Able To Communicate	6	0
(f) Awake With Neurologic Impairment (Confusion, Disorientation, Dysarthria, Gait Disturbance, Twitching, Falling, *etc.*)	20	3
(g) Nonspecific symptoms (Headache, Nausea, Vomiting, Weakness, Dizziness)	10	4
(h) Absolutely Asymptomatic	None	None
Total	56	14

[a] Pretreatment neurologic symptoms and the incidence of posttherapeutic neurologic complications.

and 23 months after the letter; and 14 had been culled from the respondents' files, representing cases seen between 10 months and 7 yr before our request for data.

Excluded Cases

We excluded five cases because data on the rate of correction of hyponatremia were absent. Three of these patients (including one young woman with a serum sodium of 96 mmol/L) recovered uneventfully. Two were elderly women who initially improved neurologically during treatment but then worsened, one lapsing into coma and the other dying of a respiratory arrest with a serum sodium level of 124 mmol/L.

Of the patients who had complete data sets, three were excluded from further analysis because of underling conditions that made interpretation of the data impossible. One of these patients died of septic shock shortly after the diagnosis of hyponatremia, and one had an acute subarachnoid hemorrhage from which he did not recover neurologically. Both patients' sodium levels rose by more than 25 mmol/L during the first 24 h of therapy. The third patient, a woman with severe biventricular heart failure, did well neurologically but died of pulmonary edema and cardiogenic shock on the fifth hospital day, when her serum sodium level was 126 mmol/L.

Data Analysis

Fifty-six patients remained for analysis. Over two thirds of the 56 patients were women, and the average age of both men and women was 59 yr. Eleven women were in their reproductive years (ages 25 to 52), a group that has recently been identified as being at especially high risk of neurologic complications from hyponatremia (8–10). The incidence of alcoholism (16.7%) was equal in men and women, but no patient had advanced liver disease.

Outcome

Forty-two of the 56 patients improved steadily during treatment of hyponatremia and had no posttherapeutic neurologic complications. Ten displayed permanent neurologic sequelae, and four had transient neurologic complications that emerged after the serum sodium concentration increased to above 120 mmol/L (Table 2; Figure 1).

Eleven of the 14 patients with posttherapeutic complications had a biphasic course. Respondents chose the term "steady improvement" (as opposed to alternative choices of "fluctuating but tending toward better," "no significant change," "getting worse no matter what therapy was given," or "getting worse until the rate of correction of hyponatremia was increased") to describe the condition of these patients during correction to a serum sodium concentration of 120 mmol/L. Beginning on the second to sixth days, the patients' neurologic condition worsened. Four of these episodes lasted for only 1 to 2 days, during which time the patient became unresponsive or exhibited psychotic behavior, and seven episodes persisted permanently or ended fatally ($N = 2$). Magnetic resonance imaging (MRI) showed pontine lesions in three of the seven patients with permanent sequelae; the others had negative MRI scans done less than 2 wk after the onset of neurologic findings (three cases) or a single negative computed tomographic scan early in the hospital course (one case).

TABLE 2. Patients with neurologic sequelae[a]

Age/Sex	Serum Na (mmol/L)	Symptoms	Use of Hypertonic Saline	Maximum Correction (mmol/L per h)	Correction in 24 h (mmol/L)	Correction in 48 h (mmol/L)	Sequelae
60/M	100	g	Yes	1	24	32	Onset Day 3/transient
60/F	97	f	No	2.5	22	27	Onset Day 3/transient
56/M	103	g	No	0.9	14	20	Onset Day 2/transient
52/F[b]	104	f	No	1.3	16	19	Onset Day 4/transient
68/M	97	b	Yes	4	29	31	Onset Day 5/permanent
72/M	99	b	Yes	1	15	25	Onset Day 3/died Day 4
31/F	98	d	Yes	2	28	37	Onset Day 6/permanent
66/F	104	f	Yes	2.5	20	23	Onset Day 4/permanent
59/F	96	g	Yes	1.4	19	32	Onset Day 6/CPM/died
40/M[b]	96	c	No	0.9	14	28	Onset Day 5/CPM
35/F[b]	91	g	No	2	26	41	Onset Day 3/CPM
42/F	105	b[c]	No	1.5	18	23	Monophasic permanent
60/F[b]	96	c	Yes	6	43	44	Monophasic permanent
80/F	95	e	Yes	1.7	25	33	Monophasic permanent

[a] Serum Na, serum sodium concentration before treatment. Symptoms before treatment are classified by letters b to g as defined in Table 1. CPM, central pontine myelinolysis, diagnosed by MRI.
[b] Alcoholism.
[c] Respiratory arrest and endotracheal intubation before treatment.

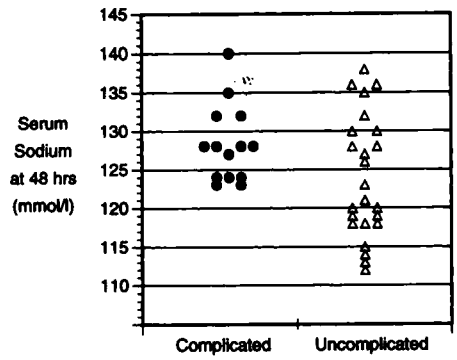

Figure 1. Serum sodium concentrations 48 h after the start of therapy in chronically hyponatremic patients. "Complicated" denotes subjects who developed posttreatment neurologic complications, and "Uncomplicated" denotes subjects who remained free of neurologic sequelae.

In three cases, the patient's course was monophasic, characterized by severe neurologic symptoms at presentation and persistent obtundation after treatment. Respondents chose the term "no significant change" to describe their patient's condition during the correction of hyponatremia. One of these patients suffered a respiratory arrest requiring intubation at the time of presentation (before treatment); she eventually awoke but demonstrated permanently disordered speech, movement, and mentation. Another patient with a monophasic course experienced the fastest correction recorded in this series (maximal rate, 6 mmol/L per hour, 41 mmol/L per 12 h, 43 mmol/L per 24 h, 44 mmol/L per 48 h).

TABLE 3. Pretreatment variables and the incidence of posttherapeutic neurologic sequelae

Variable	*N*	Neurologic Sequelae (%)	*P*
Duration of Hyponatremia			
Acute	18	0	0.003
Chronic	38	38	
Etiology of Hyponatremia			
No thiazides	31	16	0.06
Thiazides	25	36	
Iv fluids	9	0	0.07
No iv fluids	47	30	
Symptoms			
Mild	36	21	>0.1
Severe	20	35	
Sex			
Male	18	28	>0.1
Female	38	24	
Alcoholism			
No	44	23	>0.1
Yes	12	33	

Pretreatment Variables Determining Outcome

Serum Sodium Level. Patients developing posttherapeutic complications had serum sodium concentrations that were slightly but significantly lower than those of uncomplicated patients (99 ± 0.5 versus 101 ± 0.5 mmol/L; $P < 0.02$).

Chronicity. None of the patients with "acute" hyponatremia developed posttherapeutic complications (including 10 who presented with seizures and/or unresponsiveness before treatment). Patients classified as "chronic" had a 37% incidence of sequelae ($P < 0.01$ versus "acute"), including four of seven whose pretreatment symptoms were mild and nonspecific (headache, nausea and vomiting, weakness, dizziness, *etc.*) (Table 3).

Etiology of Hyponatremia. Neither alcoholism nor any of the etiologic factors responsible for hyponatremia were significantly associated with complications (Table 3).

Symptoms. Pretreatment neurologic symptoms did not differ significantly between the patients with posttreatment sequelae and those whose course was uncomplicated. This was true when symptoms were considered by their individual classification (Table 1) or by grouping into mild (lethargy, minor findings, or other) and severe (obtunded, unarousable, or seizing) (Table 3). No patient's condition worsened between the time that treatment was begun and the time that the serum sodium level had been increased to 120 mmol/L.

Hypoxic Episodes. Four patients required endotracheal intubation before the treatment of hyponatremia had begun. Three recovered uneventfully, and one developed permanent neurologic sequelae (Table 2). An additional patient (a 72-year-old man) who subsequently developed delayed neurologic deterioration was on home oxygen for pulmonary disease and had a documented Po_2 of 54 mm Hg during the correction of hyponatremia.

Age and Gender. Recently, some authors have suggested that women of childbearing age do not tolerate severe hyponatremia as well as other groups (8–10). We found no significant differences for age or sex (Table 3). In this series, there were 11 women aged 52 and younger; all survived. Their incidence of permanent (27%) or transient (9%) sequelae did not differ significantly from the incidence in older women (17 and 4%) or in men (17 and 11%). The inclusion of the three cases with incomplete data would strengthen this conclusion. However, we did not encounter young women with acute postoperative hyponatremia, and it has been in this setting that published accounts of fatal cerebral edema have occurred (8–10).

Treatment Variables Determining Outcome

Hypertonic Saline. Some patients treated with isotonic saline alone demonstrated high rates of correction (Table 2), and treatment with hypertonic saline did not preclude slow rates of correction (see Table 5). This may explain why the incidence of complications was identical (26%), irrespective of whether hypertonic saline was used (32 cases) or not used (24 cases).

Rate of Correction. This study considered a variety of measures of the rate of correction of hyponatremia. The maximal rate of correction (2.1 ± 0.2 versus 1.6 ± 0.2 mmol/L per hour) and the amount of correction at 12 h (15 ± 1 versus 13 ± 1 mmol/L), 24 h (22 ± 1 versus 18 ± 1 mmol/L), and 48 h (30 ± 1 versus 24 ± 1 mmol/L) all tended to be higher in patients with neurologic sequelae than in patients without them. However, when analyzed as continuous variables, only the amount of correction at 48 h achieved statistical significance ($P = 0.03$).

Table 4 shows the correction rates divided into dichotomous variables according to previously published criteria (2–4,11). Posttherapeutic neurologic complications did not occur in any patient corrected by <0.55 mmol/L per hour to a serum sodium level of 120 mmol/L (4) or by <12 mmol/L per 24 h (Figure 2) (2). There was a statistically significant association between posttherapeutic neurologic complications and a rate of correction exceeding either of these limits: 33 to 35% of all patients and 50 to 56% of the chronic group who were corrected "rapidly" by these criteria developed complications. Proposed cutpoints of 20 mmol/L per 24 h (11) or 25 mmol/L per 48 h (3) and a maximal correction rate of 2.5 mmol/L per hour (11) did not allow discrimination between complicated and uncomplicated cases. When the 48-h cutpoint was set at 18 mmol/L, however, there was

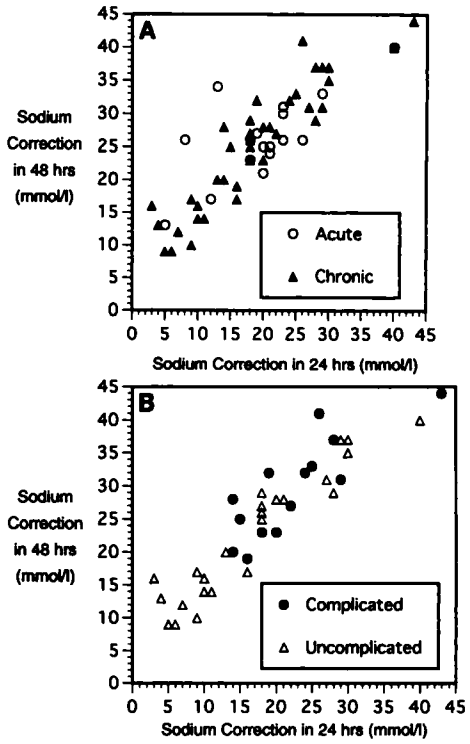

Figure 2. Increment in the serum sodium concentration during the first 24 and 48 h. (A) Patients with acute (open circles) and chronic (closed triangles) hyponatremia. (B) Chronically hyponatremic patients with (closed circles) and without (open triangles) posttreatment neurologic complications.

TABLE 4. Treatment variables and the incidence of posttherapeutic neurologic sequelae

Variable	All Patients			Chronics[a]		
	Number Treated	Number With Sequelae *N* (%)	*P*	Number Treated	Number With Sequelae *N* (%)	*P*
Maximum Correction (mmol/L per h)						
≤2.5	49	12 (24)	>0.1	32	12 (38)	>0.1
>2.5	7	2 (29)		6	2 (33)	
Correction to 120 mmol/L (mmol/L per h)						
≤0.55	16	0 (0)	0.006	13	0 (0)	0.001
>0.55	40	14 (35)		25	14 (56)	
Correction in 24 h (mmol/L)						
≤12	13	0 (0)	0.02	10	0 (0)	0.005
>12	43	14 (33)		28	14 (50)	
≤20	33	7 (21)	>0.1	24	7 (29)	>0.1
>20	23	7 (30)		14	7 (50)	
Correction in 48 h (mmol/L)						
≤18	13	0 (0)	0.02	11	0 (0)	0.003
>18	43	14 (33)		27	14 (52)	
≤25	25	5 (20)	>0.1	18	5 (28)	>0.1
>25	31	9 (29)		20	9 (45)	

[a] Chronics refers to patients with chronic hyponatremia as defined in Methods.

a significant association between complications and correction that exceeded this limit. Fourteen (52%) of the 27 chronic patients who were corrected by more than 18 mmol/L in 48 h developed complications, whereas all 11 chronic patients who were corrected more slowly had an uncomplicated course ($P = 0.003$). With two exceptions, acute patients were corrected by more than 18 mmol/L per 48 h and most were corrected by more than 25 mmol/L per 48 h; despite (or because of) rapid correction, no complications developed in this group.

DISCUSSION

In a previous study (4), we found that chronically hyponatremic patients with serum sodium concentrations ≤105 mmol/L have a high incidence of neurologic sequelae. Although we had treated only a small number of such patients, our findings suggested that complications could be avoided in this high-risk group by using slow rates of correction. This study confirms and extends these observations in a much larger series. Neurologic sequelae after the treatment of severe chronic hyponatremia were associated with increases in sodium concentration that were >12 mmol/L over the first 24 h and >18 mmol/L over the first 48 h of therapy. Neither age, sex, nor hypoxic episodes (recently proposed as the most important determinants of brain damage in hyponatremia) significantly affected the outcome.

To obtain a large series of patients with sodium concentrations ≤105 mmol/L, we prospectively gathered data on our own patients and also sought data with a letter sent to the entire membership of the ASN. Because hyponatremia of this severity is encountered extremely rarely, we anticipated that only a small fraction of the 4,100 members would be treating a case at the time they received our letter and that not all would be willing to complete a detailed report form describing their findings. In fact, data were obtained from only 1% of the membership. The low response rate is predictable and does not invalidate our findings. All members were free to submit cases, regardless of outcome or treatment strategy, and we made no special effort to seek cases that conformed to our expectations.

Our series does not appear to have been seriously affected by selection or recall bias favoring patients with or without complications. In fact, the incidence of neurologic complications is nearly identical to that of our previous study in which cases were identified by a search of laboratory records (Figure 3). Twenty-three of the cases reported here were seen by individual nephrologists within 3 months of our mailed request for data. Had we limited our analysis to these 23 cases and the 14 patients who were gathered prospectively, our conclusions would not have changed.

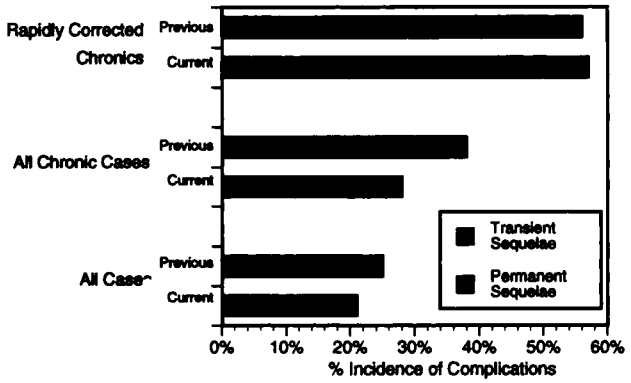

Figure 3. Incidence of complications in this survey compared with complications in a previously published survey (4); the data from the previous survey are taken from a subset of 19 consecutive patients with serum sodium levels ≤105 mmol/L. Both series define "acute" and "chronic" hyponatremia identically (see Methods); "rapidly corrected" denotes those cases in which the serum sodium concentration was increased to 120 mmol/L by >0.55 mmol/L per hour.

As in our previous report (4), we arbitrarily divided patients into those with "acute" and those with "chronic" hyponatremia. Because the precise duration of the electrolyte disturbance could not be determined, the division was based on the setting in which hyponatremia developed. Patients with psychotic polydipsia or hospital-acquired hyponatremia were designated "acute," and patients who had become hyponatremic at home drinking conventional volumes of water were designated "chronic." Acute patients remained free of posttherapeutic sequelae, despite severe presenting symptoms, whereas chronic patients, whose initial symptoms were often mild, sometimes developed devastating neurologic complications.

Over half of our "acute" patients were psychotic water drinkers. Although fatalities from cerebral edema have been reported in such patients, a review of the literature suggests that the incidence is well below 5%, regardless of age and sex (12). Although hyponatremia typically corrects rapidly in psychotic water drinkers (because of a spontaneous water diuresis), late neurologic complications are rare (4,12). To be consistent with our previously published survey (4), we also classified patients with hospital-acquired hyponatremia as "acute." In those cases in which the duration was known, hyponatremia had evolved over 48 h or more. Most published reports of fatal cerebral edema have been in patients with untreated postoperative hyponatremia of less than 48-h duration. Had we placed our hospital-acquired patients in the "chronic" group (a classification more in keeping with the actual duration of the electrolyte

disturbance), the conclusions of our statistical analysis would not have been altered.

In contrast to the acute group, our chronic patients had a high incidence of posttherapeutic neurologic complications. Neurologic complications usually appeared after 2 to 6 days of steady improvement. Delayed posttherapeutic complications with a similar time course have been reported in patients with central pontine and extrapontine myelinolysis (2). The disorder typically presents with pseudobulbar palsy and quadriparesis, but a wide spectrum of clinical manifestations has been reported, including behavioral and movement disorders (12).

As in three of our patients, MRI can often demonstrate areas of demyelination in patients who deteriorate neurologically after the treatment of hyponatremia. Pontine lesions are most typical, but associated lesions are frequently present in the periventricular white matter, basal ganglia, thalamus, and corticomedullary junction bilaterally. Sometimes, the only demonstrable lesions are extrapontine. Scans often remain normal until 3 to 4 wk after the onset of clinical findings, and positive MRI findings may eventually resolve (11–13). Milder cases of the syndrome with transient neurologic findings may be impossible to document radiographically with existing technology.

The term "osmotic demyelination syndrome" has been proposed to describe delayed-onset neurologic findings in patients who are treated for hyponatremia (2). The syndrome can be defined by its time course rather than by the specific neurologic findings that develop or by the anatomic location of brain lesions that are documented. Complications of therapy may be better defined by the clinical syndrome than by the results of imaging techniques. In this series, MRI documented pontine lesions in three patients. However, eight other patients whose symptoms followed a similar biphasic time course had negative imaging studies.

A similar syndrome of delayed neurologic deterioration develops after rapid correction of chronic (≥3 days) but not acute (≤1 day) experimental hyponatremia (14–19). Demyelinating brain lesions, similar to those of myelinolysis in humans, have been induced in animals by increasing the serum sodium concentration by at least 13 to 16 mmol/L in 24 h. The risk of demyelination increases with the rapidity and extent of correction (17). Control animals with uncorrected chronic hyponatremia do not deteriorate neurologically and do not develop brain lesions (14, 16,17).

Recent physiologic observations may explain why iatrogenic brain damage occurs when the serum sodium concentration is normalized too rapidly. Cerebral edema is avoided in severe hyponatremia by an adaptive loss of electrolyte and organic solute (osmolytes) from brain cells that begins within 24 h (12,16,20–23). During correction of the electrolyte disturbance, organic osmolyte contents return to normal. However, the rate of reuptake of these compounds by sodium-dependent transporters may be altered by chronic osmotic disturbances (24). Thus, after long-standing hyponatremia, the brain cell remains depleted of organic osmolytes for several days as the serum sodium concentration returns to normal (21). Until intracellular brain solute is restored, even a "low" serum sodium concentration may be more hypertonic than the cell. Thus, the rapid correction of hyponatremia, even to mildly hyponatremic levels, can cause cellular dehydration and, potentially, injury (16).

Consistent with observations made in experimental models, our studies identified both the chronicity of hyponatremia and the rate of correction as significant risk factors for posttherapeutic neurologic sequelae. Other unidentified variables must also affect the outcome because not all chronically hyponatremic patients who were corrected rapidly developed complications. Some investigators have emphasized hypoxia and cerebral edema as the major causes of brain damage in hyponatremia (25). Recognized hypoxic episodes and "respiratory arrests" were infrequent in our series and equally prevalent among patients with and without complications. However, we cannot completely exclude hypoxia as a contributing factor in the cause of brain damage, particularly in the three patients with a monophasic course.

In previous work, we have suggested that the correction of chronic hyponatremia by >12 mmol/L per day may cause neurologic complications (2). This series supports that conclusion. Others have emphasized that the increment over the first 2 days is a more important risk factor (3), proposing a limit of 25 mmol/L. Although our data confirm that the magnitude of correction during the first 48 h is important, they suggest that complications can occur after an increase of only 19 mmol/L. In this series, there was a close correlation between the amount of correction in the first 24 h and the amount of correction in the first 48 h of treatment (Figure 2). All patients corrected by >18 mmol/48 h had also been corrected by >12 mmol/24 h; all but one corrected by <18 mmol/L per 48 h was also corrected by <12 mmol/L per 24 h (Table 5; Figure 2). Thus, it would be premature to conclude that correction of up to 18 mmol/L per day is "safe" as long as the 2-day increment is also <18 mmol/L.

Much of the controversy regarding the relative merits of "rapid" and "slow" correction of hyponatremia can be traced to the way in which these terms have been used. Thus, several small series have reported on patients with chronic hyponatremia who have

TABLE 5. Patients corrected by <18 mmol/L in the first 48 h of treatment[a]

Age/Sex	Serum Na (mmol/L)	Use of Hypertonic Saline	Presenting Symptoms	Maximum Correction (mmol/L per h)	Correction in 24 h (mmol/L)	Correction in 48 h (mmol/L)	Sequelae
76/F[b]	103	No	g	0.3	5	13	None
80/F[b]	103	Yes	g	0.9	12	17	None
67/F	103	No	e	0.3	5	9	None
68/F	104	No	d	0.4	10	14	None
58/M	104	Yes	g	0.4	9	17	None
60/F	103	No	f	0.5	10	16	None
48/F	105	No	f	0.5	9	10	None
75/M	104	No	f	0.8	3	16	None
50/F	104	No	g	1	6	9	None
77/M	105	No	f	1	4	13	None
63/F[c]	103	No	f	1	16	17	None
66/M	104	Yes	c[d]	2	11	14	None
88/F	102	No	f	0.6	7	12	None

[a] Abbreviations are as described in Tables 1 and 2.
[b] Hospital-acquired hyponatremia.
[c] Alcoholism.
[d] Postictal; required endotracheal intubation before treatment.

been corrected "rapidly" without adverse consequences (3,24,26). The explanation for the discrepancy between this experience and ours may rest in the serum sodium levels before treatment. Successful rapid correction has been reported primarily in patients whose initial serum sodium concentrations were not much lower than 120 mmol/L (3,24,26). Although maximal rates of correction were as high as 2 mmol/L per hour (and therefore described as "rapid"), the total increase over 24 to 48 h was in a range that we, too, find to be usually free of complications.

When patients with either acute or chronic hyponatremia present with severe neurologic symptoms, we and others have recommended that the serum sodium concentration be increased by 1 to 2 mmol/L per hour during the first few hours of therapy (11,12). There is as yet no evidence that this approach is harmful as long as the total increase over 24 and 48 h is not excessive. On the surface, this recommendation would appear to conflict with our finding that correction by >0.55 mmol/L per hour is associated with a high rate of complications in chronic patients. However, in our analyses, the figure of 0.55 mmol/L per hour is not the initial or *maximal* rate of correction. Rather, it is the *average* rate of correction to a serum sodium level of 120 mmol/L (calculated by taking the difference between the presenting serum sodium level and the first sodium concentration above 120 mmol/L and dividing by the time required to achieve this increase). By this measure, correction can still be considered "slow," despite a 1 to 2 mmol/L per hour increase in sodium concentration in the first few hours.

A similar computation of rate has led some authors to link correction by <0.7 mmol/L per hour with a high mortality rate (5). This conclusion (drawn from a literature review) was not based on the maximal rate of correction; it was based on the time required to reach a sodium level of 128 to 130 mmol/L. Fatal cases (often with documented central pontine myelinolysis) that were cited by the authors initially presented with serum sodium concentrations ≤105 mmol/L and were corrected by >12 mmol/L in 24 h and >18 mmol/L in 48 h. Yet, correction was considered "slow" because the target value of 128 to 130 mmol/L was not reached for several days. As shown in Figure 1, this analysis would misleadingly classify most of our patients with complications as undergoing "slow" correction, despite large increases in sodium concentration in the first 12, 24, and 48 h (Table 2).

Our survey will not end the debate on the proper management of symptomatic hyponatremia. However, it provides a framework for more conclusive studies. As in previous reports, we find that chronically hyponatremic patients whose serum sodium concentrations are ≤105 mmol/L have a high incidence of serious neurologic sequelae. Before any therapeutic regimen is accepted as "safe," it should be tested prospectively in this high-risk group. On the basis of our findings, correction should be limited to <12 mmol/L per 24 h and <18 mmol/L per 48 h, even if the serum sodium concentration remains below 120 mmol/L for more than 2 days. If a larger prospective trial shows this approach to be free of complications, it would be difficult to justify more aggressive therapy.

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