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HYPONATREMIA, CONVULSIONS, RESPIRATORY ARREST, AND PERMANENT BRAIN DAMAGE AFTER ELECTIVE SURGERY IN HEALTHY WOMEN

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Abstract Severe hyponatremia developed after elective surgery in 15 previously healthy women who subsequently either died or had permanent brain damage. The mean age was 41 years (range, 22 to 66), and the preoperative serum sodium level was 138 mmol per liter. All the patients recovered from anesthesia, but about 49 hours after surgery, when the average plasma sodium level was 108 mmol per liter, grand mal seizures, followed by respiratory arrest requiring intubation, developed in all 15. At that time, the urinary sodium level and the osmolality averaged 68 mmol per liter and 501 mOsm per kilogram, suggesting inappropriate secretion of antidiuretic hormone. In 10 of 15 patients, an acute cerebral vascular disorder was suspected, leading to a delay in treatment and multiple diagnostic studies, including CT scanning, cerebral angiography, and open-brain biopsies. The net postoperative fluid retention was 7.5 liters, and when correction of the serum sodium level was initiated, the rate of correction was less than 0.7 mmol per liter per hour. Histologic studies of the brain in five patients were not diagnostic, and no patient had any evidence of central pontine myelinolysis on the basis of autopsy, brain biopsy, or CT scanning. Seven patients recovered from coma after the serum sodium level was increased to 131 mmol per liter, but coma recurred two to six days later and ended in either death or a persistent vegetative state. Overall, 27 percent of the patients died, 13 percent had limb paralysis, and 60 percent were left in a persistent vegetative state. (N Engl J Med 1986; 314:1529-35.)

HYPONATREMIA is probably the most common of all electrolyte disorders seen in a general hospital population.[1-5] Acute symptomatic hyponatremia has been reported in a wide variety of clinical circumstances, including that of the postoperative period.[1-19] However, permanent brain damage associated with hyponatremia appears to be infrequent, with less than a dozen cases reported.[2,9-13] Some investigators believe that other medical conditions associated with hyponatremia, rather than hyponatremia itself, are primarily responsible for brain damage.[3,7,8,14,15] Still others believe that "chronic" hyponatremia (serum sodium level below 120 mmol per liter for over 36 hours) does not generally result in cerebral damage.[3,7,8] Because of these conflicting ideas, there has developed a dichotomy of opinion about the therapy of symptomatic hyponatremia.[5-8]

It is unclear whether brain damage from hyponatremia is actually rare or merely underreported. In addition, many believe that the morbidity and mortality associated with hyponatremia are often due to associated medical conditions, such as heart, lung, liver, brain, or kidney disease.[14,15] Anderson and associates found that 1 percent of hospitalized patients[1] and 4.4 percent of postoperative patients[16] had hyponatremia (serum sodium level below 130 mM), but none of the patients in their series had brain damage. However, hyponatremia was associated with a 60-fold increase in mortality,[1] which was usually due to associated medical conditions. In the present study, my colleagues and I sought to avoid the influence of comorbid events on morbidity and mortality by restricting study subjects to patients who were essentially healthy and in whom hyponatremia developed in a hospital setting.

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METHODS

Over a period of 10 years, I was asked to see in consultation 15 patients with severe symptomatic hyponatremia who were generally healthy women who had undergone elective surgery. None had any serious underlying medical conditions before hyponatremia developed, all had had normal preoperative serum sodium levels, and all recovered from general anesthesia to the point of being able to walk, converse, and eat.

The 15 patients were seen at 15 medical centers and were followed for at least two years after their surgery, with a mean follow-up of four to six years. All the patients were ambulatory women who were either gainfully employed workers or active homemakers before their elective surgery. Only one (Patient 12) had any disability that may have interfered with an active life (coronary artery disease). In all cases, the patients were seen after the onset of seizures and coma and the diagnosis of hyponatremia. In no instance was therapy of the hyponatremia determined by me. Data were obtained both from the patient records for the period before seizure activity and from observation of the patients after the onset of seizures. The patients' age range was 22 to 66 years (mean ±SE,

41±4). Associated medical conditions included cholecystitis, vertebral fractures, migraine, pregnancy, diabetes insipidus, epistaxis, coronary artery disease, pelvic inflammatory disease, hypertension (two patients), and leiomyomatous disease of the uterus (five patients). The amount of total body water was calculated on the basis of sex, age, and weight.[17] Data are expressed as means ±SE. Significance was determined with use of the unpaired t-test.

Results

The mean weight of the 15 women was 56.8±2.6 kg, and the initial plasma sodium level before surgery was 138±1 mmol per liter. The operations these women had undergone included placement of a Stryker frame, cholecystectomy, uterine dilation and curettage, repair of a torn shoulder ligament, cosmetic dental surgery (two patients), ligation of a bleeding nasal septum, transluminal dilation of the right coronary artery, exploratory laparotomy, and abdominal hysterectomy (five patients). Anesthesia included intravenous meperidine hydrochloride (Demerol) or morphine in two patients, local anesthesia (tetracaine [Pontocaine], cocaine plus lidocaine [Xylocaine], and lidocaine plus diazepam) in three patients, enflurane (Ethrane) in six patients, and halothane in three patients. One woman did not actually undergo surgery, but was admitted to the hospital with an allergic skin reaction (to ampicillin). Her subsequent clinical course was similar to that of the other 14 patients, as was the outcome, so she has been included.

Postoperative Symptoms

All the patients awoke from general anesthesia, and all were able to walk, communicate, eat, and void spontaneously within eight hours of surgery. At 49±7 hours after surgery, grand mal seizures developed in all the patients. These seizures were generalized, but precise details of the seizure activity are not available. Within 60 minutes after the onset of seizures, respiratory arrest developed in all the patients. All were intubated but had hypoxic–anoxic intervals of various durations. At the time of seizure activity, the plasma sodium concentration was 108±2 mmol per liter. The symptoms that occurred before the seizures included nausea, headache, and emesis in all patients. Half were incontinent, and 30 to 50 percent were hostile (four patients), disoriented (four), depressed (four), or hallucinating (seven) — symptoms that resulted in psychiatric consultation in the cases of five patients. In 8 of 15 patients, the onset of seizures and respiratory arrest was explosive in nature. The patients were lying in bed, awake, with only minor symptoms. Within a period of less than 10 minutes, the eight patients went from a state in which they were alert and talking, to a grand mal seizure that was soon followed by respiratory arrest. Within two hours after the grand mal seizures, all the patients were evaluated neurologically by either a neurologist (36 percent) or an internist (64 percent). Neurologic symptoms that were observed after respiratory arrest and intubation included unequal pupils (12 patients); positive Babinski's sign (13), which was unilateral in 2 of 13 patients; hemiparesis (4); fixed dilated pupils (10); bilateral clonus of the knees and ankles (12), lethargy (9), and grand mal seizures (15).

Initial Diagnosis

After the seizures and respiratory arrest, hyponatremia was initially suspected as a cause in only 33 percent of the cases. In the other 67 percent, the initial diagnosis was either acute stroke, sagittal sinus thrombosis, arteriovenous malformation, herpes encephalitis, migraine with vascular occlusion, rupture of cerebral aneurysm, skull fracture with subdural hematoma, or coma of unknown origin. None of the aforementioned diagnoses were subsequently confirmed. The fact that hyponatremia was not usually suspected as the cause of coma led to extensive consultation. There were a total of 42 consultants for 15 patients (internal medicine, 8; neurology, 10; nephrology, 6; neurosurgery, 6; endocrinology, 4; pulmonary, 2; ophthalmology, 1; and psychiatry, 5). Largely because of the consultations and subsequent diagnostic studies, there was an average delay of 16±7 hours before therapy for the hyponatremia was begun. This interval was spent largely in diagnostic studies. Every patient had at least one CAT (computed axial tomographic) scan of the head. In addition, most patients (67 percent) had electroencephalography, 47 percent had carotid and vertebral angiography, and 60 percent had diagnostic lumbar punctures. These diagnostic studies were performed despite the fact that in 80 percent of the cases the serum sodium concentration was known. This suggests that many of the managing and consulting physicians were not aware that hyponatremia could lead to the observed symptoms. Two patients had open-brain biopsy for suspected herpes encephalitis.

Postoperative Fluid Balance

The total body water, calculated on the basis of the age, sex, and weight of the 15 patients, was 28.2±1.3 liters.[17] A review of postoperative intake and output records in the 11 patients for whom the information was available revealed that from the completion of surgery to the time of grand mal seizure activity, the average intake was 8.8±0.7 liters of 285 mM glucose (containing less than 5 mmol of sodium chloride per liter). The mean urinary output was 1.3±0.4 liters. At a time when the mean serum sodium concentration was 108 mmol per liter, the urine osmolality was 501±53 mOsm per kilogram and the urinary sodium level was 68±10 mmol per liter. The net fluid balance was thus 7.5 liters. A routine calculation[4] shows that this degree of fluid retention would theoretically lower the serum sodium level to 109 mmol per liter, which is very close to the actual value observed. The inappropriately elevated urinary sodium and osmolality in the presence of water intoxication and hyponatremia are virtually diagnostic of the syndrome of inappropriate

secretion of antidiuretic hormone,[1-3] a condition present in virtually all patients after surgery.[16]

Response to Therapy

After the diagnosis of hyponatremia was established as a possible cause of the seizures, therapy was begun with various concentrations of sodium chloride (154 mM, 515 mM, or 856 mM), often combined with furosemide. Four of the 15 patients died, three of them without regaining consciousness and in less than 24 hours. The other patient who died awoke 24 hours after her serum sodium level had been elevated to 130 mmol per liter. Thirty-six hours later, she lapsed into a coma and died two days later. Among the 11 other patients, 9 remained in a persistent vegetative state[20] after follow-up for two to six years. Two eventually regained consciousness and recovered enough of their mental faculties to lead reasonably normal lives, but both were left with permanent neurologic disability. One (Patient 3) had permanent double vision and partial paralysis of one leg. The other (Patient 12) had partial paralysis of one arm and one leg. Both can walk with a cane. In these two patients, therapy was begun within one hour of the initial grand mal seizures, and the serum sodium concentration increased to a level above 130 mmol per liter in 22 hours, as compared with 49 hours for the others.

The overall rate of correction among the 12 patients in whom the serum sodium level was elevated to 128 mM or higher was 0.5 mmol per liter per hour, a rate that has been defined as constituting "slow" correction.[6] All had permanent brain damage. Hyponatremia developed in the four who died much faster than in the group as a whole: in 28±4 hours as compared with 57±8 in the other 11 ($P<0.05$). The nine patients who remained in a persistent vegetative state after follow-up for two to six years are all institutionalized for custodial care.

Recurrent Coma

Seven of the 15 patients had an unusual clinical course, which is shown in Figure 1. These seven patients were treated with hypertonic sodium chloride in such a way that their serum sodium concentration was elevated from 105±2 to 131±1 mmol per liter in 41±7 hours. At that time, all regained consciousness to the point of being able to walk, eat, and talk. However, after a mean lucid interval of 58±8 hours, these seven patients then had a progressive clinical course characterized by decreased alertness, increasing headache, nausea, and progressive obtundation. This was followed by recurrence of grand mal seizures and a lapse back into coma. These clinical events occurred while the serum sodium level was above 128 mmol per liter in all cases. One patient died after two days, and the other six remained in a persistent vegetative state after follow-up intervals of at least two years. Such a phenomenon has not previously been well described in association with hyponatremia,[9,18] but the clinical course seems similar to that of postanoxic encephalopathy.[19-21]

Pathological Findings

Three patients died and autopsies were performed; open-brain biopsy was performed in two patients for suspected herpes encephalitis. The three patients who died in less than 24 hours all had evidence of herniation of the brain stem into the foramen magnum. In one of them (Patient 14), a CT scan before death had demonstrated edema of the brain stem. In addition, these three patients had obliteration of sulci and evidence of coning. Pathologically, the two patients who survived for several days both had evidence of necrosis of the cerebral cortex (cortical gray matter), but they had been treated with mechanical ventilation for the entire period. In all five patients, the white matter was normal, with no evidence of central pontine myelinolysis. None had evidence of encephalitis, stroke, tumor, or bleeding.

Contributory Factors

Eight of the 15 patients were not taking any drugs that might have contributed to the hyponatremia. Three were taking thiazide diuretics, which may have been a factor in the rapid onset of hyponatremia.[10,16] Another two patients were taking phenothiazines, which may have contributed to water retention. One patient had idiopathic diabetes insipidus and was given both desmopressin acetate (DDAVP) and aqueous vasopressin, which probably contributed to her water retention. One patient was taking prednisone, and two were taking propranolol. After surgery, 12 patients received parenteral narcotics (meperidine, morphine, or hydromorphone) — agents that may also result in water retention.[22-24] Thirteen patients were given at

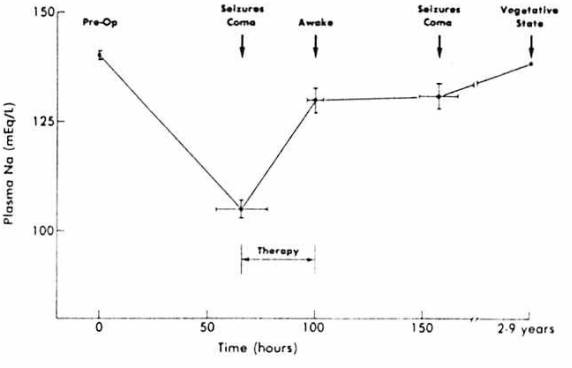

Figure 1. The Clinical Course in Seven Women Who Had Postoperative Hyponatremia with Grand Mal Seizures and Coma.
When the serum sodium level was increased from 105 to 131 mmol per liter in 41 hours, all the patients awoke. However, after a mean period of 58 hours, grand mal seizures and recurrent coma developed in all seven patients, despite the fact that the serum sodium level was above 128 mmol per liter in all cases. One patient died, and the others have remained in a vegetative state. Bars denote SE.

least 6 liters of hypotonic fluid (usually 285 mM glucose) in the first 39 postoperative hours, with urinary output of less than 650 ml per 24 hours. A routine measurement of serum sodium was not ordered for the first two postoperative days in 87 percent of the patients. Two patients (Patients 7 and 15) did not have excessive fluid intake but had received other medications (desmopressin acetate, vasopressin, or thiazides) that probably contributed to their hyponatremia.

Two patients had clinical evidence of volume contraction (postural hypotension or tachycardia) that was secondary either to excessive emesis (Patient 4) or severe epistaxis (Patient 10). One patient (Patient 13) was receiving an infusion of ACTH in 285 mM glucose in water, and another (Patient 4) received oxytocin after gynecologic surgery. Both agents have been reported to increase water retention.[25,26]

Discussion

These data show that in generally healthy women undergoing elective surgery, severe symptomatic hyponatremia can develop in two days or less. The causes of the abrupt fall in the serum sodium level are probably multiple, but the most important one appears to be excessive postoperative administration of hypotonic fluid (87 percent of the patients). However, excessive administration of free water alone does not generally result in hyponatremia. Barlow and De Wardener[27] have demonstrated that normal subjects can ingest up to 15 liters of water a day with little or no change in the serum sodium level. In subjects with hyponatremia, both total body water and sodium levels can be high, low, or normal.[9-13,23,28] In most clinical situations, hyponatremia is associated with water retention and elevated plasma levels of antidiuretic hormone. Chung and associates[16] found that among 48 postoperative patients with hyponatremia, most had elevated plasma levels of vasopressin (antidiuretic hormone). Volume contraction is a major stimulus to the release of antidiuretic hormone,[1,4,16] and most postoperative patients have a decreased extracellular volume, which is usually independent of blood loss.[29] Thus, it is not surprising that several investigators have shown that almost all postoperative patients have elevated plasma levels of antidiuretic hormone.[16,30-33] Postoperative hyponatremia is actually quite common and may affect more than 4 percent of all subjects who have undergone surgery.[9,14-16] However, it is rarely symptomatic; the plasma sodium level usually does not fall below 120 mmol per liter, and neurologic morbidity appears to be uncommon.[14-16]

There have been several reports of postoperative hyponatremia accompanied by coma and seizures. Most have appeared in the older surgical literature.[9,18,22,26,34,35] Despite the presence of a serum sodium concentration below 115 mmol per liter with symptoms, neurologic morbidity and mortality were very infrequent. Since many of the aforementioned patients were in generally good health and were undergoing elective surgical procedures, the absence of serious associated medical illness may have been a major factor in the low morbidity and mortality. Several reported cases of hyponatremia with associated brain damage have occurred in patients with other comorbid conditions.[2,7,8,10-13,36-39] However, one association may be important.

With few exceptions, most patients who have had symptomatic hyponatremia with a sodium level below 120 mmol per liter but have not had permanent neurologic damage have been men,[2,5,9-13,22] whereas those who have died or had permanent brain damage have been women.[2,4,8-13,18,37-39] If the number of previously described patients who have had well-documented postoperative symptomatic hyponatremia (serum sodium level below 120 mmol per liter) in the absence of associated medical conditions known to be frequently associated with central nervous system damage[2,9,18,22,34,35] is added to the 15 patients in the present report, the total number of such patients is 57. Eighty-eight percent were women. Furthermore, all 30 of the 57 patients who either died or had permanent brain damage were women. The mean serum sodium level was not different in the men (107±4 mmol per liter) from that in the women (109±6).

The reasons for such a female predilection to brain damage from hyponatremia are not clear. Adaptation of the brain to hyponatremia involves both an efflux of osmotically active cation (primarily potassium) and a gain of water.[2,4] Both processes act to lower the intracellular osmolality of the brain, and the rapidity of this process may ultimately help to determine survival.[2] Although the mechanism by which cation is lost from brain cells in hyponatremia has not been well studied, it probably has both active (related to a sodium–potassium pump)[40] and passive (ouabain-insensitive) components.[41] There is a potassium-conductive pathway found in several cell types (e.g., lymphocytes and Ehrlich cells) that results in a loss of cell potassium when cells are placed in a hypo-osmotic medium.[40-42] In hypo-osmolar states, the passive component of potassium influx is also reduced,[41] which would tend to increase the loss of potassium from brain cells. However, if the active component (probably efflux mediated by sodium–potassium ATPase) were to be somehow inhibited, this would impair the loss of potassium from the brain in hyponatremia, leading to increased brain swelling, with a higher morbidity. It may be that the sodium–potassium ATPase system in the brain is less efficient at extruding potassium in women than in men. This may be related to the fact that the action of sodium–potassium ATPase can be inhibited by some female sex hormones. It has recently been shown that progesterone and certain of its derivatives can inhibit this enzyme in several tissues.[43] In addition, both sexual and racial differences in the amount and the activity of sodium–potassium ATPase in red cells have been demonstrated.[44] Such effects may be present in the brain as well.

The 15 patients described here do not represent a known percentage of the total number of operations,

and there are no obvious reasons that all were women, although the literature suggests that there is indeed a definite female preponderance among patients with symptomatic hyponatremia and its neurologic sequelae.

It has been suggested that hyponatremia by itself is a benign condition and that rapid therapy is more dangerous than the condition itself.[37,45] It has also been suggested that when neurologic morbidity occurs, it is often related to co-morbid medical conditions. Brain damage has often been observed among patients with acute water intoxication.[2,18,26,34,36,38,39] Also, we have previously shown that certain groups of patients — those with alcoholism, cachexia, or hepatic cirrhosis — are much more likely to have permanent brain damage with hyponatremia than are other patients with similar serum sodium levels.[4] A serum sodium level below 130 mmol per liter is associated with an increase of 60-fold or more in the mortality of hospitalized nonsurgical or surgical patients.[1,14,15] However, despite some associated medical conditions, most of the women in this study were young and healthy. Ten were under 50 years of age and eight under 35, none were alcoholic, all had normal hepatic, pulmonary, and renal function, and only three had any important medical illness. Thus, it is unlikely that coexisting medical conditions played any part in the outcome in these patients. Furthermore, studies in animals, both in our laboratory and others, show that hyponatremia itself (a serum sodium level of 100 to 115 mmol per liter for at least two days) can result in all the clinical manifestations observed in these patients. Studies in dogs, rats, and rabbits with serum sodium levels below 120 mmol per liter for two to seven days show that lethargy, seizures, respiratory arrest, limb paralysis, anorexia, clonus, and profound weakness may develop in these animals.[2,46-49] The resultant mortality is from 58 to 100 percent. These studies in animals strongly support the contention that hyponatremia alone was responsible for the observed morbidity and mortality in our patients.

There was an average delay of 16 hours before therapy for the hyponatremia was begun, and even when it was initiated, the mean rate of correction was less than 0.7 mmol per liter per hour, a rate that has been defined as constituting "slow" correction.[6] There have been several articles over the past decade advocating such slow correction of hyponatremia.[3,7,8,37,45,48] More recently, some evidence has suggested that "overly rapid" therapy of symptomatic hyponatremia may sometimes be associated with central pontine myelinolysis,[7,8,46,48,50,51] a rare neurologic disorder of uncertain origin that is most often found in patients with alcoholism, cachexia, or malnutrition.[52] Although initial studies in laboratory animals have suggested that rapid treatment of hyponatremia could result in central pontine myelinolysis,[46,48] the lesions seen were probably not the result of rapid correction of hyponatremia alone.[2,5,53-55] Studies in both human subjects with hyponatremia[2,4,5,10,53-55] and rats[49] have demonstrated that rapid correction of symptomatic hyponatremia (serum sodium level of 95 to 120 mmol per liter) to the level of mild hyponatremia (serum sodium level of 128 to 132 mmol per liter) did not appear to result in central pontine myelinolysis. In fact, in a review of 65 patients with symptomatic hyponatremia[4] whose condition was corrected to a serum sodium level of 130 mmol per liter at a rate of about 2 mmol per liter per hour, survival was above 90 percent and central pontine myelinolysis did not develop in any patient. Rather, preliminary studies suggest that overcorrection of plasma sodium to normonatremic or hypernatremic levels may result in demyelinating lesions of the brain.[46,48,49,53] Thus, it appears that increasing the plasma sodium level by about 2 mmol per liter per hour to a level of 128 to 132 mmol per liter is appropriate at our current level of knowledge.

Seven women had an unusual syndrome, shown graphically in Figure 1. These patients were comatose while their serum sodium levels were increased from 105 to 131 mmol per liter over a mean period of 41 hours. Then, 58 hours after awakening from coma to the point of being able to communicate, eat, and walk, all seven patients had grand mal seizures and again became comatose. None recovered from this second episode of coma, which occurred when the serum sodium level was at least 128 mmol per liter. The cause of the recurrent coma is uncertain, and there have been only a few reports in which a similar syndrome has been suggested.[9,17] Such a syndrome has not been well described in association with hyponatremia, but it has been well described in patients who have had a hypoxic–anoxic episode,[19-21] such as cardiac arrest, carbon monoxide intoxication, or aspiration. Such patients are generally resuscitated quickly and appear to recover, usually within 24 hours. They seem relatively normal for 2 to 10 days, but then a characteristic syndrome occurs. This is characterized by apathy, irritability, and confusion, often with agitation or manic behavior. Motor control gradually deteriorates, and there is a progression to coma. There are no obvious features during the initial anoxic insult that serve to distinguish the patients destined to relapse from those who will have uncomplicated recoveries. The cause of anoxia seems unimportant. As in the present series, many such patients are initially misdiagnosed and are thought to have a primary cerebral disease, such as subdural hematoma.[19-21] In the present series, the diagnosis must be made on clinical grounds, but anoxia appears to be the most likely cause of the recurrent seizures and coma, with either death or a persistent vegetative state as the outcome. The pathogenesis may also be related to a similar syndrome involving brain-stem herniation secondary to a space-occupying cerebral lesion.[56,57]

In the present study, head CT scans were performed in all the patients, and pathological examination of brain tissue in five (three autopsies and two brain biopsies). No patient had any evidence of cen-

tral pontine myelinolysis, either histologically or on the CT scan. However, central pontine myelinolysis occurs most often in the central pons, a structure that would not be evaluated in a brain biopsy because of its anatomical location. In addition, special staining for central pontine myelinolysis was carried out in only one patient (Patient 2), who died within 24 hours of seizure activity, too early for myelinolysis to have developed. Thus, central pontine myelinolysis cannot absolutely be ruled out in some of the patients studied. Three patients had gross evidence of brain-stem herniation (uncal grooving and compression), and all three had died within 30 hours. Two of the others had evidence of cerebral cortical atrophy on biopsy or autopsy. However, neither histologic examination of the brain in five patients nor multiple diagnostic studies indicated any evidence of other cerebral disease, such as tumor, stroke, acute bleeding, infection, or subdural hematoma. All 15 patients had CT scans, half had carotid and vertebral angiography, and 60 percent had lumbar punctures. Three of the CT scans revealed brain-stem edema; all the other studies were negative. Thus, the neurologic disability in these patients was not associated with any lesion identifiable either by numerous diagnostic studies or by histologic studies. Preliminary studies, both from our laboratory[47] and from others,[49] show that brain lesions are generally absent in rabbits, dogs, and rats with symptomatic hyponatremia. In rats and rabbits with chronic hyponatremia (serum sodium level, 95 to 110 mmol per liter) and paralysis, seizure activity, and obtundation, the brains do not have cerebral edema and are histologically normal.[2,47,49] Thus, the neurologic lesion associated with chronic hyponatremic encephalopathy is not well defined. Hyponatremia itself may interfere with glial metabolism or affect neurotransmitter release by mechanisms still undefined.[4] In addition, hypoxia with postanoxic encephalopathy after respiratory arrest may often have a major role in the pathogenesis of the brain damage.[19-21]

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OSMOTIC DEMYELINATION SYNDROME FOLLOWING CORRECTION OF HYPONATREMIA

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Abstract The treatment of hyponatremia is controversial: some authorities have cautioned that rapid correction causes central pontine myelinolysis, and others warn that severe hyponatremia has a high mortality rate unless it is corrected rapidly. Eight patients treated over a five-year period at our two institutions had a neurologic syndrome with clinical or pathological findings typical of central pontine myelinolysis, which developed after the patients presented with severe hyponatremia. Each patient's condition worsened after relatively rapid correction of hyponatremia (>12 mmol of sodium per liter per day) — a phenomenon that we have called the osmotic demyelination syndrome. Five of the patients were treated at one hospital, and accounted for all the neurologic complications recorded among 60 patients with serum sodium concentrations below 116 mmol per liter; no patient in whom the sodium level was raised by less than 12 mmol per liter per day had any neurologic sequelae. Reviewing published reports on patients with very severe hyponatremia (serum sodium <106 mmol per liter) revealed that neurologic sequelae were associated with correction of hyponatremia by more than 12 mmol per liter per day; when correction proceeded more slowly, patients had uneventful recoveries. We suggest that the osmotic demyelination syndrome is a preventable complication of overly rapid correction of chronic hyponatremia. (N Engl J Med 1986; 314:1535-42.)

RECENTLY, the treatment of hyponatremia has become controversial. Some investigators have linked rapid correction of hyponatremia with an often fatal neurologic disorder known as central pontine myelinolysis.[1-9] Others have disputed this association, arguing that symptomatic hyponatremia is a life-threatening emergency that can result in death or permanent neurologic damage unless it is treated promptly and vigorously.[10-15] The clinician faced with a hyponatremic patient has thus been placed in a serious quandary. Allegedly, morbidity and mortality may result from treatment that is either "too fast" or "too slow."

Within the past five years we have encountered eight patients at our two institutions who have had serious neurologic complications from hyponatremia. Their presenting symptoms were severe enough to cause them to seek medical attention, but tragically, their condition worsened as their electrolyte disturbances were corrected. Each patient had similar neurologic findings, which we have termed the osmotic demyelination syndrome. We believe that this syndrome is an avoidable complication of overly rapid therapy.

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METHODS

During a 12-month period at West Virginia University Medical Center, a tertiary referral center serving a population of 600,000, three patients who did not have alcoholism and who were seen in neurologic consultation by one of us (J.E.R.) were thought to have central pontine myelinolysis. Laboratory data (with imprecise information regarding the exact timing of blood sampling) were obtained from the referring hospitals.

At the Rochester General Hospital, a 547-bed university-affiliated community hospital, the charts of adult patients in whom hyponatremia had been diagnosed during a five-year period were reviewed to identify patients with serum sodium concentrations of less than 116 mmol per liter. Of 60 patients with 62 episodes of hyponatremia, 5 were found to have had neurologic sequelae. One of us (R.H.S.) was personally familiar with the course of four of these five patients; data on the fifth patient were extracted from the