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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 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 154 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 20 cases reported.[2,9-18] Some investigators believe that other medical conditions associated with hyponatremia, rather than hyponatremia itself, are mainly 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.[6,8] 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, or kidney disease.[4,14,15] Anderson and associates found that 1 percent of hospitalized patients 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, 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.

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,

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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

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

sponse to Therapy

After the diagnosis of hyponatremia was estab- hed as a possible cause of the seizures, therapy was gun with various concentrations of sodium chloride 54 mM, 515 mM, or 856 mM), often combined with osemide. Four of the 15 patients died, three of them hout regaining consciousness and in less than 24 urs. The other patient, who died awoke 24 hours her serum sodium level had been elevated to 130 mol per liter. Thirty-six hours later, she lapsed into oma and died two days later. Among the 11 other ents, 9 remained in a persistent vegetative state[20] follow-up for two to six years. Two eventually ained consciousness and recovered enough of their tal faculties to lead reasonably normal lives, but th were left with permanent neurologic disability (Patient 3) had permanent double vision and par- paralysis of one leg. The other (Patient 12) had ial paralysis of one arm and one leg. Both can k with a cane. In these two patients, therapy was un within one hour of the initial grand mal sei- and the serum sodium concentration increased level above 130 mmol per liter in 22 hours, as pared with 49 hours for the others. The overall rate of correction among the 12 patients hom the serum sodium level was elevated to 128 or higher was 0.5 mmol per liter per hour, a rate has been defined as constituting "slow" correc- [6] All had permanent brain damage. Hyponatre- developed in the four who died much faster than the group as a whole: in 28±4 hours, as compared 57±8 in the other 11 ($P<0.05$). The nine patients remained in a persistent vegetative state after w-up for two to six years are all institutionalized, stodial care.

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ven of the 15 patients had an unusual clinical e, which is shown in Figure 1. These seven pa- were treated with hypertonic sodium chloride in way that their serum sodium concentration was ted from 105±2 to 131±1 mmol per liter in 41±7 At that time, all regained consciousness to the of being able to walk, eat, and talk. However, a mean lucid interval of 58±8 hours, these seven nts then had a progressive clinical course charac- ed by decreased alertness, increasing headache, and progressive obtundation. This was fol- d by recurrence of grand mal seizures and a lapse into coma. These clinical events occurred while rum sodium level was above 128 mmol per liter cases. One patient died after two days, and ther six remained in a persistent vegetative state follow-up intervals of at least two years. Such nomenon has not previously been well described sociation with hyponatremia,[9,18] but the clini- cal course seems similar to that of postanoxic en- cephalopathy.[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 herni- ation 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 evi- dence 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 myelinol- ysis. 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 giv- en 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

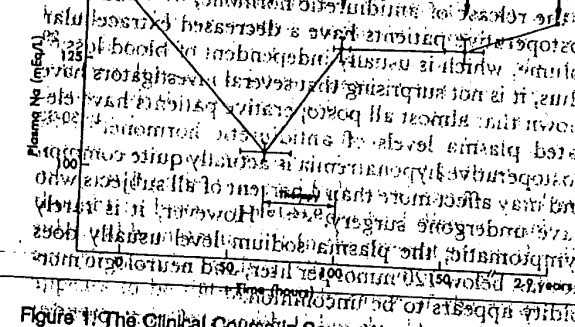

Figure 1. The Clinical Course in Seven Women Who Had Post-operative Hyponatremia with Grand Mal Seizures and Coma. When the serum sodium level was increased from 105 to 131 mmol per liter in 41 hours, all the patients awoke. However, after a mean period of 58 hours, grand mal seizures and recurrent coma 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 of 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

medical record only. Laboratory computer printouts, which included the date and time when blood samples were submitted, allowed computation of the rate of correction of hyponatremia.

Results

The patients referred to West Virginia University Medical Center (Patients 1 through 3) had initially presented with serum sodium concentrations below 110 mmol per liter, which had been raised by more than 12 mmol per liter per day before they were transferred to the center. The patients treated at Rochester General Hospital (Patients 4 through 8) had neurologic sequelae associated with correction of the serum sodium concentration by 12 mmol per liter per day or more. After 43 episodes of hyponatremia had been corrected this rapidly, five patients had sustained neurologic sequelae and three died of underlying disease (pneumonia and sepsis, acute myocardial infarction, and congestive heart failure). In 19 of the 60 Rochester cases, the serum sodium concentration was increased by less than 12 mmol per liter per day; none of the patients had any neurologic sequelae, but two died of underlying disease (hepatic failure and cardiogenic shock).

In all eight patients with neurologic sequelae who were studied, the original electrolyte disturbance had developed before hospitalization (Table 1). Seven (Patients 1 through 7) presented with both hyponatremia and hypokalemia, a complication of taking thiazide diuretics for hypertension. Only two of the eight patients were alcoholics: Patient 8 had alcoholic liver disease and peripheral neuropathy, and Patient 7 had no apparent complications of alcoholism.

All patients except one (Patient 5) could talk at the time of their initial presentation at the hospital, and only two (Patients 5 and 7) had convulsions before the hyponatremia was corrected; neither had status epilepticus. All the patients were treated for hyponatremia on the first day of hospitalization (Table 1); by the next day seven still had mild hyponatremia (serum sodium, 120 to 132 mmol per liter), and Patient 5 had a serum sodium level of 138 mmol per liter (Table 1).

Table 1. Serum Sodium Concentrations in Eight Patients with Neurologic Sequelae after Correction of Hyponatremia.

Patient No.	Age/Sex	Cause	Na on Admission	Treatment*	Maximum Na Increase	Na at Onset of Sequelae
			mmol/liter		mmol/liter/day	mmol/liter
1	54/F	Diuretic?†	102	NS	27	136–156 (Days 3–5)
2	54/F	Diuretic	109	3%	12–17	126–146 (Days 3–10)
3	60/M	Diuretic	105	NS	27	132 (Day 5)
4	68/F	Diuretic	103	NS	25	133 (Day 6)
5	74/F	Diuretic	115	5%	23	138 (Day 2)
6	75/F	Diuretic	114	3%	18	130 (Day 4)
7	77/F	Diuretic‡	98	3%	22	127 (Day 4)
8	41/M	Diarrhea‡	109	NS	13	132 (Day 3)

*NS denotes isotonic saline, 3% 3 percent saline, and 5% 5 percent saline.
†Hypertensive patient presenting with severe hypokalemia (1.9 mmol per liter); medications unknown.
‡Acute and chronic alcoholism.

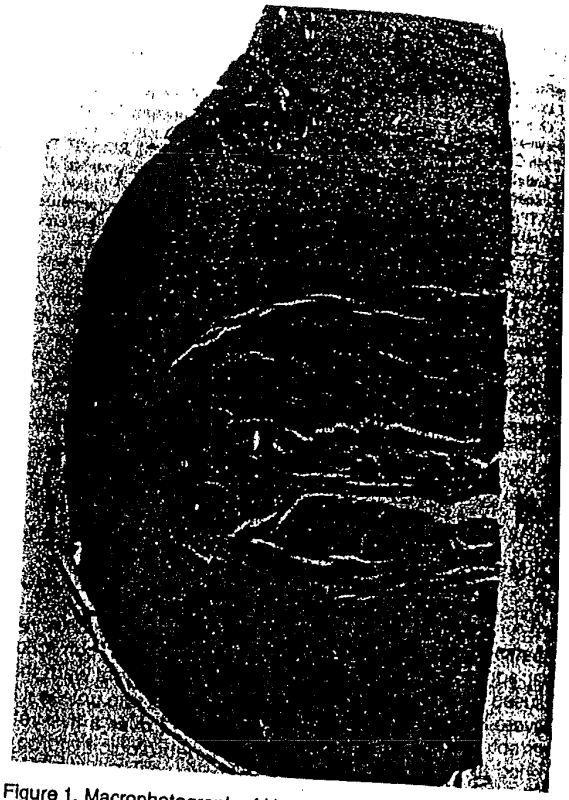

Figure 1. Macrophotograph of Hemisection of the Pons from Patient 1, Showing Extensive Central Demyelination with Preservation of Peripheral Rim of Myelin (Hematoxylin and Eosin).

Hypernatremia developed in only one patient (No. 1), late in her course after progressive obtundation had begun. All patients had neurologic deterioration after their hyponatremia was treated, with development of clinical or pathological findings of central pontine myelinolysis.

Patient 1 was obtunded but arousable on admission and never fully awoke. Beginning on the fourth day, the obtundation became progressively more severe, and from the fifth day until her death she was comatose with decorticate posturing. Results of computerized axial tomography of the brain (CT scanning) performed on the fifth hospital day were normal; at autopsy six days later, marked demyelination was found in the central pons, internal capsule, extreme capsule, lateral geniculate, and cerebellum (Fig. 1). In areas of demyelination, neurons and axis cylinders were spared.

Patient 2 was awake but disoriented on admission. She had a generalized seizure on the second day as her electrolyte levels were being

corrected, and deterioration occurred gradually over the next several days; dysarthria, difficulty in swallowing, and inability to walk were noted on the 10th hospital day. A CT scan was normal except for mild cortical atrophy. On transfer to West Virginia University Medical Center three months later, spastic quadriparesis and pseudobulbar palsy were found and a repeat CT scan showed central lucency in the pons (Fig. 2).

Patient 3 was awake and alert on admission and remained so until the fourth hospital day, when he became lethargic and had convulsions. On the fifth day he became quadriparetic. On transfer to West Virginia University Medical Center on the 20th day, spastic quadriparesis, bulbar paresis with inability to speak or swallow, and a pseudobulbar affect were found. Despite clinical findings typical of central pontine myelinolysis, neither the CT scan nor brain-stem auditory evoked responses confirmed whether it was present. Ten weeks later the patient had made a complete functional recovery, although a mild spastic quadriparesis could still be demonstrated.

Patient 4 was sent to the emergency department one day after laboratory examination showed that the serum sodium was 104 mmol per liter. On admission she was lethargic and dysarthric but oriented. With correction of her electrolytes, she became more alert. On the third day, visual and auditory hallucinations developed and later her speech was noted to be guttural and nasal. Gradually over the next several days she became increasingly less responsive and ultimately comatose, requiring mechanical ventilation. CT scans were normal. Five weeks later, she was alert and could open her eyes and blink on command but was unable to move her extremities. Over the next two months she gradually regained the use of her limbs and was able to walk with assistance but was unable to talk and had difficulty in chewing and swallowing. Vocal-cord paralysis thought to be central in origin was noted. Five years later, the patient's intellect is intact but she is confined to a wheelchair because of spastic quadriparesis. She can talk intelligibly some of the time but still has difficulty in swallowing.

Patient 5 became nonverbal, with rhythmic movements of both legs and one arm, two hours before admission; although these features were interpreted as indicating grand mal seizures, measurement of arterial blood gases showed neither metabolic nor respiratory acidosis. Treatment with diazepam and phenytoin stopped the seizure activity but caused unresponsiveness and respiratory depression requiring endotracheal intubation. When laboratory data became available, 5 percent saline was administered, increasing the serum sodium by 11 mmol per liter over two hours. After this treatment the patient was lethargic but opened her eyes when spoken to. By the next day she was flaccid and unresponsive and remained so until the sixth hospital day. After extubation she was awake but could neither talk nor swallow. CT scans were normal. Gradually over the next two months she regained the ability to talk and could walk with assistance but still had trouble with swallowing. Although she was severely confused and disoriented during her early recovery, her intellectual capacity ultimately returned to normal.

Patient 6 was lethargic and confused on presentation and became more alert and oriented after the hyponatremia was corrected. Beginning on the fourth day she became lethargic, unable to follow commands, mute, and incontinent of stool; her left arm gradually became flaccid and a swallowing dysfunction developed along with recurrent episodes of aspiration pneumonia. An area of low density involving both gray and white matter in the left posterior cerebral distribution was the only abnormality found on CT scanning. A gastrostomy was performed, and the patient was discharged to a nursing home.

Patient 7 had two brief grand mal seizures within a five-hour period at home, but on admission she was arousable and could respond to questions. After correction of hyponatremia she became alert and oriented, but on the fourth day she became increasingly lethargic and ultimately, unresponsive and quadriplegic, requiring mechanical ventilation. CT scans were normal. Two months later, shortly before her death, she was still dependent on a respirator, but alert and able to respond to questions by blinking her eyes or

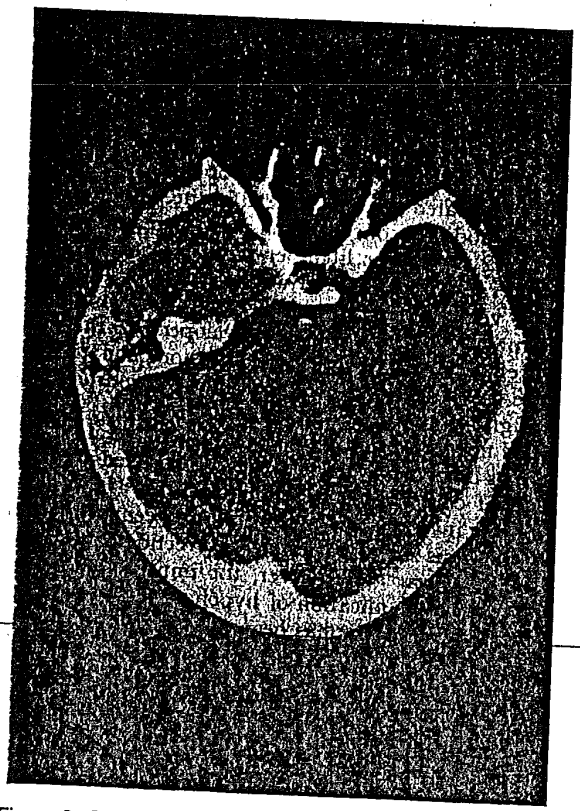

Figure 2. CT-Scan Section of Patient 2, Demonstrating Large Area of Decreased Attenuation in the Center of the Brain Stem at the Level of the Pons.

shaking her head; she could move only her left arm and right index finger. Patchy areas of demyelination in the pons were the only major abnormalities found on pathological examination of the brain.

Patient 8 was alert on admission and had only weakness. On the third hospital day, after his hyponatremia had been corrected, lethargy and dysarthria developed. On the fifth day aspiration and respiratory arrest occurred, from which the patient was successfully resuscitated. Several recurrent episodes of aspiration followed, and a neurogenic swallowing disorder was subsequently discovered. Although no anatomical lesions could be demonstrated by CT scanning, brain-stem auditory evoked responses were characteristic of pontomesencephalic dysfunction — findings consistent with a diagnosis of central pontine myelinolysis.

Discussion

When the serum sodium concentration falls rapidly to low levels, hyponatremia may be complicated by potentially fatal cerebral edema.[11] In chronic hyponatremia, brain swelling is minimized by an adaptive loss of cell solute[11,16]; despite this adaptation, serious neurologic sequelae may occur.[12] It is unclear whether these complications result from the electrolyte disturbance itself or from therapeutic measures that correct the serum sodium concentration faster than the brain can "readapt" to a higher serum osmolality.[4,7,10-15]

If uncorrected hyponatremia itself were responsible for neurologic sequelae, one would expect patients in whom hyponatremia was corrected slowly to fare less well than patients in whom it was corrected more rapidly. However, we found just the opposite: a uniformly uncomplicated course occurred in the patients whose serum sodium concentration was increased by less than 12 mmol per liter per day. In contrast, more rapid rates of correction were sometimes associated with very serious neurologic complications. These dramatic neurologic findings developed *after* the hyponatremia was corrected — a phenomenon that we have called the osmotic demyelination syndrome. Although an anatomical explanation for these findings could not always be documented, the clinical presentations of all the patients strongly suggested the diagnosis of central pontine myelinolysis.[17,18]

Other investigators have also linked central pontine myelinolysis to the speed of correction of chronic hyponatremia.[5,7,8] However, the importance of this lesion as a complication of hyponatremia is not universally accepted. It has been suggested that the disorder is extremely rare, that it primarily affects debilitated alcoholics, and that it complicates hyponatremia only when the serum sodium concentration is "overcorrected" to hypernatremic levels.[10,11,14,15] On the contrary, we find that central pontine myelinolysis is not rare and that it appears to account for most of the neurologic injury occurring in patients with chronic hyponatremia. Neither alcoholism nor overcorrection of hyponatremia was a prerequisite for this complication.

Some may question the diagnosis of central pontine myelinolysis in our patients. As originally described, this disease was accurately reflected by its name. It was defined as a selective loss of myelin (sparing neurons and axis cylinders) limited to the center of the basal pons.[17] Although the location of the demyelinating lesions in our two patients in whom autopsy was performed differed from the location in this classic description, their disorder was consistent with the constellation of pathological findings now included under the somewhat misleading label "central pontine myelinolysis." It is recognized that in many cases (as in Patient 1), myelinolysis of the central pons may be accompanied by the presence of histologically similar lesions in other areas of the brain where gray and white matter are closely admixed.[19] These extrapontine lesions are particularly common when central pontine myelinolysis complicates the treatment of hyponatremia.[19] In our patients who survived, the diagnosis rested on the clinical presentation supplemented by the results of diagnostic tests. Antemortem diagnosis of central pontine myelinolysis has recently been made possible by CT scans, brain-stem auditory evoked responses, and magnetic-resonance images.[20-24] These techniques have expanded our concepts of the clinical characteristics of the disease. Patients in whom the lesion is diagnosed during life may recover, sometimes dramatically, as might be expected of a disease that primarily affects myelin.[18,20-22,25-27] However, particularly in patients with reversible disease, anatomical lesions are difficult to document with available techniques.[26,27] This difficulty is illustrated in our first two patients. They had negative CT scans early in their course but were later found to have typical pontine myelinolysis at autopsy or repeat CT scanning. Other investigators have reported similar experiences.[22,24]

Because of the difficulties inherent in antemortem diagnosis of this disease, some reported cases, like ours, have been classified as central pontine myelinolysis solely on the basis of a typical clinical course.[18,25-27] Consequently, we believe that it may be useful to consider the complications of hyponatremia in clinical rather than anatomical terms. Since clinical findings may reflect extrapontine as well as pontine myelinolysis, we have suggested the term "osmotic demyelination syndrome" to describe the stereotypical neurologic processes that developed in our patients. This syndrome is characterized by gradual neurologic deterioration developing one to several days after complete or partial correction of chronic hyponatremia. Neurologic deterioration is often preceded by transient improvement paralleling the correction of the electrolyte disturbance. Various neurologic findings, including fluctuating levels of consciousness, convulsions, hypoventilation, and hypotension, may herald the onset of the disorder. Eventually, pseudobulbar palsy and, in

typical cases, quadriparesis develop. Swallowing dysfunction (often with episodes of aspiration) and inability to speak are usually the dominant features. In severe cases, patients are awake but unable to move or communicate — a phenomenon known as the "locked-in" syndrome. Marked improvement may occur, presumably because of remyelination. Although various

imaging techniques may be confirmatory, positive diagnostic tests are not essential to diagnose the osmotic demyelination syndrome. If pseudobulbar palsy and limb paralysis gradually develop after hyponatremia is corrected, the clinician should strongly suspect a demyelinating lesion of the pons. A negative CT scan will help to localize the disease to the brain stem. (An

Table 2. Cases of Severe Symptomatic Hyponatremia (Sodium ≤105 mmol per liter) Corrected by More than 12 mmol per liter per Day.

Reference	Cause*	Na	Symptoms	Treatment†	Maximum Na Increase	Outcome‡
Neurologic complications						
Alberca[20]	Thiazide	96	Coma	[illegible]	16	CT CPM/recovery
Ashraf[21]	Thiazide	100	Stupor	3%	≤12	Paraparesis
[illegible]	Thiazide	103	Slow speech	5%	14	Coma/death
[illegible]	Thiazide	[illegible]	Stupor	3%	25	Paralysis of one leg
[illegible]	Thiazide	104	Coma	[illegible]	[illegible]	Coma/death from MI
[illegible]	Thiazide	98	Seizure/coma	[illegible]	24	Coma/death
Berry[illegible]	SIADH	96	Coma	[illegible]	30	CPM/death
Brunner[26]	Addison	100	Slow speech	5%	28	Clinical CPM/recovery
Burcar[30]	Thiazide	96	Lethargy	[illegible]	38	CPM/death
Cambier[33]	Thiazide§	95	?	3%	15	CPM/death
Hazratji[34]	Ethanol§	94	Coma	5%	31	Improvement, then CPM/death
Kandt	Addison	100	Weakness	[illegible]	18	Clinical CPM/recovery
Lipsmeyer[16]	ARF	95	Seizure/coma	3% + PD	17	Improvement, then stupor, inability to speak or swallow
Messert[18]	Thiazide§	98	Delirium	[illegible]	14	Clinical CPM/recovery
Norenberg[8]	Thiazide?	100	?	3%	18	CPM/death
[illegible]	Thiazide?	99	[illegible]	NS	27	CPM/death
[illegible]	[illegible]	99	[illegible]	NS	20	CPM/death
Rendell	Psychosis	94	Somnolence	NS	>30	Coma, death
Schiffrin[36]	Thiazide	98	Stupor	3%	23	Improvement, then seizures, coma, death, necrosis of glial cells
Telfer[22]	Thiazide	92	Weakness	3%	20	CT CPM/recovery
Tomlinson[31]	[illegible]	100	Drowsiness	3%	24	CPM/death
[illegible]	[illegible]	96	Drowsiness	3%	18	CPM/death
No complications						
Ahmad[37]	Oxytocin	100	Coma	WR	14	Uncomplicated recovery
Ayus[13]	Psychosis	88	Seizures/coma	3%	42	Uncomplicated recovery
[illegible]	Potomania§	96	Lethargy	3%	32	Uncomplicated recovery
[illegible]	Dialysis	98	Seizures/coma	3% + HD	25	Uncomplicated recovery
[illegible]	IV plus SIADH	103	Confusion	3%	21	Uncomplicated recovery
[illegible]	Thiazide	105	Confusion	3%	22	Uncomplicated recovery
Devereaux[39]	Psychosis	100	Coma	3%	21	Uncomplicated recovery
Fichman[40]	Thiazide	98	?	WR	16	Uncomplicated recovery
Kaye[40]	SIADH	103	Confusion	3%	27	Uncomplicated recovery
Kennedy	SIADH	103	Confusion	5%	>12	Uncomplicated recovery
Langgard[42]	Psychosis	105	Stupor	WR	13	Uncomplicated recovery
[illegible]	Psychosis	94	Seizure	WR	26	Uncomplicated recovery
Sumner[43]	Psychosis	97	Coma	3%	28	Uncomplicated recovery
[illegible]	Psychosis	99	Coma	3%	29	Uncomplicated recovery
Swanson	Potomania§	101	Seizures	5%	30	Uncomplicated recovery
Walters[45]	Diarrhea	99	Confusion	3%	31	Uncomplicated recovery

*SIADH denotes syndrome of inappropriate antidiuretic hormone secretion, IV intravenous fluids, ARF acute renal failure, and Addison Addison's disease.

†PD denotes peritoneal dialysis, HD hemodialysis, WR water restriction, NS isotonic saline, 3% 3 percent saline, and 5% 5 percent saline.

‡CPM denotes central pontine myelinolysis, CT CPM CPM diagnosed by CT scanning, and MI myocardial infarction.

§Acute and chronic alcoholism.

¶Given 690 mmol of 3 percent saline in 24 hours; correction rate assumed to exceed 12 mmol per liter per day.

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area that is difficult to visualize) because such a scan tends to exclude extensive bilateral disease of the cerebral hemispheres.

A growing body of experimental and clinical evidence indicates that pontine and extrapontine myelinolysis is a consequence of rapid correction of hyponatremia rather than hyponatremia itself.[1-9,28] Demyelinating lesions virtually identical to those seen in the clinical disease have been produced in animals by correcting chronic hyponatremia rapidly.[1-3,5,9,28] Large increases in the serum sodium concentration over a short period produce the most severe lesions, and no lesions are found if hyponatremia is uncorrected or is allowed to correct itself slowly over several days.[2,3,5,9,28]

Our experience is consistent with these experimental findings. We saw no clinical evidence of neurologic injury when chronic hyponatremia was corrected very slowly. In contrast, we find that increasing the serum sodium concentration by more than 12 mmol per liter over the course of 24 hours is increasing it fast enough to do harm. The neurologic deterioration in our patients cannot be ascribed to "overcorrection" of hyponatremia. In all patients the hyponatremia was initially corrected so that it became mild, and only in Patient 1 did hypernatremia develop (in this case, after deterioration had begun). These findings are somewhat surprising and in conflict with conventional medical wisdom. The rate of correction that we have found to be potentially dangerous has usually been assumed to be safe and effective.[11,13-15,29] Indeed, some would call the treatment that some of our patients received "slow correction" since many patients have survived without incident after correction that was much more rapid.[11,13-15] Moreover, recent reviews have linked "slow correction" with a high incidence of morbidity and mortality in patients with symptomatic hyponatremia, particularly when the serum sodium concentration has fallen below 106 mmol per liter.[11,14,15] However, we find no convincing evidence that correcting hyponatremia by more than 12 mmol per liter per day is necessary, even when the serum sodium concentration is very low.

In reviewing the literature, we were able to find over 80 patients with serum sodium concentrations below 106 mmol per liter; in 51 of them, enough data were provided to allow an analysis of how treatment may have influenced outcome (Tables 2 and 3). Over half the patients undergoing "rapid" correction had neurologic sequelae. As in our experience, many of these patients initially presented with limited symptoms and subsequently had deterioration after vigorous correction of their h natremia: 14 patients had documented or suspe central pontine myelinolysis[8,18,20,22,24,26,27,30-33] clinical data on 2 others strongly suggest this diag sis.[34,36] In contrast, as shown in Table 3, all 13 tients in whom the correction rate was less than mmol per liter per day recovered without compli tions. Many of these patients were treated conser tively despite severe presenting symptoms.[46-48,53]

We conclude from our literature review, as we h from our own cases, that uneventful recovery is rule when chronic hyponatremia is managed cons vatively, whereas neurologic sequelae may be com cations of aggressive therapy. Preliminary data fro series of unselected patients with serum sodium co centrations below 111 mmol per liter support this co clusion.[57] Thus, the neurologic complications in o patients were probably the result of well-intention efforts to correct a relatively benign condition rapid —i.e., we suggest that the osmotic demyelination sy drome is an iatrogenic disease.

Recently, other explanations have been offered f the neurologic complications of hyponatremia. It h been suggested that delayed anoxic leukoencephalo athy caused by hyponatremic seizures[58] is responsib for neurologic deterioration following the apparentl successful treatment of hyponatremia. This unusu disease is observed most often after carbon monoxid poisoning, but more rarely it may complicate succes ful resuscitation from cardiopulmonary arrest or othe severe, prolonged, ischemic anoxic insult.[59] The le sions of this disease involve the deep white matter o the cerebral hemispheres (where they can be identifie by CT scanning) and spare the brain stem.[59] Anoxia i an unlikely cause of the neurologic complications i

Table 3. Cases of Severe Symptomatic Hyponatremia Corrected by Less than 1 mmol per liter per Day.

Reference	Cause*	Na	Symptoms	Treatment†	Maximum Na Increase	Outcome
		mmol/liter			mmol/liter/day	
Abramow[46]	Thiazide‡	105	Seizure/coma	NS+F	9	Uncomplicated recovery
Booker[47]	Thiazide	102	Seizure/coma	WR	3	Uncomplicated recovery
	Thiazide	105	Seizure/coma	WR	10	Uncomplicated recovery
Demanet[48]	Thiazide‡	103	Coma	WR	7	Uncomplicated recovery
De Troyer[49]	SIADH	104	Drowsiness	WR	3	Uncomplicated recovery
	SIADH	105	Drowsiness	WR	<10§	Uncomplicated recovery
Haden[50]	SIADH	105	Confusion	WR	3	Uncomplicated recovery
Ivy[51]	SIADH	105	Confusion	WR	<10§	Uncomplicated recovery
Schwartz[52]	SIADH	103	None	3%	10	Uncomplicated recovery
Stormont[53]	SIADH	103	Delirium	WR	3	Uncomplicated recovery
Thomas[54]	SIADH	102	?	?	7	Uncomplicated recovery
Weissman[55]	Thiazide	103	Confusion	WR	7	Uncomplicated recovery
West J Med[56]	SIADH	99	Lethargy	NS+F	8	Uncomplicated recovery

*SIADH denotes syndrome of inappropriate antidiuretic hormone secretion.
†NS denotes isotonic saline, 3% 3 percent saline, WR water restriction, and F furosemide.
‡Acute and chronic alcoholism.
§Exact correction rate not stated, but since patient had persistently concentrated urine and was treated with water restriction only, the rate was assumed to be below 10 mmol per liter per day.

our patients; the pathological findings in Patients 1 and 7 and the findings on CT scans in the other patients are inconsistent with this diagnosis. Moreover, only two of our patients experienced seizures before treatment; in two others, seizures developed after hyponatremia was corrected and seemed to be part of the neurologic deterioration rather than a cause of it. In summary, we believe that existing data argue strongly against correcting hyponatremia too rapidly: (1) experimentally, a characteristic, reproducible demyelinating lesion of the central nervous system develops if (and only if) chronic hyponatremia is corrected rapidly; (2) clinically, similar demyelinating lesions may occur if chronic hyponatremia is corrected at a rate of more than 12 mmol per liter per day; (3) neurologic findings typical of those in documented myelinolysis account for most of the neurologic sequelae in chronic hyponatremia; (4) recovery without complications is the rule if chronic hyponatremia is corrected by less than 12 mmol per liter per day.

There is no proved advantage to rapid correction of chronic hyponatremia. Without evidence to support this practice and with considerable evidence that it may be dangerous, we suggest that patients who present with chronic hyponatremia should be treated conservatively — primarily with water restriction and withdrawal of thiazide diuretics). We hope that in this way, the osmotic demyelination syndrome, a disease that we fear is now too common, will fade into obscurity.

We are indebted to Dr. Aaron Spital and Dr. Joshua Hollander for their helpful suggestions, to Beth Fedczuk for help in reviewing medical records, and to Carolyn Guerrera for help in preparing the manuscript.

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INTRAUTERINE INFECTION WITH VARICELLA–ZOSTER VIRUS AFTER MATERNAL VARICELLA

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Abstract We investigated the consequences of maternal infection with varicella–zoster virus in a prospective study of 43 pregnancies complicated by varicella and 14 pregnancies complicated by herpes zoster. Nine of 43 pregnant women with varicella had associated morbidity — pneumonia (4 women), death (1), premature labor (4 of 42), premature delivery (2 of 42), and herpes zoster (1). Intrauterine varicella infection was identified on the basis of clinical evidence (anomalies characteristic of the congenital varicella syndrome, acute varicella at birth, or herpes zoster in infancy) or immunologic evidence (IgM antibody to varicella–zoster in the neonatal period, persistent IgG antibody to varicella–zoster at one to two years of age, or in vitro lymphocyte proliferation in response to varicella–zoster virus antigen). The congenital varicella syndrome occurred in 1 of 11 infants of women with first-trimester varicella. Immunologic evidence of intrauterine varicella infection was present in 7 of 33 infants tested; 4 of these infants were asymptomatic. According to clinical or immunologic criteria, 8 of 33 infants had evidence of intrauterine varicella infection.

These observations show that varicella during pregnancy was associated with maternal morbidity and evidence of fetal infection, but that herpes zoster was not. (N Engl J Med 1986; 314:1542-6.)

VARICELLA during pregnancy has been associated with a congenital varicella syndrome (characterized by limb hypoplasia, cutaneous scars, microcephaly, cortical atrophy, chorioretinitis, cataracts, and other anomalies in the infant[1-18]) and with herpes zoster in otherwise asymptomatic infants.[19] Severe varicella with pneumonia and fatal dissemination has been reported in otherwise healthy pregnant women.[20,21] Birth defects following herpes zoster during pregnancy have also been described.[22-24] The risks of serious maternal infection and of fetal infection are assumed to be greater with varicella, which results from primary infection with varicella–zoster virus, than with herpes zoster. However, specific information concerning the risks of varicella during pregnancy is limited. The purpose of this study was to investigate the complications of primary and recurrent varicella–zoster virus infection in pregnant women and to evaluate the infants of these women for clinical and immunologic evidence of intrauterine varicella infection.

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METHODS

Study Population

Between July 1978 and June 1984, 44 otherwise healthy, pregnant women with varicella and 14 otherwise healthy, pregnant women with herpes zoster were enrolled in a prospective study. The diagnosis of maternal varicella or herpes zoster was made clinically by the referring obstetrician. All women with varicella had been exposed within 21 days before the onset of the rash, and none had a previous history of varicella. The diagnosis of varicella was confirmed in 11 cases serologically or by direct immunofluorescence of a lesion scraping. All women with herpes zoster had a previous history of varicella. Herpes simplex was ruled out by immunofluorescence staining if the lesions were in the lumbosacral dermatomes. There were 41 live births after maternal varicella and 14 live births after maternal herpes zoster. Informed consent for evaluation of the infant was obtained from the mothers. Newborn infants were examined for congenital anomalies. Most infants were also evaluated at one to two years of age, but 11 infants of mothers with varicella and 5 infants of mothers with herpes zoster were evaluated only at less than one year of age. The clinical evaluation at one to two years of age included a physical examination, a Denver Developmental Screening Test, and questioning for a history of herpes zoster. Most children were examined by us, but clinical data concerning five infants of mothers with varicella and two infants of mothers with herpes zoster were provided by the patient's pediatrician.

Laboratory Evaluation

Infants were studied for immunologic evidence of varicella–zoster infection with use of a solid-phase radioimmunoassay for IgG or

hypokalaemia in patients on long-term diuretic

the staff of the department of chemical pathology and tion of our clinical colleagues are much appreciated.

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lence for a primary autoimmune type of betes mellitus

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al Journal, 1978, 2, 1253–1255

y and conclusions

ght patients with longstanding diabetes and nt islet-cell antibody and 35 with coexistent and Graves's disease or primary myxoedema udied with particular reference to the HLA nd autoantibody patterns. A higher incidence of than normal was observed in the two groups. An relative risk exists when type I diabetes and mune thyroid disease coexist, indicating that HLA-linked genes may confer susceptibility to reatic and thyroid disorders. Other characteris- luding female predominance, a later onset of and a strong family history of autoimmune opathy, provide further evidence that this form es is aetiologically distinct from that generally hildren.

results support the hypothesis of a primary mune type of diabetes mellitus.

ction

rest has been focused on the biological importance of ying genetic determination and associated autoimmune a in insulin-dependent diabetes irrespective of the age (type I diabetes[1 2]). There is a significant positive between HLA-B8 and several organ-specific ne disorders including Graves's disease, Addison's nd myasthenia gravis.[3] HLA-B8 is also associated diabetes, but there is interesting evidence of a more elation in this disease, with a double axis of HLA determinants conferring susceptibility and a single axis conferring protection.[3 4] In people positive for HLA-B8 the relative risk of developing either diabetes or Graves's disease is increased two to three times.[1 3] No studies of primary myxoedema have been reported, and the association between Hashimoto's disease and the HLA system is still controversial.[1 4]

The increased prevalence of thyrogastric antibodies in patients with insulin-dependent diabetes is well recognised.[7] Islet-cell antibodies (ICA) are prominent and persistent in patients with polyendocrine disease and are found more transiently in children with uncomplicated diabetes.[8 9] Accordingly it has been suggested that pancreatic antibodies might be used as a marker for subdividing type I diabetes into two syndromes of different aetiology—namely, "juvenile" diabetes (type Ia), in which the autoimmune marker may occur in response to hypothetical viruses, and "primary autoimmune" or "polyendocrine" diabetes (type Ib).[10] Results of a recent study in children has supported this dual hypothesis, since ICA persisting for more than three years were strongly associated with the presence of other organ-specific antibodies in the patients and their families.[11]

An important question is whether the same or separate genes in linkage disequilibrium with HLA-B8 confer susceptibility to diseases in different endocrine organs. In order to elucidate this further we studied longstanding diabetics, some of whom had coexistent primary thyroid disease.

Patients and methods

We studied two groups of patients as follows:

Group 1—This group comprised 68 longstanding diabetics (mean duration of diabetes 19·5 years), with persistent ICA, whom we investigated with particular reference to clinical characteristics and other immunological features. Sixty-one patients were insulin dependent, and seven had been receiving diet and treatment by mouth for a considerable time (14–39 years). Thirty-nine of the insulin dependent group who had no clinical or biochemical evidence of other autoimmune endocrinopathy were HLA-typed.

Group 2—This group comprised 35 patients with coexistent type I diabetes and thyroid disease. All were receiving insulin. Eighteen patients had presented with classical features of Graves's disease. The diagnosis of primary myxoedema in 17 patients was made on clinical and metabolic features; none of these patients had previously been thyrotoxic or had a palpable goitre suggestive of Hashimoto's disease.

Methods—We carried out HLA-A and B typing for 34 specificities using a standard microlymphocytotoxicity method.[12] Relative risks were computed by the Woolf method[13] as modified by Haldane.[14]

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...ptoms rather than the physical signs of life-...ess that are traditionally taught in medical ...tion of these non-specific symptoms by doctors ...obtaining a careful history from the parents ...examination. Few parents, too, seem to have ...importance of unusual drowsiness, irritability, ... an altered character to the cry, or being off ...lation or as markers of deterioration in children ...or gastrointestinal illnesses.

...ggesting that all the children who had major ...d have been referred to hospital or that they ...efited from the earlier prescription of drugs. ...treatment is rarely indicated for respiratory ...stroenteritis at this age, it might be counter-...ing false reassurance to parents so that they ...alling the doctor despite the child's evident ...seems essential, however, that any child with ...ptoms which may be the only evidence of ...ngitis or septicaemia—should be kept under close ...rcumstances are satisfactory, if the parents can ...all for further help at the first sign of deteriora-... having been clearly explained to them), and ...are team can undertake closer supervision then ...rvation of the child at home will often be ...re still investigating how far these conditions ...illed and which are the crucial deficiencies in ...vision of health services for acutely ill young ...inition of which children would be safer under ...hospital is needed but not yet clear. Closer ...data and comparisons between the histories ...ents, family doctor, and health visitor may estab-...ecific symptoms should determine when hospital ...es appropriate, especially if there is already ...spiratory illness or gastroenteritis.

...ction and use of a clinical classification of deaths ...pectedly at home is only one step towards under-...mplex medical and social problem that almost certainly needs several different solutions. A later stage of the study will be to try to match the histories with the histology, so that we can interpret more precisely the importance of minor pathological changes, especially when the fatal process may have proceeded too rapidly for major tissue changes to have developed. Comparing pathological findings with the symptoms elicited may also help to indicate cases in which the observation or history was inadequate.

Once those children dying of inadequately recognised illness have been identified it should be possible to define the epidemio-logical characteristics of children who die unexpectedly despite appearing to be well. This is a crucial step before prospective investigations of cardiac, respiratory, neurological, and other physiological mechanisms of death can be undertaken in manage-able numbers of children.

Such fundamental research is a long-term commitment. The preliminary results of this study show that a large proportion of deaths might be prevented now if existing knowledge were better applied. There is an urgent need to improve the recogni-tion by both doctors and parents of non-specific symptoms as markers of severe illness in young children and their understand-ing of the necessity for rapid and appropriate action.

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...hyponatraemia in hospital inpatients

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...l, 1978, 2, 1251-1253

Conclusions

...study of severe hyponatraemia in adult ...ents showed that 44 patients had plasma ...rations below 125 mmol(mEq)/l. Eighteen ...re iatrogenic, caused by diuretic treat-...perative administration of intravenous ...or both. Chest infection, a seldom-...ill-understood cause of hyponatraemia, ...mmon than carcinoma of the bronchus. ...ents had symptoms attributable to the hyponatraemia, but these were severe in only five cases. Analysis of blood and urine was of no value in distinguish-ing the different diagnostic groups in an emergency.

Introduction

Many studies of cases of hyponatraemia have been reported, some of which have been concerned with the so-called syndrome of inappropriate antidiuretic hormone secretion. We report here an investigation into the incidence of severe hyponatraemia in an adult hospital population, the relative frequency of different causes, and the clinical importance of the condition. We have also assessed the clinical value of analyses of urine and blood in distinguishing the causes.

Methods

We were informed by the laboratory of all patients aged over 14 years with a plasma sodium concentration of under 125 mmol(mEq)/l. Patients were assessed clinically by one of us (PK or DM), with particular reference to the state of hydration, possible symptoms attributable to hyponatraemia, and the probable cause of the condition.

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..., MRCP, medical registrar (now at Brompton Hospital, ...
..., DM, FRCP, consultant physician

Simultaneous blood and urine samples were collected, and only patients with a plasma sodium concentration below 125 mmol/l in this specimen were considered further.

Plasma sodium, potassium, and urea and urinary urea concentrations were measured with a Technicon AA, autoanalyser; plasma and urinary osmolalities by freezing-point depression with an Advanced osmometer; plasma and urinary creatinine concentrations with a Technicon AA, autoanalyser; plasma and urinary magnesium and calcium concentrations by an atomic absorption spectrophotometer; and urinary sodium and potassium concentrations by a flame photometer.

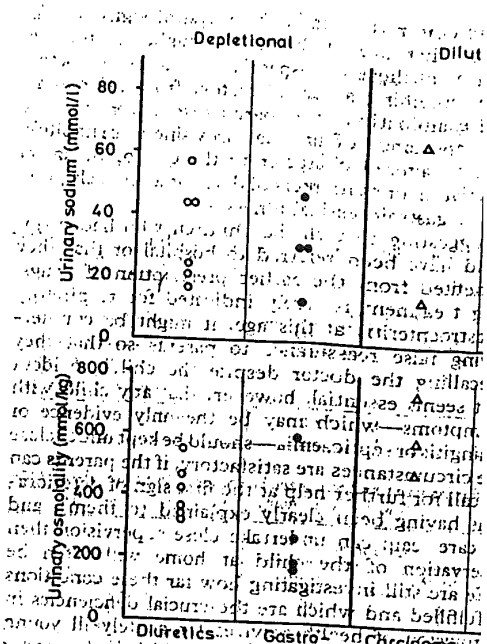
Results

We observed 44 patients (17 men, 27 women) with a plasma sodium concentration below 125 mmol/l over 10 months. This represented 0·9% and 0·4% respectively of the total medical and surgical admissions during the period. The patients were aged 23-90 (median 72) years, and the plasma sodium concentrations ranged from 110 to 124 (median 119) mmol/l.

In eight patients the hyponatraemia was attributed solely to diuretics used as maintenance treatment after previous heart failure. None of these patients had peripheral or pulmonary oedema when hyponatraemic, and only three were clinically dehydrated. Ten patients had received intravenous 5% dextrose after surgery; five of these were also receiving maintenance diuretic treatment. Nine cases were attributed to gastrointestinal and one to renal loss of salt and water. Eleven cases were associated with chest disease—seven with chest infections and four with carcinoma of the bronchus. One patient had liver failure, and in four severely ill patients there was no recognised cause of hyponatraemia.

Symptoms attributable to hyponatraemia, such as mental confusion, lassitude, anorexia, nausea, and headache,[3] are nonspecific, and it is difficult in practice to judge whether hyponatraemia or the underlying condition is responsible. Nevertheless, the hyponatraemia was considered to be the cause of symptoms in 31 patients (70%). In five cases (three iatrogenic) the symptoms were severe: three patients were grossly confused, one was comatose, and one had fits. In two of these cases and one other hyponatraemia had led to the patient's admission. The hyponatraemia and relevant symptoms cleared rapidly after diuretics or intravenous dextrose infusion had been stopped, chest infections treated, or salt and water losses replaced. Water restriction or hypertonic saline was not needed, and although 12 deaths occurred among the 44 patients hyponatraemia did not play a part in any.

Results of biochemical investigations were not received in many cases owing to administrative problems. But there was no apparent selection, and we do not believe that this invalidates our conclusions. The investigations proved unhelpful in differentiating the causes of hyponatraemia. The figure shows that urinary sodium concentrations and osmolality values overlapped considerably between groups divided arbitrarily according to whether the hyponatraemia had a "dilutional" or "depletional" cause. Similar comparisons using plasma:urine ratios and combinations of creatinine, sodium, potassium, magnesium, and calcium concentrations and osmolality showed a similar scatter. Only one of the patients with diuretic-induced hyponatraemia had a plasma potassium concentration under 3·0 mmol/l.



Urine sodium concentrations and osmolality in pa
severe hyponatraemia divided arbitrarily according
the hyponatraemia had a depletional or dilutional ca
Conversion: SI to traditional units—Sodium: 1 mEq/l. Osmolality: 1 mmol/kg = 1 mosmol/kg.

Discussion

Although all patients with a plasma sodium concentration below 125 mmol/l probably have symptoms,[3] hyponatraemia is rarely diagnosed on clinical grounds, and most of the initial blood tests in our series were routine. The true prevalence of severe hyponatraemia in an adult inpatient population may well be much greater than our data suggest. Two-fifths of our cases were iatrogenic. At least half of the cases studied by Arieff *et al*[4] were iatrogenic, though their group of patients was more selected than ours. Theoretically hyponatraemia should be less of a problem with "loop" diuretics than with thiazides.[7] Of our cases, five were associated with frusemide treatment and eight with thiazides; some patients in both groups were also receiving potassium-retaining diuretics. The absence of clinical dehydration in most of the patients with diuretic-induced hyponatraemia confirms views that sodium depletion plays a relatively minor part in this condition.[4]

There are many stimuli for release of antidiuri
after surgery.[8] The combination of postoperative wa
5% dextrose and reduced ability to excrete free wa
diuretic treatment appears to be a particularly pot
severe postoperative hyponatraemia.

Like Thomas *et al*,[3] we found that bacterial che
frequently cause severe hyponatraemia. Biochemic
blood and urine showed no characteristic values in t
consistent with the data of Thomas *et al*[3]; their da
a wide range of urine sodium and osmolality values
diagnostic groups. Reduced water excretion in sodi
states,[9] continuing sodium excretion with overhyd
variations in salt and water intakes are among factors
such variability within, and overlap between, diagno
Divalent ion excretion as a marker of plasma volume
does not appear to be of diagnostic value. Classical
biochemical criteria for the syndrome of inappropri
of antidiuretic hormone were satisfied in cases wi
aetiologies; this reinforces doubts about the clinica
of this concept in the absence of ectopic production of
hormone.[3]

This investigation did not include patients with hy
due to severe heart failure, acute renal failure, ad
deficiency and may to some extent reflect local clin
We believe, however, that many cases of hyp
hospitals are avoidable. Inappropriate treatment
more important than inappropriate secretion of
hormone. Particular care must be taken with intra
regimens in patients undergoing surgery while takin
Biochemical analysis of urine appears to play little
elucidating the cause or in the management of
natraemia in an emergency. Measurements of
trations of antidiuretic hormone are also unlikely

Although hyponatraemia only occasionally gives
symptoms in its own right, it may be a more impo

ORT REPORTS

ible hepatotoxicity of zimelidine

(Zelmid, Astra), which acts on the 5-hydroxytryptamine system, is a recent preparation for treating depression. and cardiovascular side effects are reportedly fewer than ional antidepressent drugs.[1 2] We report on a patient who hepatocellular jaundice and fever during treatment with and whose symptoms recurred on inadvertent rechallenge ug.

old insulin dependent diabetic consulted her general prac- mies over two months with varied physical symptoms including tension, nausea, dizziness, anorexia, weight loss, and paraes- She often weepy and lacked confidence. She was treated un- with lorazepam, ketazolam, betahistine, metoclopramide, and cyclizine and was then given zimelidine 100 mg twice epam 1 mg as required.

After she was admitted to this hospital with increasing nausea, d lassitude. She did not have headache. She was febrile (tem- °C) and jaundiced but did not have hepatomegaly. Serum centration was 72 μmol/l (4·2 mg/100 ml) with aspartate ate activity 235 IU/l (reference range 9-25 IU/l), alanine ase activity 300 IU/l (5-59 IU/l), lactate dehydrogenase U/l (72-395 IU/l), and alkaline phosphatase activity 176 IU/l Viral hepatitis was suspected. All drugs were stopped, and ated symptomatically. Her vomiting and fever persisted for a ek settled, and she was discharged. Results of serological tests idence of infection with hepatitis A, hepatitis B, cytomegalo- stein-Barr virus. At review six weeks later all results of liver were normal but she remained depressed and tired.

nued to complain of depressive symptoms and six months later prescribed zimelidine but in a lower dose (25 mg twice daily). eek she was readmitted with nausea, vomiting, right hypo- in, and jaundice. She was feverish (39°C) with tenderness in pochondrium but did not have hepatomegaly. Plasma bilirubin was 77 μmol/l (4·5 mg/100 ml) and activities of aspartate rase 462 IU/l, alanine aminotransferase 596 IU/l, lactate 853 IU/l, γ-glutamyltransferase 197 IU/l (6-31 IU/l), and phatase 307 IU/l. Results of blood cultures, repeat viral sts, smooth muscle and antimitochondrial antibody tests, and ultrasonography of the biliary tree were all normal. as stopped, and her temperature and symptoms settled over er one month all results of liver function tests had returned to

suffered the most severe hepatic reaction so far reported n with zimelidine. Nevertheless, on both occasions she pidly, both clinically and biochemically. Permission to er biopsy was refused. Coppen *et al*[3] described one patient y of hepatitis after treatment with chlorpromazine and who developed jaundice and fever two weeks after elidine. The patient was withdrawn from their trial and apidly subsided, but no details were given. Our patient y taken amitriptyline for over a year without ill effect. two patients[3] the principal symptom in both was transient increases in transaminase activities. Bilirubin s remained normal and the patients were afebrile.

s eliminated almost exclusively by hepatic metabolism, rzimelidine, an active metabolite with a long plasma ma concentrations are raised in elderly patients,[5] and a dose (100 mg) is recommended. Our patient was ng a day on the second occasion but the disturbance h was biochemically more severe than with the initial, his suggested a hypersensitivity reaction rather than dose.

that careful monitoring and reporting of side effects of uld continue, particularly as the drug is being increas- ed. Patients should be reviewed one to two weeks eatment, when adverse effects of this type seem most p. The drug should be withdrawn and liver function re headache, vomiting, fever, jaundice, or abdominal oped.

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Fatal brain oedema due to accidental water intoxication

Death due to water intoxication is uncommon,[1-3] though transien neurological dysfunction (confusion, headache, coma, convulsions is well recognised. Some of the earlier cases reported were iatrogenic[4] but most are psychogenic.[1 2 5] We believe the following to be th first reported case of accidental water intoxication with no psychiatri disorder and ending in death.

Case report

A 40 year old woman was brought to the casualty department confused and with incoherent speech. Initial examination showed no other abnormality. Blood pressure was 150/80 mm Hg and heart rate 88/min and regular. Shortly afterwards she had a short grand mal fit, which terminated spontaneously. During the next one and a quarter hours blood pressure rose to 220/80 mm Hg and pulse rate fell to 48/min. Respiration became irregular in depth and rhythm, and pupils were dilated and fixed; doll's eye movements were still present and the gag reflex preserved. There was no response to sternal pressure or peripheral painful stimuli. There was generalised hyperreflexia but no plantar response. We thought that a catastrophic rise in intracranial pressure was causing tentorial herniation and distortion of the upper brain stem. She was given hypertonic mannitol intravenously then intubated and ventilated. Parenteral dexamethasone was added later.

Laboratory values on admission were: serum sodium 111 mmol(mEq)/l, potassium 3·1 mmol(mEq)/l, bicarbonate 16 mmol(mEq)/l, urea 3·0 mmol/l (18·1 mg/100 ml), and glucose 9·8 mmol/l (177 mg/100 ml).

The patient's brother reported that she had drunk a small amount of diluted household bleach accidentally, mistaking it for water. He telephoned a poisons unit and was advised that she should drink large amounts of fluid. The patient drank about 15 l of water and persisted even after starting to vomit repeatedly. Two hours later she became confused and her brother called an ambulance. She had been perfectly well and had not been taking any medication.

The patient was reassessed on the ventilator. She had deteriorated: the apnoea test was not attempted, but all other brain stem reflexes were absent. A chest radiograph showed "bat's wing" pulmonary oedema. A CT scan showed cerebral and cerebellar oedema with compression of the lateral and third ventricles but without any midline shift. She had a large diuresis (8·6 l) in the first 24 hours, so that the chest *x* ray picture cleared and the serum sodium concentration rose to 129 mmol/l. Lumbar punctures on the second and fourth days gave normal results. Brain stem death was confirmed, and the ventilator was disconnected.

Results of all other investigations had been normal, including cerebrospinal fluid and blood serology and culture, and toxicology screen.

At necropsy the brain was found to be soft. The blood vessels were anatomically normal but there was massive congestion of the ventral blood

vessels and of the midbrain and pons. There was tentorial herniation, greater on the right. There was no evidence of previous cell loss or of inflammatory reaction.

Comment

Water intoxication causes hyponatraemia, which is responsible for the neurological dysfunction by causing intracellular overhydration. Symptoms may occur if the serum sodium concentration is less than 120 mmol/l, but the degree of brain dysfunction corresponds with the rapidity of development of the hyponatraemia. Intracellular potassium concentration is reduced, partly due to increased intracellular water and partly due to loss of intracellular potassium, but it is not clear whether cellular swelling alone or the potassium deficit is responsible for the encephalopathy. The accompanying brain oedema is usually transient but the intracranial hypertension may be catastrophic, causing uncal and tonsillar herniation.[1] The intracranial pressure later reverts to normal.[2]

In our patient signs developed with such rapidity that therapeutic measures succeeded in reducing the intracranial pressure only after irreversible brain stem damage had taken place.

We thank Dr A H James for permission to report this case and for helpful advice.

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Enteritis and colitis associated with mefenamic acid

Diarrhoea is a recognised side effect of treatment with mefenamic acid, although inflammatory bowel disease has not been reported. We describe two cases of acute colitis associated with treatment with mefenamic acid.

Case reports

CASE 1

A 43 year old man presented with a one year history of loose, bloodstained bowel actions up to 10 times daily, abdominal colic, and weight loss of 16 kg. He had been taking mefenamic acid (Ponstan) 250 mg by mouth three times daily for three years because of psoriatic arthropathy.

Physical examination showed only pallor and dehydration. Results of blood tests included: haemoglobin concentration (10·5 g/dl); white cells 11 600 × 10⁹/l (33% eosinophils); serum iron concentration 4·0 μmol/l (22·3 μg/100 ml); total iron binding capacity 62 μmol/l (346 μg/100 ml); erythrocyte sedimentation rate 15 mm in the first hour; and albumin concentration 31 g/l. On sigmoidoscopy the rectal mucosa appeared normal, but a biopsy specimen showed signs of mild chronic proctitis. A barium enema showed no obvious abnormality in the colon. Colonoscopy, however, showed that the mucosa of the descending colon was abnormal, with areas of aphthous ulceration and a cobblestone appearance; biopsy samples from these areas showed excessive plasma cell and eosinophil infiltration; the crypts were normal and there were no granulomas. Stool negative for salmonella, shigella, campylobacter, virus parti and *Clostridium difficile* toxin. Yersinia agglutination and an cence antibody tests gave negative results. Results of a l through examination were normal. Faecal fat excretion was (23 mmol/(6·5 g)/24 h (normal < 17 mmol (4·8 g)/24 h)). A duodenal biopsy specimen showed a chronic inflammatory c the lamina propria but was otherwise normal.

He was treated for six weeks with sulphasalazine without Mefenamic acid was therefore stopped, and within 48 hours pain and diarrhoea had stopped. His appetite improved. Ten was again given mefenamic acid; the pain and diarrhoea recu day. He did not take mefenamic acid for the following year time he was free of symptoms, he regained his former weight, variables were normal.

CASE 2

A 69 year old man presented with a two month history of d up to six bowel actions daily, and weight loss of 4 kg. He ha mefenamic acid 500 mg (Ponstan forte) intermittently for while awaiting left ureterolithotomy.

Examination was normal except for atrial fibrillation. On pus was present in the lumen and the mucosa showed loss of va A rectal biopsy specimen showed active proctitis. Stool culture results for salmonella, shigella, campylobacter and *Clostridiu* microscopy showed that no parasites were present. Full blood of thyroid function tests, and serum albumin concentration but the erythrocyte sedimentation rate was 51 mm in the seromucoid concentration was raised (2·0 g/l (normal < 1·2 enema showed only mild diverticular disease. Barium fo examination showed slight dilatation of jejunal loops. A du specimen showed normal villi with a non-specific inflammato

Mefenamic acid was stopped, and the diarrhoea resolved a He began taking mefenamic acid again after an interval of thr the diarrhoea returned within three hours. When the drug again his diarrhoea settled immediately. The erythrocyte rate, seromucoid concentrations, and sigmoidoscopic and appearances were then normal. He did not take mefenamic aci months of follow up and remained well.

Comment

Gastrointestinal side effects of mefenamic acid, althou mon, are well recognised. One of our patients had mild and both had inflammatory infiltration of the proximal both complications that have been reported before.[1 2] Coli does not appear to be a recognised complication, the m being aware of only four other possible cases (Warner-La personal communication). The unmasking of idiopathic i bowel disease has been reported with other non-st inflammatory drugs.[3] The prompt and permanent r symptoms in both our patients when treatment with me was stopped and their recurrence on re-exposure, howe suggest that this drug caused the colitis. These observatio the need for an adequate drug history in patients presentir proctitis or colitis.

We thank Dr O F W James for permission to report on t case 2.

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