SYMPTOMATIC HYPONATREMIA ASSOCIATED WITH PSYCHOSIS, MEDICATIONS, AND SMOKING

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Over a 3-year period, 15 patients with severe hyponatremia were referred to our emergency room from a nearby psychiatric institution. This article reports on 36 episodes of symptomatic hyponatremia in those 15 patients. All but two of the patients were receiving antipsychotic medications; one patient was taking a nonsteroidal anti-inflammatory drug, and one patient was taking an oral hypoglycemic agent. Thirteen patients were chronic schizophrenics, one had a bipolar depressive disorder with psychotic features, and one patient had no psychiatric disorder. Patients presented with seizures, change in mental status, and vegetative symptoms (nausea, vomiting, and diarrhea) associated with hyponatremia and water intoxication. Exacerbation of the patients' underlying illness, psychogenic polydipsia, compulsive smoking, alcoholic cirrhosis, drug abuse, and neuroleptic and other medications are thought to be the major causes of acute hyponatremia in these patients. (*J Natl Med Assoc.* 1993;85:135-140.)

Key words • hyponatremia • polydipsia • psychiatric patients • water intoxication

The prevalence of polydipsia among chronically ill psychiatric patients ranges from 7% to 18%.[1-3] Schizophrenia is the most common diagnosis in 69% to 83% of these patients.[3-5] The remainder are patients with alcohol-related organic brain syndromes, frontal or temporal lobe dysfunction, and other poorly described mental syndromes. Of these schizophrenic patients, about one half develop symptoms of water intoxication, such as polyuria, diarrhea, and hyponatremic encephalopathy, and require treatment.[1,2]

In 1933, Hoskins observed a group of schizophrenic patients with abnormally high urine output.[6,7] A higher incidence of polydipsia and polyuria in schizophrenics with a good response to neuroleptics also was reported.[8] The polyuria resolved with control of polydipsia, thus excluding diabetes insipidus as a possible cause.[9] Thirty years later, Mandell et al confirmed impaired renal free water clearance during the acute phase of psychiatric illness that returned to normal during recovery from the illness.[10]

Other authors have reported that polydipsic patients with hyponatremia tend to have lateral ventricular enlargement on computerized axial tomography (CAT) scan.[5] Vieweg et al[11] found that the onset of polydipsia in schizophrenic patients coincided with the "preterminal" stage of schizophrenia, which, according to Arieti,[12] occurs about 5 to 15 years after the onset of schizophrenia. Water intoxication subsequently follows 1 to 10 years after the onset of polydipsia.

The signs and symptoms of water intoxication are numerous. It is often difficult, if not impossible, to differentiate between exacerbation of psychosis and early signs of hyponatremic encephalopathy.[13] Early signs of water intoxication are restlessness, polyuria, hyposthenuria, retching, tremor, muscle twitching, headache, blurred vision, generalized malaise, nausea, vomiting, diarrhea, and increased salivation.[14-16] Mental status changes include lethargy, confusion, restlessness, irritability, and psychotic and manic behavior.[13,17] In addition to the neurologic complications of water intoxication resulting from cerebral edema, chronic

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uncorrected polydipsia may result in bowel and bladder dilation, hypotonicity, hydronephrosis, renal failure, and congestive heart failure.[3,16,18] If the decrease in serum sodium is precipitous, seizures and coma may be the initial presentation[19-21] and may progress to pulmonary or cerebral edema and death.[22-24] As many as 18% of deaths of schizophrenics under the age of 53 years are related to water intoxication.[24] This article reports on 36 episodes of symptomatic hyponatremia in 15 patients over a 3-year period.

MATERIALS AND METHODS

The medical records of all patients admitted to the Queens Hospital Center, Jamaica, New York, with symptomatic hyponatremia from 1986 to 1989 were reviewed retrospectively. For this study, hyponatremia is defined as a serum sodium level of 126 mEq/L or less. The following information was obtained from each medical record: age, sex, race, medical history, symptoms at hospital admission, medications, psychiatric diagnosis, treatment, hospital course, length of hospital stay, and outcome.

Laboratory studies included serum levels of sodium, potassium, glucose, bicarbonate, chloride, lactic dehydrogenase, creatine phosphokinase, urea, and creatinine. Results of CAT scans, chest roentgenograms, cerebral angiograms, liver function tests, serum osmolality, and urine analysis including osmolality and electrolytes also were examined when available. A diagnosis of hyponatremic water intoxication was made on the basis of cerebral impairment associated with excess water consumption, most often presenting as generalized seizures, and hyponatremia that was reversed after water restriction and normal saline infusion.

RESULTS

The medical records were available for 15 patients who had 36 hospitalizations for symptomatic hyponatremia (Tables 1 and 2). Fourteen of the patients were either residents of a chronic care psychiatric institution or were living at home. Patients' ages ranged from 25 to 63 years (mean: 42 years). Nine of the patients were men and six were women. One patient was black, one was Asian, one was Indian, and 13 were white. Fourteen of the 15 patients improved with treatment and were discharged (Table 1); one patient died on the day of admission. This patient was the only nonpsychiatric patient, and he presented after a 3-day alcoholic binge with polydipsia in a diabetic hyperosmolar state.

In 24 of the 36 episodes, the patient presented with seizures (14 grand mal and 10 tonic-clonic). In the remaining 12 episodes, the patient presented with bizarre behavior, change in mental status, lethargy, respiratory failure due to seizures, and status epilepticus; one patient presented with symptoms of an acute abdomen (Table 2). Treatment consisted of fluid restriction alone in 30 episodes and fluid restriction supplemented with 3% normal saline infusion in 5 episodes. In the remaining episode, the patient was treated with hydration—he was in a diabetic hyperosmolar state.

All of the patients had histories of polydipsia and were heavy smokers. Thirteen were chronic schizophrenics; one patient had a bipolar depression with psychotic features, and one patient had no psychiatric history but was a chronic alcoholic. Thirteen patients were receiving one of the following neuroleptic medications: chlorpromazine, fluphenazine, thioridazine, thiothixene, perphenazine, trifluoperazine, loxapine, and haloperidol. Two patients were not receiving any neuroleptic medication at the time of presentation, one patient was taking a nonsteroidal anti-inflammatory drug, and two patients were taking oral hypoglycemic agents (chlorpropamide and tolazamide).

Seven patients had a single hospitalization while eight patients had multiple hospitalizations: four had 2, one had 3, two had 4, and one patient had 10 hospitalizations. The admission sodium levels ranged from 105 to 126 mEq/L.

Six patients had CAT scans, and one patient had a cerebral angiogram that showed no arteriovenous malformation or aneurysm. Four patients had no significant findings on CAT scan. The CAT scan of one patient was remarkable for cerebral atrophy not consistent with his age, and another patient had an old infarct in the temporal lobe. Complete records of urine electrolytes, and serum and urine osmolality values were available for only six admissions. Urine osmolality was greater than serum osmolality in two cases and was lower in four. Lactic dehydrogenase measurements were found from review of the charts for 14 of 36 hyponatremic episodes. The value was above normal in all cases, ranging from 246 units/L to 560 units/L. Serum creatine phosphokinase was not measured in any patient.

DISCUSSION

Several theories are offered to explain the syndrome of polydipsia and symptomatic hyponatremia. Various descriptive terms are used to identify polydipsic psychiatric patients, such as "compulsive water drink-

TABLE 1. ADMISSION DATA FOR 15 PATIENTS WITH SYMPTOMATIC HYPONATREMIA

Patient	Age (Years)	Sex	Race	Primary Diagnoses	Outcome
1	25	Male	White	Hyponatremia, psychogenic polydipsia, and chronic schizophrenia	Discharged to referring institution
2	30	Female	Asian	Hyponatremia, psychogenic polydipsia, and chronic schizophrenia	Discharged to referring institution
3	31	Male	White	Hyponatremia, psychogenic polydipsia, chronic schizophrenia, and essential hypertension	Discharged to referring institution
4	33	Male	White	Hyponatremia, psychogenic polydipsia, chronic schizophrenia, and chronic drug abuse	Transferred to psychiatric institution
5	34	Female	White	Hyponatremia, psychogenic polydipsia, and bipolar depression with psychotic features	Discharged to referring institution
6	37	Male	White	Hyponatremia, psychogenic polydipsia, and chronic undifferentiated schizophrenia	Discharged to referring institution
7	41	Male	White	Hyponatremia, psychogenic polydipsia, and chronic schizophrenia	Discharged to referring institution
8	41	Male	Black	Acute pancreatitis, hyponatremia, and polydipsia	Died
9	42	Female	White	Hyponatremia, psychogenic polydipsia, and chronic schizophrenia	Discharged to referring institution
10	44	Female	White	Hyponatremia, psychogenic polydipsia, and chronic schizophrenia	Discharged home*
11	44	Female	White	Hyponatremia, psychogenic polydipsia, and chronic schizophrenia	Discharged to referring institution
12	47	Male	White	Hyponatremia, psychogenic polydipsia, and chronic undifferentiated schizophrenia	Discharged to referring institution
13	57	Female	Indian	Hyponatremia, psychogenic polydipsia, chronic schizophrenia, and unspecified acquired hypothyroidism	Discharged to referring institution
14	63	Male	White	Hyponatremia, psychogenic polydipsia, chronic undifferentiated schizophrenia, diabetic ketoacidosis, and urinary tract infection	Discharged to referring institution
15	63	Male	White	Hyponatremia, psychogenic polydipsia, chronic undifferentiated schizophrenia, and aspiration pneumonia	Discharged to referring institution

*Patient cared for at home by her father.

TABLE 2. CLINICAL DATA AND NEUROLEPTIC MEDICATIONS TAKEN PRIOR TO PRESENTATION IN 36 HOSPITALIZATIONS FOR SYMPTOMATIC HYPONATREMIA

Patient	Admission No.	Presenting Symptoms	Neuroleptic Medication(s)	Admission Sodium (mEq/L)	Hospital Treatment	Length of Hospital Stay (Days)	Other Condition(s)*
1	1	Tonic-clonic seizures	Chlorpromazine	122	FR	4	
	2	Tonic-clonic seizures	Haloperidol	114	FR + 3%NS	3	
2	1	Grand mal seizures	Haloperidol	119	FR	2	Alcoholism
3	1	Grand mal seizures	Haloperidol	110	FR	4	Hypertension
	2	Grand mal seizures	Haloperidol	116	FR	3	
	3	Grand mal seizures	Thorazine	119	FR	2	
	4	Grand mal seizures	Thorazine	114	FR	4	
	5	Grand mal seizures	Thorazine	118	FR	4	
	6	Grand mal seizures	Thorazine	116	FR	3	
	7	Grand mal seizures	Fluphenazine	117	FR	2	
	8	Grand mal seizures	Fluphenazine	121	FR	5	
	9	Grand mal seizures	Chlorpromazine	113	FR	9	
	10	Tonic-clonic seizures	Haloperidol	117	FR	16	
4	1	Psychotic episode, suicide attempt, and paranoia	None†	108	FR	12	Alcoholism and drug abuse
5	1	Grand mal seizures	Chlorpromazine	120	FR	5	
	2	Grand mal seizures	Chlorpromazine	117	FR	4	
	3	Bizarre behavior	Thiothixene	116	FR	4	
	4	Change in mental status; nausea, vomiting, and diarrhea	Thiothixene	126	FR	6	
6	1	Tonic-clonic seizures	Haloperidol	122	FR	11	
	2	Status epilepticus	Haloperidol	115	FR + 3%NS	2	
7	1	Bizarre behavior	Thiothixene	116	FR	4	Alcoholic cirrhosis
8	1	Abdominal tenderness, tachypnea, and diaphoresis	None‡	115	Hydration	<1	Alcoholism and noninsulin dependent diabetes mellitus
9	1	Tonic-clonic seizures	Haloperidol	111	FR	4	
	2	Tonic-clonic seizures	Fluphenazine	105	FR + 3%NS	3	
10	1	Change in mental status; nausea, vomiting, and diarrhea	Trifluoperazine	111	FR	3	Head trauma and brain damage in childhood
	2	Change in mental status; nausea, vomiting, and diarrhea	Fluphenazine	112	FR	15	
	3	Grand mal seizures	None	111	FR	3	
	4	Grand mal seizures	Fluphenazine	112	FR	2	

Abbreviations: FR = fluid restriction and NS = normal saline.
*All of the patients were heavy smokers.
†Patient was taking a nonsteroidal anti-inflammatory drug (naproxen).
‡Patient was taking an oral hypoglycemic drug (chlorpropamide).
§Patient was also taking tolazamide.

TABLE 2. CLINICAL DATA AND NEUROLEPTIC MEDICATIONS TAKEN PRIOR TO PRESENTATION IN 36 HOSPITALIZATIONS FOR SYMPTOMATIC HYPONATREMIA (CONTINUED)

Patient	Admission No.	Presenting Symptoms	Neuroleptic Medication(s)	Admission Sodium (mEq/L)	Hospital Treatment	Length of Hospital Stay (Days)	Other Condition(s)*
11	1	Tonic-clonic seizures	Thioridazine	108	FR + 3%NS	4	
	2	Respiratory failure secondary to seizures	Thioridazine	112	FR + 3%NS	10	
12	1	Change in mental status and lethargy	Loxapine	126	FR	3	
	2	Syncopal episode	Loxapine	123	FR	8	
	3	Tonic-clonic seizures	Loxapine	122	FR	14	
13	1	Tonic-clonic seizures	Haloperidol	106	FR	9	
14	1	Lethargy	Perphenazine§	106	FR	4	Noninsulin dependent diabetes mellitus
15	1	Tonic-clonic seizures	Haloperidol	120	FR	13	Epilepsy

Abbreviations: FR = fluid restriction and NS = normal saline.
*All of the patients were heavy smokers.
†Patient was taking a nonsteroidal anti-inflammatory drug (naproxen).
‡Patient was taking an oral hypoglycemic drug (chlorpropamide).
§Patient was also taking tolazamide.

ing,"[25] "self-induced water intoxication,"[14,26] and "psychogenic polydipsia." Polydipsia in psychiatric patients was reported well before the advent of neuroleptic medications. Therefore, thirst and dry mouth from the direct anticholinergic effects and hypotension from alpha-adrenergic blockade of these drugs play a negligible role in the causation of polydipsia.[7,25,27,28]

Furthermore, few patients describe thirst as the stimulus for their polydipsia and instead attribute their compulsive water drinking behavior to various delusions. On the other hand, some studies show a temporal relation between exacerbations of psychosis and psychogenic polydipsia and water intoxication in psychiatric patients.[28,29] Peterson and Marshall[30] propose that the increased prevalence of ventricular enlargement in schizophrenic patients may lead to structural impairment of the lateral hypothalamus and disturbances in thirst and osmolality, as well as the psychiatric balance of the patient.[31]

The polydipsic theory of dopamine supersensitivity[32] is a more recent explanation for the association of polydipsia and psychosis, first reported more than 50 years ago.[8] Dopamine is an important neurotransmitter in the area of the thirst center in the lateral hypothalamus. In animals, a hyperdopaminergic state is associated with increased fluid intake, which can be reversed by dopamine antagonists.[33,34] There is a higher incidence of tardive dyskinesia in polydipsic and hyponatremic schizophrenic patients than in controls,[35] as well as the transient occurrence of tardive dyskinesia paralleling episodes of water intoxication.[32] Like schizophrenia, polydipsia may be associated with a hyperdopaminergic state.

Why do only a small fraction of polydipsic psychiatric patients progress to develop symptoms of water intoxication and hyponatremia? The renal free-water excretion capacity of 28 L/day is more than adequate to handle even the most severe water load; thus, water intoxication develops only when such high fluid intake is coupled with an inability to excrete a maximally dilute urine, ie, a reduction in the renal free-water excretion capacity. In the absence of dehydration and any renal, cardiac, and adrenal pathology, the syndrome of the inappropriate secretion of antidiuretic hormone (SIADH) is often implicated as the cause for the renal excretion of sodium despite serum hyponatremia and hypo-osmolality. Studies have shown elevated levels of antidiuretic hormone during such episodes of hyponatremia and water intoxication.[16,29,36] This syndrome may be associated with a variety of conditions including cancer, neurologic conditions (encephalitis,

stroke, and trauma), pulmonary disorders (pneumonia and tuberculosis), and several medications such as hypoglycemic drugs, antineoplastic drugs, thiazide diuretics, nicotine, phenothiazine and nonphenothiazine neuroleptics (thioridazine, thiothixene, fluphenazine, haloperidol, and chlorpromazine), anticonvulsants (carbamazepine), and tricyclic antidepressants (amitryptiline, desipramine, and tranylcypromine).[37]

Neuroleptic medications, particularly in psychiatric patients with a history of polydipsia, must be carefully monitored. In 50% of neuroleptic drug-related hyponatremia and SIADH, the offending drug was used for less than 1 week.[38] It is therefore crucial that urine and serum electrolytes of polydipsic psychiatric patients be measured and monitored after a change in neuroleptic medication. One patient in our study presented 4 days after his old medication, nortriptyline, was changed to perphenazine. Even when SIADH resolves upon discontinuation of a particular drug, it is possible to re-administer the same drug without recurrence of SIADH.[38,39] Furthermore, a neuroleptic medication should not be implicated as the sole cause of SIADH without a controlled rechallenge with the suspected medication, and with careful daily monitoring of serum electrolytes and serum and urine osmolalities.[39] A review of several case reports of SIADH between 1974 and 1979 reveals that only once was drug rechallenge given in a controlled setting, while another rechallenge was inadvertent.[39]

Nicotine is a potent stimulator of antidiuretic hormone.[31,40-42] One study found that 69% of subjects with water intoxication were smokers.[43] All 15 subjects in our study were heavy smokers. Blum[41] found that heavy smokers all developed symptomatic hyponatremia.

Rhabdomyolysis is commonly observed in psychiatric patients even in the absence of seizures.[44] Twelve of our patients had sustained falls, extensive bruising, and cuts requiring suturing before they were brought to our emergency room. One patient living at home daily scalded his arms in boiling water as part of a "purification process." Burn wounds are associated with rhabdomyolysis. Therefore, serum creatine phosphokinase and lactate dehydrogenase levels should be checked. None of our 15 patients had a creatine phosphokinase level determined, while for 14, the lactate dehydrogenase levels were elevated.

Several drugs affecting antidiuretic hormone secretion have been tried over the years with little success. Demeclocycline may be useful in the long-term control of hyponatremia and polydipsia in psychiatric patients.[45,46]

SUMMARY

A high index of suspicion is needed when patients develop early symptoms of hyponatremia and water intoxication (vida supra) so that the patients do not go unnoticed until they develop seizures or changes in mental status. Early diagnosis is of significant clinical and economic value—the average length of hospitalization of our patients was 6 days.

Urine and serum electrolytes and osmolality should be checked when a patient's antipsychotic medication is changed, particularly if the patient develops acute changes in mental status, since most drug-induced episodes of hyponatremia present within less than a week of the medication switch. However, this testing should only serve as an adjunct to clinical evaluation. Head CAT scans on six patients showed no signs of ventricular enlargement and may not be necessary.

The incidence of rhabdomyolysis is high among psychiatric patients, especially in the presence of seizures. Serum creatine phosphokinase and lactate dehydrogenase levels are sensitive markers of rhabdomyolysis and should be routinely determined in a psychiatric patient following a seizure or in a patient who presents to the emergency room with extensive bruises, cuts, or burns.

Finally, many medications, in addition to neuroleptic agents, may cause SIADH. In our patients, oral hypoglycemic agents (chlorpropamide and tolazamide) and a nonsteroidal anti-inflammatory agent (naproxen) were associated with polydipsia and hyponatremia. No patient should be discharged on a medication that may be responsible for the patient's presentation unless it is a rechallenge done in a controlled setting, during which baseline serum and urine electrolytes and osmolalities should be determined and followed daily while the patient is taking the suspected neuroleptic agent.

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