Hypouricemia in Chronic Schizophrenic Patients With Polydipsia and Hyponatremia

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Background: Polydipsia is a common disorder among chronic psychiatric patients. Impaired water excretion due to enhanced action and secretion of antidiuretic hormone has been reported in hyponatremic patients with polydipsia. Hypouricemia coexisting with hyponatremia is a hallmark of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). The transitory coexistence of hyponatremia and hypouricemia in patients with polydipsia-hyponatremia syndrome is presented.

Method: We examined the course of hypouricemia and hyponatremia in three schizophrenic patients with a long-standing history of polydipsia resulting in the presence of these conditions. In addition, we investigated the renal clearance of uric acid in five polydipsic patients without a previous history of water intoxication or hyponatremia (simple polydipsia).

Results: Both hyponatremia and hypouricemia were demonstrated in the presence of SIADH in one patient, during an episode of acute water intoxication in another, and in association with chronic hyponatremia in a patient who was following the target weight procedure. Elevated fractional excretion of uric acid percentage (FEUA%) was detected in two patients. These states appeared to be episodic or transitory. In the five patients with simple polydipsia, serum uric acid concentrations and FEUA% were maintained within the normal range.

Conclusion: Altered uric acid regulation that resembles SIADH is present in patients with polydipsia-hyponatremia syndrome. Monitoring the uric acid concentration and FEUA% in polydipsic patients may be useful in identifying those patients with transiently impaired water excretion.

(J Clin Psychiatry 1997;58:256–260)

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Polydipsia is a common disorder among patients with chronic psychiatric illness, particularly those with schizophrenia. Eventually, some patients with polydipsia develop profound hyponatremia. The pathophysiology of episodes of acute symptomatic hyponatremia, referred to as water intoxication, is unclear.[1–7] However, it is generally accepted that in this disorder hyponatremia is coupled with impaired water excretion, presumably due to enhanced arginine vasopressin (AVP) secretion and action.[8–10]

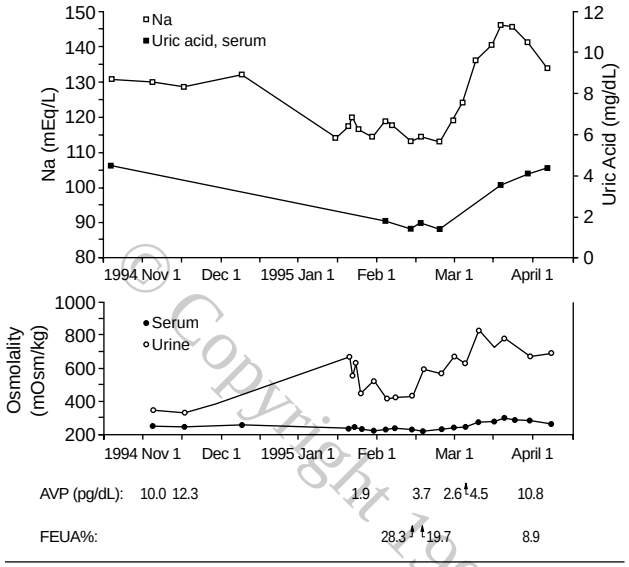
The simultaneous coexistence of hypouricemia and hyponatremia has been reported in patients with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).[11–13] We noted simultaneous changes in serum sodium and uric acid concentrations in three schizophrenic patients with a long-standing history of polydipsia, together with altered uric acid regulation due to SIADH found in polydipsia-hyponatremia syndrome.

CASE REPORTS

The three patients and five control subjects studied were hospitalized in the chronic units of Kinkoh Hospital, Kanagawa Prefectural Center of Psychiatry. For the past 5 years, both blood and urine samples were obtained simultaneously from each patient at least every 3 months.

We measured the urinary excretion of uric acid, using fractional excretion of uric acid percentage (FEUA%: the percentage of uric acid clearance relative to creatinine clearance), using these samples. The FEUA% was calculated as the (urine/serum) concentration of uric acid divided by the (urine/serum) concentration of creatinine multiplied by 100. All patients received standard treatment with neuroleptics. No patient received carbamazepine or diuretics. Only the patient in Case 3 received lithium carbonate (600 mg/day).

Figure 1. Sequential Changes in Laboratory Data in Case 1: Fractional Excretion of Uric Acid Percentage (FEUA%) and Plasma Arginine Vasopressin (AVP) Concentrations



The normal ranges for each substance are as follows: serum sodium: 135–146 mEq/L; serum uric acid: 2.6–7.5 mg/dL; serum osmolality: 285–295 mOsm/kg; urine osmolality: 50–1400 mOsm/kg; and FEUA%: 8%–12%.

Case 1

Mr. A, a 58-year-old man with a history of undifferentiated schizophrenia, had a past medical history noteworthy only for a 20-year duration of polydipsia. His first episode of water intoxication, leading to a seizure and loss of consciousness, occurred at age 46. Several subsequent episodes of water intoxication ensued. At 55 years of age, a left femoral bone fracture left him wheelchair-bound and prevented his excessive water intake. Since age 56, he had demonstrated prolonged episodes of intermittent lethargy lasting for several hours. During these periods, chronic mild hyponatremia (127 to 135 mEq/L) was noted. In November 1994, the plasma AVP was 10 pg/dL (normal range, 0.3–3.5), serum osmolality was 265 mOsm/kg, and urine osmolality was 371 mOsm/kg. These findings were consistent with a diagnosis of SIADH. Occult malignancy or drug-induced SIADH was excluded. In mid-January 1995, he suddenly lost consciousness. Laboratory data revealed profound hyponatremia (114 mEq/L). Serum osmolality was decreased, while the urine osmolality was elevated. He was given an elemental diet, and his total fluid intake was restricted to 1800 mL/day. Neuroleptics were discontinued, and demeclocycline 600 mg/day was administered. However, the patient had been unconscious for nearly a month, during which time hyponatremia persisted. During this period, his serum uric acid concentration decreased. Increased FEUA% was noted (normal range, 8%–12%)[14,15] (Figure 1).

Case 2

Mr. B, a 52-year-old man with a history of undifferentiated schizophrenia had been mildly polydipsic since his 40s. At the age of 48 in October 1992, he became agitated. Compulsive water drinking, nocturnal incontinence, and moderate diurnal weight gain were intermittently observed. On November 18, 1992, he experienced cognitive impairment and an ataxic gait. At that time, his sodium level was 131 mEq/L, serum osmolality was 252 mOsm/kg, and the urine specific gravity (SPGU) was 1.002. Water restriction according to the target weight procedure was instituted.[6,7,16,17] On December 7, 1992, he again experienced ataxic gait. For the next 2 months, despite water restriction, his serum sodium and uric acid concentrations and serum osmolality all remained below the lower limit of the normal range. Since March 1993, he has maintained his normal weight and remained free of any symptom of water intoxication, in spite of being moderately polydipsic. Routine laboratory tests documented the absence of hyponatremia and hypouricemia, and normal FEUA% (Table 1).

Case 3

Mr. C, a 52-year-old man with a history of disorganized schizophrenia, had been mildly polydipsic since his late 30s, and had experienced episodes of water intoxication once or twice a year since his 40s. On September 6, 1992, he became severely water intoxicated, with a serum sodium concentration of 118.1 mEq/L, serum uric acid concentration of 1.7 mg/dL, and SPGU of 1.001. The target weight procedure was instituted after this episode, and overnight water restriction was often imposed according to its protocol, which prevented further recurrence of water intoxication. Routine laboratory data revealed mild hyponatremia and hypouricemia with varying SPGU and urine osmolalities. In December 1995, his weight had been stable for approximately 3 weeks and his laboratory data were within the normal range. In February 1996, he presented with agitation associated with compulsive water drinking and abnormal weight gain. Mild hyponatremia and hypouricemia with elevated FEUA% were documented. After initiation of water restriction for 16 hours, both the sodium and serum uric acid levels increased. However, under conditions of free water intake, his sodium and uric acid levels and FEUA% presented marked diurnal variations. Moderate fluid restriction to 1500 mL/day for 3 days normalized his sodium and uric acid concentrations and FEUA% (Table 2).

Controls

We investigated the renal clearance of uric acid in five schizophrenic patients with polydipsia who had no pre-

Table 1. Sequential Changes in Laboratory Data in Case 2

Date	Serum Na (mEq/L)	Serum Uric Acid (mg/dL)	Serum Osmolality (mOsm/kg)	Urine Osmolality (mOsm/kg)	Urine Specific Gravity	FEUA%
Mar 9, 1990–Oct 21, 1992[a]	140.1 ± 2.8 (14)	5.85 ± 1.15 (6)	286.3 ± 5.3 (6)	287.7 ± 97.9 (3)	1.0045 ± 0.0028 (4)	…
1992						
Nov 18	131.0	…	252	91	1.002	…
Nov 26	136.5	…	278	272	1.008	…
Dec 3	137.0	4.6	280	392	1.017	…
Dec 7	137.5	2.8	…	…	1.006	…
Dec 12	134.3	2.9	270	507	1.027	…
Dec 21	135.5	2.8	270	241	1.017	…
1993						
Jan 26	130.3	4.4	258	620	1.022	…
Mar 4	141.5	6.8	283	…	1.004	…
Mar 19, 1993–Feb 28, 1996[a]	143.1 ± 2.8 (16)	4.83 ± 1.15 (12)	287.1 ± 7.5 (13)	224.3 ± 86.2 (15)	1.0058 ± 0.0020 (15)	11.24 ± 1.15 (6)[b]

[a]Values are mean ± SD followed by the number of samplings in parentheses.
[b]Fractional excretion of uric acid percentage (FEUA%) normal range = 8% to 12%.

Table 2. Sequential Changes in Laboratory Data in Case 3

Date	Serum Na (mEq/L)	Serum Uric Acid (mg/dL)	Serum Osmolality (mOsm/kg)	Urine Osmolality (mOsm/kg)	Urine Specific Gravity	FEUA%
Mar 10, 1990–Sept 6, 1995[a]	134.6 ± 5.7 (45)	3.04 ± 0.73 (16)	276.4 ± 12.5 (22)	396.9 ± 237.2 (21)	1.009 ± 0.006 (23)	…
Dec 8, 1995	141	4.0	290	637	1.015	14.33
1996						
Feb 22	133	2.9	277	241	1.005	21.35
Feb 26	135	3.2	267	107	…	…
Mar 2	129	3.1	269	142	…	26.70
Mar 7	132	3.2	268	90	…	18.64
Mar 11						
a.m.[b]	137	3.6	282	177	…	13.32
p.m.	122	2.6	252	73	…	28.15
Mar 14[c]	141	3.3	281	464	…	12.38

[a]Values are mean ± SD followed by the number of samplings in parentheses.
[b]After water restriction for 16 hours.
[c]After water restriction to 1500 mL/day for 3 days.

Table 3. Sequential Changes in Laboratory Data in Five Patients With Simple Polydipsia

Case	Age (y)	Serum Na (mEq/L)	Serum Uric Acid (mg/dL)	BUN (mg/dL)	Serum Osmolality (mOsm/kg)	Urine Osmolality (mOsm/kg)	FEUA%
4	61	140	4.1	7	288	85	9.56
5	36	138	4.8	6	277	156	6.20
6	51	140	4.9	9	290	186	7.92
7	49	142	4.3	10	285	92	10.16
8	41	139	5.0	11	287	81	10.20
Mean ± SD	47.6 ± 9.6	139.8 ± 1.5	4.62 ± 0.40	8.6 ± 2.1	285.4 ± 5.0	120 ± 47.9	8.81 ± 2.98

vious episodes of water intoxication or hyponatremia (simple polydipsia). Samples of blood and urine were taken simultaneously in the morning. The clinical and laboratory findings are summarized in Table 3. Urine osmolality and blood nitrogen concentrations were low, suggesting polyuria secondary to polydipsia. However, no hyponatremia nor hypouricemia was observed. In every patient, the FEUA% was maintained in the normal range.

DISCUSSION

The coexistence of hypouricemia and hyponatremia is one of the hallmarks of SIADH.[12–15] The cause of the hypouricemia in SIADH is elevated renal uric acid clearance. Fluid restriction usually reverses the hypouricemia and elevated uric acid clearance. It is generally considered that the elevated renal uric acid clearance is

secondary to mild expansion of the extracellular fluid, although patients with SIADH appear clinically normovolemic.[12–15,18,19] A few studies have demonstrated increased tubular urate secretion or defective presecretive and postsecretive tubular urate reabsorption in SIADH.[18,20]

This report documents simultaneous changes in the serum sodium and uric acid concentrations in three schizophrenic patients with polydipsia. In these three patients, despite variable water intake or urinary dilution, the hypouricemia always presented in association with hyponatremia. Elevation in FEUA%, verified in Cases 1 and 3, indicates that the cause of hypouricemia in polydipsia-hyponatremia syndrome is due to elevated renal uric acid clearance as in SIADH. The direct relationship of fluid intake and FEUA% was corroborated in Case 3. The five patients with simple polydipsia presented extremely diluted urine, but the serum sodium concentration, uric acid concentration, and FEUA% were maintained within the normal range. Therefore, hypouricemia with elevated FEUA% may represent transient expansion in the extracellular volume due to an inability to excrete excess water. Decaux et al.[21] have reported variable serum uric acid concentrations in 17 patients in the presence of polydipsia and hyponatremia. However, some of their patients were diagnosed with alcoholic polydipsia (beer potomania), which is potentially hyperuricemic.[22] No clearance study was performed.

Interestingly, increased renal calcium excretion, which may result in osteoporosis or pathologic fracture as seen in Case 1, was previously described in polydipsia-hyponatremia syndrome.[23,24] The presumed mechanism of increased calcium excretion is also mild volume expansion like that of uric acid.[24]

It is important to identify, among polydipsic patients, those patients with impaired water excretion, since hyponatremia combined with polydipsia may result in a potentially harmful switching in mental and physical status.[25] However, it is difficult to identify these patients using routine laboratory testing. Serum sodium levels present marked diurnal variation, and this disorder is frequently episodic in nature.[5–7] Indeed, all patients described herein appear to have an antidiuretic state with either a fluctuating or an episodic character, as other researchers have also reported.[26,27]

Diurnal weight changes and afternoon serum sodium concentrations have been used to identify these patients with impaired water excretion.[6,7,16,17] We postulate that monitoring the concentration of uric acid and FEUA% is a means of identifying those patients with temporarily impaired water excretion, and may serve as an additional marker for identifying patients at risk of developing hyponatremia. It is noteworthy that the FEUA% is usually elevated by excessive synthesis of uric acid and may be affected by a number of drugs, such as diuretics and carbamazepine, as well as several neuroleptics that alter uric acid excretion (e.g., zotepine).[28] However, these drug-induced conditions may be readily identified, with rare exceptions.[29] The sensitivity and specificity of this method in identifying these patients among the large number of chronically hospitalized patients require further investigation.

Drug names: carbamazepine (Tegretol and others), demeclocycline (Declomycin).

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