

[CASE REPORT]

SIADH with Severe Hyponatremia in an Elderly Man with Herpes Zoster Infection: A Causal or Casual Association?

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Abstract:

Syndrome of inappropriate antidiuretic hormone (SIADH) secretion is the most common cause of hypotonic hyponatremia in hospitalized patients. An elderly man with severe symptomatic hyponatremia (109 mEq/L) was diagnosed with SIADH that was likely secondary to large cutaneous herpes zoster (HZ) infection. Hypertonic saline and tolvaptan improved the patient's sodium levels and clinical condition. A one month after discharge, tolvaptan was withdrawn, due to inadequate prescription criteria, after which hyponatremia relapsed several times and was properly treated; eventually fever and sopor occurred and the patient died. SIADH secondary to HZ may induce life-threatening and long-lasting hyponatremia, which requires a prompt diagnosis and treatment.

Key words: SIADH, herpes zoster, hyponatremia, hypertonic solution, vaptans

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Introduction

Hyponatremia is the most common electrolyte disorder in hospital inpatients; the prevalence ranges from 20 to 30%, and is higher in elderly individuals (1, 2). Hypotonic hyponatremia is the variant most commonly observed in clinical practice. Patients with symptomatic hyponatremia suffer from higher rates of morbidity and mortality in comparison to normonatremic controls (1, 2). This may be due both to the illnesses that cause hyponatremia (e.g., cardiac failure, renal failure, liver disease, or tumor) and to the hyponatremia itself (1). Severe hyponatremia of acute onset (i.e., within 48 hours), may cause major neurological symptoms, including coma due to brain edema, a life-threatening complication (1, 2). However, in elderly patients, even mild hyponatremia (130-134 mEq/L) may be associated with clinical complications, such as bone demineralization or gait instability, which may increase the risk of falls and bone fractures (1, 2). The overcorrection of serum sodium levels in patients with hyponatremia may result in life-threatening osmotic demyelination syndrome (2-5).

In hospital inpatients, the most common cause of hyponatremia is syndrome of inappropriate antidiuretic hormone

(SIADH), which is a clinical and biochemical manifestation of a wide range of disease processes (1-5). Viral infections, including herpes zoster (HZ) infection, are rarely associated with SIADH (6).

We herein report the case of an elderly man with recent-onset cutaneous HZ infection who rapidly developed SIADH and severe symptomatic hyponatremia, which required multifaceted management (hypertonic saline, fluid restriction, and vaptans) in order to normalize the sodium levels during hospitalization. At one month after discharge, tolvaptan was withdrawn, due to inadequate prescription criteria and the patient's hyponatremia relapsed; despite proper treatment and the subsequent normalization of sodium levels, fever and sopor occurred and the patient eventually died.

Case Report

An 88-year-old man was taken to the emergency department of a peripheral hospital in our region following the sudden onset of achy abdominal pain. On arrival, he was suffering and confused. His vital signs were normal (blood pressure, 130/80 mm Hg; heart rate, 70 bpm; oxygen saturation on ambient air, 97%) and his abdomen was distended and tender, without signs of peritonism. Cutaneous HZ erup-

tions were present over much of the right abdominal wall (T 8-T10 thoracic dermatomes). Acyclovir and paracetamol (for HZ-induced neuralgia) had been started 3 days previously by the man's general practitioner. Regarding the patient's medical history, his relatives reported Alzheimer's disease with moderate cognitive decline, ischemic heart disease (treated with nitrates and acetylsalicylic acid) and hypertension (treated with diltiazem). A chest X-ray examination revealed no remarkable findings, whereas an abdominal X-ray showed bowel distension with multiple air-fluid levels and marked coprosthesis. Besides confirming signs of bowel sub-occlusion, contrast-enhanced computed tomography (CT) showed a 4-cm sub-renal aortic aneurysm containing a 2.5 cm thrombosed pseudoaneurysm, and minor leakage secondary to active bleeding. Blood tests revealed severe hyponatremia (105 mEq/L). The patient was urgently transferred to our hospital to be evaluated by a vascular surgeon. On arrival, he was alert but slowed and confused, his oxygen saturation on air (97%) and heart rate (90 bpm) were normal. His lung sounds were clear, his abdomen was distended and painful, bladder over-distension was detected and a catheter was inserted. No edema was present; however, however the patient's blood pressure levels were high (170/100 mm Hg); nitroglycerin infusion was started, which normalized his blood pressure (115/65 mm Hg). Laboratory testing showed that the patient's glucose levels, blood counts and renal function were normal, but confirmed severe hyponatremia (109 mEq/L), which was hypotonic (calculated osmolarity, 226 mOsm/kg) [the patient's medical records dated two weeks earlier reported normal sodium levels (135 mEq/L) (Table 1)]. The vascular surgeon, together with the radiologist, re-evaluated the abdominal CT scan, but did not find clear signs of active aneurysmal bleeding. Thus, surgery was not indicated; however, blood pressure control was recommended (target <130/80 mmHg). The patient was hospitalized in the Internal Medicine Department where he quickly fell into a soporous state and became difficult to rouse; his relatives confirmed that he was not taking any psychoactive drugs, diuretics or laxatives. A blood gas analysis with ambient air showed mild respiratory alkalosis. Acyclovir was withdrawn. Both the spot urine sodium level (65 mEq/L) and urinary specific gravity (1,031) were found to have increased, while his adrenal, renal, and thyroid functions were normal and his uric acid levels were reduced (3 mg/dL) (Table 1).

The results of the main laboratory tests are shown in Table 1. A diagnosis of SIADH was made based on the findings. Since the patient was clearly symptomatic (i.e., in a soporous state), 3% hypertonic saline infusion was started (infusion rate: 1 mEq/L/h for a few hours and 0.5 mEq/L/h thereafter) together with low-dose (20 mg) intravenous furosemide. After 48 hours, the patient's sodium levels increased to 125 mEq/L and he regained consciousness. The infusion was therefore stopped. Thereafter, fluid restriction (calculated as daily urine output minus 500 mL) was started. Brain CT showed cerebrovascular disease, whereas whole

body CT revealed no remarkable (infective or neoplastic) findings. Unfortunately, the patient's sodium levels decreased two days later (minimum level, 119 mEq/L) and sopor recurred. The infusion of 3% hypertonic saline was therefore restarted, the patient's sodium levels rose (maximum level, 132 mEq/L) after 48 hours and his condition improved (Figure). Following the withdrawal of hypertonic saline, the patient's sodium levels again declined over a few days (minimum level, 122 mEq/L). Infusion was therefore restarted and withdrawn when the patient's sodium levels reached 130 mEq/L (Figure). Following the patient's improvement, tolvaptan, kindly supplied by the hospital pharmacy, as the patient was a resident in another region, was started at a dosage of 15 mg/day, which almost normalized his sodium levels (134 mEq/L) over 2 days (Figure). A proper fluid intake was maintained. The patient regained fair autonomy and was discharged to his home town in central Italy; he was provided with a one-month supply of tolvaptan, during this month, the patient's sodium levels remained relatively normal (131-138 mEq/L) (Figure) and his clinical condition was quite satisfactory. Unfortunately, tolvaptan was withdrawn, since the local endocrinologist ascertained that the patient's examinations and clinical history did not fulfil the "Italian Drugs Agency" criteria for the regular prescription of the drug. His sodium levels subsequently dropped to 125 mEq/L; fluid restriction and oral sodium chloride supplementation were therefore started, but the patient's condition rapidly worsened and he was taken to the emergency department where hypertonic saline was infused; his sodium level normalized (135 mEq/L) within two days (Figure). The patient was discharged with home care assistance; however, sodium levels dropped again to 126 mEq/L and the patient became bedridden and required catheterization due to acute urinary retention. On the request of his relatives, the patient was managed at home. Healthcare staff started the daily infusion of mild (1.5%) hypertonic saline, which normalized his sodium levels (136 mEq/L) (Figure). Nevertheless, fever and sopor occurred. Intravenous ceftriaxone and acetaminophen were started, but the man eventually died.

Discussion

Regardless of its high prevalence and relevance in elderly hospitalized patients, hyponatremia is often overlooked, undermanaged or mismanaged (1, 2). Hyponatremia is characterized by an excess of water relative to the total body sodium level, which may be normal, increased or decreased. Hence, it is classified according to the fluid volume status of the patient (euvolemic, hypovolemic, or hypervolemic hyponatremia) or plasma osmolality (isotonic, hypotonic, and hypertonic hyponatremia) (2).

In elderly patients, acute hyponatremia is mainly characterized by neurological symptoms (confusion, delirium, seizure, lethargy until coma), but pre-existing cognitive impairment may delay the timely identification of symp-

Table 1. Main Laboratory Tests in the Patient Studied before Starting Tolvaptan.

	ER Admission	IM Admission														
		Day 0 3%HS	Day 1	Day 2 3%HS off	Day 3 3%HS	Day 4	Day 5 3%HS off	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11 3%HS	Day 12	Day 13	Day 14 3%HS off
Glucose (n.v. 70-115 mg/dL)	94	79	72	75	68	66	68	57	88	88	85	89	78	81	83	76
Creatinine (n.v. 0.6-1.2 mg/dL)	0.5	0.5	0.6	0.5	0.7	0.6	0.6	0.6	0.5	0.5	0.6	0.5	0.6	0.6	0.6	0.5
Blood nitrogen (n.v. 10-50 mg/dL)	24	22	24	-	-	32	-	-	28	28	-	-	30	-	-	28
Na (n.v. 136-145 mEq/L) AM/PM (if available)	109	111/114	120/120	125/124	122/119	123/124	127/129	132/131	132/133	128	126	125	122	124	126	130
K (n.v. 3.5-5 mEq/L)	4	4.1	3.8	3.3	3.2	3.6	3.8	3.5	4	3.9	3.8	4.6	4.2	4.1	4.7	3.9
Haemoglobin (n.v. 14.2-17.2 g/dL)	13.9	13.9	13.2	13.0	12.9	12.8	13	15.8	13	12.8	12.2	12.5	12.8	12.6	12.9	13.1
Hematocrit (n.v. 43-51%)	34.4	31.5	32.5	32.8	32.6	30.5	32.8	41.5	33.8	33.5	31.6	31.5	32.1	32.4	33.2	33.1
Calculated POsm (n.v. 275-295 mOsm/kg)	223	226	244	254	248	250	258	267	269	260	257	255	248	252	256	264
Uric acid (n.v. 3.4-7 mg/dL)	-	3.0	-	-	-	-	-	-	4.1	-	-	2.4	-	-	-	-
Total protein (n.v. 6.2-8.2 gr/dL)	-	5.8	-	-	-	-	-	-	5.7	-	-	-	-	-	6	-
U specific gravity (n.v. 1.015-1.025)	-	1.031	-	-	-	-	-	-	1.020	1.030	-	-	-	-	-	1.020
Calculated UOsm (mOsm/kg)	-	850	-	-	-	-	-	-	550	800	-	-	-	-	-	550
24-h U volume (mL)	-	900	1,900	2,100	1,600	2,500	1,100	800	900	800	1,100	1,000	1,200	1,400	1,600	1,300
Na (U) spot (mEq/L)	-	65	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Blood pressure (mmHg)	170/100	120/90	110/70	130/80	140/80	120/80	120/70	120/70	110/70	110/80	115/70	110/70	120/80	110/70	120/80	100/60
Body weight (kg)	n.m.	n.m.	n.m.	n.m.	n.m.	65	65.4	65.5	-	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	64.1
FT4 (n.v. 0.93-1.7 ng/dL)	-	1.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-
FT3 (n.v. 1.8-4.6 pg/mL)	-	1.3	-	-	-	-	-	-	-	-	-	-	-	-	-	-
TSH (n.v. 0.27-4.2 µU/mL)	-	1.74	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ACTH (n.v. 4.5-48.8 pg/mL)	-	25.5	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cortisol (n.v. 6.2-19.4 µg/dL)	-	17.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-

ER: emergency room, IM: Internal Medicine, n.v.: normal values, Osm: osmolarity, P: plasma, U: urine, HS: hypertonic saline, n.m.: not measurable due to patient's clinical condition, -: not done

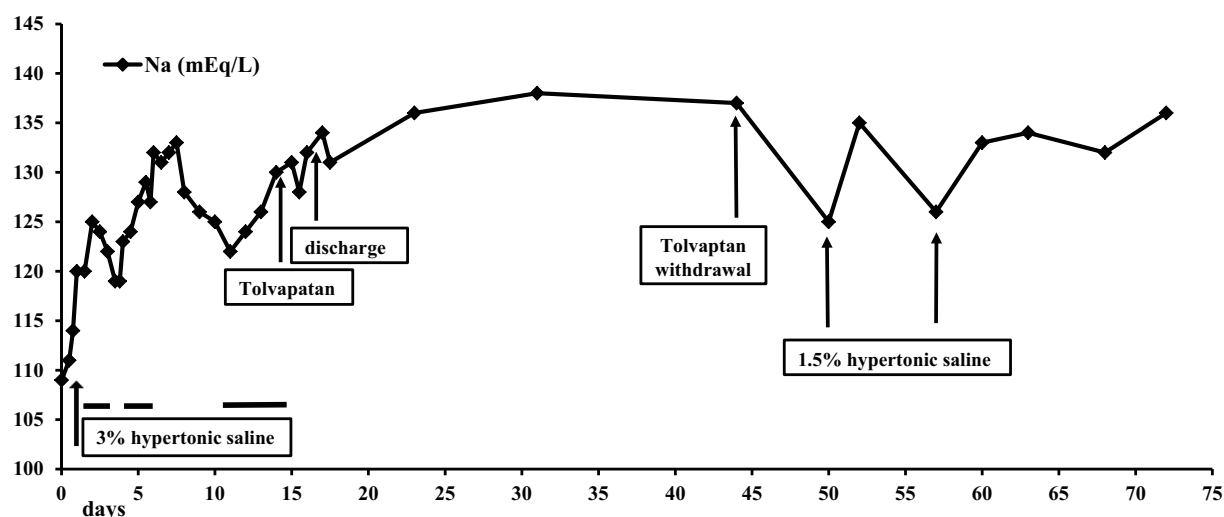


Figure. The sodium levels and therapeutic modalities in the patient.

toms (1, 2). The diagnosis itself may be challenging, due to multiple pharmacological treatments and the presence of comorbidities (2). Over 72 hours after the occurrence of cutaneous HZ eruptions, our patient, who suffered from Alzheimer's disease but who was partially autonomous at home, became confused, and eventually fell into a soporous state. On first admission to another hospital for abdominal pain, blood tests revealed severe hyponatremia (105 mEq/L). However, this finding was overlooked, since sub-renal aortic aneurysmal bleeding was detected on CT, and clinical care was initially focused entirely on this. Subsequently, in our hospital, active bleeding was excluded on an evaluation by the vascular surgeon, and symptomatic hyponatremia became the main clinical problem. An examination of the patient revealed that the diagnostic criteria of SIADH were fulfilled, including: 1) hyponatremia <135 mEq/L with decreased effective serum osmolality <275 mOsm/kg; 2) inappropriate urinary concentration ($U_{osm} > 100$ mOsmol/kg); 3) clinical euvolemia; 4) elevated urinary sodium >40 mEq/L in the presence of a normal dietary salt and water intake; 5) a normal thyroid and adrenal function; and 6) no recent use of diuretics (1-5). The most common causes of SIADH are malignancy, pulmonary disorders, central nervous system disorders, and drugs (1-5). Drugs are the most frequent cause in elderly patients, with the main culprits being selective serotonin re-uptake inhibitors, anti-epileptics and non-steroidal anti-inflammatory drugs (1-5). Our patient did not take any medications that were considered to cause SIADH; however, 3 days before his first hospital admission, he received acyclovir for a cutaneous HZ infection. This drug does not induce SIADH (7); however, it is able to cause acute tubule-interstitial nephritis with hyponatremia and metabolic acidosis. This usually occurs when the drug is administered intravenously (8, 9); however, in rare cases it has been reported after oral administration (10).

It was considered that acyclovir was unlikely to have played a role in our patient's hyponatremia because respiratory alkalosis was detected, and the severe hyponatremia

persisted after the immediate withdrawal of the drug.

Since the common causes of SIADH were ruled out and there was a strong temporal association between the onset of HZ infection and the occurrence of severe hyponatremia, it was hypothesized that a causal relationship existed. Disseminated HZ can cause SIADH by involving the central nervous system, whereas the association between localized HZ and SIADH has been less investigated. To date, the association of SIADH with localized HZ virus has been reported in 14 patients (Table 2) (6, 11-22), excluding our own. These ten women and four men were either elderly (12/14) or diabetic (5/14), both well-known risk factors for HZ virus reactivation. The dermatomal distribution in these cases was as follows: V1 (n=6), cervical (n=2), thoracic (n=5, as ascertained in our patient), and lumbar (n=1). The reported cases of HZ virus infection-associated SIADH are reported in Table 2.

The pathophysiological mechanisms through which HZ virus induces SIADH are not fully understood. The most likely hypothesis is that upon reactivation from the dorsal-root ganglia, which contains sensory neurons able to transmit messages from peripheral osmoreceptors and nociceptors, the HZ virus reaches the corresponding dermatome via the axons of infected neurons and spreads to the dorsal columns of the spinal cord, and hence to the nucleus tractus solitarius, and eventually to the hypothalamus (sopraoptic nucleus and paraventricular nucleus) with the subsequent sustained release of ADH.

In our patient, the above mentioned mechanism was considered to be likely because the cutaneous HZ lesions covered a large part of the right abdominal wall and involved the T8-T10 dermatomes, which are within the area of liver sensory nerve innervation and include osmoreceptors; and because HZ-induced neuralgia with chronic pain (and subsequent activation of nociceptors) was present (6, 12).

In the present case, the patient's hyponatremia relapsed upon the withdrawal of tolvaptan at 2 months after the onset of HZ virus infection. This finding confirms the findings of

Table 2. Published Case Reports with SIADH Associated with Localized Herpes Zoster.

References	Age/Gender	Dermatome	Latency* (days)	Na (mEq/L)	Consciousness	Duration of hyponatremia	Complications
11	72/F	T2	6	95	altered	14 days	PHN
12	67/F	T10	7	104	preserved	5 days	-
13	70/F	C4-C6	3	111	altered	5 days	-
14	78/M	V1	n.a.	108	altered	n.a.	death
15	77/M	V1	5	115	altered	n.a.	-
16	86/F	T9-T10	7	122	preserved	4	-
17	71/F	V1	4	120	preserved	9	-
18	76/F	V1	15	112	altered	7	-
19	84/F	L1-L2	n.a.	117	altered	n.a.	-
6	58/M	V1	4	114	preserved	4 months	PHN
6	38/M	V1	7	116	preserved	3 months	PHN
20	85/F	C5-C6	14	111	altered	3 day	-
21	82/F	T4-T5	12	127	altered	n.a.	-
22	82/F	T10	4	102	altered	20 days	hypokalemia
present report	88/M	T8-T10	3	105	altered	2.5 months	PHN, death*

*The time span from onset of HZ and identification of hyponatremia. ** Due to combined factors.

PHN: post-herpetic neuralgia, n.a.: not available

previous studies reporting that HZ-induced SIADH can be long-lasting (months) even if the infection is localized, particularly if neuralgia is present (6).

Hypertonic saline infusion is required for the management of SIADH in patients with severe symptomatic hyponatremia. The several formulae that are available are not reliable in predicting sodium levels and do not avoid the risk of overcorrection. The Adrogue-Madias formula enables the effect of 1 liter of a hypertonic sodium infusate on the serum sodium level to be calculated: $\Delta[\text{Na}_{\text{serum}}] = \frac{[\text{Na}]_{\text{infused}} - [\text{Na}]_{\text{serum}}}{\text{total body water} + 1}$. The appropriate hourly infusion rate can be derived by comparing this change in the serum sodium to the desired rate of correction per hour (2, 3, 23).

In patients with severe symptoms-regardless of whether hyponatremia is acute (<48 hours) or chronic-a correction rate of 1-2 mEq/L/h aimed at increasing the sodium levels by 4-6 mEq/L within 6-8 hours is recommended in order to improve the symptoms; however, the daily sodium correction should not exceed 8-10 mEq/L in the first 24 hours or sodium levels will exceed 130 mEq/L (2-4, 24).

We successfully used hypertonic saline several times during hospitalization because our patient was clearly symptomatic (in a soporous state); however, his hyponatremia relapsed with a worsening of his clinical condition. Eventually, when a target sodium level of 130 mEq/L was reached, the patient was put on tolvaptan therapy; this drug can efficiently reverse the antidiuretic effect of arginine-vasopressin by competitively binding to V2 receptors, thereby increasing free water clearance and elevating the plasma sodium levels. In our patient, this effective therapy was subsequently withdrawn for bureaucratic reasons (lack of prescription status according to the endocrinologist in the patient's town). Thereafter, the patient's hyponatremia relapsed and his clinical condition worsened despite further treatment with hyper-

tonic saline infusion and the normalization of his sodium levels, and the man eventually died.

In sum, in rare cases-mostly involving elderly individuals-SIADH may occur due to a localized HZ infection. This possibility should be considered in clinical practice, since the resulting hyponatremia can be severe and long-lasting.

The author states that he has no Conflict of Interest (COI).

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