Clinical Vignettes

Syndrome of Inappropriate Secretion of Antidiuretic Hormone Associated with Localized Herpes Zoster Ophthalmicus

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The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) associated with localized herpes zoster is rarely reported and may be under-appreciated. We describe two diabetic men with herpes zoster ophthalmicus (HZO) who developed hyponatremia (114 and 116 mmol/L) during acute illness. Both were euvolemic and had elevated urine osmolality (435 and 368 mmol/kg.H₂O) and sodium (Na⁺) concentration (61 and 63 mmol/L) along with normal cardiac, renal, liver, and endocrine function consistent with the diagnosis of SIADH. Thorough investigation for other causes of SIADH, including detailed physical examination, laboratory studies, and computed tomography of the brain, chest, and abdomen, were negative. Despite antiviral therapy (acyclovir) for herpes zoster, ophthalmoplegia, keratitis, and post-herpetic neuralgia (PHN) developed. Even with fluid restriction and high salt diet, SIADH lasted for 3 to 4 months and resolved concomitantly with resolution of PHN, suggesting an association between SIADH and HZO. These two cases raise the potential for herpes zoster infection, especially HZO, to involve the regulatory pathway of ADH secretion, contributing to SIADH. The presence of PHN, which reflects greater neural damage may, at least in part, explain the prolonged ADH secretion and hyponatremia.

KEY WORDS: herpes zoster; hyponatremia; syndrome of inappropriate secretion of antidiuretic hormone.

J Gen Intern Med 26(2):216–20

DOI: 10.1007/s11606-010-1517-4

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INTRODUCTION

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is the most common cause of euvolemic hyponatremia in hospitalized patients¹. SIADH is characterized by hypotonic hyponatremia, elevated urine osmolality, elevated urine sodium (Na⁺), absence of edema or volume depletion, and normal renal,

adrenal, and thyroid function. The most common causes of SIADH include tumors, central nervous system disorders, pulmonary diseases, and certain drugs such as carbamazepine and cyclophosphamide². Severe viral infections have also been reported to cause SIADH, including Epstein-Barr virus³, cytomegalovirus⁴, and varicella-zoster virus (VZV)^{5–16}.

VZV is a human herpesvirus that causes chickenpox (varicella) in childhood and becomes latent in cranial-nerve and dorsal-root ganglia. It frequently reactivates later as herpes zoster. The annualized incidence of herpes zoster is approximately 1.5 to 3.0 cases per 1000 persons with an estimated 600,000 new cases and 60,000 hospitalizations each year in the United States^{17,18}. VZV infection most often occurs along one dermatome (localized) but also can disseminate and involve the central nervous system (CNS) in immunocompromised patients. In localized herpes zoster, sensory nerves of the thoracic dermatomes and cranial nerves are the most commonly affected. Among the cranial nerves affected by VZV, herpes zoster ophthalmicus (HZO) in the ophthalmic division of the trigeminal nerve (V1) is the most common and accounts for 10–25% of all herpes zoster infection¹⁹. Declining cell-mediated immunity as a result of aging or immunocompromised state increases the risk of herpes zoster. Common complications of herpes zoster include post-herpetic neuralgia (PHN), encephalitis, meningitis, myelitis, cranial and peripheral-nerve palsies as well as ophthalmoplegia, uveitis, iritis and keratitis in HZO. In contrast to the approximately 5% to 15% mortality rate in immunocompromised patients with disseminated herpes zoster, mortality is extremely rare in patients with localized herpes zoster¹⁷.

Although disseminated herpes zoster is well-documented to cause SIADH by involving the CNS^{14–16}, the association between localized herpes zoster and SIADH is less appreciated and may go under-recognized. In this report, we describe two diabetic men with HZO who developed prolonged SIADH in parallel with their course of acute illness and PHN. We also thoroughly review the literature and discuss the possible mechanism of SIADH associated with localized herpes zoster.

CASE REPORT

A 58-year-old man presented to the emergency department with painful skin eruptions on his right forehead for 4 days. He

Received October 29, 2009

Revised March 26, 2010

Accepted September 8, 2010

Published online September 29, 2010

had a 10-year history of type 2 diabetes mellitus treated with mixed insulin (30% insulin aspart and 70% insulin aspart protamine) twice a day. He had fever and general malaise but denied seizure, polydipsia, nausea, vomiting or the use of diuretics before admission. His blood pressure was 148/90 mmHg, heart rate 80 beats/min, and body temperature 37.5°C on admission. Skin examination was remarkable for an eruption of dense vesicles on the right side of the face in the distribution of V1 dermatome. Ophthalmologic examination revealed a swollen right eyelid, chemosis, moderately edematous cornea, and corneal erosions but no other abnormalities of the iris, pupil, or ocular pressure. The chest, heart, abdominal, and neurologic exams were normal without nuchal rigidity or meningeal signs. The findings of moist mucous membranes, normal skin turgor, clear breathing sound, and the absence of jugular vein engorgement, pedal edema, and orthostatic hypotension suggested euvoletic status. Intravenous acyclovir (10 mg/kg/day for 7 days) was started for HZO. Nevertheless, he developed ophthalmoplegia with inability to abduct the right eye 6 days later.

As shown in Table 1, hyponatremia with serum Na⁺ concentration 114 mmol/L was the most striking laboratory abnormality. Hypouricemia (2.5 mg/dL) with increased urine uric acid excretion and normal blood urea nitrogen, potassium concentration and acid-base status also suggested euvoletic status. Based upon low serum osmolality (238 mmol/kg H₂O), increased urine osmolality (435 mmol/kg H₂O), urine Na⁺ (61 mmol/L), and normal endocrine, cardiac, hepatic and renal function, he was diagnosed with SIADH. Without apparent neurologic symptoms such as altered consciousness or seizure to suggest acute hyponatremia necessitating rapid correction, he was treated with fluid restriction 1000 ml/day and high Na⁺ diet (6 gram/day). A meticulous search for other underlying causes of SIADH, including follow-up history, physical examination, computed tomography of the chest, abdomen, and brain were all negative. On the 8th day, he was discharged with serum Na⁺ 128 mmol/L and follow-up at our clinic. His ophthalmoplegia, neuralgia, and dysesthesia over

V1 were treated with gabapentin 600 mg daily and prednisolone starting at 30 mg daily for 3 weeks with a tapering dose and blood sugar monitoring. One month after discharge, the patient presented to clinic with persistent PHN, ophthalmoplegia and a serum Na⁺ of 124 mmol/L. Despite continued fluid restriction and a high sodium diet, his serum Na⁺ concentration remained between 128–133 mmol/L for a total of four months after discharge. It is important to note that during this time, he had persistent PHN. Interestingly, his hyponatremia and PHN resolved simultaneously during the fifth month. Thereafter, hyponatremia has not recurred at subsequent follow-up.

CASE 2

A 38-year-old man with a history of hypercholesterolemia and diabetes on simvastatin 20 mg daily and insulin injection twice a day presented with fever, malaise, headache, and pain over the left eye and frontal region of the head for one week. He also reported decreased visual acuity, photophobia, and ocular pain. He denied nausea, vomiting, polydipsia, or the use of diuretics. On admission, blood pressure was 122/68 mmHg with heart rate 85 beats/min. Numerous vesiculopustular eruptions in V1 were noted. On ophthalmologic examination, visual acuity of the left eye was 20/100 and corneal erosions with moderate inflammatory reaction in the anterior chamber of the left eye were noted. Hyponatremia (116 mmol/L) with low serum osmolality (245 mmol/kg H₂O) was the most conspicuous laboratory abnormality (Table 1). He was diagnosed with SIADH based upon increased urine osmolality, increased urine Na⁺, normal endocrine, cardiac, hepatic, renal function and euvoletic status. A 7-day course of intravenous acyclovir was prescribed for HZO. Fluid restriction (1000 ml/day) and high Na⁺ diet (6 gram/day) were started for treatment of his asymptomatic hyponatremia. He was discharged on the 9th day with serum Na⁺ 131 mmol/L and gabapentin 600 mg daily for neuralgia. One month after discharge, the patient presented to clinic with a slow improvement in the skin lesions and keratitis but persisted PHN and a serum Na⁺ of 125 mmol/L. His serum Na⁺ concentration remained between 128–132 mmol/L for a total of three months after discharge and normalized concomitantly with the resolution of PHN during the fourth month. Subsequent follow-up also did not reveal any recurrence of hyponatremia.

DISCUSSION

Hyponatremia is a common electrolyte abnormality seen in hospitalized patients. These two diabetic patients developed hyponatremia during acute illnesses with HZO. Their low serum osmolality, euvoletic status, elevated urine osmolality and Na⁺ concentration, and normal cardiac, renal, liver, and endocrine function were consistent with the diagnosis of SIADH. The absence of other identifiable causes of SIADH and the simultaneous resolution of hyponatremia and PHN in both of our patients suggests an association between SIADH and HZO.

Table 1. Biochemical Studies in two Patients with HZO-Related SIADH

		Case 1	Case 2
Plasma	Normal range		
Osmolality	(285–295 mmol/kg H ₂ O)	238	245
Na ⁺	(135–142 mmol/L)	114	116
K ⁺	(3.5–5.0 mmol/L)	4.0	4.2
Cl ⁻	(96–108 mmol/L)	81	83
HCO ₃ ⁻	(23–25 mmol/L)	24	24
Uric acid	(3.4–7 mg/dL)	2.5	2.0
Glucose	(70–105 mg/dL)	121	97
BUN	(7–20 mg/dL)	11	8
Creatinine	(0.7–1.2 mg/dL)	0.7	0.6
Hemoglobin A1C	(4–6%)	6.3	6.6
TSH	(0.25–5 UIU/ml)	0.56	1.30
Free T4	(0.8–2 ng/dL)	1.09	1.72
Cortisol (8 AM)	(6–23 µg/dL)	18.1	17.2
ACTH	(0.1–46 pg/mL)	21.5	29.2
Urine			
Na ⁺	(mmol/L)	61.0	63.0
Cl ⁻	(mmol/L)	72.0	63.0
Uric acid	(µmol/L)	26.2	35.7
Osmolality	(mmol/kg H ₂ O)	435	368

Table 2. Summary of Reported Cases with SIADH Associated with Localized Herpes Zoster

Reference	Age/ Gender	Dermatome	Latency *	Serum [Na ⁺]	Conscious change	Duration [#]	Complications
Maze 1983	72/F	T2	6 days	95	+	14 days	PHN
Sato 1990	67/F	T10	7 days	104	-	5 days	-
Furuta 1996	70/F	C4-6	3 days	111	+	5 days	-
Calenda 1996	78/M	V1	n.a.	108	+	Few days	Death [†]
Han 1996	77/M	V1	5 days	115	+	n.a.	-
O'Rourke 2006	86/F	T9/10	7 days	122	-	4 days	-
Dhawan 2007	71/F	V1	4 days	120	-	9 days	-
Kucukardali 2008	76/F	V1	15 days	112	+	7 days	-
Osinga 2009	84/F	L1/2	n.a.	117	+	n.a.	-
Case 1	58/M	V1	4 days	114	-	4 months	PHN
Case 2	38/M	V1	7 days	116	-	3 months	PHN

*The time span from the onset of herpes zoster to the identification of hyponatremia, [#] Duration of hyponatremia, [†] died from unconsciousness with secondary aspiration pneumonia and sepsis. n.a. = not available, [Na⁺]=sodium concentration, mmol/L

To date, the association of SIADH with localized herpes zoster has been reported in 11 patients, including ours (Table 2)⁵⁻¹³. They, seven women and four men, were either elderly (9/11) or diabetic (3/11), well-known risk factors for VZV reactivation^{17,19,20}. The V1 dermatome (HZO) was involved in six patients, cervical in one, thoracic in three, and lumbar in one. The percentage of V1 dermatome involvement (55%) in these patients is much higher than in all herpes zoster infection (10-25%), implying that HZO particularly associated with SIADH. Their serum Na⁺ concentration ranged from 95 to 122 mmol/L. There was no correlation between serum Na⁺ concentration and the development of altered mental status. Of note, six elderly patients had altered mental status, which resolved after correction of hyponatremia, suggesting that the rate of Na⁺ decline in these elderly patients

may have been rapid enough to cause neurologic symptoms. One patient had profound hyponatremia (95 mmol/L) with altered mental status precipitated by concurrent use of a thiazide diuretic for hypertension⁵. One patient died from aspiration pneumonia and sepsis after a prolonged bout of unconsciousness. The time span from the onset of herpes zoster to the identification of hyponatremia was 3 to 7 days in most cases, but 15 days in one case. This variation may be related to the nonspecific nature of the many signs and symptoms of hyponatremia. These cases highlighted the importance of awareness of the possible association between SIADH and localized herpes zoster for early recognizing hyponatremia.

The underlying mechanism of SIADH associated with localized herpes zoster remains elusive. One possibility is that

Figure 1. Simplified schema of regulation of ADH secretion. The secretion of ADH is regulated by central and peripheral osmoreceptors as well as baroreceptors. Signals from peripheral receptors ascend via different nerves and relay in the brainstem. The nucleus tractus solitarius (NTS) in the brainstem processes signals from peripheral receptors and excites neurosecretory cells located in the paraventricular nucleus (PVN) and supraoptic nucleus (SON) to release ADH. VZV reactivation in dorsal root ganglia (shown in ①) and the first branch of the trigeminal nerve may stimulate ADH secretion via NTS (shown in ②). The NTS is also thought to be involved in pain-induced ADH secretion. VLM, ventrolateral medulla.

VZV infection may involve the regulatory pathway of anti-diuretic hormone (ADH) secretion^{5–11}. Most VZV resides latently in sensory neurons of dorsal-root ganglia composed of numerous neurons with different function such as relaying messages from peripheral thermal, pain, pressure, vibration, and proprioception receptors. Upon reactivation from dorsal-root ganglia, VZV spreads to the corresponding dermatome via axons of infected neurons and may spread centripetally to the dorsal columns of the spinal cord. Peripheral osmoreceptors also route a portion of their signals through the dorsal-root ganglia before reaching the spinal cord and CNS (Fig. 1). If the VZV-infected neurons include those responsible for peripheral osmoreceptors, the inputs and regulation of ADH secretion may be deranged. The nucleus tractus solitarius (NTS) in the brainstem plays a pivotal role in processing signals from peripheral osmoreceptors as well as baroreceptors. Studies have also shown that the NTS is also the first central relay for the primary sensory axons of V1²¹. The potential for crosstalk between trigeminal inputs and osmolar regulation has been demonstrated in animal models where stimulation of V1 increased ADH release²².

Among 11 reported cases, the duration of hyponatremia was much longer (2 weeks to 4 months) in patients with PHN than patients without PHN (4 to 9 days). During VZV reactivation, inflammatory infiltrates and necrosis have been found in histopathologic studies of affected ganglia¹⁹. The presence of PHN reflects a greater viral load and more extensive damage to the involved neural structures^{19,23,24}. PHN, by definition, represents chronic neuralgia caused by the death of infected neurons resulting in nociceptor-induced central hypersensitivity and spontaneous epileptiform discharge of damaged neurons²⁵. If the hypersensitive, damaged neurons are involved in ADH regulation, it may cause the prolonged stimulation of ADH secretion and resulting hyponatremia as shown in both cases.

Severe pain is also a possible mechanism of SIADH in patients with herpes zoster. Pain has long been thought to cause non-osmotic stimulation of ADH secretion²⁶. Despite unclear mechanisms, the NTS has also been suggested in the pathophysiology of pain-induced ADH secretion^{21,27}. Although VZV infection may involve the regulatory pathway of ADH secretion and pain develop in most patients with herpes zoster, not all patients with herpes zoster develop hyponatremia. To develop hyponatremia, one needs both a source of electrolyte-free water (water without Na⁺ and K⁺) and the action of ADH to cause retention of this electrolyte-free water. The amount of free water and Na⁺ intake, individual genetic background, severity of infection, concurrent co-morbidities or illness may alter the development of hyponatremia even in the presence of inappropriate ADH action.

Although the mainstay of treatment for SIADH is the elimination of underlying causes, hyponatremia must be treated based on the rate of its development and the associated symptoms. For symptomatic patients where hyponatremia developed within 48 hours, the goal is to rapidly raise the serum Na⁺ level by 1 to 2 mmol per liter per hour with hypertonic saline (such as 3% saline) until symptoms improve and to maintain a rise in serum Na⁺ level by 8–10 mmol per liter within the first 24 hrs². In patients with asymptomatic hyponatremia or in whom hyponatremia developed over > 48 hours, the rate of correction should be less than 6–8 mmol/L per day or 0.25–0.35 mmol/L/hr to avoid the development of osmotic demyelination syndrome (ODS). The

combination of water restriction, high Na⁺ and protein diet is effective in most cases of SIADH. High protein diet or oral urea administration induce an osmotic diuresis, increase free water excretion, and thus ameliorate hyponatremia in SIADH. The combination of loop diuretics and hypertonic saline also help correct hyponatremia. Loop diuretics can reduce hypertonic urine in SIADH to isotonic urine (osmolality close to 300 mOsm/kg H₂O). There will be a net loss of free water if all Na⁺ loss in the urine is replaced by hypertonic saline. Demeclocycline which blocks ADH action through inhibition of cAMP generation and thus increases free water excretion can be an alternative for refractory hyponatremia. Also, ADH receptor antagonists such as conivaptan or tolvaptan may be also used². Nevertheless, serum sodium level should be strictly monitored during treatment to avoid overcorrection.

In conclusion, these two cases highlighted the possible association between SIADH and localized herpes zoster, especially HZO. Besides non-osmotic stimulation of ADH by pain, VZV infection may also affect the regulatory pathway of ADH secretion. The presence of PHN which reflects a greater damage to the involved neural structures may account for the prolonged ADH secretion and hyponatremia. Awareness of this association may lead to earlier diagnosis and appropriate treatment of hyponatremia.

Conflict of Interest: None disclosed.

Funding support: None.

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