An Elderly Patient with Chronic Hyponatremia

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Summary

Hyponatremia is the most common electrolyte disorder. With the aging of the population and the greater propensity of the elderly to develop hyponatremia, this electrolyte disorder is of increasing importance to the practicing nephrologist. In this Attending Rounds, an illustrative patient with hyponatremia is presented. The reasons for the increased incidence and prevalence of hyponatremia in the elderly are discussed, with emphasis on the effects of aging on urinary dilution, the frequently multifactorial nature of hyponatremia in this population, and the absence of a definite cause for inappropriate and persistent vasopressin release in many such patients. The rationale for treating the hyponatremia, even when apparently asymptomatic, is discussed, with attention to cognitive function, gait, and bone structure disturbances that increase the risk for fractures. The various available treatment approaches, including water restriction, demeclocycline, loop diuretics with NaCl supplementation, and vasopressin antagonists are summarized, with emphasis on the efficacy and limitations of each of these therapies.

Case Description

L.G. is a 73-year-old woman referred for management of chronic hyponatremia. She was known to have had hyponatremia for several years, with serum sodium levels in the range of 121–127 mEq/L. She has had four pulmonary bacterial infections during the last 7 years and was found to have radiologic evidence of bronchiectasis. She has also had several episodes of transient cerebral ischemia leading to numbness and weakness. In the last year she has had increased gait instability and sustained a fall that resulted in a pelvic fracture. She had no history of cardiac or liver disease. She has long-standing rheumatoid arthritis. Medications included omeprazole, 20 mg daily; conjugated estrogens (Premarin), 0.3 mg daily; folic acid, 0.4 mg three times daily; aspirin, 81 mg daily; and monthly vitamin B₁₂ injections.

On physical examination she appeared to be a fragile elderly woman in no acute distress. BP was 148/78 mmHg, pulse rate was 98 beats/min, and she weighed 65 kg. She appeared to be euvolemic by examination. There were deformities of the proximal interphalangeal joints. Her neurologic examination revealed that she was fully oriented, with no focal findings, but she had an obvious gait disturbance that necessitated a walker for ambulation. Laboratory results were as follows: serum sodium, 124 mEq/L; chloride, 95 mEq/L; potassium, 4.1 mEq/L; bicarbonate, 22 mEq/L; creatinine, 0.7 mg/dl; glucose, 66 mg/dl; and uric acid, 3.8 mg/dl. Urinary sodium concentration was 75 mEq/L with a urine osmolality of 382 mOsm/kg. Result of a cosyntropin stimulation test was normal, with a baseline cortisol level of 9.2 µg/dl and a stimulated level of 18.7 µg/dl. Thyroid-stimulating hormone was normal at 0.7 mIU/L. Magnetic resonance imaging of the brain and pituitary revealed no significant abnormalities.

Discussion

Given the absence of liver or heart disease and the patient’s apparently normal volume status, she was considered to have euvolemic hyponatremia. According to an analysis of the differential diagnosis of euvolemic hyponatremia, she was taking no drugs that are associated with this disorder, and she had no evidence of thyroid or adrenal disease. The urinary sodium level (>20 mEq/L), urinary osmolality (>100 mOsm/kg), and low serum uric acid levels are findings that supported the diagnosis of the syndrome of inappropriate antidiuresis (also known as the syndrome of inappropriate antidiuretic hormone, or SIADH). Because a broad range of pulmonary disorders are associated with SIADH, bronchiectasis was considered to be the cause of the syndrome, particularly in view of the normal findings on magnetic resonance imaging of the brain.

This Attending Rounds will pose a series of questions to address the incidence and prevalence of hyponatremia in the elderly, its causes and pathogenesis, whether it should be treated, and the therapeutic options available for treatment of chronic hyponatremia.

Question 1. How Common Is Chronic Hyponatremia in the Elderly?

The prevalence of chronic hyponatremia in the elderly population is to a large extent dependent on the level of serum sodium used to define the disorder and the setting in which the measurement is made. When studying the risk factors for orthostatic hypotension in an otherwise healthy population, Caird et al. noted that approximately 7% of patients >65 years of age had serum sodium concentrations ≤ 137 mEq/L.
In contrast, with a serum sodium concentration < 135 mEq/L used as a cutoff, the prevalence of chronic hyponatremia was approximately 20% among residents of a long-term care facility (2). A similar prevalence was noted in a Veterans Affairs nursing home, whereas the prevalence was 8% in ambulatory patients in the same institution (3). Of note is that when multiple serum sodium measurements were made during a 12-month period, approximately half of the nursing home population had at least one serum sodium measurement < 135 mEq/L.

The most recent study designed to determine the prevalence of hyponatremia was limited to patients with severe decrements in serum sodium concentration to <125 mEq/L. Of 1400 elderly (≥65 years) patients admitted to an Israeli hospital, 6.2% had such a disorder (4). The increasing prevalence of hyponatremia with age is best illustrated in an analysis of >300,000 samples obtained from >120,000 patients of various ages (5). With a serum sodium concentration < 136 mEq/L used as a cutoff and a ≤30-year-old cohort as a reference group, patients >60 years had a significantly higher prevalence of hyponatremia both at presentation and as a hospital-acquired disorder (Figure 1). In summary, it is evident from multiple epidemiologic studies that the elderly are especially prone to the development of hyponatremia.

**Question 2. Why Are Elderly Patients More Prone to Hyponatremia, and What Are the Causes of Hyponatremia in This Population?**

Although changes in the renal concentrating mechanism brought about by aging have been extensively studied, the effect of aging on the renal diluting process has received much less attention. When given a water load, healthy elderly persons can readily dilute their urine to <100 mOsm/Kg, but the rate of free water excretion is slower than in younger controls (6). This decrement is further enhanced if they are receiving thiazide diuretics or nonsteroidal anti-inflammatory drugs, both of which are commonly used in this population. The subtle impairment in the excretion of water may be due to age-related reductions in GFR because creatinine clearance was substantially lower in the older cohort. A decrease in the expression of the Na-K-2Cl co-transporter in the ascending limb of the loop of Henle and the Na-Cl co-transporter in the distal tubule has been reported in aging rodents (7). These changes would result in increased delivery of solute to more distal sites of the nephron, limiting free water clearance. Whether such downregulation occurs in humans is not known, but if present it could impair both maximal concentrating and diluting abilities.

Finally, an age-related decrement in the percentage of body water content makes the elderly more prone to dysnatremias because smaller disturbances in water balance will cause greater changes in the serum sodium concentration. Nonetheless, most elderly persons have well preserved urinary diluting ability, and the development of hyponatremia is likely to supervene only when additional pharmacologic or pathologic processes are operant, as they frequently are with advancing age.

Chronic hyponatremia is frequently multifactorial in the elderly (4,8). In one observational study, more than half of the patients with hyponatremia had more than one cause for the condition. The single most common cause of hyponatremia was SIADH. Thiazide diuretic use was a common contributing factor. Heart failure is also a common comorbid condition in this age group. Also characteristic of this syndrome in the elderly is the lack of a clear underlying cause in >50% of cases (4,9).

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**Figure 1.** Increasing risk for hyponatremia (<136 mmol/L) with age at admission and acquired at hospital. *Statistical significance. Reprinted from reference 5, with permission.
**Question 3. Why Should Increasing the Serum Sodium in the Patient under Discussion Be Considered?**

Many patients with long-standing hyponatremia, even when severe (sodium < 125 mEq/L), appear by most clinical criteria to be essentially asymptomatic, probably as a consequence of the restoration of brain cell volume brought about by the exit of intracellular electrolytes and organic osmolytes. However, the loss of these solutes, although critical to the cell volume adaptive process, leaves the brain with a decreased amount of various substances, such as glutamine, a major neurotransmitter, that are important for normal neuronal function (10). Thus, although these patients may appear to be asymptomatic, more careful studies have led to the question “Does asymptomatic hyponatremia exist?” (11). In this regard, Renneboog and colleagues administered a battery of visual and auditory tests to 16 patients with chronic hyponatremia (mean age, 63 years; mean serum sodium concentration, 128 mEq/L) (12). Hyponatremia was associated with an increase in error rate and latency time that was highly significant compared with patients who had a normal serum sodium concentration. Furthermore, these investigators reported significant disturbances in gait in 12 “asymptomatic” hyponatremic patients with a mean serum sodium of 128 mEq/L that were worse than those observed in patients with blood alcohol levels of 0.05%; these gait abnormalities corrected when the serum sodium levels returned to normal. Finally, in a case-control study of 122 hyponatremic patients (mean serum sodium, 126 mEq/L; mean age, 72 years), these investigators found that the gait disturbance associated with hyponatremia culminated in an increase in risk for falls by an odds ratio of 67.4 (95% confidence interval [CI], 7.48–607.4; P<0.001).

A subsequent case-control study of >530 patients with a mean age of 81 years also found that the presence of hyponatremia (mean serum sodium concentration, 131 mEq/L) was associated with a four-fold greater risk of presenting with a fracture compared with age-matched normonatremic controls (13). A subsequent study also found this association of hyponatremia with large bone fractures in the elderly (14). A more recent prospective, population-based study of 5208 elderly patients, 399 of whom were hyponatremic (mean serum sodium concentration, 133 mEq/L), found a significant increase in nonvertebral fractures in the hyponatremic cohort (hazard ratio, 1.39; 95% CI, 1.11–1.73) (15).

The propensity for fractures in elderly hyponatremic patients may not relate solely to gait disturbance but may also be enhanced by a direct effect on bone mineralization. Verbalis and colleagues reported a significant decrease in bone mineralization in rats when their serum sodium concentration was decreased to 110 mEq/L (16). More important, adults with mild hyponatremia (mean serum sodium concentration, 133 mEq/L) displayed a significantly increased risk for osteoporosis at the hip (odds ratio, 2.85; 95% CI, 1.03–7.86) and femoral neck (odds ratio, 2.87; 95% CI, 1.41–5.81). These observations may be related to stimulation of osteoclastic activity and enhanced bone resorption in the setting of a low serum sodium concentration (17). Commensurate with the above discussion, our patient had disturbed gait and had sustained a fall and fracture. Thus, the rationale for initiating a therapeutic intervention to increase her serum sodium concentration appeared compelling.

**Question 4. What Therapeutic Options Are Available to Treat Chronic Hyponatremia in the Elderly?**

**Water Restriction**

As a disorder whose pathogenesis revolves around the retention of water and the kidney’s reduced ability to excrete it, the cornerstone of treatment of chronic hyponatremia has been restriction of water intake. This approach has the virtue of addressing the underlying responsible mechanism and is very attractive for its lack of any associated cost. However, experience has revealed that adherence with significant water restriction is problematic and that such restriction is poorly tolerated over time. Although a decrement in tonicity should in itself suppress thirst, a large portion of fluid intake is not driven by thirst but rather is determined by habit and other factors. Despite the absence of any scientific support, limitation of water intake is often strongly encouraged. Furthermore, water restriction is not always effective, particularly when the diluting defect is severe.

As was elegantly analyzed by Furst and colleagues (18), when the sum of the concentration of urinary sodium plus potassium is greater than the serum sodium concentration, no electrolyte-free water is excreted and therefore almost no amount of water restriction will result in an increase in the serum sodium concentration. Only when the diluting defect is mild and this ratio is <0.5 will a tolerable restriction of approximately 1 L/d be of any therapeutic benefit. Thus, the response to this therapeutic intervention is variably effective and is often insufficient to adequately correct significant hyponatremia.

**Demeclocycline**

Because it appears to inhibit adenylate cyclase activity after the binding of vasopressin to the V2 receptor (19), this agent also targets the mechanism underlying the pathogenesis of most water-retaining states. It is used in doses ranging from 600 to 1200 mg per day if water restriction becomes ineffective, and the underlying cause of the hyponatremia is not readily reversible or treatable. The response rate is extremely variable. The drug has significant gastrointestinal side effects, is associated with photosensitivity, and can be nephrotoxic, particularly in the presence of liver disease (20). The drug is not Food and Drug Administration (FDA) approved for treatment of hyponatremia.

**Loop Diuretics and NaCl**

The rationale for use of loop diuretics and NaCl supplementation revolves around the ability of loop diuretics to increase electrolyte-free water excretion. However, to prevent undesirable concomitant sodium depletion, this treatment also requires the administration of NaCl, typically 2–3 g daily, to supplement dietary intake. This increase in solute delivery from NaCl intake and excretion may also increase electrolyte free water clearance (or reduce negative electrolyte free water clearance). In addition, potassium repletion or use of a potassium-sparing diuretic is also often necessary to avoid clinically significant hypokalemia. Although this approach has been extensively used to treat symptomatic hyponatremia in a hospital setting, there is
Urea

The administration of urea in doses ranging from 30 to 90 g/d can successfully increase the serum sodium concentration in patients with chronic hyponatremia. It does so by inducing a solute (urea) diuresis that, by increasing urine flow rate, decreases the concentration of sodium and potassium in the urine and hence increases excretion of electrolyte-free water (22). Although a recent study by Soupart and colleagues in 13 patients with SIADH found that urea was as effective in raising serum sodium levels and was as well tolerated as the vasopressin antagonist tolvaptan (23), in my experience and in informal surveys of practicing nephrologists in North America, urea is not widely used in North America, primarily because of limited availability. There is no US Pharmacopeia–approved formulation, and it is not available at most pharmacies. Its poor palatability also leads to poor adherence. Thus, although urea is inexpensive and potentially effective, its unavailability and patient intolerance regarding its taste make it a limited treatment option.

Vasopressin Receptor Antagonists

In view of the limitations of other available therapies described above, the development of antagonists to the hydro-osmotic effect of vasopressin via its V2 receptor has received significant attention. Although peptide V2 receptor antagonists were studied initially, clinical applicability was greatly enhanced when nonpeptide oral antagonists that block activation of the receptor by vasopressin were developed (24). Since then, two competitive V2 receptor antagonists, conivaptan and tolvaptan, have been FDA approved for use in euvolemic and hypervolemic patients with hyponatremia (25). A third agent, livixavaptan, is under review by the FDA. These agents reliably increase free water excretion and, in contrast to loop diuretics, do not significantly increase urinary sodium or potassium excretion. They are best described as aquaretic agents, and as such can restore body water content to more normal levels.

The placebo-subtracted increase in serum sodium concentration on the first day of drug administration in euvolemic patients was 7.45 mEq/L in a trial with conivaptan (26), 5.60 mEq/L in a large tolvaptan trial (Study of Ascending Levels of Tolvaptan in Hyponatremia [SALT]) (27), and 6.29 mEq/L in a comprehensive meta-analysis (28). In this meta-analysis, the response was more modest in hypervolemic patients, at 4.09 mEq/L (28). Adverse effects were uncommon in most trials and were related mainly to the aquaretic effect of the drugs: polyuria, nocturia, thirst, and dry mouth (27). Rapid correction of hyponatremia occurs more frequently with vaptans than with placebo (28). Nonetheless, the goal of increasing the serum sodium concentration by 6–8 mEq/L in the first 24 hours should be attended to, and patients should be allowed free access to water in order to mitigate excessive correction rates.

An open-label trial demonstrated continued efficacy of tolvaptan to maintain serum sodium level >135 mEq/L in most treated patients for up to 4 years (Figure 2) (29). In this study as well, patients with SIADH and heart failure had a more robust response than those with cirrhosis. Because the secretion of vasopressin is sometimes transient, it would be reasonable to periodically stop the drug to determine whether it is still required. Such a trial has not yet been undertaken in the patient under discussion.

Because of interactions with drugs metabolized by the CYP3A4 hepatic isoenzyme, conivaptan is approved only for short term (4 days) intravenous administration. Therefore, at present tolvaptan is the only agent in this class available for long-term oral use. This antagonist is also metabolized by the CYP3A system, albeit to a lesser degree. Therefore, interactions with drugs that are also metabolized by this pathway result in increased concentration of both drugs and require dose adjustment.

It must be recognized that there is a serious paucity of data demonstrating that vaptans clearly improve patient outcomes. This is particularly important in view of the high cost of this treatment. The SALT trial with tolvaptan did demonstrate a significant (P=0.015) improvement in the score on the mental, but not the physical, component of the Short-Form 12 general health survey at 30 days (27). In a post hoc subgroup analysis of the euvolemic patients in this trial, the physical component of the Short-Form 12 improved and the length of hospitalization decreased significantly (30). Nonetheless, studies primarily designed to assess whether morbidity, length of hospitalization, overall well-being (preferably with a disease-specific instrument), and even mortality are urgently needed to determine whether the long-term use of these costly agents is justified.

Subsequent Clinical Course

In the patient who is the subject of this Attending Rounds, an attempt was initially made to limit her water intake to ≤1 L/d. The patient had difficulty adhering to this because of mouth dryness. During this period, her serum sodium concentration ranged between 125 and 132 mEq/L. In view of the persistent severe hyponatremia, her inability to maintain a strict water restriction, and her gait instability leading to a fracture, she was considered a good candidate for a vasopressin antagonist. Although the high cost of the drug is a frequent impediment to its long-time use, her insurance company was willing to cover the cost. During a 24-hour inpatient observation, she was given 15 mg of tolvaptan daily, which resulted in an increase in her serum sodium concentration from 126 to 134 mEq/L. Since then she has continued to receive this dose of tolvaptan, and her serum sodium levels over 20 months, without any water restriction, have fluctuated between 135 and 140 mEq/L (Figure 3). Her husband reports that her gait has significantly improved, and she has had no further falls. This dramatic improvement has led me to justify the continued use of the drug in this patient and to recommend a therapeutic trial of tolvaptan in other patients similar to
the one presented here—especially elderly patients with hyponatremia in whom water restriction is not tolerated or is ineffective, who have an obvious gait disturbance, or who are otherwise at risk for falls and fractures.

Questions

Dr. Rebecca Seshasai (Nephrology Fellow)

Once you have decided to start a patient on a vaptan, how often do you monitor serum sodium levels, and what instructions do you give your patients taking vaptans about water intake? Do you worry about these elderly patients becoming hypernatremic?

Dr. Berl

The FDA has mandated that tolvaptan be initiated in the hospital with frequent monitoring of serum sodium. Once the patient is discharged, I check the serum sodium concentration 4 days later, then weekly for 2 weeks and then monthly. One of the attractive features of the use of vaptans is that water intake need not, and should not, be restricted. As long as the thirst response is intact, significant hypernatremia should not develop. In fact, thirst was one of the more frequent complaints in the SALT trials, even when serum sodium was nowhere near the normal range. In this trial the serum sodium exceeded 146 mEq/L in fewer than 2% of the patients who received this vaptan.
Nonetheless, because the elderly are more prone to hypodipsia they may be at greater risk to develop this problem.

**Dr. Meera Nair (Nephrology Fellow)**

How significant is the burden of polyuria on patients who are receiving long-term vaptan therapy? This may be concerning in elderly patients with limited mobility.

**Dr. Berl**

Approximately 10% of the patients given a vaptan report polyuria. In my experience, this symptom occurs early in the administration of the drug and in no case was it a cause for discontinuation. Elderly patients who cannot access water should not be given these drugs. Vaptans generate a pharmacologic form of nephrogenic diabetes insipidus, and severe hypernatremia can ensue if water is not consumed.

**Dr. Stanley Goldfarb**

Would you use a vaptan in patients with lower serum sodium concentrations, such as 115 mEq/L? If so, would you worry about too rapid a rise in the level more so than in patients with more mild degrees of hyponatremia?

**Dr. Berl**

There is little if any experience with the use of vaptans in patients with serum sodium < 115 mEq/L. The SALT trial excluded patients with serum sodium < 120 mEq/L, and the original study with conivaptan enrolled patients with serum sodium as low as 115 mEq/L, but the mean was 124 mEq/L. As noted above, in some patients treated with vaptans, increments in the serum sodium concentration that exceed desired limits were exceeded. The risk for osmotic demyelination is higher with lower initial serum sodium concentration. Nonetheless, the loss of a given volume of water increases serum sodium almost equally at baselines as low as 115 and as high as 135 mEq/L. Clearly patients with more severe hyponatremia need to be monitored very closely.

**Dr. Jeffrey Berns**

Does chronic vaptan use alter sensitivity of the collecting duct to endogenous vasopressin once the vaptan is discontinued? Does the collecting duct become “hypersensitive” to arginine vasopressin or does resistance to vasopressin remain even after the drug is stopped?

**Dr. Berl**

These are intriguing questions that to my knowledge have not been studied, but certainly should be because the answers have important clinical implications.

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**References**


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