CASE REPORTS

Pseudohyponatremia in a Patient with HIV and Hepatitis C Coinfection

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Pseudohyponatremia refers to low serum sodium in the presence of normal plasma tonicity. Whereas pseudohyponatremia secondary to hyperlipidemia is a commonly recognized occurrence, falsely low sodium levels secondary to elevated protein are less frequently observed. We present in this paper the case of a man coinfecting with HIV and hepatitis C who had pseudohyponatremia from hypergammaglobulinemia. As hypergammaglobulinemia is a frequent occurrence in both HIV and HCV, we suggest that pseudohyponatremia is an important and likely underdiagnosed phenomenon in this patient population. Clinicians need to be aware of the electrolyte exclusion effect and become familiar with the techniques used by their local laboratory in the measurement of serum electrolytes. Pseudohyponatremia should also be included in the differential diagnosis of an elevated osmolal gap, as the falsely lowered sodium level will lead to a falsely low calculated serum osmolality.

KEY WORDS: pseudohyponatremia; HIV; hepatitis C; electrolyte exclusion effect.

J Gen Intern Med 23(2):202–5

DOI: 10.1007/s11606-007-0446-3

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INTRODUCTION

Pseudohyponatremia is defined as an apparently low serum sodium in the presence of normal plasma tonicity. It is a measurement artifact caused by an increase in the solid fraction of plasma, usually in the form of excess protein or lipids. Whereas pseudohyponatremia secondary to hyperlipidemia is a commonly recognized phenomenon, spuriously low sodium levels secondary to elevated protein are less frequently observed. We present in this paper the case of a man coinfecting with HIV and hepatitis C who had pseudohyponatremia from hypergammaglobulinemia. The pathogenesis of pseudohyponatremia and its potential implications for patient care are then reviewed.

CASE DESCRIPTION

A 52-year-old male with HIV/AIDS and cirrhosis secondary to both hepatitis C and alcohol abuse presented to the emergency department with a 2-day history of lower extremity weakness and fatigue. He reported subjective fevers at home and said that he had fallen 5 times in the previous 2 days. He denied head trauma or loss of consciousness in association with his falls. He had recently been discharged from the hospital with a left knee cellulitis. During that hospitalization, he was started on furosemide and spironolactone for management of ascites and sulfamethoxazole/trimethoprim for prophylaxis against *Pneumocystis jiroveci* pneumonia. His last CD4 count was 149 cells/mm³ with a viral load of 68,778 copies/mL. He was not currently taking antiretroviral therapy.

On physical examination, he was afebrile with a blood pressure of 98/62 mmHg and a pulse of 82 beats per minute. He was breathing 18 times per minute and saturating 94% on 4 L of oxygen by nasal cannula. His mucous membranes were dry and his jugular venous pressure was approximately 6 cm of water. He had scleral icterus. His chest was clear to auscultation bilaterally. Heart sounds were notable for a normal S1 and S2 with a soft one out of six systolic ejection murmur heard best at the left lower sternal border. His abdomen was minimally distended but soft with a small fluid wave. He had occasional spider nevi and no hepatosplenomegaly. His extremities revealed two-plus pitting edema with chronic stasis changes but there was no warmth or erythema. On neurologic examination, he was alert and appropriate but had bilateral asterixis, diffuse hyperreflexia, and bilateral clonus in the lower extremities.

Admission laboratory values are shown in Table 1. Serum sodium was 119 meq/L. Creatinine was 2.1 mg/dL, increased from 1.1 mg/dL 1 month before admission. Measured serum osmolality was 290 mOsm/kg (normal 285–295), calculated osmolality ($2 \times [\text{sodium (meq/L)}] + [\text{glucose (mg/dL)} / 18] + [\text{blood urea nitrogen (mg/dL)} / 2.8]$) was 261 mOsm/kg. The osmolal gap was 29 mOsm/kg (normal <10). Given his elevated osmolal gap, serum volatile and urine toxicology screens were sent and were negative. Salicylate level was less than 30 mg/L. Urine osmolality was 579 mOsm/kg. Urine sodium was 54 meq/L. Venous blood gas analysis was notable for a pH of 7.43, partial pressure of carbon dioxide of 36 mmHg, and partial pressure of oxygen of 42 mmHg. Random serum cortisol was 22.7 µg/dL. Uric acid was 14.2 mg/dL. Serum triglyceride level was 52 mg/dL. Total cholesterol was 95 mg/dL. Total protein was 11.7 g/dL with

Received May 10, 2007

Revised October 11, 2007

Accepted October 18, 2007

Published online November 10, 2007

Table 1. Admission Laboratory Values

Laboratory test	Normal values	Admission laboratory values
Sodium (meq/L)	135–148	119
Potassium (meq/L)	3.5–5.0	5.7
Chloride (meq/L)	96–109	87
BUN (mg/dL)	7–22	49
Creatinine (mg/dL)	0.6–1.3	2.1
Glucose (mg/dL)	60–109	111
Calcium (mg/dL)	8.4–10.5	9.6
Total protein (g/dL)	6.0–8.2	11.7
Albumin (mg/dL)	3.5–5.3	2.4
Total bilirubin (mg/dL)	0.1–1.2	3.9
Alanine Aminotransferase (U/L)	0–40	74
Aspartate Aminotransferase (U/L)	0–37	172
Alkaline Phosphatase (U/L)	30–120	105
Bicarbonate (meq/L)	21–31	23
Prothrombin Time (s)	9.5–11.7	15

an albumin of 2.4 g/dL. Serum immunofixation demonstrated a polyclonal hypergammaglobulinemia with beta–gamma bridging and markedly elevated IgG, IgM, and IgA levels (see Fig. 1).

Given his degree of hyponatremia, normal measured serum osmolality, and lack of evidence for any additional osmoles such as ethanol, methanol, isopropyl alcohol, or ethylene glycol, his serum sodium measurement was repeated 3 hours after his initial presentation to the emergency department. Whole blood sodium measured in the critical care laboratory was 128 meq/L, whereas sodium tested in the hospital’s main laboratory from the same sample was 120 meq/L. Based on his whole blood serum sodium, his osmolal gap was only 11 mOsm/kg. This finding suggested that his hyponatremia on presentation was, in part, because of pseudohyponatremia from elevated protein levels secondary to his HIV, hepatitis C, and cirrhosis. Therapy with both loop and potassium sparing diuretics, cirrhosis with ascites, and probable volume depletion likely further contributed to his low serum sodium level. Adrenal insufficiency was an unlikely explanation given his random serum cortisol level above 20 µg/dL.

The patient’s diuretics were held and he was gently volume resuscitated. His acute renal failure resolved and his serum sodium returned to his previous baseline of 130 meq/L. His initial symptoms of weakness and fatigue improved and were

attributed to volume depletion in the setting of increased outpatient diuretics and poor oral intake secondary to his recent infection. He was discharged on hospital day 5 to follow-up in the HIV and hepatology clinics.

DISCUSSION

Pseudohyponatremia is defined as the coexistence of hyponatremia with a normal plasma tonicity. This analytical artifact is caused by the “electrolyte exclusion effect” and arises most commonly in situations of extreme hyperproteinemia or hyperlipidemia. The explanation of the effect is the following: 93% of plasma is water and 7% is composed of solids, mostly protein and lipid. Free electrolytes are almost entirely associated with plasma water. In practice, electrolyte concentrations are defined in terms of whole plasma rather than plasma water. In most cases, these values parallel each other but in cases where the total solid content of plasma is increased, indirect measurements of whole plasma electrolytes will underestimate their plasma water concentrations. The amount of free electrolytes and water per volume of serum is reduced in cases of hyperlipidemia or hyperproteinemia because the proportion of whole plasma taken up by the solids component has increased.¹

Tests such as indirect ion-selective electrode (ISE) potentiometry and flame photometry are especially sensitive to the electrolyte exclusion effect because they dilute the plasma sample in a large volume of ionic solution before measuring the electrolyte concentration. The same amount of diluent is used each time and the concentration of the electrolyte is then adjusted by a factor of 0.93 (the average volume water fraction in plasma) to obtain the actual ion concentration in plasma.² When the solid component of plasma is elevated, the plasma water component is reduced resulting in a greater dilution for the same amount of diluent and an underestimation of the true electrolyte concentration. Direct ISE methods are not susceptible to the effect. As a result, in cases of hyperlipidemia or hyperproteinemia, serum electrolyte measurements will appear to be lower when measured by the indirect ISE or flame photometry method.^{1,3,4}

Our main hospital laboratory measures serum sodium using an indirect ISE method on the Roche Modular ANALYTICS P

Age 52 Sex M

Serum Protein Electrophoresis

Fractions	%	Ref. %	g/dl	Ref. g/dl
Albumin	21.3L	60.0 - 71.0	2.26	4.12 - 4.68
Alpha 1	1.9	1.4 - 2.9	0.20	0.13 - 0.18
Alpha 2	5.5L	7.0 - 11.0	0.58	0.52 - 0.67
Beta	7.0L	8.0 - 13.0	0.74	0.55 - 0.74
Gamma	64.3H	9.0 - 16.0	6.82	0.62 - 0.81

T.P. : 10.6
A/G: 0.27

Figure 1. Serum protein electrophoresis shows an increased total protein, an asymmetric broad-based gamma region, and beta–gamma bridging.

Module (Roche Diagnostics, Indianapolis, IN, USA). Lipemic samples are routinely screened using the lipemic index but no such trigger is used to indicate high protein levels. If a high lipemic index is found or if an astute laboratorian notices that a sample is more turbid than expected, the excess buoyant lipids can be removed from the sample before measuring the serum sodium in the aqueous phase. This can be done with carbon tetrachloride,⁵ or simply by "airfuging" the sample and removing the insoluble lipid phase from the solution surface. Such techniques are not available for elevated protein content, as the protein distributes relatively evenly and cannot be removed. As a result, the only way to obtain an accurate serum sodium measurement in the case of hyperproteinemia is to use the direct ISE method. Sodium measurements in our critical care laboratory are obtained via a direct ISE method using the Bayer Rapid Lab 865 analyzer (Bayer Corporation, Tarrytown, NY, USA). This explains the difference in our patient's serum sodium levels when simultaneously measured in the different laboratories.

A recent study by Nguyen et al.² addressed this issue by employing gravimetry to demonstrate a predictable decrease in plasma water content (PWC) as increments of albumin were added to a patient's plasma sample. This effect was mirrored by a corresponding underestimation of sodium concentration in the sample by ISE but not by direct potentiometry. The authors were able to show that PWC could be accurately assessed for sodium values measured interchangeably on ISE or direct potentiometry by using an appropriate correction factor. Assuming 93% of plasma is water, convention is that ISE employs the following dilution factor in determining the final electrolyte concentration: $(0.9333 + \text{Vol}_{\text{diluent}}) / 0.9333$ where $\text{Vol}_{\text{diluent}}$ is the assay diluent volume per unit volume of plasma. Any significant increase in plasma volume occupied by lipid or protein should predictably lead to an underestimation of sodium using this correction factor employed by ISE.

Waugh derived the following model for assessing PWC in a patient's plasma:⁶

$$\text{PWC} = 0.991 - (0.73 \times [\text{protein, kg/L}]) - (1.03 \times [\text{lipid, kg/L}]) \quad (1)$$

Substituting our patient's total protein concentration of 11.7 g/dL and total cholesterol concentration of 95 mg/dL into Eq. 1, one obtains a fractional plasma aqueous volume of 0.90 rather than the expected 0.93. This implies that the solid phase in this patient's sample is 10% by volume rather than the expected 7%. Therefore, one can see that employing a dilution factor based on a 93% PWC when the PWC volume is actually 90% for this sample leads to an underestimation of plasma sodium by ISE.

Pseudohyponatremia is more than just an intellectual curiosity. Management of fluid and electrolyte balance based on falsely low sodium levels has been reported to cause poor outcomes in hospitalized patients, including severe dehydration, hyponatremia, and even death.^{3,5} As indirect ISE measurements are commonly used in laboratories today, clinicians need to be aware of the potential for spuriously low electrolyte levels in patients at risk for hyperlipidemia and hyperproteinemia. Pseudohyponatremia should also be included in the differential diagnosis of hyponatremia and an elevated osmolal gap, as the falsely low serum sodium will lead to a lower than expected calculated serum osmolality.

Pseudohyponatremia has been reported in patients with HIV and has been attributed to hypergammaglobulinemia.⁷ Hypergammaglobulinemia has long been recognized in HIV and is the result of both virus-specific and polyclonal B cell activation.^{8,9} The significance of this hypergammaglobulinemia remains unclear, although there is some evidence to suggest that it may be related to disease progression or response to antiretroviral therapy.^{10,11}

Hypergammaglobulinemia is a common finding in patients with cirrhosis and has been linked to the generation of antibodies against bacterial endotoxin.¹² Hepatitis C in particular is known to infect and replicate in human B cells,¹³ and can cause both monoclonal and polyclonal hypergammaglobulinemia as evidenced by its role in the pathogenesis of various types of cryoglobulinemia.¹⁴ Whereas hyponatremia in end-stage liver disease is far more likely to result from cirrhosis rather than laboratory artifact, pseudohyponatremia should be considered in the differential diagnosis in patients with hypergammaglobulinemia and liver disease.

Soriana-Sarabia et al. showed that patients coinfecting with hepatitis C and HIV have higher levels of IgG than patients with HIV infection alone, despite similar elevations in total B cell counts. After the initiation of HAART therapy, coinfecting patients continued to have abnormally high numbers of B cells and circulating IgG, whereas patients with HIV infection alone normalized their B cell counts and IgG levels.¹⁵ Thus, hypergammaglobulinemia and concomitant pseudohyponatremia may be more prevalent in patients with HIV/hepatitis C coinfection, a fact which may be clinically relevant in areas where coinfection is high.

Hyponatremia is a common clinical finding in patients with HIV infection and liver disease. Clinicians need to consider the possibility of pseudohyponatremia when determining diagnostic and therapeutic strategies for patients with apparently low serum sodium levels. They must also be familiar with the methods of measuring serum electrolytes in their hospital or local laboratory to interpret results of routine testing in patients with high protein or high lipid levels.

Acknowledgements: The authors would like to thank Dr. Stuart Ray for his assistance with the manuscript. There was no financial support for this publication.

Conflicts of Interest: None disclosed.

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