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A Novel Case of Pseudohyponatremia Caused by Hypercholesterolemia

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INTRODUCTION

Pseudohyponatremia represents an artifactual reduction of blood (serum or plasma) sodium concentration measured with indirect ion selective electrode (ISE) methods. One mechanism of such artifacts is usually due to an abnormal increase in lipids or protein, the nonaqueous components of blood, that result in errors due to water displacement artifacts.[1,2] Other mechanisms that cause pseudohyponatremia may be associated with monoclonal proteins when a sample's hyperviscosity causes aspiration errors.[3]

In classic hyperlipidemia (hypertriglyceridemia)-induced hyponatremia, several equations have been published to correct errors in serum potassium, chloride, and sodium measurements. One such equation is as follows: Corrected Na^+ = Measured Na^+ + [{[0.21 × triglycerides (g/l)] − 0.6} × (Na^+/100)].[4] Using this equation, the estimated decrease of plasma sodium concentration could be as low as 3.9 mmol/l in a sample with triglyceride concentration of 1500 mg/dl (15 g/l) and sodium concentration of 130 mmol/l.

We report a case of a 41-year-old man who developed pseudohyponatremia due to hypercholesterolemia with concomitant hypertriglyceridemia and hyperglycemia. The hyponatremia was not fully accounted for by the true dilutional hyponatremia due to hyperglycemia,[5] and examination of the sample revealed that hypercholesterolemia is the culprit for the pseudohyponatremia. Institutional review was not required for this study because this case study does not provide patient identification and the blood samples used in the study were obtained for patient care, not for research purposes.

CASE PRESENTATION

A 41-year-old man with history of acute myeloid leukemia who had received an allogeneic stem cell transplant 3 years earlier developed graft-versus-host disease and liver graft-versus-host disease manifested by cholestatic jaundice. He was admitted to our institution for asymptomatic hyponatremia with complaints of polydipsia and polyuria. He denied headache, confusion, lightheadedness, fevers/chills, cough/dyspnea/chest pain, rash, nausea, diarrhea, or urinary problem. On admission, his laboratory results obtained with Roche Cobas 8000 (Roche Diagnostics, Indianapolis, IN) were as follows: sodium 118 mmol/l, potassium 3.9 mmol/l, chloride 81 mmol/l, glucose 472 mg/dl, total protein 4.0 g/dl, albumin 2.6 g/dl, total bilirubin 8.9 mg/dl, blood urea nitrogen 31 mg/dl, and alkaline phosphatase 568 U/l. Anti-mitochondrial antibodies were negative and thyroid-stimulating hormone was normal.

Osmolality measured with a freezing point depression method, Model 3320 Osmometer (Advanced Instruments, Inc., Norwood, MA), was 299 mOsm/l (reference interval: 275–295). Corrected plasma sodium concentration after accounting for true dilutional hyponatremia due to hyperglycemia was 124 mmol/l. The differential diagnosis for the patient's now moderate hyponatremia after accounting for hyperglycemia included the syndrome of inappropriate antidiuretic hormone secretion, but was more likely to be due to pseudohyponatremia, as suggested by the normal plasma osmolality of 299 mOsm/l.

After the patient was treated with 8 units of short-acting insulin and 1 liter i.v. normal saline, his serum glucose was corrected to 142 mg/dl; however, the plasma sodium concentration remained low at 122 mmol/l. The calculated osmolality was 263 mOsm/kg, resulting in an osmol gap of 36 mOsm/kg (reference interval: <10 mOsm/kg) that could not be accounted for by hyperglycemia.

On the lipid panel, the triglyceride concentration was 960 mg/dl, and cholesterol was 1449 mg/dl. Several samples from the patient were centrifuged using the Beckman Coulter Airfuge Ultracentrifuge (Beckman

Coulter, Brea, CA) and triglyceride-rich chylomicrons were separated from the aqueous phase of the plasma. The sodium concentration measured in the infranatant remained low and ranged from 124 to 130 mmol/l, indicating that triglycerides are not the sole cause for the suspected pseudohyponatremia.

Given the high cholesterol level in the sample as a potential cause of pseudohyponatremia, we used a direct ISE method on Nova 8 (Nova Biomedical, Waltham, MA) to measure sodium concentration[2] and obtained a result of 144 mmol/l in a sample with a sodium of 121 mmol/l by the indirect ISE on Cobas 8000. After the correction of sodium concentration by the direct ISE method, the calculated osmolality was 306 mOsm/kg, a value very close to the measured osmolality of 309 mOsm/kg.

Table 1 chronologically lists the sodium concentration results by the direct and the indirect ISE method, respectively, along with the cholesterol and triglyceride results in 7 samples from the patient. Samples 1, 2, 3, and 5 had high cholesterol and low sodium results by the indirect ISE method. Sample 5 had a low sodium result (121 mmol/l) by the indirect ISE and a normal sodium concentration (145 mmol/l) by the direct ISE when the cholesterol was 2419 mg/dl and triglyceride was 498 mg/dl. When the sodium concentration in the chylomicron-free infranatant was measured by the direct ISE method, the result was approximately 20 mmol/l higher than that obtained by the indirect ISE method.

These findings indicate that the very high cholesterol concentration was the cause of the pseudohyponatremia in our patient. The directly measured low-density lipoprotein (LDL) cholesterol concentration in sample 7 was 196 mg/dl, and the total cholesterol concentration was 1903 mg/dl, suggesting the vast majority of cholesterol was not contained in LDL lipid particles.

DISCUSSION

In normal blood samples, approximately 93% of plasma or serum by volume is aqueous solution and 7% is macromolecules, such as proteins or lipid particles. Sodium measurement determined with indirect ISE method is approximately 93% of that in plasma water. When plasma water volume significantly deviates from 93% due to high concentrations of protein or lipid in plasma, pseudohyponatremia can occur.[1,2] The most common cause for pseudohyponatremia is elevated plasma protein concentration. Triglyceride may be the next common cause when its concentration exceeds 1500 mg/dl.[1] In the present case, triglyceride was only moderately elevated (less than 500 mg/dl) in samples 4 and 5 whereas sodium (by the indirect ISE method) was significantly decreased, suggesting triglyceride was not the cause for the pseudohyponatremia observed in samples 4 and 5. Further, the low sodium results in the infranatant without chylomicrons strongly suggested that the highly elevated cholesterol, not the triglycerides, was responsible for the pseudohyponatremia observed in his samples.

Pseudohyponatremia due to hypercholesterolemia is extremely uncommon: 4 cases were related to graft-versus-host disease after bone marrow transplantation[6,7] or after allogeneic stem cell transplantation,[8] 3 were associated with primary biliary cirrhosis, and 1 with obstructive liver disease.[9] All of the patients presented with cholestasis characterized with markedly increased alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total and conjugated bilirubin, as well as extremely elevated serum cholesterol, ranging from 977 to 4091 mg/dl. Lipoprotein X (Lp-X) was detected in some of these samples[6–9] by lipoprotein electrophoresis. Lp-X consists of lamella lipoprotein particles with albumin in the core and a few apolipoprotein C and E molecules on the surface, which contain high contents of phospholipids (66% by weight) and large quantities of free cholesterol (22%). In cholestasis, the bile lipid complexes precursor refluxed into plasma compartment may cause Lp-X formation.[S1] Another group reported markedly decreased lipoprotein lipase and hepatic triglyceride lipase activities in a patient with severe hypercholesterolemia associated with allogeneic stem

Table 1. Test results in 7 samples of the patient

Sample no.	Na-indirect (mmol/l)	Na-direct (mmol/l)	K-indirect (mmol/l)	Cl-indirect (mmol/l)	Cholesterol (mg/dl)	Triglycerides (mg/dl)	HDL-C (mg/dl)	Bilirubin (mg/dl)	ALP (U/l)
Ref int	135–146	135–146	3.6–5.3	96–106	–	–	–	0.1–1.2	37–113
1	122	Not measured	2.9	86	1449	960	23	7.6	488
2	126	Not measured	4.0	90	1369	1487	27	6.5	462
3	121	Not measured	3.8	90	1523	1499	24	6.4	452
4	121	144	3.7	87	Not measured	357	Not measured	Not measured	Not measured
5	121	145	3.4	88	2419	498	31	14.4	1225
6	Not measured	135	3.6	Not measured	2521	304	Not measured	Not measured	Not measured
7	Not measured	138	3.5	Not measured	1903	226	29	9.8	1040

ALP, alkaline phosphatase; Cl-indirect, chloride by indirect ISE method; HDL-C, high-density lipoprotein cholesterol; ISE, ion selective electrode; K-indirect, potassium by indirect ISE method; Na-direct, sodium by direct ISE method; Na-indirect, sodium by indirect ISE method.

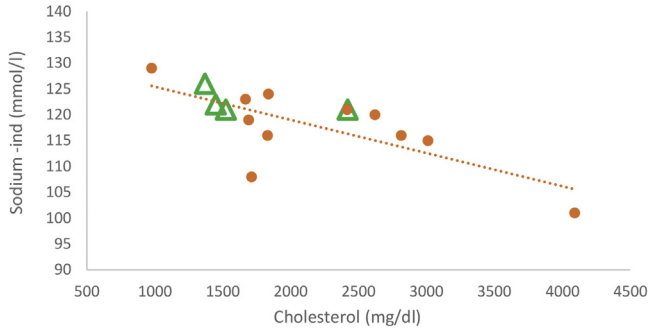

Figure 1. Results of sodium concentration by indirect ion selective electrode (ISE) method versus cholesterol in patients with primary biliary cirrhosis or liver graft-versus-host disease. Green triangles, our data; orange circles, data from previously reported cases summarized by Hussain *et al.*[9] Sodium-ind, sodium by indirect ISE method.

cell transplantation,[8] suggesting deficiencies in lipase activity also may play a role in Lp-X formation.

The extremely high cholesterol in this patient's samples are not contained in LDL lipid particles because the directly measured LDL cholesterol was only 10.3% of the total cholesterol (direct LDL of 196 mg/dl vs. total cholesterol of 1903 mg/dl in sample 7). We believe Lp-X was the major cholesterol carrier in our patient's plasma because of the similarities in hypercholesterolemia, pseudohyponatremia, and liver graft-versus-host disease that presented with cholestasis with elevated alkaline phosphatase and bilirubin between our patient and the cases in previous reports.[6–9]

In most cases of hypercholesterolemia, most of the cholesterol is contained in LDL particles. When Lp-X lipid particles become the main carrier of cholesterol, they can effectively displace more water in plasma because of their larger sizes (the diameters for Lp-X are 30 to 70 nm compared with 22 to 27 nm for LDL lipid particles). The larger size of Lp-X can explain why pseudohyponatremia occurred in a case of cholestasis when cholesterol was only 977 mg/dl.[7]

In 2015, while reporting a case of pseudohyponatremia secondary to hypercholesterolemia, Hussain *et al.*[9] plotted results of sodium versus cholesterol from 10 previously reported cases along with a case of their own. They revealed an inverse relationship between cholesterol and sodium by indirect ISE method.[9] If we add 4 pairs of sodium versus cholesterol results from our patient to their data collection and replot the figure, our data fit into the same line as shown in Figure 1. There exists an inverse relationship: the higher the cholesterol concentration, the lower the sodium result (by indirect ISE methods).

As summarized in Figure 2, pseudohyponatremia can be caused by elevated total protein, triglycerides, or very rarely by extremely elevated cholesterol. In cholestasis, Lp-X lipid particles carry most of the cholesterol in plasma and cause pseudohyponatremia.

- Pseudohyponatremia can be caused by elevated plasma protein, triglycerides, and cholesterol if measured with indirect ISE method.
- It is extremely uncommon for cholesterol to cause pseudohyponatremia. In the few cases of pseudohyponatremia associated with hypercholesterolemia, Lp-X is the carrier of cholesterol.
- Use a validated direct ISE method to measure electrolytes if pseudohyponatremia is suspected in a sample that has high protein, triglycerides, or cholesterol.

Figure 2. Take-home points. ISE, ion selective electrode; Lp-X, lipoprotein X.

DISCLOSURE

All the authors declared no competing interests. This work does not contain any human subject research material.

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SUPPLEMENTARY MATERIAL

Supplementary References.

Supplementary material is linked to the online version of the paper at www.kireports.org

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