A Woman with Primary Biliary Cirrhosis and Hyponatremia

Midhat S. Farooqi1,2 and Ibrahim A. Hashim1,2*

CASE DESCRIPTION

A 43-year-old woman with a medical history significant for hypertension, depression, and primary biliary cirrhosis (PBC)3 was admitted to the hospital after outpatient laboratory tests showed hyponatremia. Her complaints on admission included blurry vision, nausea, and significant pruritus. Her review of systems was otherwise negative. She declared no family history of hypercholesterolemia or premature heart disease. She was taking multiple medications including azathioprine, prednisone, amlodipine, losartan, prochlorperazine, sertraline, trazodone, fenofibrate, ranitidine, hydroxyzine, ursodiol, and cholestyramine. Physical exam was remarkable for scleral icterus and mild jaundice; no xanthomas were noted.

Laboratory studies were performed (Table 1). Once more, the patient was found to have hyponatremia, along with hypokalemia and hypochloremia. Her creatinine was slightly above normal limits but stable compared with past values. A liver profile test panel showed mild increases in transaminases, increased alkaline phosphatase activity, hypoalbuminemia, significant hyperbilirubinemia, and evidence of cholestasis with increased bile acids in the blood.

The patient was started on intravenous fluids (0.9% sodium chloride). Subsequently, a lipid panel was ordered (Table 1). Her most recent total cholesterol (TC) value, measured 1.5 years prior, was 322 mg/dL (8.3 mmol/L). Current testing revealed a markedly increased plasma TC concentration of 2156 mg/dL (55.8 mmol/L). This was the highest TC value ever measured by our laboratory. Furthermore, the sample appearance was clear and not grossly viscous or lipemic. An investigation took place to determine if this was an erroneous result.

DISCUSSION

LABORATORY INVESTIGATION

We first searched for possible interfering substances that could falsely increase a TC value. In our laboratory, TC is measured via an enzymatic method on a Roche Cobas® c501 instrument. Two well-known interfering substances include ascorbic acid and bilirubin; however, at high concentrations (>30 mg/dL and >5 mg/dL, respectively), both should decrease TC values (1). Furthermore, serial dilution of the specimen indicated no interferences [TC 392 mg/dL (10.1 mmol/L) and 196 mg/dL (5.1 mmol/L) after 1:5 and 1:10 dilution, respectively]. Per the manufacturers, the patient’s medications were not expected to affect the performance of this assay (2). There was no clinical reason to suspect that the patient’s plasma contained large amounts of phytosterols (as in patients with sitosterolemia), and the patient was not receiving total parenteral nutrition, both of which are possible confounding factors (1).

In general, free hemoglobin in a sample can also falsely increase TC values (2). Sample turbidity can interfere with measurement as well. Again, however, the sample appearance was clear. The hemolysis index of the sample was 3, icterus index 11, and lipemic index 73. No significant interference is expected below indices of 700, 14, and 2000, respectively (2).

1 Department of Pathology, University of Texas Southwestern Medical Center, Dallas, TX; 2 Parkland Health & Hospital System, Dallas, TX.
* Address correspondence to this author at: Department of Pathology, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX. Fax 214-648-8037; e-mail ibrahim.hashim@utsouthwestern.edu.
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QUESTIONS TO CONSIDER

1. What are possible causes of discrepant total cholesterol values?
2. What steps can be taken to determine if this was an erroneous result?
3. What are the implications for the patient if the results of her lipid panel are accurate?
4. What are the mechanisms by which lipemia can interfere with laboratory testing?
Although there was no evidence of sample misidentification or contamination, this possibility could not be entirely excluded. A new sample was obtained and tested. It showed a TC value of 2415 mg/dL (62.5 mmol/L); triglycerides, 299 mg/dL (3.4 mmol/L); HDL, 42 mg/dL (1.1 mmol/L); and LDL, unreportable. Treating these as accurate values, the patient’s serum was sent out to a reference laboratory for a lipoprotein profile.

Given the possibility that the patient’s hyperlipidemia was interfering with her electrolyte measurements, the clinical team stopped treatment with intravenous fluids. Direct ion-selective electrode (ISE) measurement of the initial sample on a Radiometer ABL825 Flex® analyzer showed a sodium concentration of 141 mmol/L (reference range 137–145); potassium, 4.4 mmol/L (3.6–5.5); and chloride, 105 mmol/L (101–111). The patient was discharged after the correct electrolyte results were obtained. Her lipoprotein profile subsequently confirmed the increased TC concentration and found a major component of lipoprotein X (LpX) (Fig. 1).

**PRIMARY BILIARY CIRRHOSIS**
PBC is an inflammatory, likely autoimmune, liver disease marked by the destruction of intrahepatic bile ducts (3). Common features of PBC include hyperbilirubinemia, pruritus, and increased plasma lipids, especially TC. In 1 study of 400 patients, 76% had TC values >200 mg/dL (5.2 mmol/L) at presentation, with an mean value of 240 mg/dL (6.2 mmol/L) and a range of 77–1037 mg/dL (2.0–26.8 mmol/L) (4). The present case is notable for the patient’s strikingly high TC value. To our knowledge, there is only 1 other report of a PBC patient with a cholesterol concentration >2000 mg/dL (51.7 mmol/L), and it, too, was associated with pseudohyponatremia significant enough to prompt clinical action (5).

PBC is also associated with a distinct lipoprotein profile (6). Earlier stages of PBC show a mild increase in LDL and marked increase in HDL, whereas later disease stages show significantly increased LDL, markedly decreased HDL, and presence of LpX. LpX is a variant lipoprotein composed of high amounts of free (unesterified) cholesterol, apolipoprotein, phospholipid, and albumin, seen in cholestatic liver disease (7). It interferes with routine lipid panel measurements, but the extent to which it does so is unclear. In contrast to LDL, LpX is not associated with increased risk of cardiovascular disease (3).

**MECHANISM OF INTERFERENCE OF ELECTROLYTE MEASUREMENT BY LIPIDS**
LpX also interferes with routine laboratory measurements (7). In general, the presence of excess lipids in a sample can impede laboratory testing in multiple ways: physical and chemical interference, absorption of light, reducing homogeneity of the sample via hydrophobic interactions, and volume displacement (8). It is important to distinguish hyperlipidemia from lipemia, as the former does not necessitate the latter. Specifically, lipemia is an accumulation of lipoprotein particles leading to sample turbidity, which is a function of lipoprotein size. An increase in larger particles such as chylomicrons is most likely to result in a turbid sample. Accumulation of only small particles, such as HDL and LDL, does not produce lipemia. LpX particles range in size and can be large enough to cause sample turbidity (7), but this is not always the case.
In this sample, the excess lipids interfered with the initial electrolyte measurement due to a volume-displacement effect, since electrolytes were measured via an ISE indirectly (i.e., after sample dilution) \( (9) \). The inaccurate result was not due to a physical interference of the electrode by lipid particles, but rather because the indirect method assumed the sample had a normal water content. A typical plasma sample contains about 93% water and 7% solids (lipids and proteins). The aqueous phase of the sample decreases in conditions where lipids are increased. In some instances, the lipid phase can be up to 25%, leaving an aqueous phase of 75% \( (8) \). Indirect methodologies rely on a sample’s water content to calculate a result from a diluted sample, but assume it is the normal value. For example, taking a measured sodium value of 105 mmol/L and presuming a sample’s water content to be 93% when, in fact, it is 75% causes the subsequently calculated sodium concentration to be falsely low [i.e., a final result of 113 mmol/L (105 divided by 0.93) as opposed to 140 mmol/L]. This problem can be circumvented by using techniques that do not require dilution (e.g., direct potentiometry).

Although an increase in solids can cause significant pseudohyponatremia, it is not intuitive that a TC concentration of approximately 2100 mg/dL would cause the degree of pseudohyponatremia seen here. Multiple formulas exist to calculate the expected drop in sodium in the setting of increased solids \( (9, 10) \). Some simple estimates are as follows: a rise of approximately 1 mg/dL of total protein falsely decreases sodium by approximately 1 mmol/L \( (9) \); similarly, an approximate 10 mmol/L increase in total lipids causes an approximate 1 mmol/L decrease in sodium \( (10) \). It is worth noting that 10 mmol/L lipids is equivalent to either approximately 900 mg/dL triglycerides or approximately 400 mg/dL cholesterol; the total lipid concentration is a variable aggregate of both. By this inference, the expected decrease in sodium in this case would be approximately 5 mmol/L (much smaller than the observed 20 mmol/L).

**Fig. 1. Lipoprotein profile and electrophoresis.**

Serum lipoproteins were assessed at a reference laboratory via a combination of ultracentrifugation, automated enzymatic and colorimetric assays, and electrophoresis. The results are shown on the left (A). β-VLDL and chylomicrons (both cholesterol and triglycerides) were not detected. Lipoprotein electrophoresis is shown on the right (B). Lane 1 is a control sample; lane 2 is the patient’s sample; HDL and LDL positions are marked (arrows). The dark, smeared nature of the band along with the observed reverse migration in the region of LDL is consistent with LpX (arrow). The amount of LDL cannot be quantified in this setting. For conversion to SI units, multiply the values by 0.02586 for cholesterol; 0.01129 for triglycerides; and 0.01 for apolipoprotein.

**POINTS TO REMEMBER**

- Patients with PBC often have increased total cholesterol concentrations, which in some cases may be extremely high.
- Lipoprotein X is an abnormal lipoprotein that may be seen in patients with obstructive biliary disease.
- A specimen may have increased lipids but not be grossly lipemic, as the latter mainly depends on an increased presence of larger lipoproteins such as chylomicrons.
- Indirect methods of measuring electrolytes show falsely decreased values in the presence of increased lipids, since they require sample dilution but do not account for changes in a sample’s water content.
- Direct methods of measuring electrolytes provide more representative results in samples with increased lipid content.
Hence, the published formulas are not reliable in this setting. We postulate that this is due to the specific nature of LpX. Further supporting this idea is that hypercholesterolemia on its own, i.e., without hypertriglyceridemia, is a very rare cause of significant hyponatremia; all reported cases thus far have involved the presence of LpX (9).

In summary, we present a case of a 43-year-old woman with a history of PBC who was admitted for hyponatremia. Laboratory results also showed hypokalemia and hypochloremia, but no acute kidney injury. She was found to have an extremely high TC concentration, which was verified by repeat testing. Subsequent lipoprotein analysis detected LpX. Using direct ISE measurement, we were able to show that the patient’s sodium concentration, as well as her potassium and chloride concentrations, were within normal range. This case is important owing to the degree of hypercholesterolemia, lack of lipemic sample appearance, and the link to multiple false electrolyte abnormalities.

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References

Commentary
Karolina M. Stepień*

This case report describes abnormal biochemical results in a patient with primary biliary cirrhosis (PBC). One of the extensive investigations carried out was of lipoprotein X, an abnormal lipoprotein in the serum of patients with obstructive jaundice (1). As shown in this case report, the presence of lipoprotein X affects cholesterol concentration. This patient had significantly raised bile acids—a hallmark of cholestasis—which have been shown to inhibit lipoprotein lipase, an enzyme participating in the degradation of lipoproteins.

An important characteristic feature of lipoprotein X is its mobility toward the cathode on agar-gel electrophoresis, which was also noted on this patient’s lipoprotein electrophoresis. Another way of confirming that lipoprotein X is probably contributing to high total cholesterol concentration is the measurement of serum apolipoprotein B. Normal apolipoprotein B concentration along with high serum LDL cholesterol and high total cholesterol indicates the presence of another particle that is contributing to the raised concentrations of those lipids.

The plasma concentration of lipoprotein X is well correlated with the plasma activity of alkaline phosphatase and serum bilirubin. Although lipoprotein X is present both in intra- and extrahepatic cholestasis, its very high concentration is indicative of intrahepatic biliary obstruction. PBC is characterized by intrahepatic cholestasis. However, of note, many of the medications this patient was taking may cause cholestatic liver disease. Hence, it would be worth considering other causes of both intra- and extrahepatic cholestasis in this case, e.g., drug-induced cholestasis.

Department of Clinical Biochemistry, Salford Royal Foundation NHS Trust, Salford, UK.
* Address correspondence to this author at: Department of Clinical Biochemistry, Salford Royal Foundation NHS Trust, Stott Lane, M6 8HD, Salford, UK. Fax: +44 (0)161-206-8583; e-mail kstepien@doctors.org.uk. Received January 10, 2015; accepted January 13, 2015. DOI: 10.1373/clinchem.2014.236844 © 2015 American Association for Clinical Chemistry.