CASE REPORT

Pseudohyponatraemia secondary to hyperlipidaemia in obstructive jaundice

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SUMMARY

A 44-year-old man with uncontrolled diabetes and chronic pancreatitis presented with abdominal pain, jaundice and unintentional weight loss. Laboratory investigations were significant for hyponatraemia, an obstructive pattern of liver enzymes. Imaging was consistent with intrahepatic and extrahepatic biliary obstruction, and endoscopic evaluation revealed a long common bile duct stricture. Intravascular volume depletion, beer potomania and syndrome of inappropriate antidiuretic hormone (with concern for biliary or pancreatic malignancy) were considered in the work-up for the aetiology of the hyponatraemia. After 4 days of conventional treatment, hyponatraemia persisted. Lipid panel obtained revealed very high levels of total cholesterol. The patient underwent a successful biliary diversion and reconstruction surgery. Follow-up after 3 months showed a clinically stable patient with resolution of elevated liver enzymes, hyperlipidaemia and hyponatraemia. We illustrate this rare case of hyponatraemia secondary to hyperlipidaemia in obstructive biliary cholestasis. It is important for physicians to thoroughly investigate the aetiology of hyponatraemia at its onset.

BACKGROUND

Hyponatraemia is one of the most common electrolyte disturbances in hospitalised patients with a prevalence of 15%–30%, if serum sodium less than 135 mmol/L is used as the diagnostic criterion.¹ Hyponatraemia associated with a normal serum osmolality has been classified as *pseudohyponatraemia*. The most common cause of pseudohyponatraemia is secondary to hyperlipidaemia.¹ Hyperlipidaemia falsely lowers the serum sodium concentration when measured using indirect ion selective electrodes (ISE), prominently employed in the hospital setting to measure electrolytes.² There are several causes of hyperlipidaemia including primary and secondary disorders.¹ Secondary disorders include obstructive biliary cholestasis. Obstructive biliary cholestasis and hyponatraemia in a patient could represent two independent conditions. However, identifying obstructive biliary cholestasis as a cause of pseudohyponatraemia is imperative to the clinician, as the management involves treating the condition causing cholestasis. Conventional treatment of hyponatraemia in a case of pseudohyponatraemia can potentially lead to serious consequences.

CASE PRESENTATION

A 44-year-old man with a history of uncontrolled type 2 diabetes mellitus and chronic pancreatitis presented to the emergency department with persistent dull aching right upper quadrant (RUQ) abdominal pain for 2 weeks and scleral icterus for 24 hours. He stated that his coworkers noticed the 'yellowness of his eyes' a day prior to presentation. He rated the pain as a 4/10, explaining that he woke up 2 weeks prior to presentation with this ache, and it has been persistent since that time. He denied any radiation of the pain elsewhere, aggravating factors or relieving factors. The patient had not tried anything for relief. He denied any prior episodes of this pain. He reported associated shortness of breath which he thought was due to the abdominal pain, as he was unable to take a deep breath. He also reported decreased appetite in the past 24 hours and an unintentional weight loss of 25 lb in the past year. The patient had an extensive alcohol abuse history, drinking 10 bottles of beer every day for the past 10 years. He denied any tobacco use or recreational and intravenous drug use. He also denied any recent travel, history of blood transfusions or high-risk sexual behaviour. He stated that 20 years ago, he underwent an open cystogastrostomy for drainage of a pancreatic cyst.

Physical examination showed scleral icterus, dry oral mucosa, midline abdominal surgical scar, moderate RUQ tenderness and decreased skin turgor. There were no other pertinent findings on examination with the other systems revealing no abnormalities.

INVESTIGATIONS

Initial laboratory results showed normocytic anaemia (haemoglobin of 10.8 g/dL, mean corpuscular volume 96.9), sodium of 110 mmol/L (reference value 136–145 mmol/L) with glucose of 492 mg/dL (reference value 74–106 mg/dL). Corrected sodium using Katz correction was 116 mmol/L.³ The Katz correction is a tool used to calculate the actual sodium level in a patient with hyperglycaemia.³ Other results were potassium 4.8 mmol/L with normal renal function. Liver enzymes were elevated; alanine aminotransferase of 285 U/L (reference value 12–78 U/L), aspartate aminotransferase of 305 U/L (reference value 15–37 U/L), alkaline phosphatase of 1810 U/L (reference value 45–117 U/L), gamma-glutamyl transferase of >8000 U/L (reference value 5–85 U/L) and total bilirubin of 3.3 mg/dL (reference value

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0.2–1.0 mg/dL), with direct bilirubin of 2.0 mg/dL (reference value 0.0–0.2 mg/dL). These values were significantly elevated in comparison with the baseline liver enzymes recorded 4 years prior. The patient was admitted for further management of his condition.

In the hospital, further diagnostic work-up for the hyponatraemia revealed thyroid-stimulating hormone and cortisol levels within normal range. Serum osmolality was 302 mOsm/kg (reference value 275–295 mOsm/kg). Urine osmolality was 826 mOsm/kg (reference value 50–1200 mOsm/kg). Urinary electrolytes were significant for urinary sodium of 49 mmol/L (reference value 40–220 mmol/L). The serum alcohol level was not measured, as the patient did not show signs of intoxication on physical exam. ECG and imaging of the chest were unremarkable. Ultrasound of the abdomen showed markedly dilated common bile duct (CBD) with intrahepatic bile duct dilatation concerning for biliary tree obstruction, and a hypoechoic appearance to the pancreas suggesting pancreatitis. Magnetic resonance cholangiopancreatography (MRCP) showed the CBD measuring 1.4 cm with a tapered narrowing of the distal CBD, and a double duct sign starting from the pancreatic head concerning for stricture secondary to chronic pancreatitis. Gallbladder was normal with no pericholecystic fluid noted, and no ascites was noted.

DIFFERENTIAL DIAGNOSIS

The patient's decreased per oral intake in the setting of hyponatraemia highlighted intravascular volume depletion as a likely diagnosis. Given the patient's history of alcohol abuse, a baseline hyponatraemic state secondary to beer potomania (dilutional hyponatraemia occurring due to excessive consumption of alcohol—poor in protein and salt) was also a possibility.⁴ However, the severely depressed sodium values were concerning. The patient was given intravenous fluids and 4 units of regular insulin in the emergency department. Repeat laboratory investigations on admission still showed significant hyponatraemia after treatment of hyperglycaemia. It was at this point that other aetiology for hyponatraemia was considered.

The presentation of this patient with significant lab findings and imaging was indicative of obstructive jaundice. This could have been a malignancy of the pancreas leading to a syndrome of inappropriate antidiuretic hormone (SIADH) secretion. It could also be a very rare case of pseudohyponatraemia in obstructive jaundice, which we read about in the books but rarely ever see clinically.

TREATMENT

In the emergency department, the initial corrected sodium was 116 mmol/L, and the patient was given a bolus of 1 L Plasma-Lyte 148 and 4 units of intravenous regular insulin. Repeat laboratory investigations 8 hours later showed serum sodium 120 mmol/L with glucose 219 mg/dL. Corrected sodium using Katz correction was 122 mmol/L.³ Given concern for rapid correction of sodium, no more intravenous fluids were given, and the patient was monitored closely. Gastroenterology was consulted to evaluate the patient because of significant findings on MRCP. The plan was to proceed with endoscopic retrograde cholangiopancreatography (ERCP) the next day. The patient was placed on 'nil per os' diet status, and sodium concentration was monitored. The patient had no significant neurological deficits on admission and throughout the hospital stay.

Lab monitoring revealed serum sodium trend in the 116–124 mmol/L range on admission prior to ERCP. Given the patient's severe hyponatraemic state, ERCP was postponed, as

the anaesthetist stated that the patient was high risk for anaesthesia. The recommendation was to proceed with sedation for ERCP only when serum sodium is >125 mg/dL. At this point, because the patient was deemed euvolaemic with better glycaemic control, serum osmolality and urine osmolality were repeated. Serum osmolality resulted as 290 mOsm/kg, and urine osmolality resulted as 888 mOsm/kg with urine sodium of 152 mmol/L. SIADH was the initial working differential with the patient restarted on diet and placed on 1 L fluid restriction. However, there was no significant improvement in serum sodium values.

On day 4 of admission, the work-up was reconsidered. The lack of significant symptoms raised the suspicion of obstructive jaundice causing a pseudohyponatraemia state. Sodium was measured on the blood gas, and the value was 132 mEq/L (reference value 135–145 mEq/L). Lipid panel resulted as total cholesterol 2118 mg/dL (reference value <200 mg/dL), triglycerides 387 mg/dL (reference value 30–150 mg/dL) and low-density lipoprotein (LDL) 2009 mg/dL (reference value <100 mg/dL). Lipid panel was repeated for confirmation, and it resulted as total cholesterol 2247 mg/dL, triglycerides 220 mg/dL and LDL 2176 mg/dL. Lipoprotein X never resulted during patient's hospitalisation.

ERCP was performed with significant findings of mid/distal CBD stricture status poststents with moderate successful dilatation. Patient was referred to surgical oncology for evaluation for a Whipple procedure as there was a concern for a malignant aetiology of the biliary obstruction.

OUTCOME AND FOLLOW-UP

The patient was discharged home to follow-up with surgical oncology for evaluation. Due to dense adhesions and significant variceal disease seen intraoperatively, it was decided that a Whipple procedure was too dangerous. The patient underwent a biliary diversion with a roux-en-y reconstruction with hepaticojejunostomy, gastrojejunostomy and jejunojejunostomy to relieve the biliary stricture. Biopsy of the tissue obtained did not reveal malignancy.

Follow-up on the patient's condition 1 week, 1 month and 3 months postsurgery revealed stable clinical condition. Hyperlipidaemia and hyponatraemia resolved as the biliary obstruction was relieved (figure 1).

Figure 1 A graphic representation of the values of serum sodium and serum total cholesterol levels. The graph shows the rise in the serum cholesterol values upon admission for obstructive biliary cholestasis and subsequent fall after surgical intervention. The corresponding sodium levels during this process are also represented.

DISCUSSION

We report a case of pseudohyponatraemia secondary to hyperlipidaemia, with total cholesterol measured as 2247 mg/dL. Lipoprotein X levels were unknown in our patient. Our patient's initial presentation was significant for biliary obstruction. This was clear given the history and physical findings, lab findings and imaging. However, the aetiology of his low serum sodium value was intriguing.

The Joint European guidelines classify hyponatraemia in adults based on the serum sodium concentration.⁵ According to this classification, the presentation of our patient falls into the profound hyponatraemia category of sodium <125 mmol/L. (Corrected sodium for our patient on presentation was 116 mmol/L.) The work-up on initial presentation showed serum osmolality of 302 mOsm/kg with the patient appearing hypovolaemic. The therapy of intravenous fluids and insulin was appropriate based on the initial presentation consistent with a hypertonic hyponatraemic state. Sodium values stayed persistently in the profound hyponatraemic range after fluid resuscitation. This prompted revisiting the work-up. The repeat serum osmolality after fluid resuscitation was 290 mOsm/kg. This was consistent with an isotonic hyponatraemic state (reference value 275–295 mOsm/kg). The serum osmolality was calculated as 251 mOsm/kg using the formula $(2 \times \text{serum [sodium, in mmol/L]} + [\text{glucose, in mg/dL}] / 18 + [\text{blood urea nitrogen, in mg/dL}] / 2.8)$.⁶ Hence, there was an osmolar gap of 39 which was significant. Calculating the serum osmolality is key because an osmolar gap can be seen in cases where there is either an accumulation of ineffective osmoles or a decrease in the plasma water content.¹ These ineffective osmoles such as urea and alcohol could be seen in patients with renal failure and alcohol intoxication, respectively, though absent in our patient. These osmoles are considered ineffective because they can cross the cell membrane without having much effect on water movement.²

Possible reasons for an osmolar gap in an isotonic hyponatraemic state include hyperlipidaemia and hyperproteinaemia. In these states, the measured serum or plasma sodium concentration appears falsely lowered because of the lipid or protein concentrations in the water content of the plasma.^{2,7} In a normal individual, plasma consists of 93% water and 7% solids.² The concentration of sodium in the physiologically significant plasma water is 154 mEq/L, which equates to a 143 mEq/L concentration when diluted in total plasma ($154 \times 0.93 = 143$).^{2,7} When the sodium level is measured using certain analysers which account for the dilution, the marked protein or lipid concentration in plasma would cause a falsely low sodium value per litre of plasma given the fall in percentage of plasma water. For example, if excessive hyperlipidaemia reduces the percentage of water in plasma to 75% while the sodium concentration in the water content remains normal (154 mEq/L), the calculated sodium concentration per litre of the plasma sample taking account for the dilution will be 115.5 mEq/L ($154 \times 0.75 = 115.5$). This false laboratory correction is termed as pseudohyponatraemia.^{1,8} There are three known methods for measuring sodium concentration. These include flame photometry, indirect potentiometry and direct potentiometry using direct ISEs.⁹ Tests that directly measure the plasma sodium concentration without dilution should be used in assessing the true sodium state of a patient with hyperlipidaemia. Direct ISEs is the only method that does not involve sample dilution. Direct ISEs, such as the point of care analyser used to measure blood gas in our case, directly measure the concentration of sodium in the water content of the plasma and are unaffected by changes in the plasma water percentage.^{7,9}

Figure 2 (A) A sample of a clear serum in a normal patient. (B) A sample of a lipaemic serum in a patient with hypertriglyceridaemia. (Adapted from Solak *et al*.¹⁰ Copyright 2017 by the BMJ Publishing Group.) (C) The sample of our patient's serum on initial presentation.

Pseudohyponatraemia can occur in patients with biliary obstruction as in the case of our patient with a biliary stricture. In these patients, there are marked elevations of the total serum cholesterol and lipoprotein X. The re-entry of unesterified cholesterol and phospholipids into the bloodstream in patients with cholestasis leads to the formation of lipoprotein X.² Lipoprotein X was measured in our patient but the laboratory reported that the quantity of sample collected for testing was not sufficient. At the time of our knowledge, the patient's obstructive jaundice had resolved. Notably, the serum sample collected by laboratory on our patient's initial presentation did not appear lipaemic (figure 2). In comparison to other hyperlipidaemic states, patients with lipoprotein X accumulation as seen in obstructive biliary cholestasis do not have a lipaemic serum.^{2,10}

There are a few case reports that have described pseudohyponatraemia in patients with hyperlipidaemia secondary to obstructive biliary cholestasis.^{11–13} However, these cases described patients with cholestasis secondary to either bone marrow transplant with graft versus host disease, primary biliary cirrhosis, hepatitis C or drugs. Only one case reported a patient with cholestasis secondary to a structural abnormality in the case of pancreatic cancer.¹³ Our case is unique from the other published cases for several reasons. First, we describe a patient with cholestasis secondary to biliary stricture, which had never been described. Second, our case was intriguing because the patient initially presented with concern for another aetiology of hyponatraemia, as the initial hypovolaemic state warranted fluid resuscitation. However, after correction back to euvolaemic status, the pseudohyponatraemic state was clinically identifiable. Making the correct diagnosis of pseudohyponatraemia in this case was important because the patient was able to proceed with surgical intervention for his clinical condition without being deemed high risk for anaesthesia.

Patient's perspective

I was very concerned about my condition. I am very thankful that my doctor was able to make the diagnosis of my abnormal cholesterol levels leading to my abnormal lab value. This was life-saving because I was able to proceed for my surgery. My symptoms have improved since my surgery, and I am now back working and happy.

Learning points

- ▶ Always obtain a serum osmolality in patients evaluated for hyponatraemia in the setting of cholestasis, as pseudohyponatraemia can result secondary to hyperlipidaemia.
- ▶ Direct ion selective electrodes such as analysers used to measure blood gas should be used to accurately measure serum sodium level in patients with pseudohyponatraemia.
- ▶ The elevated levels of lipoprotein X in cholestasis do not cause the serum to look lipaemic as seen in hypertriglyceridaemia.

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