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Case Report

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Pseudohyponatremia in a neuroblastoma patient with obstructive jaundice and review of literature

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Abstract

Background: Pseudohyponatremia is uncommonly associated with severe hypercholesterolemia. Case presentation: We report a case of pseudohyponatremia in a pediatric patient with severe hypercholesterolemia caused by obstructive jaundice. A 20-month-old female was hospitalized following a diagnosis of abdominal neuroblastoma related to asymptomatic hyponatremia.

Results: This is the first pediatric report of falsely low sodium levels in a child with severe hypercholesterolemia caused by abdominal neuroblastoma mass-related obstructive jaundice. At presentation we observed asymptomatic hyponatremia (126 mmol/L; normal range: 135-145 mEq/L), while she was later found to have 16.7 mg/dl total bilirubin and 870 mg/dL total serum cholesterol (normal range: 80-180 mg/dL). Pseudohyponatremia was diagnosed and confirmed by direct potentiometric measurement of serum osmolality (279 mOsm/kg; normal range: 275-290 mOsm/kg) and serum sodium (135 mmol/L), performed on a blood gas analyzer. It is unusual to observe an association of pseudohyponatremia with severe hypercholesterolemia.

Conclusion: We report that extreme hypercholesterolemia in cholestasis may actually be a rare cause of pseudohyponatremia. This underscores the need to carry out serum sodium evaluation with direct potentiometry when extreme hypercholesterolemia is present, and how important it is to achieve a differential diagnosis between pseudohyponatremia and hyponatremia prior to starting treatment, especially in the pediatric setting.

Introduction

Hyponatremia, defined as serum sodium concentration <135 mEq/L, is a common electrolyte disorder in children which affects between 15 and 30% of hospitalized pediatric and adult subjects [1-3].

On the basis of the underlying etiology, classification of hyponatremia may be:

1 Hypotonic hyponatremia; this is connected to reduced serum osmolality (<275 mmol/l) in the presence of increased water retention involving heart failure, nephrotic syndrome, renal failure, etc.

2 Hypertonic hyponatremia; serum osmolality increases to >295 mmol/l when high osmolar solutes including glucose, mannitol, intravenous radiocontrast agents, etc. are present.

3 Isotonic hyponatremia; pseudohyponatremia should be taken into consideration.

Pseudohyponatremia is characterized by a spurious, low serum sodium concentration against a background of normal serum osmolality [4,5]. In cases of pseudohyponatremia, hyponatremia is related to the presence of hypertriglyceridemia or hyperproteinemia and, in rare cases, to hypercholesterolemia. The above-mentioned conditions are connected to a decrease in both plasma water fraction and in measured sodium concentration [6].

Direct and indirect ion selective electrodes (ISEs) are two methods used in order to measure the electrolytes such as sodium. In clinical practice, sodium concentration in plasma water, measured by direct ISE, is important to consider as it is responsible of water movements between the liquid compartments. Knowing the difference between the two methods is important. The increase and the decrease in plasma water volume are the conditions that distort the results of the indirect ISE because, this method, after a dilution step, does not take into account the real percentage of plasma water of the patient in the determination of the concentrations. In direct ISE, the sample is not diluted, and the results are correct even if the volume of plasma water is modified as occurs with hyperlipemic and hyperproteinemic samples.

Hence, false low sodium levels may be observed when the indirect method is used. In these cases, using the direct method may prevent this issue [7]. Differentiating pseudohyponatremia from true hyponatremia is crucial since a misunderstanding regarding the discrepancy between the measured and physiological sodium concentrations may result in grave errors in managing the pediatric patient. Aggressive treatment of misdiagnosed pseudohyponatremia may result in greater morbidity and mortality.

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Case presentation

We admitted a 20-month-old girl to our institution for further investigation after she had been diagnosed with abdominal neuroblastoma and treated with one cycle of chemotherapy in her home country of Albania. The child had a history of jaundice, extremely dark urine and pale stools, and at presentation was severely jaundiced. However, there were no reports of pruritus, nausea, vomiting, bruising or bleeding, and at admission she had no fever, her pulse rate was 120 bpm, respiratory rate was 28 bpm and her blood pressure was 100/80 mmHg. Upon examination we observed jaundice, icteric sclerae, and a tender and distended abdomen, although neither hepatomegaly nor edema in the lower extremities was seen.

A CT scan confirmed the solid abdominal mass that had been seen at abdominal ultrasound as a median retroperitoneal solid mass (80×60×40 mm) incorporating the celiac trunk, superior mesenteric artery, and kidney vessels. The mass had found its way into the hepatic hilum resulting in extrinsic compression of the common bile duct, gallbladder hydrops, ectasia of the intrahepatic biliary tract and dislocation of the portal vein. The biopsy that had been carried out in Albania was reviewed and we confirmed the diagnosis of undifferentiated MYCN-amplified neuroblastoma.

Testing at admission revealed the following: blood hemoglobin concentration 10.8 g/dL, white blood cells 11.10x10.e3/µl, neutrophils 9.39x10.e3/µl, lactate dehydrogenase 834 U/L, and activated protein C 1.76 mg/dL; a severe cholestatic picture with elevated total and direct bilirubin levels (16.7 and 15.24 mg/dL, respectively), aspartate aminotransferase (AST, 191 U/L), gamma-glutamyl transferase (GGT, 1142 U/L), alkaline aminotransferase (ALT, 332 U/L); urinary catecholamine levels were pathologic (homovanillic acid and vanillymandelic acid 216 and 43 µmol/mmol creat, respectively).

Based on the European protocol, we began chemotherapy with Carboplatin and Etoposide, and at the same time molecular tests were run.

Following two cycles of chemotherapy, 123-I-meta-iodo-benzyl-guanidine (mIBG) scintigraphy was carried out which revealed focal enhancement at the tumor site that was compatible with the histological diagnosis. MYCN amplification was confirmed by molecular testing, thus, the tumor was classified as high-risk and the SIOPEN protocol NB-AR-01 was adopted.

Laboratory tests, performed after 2 cycles of chemotherapy, showed the following serum levels; sodium 126 mEq/l, potassium 4.2 mEq/l, chloride 91 mEq/l, and serum osmolality 279 mOsm/kg, while total serum cholesterol was 870 mg/dL (normal range: 80-180 mg/dL) and triglycerides were 168 mg/dL (normal range: 64 to 122 mg/dL). Supplementation with omega-3 fatty acids was started to reduce triglyceride levels.

We first believed the child had hypovolemic hyponatremia and therefore she was administered intravenous normal saline. However, since a repeat sodium evaluation showed no changes, intravenous sodium supplementation as high as 10 mEq/kg over 24 hours was given. No improvement in her sodium level was observed, hence pseudohyponatremia was taken into consideration.

Measuring serum osmolality (279 mOsm/kg; normal range: 275-290 mOsm/kg) and serum sodium (135 mmol/L) by direct potentiometric measurement, performed on blood gas analyzer, allowed us to confirm pseudohyponatremia. No lipoprotein electrophoresis was carried out.

Either direct or indirect ion-selective electrode methods may be adopted to evaluate sodium concentration. Indirect ISE involves diluting the sample prior to analysis and measuring the electrolyte concentration in the serum based on the assumption that plasma is made up of 93% water. In the presence of hyperlipidemia and hypercholesterolemia, the plasma water fraction decreases, and thus indirect ISE testing will result in falsely low sodium levels. On the other hand, no dilution is needed in direct ISE testing, and so sodium is measured directly regardless of plasma water fraction, and therefore any changes in plasma percentage concentration will not affect the results. Repeat blood tests utilizing both the direct and indirect methods were carried out at the same time to evaluate electrolyte levels, and the results are shown in Table 1.

Discussion

The low sodium concentration we observed in this patient is considered a sign of pseudohyponatremia attributable to

Table 1. Comparison between direct and indirect methods

	Indirect ion-selective electrode method			Blood gas analyzer (direct method)		
	Supplementation of sodium (mEq/kg in 24h (i.v.)			Supplementation of sodium (mEq/kg in 24h (i.v.)		
	10mEq/Kg	7mEq/Kg	6mEq/Kg	10mEq/Kg	7mEq/Kg	6mEq/Kg
	Day1	Day2	Day3	Day1	Day2	Day3
Sodium mEq/l	126	126	129	135	134	138
Potassium mEq/l	4.1	4	3.9	4.5	4.2	3.9
Chloride mEq/l	94	92	98	101	101	105
Bilirubin (total) mg/dl	17	15	14	16	14	14
Bilirubin (direct) mg/dl	15	13	13	nd	nd	nd
Plasma Osmolality mOsm/Kg	257	253	nd	279	273	279
Triglycerides mg/dl	146	145	223	nd	nd	nd
Cholesterol (total) mg/dl	791	702	635	nd	nd	nd

hypercholesterolemia. There are two ways to measure electrolytes in plasma, both of which use an ISE. The first method measures electrolyte activity in plasma with no dilution. It involves direct potentiometry and is used in point-of-care blood gas analyzers. The second method is indirect ISE, which is used in routine chemistry analyses in central laboratories, and it includes a pre-analysis serum or plasma dilution step [8,9].

Indirect ion-selective electrode potentiometry, which is used in our laboratory, is among the methods of electrolyte analysis that are based on the assumption that plasma water content does not change and that 93% of plasma is water. In the presence of hyperlipidemia or hyperproteinemia, the plasma water fraction decreases, and thus indirect ISE will show falsely low sodium levels because the decreased plasma water fraction is not taken into consideration.

The direct method measures sodium concentration directly using undiluted samples, regardless of serum plasma concentration and consequently the result is not affected by changes in plasma percentage concentration.

The exact reason hypercholesterolemia occurs with cholestasis is still not known, however there may be several contributing factors. Unesterified cholesterol, that is mainly transported as lipoprotein X (LpX), is the predominant cause of hypercholesterolemia. Hepatic lipase, lipoprotein lipase and cholesterol acyltransferase (LCAT) deficiencies may be observed in cholestasis. While LpX does not inhibit hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase (a rate-limiting enzyme in cholesterol synthesis), it does not interfere with the ability of LDL to lower HMG-CoA reductase activity either [10,11].

Indeed, cholestatic liver disease shows both enhanced HMG-CoA reductase activity (suggesting that cholesterol synthesis has been stimulated) and depressed cyp7 activity (suggesting that the conversion of cholesterol into bile is not so efficient) [12].

In cholestasis, bile lipoprotein flows into the plasma pool and binds to albumin, thus forming Lp-X. Changes in 11b-hydroxysteroid dehydrogenase (which itself contributes to electrolyte abnormalities that are similar to those observed in a mineralocorticoid excess state) are also linked to cholestasis.

Low plasma sodium levels in the context of normal osmolarity is defined as pseudohyponatremia, and it is a measurement artifact that is observed in case of an increase in the non-aqueous part of plasma.To date, only 13 cases of hypercholesterolemia-associated pseudohyponatremia have been reported, and all but one involved adults, the lone exception being a 14-year- old child, Table 2 [13-25].

All the reported patients had cholestasis and can be subdivided as follows; 4 had graft-versus-host disease following bone marrow transplantation, 3 had primary biliary cirrhosis, 2 cases were drug-induced, 2 had obstructive jaundice, 1 had hepatitis C, and 1 had pancreatic cancer. Among these cases, the lowest reported total serum cholesterol level that eventually led to pseudohyponatremia was 977 mg/dL (associated serum sodium: 129 mmol/L), while the highest value was 4091 mg/dL (associated serum sodium:101 mmol/L).

We may assume that hypercholesterolemia, with or without hypertriglyceridemia, can cause pseudohyponatremia. Our reliance on electrolytes from samples obtained from indirect ISE analysis as the sole determinant of sodium concentrations predisposed our team to treat electrolyte alterations that were, in reality, factitious. Once we compared the results obtained from direct ISE analysis, we were able to classify our results as solely a laboratory abnormality.

Our experience with this patient highlights the need to take pseudohyponatremia into consideration prior to starting treatment for suspected hyponatremia which could result in complications, especially in the pediatric setting. All hyponatremic patients with cholestasis should undergo serum osmolality evaluation, and in case of normal serum osmolality, direct potentiometry should be adopted to measure sodium levels.

Therefore, it is vital to be aware of the laboratory practices that are standard at one's own institution to properly interpret results. In such patients, we urge clinicians to compare results measured in indirect ISE

Table 2. Literature review of cases of pseudohyponatremia associated with hypercholesterolemia

Age, sex	Underlying diagnosis	Sodium Indirect method	Sodium Direct method	Total cholesterol
1, F	neuroblastoma	126 mEq/l	135 mEq/l	791 mg/dl
14, M	Acute myeloid leukemia	123 mmol/l	nd	1,667 mg/dl
27, M	Primary biliary cirrhosis	116 mmol/l	132 mmol/l	47 mmol/l 1,830 mg/dl
29, F	Obstructive liver disease	116 mmol/l	nd	72 mmol/l 2,815 mg/dl
36, M	Quetiapine-associated cholestasis	119 mmol/l	nd	219 mmol/l 1,691 mg/dl
37, M	Chronic myelogenous leukemia	129 mmol/l	135 mmol/l	25 mmol/l 977 mg/dl
40, M	Lymphoplasmacytic sclerosing cholangitis	121 mEq/l	138 mEq/l	2,109 mg/dl
41, F	Acute Hepatitis C	120 mmol/l	nd	2,621 mg/dl
43, F	Primary biliary cirrhosis	121 mmol/l	141 mmol/l	2,415 mg/dl
55, F	Acute lymphoblastic leukemia	101 mmol/l	nd	4,091 mg/dl
61, F	Pancreatic cancer	108 mmol/l	nd	1,713 mg/dl
62, F	Primary biliary cirrhosis	115 mmol/l	134 mmol/l	78 mmol/l 3,011 mg/dl
64, F	Acute myelogenous leukemia	124 mmol/l	135 mmol/l	47 mmol/l 1,836 mg/dl
69, M	Drug induced cholestatic hepatitis	119 mmol/l	132 mmol/l	1,340 mg/dl

with results obtained in direct ISE using blood gas analyzers. In our opinion, it is reasonable to simply observe pseudhyponatremia since the patient actually has normal serum sodium while working to correct the underlying causes of high triglycerides and/or high cholesterol.

Conclusion

Careful work-up should be performed to distinguish pseudohyponatremia from hyponatremia in pediatric patients presenting hypercholesterolemia, hypertriglyceridemia, or hyperproteinemia in order to prevent mismanagement that could eventually result in increased morbidity and mortality.

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