Pseudohyponatremia Associated with Severe Hypertriglyceridemia
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Abstract
The determination of serum electrolyte concentrations is a fundamental aspect of clinical laboratory testing, often accomplished through potentiometric methodologies ion-selective electrodes (ISE). Pseudohyponatremia, characterized by falsely low serum sodium levels amidst normal osmolality, poses diagnostic challenges, particularly in cases of extreme hypertriglyceridemia and hyperproteinemia. Here, we present a case of a 30-year-old woman with Congenital generalized lipodystrophy, manifesting pseudohyponatremia secondary to profound hypertriglyceridemia. Despite initial suspicion of hypovolemic hyponatremia, intravenous saline failed to rectify the sodium levels, prompting further investigation. Serum lipid profile analysis revealed markedly elevated triglyceride levels, implicating pseudohyponatremia due to lipoproteinemia. Diagnosis was confirmed through serum osmolality measurements and direct sodium analysis. Subsequent plasmapheresis sessions effectively reduced triglyceride levels and normalized serum sodium concentrations. Analytical interferences, particularly lipemia, underscore the importance of vigilant pre-analytic assessment and appropriate method selection. Mitigation strategies, including direct ISE methodologies and lipid removal techniques, are discussed in light of their implications for accurate sodium measurement. This case underscores the necessity of considering pseudohyponatremia in hyperlipidemic patients, advocating for comprehensive lipid profile assessment in hyponatremia workups. Additionally, it highlights the need for laboratory vigilance in detecting and managing analytical interferences to ensure accurate clinical interpretations and prevent potential complications associated with erroneous electrolyte corrections.

Keywords: Pseudohyponatremia; Lipemia interference; ion-selective electrodes.

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Introduction
The determination of serum/plasma electrolyte concentrations are among the most commonly performed tests in the clinical laboratory [1]. These measurements are nearly ubiquitously accomplished using potentiometric methodologies which rely on ion selective electrodes (ISE). Most high-throughput chemistry analyzers utilize an indirect ISE method which requires sample dilution; typically, 1:20 to 1:34 [3]. Pseudohyponatremia is defined as a spuriously low serum sodium concentration in the setting of normal serum osmolality. It is important to distinguish pseudohyponatremia from true hyponatremia lest injudicious treatment results in increased morbidity and mortality [4]. Pseudohyponatremia is usually seen in cases with extreme hypertriglyceridemia and hyperproteinemia [1] when serum sodium is measured using routine laboratory testing methods i.e. indirect potentiometry/flame photometry [1]. We present a case of a woman with Congenital generalized lipodystrophy who presented with pseudohyponatremia secondary to extreme hypertriglyceridemia.

Case Report
A 30-year-old woman was admitted for evaluation and treatment after routine laboratory testing revealed low serum sodium (119 mmol/L; normal range: 135 – 145 mmol/L). She was followed in endocrinology department for Congenital generalized lipodystrophy under lipid-lowering therapy. She has a history of type 1 diabetes treated with insulin since 2010 and multiples episodes of acute pancreatitis, the last one was in 2021.

Review of past laboratory testing showed normal serum sodium levels for the last 3 years; with slight reductions noted 3 months (133 mmol/L) and 1 month (130 mmol/L) prior to presentation. She had not been drinking excessive amounts of water, urine output was normal and she had no mental status changes. On physical examination her vital signs were unremarkable with a Glasgow Coma Scale (GCS) score of 15/15, a

blood pressure (BP) of 125/60 mmHg, a heart rate of 78 beats per minute (bpm), a respiratory rate of 18/min, and an oxygen saturation of 98%.

Biochemical tests were performed using the Abbott ARCHITECT c16000 system. Her laboratory results (Table 1) revealed hyponatremia, high level of total cholesterol (14 g/L; normal range: 0–1.99 g/L) and very high triglycerides levels (121 g/L; normal range: 0.1–1.49 g/L). She also had hypokalemia (3.0 mmol/L; range 3.6–5.0 mmol/L) and hypochloremia (89 mmol/L; range 98–101 mmol/L).

She was initially thought to have hypovolemic hyponatremia and was given intravenous normal saline, however a repeat sodium level was unchanged (119 mmol/L) after five hours. Review of her medical records revealed a much lower triglycerides level of 20 g/L two years ago.

The marked increase in serum triglycerides suggested pseudohyponatremia secondary to lipoproteinemia. The diagnosis of pseudohyponatremia was confirmed by measurement of serum osmolality (296 mOsm/kg H2O; normal range: 270–300 mOsm/kg H2O) and Serum Na measured using a blood gas analyzer was 139 mmol/L and thus the diagnosis of pseudohyponatremia was confirmed.

Her serum sodium by indirect potentiometry ranged from 120 – 125 mmol/L for the next two days after one session of plasmapheresis and she was discharged without any additional lipid-lowering drugs.

She underwent about 10 sessions of plasmapheresis over a four-month period before her lipid panel was rechecked. It showed improvement with preprocedure triglycerides of 50 mg/dL that decreased further to 31 mg/dL after the 10th session of plasmapheresis.

Her serum sodium level measured by indirect potentiometry normalized (139 mmol/L) with reduction in total serum cholesterol levels; as did serum potassium (3.36 mmol/L) and chloride (104 mmol/L) levels (Table 1).

<table>
<thead>
<tr>
<th>Chemistry, serum</th>
<th>Admission</th>
<th>After plasmapheresis</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium, mmol/l</td>
<td>119</td>
<td>145</td>
<td>136–145</td>
</tr>
<tr>
<td>Potassium, mmol/l</td>
<td>3</td>
<td>3.36</td>
<td>3.5–5.1</td>
</tr>
<tr>
<td>Chloride, mmol/l</td>
<td>89.47</td>
<td>104</td>
<td>98–107</td>
</tr>
<tr>
<td>Creatinine, mg/l</td>
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<td>4.05</td>
<td>6–12</td>
</tr>
<tr>
<td>Glucose, g/l</td>
<td>1</td>
<td>1.5</td>
<td>0.7–0.99</td>
</tr>
<tr>
<td>Calcium, mg/l</td>
<td>96.47</td>
<td>70.73</td>
<td>84–102</td>
</tr>
<tr>
<td>Total cholesterol g/l</td>
<td>14.081</td>
<td>4.42</td>
<td>0–1.99</td>
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<tr>
<td>LDL g/l</td>
<td>6.36</td>
<td>0.44</td>
<td>1–1.59</td>
</tr>
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<td>HDL g/l</td>
<td>0.229</td>
<td>0.14</td>
<td>0.4–0.6</td>
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<tr>
<td>Triglycerides g/l</td>
<td>121.685</td>
<td>31.14</td>
<td>0–1.49</td>
</tr>
</tbody>
</table>

Table 1: Biochemical tests results

Figure 1: Turbid appearance of the serum
Human serum is composed of 93% water and 7% non-aqueous components by volume [3]. All serum electrolytes including sodium are dissolved in the aqueous component. Increased serum lipid and protein components in blood result in a relative decrease in the water content of plasma but the proportions of serum electrolytes in the aqueous component remain unchanged. Serum sodium concentration is normally measured in milliequivalents per liter. In conditions like hyperlipidemia and hyperproteinaemia, there is a relative decrease in plasma water content as it is replaced by serum lipids or proteins [2]. In such cases, the measurement of serum sodium concentration is significantly reduced in the water component.

Flame photometry (the oldest method of measuring serum sodium) and indirect potentiometry (used in most laboratories for routine serum sodium measurements) both involve sample dilution and give similar results [4, 5]. Diluting the plasma and then correcting for the dilution gives misleading results because it does not account for the already decreased amount of plasma water and sodium as a result of the excess lipids [9]. Direct potentiometry measures the concentration of sodium in the plasma water directly with no dilution, therefore giving accurate results [6, 7]. Since potassium and chloride are also measured by indirect potentiometry, they may also be falsely lowered secondary to extreme hypertriglyceridemia.

Interferences in the clinical laboratory may lead physicians to misinterpret results for some biological analytes. The most common analytical interferences in the clinical laboratory include hemolysis, icterus and lipemia. Lipemia is defined as turbidity in a sample caused by the accumulation of lipoproteins, mainly very-low density lipoproteins (VLDL) and chylomicrons [8]. Several methods are available for the detection of lipemic samples, including the lipemic index, or triglyceride quantification in serum or plasma samples, or mean corpuscular hemoglobin (MCHC) concentration in blood samples [10].

According to the European Directive 98/79/CE, it is the responsibility of clinical laboratories to monitor the presence of interfering substances that may affect the measurement of an analyte [11].

Lipoproteins exhibit a high heterogeneity in size and not all contribute equally to turbidity. Chylomicrons are the largest lipoprotein particles (70-1000 nm) and cause the most turbidity in the sample. Based on size, there are three types of very low-density lipoproteins (VLDL): small (27–35 nm); medium (35–60 nm); and large (60–200 nm). Only large and medium VLDL cause turbidity. High-density lipoproteins (HDL) (6–12.5 nm) and low-density lipoproteins (LDL) (20–26 nm) do not cause turbidity [12, 13].

The most common pre-analytic cause of lipemia is short fasting time. However, recent studies demonstrate that non-fasting status does not induce significant changes in lipoprotein concentrations. Thus, fasting is indicated when non-fasting triglycerides are >400 mg/dL (4.56 mmol/L) [14]. Severe lipemia causing significant interference may occur in primary (familial chylomicronemia syndrome) or secondary (diabetes mellitus, insulin resistance, alcoholism, human immunodeficiency virus infection, kidney disease, among other) hypertriglyceridaemias [14]. Parenteral nutrition and diluents for poorly water-soluble medications containing lipidic emulsions may also cause lipemia [14].

Mitigation strategies described by various authors have been discussed. A common strategy for circumventing the electrolyte exclusion effect is to perform electrolyte analysis using an alternate methodology such as a blood gas analyzer or point-of-care device. These analyzers employ direct ISE methodologies, where electrolyte concentration is determined in undiluted whole blood [15]. Thus, the determination of electrolyte concentration is performed in a manner that is not dependent on the aqueous to solid ratio of the sample and is therefore not susceptible to the electrolyte exclusion effect. Despite the benefits of direct ISE, indirect ISE remains the most commonly used methodology for routine sodium measurement as it is more compatible with high-throughput chemistry analyzers. Therefore, serum and plasma sodium measurements in the central laboratory remain susceptible to error, and it is important to identify samples at risk for pseudohyponatremia so that direct ISE can be used as an alternative method to overcome the electrolyte exclusion effect [15].

In case instrument for measurement of dISE or Osm is not available, formulas for calculation of corrected sodium by free serum water or for protein-corrected-sodium may be used. These formulas, however, have not been validated on large number of samples and for their robustness [16]. Another option is removal of lipids from a lipemic sample. Several techniques are available to eliminate lipids from samples, including ultracentrifugation, high-speed centrifugation, lipid extraction using polar solvents, sample dilution, and serum blank preparation. But it requires extra reagents or instrumentation. Use of all these strategies would ultimately demand additional cost, time, and expertise [16].

**CONCLUSION**

Assessing serum sodium levels is a routine procedure in hospital labs, yet reported results may not always accurately represent actual values. Pseudohyponatremia can occur due to overcorrection, potentially leading to severe complications. Lipemia, a common source of analytical errors, can affect
biochemical test interpretation. Establishing thresholds for lipemia indices to validate or exclude results is the lab’s responsibility. This underscores the importance of considering alternative explanations when hyponatremia is detected, as lipid panels aren’t always included in the standard workup.

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