Pseudohyperkalemia and Pseudohyponatremia in Two Children with T-Cell Acute Lymphoblastic Leukemia

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Pseudohyperkalemia and pseudohyponatremia are phenomena in which hematologic disorders with high cell counts result in factitious electrolyte measurements that can result in inappropriate treatment. We describe 2 children with leukemia presenting with both disturbances to highlight the importance of correlating electrolyte results from plasma with those from whole blood before intervening. *(J Pediatr 2021;232:294-8).*

Electrolyte abnormalities are frequently encountered in critically ill patients and can be a source of alarm for clinicians as some can be life threatening. In patients with underlying hematologic malignancy, electrolyte disturbances are a frequent cause for intensive care unit admission. For instance, potassium levels and uric acid levels can be dangerously elevated in patients with tumor lysis syndrome (TLS) undergoing initial treatment for newly diagnosed leukemias and lymphomas, requiring vigilant monitoring and aggressive treatment. Two commonly encountered metabolic derangements in the pediatric intensive care unit (PICU) are those of potassium and sodium, both of which can be life threatening.

There are instances when electrolytes may be reported as abnormal although in vivo they are within a normal physiologic range. Electrolytes may be measured in serum, plasma, or whole blood. Serum samples are collected in tubes without anticoagulant. After clot formation, the sample is centrifuged and the yellow acellular supernatant is retrieved for subsequent analysis. On the other hand, plasma is the acellular fluid that is collected after tubes with anticoagulant are centrifuged to separate the cellular from noncellular components. Pseudohyperkalemia is a phenomenon where the measured serum or plasma potassium is greater than the patient's true in vivo potassium. This has been extensively reported in patients with leukocytosis and thrombocytosis.[1-8] Spurious in vitro results can also be seen with sodium levels in a variety of clinical scenarios. In patients with hyperproteinemia or hypertriglyceridemia, although the patient's osmolarity is normal, sodium levels reported from plasma or serum samples diluted for indirect ion selective electrode (ISE) analysis may be falsely depressed, a phenomenon known as pseudohyponatremia.[9] Clinicians may be quick to react to these results as hyperkalemia can cause hyperexcitability of the cardiac tissue and may lead to life-threatening cardiac arrythmias, and hyponatremia can cause serious neurologic manifestations such as altered mental status, seizures, and coma. In children with underlying hematologic processes predisposed to electrolyte derangements, a review of the literature reveals only 1 case report of pseudohyperkalemia and concomitant pseudohyponatremia. Grzych et al reported a child with newly diagnosed acute lymphoblastic leukemia (ALL) who displayed pseudohyperkalemia and pseudohyponatremia in the setting of hyperleukocytosis.[10]

We describe 2 pediatric patients admitted to our hospital with newly diagnosed T-cell ALL who presented with both pseudohyperkalemia and pseudohyponatremia. These cases highlight the importance of corroborating electrolyte results obtained from plasma separated from whole blood to results obtained from whole blood assays when evaluating patients with new hematologic malignancy and aberrant chemistry results.

ALL	Acute lymphoblastic leukemia
BMP	Basic metabolic panel
ECG	Electrocardiogram
HD	Hospital day
ISE	Ion selective electrode
PICU	Pediatric intensive care unit
RBC	Red blood cell
TLS	Tumor lysis syndrome
WBC	White blood cell

Case 1

A previously healthy 6-year-old boy was referred to our emergency department with 10 days of fever, anorexia, and sore throat with laboratory findings from an outside hospital that suggested leukemia. These results were significant for a white blood cell (WBC) count of 341 $\times$ 10^9/L with 58% lymphoblasts and a separated plasma potassium measured by indirect ISE (resulting from a basic metabolic panel [BMP]) of 5.8 mmol/L, which was reported as slightly hemolyzed. The initial platelet sample was clumped, and a repeat platelet count was 62 $\times$ 10^9/L. On presentation he was nontoxic appearing with tachycardia, 3+ submandibular and anterior cervical lymph nodes, and tender hepatosplenomegaly.

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Repeat laboratory results from our emergency department showed separated plasma electrolytes significant for a potassium level of >10 mmol/L (sample described as hemolyzed) and a sodium level of 127 mmol/L. Because of concern for TLS and hyperkalemia, a 12-lead electrocardiogram (ECG) was obtained, which showed sinus tachycardia with normal QRS interval and morphology, P wave morphology, PR interval, and T-wave amplitude.

The child was then admitted to the PICU where treatment was initiated with calcium gluconate, albuterol, and furosemide and repeat electrolytes by 2 different methods were sent to the laboratory for analysis. A blood gas sample (direct ISE) tested on whole blood resulted in 10 minutes with a potassium of 2.8 mmol/L and sodium of 133 mmol/L. A separated plasma sample measured by indirect ISE resulted 75 minutes later with a potassium of 8.6 mmol/L (not hemolyzed) and sodium 131 mmol/L. Repeat samples corroborated these results. Based on this, treatment for hyperkalemia was discontinued and no further immediate interventions were made. Of note, the total protein, glucose, and creatinine levels were normal at 7.3 g/dL (73 g/L), 83 mg/dL (4.61 mmol/L), and 0.51 mg/dL (45.09 μmol/L), respectively. Triglycerides were not checked until 1 month later but were elevated at 243 mg/dL (2.74 mmol/L) and thought to be secondary to chemotherapy. Protection against the potential for TLS was initiated with rasburicase and intravenous fluids while awaiting flow cytometry which confirmed T-cell ALL. Chemotherapy was initiated on hospital day (HD) 2 and by HD 7, the reported results from separated plasma potassium, sodium, and WBCs normalized. The blast count normalized on HD 22.

Case 2

A previously healthy 5-month-old boy presented to an outside hospital with 2 days of fever, fussiness, poor feeding, and subsequent development of melena in the setting of positive viral sick contacts. On examination, the child was nontoxic appearing with tachycardia, palpable hepatosplenomegaly, and diffuse petechial rash. Abdominal radiograph confirmed hepatosplenomegaly, and WBCs were elevated at 600×10^9/L. The child was transferred to the PICU for treatment of presumed hematologic malignancy. A repeat complete blood count was significant for a WBC count of 521×10^9/L and platelets of 48×10^9/L. A baseline separated plasma sample measured by indirect ISE was significant for a potassium level of >10 mmol/L (not hemolyzed) and sodium level of 131 mmol/L. Given concern for hyperkalemia, a 12-lead ECG was obtained which showed normal sinus rhythm with normal QRS interval and morphology, P wave morphology, PR interval, and T-wave amplitude. Nonetheless, the child then received calcium gluconate and sodium bicarbonate while a stat blood sample was sent to the laboratory for electrolytes to be analyzed in separated plasma by indirect ISE. Results were significant for a potassium of 6.6 mmol/L (not hemolyzed) and sodium 135 mmol/L. Given continued concern for hyperkalemia, the child received insulin and 10% dextrose bolus. Repeat electrolytes by 2 different methods, direct and indirect ISE, were sent. The separated plasma potassium and sodium levels measured by indirect ISE were 4.8 mmol/L and 140 mmol/L, respectively. However, the potassium measured via whole blood gas analysis (direct ISE) returned as 2.0 mmol/L (quantity not sufficient to verify), raising concern that the patient's initial potassium was falsely elevated and sodium perhaps falsely depressed. Given these results, a diagnosis of pseudohyperkalemia was made and treatment for hyperkalemia was discontinued. Of note, creatinine was elevated at 1.15 mg/dL (101.68 μmol/L) on admission and normalized within 2 hours following administration of fluids at 1.5 times the maintenance rate. Total protein and glucose levels were normal at 6.3 g/dL (63 g/L) and 79 mg/dL (4.38 mmol/L), respectively. Triglycerides were checked 3 months later and were normal at 74 mg/dL (0.84 mmol/L). Flow cytometry confirmed diagnosis of T-cell ALL. Chemotherapy was initiated on HD 1, and by HD 3 the reported results from separated plasma potassium normalized. Separated plasma sodium, WBC, and blast count normalized on HD 1, HD 8, and HD 22, respectively.

Discussion

Pseudohyperkalemia with concomitant pseudohyponatremia may be more prevalent in the clinical setting than what has been reported in the literature. Clinically, it poses a unique challenge for clinicians because patients with newly diagnosed leukemia and lymphoma are predisposed to electrolyte disturbances, especially at initial presentation. For clinicians it is important to be aware of the different electrolyte samples that can be sent and to have a heightened awareness of how these samples may be predisposed to factitious electrolyte results. This is particularly important in patients with underlying hematologic malignancy where clinicians anticipate hyperkalemia as part of TLS and may be prone to act on such values with aggressive treatment. Furthermore, clinicians may be unaware of the underlying mechanisms that may cause factitious electrolyte results and the different biochemical laboratory techniques that may be utilized to investigate the results. In this setting, a normal ECG should be very reassuring and give pause when paired with a high potassium before rushing to treat. As shown in our cases, both patients were treated for factitious electrolyte disturbances highlighting the importance of properly diagnosing these 2 phenomena in clinical practice.

Falsely elevated levels of potassium were initially described by Hartman et al in patients with thrombocytosis.[11] There have been several case reports of adults with essential thrombocytosis who presented with pseudohyperkalemia due to release of potassium during platelet clumping post-collection.[5,7,8] More frequently documented is pseudohyperkalemia attributed to fragility of leukemic cells that lyse upon collection in adult patients with acute myeloid leukemia, chronic myelogenous leukemia, and chronic lymphocytic leukemia.[2-6] There are several proposed mechanisms for

this phenomenon. Iolascon et al suggested that individuals with 'leakier' cell membranes are predisposed to developing pseudohyperkalemia because of enhanced post-collection cell lysis.[12] In addition, other potential causes of pseudohyperkalemia can occur at the time of blood collection because of repeated fist clenching,[13] traumatic venipuncture using a small gauge needle,[14] and hemolysis from mechanical trauma during venipuncture causing the release of potassium from red cells.[4] Falsely elevated potassium levels have also been attributed to lysis of cells during pneumatic tube transfer of samples to the laboratory and, hence, can be a major contributor to falsely elevated potassium levels.[15,16]

Although pseudohyperkalemia and pseudohyponatremia have been individually reported, they have rarely been reported together in patients with underlying hematologic malignancy.[10] Several hypotheses may explain this unique presentation. In red blood cells, Oh et al suggested this phenomenon may occur when there is a red cell membrane defect where "a change in serum sodium is reciprocal to a change in serum potassium."[17] In WBCs, it has been proposed that heparinized microtainers may induce lysis of WBCs in plasma which raises the extracellular ATP concentration, thereby causing an influx of sodium into lymphocytes.[18] Of note, though our patients did not experience any other significant disturbances in other biochemical measures, hyperleukocytosis may also cause other laboratory abnormalities either because of interference with laboratory assays or the presence of blasts.[19]

To develop a clinical algorithm to assess for factitious electrolyte derangements, one must first understand why there would be a discrepancy between different biochemical laboratory analysis techniques. Electrolytes may be measured in either serum, plasma, or whole blood. In separated serum samples obtained from patients with extreme thrombocytosis, potassium may be factitiously elevated when potassium is released by platelets during clotting and centrifugation process. Similarly, in separated plasma samples, sample collection, transport, and centrifugation may cause fragile cells to lyse contributing to pseudohyperkalemia. The bedside clinician must be aware that a reported hemolyzed specimen would only refer to lysed red blood cells (RBCs) and not lysed WBCs. Laboratory staff determine whether or not a specimen is hemolyzed by visually analyzing the color of the plasma, which becomes pink tinged from hemoglobin released when RBCs lyse. Because the vast majority of samples sent to the laboratory have an RBC count that is 1000-fold greater than the WBC count, lysis of WBCs normally has an insignificant contribution to release of potassium in plasma. However, in a patient with hyperleukocytosis, massive lysis of WBCs will have a significant effect on potassium levels, which would not be reported by the laboratory as "hemolysis."

On the other hand, sodium levels may be reported as factitiously low based on whether direct or indirect ISE analysis is used. Indirect ISE measures electrolytes from samples that have been diluted with a large volume of diluent. Total plasma is 93% water and 7% solids (lipids and protein). In hyperproteinemia or hyperlipidemia, the solid component of total plasma is increased causing "fewer sodium ions being presented to the electrode" for the same volume of plasma and leading to pseudohyponatremia.[20] Through a similar mechanism, the release of hemoglobin during RBC hemolysis may factitiously reduce sodium in samples measured by indirect ISE when samples are diluted for analysis.[17] In contrast, direct ISE, used in blood gas and point-of-care electrolyte analyzers, measures electrolytes from nondiluted whole-blood or plasma samples and, therefore, would not cause this phenomenon. Compared with circulating plasma, intracellular potassium is relatively high and intracellular sodium low; therefore, any cause of cell lysis tends to raise extracellular potassium and lower extracellular sodium.

Grzych et al propose an algorithm to validate hyperkalemia in patients with leukocytosis[21] and have suggested that serum samples sent in clot activator tubes may confer protection against measured electrolyte abnormalities because of leukocyte lysis when compared with plasma samples.[10] In patients with suspected hematologic malignancy and severe hyperleukocytosis, we present an alternative algorithm to manage both potassium and sodium disturbances (**Figure**). We recommend comparing electrolytes that are measured in separated plasma or serum samples using indirect ISE (commonly obtained from a BMP measuring sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, and glucose at most institutions) with electrolytes measured using a whole blood point of care blood gas analyzer (direct ISE) to minimize lysis that may occur with centrifugation and to diminish the effect of sample dilution. Our reliance on electrolytes from samples obtained from spun down plasma and indirect ISE analysis as the sole determinant of potassium and sodium concentrations in the setting of severe hyperleukocytosis predisposed our team to treat electrolyte disturbances that were, in reality, factitious. Once we compared the results obtained from separated plasma with results measured from whole blood via direct ISE analysis, we were able to classify our results as solely a laboratory abnormality. Furthermore, in these patients it may be prudent to avoid pneumatic tube transport of plasma electrolyte samples. We used the pneumatic tubing system available in our hospital to deliver the samples to the laboratory. Realizing that fragile leukemic cells are predisposed to lysis with sample vibration during pneumatic tube transport, it may have been prudent to hand carry our samples to the laboratory. Alternatively, if available, serum testing using serum separator tubes may help reduce factitious results.[22,23] While awaiting results, ECG and thorough neurologic examination should be conducted, and treatment delayed unless the patient is symptomatic or there are worrisome ECG findings. Finally, at our institution, electrolytes measured from a BMP are collected in anticoagulated tubes, centrifuged, and the plasma is then analyzed by indirect ISE. Other institutions may use serum samples as their standard for measurement. Therefore, it is vital to be aware of the laboratory practices that are

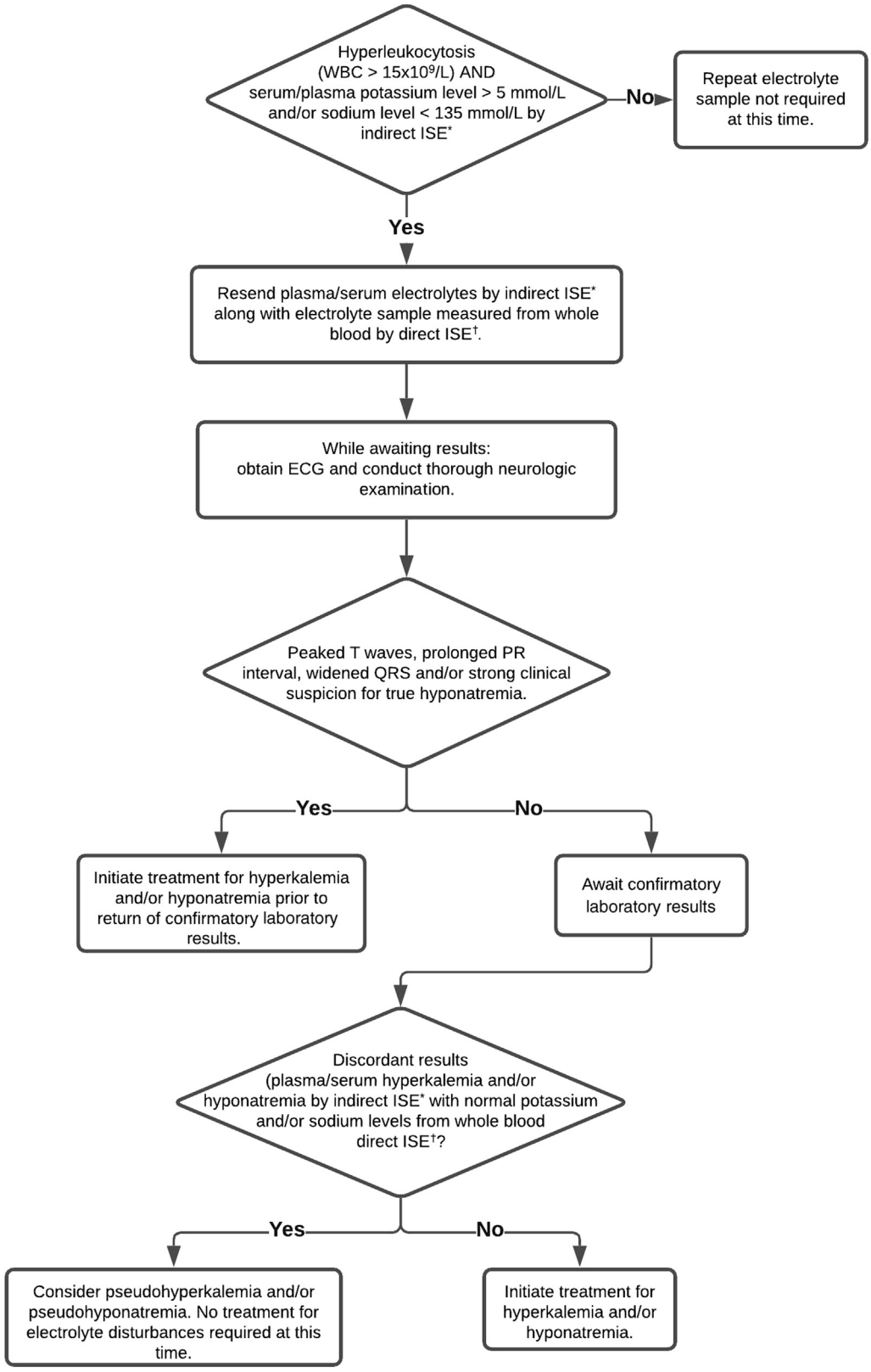

Figure. Proposed management algorithm for patients with suspected pseudohyperkalemia and/or pseudohyponatremia. *Indirect ISE is basic metabolic panel. †Direct ISE is whole blood point of care blood gas analyzer.

standard at one's own institution to properly interpret results. We believe that these 2 cases help the bedside clinician to understand the nuances of electrolyte imbalances that can be seen in hematologic malignancies because of blood sample collection technique, transport, and analysis. In such patients, we urge providers to compare results measured both in separated plasma via indirect ISE with results obtained in whole blood via direct ISE using blood gas analyzers. ■

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