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Case report

Immeasurable Levels of Serum Phosphate – An Unidentified Cause of Respiratory Failure in a Diabetic Patient

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A B S T R A C T

We report a case of immeasurable levels of serum phosphate in a patient with juvenile type Diabetes mellitus *and diabetic ketoacidosis who developed respiratory failure. A 27-year-old female with juvenile type insulin-dependent* Diabetes mellitus *was admitted because of suspected acute mediastinitis and respiratory failure, probably, among other responsible factors, caused and complicated by undetectable levels of serum phosphate. The serum phosphate concentration three days after aggressive treatment was only 0.2 mmol/L. Furthermore, a significant improvement in weakness and lethargy was observed. To the best of our knowledge, this is the first described case of immeasurable levels of serum phosphate. In patients with* Diabetes mellitus*, serum phosphate concentrations should be routinely checked in order to avoid additional complications.*

Key words: *phosphorus, phosphates, respiratory failure,* Diabetes mellitus*, severe hypophosphatemia*

Introduction

Phosphorus is the sixth most common element in the body after oxygen, hydrogen, carbon, nitrogen, and calcium and is the most abundant intracellular anion[1]. Severe hypophosphatemia (<1.0 mg/dL or 0.3 mmol/L) has significant morbidity and is associated with a very high mortality (30%)[2,3]. It can be the result of a decrease in phosphorus absorption from the gastrointestinal tract, an intracellular shift of phosphorus, or an increase in the renal excretion of phosphorus[4,5]. Hypophosphatemia is observed in approximately 28% of critically ill and 3% of hospitalized patients. The causes of hypophosphatemia in intensive care unit (ICU) can be subdivided into three categories: inadequate intake; redistribution of phosphate into cells; and loss of phosphate from the body[6].

Clinical consequences of hypophosphatemia are rhabdomyolysis; hypophosphatemic osteomalacia; hemolysis; leukocyte dysfunction; respiratory failure including impaired contractile properties of the diaphragm and refractory weaning from the ventilator; impaired myocardial performance; diabetic ketoacidosis and perturbed central nervous system[7,8].

Hypophosphatemia has been well documented in patients with severe trauma, induced hypothermia for brain-injured patients and head injury, drug- and nutrition-induced, in bulimic patient, in patients receiving specialized nutrition support, and in patients after major surgery and in particular after cardiac surgery[8–14]. Inorganic phosphate and serum albumin are two substances that act as non-volatile weak acids and have concentrations in plasma great enough so that changes in them can produce significant acid-base disturbances[15].

Hypophosphatemia has long been reported to be associated with sepsis and gram-negative infections and has been correlated with sepsis severity[16]. Shor et al.[16] found that 80.8% of the patients with sepsis with severe hypo-

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phosphatemia died, *vs.* 34.5% of the patients without severe hypophosphatemia. They also found that being in the severe hypophosphatemic group increased the risk of death by nearly 8-fold and their findings indicated that severe hypophosphatemia can serve as an independent mortality predictor in sepsis. Hoffman et al. found that sepsis was implicated as a contributing factor in 26% of patients with severe hypophosphatemia. They concluded that regular phosphate determination is recommended in ICU patients to facilitate early diagnosis of hypophosphatemia[3].

Hypophosphatemia and acute respiratory failure in a diabetic patient[17–19], as a cause of failed weaning[20], and as a reversible cause of refractory ventilatory failure[21] have been previously well documented. Several studies have suggested that diabetes is associated with impaired pulmonary function; however, previous studies have presented this relationship to be inconsistent[22].

Herein we present case of respiratory insufficiency associated with hypophosphatemia in a juvenile type *Diabetes mellitus*.

Case Report

A 27-year old female patient was transferred to our ICU because of respiratory insufficiency caused by suspected acute mediastinitis. The patient had a history of juvenile type *Diabetes mellitus*, and had been hospitalized in another hospital for 3 months previous because of sepsis caused by *Escherichia coli* in her urinary tract, poor nutritional status, diabetic gastroenteropathy, frequent vomiting and diarrhea. During cannulation of the right subclavian vein, an iatrogenic catheter-induced pneumothorax developed and chest drainage was performed. Three days later, CT findings revealed unilateral right-sided pleural effusion and anterior pneumomediastinum. Lung infiltration occurred and a diagnostic fiberoptic bronchoscopy and microbiologic analysis of endotracheal aspirates was performed. A bronchoalveolar lavage was also performed. Empirical antibiotic therapy was immediately administered with amoxicillin plus clavulanic acid and metronidazol and netromycin and the patient was transferred to our thoracic surgery ICU. On admission, the patient was confused, disorientated, barely mobile, edematous, pale, lethargic, and afebrile, with hyporeflexia and weakness of the skeletal muscle observed. Invasive measured blood pressure was 127/76 mm Hg. An electrocardiogram revealed tachycardia (126 beats/min). Arterial oxygen saturation measured by pulse oximetry was approximately 87–89%. Arterial blood gas results were pH 7.389; pCO_2 3.24 kPa; pO_2 7.23 kPa; SaO_2 89.1% and breath rate 30 breaths/min. Because of hypoxia caused by respiratory insufficiency, we applied oxygen therapy via face mask at 5 l/min, and SaO_2 was approximately 92%. Laboratory findings presented anaemia (RBC 2.72×10^{12}/L, haemoglobin concentration 8.1 g/dL, haematocrit 0.247 l/L); WBC 10.2×10^{9}/L; total serum protein content 47 g/L; blood glucose values up to 24 mmol/L refractory to insulin; and potassium 5.3 mmol/L. The central vein catheter, which had been placed in another hospital, was located beneath the skin. On admission, we have inserted a catheter into the internal jugular vein for measurement of central venous pressure (1 cm H_2O on admission) and infusions. A fiberoptic bronchoscopy and esophagoscopy with contrast were performed and spontaneous perforation of the oesophagus, as a possible cause of suspected mediastinitis was excluded. Although we have not proven respiratory infection, we continued prophylactic antibiotic therapy, which was already started in another hospital.

Initial laboratory values included a serum inorganic phosphate of 0.00 mmol/L (normal range 0.79–1.42 mmol/L). A repeat test (photometry with ammonium molybdate, Hitachi 912, Boehringer/Mannheim) revealed the same result. Serum sodium, urea, nitrogen, bilirubin and creatinine values were within a normal range. Volume resuscitation (3000 mL of saline) was initiated and four doses of packed red cell transfusion and analgesic therapy were administered. In addition, continuous IV infusion of insulin (8 i.u/h) and 0.06 mg (0.02 mmol/kg/h) of potassium phosphate salts (K_2PO_4, diluted in 250 mL of saline 0.9%) was administered. Neurologist was consulted and he found general muscle weakness caused by diabetic polineuropathy. However, on the third day after treatment was initiated, the serum inorganic phosphate concentration was only 0.2 mmol/L. At the same time, hyperglycemia and acidosis were normalized and respiratory distress and weakness were significantly improved. A control chest radiograph revealed complete re-expansion of lung parenchyma and lack of effusion. Arterial oxygen saturation was >94% without oxygen therapy. The patient's recovery was uneventful; although twelve days after phosphate replacement commenced the serum phosphate concentration was only 0.3 mmol/L.

Discussion

During a computerized search of the literature, no reports regarding serum »aphosphatemia« were found. Hypophosphatemia is observed in approximately 2–3% of hospitalized patients, but is reported to be as high as 30% in the critically ill[1]. Severe hypophosphatemia occurs in no more than 0.5% of hospitalized patients. Nevertheless, it is difficult to provide precise estimates of how many patients are seen with hypophosphatemia per annum. This is further complicated by the use of chemistry panels that do not measure inorganic phosphate unless specifically ordered. As it was in our case, this often leads to a delay in correct diagnosis, and, therefore, additional delay in management. Severe hypophosphatemia becomes clinically significant when there is underlying phosphate depletion. A high index of suspicion alone avoids the unnecessary withholding of treatment that can be life saving[2].

Hypophosphatemia is a common complication during diabetic ketoacidosis therapy where it is seldom severe and rarely causes clinical manifestations. The clinical manifestations of mild hypophosphatemia are typically

minor and nonspecific: myalgia; weakness; and anorexia. However, when the imbalance is severe, critical complications including tetany, coma, rhambdomyolysis, seizures, skeletal muscle weakness, respiratory muscles fatigue, respiratory failure and ventricular tachycardia may occur[7,10,23,24].

Phosphate is a necessary product, which provides energy for almost all cell functions. Herein, insulin-dependent *Diabetes mellitus* was further complicated as a result of long duration nutritional disorders, vomiting, diarrhea and infection. The use of additional insulin enables phosphate to re-enter the cell, thus lowering serum phosphate concentration. Hematologic abnormalities correlate with reductions in intracellular ATP and 2,3-diphosphoglycerate and may include erythrocyte microspherocytosis and hemolysis, which might explain the hemolytic anemia observed in our patient.

Hypophosphatemia is the most well known, and perhaps most significant element of the refeeding syndrome (RFS). Although nausea, vomiting, and diarrhea often predispose to RFS[25,26], we believe that RFS was not a likely cause of hypophosphatemia in our patient.

Our patient's clinical condition was seriously worsened in another hospital as a result of effusion and iatrogenic pneumothorax following cannulation of the right subclavian vein, which further contributed to the development of respiratory insufficiency and suspected mediastinitis. During the stay in our Department, we didn't confirm either respiratory infection or consequential effusion of infectious aetiology and mediastinitis. A large part of the clinical condition of our patient was caused iatrogenic. Suspicion of mediastinitis was further emphasized by history of severe vomiting that is often described as a cause of rupture of the oesophagus and the resulting mediastinitis. Sepsis caused by urinary tract infection is well known in diabetic patients, and it was certainly one of the major causes of reducing the concentration of serum phosphate in our patient, but not the only reason. Urinary tract infection was cured in another hospital, but the patient's clinical condition further deteriorated in another hospital due to vomiting, diarrhea, dehydration, and insulin refractory hyperglycaemia. All this has led to severe metabolic disorders. Consultative psychiatrist in another hospital found in our patient personality disorder from the sphere of feeding. It is well known that the juvenile type *Diabetes mellitus* causes many metabolic disorders and we reasonably suspected that the gradual loss of phosphate occurred over the years. Most likely, patient's organism was adapted to gradual fluctuations in the concentration of serum phosphate. However, a number of circumstances during the few months prior to admission to our ICU, led to immeasurable levels of serum phosphate. We assume that in this way we could explain the severe muscle weakness, which led to respiratory muscle fatigue and somnolence, and not to »tetanus cramps« and coma. Unfortunately, we didn't detect the level of parathyroid hormone, although it influences the level of phosphate.

We believe that due to severe chronic deficit of serum phosphate, a relatively aggressive substitution of the phosphate could not achieve rapid laboratory changes. However, the fact is that the recovery of our patient began following phosphate substitution. Unfortunately, low phosphorus was not identified and treated at the previous hospitals attended. Although some authors recommend the substitution of phosphate in a short time-period[7,27], we could not risk additional complications and gradually substituted phosphate by continuous IV infusion of potassium phosphate salts. Bugg and Jones concluded that further, appropriately designed trials are essential before routine correction of plasma phosphate concentrations can be recommended in ICU[6].

It is generally recommended that patients with severe hypophosphatemia (<1.0 mg/dL [0.3 mmol/L]) are treated to avoid potential detrimental consequences. Severe hypophosphatemia in critically ill, intubated patients or those with clinical sequelae should be managed with intravenous replacement therapy (0.08–0.16 mmol/kg) over 2–6 h[7].

Although the undetectable serum concentration of inorganic phosphorus seems unlikely it was confirmed on repeat testing, this may have been because of laboratory error. Depending on the assay used, it is possible that the concentration of phosphate was too low to detect using that method. Might the value have been >0.00 if performed in a different laboratory? If the measurement system could be changed to a more accurate one, a system capable of measuring concentrations from mmol/L to μmol/L, certain concentrations of serum phosphate might be present in the samples. As far as we could, we excluded laboratory error. Unfortunately, we were not able to verify the values of serum phosphate on another appliance in another laboratory.

In summary, this report describes a patient with juvenile type *Diabetes mellitus* and diabetic ketoacidosis who developed respiratory failure probably, among other responsible factors, caused and complicated by undetectable levels of serum phosphate. Continuous infusion of insulin and potassium phosphate was administered. The serum phosphate was uncorrectable despite treatment with continuous infusion of insulin and potassium phosphate and three days later, the serum phosphate concentration was only 0.2 mmol/L. Furthermore, a significant improvement in weakness and lethargy was observed. To the best of our knowledge, this is the first described case of immeasurable levels of serum phosphate. Hypophosphatemia is an underdiagnosed problem in critically ill patients, and in patients with *Diabetes mellitus*, serum phosphate concentrations should be routinely checked in order to avoid additional complications.

REFERENCES

1. HICKS W, HARDY G, Curr Opin Clin Nutr Metab Care, 4 (2001) 227. — 2. SUBRAMANIAN R, KHARDORI R, Medicine (Baltimore), 79 (2000) 1. — 3. HOFFMANN M, ZEMLIN AE, MEYER WP, ERASMUS RT, J Clin Pathol, 61 (2008) 1104. — 4. SLATOPOLSKY E, HRUSKA KA, Disorders of Phosphorus, Calcium, and Magnesium Metabolism. In: SCHRIER RW (Ed) Diseases of the Kidney & Urinary Tract. (Lippincott Wiliams and Wilkins, Philadelphia, 2001). — 5. MORAN JL, SOLOMON PJ, AY YEUNG KW, PANNALL PR, JOHN G, ELISEO A, Crit Care Resusc, 4 (2002) 93. — 6. BUGG NC, JONES JA, Anaesthesia, 53 (1998) 895. — 7. AMANZADEH J, REILLY RF, Nat Clin Pract Nephrol, 2 (2006) 136. — 8. OUD L, Med Sci Monit, 15 (2009) CS49. — 9. AIBIKI M, KAWAGUCHI S, MAEKAWA N, Crit Care Med, 29 (2001) 1726. — 10. POLDERMAN KH, BLOEMERS FW, PEERDEMAN SM, GIRBES ARJ, Crit Care Med, 28 (2000) 2022. — 11. BROWN GR, GREENWOOD JK, Ann Pharmacother, 28 (1994) 626. — 12. CLARK C, SACKS G, DICKERSON RN, KUDSK KA, BROWN RO, Crit Care Med, 23 (1995) 1504. — 13. HEAMES RM, COPE AR, Anaesthesia, 61 (2006) 1211. — 14. COHEN J, KOGAN A, SAHAR G, LEV S, VIDNE B, SINGER P, Eur J Cardiothorac Surg, 26 (2004) 306. — 15. FENCL V, JABOR A, KAZDA A, FIGGE J, Am J Resp Crit Care Med, 162 (2000) 2246. — 16. SHOR R, HALABE A, RISHVER S, TILIS Y, MATAS Z, FUX A, BOAZ M, WEINSTEIN J, Ann Clin Lab Sci, 36 (2006) 67. — 17. LIU PY, JENG CY, J Chin Med Assoc, 67 (2004) 355. — 18. RAVENSCROFT AJ, VALENTINE JMJ, KNAPPETT PA, Anaesthesia, 54 (1999) 198. — 19. HASSELTROM L, WIMBERLEY PD, NIELSEN VG, Intensive Care Med, 12 (1986) 429. — 20. AGUSTI AGN, TORRES A, ESTOPA R, AGUSTI-VIDAL A, Crit Care Med, 12 (1984) 142. — 21. VARSANO S, SHAPIRO M, TARAGAN R, BRUDERMAN I, Crit Care Med, 11 (1983) 908. — 22. WALTER RE, BEISER A, GIVELBERG RJ, O'CONNOR GT, GOTTLIEB DJ, Am J Respir Crit Care Med, 176 (2003) 911. — 23. PALMESE S, PEZZA M, DE ROBERTIS E, Minerva Anestesiol, 71 (2005) 237. — 24. MOXHAM J, Br J Anaesth, 65 (1990) 43. — 25. MARINELLA MA, J Intensive Care Med, 20 (2005) 155. — 26. SEBASTIAN S, CLARENCE D, NEWSON C, Anaesthesia, 63 (2008) 873. — 27. FRENCH C, BELLOMO R, Crit Care Resusc, 6 (2004) 175.

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NEMJERLJIVE VRIJEDNOSTI FOSFATA U SERUMU – NE PREPOZNATI UZROK RESPIRATORNE SLABOSTI U BOLESNIKA S DIJABETESOM

SAŽETAK

Prikazujemo bolesnicu s juvenilnim tipom insulin – ovisnoga dijabetes mellitusa i dijabetičkom ketoacidozom u koje se razvila respiratorna slabost uz nemjerljive vrijednosti fosfata u serumu. Bolesnicu smo hospitalizirali zbog sumnje na akutni medijastinitis i respiratorne slabosti što je vjerojatno uzrokovala i dodatno komplicirala »afosfatemija«, tj. nemjerljiva vrijednost fosfata u serumu. Ordinirali smo kontinuiranu infuziju inzulina i kalij fosfata. Unatoč intenzivnome liječenju, vrijednost fosfata u serumu nismo mogli brzo korigirati i tri dana kasnije, koncentracija fosfata u serumu bila je samo 0,2 mmol/L. Ipak, nastupilo ne značajno poboljšanje respiratorne slabosti i letargije. Koliko je autorima poznato, ovo je prvi prikaz nemjerljivih vrijednosti fosfata u serumu, uz kritički pregled literature. Koncentraciju fosfata u serumu treba rutinski kontrolirati u bolesnika s dijabetesom da bismo izbjegli dodatne komplikacije.