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Severe Protracted Hypophosphatemia in a Patient with Persistent Vegetative State on Long-Term Assisted Respiratory Support

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Female, 53-year-old
Final Diagnosis: Hypophosphatemia • respiratory alkalosis
Symptoms: Asymptomatic
Medication: —
Clinical Procedure: Mechanical ventilation
Specialty: Critical Care Medicine • General and Internal Medicine • Metabolic Disorders and Diabetics • Physiology • Pulmonology

Objective: Unusual or unexpected effect of treatment

Background: Phosphorous is an essential component of cell structure and physiology, and is required for energy conservation and expenditure. Severe hypophosphatemia can lead to profound dysfunction and injury affecting most organs and can be life-threatening. It can also compromise weaning of mechanically ventilated patients. Long-term assisted ventilatory care in ambulatory or inpatient settings is an expanding medical service for patients with various forms of persistent or progressive incapacitating diseases. Hypophosphatemia, caused by respiratory alkalosis, has been reported in critical-care settings, but its occurrence in medically stable patients requiring long-term respiratory support has not been thoroughly investigated.

Case Report: We report the case of a ventilated patient in a chronic vegetative state displaying progressive hypophosphatemia spanning over 3 months, with plasma levels gradually declining to 0.8 mg/dL. Evaluation did not reveal conditions leading to diminished phosphate absorption or enhanced urinary phosphate excretion, but it identified respiratory alkalosis related to a recent increase in target minute-volume ventilation in the adaptive support ventilation (ASV) mode as the cause of hypophosphatemia. Despite the very low plasma phosphate level, the patient was asymptomatic, probably because this type of hypophosphatemia may not represent physiologically significant intracellular phosphate depletion. The respiratory alkalosis resolved upon decreasing the target minute-volume ventilation settings, and serum phosphate was normalized.

Conclusions: Since blood gases are not routinely monitored in respiratory and hemodynamically stable patients on long-term respiratory support, hypophosphatemia may herald the development of significant respiratory alkalosis. Assessment of acid-base balance is thus warranted in patients receiving long-term ventilation, especially in those developing hypophosphatemia.

Keywords: Alkalosis, Respiratory • Hypophosphatemia • Respiration, Artificial

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/934532

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Background

Phosphorous is an essential component of cell structure, physiology, and is required for energy conservation and expenditure. Severe hypophosphatemia can be life-threatening, leading to profound dysfunction and injury affecting most organs. Central nervous system derangement, cardiac failure, rhabdomyolysis, and hemolysis are only a few examples of the potentially devastating sequelae of severe hypophosphatemia [1].

The average total body phosphorous content in adults is about 700 g, the majority of which is incorporated in the skeletal hydroxyapatite matrix, while only about 10% plays a role in organ physiology, mostly as a principal intracellular phosphate ion (PO_4^{-3}). Normal extracellular and serum phosphate concentration of 2.5-4.5 mg/dl (0.80-1.45 mmol/l) largely reflects the balance between intestinal absorption and renal excretion of phosphate. To a lesser extent, release of phosphate from bone and deposition during bone turnover also contributes to serum phosphate concentration. Compound interacting mechanisms govern these physiological processes, including vitamin D metabolites, parathyroid hormone [PTH], and fibroblast growth factor [FGF]23 [1].

Long-term assisted ventilatory care in ambulatory or inpatient settings is an expanding medical service for patients with various forms of persistent or progressive incapacitating diseases, and for some patients needing a protracted rehabilitating and weaning process [2-5], many of them recently associated with COVID-19 disease [6]. We have operated a long-term assisted ventilatory care division for 21 years, and currently are treating over 200 inpatients in 6 units, with an age range of 3 months to 100 years. Adaptive support ventilation (ASV) is a highly convenient mode of respiratory support for patients requiring long-term assisted ventilatory care [7], and about 80% of our adult patients (>18 years old) are presently treated with this mode of ventilation (Hamilton Medical AG, Rhäzüns, Switzerland). This technology provides a closed-loop controlled ventilator mode, designed to decrease patients' work of breathing. It requires the determination of the patient's ideal body weight (IBW), extrapolated from height and gender. The level of required support is defined by the healthcare team, where 100% support is IBW×100 ml minute ventilation. A sophisticated algorithm calculates the tidal volume and respiratory rate and the pressure support/control to achieve minimal work of breathing, taking into account the respiratory mechanics data from the ventilator monitoring system (resistance (R), compliance (C), time constant (R×C), auto-PEEP).

Based on our clinical judgment and goals regarding weaning, once the patients are medically stabilized, particularly regarding their hemodynamic and respiratory status, we do not routinely assess their acid-base status, but instead monitor their ventilation status principally by their oxygen saturation by a pulse-oximeter and end-tidal CO_2 using a capnograph.

Hypophosphatemia caused by respiratory alkalosis has been reported in critical-care settings [8], but its occurrence in stable patients requiring long-term respiratory support has not been thoroughly investigated. Herein we report the unusual presentation of severe progressive hypophosphatemia as the sole manifestation of concealed respiratory alkalosis in a patient in a chronic vegetative state ventilated using the ASV ventilator mode.

Case Report

A 53-year-old female patient suffering from advanced progressive multiple sclerosis reached a vegetative state and had been treated in our long-term assisted ventilatory care facilities for over 5 years with the use of the ASV mode (Hamilton C1 ventilator). Other medical problems included an episode of Guillain-Barré syndrome, epilepsy, obesity, hypothyroidism, and non-insulin-dependent diabetes mellitus. She has been treated with levothyroxine, prednisone, metformin, glargine insulin, duloxetine, apixaban, levetiracetam, as well as a cannabinoid preparation (for spasticity) and a calcium-vitamin D3 preparation. She was enterally fed with EasyDaily® 810 ml/day (Supplying 685 mg phosphorus/day; EasyLine, Caesarea, Israel). Hypophosphatemia was first noted in January 2021, and it gradually intensified over 110 days, reaching levels as low as 0.8 mg/dL (**Figure 1**). However, her medical condition and routine laboratory results remained stable, with the exception of a modest increase in total plasma Ca^{++} levels. Initial evaluation revealed vitamin D3 levels of 83.9 ng/mL (target range 75-125 ng/mL), and depressed parathyroid hormone (PTH), 10.5 pg/mL (normal range 18-80 pg/mL). Urinary 24-h phosphate excretion was 15 mg/24 h (normal >400 mg/24 h) despite the administration of phosphate supplements. Finally, blood gases revealed marked respiratory alkalosis with a pH 7.50, pCO_2 24 mmHg pO_2 94 mmHg, O_2 saturation 98%, and HCO_3 18.7 mmol/L.

In retrospect, due to declining pressure support below 10 cmH_2O and to decrease the work of breathing in the patient, who was not a candidate for weaning from the ventilator, her ASV parameters were adjusted before the substantial decline of serum phosphorus level (**Figure 1**). Parameters were moved from 70% support with a target minute-volume ventilation (MVV) of 4.3 L/min, to 90% support with a target MVV of 5.5 L/min. The target MVV was reduced accordingly, resulting in a normalized acid-base balance and transient hyperphosphatemia, which terminated upon cessation of phosphate supplements (**Figure 1**). Three weeks later, her phosphate level was 4.6 mg/dL, with a pH of 7.38, pCO_2 34 mmHg and bicarbonate 20.7 meq/L.

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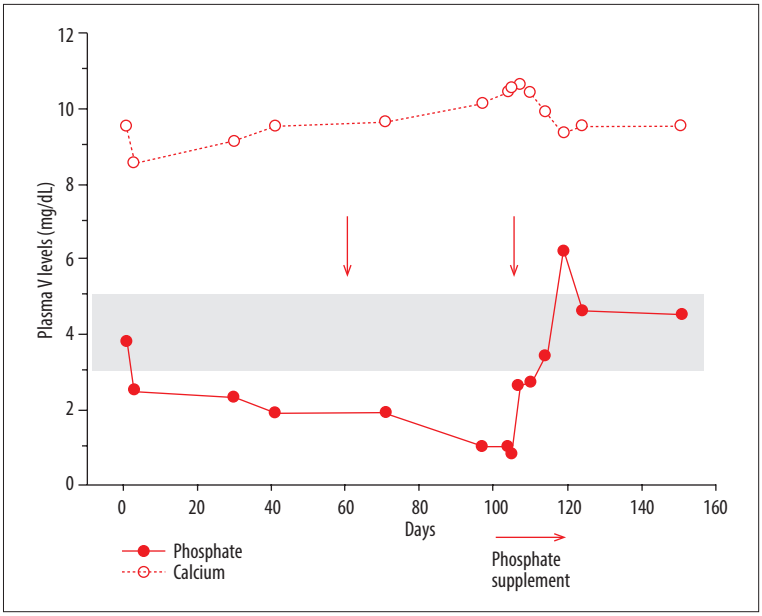

Figure 1. Serum levels of phosphorous and calcium over time, starting at January 4th, 2021. The gray area represents the normal range of phosphorous levels. Horizontal arrow indicates the period of time phosphate supplement has been administered, and the down-directed arrows denote the initial change and subsequent re-adjustment of ventilation parameters.

Discussion

Acquired hypophosphatemia is principally caused by altered phosphate absorption (for instance during malabsorption, vitamin D deficiency, or with the ingestion of phosphate-binders), or by enhanced phosphaturia (most often caused by hyperparathyroidism, and rarely by malignancy-related enhanced levels of FGF23) [1]. Intracellular translocation of phosphate is an additional often overlooked cause of reduced plasma phosphate levels [9]. It may result from enhanced cellular consumption of phosphate, as happens during refeeding of malnourished patients. Phosphate redistribution with intracellular translocation of phosphate may also be triggered by alkalosis, as it activates phosphofructokinase and increases consumption of phosphorous for glycolysis and downstream formation of glycolytic intermediate metabolites [1,10,11]. Indeed, respiratory alkalosis is the most common cause of hypophosphatemia in hospitalized patients [1], with a more modest, yet significant effect of metabolic alkalosis. Hyperventilation associated with panic disorders has been documented to cause hypophosphatemia [9,12-14], and low plasma phosphate has been proposed as a clue suggesting this condition [15]. Hypophosphatemia also accompanies other conditions characterized by intense work of breathing such as sepsis or recovery from ketoacidosis, but causative mechanisms other than alkalosis may be involved as well [1]. Hypophosphatemia is also found in mechanically ventilated patients with diminished work of breathing. Srinivasagam et al [8] reported that hypophosphatemia developed within 24-36 h in 43% of acutely ventilated patients in a critical care unit, resolving upon discontinuation of ventilation. They also detected inappropriate phosphaturia while PTH levels were unaltered, suggesting a phosphaturic impact of respiratory alkalosis unrelated to PTH. This is in contrast with observations by Krapf et al [16], who found that chronic respiratory alkalosis leads to renal PTH resistance, inhibiting phosphaturia and potentially generating hyperphosphatemia. Laaban et al [17] reported hypophosphatemia upon initiation of ventilation in 14 acutely ventilated patients with COPD, and also found a decline in urine phosphate in 2 of those patients. In another study, Watt and Silva [18] evaluated blood gases and electrolytes in 30 long-term ventilated tetraplegic patients (duration of ventilation ranging from 1 to 30 years). They found that these patients were mildly hyperventilated (mean pH 7.46). However, their average phosphate levels were within the normal range, and some had values below the 95% CI of a control group of tetraplegic self-ventilated patients. However, to the best of our knowledge, additional systematic assessment of phosphate balance among patients requiring long-term assisted ventilatory care has not been studied. Our patient presented with profound hypophosphatemia. Although blood gases and pH were not determined prior to reaching the critically low phosphate levels, it is likely that iatrogenic hyperventilation already took place during the initial days of decline in serum phosphorus levels, with further exacerbation upon adjustment of the ventilator respiratory parameters (**Figure 1**).

The clinical significance of chronic hypophosphatemia related to respiratory alkalosis and intracellular phosphorous translocation remains speculative. This type of hypophosphatemia most likely does not represent physiologically significant intracellular phosphate depletion. The clinical outcome of our patient supports this notion, as throughout the protracted period of severe hypophosphatemia there were no clinical or laboratory features indicating organ or tissue damage, such as cardiomyopathy, rhabdomyolysis, or hemolysis. Her vegetative

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state precluded the assessment of neurologic deterioration. However, concerns remain regarding decreased respiratory muscle strength caused by hypophosphatemia, particularly throughout scheduled disconnection and weaning from the respirator [19], as currently practiced in our institution in convalescing COVID-19 patients [20].

Conclusions

The current report calls into question our routine of not periodically monitoring blood gases, without which we are likely to overlook chronic respiratory alkalosis in patients on long-term assisted ventilatory care, which can lead to protracted hypophosphatemia. The central message of this case report is that the assessment of acid-base balance in such patients is indispensable even though their overall medical condition appears to be stable, especially when changing the setting of the ventilator. Hypophosphatemia might be an early indicator of evolving hyperventilation, and should particularly initiate prompt determination of blood gases.

Department and Institution Where Work Was Done

The work was done at the Long-Term Respiratory Care Division, Herzog Medical Center, Jerusalem, Israel.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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