Hypophosphatemia associated with coma

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In three cases of severe hypophosphatemia profound coma was associated. Although the occurrence of hypophosphatemia appeared to coincide with a high rate of intravenous administration of glucose and water, two of the three patients had liver disease and the other had hypothermia. In two instances the neurologic status improved with intravenous phosphate therapy. These case reports emphasize the importance of early recognition and treatment of profound hypophosphatemia in critically ill patients.

Trois cas d'hypophosphatémie sévère se sont compliqués d'un coma profond. Bien que l'apparition de l'hypophosphatémie semble avoir coincidé avec l'administration de glucose et d'eau par voie intraveineuse, deux des trois patients souffraient de maladie hépatique et l'autre présentait une hypothermie. Dans deux cas une amélioration de l'état neurologique a suivi l'administration intraveineuse de phosphate. Ces observations cliniques soulignent l'importance de reconnaître tôt et de traiter rapidement l'hypophosphatémie profonde chez les patients gravement malades.

Among other manifestations[1] hypophosphatemia has been reported to result in paresthesias, profound myopathy, seizures and even coma.[2] It must be remembered as a potential cause of coma that is clinically thought to have a metabolic basis, for such awareness can be lifesaving.[3]

In this report we describe three cases of hypophosphatemia associated with coma; in two cases intravenous phosphate therapy was followed by improvement in clinical neurologic status.

Case reports

Case 1

A 59-year-old man was admitted to the general surgical service with weakness, vomiting and excessive thirst. He had vomited on several occasions in the previous 2 weeks and four times the day before admission. Since a laryngectomy 5 years previously he had been consuming alcohol heavily. He had not taken antacids.

He was alert and well oriented, though clinically dehydrated, with orthostatic hypotension, decreased tissue turgor and a dry tongue. His liver was enlarged but not tender. Palpation of the right lower quadrant of the abdomen elicited pain. Measurement of the serum electrolyte concentrations and arterial blood gas tensions revealed hyponatremia with metabolic acidosis. The blood glucose and serum creatinine concentrations were normal (the latter was 1.5 mg/dL).

Because of profound oliguria and presumed fluid depletion, aggressive replacement was begun with intravenous fluids, primarily 0.9% NaCl alternated with 5% dextrose in water.

Over the next 24 hours the patient's level of consciousness progressively decreased. Neurologic findings were consistent with those of "metabolic" coma, no lateralizing signs being noted. An SMA 12 biochemical profile the morning after admission showed the following serum values: inorganic phosphorus 0.3 mg/dL (normal 2.5 to 4.5 mg/dL), total bilirubin 2.2 mg/dL (normal 0.15 to 1.0 mg/dL), serum glutamic oxaloacetic transaminase (SGOT) 85 mU/mL (normal 7 to 40 mU/mL) and alkaline phosphatase 65 mU/mL (normal 30 to 150 mU/mL). A clinical diagnosis of pancreatitis was confirmed by an elevated serum amylase value.

In the next 48 hours the metabolic acidosis and oliguria were treated vigorously with high-volume infusions monitored by a central venous pressure line; 5% dextrose in water and 0.9% NaCl was alternated with 5% dextrose in water, $NaHCO_3$ and KCl (for the profound hypokalemia). An SMA 12 biochemical profile 48 hours after admission again showed a serum inorganic phosphorus value of 0.3 mg/dL. Phosphorus was never given during the illness.

The patient remained deeply comatose, and 72 hours after admission had a cardiac arrest and died. Autopsy showed acute and chronic pancreatitis, a fatty liver and a previously unsuspected stone obstructing the common bile duct.

Case 2

A 56-year-old woman was admitted to the critical care unit deeply comatose and unresponsive to pain. A history of increasing confusion, lethargy, vomiting and diarrhea in the 3 days prior to admission was obtained from a friend. The patient was known to be an alcoholic.

She was dehydrated, with postural hypotension and poor tissue turgor; the blood pressure was 90/50 mm Hg with the woman supine, and the pulse rate was 130 beats/min. No lateralizing neurologic signs were present, and lumbar puncture revealed no diagnostic abnormalities. Profound metabolic encephalopathy was diagnosed.

An endotracheal tube was inserted for airway protection and a Swan-Ganz catheter was positioned for monitoring an intravenous infusion of 5% dextrose in water at 300 mL/h. The pulmonary wedge pressure before therapy was 1 mm Hg.

Biochemical investigation of the serum revealed mildly elevated values of SGOT, lactate dehydrogenase, alkaline phosphatase and total bilirubin; these disturbances were thought to be due to liver disease, probably alcohol-induced. The serum inorganic phosphorus value was elevated, at 5.4 mg/dL, as was the serum osmolality, at 303 mOsm/kg. No drugs or their metabolites were detected, and the blood glucose value was normal. Plasma cortisol and serum thyroxine values, and triiodothyronine resin uptake were normal. An electrocardiogram was normal.

The day after admission the serum inorganic phosphorus value was 0.5 mg/dL. Aggressive therapy with intravenous fluids was continued to maintain an adequate blood pressure. The pulmonary wedge pressure was still low, although other signs of dehydration dissipated that day.

On the third hospital day the serum inorganic phosphorus value was 0.8 mg/dL. She was still deeply comatose, without lateralizing signs, and neurologic evaluation suggested "metabolic" or anoxic coma. The hypotension had been corrected for 48 hours. Without any other major change in therapy she was given 45 mg of potassium acid phosphate intravenously over 8 hours and the serum inorganic phosphate concentration increased to 1.5 mg/dL. Towards the end of the infusion the coma lightened. She became fully conscious the next day, when the serum inorganic phosphorus value was 1.7 mg/dL. Over the next 3 days the serum phosphorus concentration rose to 2.3

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mg/dL with continued phosphate replacement.

The diarrhea, found to be due to ischemic colitis, continued for several more days. Hyperalimentation was begun, with careful attention being paid to the serum phosphorus concentration, and following prolonged hospitalization the woman was discharged.

Case 3

A 22-year-old woman was admitted to the critical care unit deeply comatose, unresponsive to pain and hypothermic (rectal temperature 30°C); there was evidence of sexual assault. Drug overdose was also considered a possibility.

There were no lateralizing neurologic signs, and bilateral carotid angiograms were normal. Intubation, ventilation and application of a warming blanket raised her body temperature to normal. An SMA 12 biochemical profile soon after admission showed a serum inorganic phosphorus value of 10.4 mg/dL, which was thought to be due to bowel ischemia.[4]

An intravenous infusion of 5% dextrose in water at 125 mL/h was begun. After 5 hours the infusion was changed to 5% dextrose and 0.2% NaCl in water at 200 mL/h; at this time the serum inorganic phosphorus value was only 1.0 mg/dL, as it was 8 hours later.

Later in the day, when the attending physicians became aware of the low values, another blood sample was drawn and 40 mg of potassium acid phosphate was given intravenously over 4 hours. The patient was still comatose, though she was now responding to pain and her rectal temperature was 36°C. Towards the end of the infusion she became fully conscious and appeared to be neurologically normal. The serum inorganic phosphorus values at the beginning and end of the infusion were 1.0 and 3.5 mg/dL respectively. The patient said that she had taken an unknown amount of a tricyclic antidepressant prior to the assault; it was then apparent that the cause of her coma was probably multifactorial.

Discussion

Recently, increased awareness of the clinical manifestations and pathophysiologic consequences of hypophosphatemia has been repeatedly noted.[1,5-7] This is likely due to the ease of obtaining laboratory values through the widespread use of multiple-channel autoanalysers[5] and an increased appreciation of the occurrence of hypophosphatemia, particularly secondary to intravenous hyperalimentation.[2,5,9]

Recent studies have suggested that hypophosphatemia is somewhat more common in a general hospital population than has been recognized;[5] accordingly, some of its causes and effects have subsequently been delineated. Hypophosphatemia has been divided into two types: moderate (that associated with depression of the serum inorganic phosphorus concentration to values of 1.0 to 2.5 mg/dL) and profound (that associated with depression to values less than 1.0 mg/dL).[7] Moderate hypophosphatemia has been associated with glucose infusion, recovery from hypothermia, hypomagnesemia, cirrhosis of the liver,[10] gram-negative septicemia[11] and prolonged vomiting,[5] among others. Profound hypophosphatemia, the type in our three cases, has been described in association with alcoholic withdrawal, diabetes mellitus with ketoacidosis, "hyperalimentation", "nutritional recovery syndrome" (malnutrition), pharmacologic binding of phosphate by antacids, diuretic or recovery phase of severe burns and severe respiratory alkalosis.[7]

With the widespread use of parenteral hyperalimentation and the need for serial biochemical analysis to detect occasional associated metabolic derangements, it has become evident that the sudden infusion of large quantities of carbohydrate may cause profound hypophosphatemia.[2] In most cases, whether or not the total body content of phosphorus is depleted, hypophosphatemia appears to be triggered by a shift in phosphate from the extracellular to the intracellular compartment. Most of the conditions producing such a shift seem to have in common a large and relatively sudden increase in glucose metabolism and anabolic processes. The shift occurs because most of the intermediates in both glycogen formation and glycosis are phosphorylated compounds. As a result, when these processes are extremely active, phosphate will translocate from the serum into tissue cells.

Although a relatively sudden decrease in serum phosphorus concentration in humans is believed to be due to a sudden increase in cellular uptake of phosphate,[6] this has yet to be proven. Derr and Zieve[12] approached the problem in rats, aware that previous studies of urine collections had shown that very little phosphorus is excreted through the kidneys during profound hypophosphatemia. Using radioactive phosphorus they found that with total parenteral nutrition the labelled phosphate shifted from the blood into liver, bone, muscle and carcass residue. On a weight basis liver cells took up as much phosphate as bone, and twice as much as muscle — a puzzling finding in view of the association of liver disease and hypophosphatemia in humans. It is evident that further clinical investigation is required.

Clinically hypophosphatemia is primarily manifested by abnormalities of the central nervous and musculoskeletal systems. Paresthesias, lethargy, seizures and coma associated with marked muscular weakness are seen.[6] Proximal myopathy has been described,[13] as have muscular pain and stiffness.[13] The associated myopathy appears to be occasionally severe enough to cause respiratory failure.[3]

Less clinically obvious are the effects of hypophosphatemia on erythrocytes and leukocytes. In erythrocytes the adenosine triphosphate (ATP) concentration is directly dependent and the 2,3-diphosphoglycerate (2,3-DPG) concentration indirectly dependent on the plasma concentration of inorganic phosphate.[9] It has been postulated that reduction in the erythrocyte ATP and 2,3-DPG concentrations is related to hemolytic anemia and possibly cellular hypoxia due to changes induced in the affinity of hemoglobin for oxygen. A low erythrocyte 2,3-DPG concentration is associated with a shift of the oxyhemoglobin dissociation curve[14] to the left and a subsequent reduction in the ability of hemoglobin to release bound oxygen in the periphery.

Leukocyte function is also affected by hypophosphatemia; specifically the chemotactic, phagocytic and bactericidal activity is depressed.[6] This is also believed to be due to impaired ATP synthesis in the leukocytes, which would produce improper function of the cellular microfilaments responsible for pseudopod and vacuole formation.

In two of our cases of profound hypophosphatemia deep coma was one of the primary clinical manifesta-

tions. All three patients received intravenous infusions of 5% dextrose in water as well as other crystalloid solutions for restoration of a clinically deficient intravascular volume before the onset of hypophosphatemia, and two patients had liver disease — obstruction of the common bile duct in one and cirrhosis in the other. Although reports[5,10] have indicated that liver disease may be an etiologic factor in hypophosphatemia, as it may have been in two of our cases, it is also possible that the high rate of intravenous infusion precipitated the hypophosphatemia.[5,15] In addition, patients 1 and 2 may have been extremely malnourished at the time of admission to hospital; patient 3 was hypothermic.

It seems reasonable to suggest that the profound hypophosphatemia in our patients had a multifactorial basis.

In conclusion, these cases emphasize that severe hypophosphatemia may be associated with coma in critically ill patients, and that, when found, hypophosphatemia should be recognized as an easily correctable cause of metabolic coma. Correction with intravenous phosphate therapy is safe and potentially life-saving, although hyperphosphatemia and its attendant complications should be avoided by monitoring the serum phosphate concentration. Thorough investigation is, of course, essential in all cases of coma since the underlying factors are diverse and many are treatable.

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