Neurologic signs and hypophosphatemia with total parenteral nutrition

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Hypophosphatemia in childhood is not common and often reflects disturbances in renal or hepatic function, or accompanies severe persistent vomiting, diabetic ketoacidosis or disorders of vitamin D metabolism. Protein–energy malnutrition, starvation and malabsorption may also be associated with phosphorus depletion. Patients receiving total parenteral nutrition, especially those receiving solutions low in phosphorus, have been found to have low serum phosphorus levels.[1]

Hypophosphatemia is often asymptomatic, but profound phosphorus depletion has numerous clinical presentations and can have serious or even life-threatening consequences. Hypophosphatemia can result in abnormalities in oxygen delivery, derangements in leukocyte phagocytosis, and platelet and hepatic dysfunction.[1-6] Neuromuscular symptoms, which may be mild, include anorexia, muscle weakness, paresthesia and tremors.[7-9] More dire consequences, including convulsions and fatal progressive coma, have been reported in adults and children.[8,10,11]

To our knowledge there are few reports of neurologic abnormalities related to phosphorus depletion in infants under 12 months of age. We describe two infants who had severe gastroenteritis requiring total parenteral nutrition, followed by unusual neurologic signs and profound hypophosphatemia. With phosphorus replenishment their metabolic and neurologic derangements resolved.

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Case reports

Case 1

A well nourished 11-month-old boy was transferred to our hospital because of diarrhea for 3 weeks and jaundice for 1 week. He had been born at term and had had no problems in the neonatal period. He had been breast-fed until 2 months of age; thereafter he was given a commercial infant formula and cereal. He had had four previous admissions to another hospital for recurring gastroenteritis, without a specific diagnosis having been made. Despite this, he had been gaining weight appropriately, and his development was normal. He had two older siblings who were well, and both parents were healthy.

On arrival at hospital he was noted to be less than 5% dehydrated and in no apparent distress. His weight, height and head circumference were all at the 50th percentile for his age. Apart from slight scleral icterus and mild hepatomegaly the physical findings were normal. Laboratory investigations, including a complete blood count, measurement of the blood urea nitrogen (BUN) and serum electrolyte levels, capillary blood gas analysis and chest roentgenography, all gave normal results. The total serum bilirubin level was high, at 56.4 μmol/l (3.3 mg/dl), with a direct component of 15.4 μmol/l (0.9 mg/dl). Other serum levels were: glutamic oxaloacetic transaminase (SGOT) 125 IU/l (normally less than 40 IU/l), calcium 2.3 mmol/l (9.2 mg/dl) (normally 2.0 to 2.75 mmol/l), phosphorus 0.8 mmol/l (2.5 mg/dl) (normally 1.92 to 2.20 mmol/l) and alkaline phosphatase 115 IU/l (normally less than 200 IU/l). Several stool specimens were cultured, but no bacterial pathogens or viruses were isolated, and electron microscopic examination of the stool did not demonstrate viral particles. A blood test for hepatitis B surface antigen had a negative result.

An intravenous infusion of 5% dextrose and saline solutions was begun because of poor tolerance of oral feedings. On the 12th hospital day infusions of 12% dextrose, 3% amino acid, 10% fat emulsion and multivitamins were begun through a central venous catheter. Increasing lethargy was noted at this time, and the infant's lethargic state persisted for several days.

At the beginning of the third week after admission continual coarse, myoclonic-like twitches in the right arm, shoulder and neck were noted. These were aggravated by voluntary movements and were present during sleep. There was no alteration of the infant's level of consciousness, and the results of a neurologic examination were otherwise normal. No jaundice was noted. At this time the blood glucose level, serum levels of sodium, potassium and chloride, and acid–base status were normal, and they remained normal throughout the patient's stay in hospital. Other serum levels were: calcium 2.1 mmol/l (8.4 mg/dl), phosphorus less than 0.1 mmol/l (0.3 mg/dl), magnesium 0.8 mmol/l (1.6 mEq/l) (normally 0.58 to 0.82 mmol/l), alkaline phosphatase 187 IU/l and SGOT 120 IU/l. The serum bilirubin level was now normal.

An electroencephalogram, intravenous pyelogram, skull roentgenograms, and levels of catecholamines, vanillylmandelic acid and

metanephrine in a 24-hour urine collection were normal. The protein and glucose levels and the cellular content of the cerebrospinal fluid (CSF) were normal; a culture gave negative results. A urine chromatographic screen for inborn errors of metabolism showed no abnormalities. The serum mercury level was 6 μg/dl (normally less than 2 μg/dl) and the blood lead level 0.8 μmol/l (17 μg/dl) (normally less than 1.4 μmol/l). The 24-hour excretion of copper in the urine was 0.3 μmol (18 μg) (normally less than 1.6 μmol).

When the movement disorder was recognized the total parenteral nutrition was stopped and a lactose-free formula containing phosphorus was begun. The formula was tolerated, and when the serum phosphorus level returned to normal the twitching stopped (Fig. 1).

The infant was discharged home well after 50 days in hospital. A review of his chart after discharge revealed that the infusions used for total parenteral nutrition had not contained phosphorus, apart from small amounts in the fat emulsion.

Case 2

A 12-month-old boy, who had been delivered at term without complications after a normal pregnancy, had been well until 3 weeks before admission, when a generalized maculopapular rash associated with high fever developed. He was admitted to the local hospital, where treatment included antibiotics for otitis media. Diarrhea developed; when it persisted for 2 weeks the infant was transferred to our hospital.

On arrival the infant was irritable, afebrile and 5% dehydrated. His weight was at the 25th percentile, and his length and head circumference were at the 75th percentile for his age. Except for mild hypotonia and lethargy the remainder of the physical findings were normal. Chest roentgenography, urinalysis and measurement of the BUN and serum electrolyte levels gave normal results. The serum calcium level was 2.2 mmol/l (8.6 mg/dl) and the serum phosphorus level 0.4 mmol/l (1.2 mg/dl). A titre of 1:256 for rubeola antibody confirmed a probable recent infection with the causative virus.

Initial management consisted of correcting the dehydration with the use of intravenous dextrose and saline infusions. Because of initial improvement oral feedings were started, but they soon had to be stopped because of lack of tolerance and persistent diarrhea. Total parenteral nutrition with 12% dextrose, 3% amino acid, 10% fat emulsion and multivitamins was begun through a central venous catheter.

Two weeks after admission the infant was noted to be increasingly lethargic; samples of blood, stool and CSF were obtained and antibiotic therapy was started. No bacteria or viruses were cultured, and the CSF was clear, contained no cells and had normal levels of protein and glucose. Two days later the child's condition continued to deteriorate, with decreasing muscle tone, absence of all upper and lower limb reflexes, marked lethargy, intermittent nonpurposeful movements, absent doll's eye movements, a depressed oropharyngeal gag reflex, decreased corneal reflexes and moderately dilated pupils that did not react to light. After a respiratory arrest he was resuscitated and transferred to the intensive care unit, where mechanical ventilation was begun (Fig. 2).

Investigations at that time revealed a normal acid–base status, a normal BUN level, normal serum levels of electrolytes, bilirubin, al-

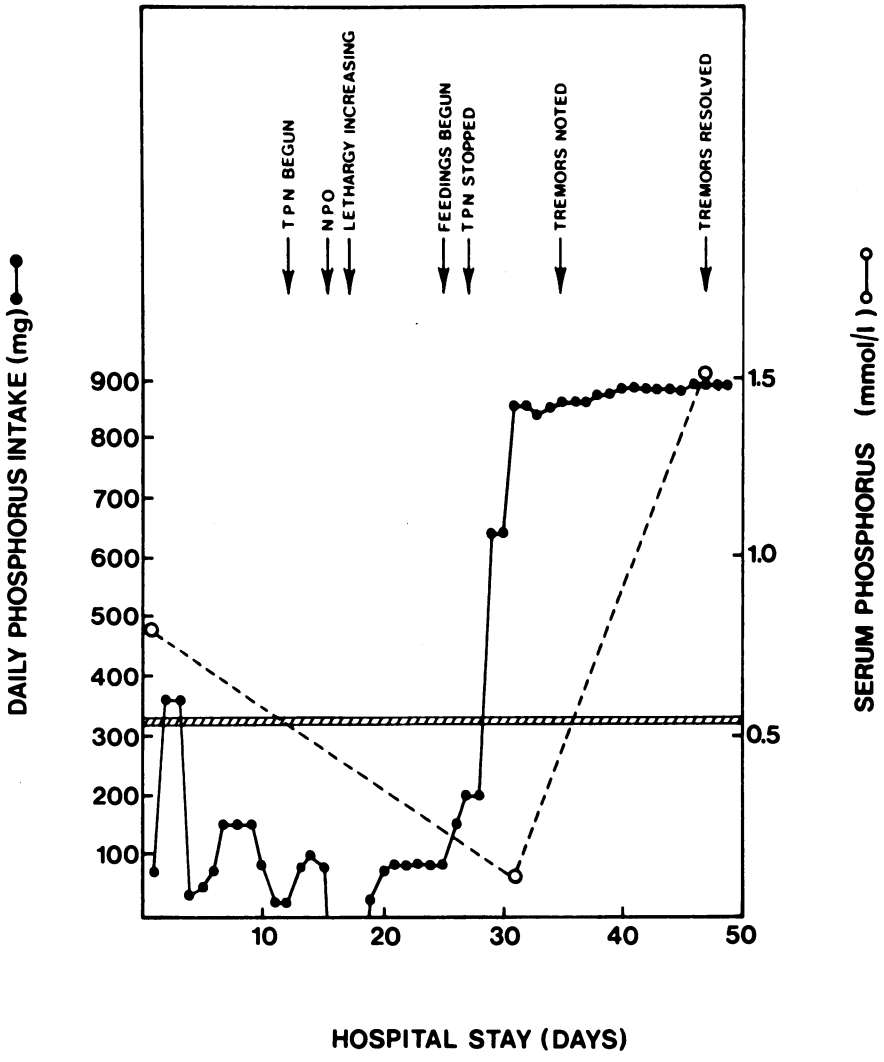

FIG. 1—Clinical course, phosphorus intake and serum phosphorus levels of patient 1. Hatched bar represents recommended daily intake of phosphorus (40 mg/kg). Normal levels of serum phosphorus 1.29 to 2.20 mmol/l. TPN = total parenteral nutrition; NPO = nothing by mouth.

kaline phosphatase and SGOT, and normal blood levels of ammonia and glucose. The serum calcium level was normal, the serum phosphorus level 0.1 mmol/l (0.3 mg/dl) and the serum magnesium level 0.7 mmol/l (1.4 mEq/l). Another specimen of CSF was normal. Computerized tomograms of the brain and a technetium 99m brain scan were entirely normal. Electron microscopic examination of the stool did not demonstrate viral particles, and serum titres of antibody to influenza A and B viruses and respiratory syncytial virus 2 weeks after the episode were less than 1:8. An electroencephalogram (EEG) demonstrated evidence of a diffuse marked encephalopathy, with diffuse high-voltage slow waves and slow background rhythms. A urine chromatographic screen for inborn errors of metabolism showed no abnormalities.

It was soon realized that the hypophosphatemia might explain the progressive lethargy, hypotonia and eventual coma. Phosphorus replacement was begun with monobasic and dibasic potassium phosphate (supplying 40 mg of phosphorus per kilogram in 6 hours) a few hours after the respiratory arrest. The serum phosphorus level rose to normal within 6 hours and remained so thereafter. Transient hypocalcemia followed but was corrected with an intravenous infusion of 10% calcium gluconate. The infant's response to the phosphorus infusion gradually improved, and 7 days after the arrest the infant was weaned from the ventilator. At this time the EEG was markedly improved. Two weeks after the event he had no evidence of lethargy and was totally alert. Prior to discharge he appeared to be in good health, and neurologic and developmental examinations gave normal results. An EEG obtained 8 months after discharge was normal.

Discussion

Despite knowledge of the major physiological and biochemical functions attributed to inorganic phosphorus in all living organisms, physicians failed to recognize until recently the diverse and serious clinical consequences of phosphorus depletion in humans. Most of the reports of patients with neurologic disturbances and hypophosphatemia have described individuals who were debilitated, received carbohydrate or total parenteral nutrition solutions that were low in phosphorus[8,11] or were in chronic renal failure and were receiving antacids and a dialysate low in phosphorus.[1,7] The neuromuscular symptoms in these individuals varied and included lethargy, malaise, weakness, intention tremor, paresthesia, anisocoria, ballismus, hyporeflexia, seizures and, rarely, coma.[8,10,11]

The variability and degree of the neuromuscular findings is probably related to the acuteness and severity of the phosphorus depletion interacting with the underlying associated disorder, but there may be a common mechanism for the symptoms. Concomitant with the depletion of serum inorganic phosphorus is a reduction in the high-energy organic phosphate compound adenosine triphosphate (ATP) and a reduction in many other important phosphate-containing enzymes, including erythrocyte 2,3-diphosphoglycerate (2,3-DPG).[2,12] Reduced intracellular ATP levels can lead to impaired contraction of muscles, interference with glycogenolysis in both muscle and liver cells and, theoretically, disturbed neuronal functioning.[5] Decreased amounts of erythrocyte 2,3-DPG can lead to a reduction in the amount of oxygen released to tissues, with subsequent tissue hypoxia. Thus, neuronal hypoxia in conjunction with neuronal "failure" may be the explanation for the neurologic symptoms in individuals with hypophosphatemia.

Solutions used for total parenteral nutrition can lead to significant phosphorus depletion by two mechanisms. The most obvious one is a reduced intake of phosphorus, especially if solutions containing little phosphorus are used. This can be corrected by adding to the solutions adequate daily maintenance amounts of phosphorus (40 mg/kg) in the form of monobasic potassium phosphate.[13] The second mechanism is a transcellular ionic shift due to intravenous carbohydrate loading: with the glucose-induced release of insulin, phosphorus is transported into peripheral cells,[14] where it is segregated, to be used in the form of high-energy phosphate compounds during glycolysis. This leads to a profound drop in the serum phosphorus level and a reduction in the amount of phosphorus available for other cellular processes.

Both of the infants we have described had very low serum phos-

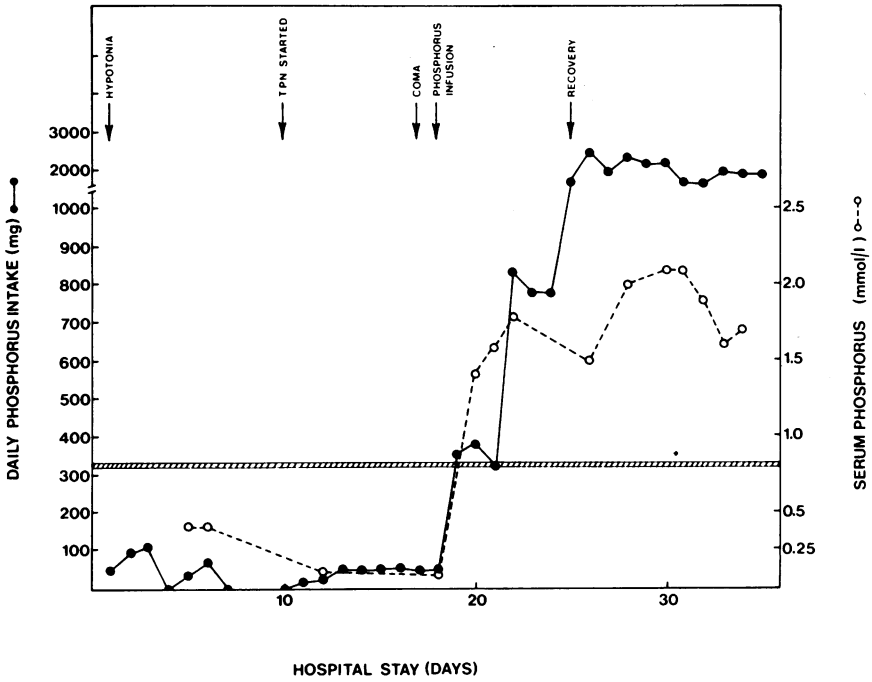

FIG. 2—Clinical course, phosphorus intake and serum phosphorus levels of patient 2.

phorus levels, and their neurologic derangements disappeared within 2 weeks of first receiving adequate amounts of phosphorus. Patient 1 had twitches in the right side of the body — a confusing presentation for a generalized metabolic disturbance. However, the absence of other potential causes for the twitches and their prompt disappearance once the serum phosphorus level returned to normal suggest phosphorus depletion as the most likely explanation. Patient 2 had a slow but steady resolution of a seemingly progressive coma after institution of phosphorus infusions. No infections or metabolic derangements apart from the hypophosphatemia were found in either patient.

Tremors, myoclonus and symptoms mimicking encephalitis that were identical to those of patient 1 were reported in children recovering from kwashiorkor.[15] The symptoms developed after 2 weeks of an improved dietary intake. No cause for the disorder was found, and all but one of the eight children completely recovered without specific therapy. Despite extensive investigation the serum phosphorus levels were apparently not measured.

Myoclonic encephalopathy of infants, as described by Kinsbourne,[16] was considered in patient 1. In this disorder there is usually an acute onset of tremors, frequently including nystagmoid movements; however, there is no history of prolonged dietary deficiency, and only one individual described received a carbohydrate infusion. Serum phosphorus levels were not reported for Kinsbourne's group, so we cannot comment on the etiologic role of phosphorus in that disorder.

Hepatic dysfunction with portal–systemic encephalopathy was excluded in patient 2, for at the peak of his coma the serum ammonia level was normal and the results of liver function tests were only mildly abnormal. An excess or deficiency of an amino acid or a trace element remains a possible but unlikely cause in both cases.

Encephalitis was unlikely in our patients in light of the normal CSF and lack of evidence of acute viral infection. Patient 2 did have suggestive clinical and serologic evidence of a recent rubeola infection; postmeasles meningoencephalitis was considered but seemed less likely than encephalopathy secondary to hypophosphatemia. Factors against a complication of measles included the 5-week interval from the onset of measles to the appearance of obvious signs of encephalopathy, the normal CSF, the diffuse metabolic-like EEG findings that rapidly cleared and the marked clinical improvement after correction of the low serum phosphorus level.

The chronic gastroenteritis and vomiting present in both infants probably contributed to the phosphorus depletion before their arrival at our hospital. These infants' neurologic disorders may have been preventable. The two errors in clinical management were the failure to add phosphorus to the solutions used for total parenteral nutrition and the failure to note the initially low serum phosphorus levels reported by the clinical chemistry laboratory.

These two cases emphasize the need to (a) periodically review basic nutritional requirements, especially in patients receiving total parenteral nutrition, (b) ensure that housestaff are supervised by individuals knowledgeable about parenteral nutrition and (c) recognize that profound phosphorus depletion can present in many ways and that correction of the metabolic derangement can be life-saving.

In neonates, infants and children with unusual neurologic disorders, including coma, hypophosphatemia should be considered and, if found, corrected.

References

1. FITZGERALD FT: Hypophosphatemia. In STOLLERMAN GH (ed): *Advances in Internal Medicine*, vol 23, Year Bk Med, Chicago, 1978: 137–157
2. LICHTMAN MA, MILLER DR, COHEN J, WATERHOUSE C: Reduced red cell glycolysis, 2,3-diphosphoglycerate and adenosine triphosphate concentration, and increased hemoglobin–oxygen affinity caused by hypophosphatemia. *Ann Intern Med* 1971; 74: 562–568
3. CRADDOCK PR, YAWATA Y, VANSANTEN L, GILBERTSTADT S, SILVIS S, JACOB HS: Acquired phagocyte dysfunction. A complication of the hypophosphatemia of parenteral hyperalimentation. *N Engl J Med* 1974; 290: 1403–1407
4. JACOBS HS: Severe hypophosphatemia. A previously ignored cause of cellular dysfunction. *West J Med* 1975; 122: 501–502
5. KLOCK JC, WILLIAMS HE, MENTZER WC: Hemolytic anemia and somatic cell dysfunction in severe hypophosphatemia. *Arch Intern Med* 1974; 134: 360–364
6. RAJAN KS, LEVINSON R, LEEVY CM: Hepatic hypoxia secondary to hypophosphatemia (abstr). *Clin Res* 1973; 21: 521
7. BOELENS PA, NORWOOD W, KJELLSTRAND C, BROWN DM: Hypophosphatemia with muscle weakness due to antacids and hemodialysis. *Am J Dis Child* 1970; 120: 350–353
8. SILVIS SE, PARAGAS PD JR: Paresthesias, weakness, seizures, and hypophosphatemia in patients receiving hyperalimentation. *Gastroenterology* 1972; 62: 513–520
9. WEINTRAUB MI: Hypophosphatemia mimicking acute Guillain–Barré–Strohl syndrome. A complication of parenteral hyperalimentation. *JAMA* 1976; 235: 1040–1041
10. PRINS HC, SCHRIJVER H, STAGHOUWER JH: Hyperalimentation, hypophosphatemia, and coma (C). *Lancet* 1973; 1: 1253–1254
11. LEE JL, SIBBALD WJ, HOLLIDAY RL, LINTON AL: Hypophosphatemia associated with coma. *Can Med Assoc J* 1978; 119: 143–145
12. YAWATA Y, CRADDOCK P, HEBBEL R, HOWE R, SILVIS S, JACOB H: Hyperalimentation hypophosphatemia: hematologic–neurologic dysfunction due to ATP depletion (abstr). *Clin Res* 1973; 21: 729
13. RICOUR C, MILLOT M, BALSAN S: Phosphorus depletion in children on long-term total parenteral nutrition. *Acta Paediatr Scand* 1975; 64: 385–392
14. FORSHAM PH, THORN GW: Changes in organic serum phosphorus during the intravenous glucose tolerance test as an adjunct to the diagnosis of early diabetes mellitus. *Proc Am Diabetes Assoc* 1949; 9: 101–122
15. KAHN E, FALCKE HC: A syndrome simulating encephalitis affecting children recovering from malnutrition (kwashiorkor). *J Pediatr* 1956; 49: 37–45
16. KINSBOURNE M: Myoclonic encephalopathy of infants. *J Neurol Neurosurg Psychiatry* 1962; 25: 271–276

BOOKS

This list is an acknowledgement of books received. It does not preclude review at a later date.

ADVANCES IN CARDIOLOGY. Vol. 28. Electrocardiology VI. 6th International Congress on Electrocardiology, Yalta, May 28–31, 1979. Edited by H. Abel and R.Z. Amirov. 247 pp. Illust. S. Karger AG, Basel, 1981. $94. ISBN 3-8055-1185-X

CURRENT CONCEPTS IN CATARACT SURGERY. Selected Proceedings of the Sixth Biennial Cataract Surgical Congress. Edited by Jared M. Emery and Adrienne C. Jacobson. 466 pp. Illust. The C.V. Mosby Company, St. Louis, 1980. $81.75. ISBN 0-8016-1527-5

DEVELOPMENTS IN BIOLOGICAL STANDARDIZATION. Vol. 47. International Symposium on Reassessment of Inactivated Poliomyelitis Vaccine. Proceedings of a Symposium Organized by the International Association of Biological Standardization and held at the Rijksinstituut voor de Volksgezondheid Bilthoven, the Netherlands, June 24–27, 1980. Edited by the International Association of Biological Standardization. Acting editors W. Hennessen and L.A. van Wezel. 364 pp. Illust. S. Karger AG, Basel, 1981. $48, paperbound. ISBN 3-8055-1820-X

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