

CASE REPORT

Severe asymptomatic hypophosphataemia in a child with T-acute lymphoblastic leukaemia

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Abstract

Hypophosphataemia is a metabolic disorder that is commonly encountered in critically ill patients. Phosphate has many roles in physiological functions, thus the depletion of serum phosphate could lead to impairment in multiple organ systems, which include the respiratory, cardiovascular, neurological and muscular systems and haematological and metabolic functions. Hypophosphataemia is defined as plasma phosphate level below 0.80 mmol per litre (mmol/L) and can be further divided into subgroups of mild (plasma phosphate of 0.66 to 0.79 mmol/L), moderate (plasma phosphate of 0.32 to 0.65 mmol/L) and severe (plasma phosphate of less than 0.32 mmol/L). The causes of hypophosphataemia include inadequate phosphate intake, decreased intestinal absorption, gastrointestinal or renal phosphate loss, and redistribution of phosphate into cells. Symptomatic hypophosphataemia associated with haematological malignancies has been reported infrequently. We report here a case of asymptomatic severe hypophosphataemia in a child with acute T-cell lymphoblastic leukaemia.

A 14-year-old Chinese boy was diagnosed to have acute T cell lymphoblastic leukaemia (ALL). His serum biochemistry results were normal except inorganic phosphate and lactate dehydrogenase levels. The serum inorganic phosphate level was 0.1mmol/L and the level was low on repeated analysis. The child had no symptoms related to low phosphate levels. The possible causes of low phosphate were ruled out and urine Tmp/GFR was normal. Chemotherapy regime was started and the serum phosphate levels started to increase. Hypophosphataemia in leukaemia was attributed to shift of phosphorus into leukemic cells and excessive cellular phosphate consumption by rapidly proliferating cells. Several reports of symptomatic hypophosphataemia in myelogenous and lymphoblastic leukaemia in adults have been reported. To our knowledge this is the first case of severe asymptomatic hypophosphataemia in a child with ALL.

Keywords: serum phosphate, hypophosphataemia, acute lymphoblastic leukaemia

INTRODUCTION

Phosphorus is an important mineral in cell metabolism. It is present in either inorganic or organic phosphate forms. Phosphate is a vital constituent of bone, cell membranes and molecules such as adenosine triphosphate (ATP), nicotinamide adenine dinucleotide (NAD), cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). It is essential for energy storage and metabolism as well as important for cell signalling and enzyme activation.¹

Plasma phosphate concentration is age-dependent. The plasma phosphate level in adults range between 0.80 and 1.45 mmol/L and children have a higher phosphate concentration than

adults. Hypophosphataemia can be divided into moderate and severe based on plasma phosphate levels of 0.32-0.65 mmol/L and <0.32 mmol/L respectively.² Symptomatic hypophosphataemia associated with haematological malignancies with blast cell crisis is infrequent.³ We report here a case of asymptomatic severe hypophosphataemia in a child with T-acute lymphoblastic leukaemia (T-ALL).

CASE REPORT

A 14-year-old Chinese boy initially presented with left lower motor neuron facial nerve palsy and was given oral prednisolone for two weeks. His symptoms did not improve and after one month, he developed high grade fever and

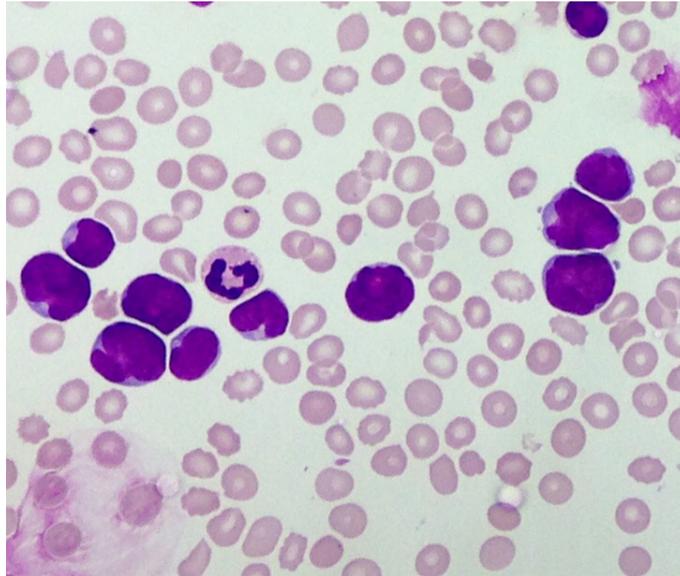


FIG. 1: Numerous blast cells in the peripheral blood smear which were heterogeneous in size, some with clefted/indented nuclei (May-Grünwald Giemsa)

bilateral epistaxis. There was no history of muscle weakness or difficulty in breathing.

On admission in our hospital, he was found to be moderately dehydrated with a body temperature of 37.2°C, blood pressure of 120/77 mmHg, heart rate of 107 beats per minute with oxygen saturation 99% under room air. Examination of the cardiovascular system and lungs were normal whereas abdominal examination revealed hepatosplenomegaly. He also had bilateral submandibular and right inguinal lymphadenopathy. Examination of the central nervous system showed no abnormality except for 7th nerve palsy.

The patient's haematological investigation results were as follows: haemoglobin, 112 g/L (130-170 g/L); total white cell count (WBC), $183 \times 10^9/L$ ($4.0-10.0 \times 10^9/L$); platelet count, 76 ($150-400 \times 10^9/L$). The peripheral blood film showed the presence of numerous blasts (93%) which were heterogeneous in size, some with clefted/indented nuclei, agranular mildly basophilic cytoplasm which was scanty to moderate in amount (Fig. 1). Flow cytometry testing performed on the peripheral blood showed these blasts to be CD45 dim to bright with low side scatter and expressing cCD3, CD2, CD4, CD5, CD7, CD8 and cTDT. There was no expression of CD34, HLA-DR or aberrant B-cell/myeloid markers. A diagnosis of T-acute lymphoblastic leukaemia (T-ALL) was made based on the morphological and

immunophenotypic features. There have been some reports of an association between facial palsy and acute leukaemia in the literature.^{4,5}

His serial biochemical blood results from admission until the commencement of chemotherapy are shown in Table 1. All biochemical parameters were normal except for serum phosphate and serum lactate dehydrogenase. Serum phosphate levels were consistently and repeatedly severely low in all samples. The laboratory notified the requesting clinician about the low phosphate level and enquired about any clinical signs and symptoms related to low phosphate level. Spurious hypokalaemia and hypophosphataemia due to extreme hyperleukocytosis in haematological malignancy has been reported by Polak *et al.*⁶ Since the serum phosphate level was very low and the patient was asymptomatic, a heparinised sample was requested to be sent in ice to exclude spurious hypophosphataemia due to high WBC counts. Serum phosphate level was found to be consistently low in heparinised sample as well. To exclude other causes of hypophosphataemia, urinary phosphate was measured. The tubular reabsorption of phosphate (TRP) was noted to be >80%. Standard ALL chemotherapy regime was started and the serum phosphate levels started to increase. He was monitored for tumour lysis syndrome. The phosphate level normalised with the complete remission of the disease.

TABLE 1: Serial monitoring of serum phosphate and other analytes

| Analyte | Reference | Sample 1 interval | Sample 2 | Sample 3 | Heparinised sample |
|--------------------------------|-----------|----------------------|----------|----------|-----------------------|
| Sodium (mmol/L) | 135-145 | 141 | 139 | 140 | 141 |
| Potassium (mmol/L) | 3.5-5.0 | 4.0 | 3.9 | 4.2 | 3.5 |
| Total CO ₂ (mmol/L) | 20-31 | 25 | 26 | 25 | 26 |
| Chloride (mmol/L) | 99-109 | 107 | 105 | 104 | 105 |
| Calcium (mmol/L) | 2.2-2.6 | 2.4 | 2.4 | 2.5 | 2.4 |
| Phosphate (mmol/L) | 0.9-1.8 | 0.1 | 0.1 | 0.1 | 0.1 |
| Albumin (g/L) | 35-50 | 35 | 37 | 35 | 36 |
| Magnesium (mmol/L) | 0.7-0.86 | 0.7 | 0.7 | 0.7 | 0.7 |
| LDH (U/L) | 120-246 | 7168 | | | |
| Urea (mmol/L) | 2.5-7.8 | 2.6 | | | |
| Creatinine (umol/L) | 55-96 | 77 | | | |
| Uric acid (mmol/L) | 0.21-0.43 | 274 | | | |

DISCUSSION

The incidence of hypophosphataemia is high in certain subgroups of patients, such as those who are hospitalized (2.2 to 3.1%), admitted to intensive care units (28.85 to 33.9%) and those with sepsis (65 to 80%), chronic alcoholism (2.5 to 30.4%), major trauma (75%) or chronic obstructive pulmonary disease (21.5%).⁷ The clinical manifestations of hypophosphataemia are primarily due to the consequences of intracellular phosphate depletion, which can affect many organ systems.²

Although most patients with hypophosphataemia do not develop symptoms, fatal complications have been described. A common mechanism in hypophosphataemia-induced complications is impaired energy metabolism, leading to cellular dysfunction in multiple organ systems. Life-threatening complications of hypophosphataemia include altered mental status, hypotension, arrhythmia or respiratory distress.¹

Hypophosphataemia can be caused by three different mechanisms: decreased intestinal absorption, increased renal excretion, or internal redistribution of inorganic phosphate.² This patient did not demonstrate any of the following conditions which can lead to phosphate depletion such as starvation, prolonged vomiting or any other conditions that could lead to decreased intestinal absorption. Hypophosphataemia and associated inappropriate phosphaturia has been described in patients with acute leukaemia. It has been suggested that in the presence of severe hypophosphataemia, depletion of intracellular phosphate can occur in renal tubular cells

potentially interfering with the reabsorption of urinary phosphate.⁶ In our patient the fractional tubular reabsorption of phosphate (TRP) and ratio of tubular maximum reabsorption of phosphate (TmP/GFR) were 0.91 and 1.45 mmol/L respectively. This shows there was no evidence of renal loss of phosphate. His serum calcium and magnesium were within normal limits. Serum PTH and vitamin D levels were not measured for this patient, since chemotherapy was commenced soon after the diagnosis of ALL.

Several reports have described hypophosphataemia in leukemic patients with blast cells proliferation.⁸⁻¹⁰ Many tumour cells consume glucose at an extraordinarily high rate compared with the tissue from which they originate – the so-called ‘Warburg effect’. Glucose has to serve as the source for a diverse array of cellular functions, including energy production, synthesis of nucleotides and lipids, membrane synthesis and generation of redox equivalents for antioxidative defence.¹¹ The increased glycolysis and synthesis of ribose phosphates by malignant cells may have increased demand for phosphorus and its uptake by the rapidly dividing cells resulting in profound hypophosphataemia.¹² The laboratory investigations probably suggest that hypophosphataemia in our case could be ascribed mainly to the transcellular shift of phosphate. The TRP value of 91%, in the presence of severe hypophosphataemia and with markedly elevated blast cells in the peripheral blood film, strongly suggest transcellular shift of phosphate as the likely cause of hypophosphataemia in this patient.

With the commencement of chemotherapy, serum phosphate levels started to increase to a maximum of 2.2 mmol/L. With complete

remission, the serum phosphate level was 1.2 mmol/L. This further confirms the fact that the reduced phosphate level in this patient could be due to transcellular shift secondary to rapidly multiplying cells. Symptoms related to hypophosphataemia have been reported in adult patients with acute leukaemia. An exhaustive literature search revealed, only Benítez *et al.*¹³ have reported hypophosphataemia in children with ALL during remission induction.

It is not clear why our patient did not have symptoms related to severe hypophosphataemia. However, to our knowledge this is the first case of severe asymptomatic hypophosphataemia in a child with ALL at the time of presentation.

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The authors have no conflict of interest to declare.

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