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Original article

Hypophosphatemia is a common complication in severely disabled individuals with neurological disorders and is caused by infection, refeeding and Fanconi syndrome

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Abstract

Aim: To describe the characteristics of hypophosphatemia in severely disabled individuals with neurological disorders and to identify its causative factors. *Method:* We retrospectively reviewed clinical data from 82 individuals with motor skills classified as sitting, rollover or bedridden. Age, gender and body mass index were compared in individuals with ($n = 19$) and without ($n = 63$) a history of hypophosphatemia (serum phosphate levels <2.0 mg/dl). The clinical course of each patient with hypophosphatemia was reviewed and the cause identified. Laboratory data during hypophosphatemia was compared with that after recovery. *Results:* The age, gender and body mass index did not differ significantly between the individuals with and without hypophosphatemia. Nineteen patients experienced 25 episodes of hypophosphatemia. The causes included febrile illnesses ($n = 17$), refeeding syndrome ($n = 4$) and Fanconi syndrome ($n = 3$), but was unidentifiable in one episode. Significant elevations in C-reactive protein levels and reductions in sodium levels were observed during hypophosphatemia episodes. *Interpretation:* Hypophosphatemia is a common complication in severely disabled individuals with frequent bacterial infections, refeeding following malnutrition and valproate administration for epilepsy treatment. Because severe hypophosphatemia is life threatening, serum phosphate levels should be closely monitored in this population.

Keywords: Hypophosphatemia; Infection; Refeeding syndrome; Fanconi syndrome; Neurological disorders; Childhood

1. Introduction

Individuals with severe disabilities due to neurological disorders often experience feeding and nutritional problems. These include vitamins and trace-element deficiencies, dumping syndrome and starvation during infectious episodes, when gastrointestinal motility is impaired and oral or tube feeding is started, eventually in respiratory distress.

We recently experienced two cases of severe hypophosphatemia that occurred while increasing nutritional intake after gastrointestinal or respiratory illness. These episodes were considered to be a part of refeeding syndrome, occurring in response to a rapid increase in

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glucose load after a starvation period [1–3]. Increased phosphorylation of glucose with usage of thiamine usage, insulin release and inhibition of lipid metabolism can result in hypophosphatemia, thiamine deficiency, intracellular shift of potassium and magnesium, water retention and decreased serum lipid levels [1–3]. All these changes are potentially life threatening [2,4]. Furthermore, refeeding syndrome may be underdiagnosed during the management of malnourished disabled patients, which may further increase the risk of developing the syndrome. Reports on the refeeding syndrome in severely disabled individuals with childhood-onset neurological disorders are very limited [5–7]. To identify more cases with this complication in this population, we retrospectively collected data of long-term institutionalized individuals with symptoms of hypophosphatemia, a hallmark of refeeding syndrome, and reviewed the clinical course in each case. Although it was not our initial aim, we also identified many episodes of hypophosphatemia that occurred during infectious episodes in individuals without a phase of nutritional recovery after starvation. Although acute infectious diseases, particularly sepsis, have been associated with hypophosphatemia [8–13], the prevalence of infection-related hypophosphatemia was surprisingly high in our case series. It is unclear whether or not malnutrition also played a role in the development of infection-induced hypophosphatemia. Furthermore, valproate (VPA) and phosphate-binding antacids are often used for treating epilepsy and gastritis in disabled individuals, which can lead to adverse effects such as Fanconi syndrome and decreased phosphate absorption, respectively [14]. Thus, there may be multiple causes of hypophosphatemia in severely disabled individuals and risk factors for these have not been fully elucidated.

In this study we investigated the characteristics of hypophosphatemia in severely disabled individuals and its potential etiological factors. We hope that the results of our study would help to improve the recognition, prevention and management of this complication in clinical settings.

1.1. Participants and methods

We surveyed the results of blood laboratory analysis between the years 2002 and 2012 from 83 (age 3–47 years, M:F = 46:36) severely disabled individuals under long-term hospitalization. The blood examinations had been done arbitrarily, i.e. during febrile episodes in most occasions, as well as for yearly check-up. The diagnoses in these individuals included brain anomalies, sequelae of birth asphyxia and meningitis, neurodegenerative and metabolic disorders, chromosomal abnormalities, post-West syndrome and muscular disorders. Patients were classified according to motor skills as sitting, rollover or bedridden. One patient with urolithiasis, recurrent urinary tract infections, and resultant persistent renal tubular dysfunction was excluded from the study. We identified 25 episodes of moderate or severe hypophosphatemia (<2.0 mg/dl) [10] in 19 patients (age 10–43 years, M:F = 11:8).

We collected data on age, gender, body mass index (BMI) and medication, including antiepileptic agents and drugs acting on the gastrointestinal tract, from 82 patients with or without a history of hypophosphatemia to determine whether any of these factors were associated with the development of hypophosphatemia. We also reviewed the clinical course of each patient with hypophosphatemia, particularly the rate of nutritional recovery after starvation. The laboratory data of blood analysis, collected during hypophosphatemia and after recovery of phosphate levels to >2.5 mg/dl, included serum levels of sodium ($n = 20$), potassium ($n = 20$), calcium ($n = 20$), glucose ($n = 10$), C-reactive protein (CRP; $n = 21$), total cholesterol ($n = 10$), triglyceride ($n = 10$), aspartate aminotransferase (AST) ($n = 18$), alanine aminotransferase (ALT) ($n = 18$), total protein ($n = 13$), pH ($n = 10$) and pCO_2 ($n = 10$). For data analysis, we used the values from the blood samples with the lowest observed phosphate level during hypophosphatemia and the values measured during the recovery phase, although these were not available in all of the patients. For statistical analysis, the chi-square test was used to compare the two groups with and without hypophosphatemia and the Mann–Whitney test was used for comparisons with subgroups of patients with hypophosphatemia. Wilcoxon signed-rank tests were used to analyze laboratory data during hypophosphatemia and after recovery. The study protocol was approved by our institutional ethics committee.

2. Results

2.1. Comparison of groups with and without hypophosphatemia

The age [mean (standard deviation, SD); 38.8 (7.16) and 31.1 (12.6) years, $p = 0.14$], gender (M:F = 11:8 and 36:27, $p = 0.91$), BMI [14.0 (2.75) and 14.3 (3.0) kg/m^2, $p = 0.73$] and administration status of VPA (5/19 and 10/63, $p = 0.58$) and phosphate-binding antacids (12/19 and 35/63, $p = 0.84$) were not significantly different between the two groups. We further divided the 25 hypophosphatemia episodes into four groups: (1) infection without an increase in post-starvation nutritional intake ($n = 17$), (2) refeeding syndrome ($n = 4$), (3) Fanconi syndrome ($n = 3$) and (4) idiopathic ($n = 1$) (Table 1). None of these groups showed significant differences with the group of patients without hypophosphatemia with regard to age, gender and BMI.