CASE REPORT

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Elemental Milk Formula as a Possible Cause of Hypophosphatemic Rickets in Wiedemann-Steiner Syndrome

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What is already known on this topic?

Nutritional phosphate deficiency is not a common cause of hypophosphatemic rickets; rather, excessive phosphate wasting, which can be caused by an excess of fibroblast growth factor 23, as in X-linked hypophosphatemic rickets, is the most common cause. Nutritional hypophosphatemia can occur in certain conditions, such as premature babies, malabsorption disorders, or if a child is taking medication that interferes with phosphate intestinal absorption.

What this study adds?

We describe a patient with multiple co-morbidities and Wiedemann-Steiner syndrome who developed hypophosphatemic rickets after being exclusively fed elemental milk formula, which was resolved by switching formulas. In the literature, this formula-associated effect was only described in a limited number of patients. Further research is needed to determine whether some patient-related factors, such as the very rare syndrome described in our patient, could influence this effect.

Abstract

Phosphate has a fundamental role in bone mineralization, and its chronic deficiency has multiple negative consequences in the body, including defects in bone mineralization that will manifest in children as rickets and osteomalacia. Here we present a young boy known to have Wiedemann-Steiner syndrome with multiple co-morbidities that necessitated gastric tube feeding. The child at 22 months was found to have hypophosphatemia and a high alkaline phosphatase level associated with rachitic skeletal manifestations that were attributed to low phosphate intake and/or gastrointestinal absorption, as there was no evidence of excessive phosphate wasting based on appropriate tubular renal re-absorption of phosphate. The primary nutritional source was an elemental amino acid-based milk formula (Neocate®) from 12 months of age. After switching from Neocate® to another elemental amino-acid based milk formula, all biochemical and radiological abnormalities returned to normal, indicating that the Neocate® formula was the possible cause of the patient's low phosphate intake. However, in the literature, this formula-associated effect was only described in a limited number of patients. Whether or not some patient-related factors, such as the very rare syndrome described in our patient, could influence this effect warrants further exploration.

Keywords: Phosphopenic rickets, osteomalacia, Neocate®

Introduction

Phosphate is mainly an intracellular anion involved in various metabolic processes that occur during normal physiologic activity (1). Serum phosphate levels in healthy individuals are kept within a narrow range, primarily regulated by fibroblast growth factor 23 (FGF23), parathyroid hormone (PTH), and 1,25 dihydroxyvitamin D [1,25$(OH)_2$D] (2).

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Acute hypophosphatemia is relatively common, particularly among pediatric patients admitted to the intensive care unit (3). Acute illnesses can result in transient hypophosphatemia, which occurs due to a number of mechanisms but does not deplete the body's total phosphate store (4). Prolonged hypophosphatemia negatively impacts multiple body systems, with bone and the musculoskeletal system bearing the brunt of the damage (5). Phosphate is required for the maturation of the growth plate and bone mineralization. Phosphate is the leading factor of apoptosis in terminally differentiated hypertrophic chondrocytes in the growth plate. It also forms hydroxyapatite crystals with calcium, the major mineral component of bone. As a result, chronic hypophosphatemia can cause hypertrophic chondrocyte accumulation at the growth plate, resulting in classic rickets signs, as well as affect bone mineralization, resulting in osteomalacia, which can lead to bone deformities and recurrent fractures (6).

Chronic hypophosphatemia commonly develops as a result of increased urinary phosphate loss caused by hyperparathyroidism secondary to vitamin D deficiency, excess FGF23, renal tubulopathy, or as a side effect of certain medications. Hypophosphatemia, due to decreased phosphate intake, is rare because most foods are high in phosphate, but it can occur in certain conditions such as premature babies, malabsorption disorders, or if a child is taking medication that interferes with phosphate intestinal absorption (2).

There is emerging evidence that Neocate® formula contributes to the development of hypophosphatemic rickets due to reduced phosphorus bioavailability (7,8,9,10). Neocate® is an elemental amino-acid-based milk formula that is used to treat gastrointestinal disorders that interfere with optimal nutritional requirements. Since 1995, the U.S. Food and Drug Administration has approved Neocate® for use, and it contains a comparable amount of phosphate to other formulas (11). We described a patient who developed hypophosphatemic rickets after being exclusively fed with Neocate® formula, which was resolved by switching formulas.

Case Report

A four-year old boy who had been diagnosed with Wiedemann-Steiner syndrome, had multiple co-morbidities including global developmental delay, hypotonia, bilateral sensorineural hearing loss, large patent ductus arteriosus status post ligation, right multicystic dysplastic kidney, chronic lung disease due to chronic micro aspiration syndrome on home oxygen, severe gastroesophageal reflux disease with severe oral dysphagia, and excessive oral secretion on esomeprazole. The patient had undergone Nissen fundoplication and gastric tube (GT) insertion at the age of 14 months.

He was born via cesarean section at 34 weeks of gestation and remained in the hospital for one month after birth due to respiratory distress syndrome. Since birth, he had difficulty feeding, was not growing well, with length and weight of 66 cm and 5.3 kg respectively at the age of one year, and was frequently admitted to the hospital due to recurrent aspiration pneumonia. In terms of nutritional management, he was fed orally and occasionally required nasogastric tube feeding. At the age of 2 months, he was started on high calorie milk formula (Infantrini®), which was changed to elemental formula (Neocate®) at the age of 12 months, and at the age of 14 months, he underwent Nissen fundoplication and GT insertion due to recurrent episodes of aspiration pneumonia.

At the age of 22 months, he was discovered to have low serum phosphate following admission to the hospital. Table 1 shows the initial laboratory findings. Based on radiological changes (Figure 1), low serum phosphate, normal PTH,

Table 1. Laboratory results at baseline and in response to changing the feeding milk formula

Variable	Reference range	Baseline	1 week follow-up	2 weeks follow-up	2 months follow-up	6 months follow-up	2 years follow-up
Calcium (mmol/L)	2.2-2.7	2.42	2.35	2.40	2.51	2.43	2.28
Phosphate (mmol/L)	1.39-1.74	0.85	2.1	1.66	1.61	1.73	1.57
Magnesium (mmol/L)	0.7-0.95	0.83	1.11	0.96	0.86	0.84	0.87
Creatinine (umol/L)	27-62	36	34	36	35	37	39
PTH (pmol/L)	1.59-7.24	2	-	-	3.17	2.86	3.63
ALP (IU/L)	156-369	1183	-	849	181	144	91
25(OH)D (nmol/L)		127.6	-	-	91.6	-	107.9
$1,25(OH)_2D$	62.6-228	552.4	-	-	-	-	-
Urine phosphate (mmol/L)		< 1.62	-	-	-	-	-
Urine creatinine (mmol/L)		7.9	-	-	-	-	-

PTH: parathyroid hormone, ALP: alkaline phosphatase, 25(OH)D: 25-OH vitamin D, $1,25(OH)_2D$: 1,25 dihydroxyvitamin D

normal calcium, normal 25-hydroxyvitamin D levels, and tubular renal re-absorption of phosphate of 99%, he was diagnosed with hypophosphatemic rickets due to low phosphate intake or reduced phosphate bioavailability.

The treatment for low phosphate was initially an oral phosphate supplement in the form of sodium glycerophosphate, which provided 55 mg/kg/day of elemental phosphate, and after the first dose of sodium glycerophosphate, serum phosphate increased to 2.33 mmol/L, which was associated with secondary hypocalcemia (serum calcium 2.17 mmol/L) and secondary hyperparathyroidism (PTH level 29.5 pmol/L). Following that, sodium glycerophosphate was reduced to provide 25 mg/kg/day of elemental phosphate, which kept calcium and phosphate within normal limits (Table 1). Neocate® was administered via GT and provided him with nearly 100 Kcal/kg/day. He had no diarrhea or other gastroenterology symptoms. Due to the suspicion that Neocate® had low phosphate bioavailability, it was replaced with another elemental amino-acid based milk formula, which resulted in a significant increase in serum phosphate levels and a decrease in alkaline phosphatase levels that persisted even after the oral phosphate supplement was discontinued. A repeat radiograph one year later revealed improved bone density and rickets signs that had healed. Currently, the phosphate level and the other biochemical profiles are normal for the patient age (Table 1).

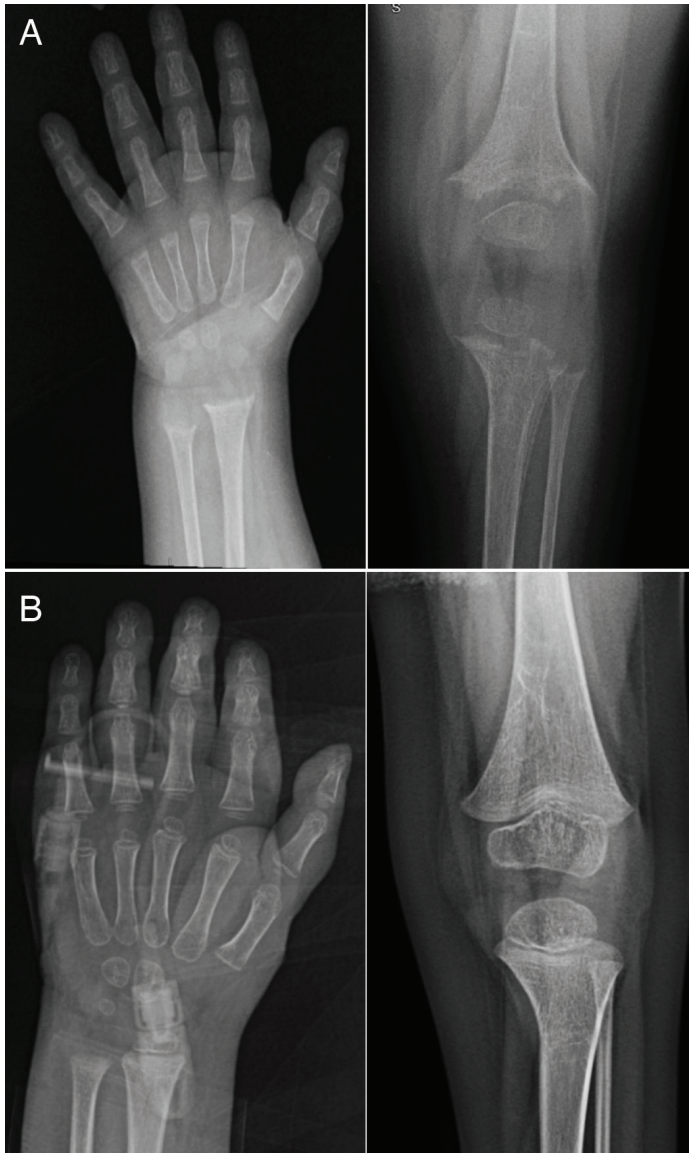

Figure 1. A and B show the baseline and follow-up radiographs of the left lower extremity and hand. A) The baseline image shows metaphyseal lucencies, cupping, and fraying of the distal femur, radius and ulna and the proximal tibia, as well as reduced osseous mineralization. B) One year follow-up shows improved mineralization and healing of rickets

Discussion

The presented patient's clinical and biochemical abnormalities are consistent with hypophosphatemic rickets, which are caused by nutritional phosphate deficiency, as evidenced by low phosphate in the urine. The fact that all biochemical and radiological abnormalities returned to normal after switching from the Neocate® formula to another formula suggests that our patient's low phosphate was possibly caused by the Neocate® formula.

Neocate® and other elemental formulas are commonly used in pediatrics to treat a variety of gastrointestinal disorders. It is an elemental amino-acid-based milk formula that is allergen-free (12). Neocate® has been used in children with milk protein allergy who are otherwise healthy, and it has not been found to cause mineral deficiencies (13). Almost all cases of hypophosphatemic rickets linked to Neocate® were in patients with multiple medical illnesses (7-10), indicating that a subset of patients may be vulnerable to impaired phosphate absorption from the Neocate® formula for reasons that are still unknown. In a recent randomized crossover trial, Neocate® was found to have comparable bioavailability of calcium and phosphorus to other elemental milk formulas in a healthy adult (14).

Our patient has multiple co-morbidities and was diagnosed with Wiedemann-Steiner syndrome, an autosomal dominant disorder caused by a mutation in the *MML* gene that results in a variety of medical problems, such as developmental delay, hypotonia, short stature, distinctive facial features, hypertrichosis cubiti and feeding difficulties that necessitate feeding support (15). In reports of a large French and Chinese cohort of patients with Wiedemann-Steiner syndrome, the observed skeletal manifestations were

advanced skeletal maturation, rib anomalies, brachydactyly, clinodactyly, tapering fingers, sacral dimple, and vertebral blocks; rickets or hypophosptaemia were not reported (16,17). The complexity of our patient's medical condition is consistent with previously reported cases of Neocate®-induced hypophosphatemic rickets, with the majority of those cases having multiple medical problems.

Given that not all patients on Neocate® develop hypophosphatemic rickets, many hypotheses have been proposed to explain these associations in a larger cohort of patients, including formula mineral bioavailability and the effect of medication such as proton pump inhibitors on absorption (10). However, these associations cannot be fully explained since the phosphorus concentration is comparable with other elemental formulas and the condition improved after substituting the formula while the patient was on the same medication, indicating that there may be other contributing factors that have yet to be discovered. A prospective study to explain these associations is needed.

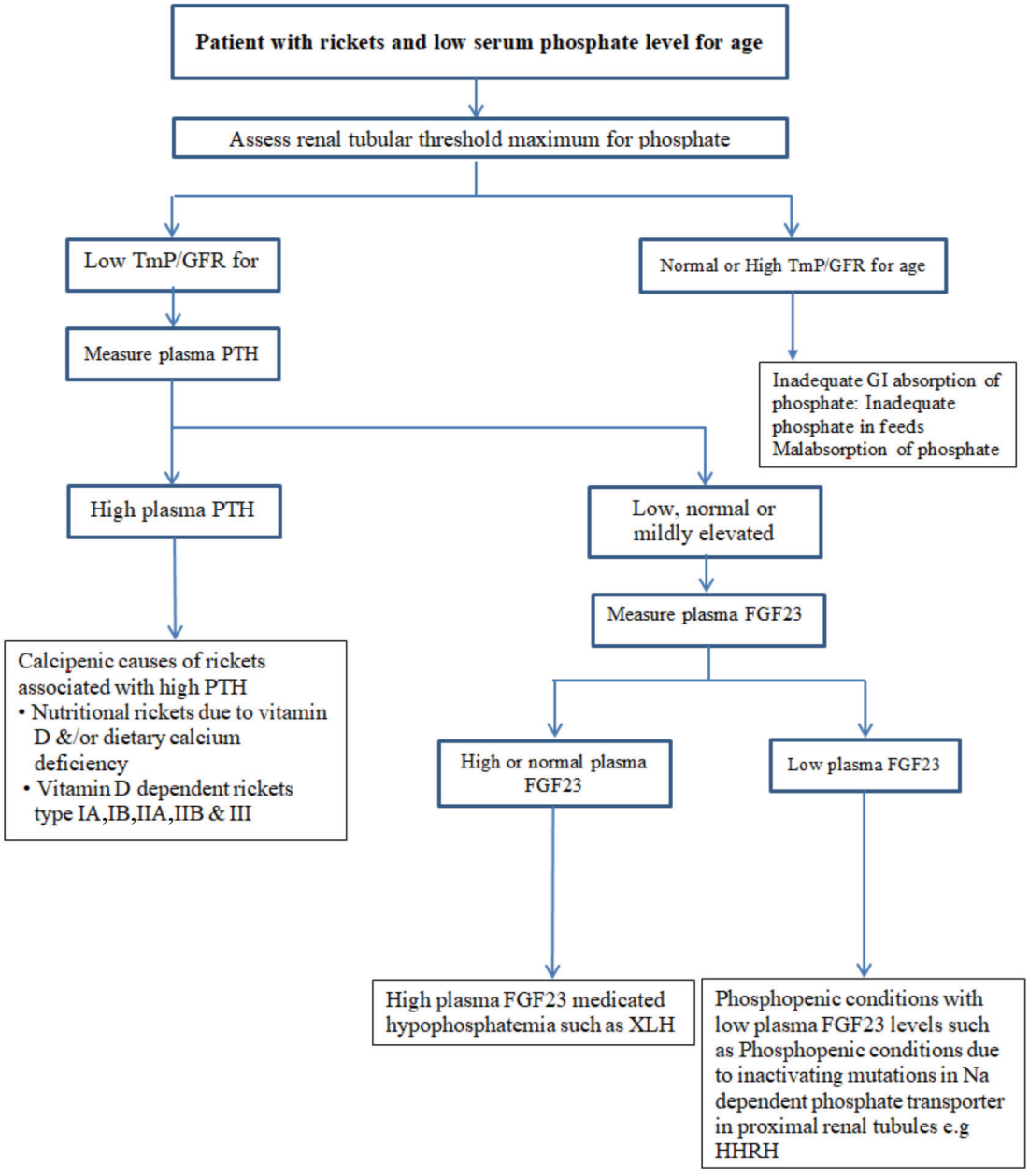

Figure 2. A biochemical algorithm for the assessment of a patient with rickets and low phosphate level for age

TmP/GFR: renal tubular threshold maximum for phosphate, PTH: parathyroid hormone, FGF23: fibroblast growth factor 23, XLH: X linked hypophosphatemic rickets, HHRH: hereditary hypophosphatemic rickets with hypercalciuria

Nutritional phosphate deficiency is not a common cause of hypophosphatemic rickets; instead, the majority of cases are caused by excessive phosphate wasting, which can be caused by an excess of FGF23, as in X-linked hypophosphatemic rickets, or by a primary defect in the Na-Po4 cotransporter, as in Dent disease (2). Given that the majority of cases reported in relation to Neocate® usually have multiple medical problems, and hypophosphatemia can be explained by a variety of factors such as prematurity and malabsorptive disorders, there is a tendency to delay in reporting these cases, which is understandable given that the majority of cases are recently reported.

Using a standard biochemical approach to hypophosphatemia treatment is one way to detect these cases early. Figure 2 depicts the stepwise biochemical approach for rickets. It is recommended that any patient with hypophosphatemia have their PTH level checked; if it is high, this means the primary defect is calcium deficiency, which could be caused by calcium or vitamin D deficiency, with nutritional vitamin D deficiency being the most common cause. If the PTH level is normal, the phosphate level in the urine should be evaluated; if it is low, it is due to nutritional deficiency or gut malabsorption; if it is high, it is due to excessive FGF23 or primary renal tubulopathy (18). The high $1,25(OH)_2D$ level observed in our patient could be confused with other vitamin D-related disorders, such as vitamin D-dependent rickets type 2, which is caused by a mutation in the vitamin D receptor. The high $1,25(OH)_2D$ level in our patient was related to a decrease in oral phosphate absorption, which leads to increased expression of one alfa hydroxylase enzyme in the kidney, which is responsible for converting 25(OH) vitamin D to its active form, $1,25(OH)_2D$.

The treatment of nutritional hypophosphatemia caused by Neocate® is not well established; there is a tendency for hyperphosphatemia after phosphate administration or formula substitution, which is explained by the expression of the Na-PO_4 cotransporter in the gut and kidney as a result of chronic hypophosphatemia and low FGF23 (19). To avoid hyperphosphatemia and secondary hypocalcemia, the phosphate dose should be gradually increased while calcium and phosphate levels are closely monitored. Rebound hypophosphatemia and hypocalcemia can also occur as a result of hungry bone syndrome caused by longstanding bone mineral depletion (20).

Conclusion

In patients with multiple co-morbidities, chronic hypophosphatemia due to the possibility of reduced phosphate bioavailability in Neocate® formula should be considered. We recommend that these patients taking Neocate® formula have their minerals and electrolytes checked on a regular basis. A prospective randomized study with a homogeneous group of patients should be performed to explore the potential patient-related factors that could increase the risk of developing hypophosphatemia, which could help in a better understanding of this association.

Ethics

Informed Consent: Informed consent was taken from the father for this material to be published.

Authorship Contributions

Concept: Fahad Al-Juraibah, Maali Melha, Azam Alromaih, Design: Fahad Al-Juraibah, Maali Melha, Azam Alromaih, Data Collection or Processing: Fahad Al-Juraibah, Maali Melha, Azam Alromaih, Analysis or Interpretation: Fahad Al-Juraibah, Fahad Al-Juraibah, Maali Melha, Azam Alromaih, Areej Al-Sunaid, Literature Search: Fahad Al-Juraibah, Fahad Al-Juraibah, Maali Melha, Azam Alromaih, Areej Al-Sunaid, Writing: Fahad Al-Juraibah, Fahad Al-Juraibah, Maali Melha, Azam Alromaih, Areej Al-Sunaid

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