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CASE REPORT

Nutritional hypophosphatemic rickets secondary to Neocate® use

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Abstract

Elemental formula is commonly used in children with feeding intolerance. We describe two, medically complex and feeding tube dependent, patients exclusively fed with Neocate® who subsequently developed hypophosphatemic rickets. Both patients had gross motor decline and pain with physical touch. They were found to have low serum phosphorus, normal calcium, and vitamin D studies, with elevated alkaline phosphatase suggestive of nutritional hypophosphatemia. Both courses were complicated by hypocalcemia following formula change and phosphorus supplementation, highlighting the need for careful management of phosphate repletion in affected individuals. Diligent serial electrolyte monitoring as well as attention to bone health is needed in conjunction with elemental nutrition. Formula change led to restoration of calcium and phosphorus homeostasis and radiographic improvement in these patients.

Abbreviations

GI	Gastrointestinal
FDA	Food and Drug Administration
GERD	Gastroesophageal reflux disease
G-Tube	Gastrostomy tube
ALP	Alkaline phosphatase
TRP	Tubular reabsorption of phosphate
EoE	Eosinophilic esophagitis
SFED	Six food elimination diet
IV	Intravenous
PPI	Proton pump inhibitors

Table of Contents Summary: We describe two patients exclusively fed with Neocate® who developed hypophosphatemic rickets. Both courses were complicated by hypocalcemia following intervention, highlighting the need for careful management in affected individuals.

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Introduction

Phosphate homeostasis plays a critical role in adequate bone mineralization in the growing child. Prolonged hypophosphatemia can lead to hypophosphatemic rickets. Signs and symptoms of rickets include impaired growth, flaring of ribs, waddling gait, and other skeletal defects as well as weakness and pain [1, 2]. The etiology of hypophosphatemia can be classified into three main categories—the most common being renal phosphate wasting due to genetic defects; second is nutritional phosphate deficiency due to decreased intestinal absorption of phosphorus seen in starvation, intestinal malabsorption, or antacid overuse; and lastly, extracellular phosphate deficiency due to shifts of phosphorus intracellularly following recovery from diabetic ketoacidosis or nutritional repletion as seen in "Hungry Bone Syndrome."

Neocate® (Nutricia) is an elemental, amino acid-based formula initially released in 1995 that was widely used in the care of children with feeding difficulties including multiple food allergies, eosinophilic gastrointestinal (GI) disorders, and intestinal malabsorption [3, 5]. Although the original formulation of Neocate® satisfied FDA requirements for phosphate content [4, 5] and was comparable to other elemental formulas on the market, recent reports link Neocate® use to the development of hypophosphatemic rickets in over 50 patients to date [6, 7].

We describe two patients exclusively fed the original formulation of Neocate® that subsequently developed hypophosphatemic rickets. Both of their courses were

complicated by delayed diagnosis followed by hypocalcemia with acute intervention, highlighting the need for careful management of phosphate repletion in affected individuals. Given the widespread use of elemental formulas, clinicians should be vigilant for similar manifestations with other elemental formulas as the exact reason for this finding remains unknown, and phosphorous should be monitored.

Case vignette 1

A 3-year-old boy with complex congenital heart disease status post Glenn repair, developmental delay, gastroesophageal reflux disease (GERD) was status post Nissen fundoplication, and gastrostomy tube (G-Tube) placement for intact protein formula intolerance in the setting of gastroparesis. He was started on Neocate® for 18 h a day at 1 year of age. Three months after starting Neocate®, he stopped attempting to walk. Over 2 years, he continued to regress and eventually refused to crawl and resorted to scooting. He struggled in physical therapy and experienced pain with physical touch. Metaphyseal widening with swelling was noted particularly on the right side. Radiographic skeletal survey revealed bilateral metaphyseal widening and growth plate irregularity, without evidence of fractures (Fig. 1).

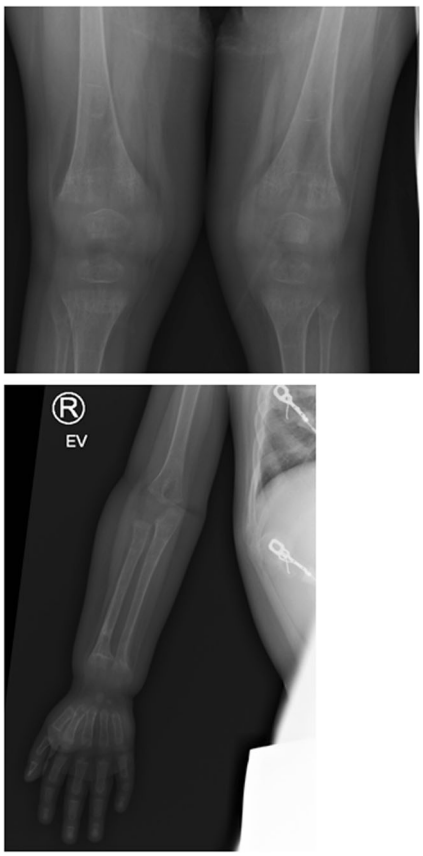

Fig. 1 Skeletal survey showing widening and fraying of the metaphases bilaterally consistent with rickets

Biochemical evaluation showed low serum phosphorus of 2.2 mg/dL (4.5–5.5 mg/dL) and elevated alkaline phosphatase (ALP) of 776 IU/L (80–220 IU/L). Serum calcium and magnesium levels were normal. Urine studies revealed low urine phosphorus of 6 mg/dL (20–60 mg/dL) and normal tubular reabsorption of phosphate (TRP) of 0.98 (normal >0.85), consistent with nutritional hypophosphatemic rickets.

Formula was changed to an alternate amino acid-based formula (EleCare®, Abbott), and he was started on enteral phosphorus supplementation with rapid correction of his hypophosphatemia. His course was complicated by hyperphosphatemia with subsequent hypocalcemia, which resolved with cessation of phosphorus supplementation and the addition of enteral calcium supplementation. Interestingly, he was not able to tolerate full transition to EleCare® due to ongoing electrolyte abnormalities of hyperphosphatemia and hypocalcemia. He was placed on a combination of both formulas (1 part EleCare® to 9 parts Neocate®) with stabilization of his electrolytes. ALP normalized 3 months after his formula transition. He has since transitioned to Peptamen Jr.® with purees through his G-tube as well as enteral calcium supplementation.

Case vignette 2

A 3-year-old boy with an undiagnosed neuromuscular disorder with hypotonia and tracheostomy dependence was status post gastrojejunostomy tube dependent for severe, recurrent, emesis unresponsive to various elimination diets. Etiology for feeding dysfunction included eosinophilic esophagitis (EoE), GERD, and intestinal dysmotility. After the failure of a blenderized six food elimination diet (SFED), transition to an elemental diet with Neocate® at 2 years, 9 months of age resulted in resolution emesis and histological remission of his EoE.

Two months following formula change, although emesis was dramatically improved, parents noted weakness, decreased activity, and abrupt changes in behavior. He stopped crawling with notable decline in his gross motor function and posture. He also had difficulty with physical therapy and tolerating minimal physical touch. These findings were initially attributed to progression of his underlying neurological disease. After 7 months of exclusive elemental diet, he sustained a left forearm fracture following minimal movement during a diaper change.

Biochemical evaluation showed low serum phosphorus of 1.3 mg/dL and elevated ALP of 1080 IU/L (81% bone specific following fractionation). Serum calcium and magnesium levels were normal. X-rays revealed left proximal radial and ulnar diaphyseal fractures as well as fraying of the metaphases (Fig. 2).

He was initially admitted for parenteral phosphorus supplementation, which led to rapid, over correction of his

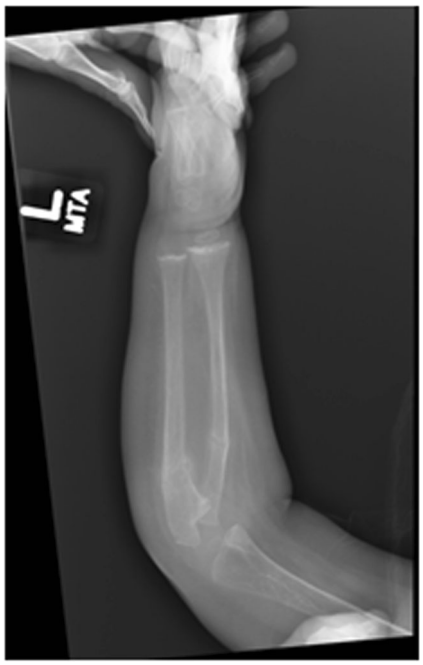

Fig. 2 Forearm X-ray showing healing radial and ulnar fractures, fraying of the metaphysis

phosphorus with subsequent hypocalcemia. This resolved with parenteral calcium supplementation. His formula was changed to EleCare® upon admission with correction of his electrolytes. He had significant clinical improvement within days of formula change including restored posture and resolved tenderness. He remains off calcium and phosphorus supplementation with near normal ALP.

Discussion

We describe two patients with hypophosphatemia secondary to Neocate® use. Baseline basic metabolic profiles were normal; however phosphorus and bone metabolic profiles were not initially obtained in either patient as they were not considered routine care at that time. Following Neocate®, both patients were found to have low serum phosphorus, normal serum calcium and Vitamin D studies, elevated ALP, and characteristic X-ray changes, consistent with hypophosphatemic rickets. The diagnosis of nutritional phosphate deficiency can be made from low phosphorus in the urine, however, only patient 1 had diagnostic urine studies ruling out renal phosphate wasting.

These cases highlight the inability of a particular subset of patients to adequately absorb phosphate in the setting of Neocate® use; the mechanism of which is not well understood at this time. Both EleCare® and Neocate® meet the FDA standard of 25 mg of phosphate per 100 kcal of formula [4, 5, 8]. Even though Elecare® does contain slightly more phosphate per liter prepared at 30 kcal/fluid ounce (854 mg versus 707.05 mg in Neocate®), both are adequate to meet nutritional needs. Neocate® has phosphate in the form of dipotassium phosphate and tricalcium phosphate, whereas Elecare® contains calcium phosphate, potassium phosphate, and magnesium phosphate. Current conjecture is that the bioavailability of these phosphates may differ, causing select patients to have poorer absorption with the prior formulation of Neocate®.

Previous case reports have noted similar, undiagnosed, hypophosphatemia leading to rickets in the setting of Neocate® use seen in Table 1. Presentation of those previously reported range from multiple fractures concerning for non-accidental trauma to incidental finding chemistry profiling. Only six have been described in detail and include elevation of ALP noted as early as 3 months of age. Most cases reported are also medically complex and feeding tube dependent. These complexities may inhibit phosphorus absorption from the gut, however, this is not observed when these same patients are transitioned to EleCare® [6, 7].

In addition to formula change, our patients received phosphorous supplementation which patient 1 received enterally and patient 2 received intravenously. In both cases, phosphate supplementation was promptly discontinued due to hyperphosphatemia. The rapid rise in phosphate levels led to excess phosphorus binding to serum calcium, resulting in hypocalcemia. Both patients required transient calcium supplementation. Patient 2 had a larger, more rapid, drop in calcium compared to patient 1 on enteral phosphorus supplementation. The danger of parenteral phosphate supplementation causing precipitous hypocalcemia has also been described in other clinical scenarios [3]. Thus, if clinically feasible, IV phosphate supplementation should not be used in the management of nutritional hypophosphatemia, as rapid correction can lead to profound hypocalcemia as seen in our patients.

Ongoing electrolyte abnormalities following formula change to full strength EleCare® has not been previously reported. These cases underscore the importance of diligent serial electrolyte monitoring as well as attention to bone health in these patients, both acutely during initial transition to elemental therapy as well as long-term follow-up. Patient 1 required close outpatient monitoring for the first 3 months to tailor both mineral supplements and formula to maintain normal calcium and phosphorus levels. Exclusive formula change may not be sufficient in correcting electrolytes and should be in conjunction with enteral mineral supplementation when needed.

As most cases are in the setting of medical complexity, it seems likely that host factors mitigate the absorption of phosphate and should be further explored. Both of the described patients were taking acid suppressive medication—proton pump inhibitors (PPI) which decrease the gastric acidity and may alter phosphate uptake. Similarly, Gonzalez Ballesteros, et al. reported 91% of patients with elemental formula associated hypophosphatemia and medication documentation were on PPI's [6]. Long-term antacid use has been associated with

Table 1 Clinical characteristics of patients with hypophosphatemic rickets on exclusive Neocate®

	Age at presentation	Diagnoses	Duration on exclusive Neocate®	Phosphorus (mg/dL)	ALP (IU/L)
Gonzalez Ballesteros et al.*					
Case 1	18 months	Esophageal atresia/tracheoesophageal fistula repair and NEC	1 year	1.3	1137
Case 2	4 years	HIE, gastric dysmotility, developmental delay, seizures	2.6 years	1.7	1014
Case 3	3.5 months	Bronchopulmonary dysplasia feeding intolerance	1.5 months	2.9	776
Case 4	8 months	Retinopathy of prematurity, microcephaly, reflux, hypertonia	6 months	2.9	1510
Case 5	6.5 years	Epidermolysis bullosa, global developmental delay	3.5 years	0.6	–
K. Abulebda et al.					
Case 1	2 years	Pierre-Robin sequence, HIE, global developmental delay, recurrent pneumonia, and feeding difficulties	–	1.1	3777
Our Case Series					
Patient 1	3 years	Tricuspid atresia and VSD status post bidirectional Glenn repair), motor and speech delay, and GERD with feeding intolerance	2 years	2.2	776
Patient 2	3 years	Neuromuscular disorder with hypotonia, tracheostomy dependence, oculomotor apraxia, eosinophilic esophagitis, gastrostomy tube dependence	7 months	1.3	1080

NEC, necrotizing enterocolitis; *HIE*, hypoxic ischemic encephalopathy; *GERD*, gastroesophageal reflux; *VSD*, ventricular-septal defect

*An additional 46 patients were described in supplemental data without sufficient details to be included in this summary

osteoporosis in young adults [9] with one reported pediatric case of hypophosphatemic rickets after chronic PPI [10]. No systematic studies have been done to investigate this correlation. Additionally, both of these patients had normal vitamin D levels, however, if present vitamin D deficiency could exacerbate bone demineralization.

As these cases are only coming to light after years of widespread use, research is needed to delineate risk factors and mechanisms. Neocate® has been reformulated in response to these reports. Watchfulness should still be implored with any elemental formula use as this phenomenon may occur with other products. Clinicians should especially consider this entity in children who are on exclusive enteral nutrition. In patients who are medically complex and elemental formula dependent via G-tube, we suggest baseline chemistry including sodium, potassium, bicarbonate, total calcium, albumin, and phosphorus as well as vitamin D levels at time of formula initiation, followed by periodic electrolyte monitoring every 3 to 6 months until further recommendations with larger studies are made. If electrolyte abnormalities are present, would recommend consultation for endocrinologist for further evaluation.

Conclusion

This report, together with existing literature, highlights the risk of hypophosphatemia in patients exclusively fed Neocate®, a widely used elemental formula [11, 12]. Although not all cases with documented hypophosphatemia progressed to rickets, prolonged nutritional hypophosphatemia can go unrecognized. Thus, periodic electrolyte monitoring that includes phosphorous, in conjunction with clinical vigilance for bone health is needed in patients dependent on elemental formula. Prompt formula change can prevent rickets, although in some cases, supplementation is also required. Phosphorus supplementation should be approached cautiously, and with the assistance of a pediatric endocrinologist, to avoid drastic swings in serum calcium and phosphorus. Enteral phosphorus supplementation is preferred over IV to avoid precipitating rapid hypocalcemia. Restoration of calcium and phosphorus homeostasis leads to biochemical and radiographic improvement in these patients.

Compliance with ethical standards

Conflicts of interest None.

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