10.4274/jcrpe.galenos.2022.2022-8-23

Case report

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

Al Juraibah F et al. Elemental Formula and Hypophosphatemic Rickets

Fahad Al Juraibah[1,2,3*] Maali Melha[1], Azam Alromaih[2] Areej Al-Sunaid[1,2,3], Hamad Abdullah Alkhalaf[1,2,3]
[1]Pediatric Department, King Abdullah Specialist Children's Hospital, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia
[2]College of Medicine, King Saud bin Abdul-Aziz University for Health Sciences, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia
[3]King Abdullah International Medical Research Center, Ministry of National Guard Health Affairs Riyadh, Saudi Arabia

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 FGF23, 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 described 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. We present here 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

Fahad Al Juraibah MD, Head, Pediatric Endocrinology Division, Department of Pediatrics, King Abdullah Specialized Children's Hospital, King Abdulaziz Medical City, Riyadh11426, Saudi Arabia
+(011)8011111 Ext. 53549
juraibahf@ngha.med.sa
05.09.2022
12.12.2022

Published: 16.02.2023

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).
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 medication. 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 (7–10). 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 US Food and Drug Administration (FDA) has approved Neocate® for use, and it contains a comparable amount of phosphate to other formulas (11). We described a patient who has developed hypophosphatemic rickets after being exclusively fed with Neocate® formula, which was resolved by switching formulas.

Case presentation:

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 (SNHL), large patent ductus arteriosus (PDA) status post ligation, right multicystic dysplastic kidney, chronic lung disease due to chronic micro aspiration syndrome on home oxygen, severe gastroesophageal reflux disease (GERD) 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; at the age of one year, his length and weight were 66 cm and 5.3 kg respectively, 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 caloric 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 gastric tube 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 parathyroid hormone (PTH), normal calcium, normal 25-hydroxyvitamin D levels, and tubular renal re-absorption of phosphate (TRP) 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 gastric tube and provided him with nearly 100 Kcal/kg/day. He had no diarrhea or other gastroenterology symptoms. Because it was suspected 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 1 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).

Discussion

Our 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 a large French and Chinese cohort of patients with Wiedemann-Steiner syndrome reports, 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 and that a prospective study to explain these associations is needed.

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)2 D level observed in our patient could be confused with other vitamin D-related disorders, such as vitamin D-dependent rickets type II, which is caused by a mutation in the vitamin D receptor. The high 1.25(OH)2 D level in our patient is related to a decrease in oral phosphate, 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)2 D.

The treatment of nutritional hypophosphatemia caused by Neocate® is not well established; there is a tendency of hyperphosphatemia after phosphate administration or formula substitution, which is explained by the expression of the $Na\text{-}PO_4$ 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. S Rebound hypophosphatemia and hypocalcemia can also occur as a result of hungry bone syndrome caused caused by longstanding bone mineral depletion **(20).**

Conclusion

In patients with multiple co-morbidities, chronic hypophosphatemia due to possibility of reduced phosphate bioavailability in Neocate® formula should be considered. We recommend that patients taking Neocate® formula have their minerals and electrolytes checked on a regular basis. A

prospective randomized study on 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.

Data Availability

The data used to support the finding of this study are included with the article.

Consent

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

Conflict of Interest

The authors declare that they have no conflicts of interest.

Author contributions

FA, MM, AA, conceived and designed the study, acquired the data, analyzed and interpreted the data, and drafted the article. FA, AAS, HA revised it critically for important intellectual content. All authors approved the final version to be published.

References

1. Aljuraibah F, Bacchetta J, Brandi ML, Florenzano P, Javaid MK, Mäkitie O, Raimann A, Rodriguez M, Siggelkow H, Tiosano D, Vervloet M, Wagner CA. An Expert Perspective on Phosphate Dysregulation With a Focus on Chronic Hypophosphatemia. J Bone Miner Res. 2022 Jan;37(1):12-20. DOI: 10.1002/jbmr.4486. Epub 2021 Dec 23. PMID: 34870347.

2. Florenzano P, Cipriani C, Roszko KL, Fukumoto S, Collins MT, Minisola S, Pepe J. Approach to patients with hypophosphataemia. Lancet Diabetes Endocrinol. 2020 Feb 1;8(2):163-74. DOI: 10.1016/S2213-8587(19)30426-7

3. De Menezes FS, Leite HP, Fernandez J, Benzecry SG, de Carvalho WB. Hypophosphatemia in Children Hospitalized Within An Intensive Care Unit. J. Intensive Care Med. 2006 Jul;21(4):235-9. DOI: 10.1177/0885066606287081

4. Amanzadeh J, Reilly RF. Hypophosphatemia: An Evidence-Based Approach to Its Clinical Consequences and Management. Nature clinical practice Nephrology. 2006 Mar;2(3):136-48.

5. Michigami T, Ozono K. Roles of phosphate in skeleton. Front. Endocrinol. 2019 Mar 26;10:180. DOI: 10.3389/fendo.2019.00180

6. Carpenter TO, Shaw NJ, Portale AA, Ward LM, Abrams SA, Pettifor JM. Rickets. Nat. Rev. Dis. Primers. 2017 Dec 21;3(1):1-20. DOI: 10.1038/nrdp.2017.101

7. Akhtar Ali S, Mathalikunnel A, Bhardwaj V, Braskett M, Pitukcheewanont P., Nutritional Hypophosphatemic Rickets Secondary to Neocate® Use. Osteoporos Int. 2019 Sep;30(9):1887-1891. doi: 10.1007/s00198-019-04836-8. Epub 2019 May 29. PMID: 31143989.

8. Uday S, Sakka S, Davies JH, Randell T, Arya V, Brain C, Tighe M, Allgrove J, Arundel P, Pryce R, Högler W, Shaw NJ. Elemental Formula Associated Hypophosphataemic Rickets. Clin Nutr. 2019 Oct;38(5):2246-2250. doi: 10.1016/j.clnu.2018.09.028. Epub 2018 Sep 28. PMID: 30314926.

9. Ang KH, Patel AD, Berkwitt AK. An Unusual Presentation of Hypophosphatemic Rickets. AACE Clin. Case Rep. 2018 Jan 1;4(1):35-8. DOI:10.4158/EP171853.CR

10. Gonzalez Ballesteros LF, Ma NS, Gordon RJ, Ward L, Backeljauw P, Wasserman H, Weber DR, DiMeglio LA, Gagne J, Stein R, Cody D, Simmons K, Zimakas P, Topor LS, Agrawal S, Calabria A, Tebben P, Faircloth R, Imel EA, Casey L, Carpenter TO. Unexpected Widespread Hypophosphatemia and Bone Disease Associated with Elemental Formula Use in Infants and Children. Bone. 2017 Apr;97:287-292. doi: 10.1016/j.bone.2017.02.003. Epub 2017 Feb 4. PMID: 28167344; PMCID: PMC5884631.

11. Nutricia North America. Neocate junior. Available at: https://www.neocate.com/shop/cat egory/9/neocate-junior. Accessed 25 February 2018

12. Verduci E, Salvatore S, Bresesti I, Di Profio E, Pendezza E, Bosetti A, Agosti M, Zuccotti GV, D'Auria E. Semi-Elemental and Elemental Formulas for Enteral Nutrition in Infants and Children with Medical Complexity—Thinking about Cow's Milk Allergy and Beyond. Nutrients. 2021 Dec;13(12):4230. DOI: 10.3390/nu13124230

13. Harvey BM, Eussen SRBM, Hartheorn LF, Burks AW. Mineral Intake and Status of Cow's Milk Allergic Infants Consuming an Amino Acid-based Formula. J Pediatr Gastroenterol Nutr. 2017 Sep;65(3):346-349. doi: 10.1097/MPG.0000000000001655. PMID: 28604516; PMCID: PMC5559186.

14. Bergwitz C, Eussen SR, Janssens PL, Visser M, Carpenter TO, van Helvoort A. Different Elemental Infant Formulas Show Equivalent Phosphorus and Calcium Bioavailability in Healthy Volunteers. Nutr Res. 2021 Jan 1;85:71-83. DOI 10.1016/j.nutres.2020.11.004

15. Fontana P, Passaretti FF, Maioli M, Cantalupo G, Scarano F, Lonardo F. Clinical and Molecular Spectrum of Wiedemann-Steiner Syndrome, An Emerging Member of the Chromatinopathy Family. World J Med Genet 2020 Jun 20;9(1):1-1. DOI:10.5496/wjmg.v9.i1.1

16. Li N, Wang Y, Yang Y, Wang P, Huang H, Xiong S, Sun L, Cheng M, Song C, Cheng X, Ding Y. Description of the molecular and phenotypic spectrum of Wiedemann-Steiner syndrome in Chinese patients. Orphanet J Rare Dis. 2018 Dec;13(1):1-3.

17. Baer S, Afenjar A, Smol T, Piton A, Gerard B, Alembik Y, Bienvenu T, Boursier G, Boute O, Colson C, Cordier MP. Wiedemann-Steiner syndrome as a major cause of syndromic intellectual disability: A study of 33 French cases. Clin Genet. 2018 Jul;94(1):141-52.

18. Al Juraibah F, Al Amiri E, Al Dubayee M, Al Jubeh J, Al Kandari H, Al Sagheir A, Al Shaikh A, Beshyah SA, Deeb A, Habeb A, Mustafa M, Zidan H, Mughal MZ. Diagnosis and Management of X-linked Hypophosphatemia in Children and Adolescent in the Gulf Cooperation Council Countries. Arch Osteoporos. 2021 Mar 4;16(1):52. doi: 10.1007/s11657-021-00879-9. PMID: 33660084; PMCID: PMC7929956.

19. Hattenhauer O, Traebert M, Murer H, Biber J. Regulation of Small Intestinal Na-Pi type IIb Cotransporter By Dietary Phosphate Intake. Am. J. Physiol. Gastrointest. Liver Physiol. 1999 Oct 1;277(4):G756-62. DOI: 10.1152/ajpgi.1999.277.4.G756

20. Witteveen JE, Van Thiel S, Romijn JA, Hamdy NA. Hungry Bone syndrome: Still a Challenge in the Post-Operative Management of Primary Hyperparathyroidism: A Systematic Review of the Literature. Eur J Endocrinol. 2013 Mar 31;168(3):R45-53. DOI: 10.1530/EJE-12-0528

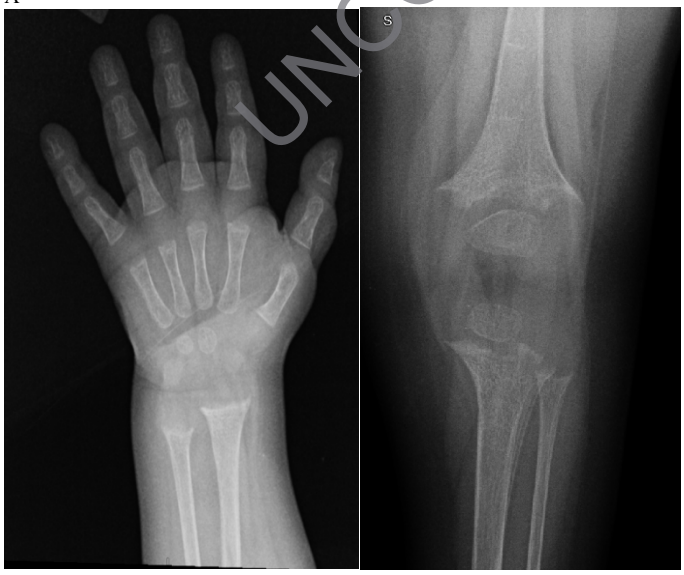
Table1. Laboratory results at baseline and in response to changing the feeding milk formula

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
25OHD (nmol/L)		127.6	-	-	91.6	-	107.9
1,25 $(OH)_2$ D	62.6-228	552.4	-	-	-	-	-
Urine phosphate (mmol/L)		<1.62	-		-	-	-
Urine creatinine (mmol/L)		7.9	-	-	-	-	-

PTH, Parathyroid Hormone; ALP, Alkaline Phosphatase; 25OHD, 25-OH Vitamin D; 1, 25 $(OH)_2$ D, 1,25 Dihydroxyvitamin D.

Figure 1. A & B show the baseline and follow-up radiographs of the left lower extremity and hand. Figure 1A 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. Figure 1B 1 year follow-up shows improved mineralization and healing of rickets

A



B

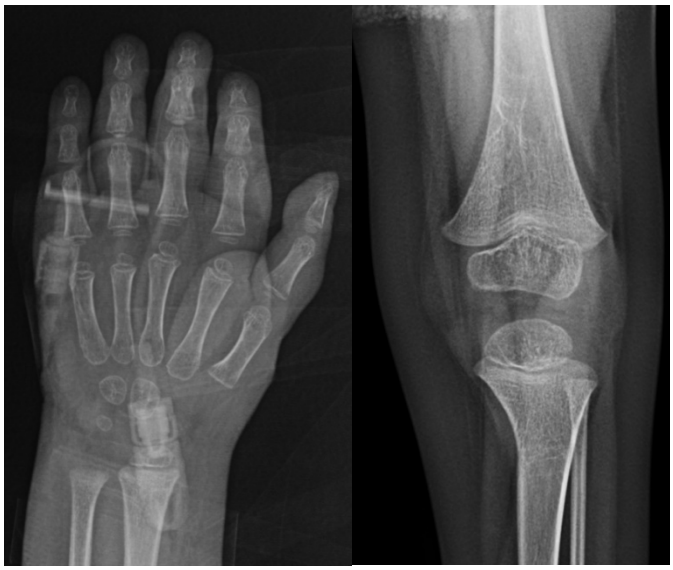


Figure 2. A biochemical algorithm for the assessment of a patient with rickets and low phosphate level for age. TmP/GFR, renal tubular threshold maximum for phosphate; PTH, parathyroid hormone; FGF23, fibroblast growth factor 23; XLH, X linked hypophosphatemic rickets; HHRH, hereditary hypophosphatemic rickets with hypercalciuria