Title
Copper Deficiency Anemia and Neutropenia Due to Ketogenic Diet

Journal
Pediatrics, 141(5)

ISSN
0031-4005

Author
Chin, Alan

Publication Date
2018-05-01

DOI
10.1542/peds.2017-3286

Copper Deficiency Anemia and Neutropenia due to Ketogenic Diet

Alan Chin, MD

Affiliations: UCLA Mattel Children's Hospital, Los Angeles, California

Address correspondence to: Alan Chin, Department of Pediatrics, UCLA Mattel Children's Hospital, 757 Westwood Plaza, 3018, Los Angeles, CA, 90095-1752, aschin@mednet.ucla.edu, 310-267-0119

Short title: Copper Deficiency in Ketogenic Diet

Funding Source: No funding was secured for this study

Financial Disclosure: The author has no financial relationships relevant to this article to disclose

Conflict of Interest: The author has no conflicts of interest to disclose

Table of Contents Summary: Copper deficiency is an uncommon cause of anemia and neutropenia and can present due to restrictions of a ketogenic diet.

Abbreviations: MCV – mean corpuscular volume, PCR – polymerase chain reaction, TPN – total parenteral nutrition, WBC – white blood cell count, ANC – absolute neutrophil count, Hgb – hemoglobin, Plt – platelet

Abstract

Copper deficiency is an uncommon cause of hematologic abnormalities in children that is often overlooked or misdiagnosed. While cases have been reported due to malabsorption syndromes or following gastrointestinal surgeries, we report a case of copper deficiency associated anemia and neutropenia in a child due to dietary restrictions, specifically transitioning from a formula-based ketogenic diet to pureed food-based ketogenic diet. Upon copper supplementation, patient's anemia and neutropenia resolved. To our knowledge, this report is the first showing copper deficiency anemia and neutropenia developing due to ketogenic diet.

Introduction

Copper is an essential element in the functioning of the hematologic system. Often misdiagnosed as myelodysplastic disease, copper deficiency is an uncommon cause of hematologic abnormalities in children. Most often, copper deficiency is associated with total parenteral nutrition without copper supplementation, protein-losing enteropathies, gastrointestinal surgeries, malabsorption syndromes, and zinc toxicity.[1] However, in a recent review, 30% of patients that presented with hematologic abnormalities due to copper deficiency had no identified cause.[2] Additionally, median time to diagnosis of copper deficiency was one year.[2] This illustrates the difficulty in diagnosing copper deficiency, even though it is a known cause for hematologic abnormalities.

Ketogenic diets are an effective treatment for drug-resistant epilepsies in children. However, the mechanisms of action in controlling seizures are not well understood.[3] All ketogenic diets are essentially high fat, low carbohydrate diets that induce the production of ketone bodies through fatty acid catabolism.[4] An all liquid ketogenic formula is available, however transition to solid foods is possible as long as patients can adhere to a restricted diet of approximately 90% of calories from fat and only 10% from carbohydrates and proteins.[3]

In this report, we describe a 2-year-old girl who presented with neutropenia and anemia, which was found to be caused by copper deficiency due to dietary restrictions related to her ketogenic diet.

Case Report

A 2-year-old girl with a past medical history of microcephaly, lissencephaly, cerebellar hypoplasia, agenesis of corpus collosum, and seizure disorder, presented to our medical center in March 2016 with lethargy and hypothermia to 91 degrees Fahrenheit. Blood counts revealed leukopenia, with a white blood cell count of 2830/uL, neutropenia, with an absolute neutrophil count of 255/uL, and a macrocytic anemia, with a hemoglobin of 9g/dL and MCV 113.4fL. Platelet count, chemistry profile, and urinalysis were all normal. Of note, six months prior, the patient had completely normal blood counts.

In evaluating the patient's new onset neutropenia and anemia, we performed an extensive work-up. Viral or other infection induced bone marrow suppression was considered, however, blood culture, urine culture, respiratory virus polymerase chain reaction (PCR) panel, cytomegalovirus PCR, Ebstein-Barr virus PCR, and parvovirus B19 PCR drawn at the time of admission were negative. Folate and vitamin B12 deficiencies were considered, but levels obtained two weeks prior to presentation were normal. Hypothyroidism was ruled out as thyroid stimulating hormone and free thyroxine levels were normal. In specifically evaluating anemia, direct antibody testing was negative and haptoglobin and lactate dehydrogenase were normal, making hemolysis unlikely, and an iron panel was normal, ruling out iron deficiency. Myelodysplastic syndromes and other hematologic malignancies were ruled-out with a peripheral smear showing neutropenia with no blasts and an appropriate reticulocytosis, and a bone marrow biopsy showing

normocellular marrow with reduced and left-shifted myelopoiesis, adequate megakaryopoiesis, moderate hematogone hyperplasia, and occasional ring sideroblasts.

After review of initial work-up, we determined there were two possible etiologies for the patient's neutropenia and anemia: drug-induced from patient's anti-epileptic medications or a nutritional deficiency of trace elements, specifically copper, which may present with ringed sideroblasts.[5,6] The patient was taking two anti-epileptic medications known to cause neutropenia: levetiractem[7-9] and zonisamide.[10] However, she had been on stable doses of these medications for more than one year prior to the development of neutropenia and anemia and had normal blood cell counts while on these medications, suggesting these would not be the cause for her acute hematologic abnormalities.

The patient was also noted to be on an oral ketogenic diet as part of her seizure management, without the need for supplemental gastric or transpyloric feeds. Detailed diet history revealed that in the past six months, she had transitioned from a powdered ketogenic formula to pureed foods. Given the restrictions of her ketogenic diet, her pureed foods were limited to green beans, turkey, chicken, and olive oil. While the pre-formulated ketogenic formula contained adequate amounts of copper, the pureed foods did not. Based on the pureed ketogenic diet recipes, the patient received a range of 55-75mcg of copper per day, when the recommended daily amount is 350mcg/day for her age and weight (40mcg/kg daily).[11] Though the patient was taking a pediatric multivitamin suspension, the specific formulation contained no copper. Our patient's serum copper was found to be <10mcg/dL (normal 12-67mcg/dL). She was treated for copper deficiency with intravenous copper 20mcg/kg for two doses and discharged on oral copper glycinate powder 40mcg/kg daily. At her follow-up visit one month later, her complete blood

count improved with a white blood cell count of 8740/uL, absolute neutrophil count of 1520/uL, hemoglobin 10.6g/dL, and MCV 98.3 fL. Her serum copper level was 76mcg/dL. Table 1.

Discussion

Copper is an essential trace element that plays a crucial role in the normal functioning of the hematologic system.[2,5,6,12,13] Copper is absorbed in the stomach and proximal duodenum, but absorption can be impaired after gastrointestinal surgery[12] and in malabsorption syndromes, such as celiac disease and short bowel syndrome.[14,15] Copper deficiency can also occur in prolonged total parenteral nutrition (TPN) in the absence of copper supplementation,[15] protein-losing enteropathies, and zinc toxicity as zinc competes with copper for absorption in the gastrointestinal tract.[1]

The mechanism of copper deficiency neutropenia and anemia is not well understood.[1,16] However, the hematologic manifestations are well described – including microcytic, normocytic, and macrocytic anemia, severe absolute neutropenia, and rarely thrombocytopenia.[17] Given the low incidence of copper deficiency and usual adequate intake in children from developed countries, copper deficiency as the cause of anemia and neutropenia is often overlooked.[5,13,14,18] While we have focused on the hematologic abnormalities of copper deficiency, neurologic manifestations have also been described. Copper deficiency neuromyelopathy, including lower limb parethesias and gait disorders with sensory ataxia or spasticity, if present, may help identify this uncommon cause of hematologic abnormalities.[6] Other symptoms of copper deficiency may include fragile, abnormally-formed hair, depigmentation of the skin, edema, hepatosplenomegaly, and osteoporosis.

Once a patient is diagnosed with copper deficiency, management includes copper supplementation with copper salts, which can be given orally or intravenously. While there is no standard supplementation regimen, current practices are to supplement with a recommended daily amount of 40-50mcg/kg of elemental copper.[6,11,12] The hematologic abnormalities resolve within four to 12 weeks of therapy.[6,19,20]

Most reported cases of copper deficiency associated neutropenia and anemia in the pediatric population have been due to inadequate supplementation while receiving TPN, malabsorption, or in rare cases zinc toxicity.[18] However, in up to 30% of cases in adults, there is no identified cause of copper deficiency.[2] Previously, Carballo et al reported one case of low serum copper without hematologic manifestations in a cohort of 216 children prescribed ketogenic diet,[21] suggesting that copper deficiency is relatively rare in this patient population. Recently, a case report by Rashidian et al describes a similar case of severe neutropenia and anemia due to copper deficiency in a patient prescribed a ketogenic diet. However, in that case, the patient did receive adequate copper intake from her diet, and required supra-therapeutic supplementation of copper for resolution of the hematologic manifestations, suggesting copper metabolism may have been atypical in this patient.[22] Our case illustrates a novel etiology with the development of copper deficiency associated neutropenia and anemia due to dietary restrictions in transitioning from a formula-based to pureed food-based ketogenic diet.

Ketogenic diets are highly restrictive, which put patients at risk for nutritional deficiencies. Comprehensive nutritional evaluation and follow-up is very important in these patients, including regular evaluation for vitamin and mineral deficiencies.[3] Multivitamins with minerals should be recommended for all patients on ketogenic diets.

In evaluating neutropenia and anemia of unknown etiology, our case highlights the need to elucidate a thorough dietary history and to consider copper deficiency in not only patients with risks of malabsorption, but also in those with restrictive diets.

References

1. Lazarchick J. Update on anemia and neutropenia in copper deficiency. *Current opinion in hematology.* Jan 2012;19(1):58-60.
2. Halfdanarson TR, Kumar N, Li CY, Phyliky RL, Hogan WJ. Hematological manifestations of copper deficiency: a retrospective review. *European journal of haematology.* Jun 2008;80(6):523-531.
3. Luat AF, Coyle L, Kamat D. The Ketogenic Diet: A Practical Guide for Pediatricians. *Pediatric annals.* Dec 01 2016;45(12):e446-e450.
4. Youngson NA, Morris MJ, Ballard B. The mechanisms mediating the antiepileptic effects of the ketogenic diet, and potential opportunities for improvement with metabolism-altering drugs. *Seizure.* Sep 13 2017;52:15-19.
5. Dalal N, Hooberman A, Mariani R, Sirota R, Lestingi T. Copper deficiency mimicking myelodysplastic syndrome. *Clinical case reports.* May 2015;3(5):325-327.
6. Gabreyes AA, Abbasi HN, Forbes KP, McQuaker G, Duncan A, Morrison I. Hypocupremia associated cytopenia and myelopathy: a national retrospective review. *European journal of haematology.* Jan 2013;90(1):1-9.
7. Bunnell K, Pucci F. Levetiracetam-induced neutropenia following traumatic brain injury. *Brain injury.* 2015;29(1):115-117.
8. Oh SJ, Kwon HI, Moon SH, Ro YS, Ko JY. Toxic epidermal necrolysis with isolated neutropenia related to the use of levetiracetam. *The Journal of dermatology.* Aug 2016;43(8):969-971.
9. Taberner Bonastre MT, Peralta Munoz S, Boza FM, Guma IPJ. Neutropenia secondary to exposure to levetiracetam. *Tumori.* Sep 09 2015;101(5):e145-146.
10. Zonegran (zonisamide) [prescribing information]. Woodcliff Lake, NJ: Eisai Inc. January 2012.
11. Hughes G, Kelly VJ, Stewart RA. The copper content of infant foods. *Pediatrics.* Mar 1960;25:477-484.
12. Chhetri SK, Mills RJ, Shaunak S, Emsley HC. Copper deficiency. *BMJ case reports.* Jun 17 2014;348:g3691.
13. Gregg XT, Reddy V, Prchal JT. Copper deficiency masquerading as myelodysplastic syndrome. *Blood.* Aug 15 2002;100(4):1493-1495.
14. Khera D, Sharma B, Singh K. Copper deficiency as a cause of neutropenia in a case of coeliac disease. Sep 15 2016;2016.
15. Mullally AM, Vogelsang GB, Moliterno AR. Wasted sheep and premature infants: the role of trace metals in hematopoiesis. *Blood reviews.* Dec 2004;18(4):227-234.
16. Percival SS. Neutropenia caused by copper deficiency: possible mechanisms of action. *Nutrition reviews.* Mar 1995;53(3):59-66.
17. Sutton L, Vusirikala M, Chen W. Hematogone hyperplasia in copper deficiency. *American journal of clinical pathology.* Aug 2009;132(2):191-199; quiz 307.
18. Sochet AA, Jones A, Riggs CD, Jr., Weibley RE. A 3-year-old boy with severe anemia and neutropenia. *Pediatric annals.* Jan 2013;42(1):15-17.

19. Huff JD, Keung YK, Thakuri M, et al. Copper deficiency causes reversible myelodysplasia. *American journal of hematology.* Jul 2007;82(7):625-630.
20. Naismith RT, Shepherd JB, Weihl CC, Tutlam NT, Cross AH. Acute and bilateral blindness due to optic neuropathy associated with copper deficiency. *Archives of neurology.* Aug 2009;66(8):1025-1027.
21. Caraballo R, Vaccarezza M, Cersósimo R, et al. Long-term follow-up of the ketogenic diet for refractory epilepsy: Multicenter Argentinean experience in 216 pediatric patients. *Seizure.* 2011/10/01/ 2011;20(8):640-645.
22. Rashidian H, Liu YMC, Geraghty MT, Kobayashi J, Donner EJ, Klaassen RJ. Severe Neutropenia and Anemia in a Child With Epilepsy and Copper Deficiency on a Ketogenic Diet. *Pediatric neurology.* Nov 2017;76:93-94.

Figures

Table 1: Laboratory Values

		Admission		Initiated Cu Supplement	
	2/22/2016	3/3/2016	3/10/2016	3/11/2016	4/4/2016
WBC (K/µL)	5	2.83	3.17	7.05	8.74
Hgb (g/dL)	7.6	9	7.1	7.7	10.6
MCV (fL)	107	113.4	111.7	112.1	98.3
Plt (K/µL)	349	213	228	350	401
ANC (K/µL)		255	0	250	1520
B12 (pg/mL)	3912	(Normal range 254-1060)			
Folate (ng/mL)	32	(Normal range 8.1-30.4)			
Copper (µg/dL)		< 10	(Normal range 12-67mcg/dL)		76