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Hematologic Manifestations of Nutritional Deficiencies: Early Recognition is Essential to Prevent Serious Complications

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Summary:

Nutritional deficiencies, including deficiencies of vitamin B_{12}, copper, and vitamin C, may result in cytopenias and hematologic symptoms. Early recognition of these deficiencies is imperative for prompt treatment and improvement in hematologic and other manifestations. We describe 5 cases which illustrate the hematologic manifestations of nutritional deficiencies and challenges to initial diagnosis and management. Supplementation of the deficient vitamin or micronutrient in all of these cases resulted in rapid resolution of cytopenias, hemorrhage, and other associated hematologic symptoms. We also review other nutritional deficiencies that manifest with hematologic symptoms and compile recommendations on treatment and expected time to response.

Keywords

cytopenias; hemorrhage; vitamin B_{12}; copper; nutritional deficiencies

Nutritional deficiencies are known to cause hematologic problems such as cytopenias and hemorrhage. However, there may be a delay in diagnosis if nutritional deficiencies are not included on the initial differential diagnosis of single or multiple cytopenias or bleeding. Vitamin B_{12} deficiency is the most common cause of megaloblastic anemia,[1] while copper deficiency is associated with anemia and neutropenia and can mimic myelodysplastic syndrome.[2] Both can cause serious, irreversible neurological effects if left untreated.[1,3] Scurvy, or vitamin C deficiency, is a forgotten disease as it is uncommon in our current environment, but children can present with acute illness including dermatologic, orthopedic, dental, and hematologic manifestations.[4]

It is important to appreciate that nutritional deficiencies are part of the differential diagnosis of cytopenias and hemorrhage. We describe 5 representative patients with nutritional

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deficiencies who presented with hematologic manifestations. This case series reviews the clinical presentation, diagnostic evaluation and management of nutritional deficiencies in pediatric patients at a single institution.

RESULTS

Case descriptions are detailed below and summarized in Table 1.

Case 1-Vitamin B_{12}

A 15-month-old female of south Indian descent initially presented to her primary doctor for her 12-month well child check and was noted to have mild anemia that persisted on recheck at her 15-month check. A complete blood count with differential and reticulocyte count showed normocytic anemia with reticulocytopenia and neutropenia. She was then referred to hematology clinic. On further history, the family was strictly ovo-vegetarian with a family history of anemia. Differential diagnosis included transient erythroblastopenia of childhood, congenital dyserythropoietic anemia, Diamond-Blackfan Anemia, and Shwachman-Diamond Syndrome. She required 1 packed red blood cell (pRBC transfusion for symptomatic anemia (hemoglobin of 6.6 g/dL). Vitamin B_{12} level was borderline low and serum methylmalonic acid (MMA) level was high, consistent with vitamin B_{12} deficiency. Within 5 days of her initial visit she began vitamin B_{12} 1000 mcg intramuscular (IM) injections monthly for 3 doses and was prescribed a multivitamin containing vitamin B_{12}. Anemia, reticulocytopenia, and neutropenia normalized within 16 days after supplementation.

Case 2-Vitamin B_{12}

A 9-month-old Hispanic female presented with pancytopenia and coagulopathy requiring admission to the pediatric intensive care unit (PICU) for which she received pRBC, platelets, and fresh frozen plasma. Before this episode she had been exclusively breastfed due to oral aversion with solid foods. She had a history of persistent thrush at 6 months and anemia. There was no family history of blood disorders. The initial differential diagnosis included thrombotic thrombocytopenic purpura, leukemia, toxic ingestion, and hemophagocytic lymphohistiocytosis. ADAMTS13 level was normal, bone marrow aspirate and biopsy did not show evidence of malignancy, toxicology screen was negative, and she did not meet criteria for hemophagocytic lymphohistiocytosis. Her coagulopathy was attributed to vitamin K deficiency, and she was started on IV vitamin K in the PICU, and transitioned to oral vitamin K after 3 days. As she did not have any signs of malabsorption, her vitamin K deficiency was attributed to dietary insufficiency and persistent thrush causing pain and decreased PO intake. Laboratory testing was sent to evaluate for vitamin B_{12}, folate, and copper deficiencies due to macrocytosis. Serum vitamin B_{12}, MMA, and cystathionine levels were consistent with vitamin B_{12} deficiency. After reviewing these test results, she was started on a multivitamin containing vitamin B_{12}, and her neutropenia and thrombocytopenia corrected within 1 week and anemia corrected within 2 months. Given how quickly her hematologic abnormalities corrected, she did not require IM injections of vitamin B_{12}. She was further evaluated in metabolic clinic, and also received occupational therapy to treat her oral aversion.

Whole-exome sequencing was sent as part of the Rady Children's Institute for Genomics Medicine research study due to the severity of her presentation. Four weeks after initial admission, whole-exome sequencing identified a heterozygous variant of unknown significance in the MMA metabolic pathway, which may be related to her vitamin B_{12} deficiency becoming clinically significant at such a young age.

Case 3-Vitamin C

A 12-year-old Hispanic female with Jacobsen syndrome, iron deficiency anemia, developmental delay, and autism spectrum disorder was admitted to the hospital for evaluation and management of gingival bleeding and left lower extremity edema, knee effusion, and refusal to bear weight. The differential diagnosis included nonaccidental trauma, platelet dysfunction secondary to Jacobsen syndrome, bleeding disorder, side effect of sertraline (which she was on for management of aggressive behaviors and anxiety), and leukemia. Evaluation included child protection team, orthopedics, dental, and nutrition consults, and extensive laboratory testing. On admission, sertraline was held, and she was transfused platelets for management of suspected platelet dysfunction associated with Jacobsen syndrome and pRBCs for an acute drop in hemoglobin. Magnetic resonance imaging of the lower extremities demonstrated bilateral femoral and tibial metaphyseal T1 hypointensity and T2 hyperintensity with patchy, near-symmetric areas of contrast enhancement. Periosteal elevation without definite subperiosteal collections suggested periosseous edema. There were multifocal areas of ill-defined T2 hyperintensity involving the soft tissues and muscles suggesting edema or hemorrhage, but no focal hematoma. There was also a left knee effusion. Nutrition assessment identified a very limited diet of potatoes, pasta and bean and cheese burritos. Because of the extent of gingival bleeding, poor nutrition, and magnetic resonance imaging findings, vitamin C deficiency was suspected and confirmed. Vitamin C was started 7 weeks after initial presentation, and bleeding symptoms resolved within 2 weeks of supplementation. Of note, she did have platelet function testing that was initially abnormal, but this was thought to be spurious due to thrombocytopenia. Repeat platelet function testing has been normal.

Case 4-Copper

A 5-year-old Hispanic female with short gut syndrome due to gastroschisis was evaluated by hematology due to a 5-week history of neutropenia and anemia. She had a history of total parenteral nutrition (TPN) dependence, but was receiving G-tube feedings for 1 year before presentation. She did have persistent diarrhea and failure to thrive. Initial workup included a negative antineutrophil antibody, normal folate, vitamin B_{12}, iron levels, and no evidence of hemolysis. Bone marrow evaluation was significant for erythroid elements with vacuoles, hemosiderin-laden macrophages, markedly increased stainable storage of iron and rare ring sideroblasts, suggestive of copper deficiency;[5] there was no evidence of malignancy or bone marrow failure. Copper and ceruloplasmin were low. Three months after initial detection of cytopenias, she was started on oral copper until 8 days later when a central venous catheter was placed for TPN at which point copper was given parenterally. Her copper deficiency was believed to be secondary to malabsorption due to her short gut syndrome. Two weeks after initiation of IV copper supplementation, copper levels normalized, neutropenia resolved within 3 days, and anemia improved after 1 month.

Case 5-Multiple

A 9-month-old previously healthy white female with decreased energy and pancytopenia for 1 month was admitted to the PICU for worsening fatigue, failure to thrive and hypotonia. Bone marrow evaluation was significant for 70% to 80% cellularity, megaloblastic changes, and no evidence of malignancy. She remained pancytopenic and was subsequently found to be coagulopathic with a subdural hematoma and global cerebral volume loss. Management of her coagulopathy in the PICU included fresh frozen plasma, pRBC, and platelet transfusions and vitamin K. Further diagnostic testing revealed markedly low serum B_{12} with elevated MMA and homocysteine levels, mildly low folate and copper levels, and markedly low vitamin D level. Mitochondrial and genomic testing were negative, and given that she had multiple vitamin deficiencies along with failure to thrive her overall picture was suspicious for malabsorption. The diagnosis of multiple vitamin deficiencies was made 5 weeks after initial presentation. Her pancytopenia and coagulopathy improved within 7 days on oral vitamin K, 2 doses of IM vitamin B_{12}, vitamin ADEK, and IV copper in TPN. Gastroenterology diagnosed her with a milk protein allergy. She was started on hypoallergenic feeds via nasogastric tube due to dysfunctional swallow, and received occupational therapy for her poor swallow. She has been tolerating enteral nutrition and her nasogastric tube has since been removed. She was weaned off oral vitamin K and vitamin ADEK and never required oral copper or vitamin B_{12} supplementation. On follow-up her complete blood count with differential has remained normal.

DISCUSSION

Now that the typical American diet is fortified with vital vitamins and minerals, nutritional deficiencies are less common and therefore often forgotten in the workup of cytopenias and hemorrhage. Clinicians should be aware of patients who are at risk for nutritional deficiencies, including patients with gut malabsorption,[6] such as our patient with short gut syndrome, or restricted diet due to behavior, such as our patient with autism spectrum disorder, personal choice, such as vegan diet, or food allergy, as in our patient with multiple nutritional deficiencies due to malabsorption and milk protein allergy. Moreover, it is important to note that normocytosis does not exclude the diagnosis of vitamin B_{12} deficiency, as demonstrated in case 1. Treatment includes managing the underlying cause of nutritional deficiency as well as prescribing the appropriate supplement. If malabsorption is present parenteral administration should be considered. Early identification is important to avoid unnecessary invasive interventions as well as preventable and sometimes irreversible complications of untreated deficiencies, such as neurologic effects in copper[7] and vitamin B_{12} deficiency,[8] or bleeding complications in vitamin C deficiency.[4] Current literature lacks consensus on appropriate management for patients with nutritional deficiencies and expected time to response.[9] Recommendations for treatment of vitamin deficiencies are derived from medication information resources[10-12] and limited published data.[1,4,6] Vitamin B_{12} can be given orally, via IM injection or subcutaneous injection. These reported cases illustrate that repletion of the deficient nutrient and subsequent correction of the hematologic abnormality occurs swiftly after initiation of the proper supplementation.

These cases also show that the diagnosis of nutritional deficiencies is not at the forefront of our differential diagnoses for hematologic abnormalities, and patients can go weeks to months before a diagnosis is discovered. Table 2 provides a summary of testing, management, and outcomes. There are other nutritional deficiencies not demonstrated by these 5 cases that can lead to hematologic abnormalities, such as iron, folate, vitamin K, and vitamin E. These are also included in Table 2. Iron deficiency anemia is the most common cause of anemia worldwide. The microcytic anemia seen with iron deficiency can be managed by general pediatricians, but often presents to the hematologist due to poor response to iron or for evaluation of thalassemia trait, and should be considered in conjunction with other nutritional deficiencies as it could obscure the overall picture. Folate deficiency, which can cause macrocytic anemia, is much less common in this era due to the fortification of many of our everyday foods as folate deficiency is associated with neural tube birth defects.[17] There has been a resurgence of Vitamin K deficiency due to increasing parental refusal of vitamin K prophylaxis at birth.[18] Thus, it is essential to recall that vitamin K deficiency can present with coagulopathy and bleeding, including intracranial hemorrhage in infants. Vitamin E deficiency can cause high turnover anemia and is more common in patients with cystic fibrosis.[19] Neurological abnormalities and increased infections can also be seen by vitamin E deficiency, and symptoms are reversible with vitamin E supplementation. Curation of additional cases over time may lead to a better understanding of complications and outcomes of nutritional deficiencies.

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TABLE 1.

Clinical Features of Nutritional Deficiencies

Case no, Nutritional Deficiency	Age at Diagnosis	Medical History and Contributing Factors	Presenting Symptoms	Relevant Laboratories at Dx	Nutritional Evaluation	Time to Diagnosis (wk)	Treatment	Time to Resolution (d)
1, Vit B_{12}	15 mo	Strictly ovo-vegetarian diet	Anemia, neutropenia; normal growth and development	WBC, 5.4[*] **Hgb, 6.6**[†] MCV, 78.3[‡] Plt, 230 k[§] **ANC, 840**[//]	Folate, > 24[¶] **Vit B_{12}, 267**[#] **MMA, 705**[**]	< 1	Vit B_{12}, 1000 mcg IM monthly ×3; PO multivitamin	16
2, Vit B_{12}	9 mo	Refusal to take solids, exclusively breastfed	Anemia, pancytopenia, coagulopathy, fever, cough, vomiting, diarrhea	WBC, 6.1 **Hgb, 3.9** MCV, 87.0 **Plt, 34 k ANC, 427 PT, > 120 INR, > 13.2 PTT, 88**	**Vit B_{12}, 129**[#] **MMA, 9481**[**] **Homocysteine, 66.8**[††] **Cystathionine, 1287**[‡‡]	4	Multivitamin PO daily	60
3, Vit C	12y	Jacobsen syndrome, autism spectrum disorder, history of iron deficiency anemia, restrictive diet	Increased bruising, swelling and pain of left calf, gingival bleeding	**WBC, 2.4 Hgb, 7.7** MCV, 77.7 **Plt, 99** ANC, 1176	**Vit C, <0.12**[§§]	7	Ascorbic acid 250 mg PO daily, then increased to twice daily	14
4, Copper	5y	Gastroschisis, short gut, gut motility disorder	Fatigue	**WBC, 2.9 Hgb, 7.2 MCV, 106.3** Plt, 451k **ANC, 490**	Folate,11.8[¶] Vit B_{12},408[#] **Copper,11**[///]	12	Copper 2 mg, PO daily ×7 d IV copper 20 mcg/kg/day in TPN	28
5, Multiple	9 mo	Previously healthy	Pancytopenia, fatigue, hypotonia; coagulopathy with subdural hematoma	**WBC, 1.3 Hgb, 4.9** MCV, 83.5 **Plt, 19 k ANC, 182**	**Vit B_{12}, 174**[#] **MMA, 11140**[**] **Homocysteine, 85.9**[‡‡] **Copper, 29**[///] **Ceruloplasmin, 9**[¶¶]	5	Vit K 2.5 mg PO, daily Vit B_{12}, 1000 mcg IM ×2 Vit ADEK Copper, 5 mcg/kg/day in TPN ×1 wk	8

Values in bold are outside the normal range.

[*] WBC: white blood cell, normal range is 4.0 to 10.5 TH/μL.

[†] Hgb: hemoglobin, normal range is 12.0 to 15.0 g/dL.

[‡] MCV: mean corpuscular volume, normal range is 78.0 to 95.0 fL.

[§] Plt: platelets, normal range is 140 to 440 TH/μL.

[//] ANC: absolute neutrophil count, normal range by age: term newborn 6000 to 26000/μL, infant (1 wk to 2 y) 1100 to 9500/μL, > 2 year 1500 to 7500/μL.

[¶] Folate, normal ranges by age: <5 year not established; 5 to 9 year > 7.1 ng/mL; 10 to 17 year > 8.0 ng/mL.

[#] Vit B12, normal ranges by age: <5 year not established; 5 to 9 year 250 to 1205 pg/mL; 10 to 17 year 260 to 935 pg/mL.

[**] Methylmalonic acid (blood), 0 to 378 nmol/L, but may depend on laboratory.

[††] Homocysteine normal range, <10.4 μmol/L.

[‡‡] Cystathionine, 44 to 342nmol/L.

[§§] Vit C, normal range is 0.2 to 1.9 mg/dL.

[///] Copper, normal range is 56 to 191 mcg/mL.

[¶¶] Ceruloplasmin, normal range is 15 to 43 mg/dL.

Dx indicates diagnosis; GI, gastrointestinal; IM, intramuscular; MMA, methylmalonic acid; PO, oral; TPN, total parenteral nutrition; Vit, Vitamin.

TABLE 2.

Summary of Nutritional Deficiency Diagnoses, Management, and Expected Time to Resolution

Nutritional Deficiency	Hematologic and Other Notable Manifestations	Diagnostic Testing	Management	Expected Time to Resolution of Laboratory Abnormalities and Symptoms
Vitamin B_{12}	Macrocytic anemia	Vitamin B_{12} Serum Methylmalonic acid Homocysteine	Vitamin B_{12} 1000 mcg IM/SC Daily ×3 d;[1] or multivitamin daily Diet modifications	Neutropenia and thrombocytopenia—within 7 to 10d Anemia—within 16 to 60 d
Copper (can be seen in zinc excess)	Normocytic anemia Neutropenia	Copper Ceruloplasmin	Copper 20 to 40 mcg/kg/d IV; or copper 2 mg/kg/d PO; or if zinc excess: stopping zinc[9]	Neutropenia—within 3 d Anemia—within 4 wk
Vitamin C	Excessive bleeding and bruising	Vitamin C	Vitamin C 100—300 mg, PO daily;[4] Diet modifications	Bleeding symptoms—within 2wk
Iron	Microcytic anemia	CBCD Serum iron Total iron binding capacity Ferritin	Ferrous sulfate 3 to 6 mg elemental iron/kg/d PO IV iron (dose depends on iron deficit)	Anemia—3 to 6 mo[13]
Folate	Macrocytic anemia	CBCD Folate serum	Folic acid 0.1 mg daily (infants), 0.3 mg daily (1 to 4 y), 0.4 mg daily (> 4y)	Anemia—4 to 8 wk
Vitamin K	Coagulopathy	PT, PTT	Vitamin K PO/IM/IV/SC 2.5—5 mg daily	Coagulopathy–2 to 6h if administered IV, 6 to 8 h if PO[14]
Vitamin E	Hemolytic anemia, thrombocytosis	CBCD CMP, LDH, Haptoglobin Alpha-tocopherol, vitamin E to serum lipid ratio	Vitamin E 1 U/kg PO daily[15]	Reticulocytosis—1 to 2 wk Anemia—within 4 wk Thrombocytosis—up to 3 mo[16]

CBCD indicates complete blood count with differential; IM, intramuscular; PO, oral; SC, subcutaneous.

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