Abstract:

Hemolytic crises and aplastic crises in hereditary spherocytosis (HS) are typically triggered by viral infections. We present the case of an adolescent with HS who developed unexpected and life threatening consequences of her hemoglobinopathy as a consequence of anorexia nervosa and severe malnutrition.

Keywords: feeding and eating disorders, anorexia nervosa, malnutrition, weight loss, nutrition disorders, hemoglobinopathies, hemolysis, bone marrow diseases, chronic disease, adolescent

Introduction:

Adolescents with chronic health conditions (CHCs) may be more likely to engage in disordered eating than their peers (Neumark-Sztainer et al., 1998). However, their underlying conditions may place them at higher risk for more severe complications from malnutrition. In this report we present an illustrative example of an adolescent with hereditary spherocytosis (HS) who developed anorexia nervosa and severe malnutrition which precipitated unexpected and life-threatening complications of her hemoglobinopathy.

Hereditary spherocytosis (HS) is the most common inherited cause of hemolytic anemia (Eber & Lux, 2004). It is characterized by an erythrocyte membrane defect leading to chronic normocytic hemolytic anemia and, if moderate or severe, jaundice and/or splenomegaly. Most patients with HS have elevated reticulocytes at baseline to compensate for ongoing hemolysis. However, if reticulocytosis in the bone marrow is suppressed, serious aplastic crises and illness may occur. The most typical triggers for hemolytic and aplastic crises are viral infections (Eber & Lux, 2004). Since viral infections resolve relatively quickly, most hemolytic and aplastic crises can be managed conservatively with only occasional need for blood transfusions in severe cases.

In this report we describe the case of an adolescent girl with HS who presented with an aplastic crisis from an unusual trigger: severe malnutrition and copper deficiency associated with anorexia nervosa (AN). This resulted in prolonged bone marrow suppression and severe, uncompensated hemolytic anemia that complicated her eating disorder treatment course. This is the first report that we are aware of demonstrating the unusual and significant repercussions that eating disorders and severe malnutrition can have in patients with underlying hemoglobinopathy, and highlights the increased risk that youth with chronic health conditions may face if they develop eating disorders.

Clinical Observation:

A 14-year-old girl with a history of moderate HS was admitted to an eating disorder inpatient unit with severe malnutrition, dehydration, fatigue, headache, dizziness and 18 kg of weight loss. Her weight loss began 18 months earlier but was more precipitous immediately prior to admission. By time of admission, she was restricting her intake to under 500 calories per day, which was only 20% of her estimated nutritional needs. She had been afebrile without any recent infections, diarrhea, vomiting or any known viral illnesses for months prior to admission. She had been previously evaluated for organic causes of weight loss including celiac disease, thyroid

disease, malignancy, gallbladder disease and systemic inflammatory conditions, without any contributors identified. She reported intentional dietary restriction to lose weight, fear of weight gain and poor body image; psychopathology was consistent with anorexia nervosa restrictive subtype. Her expected body weight (EBW) was 56.1 kg using the 75th percentile body mass index (BMI) for her age and sex, consistent with her previous growth curve. Her admission weight was 31 kg, which was 55.5% of her EBW. She had symptomatic orthostatic hypotension and tachycardia, with blood pressure dropping from 107/60 to 81/51 and heart rate increasing from 57 bpm to 91 bpm when she changed positions from supine to standing.

She had been diagnosed with HS as a newborn when she presented with neonatal jaundice and hemolytic anemia. There was a known family history of HS in her father and paternal relatives. In infancy she had required several packed red blood cell (pRBC) transfusions for aplastic or hemolytic crises thought to be induced by viral infections. Subsequently, until the time of her admission, she had required only two additional transfusions at age 11 years and 13 years when she experienced hemolytic and aplastic crises, also associated with viral infections. In all cases, the crises lasted a few days and only a single blood transfusion was required resulting in rapid symptomatic improvement. She had no history of gallstones, nor had her HS been severe enough to warrant splenectomy. She was followed by a pediatric hematologist. Her only home medication was folic acid to prevent megaloblastic anemia.

When she was admitted to the eating disorder unit, in addition to appearing pale and emaciated with cold extremities, she also was found to have scleral icterus and splenomegaly worsened from her baseline. Initial laboratory testing revealed macrocytic anemia, neutropenia, leukopenia, and unconjugated hyperbilirubinemia **(Table 1)**. Her reticulocyte count was suppressed at 2.8%, significantly lower than her baseline of 9% and lower than it had ever been during previous aplastic crises.

The patient reported no symptoms of cough, congestion sore throat, rhinorrhea, vomiting or diarrhea for months prior to her presentation. Inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) were normal upon admission. Additionally, her electrolytes, renal function and urinalysis were normal. A serum copper level was obtained, as copper deficiency has been associated with cytopenias (Kharel et al., 2019). She was found to have copper deficiency **(Table 1)** and was started on oral copper supplementation.

Due to worsening anemia and hemodynamic instability, she was transfused with 1 unit of pRBCs. Unlike previous transfusions which had resulted in rapid symptomatic improvement, this transfusion provided only minimal relief of her fatigue and dizziness. Over the following days, her hemoglobin gradually decreased again and reticulocytes remained suppressed. One week later, when her hemoglobin dropped to 7.0 g/dL and symptoms worsened further, she required a second pRBC transfusion. The patient's reticulocytopenia gradually improved with nutritional rehabilitation and copper supplementation, with reticulocytes eventually reaching baseline values by hospital day 23 and ultimately reaching as high as 12.9% by the day of discharge (hospital day 55). In addition to improvement of reticulocytosis, her fatigue and dizziness also improved as her weight normalized. After a 55-day hospitalization, she was discharged to a residential eating disorder treatment program. At discharge, her weight was 42.4 kg (76% EBW), hemoglobin was 8.9 g/dL and serum copper had normalized with supplementation to 78 mcg/dL.

Discussion:

We present the case of an adolescent with moderate HS who developed a prolonged hemolytic and aplastic crisis that appeared to be triggered by severe malnutrition and dietary copper deficiency associated with anorexia nervosa.

This hemolytic crisis differed from our patients' previous crises in a number of ways. Previous crises had been triggered by viral illnesses, which are the most common precipitant of hemolytic crises in individuals with HS. However, the patient did not have any recent clinical symptoms suggestive of a viral illness prior to admission, her inflammatory markers were within normal limits, and she was not immunocompromised in a way that might suppress her clinical or biochemical immune response to a viral illness. She was consistently afebrile at recent clinic visits and throughout her hospitalization. Second, previous crises had only occasionally required single blood transfusion for supportive management, which resulted in rapid symptomatic improvement. However, this crisis required multiple pRBC transfusions that did not significantly improve her symptoms of dizziness and fatigue. Previous crises resolved within several days, but this episode was associated with more profound reticulocytopenia that took weeks to resolve. Finally, previous crises were never associated with other cytopenias, but her current crisis was associated with leukopenia and neutropenia.

As reported in studies of hematologic manifestations in eating disorders, we hypothesize that her starvation state triggered her aplastic crisis by causing chronic and generalized bone marrow suppression resulting in reticulocyte suppression and other cytopenias that were not easily reversible and took weeks of nutritional rehabilitation to resolve (Abella et al., 2002). She was found to have copper deficiency, a relatively uncommon micronutrient deficiency that is associated with leukopenia, neutropenia and anemia (Abella et al., 2002; Myint et al., 2018; Yu et al., 2019). Her poor dietary intake was the only identifiable cause of her copper deficiency. With weight gain and copper supplementation, her cytopenias eventually resolved and her reticulocytes finally rose sufficiently to adequately compensate for her hemolysis.

To our knowledge, this is the first reported case of chronic and severe malnutrition associated with an eating disorder as the most probable trigger of hemolysis and aplastic crisis in a patient with a hemoglobinopathy. Adolescents with CHCs may be more likely to experience body image concerns or to engage in disordered eating to cope with the effects of the CHCs on their lives (Schlundt et al., 1999). Many previous studies have described an association between anorexia nervosa and other CHCs such as cystic fibrosis, diabetes mellitus, inflammatory bowel disease and celiac disease (Quick et al., 2013; Rome & Ammerman, 2003). Conditions like these, which require changes in diet and physical activity or are associated with weight changes, may particularly increase the risk of developing an eating disorder. However even among youth with underlying health conditions that have a less direct relationship with diet or exercise (such as hemoglobinopathies as in this case), dietary restriction may still be used as a coping strategy and malnutrition could have a catastrophic disease-specific consequences. Providers who treat adolescents with any CHC should consider screening them regularly for body image concerns and disordered eating behaviors. They should also provide anticipatory guidance about condition-specific complications that may result from disordered eating behaviors, just as they

would counsel on condition-specific complications that could arise from other risk behaviors such as substance use or unsafe sexual practices.

In summary, this case highlights how adolescents with CHCs who develop eating disorders may experience more severe complications of malnutrition than their peers as a consequence of their underlying condition. Providers should consider universal screening for body image problems among adolescents with CHCs and provide anticipatory guidance about condition-specific complications that could arise from disordered eating behaviors.

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Authorship

AMT: Direct patient care, preparation, editing and submission of manuscript
ZDD: Direct patient care, manuscript writing, editing and submission guidance
JK: Direct patient care, manuscript contributions
JY: Direct patient care, manuscript contributions
MMK: Direct patient care, manuscript writing and editing, submission guidance and final approval

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