A Toddler With Treatment-Resistant Iron Deficiency Anemia

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abstract

A 19-month-old girl with a history of asthma and atopic dermatitis presented to her pediatrician because of parental concerns of pallor and fatigue. On dietary history, it was discovered that she was a picky eater and consumed 26 oz of homogenous milk daily. Her physical examination was unremarkable aside from pallor, and both her height and weight plotted between the 50th and 75th percentile for age. Therefore, she was investigated for iron deficiency anemia and indeed her blood work was consistent. Despite appropriate iron supplementation and dietary milk restriction, there was no improvement in her hemoglobin or iron studies. Our expert panel examines the case and offers a differential diagnosis for a child presenting with treatment-resistant iron deficiency anemia.

CASE HISTORY WITH SUBSPECIALTY INPUT

Dr Meinert, Consultant Pediatrician

A 19-month-old girl was referred to a consultant pediatrician with concerns of pallor and fatigue. In looking at her history, it was discovered that she consumed 26 oz of homogenous milk daily and few iron-rich foods. Her physical examination was unremarkable aside from pallor, and both her height and weight plotted between the 50th and 75th percentile for age. Her investigations were consistent with iron deficiency anemia (IDA), specifically a hemoglobin of 7 g/dL, mean cell volume (MCV) of 61 fl oz, red cell distribution width of 21.4%, thrombocytosis of 870×10^9/L, and ferritin of 5 μg/L (Table 1). The family was advised to decrease milk intake to no more than 16 oz daily and to start iron supplementation at 6 mg/kg per day. Although there are many causes for IDA, no further investigations were pursued at this visit, as the patient did not have any "red flags" to suggest a more sinister etiology. Specifically, there was no melena, hematochezia, or hematemesis to suggest gastrointestinal bleeding. Moreover, her growth was normal, thereby lowering the suspicion for malabsorption.

The patient's blood work was repeated 3 weeks later, revealing minimal rise in the hemoglobin to 7.5 g/dL. Initially, adherence with dietary advice and iron supplementation was suboptimal, and the importance of these measures was reinforced. Repeat blood work 4 weeks later showed lack of response, with a hemoglobin of 7.6 g/dL. Her parents verified that she was only receiving 16 oz of milk daily and had not missed any doses of iron supplementation. They were referred to a dietician to discuss ways of optimizing their daughter's iron intake, but persuading her to accept new foods was an ongoing struggle. At this time, she was referred to a hematologist and gastroenterologist.

Dr Weinstein, Moderator, Pediatric Hospital Medicine

Does this patient qualify as having treatment-resistant IDA? If so, what are the diagnostic considerations?

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Drs Conway and Weinstein drafted the initial manuscript and reviewed and revised the manuscript; Drs Marcon, Meinert, Durno, Upton, and Kirby contributed to the conception and design of the manuscript and critically revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: https://doi.org/10.1542/peds.2017-2971

Accepted for publication Nov 20, 2017

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

To cite: Conway M, Marcon P, Meinert P, et al. A Toddler With Treatment-Resistant Iron Deficiency Anemia. *Pediatrics*. 2018;142(1):e20172971

TABLE 1 Initial Hematologic, Immunologic, and Nutritional Laboratory Data

Variable	Reference Range	Laboratory Test Results
Red blood cells	5.0–12.0 × 10^9/L	3.97 × 10^9/L[a]
Hemoglobin	11.0–14.0 g/dL	7.0 g/dL[a]
MCV	70–86 fl	61.0 fl[a]
RDW	11.5%–14.5%	21.4%[a]
Platelets	150–400 × 10^9/L	870.0 × 10^9/L[a]
Ferritin	10–99.9 μg/L	5.0 μg/L[a]
Iron	5.2–26.6 μmol/L	2.1 μmol/L[a]
Albumin	3.5–4.7 g/dL	3.7 g/dL
Protein	6.3–7.9 g/dL	66.0 g/dL
IgG	3.2–11.5 g/L	1.34 g/L[a]
IgA	0–0.9 g/L	0.0 g/L
IgM	0.5–1.9 g/L	0.6 g/L
Anti-tTG	<20 CU	0.0 CU
Antitetanus toxoid	>0.1 total IgG	1.18 total IgG
CD19 B lymphocytes	600–1300 cells/μL	931.0 cells/μL
ESR	1–10 mm/h	5 mm/h
CRP	0.1–1.0 mg/L	0.1 mg/L

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RDW, red cell distribution width.
[a] Laboratory values outside of the normal reference range for age.

Dr Kirby, Pediatric Hematology

IDA is the most common cause of anemia worldwide, and in toddlers this is often attributed to excessive cow's milk consumption. Diets with excess milk provide adequate calories, thus growth is often unaffected, but it can cause children to be satiated, thereby limiting intake of solid foods. It is therefore recommended to restrict cow's milk consumption to a maximum of 16 to 20 oz daily and to start iron supplementation at a dose of 3 to 6 mg/kg per day of elemental iron.[1] Signs of improvement include reticulocytosis as soon as 3 days after supplementation, a rise of hemoglobin by 1 g/dL within 2 to 4 weeks, and repletion of iron stores by 3 months.[2]

Once compliance is verified, most toddlers will respond to oral iron. When the expected improvement is not observed, consider inappropriate administration. In children who consume excessive amounts of milk, it is common for the iron supplement to be taken with milk-containing products, which is problematic because calcium can inhibit iron absorption. Ideally, it should be taken with foods containing vitamin C, to enhance absorption. Once compliance and administration are adequate, the patient is considered to have treatment-resistant IDA. At this point, gastrointestinal, respiratory, and urinary losses should be excluded and evidence for malabsorption or a chronic inflammatory condition should be sought. To start, one should rule out red flags as Dr Meinert mentioned. Additionally, erythrocyte sedimentation rate and C-reactive protein can serve as a basic screen for inflammatory conditions. In our patient, these values were normal (Table 1).

An uncommon diagnosis to be entertained is iron-refractory IDA. This is an autosomal recessive disorder characterized by IDA, which is unresponsive to oral iron supplementation and partially responsive to parenteral iron. This is caused by a mutation in the gene *TMPRSS6*, a transmembrane serine protease expressed in the liver. TMPRSS6 acts to cleave hemojuvelin, a membrane protein that promotes hecidin signaling in hepatocytes. Without TMPRSS6, excess hepcidin is produced, resulting in inhibition of iron absorption and reduced release of iron from macrophages. Key features of iron-refractory IDA include congenital hypochromic and microcytic anemia, low transferrin saturation, and abnormal iron absorption and utilization. Growth and development are generally unaffected in the long-term. Anemia is often an incidental finding.[3]

Dr Weinstein

Dr Kirby mentioned that malabsorption is a key consideration for treatment-resistant IDA. Which gastrointestinal diseases should be considered? Is it possible for these diseases to occur in the absence of overt gastrointestinal symptoms such as diarrhea or failure to thrive?

Dr Durno, Pediatric Gastroenterology

At the gastroenterology appointment, the patient's only reported gastrointestinal symptom was constipation, and it was explained to the family that this is a common side effect of iron supplementation.

There is a broad differential diagnosis of gastrointestinal etiologies for IDA. Meckel's diverticulum is the most common congenital anomaly of the gastrointestinal tract and a relatively common cause of gastrointestinal bleeding in this age group. Affected children typically present with maroon-colored stools, although sometimes the bleeding is chronic and insidious. Peptic ulcer disease is another common cause for gastrointestinal bleeding and may be attributable to *Helicobacter pylori* infection or nonsteroidal antiinflammatory drug use. *H pylori* can also alter the composition of gastric juices, thereby impairing iron absorption.[4] Patients with peptic ulcer disease may experience melena, which can be difficult to distinguish from darkened stools caused by iron supplementation. Additionally, vascular anomalies in the gut and polyps can present with IDA without overt signs of bleeding.

Celiac disease (CD) can present with IDA without significant clinical symptoms. In fact, anemia alone may be the only clue to a diagnosis

of CD. In a review of 347 children with CD, 18% presented with only extraintestinal symptoms of which IDA was common.[5] Many children experience a delay in the diagnosis because the anemia is attributed to nutritional causes. However, if there is no resolution of the anemia despite dietary adjustment and iron supplementation, then CD should be screened for.

Inflammatory bowel disease (IBD) is another important consideration, especially in the setting of IDA paired with low serum albumin. In a review of 497 children with IBD, 69% of those with Crohn disease and 64% of those with ulcerative colitis had anemia at presentation.[6] However, early-onset IBD is more likely to be associated with bloody stools, significantly reduced weight-for-age,[7] and a family history,[8] none of which were present in our patient. Lastly, in younger children, there are other rare causes of IDA due to malabsorption, such as autoimmune enteropathies, transporter defects, and cystic fibrosis.

Dr Conway, Pediatric Resident

As Dr Kirby mentioned, the family admitted that it was difficult to persuade the patient to take her iron supplement; therefore, they had resorted to mixing it in with her milk. They were counseled regarding the importance of administering the iron separate from any calcium-containing foods. In the meantime, at her gastroenterology appointment, the patient was tested for CD. Her anti-tissue transglutaminase (anti-tTG) was negative (0.0 chemiluminescent units); however, this was in the context of an immunoglobulin A (IgA) of 0.00 g/L (Table 1). One consideration at the time was to order an anti-tTG immunoglobulin G (IgG); however, her IgG was found to be significantly below normal range at 1.34 g/L (Table 1). Consistently decreased immunoglobulin levels were confirmed on a repeat blood sample; therefore, she was referred to immunology to rule out primary immunodeficiency.

Dr Weinstein

Are there any primary immunodeficiencies that could explain her hypogammaglobulinemia? Would selective IgA deficiency be a consideration?

Dr Upton, Pediatric Immunology

At her immunology appointment, she was screened for immunodeficiency, but her history and physical examination revealed no red flags. Specifically, there was no history of recurrent, unusual, or severe infections. Additionally, there was no family history of immunodeficiency and her physical examination was unremarkable except for some scattered bruises on her lower legs. Immunologic investigations confirmed hypogammaglobulinemia but with reassuring B cell function because she had positive vaccine titers to tetanus (Table 1). Additionally, she had normal B cell numbers on lymphocyte immunophenotyping (Table 1).

It is important to remember that secondary causes of hypogammaglobulinemia are far more common than primary causes. Therefore, we always order a total protein and albumin when measuring immunoglobulins to evaluate for disorders of protein loss.[9] Protein loss can cause low IgG and IgA with relatively preserved immunoglobulin M (IgM) because IgM is larger in size. We noted that her total protein and albumin were within normal limits (Table 1).

Another consideration could be transient hypogammaglobulinemia of infancy (THI). The pathogenesis of THI is unknown. Historically, the 2 most commonly reported features are upper and lower respiratory tract infections and atopic disorders. Both of these were present in this patient because she had a history of viral-induced asthma and atopic dermatitis. Diagnostic criteria include serum IgG at least 2 SDs below age-matched controls and normalization of immunoglobulins during childhood. Many patients also have low IgA and/or low IgM, but this is not required for the diagnosis. Normal vaccine titers and lymphocyte immunophenotyping are expected.[10] Nevertheless, this is a diagnosis of exclusion, which can only be made retrospectively once immunoglobulins have normalized. Therefore, it was important to arrange ongoing follow-up in the immunology clinic until her IgG normalized or an alternative diagnosis was made.

Selective IgA is the most common primary immunodeficiency. It is associated with a higher prevalence of malabsorptive gastrointestinal diseases, including celiac sprue and IBD, which were already mentioned as potential considerations for this patient. Additionally, atopic diseases such as asthma are also more prevalent in patients with selective IgA deficiency. However, transient low IgA levels are common in children <4 years old because of immaturity of the immune system.[11] In fact, at her age, the reference range for IgA is 0 to 0.9 g/L. For this reason, we do not make a diagnosis of selective IgA deficiency in children <4 years old. Moreover, as the name suggests, in selective IgA deficiency, the other immunoglobulin (IgG and IgM) levels are normal.

Lastly, because the hypogammaglobulinemia was occurring in the context of IDA, there are several genetic immunodeficiencies in which colitis or enteropathy is a key feature.[12] However, these diseases are rare, and were felt to be unlikely in the setting of a thriving patient with no diarrhea.

TABLE 2 Report of Patient's Dietary Intake

Food Item	Vitamin or Mineral, % of Recommended Daily Intake	
	Vitamin C	Iron
Grilled cheese	2	14
Cheese pizza	1	12
Corn	0	15
Peanut butter sandwich	0	10
Pancakes	0	9
Macaroni and cheese	0	6
Hot dogs	0	6
Fish sticks	0	5
Yogurt	0	0

Dr Conway

Two weeks after her immunology appointment (16 weeks from initial presentation), the patient's mother reported that the patient had been experiencing daily gum bleeding for the past 8 days. A more detailed dietary history revealed an important clue. The patient's diet was limited to the following foods: grilled cheese, pizza, corn, peanut butter sandwiches, pancakes, macaroni, hot dogs, fish sticks, and yogurt (Table 2). Her parents described her as a picky eater who refused to eat fruits or vegetables. Because of concerns for possible vitamin C deficiency, a serum ascorbic acid level was sent and came back at <5 μmol/L (normal >24 μmol/L). The patient was started on vitamin C 100 mg 3 times daily for 1 week, followed by 100 mg daily thereafter, and the family was counseled about introducing vitamin C–rich foods into her diet. Within several days of starting the vitamin C supplementation, her gum bleeding ceased.

Dr Weinstein

At this time, the patient was diagnosed with scurvy on the basis of clinical symptoms of gum bleeding and easy bruising, as well as an undetectable serum ascorbic acid level. Although rare, scurvy has been reported in patients with restricted diets, including children with autism spectrum disorder, developmental delay, and parental neglect.[13–15] The symptoms can range from mild to severe. Some of the classic symptoms include mucocutaneous bleeding, gingival hypertrophy, perifollicular petechial rash, corkscrew hairs, and musculoskeletal pain. Our patient's gum bleeding and bruising can be explained by capillary fragility because of vitamin C's essential role in collagen synthesis and cross-linking. Additionally, ascorbic acid promotes the uptake of nonheme iron from transferrin by reducing it to the ferrous state and its deficiency may be a factor in persistent IDA.

In my clinical experience, one can expect normalization of the patient's hemoglobin within 2 to 8 weeks of starting vitamin C supplementation.[13,14] However, in this patient, the hemoglobin initially improved significantly but plateaued at 10.2 g/dL after 8 weeks of vitamin C supplementation. As well, only minimal improvement was noted in the iron studies (Table 3). In contrast, the ascorbic acid level normalized to 58 μmol/L within 4 weeks of starting supplementation.

Dr Conway

Twenty-six weeks after initial presentation, the patient returned for follow-up in the gastroenterology clinic. She had been taking vitamin C supplementation for 10 weeks without normalization of her hemoglobin and there had been a plan in place to repeat her celiac serology and possible endoscopy if her IDA was persistent. At this visit, her parents reported a 3-week history of spontaneously appearing painful nodules on the extensor aspects of her lower extremities (Fig 1). The appearance was concerning for erythema nodosum.

Dr Weinstein

What is the differential diagnosis for erythema nodosum?

Dr Marcon, Pediatric Gastroenterology, Celiac Specialist

Erythema nodosum is characterized by raised erythematous tender nodules, usually appearing on the shins. There are many triggers for these lesions, which are caused by inflamed fat nodules under

TABLE 3 Trending Hemoglobin, MCV, Iron, Ferritin, and Ascorbic Acid Level Before and After Initiation of Nutritional Supplements With Iron and Vitamin C

Variable	Initial Blood Work[a]	3 wk	7 wk	16 wk[b]	20 wk	24 wk
Hemoglobin, g/dL	7.0[c]	7.5[c]	7.6[c]	7.9[c]	9.9[c]	10.0[c]
MCV, fl	61[c]	62[c]	57.6[c]	61.1[c]	65[c]	70
Iron, μmol/L	2.1[c]	3[c]	3[c]	2.6[c]	5[c]	5[c]
Ferritin, μg/L	5.0[c]	3.1[c]	4.5[c]	5.5[c]	6[c]	6.4[c]
Ascorbic acid, μmol/L	ND	ND	ND	<5[c]	58	ND

ND, not done.

[a] Iron supplementation at 6 mg/kg per day initiated.

[b] Vitamin C supplementation initiated.

[c] Laboratory values outside of the normal reference range for age.

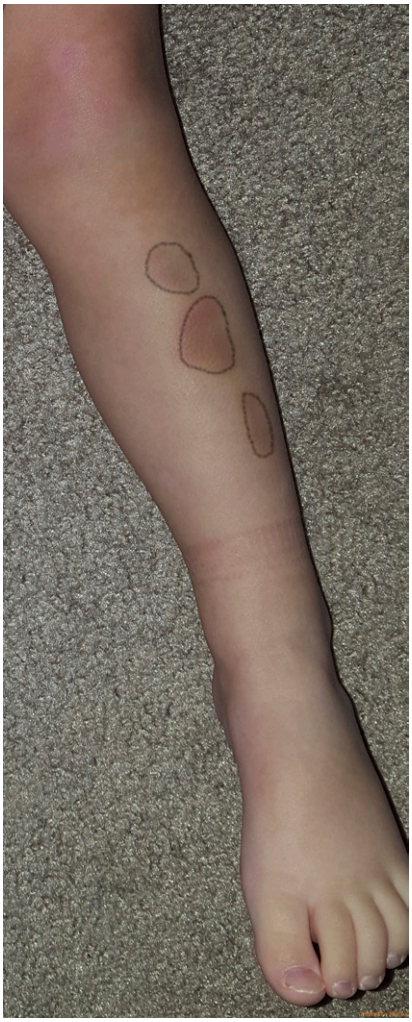

FIGURE 1
Erythema nodosum on the left anterior shin.

the skin. The most common cause is idiopathic, which accounts for ~50% of cases. Other etiologies include infections such as group A *Streptococcus*, tuberculosis, or *Yersinia enterocolitica*; rheumatologic conditions such as sarcoidosis or systemic lupus erythematosus; medications such as oral contraceptives; and of course, gastrointestinal disease, such as IBD, Behçet disease, and CD. Specifically, CD has been reported as a trigger for the nodules, which then resolve on a gluten-free diet.[16]

At this appointment, the patient had her celiac serology repeated, and the anti-tTG was positive at 1160 CU in the context of an IgA

TABLE 4 Nutritional Markers at Time of Diagnosis of CD

Variable	Reference Range	Laboratory Test Result
25-OH-vitamin D	70–250 nmol/L	68 nmol/L[a]
Ascorbic acid	>24 μmol/L	88 μmol/L
Iron	5.2–26.6 μmol/L	5 μmol/L[a]
Ferritin	10–99.9 μg/L	6.8 μg/L[a]
Red cell folate	182–834 nmol/L	608 nmol/L
Vitamin B_{12}	218–1305 pmol/L	561 pmol/L
Zinc	10.3–18.1 μmol/L	12.4 μmol/L

25-OH-vitamin D, 25-hydroxyvitamin D.
[a] Laboratory values outside of the normal reference range for age.

that had normalized (0.30 g/L). Her hemoglobin had plateaued at 10.2 g/dL and although her ascorbic acid level had normalized to 88 μmol/L, her iron and ferritin levels remained low at 5 μmol/L and 6.8 μg/L, respectively. Additional nutritional blood work revealed normal folic acid, zinc, and vitamin B_{12} levels but a decreased 25-hydroxy-vitamin D level of 68 nmol/L (Table 4), despite taking 600 IU of vitamin D daily. A diagnosis of CD was then confirmed via upper endoscopy with duodenal biopsies. Histology revealed subtotal villous atrophy with marked increase in intraepithelial lymphocytes consistent with a Marsh score of 3. Therefore, a gluten-free diet was instituted.

CD is an immune-mediated gastrointestinal disease leading to inflammatory damage to the small intestinal villi. It is triggered by dietary gluten in patients who are genetically susceptible, such as those with HLA antigens DR3-DQ2 and DR4-DQ8.[17] The prevalence of CD is increased in patients with Down syndrome, Turner syndrome, and William syndrome. It is also increased in patients with other autoimmune conditions, such as type 1 diabetes mellitus and autoimmune thyroiditis.

Classically, CD presents in infancy shortly after introduction of solid foods containing gluten. Symptoms include abdominal pain, distention, diarrhea, vomiting, and failure to thrive. In ~8% of cases, constipation may be the predominant gastrointestinal symptom,[18] as was the case in our patient. However, many cases of CD present more subtly or may present with nongastrointestinal symptoms. This might include anemia, behavioral abnormalities, elevated aminotransferases, dermatitis herpetiformis, osteomalacia, and dental enamel defects. Intestinal biopsies may reveal increased intraepithelial lymphocytes, villous atrophy, and crypt hyperplasia.

Micronutrient deficiencies due to malabsorption are common in CD, including iron, zinc, folic acid, vitamin B_{12}, and vitamin D. Vitamin D deficiency was the most common deficiency identified at diagnosis (69.4%) according to 1 study.[19] Additionally, it was the least likely micronutrient to normalize on a gluten-free diet at 6 and 18 months after diagnosis.[19] Therefore, in addition to instituting a gluten-free diet, our patient's vitamin D supplementation was increased to 1000 IU daily.

Dr Weinstein

The patient's celiac serology was initially negative in the context of an undetectable IgA level. How do you explain this negative result? What are alternative ways to diagnose CD in patients with low IgA?

Dr Marcon

One possibility is that when she was first seen, she did not yet have CD. On the basis of managing and rescreening at-risk populations, it is known that CD can develop anytime over a lifetime if one carries the

genetic risk. Another more likely possibility is that she had a falsely negative test because of her IgA deficiency at the time she presented.

The current recommendation for the most cost-effective and reliable serologic test for CD is the immunoglobulin A tissue transglutaminase (tTG-IgA). A serum IgA level should also be drawn to ensure proper interpretation. Panels of multiple serologic tests are not recommended as they add cost without improving diagnostic yield.[20] If the titer is low-positive, it can be confirmed with IgA antiendomysial antibody testing.

In IgA-deficient subjects, there is a role for the IgG antibodies although their overall sensitivity and specificity are lower. The newer IgG deamidated gliadin can be used if there is a clinical suspicion of CD.[20] The authors of a few small studies have suggested that the tTG-IgA may not be as accurate in patients <2 years of age; therefore, performing an IgG deamidated gliadin should be considered in addition to the tTG-IgA in this younger population.

Dr Weinstein

To summarize, this patient had treatment-resistant IDA that was explained by 2 etiologies: vitamin C deficiency and CD (Fig 2). Are there any previously published reports of a connection between vitamin C deficiency and CD?

Dr Conway

A thorough literature review was conducted, and only 2 cases of vitamin C deficiency in association with CD were identified.[21,22] One of these cases was published in French in 1986 and the abstract was not available.[21] The second case was published in Spanish in 2002. This case described a 2-year-old girl with a restricted diet who initially presented with symptoms of scurvy

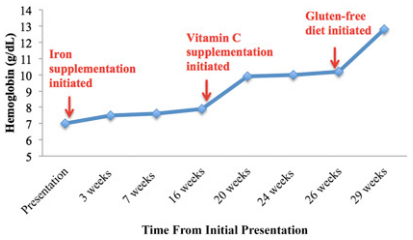

FIGURE 2
Trending hemoglobin values with iron supplementation, vitamin C supplementation, and gluten-free diet.

and was subsequently found to have IDA and then CD. Interestingly, she had more fulminant signs of scurvy, including pseudoparalysis, gingival hypertrophy, petechiae, and ecchymosis, although her anemia was comparably mild (hemoglobin of 10 g/dL). Similar to our case, the vitamin C deficiency improved with vitamin C supplementation, even before initiation of a gluten-free diet.[22]

Vitamin C deficiency has been reported in several patients with Crohn disease. In some cases, the vitamin C deficiency was due to self-imposed restricted diets adopted by the patients in an attempt to reduce gastrointestinal symptoms. In other cases, there was adequate dietary intake, and the vitamin C deficiency was attributed to malabsorption and increased demand.[23]

In our case, the patient's vitamin C deficiency was likely caused by poor diet lacking in fruits and vegetables (Table 2) rather than malabsorption. This is evident because her serum ascorbic acid level normalized with vitamin C supplementation before initiation of a gluten-free diet. However, we wonder if her picky eating may have been partially attributable to subtle symptoms of CD such as abdominal discomfort or bloating. One study of patients with IBD found that 65% of patients reported food intolerance defined by symptoms such as diarrhea, abdominal pain, and meteorism. The most common food category implicated was vegetables followed by fruits, and specifically ones that are rich in vitamin C, such as cabbage and citrus fruits.[24] It is plausible to consider similar factors in the connection between CD and vitamin C.

Dr Weinstein

This case illustrates several important take-home points for clinicians. Firstly, it is imperative to maintain a high index of suspicion for CD in IDA not responding to dietary modification and supplementation, even in the absence of growth impairment or diarrhea. Serologic testing for celiac is both sensitive and specific, but has limitations, such as in the case of hypogammaglobulinemia, and thus should not be relied on exclusively. Furthermore, although vitamin C deficiency is not common in typically developing children, it is nevertheless important for clinicians and dieticians to screen for sources of vitamin C in the diet when evaluating patients with IDA rather than solely focusing on dietary iron intake. Lastly, although abnormal laboratory results should not be ignored, clinicians must keep in mind that these can sometimes act as red herrings. For example, clinicians in this case were distracted by the low immunoglobulins and embarked on pursuit of other rarer disorders. Thus, when encountering diagnostic dilemmas, a helpful maxim is that an uncommon presentation of a common disease is more likely than a typical presentation of rare disorders.

How is the patient doing?

Dr Conway

She is doing well. After starting a gluten-free diet, there was substantial improvement in her clinical picture.

Her erythema nodosum disappeared, and finally there was resolution of her IDA (Fig 2), as evidenced by a hemoglobin of 12.8 g/dL, an MCV of 83.5 fl, serum iron of 15.8 μmol/L, and ferritin of 16.1 μg/L. Furthermore, her 25-hydroxy-vitamin D level normalized to 101 nmol/L. Additionally, although she remains on iron supplementation, her constipation is markedly improved. Her IgA and IgG had normalized before starting a gluten-free diet, and so the immunology team retrospectively confirmed a diagnosis of THI, which did not require further follow-up. She continues to plot between the 50th and 75th percentile for weight and height and continues to achieve her developmental milestones.

ACKNOWLEDGMENT

We thank Stephanie Erdle, MD.

ABBREVIATIONS

anti-tTG: anti-tissue transglutaminase
CD: celiac disease
IBD: inflammatory bowel disease
IDA: iron deficiency anemia
IgA: immunoglobulin A
IgG: immunoglobulin G
IgM: immunoglobulin M
MCV: mean cell volume
THI: transient hypogammaglobulinemia of infancy
tTG-IgA: immunoglobulin A tissue transglutaminase

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DOI: 10.1542/peds.2017-2971 originally published online June 27, 2018;

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