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CASE REPORT | INFLAMMATORY BOWEL DISEASE

Severe Crohn's Disease Manifestations in a Child with Cystathionine β-Synthase Deficiency

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ABSTRACT

Inflammatory bowel diseases (IBDs) are idiopathic autoimmune diseases that are characterized by inflammation of both the small and large intestine. Although IBD is common in the general population, the pathophysiology remains ambiguous. Clear understanding of IBD pathophysiology would be a major step toward curative treatment in the future. Hyperhomocysteinemia has been associated with multiple autoimmune diseases including IBD, but homocystinuria has not been associated with IBD before. We report a 9-year-old girl with Crohn's disease and homocystinuria. Her gastrointestinal symptoms improved significantly upon classical homocystinuria treatment, and her last colonoscopy showed a pronounced remission. This case supports the inflammatory role of homocysteine in the gastrointestinal tract and the association between hyperhomocysteinemia and IBD manifestations.

INTRODUCTION

Inflammatory bowel disease (IBD) is an umbrella term that encompasses Crohn's disease (CD) and ulcerative colitis (UC), and is characterized by inflammation of various sites in the gastrointestinal (GI) tract.[1] The prevalence of CD is relatively high in many western countries, estimated to be 30–50 out of every 100,000 people, while the incidence of pediatric IBD is approximately 10 per 100,000 children in the United States and Canada.[2,3] Patients with CD typically experience pain in the lower right abdomen, diarrhea, and bleeding from the rectum, and the typical clinical course is recurrent flares and remission of symptoms.[4] Homocysteine is a sulfur-containing amino acid that is not obtained from the diet. Instead, it is biosynthesized from methionine via 2 intracellular pathways: remethylation to methionine, which requires folic acid and vitamin B_{12}, and transsulfuration to cystathionine, which requires vitamin B_6 (Figure 1).[5] Classical homocystinuria is an inborn error of metabolism that results in elevated levels of homocysteine, and it is caused by cystathionine β-synthase (CBS) deficiency.[6] The age of onset and the severity of homocystinuria vary widely among patients with CBS deficiency. While the symptoms can involve any system, they mainly involve the ocular (eg, ectopia lentis and high myopia), skeletal (eg, tall stature, long limbs, scoliosis, pectus excavatum, and osteoporosis), neuronal (eg, intellectual disability, seizures, and psychiatric problems), and vascular

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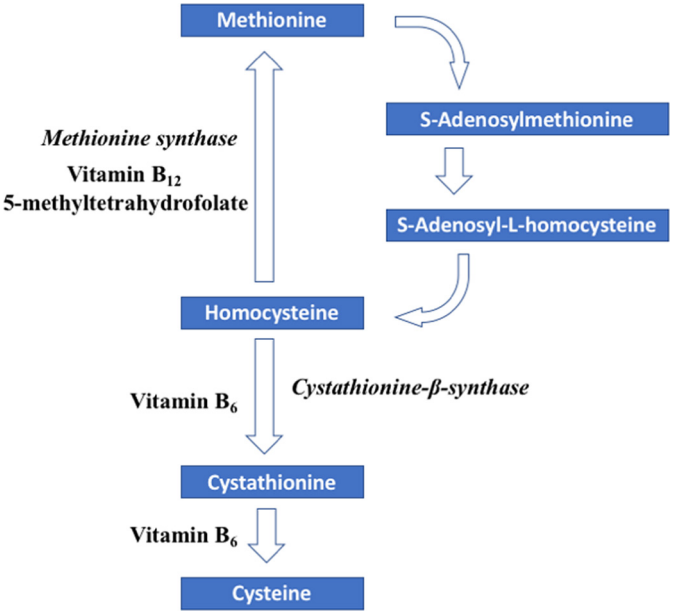

Figure 1. Representation of homocysteine metabolism pathway.

(eg, thromboembolic events and cerebrovascular accidents) systems.[7] CBS deficiency is typically not associated with active chronic inflammatory disease of the GI tract; however, there has been cumulative evidence linking hyperhomocysteinemia with IBD.[8,9]

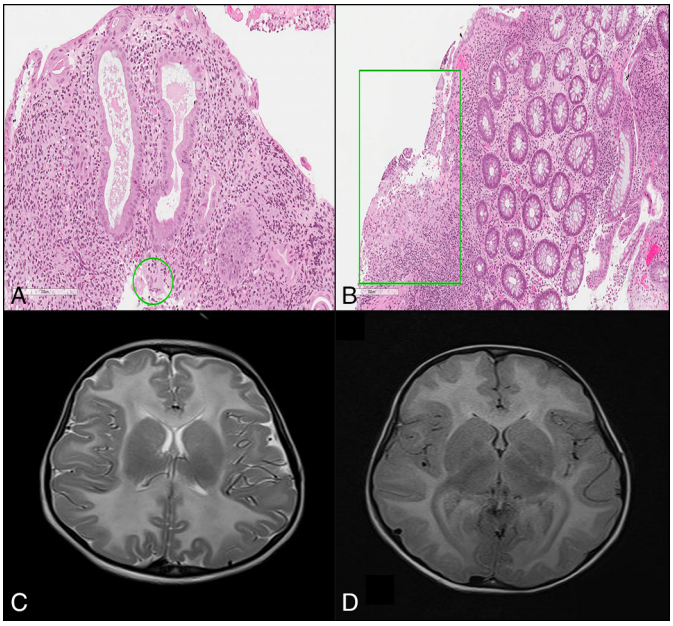

Figure 2. Pretreatment histological and radiological findings of the initial lower gastrointestinal (GI) biopsies revealed normal terminal ileum (not shown) and patchy moderate chronic active colitis with granulomas showing (A) ascending colon with moderate chronic active colitis with granuloma and (B) rectum with erosion and granuloma (hematoxylin and eosin stained). (C) Axial magnetic resonance imaging (MRI) T2WI and (D) fluid-attenuated inversion recovery (FLAIR) images show bilateral symmetrical hyperintense signal in the periventricular, deep, and subcortical white matter with sparing of the corpus callosum and internal capsule.

CASE REPORT

The patient is a 9-year-old girl who was born post-term via C-section following an uneventful pregnancy. Her parents are a first-degree consanguineous couple with medically unremarkable family history. She was developmentally normal with normal growth parameters until 5 years of age, when she presented with abdominal pain, an increase in bowel habits, rectal bleeding, weight loss, and joint pain. IBD was suspected. Enhanced computed tomography enterography showed abnormal enhancement of the terminal ileum mucosa and proximal part of the ascending colon, with surrounding minimal mesenteric fat stranding, and no signs of thrombosis in the portal vein or superior mesenteric vein. Upper GI endoscopy revealed normal esophagus but showed gastritis and multiple ulcers in the antrum, pylorus, and duodenum. Colonoscopy revealed pancolitis with multiple ulcers and pseudopolyps in the rectum; the anus and ileum were normal. Subsequent histological examination of the lower GI biopsies revealed normal ileal mucosa and moderately active chronic colitis, with patchy granulomatous inflammation in the cecum and ascending, transverse, and descending colon (Figure 2). Her erythrocyte sedimentation rate (ESR) was elevated at 58 mm/h, as was her stool calprotectin level at >1,000 µg/g. C-ANCA and P-ANCA were normal. All other routine laboratory investigations were within normal limits, and other infectious causes were ruled out.

The patient was diagnosed with CD and was started on prednisolone and azathioprine; her GI symptoms improved. She relapsed in the following year; a second colonoscopy was not significantly different from the previous one, showing focal cryptitis and mild crypt architecture distortion. Infliximab infusion was added to her regimen, but her clinical course did not improve significantly. A few months later, she started complaining of decreased visual acuity, and she was found to have bilateral lens subluxation. After another few months, she had a significant flare-up, and she presented with abdominal pain, distention, weight loss, and bloody diarrhea. In the same period of her relapse, she developed neurological symptoms, and she started to regress developmentally and lose her ability to ambulate, with her lower limbs being more affected than the upper limbs. She started to have spasticity in the lower limbs, while the upper limbs remained normal. Furthermore, her growth parameters started to lag, and she started to cross down the percentiles.

The patient was admitted to the pediatric ICU, where portal vein thrombosis, superior mesenteric vein thrombosis, and lesser sac hematoma were identified. An investigation for hypercoagulable causes revealed elevated homocysteine levels at 152 µmol/L. Urine homocysteine excretion was

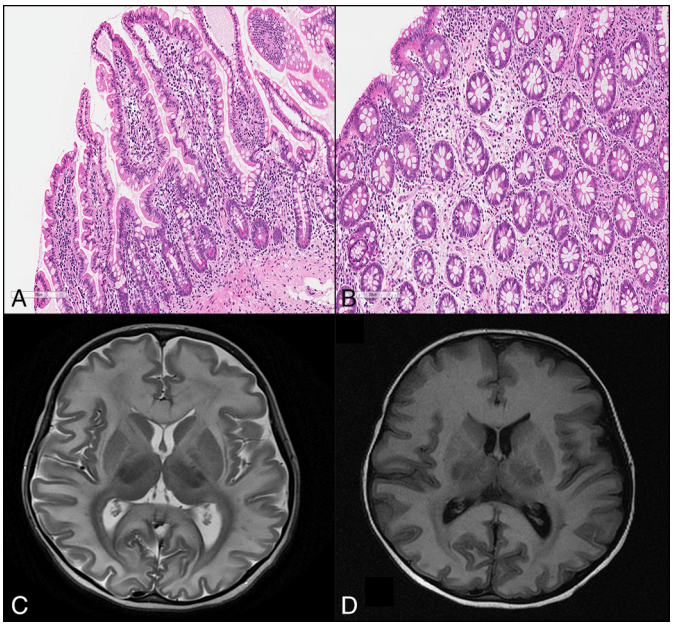

Figure 3. Post-treatment histological and radiological findings of the lower GI biopsies after homocystinuria therapy revealed significant improvement. Focal chronic active inflammation with foreign body giant cell reaction in the colon is noted. Normal mucosa is seen in (A) the terminal ileum and (B) the ascending colon (hematoxylin and eosin stained). (C) Axial MRI T2WI and (D) FLAIR images show the progression of the bilateral, symmetrical, hyperintense signal involving the white matter, corpus callosum, internal capsule, external capsule, and extreme capsule. Hypointense signal is noted in the ventral part of the thalami.

extremely high 180 mg/d, and amino acid analysis showed an increased methionine level at 2,353 umol/L. Because of her complex condition, we did whole exome sequencing, which revealed a homozygous pathogenic variant c.1039G>A (p. Gly347Ser) in the *CBS* gene. This variant has been previously described as causing CBS deficiency.[10] No other pathogenic mutations were found in genes associated with IBD (eg, *NOD2*, *IRGM*, and other IBD genes). Magnetic resonance imaging (MRI) of the brain showed diffusely abnormal white-matter signal extending to involve the U-fibers (Figure 2). She was started on a methionine-restricted diet and classical homocystinuria regimen: pyridoxine, betaine, hydroxocobalamin, aspirin, and folic acid. As a result, her CD GI symptoms improved. A third colonoscopy showed significant improvement of her pancolitis, and succeeding colonic biopsies showed normal ileal mucosa and mild active chronic colitis (Figure 3). Her GI symptoms appeared to ameliorate with homocystinuria management. She still has occasional mild flares of abdominal pain and mild bleeding that show a linear correlation with increased homocysteine, methionine, and stool calprotectin levels. At the age of 9 years, she is below the fifth percentile for weight and height (21 kg and 121 cm, respectively). Her ESR level dropped to 25–29 mm/h (normal: 2–20 mm/hr), and stool calprotectin was 47–149 µg/g (normal <50 µg/g). Repeat brain MRI 1 year later showed interval worsening of bilateral, symmetrical, and diffusely abnormal white-matter signal intensity involving the U-fibers, deep white matter, internal capsule, and spinothalamic tract (Figure 3). Clinically, the patient's neurological status is deteriorating slowly, and she is wheelchair-bound, but she still can communicate and take care of her dressing and toileting.

DISCUSSION

Hyperhomocysteinemia has been associated with IBD and many autoimmune diseases.[11,12] In a meta-analysis of 28 studies, homocysteine levels were significantly higher in patients with IBD compared to controls.[13] The pathophysiological mechanisms leading to vascular damage in hyperhomocysteinemia are multifactorial and are still poorly understood. Homocysteine enhances the release of cytokines and other mediators of inflammation, which may damage cells and tissues in arteries.[14] Homocysteine also causes endothelial dysfunction, which has been attributed to impaired bioavailability of nitric oxide by many mechanisms.[15] One possible mechanism is mediated by asymmetric dimethylarginine, an endogenous inhibitor of endothelial nitric oxide synthase that competes with L-arginine and limits the synthesis of nitric oxide.[16] Studies have also shown that IBD patients' colonic mucosa has a higher level of homocysteine.[17] It has been hypothesized that lamina propria mononuclear cells play an important role in homocysteine production. Synergistically with TNF-α, homocysteine triggers human intestinal microvascular endothelial cell inflammation, resulting in upregulation of vascular cell adhesion molecule 1, chemoattractant protein-1 production, and p38 phosphorylation. Together, these events lead to T-cell and monocyte recruitment to the GI tract.[18]

The patient described herein developed progressive neurological symptoms in the form of neuroregression, spasticity in the lower limbs, and decreased cognition. These symptoms may be extraintestinal manifestations of CD, anti-TNF-α therapy side effects, which can cause neurological disease characterized by central demyelination, or CBS deficiency.[19,20] It was noted that the child's GI symptoms improved by decreasing homocysteine levels, and the significant clinical improvement that she experienced when CBS deficiency was controlled supports this association. Further prospective or experimental studies using homocysteine-lowering agents may give promising treatment options to control GI vascular complications in patients with IBD.

DISCLOSURES

Author contributions: S. Alsahli wrote the manuscript. A. Al Anazi, MM Al Hatlani, A. Kashgari, M. Alfadhel, and F. Al Mutairi edited the manuscript. F. Al Sufiani provided the biopsy images. F. Al Mutairi is the article guarantor.

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