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Celiac disease in a child with ulcerative colitis. A possible genetic association

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Abstract

Celiac disease and Inflammatory bowel disease (IBD) including ulcerative colitis (UC) and Crohn's disease are both immune-mediated enteropathies. It is rare for both celiac disease and IBD to occur together in an individual patient. This association has been reported in adults, but very rarely in children. Here, we report an unusual case of an eight-year-old child with a history of anemia and failure to thrive who presented with bloody diarrhea. His evaluation showed anemia, elevated inflammatory markers and positive celiac antibodies. Endoscopic evaluation revealed partial duodenal villous atrophy and pancolitis. He was diagnosed with celiac disease and UC and responded well to a gluten-free diet and steroid/mesalamine therapy. The patient's genetic testing revealed markers showing susceptibility for both celiac disease and UC. It is important to be aware of this association as both conditions can present with similar clinical features, but require different therapeutic approaches.

Keywords

celiac disease; Crohn's disease; ulcerative colitis

PRESENTATION OF CASE

Dr Sam Cheng and Dr Aileen Raizner: An 8 year-old Caucasian boy presented with a 2-month-history of bloody diarrhea occurring up to 10 times daily with lower abdominal pain. He had urgency and tenesmus associated with defecation. Prior to the development of hematochezia, he had a one year history of intermittent diarrhea, anemia and failure to thrive. His weight had dropped from the 50th percentile to the 25th percentile. His past medical history was significant for walnut allergy and there was no family history of IBD or celiac disease.

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There is no conflict of interest.

Physical examination was significant for a pale-looking child with a weight of 23.9 Kg at the 25th percentile and height of 124 cm at the 10th percentile. His abdomen was soft and non tender without any masses. Systemic examination was otherwise unremarkable. Laboratory testing revealed a hemoglobin of 9.2 g/dl, platelet count of $522 \times 10^9/L$, normal liver function tests with serum albumin of 3.7 g/dl. Both erythrocyte sedimentation rate (31 mm/h) and C-reactive protein (5.1 mg/L) were elevated. Stool cultures were negative for infection.

Upper endoscopy revealed duodenal erythema, normal stomach and esophagus. Duodenal histology showed moderate inflammation, intraepithelial lymphocytosis, and partial villous atrophy. These changes were consistent with celiac disease. Colonoscopy revealed continuous inflammation, multiple ulcerations with bloody exudates, and friable mucosa throughout the colon. Colon histology revealed moderate chronic active colitis without any granulomas. Terminal ileum histology was unremarkable. The upper gastrointestinal contrast study did not show any small bowel abnormalities. In view of the duodenal pathology, celiac serologies were obtained which revealed positive tissue transglutaminase IgA (TTG) titers of 146 units/ml (normal < 20 units/ml) and positive endomysial antibody. Repeat testing confirmed high TTG antibody titers. IBD serology was positive for anti-neutrophil cytoplasm antibody (pANCA) (54.7, normal <18.7 EU/ml) and negative for anti-Saccharomyces cerevisiae antibody.

Steroid therapy was initiated for ulcerative colitis and the patient was started on a gluten free diet for celiac disease. Steroids were tapered off gradually following improvement in clinical symptoms and weight gain. The patient was started on mesalamine. He has remained asymptomatic and has been growing well on a gluten-free diet and mesalamine therapy for the past 2 years. Repeat evaluation on gluten free diet revealed normal duodenal histology and normal TTG titers (11 units/ml).

PRESENTATION OF GENETIC ANALYSIS FINDINGS

Dr Judy Cho: The patient's genotypes at selected positions were determined by chip-based oligonucleotide hybridization using genomic DNA in our laboratory.¹ We assessed for single nucleotide polymorphisms (SNPs) at different loci including *NOD2*, *IL18RAP*, *PTPN2*, *TAGAP* (risk for celiac disease and Crohn's disease)² and *IL2/IL21* (association with celiac disease and UC).³ Our patient did not have any of the three risk alleles (at rs2066844, rs2066845, rs5743293) within *NOD2* that show well-replicated association with Crohn's disease.⁴ Among three other loci (*IL18RAP*, *PTPN2*, *TAGAP*) that show association to celiac disease and Crohn's disease (markers rs6708413, rs16939895, rs212388, respectively), our patient's genotypes conferred risk at only *PTPN2*, where the genotype was homozygous for the risk allele.² Finally, within a previously identified haplotype block containing *IL2* and *IL21*, the patient was homozygous for all four of the common alleles (rs13151961, rs13119723, rs6822844, rs6840978) that are associated with celiac disease and confer risk for UC.³ Thus, the patient's genetic data supports the diagnosis of celiac disease and UC.

DISCUSSION

Dr Sam Cheng and Dr Dinesh Pashankar: We report a child with classical clinical, serological and pathological features of celiac disease and UC. His symptoms of colitis improved with treatment with corticosteroids and mesalamine. A gluten-free diet led to improvement in growth, celiac antibody titers, and duodenal histology. Therefore, we believe that our patient has confirmed diagnoses of celiac disease and UC.

Audience: Is there any association between celiac disease and IBD reported in the literature?

Dr Sam Cheng: The association of celiac disease and IBD has been described in adults. Yang et al diagnosed 10 patients with IBD (5 UC and 5 Crohn's disease) in a cohort of 455 adult patients with confirmed celiac disease in the United States.⁵ They reported that IBD is more common in patients with celiac disease than the general population with adjusted prevalence rate ratio of UC and Crohn's disease of 3.56 and 8.49, respectively.⁵ Leeds et al reported that the risk of developing IBD was tenfold higher in British patients with celiac disease than in the general population.⁶ On the other hand, celiac disease was diagnosed in only 0.5% of adults with IBD in a recent multicenter study in Italy.⁷ This prevalence rate was lower than the rate of 1% seen in the general population. It is possible that the association between celiac disease and IBD varies depending on the population studied.

Compared to adults, the occurrence of celiac disease and IBD together in children is extremely rare and has not been reported in the United States. The first three case reports^{8–10} published more than 12 years ago do not provide convincing evidence of the diagnoses of both conditions (Table 1). Proctosigmoiditis in the two children reported by Ansaldi *et al* was most likely induced by a milk-protein allergy.⁸ The patient reported by Glasgow *et al* did not have convincing evidence of Crohn's disease.⁹ The patient reported by Lacaille *et al* had microscopic colitis without convincing evidence of UC.¹⁰ Similar to our patient, three other reports describe convincing evidence of celiac disease and ulcerative colitis.^{11–13} All children including our patient responded well to a gluten-free diet and steroid/mesalamine therapy.

Audience: Given the difference in treatment, early recognition of this association becomes important. How do we recognize it?

Dr Dinesh Pashankar and Dr Uma Phatak: Despite a number of publications in adults, it is interesting that there are so few pediatric reports as both conditions can start in childhood. It is possible that the diagnosis of celiac disease may be overlooked in children with IBD as symptoms of both conditions are so similar and may be attributed to IBD only. Children with UC and duodenal involvement can be misdiagnosed as Crohn's disease. Although more common in patients with Crohn's disease, duodenitis is also reported in patients with UC.¹⁴ In one review of duodenal histology in adult patients with Crohn's disease, villous atrophy and intraepithelial lymphocytosis were seen in 23% and 22% of patients respectively.¹⁵ These findings are suspicious of celiac disease although the authors did not consider the possibility of celiac disease nor did they comment on celiac serology. In one study TTG antibody titers were assessed in adults with IBD and celiac disease.¹⁶ Authors reported low positive TTG titers in patients with IBD, but none of them had high positive titers as seen in

patients with celiac disease. Additionally none of the patients with IBD had positive endomyseal antibody titers.¹⁶ We recommend obtaining celiac serology titers (including TTG antibody and endomyseal antibody) in patients with IBD and duodenal involvement.

Audience: Is there a genetic association between celiac disease and IBD?

Dr Judy Cho: Both celiac disease and IBD are known to have a strong genetic predisposition. Recent genome-wide association studies report several common candidate genetic markers that have been associated or functionally linked with celiac disease and only one form of IBD (Crohn's disease or UC).^{2, 3} Glas *et al* analyzed five SNPs strongly associated with celiac disease in patients with IBD and healthy controls.³ They reported novel genetic risk markers for UC and celiac disease in the *IL2/IL 21* region on chromosome 4q27 region.³ Recently Feston *et al* reported *IL18RAP*, *PTPN2*, and *TAGAP* as shared risk loci for Crohn's disease and celiac disease in a meta-analysis of genome-wide association study datasets.² Our patient's genetic analysis supports our diagnoses of celiac disease and UC.

Dr Sam Cheng: In summary, we report a rare case of a young child who presented with features of both celiac disease and UC. It is important to be aware of this association as both diseases require different therapeutic approaches even though both can present with similar gastrointestinal symptoms. The possibility of co-existent celiac disease should be considered when children with IBD have duodenal involvement or symptoms that are not responsive to the standard therapeutic approach. The diagnosis of celiac disease is suggested by a positive serology, particularly endomyseal antibody. Genetic analysis studies can also be useful to support the diagnosis. Further studies are required to assess prevalence of this association in children.

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References

1. Gunderson KL, Steemers FJ, Lee G, et al. A Genome-wide scalable SNP genotyping assay using microarray technology. *Nature Genet.* 2005; 37(5):549–554. [PubMed: 15838508]
2. Festen EA, Goyette P, Green T, et al. A meta-analysis of genome-wide association scans identifies *IL18RAP*, *PTPN2*, *TAGAP*, and *PUS10* as shared risk loci for Crohn's disease and celiac disease. *PLoS Genet.* 2011; 7(1):e1001283. [PubMed: 21298027]
3. Glas J, Stallhofer J, Ripke S, et al. Novel genetic risk markers for ulcerative colitis in the *IL2/IL21* region are in epistasis with *IL23R* and suggest a common genetic background for ulcerative colitis and celiac disease. *Am J Gastroenterol.* 2009; 104(7):1737–1744. [PubMed: 19455118]
4. Hugot JP, Chamaillard M, Zouali H, et al. Association of NOD2 leucinerich repeat variants with susceptibility to Crohn's disease. *Nature.* 2001; 411(6837):599–603. [PubMed: 11385576]
5. Yang A, Chen Y, Scherl E, et al. Inflammatory bowel disease in patients with celiac disease. *Inflamm Bowel Dis.* 2005; 11(6):528–532. [PubMed: 15905699]
6. Leeds J, Hroldt B, Sidhu R, et al. Is there an association between coeliac disease and inflammatory bowel diseases? A study of relative prevalence in comparison with population controls. *Scand J Gastroenterol.* 2007; 42(10):1214–1220. [PubMed: 17918008]
7. Casella G, D'Inc R, Oliva L, et al. Prevalence of celiac disease in inflammatory bowel diseases: An IG-IBD multicentre study. *Dig Liver Dis.* 2010; 42(3):175–178. [PubMed: 19786375]

8. Ansaldi N, Santini B, Dell'olio D, et al. Proctosigmoiditis and coeliac disease. *Arch Dis Child*. 1978; 53(8):645–648. [PubMed: 708100]
9. Glasgow JF, Pinkerton CR, Sloan JM. Serosal miliary Crohn's disease in association with probable coeliac disease. *Arch Dis Child*. 1983; 58(2):149–151. [PubMed: 6830294]
10. Lacaille F, Canioni D, Bernard O, et al. Celiac disease, inflammatory colitis, and primary sclerosing cholangitis in a girl with Turner's syndrome. *J Pediatr Gastroenterol Nutr*. 1995; 21(4): 463–467. [PubMed: 8583302]
11. Cadaha V, Rodrigo L, Fuentes D, et al. Celiac disease (CD), ulcerative colitis (UC), and primary sclerosing cholangitis (PSC) in one patient: a family study. *Rev Esp Enferm Dig*. 2005; 97(12): 907–913. [PubMed: 16454610]
12. Day AS, Abbott GD. Simultaneous presentation of coeliac disease and ulcerative colitis in a child. *J Paediatr Child Health*. 1999; 35(2):204–206. [PubMed: 10365362]
13. Skora J, Varvarovsk J, Pomahacov R, et al. Simultaneous presentation of celiac disease, ulcerative colitis and autoimmune thyroiditis in childhood. *J Clin Gastroenterol*. 2004; 38(7):613–614. [PubMed: 15232370]
14. Sonnenberg A, Melton S, Genta R. Frequent occurrence of gastritis and duodenitis in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2011; 17(1):39–44. [PubMed: 20848539]
15. Wright CL, Riddell RH. Histology of the stomach and duodenum in Crohn's disease. *Am J Surg Pathol*. 1998; 22(4):383–390. [PubMed: 9537465]
16. Di Tola M, Sabbatella L, Anania M, et al. Anti-tissue transglutaminase antibodies in inflammatory bowel disease: new evidence. *Clin Chem Lab Med*. 2004; 42(10):1092–1097. [PubMed: 15552265]

Table 1

Published cases with combined presentation of celiac disease and IBD in children

Authors	Age/Sex (Nation)	Diagnosis	Comments	Refs
Ansaldi et al (1978)	5 mo girl (Italy)	Celiac & ?UC	?milk protein-induced colitis	8
	29 mo girl (Italy)	Celiac & ?UC	?milk protein-induced colitis	8
Glasgov et al (1983)	2 yr boy (U.K.)	Celiac & ?Crohn's	?miliary Crohn's	9
Lacaille et al (1995)	24 yr girl (France)	Celiac & ?UC	?microscopic colitis	10
Day & Abbott (1999)	7 yr girl (New Zealand)	Celiac & UC	Confirmed diagnoses	12
Skora et al (2004)	15 yr girl (Czech)	Celiac & UC	Confirmed diagnoses	13
Cadahia et al (2005)	17 yr boy (Spain)	Celiac & UC	Confirmed diagnoses	11