Degree of Villous Atrophy and Outcomes in Children

Celiac disease (CD) is an immune-mediated disease typically associated with gastrointestinal inflammation in response to gluten exposure. Esophagogastroduodenoscopy (EGD) with duodenal biopsies has been considered "gold standard" for CD diagnosis; however, recent pediatric guidelines such as the European Society for Paediatric Gastroenterology Hepatology and Nutrition Guidelines for the Diagnosis of Coeliac Disease (https://journals.lww.com/jpgn/Fulltext/2012/01000/European_Society_for_Pediatric_Gastroenterology,.28.aspx) suggest that serology screening may be an adequate substitute for EGD with duodenal biopsy. In particular, a tissue transglutaminase IgA antibody (TTG IgA) level greater than 10 times the upper limit of the measured laboratory value has a high association with CD. It is unclear if the degree of villi damage seen in CD corresponds well with TTG IgA antibody titer levels, and the authors of this study evaluated the effectiveness of determining intestinal villi length (disease severity) in pediatric patients with a new diagnosis of CD in regards to their long-term health outcomes as adults.

This study occurred at a single tertiary hospital in Finland, and retrospective data was obtained from a CD database containing the records of 906 pediatric patients from 1966 to 2014. Medical data at the time of CD diagnosis was reviewed such as the presence of gastrointestinal symptoms and other extra-intestinal disease manifestations, and duodenal biopsy results from these patients were divided into three groups: partial atrophy, subtotal atrophy, and total atrophy. Growth impairment was determined by decreased growth velocity noted on growth charts. TTG IgA and endomysial antibodies (EMA) were recorded from patients from 2000 onward when such serum testing had become available. Finally, pediatric patients with CD who were now adults completed three questionnaires including a questionnaire reviewing complications and co-morbidities associated with CD, the Gastrointestinal Symptom Rating Scale (GSRS) to evaluate the presence of gastrointestinal symptoms, and the Psychological General Well-Being questionnaire (PGWB) to evaluate quality of life.

The duodenal biopsies of the 906 pediatric patients demonstrated partial villous atrophy in 34%, subtotal villous atrophy in 40%, and total villous atrophy in 26% of patients. Children with total villous atrophy had significantly more extra-intestinal manifestations, anemia, and impaired growth while patients with less severe atrophy had less abdominal pain and less CD detected by serum screening. Children with more advanced stages of villous atrophy were diagnosed during the earlier years of the study although there was no difference in patient age throughout the study at the time of CD diagnosis. More severe villous atrophy was identified in patients with significantly shorter height, lower body mass index (BMI), lower hemoglobin levels, and higher celiac antibody levels (TTG IgA and EMA) at time of CD diagnosis.

A total of 503 adult patients with CD diagnosed as children were asked to participate in this study, and 212 of these patients (42%) completed all questionnaires. The adult patients with partial and subtotal villous atrophy were significantly younger than the adult patients with total villous atrophy. However, all three villous atrophy groups had no difference as adults in regards to comorbid conditions, complications from celiac disease, self-reported symptoms, overall health, adherence to a gluten-free diet, GSRS score, and PGWB score even after adjusting for current age, sex, year of CD diagnosis, and median BMI.

This study demonstrates that pediatric patients with CD and more severe villous atrophy (and more health-related issues as children) appear to have similar long-term outcomes as adults when compared to pediatric patients with less severe villous damage. We can use this information to inform pediatric patients with CD and their families about the importance of continuing a gluten-free diet throughout their lives in order to have good health outcomes.

Kroger S, Kurppa K, Repo M, Huhtala H, Kaukinen K, Lindfors K, Arvola T, Kivela L. Severity of villous atrophy at diagnosis in childhood does not predict long-term outcomes in celiac disease. Journal of Pediatric Gastroenterology and Nutrition 2020; 71: 71-77.

(continued on page 44)

(continued from page 42)

More Data on C. difficile and Pediatric IBD Outcomes

Clostridioides difficile (C. diff), previously known as *Clostridium difficile* is a relatively common gastrointestinal tract infection and has a significant association with inflammatory bowel disease (IBD). C. diff infection and the C. diff carriage state may be difficult to differentiate in patients in IBD due to similar symptoms occurring with active IBD as well as with an active C. diff infection (diarrhea, abdominal pain, etc.). The authors of this study evaluated the progression to intestinal resection in pediatric patients with IBD diagnosed with C. diff carriage within one year of IBD diagnosis, and they evaluated fecal microbiome samples in such pediatric patients in relation to C. diff carriage state as well as in relation to a history of intestinal surgery.

Patients with Crohn disease (CD) from a single tertiary children's hospital (age 21 years old or less) were retrospectively included in the study if they had stool samples as part of that institution's IBD Biorepository and if they had C. diff testing within one year of the CD diagnosis. At the same time, a prospective study occurred for patients who were diagnosed with CD and who subsequently could provide stool sampling. Stool samples were analyzed for calprotectin levels and had C. diff polymerase chain reaction (PCR) testing as well as microbiome sampling performed by high throughput shotgun metagenomic sequencing (rapid parallel DNA sequencing). Metabolic pathways of bacteria were analyzed using nucleotide and peptide databases.

The retrospective aspect of the study demonstrated a C. diff positivity rate of 19% in the CD group with significantly more patients with C. diff having had antibiotic exposure within 30 days of testing. Most patients with CD were in the age range of 10 to 17 years, and the percentage of steroid exposure in the first year of life was not statistically different regardless of C. diff status. The rate of intestinal resection was significantly lower for patients with negative C. diff testing (21%) compared to patients with positive C. diff testing (67%). Additionally, patients with positive C. diff testing had a shorter mean time to intestinal resection (527 days) compared to patients with negative C. diff testing (1268 days). Univariate analysis showed that steroid or anti-tumor necrosis factor (anti-TNF) medication exposure did not change results. Multivariate analysis demonstrated that only positive C. diff testing was associated with the need for intestinal surgery in patients with CD.

The subsequent prospective study demonstrated that 14% of patients with CD had positive C. diff testing, and 9% of patients with CD had a history of intestinal surgery. Similar to the retrospective cohort, patients with positive C. diff testing were significantly more likely to have had prior intestinal surgery. There was no difference in fecal calprotectin levels or reported IBD symptoms between groups. High throughput shotgun metagenomic sequencing demonstrated no overall difference in the fecal microbiome profile between patients with or without C. diff although there was a significant decrease in 123 taxa in patients with a positive C. diff infection. These taxa tended to be commensal organisms that had a potential mucosal protective effect. Metabolic profiles were not significantly different between patients regardless of C. diff status although patients that underwent intestinal surgery had 95 metabolic pathways that were altered compared to patients who had not had surgery (such as downregulated methionine biosynthesis pathways). Finally, patients with positive C. diff testing and a history of intestinal surgery had 47 bacterial species that were significantly reduced. These taxa were associated with protective gut function.

This study appears to show that young patients with CD and positive C. diff testing are at an increased risk of intestinal resection. These patients had microbiome changes noted as well suggesting the potential loss of a protective gut microbiome. The authors theorize that the early presence of C. diff in a young person with CD may be due to significant alterations in the microbiome leading to bowel inflammation and subsequent surgery.

Hellmann J, Andersen H, Fei L, Linn A, Bezold R, Lake K, Jackson K, Meyer D, Dirksing K, Bonkowski E, Ollberding N, Haslam D, Denson L. Microbial shifts and shorter time to bowel resection surgery associated with C. difficile in pediatric Crohn's disease.

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