

ISSUES IN PEDIATRICS

Addressing the Special Needs of Children in Gastroenterologic Practice

The Diagnosis and Treatment of Celiac Disease

Ivor Hill, MD
Department of Pediatrics
Wake Forest University School of Medicine

G&H Is celiac disease a genetic disorder, a syndrome brought on by environmental factors, or some combination of both etiologies?

IH Our current understanding of celiac disease describes it as an autoimmune enteropathy. We have identified specific genetic factors that predispose patients and we know the environmental factors that actually initiate disease.

There is no doubt that the inheritance factor is present at birth but patients do not develop the disease until they are exposed to the dietary toxic factors, which are found in wheat, barley, and rye. There has been considerable debate over the years as to whether there are other factors involved in initiating onset of disease, as the age of onset of symptoms and clinical manifestations varies widely among patients. There has been interest in associated viral infections and parasitic infections, as well as stress factors such as pregnancy, which have been proposed as contributing to onset. None of these theories has ever been proven and researchers are still looking for a definitive answer.

G&H Can you describe the pathophysiologic mechanism of celiac disease?

IH When patients predisposed to celiac disease are exposed to gluten or gluten-related products, the innate and adaptive immune systems both react. The innate system is triggered very early and is driven largely by cytokines, which initially cause very little damage to the intestinal mucosa. The exact pathways are unknown but interleukin-15 plays a very important role in the innate pathway and is probably responsible for the early migration of T-lymphocytes into the intraepithelial compartment from the deeper layers of the lamina propria of celiac patients. There is also a simultaneous upregulation of DQ2 and DQ8 molecules on the antigen-presenting cells.

In the adaptive arm of the disease process, tissue transglutaminase plays a critical role. Tissue transglutaminase deamidates glutamine to glutamic acid, which increases the negative charge on the gluten peptides and strongly binds them to the DQ2/DQ8 molecules on the antigen-presenting cells. This, in turn, triggers both a T- and a B-cell response of humoral antibodies and cytokines, particularly interferon gamma. There is then a progressive remodeling of the intestinal mucosa characterized by flattening of the villi and elongation of the crypts, leading to further complications related to malabsorption of nutrients.

G&H What are the presenting symptoms of patients with celiac disease?

IH Symptoms are extremely variable. In order to aid in diagnosis, we can divide them into gastrointestinal symptoms, nongastrointestinal symptoms, and associated conditions and other risk factors.

The gastrointestinal symptoms of celiac disease include diarrhea, frank steatorrhea, bloating, abdominal discomfort, excessive gas, nausea, vomiting, and elevated liver enzymes, which can occur singly or in combination. In some cases constipation can be a problem, as opposed to diarrhea. There are a very wide variety of gastrointestinal manifestations and their severity is highly variable. They can be characterized as mild and intermittent or severe and protracted.

With regard to nongastrointestinal symptoms, one could choose virtually any system in the body and associate a problem with celiac disease. In the hematologic system, iron deficiency anemia that responds poorly to iron therapy is a very well-described presentation of celiac disease in adults, which we believe is related to the mucosal damage, which causes malabsorption of iron. Although children with celiac disease are often anemic as well, it

is not generally thought of as a presenting symptom for this age group. In dermatology, dermatitis herpetiformis is now recognized as a skin manifestation of celiac disease. Dental enamel hypoplasia that affects the secondary dentition is well recognized by dentists in Europe, who will refer pediatric patients to physicians for definitive diagnosis. In adults, osteoporosis and osteopenia are often seen. Children with active disease may have poor growth and present with shorter than average stature. There are also generalized features including loss of appetite, loss of energy, and feelings of chronic ill health.

A number of both autoimmune and non autoimmune conditions are strongly associated with celiac disease. Type-1 diabetes is the most prominent autoimmune celiac disease-associated disorder. Others include thyroiditis, Sjogren syndrome, autoimmune hepatitis, and primary biliary cirrhosis. Associated nonautoimmune conditions include Down syndrome, Turner syndrome, and Williams syndrome. First-degree family members of patients with celiac disease are also at much higher risk.

G&H With the wide variety of manifestations of celiac disease, how can it be differentiated from other gastrointestinal disorders and a positive diagnosis made?

IH At this time, a definitive diagnosis for celiac disease still requires demonstration of the characteristic small intestinal histologic features coupled with a positive response to treatment. Obviously, every patient presenting with any of the wide variety of manifestations of celiac disease cannot undergo endoscopy. However, there are sensitive serologic screening tests to identify patients in need of biopsy for definitive diagnosis. Having said that, if the clinical index of suspicion for celiac disease is high, (eg, a child with chronic diarrhea who's failing to thrive) biopsy should be considered even with a negative serologic test because these tests are not 100% accurate.

G&H What treatments are available for patients with celiac disease?

IH The only proven form of therapy for celiac disease is adherence to a strict gluten-free diet for life. In theory, it sounds simple to exclude any foods that contain products from wheat, barley, or rye. However, in practice it can be extremely difficult because gluten is hidden in many food-stuffs. Successful dietary adherence requires an enormous amount of education and consultation with a skilled nutritionist. Also, it should be noted that oats, in their pure form, are safe. However, harvesting, milling, and production processes in the United States can contaminate oats with traces of wheat products and, therefore, we cannot endorse them without reservations.

G&H Why is it important to diagnose and successfully treat celiac disease in pediatric patients?

IH The ideal stage to make a diagnosis of celiac disease is in the young child. The younger the patient, the better the chance of complete resolution of celiac disease with a strict, gluten-free diet.

Many children at the time of diagnosis have decreased bone mineralization. On a gluten-free diet, the vast majority of these patients will completely resolve any bone density issue within a year and their levels will return to normal for their age. However, if the patient is diagnosed later in life, in their 40s or 50s, many will already have osteoporosis or osteopenia. Although their bone mineral density can be improved, they will never return completely to optimal, healthy levels.

A recent study of children who were evaluated for short stature in an endocrinology clinic found that 10% of these patients could retrospectively be diagnosed with celiac disease. Again, if these children are diagnosed early and treated, they will demonstrate catch-up growth and ultimately reach their full growth potential. If, however, they are not diagnosed and treated until after puberty, they will be permanently stunted.

It is also important for women of child-bearing age (ie, late adolescence and early adulthood) to be diagnosed and treated as those with untreated celiac disease have a much higher incidence of infertility, recurrent spontaneous abortions, and low birth-weight babies. Again, on a gluten-free diet these patients revert back to normal statistics.

G&H How do you approach pediatric patients in terms of achieving adherence and effective treatment of celiac disease?

IH The main focus for patients with celiac disease is education. In the beginning, I see these patients frequently, to reinforce the importance of strict dietary adherence and emphasize the long-term adverse health implications of nonadherence. Because the dietary issues are so complex, I rely on an expert nutritionist, as should most physicians, to work with these patients. In addition, there are patient support groups throughout the country that are extremely well educated and provide an excellent resource for both patients and parents.

Many pediatricians have concerns about imposing these dietary restrictions on children and the psychological issues involved in making them feel somehow different from their peers. In my experience, children are adaptable and they learn very quickly what they can and cannot eat. In the long run, it does not seem to phase them at all.

G&H What research is currently ongoing in the diagnosis and treatment of celiac disease?

IH Although we know there are only two HLA types, HLA/DQ2 and HLA/DQ8, that have been associated with the vast majority of celiac patients, these genes alone account for only about 40% of the genetic predisposition to the disease. We believe that non-HLA genes are involved and the ability to identify them would provide a huge boost to our understanding. There is also ongoing work to fully understand the intricacies of the pathways involved in immunopathogenesis. This would not only help us understand celiac disease, but also allow us to better understand autoimmune diseases in

general. It might also provide us with potential for future therapeutic interventions.

Suggested Reading and Resources

Hill ID, Dirks MH, Liptak GS, et al for the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr.* 2005;40(1):1-19.

Hopman EG, le Cessie S, von Blomberg BM, Mearin ML. Nutritional Management of the Gluten-free Diet in Young People with Celiac Disease in The Netherlands. *J Pediatr Gastroenterol Nutr.* 2006;43:102-108.

Children's Digestive Health and Nutrition Foundation: <http://www.cdhnf.org> or <http://www.celiachealth.org>.

Celiac Disease Awareness Campaign: www.celiac.nih.gov.