

More: **Digestive Disease Week (DDW) 2008**

News on Celiac Disease: Where Are We? Where Are We Going?

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San Diego, California; Wednesday, May 21, 2008 - The trend of exponential growth in the reports and special sessions on celiac disease continued at this year's Digestive Disease Week (DDW) meeting. A total of 75 American Gastroenterological Association-sponsored sessions (Clinical Symposia, Meet-the-Professor Lunches, Focused Clinical Updates, Research Roundtables, and Sunrise Discussions) and abstracts were presented throughout the course of the meeting and were summarized, as is the tradition, by Drs. Carol Semrad and Robert Anderson at a well-attended Sunrise Discussion on advances in celiac disease.^[1] The wealth of basic, translational, and clinical information reported this year and the quality of these data are testimonial to the fact that celiac disease is closing in on other gastrointestinal disorders that have historically been at the forefront of the field.

Celiac disease is now considered an autoimmune disorder triggered by the ingestion of gluten and similar proteins of barley and rye in genetically susceptible subjects. It is the gliadin fraction of wheat gluten and similar alcohol-soluble proteins in other grains that is associated with the development of intestinal damage. The interplay between genes and environment (ie, gluten) leads to the onset of intestinal and/or extraintestinal symptoms. The major breakthroughs reported at DDW 2008 were in regard to the pathogenesis of celiac disease and, most important, focused on new strategies for its prevention and treatment.

Celiac Disease: Where Did It Come From and How Does It Work?

For most of the history of the human race, gluten was not part of the equation. About 10,000 years ago, a fraction in the 2.5 million years of human history, gluten made its appearance with the advent of agriculture, providing the second "ingredient" (the first being genetic predisposition) necessary to develop celiac disease. However, we are still struggling with a key unanswered question: Why, despite the fact that 30% to 40% of the population worldwide has the necessary HLA DQ2/DQ8 genes (ie, class II human leukocyte antigen HLA genes DQ2 or DQ8) and despite that virtually everyone is exposed to gluten, do only 1% of individuals develop celiac disease? Several studies presented at this year's DDW meeting attempted to answer this question. Three of these studies advocated a third element, the loss of the intestinal barrier function, as an integral part of the problem.

A group from the University of Adelaide in Australia reported that gliadin causes increased intestinal permeability by inducing redistribution of claudins, proteins that are an integral part of the tight junction complex that governs intestinal permeability.^[2] By using a transgenic mouse model of celiac disease, another group from McMaster University in Canada presented 2 abstracts in which they showed that gluten ingestion in sensitized animals caused an increased intestinal permeability that was aggravated by the administration of nonsteroidal anti-inflammatory drugs^[3] and attenuated by treatment with an inhibitor of zonulin, a molecule that regulates intestinal permeability.^[4] It is interesting to note that correction of the intestinal barrier defect caused a decrease in intraepithelial immune cell infiltration (a sign of celiac disease activation),^[4] suggesting that increased intestinal permeability is an integral part in the pathogenetic cascade of the disease.

The intestinal microbiota has also been hypothesized as an additional element involved in the pathogenesis of celiac disease. A group from Italy showed that the duodenal microbiota of children with celiac disease who were exposed to gluten was radically different from the microbiota of children with celiac disease who were on a gluten-free diet.^[5]

Both the innate and adaptive immune responses seem to be involved in the pathogenesis of celiac disease. Junker and Schuppan^[6] provided convincing evidence that the innate immune response elicited by not yet identified gliadin peptides involves the signal transduction molecule MyD88. Also intriguing were data reported by a group from Stanford University suggesting that transglutaminase 2, the enzyme that potentiates the adaptive immune response to gluten, is constitutively inactive and is transiently activated upon tissue injury.^[7] A Hungarian group presented very provocative

data suggesting that haptoglobin, once considered a marker of acute inflammation, may represent a novel genetic risk factor involved in the development of celiac disease.^[8]

Diagnosis: Can We Eliminate the Intestinal Biopsy?

Still today, a small intestinal biopsy showing the typical celiac enteropathy is considered the gold standard for proper diagnosis of celiac disease. However, several studies presented at DDW 2008 suggested that the histologic findings may not be so conclusive. In this context, a report from Argentina, which suggested that a very accurate serologic algorithm may obviate the need for an intestinal biopsy in selected celiac disease cases,^[9] should be welcomed as a provocative finding to stimulate a debate on the need to revise the diagnostic criteria for celiac disease.^[10]

Reaction to Gluten: Not Always Celiac Disease

Many patients report that their symptoms resolve once they embrace a gluten-free diet even when celiac disease has been ruled out. Growing clinical evidence, still awaiting rigorous validation studies, suggest that these cases may be related to gluten sensitivity, a new form of food reaction. Preliminary data presented this year suggest that this form of disease may be related to activation of the innate immune system without the involvement of the adaptive immune response.^[11]

Potential New Therapy Alternatives to the Gluten-Free Diet: The Future Is Coming

The cornerstone of treatment of celiac disease for decades has been a lifelong adherence to a strict gluten-free diet devoid of proteins from wheat, rye, barley, and related cereals. However, gluten is a common (and in many countries, unlabeled) ingredient in the human diet, presenting a great challenge for patients with celiac disease. Further complicating the situation is the evidence that a high percentage of patients with celiac disease who are on a gluten-free diet, are symptom-free, test negative for celiac disease serology show persistence of severe intestinal damage. Therefore, there is a strong demand for alternatives to the gluten-free diet.

During this year's DDW meeting, 3 groups presented different yet complementary approaches for the management of celiac disease. A group from Ireland showed that the combination of bacterial- and barley-derived proteases given orally to celiac disease patients can degrade gluten to nontoxic fragments and therefore may represent a good treatment strategy.^[12] Similar promising results were obtained by a Finnish group that showed that proteases from germinating wheat decrease the toxic effects of gliadin in vitro.^[13] A third group from the United States presented data from a phase 2b study using the same zonulin inhibitor used in an animal model of celiac disease as mentioned above; it showed promising efficacy and a reduction in gluten toxicity.^[14] These studies were elegantly summarized by Dr. Khosla in a State-of-the-Art-Lecture.^[15] Finally, an intriguing study from an Italian group showed preliminary data suggesting a protective role for delayed gluten introduction on the onset of celiac disease in genetically at-risk infants.^[16]

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