Celiac Disease

Celiac Disease affects one out of 133 people in the United States. Unlike a wheat allergy or food sensitivity, diagnosed Celiac Disease is not a temporary food intolerance, but a life long autoimmune disease. Left untreated CD has the potential to lead to a host of other problems such as iron deficiency anemia, vitamin and mineral deficiencies, early onset osteoporosis/osteopenia, and even infertility. Fortunately the complete exclusion of very culprit of the symptoms - gluten - from the diet, can reverse such manifestations as inflammation of the small intestine, thus eliminating the symptoms of the disease.

Detecting Celiac Disease

As stated above, roughly two million people are said to have CD. This number may seem shocking, especially since the general population does not discuss CD as they do other autoimmune or gastrointestinal diseases such as Type 1 diabetes, Irritable Bowel Disease or even Crohn's Disease. One can assume there are several people suffering from symptoms of CD who are undiagnosed. In fact, a survey completed in Canada reported that the average delay from symptoms to detection of CD is 11.7 years.[1] This maybe due to the diversity and variability of symptoms in each patient. Common symptoms in children and babies include abdominal pain, bloating constipation, diarrhea, weight loss, and vomiting. Diarrhea is not as common is adult diagnoses, with only fifty percent suffering from this indicator. Adults can manifest other symptoms such as anemia, arthritis, bone loss, mouth ulcers, depression, fatigue, infertility, joint pain, seizures and numbness in the extremities.

Noting discomfort after certain gluten containing foods is only the start. Real detection occurs with a series of tests. The endomysial antibody (EMA) test has been associated with testing for Celiac. Yet, it relies on an experienced technician to interpret the results of the immunofluorescence results. As a result, some health professionals will reserve this test for the more challenging to diagnosis cases.

Blood tests are a straightforward initial test for the detection of CD. The patient must be consuming gluten containing foods before testing. Patients are advised that a blood panel does not confirm CD, but screens for the risk of the disease. They are further informed that blood tests should screen for the following:

- Endomysial antibody (EMA-IgA)
- Tissue transglutaminase antibody (tTG - IgA/IgG)
- Anti-gliadin antibody (AGA-IgG, AGA-IgA)
- Total serum IgA[2]

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[1] Cranney, Ann, et al. "The Canadian Celiac Health Survey. *Digestive Diseases and Science"* (2007);52:1087-1095

[2] Celiac Disease Diagnosis. Retreived December 5, 2009, from http://www.celiac.org/cd-diagnosis.php.

To understand how a test works, look at IgA. Immunoglobulin A deficiency is normally detectable in CD sufferers. For instance in the general population IgA levels vary from .05% to .1%, whereas they rise to 1.7% to 3.0% in test positive for CD. If a patient falls in this range, the next step is to have a duodenal biopsy to observe potential damage to the villi in the small intestine. For further (and perhaps final) confirmation, tests are done for the presence of human leukocyte antigen (HLA) DQ2 or DQ8. These tests are extremely accurate and sensitive for CD. One third of the population have these genes. However, it is not the presence of DQ2 or DQ8 that mark the development of CD, but the *lack* of these two genes that practically rules out the possibility.

It is a combination of experiencing and reporting symptoms, a series of antigen detection blood tests, a physical biopsy to detect the actual damage to the small intestine, and a genetic confirmation of susceptibility to the disease to fully detect and diagnose this autoimmune disease.

Looking inside – the autoimmune response of Celiac Disease

If CD sufferers need a moral boost, then they may take to heart a comment by leading researcher, doctor, and innovator Alessio Fasano who stated "Celiac Disease provides an enormously valuable model for understanding autoimmune disorders because it is the only example where the addition or removal of a simple environmental component, gluten, can turn the disease on or off." [3]

Gluten is composed of proteins called gliadins and glutenins. When they are digested, peptides, protein fragments, in the gluten molecule are still kept intact. For 99% of the population, the protein fragment passes through the gastrointestinal tract and is then excreted without consequence. In the remaining 1% of the nation, the host of symptoms previously mentioned occurs due to the presence of this small gluten fragment.

How does the fragment pass through the barrier wall of the small intestine? In the last decade, much intention has been given to the role of tight junctions. It was formerly believed that tight junctions were impermeable, and thus molecules could not pass through. Current research has shown tight junctions to be complex structures vulnerable to a change in shape and form, and thus *function.* [4] After the perpetrating gluten peptide left in the GI tract elevates the amounts of a certain protein called Zonulin. It is relevant to note that Zonulin is present in all humans, but elevated levels exist in people with autoimmune disorders such as CD, rheumatoid arthritis, and multiple sclerosis. Zonulin acts on tight junctions, loosening them and allowing the passage of fluids, large molecules, and immune cells. Once the gluten crosses the intestinal lining they accumulate under the epithelial cells (enterocytes). Their presence entices the enterocytes

[3] Alessio Fassano "Surprise from Celiac Disease. *Scientific American,"* (2009, August) pp. 54- 61.
[4] Alessio Fassano, Terez Shea-Donohue. "Mechanisms of Disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases. *Nature Clinical Practice Gastroenterology and Hepatology*"(2005) 2; 416-22.

to secrete interleukin–15 (IL-15) which elicits lymphocytes against epithelial cells. These cells are now damaged and start releasing their own enzyme called tissue transglutaminase (TTG). TTG modifies the gluten fragment. Next an antigen presenting cell binds the modified gluten to HLA molecules. What are HLA molecules?

The major histocompatibilty complex on chromosome 6 contains human leukocyte antigen (HLA) class I and class II genes. This genes are associated with a least 50 autoimmune disorders. In the case of CD, HLA DQ2 and HLA DQ8 are present in 95% of diagnosed patients. Recall that when gluten is broken down into amino acids, the peptides are kept intact. HLA DQ2 and DQ8 encode glycoproteins that bind peptides (in this case, gliadin), and the result is a HLA-peptide complex.[5] The complex presents itself to helper T cell lymphocyte receptor in the intestinal mucosa. If the HLA-peptide complex was advertising a warning, then the helper T cell is the town crier, summoning more immune cells to elicit their response on the foreign invader.

From there the immune system continues to attack in full force. Cytotoxic T cells directly target the epithelial cells. The release of cytokines and chemokines stimulate further immune response. B cells play a part by "ingesting" TTG and making antibodies against it. As a result higher levels of antibodies, such as anti-gliadin, anti-endomysium and anti-tissue transglutaminase are present in the blood of a Celiac patient. The physical damage due to multidirectional invasion on the enterocytes is damage directly on the surface of the small intestine. Fingerlike projections called villi located on the enterocytes house some of the enzymes necessary to breakdown food so they can pass into the bloodstream. The immune response to an invading gluten protein damages the lining of the small intestine by flattening the villi. With less surface area, the small intestine is less efficient at nutrient absorption.

How to treat Celiac Disease

As mentioned the complete removal of gluten from the diet can almost completely reverse the symptoms of Celiac patient. For most people following a strict diet, the problem lies in "hidden" sources of gluten. These include, but are not limited to, contamination of gluten free products with gluten containing ones, flour dusted on items such as frozen vegetables or fruit, or unspecified additives in soups, sauces, and dressings. These scenarios encouraged a double blind, placebo controlled study conducted in Italy in 2007.[6] The researchers attempted to discover the "gluten threshold" that one could tolerate in their diet. They estimated that average vigilant gluten free diet follower still consumed between 5 to 50 mg of gluten per day. Unfortunately, the study started out small and some participants dropped out. However, the small sample did

[5]Victorien Wolters, Cisca Wijmenga "Genetic background of Celiac Disease and its clinical implications. *American Journal of Gastroenterol"* (2008) 103: 190-5

[6]Carlo Catassi. et al. "A prospective, double blind, placebo- controlled trail to establish a safe gluten threshold for patients with celiac disease. *American Journal of Clinical Nutrition"* (2007) 85;160-6.

determine the ingestion of gluten should be kept to less than 50mg per day. To the average Italian dinner 50 mg is a trace amount!

To date, avoidance of gluten containing food is the only reliable treatment for CD. Scientists are seeking alternatives. Most interventions are trying to manipulate certain stages of the pathway. For instance, can researchers block epithelial ZOT receptor (Zonulin) to decrease intestinal permeability? Can they inhibit intestinal TG2 activity with transglutaminase inhibitors? Would it be possible to block the gluten peptide presentation by HLA-DQ2 antagonists or modulate proinflammatory cytokines? The treatments are still hypotheses but as of this year some await phase 1 or 2 of clinical trails. [7]

The medical community has been criticized for a lack of attention and proper screening of CD.[8] Positive implications abound for earlier detection and treatment. Not only would less people suffer from mild to severe gastrointestinal discomfort, but also doctors and specialists my find answers to former undiagnosed symptoms. Health care costs would drop if patients could be treated in a timely fashion and avoid several trips to their health care professional. Perhaps most important incentive is preventative care. CD has been linked with several other conditions with varying degrees of severity and morbidity. To treat CD could also mitigate other conditions or lessen their severity.

Though some examples were stated earlier, the following is a complete list from the Celiac Foundation[9] of long-term conditions that can result from CD left untreated:

- Iron deficiency anemia
- Early onset osteoporosis or osteopenia
- Vitamin K deficiency associated with risk for hemorrhaging
- Vitamin and mineral deficiencies
- Central and peripheral nervous system disorders - usually due to unsuspected nutrient deficiencies
- Pancreatic insufficiency
- Intestinal lymphomas and other GI cancers (malignancies)
- Neurological manifestations
- Gall bladder malfunction
- Lymphoma

It is also necessary to highlight another aspect of the genetic link of CD. Because the same genetic markers could be present among family members, there is a 5-15% chance a child of a Celiac patient will contract the disease. In identical twins, 70% both have CD.

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[7] S. Detlef et al. Celiac Disease: From Patogénesis to Novel Therapies. *Gastroenterol* 2009; 137:1912-1933.

[8] Rosemary Frei. (2007, May). New Study Highlights Need for Proper Screening For Celiac Disease in Patients with GI Symptoms. *Gastroenterology and Endoscopy News*. Retrieved from http://www.gastroendonews.com

[9] Celiac Disease Symptoms. Retrieved December 5, 2009. http://www.celiac.org/cd-symptoms.php

Finally, those have previously been diagnosed with another autoimmune disease have a 25% increased risk of development. Other associated autoimmune disorders include:

- Dermatitis Herpetiformis (DH)
- Insulin-dependent Type I Diabetes Mellitus
- Thyroid Disease
- Systemic Lupus Erythematosus
- Liver Diseases

If this genetic component exists, how do researchers explain "late onset" CD? There are different answers to this provocative question. Some believe the disease was occurring early in life, but mild enough to not manifest symptoms. However, another hypothesis looks at the bacteria in the digestive tract. Also referred to as a microbiome, microbes that live in the digestive tract may vary throughout life. They also may influence which genes in their hosts are active at a particular time. This versatility may leave them tolerant of certain substances (like gluten) for several years, and then suddenly intolerant if "dormant" genes become active. If this is true, perhaps people suffering from CD could one day be treated with probiotics! [10]

The Future of Celiac Disease

With 1% of the nation suffering with CD, a continued effort to find reliable tests and markers, and a growing awareness among health professionals and patients alike, it can be assumed the outlook of CD will improve. Perhaps there will be routine preventative screening for family members predisposed to the illness. Clinical research and trials on preventing the immune response to gluten may prove successful and give patients alternatives to coping with CD. Until then they can rest assured that they have one advantage of having CD over any other autoimmune disorder. With the removal of that small little protein fragment – gliadin – they have the power to completely eradicate the manifestations of their disease.

[10] Alessio Fassano, Terez Shea-Donohue. 416-22.

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Mechanisms of Disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases

Alessio Fasano* and Terez Shea-Donohue

Summary

The primary functions of the gastrointestinal tract have traditionally been perceived to be limited to the digestion and absorption of nutrients and electrolytes, and to water homeostasis. A more attentive analysis of the anatomic and functional arrangement of the gastrointestinal tract, however, suggests that another extremely important function of this organ is its ability to regulate the trafficking of macromolecules between the environment and the host through a barrier mechanism. Together with the gut-associated lymphoid tissue and the neuroendocrine network, the intestinal epithelial barrier, with its intercellular tight junctions, controls the equilibrium between tolerance and immunity to nonself-antigens. When the finely tuned trafficking of macromolecules is dysregulated in genetically susceptible individuals, both intestinal and extraintestinal autoimmune disorders can occur. This new paradigm subverts traditional theories underlying the development of autoimmunity, which are based on molecular mimicry and/or the bystander effect, and suggests that the autoimmune process can be arrested if the interplay between genes and environmental triggers is prevented by re-establishing intestinal barrier function. Understanding the role of the intestinal barrier in the pathogenesis of gastrointestinal disease is an area of translational research that encompasses many fields and is currently receiving a great deal of attention. This review is timely given the increased interest in the role of a 'leaky gut' in the pathogenesis of gastrointestinal diseases and the advent of novel treatment strategies, such as the use of probiotics.