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Pathophysiology and approaches in celiac disease management

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Abstract
Celiac disease (CD) is a common autoimmune disorder characterized by an immune response to ingested gluten and has a strong HLA association with HLADQ2 and HLA-DQ8 molecules, but human HLA-DQ risk factors do not explain the entire genetic susceptibility to gluten intolerance. CD is caused by the lack of immune tolerance (oral tolerance) to wheat gluten. The expression of soluble HLA-G in CD molecule plays an important role in the induction of immune tolerance. At present, strict and lifelong gluten free diet is the only effective treatment for celiac disease. Even small amounts of gluten (50mg/day) can be immunogenic; therefore all food and food items and drugs that contain gluten and its derivatives must be eliminated completely from the diet. In recent times, a number of targets to halt the process of immunological injury have been explored to find out alternative treatment for celiac disease. These targets include exploration of ancient wheat if they are less immunogenic, intra-luminal digestion of gluten using prolylendo peptidases, pretreatment of whole gluten with bacterial-derived peptidase before ingestion; prevention of passage of immunogenic peptides through the tight junctions such as zonulin antagonists, Blocking of HLA-DQ2 to prevent binding of immunogenic peptides, inhibition of transglutaminase-2, immune-modulation and induction of tolerance to gluten using gluten tolerating vaccines, use of gluten-sequestering polymers, use of anti-inflammatory drugs (glucocorticoides, budesonides) and anti-cytokines such as anti TNF-α, and anti-interleukin-15.

Keywords: autoimmune disorder, Celiac disease, Cytokines, Gliadin peptide, gluten, glucocorticoides

Introduction
Celiac disease (CD) is a chronic inflammatory disease in genetically predisposed individuals. It is a T cell-mediated inflammatory disorder with autoimmune features. It has environmental and immunologic component [1, 2]. It is characterized by an immune response when an individual ingest wheat gluten and related proteins of rye and barley that leads to villous atrophy in the proximal part of the small intestine, inflammation and crypt hyperplasia [2,3]. In healthy patients with typical enteropathy, CD is described as silent. Potential CD refers to risk for developing a typical CD later in life; the patients have tissue transglutaminase antibody and Endomysial antibody (EMA) with HLA DQ2 or DQ8 as predisposing genotype [4, 5]. Diarrhea, abdominal pain, malnutrition, abdominal distension, weight loss and fatigue are the common presentation signs and symptoms of CD [6].
Although there have been major advances according to our knowledge of the disease, there are few advances in the therapy. Nutritional therapy with a gluten-free diet for lifelong is the only acceptable treatment for CD [7].

Epidemiology
Not so long ago, it was thought that CD was a rare condition. Caucasians are the only one who are affected with CD, mostly found in children, with a typical presentation of diarrhea and weight loss. We know now that this is not true.

- In world CD is common and affects around 300 of the population it causes 100 to one.
- The female-to-male ratio is 2: 1.
- CD occurs frequently without gastrointestinal symptoms.
- There are no substantial differences between symptomatic patients and "not-at risk" patients in all the countries or geographic areas in which epidemiological studies have been carried out.
- CD epidemiology has few characteristics — the undiagnosed case(below the waterline) are far more than diagnosed cases (above the waterline)
- There is a greater risk in first-degree relatives (up to 10%) and less so in second-degree

- relatives, as well in people with diabetes and other autoimmune diseases, Down's syndrome, and a number of other associated diseases
- Fertility can be affected in a subset of celiac disease patients.
- In undiagnosed CD patients pregnancy may present with an unfavorable course in, especially in those who have had symptoms earlier. • During pregnancy or puerperium a clinically severe picture can develop in up to 17% of women patients [8].

Etiology

CD can be differentiated from other autoimmune diseases in that it encompasses several factors known to provoke a response. There is a clearly identified environmental trigger (gluten, a protein found in wheat, barley, and rye), auto antibodies against tissue transglutaminase (tTG) (detectable in over 95% of celiac patients) and a required dominant Human Leukocyte Antigen (HLA) contribution [9]. Although all of these have been identified as contributing factors to celiac disease the exact mechanism is still under investigation. Additional environmental factors, such as hepatitis B, hepatitis C, adenovirus, and others have been shown to have a role in celiac disease.

Clinical Features

Childhood:

In infants, celiac disease is usually very distinguishable. The symptoms generally appear in the first 1-2 years of life or after weaning when cereals are introduced into the diet. The child with irritable appearance, failing to thrive, and apathetic, and presentation of hypotonic, muscle wasting, and abdominal distention are the classic symptoms. Sometimes the child may present with watery diarrhea or constipation [10]. Especially in older children Nutritional deficiency, such as anemia, is another common presentation. In adolescence for many patients a brief, spontaneous remission of symptoms occur [11].

Adulthood

The mean age of diagnosis is approximately 45 years old in adults. In past perception the increase in newly diagnosed adults with CD contradicts that celiac disease was mainly a pediatric complication. Some of the adults diagnosed may have had evidence of unrecognized gluten sensitivity in childhood, such as short stature and a symptom history consistent with unrecognized sensitivity. However; many adults do not have a history of celiac disease, indicating that they developed gluten sensitivity for the first time in adult life. For these adults there seems to be a correlation with the development of celiac disease and increased obesity and body mass index [11].

Symptoms of Celiac Disease [11].

Gastrointestinal:

- Steatorrhea,
- Diarrhea,
- Weight Loss,
- Abdominal Distension and
- Flatulence and

Extra intestinal:

- Anemia,
- Osteopeni,
- Neurologic (Ataxia, neuropathy),
- Dermatitis herpetiformis.

Pathogenesis

The HLA-DQ haplotype of the individual, as well as a defect in antigen processing by epithelial cells, together with the intrinsic properties of the gliadins are considered the principal factors involved in the pathogenesis of CD [3]. CD is strongly associated with HLA class II genes that map to the DQ locus. It has been shown that CD is associated with the expression of HLA-DQ8 and HLA-DQ2 [4, 5]. Several studies found that the majority of celiac patients carry DQ2 (DQA1*05/DQB1*02), with the remaining patients displaying an association with DQ8 (DQA1*0301/ DQB1*0302). Collectively, these HLA genes confer up to 40% of the genetic risk for CD development. Gliadin peptide and T-cell activation presentation are critical events in the pathogenesis of CD. Gluten peptides are not fully digested by the action of gastric, intestinal and pancreatic enzymes in CD patients. A 33-mer peptide was isolated and identified as the primary initiator of the inflammatory response to gluten in celiac patient [12]. This peptide reacted with tissue transglutaminase (tTG), the major auto antigen in CD that deamidates certain glutamine residues of gluten to glutamic acid. This in turn produces a negative charge that favors' binding and presentation by HLA-DQ2 and DQ8 molecules, which are responsible for T-cell activation and subsequent production of cytokines, leading to tissue damage [13, 14].

The inappropriate CD4+ T-cell activation in the lamina propia commonly observed in CD is triggered by specific gluten peptides bound to DQ2 and DQ8 heterodimers on the surface of antigen presentation cells [2, 4]. The mucosal intestinal lesion is believed to be mainly induced by the production of IFN gamma from these gluten specific T cells [1, 2]. Moreover, changes in intestinal permeability, secondary to alterations in intercellular tight junctions or in the processing of the food antigen, have also been recently implicated in the loss of tolerance to gluten [15].

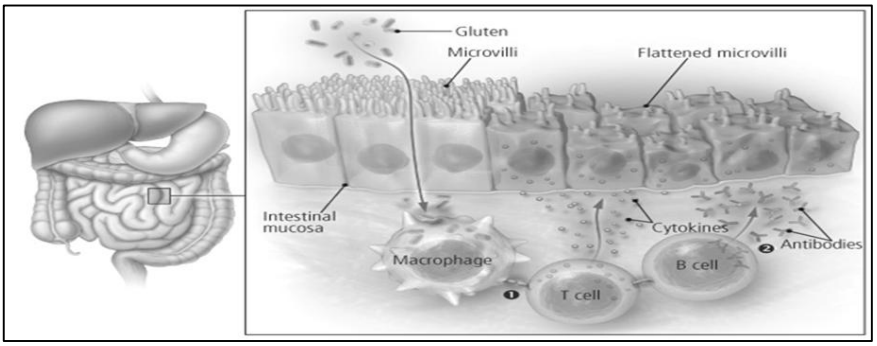

Fig. 1: Normal Villi and Damaged Villi

Immune (oral) tolerance

The immune system of the gut is exposed to a wide variety of antigens derived from foods, resident bacteria and invading microorganisms. Oral tolerance is a physiological condition characterized by induction of immune unresponsiveness toward intestinal alimentary and bacterial antigens of the intestinal flora. Multiple cellular and molecular mechanisms are involved in the regulation of this fundamental property of the gut immune system [16]. CD is the most common food-sensitive enteropathy in humans and is caused by the lack of immune tolerance (oral tolerance) to prolamin fractions of rye and barley wheat gluten. Many different gluten peptides recognized by intestinal T cells have been identified [17]. The activation of these gluten-reactive T cells represents a key event in the pathogenesis of CD [1, 2]. The CD patient's mucosa is characterized by a high proportion of intraepithelial T cells bearing gamma-delta chain of the antigenic T cell receptors (γδ IEL) [18]. Ingested gliadin, the triggering agent of the disease, can cross the epithelial barrier and elicit a harmful T cell mediated immune response. Dendrite cells are supposed to play a pivotal role in shaping the immune response [19]. Immature dendrite cells are characterized by low levels of MHC class II expression and co-stimulatory molecules and can mediate tolerance presumably by induction of T regulatory cells (Treg cells) [20].

Therefore, the direction of the immune response toward immunity or tolerance depends on the functional properties of the dendritic cells and the stage of maturation. Gliadin peptides can contribute to overcoming the stage of unresponsiveness of immature dendritic cells by inducing phenotypic and functional dendritic cell maturation, resulting in presentation of gliadin peptides to specific T lymphocyte [21].

HLA-G: molecule of immune tolerance

HLA-G is a non-classical major histocompatibility complex class I molecule selectively expressed at the maternal-fetal interface on cytotrophoblast cells, protecting the fetus from the maternal immune rejection, and creating a general state of tolerance [22]. HLA-G exhibit tolerogenic properties via interaction with inhibitory receptors presented in natural killer (NK) cells, T cells and antigen-presenting cells (APC) [23].

Interestingly, work from our lab and others have suggested that HLA-G antigens may play a protective role in inflammation [24, 25]. Further analysis revealed that, sHLA-G are the molecules inhibit lytic activity of NK cells, induce apoptosis of CD8+ CTLs and affect CD4+ all proliferation [26]. Thus, the immune modulatory properties of sHLA-G may suggest a potential role in CD. The expression of soluble HLA-G in CD is of special interest because its molecule plays an important role in the induction of immune tolerance [26]. HLA-G may act through inhibitory receptor (ILT) interactions that lead to development of tolerogenic dendrite cells with the induction of anergic and immunosuppressive T cells, and an arrest of maturation/ activation of dendrite cells. The expression of these ILT receptors on dendrite cells is tightly controlled by inflammatory stimuli, and by cytokines [27].

Thus, a powerful anti-inflammatory response to gliadin might occur during the development of the CD with uncontrolled production of HLA-G and anti-inflammatory cytokines, such as IL-10 and TGF-beta, which counteract the inflammation and/or may cause recruitment of intraepithelial lymphocytes, maintaining the intestinal lesions presented in CD [28].

Cytokines

The characteristics of an intestinal inflammatory response depend on the cytokines which are produced during this response. The production of cytokines from T cells and macrophages is of potential importance for the histological lesions that appear in CD. The CD lesions are associated with a marked infiltration of Th1 cells dominated by the synthesis of the pro-inflammatory cytokines, IFN-gamma and TNF-alpha [37]. IL-15 plays an important role in CD, because it orchestrates intraepithelial lymphocytes changes in the disease. Certain parts of gluten may stimulate the innate part of the immune system, and IL-15 is a central player in this immune response-induced by gluten, inducing the activation of IEL in CD [25].

Diagnosis

A common theme in the presentation of celiac disease is patient variability based upon, the diagnosis of the disease is no exception and severity and extent of the intestinal lesions. Over the years the frequency of celiac disease diagnosis has increased, but it is estimated that 97% of patients with celiac disease have not been diagnosed.

The most accurate diagnostic tests are serum IgA EMA or tTG antibody and the performance of a small intestine biopsy. A confirmed diagnosis of celiac disease requires both improvement in response to gluten-free diet and a positive histological finding on the biopsy, which is usually carried out via serologic tests.

Serology

There are many different assays that can be used to determine the presence of celiac disease, but the IgA EMA is the most sensitive (90%) and specific (99%), therefore, it is considered the gold standard. Due to the high specificity of the assay, the results are interpreted as a simple positive or negative. Upon the initiation of a gluten-free diet, antibody levels usually fall with the test often becoming negative in treated patients Both the IgA EMA and tTG target the tTG antigen, while other assay tests such as the IgA and IgG AGA tests target the antigladin antibody [29].

Small Intestine Biopsy

Diagnosis of celiac disease may be apparent via positive serologic tests and clinical observation, but a confirmed diagnosis cannot be accomplished unless a positive biopsy for the disease is established. Endoscopic biopsy is the standard procedure, which takes multiple small samples from the distal duodenum. The mucosa of the small intestine is then analyzed via a dissecting microscope [10]. Normal small intestine mucosa have a villous structure, but in untreated celiac disease the mucosa takes on a flat and featureless shape, which is easily recognizable [29].

Other Diagnostic Tools

Blood Tests

Specific types of antibody blood tests are used to diagnose patients with CD. These blood tests are also used to test people who may be at risk for having CD but have no symptoms (relatives of patients with CD). The most used tests are the tissue transglutaminase antibody tests and endomysial antibody. Other tests such as tests for gliadin antibodies are not as accurate because in healthy patients they can be abnormal who do not have celiac disease or in people with

other digestive problems. Other tests for allergies will not detect celiac disease. Tests on saliva or stool for antibodies are not good substitutes for the blood-based tests. Genetic tests are available to assist doctors when the blood tests are unclear, or when patients continue to have symptoms while on a gluten free diet [30].

Physical Examination

Like the gastrointestinal and extra intestinal symptoms, the physical findings in CD patients are variable. In general, people with mild disease exhibit normal physical symptoms, but as the however, the tTG test is more readily available and less expensive, therefore more widely used. The same is true when used for monitoring the adherence of celiac patients. Antibody levels decrease upon initiation of a gluten-free diet, which makes the serology, assays a perfect tool to monitor the compliance of celiac disease patients [29].

Differential Diagnosis

There are other malabsorption and gastrointestinal disorders that share similar characteristics as celiac disease, requiring the need to rule out these disorders when diagnosing celiac disease. The easiest way to do this is by performing one of the serologic tests mentioned above, as the IgA EMA and tTG are very specific in identifying celiac disease [29].

Genetic Testing

Nearly all individuals with CD carry the type II class Human Leukocyte Antigen (HLA) DQ2 and/or DQ8 haplotypes. These molecules are requisite for the high affinity binding of deamidated gluten peptides necessary to generate an immune response [31, 32]. Less than 1% of the CD population carries half of the HLA-DQ heterodimer [31]. However, HLA DQ2 and DQ8 are highly prevalent, and can be found in 20%–40% of the general population [33]. For this reason, it is estimated that only 3% of individuals with these haplotypes will go on to develop CD giving this test a very low positive predictive value [34, 35]. At the same time, HLA typing has a negative predictive value of >99% and is useful for ruling out CD in patients with a gluten free diet (GFD), for patients with an uncertain diagnosis of CD as recommended by ESPGHAN [36] and for risk stratifying CD in at risk family members.

Treatment

Introduction

At present, lifelong gluten free diet is the only effective treatment for celiac disease [37]. Even small amounts of gluten (50mg/day) can be immunogenic; therefore all food and food items and drugs that contain gluten and its derivatives must be avoided in the diet completely [38].

The overall goals of treatment include relieving symptoms, healing the intestine, and reversing the consequences of malabsorption. Currently, the only accepted treatment for celiac disease is a lifelong strict adherence to a gluten-free diet. Celiac patients must recognize the importance of completely avoiding gluten in their diet. This means not ingesting products containing gluten or any products that have been contaminated with gluten. Rye, Wheat, and barley must be avoided. Oats are from a different plant family, but they have also been problematic in celiac patients. Patients must also commit to avoiding the ingestion of gluten found in nonfood items such as toothpaste, lip balm, lipstick, etc. Other potential sources of gluten that should not be overlooked are oral prescription or nonprescription drugs, vitamin supplements and mineral supplements, health and beauty aids and cosmetics that have oral ingestion [39].

It is hard to determine a universal threshold under which patients need to keep their daily gluten, but as little as 10 to 50 mg/day is the minimum dose required to produce measurable damage to the small intestinal mucosa. The FDA has recently determined the tolerable daily gluten intake in celiac patients to be less than 0.4 mg/day for adverse morphological effects and less than 0.015 mg/day for adverse clinical effects [39].

One study showed that cognitive impairment or "brain fog" was significantly improved in celiac patients who adhered to a gluten-free diet [40].

Newly diagnosed patients should be evaluated for nutritional deficiencies associated with vitamin and mineral malabsorption. Possible nutritional deficiencies include folic acid, vitamin B12, fat soluble vitamins, iron, and calcium. Iron-deficiency anemia may be the only presenting sign of disease in patients without diarrhea. If detected, these deficiencies should be supplemented in addition to treating the disease [39].

The bone disorders that result from the disease pose their own challenge for comprehensive treatment of celiac patients. The two main mechanisms are chronic inflammation and intestinal malabsorption. A gluten-free diet in addition to calcium and vitamin D supplementation is usually the initial approach for treating these bone disorders. However, in many cases, especially in severe osteoporosis, it might be useful to begin treatment with hormones or bisphosphonates [41].

The following are the grains which contain Gluten and are Not Allowed in Any Form:

Barley, Triticale, Kamut, Rye, Einkorn, Spelt, Wheat

Frequently overlooked foods that often contain gluten

Breading, Communion wafers, Imitation bacon, Broth, Processed meats, Imitation seafood, Coating mixes, and Marinades Commercial cereals, Sauces, Basting Pastas, and Croutons Stuffings.

Some lifestyle changes are needed for gluten free diet. The way to understanding the gluten free diet is to become a good ingredient label reader. If a food has questionable ingredients avoid it and try to find a similar product that you know is gluten free. Foods containing the following ingredients are questionable and should not be consumed unless it is verified that they do not contain or are not derived from prohibited grains. These products are:

Unidentified:

Hydrolyzed plant protein (HPP), Modified food starch, Hydrolyzed vegetable protein (HVP), Malt vinegar, Soy sauce or soy sauce solids, Textured vegetable protein (TVP), Dextrin, Vegetable gum, brown rice syrup.

Be aware that medications may contain gluten ingredients. Gluten containing fillers may be in both in over the counter medications and prescription medications. It is essential to ensure that any medications being taken are gluten free.

Allowed:

Quinoa, Corn, Buckwheat, Rice, Millet, Soy Nut Flours, Sorghum, Bean, Tapioca, Potato Tef [42].

Future Therapies

Because of the shortcomings of the gluten-free diet mentioned

above, this approach is not the perfect solution for all celiac patients and leaves desire for additional treatment options for the disease. A few studies have addressed the use of small intestinal release mesalamine, or immunosuppressive agents (eg, azathioprine) systemic steroids (e.g. prednisone or enteric-coated budesonide), in patients with RCD. Unfortunately, these agents are not always successful in achieving symptom relief or mucosal healing [43].

Due to an improved understanding of the pathogenesis of celiac disease potential therapeutic targets have emerged. Most of these novel therapeutic approaches are aimed at the treatment of patients with refractory celiac disease since the gluten-free diet is not effective for these patients. Future therapies can be directed at two general mechanisms for treating the disease:

1) Decreasing the antigenic load and 2) modulating the immune response [39].

Decreasing Antigenic Load

Potential methods include antigen presentation blockade via tTG inhibitors. However, their safety is questionable due to the presence of the enzyme throughout the body and its role in many functions necessary for homeostasis. In the intestinal lumen, gluten could potentially be detoxified by polymeric binders, probiotic bacteria, or glutenases that decrease the harmful effects of gluten peptides. Another approach to decrease the toxicity of gluten peptides is through the development of gluten proteins in which the proline residues were replaced by azidoprolines. These novel gluten peptides bound HLA-DQ2 but did not stimulate an immune response [39, 41].

Modulating the Immune Response

Methods for modulating the immune response include the neutralization of inflammatory cytokines and regulation of T cells. Several endopeptidases have been developed which promote a more complete digestion of gluten peptides and thus destroy T cell activating epitopes. Lymphocyte blocking or anticytokine therapy may also be a potential approach to therapy. Finally, anti-inflammatory drugs and monoclonal antibodies that play a major role in immune modulation have been tested and might become an approach in the future [39, 44].

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