CELIAC DISEASE: FROM PATHOPHYSIOLOGY TO TREATMENT

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Abstract:
Celiac sprue is another name of celiac disease. It is a severe inflammatory disorder of small intestine, which is caused by ingestion of gluten items in susceptible people. This disease is multifactorial and includes environmental as well as genetic factors. Gluten falls under environmental factors and genetic predisposition is considered as the major complex histocompatibility region. Celiac disease is not rare anymore and has 1% of global prevalence. The reason it is not highly recognized is that most of the people do not have classic GIT symptoms, but they do show some nutritional deficiency or sometimes no symptoms at all. Here, in this review paper recent data encapsulating epidemiology, clinical presentation and therapeutic management of celiac disease is presented.

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Please cite this article in press Anam Sadia et al. Celiac Disease: From Pathophysiology To Treatment., Indo Am. J. P. Sci, 2020; 07(09).
INTRODUCTION:
An aberrant adaptive immune response against gluten containing grains become the cause of autoimmune disorder, celiac disease, in susceptible patients. 1 It was first explained by Samuel Gee in 1888, but by 1953 its importance was highlighted in the context of pathology. In patients with celiac disorder, gluten ingestion causes an enteropathy impairment of mucosal surface, and, aberrant nutrient absorption. 2-3 Various human systems are involved as well as wide range of clinical manifestations owing to which celiac disease is often referred as a syndrome. Peculiar features like complete recovery from mucosal damage or reversibility of its progression and chronic dynamics, in comparison to other autoimmune disorders, are shown by celiac disease. It is depicted that if celiac disease remain undiagnosed then it can have serious consequences. Another type of disease, besides celiac disease and wheat allergy, NCGS has been found which is non-celiac gluten sensitivity. 4

Epidemiology
In the recent years, large data have been reported on celiac epidemiology. Nowadays, celiac disease falls in the most prevalent genetically based disorder. Europe is considered its hot hub with a prevalence of 1 to 2%. Despite medical advances, this disease remains least diagnosed, and its prevalence still remains unclear. 5 It is not known that either this is owing to screening tool or real variability of disease prevalence. 6

A multicellular study has shown occurrence rate as 1 out of 133 in healthy people, and this frequency is confirmed in the US, European, Australian and Asian populations. Moreover, the chances of celiac disease prevalence ranges from 4.5% in high risk people to 0.75% in low or not at risk patients.

People who are at higher risk include the relatives of patients with this disease, adults or children with celiac linked symptoms like abdominal pain, constipation or diarrhea; and adults or children with celiac related disorders like anemia, infertility, osteoporosis, Down syndrome, and Diabetes Mellitus type-1. 7

• Genetic Susceptibility
The most prominent genetic character which characterizes for 35% of the total celiac disease genetic factor, is the MHC encoding genes for class II proteins including leukocyte antigen (HLA) DQ 2 and HLA-DQ8. Only 10% patients show HLA-DQ8 molecule effect, while 90% subjects express HLA_ DQ2 molecules. Only 1 to 3% subjects develop the disease while the frequency of celiac disease occurrence based on HLA genotype is about 30%. 8,9

Based upon the given evidence, it is visible that genetic factor HLA is among the main but not sufficient factor for the celiac disease development. But, multitude genetic factors collectively contribute towards this disease. Recently, another genome based study has revealed that 39 non HLA loci also contribute to celiac disease. 10 one of these genes are related to chromosome 19 genetic structure and myosin IXB gene, and may be involved in response towards gluten or gluten free diet. However, both HLA- DQ8 and HLA- DQ2 codifies for heterodimers which are located on APCs Antigen Presenting Cells. It has been found that gluten peptides are present in the intestinal mucosa on antigen specific t lymphocytes, which induce cytokine production and their proliferation.

• Environmental Factors
Diet plays an important role. The eating pattern in the early life and viral infections like rotavirus might be involved in the celiac disease development. A medical disease linked investigation has shown that specific infectious agents increases the risk of celiac disease autoimmunity in children. Gluten is composed of glutenin and prolamines, which are common parts of human nutrition. The wheat prolamines are gliadins, in rye these are secalines and in barely hordeins. It is prosposed that 50mg gluten/ day is the minimum amount enough to determine the alterations to small intestine in celiac disease patients.

Other environmental factors include milk feeding types i.e., breast feeding which can influence the small intesteine microenvironment. Moreover, reduced Bifidobacteria and increased gram negative bacteria in intestine rises the celiac disease risks. Heavy metals and bacterial TG in food stuff also contribute towards this disease. 11

Celiac Disease: Clinical Presentation
This disease is highly heterogenous, especially when it comes to factors like age, duration and extent of disease as well as the presence of extra intestinal comorbidities. Initially it was considered aa pediatric disorder, the prevalence is higher in adults.

Classical or typical form, it is described by common clinical symptoms associated to aberrant intestinal absorption. After the introduction of weaning items containing prolamines, this disorder occurs between 6 to 18 months of age.

• Atypical Form
This form is characterized by the presence of extra intestinal symptoms with no or few gastrointestinal symptoms. Usually, the common features of abnormal absorption are absent and it occurs in older children or adults.
• **Silent Form**
  It is characterized by histological abnormalities and serological issues without prominent clinical symptoms. This subtype is often present in subjects with family history of celiac disease, or patients with associated autoimmune (type 1 diabetes) or genetic disorders (Williams syndrome or Down’s syndrome).

• **Latent Form**
  This subtype has characteristics associated with previous asymptomatic celiac disease. No villous atrophy or histology abnormalities are prominent in it, but has positive serology. Troncone et al has postulated that increased level of endomysial antibodies in these subjects can act as predictor of disease progression. 12

• **Potential Form**
  Persons who have never diagnosed with celiac disease, the word potential is used for those patients, but they show appropriate genetic background (HLA- DQ2/DQ8), normal or mildly aberrant histology and positive serology.

• **Refractory Form**
  The presence of malabsorptive symptoms and villous atrophy persistent for 1 year after gluten free diet defines this refractory form. Many refractory form patients do not response to gluten free diet, while others might respond but recurrence of symptoms and intestinal damage is prominent. This form has two different types; “Type 1” showing normal intraepithelial lymphocyte count and “Type 2” showing abnormal intraepithelial lymphocyte count. 13

Celiac disease can affect person of any age, but the two peak ranges are less than 6 years old and 4th or 5th decade. Classical presentation is frequent in pediatric and occurs in early life, 6 to 24 months, while atypical one occurs at later age in adults or children with age greater than 5 years.

**Current Treatments of Celiac Disease**

• **Life Long Gluten Free Diet**
  The current treatment is the life long gluten free diet, as clinical improvement can be achieved within a few weeks and mucosal damage recovers in 1 to 2 years. Patients with this disease have damaged surface of epithelial cells and brush border lactase deficiency, milk and dairy products are advised to avoid in the first week of therapy. Gluten free multivitamin are also recommended to overcome nutritious deficiency.

Early diagnosis and treatment is beneficial in pediatric celiac disease, as later on some complications are irreversible: abnormal dentition, osteoporosis, growth retardation. Prolonging breast feeding and delaying the introduction of gluten diet in babies might lower the risk of this disease.

As some specifically targeted diet might also contain tiny amounts of gluten in them, specific considerations must be taken into account for its diet recommendation. In minority of patients affected by RCD, GFD is ineffective. It shows higher mortality rate in comparison to RCD type 1, owing to more severe malnutrition along with risk of overt lymphoma development. These disease forms require immunosuppressant and corticosteroids, like cyclosporine or azathioprine which can improve symptoms in most patients. Furthermore, these drugs might increase the risk of overt T cell lymphoma progression, so it is advisable to use drugs and agents in chemotherapy with caution.

• **Gluten Degrading Enzymes**
  Enzyme supplement treatment including bacterial prolyl endopeptidase has been proposed to enhance gluten digestion in the GIT and to destroy T cell epitopes. Prolyl endopeptidase are peoline specific enzymes which have the ability to cleave gluten peptides. These are under clinical trials on two drug candidates, ALV003 and AN-PEP (Aspergillus niger prolyl-endoprotease). Recent data based on these trials has depicted that therapy with AL V003 eradicate the peripheral blood T cell response in celiac patients. The current triasli with this therapy is showing positive outcomes with reduced symptoms in patients with typically induced by gluten. AN-PEP is an enzym which can thrive in stomach acidic pH and degrades gluten peptides effectively. Therefore this enzyme might show promising outcomes in the long run. 14

• **Modified Grains**
  These can be introduced either by selective grain breeding of early wheat species or using siRNA technology to mutate or silence immunostimulatory sequence. 15

• **Blocking gluten entry across the intestinal epithelium**
  Zonulin inhibitor larazotide (AT-1001) modifies and corrects intestinal barrier defects. It is currently studied to treat celiac patients. It is observed that patients treated with AT-1001 had improvement in symptom score, less pro-inflammatory production and autoantibody response, less urinary nitrate excretion as comparison to placebo controls. 16

• **Rho/Rho kinase inhibition**
  The increase in intestinal permeability depends upon Rho kinase (ROCK) activity. ROCK is known to regulate axon growth, tight junction structure and function. The drug can be used to reverse gluten dependent increase in intestinal permeability or ROCK inhibition in these patients. Vaccines and immunotherapy are under testing phase, so these are not discussed in this review paper.
CONCLUSION:
It is indubitable that celiac disease is like a mystery with controversial and complex explanation. Further research is required to establish evidence based treatment and diagnostic methods. Breast feeding has found to be effective in lowering the risk, but the data are controversial. What is to be elucidated is if current treatments offer a permanent protection or only delay the occurrence of disease.

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