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Celiac Disease – A Review

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Abstract:- One percent of people have celiac disease (CD), a prevalent autoimmune illness. When gluten is consumed by vulnerable people, an immune-mediated enteropathy may arise. In order to provide energy and nutrition, a major grain crop called wheat is used by billions of people worldwide. Gluten, a structural element of wheat, is crucial to the grain's capacity to produce dough, but it can also make some people susceptible to certain intolerances.The three primary genetic components of CD differentiate it from other autoimmune illness. These components include the auto-antigen responsible for the disease (tissue transglutaminase [tTG], the environmental trigger (gluten), and human leukocyte antigen (HLA)-DQ8.A gluten-free diet (GFD) is the only treatment for celiac disease (CeD), while it may also assist those with non-celiac gluten/wheat sensitivity feel less symptomatic. Different diseases have different causes for when they start and manifest; some, like type 1 diabetes mellitus (T1D), have comparable pathogenic pathways, while others have no known etiology. It is important for general practitioners and other specialists to remember that CD might present with extraintestinal symptoms at initially and that the disease can worsen concurrent conditions even as it advances.

Keywords:- *Celiac Disease, Gluten Allergy, Rho/Rho Kinase Inhibition, Tissue Transglutaminase, Deamidated Gliadin Peptides, Recurrent Aphthous Stomatitis.*

I. INTRODUCTION

In people with a genetic predisposition, eating gluten can cause celiac disease (CeD), a chronic immune-mediated enteropathy (1). Based on the existence of circulating CeD-Specific antibodies to endomysium (EMA), tissue transglutaminase (tTG), and deaminated gliding peptides (DGP), as well as the enteropathy shown in small intestinal biopsies with villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis, the current diagnosis is made. If a child has strong positive tTG antibody (tTGA) titer, CeD-associated HLA genotype, and CeD-related symptoms, the diagnosis of CeD can be made without the need for a small intestinal biopsy.(2). Since gluten was discovered to be the primary cause of CeD in the 1950s, the mainstay of therapy has been a rigorous, lifelong gluten-free diet (GFD). Although CeD is widespread around the world and is becoming more prevalent in various groups, it is commonly missed in clinical settings . Untreated symptoms of the disease are linked to higher morbidity and death rates as well as lower quality of life (3-6). Numerous clinical symptoms, such as gastrointestinal distress, persistent weariness, nutrient deficits, poor growth, and failure to thrive, are evident. Extraintestinal manifestations are widespread, and although they were originally thought to occur more frequently in adults than in children with CeD, current research suggests that frequency is comparable in children with CeD, despite the fact that the forms and rates of recovery vary (7). A higher incidence of autoimmune disorders such as Hashimoto's thyroiditis, Graves' disease, and type 1 diabetes (T1D) is also linked to CeD (8-11). CeD cannot develop without the ingestion of foods that contain gluten. Alcohol-soluble gliadins and alcohol-insoluble glutenins make up the viscoelastic protein known as gluten, which is what is left over after washing dough. Gluten is highly valued in the food business because of its rheological characteristics, which enable it to give food a light and extensible texture. Modern wheat gluten is diverse and has a more complex genetic makeup than the human genome since it develops from a hexaploid genome. Prolamins, a collective word for similar proteins high in glutamine and proline present in barley and rye and known as hordeins and scaling, respectively, are toxic to CeD.Oat prolamin, known as avenin, differs phylogenetically from wheat, barley, and rye prolamin. Oats are generally regarded as safe for eating by persons with CeD, despite some reports of negative immunological and clinical effects(12-14). The clinical spectrum of CD is broad and includes typical ,malabsorption with diarrhea, nonclassical extraintestinal symptoms, subclinical or silent forms, and prospective disease indicated by positive serology with normal intestinal mucosa on biopsy (15,1). Early diagnosis and a family history of autoimmunity are risk factors for the emergence of additional AD in celiac patients, whereas the gluten-free diet (GFD) has a protective effect (16). In contrast, the frequency of AD increases with age in relatives of CD suffers. Contrarily, people with other AD have been shown to have a much higher prevalence of CD (17,18).

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II. EPIDEMIOLOGY

The total prevalence of CD in the general population varies across several nations from 0.5% to 2%, with an average of about 1%. CD can happen at any age, with a female predominance, from childhood after two years old to the second and third decades or later in life. A male-to-female ratio of 1:2 means that women are two to three times more likely than men to receive a CD diagnosis[19]. Children are more likely to have CD (0.9% vs. 0.5%) than adults. Autoimmune disorders are present in 25% of CD patients (autoimmune thyroiditis accounts for 10% of cases), whereas herpetiform dermatitis and infertility are less common[20]. Estimates show that the prevalence of celiac disease among people with autoimmune hepatitis was 3.5%, much higher than the estimated prevalence of 0.5–1% in the general population[21]. The mean prevalence of CD in patients with T1D is about 8 %[22].

III. ETIOLOGY

A genetically vulnerable population is affected by celiac disease (CD), an immune-mediated enteropathy brought on by exposure to wheat gluten and other related proteins found in rye and barley[23]. Due to an abnormal immune reaction to the digestion of the gliadin present in wheat, patients with the condition have various degrees of chronic inflammation within the small intestine[24]. The celiac disease-causing epitopes in gluten, notably the highly immunogenic alpha-gliadins, are responsible for the condition. Another gluten-related disease called non-celiac gluten sensitivity causes individuals to have innate immune reactions along with gastrointestinal and non-gastrointestinal symptoms, which go away when gluten is removed from the diet. After inhaling or ingesting wheat, people with wheat allergies develop an immunological response that is either IgE- or non-IgE-mediated[25]. The onset of a disease maybe influenced by a number of factors, including infections, some medications, smoking, lactation, and the first time gluten is consumed[26].

IV. PATHOPHYSIOLOGY

Celiac disease is a relatively well-understood immunopathogenesis compared to other HLA-associated diseases. The disease lesion is confined to the gut and is characterized by hypersensitivity to cereal gluten proteins. However, the diagnosis can still be established through the blood's identification of highly disease-specific autoantibodies to transglutaminase 2[27]. HLA-DQ, a subclass of the HLA class II gene, provides peptides to T cells that are specific for an antigen. It is understood that HLA-DQ can bind to and present gluten peptides and that these HLA-DQ-peptide complexes exacerbate disease by inducing inflammatory T cells[29]. It develops as a result of an immunological reaction to gluten proteins found in a few cereals in people with particular genetic predispositions (HLA-DQ2 and/or HLA-DQ8). Its pathophysiology involves both innate and adaptive immunity, with an IL-15-mediated response elicited in the intraepithelial compartment (HLA molecules, transglutamase 2,dentritic cells, and CD4+ T-cells) [28]. The complex and dynamic environment of the human digestive tract is home to a wide variety of commensal microorganisms. It is crucial to remember that this healthy micro-ecosystem acts as a natural defense against disease invasion given the recent attention on the function of the microbiome in the pathophysiology of CD[29].

V. CLINICAL MANIFESTATION

A. Cutaneous and mucosal manifestation:

The oral cavity, where enamel deficiencies (ED), delayed dental emergence, and recurrent aphthous stomatitis (RAS) can be evident, is one of the most frequently injured body areas in CD patients [30].

B. Neurological manifestation:

Neurological symptoms include cerebellar ataxia, epileptic seizures, dementia, neuropathy, myopathy, and multifocal leukoencephalopathy [31].

C. Liver manifestation:

Asymptomatic increases in liver enzyme levels, non-specific hepatitis, non-alcoholic fatty liver disease, and autoimmune and cholestatic liver disease are among the liver manifestations[32].

D. Neuropsychiatric manifestation:

Among the psychological symptoms typically stated by CD patients are depressive symptoms, apathy, excessive anxiety, irritability, eating disorders, and attention-deficit/hyperactivity disorders (ADHD)[33].

E. Extraintestinal manifestation :

Common extraintestinal symptoms include short stature, delayed puberty, osteopenia, neuropsychiatric manifestations, iron-deficiency anemia, and increased liver enzymes[34].

F. Reproductive manifestation:

Because of malabsorption, women with celiac disease who are consistently in their reproductive years may have problems with growth, nutrition, and embryogenesis. Numerous gynecologic and obstetric conditions, including delayed puberty, early menopause, infertility, intrauterine growth restriction, recurrent spontaneous abortion, and stillbirth, have been associated to latent celiac disease [35].

VI. DIAGNOSIS

Serologic tests are helpful because they can be used to monitor GFD compliance when there is a suspicion of CD[39]. In comparison to EMA and tTG test findings, the recently developed deamidated gliadin peptide antibody (DGP) has demonstrated promising performance[36].
Numerous pieces of evidence support the use of TTG-IgA assays as the initial test for the diagnosis of celiac disease.[37]. The following five criteria must be satisfied for a celiac disease diagnosis:

- A history of success in treating celiac disease symptoms that are typically present.

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- Positive serological markers that are frequently connected to celiac disease, such as TTG or IgA EMA.
- The outcome of a genetic test for the HLA-DQ2 or DQ8 allele.
- Cluster of differentiation 3+ intraepithelial lymphocytosis with blunting as seen in a small intestinal biopsy.
- Reduction of symptoms by a gluten-free diet [38].

Flow cytometry for IEL phenotyping plays a vital role in diagnosing CD. It serves as a highly sensitive and specific addition to serological and histological examinations for CD diagnosis, particularly in individuals adhering to a gluten-free diet with normal duodenal histology. While the celiac lymphogram isn't considered a definitive diagnostic tool, flow cytometry analysis of IELs can validate the diagnosis of CD. [39].

VII. COMPLICATIONS

Low bone mineral density is the most likely reason for the 1.4-fold increased risk of fractures linked to celiac disease. Additionally observed are poor pregnancy outcomes and a link between infertility and celiac disease[40]. The most well-known sign that can affect both adults and children is a stroke .In addition to cardiovascular issues, dilated cardiomyopathy, pulmonary thromboembolism, hepatic vein thrombosis, atrial fibrillation, deep vein thrombosis, hepatic vein thrombosis, Bad-Chiari syndrome, portal vein thrombosis, and anticardiolipin syndrome are side effects of CD. CD patients are more likely to develop thromboembolic events since CD is an autoimmune disease associated with many hypercoagulable illnesses. Examples include a stroke, central and peripheral vein thrombosis, and miscarriage[41]. Osteoporosis is the most prevalent consequence and is caused by inadequate vitamin D levels as well as improper calcium absorption as a result of damaged calcium transport through the diseased small intestine. Collagenous sprue: Patients do not respond to diet and histology reveals extra-cellular matrix components in the intestinal wall at the level of the superficial sub-epithelial layer. It is one of the most serious complications of enteropathy[42].

A. *Refractory celiac disease:*

RCD is defined as the presence of malabsorptive symptoms and mucosal atrophy for at least 12 months in patients despite an intense GFD and after other causes of nonrecovery have been ruled out. It's regarded as a rare complication[43].

B. *The risk of malignancies*

According to one of the most recent state-wide cohort studies in Sweden, people with CD are generally at a higher risk of acquiring malignancies, especially if they are diagnosed after the age of 40. People with CD are particularly prone to lymphoma, oropharyngeal, and intestinal cancer[44]. A digestive chronic inflammatory illness with an elevated risk of gastrointestinal malignancies is celiac disease (CD). Although small intestinal T lymphomas are the most prevalent tumor in CD patients, small bowel carcinoma has been reported to occur more frequently[45].

VIII. TREATMENT

A. *Life-long gluten-free diet:*

Celiac disease individuals are required to maintain a strict gluten-free diet (GFD) for the remainder of their lives. This diet restricts the intake of any prepared meals manufactured from the following grains: wheat, rye, barley, spelled, kamut, emmer wheat, einkorn wheat, and green spelled [46]. Whole grains must be naturally free of gluten in addition to naturally gluten-free foods in their whole, such as fruits, vegetables, legumes, nuts, seeds, fish, eggs, and chicken. These grains include Arrowroot, Quinoa, Millet, Sorghum, and Teff. Buckwheat, Brown, Black, and Red Rice, as well as Oats, are also free of gluten. Celiac disease individuals can use the gluten-free starch arrowroot powder as a starch alternative[47]. When walnut, peanut, or their combination was added to corn flour biscuits in proportions ranging from 5 to 20%, the nutritional value, physical characteristics, and organoleptic acceptability of the gluten-free products were improved. Maize flour biscuits with 15% nut meat are suggested as a less expensive alternative for making biscuits as a snack food with great nutritional content and increased organoleptic features for celiac patients[48].

B. *Gluten-degrading enzymes:*

Examples of gluten-degrading enzymes that can both increase and decrease the immunogenicity of gluten peptides includes peptidases and prolyl endopeptidases, which are produced by commensals in the human gastrointestinal tract[49].

C. *Rho/Rho kinase inhibition:*

The only clinically utilised ROCK inhibitor, fasudil, a new isoquinoline sulfonamide derivative,

Has been used to stop cerebral vasospasm during subarachnoid haemorrhage. Numerous proinflammatory cytokines, such as TNF-, IFN-,IL-1.family members such as IL-1 and IL-13, affect barrier function in chronic inflammatory illness like IBD by encouraging the endocytosis of epithelial AJC proteins. The contraction of the perijunctional actomyosin ring, which is regulated by Rho-/ROCK-/MYPT-/MLC, regulates the internalisation of the AJC protein inflamed colonic mucosa from CD patients and rats with TNBS(2,4,6- trinitrobenzene sulfonic acid) colitis,increased RhoA/ROCK activation has been seen[50].

D. *Gluten modification:*

In order to make gliadin non-toxic, dietary gluten has been modified in non-invasive ways that are safe for CD patients.

Due to the loss of baking properties, public opposition to genetically modified crops, contamination of genetically modified crops with gluten-containing crops grown nearby, heterogenous uncharacterized immunostimulatory epitopes in gluten, and variations in patient response to

immunostimulatory epitopes and gluten levels, this approach has been appealing[51].

E. Vaccines:

The only vaccination for celiac disease that is presently undergoing clinical testing is NexVax2, which was developed by Immunosan T, Inc. It has three 15–16 amino acid long immunogenic gliadin peptides, including the five most powerful gluten peptides linked to celiac disease caused by the HLA-DQ2.5 gene. They include DQ2.5-glia-1 and DQ2.5-glia-2, which are both found in hordein proteins. The HLADQ2.5-TCR complex, which connects CD4+ T cells to antigen-presenting cells to produce specific immunity to gluten, is the focus of the vaccine. This vaccination is administered via injection with a dose that is gradually increased to create immunological tolerance, unlike the other two vaccines mentioned above[52].

IX. DISCUSSION

A long-term immunological condition brought on by consuming gluten. It damages the lining of the intestines and resulting in diarrhoea, tiredness, weight loss, bloating and anaemia. With a mean frequency of 0.9% worldwide, CD is one of the most prevalent, lifelong illness affecting people all over the world, including many emerging regions, and its prevalence is actually rising. Given that causes(consumption of gluten-containing cereals and HLA-predisposing genotypes) are common, this is not surprising.

X. CONCLUSION

Since wheat is a staple grain in the majority of countries, people frequently consumes it. Many patients go misdiagnosed because they are unaware of the prevalence or danger of celiac disease, and they continue to eat normally even if they have it.if they have any symptoms, visit a doctor as they could not be aware of this disease. In order to prevent CD misdiagnosis and missing cases, diagnostic criteria should be used by doctors. CD is still mostly treated with a GFD, which takes a lot of patient education, motivation, and follow-up. The very risky diagnoses in adulthood can be avoided with early diagnosis.

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