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Celiac Disease: Diagnostic dilemma

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Celiac disease, an autoimmune disorder, occurs in genetically susceptible individuals and is triggered by the ingestion of well-idenfined autoantigen- gluten. It affects primarily the small intestine, where it progressively leads to flattening of small intestinal mucosa. Three cereals contain gluten and are toxic for Celiac patients – wheat, rye and barley. It occurs more commonly in relatives of celiac patients and some at risk groups. It causes gastrointestinal symptoms, predominantly chronic diarrhea with wastings, but also many extra-intestinal manifestations can be present alone. Suspected patient should be screened with transglutaminase + total serum IgA and if positive, confirmed by biopsy before the gluten-free diet is started. A gluten free diet typically reverses all signs and symptoms within a short time. Monitoring of the patient to verify ongoing dietetic compliance is fundamental in order to ensure that all possible complications, including malignancies, are avoided.

Introduction: Celiac disease (CD) is an autoimmune disorder occurring in genetically susceptible individuals on exposure to gluten. Gluten is a general term for insoluble prolamine Celiac disease (CD) is an autoimmune disorder occurring in genetically susceptible individuals on exposure to gluten. Gluten is a general term for insoluble prolamine polypeptides found in wheat (gliadins and glutenins), rye (secalin), barley (hordein), and other closely related grains. Clinical descriptions of CD were first made by Samuel Gee in 1887, but its association with wheat was established by Dicke only in 1944 and gluten as the offending protein was proven by Van De Kamer 10 years later. Gee adopted the same term as Greek physician Areataeus (Celiac disease) Gee made an important statement: "If patients can be cured at all, it must be utilizing diet. Gee recognized that milk intolerance is a problem with Celiac children. Screening studies have shown that CD has a very high prevalence, occurring in about 1% of general populations through Europe and North America. It must be emphasized that not all those affected by CD are symptomatic and that even symptomatic patients may present diverse problems, not everyone showing with the classical presentation with gastrointestinal complaints. However diagnosing CD in all affected individuals is imperative, as the condition can be fully reverted to normal with the timely institution of a Gluten-free diet (GFD)and thus preventing the many complications.

Epidemiology:

In Europe and North America, the CD is estimated to be present in as high as 1 % of the population. In India is most commonly noted in Wheat consuming states such as Punjab, Haryana, Delhi, Rajasthan, Uttar Pradesh, Bihar, and Madhya Pradesh. Two recent population-based studies in Punjab and Delhi estimated that the prevalence is around 0.3% and 1% respectively which is similar to that in Europe. However, the disease is extremely uncommon in South India, because of the very low prevalence of the disease-causing gene and CD associated HLA-class II in South Indian communities (only 10% as against 32% in North India). The increasing prevalence of CD all over the world is attributed to changing Infant feeding practices with early gluten exposure, environmental risk factors, increased awareness, and wide availability of testing in a a genetically susceptible populations.

Pathophysiology:

CD occurs in genetically predisposed individuals (HLA-DQ2 or HLA-DQ8 positivity)due to an inappropriate immune response and characterized by antibodies against the enzyme tissue transglutaminase (TG2). Wheat eating communities consume around 10-20g gluten per day. Gluten proteins are rich in glutamines and prolamines that are incompletely digested by gastric, pancreatic and brush border peptidases, leaving large peptides. These peptides pass through the epithelial barrier of the intestine and enter the lamina propria through the transcellular or paracellular route. They are presented on the antigen-presenting cells with HLA types HLADQ2 or HLADQ8 and stimulate gluten-specific T cells. TG2 change the antigenicity of gluten by changing the neutral glutamine to produce an acidic glutamic acid residue; thereby promoting the binding of gluten peptides to HLADQ2 orHLADQ8.This induces inflammatory T-cell reaction by producing pro-inflammatory cytokines like interferon ã. The activated T cells in lamina propria release metalloproteinases that are cytotoxic and cause apoptosis of enterocytes, atrophic remodeling of the mucosa, and malabsorption. The presence of increase intraepithelial lymphocytes (IELs) reflects the role of the innate immune system in Celiac disease because IELs express the natural killer (NK) T cell receptors, NKG2D, and CD9/NKG2A. The gluten-HLA complex also induces activation of plasma cells leading to the production of autoantibodies like anti-deamidated gliadin peptide (DGP), anti-endomysial (EMA) and anti-tissue transglutaminase (tTG). The role of the antibodies in disease modulation is uncertain, but is thought to contribute to the systemic manifestation of CD.

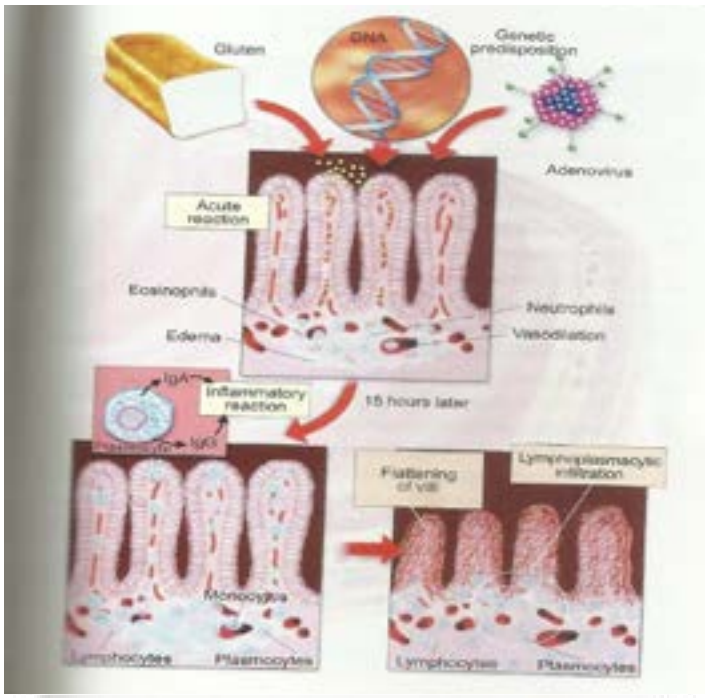


FIGURE 1: PATHOPHYSIOLOGY OF CD

Clinical features

The clinical features depend on the age of the presentations.

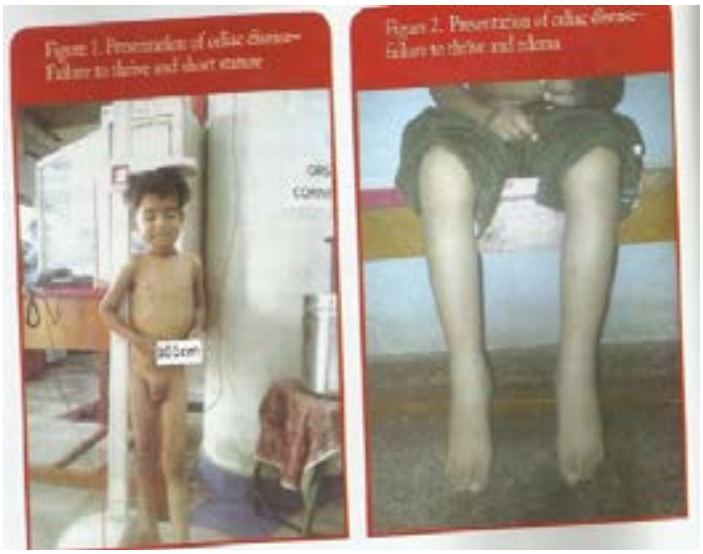
Young children present with diarrhea, steatorrhea, and cramping abdominal pain after cereals are introduced into the diet.

Classically the child failure to thrive, apathetic, irritable and has muscle wasting with hypotonia and abdominal distension. Atypical clinical presentations of CD are increasingly being recognized and may occur in 40% to 50% of patients in India. Short stature, and nutritional anemia or rickets that are refractory to treatment are the comments a typical presentations.

In India the mean age of onset of symptoms is 2-3 years (9-18 months in western world) due to prolonged breastfeeding and delayed introduction of weaning foods.

Mean age at the diagnosis unfortunately is 6-8 years mainly due to poor awareness and inadequate diagnostic facilities.

The possibilities of gluten sensitivity should be considered in children in endemic areas who present with short stature or failure to thrive, even when there are no gastrointestinal symptoms.



Clinical presentation of Celiac disease

Types	Presentations
Classic/ Gastrointestinal	Diarrhea, Steatorrhea, Non-specific abdominal pain, vomiting, Failure to thrive, Anorexia, Constipation
Non classical/ atypical (common)	Dermatology – Dermatitis herpetiformis follicular hyperkeratosis Hematology Refractory Iron deficiency Anemia Vitamin B12 deficiency Endocrinology Idiopathic short stature Refractory rickets Primary amenorrhea/infertility Autoimmune diseases Type 1 diabetes mellitus Autoimmune thyroiditis Autoimmune hepatitis Primary biliary cirrhosis Neurological Primary ataxia white matter focal lesion Peripheral neuropathy Epilepsy with occipital calcifications Psychiatric disorders Bones & teeth Arthritis Osteopenia Osteoporosis Permanent enamel hypoplasia

Celiac disease current nomenclature:

Classical CD: with signs and symptoms of malabsorption diarrhea, steatorrhea, weight loss, iron deficiency anemia, growth failure

Non classic CD: without specific symptoms and signs of malabsorption abdominal pain, constipation, transaminitis etc.

Symptomatic CD: with gastrointestinal or extra-intestinal symptoms

Subclinical CD: asymptomatic, but are detected by screening tests, wherein both serology and histology are positive previously called silent CD.

Potential CD: with positive celiac serology but with normal small intestinal biopsies.

They are at high risk of progressing to Celiac disease and regular follow-up.

Refractory CD: persistence or recurrence of malabsorption associated with villous atrophy on biopsy despite being on adequate gluten free diet for over 12 months.

Non-celiac gluten sensitivity (NCGS) : Gluten ingestion leads to symptoms suggestive of celiac disease,but serology and histology are normal. Gluten challenge is required for diagnosis and could represent non IgA-mediated food allergy.

Gluten related disorders : Examples are gluten ataxia, dermatitis herpetiformis and NCGS.s

Complications:

Celiac crisis: Celiac crisis is rare, life-threatening complication in which children and adult with untreated Celiac disease present with profuse diarrhea that leads to severe dehydration, metabolic disturbances, renal dysfunction and in some instances, hemodynamic instability. Early diagnosis is important and management includes IV fluids, glucocorticoids and/or parentral nutrition where indicated.

Intestinal malignancies: Recent studies have shown that adults with CD have a 3 times higher risk of Non Hodgkin lymphoma and 40 times higher risk of small bowel lymphoma compared to general population. However no such risk observed in children. European data show that children diagnosed before 10 years of age had no increase in the risk of cancer compare to those diagnosed later. It is likely that many years of delay in diagnosis is predisposing factor for intestinal lymphoma, rather than the disease as such.

Diagnosis:

Serological tests : Serological tests are used for screening those with Suspected CD and should be done only if the patient has been on a gluten containing diet for at least a month, since serum antibodies have half –life of 30-60 days.

The three most commonly used are 1. IgA-tTG (Tissue transglutaminase): It is an ELISA test and preferred in children above 2 years. It has sensitivity of 90%-98% and specificity of 94%-97% which are comparable to IgA-EMA and the cost is comparatively lower.

IgA-EMA(Endomysialantibodies):Itisanindirectimmunofluorescence test and is technically difficult. It has the highest specificity (97%-100%) but sensitivity is only 85%-98%.

IgG-DGP (De-amidated gliadin peptide): It is prefered test in those with IgA deficiency and children below 2 years. It has a sensitivity of 79%-98% and specificity of 80%-95%.

Point of care testing (POCT) is a kit test done on a finger prick sample of blood, to detect both IgA and IgG antibodies against tTG. Results are obtained within 10 minutes, but it has lower sensitivity (80%-98%) and specificity (91%-93%).Therefor a positive POCT should be comfirmed with IgA-tTG before duodenal biopsy.

Endoscopy and Histology:

The diagnosis is confirmed by upper GI endoscopy and biopsy. Endoscopic findings in the proximal portion of the small intestine include scalloping of of duodenal folds, mosaic mucosal pattern, isible submucosal vessels and loss of macroscopic villi, as well as mucosal atrophy. Histological evaluations of at least four duodenal biopsies are necessary, since mucosal involvement is often patchy (mosaic pattern). Biopsies should take from the four quadrants of the descending duodenum and preferably, one or two from the duodenal bulb. Histology is interpreted based on modified Marsh grading system.

Marsh type 1: Increased IELs with normal villous architecture is non-specific for CD but diagnosis can be strengthened by strongly positive serology.

HLA in Celiac disease HLA-DQ2 & HLA-DQ8 are found in 99% cases of CD against 30% in general population. Thus it has a high negative predictive value in diagnosis and therefore it can be used to rule out the disease rather then make a positive diagnosis.

Marsh type 3: Villous atrophy with crypt hyperplasia and increased intraepithelial lymphocytes (IELs) >30/100 epithelial cells is characteristic of CD.

Marsh type 2: Increased IELs with crypt hyperplasia is computable with CD if supported by a positive serology. In case of negative serology other causes should be excluded to make the diagnosis of CD.

Changing face of Celiac disease:

- No longer a diagnosis of childhood.
- Many facets of presentation.
- Often present in young adults.
- 20% in adult > 60 years of ages
- Diagnostic dilemma
- Reasons:

Celiac like lesions could be due to:

- Persistent enteric infection or infestation.
- Tropical sprue.
- Severe oedematous malnutrition.
- Small bowel bacterial overgrowth

Figure: Algorithm for diagnosis of suspected CD

- Diagnostic criteria for Celiac disease
- Villous atrophy in small intestinal biopsy.
- Positive Celiac serology (tTG or EMA).
- Genetic markers HLA-DQ2 and HLA-DQ8
- Unequivocal clinical response to Gluten free diet in weeks

The diagnostic guidelines of the European society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) are widely used, but their recent modifications may not be applicable in developing countries.

According to modified ESPGHAN criteria, characteristic small bowel histology (showing villous atrophy) and unequivocal clinical response to Gluten free diet in weeks are enough to make diagnosis of Celiac disease.

A recent modification proposed that intestinal biopsy is not essential

to diagnose CD in subset of symptomatic patients who have tTG > 10 times upper limit of normal along with HLA-DQ2 and HLA-DQ8 and EMA positivity.

However, in developing countries like India where enteric infection and malnutrition are rampant, villous atrophy has varied etiology and so diagnosing CD based on histopathology alone is fraught with risk of misdiagnosis. In addition, the expertise required in interpreting histopathology is not widely available.

Combination of serology and histology as essential criteria to confirm the diagnosis of CD in India. Genetic studies are expensive and are not widely available in developing countries.

Symptomatic patients: Positive serology along with villous atrophy on histology followed by disappearance of symptoms and negative serology on gluten free diet would make diagnosis of CD definite. As selective IgA deficiency is common in CD, serum IgA level should be done before confirming that serology IS truly negative.

Asymptomatic/High risk patients: Screening test if possible should be HLA-DQ2Aand HLA-DQ8 and if positive then serology (tTG) and if tTG is > 3 times upper limit of normal then duodenal biopsy. An approach to diagnosis of suspected CD is shown in Fig 1

Population screening: Can be done with serology test (tTG), but duodenal biopsy is essential to confirm the diagnosis.

Gluten challenge: A gluten challenge under medical supervision is indicated only if CD is strongly suspected but diagnostic criteria are not unequivocally met. It is performed in 6-7 years age children or when pubertal growth is complete.HLA typing and a duodenal biopsy should first be performed. The patient is then started on normal gluten containing diet. Serological testing and duodenal biopsy are performed if symptoms arise or by six months if normal, again at 24 months.

Treatment:

Total lifelong avoidance of gluten ingestion is cornerstone treatment of Celiac disease. Treatment should only be initiated once definitive diagnosis is made. The mainstay of treatment remains the institution of a strict gluten-free diet. At present there is no cure for the disease.

Principles of the gluten free diet include:

Avoid all foods made from wheat, rye and barley. Beware of many names of wheat.

Avoid oats. Consensus on oats is mixed. Some patients with Celiac disease can tolerate oats in their diet. There are chances that oats might be contaminated with wheat.it is best avoided initially while remission is being achieved.

Processed foods: Wheat is a common ingradient in many foods. To named a few – canned foods, luncheon meats, candy, ice-cream, sauces, pasta, instant coffee and some brands of yoghurt.

Medications: Several tablets, capsules and vitamins preparation contain gluten. Wheat starch is commonly used as a binding agent in tablets and capsules.

Cosmetics: Several cosmetics products contain gluten. Especially lip balms, ointments should check for their gluten content.

Alcohol: Avoid regular beer; however, wine, brandy and whisky are permissible.

Gluten free products are often low in vitamin B, calcium, vitamin D, Iron, zinc, magnesium, and fiber these should be supplemented.

Avoid food containing lactose initially.

Use only rice, bajara, corn, maize, jawar, potato, soybean or tapioca flours, meals and starches and rajgiri 70% of patients with classic CD will show improvement in symptoms within 2 weeks of the initiation of strict gluten free diet.

10%-30% of patients with celiac disease will have persistent symptoms, signs laboratory abnormalities despite being on a gluten-free diet for 12 months and would be classified as non-responders. The commonest cause of non response or inadequate response is poor diet compliance or inadvertent exposure to gluten. Other causes include lactose and fructose intolerance, small intestine bacterial overgrowth, pancreatic insufficiency, and irritable bowel syndrome, all which are rare in children.

Two major problems with GFD diet in developing countries are poor patient compliance and lack of food standardization and labeling. Poor compliance observed in at least a third of patient while on follow up and is more with subclinical CD and adolescents

Monitoring and follow up:

A gluten-free diet has been shown to protect against all complications of the classic form of CD including dermatitis, herpeticformis and osteoporosis.

CD treatment is lifelong commitment and needs regular follow up to monitor growth to ensure adequate diet compliance. After documenting initial response to GFD, the child should be reviewed once in 3to6 months with growth chart. Supplementation with minerals and multi vitamins is required only in initial phase of treatment. Catch-up growth occurs in 6 months and catch-up height in 12 months. Serological tests normalized in 3 months to a one year, but the Anti –tTG should be repeated yearly to look for adherence to GFD. Every review visit should include dietary reinforcement to ensure strict adherence to GFD.

Prevention:

There is new evidence showing that Celiac disease onset can be prevented, or at least markedly delayed, when gluten is introduced in small amounts in genetically predisposed individual and while the infant is still being Breastfed, and possibly during to the 4-6months life window. Additionally, since the role of gastrointestinal infection, especially by rota virus in early infancy, has also been proposed, it is possible that diffusion of new anti-rotavirus vaccine may also contribute to reduce the prevalence of Celiac disease.

Into the future:

Several medical therapies are being investigated as non-dietary therapy for celiac disease. With the increased identification of specific gluten epitopes and understanding of the pathogenesis of Celiac disease, future therapy may be rely on genetically altered gluten proteins, immunization techniques, or therapies focused on either the development of specific immune tolerance or regulation of mucosal inflammation. Currently, the most attractive alternative involves the use of recombinant enzymes that digest the toxic gliadin fraction in stomach or upper small intestine.

Genetically engineered grains have been studied to reduce gluten toxicity. Wheat grain with a low content of gluten may reduce immunogenicity. Some other approaches to drug treatment include:

a) “Glutens for the degradation of the immune dominant gluten peptides to prevent proteolytic degradation in the intestinal lumen

b) Drugs to lower intestinal permeability of gluten,

c) “Gluten vaccinations to induce oral tolerance. Nexvax 2 a gluten specific therapeutic vaccine is a combination of three peptides (gliadin, hordein, secalin) commonly identified by T- cell in HLA-DQ2

genotype patient that will ultimately reprogram Gluten-specific T-cell.

d) Inhibition of intestinal TG2 with specific TG2 blockers

e) Blockade of antigen- presenting HLADQ2/HLADQ8

f) Modulation of pro inflammatory intestinal cytokines with biological agents like monoclonal antibodies.

Concluding remarks

Celiac disease occurs due to gluten sensitivity in genetically predisposed individuals.CD is an autoimmune inflammatory disorder of small intestine triggered by gluten and is a very common chronic disease. It occurs more commonly in relatives of Celiac disease patients and some at risk groups. Classic celiac disease is characterized by malabsorption and non-classic celiac disease is equally common. A combination of serology and duodenal histology is mandatory for diagnosis. IgA-tTG is the preferred serological test for diagnosis. The only accepted treatment is life-long avoidance of gluten in diet. Monitoring of the patient to verify ongoing dietetic compliance is fundamental in order to ensure that all possible complications, including malignancies, are avoided New data show the possibility of prevention.

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