Celiac Disease in Children: Recent Concepts

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Food allergies/intolerances are not much talked about in tropics because infections are very common (1-3). Out of food allergies, wheat allergy also known as celiac disease (CD) is well documented from centres in North India, whereas other centres are silent (4). I am sure the disease might be occurring in other parts of India though, with much less frequency. Now with spreading knowledge and presence of expertise in field of Pediatric Gastroenterology, more studies are being reported from other centres. In UK, the disease was recognised in the immigrant population from India and Pakistan (5). Wheat allergy is having protean clinical manifestations.

Definition

Wheat allergy also known as celiac disease is a permanent hypersensitivity to gluten, a wheat product and is a life long disease. Classically in children it manifests with growth failure, chronic diarrhea and anemia. On withdrawal of gluten from diet there is reversal of clinical, biochemical, pathological and serological alterations in the body (4,5).

Nomenclature

This been described in literature by various names like wheat allergy, gluten allergy, gluten sensitive enteropathy (GSE), permanent gluten enteropathy, celiac disease, non-tropical sprue, celiac sprue, Gee Herter’s disease etc. All these terms have been well accepted in literature and are used in the text.

Historical events

First clinical description of celiac disease in children was published 112 years back by Gee in 1988 (6). This was named as Gee Herter's disease. Thaysen in 1932 gave the detailed description of disease in children and adults (7). Dicke in 1950, recognised that celiac disease is due to intake of wheat or rye (8). This idea was conceived from observation made in thesis by one of the student of Dicke. Things became quite evident after IIInd world war, when there was nothing left to eat apart from some fruits and vegetables. During this period patients suffering from celiac disease improved and when wheat again became available, their symptoms reappeared. This virtually confirmed that wheat is responsible for the development of the disease. In 1952 Van de kamer, Dicke and their associates isolated harmful protein moiety gluten responsible for disease (9). Subsequently specific toxic protein gliadin was isolated from gluten. Gliadin is having alpha, beta, gamma and omega components. Alpha gliadin is the most allergenic. Paulley in 1954 for the first time described surgical specimen of small intestine and classical histopathology of jejunum in celiac disease (10). In 1958, Butterworth, Perez and Grosby, developed oral suction jejunal biopsy instrument also

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Genetic susceptibility to develop CD is well known. This has been documented in families. We also have few families on follow up. The prevalence of CD in first degree relations is 10-20% described from west, whereas 75% of monozygotic twins have been found to be Alpha gliadin in HLA DQ positive. Genetic susceptibility to develop CD is well known. This has been documented in families. We also have few families on follow up. The prevalence of CD in first degree relations is 10-20% described from west, whereas 75% of monozygotic twins have been found to be

**Etiopathogenesis**

Wheat is the main cereal that is toxic to intestinal mucosa in celiac disease patients. Other known harmful cereals are rye, barely and oat. In the wheat, the main antigenic protein is gliadin, which is product of gluten an extract of wheat. It is the alpha component of gliadin which is most allergenic as shown in figure 1. The counterpart of gliadin is another peptide known as prolamin and this is present in rye, barley and oat. Immunogenicity of prolamin is similar to that of gliadin and crossreacts as shown in vitro experiments (31-34).

Figure-I Showing cereals and their antigens responsible for mucosal injury resulting into Celiac disease.

- Cereals
  - Wheat
  - Rye, Barely and Oat
  - Gluten
    - Gliadin (Allergenic moiety)
      - Alpha gliadin in HLA DQ positive
        - Potent Immunogenic
          - Jejunal mucosal injury
            - Celiac disease
  - Glutenin (Not allergenic)
  - Prolamine (Allergenic)
  - Cross reacts

Celiac disease in India was first described in 1966 from New Delhi (17,18,21,22). Subsequently many reports appeared in the literature from this part of country including our center. The criteria laid down by Anderson and Cameron were used (19,20).

In 1972, there was one report from UK, describing celiac disease in Asian migrant population (23). In India, flexible endoscopic facilities became available to children during second half of 1980's. There is no difference in the histopathological changes in the biopsies from duodenum versus jejunum. This has been shown from our center also. To take biopsy from jejunum with Crosby capsule is difficult and it is a traumatic experience for the child. Moreover, fluoroscopic help is also needed for this procedure (13,24). But these facilities are not available in all the centers in our country. There is lack of expertise also.

In 1980's, the role of antigliadin antibodies, antireticulin antibodies and anti-endomysial antibodies was defined and it was shown that these are very sensitive and specific in diagnosing celiac disease. These can be repeated on follow up, to judge the response to gluten free diet (25-30). Recently antibodies to tissue transglutaminase have been reported to be very sensitive and specific of celiac disease.
concordant with CD. Possibly genetic susceptibility maps to the HLA region on chromosome 6.

Primary association of GSE has been found to be with DQ molecule in 95% CD patients in comparison to 20-30% controls. Celiac disease patients invariably express the HLA alleles DR4 DQW8 whereas DQ B1 0201 have greater risk of developing CD. HLA class II genes and DQ molecule peptide binds to antigen involved in pathogenesis of CD and present it to T cells. T cells in lamina propria recognise gliadin peptide in presence of relevant DQ molecule. In case of HLA DQ A1 0501, B1 0201 thymus T cells may have set of receptors involved in pathogenesis of CD. Other non-HLA genes could also confer susceptibility to CD. These genes are responsible for transport of the peptides to T cell receptors and control the synthesis of cytokines and cytokine receptors (31,33). Pathogenesis of CD is given in figure-II.

**Figure-II Pathogenesis of celiac disease**

**Immunological response**

![Pathogenesis of celiac disease](image)

Recently this has been shown that tissue transglutaminase (tTG) is the enzyme involved in pathogenesis of CD. This enzyme accepts gliadin as its substrate and activates transforming growth factor \( \beta \). It has been shown that tTG specifically deamidates gliadin peptides and results into better binding of gliadin peptides to HLA and enhances the recognition by T-cells in celiac patients.

Celiac disease in immunologically mediated small bowel enteropathy. Mucosal lesions suggest over stimulation of cell-mediated and humoral immunity. Gliadin is potent antigenic peptide that is responsible for stimulation of T-cells in lamina propria by involving HLA II restricted antigen presenting cells. Antigen recognition leads to upregulation of interleukin-2 receptor expression and production of cytokines. Hybridization and histochemistry studies have shown enhanced activity of interferon and tumor necrosis factor \( \alpha, \beta \) IL2, IL4, IL6 and IL10 in the cells in CD. This shows that different kind of cytokines have role to cause mucosal injury. More evidence in needed to support this fact (31,34).

In celiac disease the lymphocytic infiltration is constituted by intraepithelial lymphocytes (IEL). More than 90% of IEL express CD 8 and 10% express CD4. In normal mucosa T-IEL express 90% \( \gamma/\delta \) of cells whereas \( \alpha/\beta \) form 10% of T-cell receptors. In CD treated or untreated \( \gamma/\delta \) TIELS are increased. These cells possess lytic potential, cytokine profile and cytotoxic function.

There is enhanced humoral immunity in celiac disease. This is characterised by rise of antigliadin IgA and IgG antibodies. The production of autoantibodies triggered by gliadin to noncollagenous proteins of the extracellular matrix are anti-reticulin, antiendomysial antibodies and tissue transglutaminase. This is not clear that these antibodies have some role in causation of mucosal damage. These antibodies decrease on gluten free diet and rise on gluten challenge. This is possible that gliadin has great affinity for jejunal mucosa lamina propria reticulin, unmask cryptic reticulin and
endomysial epitopes and continuous gliadin ingestion is responsible for self maintenance of disease (31-34).

Pathology

Endoscopic gross change in duodenum and jejunum seen are sparse thin and scalloping folds. Histopathological distinct changes have been described in classical case are: (1) partial to sub-total villous atrophy, (2) elongated crypts (3) increased mitotic index in crypts (4) increased IELS, (5) infiltrations of plasma cells, lymphocytes, mast cells, eosinophils and basophils, (6) loss of nuclear polarity with pseudostratification of epithelial cells and (7) absence of identifiable brush border and abnormalities in epithelial cells, which become flattened and cuboidal. In severe cases these changes are seen in ileum also. These changes are not pathognomonic of CD and can be seen in other conditions given in table I. People have tried to grade these histopathological changes based upon the degree of infiltration and the atrophy of mucosa. Varying grades of lesion also depend upon the genetic predisposition and exposure to the quantity of gluten. Heavy infiltrate has been seen in rectal and gastric mucosa in these patients (31-34).

Table-I Condition that cause villous atrophy other than CD

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Cow milk or soya protein hypersensitivity</td>
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<tr>
<td>Eosinophilic gastroenteritis</td>
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<tr>
<td>Transient gluten enteropathy</td>
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<tr>
<td>Persistent diarrhea</td>
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<tr>
<td>Giardiasis</td>
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<td>Bacterial infection/overgrowth of bacteria</td>
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Clinical Features

Clinical presentation of celiac disease depends upon the severity and extent of small intestinal pathology (31). There is usually a variable latent interval between the introduction of gluten into the diet and the development of clinical manifestations. This interval varies between months to years and even for decades but few children may develop symptoms immediately after gluten ingestion. Walker-Smith has reported that 19.6% had symptoms on their first contact with gluten (5). But others have not found such rapid onset on symptoms. Classically celiac disease presents between 9 to 18 months of age (5). But in our country there is a significant delay in the onset of symptoms and the age of presentation. The age of onset of symptoms is varying from 3-5 years and age of presentation is 6-9 years (4). This delay is probably because of delayed introduction of cereals, prolonged breast feedings, late introduction of wheat products, delayed referral and lack of awareness about the disease.

Though female preponderance (3:1) has been reported from the West (33) but in India both males and females are equally affected. Clinical features of Indian children (4) and of West (5) are given in table II. Main differences being failure to thrive, anemia and muscle wasting which are the features of severe disease, are more common in our children given in table-II (4). This reflects delayed diagnosis. In our set up the diarrhea is present in 93-100% whereas 7% cases may have short stature, refractory anemia, rickets, constipation, alopecia etc. with poor growth. These cases may be attending other clinics and waste lot of time before exact diagnosis is made. This shows high index of suspicion is very important to look for celiac disease. In our series there was one case of multiple jejunal intussusceptions. On gluten free diet (GFD), all his symptomatology and features of obstruction disappeared (4). Other atypical manifestation reported in literature are aphthous stomatitis, enamel hypoplasia, infertility, intractable seizures, unexplained anemia or rise of transaminases, osteoporosis, alopecia and lymphoma (31).
Silent celiac disease patients are those who are asymptomatic but small intestinal biopsy show villous atrophy. Silent cases are detected by population screening. Patients suffering from other diseases like various autoimmune endocrinopathies, IgA deficiency, insulin dependent diabetes mellitus, connective tissue disorders, Down's syndrome, cystic fibrosis, IgA nephropathy etc. are also prone to develop CD (31).

### Spectrum of Celiac Disease

Celiac disease is having varied manifestations responsible for wide spectrum of clinical presentations. The varying picture is difficult to understand. Clinical presentations are in form of (1) classical or active form, (2) silent, (3) potential and (4) latent CD. The classical or active form is one which manifests with overt clinical picture characterised by chronic diarrhea with malabsorption, failure to thrive and anemia. This clinical disease constitutes the tip of the iceberg. There is large submerged group comprised of asymptomatic, silent, potential and latent celiac disease. The occurrence of asymptomatic disease has been shown in a cohort of school children from Italy. This shows celiac disease can be divided into symptomatic and asymptomatic (subclinical) disease to understand it in a better way (31, 35-37).

#### 1. Silent celiac disease

Silent celiac disease patients are those who are asymptomatic but small intestinal biopsy show villous atrophy. Silent cases are detected by population screening of first degree relatives of celiac disease, 10% of whom are found to have CD. Serological tests are positive in them (35,38).

#### 2. Latent celiac disease

These are the patients who have a normal jejunal biopsy while on a normal diet but at some other time, before or since, have recovered from a flat jejunal biopsy while on gluten free diet. These patients are in a latent phase of the disease or pre-celiac state that may become symptomatic when exposed to high dose of gluten. They have cellular infiltrate and immunologic response equivalent to active CD. (35, 37).

#### 3. Potential celiac disease

These are the patients who have a normal jejunal small bowel villous architecture on gluten, but still gluten sensitive. They have the potential to develop celiac disease. In a study, Collin et al. have shown that 30% developed villous atrophy over a period of 7 years (39). Probably potential celiac disease cases would require a second insult to evolve to the full blown picture of severe mucosal damage. Factors which have been postulated to act as a second insult are, temporary increase in intestinal permeability, an increased gluten intake or adjunct effect of intestinal infections. Potential celiac disease may be suspected in individuals who show positive serological tests (positive EMA, AGA or tTGA), a high positive immunological response as seen in active CD and a positive rectal gluten challenge (34, 35, 37).

### Associations of celiac disease

**IgA deficiency**: It has been shown that the prevalence of selective IgA deficiency in celiac disease patients is 10 times higher than expected. It causes problem in interpreting serology of IgA class. All IgA deficient patients should be screened for celiac disease (40).

**Diabetes mellitus**: Prevalence of celiac disease...
among patients with type I diabetes mellitus is around 4% (32, 41).

**Dermatitis herpetiformis (DH):** Small intestinal biopsy of 75% cases of dermatitis herpetiformis show villous atrophy. On the other hand only 10% of celiac disease patients develop dermatitis herpetiformis (32,41). Gluten free diet improves both skin lesions of DH and villous atrophy.

**Other associations** are autoimmune thyroiditis, IgA nephropathy, ulcerative colitis, primary sclerosing cholangitis, primary biliary cirrhosis, autoimmune hepatitis, arthropathy and Down syndrome as mentioned.

**Transient gluten enteropathy:** This has been documented in infants and younger children with persistent diarrhea and results due to absorption of macromolecules of proteins and lead to sensitisation. Subjects do not tolerate wheat and on withdrawal of wheat become asymptomatic and on reintroduction of wheat there is no problem. This shows that this is a temporary phenomena. The long term follow up of these patients is not known (4,5).

**Celiac Crisis**

This is a rare life threatening complication of CD. This may be precipitated by reintroduction of gluten in diet, intercurrent infections, prolonged fasting or anticholenergic drugs. This is characterised by severe watery diarrhea, dehydration, acidosis, abdominal distension, vomiting, pedal edema, hypokalemia and shock. This should be promptly recognised and treated (4,5,42,43).

**Complications of Celiac Disease**

In long standing and untreated cases, the complications like lymphoma, carcinoma, refractory sprue, ulceration and strictures of small bowel have been reported during adulthood (4,5).

**Diagnostic Criteria**

In 1969, ESPGAN, at the Interlaken meeting, first laid down some criteria to make a diagnosis of celiac disease. These are also known as Interlaken criteria. These are: (i) structurally abnormal jejunal mucosa when taking a diet containing gluten, (ii) clear improvement of villous structure when taking a gluten free diet (iii) deterioration of the mucosa during challenge and (iv) on withdrawal of gluten, improvement. According to these criteria 3 sequential biopsies are required to make a diagnosis of celiac disease (14). The Interlaken criteria were reviewed by ESPGAN in 1975 and it was shown that gluten challenge confirmed initial diagnosis of celiac disease in 95% cases. But in 1989 in another workshop on diagnostic criteria of celiac disease, criteria were modified (16). According to modified ESPGAN criteria, there is no need to document histological improvement while on GFD and also on challenge. The first requirement for the diagnosis of celiac disease is the demonstration of characteristic histological changes on small intestinal biopsy to document histological improvement while on GFD is required in cases of asymptomatic patients and when clinical response to GFD is equivocal. Gluten challenge is needed when, (i) there is any doubt about the initial diagnosis like, when no initial diagnostic biopsy was done or when the biopsy specimen was inadequate or not characteristic of celiac disease, (ii) diagnosis of celiac disease is made in < 2 years of age when other causes of enteropathy like cow’s milk protein intolerance (CMPI), persistent diarrhea, giardiasis and transient gluten intolerance are common (iii) in older children and teenagers who intend to abandon the GFD in an uncontrolled way by themselves, it is preferable to do challenge.

It has also been emphasised that IgA antigliadin, antireticulin, tTGA and antiendomysial antibodies, if present at the time of diagnosis in a child with a typical small intestinal histology and they disappear in parallel
to a clinical response to GED, add weightage to the diagnosis of celiac disease. However, the diagnosis of celiac disease can not be made on the basis of these antibodies alone without histological, biochemical change and clinical counterpart.

The problem in developing countries like India is that there are so many other conditions which can give rise to villous atrophy. If we follow the modified ESPGAN criteria, then we will over-diagnose celiac disease. In a series of cases with protracted diarrhea from Delhi, it has been shown that 26% of them had severe villous atrophy due to enteropathogenic E. Coli, giardia, CMPI, salmonella, bacterial overgrowth and transient gluten intolerance (30). Similar observations have been made by other authors also. Various causes of villous atrophy are given in table-I. It seems that modified criteria supplemented with serological tests like AGA or EMA or iTGA estimation seem to be very good adjunct to make diagnosis of CD in our country.

Practical Approach

I. Clinical Suspicion
High index of suspicion should be based on sound clinical knowledge about the disease. It is not difficult to pick up the diagnosis in a child coming with chronic diarrhea with malabsorptive stools, stunted growth and anemia. This is picture of an active or classical case of celiac disease. However the atypical presentation or associated diseases as discussed earlier should be kept in mind but growth failure is a universal finding with these conditions also. In our set up, microscopic examination of stool for 3 consecutive days should be carried out routinely to rule out giardiasis (4).

II. Hemogram
Hemogram includes estimation of hemoglobin/PCV along with reticulocyte count and peripheral smear to see for type of anemia. There is dimorphic anemia suggesting iron and folic acid deficiency in CD. There may be thrombocytosis suggesting asplenia in long standing cases of CD. Estimation of serum levels of iron, folic acid and Vit. B₁₂ may be done if feasible. Prolongation of prothrombin time may suggest vitamin K deficiency.

III. Biochemical Tests
Blood biochemistry includes estimation of serum proteins, transaminasses, calcium, phosphorus, magnesium and potassium. These are not done routinely in all the cases.

IV. D-Xylose Test
This is very useful test to see the integrity of jejunal mucosa. This is done by estimation of D-xylose in urine or serum after loading the child with 5g of D-xylose.

V. Fecal Fat
Quantitative fecal fat estimation is done to see the state of steatorrhea. This is done by Van de Kamar method or ¹⁴C-Trilein or ¹³C-Trilein breath test (4,5).

VI. Intestinal Biopsy
Endoscopic mucosal biopsy from second part of duodenum or deep from jejunum has replaced cumbersome method of taking jejunal biopsy by Crosby capsule. In most of the centres people are doing mucosal biopsy with UGI endoscope. Various histopathological changes described in CD are mentioned under pathology given earlier (31,34).

VII. Serological Tests
Serological tests are replacing now the most cumbersome tests to diagnose and to prognosticate CD. These are antireticulin antibodies (ARA), antigliadin antibodies (AGA) and endomysial antibodies (EMA). Antireticulin antibodies have low sensitivity 65-83% (74%) but very high specific (100%) hence, not used routinely for diagnosis of CD. Antigliadin antibodies IgA have
Estimation of antibody titres is very important to see the serological response while on gluten free diet. These antibodies come down while on wheat free diet and non-complaint patient can also be picked up if antibody levels are not falling. Antibody levels should be repeated after 3 months of the wheat free diet.

**Treatment**

**Gluten free diet**

Meticulous treatment of CD is mandatory. Since disease is permanent and life long, it should be explained to parents and child thoroughly by senior and experienced person. The manipulations in the dietary adjustments have to be encouraged. Proper counselling of whole family and possibly school teachers is very important. Cereals like wheat and wheat products, rye, barley and oat are avoided. Various gluten free dietary recipes should be given as hand out to follow at home. Response to GFD is dramatic and within week’s time appetite returns, patient starts feeding well, becomes alert, develops smile on the face, starts playing, diarrhea subsides and catch up of the growth follows. The weight and height gain are observed over one month on follow up and remain constantly progressive if GFD is continued. Other diets to be avoided broadly include all bakery products, confectionery products, chocolates, chocolate toffees, ice creams, soups, noodles, maggi etc., because all these are thickened by adding maida, a product of wheat. The details of this are given to patients as handout in our centre. Preferably parents should grind various articles at home in a grinding machine. Everything should be prepared at home for the affected child (4,5,46,47). Great care should be observed in out door parties, where all sort of food items are displayed and there is lot of mixing. So parents should guide the children during these occasions and choose appropriate wheat product free food items.

**Lactase deficiency**

Small percentage of younger age patients or during acute crisis may not tolerate milk and thus should stop
milk and milk products for 3-4 weeks initially.

Supplemental therapy

Iron and folic acid should be given to treat associated anemia. Vitamin B₁₂ is given, if there is evidence of its deficiency. Other vitamins like A, D, K and E and B complex vitamins are given in adequate amount. In case of tetany, injectable calcium should be given followed by oral administration of Ca++ and Mg++.

Celiac Crisis

Celiac crisis should be recognised and treated promptly. This needs intravenous fluids for expansion of volume, potassium replacement and treatment of associated acidosis, infections or hyponatremia should be started simultaneously. In severe cases, steroids for short period are recommended (4, 46).

Refractory Sprue

Very rarely patients do not respond to GFD and may need steroids and immunosuppressive therapy. Reasons for this condition are not clear and condition often proves fatal.

Prognosis and follow up

Prognosis is excellent if GFD is strictly followed. The diarrhea disappears and growth is achieved at faster rate. Within few months whole clinical picture changes. Prognosis is not good in situations where patient is noncompliant, parents don’t follow instructions and disease is not understood properly. Major problems are growth faltering and complications of CD during later life.

Follow up of these patients on GFD should be done very closely and from time to time. Importance of GFD, growth measurements and serological tests are to be emphasised

In conclusion, CD is a common cause of chronic diarrhea with malabsorption in our centre. Diagnosis is based on clinical features, abnormal malabsorption tests and positive AGA or EMA or tTGA (45, 48). Treatment with GFD is excellent and prolonged follow up is mandatory. Compliance to GFD and frequent follow up have key role to play in management of celiac disease.

For better interaction among patients, there is need of making “Celiac Society”.

References