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DIFFICULT CELIACS IN CENTRAL INDIA.

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Introduction:

Celiac disease is gluten hypersensitivity with multisystem involvement. Though considered to be more prevalent in Northern India, still unfortunately follows the tip of iceberg phenomenon in diagnosis everywhere.

In Central India which includes Maharashtra, Chattisgarh, Madhyapradesh exact incidence and prevalence is not known. In this volume 37 OF Pedgihep E-JOURNAL I take this opportunity to discuss difficult celiac pathophysiology and their implications on our clinical day to day practice.

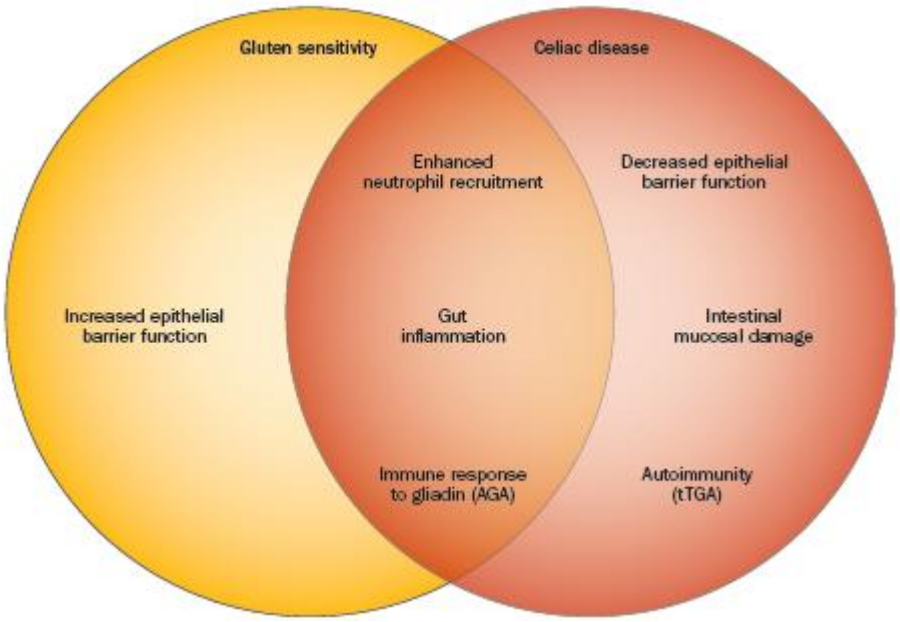

Figure : Volta, U. & De Giorgio, R. *Nat. Rev. Gastroenterol. Hepatol.* advance online publication 28 February 2012; doi:10.1038/nrgastro.2012.15

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DEFINATION OF DIFFICULT CELIAC DISEASE:

Inclusion:

1. Potenial celiacs .

2. Refarctory Celiacs.

Exclusion criteria :

Non-compliant on gluten free diet patient not included in the discussion of refractory celiac. Initial wrong diagnosis of celiac diseases are excluded.

Potenial Celiacs:

By definition: serology positive IgA TTG +ve / Duodenal biopsy : marsh 0/Clinical features : consistent with celiac disease

Number of patients:

What's not done :

1. Immuno-phenotyping of duodenal mucosal biopsy samples CD differentation
2. TTG in-situ staining.

What's important?

1. Exact incidence of potential celiac changing to celiac disease is not known.
2. Are potential celiac are subset of non-celiac gluten intolerance ?
3. What should be the cut off of serum IgA TTG for diagnosing Potenial celiacs while serological monitoring to avoid unnecessary duodenal biopsy?

Analysis:

A Double blind RCT published recently confirmed the entity of non-celiac gluten hypersensitivity manifesting as Irritable bowel, duodenal malabsorption .Though authors could-not explain mechanism behind it [1]Gluten intolerance in individuals without celiac disease, has also been described as NON MAN'S LAND.[2]

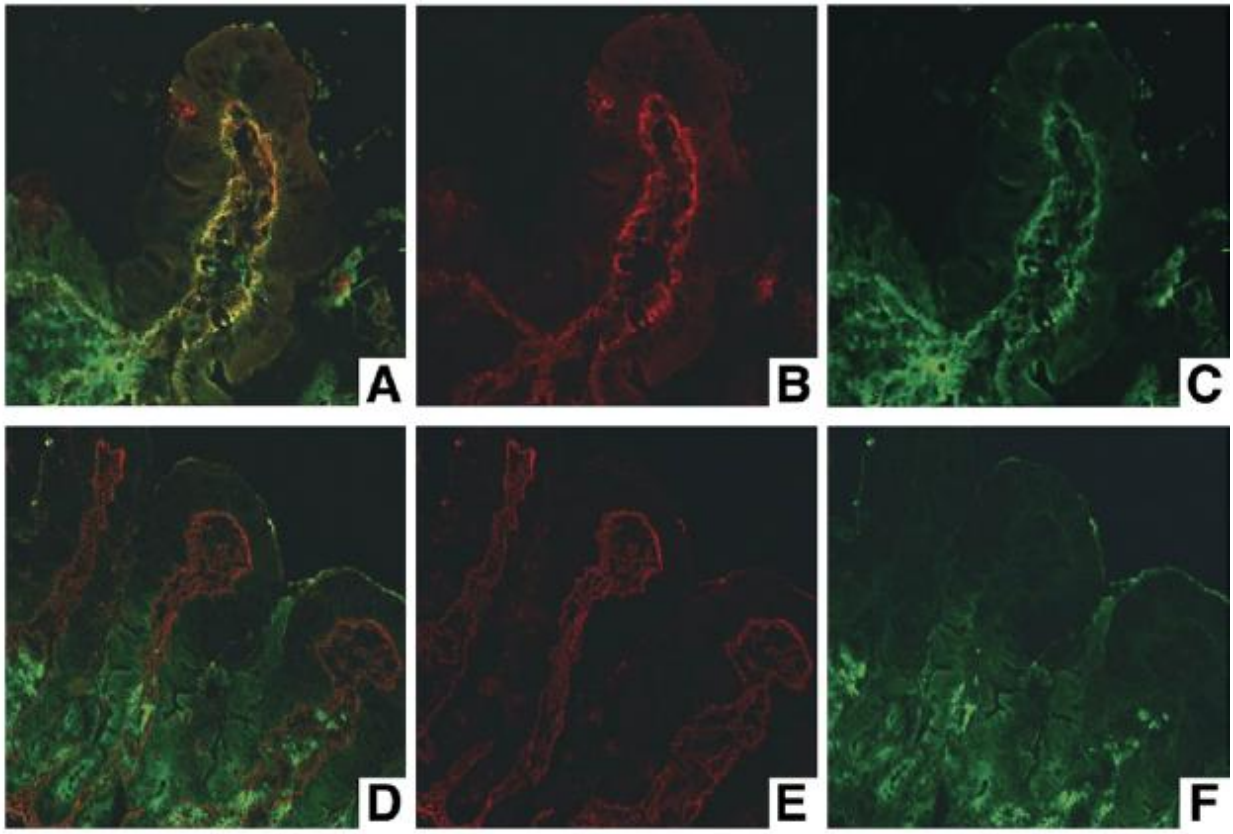
Most of published evidence, label the patient as potential celiac who do not follow serological/biochemical/endoscopic criteria of published guidelines ESPGHAN on definition of celiac disease for diagnosis.

Any dietary product like Gluten can induce functional gut symptoms include induction of intestinal distension through the fermentation of poorly absorbed gluten peptides. Alternatively, some studies reinforce that gluten may mediate cholinergic activation as has been shown in murine models of gluten sensitivity.[3]

Gluten indeed can trigger of gut symptoms and tiredness in persons with Potential celiac . How to interpret this situation in children is questionable and debateable.

Are we over justified in recommending trial of gluten withdrawal in children with functional abdominal pain and irritable bowel syndrome needs to be further studied.

One of the landmark studies in children with potential celiac reinforces that most of these children remain healthy. Over the period of 3 years 1/3 would develop villous atrophy. Use of Intestinal deposits for ANTItG2 IgA as screening test is recommended.[4]



Detection of IgA depositsin duodenal mucosa from a potentialCD patient. TG2 (in *red*) shows a subepithelial localization (*B*), IgA in*green* (*C*) are present inside plasmacells; thin layers of anti-TG2 antibodymucosal deposits are visible in subepithelialareas. In *panel A*, *yellow color*indicates colocalization of IgA anti-TG2 mucosal deposits and TG2.(*D–F*) Duodenal mucosa from a potentialCD patient negative for deposits ofIgA anti-TG2. IgA are visible, in *green*,only inside plasma cells and epithelialcells (*F*), TG2 in *red* presents a subepithelialdistribution (*E*). No area of colocalizationis evident (*D*).

figure: CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2011;9:320–325

The natural history of gluten sensitivity is unknown. Whether this disorder is permanent or transient and whether it is linked to autoimmunity.

To include patients and better define them as NONCELIAC GLUTEN HYPERSENSITIVITY OR GLUTEN SENSITIVITY where classic definition by ESPGHAN do-not clarify or distinguish the patient as Celiac disease may we start using following criteria:[5]

Box 1 | Diagnostic criteria for gluten sensitivity*

- Gluten ingestion elicits the rapid occurrence of intestinal and extraintestinal symptoms
- Symptoms disappear rapidly after gluten withdrawal
- Reintroduction of gluten causes symptoms
- Specific IgE to gluten and wheat and skin prick tests results are negative
- Celiac disease serology (IgA endomysial antibodies, IgA tissue transglutaminase antibodies, IgG deamidated gliadin antibodies) results are negative
- Antigliadin antibodies (mainly of IgG class) are positive in about 50% of patients
- Normal mucosa or mild increase in the number of intraepithelial lymphocytes at histopathology
- HLA-DQ2 and/or HLA-DQ8 possibly positive in ~40% of patients

*Criteria proposed by the authors.

By using above criteria I propose we can better investigate /approach celiac syndrome. Data from India in children is richly awaited to be tapped.

IS Gluten sensitivity, potential celiac reversible? It would also give us clue is it muti-factorial or completely genetic based.

Refractory celiac disease:

What's important?

What is the incidence of missed refractory celiac from India?
Can we take help of immune-staining CD s early in diagnosis for better prognostication?

Refractory CD has been defined as persistent or recurrent villous atrophy with crypt hyperplasia and increased intraepithelial lymphocytes (IELs) despite a strict GFD for greater than 12 mo (or if severe persisting symptoms necessitate intervention independent of the duration of the GFD.[6] Refractory celiac disease is further classified as type 1: normal pattern of Intra epithelial lymphocytes . and type 2 : abnormal pattern of Intra epithelial lymphocytes .Type 2 being more chances of developing lymphoma and poor prognosis. Patients with both types may benefit from immunosuppressive therapy.[7]

Recurrent symptoms develop in biopsy-proven CD patients on a GFD. The most common cause of nonresponsive CD, which occurs in about 30% of CD patients, is non-adherence to a GFD.

About 10% of CD patients diagnosed in childhood may develop temporary tolerance to gluten[8] But still we do find patients with refractory celiac disease.

By Common justified approach before labeling as refractory celiac disease primary or secondary pancreatic insufficiency, small intestinal bacterial overgrowth, collagenous sprue, or lymphocytic or collagenous colitis needs to be excluded. Similarly Gluten free diet need to be reinforced. Inspite of all the above measures if problem persist we need to reconsider the diagnosis of celiac disease. All through….. ultimately refractory celiac label should be considered.

Origin of refractory celiac disease types has been traced to Different cluster of differentiation as per the recent study and it has to deal with thymic migration of intra epithelial lymphocytes which is post- natal. Simple genetic causation would be difficult to explain these observations in new studies

Schmitz et al[9] defined a subpopulation of lineage-negative (Lin-) CD7CD127− CD34− lymphocytes as likely precursors of aberrant IELs in type 2 . They showed that their RCDII lymphocytic cell lines expressed far more NK-cell associated transcripts compared to mature TCR+ CD3 IELs and then defined a subpopulation of these lineage-negative (Lin-) CD7CD127− CD34− lymphocytes that highly expressed the interleukin (IL)-2/15Rβ chain (CD122)as likely precursors of aberrant IELs in type 2 .

Interestingly Type 2 lineage 18-fold more frequent in the duodenum of non-coeliac compared to coeliac children, and less frequent in adults .Rich expression of NATURAL KILLER CELLS and Il15 /2 AXIS is underlying basis of type 2 celiac disease.

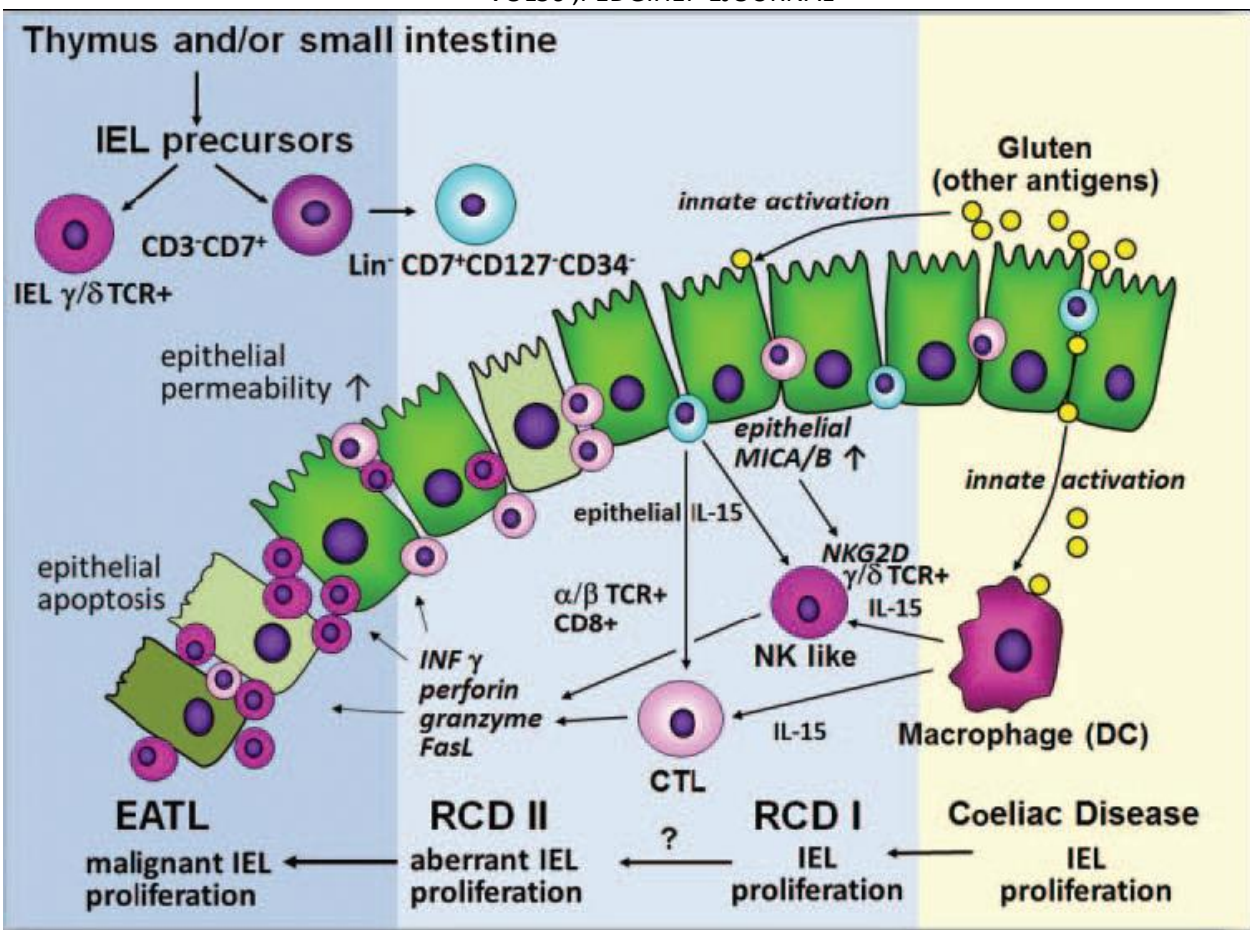


Figure : Gut 2012;0:1–2. doi:10.1136/gutjnl-2012-303030

BOTH COMBINED: POTENTIAL / REFRACTORY CELIAC?

Should we try gluten free trial in patients of functional abdominal pain/CHILDHOOD IBS who are diagnosed as gluten sensitivity as discussed earlier in the criteria? Should we introduce immune-staining early to diagnose potential celiac? Can we propose understanding of refractory celiac for prognostication?

At least we should have NATIONAL academic committee with histopathologist / immunocytochemist where we could send all the samples for analysis to understand celiac disease better in children.

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ESPGHAN GUIDELINES ON CELIAC DISEASE, SHORT SUMMARY

There is a strong genetic predisposition to CD with the major risk attributed to the specific genetic markers known as HLA-DQ2 and HLA-DQ8. LOE: 1.

The main role of HLA-DQ typing in the diagnosis of CD is to exclude the disease. LOE: 2.

HLA-DQ2 and/or HLA-DQ8 have poor specificity for CD (median 54%), indicating a low positive predictive value for CD.LOE: 2.

groups at risk for CD. A negative result for HLA-DQ2/HLA-DQ8 renders CD highly unlikely in these children, and hence there is no need for subsequent CD antibodies testing in such individuals. LOE: 2.

Offer HLA-DQ2 and HLA-DQ8 typing in patients with uncertain diagnosis ofCD, for example, in patients with negativeCDspecific antibodies andmild infiltrative changes insmall-bowel specimens. Negative results render CD highly unlikely in these children.

HLA-DQ2/HLADQ8 typing in children WITHOUT intestinal biopsies to add strength to the diagnosis.

In subjects with normal serum IgA values for age, a positive IgA class EMA result or a positive IgA class anti-TG2 antibody result is considered to be a CD-relevant antibody positivity. In the case of IgA deficiency, a positive IgG class EMA result, a positive IgG class anti-TG2 antibody, or a positive IgG class anti-DGP antibody is diagnostically relevant. LOE: 1.

For blood anti-TG2 antibody tests that use calibration curves to express antibody concentration, values exceeding 10 times ULN may be denoted as high antibody positivity. LOE: 3.

It is more likely that CD is present if the EMA result is positive than if another CD antibody result is positive. LOE: 1.

Isolated positivity for anti-TG2, especially in the low positivity range, can occur in conditions that are unrelated to CD, such as other autoimmune conditions, infections, tumours, or tissue damage. LOE: 1.

High concentrations of anti-TG2 antibodies in blood (as defined in statement 2.3.5) predict villous atrophy better than low positive or borderline values. LOE: 2

The evaluation of rapid tests is less reliable if done by untrained or laypeople.LOE 1

Anti-TG2 antibody or EMA testing from a blood sample has a higher accuracy than antibody testing against DGP, unless special patient characteristics are present (IgA deficiency, age younger than 2 years).LOE: 1.

Tests for the detection of IgG or IgA antibodies against native gliadin (conventional gliadin antibody test) are neither sufficiently sensitive nor sufficiently specific for the detection of CD. LOE: 1.

Tests for the detection of CD antibodies of any isotype (IgG, IgA, secretory IgA) in fecal samples are unreliable. LOE: 3.

For initial testing in symptomatic patients, a quantitative test detecting IgA class anti-TG2 or EMA from a blood sample is recommended. If total serum IgA is not known, measurement is recommended. In subjects with either primary or secondary humoral IgA deficiency, at least 1 additional test measuring IgG class CD antibodies (IgG anti-TG2, IgG anti-DGP, or IgG EMA, or blended kits for both IgA and IgG antibodies) is recommended.

Children found to test positive for CD-specific antibodies should be evaluated by a paediatric gastroenterologist to prove or to exclude the presence of CD.

Histological assessment may be omitted in symptomatic patients (see list in Who to Test) who have high IgA anti-TG2 levels (10 times above ULN), verified by EMA positivity, and are HLADQ2 and/or HLA-DQ8 heterodimer positive.

If anti-TG2 antibodies are positive only in low concentrations and EMA testing is negative, then the diagnosis of CD is less likely. A small intestinal biopsy should be performed to clarify whether CD is present.

In seronegative patients with strong clinical suspicion of CD, small-intestine biopsies are recommended.

Biopsies should be taken from the bulb (at least 1) and from the second or third portion of the duodenum (at least 4).

Gluten challenge is not considered mandatory, except under unusual circumstances. These circumstances include situations in which there is doubt about the initial diagnosis, including patients with no CD-specific antibodies before starting a GFD.

Gluten challenge should be performed under medical supervision, preferably by a paediatric gastroenterologist.

HLA typing and assessment of duodenal histology should be considered before gluten challenge is instituted

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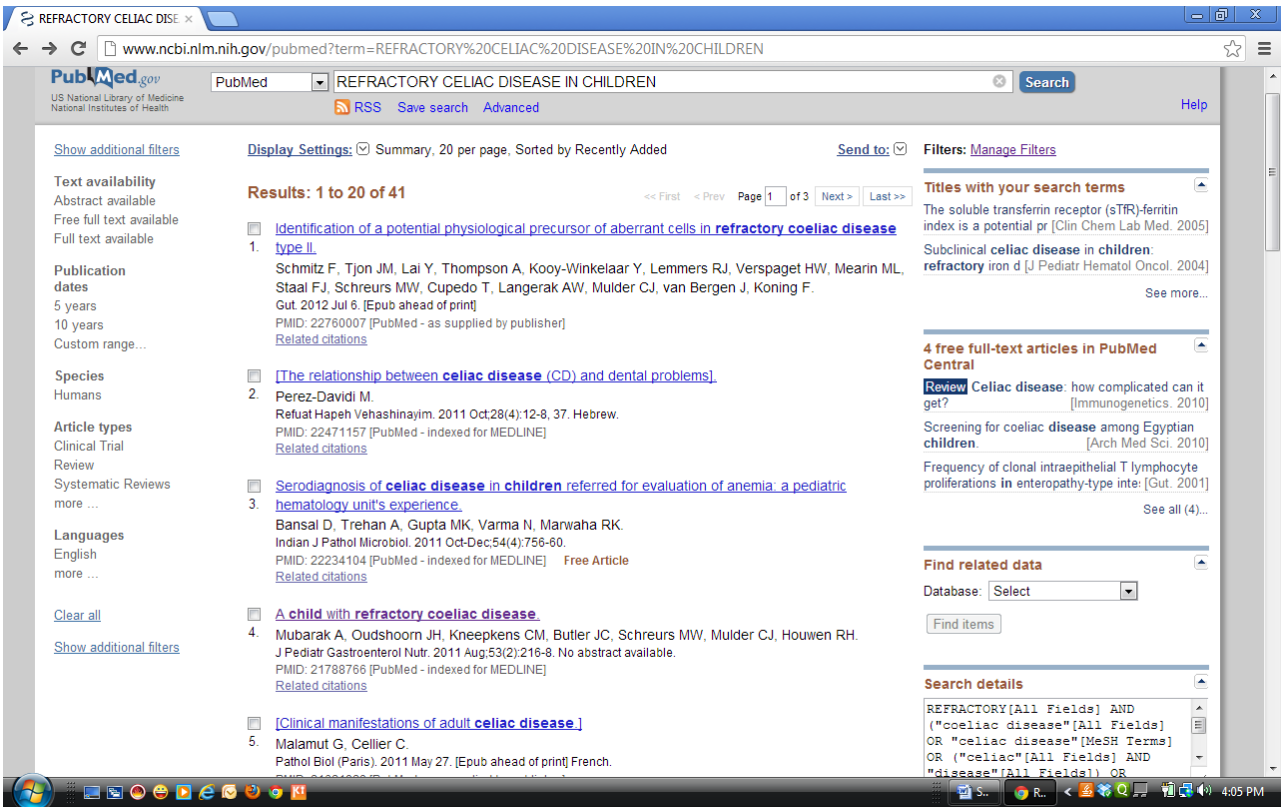

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