In the name of God

Celiac Disease(CD)

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Case presentation

1-In a 53 yr old man , a pediatrician (Dr) with unexplained Wt.loss and refractory Fe def.anemia.

tTG-IgA was positive.

Intest.Bx. → *CD* → *GFD* → *Responded*

2-. In a boy with CAP and obesity ,tTG-IgA was positive

Intest. Bx. → *CD* → *GFD*

3-In a 9 yr old child with chronic functional constipation, dependent on medical therapy , tTG-IgA was positive

Intest.Bx. → *CD* → *GFD* → *Responded*

Case presentation

4- In an adolescent girl with delayed puberty,

tTG-IgA was positive

Intest.Bx → CD → GFD → Responded

5-In a young boy with impression of JRA, tTG-IgA was positive.

Intest.Bx . → CD → GFD → Responded

6-In a young lady with infertility , tTG-IgA was positive

Intest.Bx. → CD → GFD → became pregnant

Case presentation

7- In a young girl with Hx. of chronic headache, tTG-IgA was positive.

Intest. Bx. → CD → GFD → Improved

8- In an 8 yr old boy with ADHD, tTG-IgA was positive.

Intest.Bx. → CD → GFD → Improved

9-In a 7 yr old child with unexplained abnormal AST/ALT elevation for a few mo. tTG-IgA was positive

Intest.Bx → CD → GFD → Nl

10-In a12yr old boy with Hx. of recurrent aphthous lesions for 2-3 weeks each time for a long time. tTG-IgA was positive.

Incest. BX → CD → GFD → improved

11-In a 9 yr old boy with Hx. of abd. protrusion, flatulence and malodor gas passing for a long time. tTG-IgA was pos.

Intest. Bx → CD → GFD → improved

These cases are known as monosymptomatic , non-classic or atypical CD.

12-A 36 yr old woman, a pediatrician with Hx.of on and off abdominal pain, cramps, flatulence and diarrhea a few hrs after eating bread for a long time.

She was treated as a case of IBS.

She noticed that her symptoms improve with restriction of ingestion of bread (GFD).

tTG-IgA was Nl , and intestinal Bx.for CD was negative.

What is the Dx.?

Non-Celiac Gluten Sensitivity (NCGS)

Considering the different types of clinical presentations of CD and affecting different organs ,it is better to be known as a syndrome ,rather than a disease.

Introduction

CD (Gluten-sensitive enteropathy , Nontropical sprue) was first described by Samuel Gee in 1888.

The association between CD and bread and cereals was recognized by Willem K Dicke , a Dutch pediatrician.

The Second World War and CD.

Introduction

Types of adverse reactions to wheat (gluten):

1-wheat allergy (IgE/IgG mediated)

2- CD (T cell mediated)

3- Non celiac gluten sensitivity (NCGS)

Introduction

CD is a chronic , multiorgan, autoimmune disease, that affect proximal small bowel in genetically predisposed persons, precipitated by ingestion of gluten.

The immune response is mediated by gliadin reactive T cells.

Introduction

Prevalence:

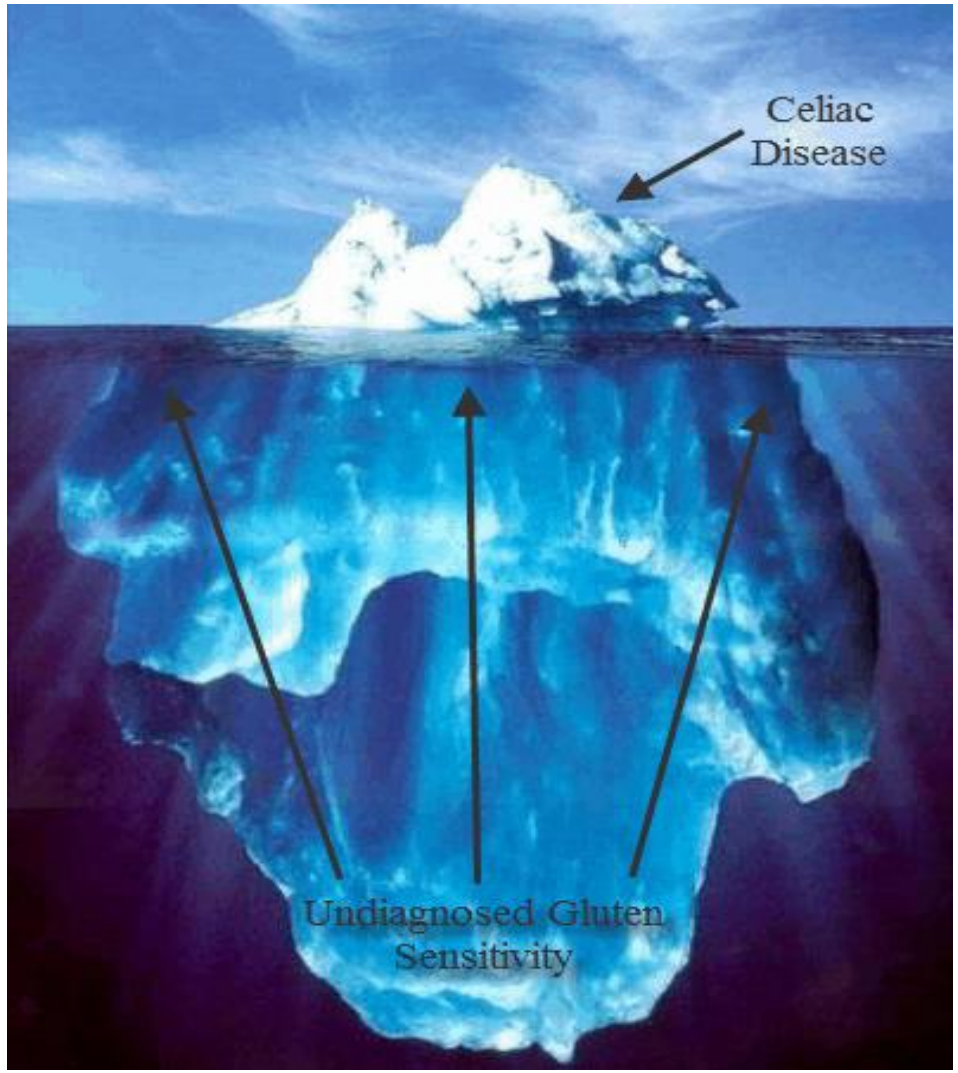
CD presents such as an iceberg, most of the cases are not detected.

The CD affects about 0.5 -1% of the general population in many parts of world in genetically susceptible people.

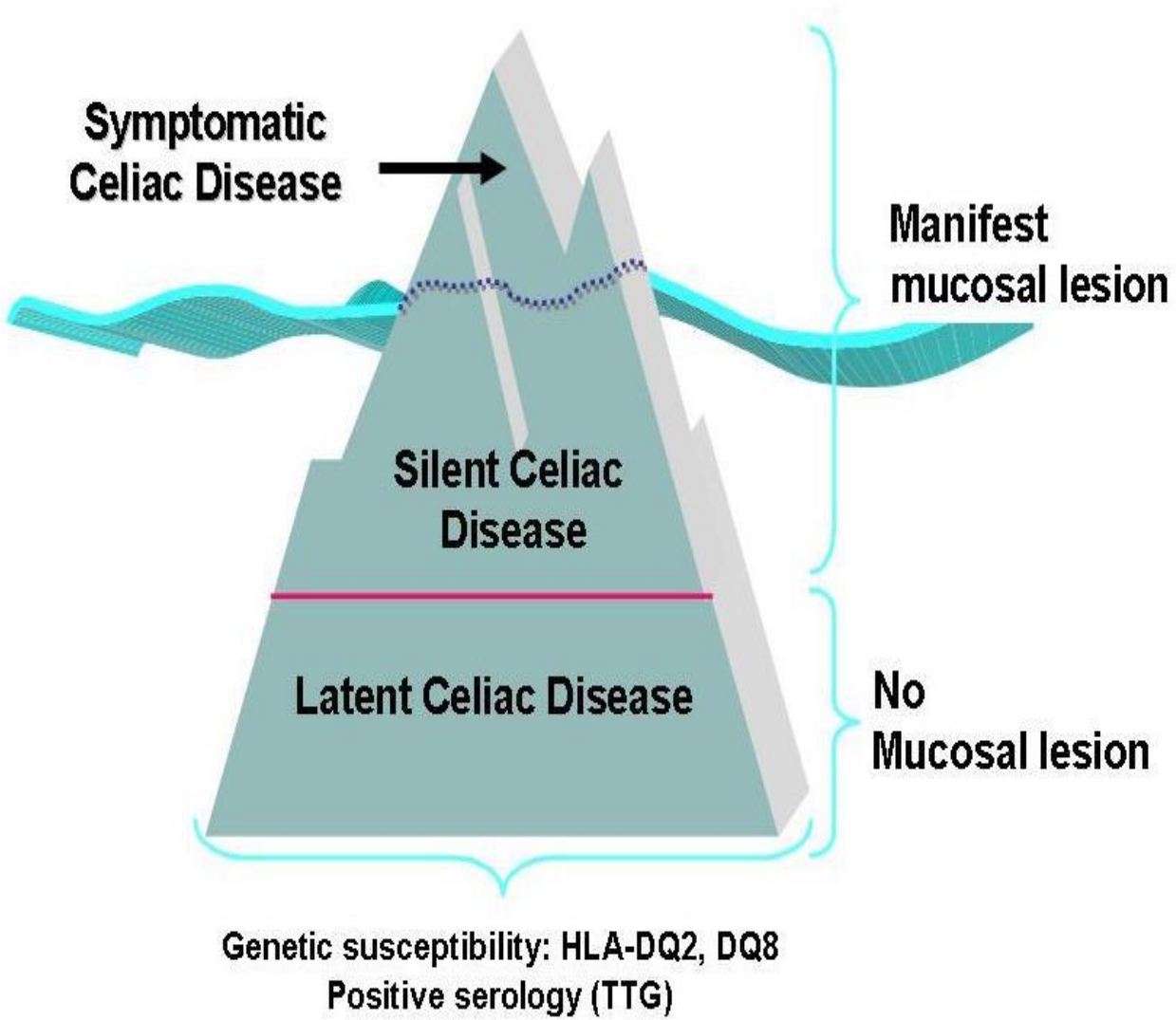
CD affects all age groups.

The female/male ratio is about 2/1

CD iceberg



The Celiac Iceberg



Introduction

High risk groups:

1- All individuals with HLA DQ2/DQ8

2- Following groups:

1-Fisrt and second degree relatives

2- DM1 *3- AI thyroiditis*

4- IgA def. *5- Chronic juvenile arthritis*

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6- Down , Turner and William synd.

CD and infants feeding practice

1-Timing:

The time of initial gluten exposure

2- Quantity:

The quantity of gluten in infants diet

3-Breast feeding

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CD and infants feeding practice

1- There is no association between the timing of gluten introduction or breastfeeding with CD risk

2- Later introduction of gluten does not alter the CD risk, but it modestly delays the onset of CD presentation.

Additional trigger factors

Prior intestinal infection, in particular rotavirus and enterovirus infection and previous exposure to antibiotics are more common in children with CD than those without.

If true, the precise mechanisms by which these events affect the onset of disease remain unclear.

Classification

The umbrella of CD:

1- *Classic*

2- *Non-GI(atypical) (the most common)*

3- *Silent/Subclinical*

4- *Potential*

5- *Latent*

Classic type CD

Characteristics:

1-Presents with signs of malabsorption :

Diarrhea/ steatorrhea, Wt. loss, abd. Protrusion and Signs of nutrient and vit. Deficiency (usually present between 6-24 mo of age).

2- Characteristic histologic changes on small intestinal Bx.

3- Resolution of symptoms and mucosal lesions on GFD (usually within a few weeks or months).

GI symptoms

1-Chronic/ persistent diarrhea, steatorrhea and malabsorption

2-CAP/RAP

3-Chronic constipation

4-GERD/Vomiting

5-IBD

2 and 3 are the most common GI presentations in this period.

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Non-GI (Extra-GI) CD

1- G/D:

Short stature and delayed puberty

2- Neurologic and behavioral (neuropsychiatric) symptoms:

Hypotonia , DD, learning disorders ,headache, epilepsy and cerebellar ataxia(gluten ataxia), ADHD, autism ,..

3- Liver disease:

Isolated increased liver enz.s, acute hepatitis, chronic hepatitis , AIH, cirrhosis

Non-GI (Extra-GI) CD

4- Fe def. anemia

5-Skin :

DH is the most specific specific extra-GI symptom

6- Dental enamel defect

7- Metabolic bone disease

Non–GI (Extra-GI) CD

8- Chronic arthritis

9- Gynecological problems

(infertility , recurrent abortion, stillbirth, IUGR,..)

10 – Hyposplenism

11- Kidney disease

Non-GI (Extra-GI) CD

12-Pulmonary hemosiderosis (Lane-Hamilton syndrome)

13-Myocarditis and Cardiomyopathy

14-Atrophic Glossitis/oral lesions (aphthous lesions)

15-Pancreatitis

Dental enamel hypoplasia

1- Occurs symmetrically in permanent teeth

2- May occur in the absence of GI symptoms

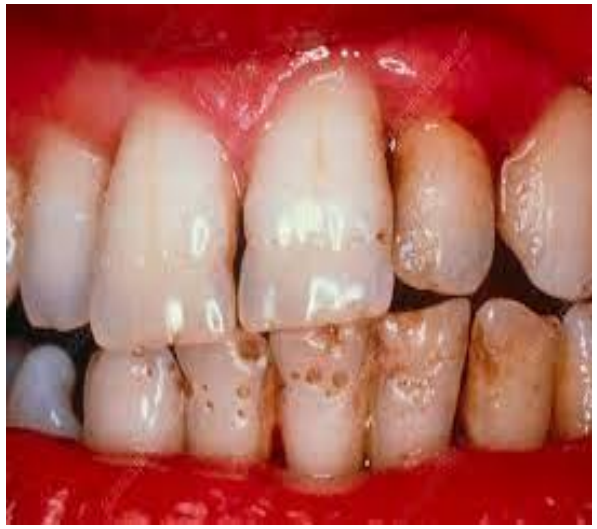
3-Consists of:

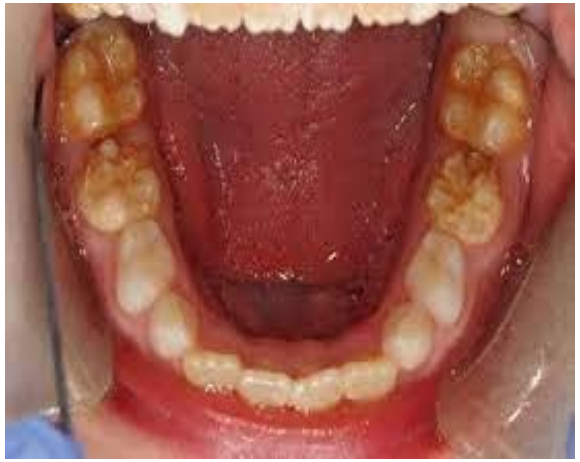
1- Cream, yellow or brown opacities

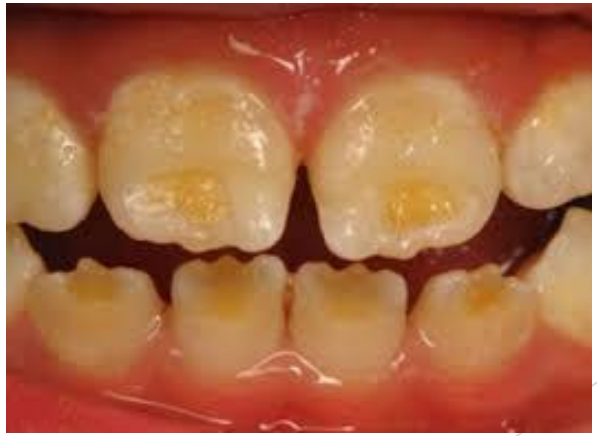
2- Loss of enamel glaze

3- Horizontal groves or yellow pits

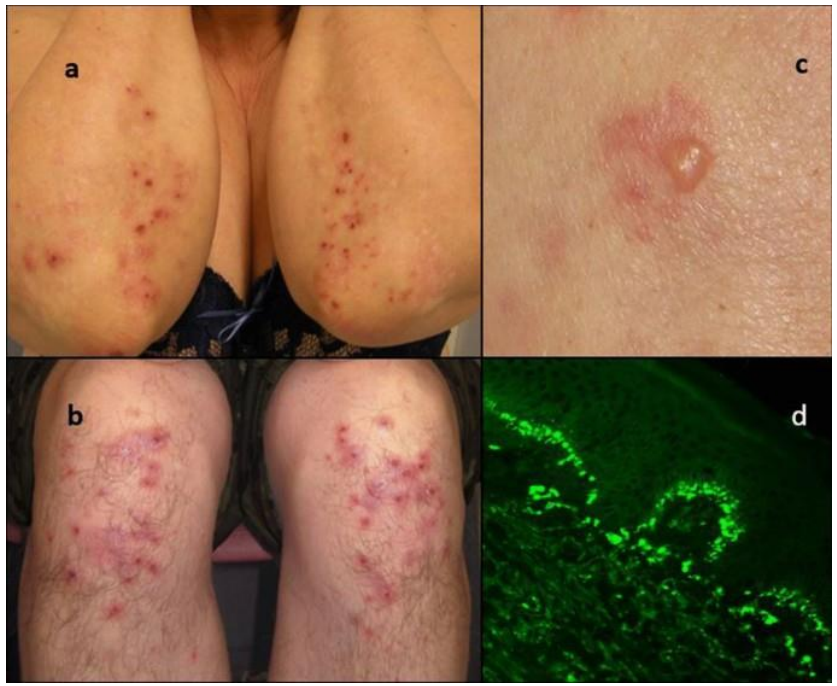
Dental enamel hypoplasia

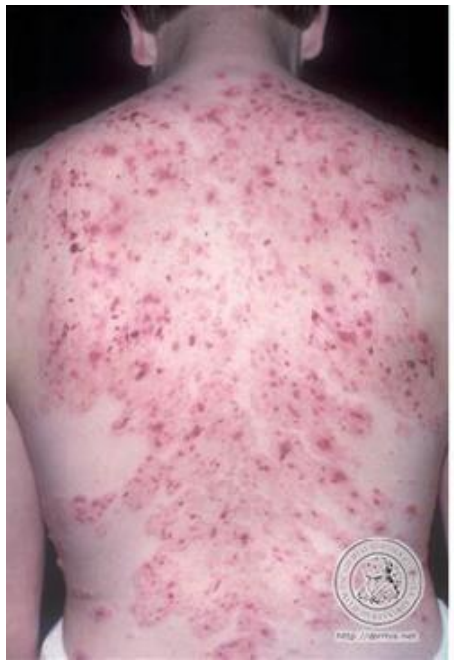


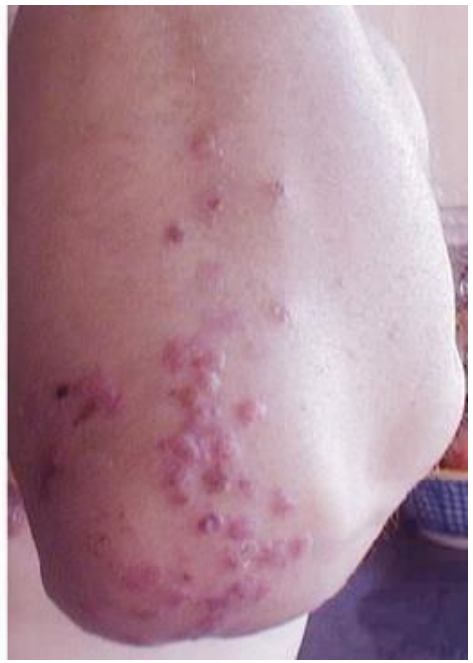


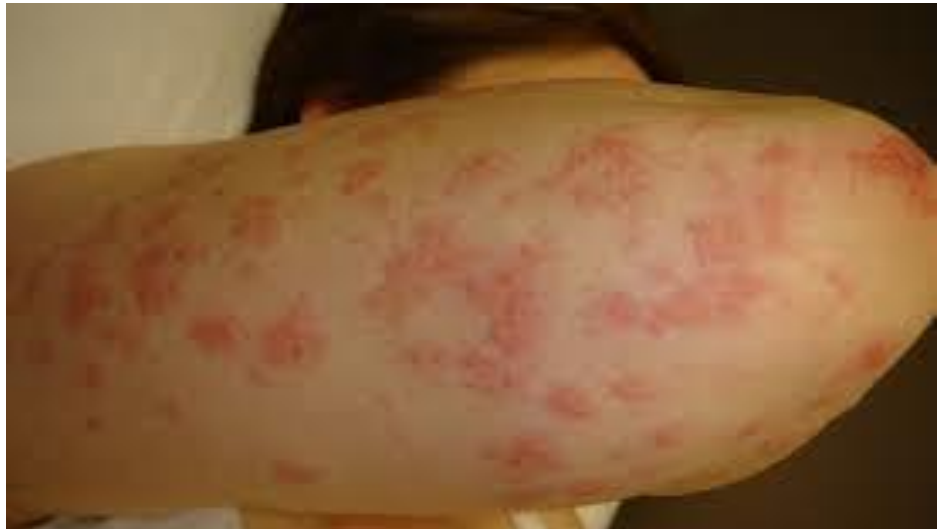


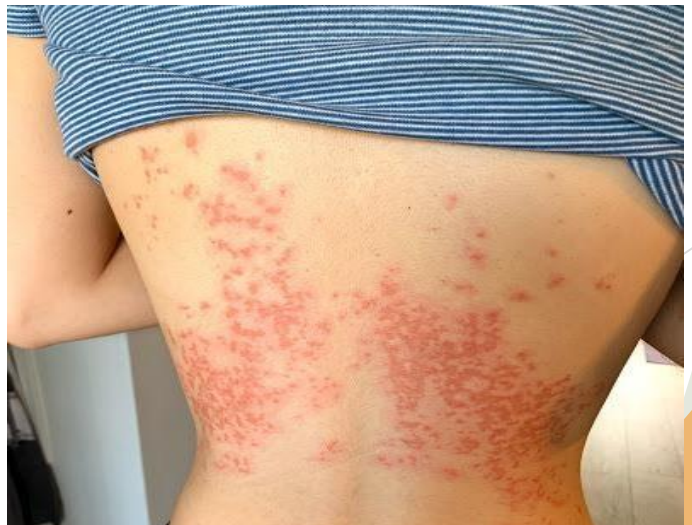
DH











Silent/Subclinical CD

Characteristics:

1-No discriminable symptoms

2-Positive serologic tests for CD

3-Hiatologic changes compatible with CD

These cases are usually detected by screening of high risk groups.

The term silent may be a misnomer.

Potential CD

Characteristics:

1-Asymptomatic (usually) or symptomatic

2- Positive serologic tests

3- Nl. Histology

1-These are usually identified in screening of high risk groups.

2- The majority of asymptomatic children in this group do not develop CD.

Latent CD

Characteristics:

1-They have had all diagnostic criteria of CD at some time

2- Have few or no symptom while ingesting gluten containing diet

3- Have normal histology and negative serology

In many of these cases the CD was initially diagnosed during childhood and was treated with a GFD, then the disease was remained quiescent despite ingestion of normal diet.

NCGS

Characteristics:

1- NCGS is a dose dependent intolerance to gluten containing grains.

2- GI symptoms (abd. Pain, bloating, diarrhea, ..) occur with gluten ingestion

3- No serologic or histologic evidence of CD

4- The onset of symptoms are typically within hrs or a few days of gluten ingestion

Diagnosis:

CD , wheat allergy ,CHO malabsorption and IBS should be excluded.

Risk of malignancy

The risk of GI malignancy , particularly, non-Hodgkin lymphoma and GI cancer are increase in adults with CD.

The incidence of cancer does not appear to be increased during childhood.

The risk of malignancy is reduced by long term treatment with GFD (it is one of the rationales for recommendation for lifelong GFD in all cases of CD).

Diagnosis

1-Provisional Dx., based on:

1- clinical symptoms

2- Positive serologic tests

3- typical histologic changes

2-Confirmed Dx.:

Based on clinical response and normalization of serologic tests on GFD.

Diagnosis

1- Whom to test?

2- How to test?

3- when to test?

Whom to test?

Screening for CD is recommended for :

1-Symptomatic patients suspected to CD

2-High risk groups

In asymptomatic high risk groups, screening should be performed at three yr of age or older and on gluten diet for least one yr. and should be repeated every 3-5 yr during childhood.

How to test?

1-Serologic tests

2- Histologic study

3-HAL-DQ2/DQ8 determination

How to test?

In most cases the first step is to perform serologic test.

Serologic tests:

1-tTG-IgA (first screening test)

2-EMA

3-DGP -ab

Note:

1- AGA is no more recommended

2- 2-15% of CD are seronegative

How to test?

1-serologic tests should be done while on a gluten containing diet.

2- False positive and false negative tests may occur.

3- Serologic tests may become negative within weeks of beginning GFD, but may take up to a yr or even more in some cases.

How to test?

Is it necessary to perform total IgA in all cases?

About 2% of children with CD have IgA deficiency

Total IgA should be measured only in children with negative level of tTG-IgA but a high clinical suspicion of CD.

Routine measurement of total IgA for CD screening is not cost effective and therefore is not recommended.

How to test?

Asymptomatic high risk group:

tTG-IgA:

1->3ULN → *intestinal Bx.*

2-Positive (<3ULN) → *EMA(+)* → *Bx.*

3- Nl: CD is unlikely

How to test?

Asymptomatic high risk groups:

An alternative strategy is HLA-DQ2/DQ8 measurement.

Those positive for above HLA, should undergo serial antibody screening every 3-5 yrs.

How to test?

Is intestinal Bx.necessary for all pat.s ?

1-Bx.is not needed for Dx.of CD in DH pat.s

2- Bx.is optional for pat.s with all of the following characteristics:

1-tTG-IgA>10 ULN

2- Positive EMA/DGP

3- GI symptoms typical for CD

The Dx.is only confirmed if there is a clear clinical response on GFD and normalization of serologic tests.

How to test?

Abnormal histologic findings (*Marsh classification*):

1-Marsh1: increased intraepithelial lymphocytes

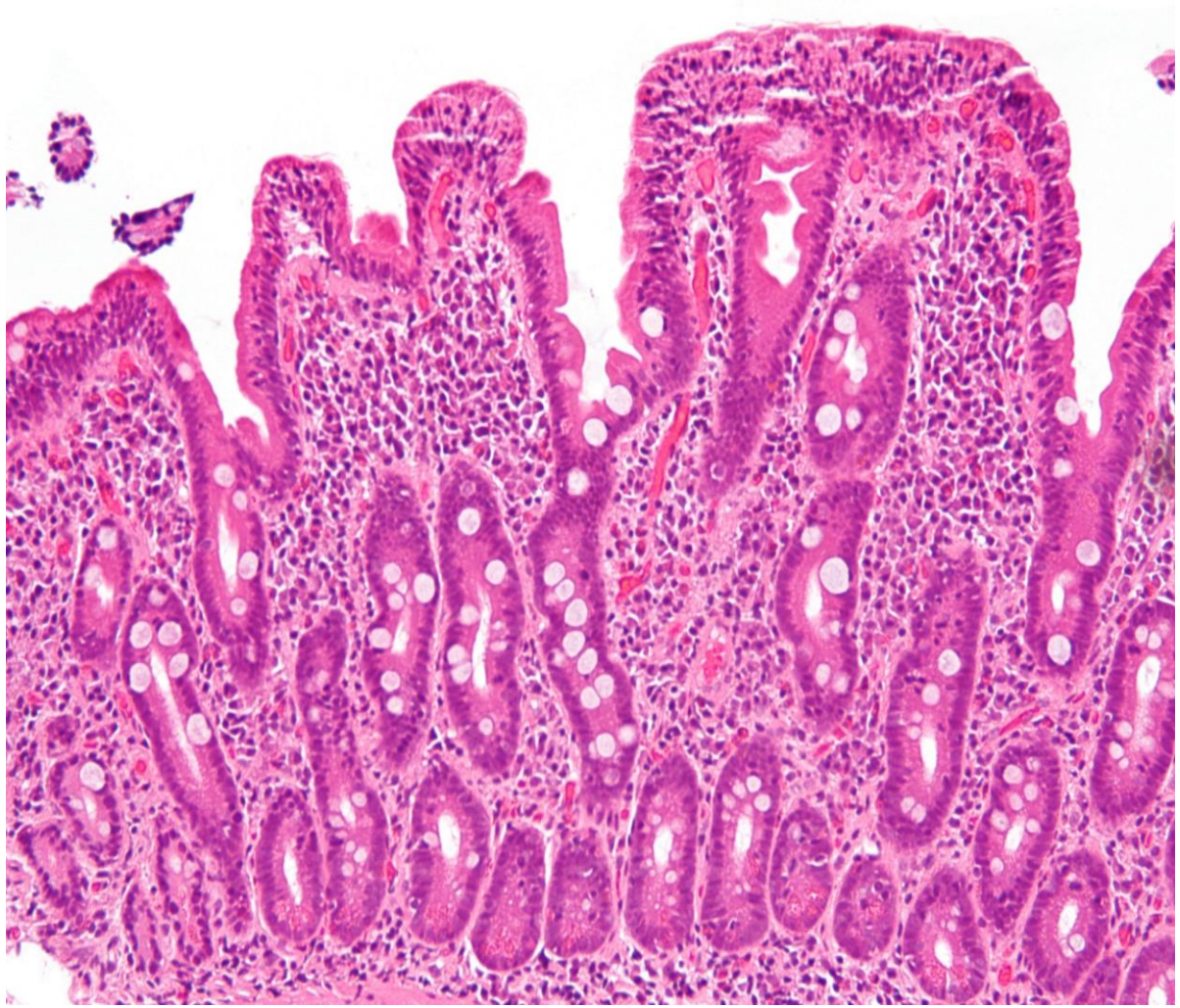
2- Marsh2: Crypt hyperplasia

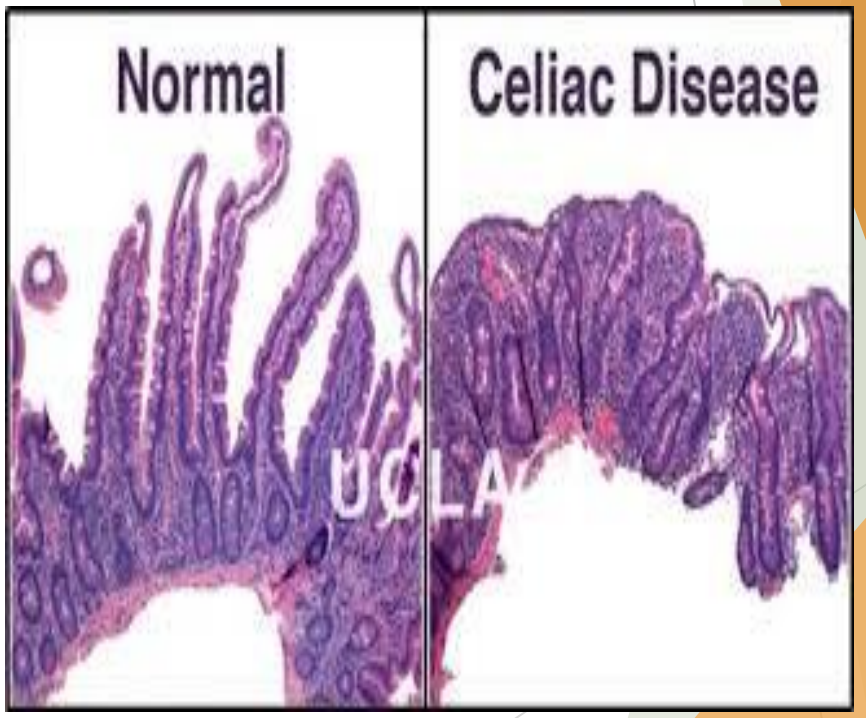
3-Marsh3: Villous atrophy

(partial,3a, subtotal,3b and total,3c)

4-Marsh 4: Crypt hypoplasia

Mucosal changes in CD





The degree of villous atrophy does not necessarily correlate with the severity of clinical symptoms

Management

The main challenges of patient and family after Dx.of CD:

Telling the Dx.of CD is a very bad news

1- The Poor compliance of patients

2-Has significant psychosocial burdens

3-Has significant economic burdens

Management

A strict GFD is recommended for both diagnostic and therapeutic purposes in individuals with a provisional Dx.of CD.

If CD is confirmed, the GFD should be continued lifelong.

The principle sources of gluten are:

wheat ,rye and barley

Is it possible to treat or prevent CD?

Gliadin receptors on intestinal epithelial cells may mediate the transport of gliadin peptides to the lamina propria where T-cell activation occurs.

Identification of the receptors could lead to non-dietary therapies of CD by creating drugs that interfere with receptor function.

With thanks

Non-responders

The majority of CD pat.s respond to GFD.

Those who do not respond , fall in to 4 main groups:

1- Those who are ingesting gluten (the most common cause)

2- Concurrent GI disorders that causing similar symptoms

3- Diseases that mimic clinical and histologic features of CD

4- Refractory CD (very rare in children)

Management

The 6 key elements in the management of pat.s with CD:

1-Consultation with a skilled dietitian

2-Education about the disease

3-Lifelong adherence to GFD

4-Identification and treatment of nutritional def.

5-Access to an advocacy group

6-Continuous long term FU by a multidisciplinary team

Management

Response to GFD:

The rapidity of response to GFD is variable.

Approximately 70% of pat.s have clinical improvement within two weeks.

The Dx. of CD is confirmed if a patient with presumptive Dx. of CD responds to a GFD.

Management

Response to GFD:

A positive response to a GFD is based on the:

1-Symptom resolution

2- Normalization of antibodies

Management

Monitoring on GFD:

1-For all pat.s antibody level should be measured about 6 mo. after beginning a GFD.

2- Test pat.s with recurrent symptoms at any time after starting a GFD.

3- Antibody level is not a reliable predictor of mucosal healing.

Management

Immunizations:

1-HBV vaccine:

Pat.s with CD may not respond to the HBV if administered prior to treatment with GFD.

Therefore, pat.s should undergo serologic screening to determine immune status.

If they are nonimmune , must undergo immunization when they are on GFD.

Management

Immunization:

Pneumococcal vaccines:

Because pat.s with CD may be at increased risk for invasive pneumococcal disease , they must receive the standard pneumococcal vaccination.

Non-responders

The majority of CD pat.s respond to GFD.

Those who do not respond , fall in to 4 main groups:

1- Those who are ingesting gluten (the most common cause)

2- Concurrent GI disorders that causing similar symptoms

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4- Refractory CD (very rare in children)

Management

A GFD must contain < 20 ppm gluten

Dairy products may be avoided ,since many cases with CD have secondary lactose intolerance.

A GFD is low in fiber and may induce constipation.

Daily Ca and vit.D need:

calcium: 1-3 yr: 700mg , 4- 8yr:1000mg, 9-18yr:1300mg

Vit D: with15 microgram(600INU)/day

Management

Second Bx.:

In typical cases there is no need for second Bx.

In pat.s who do not respond to a GFD (not typical) , a second Bx. should be done 9-12 mo. after beginning a GFD to demonstrate mucosal healing.

Management

Gluten rechallenge:

Is reserved for cases in which the initial Dx. of CD is doubtful.

This includes:

1- children already on a GFD without prior any testing for CD.

2- When there is discrepancy between the antibody level and histologic findings.

To perform gluten rechallenge, pat should ingest gluten containing diets (at least 10gm gluten/day) for 4-6 weeks, followed by intestinal Bx.

Management

Monitoring:

1-Ht and Wt (growth indexes)

2-CBC

3-TFT

4-Vit D status (by measuring vit.D level)

Genetic factors

CD occurs in genetically susceptible cases.

More than 99% of individuals with CD have
HLA DR3-DQ2/or DR4-DQ8.

Approximately 40% of general population have these HAL.

CD and overweight and obesity

About 40% of CD cases are overweight/obese at time of Dx.

CD should be considered in children with excessive Wt. gain.

They may have significant Wt. gain after starting GFD.

They need careful FU of nutritional status after Dx. and treatment with GFD.

How to test?

For most cases ,the most valuable test is tTG-IgA, which is recommended as the first screening test.

Sensitivity and specificity of tTG-IgA is: >96%

The sensitivity in younger children is near 90%

Case reports suggest that tTG-IgA may be falsely elevated during a febrile illness.

In IgA deficient cases , tTG-IgG should be performed.

How to test?

EMA:

Is as accurate as tTG-IgA, but is more expensive and operator dependent.

As a result, EMA is used as a second line test.

DGP:

Has good diagnostic accuracy and may be useful in younger children.

How to test?

In pat.s suspected to CD with Nl.IgA and Nl.tTG-IgA (seronegative CD)

2-15% of CD are seronegative.

They need intest.Bx for Dx.

Causes:

1- Low gluten diet ingestion

2- Immun. suppressive drugs

3-Extra- GI manifestation

How to test?

Children < 2yrs:

Concurrent assessment of tTG-IgA and DPG-IgG is recommended.

How to test?

Intestinal Bx.:

pat.s with positive serologic tests, should undergo intestinal Bx.

Multiple Bx.s should be obtained (four from the distal duodenum and at least one from bulb).

Endoscopy and Bx.are also appropriate for pat.s with negative serologic tests if there is a strong suspicion of CD.

Management

A strict GFD is recommended for both diagnostic and therapeutic purposes in individuals with a provisional Dx. of CD.

If CD is confirmed, the GFD should be continued lifelong.

The principle sources of gluten are:

wheat ,rye and barley

Gluten (prolamin) consists of :

1- gliadin , 2- glutenin

How to test?

Pat.s already on a GFD:

1-Serologic testing for tTG-IgA /EMA → if positive → Bx.

2- If Nl, testing for HLA-DQ2/DQ8:

1- If negative → CD excluded

2-If positive → gluten challenge

Pat.should be tested for tTG-IgA when symptoms recur or after 6 mo. on gluten if remains asymptomatic.