Doença Celíaca

Nutrição e Imunogenética

Helena Alves

UPSPDNT
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Doença Celíaca

- Considerada a doença mais subdiagnosticada nos EUA.
- Afecta ~1/100 pessoas., Só nos EUA há mais de 1 milhão de pessoas com D. Celíaca
- Os doentes têm sintomas durante anos sem serem diagnosticados, demorando em média 8 anos até ao diagnóstico.
- Os doentes não diagnosticados estão predispostos para osteoporose, têm anemia e desconforto gastrointestinal crónico, com atraso de desenvolvimentop e de aprendizagem nas crianças e cancros linfáticos.
- Chamada “enteropatia sensível ao glúten”.
- Ocorre como consequência de ingestão de grão que contém glúten tal como o trigo, cevada, centeio, aveia, kamut, espelta, bulgur.

Pathogenesis:

1. A component of gluten, **gliaden, interacts** with a specific genetic form of **HLA** receptor on an **antigen presenting cell.**

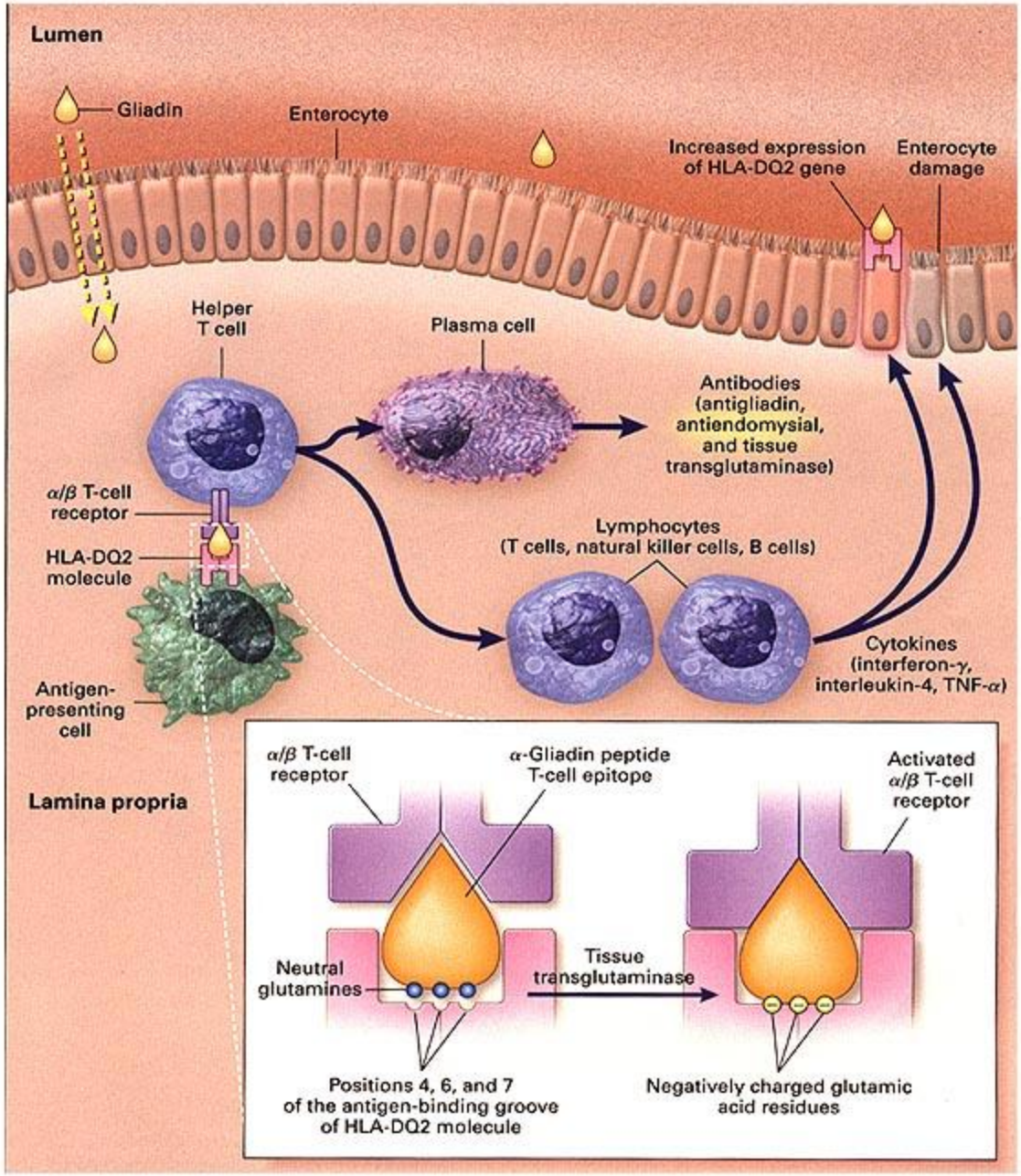
2. **Tissue transglutaminase** converts **glutamine residues to glutamic acid residues** making an even more potent antigen.

3. **T helper cells are activated** and, in turn, **activate B and killer T cells**.

4. Plasma cell **antibodies bind to gliadin bound to enterocytes**, **tissue transglutaminase and reticular fibers** surrounding gut smooth muscle (**endomysial ab's**).

5**. T cells release** (inappropriate) **inflammatory cytokines** as well as inflict **tissue damage**.

Source:NEJM 346:180, 2002



Celiac disease (CD)

- It is an **immune-mediated disease of the intestines** that is triggered by the ingestion of **gluten in genetically susceptible** individuals. Gluten is the major protein component of wheat, rye, and barley.

- **Inflammation** resulting from **immune system overactivity** may cause a wide variety of signs and symptoms involving many parts of the body.

- Celiac disease **can develop at any age**

- The classic symptoms result from **inflammation affecting the gastrointestinal tract**, that damages the villi, reducing the surface area to absorb nutrients.

- **The villi become shortened** and eventually flatten out.
- Intestinal damage **causes diarrhea and poor absorption of nutrients**, which may lead to we**ight loss.**
- **Abdominal pain, swelling (distention), and food intolerances** are common.

- Inflammation may lead to **an increased risk** of developing certain **gastrointestinal cancers** such as cancers of **the small intestine or esophagus.**
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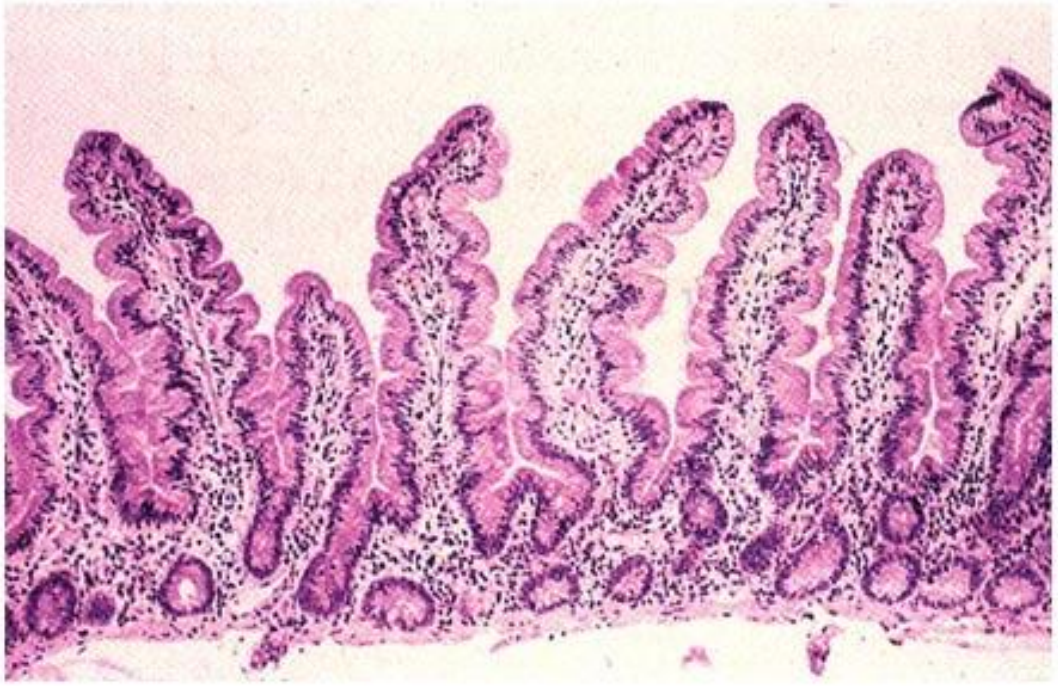
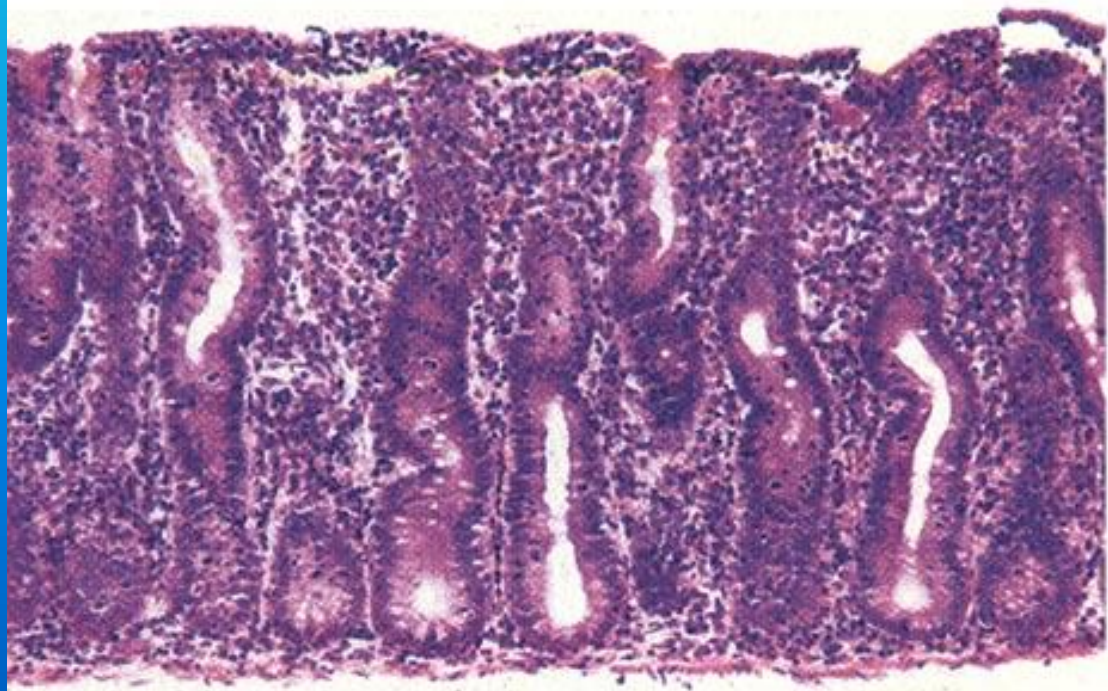
Normal intestinal biopsy



<u>Small</u> intestinal biopsy in a patient with active celiac disease



Source:NEJM

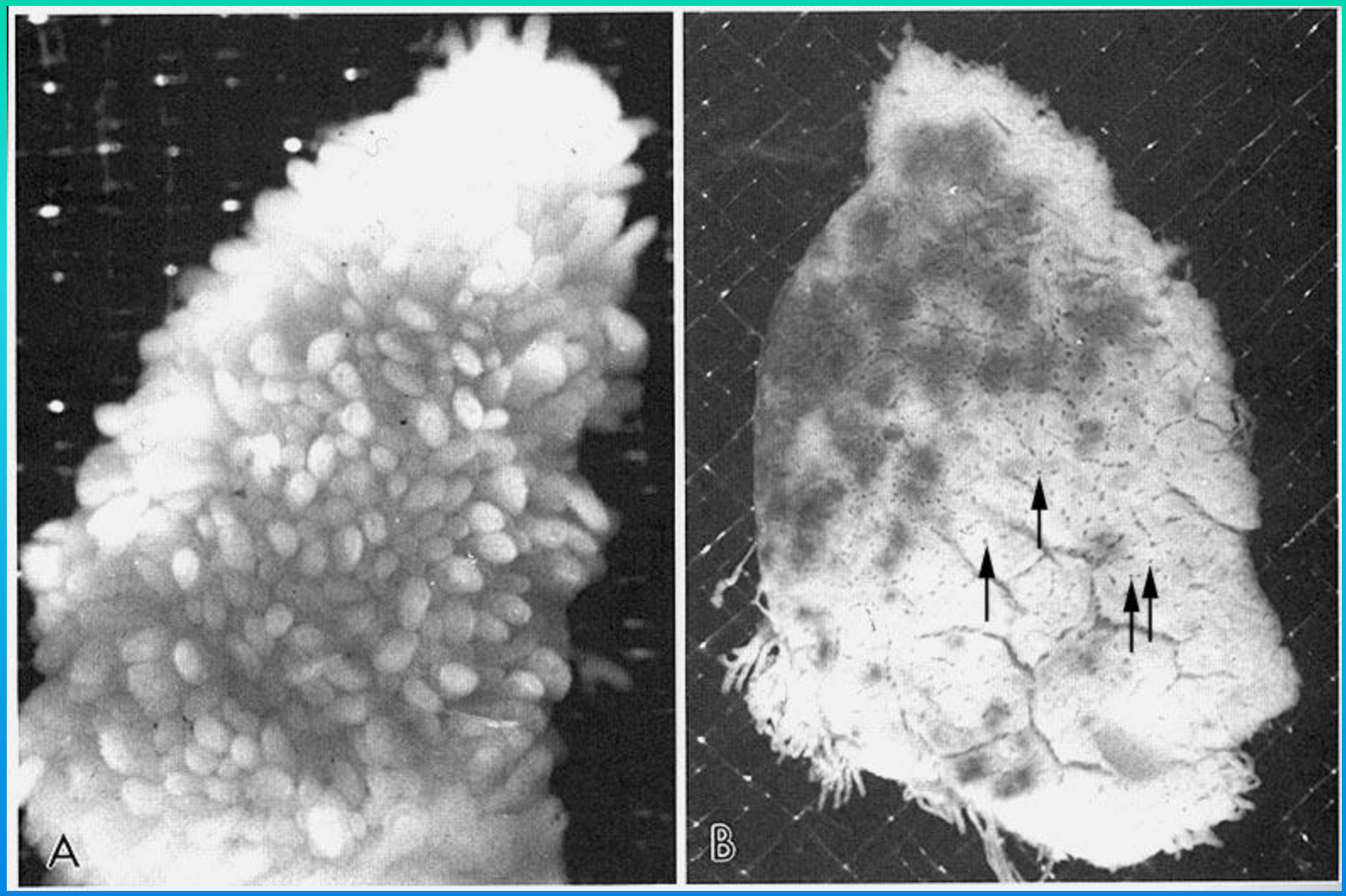
Celiac disease (CD)

- **Iron deficiency** (**anemia)**, **vitamin deficiencies, osteoporosis, dermatitis herpetiformis, defects in the enamel of the teeth, chronic fatigue, joint pain, poor growth, delayed puberty, infertility, or repeated miscarriages.**

- **Neurological problems** have also been associated with celiac disease; these **include migraine headaches, depression, attention deficit hyperactivity disorder (ADHD), and recurrent seizures (epilepsy)**.

- Many people with celiac disease have one or more of these varied health problems but do not have gastrointestinal symptoms. This form of the condition is called **nonclassic celiac disease.**

- Researchers now believe that **nonclassic celiac disease is actually more common than the classic form.**



Normal intestinal surgical specimen with distinct villi

Celiac disease specimen with total loss of villi, the arrows indicate crypt openings

Source: Pathology of the Gastrointestinal Tract, 2nd Ed., 1998, Ed. by Ming and Goldman

Genetic predisposition to CD

- **Genetic predisposition** plays a key role in CD and considerable progress has been made recently in identifying genes that are responsible for CD predisposition.
- **CD is strongly associated with specific HLA class II genes *HLA-DQ2* and *HLA-DQ8* located on chromosome 6p21**.
- **Approximately 95% of CD patients express *HLA-DQ2*, and the remaining patients are usually *HLA-DQ8* positive**.
- The ***HLA-DQ2* allele is common and is carried by approximately 30%** of Caucasian individuals.
- Thus, ***HLA-DQ2* or *HLA-DQ8* is necessary for disease development but is not sufficient for disease development**;
- Its **estimated risk effect** is only **36-53%.**

Celiac disease risk loci

- Trynka et al comprehensively surveyed the genetic architecture of all known risk loci previously associated with immune-mediated diseases **in 12,041 patients with celiac disease and 12,228 controls. They identified 13 new celiac disease risk loci reaching genome-wide significance, some being present in single genes or regulatory genes.** Even if each of the identified genes have little "weight" in defining a celiac disease genetic trait, they add to the growing pieces (now approximately **40 genes**) of the celiac disease genetic puzzle.[3]

- Guidelines for CD diagnosis from the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) propose the option **to omit the duodenal biopsy in the diagnosis of CD if all 4 of the following criteria are met in children and adolescents**[4, 5, 6, 7] :

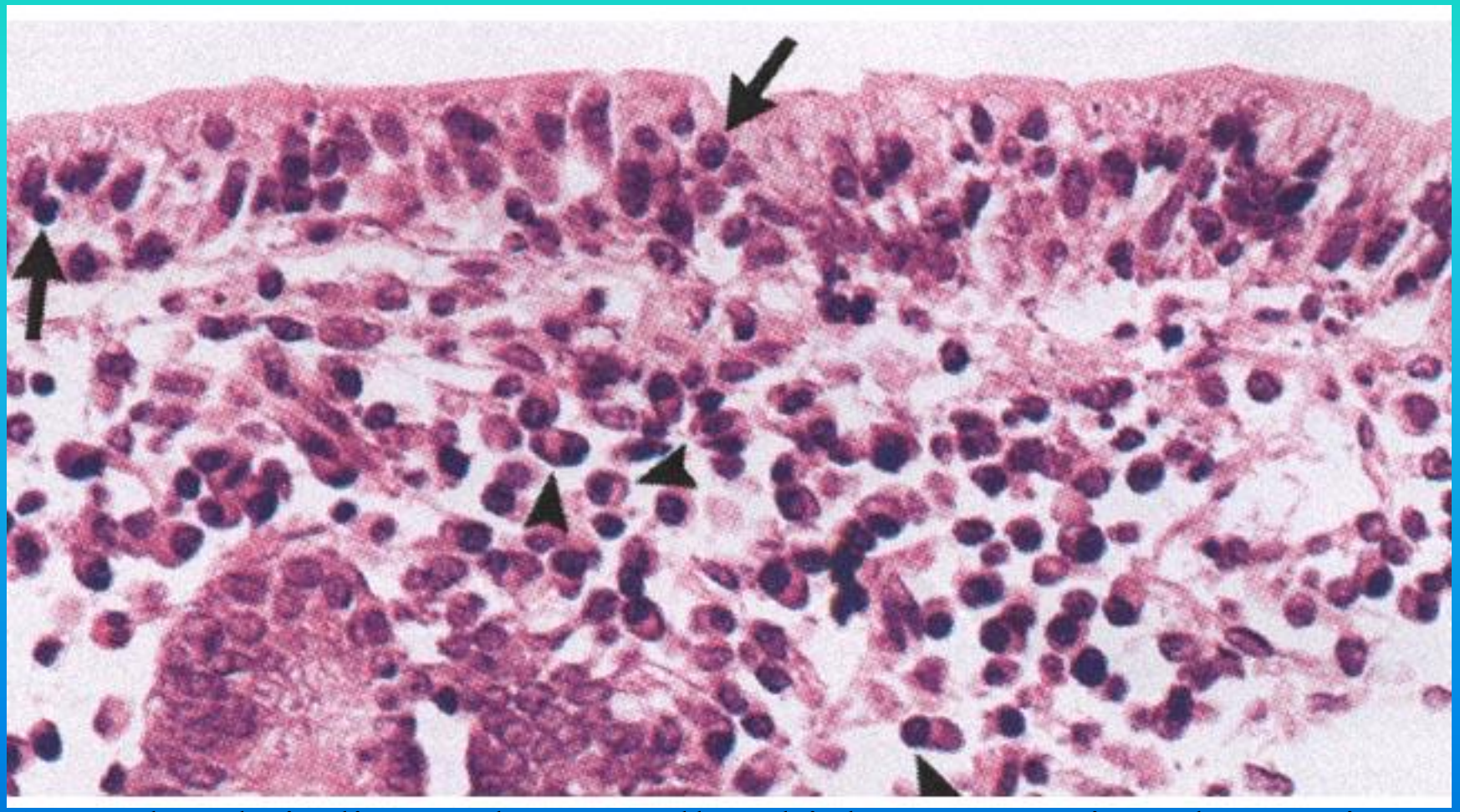
- Ref - emedicine.medscape.com/article/1790189-overview

To omit the duodenal biopsy in the diagnosis of CD if all 4 of the following criteria are met in children and adolescents:

- **Signs and symptoms** suggestive **of CD**
- **Anti-transglutaminase type 2** antibody **(anti-TG2)** levels more than **10 times** the upper limit of normal
- **Positive confirmation** tests of **anti-endomysium-IgA antibodies (EMA)**
- At-risk **HLA-DQ2** or **HLA-DQ8**

Ref - emedicine.medscape.com/article/1790189-overview

Arrows indicate intraepithelial lymphocytes which, in this disease, are destructive.



Arrowheads indicate plasma cells which are secreting ab's against gliaden bound to enterocytes as well against reticulin and tissue transglutaminase resulting in tissue destruction. Source:NEJM

HLA-DQ2 and DQ8 alleles

- About **95%** of people with celiac disease have the **HLA-DQ2** allele and most of the remaining **5%** have **the HLA-DQ8 allele.**
- **Having the alleles means you are *at risk* for developing celiac disease, but does *not* mean that you *definitely have* the disease.**
- A positive genetic test should be followed up with a celiac blood panel to determine if you have celiac disease.
- If genetic test has a negative result, you can virtually rule out celiac disease.

Haplotypes
HLA DR3–DQ2 or HLA DR4–DQ8

- The presence of **HLA haplotype DR3–DQ2 or DR4–DQ8** is associated with an **increased risk of celiac disease.**

- In addition, nearly all children with celiac disease have serum **antibodies against tissue transglutaminase (tTG).**

- **Children with the HLA haplotype DR3–DQ2, especially homozygotes,** were found to be at **high risk** for celiac disease **early in childhood**.

- **The higher risk in Sweden** than in other countries highlights the importance of studying **environmental factors associated with celiac disease.**

Others autoimmune diseases

- Having an autoimmune disorder makes you more likely to develop other autoimmune diseases, like celiac disease.

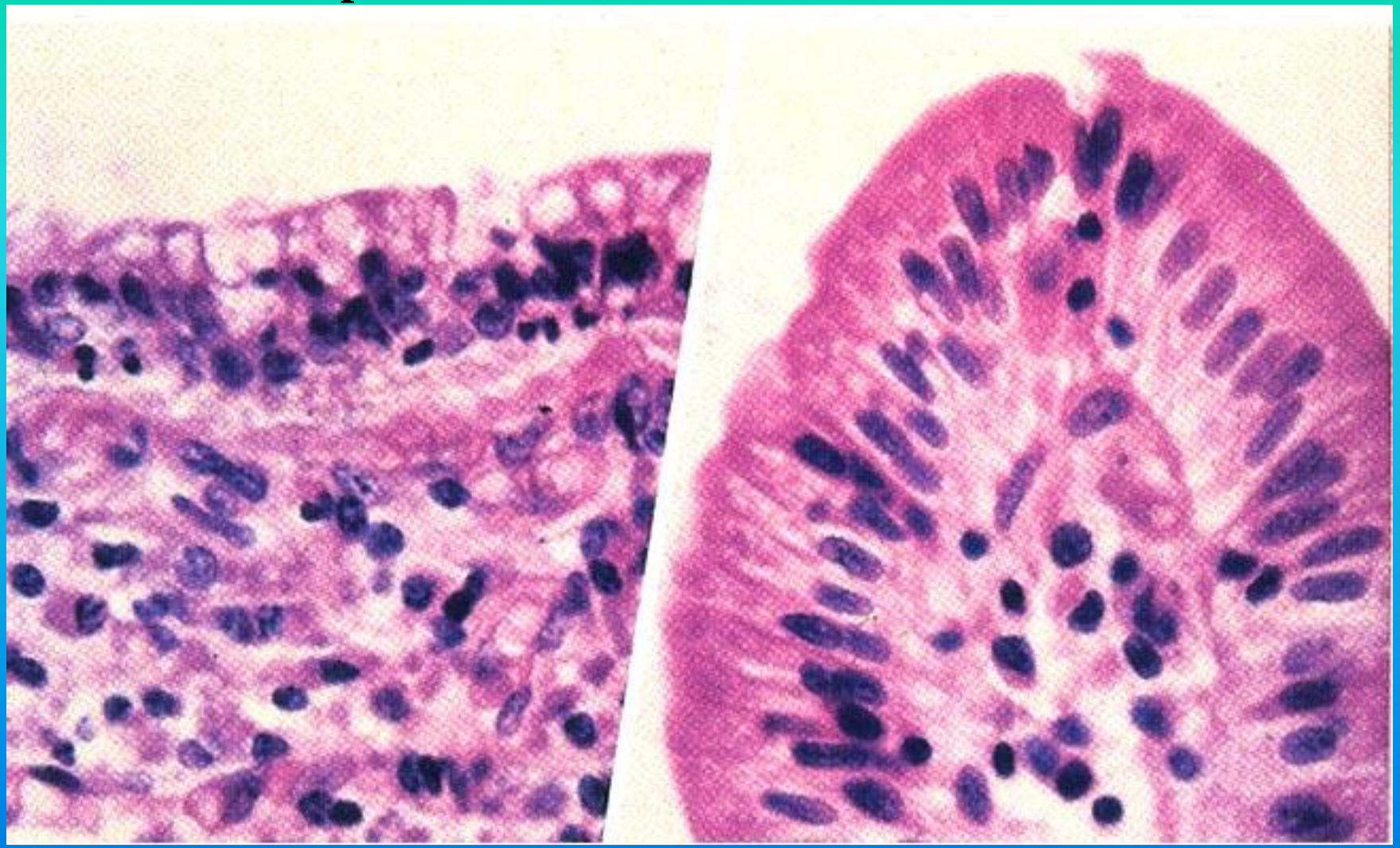
- Thyroid disease, Type 1 diabetes mellitus, primary biliary cirrhosis, etc...

Treatment

- There is only one treatment, **strict adherence to a gluten-free diet.**
- **Gluten-free foods** are **limited**, and frequently **unavailable**.
- Gluten-free foods **cost 2-3X** that of normal foods.
- Unfortunately, **purchase** of gluten-free products is **rarely covered by health insurance.**
- The good news is that strict adherence to a gluten-free diet can have an extraordinary outcome as seen on the next slide.
- Source:www.glutin.net

When the patient adheres to a strict gluten-free diet, the damaged intestinal mucosa (often but not always) completely regenerates including reformation of normal villi. This is a normal biopsy; see screen 11 for a complete biopsy series. Source:NEJM

Sprue **Normal**



As the damage recedes, the ragged, lymphocyte infiltrated-enterocytes are replaced by normal columnar ones, thus assuring normal transport from the lumen into the body.

Source:NEJM

Alimentos sem glúten

- Arroz e milho
- Quinoa
- Millet (panicum miliaceum)
- Amaranto (Amaranthus hypochondriacus)
- Trigo sarraceno (Fagopyrum esculentum)
- Sorgo (Sorghum)
- Flocos de batata, tapioca, farinha de amêndoa, avelã, noz, ... (só precisa de triturar os frutos ao natural)

Shared immunological mechanisms in several immune-related disorders

- **Newly identified genetic risk variants for celiac disease related to the immune response**
  Nature Genetics **40**, 395 - 402 (2008)

  – **Type 1 diabete**s and celiac **disease share *HLA-DQ*, *IL2–IL21*, *CCR3* and*SH2B3* risk regions. Thus, this extensive genome-wide association follow-up study has identified additional celiac disease risk variants in relevant biological pathways.**

- **Detecting shared pathogenesis from the shared genetics of immune-related diseases**
  Nature Reviews Genetics **10**, 43-55 (January 2009) |

  – Recent genetic studies have revealed **shared immunological mechanisms in several immune-related disorders**

HLA DQ

- HLA class II region

  (**either** **DQ2** [DQA*0501-DQB*0201]

  or **DQ8** [DQA*0301-DQB1*0302])

  confer a large part of the genetic susceptibility to celiac disease.

- Celiac disease originates as a result of a combined action involving both adaptive and innate immunity.

- **Anti-endomysium-IgA antibodies (EMA)**
- **Teste de imunofluorescência com esófago de macaco**

- Anti-transglutaminase type 2 antibody **(anti-TG2)**
- Teste ELISA

Spectrum of gluten-related disorders: consensus on new nomenclature and classification

Sapone et al. BMC Medicine 2012, 10:13

- The toxic protein fractions of gluten include **gliadins and glutenins**, with gliadins containing monomeric proteins and glutenins containing aggregated proteins

- **3 main forms of gluten reactions**:
  - allergic (wheat allergy),
  - autoimmune (celiac disease, dermatitis herpetiformis and gluten ataxia) and
  - possibly immune-mediated (gluten sensitivity)

- **Mediated by the adaptive immune system**: **wheat allergy (WA) and celiac disease (CD).**
- In both conditions the reaction to gluten is mediated by T-cell activation in the gastrointestinal mucosa.
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- However, **in WA it is the cross-linking of immunoglobulin (Ig)E** by repeat sequences in gluten peptides (for example, serine-glutamine-glutamine -glutamine-(glutamine-)proline-proline-phenylalanine**) that triggers the release of chemical mediators, such as histamine, from basophils and mast cells [1].**
- In contrast, **CD is an autoimmune disorder**, as demonstrated by **specific serologic autoantibodies, most notably serum anti-tissue transglutaminase (tTG) and anti-endomysial antibodies (EMA).**

Spectrum of gluten-related disorders: consensus on new nomenclature and classification

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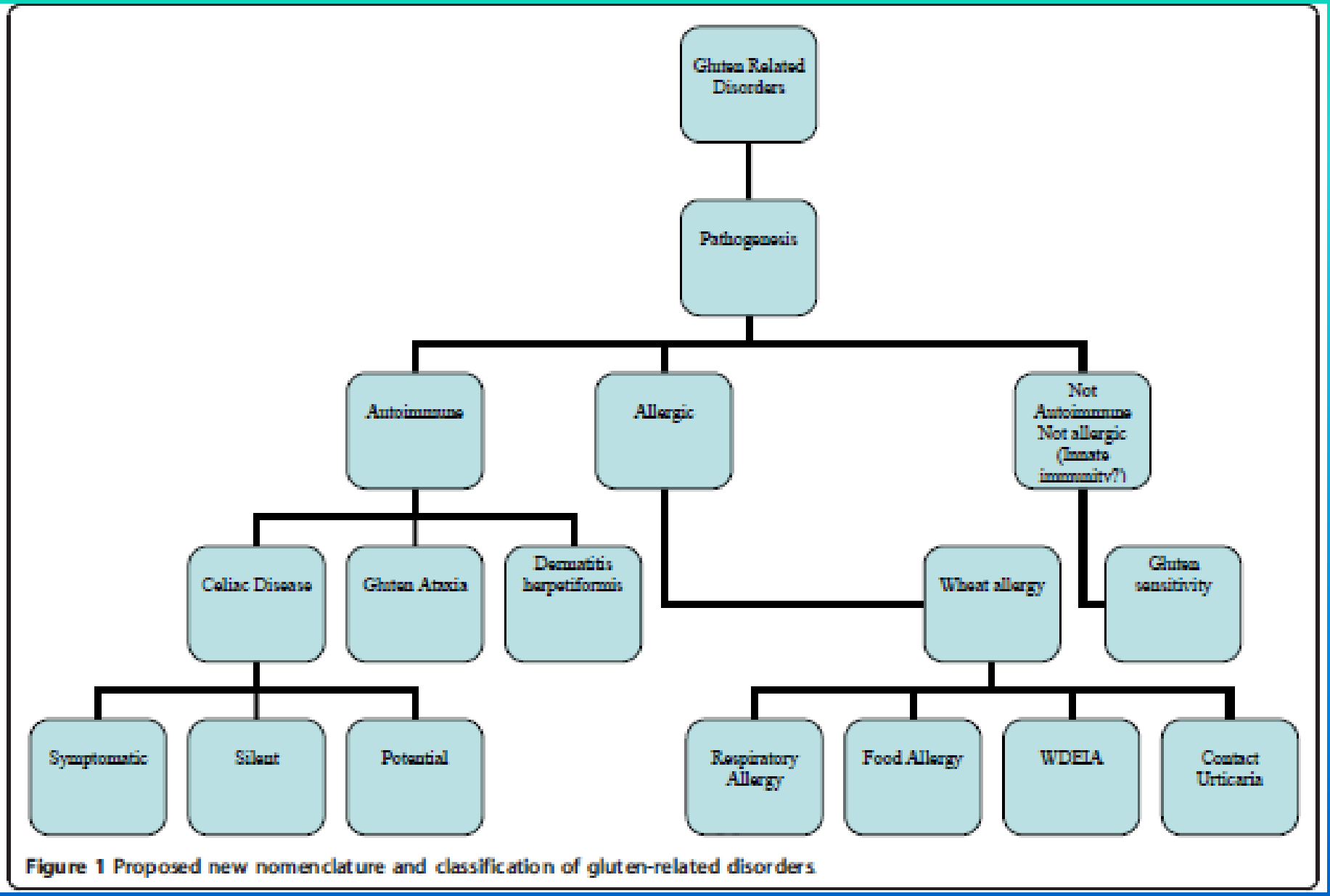

Figure 1 Proposed new nomenclature and classification of gluten-related disorders.