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CELIAC DISEASE IS NO LONGER A CHALLENGE: DEVELOPMENT FROM DIAGNOSIS FOR A BETTER QUALITY OF LIFE

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RESUME

Celiac disease (CD) is a dysimmune disease causing intestinal inflammation caused by the ingestion of gluten, in predisposed patients. Its prevalence is nearly 1% in France,[1] but it is underdiagnosed, given the multifaceted nature of its clinical manifestations. The diagnosis is easily accessible by serology and biopsies, and the treatment consists only of a strict elimination of gluten for life. It can be associated with digestive and extra-digestive complications as well as an alteration of the quality of life. The objective of our article is to make a point on the pathology in the light of the new recommendations to make its management more easy and to improve the quality of life of patients.

Definitions

According to the Oslo 2013 definitions[2]

- Symptomatic CD: classic or non-classic, depending on the presence or absence of signs of malabsorption.
- Subclinical CD: includes patients with celiac disease below the clinical detection threshold.
- Asymptomatic CD: describes the situation of an individual without symptoms of CD, but with the presence of antibodies associated with CD and histological evidence of CD on intestinal biopsy.
- Potential CD: this term applies to subjects without signs or symptoms of CD, but who have antibodies associated with CD, without histological lesions on the intestinal biopsy.
- Refractory CD: describes an individual with definite CD who continues to have signs or symptoms of active CD, despite continued GLI.

Epidemiology

The prevalence in the United States and Europe is approximately 3 to 13 cases per 1000 people.[3] There is a female predominance with a ratio of approximately 2/1.[3] Recent screening studies suggest that in developing countries of Africa, Asia and South America, the frequency is similar to that of the United States and European countries.[4]

Pathophysiology:[5]

Gluten is only toxic in genetically predisposed subjects. The toxic peptide sequences of gliadin are relatively resistant to digestive enzymatic capacities and can come into contact with the intestinal mucosa intact. These fragments are then absorbed by the epithelium and arrive in the chorion in contact with the tissue transglutaminase of which they are substrates due to their richness in glutamine. Transglutaminase converts positively charged glutamines into negatively charged glutamic acid residues by deamidation. This then allows their binding to the positively charged peptide pockets of the HLA DQ2 or DQ8 molecules which are located on the surface of antigen-presenting cells. These deamidated peptides are recognized by intestinal CD4+ T lymphocytes which then produce cytokines such as interferon, IL 4 and TNF, responsible for inflammatory lesions and villous atrophy.[5]

In summary: the different stages of the pathophysiological mechanism of the disease

- crossing of the epithelial barrier by gliadin
- formation of the gliadin-transglutaminase complex in the lamina propria: deamination of gliadin and increase in its immunogenicity
- formation of the gliadin-transglutaminase-HLA II complex and presentation by macrophages to CD4+ T cells
- activation of CD4+ T cells
- activation of immunoglobulin A plasma cells in the mucosa: formation of anti-endomysium antibodies and secretion of cytokines (including interleukins IL 8)
- IL 8 activation of macrophages that synthesize metalloproteins
- destructuring of the extra-cellular matrix by metalloproteins: crypt hypertrophy

Positive diagnosis

What are the indications for celiac disease?[6]

Digestive signs	Extra-digestive signs	Specific situations
Chronic or intermittent diarrhea Chronic constipation resistant to usual treatment Chronic abdominal pain Abdominal distention	Weight loss, delay in weight and/or stature growth Puberty delay, amenorrhea, chronic fatigue, Neuropathy Arthritis, arthralgia, Chronic iron deficiency anemia, Bone demineralization (osteopenia, osteoporosis), Repeated fractures Recurrent ulcers, stomatitis, Dermatitis herpetiformis (type rash) Lesions of tooth enamel, Abnormal liver function tests	Celiac disease in first-degree relatives Autoimmune disease: type 1 diabetes, thyroiditis, liver disease Trisomy 21, Turner syndrome Williams syndrome Ig A deficiency

What serological tests and what is the diagnostic procedure?[1]

- If the IgA ATG are ≥ 10 times the upper limit of normal (ULN), and a 2nd sample shows positive anti-endomysial IgA (EMA), the diagnosis of celiac disease can be confirmed without performing biopsies.
- If the IgA ATG are positive at a rate lower than 10 times ULN, an upper digestive endoscopy with digestive biopsies should be performed.
- In case of low concentration, a serological assay of IgG (IgG anti deaminated peptide of gliadin or EMA or ATG) will be done in 2nd intention. If one of these first tests is positive, it is recommended to perform an upper digestive endoscopy with biopsies.
- In the event of latent celiac disease (ATG + and HLA + but normal biopsies), a trial of a gluten-free diet can be proposed in agreement with the family in the event of symptoms related to gluten consumption. In the case of a normal diet, annual follow-up is necessary with evaluation of nutritional, bone and growth status. An upper digestive endoscopy is performed in the event of an increase in the elevation of ATG or the appearance of symptoms.
- See Figure 1.

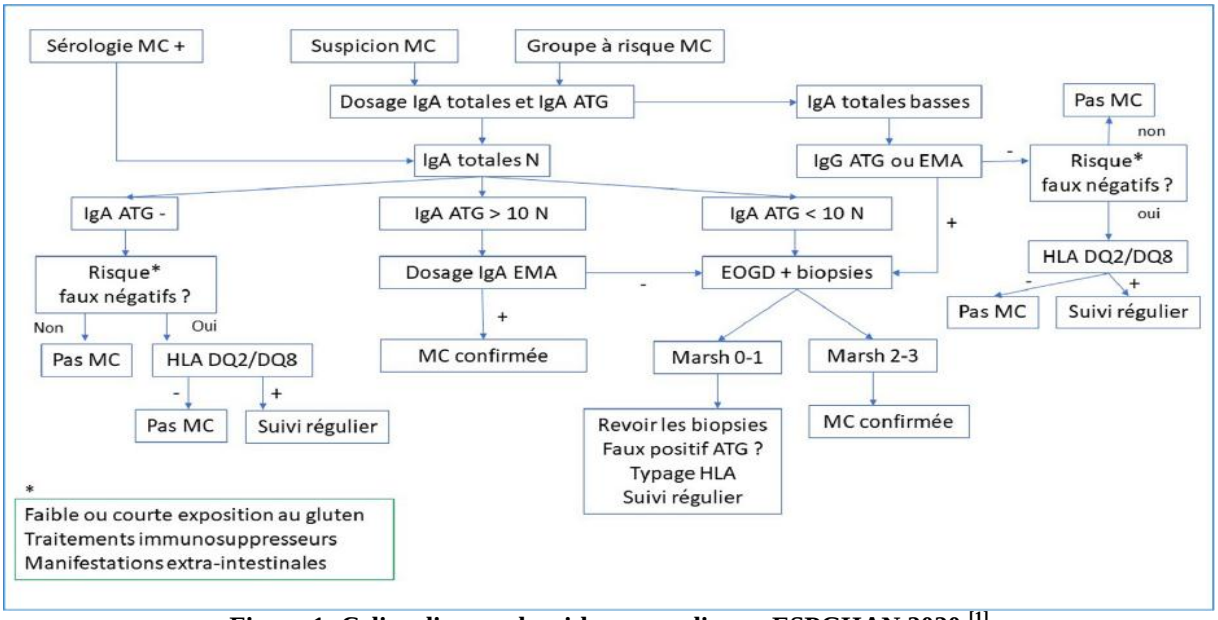


Figure 1: Celiac disease algorithm according to ESPGHAN 2020.[1]

Endoscopy for whom?[1]

- If IgA ATG ≥ 10 N: No interest of FOGD.
- If IgA ATG ≥ 10 N with IgA EMA Negative: FOGD with biopsy is indicated.
- If no clinical or biological improvement: FOGD with biopsy is indicated.
- If doubt about complication: FOGD with biopsy is indicated.

How to perform duodenal biopsies for diagnosis?[7]

It is recommended to perform at least four duodenal biopsies, and at least one bulbar biopsy because of the existence of "ultra-short celiac disease" limited to the bulb.

Histology and MC[7]

What are the histological signs suggestive of celiac disease?

- Villous atrophy (partial total or subtotal).
- Epithelial alterations:
- Increase in epithelial lymphocytes (LEI) > 25 per 100 epithelial cells.
- Cryptic hyperplasia.
- Lamina propria hypercellularity.
- The subepithelial basement membrane may be thickened.

What classification is used in histology for MC?[7]

Marsh I: Intraepithelial lymphocytosis

Marsh II: Intraepithelial lymphocytosis with crypt hyperplasia

Marsh III: A: partial villous atrophy

B: subtotal villous atrophy

C: total villous atrophy

Histological false positives and false negatives?[8]

False Negatives: possible if the patient was already on a gluten-free diet.

Faux positifs:
Maladie de Crhon

Malnutrition

Entéropathies infectieuses: Giardia

Sprue tropicale

Cryptosporidiose intestinale

Coccidiose /Schistosomiase /Stongyloidose /Microsporidiose.

Déficit en IgA / immunodéficience

Entéropathie allergique au lait / lait de soja

Entéropathie auto-immune

Syndrome de Zollinger-Elisson

Histological false positives and false negatives?[8]

HLA DQ2-DQ8 typing has an excellent NPV (> 99%): it has an interest in excluding CD, in four situations:

1) in patients already on a gluten-free diet (RSG), in whom serological abnormalities and villous atrophy can be corrected, and who do not wish perform a gluten reintroduction test

2) when the diagnosis of CD is uncertain (serology negative but compatible histology);

3) distinguish between brothers and sisters in whom the development of CD is unlikely of those to be monitored;

4) in patients with other autoimmune diseases or genetic predispositions that must be screened for the MC.

The iceberg of clinical forms of gluten intolerance.
What is the assessment to be made once the diagnosis of CD is retained??[8]

- A blood count (NFS);
- A dosage of serum iron and ferritin: frequent anemia, it can be the only symptom of a silent disease;
- Folate dosage: frequent deficiency;
- A dosage of vitamins B12: frequent deficiency;
- The dosage of prothrombin: it decreases with conservation of factor V, due to malabsorption of vitamin K
- A liver test: frequent increase in transaminases;
- A determination of serum calcium, magnesium and vitamin D, and
- A bone densitometry for the evaluation of osteopenia;
- A weight assay of immunoglobulins: strong decrease in immunoglobulins M and increase in immunoglobulins A
- A dosage of proteins and albumin: hypoproteidemia and hypoalbuminemia are responsible for edema.

What support ?

Gluten-free diet [9]

- For life
- Eliminate all cereals containing gluten (wheat, rye, barley, spelled, Kamut, etc.)
- Possibility of taking: Corn, Rice, soybeans, potatoes.
- Current recommendations allow oats

Therapeutic education (EDT)[10]

Increase TDS on disease progression, gluten-free products, and follow-up to improve adherence and establish healthy diets to reduce increased risk of morbidity and mortality.

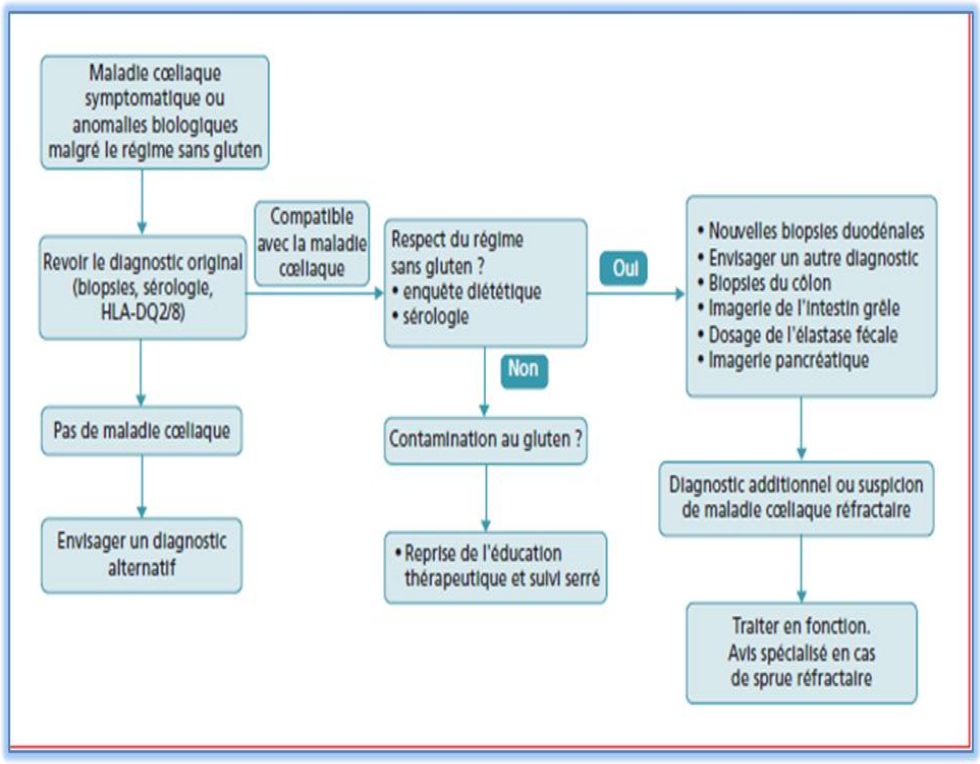
Quality of Life [10]

In addition to the duration of the RSG, the factors significantly associated with a better QoL are: age at diagnosis, socio-professional category, frequency of follow-up, good observance of the RSG, and liking products without gluten.

Therapeutic perspectives [11], [12]

- Bacterial prolyl-endo peptidases
- Inhibition of intestinal tTG
- Anti-inflammatory cytokines
- Genetically modified wheat

What should be done in case of clinical or biological non-response?[8]



CD follow-up

How to follow up in a celiac patient?[8]

At the time of diagnosis	− Gastrological consultation as well as a dietician doctor. − Dietary advice by a qualified dietitian. − Physical examination including BMI. − Therapeutic education on MC. − Recommend family screening (DQ2/D8 and celiac serology). − Routine tests (complete blood count, iron status, folate, vitamin B12, thyroid function tests, liver enzymes, calcium, phosphate, vitamin D) − Bone densitometry at diagnosis
2nd consultation at 3-4 months	− Assess symptoms and coping skills − Diet review − Celiac serology (IgA-ATG)
3rd consultation at 6 months	− Assess symptoms − Diet review − Celiac serology − Repeat routine tests (if previously abnormal)
4th consultation at 12 months	− Gastrological and dietary consultation. − Evaluate symptoms and physical examination (if indicated) − Diet review − Celiac serology − Repeat routine tests − Small bowel biopsy (not routinely recommended)
5th consultation at 24 months	− Assess symptoms − Consider a dietary review − Celiac serology − Thyroid function tests − Other tests as clinically indicated
6th consultation at 36 months	− Medical consultation every 1 to 2 years. − Bone densitometry (if previously abnormal) − Assess symptoms − Consider a dietary review − Celiac serology − Thyroid function tests − Other tests as clinically indicated

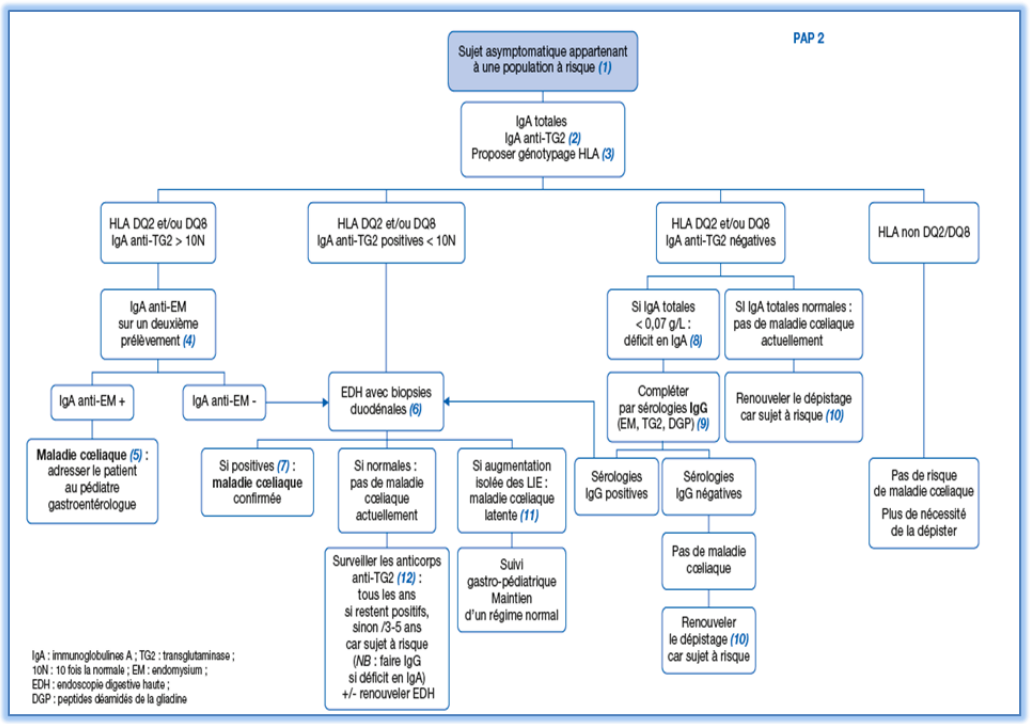
Special Situations[13,14]

In the event of negative serology in a patient belonging to a population at risk and having HLA DQ2 and/or DQ8 genotyping, the dosage of anti-TG2 IgA must be repeated every 3 to 5 years in the event of a family history of disease celiac, and more frequently (annual screening proposal) in the event of type I diabetes, other autoimmune diseases or genetic pathology at risk.

In an asymptomatic subject belonging to a population at risk, the association of positive anti-TG2 IgA with an isolated increase in intraepithelial lymphocytes (without villous atrophy) establishes the diagnosis of latent celiac disease. In this case, the patient can be left on the normal diet but should be monitored regularly. Depending on the evolution of the antibody level, endoscopic reassessments are then desirable in order to look for the evolution towards silent or symptomatic celiac disease (development of villous atrophy +/- associated with clinical signs).

In the case of normal biopsies, the anti-TG2 IgA (or IgG in the event of a deficiency) must be checked every year if they are positive or every 3 to 5 years if they are negative since we are talking about subjects at risk. The performance of an upper digestive endoscopy control will be decided according to the evolution of the level of antibodies: if they remain high, a control at 1 year seems desirable.

Screening[15]



CONCLUSION

Celiac disease is the result of digestive hypersensitivity with an inappropriate mucosal immune response to gluten proteins, occurring in genetically predisposed subjects. The gluten-free diet is the only treatment currently recommended. Regular monitoring is of paramount importance. With the new recommendations, diagnostic and therapeutic management becomes more codified for the clinician but also for the patient.

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