

## PRESENT INTERESTS IN THE CELIAC DISEASE. CLINICAL AND LABORATORY ASPECTS

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**Abstract:** Celiac disease is a consequence of gluten hypersensitivity translated into subtotal or total villous atrophy. The classic clinic symptoms correspond to the chronic diarrhoea syndrome (steatorea), but there are also cases with nonspecific symptoms ("constitutional ones", mono-symptomatic celiac disease). The serologic tests have as their purpose the determination of antigliadina, antiendomysial and anti-transglutaminase antibodies. The final diagnosis is established by intestinal biopsy.

**Keywords:** Celiac disease, serologic tests, intestinal biopsy.

**Rezumat:** Boala celiacă este consecința unei hipersensibilități digestive la gluten tradusă prin atrofie vilozitară totală sau subtotală. Simptomatologia clinică clasică corespunde sindromului diareic de tip steatoreic, dar există și cazuri cu manifestări nespecifice ("constituționale", boală celiacă monosimptomatică). Testele serologice vizează determinarea anticorpilor antigliadină, antiendomysium și antitransglutaminază. Diagnosticul de certitudine este stabilit de biopsia intestinală.

**Cuvinte cheie:** boală celiacă, teste serologice, biopsie intestinală.

Celiac disease is a consequence of gluten digestive hypersensitivity linked to an anomaly of cellular immunity and which occurs in genetically predisposed subjects. Hypersensitivity is translated into subtotal or total villous atrophy of the small intestine mucosa which becomes normal after gluten exclusion from food and villous atrophy reappearance after the reinsertion of gluten (the relapse test). After years of gluten exclusion, the relapse is the witness of the permanent character of the intestinal mucosa sensibility to gluten, differentiating the celiac disease from food intolerance.

Although the "classic" celiac disease is commonly described, recent data show that the majority of the patients present "atypical" forms, identified as a result of investigating a sideropenic anemia, osteoporosis, stature deficit or infertility or "silent" forms to the asymptomatic patients through serological screening or endoscopy made for investigating other affection.

Other authors describe a latent form of the celiac disease characterized by a previous diagnosis, with favourable response to the gluten-free diet and presenting normal mucosa from the histological point of view after the reinsertion of gluten in food.

From the **symptomathology** point of view, the patients with celiac disease are classified as follows:

- Patients with classic celiac disease which starts 8-24 months after the gluten insertion in food, who present a characteristic aspect with reduced subcutaneous cellular tissue, voluminous abdomen, gracile limbs, diarrhoeic syndrome of steatorea type with numerous voluminous stools, presence in stools of undigested food, sometimes aqueous diarrhoea after milk drinking (by the existence of the secondary deficit of lactase), deficiency syndrome characterised by somatic development deficit, anemia, rickets, hemorrhagic manifestation;
- Patients with "constitutional" manifestations or unspecific gastrointestinal symptoms with alternation between the relative health and disease intervals manifested by chronic diarrhoea, anemia, unsatisfactory stature and weight, psychical disorders;
- Patients with monosymptomatic celiac disease where clinical and biochemical manifestations could be seen, such as: delayed menarche, bones pain, paraesthesia, premature osteoporosis in young women, axonic degeneration partially reversible after the gluten exclusion from food;
- Patients presenting diseases associated with the celiac disease;
- Endocrine diseases: diabetes mellitus type I, hyperthyroidism, Addison disease;
- Haematological and immunological diseases: IgA selective deficit, immune thrombocytopenic purpura, self immune hemolytic anemia;
- Pulmonary diseases: cryptogenic pulmonary fibrosis;
- Cardiac diseases: idiopathic recurrent pericarditis;
- Renal diseases: IgA primary mesangial nephropathy;
- Digestive diseases: exocrine pancreatic insufficiency, intestinal chronic inflammatory disease, chronic hepatitis, intolerance to the milk cow proteins;
- Psychical neuromuscular diseases: cerebral ataxia, peripheral neuropathy, myopia, epilepsy, schizophrenia;
- Neoplastic diseases: malign lymphoma, malign histiocytosis, carcinoma; the major complications of the

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celiac disease include intestinal or extraintestinal malignancies, ulcerative rectocolitis and collagen sprue; Other diseases: cystic fibrosis, Down syndrome, ARJ, LES, Sjogren's syndrome;

- Patients with asymptomatic celiac disease who present folate or iron deficit and minimal histologic injuries;

- Patients with atypical celiac disease – it may evolve towards constipation.

**Laboratory examinations** involve the evaluation of the nutritional impact. Anemia is observed in 1/3 cases and usually, it is microcitary, hypochomic and hypsideremic; it is rarely microcitary as a result of folates deficit. The decrease of the coagulation factors level can be observed. Hypoproteinemia affects almost half of the cases, being moderate in most cases, without clinical consequences. Hypercholesterolemia is the proof of lipids loss in stools and is inconstant in almost 1/3 cases. The malabsorption of vitamin D and of calcium is responsible for the anomalies of the phosphocalcic metabolism. The seric level of calcium and phosphorous is decreased while the FA level is normal or increased. Other useful tests are the stool biochemical determinations, D - xylose absorption test, barium transit.

**Immunological tests.** – show a large applicability by measuring IgG and IgA anti gliadina, antireticuline, antiendomysium, antitransglutaminase antibodies. The practical problem related to the IgA antibodies dosing is the existence of the IgA deficit in patients with celiac disease. Antibodies dosing simplifies the diagnostic procedure and follows the celiac disease evolution, not being able to replace the jejunal mucosa biopsy.

The serological tests aim at:

- IgA tissue antitransglutaminase antibodies;
- Anti gliadina antibodies;
- Antiendomysium antibodies.

Transglutaminase (tTG) represents the major autoantigen in the celiac disease (Celikey test). It represents calcium dependent enzyme, playing a part in assembling the extra cellular matrix and in tissue recovery systems. High levels of tTG may be registered in the affected tissues. IgA antibodies against tTG are the serologic markers with high specificity for the celiac disease. The test sensibility if of 96 %, and the specificity is between 93 – 100 %.

Anti gliadina antibodies represent a useful complementary investigation, especially for the patients with IgA selective deficit which associates the celiac disease.

It is a non-invasive instrument for the celiac disease screening and for monitoring the diet compliance. Disappearance of Ac anti gliadina is registered 6-12 months after beginning the gluten-free diet and indicates a good diet compliance; the persistence of certain high levels indicate a reduced compliance.

Celikey test is not recommended to the patients with IgA deficit. Anti gliadina antibodies may give possible false positive results.

For these reasons, the final diagnosis remains the intestinal biopsy.

*The intestinal biopsy* precisely indicates the celiac diagnosis, the specific histological lesions being the following:

- Total or subtotal villous atrophy;
- Intestinal crypta hyperplasia;
- Decrease of the relation between the surface epithelium and the crypta epithelium;
- Increase of the number of intraepithelial lymphocytes;
- Increase of the cellular population of lamina propria;
- The results of the intestinal biopsy are interpreted according to Marsh classification as follows:

Marsh Classification	Histologic characteristics
0	Normal architecture of the intestinal mucosa with minimum intraepithelial lymphocytes infiltrate
I (lymphocitary enteritis)	Normal architecture of the intestinal mucosa with villous lymphocitary infiltrate, 30 lymphocytes/100 enterocytes.
II (lymphocitary enteritis with cryptic hyperplasia)	Intraepithelial lymphocytosis with the increase of the epithelial cells proliferation.
III	Intraepithelial lymphocytosis, cryptic hyperplasia and villous atrophy.
	A Partial villous atrophy with moderate villous (relation villi/crypta < 1/1)
	B Subtotal villous atrophy
	C Total villous atrophy

The possibility of establishing anti gliadina, antireticuline, antiendomysium, antitransglutaminase antibodies simplify the diagnosis algorithm of the celiac disease and observes the evolution in time of the patients without replacing the jejunal mucosa biopsy.

The intestinal mucosa biopsy represents the gold standard, proving the villous atrophy with crypta hyperplasia and the anomalies of the surface epithelium specifying the celiac disease diagnosis. The control biopsy is necessary for the patients with ambiguous response to the diet. The relapse test with the reappearance of the stigmas upon the reinsertion of gluten is recommended especially to the children under 2 years old.

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