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The role of laboratory testing in the diagnosis and follow-up of coeliac disease

Coeliac disease is an autoimmune enteropathy that is induced by a food antigen known as gliadin (found in wheat, barely and rye) in genetically predisposed individuals. This disease is most frequent cause of malabsorption in adults and children.

Epidemiology

Its prevalence has, for a long time, been under estimated: its prevalence in Europe would be, on average 1%, yet there are large differences depending on the country as well as a north-south decreasing gradient. In France, the prevalence has been estimated as between 0.1 and 0.25%. Coeliac disease is very rare in Asia and sub-Saharan Africa. The male to female gender ratio in children is 1:1 and 1:2-3 in adults.

Physiopathology

The detection of transglutaminase as a target antigen for anti-endomysial antibodies, the characterisation of enzymatic changes in gliadin induced by transglutaminase and the presence of T lymphocytes specific for modified gliadin and presented by HLA DQ2/8 (95% of coeliac disease suffers are HLA DQ2, 5 - 10% are DQ8) explains how the breakdown in tolerance to an oral antigen - gliadin, leads to the development of autoimmune coeliac disease of the intestinal mucosa. Other factors seem to play a role: genetic factors (besides HLA, MICA and CTRL4 etc.), environmental factors (rotavirus etc.), personal factors (stress etc.) and immune system factors (e.g. pregnancy).

Clinical forms

Symptomatic coeliac disease in children

The onset of this disease can occur in infants (aged between 6 and 24 months) following the introduction of gluten into the diet. Usually, the clinical picture demonstrates a stunt in the growth curve, chronic diarrhoea with malabsorption, abdominal distension, a decrease in muscular mass, hypotonia, loss of appetite and irritability amongst other things.

Symptomatic coeliac disease in adults (usually aged between 20 and 40)

The disease is characterised by abdominal pain, diarrhoea, malabsorption, weight loss and hair and nail problems etc. In addition, there are biological symptoms of malabsorption: deficit in iron, Ca, Mg, vitamins ADEK, folates and B12.

Pauci-symptomatic coeliac disease

No or few digestive symptoms are experienced. In children, growth retardation and/or a delay in puberty, osteopenia, hypoplasia of the dental enamel and anaemia. In adults, a deficiency in iron (hypochromic anaemia that is unresponsive to treatment), folates, vitamin B12 or a combination, often severe osteopenia, hepatic disorders (increase in transaminase levels), hormonal disorders (infertility, amenorrhea and delayed puberty), migraine type neurological disorders, headaches, depression, and irritable bowel syndrome (5% of which is coeliac disease).

Asymptomatic coeliac disease

Asymptomatic coeliac disease is often a fortuitous discovery revealed during endoscopy for other reasons that shows destruction of the intestinal villi. Alternatively, the disease can be identified during systematic serology screening of patients considered to be at risk.

Coeliac disease should be considered:

In overweight patients and the elderly.

Diagnosis

First-line serology testing can be requested as high-performance markers produce a reliable diagnosis.

- **Anti-reticulin antibodies:** these are totally obsolete.
- **Anti-gliadin antibodies IgG and IgA:** screening by ELISA, their specificity is insufficient and their sensitivity is mediocre. They are not covered or recommended by the French National Health Service.

Anti-endomysial antibodies IgA and IgG

These antibodies are revealed using indirect immunofluorescence (IF) on sections of monkey oesophagus when a fibrillar fluorescent pattern is seen around smooth muscle fibres. These antibodies have a high level of diagnostic performance (see table below). Their main disadvantage is the use of the IF method (reading is operator dependant and costly in terms of use of the technician's time).

Anti-transglutaminase IgA antibodies

These antibodies react with tissue transglutaminase (tTG), which has been identified as the target of anti-endomysial antibodies. Due to their high diagnostic performance (see table), they are recommended for first-line testing for diagnosis in both adults and children and they are useful in monitoring the patient's adherence to a gluten-free diet. Rarely encountered false positives have been described in patients suffering from liver disease and/or cases of massively increased levels of circulating IgA (steatosis/hepatic cirrhosis). The techniques available are ELISA, Luminex®, dot blot or "biocards" (doctor test).

Anti-transglutaminase IgG antibodies

Screening for these antibodies is recommended in patients suffering from a deficiency in IgA (or in cases of a suspected deficit). False positives are possible in cases of hypergammaglobulinemia, chronic liver disease and cirrhosis.

Diagnostic performances of different auto-antibodies in coeliac disease

	Sensitivity (%)	Specificity (%)
Anti-reticulin IgA antibodies	40 - 60	95 - 100
Anti-gliadin IgA antibodies	68 - 90	42 - 80
Anti-gliadin IgG antibodies	65 - 100	50 - 90
Anti-endomysial IgA antibodies	85 - 100	95 - 100
Anti-tissue transglutaminase IgA antibodies	95 - 100	90 - 100
Anti-tissue transglutaminase IgG antibodies	98	95

From the J.O. dated 25 November 2008, the NABM (nomenclature of medical treatment) has been changed following the HAS (French National Authority for Health) recommendations dated 2007

Anti-reticulin antibodies and anti-gliadin antibodies are no longer covered by the French National Health Service. IgA and IgG anti-transglutaminase antibodies are listed; anti-endomysial IgA antibodies are covered by the French National Health Service (for residents only) for children, but not for adults (› 15 years old); anti-endomysial IgG antibodies are always covered by the French National Health Service (for residents only), however, please be warned that they are less efficient. They should only be screened for in cases of total IgA deficit (otherwise, there is a risk of false negatives).

What laboratory tests should be performed when confronted with coeliac disease?

FBC-platelets, blood electrolytes, serum iron, serum protein electrophoresis, IgA quantification, ionised calcium, serum albumin, Mg++, prothrombin, full liver profile, vitamin B12 (a deficit is frequently encountered) and a phosphate and calcium profile.

A D-xylose test or a steatorrhea test is not recommended. The same can be said for transit explorations of the small intestine or push-type enteroscopy. Examination by video capsule is abnormal in 2 out of 3 cases; however, it does not allow duodenal biopsies to be collected. This test remains the benchmark examination used to confirm the diagnosis, but continues to be invasive and is not infallible (biopsies from several areas are required to obtain good sensitivity for this examination). Its necessity remains questionable today in patients with positive serology results as the currently available serological markers are both sensitive and specific.

Treatment: gluten-free diet

This means removing wheat, barely and rye flour from the patient's diet for life. The cost of this is high and can be covered by the French National Health Service (for residents only) depending on the biopsy result. This treatment is combined with iron, folates and calcium supplements. The efficacy is judged on the patient's clinical picture (improvement in symptoms after just a few days or weeks), the laboratory results (anti-tTG/anti-endomysial antibody results as follows: 100% after 1 month, 50% after 3 months, 20% after 6 months, 10% after 9 months followed by negative results) and the histology result (normalisation of the result with villi regrowth after just a few months).

Pitfalls to be avoided

Don't only think of coeliac disease when faced with a typical digestive form; prescribe a gluten-free diet before a serology and histology diagnosis; make a diagnosis when confronted with positive isolated anti-gliadin IgG antibodies; exclude the diagnosis when confronted with negative IgA markers (2% total IgA deficit in the general population).

Coeliac disease: the key points

- **First-line test:** screen for **anti-transglutaminase IgA antibodies**. Should a negative result be found, check the patient's diet and quantify total IgA. Should a deficit in IgA be revealed, screen for anti-transglutaminase IgG antibodies and possible anti-endomysial IgG antibodies. In reality, screens for anti-transglutaminase IgA antibodies and anti-endomysial antibodies are the same test but use a different technique (Elisa is easier to perform and more robust that IF). IgG markers should only be screened for in cases showing a deficit in total IgA. If no deficit is found and yet the clinical suspicion is high, a 2nd measurement of anti-transglutaminase IgA antibodies and/or anti-endomysial IgA antibodies can be carried out, especially for children.
- Anti-reticulin antibody and anti-gliadin antibody (less specific and not covered by the French national health service) screens should no longer be performed.

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