The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

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Coeliac disease

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1 Introduction

Coeliac disease is an autoimmune enteropathy related to gluten intolerance and linked to a strong genetic susceptibility background: DQA1*05-DQB1*0201 (HLA-DQ2) or DQA1*301-DQB1*302 (HLA-DQ8). This disease is characterised by inflammation of the intestinal mucosa causing total or subtotal villous atrophy.

Coeliac disease is usually considered to be rare but its prevalence needs to be re-evaluated in the light of recently developed screening tests. In reality, the majority of patients are either asymptomatic or with few or atypical symptoms. Coeliac disease mostly affects the populations of Northern Europe, the Maghreb countries, Australasia and the United States. It is very rare in Asia and sub-Saharan Africa. Epidemiological studies have shown that 0.5 to 1 % of individuals suffer from coeliac disease in Western European and North American populations.

The sex ratio of coeliac disease in children is 1/1. In adults, coeliac disease is 2 to 3 times more frequent in women than in men.

The disease is diagnosed at any age with two frequency peaks. Classically, the onset is in childhood, between the ages of six months and two years, and after gluten has been introduced into the diet (baby cereals containing gluten, pasta, bread …), or in adulthood, mainly between the ages of 20 and 40 years. However, late-onset forms, after the age of 65, are not exceptional. The first clinical signs appear before the age of one year in 73 % of cases. The diagnosis is established before the age of two years in 58 to 77 % of cases.

2 Diagnostic measurements for specialised physicians

The Federation of International Societies of Paediatric Gastroenterology, Hepatology and Nutrition (FISPGHAN) proposed guidelines for the diagnosis and treatment of coeliac disease which have been re-evaluated in 2011 by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) [1, 2].

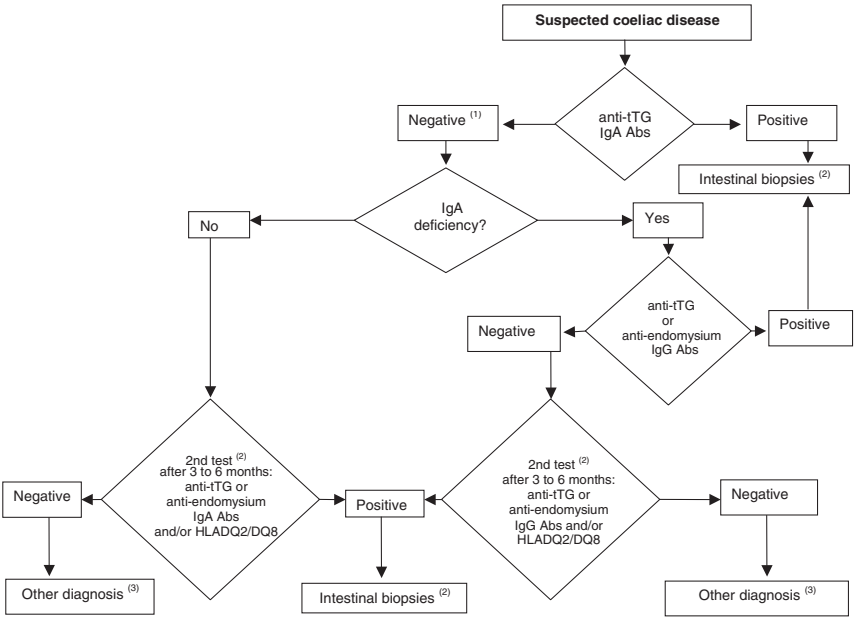
When coeliac disease is suspected in adults and children, serum should be tested for anti-tissue transglutaminase (tTG) IgA antibodies by a technique which uses human recombinant tissue transglutaminase as the antigen. Antibody and histological (biopsy) testing should only be carried out when the patient is on a gluten inclusive diet or the results may be falsely negative. When an anti-tTG IgA antibody test is negative or close to the threshold of positivity, testing for anti-endomysium IgA antibodies is recommended. After a first negative test for anti-tTG IgA antibodies in children suspected of coeliac disease who are not following a gluten-free diet and who do not have IgA deficiency, a second screening for anti-tTG IgA antibodies or anti-endomysium IgA antibodies is recommended within 3 to 6 months. In subjects with IgA deficiency, screening for anti-tTG IgG antibodies or anti-endomysium IgG antibodies is recommended in the same way as for IgA.

The formal diagnosis of coeliac disease is established when total or subtotal villous atrophy accompanied by cryptic hyperplasia and lymphocytic infiltration of the surface epithelium is demonstrated on small intestinal biopsies. Because these histological lesions may be patchy, it is recommended that multiple biopsy specimens be obtained. Due to the high sensitivity and specificity of anti-tTG and anti-endomysium tests, it is no longer necessary to perform control biopsies after initiation of a gluten-free diet. These second biopsies are reserved for patients who have an unsatisfactory response to a strict gluten free diet.

A summary of the diagnostic criteria of celiac disease and an algorithm for the diagnosis are presented on Table 1 and Fig. 1 respectively.

Table 1. Diagnostic criteria of coeliac disease.

Clinical signs
Chronic diarrhoea
Abdominal pain
Malabsorption syndrome
Complete resolution after treatment with a strict gluten-free diet
Histological criteria (small intestinal biopsy)
Villous atrophy
Cryptic hyperplasia
Intraepithelial lymphocytosis
Serological criteria
IgA anti-tissue transglutaminase or IgA anti-endomysium antibodies (IgG anti-tissue transglutaminase or IgG anti-endomysium antibodies in patients with IgA deficiency)



(1) Interpretation depending on the gluten-free diet compliance;
(2) Medical decision according to clinical context;
(3) Small intestinal biopsy may however be requested in certain circumstances, in the adult and if there is a strong suspicion of coeliac disease.

Abs, antibodies; **tTG**, tissue transglutaminase

Figure 1. Algorithm for the diagnosis of coeliac disease.

3 Requirements for family practitioners

Symptoms may arise from the gastrointestinal involvement with malabsorption of nutrients and vitamins, or may be related to the immune dysfunction which is responsible for extraintestinal symptoms. The clinical manifestations differ from one patient to another (Table 2) [3–5].

Three clinical forms are found:

- asymptomatic, completely silent form, which is detected from serological or histological findings;
- presenting few symptoms, or sub-clinical form;
- symptomatic, the classic form of the disease.

The asymptomatic forms or those with few symptoms are more frequent than the symptomatic forms. The severity of the disease is not necessarily proportional to

Table 2. Main signs and symptoms of coeliac disease.

Infant	Diarrhoea or constipation
	Anorexia
	Vomiting
	Extraintestinal manifestations (Table 3)
	Abdominal distension
Child	Chronic diarrhoea or constipation
	Abdominal pain
	Vomiting
	Extraintestinal manifestations (Table 3)
Adult	Chronic diarrhoea
	Steatorrhoea
	Abdominal pain
	Extraintestinal manifestations (Table 3)

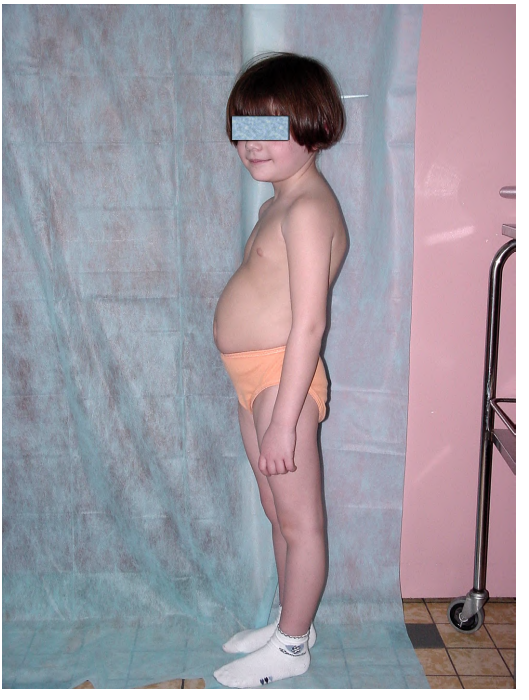


Figure 2. Abdominal distension in a child with coeliac disease.

the severity of the intestinal mucosal lesions, as a patient with total villous atrophy may be asymptomatic.

In the infant, the most classic presentation associates chronic diarrhoea with malabsorption and signs of malnutrition of varying severity and abdominal distension (Fig. 2). Anorexia is almost always present. Vomiting is frequent. When gluten has been introduced into the diet, any slowing of weight gain should suggest the diagnosis of coeliac disease.

In the child, the symptoms are misleading, as diarrhoea often plays a secondary role. Gastrointestinal problems such as abdominal pain, vomiting or constipation may be observed. Sometimes, only fatigability, growth retardation or delayed puberty, or extraintestinal manifestations may be observed (see following paragraph).

In the adult, coeliac disease is easily diagnosed when clinical gastrointestinal signs are present (chronic diarrhoea with steatorrhoea and abdominal pain), but diagnosis is much more difficult when the symptoms are minor or when they are related to extraintestinal manifestations.

Extraintestinal manifestations secondary to the malabsorption syndrome are presented in Table 3: anaemia, delayed growth or puberty in the child, bone and joint pain related to osteopenia and osteoporosis, neurological disorders such as peripheral neuropathy, muscular disorders such as muscle cramp or tetany, weight loss or even malnutrition, sometimes with oedema, fatigue, bleeding and haematomas.

Extraintestinal manifestations which are probably not secondary to the malabsorption syndrome, observed in the atypical forms of the disease, are also presented in Table 3: neurological disorders, dermatitis herpetiformis, liver dysfunctions, reproductive disorders, aphthosis, IgA nephropathy, myocarditis, haemorrhagic alveolitis, arthritis.

Lastly, coeliac disease may be associated with other non-intestinal diseases: organ-specific autoimmune diseases such as insulin-dependent diabetes (3.6 to 6.2 %), autoimmune thyroiditis (3 %), primary biliary cirrhosis (2 %), or systemic autoimmune diseases (systemic lupus, Sjögren's syndrome …). There is also an increased risk of coeliac disease in first-degree relatives of coeliac disease patients (5 to 10 %).

When the diagnosis of coeliac disease is suspected, serological testing should be performed. In case of positivity, the patient should be referred to a paediatric or adult gastroenterology unit for a small intestinal biopsy. Most recent guidelines indicate that these biopsies may be avoided in symptomatic children with high level of anti-tTG or anti-endomysium IgA antibodies especially if they are HLA-DQ2/DQ8 positive.

Table 3. Main extraintestinal manifestations of coeliac disease.

Secondary to the malabsorption syndrome	
Iron, folates, vitamin B12 deficiency	Anaemia
Vitamin D and calcium deficiency	Delayed growth or delayed puberty
	Bone and joint pain related to osteopenia and osteoporosis
Vitamin B12 and B1 deficiency	Neurological disorders such as peripheral neuropathy
Magnesium and calcium deficiency	Muscular disorders such as muscular cramp or tetany
Malabsorption of the majority of nutrients	Weight loss
Hypokalaemia and electrolyte depletion	Fatigability
Vitamin K deficiency	Bleeding and haematomas
Probably not secondary to malabsorption	Neurological disorders: depression, epilepsy, migraine…
	Dermatitis herpetiformis
	Liver dysfunctions: elevated transaminases…
	Reproductive disorders: infertility, amenorrhoea, recurrent miscarriage…
	Aphtosis
	IgA nephropathy
	Myocarditis
	Haemorrhagic alveolitis
	Arthritis

4 Follow up

Clinical observations

The response to gluten withdrawal from the diet is generally rapid: gastrointestinal symptoms improve within 2 to 3 weeks. Gluten-free diet allows restoration of the intestinal villi in patients with coeliac disease and healing of skin lesions in patients with dermatitis herpetiformis. Children with coeliac disease should be monitored for assessment of symptoms, growth, physical examination and adherence to a gluten-free diet. Lack of improvement of symptoms within a few (six to eight) weeks after initiation of a gluten-free diet should prompt the physician to look for involuntary or deliberate gluten ingestion.

Expectations

Early detection of coeliac disease and subsequent initiation of a gluten-free diet reduce the risk of developing some important complications such as osteoporosis, vitamin deficiency, spontaneous abortions, low birth weight infants, intestinal lymphoma and cancer.

Blood tests

Total adherence to a gluten-free diet usually induces a steady decrease of tissue transglutaminase and endomysium antibodies within 6 to 18 months, and they eventually disappear. So, testing for anti-tTG IgA or anti-endomysium IgA antibodies (anti-tTG IgG or anti-endomysium IgG antibodies in patients with coeliac disease and IgA deficiency) is recommended after 6 and 12 months of a gluten-free diet in patients whose first test was positive. Persistently high antibody levels are suggestive of poor compliance to the gluten-free diet. A decrease or disappearance of antibodies should encourage the patient to continue to adhere to the gluten-free diet.

5 Management

At the time of diagnosis, several biological parameters should be screened to detect possible deficiencies: full blood count, electrolytes, serum iron, vitamin B12, phosphocalcic profile, protein electrophoresis, magnesium, liver function tests and prothrombin rate. Diet supplementation with iron, folates, vitamin D and calcium is sometimes necessary at the beginning of treatment to correct a deficiency.

Coeliac disease is not curable but can be treated effectively by lifelong adherence to a gluten-free diet. This is based on the withdrawal of wheat, rye and barley. Corn, rice and potato are allowed. Complete compliance to the diet is difficult as, in addition to products containing flour, gluten is also used to bind foods and as an additive in industrial meals and in certain drugs.

6 Diagnostic tests

Initial testing for coeliac disease should be performed by measurement of anti-tTG IgA or anti-endomysium IgA antibodies [1, 2].

Anti-tTG IgA antibodies tests have very good diagnostic performances both in children and in adults: sensitivity is more than 90 % and specificity is more than 95 %. Anti-tTG antibodies are mostly detected by enzyme linked immunosorbent assay (Elisa). These quantitative tests are automated, and now widely available. The nature of the antigen used is important. Tests using human recombinant antigen have shown the best performance.

Sensitivity and specificity of anti-endomysium IgA antibodies detection are similar to anti-tTG IgA antibodies detection. This reference test, despite the inherent limitations of the indirect immunofluorescence method (time consuming, non automated test, observer dependent results) is recommended the first time anti-tTG antibodies are found to be positive. Indeed, some false positive anti-tTG antibodies have been described, especially in adults [2].

When an anti-tTG IgA antibody test is negative or close to the threshold of positivity, testing for anti-endomysium IgA antibodies is also recommended. The overall performances of both tests are equivalent, but their results are not entirely identical.

Measurement of anti-tTG IgG or anti-endomysium IgG antibodies should be limited to patients with IgA deficiency. Serum IgA levels, when unknown, should be measured at the same time as screening of anti-tTG IgA antibodies to exclude IgA deficiency [2].

During follow-up, all tests should be carried out in the same laboratory since variations of antibody levels cannot be interpreted when different reagents are used.

Tests for anti-reticulin and anti-native gliadin antibodies have low sensitivity and specificity respectively and should no longer be used in routine practice. Although a new generation of serological tests using antigen derived from gliadin or synthetic deamidated gliadin peptides are now available, the benefit of these new tests in patients without anti-tTG IgA or anti-endomysium IgA antibodies needs to be evaluated on large populations. Finally, adding HLA-DQ2/DQ8 typing into the diagnosis of coeliac disease may be useful to avoid biopsies in some cases.

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