Edition no. 3

PATHCHAT

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Endorsed by the Infectious Diseases Peer Group

The diagnostic approach to coeliac disease

Coeliac disease (CD) is an immune mediated inflammatory disease triggered by an environmental agent (the gliadin component of gluten) in genetically predisposed individuals.

The pathogenesis is a complex interplay between genetic factors (remarkable close association with the HLA-DQ2 and/or HLA-DQ8 gene loci), serum auto-antibodies (tissue transglutaminase IgA and endomysium IgA), the innate immune system and gliadin reactive T cells. Tissue transglutaminase is released in response to mechanical irritation or inflammation and subsequently cross links and deamidates glutamine proteins found in wheat. Deamidation produces a negative charge in gluten peptides and increases their affinity for HLA-DQ2 and/or DQ8, which in turn stimulates T helper cells. An immune reaction is triggered, causing villous atrophy and hypertrophic crypts.

Gluten is found in various cereals (e.g. wheat, barley, rye). If patients with CD consume food containing gluten, it will eventually lead to damage to the mucous membranes of the small intestine.

Epidemiology

Individuals of North European descent are mostly affected and a prevalence of 1:70 to 1:300 has been reported, but people from the Middle East, Asia, South America and North Africa are also affected. On large scale screening, it was found that recognised cases only represented a small proportion of the coeliac problem.

Clinical presentation

Coeliac disease used to be a disease of infancy, with children presenting with life-threatening malabsorbtion. Currently and more commonly, the disease presents between the ages of 10 and 40 with milder manifestations.

Gastrointestinal manifestations

- Steatorrhea and flatulance
- Consequences of malabsorbtion, including growth failure, weight loss, severe anaemia, neurologic manifestations due to vitamin B deficiencies and osteopaenia due to vitamin D and calcium malabsorbtion

Subclinical disease

Symptoms include fatigue, unexplained elevation of serum aminotransferase and borderline iron deficiency. It is important to detect subclinical disease, for these patients have an increased risk of developing malignancies. They may have nutritional deficiencies, affected mothers may have infants with a low birth weight and the disease is associated with other autoimmune disorders.

Other clinical associations

Associated conditions include dermatitis herpetiformis, Down syndrome, selective IgA deficiency and disorders with an autoimmune component, including thyroid disease, liver disease and type 1 diabetes mellitus (T1DM). Several large population-based studies also demonstrated an increased risk of developing lymphoma (especially non-Hodgkin's lymphoma) and gastrointestinal tract cancers. Neuropsychiatric disease, hyposplenism and idiopathic pulmonary heamosiderosis have also been reported.

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Women with untreated CD may have an increased frequency of reproductive abnormalities including later menarche, secondary amenorrhoea, repeated foetal losses during the first trimester of pregnancy, infertility and earlier menopause. In women with repeated early miscarriages, it has been shown that a subclinical form of coeliac disease is the cause in 5% of cases. Since the foetal loss can probably be avoided with a gluten-free diet, a serological screening test is particularly important in these patients, especially given that the disease is only diagnosed in 10% of affected individuals.

Who should be tested?

- Patients with unexplained symptoms and signs of chronic or intermittent diarrhoea, weight loss, iron-deficiency anaemia, nausea or vomiting, chronic abdominal pain, cramping or distension, chronic constipation, chronic fatigue, recurrent aphtous stomatitis, dermatitis herpetiformis-like rash, fracture with inadequate traumas, osteopaenia, osteoporosis, abnormal liver biochemistry and failure to thrive, stunted growth, delayed puberty and amenorrhoea in children and adolescents
- Asymptomatic patients with increased risk for CD, i.e. T1DM, Down syndrome, autoimmune thyroid disease, Turner syndrome, William's syndrome, selective IgA deficiency and autoimmune liver disease
- Asymptomatic patients with first-degree relatives with CD

Diagnostic tests

1. CD-specific antibodies

These antibodies include autoantibodies against tissue transglutaminase (TTG), endomysial antibodies (EMA) and antibodies against deamidated forms of gliadin peptide (DGP).

Positive anti-TTG and/or EMA is associated with a high probability for CD, although low levels of anti-TTG have been noted in other conditions, including other autoimmune disorders, tumours, infections, myocardial damage, liver disorders and psoriasis. Endomysial antibodies have not been associated with the above and are therefore considered to be more reliable.

Several studies suggested that high anti-TTG antibody levels, defined as exceeding 10 x upper limit of normal (ULN), correlate better with villous atrophy and should be used in the initial approach to diagnose CD.

Recommendations for antibody testing:

- IgA class anti-TTG or EMA should be used as first line investigation in patients with suspected CD. Patients should ideally be on a gluten-containing diet.
- IgA levels should be determined to exclude IgA deficiency, as first-line CD-antibody testing is IgA based
  - In patients with either primary or secondary IgA deficiency, testing for at least one IgG class, including IgG anti-TTG, IgG EMA and IgG DGP, is indicated.
- IgG or IgA class deamidated gliadin peptiede (DGP) should be measured in patients negative for anti-TTG or EMA with strong suspicion of CD, especially in children <2 years of age.
- If IgA class CD antibodies are negative in an IgA-competent individual, it is unlikely that the current symptoms are caused by CD. Further testing is advised in children <2 years, individuals with restricted gluten consumption, severe symptoms, family predisposition or predisposing diseases, use of immunosuppressants.
- Individuals found to be CD-specific antibody positive should be further evaluated by a gastroenterologist.

Suggestive clinical features of CD but negative serological tests:

- Selective IgA deficiency (total serum IgA <0.2 g/L)
- Immunosuppressive drugs
- If gluten exposure was short or the individual was on a low gluten diet (several weeks to years)
- The serologic test could be falsely negative, in which case a small bowel biopsy is necessary
- Not CD; other causes of symptoms or villous atrophy should be considered

2. HLA testing for HLA-DQ2 and HLA-DQ8

HLA DQ2/DQ8 typing is a useful tool to determine if the patient is genetically susceptible to CD. If HLA DQ2/DQ8 testing is negative, CD is excluded or highly unlikely. The HLA-DQ2 allele is found in 90-95% of individuals with CD and the remaining 5-10% possesses the HLA-DQ8 allele. It must be kept in mind, however, that CD is a multigenetic disorder, for example, the expression of HLA-DQ2 or HLA-DQ8 molecules is necessary, but not sufficient to cause disease and approximately 30-40% of the European population holds the HLA-DQ2 haplotype, but only 1% develops CD.

Recommendations for HLA-DQ2 and HLA-DQ8 typing:

- HLA typing may be offered as a first line test to select individuals for further antibody testing, especially in asymptomatic people.

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- If CD is strongly suspected in a child with high specific antibodies present and a small bowel biopsy is not going to be performed, it is then recommended to perform HLA DQ2/DQ8 typing in order to add strength to the diagnosis.
- Offer HLA-DQ2/HLA-DQ8 typing in patients with uncertain diagnosis, for example, in patients with negative antibody levels and mild infiltrative changes in small bowel biopsy.
- If HLA-DQ2/HLA-DQ8 typing is negative, offer investigations for other causes of symptoms.

3. Duodenal biopsies

Histological features may be patchy, may only appear in the duodenal bulb and may be of variable severity. The pathology report usually grades the pathology according to the Marsh-Oberhuber classification.

Recommendations for performing duodenal biopsies:

- In symptomatic patients with high anti-TTG IgA levels (>10x ULN), verified by EMA positivity and who are HLA-DQ2 and/or HLA-DQ8 positive, histological assessment may be omitted.
- Follow-up of the above patients after initiation of GFD should include significant symptom improvement and normalisation of CD-specific antibody levels.
- A small bowel biopsy should be performed in individuals with only low concentrations of anti-TTG and negative EMA.
- In patients with a strong clinical suspicion, but negative antibody levels, a small intestinal biopsy should be performed. With CD compatible lesions, HLA typing should be performed. In HLA-DQ2 and/or HLA-DQ8 positive patients, the diagnosis should be confirmed with gluten challenge and repeat biopsy.
- If a Marsh type 1 lesion was observed, additional supportive evidence should be looked for (extended serology, HLA, IgA anti-TTG intestinal deposits, high intra-epithelial lymphocyte γδ count) before establishing the diagnosis.
- When biopsy was performed as part of a diagnostic workup and Marsh type 1 to 3 lesions were observed with negative antibody levels or compatible HLA typing, other causes for enteropathy should be considered (including food allergy, autoimmune enteropathy, bacterial overgrowth, giardiasis, lymphoma, tropical sprue, Zollinger-Ellison syndrome, CVID, post gastroenteritis).
- It is preferable to take biopsies from the bulb (at least one) and from the second or third portion of the duodenum (at least four).
- Gluten challenge is only necessary in unusual circumstances and should not be performed in children younger than five to six years old or during the pubertal growth spurt. HLA typing should be considered before gluten challenge.
- For a gluten challenge, the daily gluten intake should contain at least the normal amount of gluten advised (~15g/day). IgA anti-TTG antibody (IgG in selective IgA deficiency) should be measured during the challenge. If antibodies become positive, the diagnosis can be confirmed. The challenge should be considered complete after a two-year period without symptoms or positive antibodies, however, additional biopsies on a normal diet are recommended because delayed relapse may occur later in life.

A diagnostic approach to CD

Flow diagrams with a diagnostic approach to CD in the symptomatic and asymptomatic person are proposed (figures 1 and 2, adapted from *Hepatology and Nutrition Guidelines for the Diagnosis of Coeliac Disease*, JPGN; 2012: 136-160).

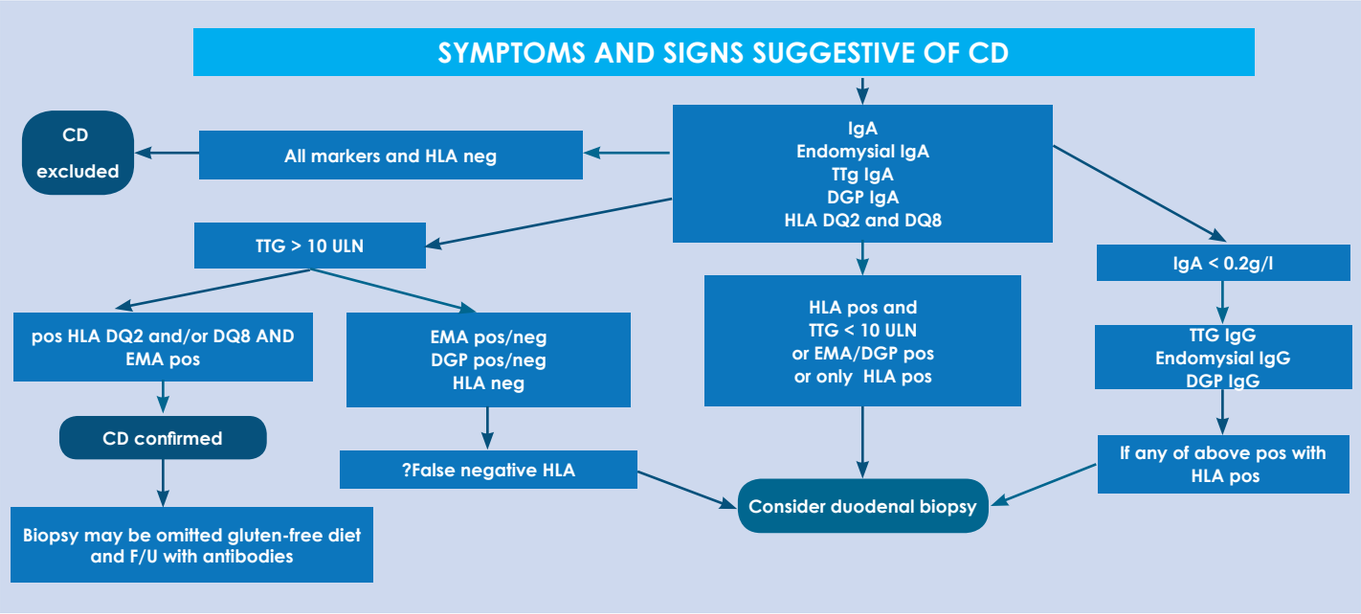

Figure 1: Diagnostic approach to a person with symptoms and signs of CD
TTG: Tissue transglutaminase; EMA Endomysial antibodies; DPG Deamidated gliadin peptide; ULN: upper limit of normal; F/U: follow up

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Follow-up

If a diagnosis of CD has been made, a gluten-free diet (GFD) should be instituted. Follow up regularly for symptom improvement and normalisation of CD-specific antibodies. In general, this is achieved within 12 months of starting a GFD.

Conclusion

A diagnosis of CD can be made when gluten-dependent symptoms, CD-specific antibodies, HLA-DQ2 and/or DQ8 and characteristic histological changes (villous atrophy and crypt hyperplasia) are present. High anti-TTG levels (>10x ULN) show high diagnostic accuracy and with the presence of these together with suspicious symptoms, a positive EMA and HLA, biopsy may be omitted. The diagnosis is confirmed with a decline in antibody levels and symptom improvement on GFD.

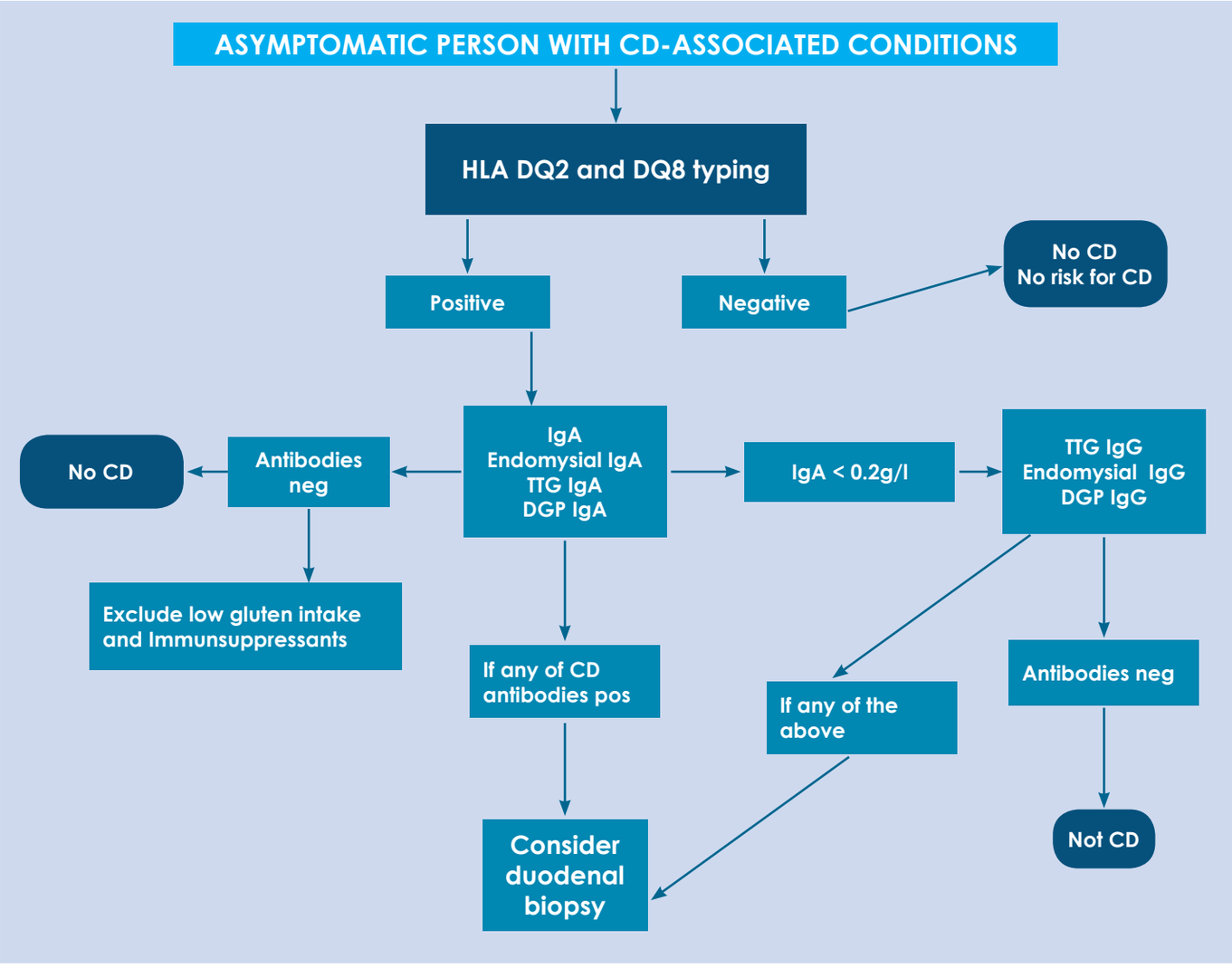

Fig 2: Diagnostic approach to the asymtomatic person with CD-associated conditions.
TTG: Tissue transglutaminase; DGP: Deamidated gliadin; CD: Coeliac disease

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