Review Article

WHEAT-RELATED DISORDERS: MAKING SENSE OF COELIAC DISEASE AND OTHER REACTIONS TO WHEAT AND GLUTEN

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INTRODUCTION

Globally, wheat-free and gluten-free products and diets have become fashionable, indicating at first glance that the prevalence of gluten-related disorders is very high. Clinicians will therefore regularly be confronted with patients who suspect that they react to wheat or gluten. Most patients attribute any adverse reaction to wheat or gluten to an allergy. The greatest challenge to the clinician is to distinguish between the different gluten-related disorders like Coeliac Disease, wheat allergy, wheat intolerance and other gut complaints like irritable bowel syndrome (IBS).¹,²

Gluten-related disorders are broadly categorised into allergic reactions (e.g. wheat allergy), autoimmune reactions (e.g. Coeliac Disease) and reactions not involving the immune system (wheat/gluten intolerance) (Figure 1).¹-⁵ This article provides a summary of the most current diagnostically relevant information on wheat-related disorders and their distinctions. A practical approach to a patient presenting with a history of wheat/gluten allergies is also proposed.

WHEAT ALLERGY

Patients with wheat allergy (WA) may present with a wide range of IgE-mediated, non IgE-mediated and mixed immunological allergic reactions.¹,²,⁴ IgE-mediated reactions may occur within minutes to two hours of ingestion and include symptoms like itching and irritation of the mouth and throat, gastrointestinal symptoms, rhinitis, asthma or severe cardiovascular reactions. Reactions can vary from mild oral or cutaneous reactions to life-threatening anaphylaxis. In addition, WA may also cause basophil-mediated reactions and mixed reactions.

TABLE I: MAIN WHEAT ALLERGEN COMPONENTS AND THEIR ASSOCIATIONS

<table>
<thead>
<tr>
<th>Gladin</th>
<th>Pig β-glucan</th>
<th>α-amylase</th>
<th>PR-10</th>
<th>LTP</th>
<th>CCD</th>
</tr>
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<tbody>
<tr>
<td>15S Gladin</td>
<td>Associated with wheat allergy persistence.</td>
<td>Marker of gluten intolerance.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31S Gladin</td>
<td>Associated with wheat-dependent exercise induced anaphylaxis.</td>
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Mixed and non IgE-mediated immunological WA reactions may involve either humoral and/or cellular immune mechanisms and may present with acute and/or chronic symptoms. Some of the clinical conditions which may be associated with these reactions include a subset of atopic dermatitis, allergic eosinophilic gastrointestinal disorders and food protein-induced enterocolitis syndrome (FPIES).¹-⁵ Immediate wheat allergy affecting the gastrointestinal tract, skin or respiratory system is mainly seen in children and is commonly outgrown by school age, yet can persist in some patients causing severe reactions. In teenagers and adults, anaphylaxis may also result from the ingestion of wheat in conjunction with stress triggers (including exercise, severe stress, alcohol consumption and concomitant NSAID intake). This is called co-factor induced anaphylaxis. Occupational and household exposure to processing or cooking vapours containing wheat proteins may cause adult-onset wheat allergy with respiratory symptoms like asthma (baker’s asthma) and rhinitis. Casual touching of wheat allergens may cause localised contact urticaria.¹,²,⁷,⁹

Oral allergy syndrome (OAS) or food-pollen-syndrome may occur in patients with pollen allergy with IgE antibodies to certain cross-reacting protein components in foods of plant origin, e.g. nuts, fruits and vegetables. The symptoms of OAS are typically itching and/or mild swelling of the mouth and throat immediately after ingestion of uncooked fruits or vegetables. Only a small portion of these patients experience systemic allergic reactions. OAS does not frequently occur after ingestion of wheat, presumably because wheat is mainly ingested in cooked forms. However, symptoms of OAS have been reported in patients consuming whole-wheat bread products.¹⁰
Wheat allergy may play a role in several mixed and non IgE-mediated food allergic disorders. Wheat allergy may play a pathogenic role in a subset of patients, primarily infants and children, with atopic dermatitis. Wheat is also a major allergen which may be involved in allergic eosinophilic oesophagitis, a disorder characterised by eosinophilic inflammation of the oesophagus. Patients experience symptoms of gastro-oesophageal reflux unresponsive to conventional therapies. Severe cases may present with vomiting, abdominal pain, dysphagia and feeding disorders. Some patients may also experience eosinophilic gastroenteropathy of the stomach and intestines (allergic eosinophilic gastroenteritis) and present with symptoms of abdominal pain, nausea, vomiting, diarrhoea and weight loss.

Patients with FPIES typically present with severe vomiting and diarrhoea within one to three hours after ingestion of the offending allergen, causing dehydration, lethargy and sometimes shock. FPIES is usually seen in young children in response to milk or soy consumption, but may also occur in response to wheat.

**DIAGNOSIS OF WHEAT ALLERGY**

The diagnosis of wheat allergy is based on the patient history and laboratory testing, where available. It may also be necessary to perform an oral food challenge to make the final diagnosis.

**DIAGNOSTIC TOOLS FOR THE ASSESSMENT OF A POSSIBLE WHEAT/GLUTEN ALLERGY**

- Proper history and examination;
- Skin prick tests (SPT) or blood tests (ImmunoCap IgE) to wheat, gluten and/or grass pollen;
- IgE allergen components after initial wheat and/or pollen IgE test is positive: omega 5 gliadin, α/ω gliadins, alpha amylase, prolin, Proteinase-10 (PR-10), Lipid Transfer Protein (LTP), Cross-reactive carbohydrate determinants CCD;
- Basophil activation tests to wheat/gluten (available in the form of the CAST (Cellular Antigen Stimulation Test) in South Africa);
- Elimination diets and food challenges.

**WHEAT ALLERGEN COMPONENTS RELEVANT TO THE APPROPRIATE DIAGNOSIS OF WHEAT ALLERGY**

Foods are comprised of numerous proteins and an individual with a food allergy may have immune responses to any of these individual proteins. The specific proteins that the patient is sensitised to are important, as some may be cross-reactive between different plant species, some may be heat-labile and some may be associated with severe reactions or certain clinical presentations.

Wheat, like all other foods, contains a number of proteins. However, not all of these proteins are allergenic. The main al-

Glutens are the main wheat allergens and consist of gliadins and glutenins. The wheat component Tri α 19 (omega-5 gliadin) is associated with true wheat allergy and is an important risk marker for immediate reactions to wheat in children and for exercise-induced anaphylaxis after wheat ingestion in adults. Sensitisation to other gliadins (α/ω) may also be associated with severe and/or persistent wheat allergy. Another marker for clinical reactions to wheat is the wheat component Tri α 14 (a lipid transfer protein), which lacks cross-reactivity to grass pollen allergens. IgE to the Alpha-amylase/Trypsin inhibitor component in wheat is associated with respiratory symptoms to wheat after...
Patients with pollen allergies are often immunologically sensitised to cross-reactive components that occur in pollens as well as in foods of plant origin. The most common pollen cross-reactive components are cross-reactive carbohydrate derivatives (CCD), profilins, proteinase-10 (PR-10) and lipid transfer proteins (LTP). Cross-reactivity is due to molecular similarity of allergen components in multiple allergen sources and patients may test positive to multiple allergen-specific IgE tests, including other pollens and foods of plant origin. IgE-mediated allergy to some cross-reactive components may either be asymptomatic, cause mild symptoms (e.g. OAS) or rarely cause severe systemic reactions. Patients with wheat allergy may also react to other cereals such as rye and barley due to cross-reactivity between gluten proteins (gliadins and glutenins).

A summary of the main wheat allergen components and their associations is demonstrated in Table I. A word of caution on interpretation of wheat allergy tests is that a positive allergy test result to wheat-flour extract does not always correlate with clinical symptoms, as cross-reactivity with grass pollen is common. This is a particular problem in South Africa, where incorrect over diagnosis of wheat allergy occurs frequently in patients with actual grass allergy.

AUTOIMMUNITY

The onset of symptoms in patients with autoimmune reactions to gluten are somewhat more delayed than those in wheat allergy. The most commonly recognised disorder is Coeliac Disease (CD), an autoimmune inflammatory multisystem disorder with a wide range of clinical manifestations, affecting in particular the small intestine. In addition, Dermatitis Herpetiformis (DH) and Gluten Ataxia are also recognised.

COELIAC DISEASE

Coeliac Disease (CD) is an autoimmune enteropathy triggered by the ingestion of gluten in a genetically susceptible individual.
The pathogenesis of CD is a complex interplay between genetic factors, serum auto-antibodies (specifically tissue transglutaminase (TTG) IgA and endomysium (EMA) IgA), the innate immune system and gliadin-reactive T cells. When patients with CD consume foods containing gluten an immune reaction, causing villous atrophy and damage to the mucous membranes of the small intestine, is triggered.

CD occurs relatively commonly in individuals of Northern European descent, where a prevalence of 1:70 to 1:300 has been reported, but CD is also described in people from the Middle East, Asia, South America and Africa. However in most countries, the diagnosis of CD is not readily considered, therefore the majority of CD patients remain undiagnosed. Although CD used to be considered to be a disease of infancy, with children presenting with life-threatening malabsorption, more commonly, the disease presents between the ages of 10 and 40 with milder manifestations.

The onset of symptoms is usually gradual with a time lag of months or years after gluten introduction. However, early presentation as well as immediate symptoms such as vomiting...
and abdominal pain have been described.\cite{1,3,11,13,15-17} The majority of patients with CD will present with common gastrointestinal symptoms (diarrhoea, abdominal pain, flatulence, constipation, vomiting and loss of appetite). Patients may experience severe weight loss, malabsorption and failure to thrive, and more rarely haemosiderosis.\cite{15,17}

A significant subgroup of patients with CD presents with subclinical disease. Symptoms include fatigue, reduced bone-mineral density, peripheral neuropathy, neuropsychiatric disease, unexplained elevation of serum aminotransferase and iron deficiency anaemia. There is a strong association between CD and dermatitis herpetiformis, IgA deficiency, other autoimmune diseases (Type 1 diabetes, autoimmune thyroid disease and Sjögren’s disease) and syndromic disorders like Down’s syndrome, Turner’s syndrome and William’s syndrome.\cite{11,12,16,17}

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, low birth-weight infants, infertility and earlier menopause.\cite{15,18} Since the foetal loss can probably be avoided with a gluten-free diet, a screening test for CD is particularly important in patients with recurrent miscarriages, especially given that CD is only diagnosed in 10% of affected individuals.\cite{16,17}

It is important to detect subclinical CD, as these patients have an increased risk to develop malignancies (e.g. lymphoma, GIT tract malignancies), nutritional deficiencies, reproductive abnormalities and other autoimmune disorders. It is also essential to identify and follow up asymptomatic relatives of CD patients.\cite{1,2,4,11,12,16,17}

WHO SHOULD BE TESTED FOR CD?

- 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 aphthous stomatitis, dermatitis herpetiformis-like rash, fracture with minor trauma, osteopaenia, osteoporosis, abnormal liver biochemistry and failure to thrive and stunted growth in children, delayed puberty and amenorrhoea.\cite{19}
- Asymptomatic patients with increased risk for CD, i.e. Type 1 diabetes, autoimmune thyroid disease, autoimmune liver disease, Sjögren’s syndrome, Down syndrome, Turner syndrome, William’s syndrome and selective IgA deficiency.
- Asymptomatic patients with first-degree relatives with CD.

DIAGNOSTIC TESTS

CD-SPECIFIC ANTIBODIES

Worldwide the first line of testing in patients with suspected CD are the CD-specific antibodies.\cite{12} These include auto-antibodies against tissue transglutaminase (TTG), endomysial antibodies (EMA) and deamidated forms of gliadin peptide (DGP).

Positive anti-TTG and/or EMA is associated with a high probability for CD, though low levels of anti-TTG have been noted in other conditions including other autoimmune disorders, tumours, infections, myocardial damage, liver disorders and psoriasis.\cite{12} Several studies, however, suggest high anti-TTG antibodies levels, defined as exceeding 10 x upper limit of normal, correlate better with villous atrophy and should be used in the initial approach to diagnose CD.\cite{1,2,12,13,16}

In contrast, endomysial antibodies have not been associated with the above and are therefore considered to be more specific.\cite{12}

RECOMMENDATIONS FOR ANTIBODY TESTING:

- IgA class anti-TTG and/or EMA should be used as first line investigation. Patients should ideally be on a gluten-containing diet when testing is performed, as antibody levels may become negative during periods of gluten avoidance. TTG can also be used as a test for compliance with a gluten-free diet and monitoring of disease activity.
- Total IgA levels should always be determined to exclude IgA deficiency. In patients with either primary or secondary IgA deficiency, testing for IgG-mediated Coeliac antibodies, e.g. IgG anti-TTG, IgG EMA and IgG DGP, is indicated.
- IgG or IgA class deamidated gliadin peptide (DGP) should be measured in patients negative for anti-TTG or EMA with strong suspicion of CD, especially in children younger than 2 years of age. These markers are more sensitive than TTG and EMA in young children.
- If IgA class CD antibodies are negative in an IgA-competent individual consuming a diet rich in gluten, it is unlikely that the current symptoms are caused by CD. Further testing is advised particularly in children younger than 2 years of age, individuals with restricted gluten consumption, severe symptoms, familial predisposition, predisposing diseases and in patients using immunosuppressants.
- Individuals found to be CD-specific antibody positive, should be further evaluated by a gastroenterologist or gastrointestinal surgeon, as in the majority of cases the disease needs to be confirmed on biopsy of the upper small bowel.

Consider the following in patients with suggestive clinical features of CD but negative serological tests:

1. Selective IgA deficiency (total serum IgA <0.2 g/L).
2. Immunosuppressive drugs.
3. If gluten exposure was short or the individual was on a low gluten diet (several weeks to years) tests may be false negative.
4. The serologic test could be falsely negative in which case a small bowel biopsy is necessary. Please note that a combination of negative TTG, EMA and DGP is required before serologic tests are deemed negative.
5. Consider testing for genetic predisposition to CD (HLA-DQ2 and HLA-DQ-8).
6. Refer to a gastroenterologist when in doubt.
7. The patient may not have CD and alternate causes of symptoms or villous atrophy should be considered.

**HLA TESTING FOR HLA-DQ2 AND HLA-DQ8**

Genetic testing of the HLA DQ2/DQ8 alleles is a useful tool to determine if the patient is genetically susceptible to CD. If HLA DQ2/DQ8 testing is negative, CD is highly unlikely. The HLA-DQ2 allele is found in 90-95% of individuals with CD and 5-10% possesses the HLA-DQ8 allele.\textsuperscript{12,17,20} Given that CD is a multigenetic, multifactorial disorder, the expression of HLA-DQ2 or HLA-DQ8 molecules is necessary but not sufficient to cause disease.

**RECOMMENDATIONS FOR HLA-DQ2 AND HLA-DQ8 TYPING:**

- Depending on cost, HLA typing may be offered as first line test to select individuals for further antibody testing, especially in asymptomatic patients. This is also the recommended screening tool for asymptomatic first degree relatives of CD patients.
- If CD is strongly suspected in a child with high specific antibodies present (TTG 10 x above upper limit), a positive HLA DQ-2/HLA DQ-8 test can confirm the diagnosis of CD and an invasive small bowel biopsy may not be necessary.
- HLA-DQ2/HLA-DQ8 typing is also recommended in patients with an uncertain diagnosis, i.e. in patients with negative antibody levels and mild infiltrative changes in small bowel biopsy. This can help to exclude a diagnosis of potential CD.
- If HLA-DQ2/HLA-DQ8 typing is negative, offer investigations for other causes of symptoms.

**DUODENAL BIOPSIES**

In patients with CD a duodenal biopsy is the confirmatory diagnosis. In order to avoid sampling bias, multiple biopsy samples are required. Histological features of CD 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.\textsuperscript{3,11,16,17}

**RECOMMENDATIONS FOR PERFORMING DUODENAL BIOPSY:**\textsuperscript{21}

A small bowel biopsy should be performed in individuals with low positive concentrations of anti-TTG (less than 10 x upper limit of normal) and/or negative EMA.
- In patients with a strong clinical suspicion but negative antibody levels, 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 is observed, additional supportive evidence should be looked for (extended serology, HLA, IgA anti-TTG intestinal deposits, high intra-epithelial lymphocyte y6 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, Common Variable Immunodeficiency (CVID), post-gastrectomy).
- It is preferable to take biopsies from the bulb (at least 1) and from the second or third portion of the duodenum (at least 4).
- A gluten containing diet before biopsy will increase the diagnostic accuracy of biopsies and CD serology.
- A gluten challenge is not necessary in most cases to diagnose CD, but may be performed when doubt exists regarding the initial diagnosis on patients following a gluten-free diet. A gluten challenge should preferably not be performed in children younger than 5 to 6 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 (15 g/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.
- If a patient does not experience symptoms or develop positive antibodies (relapse) on a diet containing a normal amount of gluten within the next 2 years, the diagnosis of CD can be excluded with a reasonable degree of certainty. However, additional biopsies on a normal diet are recommended in individuals at risk for CD (e.g. HLA DQ2/DQ8 positive), because delayed relapse may occur later in life.
- In symptomatic patients with high anti-TTG IgA levels (>10 x upper limit of normal), 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 a gluten-free diet should include significant symptom improvement and normalisation of CD-specific antibody levels.

**A DIAGNOSTIC APPROACH TO CD**

Flow diagrams with a diagnostic approach to CD in the symptomatic and asymptomatic person are proposed (Figures 2 and 3, adapted from Hepatology and Nutrition Guidelines for the Diagnosis of Coeliac Disease, JPGN; 2012: 136-160).

A diagnosis of CD can be made when gluten-dependant symptoms, CD-specific antibodies, HLA DQ-2 and/or HLA DQ-8 and characteristic histological changes (villous atrophy and crypt hyperplasia) are present. High anti-TTG levels (>10 x ULN) show high diagnostic accuracy and with the presence of these together with suspicious symptoms, positive EMA and HLA; biopsy may be omitted. The diagnosis is confirmed with a decline in antibody levels and symptom improvement on a gluten free diet.
FOLLOW-UP OF COELIAC DISEASE
If a diagnosis of CD has been made, a life-long 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.

DERMATITIS HERPETIFORMIS
Dermatitis Herpetiformis (DH) is a skin manifestation of gluten-driven autoimmunity and inflammation and presents with an intensely itching and burning blistering rash. The elbows and upper forearms are affected in approximately 90% of patients, but the rash may also be wide-spread and is often symmetrical.1,2,21,22,23

The inflammatory reaction is driven by IgA autoantibodies to epidermal transglutaminase with granular or fibrillar IgA deposits in the dermal papillae of the skin. The diagnosis of DH is based on skin biopsy and demonstration of serologic markers of CD. Only a minority of patients (approximately 10%) have gastrointestinal symptoms and these are usually mild. DH patients may demonstrate the same manifestations and complications seen in patients with CD. After the diagnosis of DH has been established, a gluten-free diet should be implemented, regardless of gastrointestinal symptoms and involvement.22,23
GLUTEN ATAXIA
Gluten Ataxia (GA) is defined as idiopathic sporadic ataxia with positive serological markers for Coeliac Disease. Antibodies to brain-expressed transglutaminase have been found in patients with GA, but the diagnosis is not as straightforward as that of CD. Anti TTG IgA antibodies only occur in approximately 38% of patients with GA and unlike CD, IgG antibodies to TTG occur more frequently. Patients with positive TTG antibodies should receive a duodenal biopsy. Regardless of the endoscopy results, a gluten-free diet should be offered with regular follow-up until TTG antibodies disappear, which usually takes 6-12 months. Stabilisation or improvement of ataxia after one year of a gluten-free diet will confirm the diagnosis.

NON-ALLERGIC REACTIONS
WHEAT INTOLERANCE
The onset of symptoms in these patients is usually hours to days after gluten exposure. The definition of wheat intolerance (WI) is patients with challenge proven reactions to gluten in which allergy and autoimmunity have been excluded. Practically, this means patients in which Coeliac serology is negative (TTG, DGP, EMA), the patient has negative HLA DQ2/DQ8, IgA deficiency has been excluded, patients have normal duodenal histopathology, wheat immune-allergy tests are negative (IgE/CAST) and patients show a resolution of symptoms on a gluten-free diet which can be confirmed with an open food challenge. Currently there are no laboratory biomarkers for WI.

REFERENCES