

The changing face of coeliac disease: links with other autoimmune disorders

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The onset of coeliac disease, together with type 1 diabetes, influences glycaemic control, and more precisely the development of hypoglycaemia. These conditions share a similar genotype. The main problem of coeliac disease is intolerance to gliadin, a gluten protein found in cereals such as wheat, rye and barley; the only treatment is a gluten-free diet. Spomenka Ljubic and Zeljko Metelko report on the growing body of evidence linking coeliac disease and other autoimmune disorders, including type 1 diabetes, and describe recommended procedures for its diagnosis and treatment.

Coeliac disease is an autoimmune disorder of the small intestine which is accompanied by inflammation. It occurs in children and adults with a genetic predisposition, in interaction with environmental factors. Coeliac disease is more common than was previously thought.¹ In the USA, more

than 60 000 people are diagnosed every year.² Indeed, coeliac disease is the most common genetically pre-determined condition in people, with a prevalence of up to 1% in the tested population.³ The incidence of symptoms of the disease are reduced during periods of starvation, as was

observed in children during the second world war.⁴

Pathogenesis

Ingestion of gliadin in food causes inflammation in people who are susceptible. An abnormal T-cell-mediated immune response is followed by inflammatory damage to the small intestine.⁴ This inflammation can result in mucosal damage and consequent difficulty in digesting or absorbing nutrients from food (malabsorption).²

Coeliac disease involves difficulty digesting or absorbing nutrients from food.

Genetic markers on chromosome 6, known as human leukocyte antigen HLA-DQ2 and HLA-DQ8 are very frequent in these people. T-cells (a type of white blood cell), together

Table 1: Clinical disorders associated with coeliac disease

<p>Gastrointestinal</p> <ul style="list-style-type: none"> Liver disease Aphthous mouth ulcers Irritable bowel disease Lymphocytic gastritis Small bowel adenocarcinoma <p>Neurological</p> <ul style="list-style-type: none"> Peripheral neuropathy Epilepsy Ataxia <p>Endocrine</p> <ul style="list-style-type: none"> Type 1 diabetes Infertility Recurrent abortion Thyroid disorders Addison's disease <p>Renal</p> <ul style="list-style-type: none"> IgA nephropathy <p>Dermatological</p> <ul style="list-style-type: none"> Dermatitis herpetiformis Psoriasis Brown pigmentation of the face <p>Dental</p> <ul style="list-style-type: none"> Damage to tooth enamel 	<p>Haemopoietic</p> <ul style="list-style-type: none"> Anaemia Coagulation disorders IgA deficiency Hyposplenism T-cell lymphoma <p>Locomotor</p> <ul style="list-style-type: none"> Osteopenia Arthralgia <p>Psychiatric</p> <ul style="list-style-type: none"> Depression Schizophrenia <p>Genetic</p> <ul style="list-style-type: none"> Down's syndrome <p>Cardiovascular</p> <ul style="list-style-type: none"> Cardiomyopathy <p>Other</p> <ul style="list-style-type: none"> Alopecia areata Sjögren syndrome Finger clubbing Pharyngeal and oesophageal carcinoma
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Cancer risk

It is believed that coeliac disease represents the beginning of a range of conditions that, for a small percentage of people, might lead to a form of cancer, enteropathy-associated T-cell lymphoma. Most people with coeliac disease respond to a gluten-free diet and do not progress to the later stages. However, people who do not respond to the therapeutic diet experience changes in their immune system and in the cells lining their small intestine. Severe inflammation of the small intestine is known as refractory sprue. People with refractory sprue are at high risk from enteropathy-associated T-cell lymphoma and need to be treated with corticosteroids and immuno-suppressants.⁴

Most people respond to a gluten-free diet and do not progress to the later stages of the disease.

The proportion of people with coeliac disease presenting with gastrointestinal symptoms is decreasing.³ Widely used serological tests facilitate the diagnosis of 'milder' and asymptomatic cases of coeliac disease at a later age. This trend is expected to continue in the future.⁴

Associated conditions

The most common skin-related symptom of coeliac disease is dermatitis herpetiformis – an extremely itchy rash, which is present in approximately 25% of people with the disease; 90% of people with dermatitis herpetiformis also suffer from coeliac disease.² Extended exposure to gluten can result in increased incidence of autoimmune hepatitis, autoimmune thyroid disease,

with HLA-DQ2 and HLA-DQ8, stimulate the production of cytokines (proteins and peptides that are used as signalling compounds) by stimulating plasma cells. As a result, further antibodies to gliadin, tissue transglutaminase and endomysium are produced.^{2,4} The predisposing genotypes HLA-DQ2 and HLA-DQ8 have been found in approximately 98% of people with coeliac disease. The risk of coeliac disease is higher in people with first-degree relatives with the disease.³

Clinical symptoms

Important symptoms and signs of

coeliac disease include anaemia, joint pain, fatigue, infertility, weight loss, and especially gastrointestinal symptoms such as abdominal pain, anorexia, bloating, constipation, and diarrhoea.^{2,4} In children, the clinical picture is more typical: they are likely to suffer from bloating, diarrhoea, oedema, impaired growth and vomiting. The onset of coeliac disease is associated with the consumption of cereals.⁴ In severe cases of coeliac disease, delays in the onset of puberty, anaemia, and deficiencies in iron, folic acid, calcium and vitamin D can also occur, as can elevated levels of transaminase (a liver enzyme).³

connective tissue disease (Sjögren syndrome, rheumatoid arthritis), Addison's disease, and type 1 diabetes.²

About 15% to 30% of people with type 1 diabetes also have autoimmune thyroid disease; 4% to 9% have coeliac disease; and 0.5% have Addison's disease. Up to 10% of people with type 1 diabetes are found to be positive for endomysial and transglutaminase autoantibodies.⁵ Coeliac disease, together with type 1 diabetes, can also form a part of the autoimmune polyendocrine syndrome II.

Extended exposure to gluten can provoke hepatitis, thyroid disease, and type 1 diabetes.

One possible explanation for this might be that coeliac disease and other disorders share the same autoimmune mechanism or gene. It is possible that chronic lymphocyte stimulation in people with coeliac disease acts as a trigger for other autoimmune diseases. Untreated people suffer from more serious autoimmune diseases, probably because the risk of developing antibodies is associated with exposure to gluten.

Hypoglycaemia

Mucosal damage and inflammation can change the absorption of nutrients, affecting glycaemic control and thus provoking hypoglycaemia.³ Changes in a person's body mass index may occur, also affecting glycaemic control. The diagnosis of coeliac disease can be made prior to, at the diagnosis of, or after the diagnosis of type 1 diabetes, but usually occurs within 5 years of diagnosis.¹

In people with type 1 diabetes, hypoglycaemia and diarrhoea might serve as an indication for a diagnosis of coeliac disease. Clinical disorders associated with coeliac disease are presented in Table 1.

Diagnosis

Serological tests should be performed prior to initiating a specific diet. People with coeliac disease often lack the IgA anti-gliadin antibody.⁵ Initially, therefore, tests should be carried out to determine IgA-tissue and total serum transglutaminase. If these are negative, despite strong suspicion of the presence of coeliac disease, a test for IgA anti-endomysial antibody should be carried out. Tests for IgA anti-gliadin antibody and IgG anti-gliadin antibody should also be added to the diagnostic procedure, although these can also be found in healthy people.⁴

The combination of tissue transglutaminase and anti-endomysial antibody has been established as being sensitive and specific in almost all cases. The genetic markers, HLA-DQ2 and HLA-DQ8, are important in the diagnosis of coeliac disease. However, a tissue biopsy of the second or third sections of distal duodenum remains the gold standard.

Treatment

The only treatment for people with coeliac disease is a gluten-free diet. Strict adherence to a gluten-free diet results in the absence or attenuation of both the intestinal and extra-intestinal symptoms of coeliac disease.² Indeed, it is essential for those with the disease to be aware that they need to adhere to a gluten-free diet for their entire life.

Persistent symptoms despite adherence to this diet may be associated with disorders like colitis or irritable bowel disease. People with coeliac disease can benefit from supplementing their diet with calcium, vitamin D, iron, and folic acid.

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