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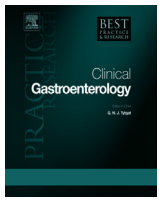

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Adaptive diagnosis of coeliac disease

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Selective immunoglobulin A deficiency

A B S T R A C T

Coeliac disease has for a long time simply been regarded as a gluten-dependent enteropathy and a duodenal biopsy was required in all patients for the diagnosis. It is now accepted that autoimmunity against transglutaminase 2 is an earlier, more universal and more specific feature of coeliac disease than histologic lesions. Moreover, high serum levels of combined anti-transglutaminase 2 and anti-endomysium antibody positivity have excellent predictive value for the presence of enteropathy with villous atrophy. This makes the histology evaluation of the gut no longer necessary in well defined symptomatic paediatric patients with compatible HLA-DQ2 and/or DQ8 background. The biopsy-sparing diagnostic route is not yet recommended by gastroenterologists for adults, and certain clinical circumstances (immunodeficiency conditions, extraintestinal manifestations, type-1 diabetes mellitus, age less than 2 years) may require modified diagnostic approaches. Coeliac patients with preserved duodenal villous structure do exist and

Abbreviations: CD, coeliac disease; GFD, gluten free diet; HLA, Human Leucocyte Antigen; TG2, type 2 (tissue) transglutaminase; TGA, anti-transglutaminase 2 antibodies; DGP, antibodies against deamidated gliadin peptides; EMA, anti-emdomysium antibodies; ESPGHAN, European Society for Pediatric Gastroenterology Hepatology and Nutrition; AGA, anti-native gliadin antibodies; T1D, type-1 diabetes mellitus; DH, dermatitis herpetiformis; IELs, intraepithelial lymphocytes; γδ, gamma delta T cells; Reg3α, Regenerating islet-derived 3-alpha; TCR, T cell receptor; SNP, single nucleotide polymorphism; PCR, polymerase chain reaction; IFN, interferon.

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these need a more extended evaluation by immunologic and molecular biology tools.

Introduction

The burden of diagnosing coeliac disease (CD) is high: when made, the patient has to follow a gluten-free diet (GFD) for life and, when missed, exposes the patient to elevated risk of complications which could be avoidable. Today, the symptoms are highly variable and may be even absent and the most consistent finding is autoimmunity indicated by the presence of anti-transglutaminase antibodies (TGA) accompanied in most, but not all, cases by enteropathy with villous atrophy. The diagnostic findings are gluten dependent and premature changes in the diet may interfere with the diagnosis. Nowadays, information on CD and suggestions to reduce gluten intake are abundant from the internet and other media, thus delays in appointments and diagnostic procedures may decrease diagnostic success.

Evolution of diagnostic criteria

CD was initially defined as steatorrhoea on a gluten-containing diet. The first accurate diagnostic criteria were published in 1969 by the European Society of Paediatric Gastroenterology and Nutrition (ESPGAN), which were based on three histology evaluations of the small intestinal mucosa establishing the presence of a gluten-dependent enteropathy (severe villous atrophy at diagnosis, remission on a gluten-free diet and relapse after gluten provocation) [1]. Even after the recognition of disease-specific antibodies and the reduction of required biopsies in 1990 [2], for many years CD has been defined, and thus simply considered, as a gluten dependent enteropathy. However, the most recent ESPGHAN diagnostic guidelines (2012) [3] for the first time defined CD as an immune-mediated systemic disorder elicited by gluten and related prolamines, occurring only in genetically susceptible individuals carrying the human leucocyte antigen (HLA) class II haplotypes -DQ2 and/or -DQ8 and characterised by the presence of a variable combination of gluten-dependent clinical manifestations including gastrointestinal and extra-intestinal signs and symptoms, elevated titers of coeliac-specific antibodies, autoantibodies against the enzyme type-2 (tissue) transglutaminase (TG2), endomysium and deamidated gliadin peptides (DGP) and a small intestinal enteropathy [3].

Tools for the diagnostic evaluation

Antibodies

Primary antibodies

CD is an immune-mediated disorder orchestrated by DQ2 and/or DQ8-restricted gluten-specific T cells. These T cells recognise mostly, but not exclusively, modified gliadin peptides bearing deamidation pattern specific for the enzyme TG2 and provide help for antibody production upon gluten exposure [4]. Gliadin presentation to specific T cells and anti-gliadin antibody production may occur in many people [5], but the immune response coupled with antibody production against TG2 is unique for CD. Gluten-dependent TGA are specific biomarkers of CD and they are predominantly of IgA class [6,7]. Patients with selective humoural IgA deficiency (total serum IgA <0.05g/l) produce IgG and IgM class TGA [8,9]. Recently, disease-specific epitopes of TGA have been identified and they show a very conservative pattern common in all CD patients [10,11].

TGA are produced in gut plasma cells [12] and the antibodies locally bind to the TG2 autoantigen in the mucosa [13]. TGA are first accumulating in tissues expressing TG2 (gut, liver, spleen, heart, kidney, brain, endocrine glands, placenta) and also may appear in the circulation, duodenal juice [13] and saliva [14]. It is important to note that serum TGA levels reflect only the tip of an iceberg, and TGA can be