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Research paper

Strategies to improve the efficiency of celiac disease diagnosis in the laboratory

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ABSTRACT

The demand for testing to detect celiac disease (CD) autoantibodies has increased, together with the cost per case diagnosed, resulting in the adoption of measures to restrict laboratory testing. We designed this study to determine whether opportunistic screening to detect CD-associated autoantibodies had advantages compared to efforts to restrict testing, and to identify the most cost-effective diagnostic strategy. We compared a group of 1678 patients in which autoantibody testing was restricted to cases in which the test referral was considered appropriate (G1) to a group of 2140 patients in which test referrals were not reviewed or restricted (G2). Two algorithms A (quantifying IgA and Tissue transglutaminase IgA [TG-IgA] in all patients), and B (quantifying only TG-IgA in all patients) were used in each group, and the cost-effectiveness of each strategy was calculated. TG-IgA autoantibodies were positive in 62 G1 patients and 69 G2 patients. Among those positive for tissue transglutaminase IgA and endomysial IgA autoantibodies, the proportion of patients with de novo autoantibodies was lower ($p = 0.028$) in G1 (11/62) than in G2 (24/69). Algorithm B required fewer determinations than algorithm A in both G1 (2310 vs 3493; $p < 0.001$) and G2 (2196 vs 4435; $p < 0.001$). With algorithm B the proportion of patients in whom IgA was tested was lower ($p < 0.001$) in G2 (29/2140) than in G1 (617/1678). The lowest cost per case diagnosed (4.63 euros/patient) was found with algorithm B in G2. We conclude that opportunistic screening has advantages compared to efforts in the laboratory to restrict CD diagnostic testing. The most cost-effective strategy was based on the use of an appropriate algorithm.

1. Introduction

Celiac disease (CD) is a relatively common autoimmune disorder that affects both children and adults, with an estimated prevalence of 0.5% to 1% in the general population (Rewers, 2005). It is strongly linked to alleles DQ2 and DQ8 (Lundin et al., 1990), which are present in 95%–98% of persons with CD, and are expressed in 25%–30% of the population in western countries. The risk of CD is 3-fold to 5-fold greater in persons with autoimmune thyroiditis, type 1 diabetes, Down syndrome and IgA deficiency.

In children, CD presents with abdominal distension and/or pain, diarrhea and weight loss between the ages of 6 to 24 months after gluten is introduced in the diet. In adults the most common symptom is iron deficiency anemia. Most patients present manifestations related with malabsorption. Early diagnosis and a gluten-free diet are fundamental to prevent complications (Fasano et al., 2003) and it also has economic advantages (Long et al., 2010). The gold standard for definitive diagnosis is based on typical histological alterations in the intestine and clinical improvement with a gluten-free diet. In 75% of all cases CD remains undiagnosed (West et al., 2014). An increase in the incidence of diagnosis has been reported in people older than 65 years (Murray et al., 2003), and diagnosis in adults is often delayed by as long as 15 to 17 years (Patel et al., 2005; Fuchs et al., 2014).

Autoantibodies specific for CD belong to the IgA class, and

Abbreviations: CD, Celiac disease; TG-IgA, Tissue transglutaminase IgA; EmA-IgA, Endomysial IgA; DGP-IgG, Deamidated gliadin peptide IgG; FEIA, Fluorescence enzyme immunoassay; CLIA, Chemiluminescence immunoassay

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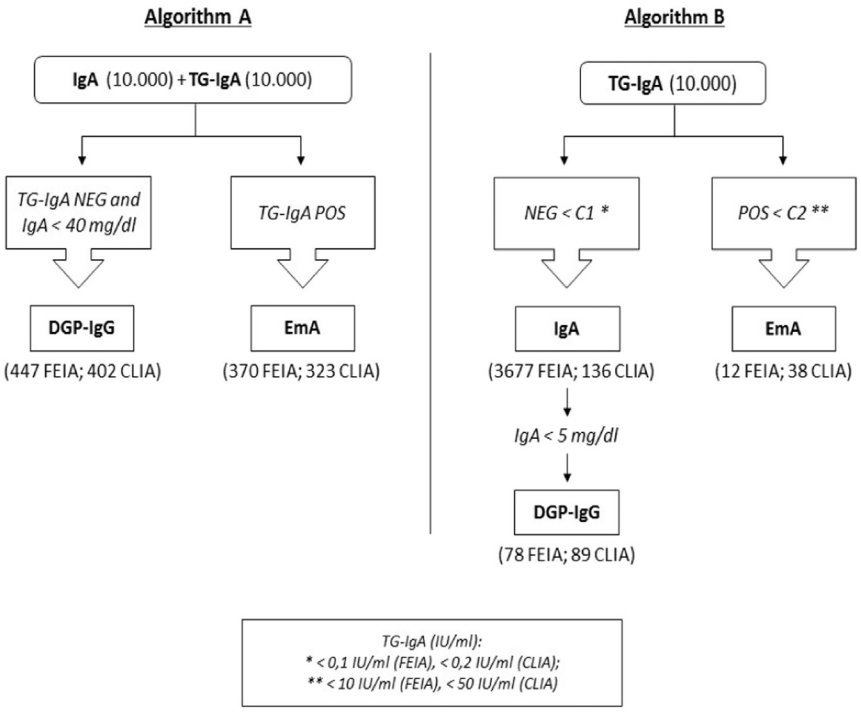

Fig. 1. Two laboratory working algorithms, A and B were evaluated.

recognize tissue transglutaminase (TG) (Dieterich et al., 1997) and deaminated gliadin peptides (DGP) (Rashtak et al., 2008a, 2008b; Prause et al., 2009). Clinical guidelines have been published for the diagnosis and management of CD in children and adolescents (Hill, et al., 2005; Husby et al., 2012), and in adults (Ludvigsson et al., 2014). These sources recommend algorithms based on determinations of TG and EmA-IgA, whereas the role of DGP antibodies is less well established (Husby et al., 2012; Ludvigsson et al., 2014). Because CD is defined as a common multiorgan disease (Husby et al., 2012), there has been growing interest in optimizing the use of autoantibody testing, with a consequent increase in the cost per case diagnosed and the adoption of measures to restrict testing. The most widely used laboratory methods for antibody detection are fluorescence enzyme immunoassay (FEIA), enzyme-linked immunosorbent assay (ELISA), chemiluminescence (CLIA), the Luminex® system, and indirect immunofluorescence (IFI) (http://www.immqas.org.uk/).

The aims of this study were to determine whether opportunistic screening to detect CD-associated autoantibodies had advantages in comparison to restricted testing, and to determine the most cost-effective strategy for diagnosis.

2. Material and methods

2.1. Patients

Celiac disease-associated autoantibodies were determined in 3818 patients selected with a random start and consecutive recruitment method. We enrolled all patients who were tested at our clinical laboratory during two 3-month periods from 1 April to 30 June in 2015 and 2016. The study was approved by the Bioethics Committee of Nuestra Señora de la Candelaria University Hospital, which serves as the reference center for a population of 600.000 inhabitants in the island of Tenerife.

Two groups were compared:

Group 1 was studied in 2015 and consisted of all 1678 patients who met the criterion for restricted testing, i.e., only those whose referrals for autoantibody testing were considered appropriate and justified (Their diagnostic suspicion was reported to the laboratory). Patients whose test referrals were considered inappropriate (Their diagnostic suspicion was not reported to the laboratory) were excluded (n = 132, of whom 93 were referred by their primary care physician). In all patients, we simultaneously tested for IgA and TG IgA. If IgA deficit or low IgA was detected, DGP-IgG antibodies were tested. Patients with an uncertain or positive TG-IgA test result were also tested for EmA-IgA antibodies. Antibodies to TG-IgA and DGP-IgG were quantified by FEIA.

Group 2 was studied in 2016 and consisted of 2140 patients whose test referrals were not checked to exclude inappropriate requests (Opportunistic screening). In all patients, we simultaneously tested IgA and TG-IgA. If IgA deficit or low IgA was detected, DGP-IgG antibodies were tested. Patients with a positive TG-IgA test result were also tested for EmA-IgA antibodies. Antibodies to TG-IgA and DGP-IgG were quantified by CLIA.

2.2. Methods

2.2.1. Laboratory parameters

TG-IgA antibodies in group 1 were measured with the EliA Celikey IgA technique (Phadia, Freiburg, Germany). This FEIA was carried out automatically in a Phadia 250 autoanalyzer. Values between 7 and 10 IU/mL were considered uncertain, and values > 10 IU/mL were considered positive. In group 2, TG-IgA antibodies were determined with the ZENIT RA t-TG IgA kit (Technogenetics S.r.l., Milan, Italy). This CLIA was carried out automatically in a dedicated ZENIT RA Analyzer. Values > IU/mL were considered positive. The correlation between both techniques (r = 0.96) has been published (Farré Massip, 2013).

DGP-IgG antibodies were measured in all patients with IgA < 40 mg/dL. In group 1 were measured with the Elia Gliadin DP IgG technique (Phadia). This FEIA was carried out automatically in a Phadia 250 autoanalyzer. In group 2, the ZENIT RA Deamidated Gliadin IgG kit (Technogenetics) was used; this CLIA was run automatically with a ZENIT RA Analyzer.

To detect EmA-IgA antibodies we used an IFI technique in monkey esophagus sections (Eurospital Spa, Trieste, Italy).

For IgA analysis we used an automated immunoturbidimetric method with a Roche/Hitachi Cobas c system (Roche Diagnostics Ltd., Rotkreuz, Switzerland). The results were recorded in five concentration ranges of (mg/dL) < 5 (IgA deficit), 5–39 (low IgA), 40–99, 100–400