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Molina Arias M[1], Pérez-Moneo Agapito B[2]
[1]Department of Gastroenterology and Nutrition. Hospital Infantil Universitario La Paz. Madrid. Spain.
[2]Hospital Universitario Infanta Leonor. School of Medicine. Universidad Complutense de Madrid. Madrid. Spain.

Correspondence: Manuel Molina Arias, mma1961@gmail.com

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Can the diagnosis of celiac disease be based on serologic tests alone?

Molina Arias M[1], Pérez-Moneo Agapito B[2]

[1]*Department of Gastroenterology and Nutrition. Hospital Infantil Universitario La Paz. Madrid. Spain.*

[2]*Hospital Universitario Infanta Leonor. School of Medicine. Universidad Complutense de Madrid. Madrid. Spain.*

Correspondence: Manuel Molina Arias, mma1961@gmail.com

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Abstract

Authors' conclusions: in a prospective study, we validated the IgA anti tissue transglutaminase procedure and the IgA anti tissue transglutaminase-IgG anti deamidated gliadin procedure in identification of pediatric patients with or without celiac disease, without biopsy.

Reviewers' commentary: although serological determinations are useful for the diagnosis of celiac disease and can allow diagnosis without duodenal biopsy, it seems reasonable to continue with the current recommendations, especially in groups of patients with low risk of disease.

Key words: endoscopy; ELISA; gluten; antibodies.

¿Se podría diagnosticar la enfermedad celíaca solo con serología?

Resumen

Conclusiones de los autores del estudio: se validan, mediante un estudio prospectivo, dos procedimientos basados en la determinación de anticuerpos antitransglutaminasa y anticuerpos antigliadina-deaminada para la identificación de pacientes pediátricos con y sin enfermedad celíaca, sin necesidad de biopsia.

Comentario de los revisores: aunque las determinaciones serológicas son útiles para el diagnóstico de enfermedad celíaca y pueden permitir el diagnóstico sin necesidad de recurrir a la biopsia duodenal, parece razonable continuar con las recomendaciones actuales, especialmente en grupos de pacientes de bajo riesgo de enfermedad.

Palabras clave: endoscopia; ELISA; gluten, anticuerpos.

STRUCTURED ABSTRACT

Objective: to validate the positive and negative predictive values of two diagnostic procedures for celiac disease (CD) based on the use of antibodies without the use of biopsy.

Design: multicentre cohort study for diagnostic test validation.

Setting: 13 paediatric gastroenterology units in hospitals in Europe.

Study participants: children aged 5 months to 18 years scheduled for duodenal biopsy to confirm or refute CD. The following patients were excluded: patients already diagnosed with CD, on a gluten-free diet, who had received immunosuppressive therapy within the past 8 weeks, expected to be non-compliant or participating in other trials. A total of 949 participants were enrolled, and 898 were included in the final analysis.

Evaluation of diagnostic procedures: each participating centre continued its standard practices to prescribe a gluten-free diet and make the final diagnosis. For each patient, data

on clinical manifestations, local antibody, HLA typing and IgA results were documented, with collection of local serology samples and samples for the blinded measurement of IgA antibodies against tissue transglutaminase (TTG) and IgG antibodies against deamidated gliadin peptides (DGL). The study evaluated two diagnostic procedures and their results. The first procedure involved the investigation of TTG. Three diagnostic categories were defined: no CD if assay results were < 1-fold the upper limit of normal (ULN), uncertain between 1- and 10-fold the ULN, and CD if results were > 10-fold the ULN. The second procedure involved the investigation of TTG-DGL: CD was ruled out if both were < 1-fold the ULN, confirmed if both were > 10-fold the ULN, and results were otherwise considered inconclusive (with biopsy required for diagnosis).

Outcome measurement: the authors calculated positive predictive values (PPVs) and negative predictive values (NPVs). The diagnosis of CD, no CD or no final diagnosis was made based on biopsy results, serologic test results and follow-up data. Patients without a final diagnosis were considered false positives or false negatives based on the results of serologic testing. The diagnostic procedure was considered reliable if the estimated PPV and NPV were greater than 95% and the lower bounds of their confidence intervals (LCBs) were greater than 90%.

Main results: the study analysed 898 patients, with a final diagnosis of CD in 529 and of no CD in 345, with 24 patients remaining undiagnosed at the end of the study.

Of all patients with CD, 76.4% had TTG results that were at least 10-fold the ULN (404 out of 529), while the results of TTG were negative in 84.9% of patients without CD (293 of 345). Based on this criterion, less than one fourth of patients required a biopsy.

The PPV for the TTG procedure was 0.988 (95 LCB: 0.975) and the NPV was 0.934 (95 LCB: 0.908). For the TTG-DGL procedure, the PPV was 0.988 (95 LCB: 0.975) and the NPV was 0.958 (95 LCB: 0.934). The authors created a model for the extrapolation of the predictive values to determine the prevalence range for which these procedures would be reliable. Applying the established criteria, the procedures were estimated to be reliable for prevalences ranging between 0.04 and 0.53 for TTG, and from 0.04 to 0.63 for TTG-DGL.

Five patients had false positive results, two of whom had associated autoimmune disease. The other three did not have a final diagnosis by the time the study ended.

Twenty-one patients had false negative (FN) results with the TTG procedure, 20 of who were symptomatic. Fifteen received a diagnosis of CD and achieved remission with resolution of symptoms with a gluten-free diet. Using the TTG-DGL procedure, there would be 13 FN, 9 of them with CD.

In all patients with CD and TTG more than 10-fold the ULN, the levels of antiendomysium antibodies were positive and HLA status was compatible with CD (in those patients in who it had been performed).

The study included asymptomatic patients who had risk factors for CD, such as a family history of CD or a personal history of disease associated with an increased risk of CD (e.g. type 1 diabetes). Of the 47 patients with TTG > 10-fold the ULN, 46 received a diagnosis of CD. Symptomatic patients with CD were not more likely to be classified as positive than asymptomatic patients with CD using the diagnostic procedures based on TTG and TTG-DGL (76% versus 80%).

Conclusion: this prospective study validated the TTG and TTG-DGL procedures for the identification of patients with and without CD without the use of biopsy.

Conflicts of interest: two authors received grants from EUROIMMUN unrelated to this study, and two authors had registered the patent for the use of peptides for the diagnosis of CD.

Funding source: the study was funded by the European Regional Development Fund and an unrestricted grant from EUROIMMUN (Lübeck, Germany; the laboratory that performed the analyses).

COMMENTARY

Justification: traditionally, the diagnosis of CD has been based on the morphology of repeated duodenal biopsies combined with the withdrawal of gluten from the diet with its subsequent reintroduction. With the increasing knowledge on genetic factors and the development of serologic methods, the number of biopsies required for diagnosis continued to decrease, eventually leading to the 2012 guidelines of the ESPGHAN,[1] which allow the diagnosis of CD without the need for duodenal biopsy in a majority of patients. This study was relevant in that it validated the serologic procedures that are commonly used to diagnose CD.

Validity or scientific rigour: the diagnostic procedures under study and the population in which they were used were clearly defined. Both the procedures under study and the reference standard were performed almost simultaneously in every analysed patient. The sample was obtained by selecting patients at high risk of disease (prevalence of 0.59), which must be taken into account when extrapolating the results to populations with a lower prevalence. Selection bias may have been at play, as individuals with negative TTG results were less likely to be included in the study, since this finding usually leads to referral of the patient for biopsy, and this may have resulted in the exclusion of cases that would have corresponded to false negatives.

The reference diagnostic standard was a composite (final diagnosis based on biopsy, HLA typing and clinical followup) and included among its parameters the results of serologic testing (the method under study), which could have been a source of incorporation bias.

The data were analysed correctly, and the authors extrapolated the validity of predictive values based on the prevalence of disease by means of a Bayesian linear model. For this purpose, it may have been simpler and more useful to calculate likelihood ratios, which in turn would allow the calculation of the positive post-test probability in populations with prevalences different from the one found in the study.

Clinical relevance: the determination of antibodies for the diagnosis of CD, be it TTG alone or in combination with DGL, proved to be a useful test in patients at high risk of disease, with the lower bounds of the 95% confidence intervals for PPVs and NPVs exceeding 90%. Using data from the study, we calculated positive likelihood ratios of 9.07 for TTG and 7.66 for TTG-DGL, with a post-test probability for the presence of diseases of approximately 95% in this population*, which seem sufficient to confirm the diagnosis of disease without the need for duodenal biopsy. The negative likelihood ratios were 0.03 for TTG and 0.8 for DGL (while the latter test was less powerful than the former, its routine inclusion in the diagnostic workup allowed the detection of 6 patients with negative TTG results).

These results are similar to those reported by previous studies conducted in populations with a high prevalence of CD, such as the one by Werkstetter *et al*,[2] with a prevalence of 35%. However, they cannot be extrapolated to patients with a lower risk of disease, such as the general population or asymptomatic patients. Assuming a prevalence of 2% (the one in the general population of Spain), the positive post-test probability would drop to 15%,* which is insufficient for diagnosis, and performance of biopsy would be required in adherence to the current guidelines of the ESPGHAN.[1,3]

Applicability to clinical practice: the findings of this study are applicable to Spain. Serologic testing is a useful tool in the diagnosis of CD without the additional need for biopsy, especially in patients at risk and with obvious symptoms. At any rate, it seems reasonable to continue applying the currently accepted criteria (serologic, genetic and clinical), resorting to histological examination in cases where non-invasive tests are inconclusive for the purpose of diagnosis.

Conflicts of interest: the authors of the commentary have no conflicts of interest to declare.

REFERENCES

1. Husby S1, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips A, Shamir R, *et al.* European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr. 2012;54:136-60.
2. Werkstetter KJ, Korponay-Szabó IR, Popp A, Villanacci V, Salemme M, Heilig G, *et al.* Accuracy in diagnosis of celiac disease without biopsies in clinical practice. Gastroenterology. 2017;153:924-35.
3. Klapp G, Masip E, Bolonio M, Donat E, Polo B, Ramos D, *et al.* Celiac disease: the new proposed ESPGHAN diagnostic criteria do work well in a selected population. J Pediatr Gastroenterol Nutr. 2013;56:251-6.

* Figures calculated by the reviewers from study data.