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Editorial

Is the use of biopsy in celiac disease coming to an end?

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Reception date: November 22, 2017 • **Acceptance date:** November 24, 2017
Publication date: November 29, 2017

Evid Pediatr. 2017;13:49.

HOW TO CITE THIS ARTICLE

Martínez-Ojinaga Nodal E. Is the use of biopsy in celiac disease coming to an end? Evid Pediatr. 2017;13:49.

This article is available at http://www.evidenciasenpediatria.es/EnlaceArticulo?ref=2017;13:49
 • ISSN: 1885-7388

Is the use of biopsy in celiac disease coming to an end?

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Celiac disease (CD) is an immune-mediated systemic disorder triggered by the consumption of gluten and prolamines in genetically susceptible individuals, and characterised by a variable combination of gluten-dependent clinical manifestations, the presence of specific antibodies, high-risk HLA DQ2 or DQ8 haplotypes and enteropathy.[1]

The pathogenic cascade starts in the small intestine, with an enhanced permeability to gluten gliadin and loss of tolerance giving rise to innate and adaptive humoral and cell-mediated immune responses triggered by an external element, gluten, after it is deamidated by tissue transglutaminase type 2 (TTG2), which is the main autoantigen in CD.[2,3]

Thanks to the guidelines published by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in 2012,[1] it is now possible to diagnose CD in the paediatric population without performance of biopsy as long as patients have obvious symptoms consistent with active CD along with clearly positive (> 10 times the upper limit of normal) antitransglutaminase antibodies, as well as positive antiendomysium antibodies (EMA) in a subsequent test, combined with a high-risk HLA haplotype (DQ2 or DQ8). These guidelines underscore two key aspects: the systemic nature of the disease, in which enteropathy is considered just one of the elements to consider in diagnosis, and a high-risk HLA haplotype a required factor.

However, the development and application of these guidelines would not have been possible without the currently available serology tools: assays for TTG2 and EMA IgA antibodies, both of which target the same antigen (TTG2). Since enteropathy is no longer considered a necessary criterion for diagnosis, recent efforts have focused on the development and improvement of non-invasive methods and the combination of serologic markers for the diagnosis of CD.

Anti-gliadin antibodies (AGA) of the IgA class have a high sensitivity (Sen) but are also found in healthy individuals and individuals with enteropathies other than CD. Their titres correlate to gluten intake and their presence is considered part of the mucosal immune response. Since the identification of other antibodies (EMA and TTG2 antibodies), the use of AGA has become infrequent and is restricted to children aged less than 2 years, as approximately 10% of those affected in this age group have not yet developed anti-TG2 or endomysial antibodies when CD is first suspected.[4]

The determination of EMA is the most specific method (97-100%), with a positive predictive value (PPV) of 98-100% for the diagnosis of CD. However, it has several technical drawbacks that impede the simultaneous performance of multiple tests, such as its manual processing and its subjective interpretation. Since detection of anti-TG2 by ELISA became available, a much simpler method with almost the same specificity (Spe), determination of EMA is now mainly used to identify potential TTG2 antibody false negatives[4,5] and confirm the positive TTG2 antibody results in a second sample to avoid biopsy, in adherence with the new guidelines.

Determination of TTG2 antibodies is currently the gold standard for diagnosis because while it is less specific (Sen of 91-95% and Spe of 95-97%) than EMA, it can be performed rapidly. Evidence associating TTG2 antibody titres with the degree of histologic damage in CD has existed for years,[6] even suggesting a directly proportional association between antibody titres and the grade of duodenal histopathology. Patients with TTG2 antibody titres > 100 U/ml have at least Marsh 2 histology, and subsequent studies, prospective[7] as well as retrospective,[8-10] have found a nearly perfect correlation between anti-transglutaminase antibody titres and the diagnosis of CD confirmed by biopsy, which led the ESPGHAN to establish a minimum of 10 times the reference value to allow the omission of intestinal biopsy.

Later on, evidence emerged on the high affinity of HLA-DQ2/8-restricted T lymphocytes for peptides deamidated by TTG2, a reaction that does not take place in healthy individuals, leading to the analysis of deamidated gliadin peptides (DGP), initially by determination of IgG antibodies with ELISA, with a sensibility (Sen) of 70-95% and a specificity (Spe) of 80-94%. This method is useful in cases in which the diagnostic yield of the TTG2 antibody assay may be lesser, as happens in children aged less than 2 years or with IgA deficiency, but the positive predictive value (PPV) of this test in isolation is low (30%), so its use is not recommended unless it is combined with the determination of TTG2 antibodies or EMA.[11] Furthermore, the ESPGHAN guidelines do not currently consider contemplate DGP antibodies. In the past decade, rapid kits for the detection of DGP in capillary blood samples have become commercially available that are useful for initial screening, with a high Sen and Spe and an excellent NPV.[12] Nevertheless, they are not equivalent to the TTG antibody and EMA assays,[13] so positive results obtained through these kits (or negative results in patients in who there is a strong

clinical suspicion) should be confirmed by means of conventional serology.

It is worth highlighting two studies published this year whose aim was to assess the efficacy of serologic testing and the pertinence of the new ESPGHAN guidelines. The first one assessed the efficacy of TTG2 antibodies alone using titres > 10 times the reference value as the criterion for reliable diagnosis and omission of duodenal biopsy in symptomatic patients,[14] and the authors countered the new ESPGHAN guidelines in regard to HLA typing, which they considered unnecessary; the second is the retrospective study reviewed in the current issue of Evidencias en Pediatría comparing the determination of TTG2 antibodies alone to determination of both TTG2 and DGP antibodies.[15] This study also reported excellent positive and negative predictive values for the combination of both assays, although it did not resolve the gaps left by intermediate titres when it comes to the decision whether to perform biopsy in patients with seronegative CD,[16] with associated diseases or risk factors or who are asymptomatic. Furthermore, these results are only reliable in populations where the prevalence is of at least 4%, so they cannot be extrapolated to general populations with lower prevalences, as is the case in Spain, or to asymptomatic patients, which was the conclusion reached by the authors that reviewed this study.[17]

This is one of the reasons why duodenal biopsy continues to be the gold standard for diagnosis in adults or, outside Europe,[18] in both children and adults.[19,20]

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