The CD That Pays Dividends: More Than 15 Years of Deamidated Gliadin Peptide Antibodies

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Published online: 17 March 2017
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“...That twenty years is nothing...”

Lyrics from the tango “Volver” (To Return), by Carlos Gardel, 1930.

Celiac disease (CD) is a unique disorder in gastroenterology because, among other clinical and pathophysiological features, highly sensitive and specific serological tests are available that enable its precise diagnosis [1]. Current guidelines recommend that the diagnosis of CD should be based on a combination of intestinal (duodenal) biopsies and CD antibodies, which are specific surrogate biomarkers of gluten-dependent mucosal damage [1].

One of the milestones in CD history was marked by the discovery in the 1980's of a specific serological biomarker of CD enteropathy, the endomysial antibodies (EmA) [1]. In 1997, Dieterich et al. [2] identified transglutaminase 2 (TG2) as the autoantigen targeted by EmA. As a consequence, detection of tissue transglutaminase (tTG) autoantibodies, by using the enzyme-linked immunosorbent assay (ELISA) platform, became the reference serology for diagnosing CD with very high sensitivity and specificity [3], which in turn led to a profound revolution in the recognition of CD as a globally prevalent disease.

Deamidated gliadin peptide (DGP) antibodies were identified in 2001, soon after the recognition of pathophysiological events involving the deamidation of gluten peptides by TG2, which initiates the pro-inflammatory T cell response in CD [4]. DGP antibodies measured by ELISA came to be considered an additional or complementary serological tool in the diagnostic algorithm of CD [5, 6]. In some studies, IgG DGPs had the highest sensitivity for the diagnosis of CD [6] in addition to potential diagnostic advantages over other antibodies [7]. Despite this, the topic has remained controversial [8]. Limitations in study design are partly responsible for the lack of consensus as evidenced in a recent guideline [9].

In this issue of *Digestive Diseases and Sciences*, Hoerter et al. [10] provide new evidence supporting the use of DGP antibodies as part of the diagnostic algorithm for CD. They retrospectively evaluated 84 patients from two well-recognized referral centers who had positive IgG and/or IgA DGP but negative IgA tTG antibodies, and a duodenal biopsy. The authors reported that biopsy-proven histological changes enabled the identification of CD in 15.5% of the patients. Since the diagnostic algorithm employed by the authors of the study differed from the recommended conventional strategy, their strategy should be emphasized. A key finding in this study was that the concomitant measurement of IgA tTG and DGP antibodies may help in the identification of seronegative CD (SNCD), a diagnosis that could be overlooked if a conventional serological algorithm was followed (i.e., total serum IgA plus IgA tTG). Therefore, the authors concluded that adding DGP antibodies to the algorithm increases the sensitivity for the detection of CD.

Seronegative CD is defined as a gluten-dependent enteropathy with negative tTG and/or EmA. Other

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Fig. 1 Comparison of first serological strategies, with and without DGP antibodies in the diagnosis of celiac disease

potential causes of duodenal atrophy need to be considered in patients with conventional negative CD serology, such as giardiasis, other infections, common variable immunodeficiency, autoimmune enteropathy, or drug-induced enteropathy [11, 12]. While IgA deficiency occurs in <2% of the general population, the prevalence of CD in IgA-deficient individuals is 6.7–20.6% [12, 13]. Nevertheless, the true prevalence of SNCD is unknown; the relevance of IgA deficiency as a cause of SNCD may be overestimated due to diagnostic bias. SNCD is diagnosed based on low serum concentrations of tTG IgA and total IgA as the first-line tests in the diagnostic algorithm of CD. In this context, detection of SNCD in immunocompetent individuals is only possible when there is strong clinical suspicion, as this may promote the use of additional strategies, such as concomitant measurement of DGP antibodies (as a first serologic step) and/or duodenal biopsy. Indeed, previous studies suggest that DGP IgG isotype may be useful to detect CD in patients with isolated IgA deficiency [5, 6]. Compared with symptomatic CD patients, specific serological tests have inferior performance characteristics to diagnose populations with a low pretest risk and patients with mild enteropathy [6, 8]. Patients with ultra-short CD and a proportion of patients with dermatitis herpetiformis may fulfill criteria for SNCD [14]. Taking into consideration all of these observations, it seems likely that an unknown number of patients may have a subclinical or

silent clinical course and minimal gluten-induced enteropathy but have a high probability of being seronegative for one or more CD-specific antibodies.

Notably, as shown in Fig. 1 of the study by Hoerter et al., the serum concentration of DGP antibodies cannot discriminate between DGP-positive CD patients and cases regarded as “false positives.” Therefore, patients with discrepant results (tTG negative and DGP positive, or vice versa) should undergo duodenal biopsy. Although cost-effective analyses comparing different serological strategies (IgA tTG plus total serum IgA versus IgA tTG plus IgG DGP) are not available, the last combination, used as the first step in the algorithm, seems a prudent and cost-effective strategy. Most guidelines recommend the use of IgA EmA as confirmatory serology after obtaining IgA tTG [9]. Although EmA IgA is specific to CD, both tTG and EmA target the same antigen although EmA has a lower sensitivity than does tTG. This self-fulfilling prophecy is confirmed by Hoerter et al. showing that all SNCD cases detected were also negative for EmA IgA. Thus, the strategy used by Hoerter et al. will likely increase diagnostic accuracy. Figure 1 depicts the conventional diagnostic strategy and the strategy proposed by Hoerter et al. [10] in the diagnosis of CD. One drawback that needs to be elucidated in the future relates to the utilization of slightly different tests at the Boston (IgA or IgG DGP antibodies) and New York sites (blend combination of both DGP subtypes, single test). At this point, the study is not

able to identify which of the DGP subtypes (IgA, IgG or their combination in a single assay) have the best performance characteristics.

The interpretation of a positive DGP test in the absence of villous atrophy (“false positive”) deserves some discussion. 14.3% of DGP antibody positive patients in this study had mild enteropathy (Marsh stages I or II). Although the authors did not report clinical and histological changes after administration of a gluten-free diet, which could help in identifying these patients as having CD, Hoerter et al. also recognize that a prospective design could clarify whether DGP-positive cases are truly “false positive” or they represent potential CD cases where a positive serology presages a future CD diagnosis. A recent paper [15] studied CD children in whom serology was obtained as a mean of 1 year before diagnosis was available (and while CD was not suspected). In this context, 35 out of 48 children fulfilling these criteria had positive DGP tests 1 year before definitive CD diagnosis, but had negative IgA tTG [15]. The study suggests that, in a proportion of cases, DGP antibodies could predict CD in children at least 1 year before tTG seroconversion and development of enteropathy.

In conclusion, the study of Hoerter et al. [10] adds to the growing evidence in favor of the use of DGP antibodies in the diagnosis of CD. The study shows that DGP antibodies can detect CD in patients recognized as seronegative for the most commonly used serologic strategy (IgA tTG plus total serum IgA). Although the study confirms that isolated total IgA deficiency is an important cause for SNCD, cases with a minor degree of enteropathy should also be considered. The results from Hoerter et al. [10], in conjunction with those from previous studies, suggest that replacing total serum IgA measurement for DGP antibodies (mainly the IgG subtype), might have the advantage of detecting CD cases where the conventional strategy would exclude patients from further investigations. In the event of discordant serology (only IgA tTG or IgG DGP positive), intestinal biopsy assessment should be performed. Future studies will confirm whether, almost 20 years after their development, DGP antibodies have found their place in the serological algorithm of CD.

Compliance with ethical standards

Conflict of interest None.

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