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Research Article

Anti-Endomysial Antibody May Predict a Second Endoscopy in Coeliac-Suspected Patients with False Negative Index Duodenal Biopsies

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Abstract

Background/aims: A subset of coeliac-suspected patients requires 2 Oesophagogastroduodenoscopies (OGDs) to achieve histological confirmation. Their index OGD would fail to reach diagnosis despite 4 duodenal biopsies suggested by guidelines. We compared this subgroup of patients with other coeliac patients requiring 1 endoscopy and recognize any predictors to identify the former group.

Methods: Coeliac-suspected patients at our department underwent an OGD. Clinical, serological and histological data were retrieved from medical notes. Group 1 comprised patients who achieved diagnosis with 1 OGD. Group 2 required 2 OGDs.

Results: 178 patients underwent an OGD (mean age 47 years; 73.6% females). 12 patients (6.7%) required 2 OGDs. Both groups had the same mean number of duodenal biopsies at their index endoscopy (4.6 vs 4.5, P=0.76). In Group 2, the number of biopsies was higher at the second endoscopy (6.4 vs 4.5, P=0.028). Group 2 showed a negative or lower positivity for anti-EMA (P=0.039) and a lower anti-tTG IgA level (P=0.06) than Group 1.

Conclusion: Anti-EMA seronegativity or low positivity in coeliac-suspected patients indicates the need for more duodenal biopsies to achieve diagnosis and avoiding subsequent OGDs. This finding makes anti-EMA testing crucial in coeliac diagnostics.

Keywords: Anti-endomysial antibody; Anti-tissue transglutaminase IgA antibody; Coeliac disease; Duodenal biopsies

Abbreviations

Anti-Endomysial Antibody; Anti-EMA; Anti-Tissue Transglutaminase IgA, Anti Ttg-IgA; Coeliac Disease CD; Gastrointestinal GI; Second Part of Duodenum D2

Introduction

Small bowel biopsies have been the gold standard investigation for the diagnosis of Coeliac Disease (CD). These would usually follow the clinical suspicion such as diarrhoea, malabsorption or iron deficiency anaemia, together with a positive CD-specific serological test, with the most sensitive and specific being anti-tissue transglutaminase IgA (tTG-IgA) antibody in non-selective IgA deficient patients. The number of duodenal biopsies to be taken at endoscopy in coeliac suspected patients has been well studied, with international guidelines suggesting at least four biopsies from the second part of the Duodenum (D2) [1,2]. Despite these recommendations, a subgroup of such patients fail to show any duodenal histological abnormalities consistent with coeliac disease because their disease would manifest in a patchy distribution, a type of CD phenotype which is well described [3], and the obtained biopsies would not have targeted the diseased parts of the small bowel (false negative result). In such cases, if the clinical suspicion remains high or coeliac serology remains elevated, they would need to be subjected to a second upper Gastrointestinal (GI) endoscopy to obtain further duodenal biopsies for diagnostic histological confirmation. From studies carried out so far, such patients with a patchy distribution cannot be predicted prior to undergoing their index upper GI endoscopy. This would be very useful as more duodenal biopsies could be taken during their initial endoscopy (rather than the recommended four biopsies), aiming to get a histological diagnosis with one procedure, and avoiding unnecessary subsequent endoscopies with its associated risks and burden on endoscopic services.

We thus aimed to study and compare this subgroup of coeliac patients, requiring more than one upper GI endoscopy for diagnostic histological confirmation, with other coeliac patients in whom histological diagnosis was made with one endoscopy. We also aimed to identify any potential predictors, mainly serological antibodies, to identify this subgroup of coeliac patients that would benefit from additional number of duodenal biopsies at their index endoscopy to achieve diagnosis, thereby avoiding subsequent repeat endoscopies.

Materials and Methods

We retrospectively enrolled 178 patients, between January 2008 and April 2013, who were referred to the gastroenterology department either with clinical history suspicious for coeliac disease or with positive coeliac serology, for consideration of

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Table 1: Demographical, serological and histological differences between Group 1 and 2.

	Group 1	Group 2	p value
Total cohort of patients	166	12	
Gender - males - females	 45 (27.1%) 121 (72.9%)	 2 (16.7%) 10 (83.3%)	
Age (years) - mean - median	 46.5 47.5	 50.6 55	 0.39
Mean number of distal duodenal biopsies taken during the index endoscopy	4.6	4.5	0.76
Mean number of distal duodenal biopsies taken during the second endoscopy	-	6.4	*0.028*
Modified Marsh classification - Classification not reported, but features of coeliac disease noted - Marsh 1 - Marsh 2 - Marsh 3a - Marsh 3b - Marsh 3c	 39 3 3 36 50 35	 3 1 0 5 3 0	 0.135
Anti-tTG IgA antibody level (U/mL) - total no. of patients tested* - seronegative - seropositive but ≤165U/mL - seropositive >165U/mL	 156 15 62 79	 10 0 8 2	 0.06
Anti-endomysial antibody level - total no. of patients tested* - negative - positive + - positive ++ - positive +++	 136 6 15 31 84	 9 2 2 3 2	 *0.039*

*The patients who were not tested for coeliac serology had endoscopy based on clinical symptoms.

gastro duodenal biopsies. Their demographic, clinical, serological, endoscopic and histological data were retrieved from their medical notes. The serological data obtained were the ones requested up until 6 months prior to their index endoscopy. HLA typing is not routinely tested at our centre. A second endoscopy was performed in cases where the clinical suspicion and/or the anti-TTG IgA remained high, despite the index histological biopsies failing to show any intestinal abnormalities, including any villous atrophy or increased intraepithelial lymphocytes. The prevalence of newly diagnosed coeliac patients in the study period after one endoscopy (Group 1) or more than one endoscopy (Group 2) was calculated and the two groups compared together. Potential predictors for Group 2 were studied.

Results

A total of 178 patients were histologically diagnosed with CD in the study period. The mean age was 47 years ±16.02SD (median age 48 years, range 18 – 84 years) and 131 patients (73.6%) were females. Their clinical presentation varied from diarrhea or bloating after ingesting gluten-containing products, weight loss or iron-deficiency anaemia. Among this cohort, 12 (6.7%) (Mean age 50.6 years ±17.56SD; 10 females, 83.3%) required a second Gastroduodenoscopy (Group 2) for histological confirmation of the disease. Table 1 shows the patient characteristics between Group 1 and Group 2. The mean age between both groups was not statistically significant (46.5 vs 50.6, P=0.39, Independent T test). The mean number of distal duodenal biopsies taken from Group 1 and at the index endoscopy of Group 2 was also not statistically significant (4.6 vs 4.5, P=0.76, Mann Whitney test), thus confirming that in both groups the recommended guidelines were followed but were not enough to make the diagnosis in Group 2. However, the mean number of distal duodenal biopsies taken at the second endoscopy in Group 2 was statistically significant compared to the ones taken from the first endoscopy (6.4 vs 4.5, P=0.028, Wilcox on test). All patients in Group 2 had positive histology for coeliac disease from their second endoscopy. The severity of CD as described by the Modified Marsh classification was also not statistically different between both groups (P=0.135, Chi squared), confirming that Group 2 did not have milder disease, which could have possibly explained the need for more tissue acquisition to achieve a diagnosis.

On the contrary, the only potential predictor found to differentiate between the two groups was antibody serological testing. Anti-tTG IgA antibody and anti-Endomysial Antibody (EMA) were carried out in 166 patients (93.3%) and 145 patients (81.5%) respectively within six months prior to endoscopy. We found that Group 2 was associated with a negative or lower positivity for anti-EMA than Group 1, reaching statistical significance (P=0.039, Chi squared). In the two cases from Group 2 who had a negative anti-EMA (Table 1), both had elevated anti-TTG IgA and thus the reason for performing the second endoscopy. A study by Abrams et al had found that anti-EMA sensitivity was lower in those with less severe lesions [4]. Furthermore, there was only a tendency, rather than an association, for Group 2 to have a lower anti-tTG IgA level than Group 1 (P=0.06), marginally missing statistical significance. This tendency was only observed when an anti-tTG IgA level cut off of 165 U/mL was taken.

Discussion/Conclusion

In this study, we have found that high anti-EMA positivity is associated with a positive histological diagnosis when international guidelines are followed and 4 distal duodenal biopsies are taken (Group 1). What is more useful for clinical practice is that a

negative anti-EMA (in the context of a positive anti-TTG IgA) or low anti-EMA positivity seems to predict the need to obtain more distal duodenal biopsies to achieve histological diagnosis than the guidelines would suggest, and thus avoiding repeated endoscopies for diagnostic confirmation. All patients in Group 2 had histological confirmation when 6 distal duodenal biopsies were taken. At this stage, given the small sample size of Group 2, we cannot commit to a definite number of biopsies required to achieve diagnosis in this subgroup of patients, but rather a higher number of biopsies than the standard recommended (4) is required. To our knowledge, this is the first study, albeit small and retrospective, to explore the relationship between serological testing and protocol biopsy tissue sampling in coeliac-suspected patients. Although anti-tTG IgA antibody has a very high sensitivity and specificity for CD, triggering various centres to request it in isolation, the advantage of anti-EMA over anti-tTG to predict the above subclass of coeliac patients should make anti-EMA testing crucial in coeliac-suspected patients. Notwithstanding the small sample size in Group 2, this study did show a tendency for CD-specific serological testing to predict a subgroup of patients requiring more duodenal biopsies than the guidelines would suggest, especially anti-EMA, making this a further benefit of CD-specific antibodies in coeliac diagnostics. Validation of the above findings is therefore recommended using larger cohorts. Coeliac patients with low anti-EMA positivity and high anti-tTG IgA, such as in Group 2, clearly shows the subjectivity of the anti-EMA immunofluorescence test and the objectivity of the anti-tTG ELISA test. Thus, patients with a strong clinical suspicion for coeliac disease or with a high anti-tTG IgA should have a second endoscopy if the index biopsies fail to show duodenal abnormalities compatible with coeliac disease, irrespective of the anti-EMA result.

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