Celiac Disease: Are Endomysial Antibody Test Results Being Used Appropriately?

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Background: The aim of this study was to retrospectively examine how positive IgA-endomysial antibody (EMA) test results for celiac disease were being interpreted and acted on by physicians in the Calgary Health Region.

Methods: We reviewed consecutive EMA test results, with or without a serum IgA, obtained during a 17-month period. Seropositive tests were cross-referenced to the surgical database to determine the number of patients who underwent intestinal biopsy and the results of the biopsy. We sent questionnaires to the ordering physicians of positive tests with no record of intestinal biopsy.

Results: Among 11,716 EMA tests in 9,533 patients, 349 results were positive in 313 patients (3%). Intestinal biopsies were performed in 218 (70%) of the seropositive patients; 194 of them were diagnostic of celiac disease. Celiac disease was also found in 10 EMA-negative patients. Of the 109 positive tests performed in 95 patients with no subsequent biopsy, 28 had appropriate indications to not perform a biopsy; the most common reason being that the test had been ordered to follow up on a previous biopsy-proven diagnosis of celiac disease (n = 21). For 33 other positive test results without a subsequent biopsy, management appeared to be inappropriate, most commonly (n = 21) because of a recommendation to follow a gluten-free diet despite lack of a tissue diagnosis of celiac disease. For the remaining 48 positive EMA results, administrative issues prevented evaluation (n = 19), the patients refused further evaluation (n = 11), or physician surveys were not returned (n = 18).

Conclusions: Celiac disease affected 2% of patients, with a similar prevalence in male and female patients. Most positive EMA tests (77%) were appropriately managed by physicians. Beginning a gluten-free diet without biopsy or failing to follow up on a positive EMA test remain common errors of management.

The development and broader application of accurate serologic testing has dramatically altered the medical community’s conception of celiac disease (1). Traditionally, celiac disease was considered a rare disorder, estimated to occur in approximately 1 of 4500 persons in the US (2). Population screening studies revealed that celiac disease is common, however, with a prevalence reaching 1% in North American and European populations (3). Furthermore, it is now clear that celiac disease encompasses multiple clinical presentations not limited to the gastrointestinal tract. Patients display signs and symptoms involving a variety of organ systems, minor symptoms, or no apparent symptoms in conditions with an increased risk of celiac disease (4). Thus, serologic testing plays an increasingly critical role in the identification of patients with celiac disease.

Despite its high prevalence in the general population, celiac disease remains largely undiagnosed because of lack of awareness of its atypical manifestations and associated conditions, as well as the underutilization of serologic tests (5–7). The early diagnosis of celiac disease is critical not only to resolve symptoms and improve quality of life (8, 9), but also to prevent long-term complications, including anemia, osteopenia, infertility, intestinal lymphoma, and perhaps other autoimmune diseases (10).

Clinical guidelines report that serologic testing for celiac disease can play a major role to improve recognition in at-risk groups. Because serologic tests are not a perfect tool, intestinal biopsy remains the gold standard to diagnose celiac disease (10). Nonetheless, translating clinical guidelines into routine daily practice often does not occur (11). Given the difficulty in improving physician practice patterns, coupled with the general lack of awareness of celiac disease among clinicians (12) and the frequent
reports of delayed and failed diagnoses (5, 13–15), serologic testing for celiac disease may not be optimally used.

Although numerous investigations have assessed the diagnostic value of serologic testing for celiac disease, examination of what happens to seropositive patients in clinical practice remains underreported. In 1999, IgA-endomysial antibody (EMA) test utilization was evaluated in the Calgary Health Region. During a 1-year period, 939 EMA tests were ordered, and 101 positive EMA patients were identified. Surprisingly, 52% of the seropositive patients did not undergo an intestinal biopsy within 12 months after the EMA test was performed (R. McKenna, unpublished data). Other investigators also observed that up to 82% of seropositive patients do not undergo intestinal biopsy (16–18). This study evaluated how positive EMA tests were being interpreted and acted on by physicians.

**Materials and Methods**

**STUDY GROUP**
We reviewed consecutive EMA test results, with or without measurement of serum IgA, from the Calgary Laboratory Services computer database from March 1, 2003 to July 31, 2004. Serum samples submitted to the laboratory for EMA testing from laboratories outside the Calgary Health Region were excluded from the study.

**CELIAC DISEASE SEROLOGY**
At the time of this study, Calgary Laboratory Services offered the EMA assay for celiac disease serologic testing. Experienced technicians tested samples for EMA by an indirect immunofluorescence method from a commercial test system using monkey distal esophagus as substrate (IMMCO Diagnostics). Positive samples were serially diluted from titer of 1:2.5 to 1:1280, and a titer of 1:2.5 was considered to be the threshold for positivity, as established by the manufacturer. Positive and negative control samples were analyzed with each run. Serum IgA was measured using the Integra Immunoturbidimetric assay according to the manufacturer’s procedure (Roche Diagnostics). The laboratory measured serum IgA or performed an IgG-tissue transglutaminase (tTG) only if requested by the physician. IgA deficiency was defined as a serum IgA <0.06 g/L in patients ≥2 years old (19). External quality assessment of the EMA test through the College of American Pathologists was acceptable over the study period.

**HISTOLOGIC ASSESSMENT**
To determine the number of seropositive patients who underwent small-intestine biopsy and the biopsy results, we searched the Calgary Laboratory Services surgical pathology database by name and healthcare number of seropositive patients for records of small-intestine biopsies and skin biopsies performed between January 1, 2003, and May 11, 2005. An additional search of the pathology database including the terms “villous atrophy”, “celiac disease”, “sprue”, or “gluten-sensitive enteropathy” identified all small-intestine biopsies diagnostic of celiac disease, irrespective of EMA testing. All specimens were re-reviewed and graded according to the modified Marsh criteria (20) by an experienced pathologist unaware of the clinical information, EMA results, or initial diagnosis. If the diagnoses differed, a 3rd physician reassessed the biopsy specimens to make the final diagnosis. We made a diagnosis of celiac disease in intestinal biopsies with Marsh IIIα to IIIc lesions and skin biopsies demonstrating dermatitis herpetiformis. In biopsies with a Marsh I or II lesion, we also made a diagnosis of celiac disease in light of EMA positivity and response to a gluten-free diet (GFD) as determined by physician interview. The original pathologic assessment and the blinded review were considered discrepant if the diagnosis was changed from Marsh 0 to Marsh I, II, or III or vice versa. A change in diagnosis from Marsh I or II to Marsh III, and vice versa, was also considered discrepant. An additional search for apparently false-positive EMA patients between May 11, 2005, and May 15, 2007, determined how many received follow-up and if any developed celiac disease.

**QUESTIONNAIRE**
We sent a questionnaire to the EMA ordering physician to evaluate the management of EMA-seropositive patients with no record of intestinal biopsy. The questionnaire (see Supplemental Data that accompanies the online version of this article at http://www.clinchem.org/content/vol53/issue10) included a variety of multiple choice explanations as well as free space to explain why an intestinal biopsy had not been performed and how the patient was managed. After 6 weeks, we sent a reminder letter to nonresponding physicians.

**DATA ANALYSIS**
We classified responses from ordering physicians as appropriate management, inappropriate management, patient refusal, or administrative error. Appropriate management of seropositive patients included use of the EMA test to monitor histologic recovery and dietary compliance at least 3 months after the intestinal biopsy or in seropositive patients with other medical conditions that prohibited intestinal biopsy. Inappropriately managed patients included patients who began GFD without an intestinal biopsy as well as patients who received no further evaluation by their physician. Patients with celiac disease require 3–12 months on GFD for their EMA titer to become undetectable (21, 22). Thus, EMA tests ordered <3 months after an intestinal biopsy diagnostic of celiac disease were also classified as inappropriate. Administrative error included cases in which the ordering physician received the result but could not contact the patient, did

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4 Nonstandard abbreviations: EMA, IgA-endomysial antibody; tTG, tissue transglutaminase; GFD, gluten-free diet.
not receive the result, or could not be identified. Patient refusal denoted seropositive patients who refused intestinal biopsy and remained on a full diet or adopted GFD.

STATISTICAL ANALYSIS
A 2-tailed test of proportions (Stata for Windows) was used to compare proportions of EMA tests by age and sex. \( P < 0.05 \) was accepted as statistically significant.

Approval for this study was received from the Conjoint Medical Research Ethics Board of the University of Calgary. The granting agencies of this study had no involvement in study design or preparation of the manuscript and possessed no rights to approve, delay, or disapprove this publication. With the exception of the Calgary Laboratory Services, who released EMA data, IgA data, and pathology results, the data collection, analysis, and interpretation were performed solely by the investigators.

Results
STUDY GROUP DEMOGRAPHICS
During the 17 months for which we reviewed data, 11 716 EMA tests were ordered in 9533 individuals. Among these, 349 EMA test results were positive in 313 individuals (3%). Serum IgA was measured in only 4698 patients (49%), and 35 patients (0.7%) had IgA deficiency. At all age groups, significantly more female than male patients underwent EMA testing \( (P < 0.001) \) (Fig. 1).

The specialty distribution of the physicians ordering EMA tests included family practitioners (36%), adult gastroenterologists (36%), internists (13%), pediatricians (8%), pediatric gastroenterologists (2%), and other specialties (5%).

PATHOLOGY
A search of the pathology database revealed intestinal or skin biopsy records for 218 (70%) of the seropositive individuals and a diagnosis of celiac disease in 194 (89%) of patients who underwent biopsy (193 intestinal, 1 skin). Among the biopsies diagnostic of celiac disease, 8 (4%) were from patients previously diagnosed with celiac disease and were performed for follow-up or to assess dietary compliance. The remaining records included 8 (4%) with nonspecific duodenitis (<30 intraepithelial lymphocytes per 100 enterocytes) and 10 (5%) with no pathologic diagnosis. In addition, a normal biopsy was observed in 5 seropositive patients on GFD. One specimen was inadequate for histologic assessment. Thus, the positive predictive value of the EMA test was 91% (186 of 204), excluding the 8 patients previously diagnosed with celiac disease, 5 patients on GFD, and the inadequate specimen. During the same time period, intestinal biopsy records diagnostic of celiac disease (Marsh IIIa to IIIc) were identified in 10 IgA-sufficient patients with a negative EMA test. Physician interview confirmed that patient diets included gluten at the time of the EMA test. This approach represents the minimum number of false-negative EMA test results. Thus, the “maximum” sensitivity and specificity of the EMA test were 94.9% and 99.8%, respectively. Because we were unable to determine the number of seronegative patients who underwent intestinal biopsy, the maximum sensitivity and specificity assume that all other seronegative patients were true negatives. A 2.1% (196 of 9519) prevalence of biopsy-proven celiac disease was observed in this population. The proportions of EMA-tested females (140 of 6480, 2.2%) and males (56 of 3039, 1.8%) with biopsy-proven celiac disease did not differ. However, more 21- to 40-year-old women (67 of 2065, 2.1%) had biopsy-proven celiac disease than men (22 of 763, 0.8%, \( P < 0.05 \)). No differences in the prevalence of celiac disease between female and male patients were noted in other age groups. An additional 35 patients who did not undergo EMA testing had an intestinal biopsy consistent with celiac disease.

The distribution of Marsh scores between the original pathologic assessment and blinded pathology review revealed no significant differences (data not shown). Of all 218 biopsy records, the final diagnosis between the original pathologic assessment and the 2nd pathologist’s review differed in only 14 (6%). After review of these 14 discrepant cases by a 3rd physician, the final diagnosis changed in 3 seropositive patients. Among these 3 patients, 2 diagnoses changed from Marsh 0 to celiac disease (both Marsh I and confirmed by physician interview), and 1 diagnosis changed from Marsh IIIa to Marsh 0 (clinical information indicated the patient was on GFD at the time of biopsy).

The 18 patients with a false-positive EMA were found at all titers, with the exception of 1:160 and 1:320 (Fig. 2). The majority (58%) of false positives occurred at a titer of 1:10 or less, but >77% of seropositive patients at the lowest titers (1.2.5 to 1:10) were true positives. The single false-positive EMA result with a titer of 1:1280 suggested laboratory error, because a normal intestinal biopsy and a negative EMA test result were obtained within 6 weeks of

Fig. 1. EMA testing by age and sex.
In all age groups, a significantly greater proportion of females than males underwent EMA testing \( (P < 0.001) \).
the initial positive EMA. Physician interview revealed
that the patient did not begin GFD, and the patient’s
history was negative for other causes of a false-positive
EMA. The single false-positive EMA result with a titer of
1:640 was found in an asymptomatic patient with type 1
diabetes. An initial capsule biopsy, followed by endos-
copy with multiple biopsies, revealed mild villous atro-
phy without increased intraepithelial lymphocytes. This
case represented latent celiac disease, however, because
biopsies obtained 19 months after the inconclusive biop-
sies were diagnostic of celiac disease. Among the 16
remaining patients with false-positive EMA results (1:2.5
to 1:80), 8 were lost to follow-up and 4 had a negative
EMA up to 9 months after the initial positive EMA and
normal biopsy. An intestinal biopsy was repeated on 2
seropositive patients (1:2.5 and 1:5) 36 and 29 months,
respectively, after the initial biopsy; both results were
normal. One seropositive patient (1:5) with a normal
biopsy received a clinical diagnosis of celiac disease based
on increased small intestinal permeability, family history
of celiac disease, and response to GFD. In addition, 1
apparently false-positive patient (1:2.5) decided not to
pursue further testing for celiac disease. The median
number of biopsy specimens obtained from these appar-
ently false-positive EMA patients was 3 (range 1–7).

PHYSICIAN SURVEY RESULTS
Of the 349 positive EMA results, 240 (69%) tests were
performed in 218 patients who underwent intestinal bi-
opzy. No record of intestinal biopsy was found for 109
(31%) positive EMA tests in 95 patients. Only 18 (5%) surveys were not returned by physicians, giving a physi-
cian response rate of 81% (77 of 95). Physician survey
responses revealed apparently inappropriate manage-
ment in 33 (10%) and appropriate management without a
biopsy in 28 (8%) (Table 1).

Among the 28 appropriately managed positive EMA
tests with no record of intestinal biopsy, 21 tests were
ordered to provide follow-up care for celiac patients who
had undergone intestinal biopsy before January 2003. An
additional 3 tests were ordered for 3 patients who were
unable to undergo intestinal biopsy for medical reasons
including myocardial infarction, esophageal stricture, and
not specified. Two of these patients began GFD following
the positive EMA test, and 3 additional tests were per-
formed to demonstrate improvement on GFD. In addi-
tion, an asymptomatic patient with type 1 diabetes had an
EMA titer of 1:2.5. One year later, repeat EMA was
negative and annual EMA testing was recommended.

Apparently inappropriate management occurred in 33
(10%) of the 349 positive tests. In 21 cases, physicians
recommended GFD without an intestinal biopsy, because
of concern regarding long endoscopy waiting lists or
because they considered a biopsy unnecessary. In 6 other

Table 1. Responses to positive EMA test results (n = 349)

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<tr>
<th>Response to positive EMA test</th>
<th>Positive EMA results, n (%)</th>
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<tbody>
<tr>
<td>Appropriate—biopsy</td>
<td>240 (69)</td>
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<tr>
<td>Appropriate—no biopsy</td>
<td>28 (8)</td>
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<tr>
<td>Inappropriate</td>
<td>33 (10)</td>
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<tr>
<td>Administrative error</td>
<td>19 (5)</td>
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<tr>
<td>Patient refusal</td>
<td>11 (3)</td>
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<tr>
<td>No response to survey</td>
<td>18 (5)</td>
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cases, physicians did not recommend an intestinal biopsy because the patient became asymptomatic or did not experience classic celiac disease symptoms. The remaining 6 positive tests in this group were ordered <3 months after intestinal biopsy. The percentage of inappropriately managed tests did not differ when evaluated at each EMA titer (P >0.05, data not shown).

Patient refusal to undergo intestinal biopsy occurred in 11 (3%) of patients with positive EMA results. In 5 of these cases, the physician reported that the patient chose to begin GFD. Administrative error occurred in 19 (5%) of positive EMA tests. Within this group, 8 physicians indicated that they did not receive the serology results, and the other 7 physicians could not reconnect the patient. In the remaining 4 cases, the ordering physician could not be identified from the database.

**Discussion**

With a prevalence of 1:100 to 1:300, celiac disease is now recognized as an important health problem in North America (23, 24). Similar to the prevalence observed using a case-finding strategy (25), we observed a 1:47 prevalence of celiac disease in the population tested. This result likely underestimates the true prevalence of celiac disease in this population, because nearly one-quarter of patients with positive EMA results were not managed appropriately. Furthermore, only one-half of patients tested had their IgA measured; among these, 35 patients were IgA deficient. For a negative IgA-EMA or -tTG result to be accurately interpreted, the patient must be IgA sufficient. Failure to evaluate for IgA deficiency and inappropriate management of IgA-deficient, negative EMA patients is another source of inappropriate EMA testing (26).

A 10-fold increase in EMA testing between 1999 and 2004 was observed in our health region, likely because of increased celiac disease testing by family physicians. Even so, the percentage of EMA tests ordered by adult and pediatric gastroenterologists accounted for a high proportion (38%) of the tests ordered. Primary care physicians must receive additional education to improve the detection of celiac disease despite the diverse clinical presentations.

Previous studies suggest a female predominance of celiac disease (approximately 2:1) based on cases diagnosed in clinical practice (27, 28). The absolute number of EMA-tested females with biopsy-proven celiac disease was more than twice that of males in this study. However, the similar percentage of EMA-tested males and females with biopsy-proven celiac disease was consistent with North American and European celiac disease prevalence data, suggesting that the condition affects each sex equally (24, 29). The increased number of females undergoing EMA testing likely reflects a higher frequency of women seeking healthcare (30) and may suggest that sex influences the clinical presentation of celiac disease, with females displaying symptoms that are more likely to trigger the physician to test for celiac disease (28). However, patients in the 21- to 40-year age group were exceptions, because the prevalence of celiac disease in women in this age group was significantly higher than in men of the same age. This increased prevalence of celiac disease in females 21–40 years old may be due to the recognized onset of celiac disease during pregnancy or breastfeeding (31).

Despite the observed overall accuracy of the EMA test, as evidenced by a 91% positive predictive value, our results indicate that histologic assessment remains mandatory for the final diagnosis. Without an intestinal biopsy, celiac disease would be incorrectly diagnosed in up to 9% of seropositive patients. It is unacceptable to impose on individuals with a false-positive serology the dietary restrictions, social challenges, and increased expense associated with lifelong GFD. These limitations outweigh the convenience and decreased healthcare expenditures achieved by omitting an intestinal biopsy (32). Although most false-positive EMA tests occurred at low titers, more than three-quarters of seropositive patients at the 3 lowest titers were true positives, demonstrating that weak-positive EMA titers cannot be assumed to be falsely positive.

The absence of characteristic changes of celiac disease observed in small intestinal biopsy specimens from seropositive patients creates a diagnostic dilemma (33). Misinterpretation of biopsy results was ruled out by the blinded pathology review. However, fewer than half of patients with a false-positive EMA had an endoscopy with an adequate number of specimens. Because of inadequate tissue sampling, celiac disease may have been missed in these patients (10).

False-positive EMA test results may be an indication of latent celiac disease (10, 33). Fewer than half of false-positive EMA patients received adequate follow-up. Physicians need to be aware of the many causes of an apparently false-positive EMA and of the importance of serial follow-up. This follow-up may include repeat serology, additional intestinal biopsies, or analysis for susceptibility genes in the HLA class II DQ region (33).

This study confirms previous evidence that the EMA test does not identify all patients with celiac disease (34, 35). This limitation is especially true in patients with milder intestinal lesions, in whom the sensitivity may be <50% (35). In light of a negative EMA test, physicians may not further evaluate their patients for celiac disease despite suggestive clinical history (7). Thus, physicians must be aware that when a high clinical suspicion of celiac disease exists, an intestinal biopsy should be recommended regardless of the EMA test result (35).

The majority (77%) of positive EMA tests were interpreted and acted on appropriately by physicians in the Calgary Health Region. In many of the cases in which the EMA-positive patient did not subsequently undergo intestinal biopsy, valid clinical rationales were applied, such as for EMA tests to monitor dietary compliance in patients with previously diagnosed celiac disease, as well as...
reasons beyond the control of the physician. Although the high prevalence of appropriate use of the EMA tests is promising, in approximately 1 in 7 cases with positive EMA tests inappropriate patient management occurred, including recommendation for GFD with no intestinal biopsy, inaction because of symptom resolution or atypical symptoms, and administrative error. Thus opportunities remain to improve practice patterns, reduce administrative error, and decrease the risk that seropositive patients will be placed unnecessarily on an expensive, restrictive, and challenging diet for life and not seek medical attention for another underlying ailment (32, 36). In addition, patients with celiac disease diagnosed by intestinal biopsy are more likely to adhere to GFD (37). An intestinal biopsy also provides a baseline assessment, should additional biopsies be required for patients who do not respond to GFD (37).

It has been estimated that approximately 30%–40% of patients do not receive care consistent with current evidence (11). Our findings lend support to previous studies, which suggest that not all patients with celiac-related antibodies undergo intestinal biopsy. Lock et al. (17), while evaluating the performance of the IgA-tTG, incidentally observed that only 32% of seropositive patients underwent an intestinal biopsy. Pearce et al. (18) found that only 18% of patients with a positive EMA result underwent an intestinal biopsy. These investigations did not examine why biopsies were not performed in the majority of seropositive patients. A recent follow-up study revealed that the addition of an interpretive comment to positive antibody results that recommended “referral for further gastroenterological investigations including duodenal biopsy” increased the biopsy rate from 18% to 80% (16, 18). The reasons seropositive patients did not undergo biopsy in this interventional study were similar to those found in the present study (16).

A lack of awareness of the subtle and atypical forms of celiac disease remains a common barrier to the appropriate management of positive EMA results. In nearly one-fifth of cases with inappropriately managed positive EMA test results, the physicians indicated that a biopsy was not pursued because the patient was no longer experiencing symptoms of celiac disease. Physician responses also indicated, however, that the patient had a celiac-associated condition or a family history of celiac disease. It is not known if the consequences of untreated celiac disease in asymptomatic patients or patients with only minor symptoms are the same as those in symptomatic patients (23). However, patients with “silent” celiac disease may actually have unrecognized symptoms that improve on GFD (8, 9).

To address our findings, recommendations were made to adopt a celiac disease screening strategy that is consistent with current evidence (38) and create a clinical environment that will facilitate appropriate laboratory test use and interpretation. In this system, when the physician marks “celiac disease screen” on a laboratory requisition, the patient will be tested with an IgA-tTG. Positive IgA-tTG results will be confirmed with an EMA (38). To screen for IgA deficiency, serum IgA will be measured in all patients. Alternatively, to reduce the number of serum IgA measurements, an IgA-tTG absorbance cutoff level can be established to effectively exclude IgA deficiency. Studies have demonstrated this process to be a cost-effective and practical protocol (39, 40). IgA-deficient patients will have an IgG-tTG performed. This reflexive system, performed by laboratory personnel and combined with interpretative comments, will ensure that the appropriate celiac disease serologic tests are conducted and will facilitate appropriate interpretation and management of test results.

Positive celiac disease tests will include the following comments: “Celiac screen is positive. Guidelines advise that your patient be referred to a gastroenterologist for an intestinal biopsy because false positives occur with a 10% frequency in this laboratory. Treatment without biopsy is not recommended and initiating a GFD before biopsy interferes with results. The diet for celiac disease is complicated, expensive, and must be followed for life.” These clinical laboratory modifications, coupled with ongoing efforts to improve awareness of celiac disease and its myriad clinical presentations, will aid physicians in appropriate evaluation and diagnosis in patients with celiac disease.

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