Celiac Disease and IgA Deficiency: Complications of Serological Testing Approaches Encountered in the Clinic

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BACKGROUND: IgA deficiency causes false-negative IgA-based celiac serology results in patients with celiac disease. Using a case-finding strategy, we examined the prevalence of IgA deficiency, physician evaluation, and management of IgA deficiency during serological testing for celiac disease.

METHODS: We reviewed consecutive IgA-endomysial antibody (EMA) and serum IgA results from the laboratory database over 17 months. We cross-referenced seronegative patients with IgA deficiency (IgA <0.06 g/L) to the pathology database to evaluate intestinal biopsy results. Ordering physicians received a questionnaire regarding the management of seronegative patients with IgA deficiency who had no biopsy record.

RESULTS: Among the 9533 patients tested for IgA-EMA, 4698 (49%) were tested for IgA deficiency. IgA deficiency occurred in 35 of 4698 (0.75%) patients screened for IgA deficiency. Only 19 of 35 (54%) IgA-deficient patients were diagnosed appropriately with either intestinal biopsy (17 patients) or measurement of IgG-tissue transglutaminase (2 patients). Thirteen (76%) of the 17 IgA-deficient patients who underwent upper endoscopy with or without colonoscopy displayed gastrointestinal pathology on biopsies, including 3 (18%) with celiac disease. No further evaluation to exclude celiac disease was performed for the remaining 16 of 35 (46%) IgA-deficient, EMA-negative patients because of inappropriate management (6 patients), administrative error (7 patients), or patient/physician refusal (3 patients).

CONCLUSIONS: IgA deficiency occurred in 1:131 patients tested for celiac disease, and celiac disease occurred in 1:6 of those properly evaluated. Inadequate evaluation of IgA deficiency while testing for celiac disease occurred frequently and resulted in the underdiagnosis of both. Changes in testing algorithms and reporting of results were made to improve testing for celiac disease and IgA deficiency.

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Selective IgA deficiency occurs in 1 of 39 to 57 patients with celiac disease (1–3). This is much higher than the prevalence of selective IgA deficiency in the general population, which is estimated to be approximately 1 in 400 to 18 500, depending on ethnic background (4, 5). Little is known about the prevalence of IgA deficiency in a North American population that undergoes testing for celiac disease by a case-finding strategy. The prevalence of celiac disease in patients with selective IgA deficiency ranges from 10% to 30%, depending on the evaluated population (6–10). This association between celiac disease and IgA deficiency complicates serological testing for celiac disease. Most laboratories offer IgA-based assays only to accomplish serological testing for celiac disease and monitor response (6). If IgA deficiency is not excluded, the physician may not recognize a false-negative celiac serological test result attributable to IgA deficiency (3). Thus, patients with IgA deficiency and celiac disease will remain undetected by the conventional IgA-based serological tests unless IgA concentrations are simultaneously assessed (11, 12).

Recommendations regarding the importance of measuring serum IgA concentrations when using an IgA-based test are inconsistent and not always addressed in working group proceedings or practice guidelines (13–18). Some authors advise excluding IgA deficiency in all patients undergoing serological testing for celiac disease to improve the reliability of a negative test result (1, 3, 18, 19). Others propose that assessment of serum IgA concentrations should be performed only in symptomatic patients because IgA deficiency plus celiac disease occurs in only 1 of 8500
individuals in the general population (14–17). In contrast, some studies conclude that excluding IgA deficiency in all patients adds little value in the detection of celiac disease (20, 21). Confusion about whether celiac disease serological testing should include measurement of serum IgA concentrations is due, at least in part, to the assumption that the issue is the risk of IgA deficiency in the general population rather than the risk in a population that is undergoing testing for celiac disease by a case-finding strategy. To our knowledge, examination of physician practice patterns regarding evaluation and management of IgA deficiency while testing for celiac disease has not been reported. Thus, we evaluated the frequency with which physicians assessed IgA concentrations while performing IgA-based celiac disease serology and the management of negative serology results in IgA-deficient patients. We also examined the prevalence of selective IgA deficiency in a population undergoing celiac disease serological testing by a case-finding strategy and the effect of partial IgA deficiency on the accuracy of IgA-endomysial antibody (EMA) tests.

Materials and Methods

STUDY GROUP

We reviewed consecutive IgA-EMA test results, with or without measurement of serum IgA, from the Calgary Laboratory Services computer database over 17 months from March 1, 2003, to July 31, 2004. Selective IgA deficiency was defined as a serum IgA concentration of <0.06 g/L in patients 2 years of age and older (5). Partial IgA deficiency was defined as a concentration ≥0.06 g/L but <2 SDs below the normal mean concentration for their age (5). Samples submitted to the laboratory from outside the Calgary Health Region were excluded.

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identified. Patient refusal denoted IgA-deficient patients who refused intestinal biopsy.

STATISTICAL ANALYSIS
We used a 2-tailed test of proportions (Stata for Windows) to evaluate group comparisons. Statistical significance was accepted as $P < 0.05$, and 95% CIs were used.

ETHICS
The Conjoint Medical Research Ethics Board of the University of Calgary approved the study. The granting agencies of this study had no involvement in its design or preparation of the manuscript and possessed no rights to approve, delay, or disapprove of this publication. Calgary Laboratory Services released EMA and IgA serology and pathology results. Otherwise data collection, analysis, and interpretation were performed solely by the investigators.

Results

STUDY GROUP DEMOGRAPHICS
Over the 17 months reviewed, IgA-EMA tests were performed in 9533 patients, and 313 (3%) patients were seropositive. Physicians ordered a serum IgA concentration for only 4698 of 9533 (49%) of these patients, and 124 of 4698 (2.6%) displayed a positive IgA-EMA. Among the 4574 IgA-EMA–negative patients, selective IgA deficiency was identified in 35 (0.8%; 95% CI 25–50) patients. The median age of IgA-deficient patients was 34 years (range 2–69 years) including 9 children under 18 years of age. In the population evaluated, the proportion of females with IgA deficiency (23 of 3199, 0.7%; 95% CI 15–34) did not differ from the that of males (12 of 1499, 0.8%; 95% CI 6–21) ($P = 0.762$).

MANAGEMENT
Physicians appropriately managed only 19 (54%) of the 35 seronegative patients with IgA deficiency with an intestinal biopsy (17 patients) or measurement of IgG-tTG (2 patients with negative results). The clinical information provided at the time of upper endoscopy, with or without colonoscopy, and the gastrointestinal pathology results of each of the 17 biopsied patients are shown in Table 1. Upper intestinal biopsies demonstrated celiac disease in 3 of 17 (18%) patients, 1 of whom was previously diagnosed with celiac disease and was likely consuming gluten. Furthermore, 3 of 17 duodenal biopsies (18%) demonstrated other diagnoses, including 2 patients with nonspecific duodenitis (<30 intraepithelial lymphocytes per 100 enterocytes) and a bone marrow transplant recipient with graft-vs-host disease. The remaining 11 of 17 (65%) duodenal biopsies had no pathological diagnosis. In addition, abnormal pathology outside the duodenum was observed in 12 of 17 patients (Table 1). Pathology included chronic gastritis (8 patients), lymphocytic colitis (2 patients), gastric and colonic graft-vs-host-disease (1 patient), and a hyperplastic polyp (1 patient). This included 1 IgA-deficient patient with celiac disease who had chronic gastritis and lymphocytic colitis. Of note, 13 of 17 (76%) patients displayed pathological abnormalities on their biopsies. An additional 3 patients with IgA deficiency and gastrointestinal symptoms were investigated only with colonoscopy, which yielded the following results: no pathologic diagnosis (1 patient), idiopathic inflammatory bowel disease of the colon (1 patient), and ileal Crohn disease (1 patient). Thus, 15 of 20 (75%) of patients with chronic gastrointestinal symptoms and IgA deficiency displayed gastrointestinal pathology. Of the 2 IgA-deficient patients managed appropriately without a biopsy, 1 IgG-tTG–negative patient was an asymptomatic relative of a patient with celiac disease. The other had mild dyspeptic symptoms that resolved. Continued monitoring was favored for these 2 patients.

PARTIAL IgA DEFICIENCY
Among the 4698 patients with a known serum IgA concentration, partial IgA deficiency occurred in 106 (2.3%). Concomitant EMA positivity and partial IgA deficiency occurred in 2 of 106 patients (1.9%; 95% CI 0.5–13), which did not differ from the EMA positivity observed in IgA-sufficient patients (120 of 4555, 2.6%; 95% CI 100–143; $P = 0.227$). Intestinal biopsy demonstrated no pathologic diagnosis in 1 patient who was on GFD. This patient had previously diagnosed, biopsy-proven celiac disease. The other patient with partial IgA deficiency refused intestinal biopsy. A search of the gastrointestinal pathology database revealed that 31 of 104 (30%) seronegative patients with partial IgA deficiency underwent intestinal biopsy. Celiac disease (Marsh IIIa) was found in 1 (3.2%) seronegative patient with gastrointestinal symptoms and partial IgA deficiency. Nonspecific duodenitis was observed in 3 patients (9.7%) and a mild increase in eosinophils in 1 patient (3.2%). No pathologic diagnosis was found in 26 of the 31 (84%) seronegative patients with partial IgA deficiency.

In addition to the 35 IgA-EMA–negative patients with IgA deficiency, strong positive IgA-EMA results (1:320, 1:1280) were observed in 2 patients with IgA deficiency (<0.06 g/L). Intestinal biopsies confirmed celiac disease (Marsh IIIc) in both. The first, a 9-year-old boy, was referred with anemia and classic symptoms of celiac disease. The second, a 7-year-old girl, also presented with classic symptoms, a history of IgA deficiency associated with recurrent sinus infections, and a positive family history of celiac disease. In both
seropositive IgA-deficient patients, GFD led to a fall in IgA-EMA titers (negative and 1:2.5, respectively) by 12 months after the biopsy and no increase in serum IgA concentrations.

### PREVALENCE OF IgA DEFICIENCY AND CELIAC DISEASE

Including the 2 seropositive IgA-deficient patients, the prevalence of IgA deficiency in patients undergoing testing for celiac disease was 0.8% (37 of 4698; 95% CI 0.2–5.1). During the 17-month study period, 196 patients were diagnosed with celiac disease by intestinal biopsy. Of these patients, 186 displayed positive IgA-EMA tests, including the 2 IgA-deficient children mentioned above, and 10 were IgA sufficient with negative IgA-EMA tests (22). Thus, the prevalence of IgA deficiency in patients diagnosed with celiac disease by intestinal biopsy was 2.5% (5 of 199; 95% CI 2–11). Three of the IgA-deficient patients with celiac disease were IgA-EMA negative and 2 were positive.

### PHYSICIAN SURVEY RESULTS

No record of intestinal biopsy or IgG-tTG was found in the remaining 16 of 35 (46%) negative IgA-EMA patients with selective IgA deficiency. Physician survey responses indicated that 6 of 35 (17%) of these were inappropriately managed due to failure to recognize that IgA deficiency may cause a false-negative IgA-EMA result. In all 6, the physician ordered the IgA-EMA because of gastrointestinal symptoms. Three inappropriately managed patients underwent a colonoscopy and, as described above, 2 were abnormal. Despite undergoing colonoscopy, all were considered inappropriately managed because they received no further celiac disease testing. Administrative errors pre-

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**Table 1. Gastrointestinal pathology and clinical findings of negative IgA-EMA patients with selective IgA deficiency.**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age, years</th>
<th>IgA, g/L</th>
<th>Duodenal biopsy result</th>
<th>Gastric biopsy result</th>
<th>Colon biopsy result</th>
<th>Clinical information</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>&lt;0.04</td>
<td>Marsh I</td>
<td>NP</td>
<td>NP</td>
<td>Known celiac, anemia, receiving gluten</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>&lt;0.04</td>
<td>Marsh IIic</td>
<td>Chronic gastritis</td>
<td>Lymphocytic colitis</td>
<td>Fe and B_v deficiency, diarrhea</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>&lt;0.04</td>
<td>Marsh IIib</td>
<td>NP</td>
<td>NP</td>
<td>“Likely celiac”</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>&lt;0.04</td>
<td>Marsh 0, duodenitis^b</td>
<td>Chronic gastritis</td>
<td>Mild edema of lamina propria</td>
<td>Fe deficiency</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>&lt;0.04</td>
<td>Marsh 0, duodenitis^b</td>
<td>Chronic gastritis</td>
<td>NP</td>
<td>Weight loss, anemia</td>
</tr>
<tr>
<td>6</td>
<td>9</td>
<td>0.04</td>
<td>GVHD</td>
<td>GVHD</td>
<td>GVHD</td>
<td>Bone marrow transplant, diarrhea</td>
</tr>
<tr>
<td>7</td>
<td>24</td>
<td>&lt;0.04</td>
<td>Marsh 0</td>
<td>Chronic gastritis</td>
<td>Normal</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>8</td>
<td>30</td>
<td>&lt;0.04</td>
<td>Marsh 0</td>
<td>Chronic gastritis</td>
<td>NP</td>
<td>Weight loss, Fe deficiency, family history celiac</td>
</tr>
<tr>
<td>9</td>
<td>39</td>
<td>&lt;0.04</td>
<td>Marsh 0</td>
<td>Chronic gastritis</td>
<td>NP</td>
<td>Dyspepsia, Fe deficiency</td>
</tr>
<tr>
<td>10</td>
<td>56</td>
<td>&lt;0.04</td>
<td>Marsh 0</td>
<td>Chronic gastritis</td>
<td>NP</td>
<td>Dyspepsia</td>
</tr>
<tr>
<td>11</td>
<td>60</td>
<td>&lt;0.04</td>
<td>Marsh 0</td>
<td>Chronic gastritis</td>
<td>NP</td>
<td>Crohn’s, early satiety, and diarrhea</td>
</tr>
<tr>
<td>12</td>
<td>21</td>
<td>&lt;0.04</td>
<td>Marsh 0</td>
<td>NP</td>
<td>Lymphocytic colitis</td>
<td>Food intolerance, weight loss</td>
</tr>
<tr>
<td>13</td>
<td>41</td>
<td>&lt;0.04</td>
<td>Marsh 0</td>
<td>NP</td>
<td>Hyperplastic polyp</td>
<td>Not provided</td>
</tr>
<tr>
<td>14</td>
<td>13</td>
<td>&lt;0.04</td>
<td>Marsh 0</td>
<td>Normal</td>
<td>NP</td>
<td>Abdominal pain, diarrhea, type 1 diabetes</td>
</tr>
<tr>
<td>15</td>
<td>18</td>
<td>&lt;0.04</td>
<td>Marsh 0</td>
<td>Normal</td>
<td>NP</td>
<td>Abdominal pain, Fe deficiency</td>
</tr>
<tr>
<td>16</td>
<td>49</td>
<td>&lt;0.04</td>
<td>Marsh 0</td>
<td>NP</td>
<td>NP</td>
<td>Not provided</td>
</tr>
<tr>
<td>17</td>
<td>65</td>
<td>&lt;0.04</td>
<td>Marsh 0</td>
<td>NP</td>
<td>NP</td>
<td>Weight loss, malnutrition, liver disease</td>
</tr>
</tbody>
</table>

* NP, not performed; GVHD, graft-vs-host-disease.  
^b <30 intraepithelial lymphocytes per 100 enterocytes.
vent ed 7 (20%) negative IgA-EMA patients with IgA deficiency from receiving further investigation. Among these, 2 physicians could not contact their patients, 2 physicians did not receive serum IgA results, and in 3 cases the database could not identify ordering physicians. One (3%) IgA-deficient patient refused to undergo biopsy, and 2 physicians (6%) did not respond.

Discussion

The 1:131 prevalence of selective IgA deficiency in this population screened by a case-finding strategy is much greater than the 1:400 to 1:18500 prevalence of IgA deficiency observed in the general population (4, 5). This is likely due to an increased frequency of gastrointestinal symptoms observed in patients who undergo testing for celiac disease. Similar to the increased prevalence we observed, Sinclair et al. (24) noted a prevalence of IgA deficiency of 1 of 152 patients tested for celiac disease. Individuals identified with selective IgA deficiency and gastrointestinal symptoms should be considered for upper endoscopy and colonoscopy, regardless of celiac serological test results, because gastrointestinal pathology was observed in three quarters of those evaluated with endoscopy. The nonspecific duodenitis and chronic gastritis found in 2 IgA-deficient patients may represent latent celiac disease (25–28). These patients require serial follow-up to clarify the significance of these findings. Our study and the one reported by Sinclair et al. demonstrate that the prevalence of IgA deficiency is between 3 and 140 times higher in a population that undergoes testing for celiac disease by a case-finding strategy compared with testing the general population for IgA deficiency (4, 5, 24).

The prevalence of celiac disease in IgA-deficient patients who were properly evaluated (18%) was within the range of previous estimates (12% to 31%) obtained from highly selected patient groups with gastrointestinal symptoms (7–9). Recent investigations report an 8% to 10% prevalence of celiac disease in IgA-deficient patients among blood donors and consecutively diagnosed cases of IgA deficiency (6, 10). If one assumes that the 16 IgA-deficient patients who were not appropriately investigated in this study did not have celiac disease, the “minimum prevalence” of celiac disease in IgA-deficient patients (9%) would be similar to the reported 8% to 10% (6, 10). Thus, the prevalence of celiac disease likely falls between 9% and 18% in IgA-deficient patients identified using a case-finding strategy to test for celiac disease. The minimum prevalence of celiac disease among negative IgA-EMA patients with IgA deficiency (9%) is greater than the 2% prevalence of celiac disease in all patients undergoing celiac disease testing over the same period in our health region (22) and 10 times the estimated prevalence of 0.75% in the general North American population (29). The sharing of HLA-DQ2 and -DQ8 alleles in both conditions may explain the increased risk (3, 6, 30). Furthermore, the absence of the protective effects of IgA on mucosal surfaces may increase the risk of celiac disease (3). IgA-deficient patients represent an important case-finding group for celiac disease (3, 6).

Partial IgA deficiency usually does not interfere with the diagnostic reliability of IgA-EMA test results, as evidenced by a similar prevalence of celiac disease in IgA-sufficient and partially IgA-deficient patients. This confirms 2 reports with smaller sample sizes (31, 32). Residual capacity for antigen-specific IgA production remains in patients with partial IgA deficiency (32). As previously reported, IgA-EMA positivity and absolute IgA deficiency were not mutually exclusive, as observed in the 2 IgA-deficient children with positive IgA-EMA tests and biopsy-proven celiac disease (6, 31, 33). Alterations in cytokines due to inflammation may cause a temporary loss of IgA (6). However, both patients remained IgA deficient after 1 year on GFD with complete resolution of symptoms. Alternatively, in a minority of IgA-deficient patients, IgG-EMA binds to monkey esophagus and cross-reactive immunofluorescent staining occurs.

The proportion of negative IgA-EMA patients with IgA deficiency who were appropriately evaluated and managed by physicians (54%) was significantly less than that of IgA-sufficient, IgA-EMA–positive patients (77%; P = 0.004) simultaneously evaluated in our health region (22). Almost 50% of patients with IgA deficiency did not undergo further evaluation for celiac disease, either with additional serological evaluation (IgG-tTG) or referral for consideration of intestinal biopsy. Most displayed gastrointestinal symptoms of unknown severity. This lower rate of appropriate physician action is not unexpected, because celiac disease practice guidelines either omit or vary in recommendations for evaluation of the IgA-deficient patient (13–18). Others have noted that the discovery of IgA deficiency observed during the evaluation of patients for multiple clinical reasons often does not trigger appropriate investigation of diseases associated with IgA deficiency (34). Furthermore, regardless of celiac serology test results, these data suggest that patients with chronic gastrointestinal symptoms and IgA deficiency should be referred for further gastrointestinal evaluation.

Practice guidelines recommending measurement of serum IgA concentrations only in symptomatic patients assume that all physicians will correctly adhere to these guidelines (1, 3, 18, 19). However, physician practice patterns often differ from guidelines (22, 35, 36). Furthermore, celiac disease guidelines are inconsistent in their recommendations for IgA defi-
ciency testing, and this adds to physician confusion about managing IgA-deficient patients. Thus, the most effective way to ensure that IgA-deficient patients receive appropriate testing for celiac disease and other gastrointestinal disorders is to measure serum IgA in all patients who undergo testing for celiac disease by a case-finding strategy. When IgA deficiency is found, the clinical laboratory can conduct additional testing for celiac disease. We and others have developed a celiac disease serological testing algorithm (24, 37). In our algorithm, all patients will be screened for IgA deficiency. This can be accomplished by measuring serum IgA in all patients, or by measuring serum IgA only in patients who have an IgA-tTG measurement below an absorbance cutoff concentration established to exclude IgA deficiency (24, 38). An IgG-tTG will be automatically performed on patients with low or undetectable serum IgA concentration to test for celiac disease (6, 12). Thus all patients with IgA deficiency will be identified and appropriately tested for celiac disease.

These changes alone will not lead to the appropriate management of IgA-deficient patients. Ordering physicians inappropriately managed 1 in 6 negative IgA-EMA patients with IgA deficiency. Others have demonstrated that the rate of intestinal biopsy increased from 18% to 80% after the introduction of a comment recommending biopsy for positive celiac disease testing results (37). To improve patient care, positive IgG-tTG test results in IgA-deficient patients will include the following comment: “Your patient is IgA deficient. There is an increased risk of celiac disease in individuals with IgA deficiency. An IgG-tTG is positive in your patient. This is suggestive of celiac disease and we recommend your patient be referred for an intestinal biopsy. Treatment without biopsy is not recommended, and initiating a gluten-free diet before biopsy interferes with results. The diet for celiac disease is complicated, expensive and must be followed for life.” For IgA-deficient patients with a negative IgG-tTG, the following comment will be included: “Your patient is IgA deficient and screens negative for celiac disease with testing of the IgA-deficient patient. False-negative celiac disease screens can occur. If you still suspect celiac disease or another gastrointestinal disease, your patient should be referred to a gastroenterologist for further evaluation.”

In conclusion, IgA deficiency creates challenges in the management of patients undergoing evaluation for celiac disease. Our results suggest that IgA deficiency and celiac disease occur more commonly when using a case-finding strategy to test for celiac disease compared with testing the general population. Furthermore, many physicians who test patients for celiac disease are unaware that additional testing is required to exclude celiac disease in patients with IgA deficiency. Patients with gastrointestinal symptoms and IgA deficiency frequently have gastrointestinal pathology, and endoscopic evaluation must be considered. Testing algorithms and comments designed by clinical laboratories to address these issues will likely improve the detection of celiac disease in the clinic.

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References


Celiac Disease Testing and IgA Deficiency


