Systematic review: the use of serology to exclude or diagnose coeliac disease (a comparison of the endomysial and tissue transglutaminase antibody tests)

N. R. LEWIS & B. B. SCOTT

Department of Gastroenterology, Lincoln County Hospital, Lincoln, UK

Correspondence to:
Dr B. B. Scott
Department of Gastroenterology, Lincoln County Hospital, Lincoln, LN25QY, UK.
E-mail: brian.scott@ulh.nhs.uk

SUMMARY

Background
With the appreciation of the high prevalence of coeliac disease there is increasing use of serology in screening asymptomatic people and testing those with suggestive features.

Aim
To compare the sensitivities and specificities of the endomysial antibody and the tissue transglutaminase antibody tests.

Methods
Using electronic databases a search was made for relevant papers using the terms tissue transglutaminase and endomysial antibody.

Results
Both the endomysial antibody and tissue transglutaminase antibody have very high sensitivities (93% for both) and specificities (>99% and >98% respectively) for the diagnosis of typical coeliac disease with villous atrophy. Human recombinant tissue transglutaminase performs much better than guinea pig tissue transglutaminase. Review of studies comparing endomysial antibody with human recombinant tissue transglutaminase antibody shows that endomysial antibody more often has a higher specificity and human recombinant tissue transglutaminase antibody more often has a higher sensitivity.

Conclusion
The human recombinant tissue transglutaminase antibody is the preferred test for screening asymptomatic people and for excluding coeliac disease in symptomatic individuals with a low pretest probability (i.e. <25%) for coeliac disease. Furthermore, it has a number of practical and financial advantages. If the pretest probability is >25%, biopsy is preferred as the post-test probability of coeliac disease with a negative test is still >2%.

Aliment Pharmacol Ther 24, 47–54
INTRODUCTION
Coeliac disease has assumed increasing importance with the realization of its high prevalence (approximately 1% of the UK population), its association with many other disorders such as type 1 diabetes, primary biliary cirrhosis and dermatitis herpetiformis, and it being a cause of common conditions such as iron deficiency anaemia. Consequently, screening tests have assumed greater importance because histology of small bowel biopsies (still regarded by most as the gold standard) is inconvenient, expensive, unpleasant and not without risk. The first reliable screening test was the endomysial antibody (EMA) devised by Chorzelski et al. in 1983. In a systematic review of published studies in 2000, we calculated the pooled sensitivity and specificity to be 94% and 98% respectively. It is hard to think of a better performing screening test for any condition. However, there are problems with the EMA test – it is subjective, labour intensive, and one common substrate (monkey oesophagus) is from an endangered species. In 1997, Dieterich et al. found that tissue transglutaminase (tTG) is the antigen recognized by the EMA. A test for detecting antibodies to tTG was soon devised using either guinea pig (gpT) or human recombinant tTG (rhT), and it was assumed that this test would perform even better than the EMA test, and at the same time obviate the above problems associated with the EMA test. Certainly the enzyme-linked immunosorbent assay test used is objective and lends itself to automation. Thus, there is a widespread move to replace the EMA test. Before the EMA test disappears, it was thought important to compare the performance of the EMA test with the two types of tTG antibody test with regard to sensitivity and specificity, to make recommendations for the most appropriate screening test and to determine the likelihood ratios (LRs) for the preferred test.

METHODS
A literature search was conducted using PubMed, Medline and Ovid databases up to September 2005 to identify relevant articles in English. The search terms used were tTG and EMA. The reference lists of selected articles were also used to identify other relevant articles. Criteria for inclusion were all of the following:
1. The published study was peer reviewed.
2. The study included untreated coeliac patients and controls.
3. Both EMA and tTG antibody were tested in the same patients and controls.
4. All coeliacs had had a biopsy and the biopsy criteria for diagnosis were given.
5. It was clear which controls were biopsy negative and which had not been biopsied.

It was hoped to exclude studies in which there was ascertainment bias (i.e. where the coeliac group was identified by EMA or tTG antibody tests) but unfortunately very few papers specified how the coeliac patients were identified and thus this criterion was abandoned. This will, inevitably, lead to an overestimation of sensitivity. E-mails were sent to 14 authors of studies using rhT enquiring about the use of serology to detect the coeliac patients.

For each study, the sensitivity and specificity for EMA and the two types of tTG antibody test (i.e. human recombinant and guinea pig) was calculated. Each study was then assessed to determine whether the tTG antibody test or the EMA test gave the higher sensitivity and specificity in that particular study. The number of studies in which each test gave the higher sensitivity and the higher specificity was then added up. All the subjects were then pooled and the overall sensitivity and specificity were calculated with 95% confidence intervals (CIs) for both tTG antibody and EMA. In addition, the overall sensitivities and specificities were calculated for different types of tests and also separately for studies of adults and for those studies using commercial kits as opposed to in-house tests. From them the positive and negative LR were calculated using the formulae: LR + = sensitivity/100–specificity; LR– = 100–sensitivity/specificity. The LR (positive or negative) indicates how much more likely or less likely is a particular diagnosis if the test is positive or negative. A LR of 1 indicates that the test result makes the diagnosis neither more nor less likely.

RESULTS
Thirty-four studies fulfilled our criteria and the details are shown in Table 1. The histological criterion for diagnosing coeliac disease was partial or more severe villous atrophy in the majority. In four, total villous atrophy was required, and in two an abnormality ranging from an increase in intraepithelial lymphocytes alone to total villous atrophy was allowed. Two studies were vague simply saying that the diagnosis was histologically proven and therefore some degree of villous atrophy was assumed.
<table>
<thead>
<tr>
<th>Study</th>
<th>Type of tTG assay</th>
<th>Source of antigen</th>
<th>Biopsy negative*</th>
<th>Not biopsied*</th>
<th>tTG Ab positive</th>
<th>EMA positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baudon et al.</td>
<td>Eu-tTG rh</td>
<td>Children, adults or mixed</td>
<td>17†</td>
<td>92</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Lorente et al.</td>
<td>Celikey rh</td>
<td>Not biopsied*</td>
<td>64</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Tesei et al.</td>
<td>Eu-tTG rh</td>
<td>tTG Ab positive</td>
<td>176</td>
<td>0</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Tonutti et al.</td>
<td>Eu-tTG rh</td>
<td>EMA positive</td>
<td>6316</td>
<td>0</td>
<td>52</td>
<td>10</td>
</tr>
<tr>
<td>Burgin-Wolff et al.</td>
<td>Celikey rh</td>
<td>tTG Ab positive</td>
<td>157</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Carroccio et al.</td>
<td>Eu-tTG gp</td>
<td>EMA positive</td>
<td>183</td>
<td>0</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Baudon et al.</td>
<td>In-house gp</td>
<td>Controls</td>
<td>49</td>
<td>0</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Dickey et al.</td>
<td>Quanta Lite gp</td>
<td>Untreated Coeliac Disease</td>
<td>58</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Bardella et al.</td>
<td>Genesis gp</td>
<td>Children</td>
<td>110</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Dahele et al.</td>
<td>In-house gp</td>
<td>Mixed</td>
<td>65</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Salmaso et al.</td>
<td>In-house gp</td>
<td>Adults</td>
<td>106</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Chan et al.</td>
<td>unspecified ?</td>
<td>Adults</td>
<td>66</td>
<td>0</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Leon et al.</td>
<td>In-house gp</td>
<td>Mixed</td>
<td>53</td>
<td>99</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Fabiani et al.</td>
<td>Eu-tTG rh</td>
<td>Adults</td>
<td>186</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Bonamico et al.</td>
<td>Eu-tTG gp</td>
<td>Children</td>
<td>56</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Picarelli et al.</td>
<td>Eu-tTG rh</td>
<td>Adults</td>
<td>26</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Biagi et al.</td>
<td>In-house gp</td>
<td>Adults</td>
<td>52</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Vittori et al.</td>
<td>Celikey gp</td>
<td>Adults</td>
<td>28</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hansson et al.</td>
<td>In-house gp</td>
<td>Children</td>
<td>17</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Baldas et al.</td>
<td>In-house gp</td>
<td>Mixed</td>
<td>17</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Stern and Working</td>
<td>In-house rh</td>
<td>Adults</td>
<td>0</td>
<td>196</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Group on Serologic Screening for Celiac Disease</td>
<td>In-house rh</td>
<td>Mixed</td>
<td>89</td>
<td>60</td>
<td>7</td>
<td>1</td>
</tr>
</tbody>
</table>

**Controls**
- tTG Ab sensitivity: 93.3
- tTG Ab specificity: 97.4
- EMA sensitivity: 90.0
- EMA specificity: 100

**Untreated Coeliac Disease**
- tTG Ab sensitivity: 96.4
- tTG Ab specificity: 100
- EMA sensitivity: 96.9
- EMA specificity: 70.5

**Children**
- tTG Ab sensitivity: 90.0
- tTG Ab specificity: 94.9
- EMA sensitivity: 85.6
- EMA specificity: 100

**Mixed**
- tTG Ab sensitivity: 94.8
- tTG Ab specificity: 92.1
- EMA sensitivity: 99.8
- EMA specificity: 100

*Biopsy negative* and *Not biopsied* refer to the status of biopsy in the study.
<table>
<thead>
<tr>
<th>Study</th>
<th>Type of tTG assay</th>
<th>Source of antigen</th>
<th>Controls (Biopsy negative*)</th>
<th>Untreated Coeliac Disease (tTG Ab positive EMA positive Total)</th>
<th>Children, adults or mixed</th>
<th>tTG Ab sensitivity</th>
<th>tTG Ab specificity</th>
<th>EMA sensitivity</th>
<th>EMA specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataldo et al. 31</td>
<td>In-house rh</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>100</td>
</tr>
<tr>
<td>Koop et al. 32</td>
<td>In-house gp</td>
<td>23</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>20</td>
<td>18</td>
<td>19</td>
<td>100</td>
</tr>
<tr>
<td>Lock et al. 33</td>
<td>In-house gp</td>
<td>65</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>27</td>
<td>23</td>
<td>27</td>
<td>90</td>
</tr>
<tr>
<td>Troncone et al. 34</td>
<td>In-house gp</td>
<td>63</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>48</td>
<td>44</td>
<td>42</td>
<td>90</td>
</tr>
<tr>
<td>Sardy et al. 35</td>
<td>In-house gp</td>
<td>0</td>
<td>53</td>
<td>2</td>
<td>1</td>
<td>55</td>
<td>51</td>
<td>55</td>
<td>90</td>
</tr>
<tr>
<td>Vitoria et al. 36</td>
<td>In-house gp</td>
<td>0</td>
<td>53</td>
<td>1</td>
<td>1</td>
<td>55</td>
<td>54</td>
<td>55</td>
<td>98.1</td>
</tr>
<tr>
<td>Biagi et al. 37</td>
<td>In-house gp</td>
<td>61</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>39</td>
<td>37</td>
<td>39</td>
<td>98.1</td>
</tr>
<tr>
<td>Bazzigaluppi et al. 38</td>
<td>In-house gp</td>
<td>0</td>
<td>92</td>
<td>8</td>
<td>1</td>
<td>112</td>
<td>95</td>
<td>109</td>
<td>98.4</td>
</tr>
<tr>
<td>Dieterich et al. 39</td>
<td>In-house gp</td>
<td>0</td>
<td>114</td>
<td>6</td>
<td>0</td>
<td>106</td>
<td>104</td>
<td>105</td>
<td>90</td>
</tr>
<tr>
<td>Sulkanen et al. 40</td>
<td>In-house gp</td>
<td>207</td>
<td>0</td>
<td>13</td>
<td>1</td>
<td>136</td>
<td>129</td>
<td>126</td>
<td>90</td>
</tr>
</tbody>
</table>

EMA, endomysial antibody; tTG, tissue transglutaminase; Ab, antibody; rh, human recombinant; gp, guinea pig.

* ‘Biopsy negative’ controls were those controls who had a small bowel biopsy which was negative for coeliac disease on histology. ‘Not biopsied’ controls were those who did not have a small bowel biopsy to exclude coeliac disease.

† Twenty-four of the controls had small bowel biopsy of which 17 had completely normal histology, six had minor histological changes and one had partial villous atrophy from cow’s milk allergy. Ninety-two of the controls had no biopsy.
Most studies did not give sufficient information to determine whether there was ascertainment bias. Some, either in the paper or on subsequent email communication, admitted a partial ascertainment bias whereas it was specifically excluded in two.

Nearly all the control groups consisted of patients in whom coeliac disease was suspected for various reasons. Most had symptoms but some were asymptomatic and studied because they had a condition associated with coeliac disease (e.g. type 1 diabetes, iron deficiency anaemia) or were related to patients with coeliac disease.

The sensitivities for both tTG antibody and EMA ranged from 70% to 100%. The specificities for tTG and EMA ranged from 91% to 100% and from 90% to 100% respectively.

The result of head to head studies of EMA with tTG antibody (Table 2) shows that EMA performed better more often for both sensitivity and specificity. However, when only the 18 head to head studies using rhTtTG are looked at (Table 3), the tTG antibody test performed better more often with regard to sensitivity but not specificity.

In Table 4 all the results are pooled. The total numbers of controls for the tTG antibody and EMA studies were 10 465 and 9741 respectively. The total numbers of untreated coeliac patients for the tTG antibody and EMA studies were 3745 and 3296 respectively. The pooled sensitivities and specificities (with 95% CIs) are given for all tTG antibody and EMA studies and also separately for adults and for the different types of tTG protein (i.e. rhTtTG or gpTtTG) and EMA substrates (i.e. monkey oesophagus or human umbilicus). From the sensitivities and specificities the positive and negative LR are also calculated and presented.

The tTG antibody tests perform much better using rhTtTG rather than gpTtTG. The sensitivity is higher in adults than in children. The EMA test gives a higher sensitivity using monkey oesophagus and a higher specificity when using human umbilicus as substrate. These differences tend to be more marked in adults.

### Table 2. The result of head to head comparisons of tissue transglutaminase (tTG) antibody with endomysial antibody (EMA) in all 42 studies (number of studies in parentheses)

<table>
<thead>
<tr>
<th></th>
<th>EMA better</th>
<th>Equal</th>
<th>tTG antibody better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>48% (20)</td>
<td>24% (10)</td>
<td>28% (12)</td>
</tr>
<tr>
<td>Specificity</td>
<td>62% (26)</td>
<td>21% (9)</td>
<td>17% (7)</td>
</tr>
</tbody>
</table>

### Table 3. The result of head to head comparisons of only recombinant tissue transglutaminase (rhTtTG) with endomysial antibody (EMA) in all 18 studies (number of studies in parentheses)

<table>
<thead>
<tr>
<th></th>
<th>EMA better</th>
<th>Equal</th>
<th>rhTtTG antibody better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>28% (5)</td>
<td>28% (5)</td>
<td>44% (8)</td>
</tr>
<tr>
<td>Specificity</td>
<td>56% (10)</td>
<td>22% (4)</td>
<td>22% (4)</td>
</tr>
</tbody>
</table>

Table 4. The pooled sensitivities and specificities together with the positive and negative likelihood ratios derived from them

<table>
<thead>
<tr>
<th>Analysis</th>
<th>No. studies</th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
<th>LR+</th>
<th>LR−</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EMA studies</td>
<td>34</td>
<td>93.0 (92.1–93.8)</td>
<td>99.7 (99.5–99.9)</td>
<td>310</td>
<td>0.070</td>
</tr>
<tr>
<td>EMA studies; monkey oesophagus</td>
<td>25</td>
<td>93.1 (92.1–94.0)</td>
<td>99.1 (98.8–99.4)</td>
<td>103</td>
<td>0.070</td>
</tr>
<tr>
<td>EMA studies; human umbilical cord</td>
<td>9</td>
<td>92.9 (90.7–94.7)</td>
<td>99.7 (99.2–99.9)</td>
<td>310</td>
<td>0.071</td>
</tr>
<tr>
<td>EMA studies in adults; monkey oesophagus</td>
<td>4</td>
<td>98.0 (94.2–99.3)</td>
<td>99.3 (97.9–99.8)</td>
<td>140</td>
<td>0.020</td>
</tr>
<tr>
<td>EMA studies in adults; human umbilical cord</td>
<td>4</td>
<td>91.5 (86.6–94.7)</td>
<td>100 (97.8–100)</td>
<td>∞</td>
<td>0.085</td>
</tr>
<tr>
<td>All tTG studies</td>
<td>42</td>
<td>92.8 (91.9–93.6)</td>
<td>98.1 (97.8–98.4)</td>
<td>49</td>
<td>0.073</td>
</tr>
<tr>
<td>rhTtTG studies</td>
<td>19</td>
<td>93.8 (92.8–94.7)</td>
<td>98.7 (98.5–98.9)</td>
<td>72</td>
<td>0.063</td>
</tr>
<tr>
<td>gpTtTG studies</td>
<td>23</td>
<td>90.4 (88.8–91.9)</td>
<td>92.4 (90.8–91.8)</td>
<td>12</td>
<td>0.103</td>
</tr>
<tr>
<td>rhTtTG studies in adults; commercial</td>
<td>2</td>
<td>100 (97.2–100)</td>
<td>97.1 (93.9–98.7)</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>gpTtTG studies in adults; commercial</td>
<td>3</td>
<td>100 (94.9–100)</td>
<td>94.7 (91.7–96.7)</td>
<td>19</td>
<td>0</td>
</tr>
</tbody>
</table>

EMA, endomysial antibody; tTG, tissue transglutaminase; rhTtTG, human recombinant tTG; gpTtTG, guinea pig tTG; LR, likelihood ratio.
The highest positive LR (i.e. the most powerful at confirming a diagnosis of coeliac disease) is provided by EMA especially using human umbilical cord (310) and in adults (infinity). The lowest negative LR (i.e. most powerful at excluding coeliac disease) is provided by the rhTg test (0.063 compared with 0.069 for EMA monkey oesophagus). Both tests tend to perform better in adults but the numbers are too small to be reliable and the 95% CIs are wide.

Most gastroenterologists will be testing adults with commercial tTG antibody kits and such studies were looked at separately. Although there were only two or three such studies the specificities were 100% and the sensitivities were 97.1% for rhTg and 94.7% for gptTg giving very useful LRs.

DISCUSSION

We have shown that the EMA test has greater specificity than the tTG antibody test, whether human umbilicus or monkey oesophagus is used. We have also shown that the tTG antibody test, using human recombinant protein, has greater sensitivity than EMA. The rhTg antibody test is therefore the preferred test to screen asymptomatic people and to exclude coeliac disease in those with symptoms if the pretest probability is low (e.g. <25%). If the pretest probability is higher (i.e. >25%), the post-test probability of coeliac disease with a negative test is >2% (using a negative LR of 0.06 – see below) and therefore small bowel biopsy is still required. Moreover, the rhTg antibody test has a number of practical and financial advantages over the EMA test. The EMA test could be reserved for confirming coeliac disease in those with a positive rhTg antibody test but, as many gastroenterologists would take small bowel biopsies if the tTG antibody test is positive, it would not be necessary unless the patient refused biopsy.

When applying the rhTg antibody test to exclude coeliac disease with a particular pretest probability, a negative LR of 0.06 could be used in conjunction with Fagan’s nomogram (Figure 1). This will readily give the post-test probability for coeliac disease. In the example given in the Figure, a patient with iron deficiency anaemia is considered. As we know that the pretest probability (or prevalence) of coeliac disease in iron deficiency anaemia is 5%; the post-test probability of coeliac disease, if the test is negative, is about 0.4%, which effectively excludes the diagnosis. However, it should be borne in mind that most recent studies are likely to give falsely high sensitivities because of the ascertainment bias, which is inevitable if serology is the main way of detecting coeliac disease. Thus, this and all the other negative LRs given in Table 4 are likely to be lower (i.e. more powerful) than they should be.

When confirming coeliac disease using the EMA test, a positive LR of 300 would be appropriate (or 100 if monkey oesophagus is used), and can be similarly used with Fagan’s nomogram in conjunction with the pretest probability to obtain the post-test probability of coeliac disease.

As the detection of at least partial villous atrophy was used to make a diagnosis of coeliac disease in the vast majority of studies, we can’t assume that the same LRs apply to coeliac patients with lesser abnormality such as an increase in intraepithelial lymphocytes or electron-microscopic changes only. In fact, if such lesser abnormalities were used as criteria for diagnosing (and excluding) coeliac disease, the sensitivity of the
tests could be lower (i.e. more false negatives), especially since a number of studies suggest that the EMA and tTG antibody tests are less sensitive with lesser degrees of mucosal abnormality. On the other hand, many patients have been shown to have positive EMA tests with normal villous and crypt architecture and just an increase in intraepithelial lymphocytes or just electron microscopic changes and so the specificity could be higher (i.e. fewer false positives). However, do we want to label people with minor changes as coeliac disease? There is no agreement on what is meant by disease – are symptoms, or an abnormality of structure or function, or an abnormal serological test required? One reason for diagnosing a disease is to offer treatment. Would we want to offer treatment (i.e. a strict lifelong gluten-free diet) to people with just minor abnormalities on biopsy and no symptoms, or even with just positive serology? These questions need answering before embarking on screening of, say, relatives of coeliac patients. When dealing with asymptomatic people many would be reluctant to advise treatment if there is no villous atrophy. Therefore, the LRs given above and obtained from coeliacs predominantly with villous atrophy will be appropriate.

To use these tests for detecting people with minor changes in the small bowel mucosa (such as an increase in intraepithelial lymphocytes or electron-microscopic change), it will be necessary to determine the sensitivity in a large study of such people who had not been selected by positive serology. This may not prove possible with the present widespread reliance on serology and the consequent ascertainment bias.

Another complicating factor is immunoglobulin (Ig) A deficiency which is found in 2% of coeliacs and 0.2% of the general population. Since the usual serology tests (tTG antibody and EMA) are for IgA antibodies, there will be more false negatives thus slightly reducing the sensitivity. It is therefore probably best to follow the advice of Hill et al. to test for IgA if low absorbance readings are shown in the tTG assay, and rely on biopsy if IgA deficient, although, alternatively, testing for IgG tTG antibodies has been found useful.

In conclusion, we recommend the use of rhTGG antibody test to exclude coeliac disease if the pretest probability is low (e.g. <25%). If the rhTGG antibody test is positive we recommend small bowel biopsy to confirm the diagnosis. If for any reason biopsy is precluded then the EMA test could be used to confirm the diagnosis.

ACKNOWLEDGEMENT

No external funding was received for this study.

REFERENCES
