

ORIGINAL ARTICLE

The role of antitissue transglutaminase assay for the diagnosis and monitoring of coeliac disease: a French–Italian multicentre study

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Aims: Tissue transglutaminase (tTG) was recently identified as the major autoantigen in coeliac disease. The aim of this multicentre study was to evaluate the impact of a new immunoenzymatic assay for the detection of IgA anti-tTG antibodies.

Methods: Seventy four Italian and French clinical laboratories participated in this study; anti-tTG IgA with an enzyme linked immunosorbent assay (ELISA) method using guinea pig liver extract as the coating antigen, anti-endomysium IgA autoantibodies (EMA), and total serum IgA were determined in 7948 patients, 1162 of whom had coeliac disease (737 untreated cases and 425 on a gluten free diet). A proportion of the sera were then sent to a reference laboratory for anti-tTG retesting with an ELISA method using recombinant human tTG antigen.

Results: Seven thousand four hundred and fifty eight (93.8%) sera were EMA/antiguinea pig tTG concordant (positive or negative); 490 (6.2%) were non-concordant. The sensitivity of EMA and antiguinea pig tTG in the 737 untreated patients with coeliac disease was 92.1% and 94.8%, respectively, and the specificity was 99.8% and 99.2%, respectively. Retesting of the discordant sera showed that of the 162 sera classified as EMA negative/antiguinea pig tTG positive, only 49 were positive for human recombinant anti-tTG, and that 39 of these were also EMA positive. Furthermore, of the 36 sera classified as EMA positive/antiguinea pig tTG negative, only two were confirmed as EMA positive.

Conclusions: The antiguinea pig tTG assay is more sensitive but less specific than EMA, whereas the antihuman recombinant tTG assay is far more specific and just as sensitive as antiguinea pig tTG. Testing for EMA presents considerable interpretative problems and is difficult to standardise.

Coeliac disease (CD) is a gluten dependent disorder characterised by small intestinal damage with loss of absorptive villi.^{1,2} IgA and IgG antigliadin (AGA), IgA antireticulin (ARA), and IgA anti-endomysium antibodies (EMA) are valuable serological tests for the identification of patients with CD and treatment control.^{3–6} However, the final requirement for the diagnosis of CD is the histological finding of a characteristic mucosal abnormality in an intestinal biopsy specimen.^{7,8} The enzyme tissue transglutaminase (tTG) was recently identified as the major autoantigen in CD,⁹ and the antigenic target recognised by EMA.¹⁰ tTG induces the deamidation of gluten peptides and the formation of novel epitopes that, in association with human leucocyte antigen class II antigens, drive the antibody response to both gliadin and tTG.^{11,12} Newly available enzyme linked immunosorbent assay (ELISA) methods to identify IgA anti-tTG antibodies have increased the sensitivity of laboratory tests in detecting CD, but data regarding their specificity are, at times, contradictory,^{13–15} probably because of differences in the antigenic source used (purified extracts from guinea pig liver or human tissues).^{16,17}

“The enzyme tissue transglutaminase was recently identified as the major autoantigen in coeliac disease, and the antigenic target recognised by anti-endomysium antibodies”

The main aim of our study was to evaluate the diagnostic impact of an ELISA assay that uses guinea pig liver extract as the coating antigen (tTGgp) for the identification of anti-tTG autoantibodies, in a large number of Italian and French clinical

laboratories, and to compare the results with the EMA method. The subsequent availability of a new ELISA assay with human recombinant tTG (tTGhr) when our study was already in progress made it possible to re-evaluate some sera samples in a reference laboratory, and to compare the performances of the anti-tTGgp and anti-tTGhr assays.

PATIENTS AND METHODS

Seventy four laboratories (64 Italian and 10 French) participated in our study. The sera, which were collected from January to October 2000, were obtained from: (1) patients with a clinical diagnosis of CD, who were either untreated or on a gluten free diet (GFD), and (2) patients without a previous diagnosis of CD, whose sera were sent for EMA and AGA testing.

Demographic characteristics (name, address, date of birth, and sex), in addition to serological and clinical data (symptoms, diagnosis of active coeliac or non-coeliac disease both confirmed by intestinal biopsy, or patient with CD on diet), were collected on a standard report form. Only patients who fulfilled the diagnostic criteria of the European Society

Abbreviations: AGA, antigliadin antibodies; ARA, antireticulin antibodies; AU, arbitrary units; CD, coeliac disease; CI, confidence interval; ELISA, enzyme linked immunosorbent assay; EMA, anti-endomysium antibodies; GFD, gluten free diet; ILF, indirect immunofluorescence; tTG, tissue transglutaminase; tTGgp, guinea pig liver tissue transglutaminase; tTGhr, human recombinant tissue transglutaminase

Table 1 Number of patients studied and male to female ratio for age group

Age	Number	Male:female ratio
<2 years	1246	1:1.10
2–14 years	4264	1:1.16
>14 years	2438	1:1.66
Total	7948	1:1.28

for Paediatric Gastroenterology, Hepatology, and Nutrition⁷ were defined as being affected by CD.

In total, 7948 patients (male to female ratio, 1/1.28) were recruited. These were further subdivided into three age groups (< 2 years, between 2 and 14 years, and > 14 years) to discern the possible presence of different antibody reactivities in different age groups (table 1).

IgA anti-tTG, IgA EMA, and total serum IgA values were determined in all subjects. IgA and IgG AGA were tested in all children < 2 years of age, and in all patients with CD. All laboratories tested for IgA anti-tTG using a commercial ELISA (Eu-tTG® IgA; Eurospital, Trieste, Italy) that uses tTGgp as the coating antigen, and anti-human IgA peroxidase conjugate as the secondary antibody; as indicated by the manufacturer, sera with a concentration > 5 arbitrary units (AU)/ml were considered positive. IgA EMA, IgA and IgG AGA, and total serum IgA antibodies were determined by the method used routinely in each laboratory. All sera were tested immediately and then stored at -20°C for further investigation.

One hundred and ninety eight available sera for which discordant results were obtained by the participating laboratories (162 EMA negative and anti-tTGgp positive, and 36 EMA positive and anti-tTGgp negative) were retested in a reference laboratory for EMA (antiendomysium; Eurospital) by indirect immunofluorescence (IIF) on monkey oesophagus and for anti-tTG using both the above assay and a new ELISA test (Eu-tTG-humana® IgA; Eurospital) that uses tTGhr as the coating antigen; for this last method, the cut off point was set at 7 AU/ml, as proposed by the manufacturer.

Furthermore, to verify the consistency of the preliminary test results and to compare the sensitivity and specificity of the anti-tTGgp and anti-tTGhr assays, 400 randomly selected sera for which concordant results had been obtained (300 EMA and anti-tTGgp negative, and 100 EMA and anti-tTGgp

positive) were also retested in the reference laboratory. Two different operators independently interpreted the immunofluorescence pattern of EMA.

Statistical analysis was carried out by calculating the sensitivity of each method in identifying sera of patients with CD; the specificity of each method was calculated in the group of patients in which CD was excluded. The χ^2 test was used to see whether there were differences between the assays in the different age groups, and a p value < 0.05 was considered significant. Confidence intervals (CI) were calculated where appropriate.

All the patients gave their informed oral consent to be included in our study. Results of the assays were given to individual patients. When there were discrepancies between the anti-tTG and EMA assays, the patients were notified that confirmatory tests were in progress. Results obtained in the reference laboratory were communicated to the patients and proper counselling was given.

RESULTS

Of the 7948 patients studied, 1162 had CD (737 were untreated, and 425 were on a GFD), and 6316 were classified as non-CD; in 470 (5.9%) cases the diagnosis remained undefined because of a lack of clinical information or refusal to undergo intestinal biopsy, or because biopsy findings were not discriminant (latent CD?).¹⁸ The patients were then divided into two groups based on EMA and anti-tTGgp results: 7458 (93.8%) were EMA and anti-tTGgp concordant (group A), and 490 (6.2%) were EMA and anti-tTGgp discordant (group B) (fig 1).

Group A: EMA/anti-tTGgp concordant results

This group of 7458 patients was further subdivided in two subgroups, according to whether the EMA and anti-tTGgp tests were both negative (group A1) or both positive (group A2).

Group A1: 6528 patients were negative for both tests; of these, 6254 were non-CD, 245 had CD and were on a GFD, and 29 had untreated CD (six with an IgA selective deficiency). In these 29 seronegative patients a definitive diagnosis was made on the basis of intestinal biopsy results showing typical villous atrophy, and the subsequent normalisation of the intestinal mucosa after an adequate GFD period.¹⁹

Group A2: concordant positive results were obtained in 930 patients, of whom 670 had untreated CD, 110 had CD and were on a GFD, and 150 cases were undefined.

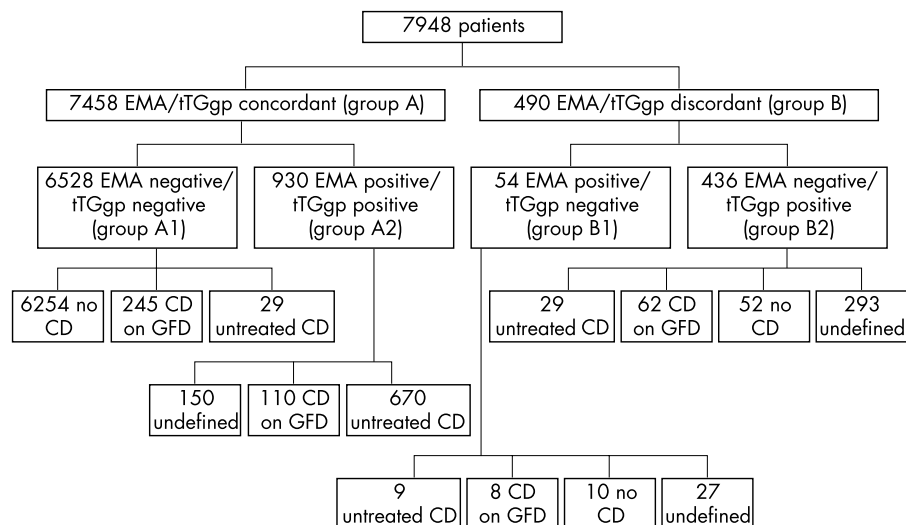


Figure 1 Flow diagram of test results according to the clinical diagnosis. CD, coeliac disease; EMA, anti-endomysium antibodies; GFD, gluten free diet; tTGgp, guinea pig tissue transglutaminase.

Table 2 Sensitivity of the EMA, anti-tTGgp, IgG AGA, and IgA AGA assays in 737 untreated patients with coeliac disease, subdivided by age group

Age (years)	Number of patients	EMA positive (%)	Anti-tTGgp positive (%)	AGA IgA positive (%)	AGA IgG positive (%)
<2	74	89.2	87.8	82.4	95.9
>2<14	369	94.3	96.7	66.3	75.1
>14	294	90.1	94.2	71.4	67.3
Total	737	92.1	94.8	70.0	74.1

AGA, antigliadin antibodies; EMA, anti-endomysium antibodies; tTGgp, guinea pig tissue transglutaminase.

Table 3 Specificity of the EMA, anti-tTGgp, IgG AGA, and IgA AGA assays in 6316 individuals without coeliac disease, subdivided by age group

Age (years)	Number of patients	EMA negative (%)	Anti-tTGgp negative (%)	AGA IgA negative (%)	AGA IgG negative (%)
<2	1147	100	99.7	93.5	76.6
>2<14	3343	99.8	99.1	93.5	84.0
>14	1826	99.8	99.0	95.0	85.7
Total	6316	99.8	99.2	94.0	82.7

AGA, antigliadin antibodies; EMA, anti-endomysium antibodies; tTGgp, guinea pig tissue transglutaminase.

Group B: EMA/anti-tTGgp discordant results

The 490 sera with discordant results for EMA and anti-tTG testing were also subdivided into two subgroups.

Group B1: 54 patients were EMA positive/anti-tTGgp negative (nine untreated CD, eight with CD on a GFD, 10 not CD on biopsy, and 27 undefined).

Group B2: 436 patients were EMA negative and anti-tTGgp positive (29 untreated CD, 62 with CD on a GFD, 52 no CD on biopsy, and 293 undefined).

The sensitivity of anti-tTGgp in the 737 untreated patients with CD was higher (94.8%; CI, 93 to 96) than that of EMA (92.1%; CI, 90 to 94) (table 2), whereas the specificity of anti-tTGgp in the 6316 non-CD subjects was 99.2% (CI, 98.9 to 99.4) and that of EMA was 99.8% (CI, 99.6 to 99.9) (table 3). In the 425 patients with CD on a GFD, EMA was positive in 27.7%, and anti-tTGgp was positive in 39.5%. It must be noted that clinically undefined cases were excluded from the statistical analysis, and that sensitivity and specificity values were calculated using the data provided by the participating laboratories and not after retesting in the reference laboratory (see below).

AGA IgA and IgG

AGA IgA and IgG were positive in 6% and 17.3%, respectively, of the 6254 concordant negative patients, in 70% and 74.1%, respectively, of the 737 untreated patients with CD, and in 43.5% and 55.5%, respectively, of the patients with CD who were on a GFD, thus showing that these tests are both less sensitive and less specific than EMA and anti-tTG. However, an excellent sensitivity (95.9%; CI, 91 to 100) of AGA IgG was seen in the 74 patients with CD who were < 2 years old (table 2).

Results of sera retesting in a reference laboratory

Five hundred and ninety eight sera were re-evaluated: 300 were EMA and anti-tTGgp concordant negative (group A1), 100 were EMA and anti-tTGgp concordant positive (group A2), 36 were EMA positive and anti-tTGgp negative (group B1), and 162 EMA negative and anti-tTG positive (group B2).

The 300 concordant negative and the 100 concordant positive sera were all confirmed by EMA and anti-tTGhr retesting.

All 36 sera of group B1 (EMA positive/anti-tTGgp negative) were confirmed negative when retested by the anti-tTGgp assay, but one sample was positive for anti-tTGhr. More noteworthy, EMA positivity was confirmed in only two of the 36

Table 4 EMA and anti-tTGhr retesting of 36 sera that were classified as EMA positive/anti-tTGgp negative by the participating laboratories

	EMA positive	EMA negative
Anti-tTGhr positive	1	0
Anti-tTGhr negative	1	34

EMA, anti-endomysium antibodies; tTGgp, guinea pig tissue transglutaminase.

Table 5 EMA and anti-tTGhr retesting of 162 sera that were classified as EMA negative/anti-tTGgp positive by the participating laboratories

	EMA positive	EMA negative
Anti-tTGhr positive	39	10
Anti-tTGhr negative	0	113

EMA, anti-endomysium antibodies; tTGgp, guinea pig tissue transglutaminase; tTGhr, human recombinant tissue transglutaminase.

sera (table 4), showing that most of the discordant results in this group were caused by a false positive interpretation of the EMA patterns.

In group B2 (EMA negative/anti-tTG positive), 152 of the 162 sera were confirmed positive when retested for anti-tTGgp, but only 49 were anti-tTGhr positive, showing that the tTG assay using the human recombinant antigen had a higher specificity. Moreover, 39 of these 49 sera were also EMA positive (table 5), indicating once again that the false negatives resulted from the misinterpretation of the EMA test. Thus, although the data are biased by the fact that not all the samples were retested by the anti-tTGhr assay, after retesting, specificity increased from 99.8% to 99.9% for EMA, and decreased from 99.2% to 94.7% for the anti-tTGgp assay.

DISCUSSION

The incidence of CD in white individuals is very high (1/100–200 people).^{20–24} Its clinical manifestations vary greatly and there are often no specific gastrointestinal symptoms.^{25, 26} Therefore, it is very important to have sensitive and specific diagnostic tests that can enable the accurate and early identification of patients with CD so that a GFD can be instituted,

thus avoiding a wide range of associated pathological conditions.²⁷⁻³¹ For the past 10 years, IgA EMA has been the reference test for the diagnosis and monitoring of patients with CD because of its high sensitivity and specificity.³² This test is based on the identification of specific antibodies on monkey oesophagus sections by IIF; however, it requires skilled personnel for the correct interpretation of the fluorescence pattern and its reproducibility is poor.³³ For this reason, several laboratories measure EMA in association with AGA IgA and IgG, and ARA, and this involves a large expenditure of time and resources.³⁴

Assays for anti-tTG detection have been developed recently and have been proposed as an alternative method. Our study was designed to verify the diagnostic accuracy of the anti-tTGgp test, and its role as a possible substitute for the older tests.

We found that the anti-tTGgp test has a higher sensitivity than the EMA test, which in turn is slightly more specific, and is more efficient than EMA in monitoring patients with CD who are on a GFD (39.5% v 27.7% sensitivity, respectively). A more sensitive method to monitor patients on a GFD is needed, because recent research has shown that a negative EMA test does not always indicate a normalisation of the intestinal mucosa.³⁵ In this context, the anti-tTG test can be useful even at lower cut off values than those used for diagnostic purposes.

The IgA and IgG AGA assays had a lower sensitivity and specificity, in line with those reported in previous studies.³⁶⁻³⁷ However, the IgG AGA test was positive in 95.9% of patients with CD aged less than 2 years; this indicates that an IgG class marker can be very useful in situations where low amounts or a deficiency of IgA is suspected.³⁸ Furthermore, it was shown recently that some patients with CD may be positive for the IgG class only, even though they do not have IgA deficiency.³⁹ Thus, if anti-tTG replaces the AGA assay, both the IgA and IgG isotypes should be determined.

Another interesting feature of the anti-tTG test relates to the 47 patients who were affected by IgA deficiency and in whom IgA anti-tTGgp values were constantly below 1 AU; this aspect could be useful for the selection of sera to test for total IgA.

"The use of antitissue transglutaminase testing, particularly if a human recombinant antigen is used, will probably lead to a more precise diagnosis of coeliac disease"

The results obtained after a re-evaluation of a proportion of the non-concordant EMA/anti-tTGgp sera deserve some comments. Although anti-tTGgp positive results were re-confirmed in 92.3% of the cases, positivity was confirmed by anti-tTGhr in only 49 of the 162 anti-tTGgp positive/EMA negative sera, thus suggesting that anti-tTGhr is significantly more specific than anti-tTGgp. Among the 113 sera in which positive results were not confirmed by anti-tTGhr, 56 had low anti-tTGgp values (5-7 AU), but 57 had high or very high values. This discrepancy probably results from contamination of the antigen extracted from guinea pig liver by other proteins.¹⁷ Of the 49 sera that were confirmed positive by the anti-tTGhr assay, 39 that had been classified as EMA negative were in fact EMA positive, and of the 36 sera classified as EMA positive and anti-tTGgp negative, only two were really EMA positive. This indicates that EMA is a difficult test to interpret, and some patients may be mistakenly classified as negative. In addition, false positive results may be the result, at least in part, of an erroneous interpretation of the fluorescence pattern, as may occur (for example) when anti-smooth muscle autoantibodies are present.³⁴

Our study has also shown that some patients with CD may be anti-tTG positive but EMA negative, and that the ELISA

method enables the identification of autoantibody reactivity that is not detectable by the IIF EMA method.¹⁹ Thus, although the re-evaluation of sera indicates that EMA and anti-tTGhr are equally reliable diagnostic tests, the introduction of the anti-tTGhr assay in clinical laboratories would eliminate the intrinsic problems related to the IIF method, and provide a more accurate diagnostic procedure. In addition, the ELISA method is less expensive than the EMA assay, less labour intensive, and can be automated, thus providing a more cost effective test to be used on a wide scale.

Taken together, the results of our study indicate that the most efficient use of laboratory tests for the diagnosis of CD consists of IgA anti-tTG as the screening test; if anti-tTG is negative and serum IgA values are normal, CD can be excluded. Positive anti-tTG sera must be tested for EMA; if positivity is confirmed, an intestinal biopsy should be performed, although some recent papers suggest that when CD symptoms are typical and both antibodies are present, an intestinal biopsy is not mandatory.³⁹

Furthermore, if an anti-tTG assay with guinea pig antigen is used, a certain number of false positives should be expected; alternatively, if an anti-tTG assay with human recombinant antigen is used, a higher specificity will be obtained, and there will be a higher correlation with EMA. Finally, testing for IgG class antibodies (either anti-tTG or EMA) is necessary when serum IgA concentrations are low or this class is absent, and in patients aged less than 2 years (V Kiren, *et al.* New dimension of coeliac iceberg in childhood by using human tissue transglutaminase based ELISA test. Abstract of the 34th Annual Meeting of ESPGHAN, Geneva, Switzerland, May 9-12, 2001).³⁵⁻⁴⁰

The need for continuous monitoring of assay accuracy by external quality assessment programmes also emerged from this multicentre survey, especially for the detection of EMA, because of its subjectivity of interpretation and standardisation problems. The use of anti-tTG testing, particularly if a human recombinant antigen is used, will probably lead to a more precise diagnosis of CD.

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APPENDIX 1

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Take home messages

- The tissue transglutaminase (tTG) antibody assay is more sensitive than the antigliadin and anti-endomysium assays in the diagnosis of coeliac disease (CD)
- The tTG antibody assay using human recombinant antigen is more specific than the guinea pig tTG antibody assay
- The most specific test for the diagnosis of CD is the anti-endomysium antibody assay
- We suggest that samples should be screened with the human recombinant tTG antibody assay and positive results confirmed with the anti-endomysium antibody assay

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Conflict of interest: Dr Caradonna and Dr Cerni are employed by Eurospital S.r.l.

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