CLINICAL UTILITY OF ANTI-TISSUE TRANSGLUTAMINASE ANTIBODIES FOR DIAGNOSIS AND MONITORING OF COELIAC DISEASE IN CHILDREN AND ADOLESCENTS

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Summary

Identification of tissue transglutaminase (tTG) as a major target antigen of IgA anti-endomysial antibodies and detection of auto-antibodies against tTG in the serum pointed out a new direction in the serologic diagnosis of coeliac disease.

Clinical utility of determination of anti-tTG IgA antibodies, with recombinant human tTG used as antigen, was evaluated for the diagnosis of coeliac disease and monitoring the adherence to the diet in children and adolescents.

Patients: The study was performed in 169 patients aged 2-24 years, including 42 children (26 girls, 16 boys, mean age 8.01 ± 5.69, range 2-18) with newly diagnosed coeliac disease (CD) (group I), 60 patients (39 females, 21 males, mean age 15.68 ± 4.74, range 5-24) with CD recognized at least 3 years before entering the study, non-compliers with gluten-free diet (group II) and 67 children (34 girls, 33 boys, mean age 6.28 ± 4.48, range 2-16) suspected of malabsorption, in whom diagnosis of CD had been excluded.

Methods: Serum samples were taken from all patients and tested for total IgA, anti-endomysial IgA (IgAEmA) or IgG autoantibodies (IgGEmA), only in cases with IgA deficiency, by indirect immunofluorescence method and anti-tTG IgA antibodies by ELISA.

Results:

| Anti-tTG IgA | IgAEmA | Group I | Group II | Group III | Total |
|--------------|--------|---------|----------|-----------|-------|
| **positive** | 85.7%  | 89%     | 1.7%     | -         | 52.1% |
| **borderline** | 2.4%   | 95%     | -        | 3%        | 3.9%  |
| **negative** | 4.8%   | 7.1%    | 6.8%     | 1.7%      | 97%   |

Strong significant associations between anti-tTG IgA present in the serum and IgAEmA (Kendall τ = 0.7748, p<0.0001) and good correlation between the levels of anti-tTG IgA and IgAEmA (r=0.488, p=0.001) were found in group I. We have not shown the relationship between the presence of both types of antibodies in patients of group II (Kendall τ = 0.2102, p=0.0937). However, a good significant correlation between the levels of these parameters was observed (r=0.813, p<0.0001). Anti-tTG IgA concentration was significantly higher in patients of group I compared to group II (38.35 U/ml v. 23.13 U/ml, p<0.0056). The sensitivity of anti-tTG IgA test in group I was 88.1%, in group II - 91.7% while specificity reached 97%.

Conclusions: Determination of anti-tTG IgA shows high sensitivity (88.1%) and specificity (97%) for the detection of coeliac disease. This test can be used alternatively with the immunofluorescent IgAEmA in diagnosis of coeliac disease, and also as a marker of compliance with gluten-free diet. However, both IgAEmA and anti-tTG IgA tests do not reach 100% sensitivity and specificity for diagnosis and monitoring of celiac disease. Therefore small intestinal biopsy is still recommended as a gold standard.

Key words: coeliac disease, anti-endomysial antibodies, anti-tissue transglutaminase antibodies

Introduction

Coeliac disease (CD) is a genetically determined chronic inflammatory intestinal disease induced by gluten, the storage protein of wheat (gliadin), barley (hordein) and rye (secalin). It can be diagnosed in the presence of characteristic abnormalities in a small intestinal biopsy sample and by improvement on a gluten-free diet. The major histopathological changes are suggestive of coeliac disease in different grades of villous atrophy with crypt hyperplasia and intraepithelial lymphocytosis [1].
The clinical classification of coeliac disease is based on the presence of gastrointestinal symptoms. Difficulties in the diagnosis of atypical forms of the disease where gastrointestinal symptoms are absent or not prominent, along with the need for identification of CD cases in high-risk populations and monitoring the effects of adherence to the diet, led to the development of sensitive, specific and simple in vitro serologic assays [1].

Until now, testing for anti-endomysial antibodies (EmA) and anti-reticulin antibodies (ARA) seemed to be the most useful in the diagnosis and the treatment of CD patients with gluten-free diet. However, the indirect immunofluorescence methods for the detection of these antibodies have some disadvantages like observer-dependence, interferences with anti-nuclear or smooth muscle antibodies and difficulties in inter-laboratory standardization [2,3]. Moreover, there are ethical concerns about the use of monkey oesophagus as a substrate [4]. It is well known that EmA testing alone has no sufficient diagnostic accuracy for CD and for monitoring the effects of gluten-free diet, because the presence of these antibodies depends on villous and crypt architecture of small intestinal mucosa [5]. Lower sensitivity of EmA screening in cases with moderate abnormalities of mucosal pattern may result in worse detection of CD cases [5,6]. EmA seems to be not a reliable enough marker for slight dietary transgressions [4].

A most frequent pitfall of serological testing of EmA is selective IgA deficiency which occurs 10- to 16-fold more often than in the general population. Selective IgA deficient individuals usually have a raised concentration of IgG antibodies; so IgG-EmA test appears to be useful for identification of coeliac disease in these patients [7]. Another pitfall of serological testing is that children younger than 2 years of age are often negative for anti-endomysial antibodies. In this group of patients antibodies against gliadin (AGA) seem to be more specific and sensitive. The results of serological analysis will alter the use of immunosuppressive therapy and the amount of gluten consumed by patients; so after one month of gluten-free diet they can be negative [1].

Identification of tissue transglutaminase (tTG) as the major autoantigen in coeliac disease and the antigenic target recognised by anti-endomysial antibodies and detection of anti-tTG antibodies in the serum of CD patients has allowed a new diagnostic approach to serologic testing [8]. Most studies evaluating sensitivity and specificity of anti-tTG antibodies for diagnosis and follow-up were promising, especially, after introducing human recombinant tTG (rh-tTG) instead of tissue transglutaminase from guinea pig (gp-tTG) as antigen in commercially available tests [9,10]. It has been suggested that simple and less expensive ELISA tests could be useful for identification of coeliac disease in these patients [7].

The mean value of anti-tTGIgA in children of group I was 38.35 U/ml, in group II - 31.79 U/ml, in group III - 28.35 U/ml. According to the manufacturer recommendation, we considered negative, 4-9 U/ml - borderline, > 9 U/ml were considered positive. Anti-tTG IgA antibodies were detected in 36 of 42 children (85.7%) with newly diagnosed CD (group I, Table 1). Total IgA values in this group were within a reference range, except in one case which showed a decreased value for its age. In 6 patients (14.3%) negative or borderline results were found. Four of them were IgA deficient but only 3 were negative with anti-tTG IgA; in one patient a borderline result was shown (4.66 U/ml).

EmA were detected in all patients positive with anti-tTGIgA but also in 10 children were EmA negative. EmA were detected in 84.6% of children with grade III or grade IV of villous atrophy (Table 2). Two patients had high IgAEmA titers (+2560 IF and +640 IF; in histopathological findings, grade II in 1 case and grade III in 1 case). Positive results with anti-tTG IgA were found in all children with grade IV of villous atrophy.

The mean value of anti-tTG IgA in children of group I was 38.35 U/ml (quartile 1 and quartile 3 - 2.18 and 107.14, respectively). Statistically significant association was found between the presence of both types antibodies (Kendall’s τ coefficient 0.7748, p=0.0001) and their levels (r=0.4880, p=0.001). Among 42 children of group I, total villous atrophy in histopathological findings of small intestine was observed in 30 cases (71.4%), grade III/IV in 6 (14.3%), grade III in 5 (11.9%) and grade II in 1 case (2.4%). Positive results with anti-tTG IgA test were found in 90% of children with grade IV, 66.7% with grade III/IV and in 100% of children with grade III of villous atrophy. Statistical analysis has shown that the relationship between the degree of morphological damage of small intestinal mucosa and positive result of anti-tTG IgA test was rather weak (p=0.2741) (Table 2).

In 60 CD patients of group II, monitored for at least 3 years, non-compliance with gluten-free diet and normal IgA levels were found. Of 60 patients, 52 were positive with anti-tTG IgA (86.7%). In all study protocol was approved by the Bioethics Committee at L.Rydygier Medical University and informed consent was obtained from each patient.
these cases but one EmAs were detected (+2.5 IF to + 640 IF).
Borderline results with anti-tTGIgA were found in 3 patients with
EmA titers +2.5 IF, +5 IF and + 40 IF. Among 3 cases with negative
anti-tTG IgA 4 were positive with IgAEmA (+2.5, +5, +5 and +40 IF).
IgAEmA were detected in 58 of 60 patients (96.7%). Two patients of
this group were reported to be on a gluten-rich diet. Nevertheless,
they had normal total IgA levels and were negative with IgAEmA
and IgG EmA. In these 2 patients anti-tTG IgA were negative or
borderline (0.542 and 4.257 U/ml).

The mean level of anti-tTG IgA in group II was 23.13 U/ml [(Q1;Q3)
(12.07; 55.22)]. There was no association between the presence of
both types of antibodies (p=0.0937, Kendall τ 0.2102) but a good
positive correlation between the levels of these variables was
observed (r=0.8134, p<0.0001). Results are presented in Table 3.

Interestingly, statistical analysis has revealed significantly higher
level of IgAEmA and anti-tTG IgA in patients with newly diagnosed
CD than in patients which reported non-compliance with the gluten-
free diet (p=0.0008 and p=0.0356, respectively) (Figure 1).

In 67 children (group III) with other gastrointestinal diseases, in
which CD was excluded, EmA were not detected and borderline
anti-tTG IgA was found only in 2 cases (5.59 and 14.4 U/ml).

The sensitivity of 88.1% in group I (85.1% positive, 2.4% borderline
as positive) and 91.7% in group II (96.7% positive, 5% borderline as
positive) was obtained, while specificity reached 97% for anti-tTG
ELISA (Table 5). Positive and negative predictive value were in
group I - 94.9 and 92.9%, in group II - 96.5 and 92.9%, respectively
(Table 4).

Discussion

Tissue transglutaminase belongs to a diverse family of enzymes
that are widely distributed in tissues and body fluids of mammals
and some plants. In humans, there are several other enzymes which
belong to this family: three of epithelial origin and two
extracellular (coagulation factor XIII and prostate TG). Tissue
transglutaminase is found in the small bowel mucosa, endothelial
cells, smooth muscle cells and thymus. Tissue TG is a cytosolic
enzyme, physiologically inactive. In the tissues damaged after
mechanical injury, inflammation or during apoptosis TG is
released from the cells. TG plays a role in the aetiopathogenesis of
several diseases like these of the central nervous system (Huntington’s
toxaemia, malignancies, HIV infections, thrombocytopenia,
non-specific enteritis, cirrhosis, cataract or several autoimmune
diseases [12, 13, 14]. The finding of anti-TG antibodies is of special
interest in the pathogenesis of CD. TG is present in all layers of
the intestine wall with the highest activity in the submucosa but almost
undetectable in the epithelium. Transglutaminase is absent from
crypt epithelium but increased expression of the enzyme was shown
in mature epithelial cells migrating to small intestine villi [15].

TG induces the deamination of gluten peptides present in the diet
and the formation of neoepitopes that, in association with HLA-
DQ2 molecules on the surface of T-lymphocytes, presents antigen
drive of the antibody response to both gluten and TG [12,16].

Since identification of TG in 1997 as a major autoantigen
recognized by anti-endomysium antibodies [17] commercially
available tests for IgA class anti-TG [10], using guinea pig TG as an
antigen were developed. However, recently recombinant human
antigen was recommended because of higher sensitivity and
specificity [18-23]. In our study the ELISA test, using rhTG, provided encouraging
results with 88.1% sensitivity in children with newly diagnosed CD,
which was comparable to 75-100% in the previous data [10, 11, 19,
21-32]. Test sensitivity could probably be increased by measuring
IgG class anti-TG antibodies in cases with decreased or deficient
IgA, which is often found in CD patients. Therefore, it is suggested
that in suspected cases first total IgA should be measured and then
patients with IgA deficiency checked for anti-TG IgG antibodies
[7,29,33-34].

A weak association between anti-tTG IgA positivity and mucosal
pattern in children with CD may result from a small number of
cases with moderate villous atrophy (11 patients). Presumably, test
sensitivity increases in cases with total villous atrophy while
decreases in patients with subtle changes of mucosal architecture as
reported by others [31, 35]. This may lead to negative results in
patients with gluten-sensitive enteropathy with normal or slightly
changed mucosa.

In CD patients monitored for 3 years, which reported high gluten
consumption, anti-TG IgA sensitivity of 91.7% was achieved; this was
lower than the IgAEmA sensitivity (96.7%) found by us earlier [36].
EmAs seem to be a better marker of gluten-free diet compliance.
According to data reported elsewhere, anti-tTG IgA show positive
correlation with the amount of gluten in the diet before CD
recognition and during the gluten challenge [37]; also with duration
of gluten-free diet or gluten challenge [28]. Several CD patients
committing dietetic errors are negative with anti-tTG IgA; on the
other hand negative serology in CD patients is not related to
histologic regeneration of small intestine mucosa [38].

CD patients on gluten-free diet present significantly lower values
of anti-tTG IgA compared with non-compliants [31]; that is also
observed in our study.

The anti-tTG IgA test in our hands had 97% specificity which was very
high and comparable to other data -90.1 to 99.2% [10, 18, 19, 21-
31, 39]. In two cases with diverse gastrointestinal diseases borderline
positive anti-tTG IgA values were found while IgAEmA results were
negative. One of these two patients, a 12 years old girl with a family
history of CD and gastrointestinal symptoms of unknown etiology,
had a normal biopsy, trace amounts of IgAEmA (+2.5 IF) and
recently found borderline anti-tTG IgA of 7.44 U/ml which may not
be a false positive but suggests an early silent atypical form of CD.

Indeed, very recent data suggest that anti-tTG IgA test can be used to
detect CD in patients unrecognized by IgAEmA [21,40].

The 94.1% accordance of anti-tTG IgA detection with the presence of
IgAEmA, measured by immunofluorescence method, observed in
all patients in the study was quite high, however does not allow the
complete replacement of EmA testing with rh anti-TG ELISA, that is
in agreement with previous reports [18,20,22,37,41]. We suggest,
with agreement with some others, that anti-TG antibodies can be used
as the first-step tool in the routine diagnostic panel for CD and in
doubtful cases EmA should be tested [29,32]. According to Dickey
et al. serology screening should be based on both EmA and anti-
tTG IgA detection because in every third patient only one type of
antibody is present [30]. It is worth noting that, at present,
serologic markers are not reliable enough to become a “gold
standard” in diagnosis and monitoring of coeliac disease. In fact, a
proportion of CD cases, especially these with subtotal villous
atrophy, is negative for any antibodies characteristic for CD that
makes avoiding biopsy by clinicians, impossible [24,30].

We have shown that anti-tTG IgA ELISA with recombinant human
antigen may be used interchangeably with IgAEmA in serology.
screening for diagnosis of CD and adherence to the gluten-free diet but, providing sensitivity and specificity below 100%, should not replace small intestinal biopsy.

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Table 1. Number of cases positive, negative or borderline for serum IgAEmA and anti-tTGIgA in children with newly diagnosed coeliac disease (group I)

| IgAEmA | Anti-tTGIgA | positive | borderline | negative |
|--------|------------|----------|------------|----------|
|        |            | N %      | N %        | N %      |
| Positive| 36         | 100.00   | 2          | 40.00    | 38       |
| negative| –          | 100.00   | 3          | 60.00    | 4        |
| All     | 36         | 100.00   | 5          | 100.00   | 42       |

Chi² = 28.0737 (p < 0.0001)
Contingency coefficient = 0.4338
Rendall r = 0.7482

Table 2. Relationship between anti-tTGIgA and degree of villous atrophy in children with newly diagnosed CD

| Anti-tTGIgA | Degree of villous atrophy in histological picture of internal intomorphy |
|------------|---------------------------------|
|            | N % | N % | N % | N % | N % |
| positive    | 27  | 36  | 4   | 66.67 | 5   |
| borderline  | 1   | 33  | –   | –    | –   |
| negative   | 2   | 66.67 | 2  | 33.33 | –   |
| all        | 30  | 100.00 | 6  | 100.00 | 1  |

Chi² = 11.844 (p = 0.0062)
Contingency coefficient = 0.4669
Spearman's rank correlation = 0.2727 (p = 0.2741)

Table 3. Number of cases positive, negative and borderline for serum IgAEmA and anti-tTGIgA in patients non-compliants with gluten-free diet (group II)

| IgAEmA | Anti-tTGIgA | positive | negative | negative % |
|--------|------------|----------|----------|------------|
|        |            | N %      | N %      |            |
| Positive| 22         | 100.00   | 4        | 20.00      |
| Negative| 1          | 100.00   | 2        | 20.00      |
| all     | 23         | 100.00   | 6        | 20.00      |

Chi² = 8.7347 (p = 0.0037)
Contingency coefficient = 0.2704
Rendall r = 0.2702

Page 121
Figure 1. Comparison between anti-tTG IgA in both groups of patients with coeliac disease

Table 4. Assessment of the utility of anti-tTG IgA-ELISA for diagnosis and monitoring of coeliac disease

|                        | Patients with newly diagnosed coeliac disease | Patients not-compliant with gluten-free diet | All patients |
|------------------------|---------------------------------------------|--------------------------------------------|--------------|
| Sensitivity            | 80.30%                                      | 91.67%                                     | 90.21%       |
| Specificity            | 91.07%                                      | 97.01%                                     | 91.01%       |
| Positive predictive value | 94.02%                                    | 96.49%                                     | 97.01%       |
| Negative predictive value | 92.88%                                    | 92.88%                                     | 98.61%       |
| Precision              | 93.52%                                      | 94.49%                                     | 92.94%       |