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Research Article

A Point-of-Care Test for Anti-Transglutaminase (tTG2A) IgA, IgG, IgM Antibodies (Celiac Quick Test®) Validated in Diagnosis of Incident Celiac Disease (CD) in Pediatric Patients

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Abstract

Background: Testing for tTG2A (tissue transglutaminase 2A) in serum has become a standard in diagnosis and follow-up of celiac disease (CD). To avoid unnecessary delays in diagnostic laboratories, a series of commercial point-of-care (POC) tests for tTG2A have been developed.

Objective: To assess the performance of a novel POC test measuring IgA-, IgG- and IgM antibodies to tTG2A (Celiac Quick Test®, Biohit Oyj, Helsinki) (CDQT) in pediatric patients who underwent full diagnostic setup for suspected incident CD.

Study Design and Methods: The cohort comprises 21 children who completed the diagnostic setup for incident CD because of protean clinical symptoms. All 21 subjects were screened for total IgA and tTG2A IgA antibodies by a serum ELISA test (Diametra Diagnostics Srl, Milan, Italy) as a reference to CDQT. All ELISA-positive, all IgA-deficient children as well as those with persistent clinical suspicion underwent upper gastrointestinal endoscopy with small bowel biopsies.

Results: After complete diagnostic setup, CD was confirmed in 9/21 children and excluded in 11, one case remaining inconclusive because of no histological signs of CD. Clinical symptoms were not helpful in distinguishing CD from non-CD patients. CDQT was 89% sensitive and 100% specific for CD, while the ELISA test was 100% sensitive but only 83% specific, with the respective AUC (area under ROC) of 0.944 and 0.917 (p = 0.752).

Conclusions: These results confirm the performance of CDQT reported in a larger series of pediatric CD patients on gluten-free diet (GFD). The 100% specificity (with no false positive results) makes CDQT an excellent candidate POC test for population-based screening for CD, where high PPV is an advantage.

Keywords: *Celiac Disease; Tissue Transglutaminase 2A (tTG2A); IgA, IgG, IgM Antibodies; Celiac Quick Test®; Incident Disease; Pediatric Patients; Test Performance; tTG2A Serum ELISA Test; Gold Standard; Marsh's Classification; Duodenal Biopsies; Endoscopy; Gluten-Free Diet; Population-Based Screening*

Introduction

Celiac disease (CD) is an autoimmune disorder of the small intestine that occurs in genetically predisposed people of all ages [1-3].

Symptoms include pain and discomfort in the digestive tract, chronic constipation and diarrhea, failure to thrive (in children), anemia and fatigue, but these may be absent, and symptoms in other organ systems are not uncommon [4,5]. CD is a chronic disorder affecting 1 - 3% of the Western population [1,6-8]. Currently, more and more diagnoses are made in asymptomatic persons as a result of systematic screening which has gained increasing popularity [9].

CD is caused by a reaction to gliadin, a prolamin (gluten protein) found in wheat, and similar proteins found in the crops of other common grains such as barley and rye [10-14]. Upon exposure to gliadin, and specifically to three peptides found in prolamins, the enzyme tissue transglutaminase type 2 (tTG2A) modifies the protein, and the immune system cross-reacts with the small-bowel tissue, causing an inflammatory reaction. That leads to a truncating of the villi lining the small intestine (called villous atrophy), which interferes with the absorption of nutrients. The only known effective treatment is a life-long gluten-free diet (GFD) [10]. tTG2A usually disappears in serum 9 - 12 months after initiation of GFD [10-14]. Therefore, detection of tTG2A in serum is not only useful in diagnosis and screening of CD, but also in monitoring the remission and patient's compliance with the GFD [14-19].

However, the conventional tTG2A measurement requires specialized laboratories and the results are usually delayed by several days. The clear need for point-of-care (POC) testing has resulted in the emergence of several commercial POC tests for tTG2A [20,21]. In POC testing, there is no need for purified or recombinant TG2 or serum separation, because TG2 is also found in the red blood cells (RBCs). Therefore, the patient's own TG2 can be used in anti-tTG2A detection by hemolysing a whole blood sample and liberating the self-TG2A from RBCs. Test results are available within 10 minutes, and the test can be performed at home, which is a clear advantage in the follow-up of CD patients on GFD [21-25].

Several studies have investigated the accuracy of tTG2A POC tests in screening and diagnosis of CD, and sensitivities and specificities similar to tTG2A serum ELISA tests have been reported: 70.1 - 97% and 76 - 100%, respectively [21-24,26-31]. There is, however, less consensus over the accuracy of POC testing in monitoring CD treated by GFD [21,28], because these patients usually have much lower titers of tTG2A than the untreated patients [22,32].

The aim of this study was to assess the performance of a novel tTG2A POC test (CELIAC Quick Test®, Biohit Oyj, Helsinki, Finland; CDQT) in diagnosis of CD in children completing the diagnostic setup for a suspected disease. CDQT is an immunochromatographic test designed for a qualitative detection of IgA/IgG/IgM antibodies against human tTG2A in whole blood. So far, this test has been compared only in pediatric patients with prevalent CD who are on GFD [21]. Clinically confirmed CD was used as the gold standard, and a commercial tTG2A IgA ELISA as the reference test.

Material and Methods

Patients and their testing

The study was conducted in the Second Pediatric Clinic, Children's Emergency Hospital, University of Medicine and Pharmacy, Cluj-Napoca (Romania). All consecutive children with clinically suspected incident CD were included. The suspicion was based on their clinical presentation, including 1) gastrointestinal symptoms (diarrhea, constipation, vomiting, decreased appetite), 2) signs of malabsorption (failure to thrive, anemia, rickets/thin bones), 3) other clinical signs of CD such as depression, dermatitis herpetiformis (DH), as well as 4) family or personal history of an autoimmune disease.

All subjects were first screened for total IgA and tTG IgA antibodies by an ELISA test. Children with positive anti-tTG antibody or those with IgA-deficiency underwent upper gastrointestinal endoscopy with small bowel biopsies. If tTG2A serology was negative but clinical suspicion persisted (failure to thrive, with persistent diarrhea or constipation, anemia, positive family history), endoscopy with duodenal biopsies was performed. All patients who refused to sign the consent or to undergo upper gastrointestinal endoscopy with duodenal biopsies (the gold standard) [33] were excluded from the study. Using this diagnostic setup, 21 eligible children were enrolled during a 20-month period (2014 - 2016). The study protocol was approved by the medical ethical committee of the Iuliu Hatieganu University of Medicine and Pharmacy in Cluj-Napoca. All patients (or their parents) signed an informed consent.

Methods

Gold standard laboratory test for CD

As the gold standard laboratory test for CD, we tested the IgA antibodies to tTG2A, using commercially available ELISA kits (Diametra Diagnostics Srl, Milan, Italy), performed in the hospital laboratory following the manufacturer's instructions. IgA tTG value > 20 AU/ml was considered as positive.

Celiac Quick test® (CDQT)

In all steps of performing the CDQT, the manufacturer's instructions were strictly followed, including the sampling and its processing as well as the interpretation of the results [34]. The results were visually read 10 minutes after adding the dilution buffer. In a positive test, a clearly distinguishable pink-red band must appear across the result window close to the letter "T" (test line), in addition to the blue control band. Although the intensity of the line depends on the concentration of tTG2A antibodies in the sample, CDQT is only qualitative when interpreted by visual inspection [34].

Endoscopy and biopsies

Biopsy samples were taken from the duodenum (the bulb and second part of the duodenum), two to four biopsies, as currently recommended [35]. The biopsy specimens were routinely processed for hematoxylin-eosin (HE) and Alcian Blue PAS-stained sections. All biopsies were examined by one expert pathologist at the Pathology Department of Children's Emergency Hospital, Cluj-Napoca, among the daily routine samples. The diagnoses were reported using the Marsh classification of duodenal histology in CD, classified into one of the 5 categories [36,37], subsequently modified by splitting the previous stage 3 into three sub-stages [38].

Statistical Analysis

For statistical analyses, three software packages were utilized (for specific purposes): SPSS 24.0.0.1 for Windows (IBM, NY, USA), STATA/SE 14.2 (STATA Corp., Texas, USA), and MedCalc 17.4.4. (MedCalc Software, Ostend, Belgium). The descriptive statistics were conducted according to routine procedures. Performance indicators [sensitivity (SE), specificity (SP), positive predictive value (PPV), negative predictive value (NPV) and their 95%CI] of the two tests (CDQT and tTG2A ELISA) were calculated for the clinical CD endpoint, using the diagti module (in STATA). This also calculates the area under ROC (Receiver Operating Characteristics) called Area Under Curve (AUC) [(SE+SP)/2]. Concordance between the CDQT and the gold standard tTG2A ELISA serology was calculated using regular and weighted kappa (ICC). Significance of the difference between AUC values was estimated using the ROC comparison test (MedCalc) with 95%CI. The results were interpreted significant at $p < 0.05$ level.

Results

After the completion of all diagnostic procedures, 9 out of 21 patients (42.9%) had an incident CD confirmed (CDQT, ELISA, histology all +), whereas the disease could be excluded in 11/21 (52.4%) children (CDQT, ELISA, histology, all-). In the remaining child, CDQT and serology were positive for tTG2A, but duodenal biopsies failed to confirm CD, thus leaving the diagnosis uncertain. This patient was classified into the group of non-confirmed CD (non-CD) in all statistical analyses.

The key clinical characteristics of the study subjects stratified by the CD and non-CD groups are given in Table 1. The two groups are very similar in most of the recorded characteristics, including their mean age, gender distribution and body mass index (BMI). The same applies to the clinical symptoms recorded during the clinical examination. In fact, there were no differences at all ($p = 1.000$) regarding several key symptoms of CD including: failure to thrive, vomiting, poor appetite, and irritability. On the other hand, constipation (OR = 4.00, NS), autoimmune disease (OR = 3.14, NS) and family history of autoimmune disease (OR = 4.00, NS) were reported more frequently to the children with confirmed CD. Also, the duration of the symptoms, 17.6 months in the CD group was longer than that (9.6 mo) in the non-CD group, but the difference was not statistically significant ($p = 0.223$).

Variable/Symptom	Children with confirmed CD (n = 9)		Children with CD not confirmed (n = 12)*		OR (95%CI)	p - value
	Number	Per cent	Number	Percent		
Age	8.3 (4.9)	NA	8.4 (6.2)	NA	NA	0.972
Gender:						
F	4	44.4	9	75.0	0.267 (0.042 - 1.70)	0.203
M	5	55.6	3	25.0		
BMI	14.3 (2.1)	NA	14.4 (2.4)	NA	NA	0.890
BMI within normal range:						
Yes	5	55.6	8	66.7	0.625 (0.10 - 3.70)	0.673
No	4	44.4	4	33.3		
Diarrhea						
Yes	2	22.2	4	33.3	0.571 (0.08 - 4.12)	0.659
No	7	77.8	8	67.3		
Constipation						
Yes	7	77.8	5	41.7	4.90 (0.70 - 34.3)	0.184
No	2	22.2	7	58.3		
Failure to thrive						
Yes	7	77.8	9	75.0	1.17 (0.15 - 9.00)	1.000
No	2	22.2	3	25.0		
Vomiting						
Yes	1	11.1	2	16.7	0.625 (0.05 - 8.20)	1.000
No	8	88.9	10	83.3		
Poor appetite						
Yes	4	44.4	6	50.0	0.800 (0.14 - 4.53)	1.000
No	5	55.6	6	50.0		
Irritability						
Yes	5	55.6	7	58.3	0.89 (0.15 - 5.11)	1.000
No	4	44.4	5	42.7		
Anemia						
Yes	2	22.2	6	50.0	0.286 (0.04 - 1.98)	0.367
No	7	77.8	6	50.0		
Rickets (thin bones)						
Yes	1	11.1	5	42.7	0.175 (0.016 - 1.88)	0.178
No	8	88.9	7	58.3		
Depression						
Yes	1	11.1	0	0.0	NA	0.429
No	8	88.9	12	100		
Autoimmune disease (AI)						

Yes	2	22.2	1	8.3	3.14 (0.23 - 41.50)	0.553
No	7	77.8	11	91.7		
Family history of AI						
Yes	4	44.4	2	16.7	4.00 (0.53 - 29.80)	0.331
No	5	55.6	10	83.3		
Duration of symptoms (mo)	17.6 (16.3)	NA	9.6 (10.4)	NA	NA	0.223

Table 1: *Key clinical characteristics of the children with confirmed CD and those with no CD confirmed.*

**Includes the single patient with CD diagnosis not confirmed by histology.*

Table 2 summarizes the performance indicators of the CDQT and the IgA tTG2A ELISA test, with the clinically confirmed CD as the end-point. CDQT successfully competes with the IgA ELISA test as measured by the ROC analysis (AUC) that reflects the sensitivity/specificity balance. Albeit CDQT is less sensitive (88.9%) than the ELISA test (100%), it is far more specific (100%) than the ELISA (83.3%), resulting in AUC = 0.944 and AUC = 0.917, respectively. This difference is not statistically significant, however (p = 0.752). The two tests are highly concordant (85.7% overall concordance), and their inter-rater agreement exceeds the limit (0.8) of almost perfect by the weighted kappa (ICC, intra-class correlation) test (ICC = 0.856). When CDQT was compared against the IgA tTG2A ELISA test (endpoint), the sensitivity was only 72.7%, but specificity still 100%, AUC falling below 0.9 (Table 2).

Test	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	Area under ROC (AUC)
CDQT IgA/IgG/IgM (tTG2A)	88.9 (51.8 - 99.7)	100 (73.5 - 100)	100 (63.1 - 100)	92.3 (64.0 - 99.8)	0.944 (0.836 - 1.000)#
IgA ELISA (tTG2A)	100 (66.4 - 100)	83.3 (51.6 - 97.9)	81.8 (48.2 - 97.7)	100 (69.2 - 100)	0.917 (0.807 - 1.000)#
CDQT IgA/IgG/IgM (tTG2A)*	72.7 (39.0 - 94.0)	100 (69.2 - 100)	100 (63.1 - 100)	76.9 (46.2 - 95.0)	0.864 (0.726 - 1.000)

Table 2: *Performance of CDQT and IgA tTG2A ELISA serology in diagnosis of clinically confirmed incident CD in pediatric patients.*

*Overall Concordance between the two tests: 18/21 (85.7%); Regular (Cohen's) kappa: 0.717 (95% 0.572 - 0.862); Weighted kappa (ICC): 0.856 (95%CI 0.644 - 0.941); #ROC comparison test (significance between the two AUC values): p=0.752; *CDQT as compared to "the gold standard" (tTG2A ELISA test).*

Discussion

Severe CD leads to the characteristic symptoms of pale, loose and greasy stool (steatorrhea) and weight loss or failure to gain weight (in young children). It is also possible to have CD without any symptoms whatsoever [1,9-11,39,40]. Approximately 2-8% of children and adolescents referred for evaluation of a short stature have evidence of CD [41]. Once endocrine causes have been excluded, rates of CD increase 2- to 4-fold depending upon the referral criteria [41]. In the setting of declining growth percentiles or where the data are not available, the possibility of CD should justify the testing for autoantibodies [13,33,42].

CD patients also present with extra-intestinal manifestations, all sharing a feature in common, i.e., they are at least partially responsive to GFD [3,9,13,43]. Abnormalities of the dental enamel including pitting and/or grooving may be present in up to 20 - 70% of CD patients [44]. Therefore, the diagnosis of CD may be raised first by the dentist finding dental enamel hypoplasia. The recurrent aphthous stomati-

tis has been attributed to nutritional deficiencies and generally resolves with GFD [44]. Neurological and psychiatric disorders including depression, anxiety, irritability, peripheral neuropathy, cerebellar ataxia and migraines have all been reported [3,13]. More seldom, CD patients can report hypotonia, developmental delay, epilepsy, headache, and ataxia, which, unfortunately, do not invariably improve with GFD [45]. Furthermore, CD is associated with a number of other medical conditions, many of which are autoimmune disorders: diabetes mellitus type 1, autoimmune thyroiditis, primary biliary cirrhosis, and microscopic colitis [3,11,13,43]. As to 1) IgA deficiency; 2) DH; 3) growth failure and/or pubertal delay; 4) recurrent miscarriage and unexplained infertility; 5) hyposplenism, it is unclear whether the gluten-induced bowel disease is a causative factor or whether these conditions share a common predisposition [3,11,13,43].

In the present study, a thorough recording of the clinical symptoms was completed (Table 1), including symptoms of both intestinal and extra-intestinal origin. Based on these protean symptoms, all the study subjects were referred for an expert clinic with a suspicion of CD, strong enough to warrant the execution of the standard diagnostic setup. Such a diagnostic setup, proposed by Catassi and Fasano [33] currently consists of a 5-point scoring system that incorporates 1) symptoms of CD; 2) positive tTG2A serology at high titer; 3) the presence of a DQ2 or DQ8 haplotype; 4) characteristic histopathological findings in duodenal biopsy; and 5) a serological or histological response to GFD. The presence of 4/5 criteria (or 3/4, if the gene testing is not included) would meet the diagnostic criteria of CD [3,6,9-11,13,33,35-37,46] Indeed, when this setup was completed, 9/21 children were confirmed to have CD, while in 11/21 patients, CD could be reliably excluded. This clearly confirms the complexity of the disease, with most (if not all) of the symptoms being non-diagnostic to CD. This is demonstrated by the clinical data in Table 1, which was practically equal in the CD and non-CD patients, clearly emphasizing the fact that the diagnosis of CD cannot be made on the basis of clinical symptoms [3,6,9-11,13, 33,35-37,46].

To obviate the excessive use of invasive endoscopic procedures (EGD-esophago-gastroduodenoscopy) particularly among children, non-invasive diagnostic tools (POC tests) capable of diagnosing CD without an unnecessary laboratory delay have been introduced on the market [21-24,26-31]. There are two special groups that need particular attention while diagnosing CD with the POC tests: i) children, and ii) individuals with IgA-deficiency. In children, the current concepts suggest that tTG2A IgA and deamidated gliadin peptide (DGP) IgA and IgG are equivalent in detecting CD, and DGP IgG is also as good as tTG2A IgG in detecting CD in IgA-deficient patients [1,21,46]. However, the superiority of DGP or tTG2A in screening of very young children for CD, as well as in monitoring of the dietary compliance remains rather controversial [46]. When CD is suspected in patients with IgA-deficiency, endoscopy with biopsies is usually recommended, regardless of the autoantibody status [1,10,11,13,21,33,35-37,46]. To minimize the risk of missing the IgA-deficient patients in POC testing, who have 10-fold higher risk of CD [47], Biohit Oyj developed its Celiac Quick Test®, that detects anti-tTG2A IgA-, IgG- and IgM antibodies. This test is performed in a blood sample taken from the fingertip, which makes CDQT very user-friendly for small children [21,34].

Until now, CDQT has been evaluated only in one study, comparing three different commercially available POC tests for anti-tTG2A in children with treated CD [21]. These authors designed a cross-sectional study, evaluating 1) BIOCARD™, Celiac Test for IgA TG2A (Ani Biotech Oy, Vantaa, Finland), 2) CDQT (Biohit, Helsinki), and 3) Eurospital, Xeliac Test Professional for IgA and IgG TG2A (Eurospital SpA, Trieste, Italy) (referred to X, Y and Z, respectively in the text), in 142 blood samples from IgA-competent CD patients aged ≤ 18 years [21]. Serum tTG2A ELISA (the reference test) was positive in 47/142 samples. Test Y (CDQT) had a higher sensitivity than the other two tests: 89%, (95% CI 0.81-0.98) vs. test X: 34%, (95% CI 0.20 - 0.48) and Z: 55% (95% CI 0.41 - 0.70), and its specificity was 96% (95% CI 0.90 - 1.0) [21]. The authors concluded that different POC tests currently on the market do show different sensitivities for the relatively low positive tTG2A levels in treated pediatric CD patients [21]. The authors also recommended that before implementation of any POC test in the follow-up of treated CD patients, the test should be validated for this specific purpose [21].

The present setting is different from that used by the Dutch group [21], in that all the patients enrolled represent children with clinically suspected CD on the basis of their protean clinical symptoms (Table 1). Thus, in these untreated (naïve) CD patients, one would expect higher titers of serum antibodies for tTG2A that should be readily detectable by the POC and ELISA tests [1,4-7,13]. Having underwent a complete diagnostic setup [33], CD was confirmed in 9 children, all being correctly identified by the serum ELISA reference test, but one being missed by the CDQT. Importantly, however, the ELISA test gave a false positive result in two cases, which were correctly identified

by CDQT. These data translate to 88.9% sensitivity and 100% specificity for the CDQT, which are practically identical with (and even exceed) the figures (89% and 96%, respectively) reported in the follow-up study of pediatric CD patients, discussed above [21] (Table 2). However, CDQT and serum ELISA test were well concordant (85.7%) and also showed a high agreement in weighted kappa analysis (ICC = 0.856), which falls into the rank "almost perfect". Due to the lower specificity of the ELISA reference test, though, using it as the gold standard test for CD, resulted in compromised sensitivity (72.7%) for CDQT.

The indications of CD testing by serological markers are well defined [3,46]: 1) individuals with suspected CD, 2) those at high risk for CD (e.g. family history or another autoimmune disease), and 3) monitoring the compliance of GFD [3,21,22,26-31,43]. On the other hand, population-based screening for CD is a more controversial issue [9,48]. Given that CD has a population prevalence between 1% - 2%, with such a variety of symptoms also affecting life expectancy [1,3,9-11,40,41], the idea of an organized screening by serological tests is not incongruous [48]. As with all population-based screening, the issues are whether the screening is cost-effective and has an impact on mortality. Much of the success depends on the screening test, which should ideally have a high PPV [49]. With such a test, the maximum number of true disease is being detected with the minimum wasting of resources for triaging of the false positive results with other (expensive) tests [49]. Although not applied for systemic population-based screening of CD yet, CDQT would look a promising candidate test for such a purpose. If the results of the present diagnostic setting are translated to a hypothetical screening setting of 10.000 subjects, one can calculate the test performance in populations with different prevalence of CD, e.g. 1% and 2% CD prevalence. In the former (1%), CDQT would have sensitivity of 89%, specificity 100%, PPV 100% and NPV 99.9%. In the latter (2%), the respective figures would be 89%, 100%, 100% and 99.8%. In doing this, we presume that the CDQT sensitivity is similar in a diagnostic and a screening setting. In planning any such pilot, it is imperative to confirm by the gold standard not only all CDQT positives, but also a random sample of 2-3% test-negatives to control for the verification bias, which is inherent to all screening studies with incomplete design (i.e., not all cases being verified by the gold standard).

Conclusions

Taken together, the CDQT test with anti-tTG2A (IgA- IgG and IgM antibodies) was validated in a diagnostic setting of pediatric patients with clinically suspected CD, who all underwent the state-of-art diagnostic setup with biopsy confirmation [46]. Although the study is small in sample size, the results are encouraging. These data in children with incident CD fully confirm the figures obtained in a larger study of prevalent CD patients on GFD [21], indicating that CDQT is 89% sensitive and 100% specific for CD. In fact, the sensitivity/specificity balance measured by ROC analysis was better (AUC = 0.944) than that (AUC = 0.917) obtained for the tTG2A IgA ELISA test used as the gold standard in the study. The fact that no false positive results were reported for CDQT, this 100% PPV makes the test an excellent candidate POC test in population-based screening for CD, where high PPV is an advantage.

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Volume 3 Issue 1 May 2017