DOI: https://doi.org/10.2298/SARH230113064P
UDC: 616.341-008.1-097

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Assessment of diagnostic value of *HLA-DQ2/DQ8* typing and anti-tissue transglutaminase antibodies as an alternative to duodenal biopsy in pediatric celiac disease

Dragan Prokić[1], Slaviša Đuričić[2,3], Ivana Kitić[1,4], Marija Kocić[1], Srđan Pašić[4,5], Biljana Vuletić[6]

[1]Dr. Vukan Čupić Mother and Child Health Care Institute of Serbia, Department of Gastroenterology, Belgrade, Serbia;
[2]Dr. Vukan Čupić Mother and Child Health Care Institute of Serbia, Department of Clinical Pathology, Belgrade, Serbia;
[3]University of Banja Luka, Faculty of Medicine, Banja Luka, Republic of Srpska, Bosnia and Herzegovina;
[4]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[5]Dr. Vukan Čupić Mother and Child Health Care Institute of Serbia, Department of Immunology, Belgrade, Serbia;
[6]University of Kragujevac, Faculty of Medical Sciences, Department of Pediatrics, Kragujevac, Serbia

SUMMARY

Introduction/Objective The objective of the paper is to assess the applicability of serum anti-tissue transglutaminase (tTG) antibodies IgA and IgG concentration and *HLA-DQ2/DQ8* typing as a non-invasive alternative to duodenal biopsy in diagnosing celiac disease (CD) in pediatric population.

Methods A prospective cohort study included a total of 179 pediatric patients aged 1–18 years. Determination of tTG IgA and tTG IgG antibodies and human leukocyte antigen (*HLA*) *DQ2/DQ8* typing was performed for all patients. Histology of duodenal biopsies was interpreted by the modified Marsh scoring system.

Results The diagnosis of CD was confirmed in 101 (56%) patients of the studied population. In cases of CD, *HLA-DQ2/DQ8* was positive in 100 patients (99%). The tTG IgA antibodies in concentration higher than 100 U/ml were detected in 77 (76.2%) of the CD patients and in significantly smaller number for tTG IgG [29 (28.7%)] ($p < 0.001$). Statistically highly significant association of duodenal lesions Marsh grade 3 with concentration of tTG IgA 10-fold higher than the upper level of normal (ULN) was established ($p < 0.001$)

Conclusion Concentration of tTG IgA 10-fold higher than ULN is significantly positively correlated with Marsh grade 3 histopathology findings. Specific antibodies determination in combination with *HLA-DQ2/DQ8* typing proves to be sufficient for a diagnosis of CD, supporting the fact that duodenal biopsy may be avoided in a significant majority of patients – 75%.

Keywords: celiac disease; tissue transglutaminase antibodies; *HLA-DQ2/DQ8* typing; non-invasive

INTRODUCTION

Celiac disease (CD) is an autoimmune disorder that primarily affects the small intestine, and is caused by the ingestion of gluten in genetically susceptible individuals. Prevalence in the general population ranges 0.5–2%, with an average of about 1% [1, 2]. The development of the coeliac enteropathy depends on a complex immune response to gluten proteins. Clinical presentation of CD is highly variable and includes classical and non-classical gastrointestinal symptoms, extraintestinal manifestations, and subclinical cases. Familial occurrence was found to be present in 5–15% of patients, more often female in ratio 2–3:1, usually disclosing in children; however, up to 20% of cases may be diagnosed in patients over 60 years of age [3, 4, 5].

The reasons for the rising number of CD cases in recent decades are unknown, but may be related to environmental factors that may promote loss of tolerance to dietary gluten. Therefore, the quantity of early-life gluten exposure has been a major focus of prevention efforts.

The criteria for the diagnosis of CD are changing, but in adults, diagnosis still depends on the presence of duodenal villous atrophy, along with findings from serology analysis. Although guidelines in the United States continue to mandate a biopsy at all ages, some children receive a diagnosis of CD without a biopsy [6].

A strong association of CD with *HLA-DQ2* and *HLA-DQ8* genetic haplotypes has been well documented. In general population, *HLA-DQ2/DQ8* phenotype is present in 30–40% of individuals, but only 3% develop CD [7]. Globally, 95–99% of CD patients carry *HLA-DQ2* and/or *HLA-DQ8* haplotypes. Prevalence of *HLA-DQ2* phenotype ranges 90–95% among CD patients from European Caucasian population [8]. The presence of at least 1 of these haplotypes is necessary but insufficient for development of CD. Two twin studies have found concordance rates of only 49–83% among monozygotic twins,

Received • Примљено: January 13, 2023
Revised • Ревизија: June 5, 2023
Accepted • Прихваћено: June 11, 2023
Online first: July 3, 2023

Correspondence to:
Dragan PROKIĆ
Dr. Vukan Čupić Mother and Child Health Care Institute of Serbia
Radoja Dakića 6–8
11070 Belgrade, Serbia
prokic.gastro@gmail.com

indicating the existence of environmental risk factors [6, 9]. Therefore, human leukocyte antigen (*HLA*) typing could not be recommended as the sole marker for diagnosis of CD since positive predictive value reaches only 57%, while sensitivity does not exceed 63% [10]. The European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) proposed in 2012 and 2020 that it might be possible to avoid intestinal biopsy in children who meet the following criteria: have characteristic symptoms of CD, levels of tTG IgA greater than 10-fold the upper limit of normal, confirmed with a positive serologic result for anti-endomysial antibodies (EMA) [10, 11]. According to guidelines from 2012/2020, *HLA-DQ2/DQ8* typing was also recommended as a useful tool for CD diagnosis exclusion as well as for adding strength to the diagnosis of CD [11].

Considering the invasive nature of endoscopy and its potential complications, it has been postulated that an increase of both tTG IgA and/or IgG antibodies is predictive of the grade of small intestine villous atrophy, thus making intestinal biopsy unnecessary in two-thirds of the patients [10].

Presence of tTG IgA in different concentrations has been described in several autoimmune disorders, such as autoimmune hepatitis (AIH), inflammatory bowel disease (IBD), autoimmune thyroiditis and systemic lupus erythematous. However, elevation of tTG IgA in autoimmune disorders is not always associated with CD. Therefore, in this particular clinical setting determination of EMA was reported as a better choice [12].

The aim of our study was to estimate the accuracy of non-invasive diagnostic methods in pediatric patients with CD proposed by the ESPGHAN criteria. Our approach included a determining both IgA tTG and IgG tTG serum concentrations and correlating these values to the Marsh histology. The other goal of our study was to determine the usefulness of *HLA-DQ2/DQ8* typing in adding diagnostic accuracy to the aforementioned serologic analysis for confirmatory diagnosis of CD [11].

METHODS

This prospective study was conducted at Dr. Vukan Čupić Mother and Child Health Care Institute, Belgrade, Serbia during an observational period between January 2017 and December 2020. A total of 179 patients, aged from 12 months to 18 years, were included. The study group consisted of two major subgroups: a) children with at least one clinical or laboratory finding suggestive of CD: chronic diarrhea, bloating, chronic constipation, dyspepsia, failure to thrive, chronic weight loss, anemia and elevated serum transaminases, and b) asymptomatic children with positive family history for CD or previously diagnosed conditions associated with an increased risk for CD: immunoglobulin A deficiency (IgAD), AIH, Crohn's disease, diabetes mellitus type 1, Down syndrome.

Inclusion criteria of our study were the following: a) status of tTG IgA and tTG IgG antibodies determined before initiation of treatment; b) determined *HLA-DQ2/DQ8* typing; c) duodenal biopsy done within four weeks before the initiation of treatment.

Prior use of gluten-free diet (GFD) or the presence of IgAD (serum concentration of IgA ≤ 0.07 g/l) were considered to be the exclusion criteria. IgA antibodies in IgAD are not a reliable parameter due to their abnormally low concentrations, which would disrupt statistical analysis, and were excluded from this study [13].

Serum concentrations of the tTG IgA and tTG IgG antibodies were measured by using ELISA kit ORG 540 (Organon, USA) with recommended cut-off concentrations of tTG IgA and IgG antibodies > 10 U/ml (maximum operating range, 200 U/ml).

HLA typing for *DQ2* and *DQ8* haplotypes and was performed by the standard Complement Dependent Cytotoxicity assay [14].

Histological evaluation of intestinal forceps biopsies consisted of at least four specimens: three from the D2 section and one from a bulb of the duodenum. The results of histologic evaluation were classified using the Marsh scoring system modified by Oberhuber: Marsh 0 – normal mucosa; Marsh 1 – infiltrative lesions with at least 25 lymphocytes per 100 examined epithelial cells; Marsh 2 – hyperplastic lesions; Marsh 3 a, b, c stages were interpreted as partial, subtotal, and total villous atrophy, respectively [15, 16].

All statistical data were analyzed using IBM SPSS Statistics, Version 20.0 (IBM Corp., Armonk, NY). The data are presented as frequencies and median values depending on the type. The χ^2 test and the Mann–Whitney U test were used to assess the difference between the groups. Spearman correlation analysis was used to test the association between two variables. Diagnostic accuracy was presented with sensitivity, specificity, positive predictive value, and negative predictive value. We used receiver operating characteristic (ROC) analysis to find the optimal cut-off values. All p-values below 0.05 were considered statistically significant.

The study was conducted with the approval of the institutional ethics committee.

RESULTS

In the study cohort of 179 patients, the diagnosis of CD was established in 101 (56.4%). Basic demographic characteristics of the study subjects along with *HLA-DQ2/DQ8* typing profiles are presented in Table 1. In patients younger than two years (n = 35), CD was confirmed in 60% (n = 21), while in older than two years (n = 144), the same diagnosis was established in 63% (n = 91). Statistical analyses showed that *HLA-DQ2/D8* typing provided high negative predictive value of 99% for the diagnosis of CD, with specificity of 56%, positive predictive value of 75%, with test accuracy estimated at 82%.

Diagnostic accuracy of tTG IgA and IgG at different values of interest (10, 50, and 100 U/ml) was tested (Table 2), while optimal cut-off value was determined by ROC: for tTG IgA at 13 U/ml, and for TTG at IgG 5 U/ml, as

Table 1. Basic demographic data and status of *HLA-DQ2/DQ8* typing in the studied group

Demographic data	CD		p
	Yes (n = 101)	No (n = 78)	
Age (years)	7 (3–13)	7.5 (3–11)	0.984
Sex, male (n, %)	29 (28.7%)	41 (52.6%)	0.001
Positive *HLA-DQ2* and/or *DQ8* (n, %)	100 (99%)	33 (42.3%)	< 0.001
Positive *DQ2* (n, %)	97 (96%)	27(35%)	
Positive *DQ8* (n, %)	3 (3%)	6 (7%)	
Negative *HLA-DQ2* and *DQ8*	1 (1%)	45 (58%)	

Table 2. Serological and histopathological features of the studied group; all data were calculated without patients with IgA deficiency (tTG IgA is 0)

Features	CD		p
	Yes (n = 101)	No (n = 78)	
tTG IgA (U/ml)			
0–10	1 (1%)	70 (89.7%)	< 0.001
11–50	10 (9.9%)	5 (6.4%)	
51–100	12 (11.9%)	1 (1.3%)	
> 100	77 (76.2%)	2 (2.6%)	
tTG IgG (U/ml)			
0–10	27 (26.7%)	68 (87.2%)	< 0.001
11–50	32 (31.7%)	8 (10.3%)	
51–100	13 (12.9%)	2 (2.6%)	
> 100	29 (28.7%)	0	
Marsh histopathology	95 (94.1%)	10 (12.8%)	< 0.001
Marsh grade			
0	3 (3%)	62 (79.4%)	< 0.001
I	2 (2%)	6 (7.7%)	
II	1 (1%)	2 (2.6%)	
IIIa	15 (14.9%)	6 (7.7%)	
IIIb	18 (17.8%)	2 (2.6%)	
IIIc	62 (61.4%)	0	

Table 3. Determination of the cut-off values of tTG IgA and tTG IgG concentrations optimal for diagnosing celiac disease

Test	p	AUC	Cut-off	Sn	Sp
tTG IgA	< 0.001	0.984 (0.968–1.000)	13	99.9%	91%
tTG IgG	< 0.001	0.832 (0.771–0.892)	5	74.3%	87.2%

Sn – sensitivity; Sp – specificity; AUC – area under the curve

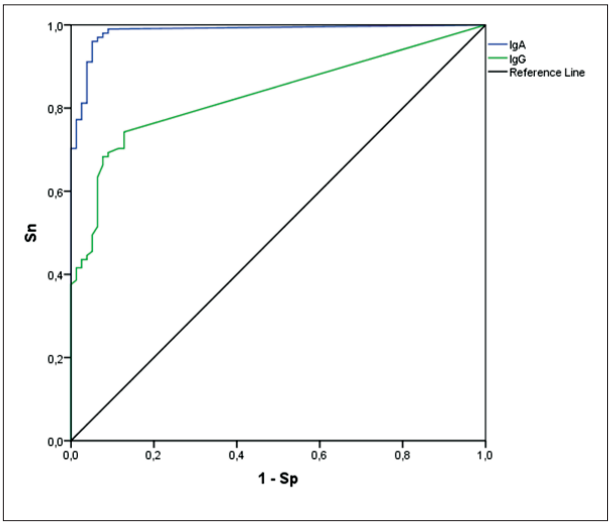

Figure 1. Receiving operating curve and area under the curve determine the best cut-off value for both tTG IgA and tTG IgG

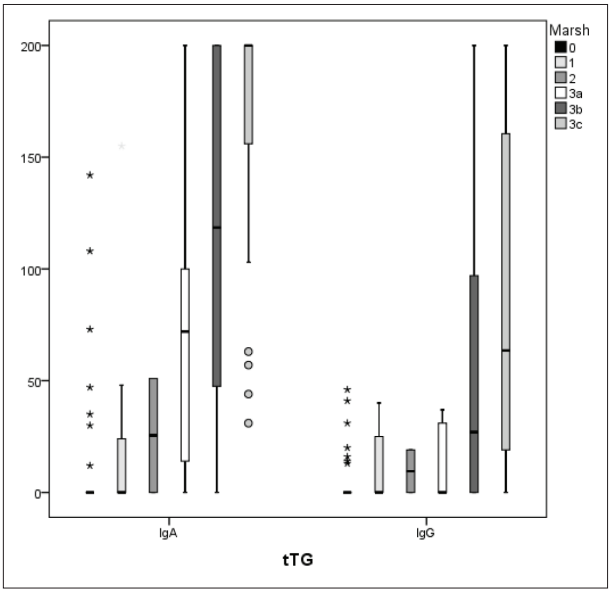

Figure 2. Correlation of tTG IgA (left) and tTG IgG (right) levels, with lesions of enteral mucosa graded by Marsh criteria (p > 0.001)

presented in Figure 1 and Table 3. As shown in Table 4, the highest sensitivity of tTG was found at IgA > 10 and IgG > 50, respectively. On the other hand, the highest specificity was detected both for tTG IgA and tTG IgG at levels higher than 50 U/ml.

There is statistically significant correlation of tTG IgA and tTG IgG concentrations with the extent of enteric mucosa lesions graded by the Marsh criteria ($p < 0.001$). The most significant association was observable for Marsh grade 3a lesions and tTG IgA concentration and also for Marsh grade 3b and tTG IgG concentration. Concentration of tTG IgA above 100 U/ml (10-fold higher than the ULN)

Table 4. Diagnostic accuracy of anti tTG IgA and tTG IgG for celiac disease at different concentration values of interest (10, 50, and 100 U/ml)

	Sn	Sp	PPV	NPV
IgA > 10	99 (93.8–99.9)	89.7 (80.3–95.1)	92.6 (85.5–96.5)	98.6 (91.3–99.9)
IgG > 10	73.3 (63.4–81.3)	87.2 (77.2–93.3)	88.1 (78.7–93.8)	71.5 (61.2–80.1)
IgA > 50	89.1 (80.9–94.2)	96.1 (88.4–99)	96.7 (90.2–99.2)	87.2 (77.8–93.1)
IgG > 50	41.6 (31.9–51.8)	97.4 (90.2–99.5)	95.4 (83.3–99.2)	56.3 (47.5–64.7)
IgA > 100	77.2 (67.6–84.7)	97.4 (90.2–99.5)	97.5 (90.4–99.5)	76.7 (67.0–84.4)
IgG > 100	28.7 (20.4–38.7)	1 (94.1–1)	1 (85.4–1)	52 (43.7–60.2)

Sn – sensitivity; Sp – specificity; PPV – positive predictive value; NPV – negative predictive value

was present in CD patients with enteric mucosa lesions Marsh 3c, with few exceptions (Figure 2 left). Although statistically significant, tTG IgG variation in relation to Marsh grade was lower (Figure 2 right).

DISCUSSION

Our study reiterated female predominance in the population of CD patients, as demonstrated by previous studies [5].

The age at the onset of CD did not affect the accuracy of the final diagnosis. It has been reported that tTG has limited diagnostic value in children younger than two years of age in establishing the CD diagnosis, suggesting that the concentration of antibodies on deamidated gliadin peptide could be of higher accuracy [11]. We should consider two possible causes of lower sensitivity of tTG in younger age. Namely, children under two years of age tend to have lower values of total IgA, which impacts the levels of tTG IgA. On the other hand, tTG antibodies could be less sensitive to gluten stimulation in younger age. Additionally, lower amount of gluten in an infant diet represents weak stimulus for tTG rise, but nevertheless causes abnormal gut histopathology [17]. Since we have excluded children with IgA deficiency from the statistical analysis, our study found that the diagnostic value of tTG should be considered reliable, without any effect of the age ($p = 0.984$). Therefore, we may assume that tTG in very young children is not inferior to AGA.

Our results in regard to *HLA-DQ2/DQ8* typing in CD patients showed almost complete correspondence to the similar study from 2014 conducted on a Serbian population [8]. Namely, both studies show that above 94% of patients diagnosed with CD carry the *HLA-DQ2* haplotype. In comparison with other studies in our geographic regions, there is also high degree of data similarity: e.g., in Croatia, 93.7% children with diagnosed CD carry *DQ2* [8]. In other parts of Europe, the prevalence of *HLA-DQ2* among CD patients may vary from nearly 85% in Greece and 87% in France to 92% in Scandinavia [8, 18]. In other parts of the world, *HLA-DQ* types in affected population are distinctly different, as shown in a Brazilian study: *HLA-DQ2* at 68.5%, *HLA-DQ8* at 17.8%, and both *DQ2* and *DQ8* at 6.8% [19]. The negative predictive value of *HLA* typing of 99% is in full accordance to the results of previous studies [8]. In the group of patients without confirmed CD, 42% were positive for *HLA-DQ2/DQ8*. This result is slightly exceeding the prevalence of aforementioned haplotypes of 30–40% in the general population, and it could be attributed to familial aggregation [7].

As shown in our results, the concentration of tTG IgA antibodies above 100 U/ml was highly suggestive of CD. Total serum IgA, tTG IgA and IgG antibodies as well as EMA antibodies all correlate to intestinal villous atrophy. Sensitivity of tTG IgA in the diagnosis of CD has been found to range 71–100%, while for EMA it is estimated at 86–100%; specificity is similar in both, ranging 90–100%. American College of Gastroenterology recommended the tTG IgA antibody as the most cost-effective and reliable screening test to identify CD. Obtaining a total serum IgA level at the initial testing is also recommended to identify those with selective IgAD in whom a tTG IgG-based test should be used [17]. In our study, tTG IgA above 100 U/ml (10 × ULN) showed high sensitivity (77.2) and specificity (97.5), with the optimal cut-off value at 13 U/ml. In contrast, tTG IgG above 100 U/ml (10 × ULN) showed significantly lower sensitivity of only 28.7, with absolute specificity and cut-off value optimally estimated at 5 U/ml. This observation could be explained by immunogenity of different isotypes: tTG IgG shows slower kinetics after gluten challenge especially if the stimulus contained a low gluten concentration. Moreover, tTG IgA and IgG share affinity for the same epitopes, and competition between these favors IgA antibodies. Circulating tTG IgG falls very slowly, and could be positive for over two years, which could be of importance in prolonged monitoring of patients with CD and associated IgAD [17].

We determined EMA antibodies only in special situations, such as the following: a) a finding of low concentration of the IgA tTG antibody with positive *HLA-DQ2/DQ8* typing; b) positive IgA tTG antibodies associated with negative *HLA-DQ2/DQ8* typing; c) patients with comorbid autoimmune diseases. At the time of our study, the determination of EMA IgA and IgG antibodies was not available at our hospital. Therefore, for 59 of our patient, the EMA were analyzed in different laboratories (by operator dependent methods). Due to this shortcoming, EMA antibodies status was excluded from statistical analysis. The analysis of EMA antibodies status in patients with clinical signs of CD is required by ESPGHAN recommendations [11]. However, our study demonstrates that the lack of EMA availability did not significantly affect the yield of non-invasive approach combining tTG serology and HLA typing.

False positive serology for tTG was reported in approximately 10% of the patients with food intolerance, post-infectious enteritis syndrome, sprue and kwashiorkor, and without evidence of CD [20, 21]. We found false positive results for tTG IgA in 3% of our patients, and in 12.9% for tTG IgG. In these cases, the importance of HLA typing is reflected in selecting patients in need of further investigation, such as EMA antibody testing and duodenal biopsy.

By contrast, false negative serology for tTG antibodies is only rarely described (~1%) in CD patients, especially in those with sufficient total IgA activity [21]. In our study, only one patient (1%) had false negative both tTG IgA and tTG IgG, with normal total serum IgA, positive *HLA-DQ2/DQ8*, and subsequent Marsh 3c histopathology; in the same patient, six months of GFD resulted in the resolution of histopathology findings to Marsh grade 0.

In our cohort of patients with confirmed CD, tTG IgA above 100 U/ml was found in 71% ($n = 73$) of the patients. Nevertheless, the tTG IgA concentration above 100 U/ml (10 × ULN) should be considered a good predictor of Marsh lesion grade 3, and especially of 3c (Figure 2, left).

The presence of duodenal damage, even Marsh 3 lesions, is not strictly correlated to the CD diagnosis, especially in children younger than two years [10]. Differential diagnosis in these cases is broad and includes other conditions, such as milk protein allergy, immune enteropathy,

Giardia infestation, post-infectious enteritis, malnutrition, etc. It should also be noted that in 13% of our patients Marsh 3a and 3b lesions were not associated with final diagnosis of CD. However, all Marsh 3c patients had definitive CD. Thus, only Marsh 3c lesions could be accepted as the "gold standard" in the histopathologic diagnosis of CD.

Crohn's disease and CD are two immune disorders with diverse genetic background. There is a strict correlation between *HLA-DQ2/DQ8* and CD, but this correlation is lacking in Crohn's disease [19]. However, patients with comorbidities of CD and Crohn's disease are expected to be *HLA-DQ2/DQ8*-positive. The prevalence of CD is not increased in children with IBD when compared to the general population [22]. False positive tTG antibodies' values can occur in children with IBD. Some patients with IBD, especially with Crohn's disease, show tTG IgA positivity in the absence of CD. In these patients, positivity of tTG antibodies may be a consequence of induced apoptosis and undergoing tissue damage in the bowel [23].

In our study, two patients had comorbidities of CD and Crohn's disease. One of them was diagnosed by the finding of increased tTG (IgA and IgG > 200 U/ml) antibodies, positive EMA antibodies, *HLA-DQ2/DQ8*-positive typing, and Marsh 3c score on histopathology; GFD resulted in a significant decrease of tTG. However, a single patient from our study had Crohn's disease and slightly positive tTG IgA (51–100 U/ml), negative both tTG IgG and EmA, as well as negative *HLA-DQ2/DQ8* typing and Marsh 0 histopathology. In this non-CD patient, tTG IgA gradually fell to normal levels after three months of follow-up, without GFD.

The correlation of AIH and chronic liver disease with CD seems to be complex as well. Some data demonstrated that CD prevalence does not differ significantly between the general population and patients with chronic liver disease such as AIH (comorbidity with CD in about 4–6% of cases) [24]. Furthermore, similarly to other autoimmune conditions, AIH could be associated with nonspecific positivity of tTG antibodies. In such a scenario, it would be important to determine EMA and rely on high sensitivity and specificity of this marker [25]. Interestingly, in our study, two of the patients with AIH had tTG IgA above 100 U/ml, with negative tTG IgG, EMA, *HLA-DQ2/DQ8* typing, and Marsh 0 histology. Also, the same two patients failed to demonstrate a decrease of tTG IgA during GFD, so the CD diagnosis could be excluded. In the third patient with AIH from our cohort, high concentrations of both tTG IgA and IgG antibodies (> 200 U/ml), positive EMA antibody, and positive *HLA-DQ2/DQ8* typing correlated to Marsh 3 histopathology. This CD patient responded to GFD and his tTG gradually decreased.

CONCLUSION

We confirmed previous findings that positive *HLA-DQ2/DQ8* typing combined with tTG IgA in concentration 10-fold higher than ULN should be regarded as sufficient for the diagnosis of CD. Furthermore, we showed that a duodenal biopsy may not be necessary in approximately 75% of pediatric patients with suspected CD. An increased concentration of tTG IgA antibodies significantly correlated with the grade of Marsh histopathology lesions. We report that the concentration of tTG IgA higher than 100 U/ml (10-fold higher than ULN) is a good predictor of more extended Marsh lesions (grade 3a, 3b or 3c) in children. By contrast, the measurement of tTG IgG antibodies was found to be of weaker sensitivity, although it remains an important diagnostic tool in special conditions such as IgAD or certain autoimmune diseases. Finally, EMA concentration was of particular importance for confirmation of CD diagnosis in challenging patients, but the pitfall of our study was the incomplete testing of the whole group. Therefore, determination of EMA should be regarded as an important part of the diagnostic algorithms for CD based on non-invasive approach.

Conflict of interest: None declared.

REFERENCES

1. Catassi C, Verdu EF, Bai JC, Lionetti E. Coeliac disease. Lancet. 2022;399(10344):2413–26. [DOI: 10.1016/S0140-6736(22)00794-2] [PMID: 35691302]
2. Machado MV. New Developments in Celiac Disease Treatment. Int J Mol Sci. 2023;24(2):945. [DOI: 10.3390/ijms24020945] [PMID: 36674460]
3. Zubkiewicz-Kucharska A, Jamer T, Chrzanowska J, Akutko K, Pytrus T, Stawarski A, et al. Prevalence of haplotype DQ2/DQ8 and celiac disease in children with type 1 diabetes. Diabetol Metab Syndr. 2022;14(1):128. [DOI: 10.1186/s13098-022-00897-8] [PMID: 36096955]
4. Durazzo M, Ferro A, Brascugli I, Mattivi S, Fagoonee S, Pellicano R. Extra-Intestinal Manifestations of Celiac Disease: What Should We Know in 2022? J Clin Med. 2022;11(1):258. [DOI: 10.3390/jcm11010258] [PMID: 35011999]
5. Galli G, Amici G, Conti L, Lahner E, Annibale B, Carabotti M. Sex-Gender Differences in Adult Coeliac Disease at Diagnosis and Gluten-Free-Diet Follow-Up. Nutrients. 2022;14(15):3192. [DOI: 10.3390/nu14153192] [PMID: 35956368]
6. Lebwohl B, Rubio-Tapia A. Epidemiology, Presentation, and Diagnosis of Celiac Disease. Gastroenterology. 2021;160(1):63–75. [DOI: 10.1053/j.gastro.2020.06.098] [PMID: 32950520]
7. Sallese M, Lopetuso LR, Efthymakis K, Neri M. Beyond the HLA Genes in Gluten-Related Disorders. Front Nutr. 2020;7:575844. [DOI: 10.3389/fnut.2020.575844] [PMID: 33262997]
8. Stanković B, Radlović N, Leković Z, Ristić D, Radlović V, Nikčević G, et al. HLA genotyping in pediatric celiac disease patients. Bosn J Basic Med Sci. 2014;14(3):171–6. [DOI: 10.17305/bjbms.2014.3.28] [PMID: 25172978]
9. Gnodi E, Meneveri R, Barisani D. Celiac disease: From genetics to epigenetics. World J Gastroenterol. 2022;28(4):449–63. [DOI: 10.3748/wjg.v28.i4.449] [PMID: 35125829]
10. Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips A, et al; ESPGHAN Working Group on Coeliac Disease Diagnosis; ESPGHAN Gastroenterology Committee; European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr. 2012;54(1):136–60. [DOI: 10.1097/MPG.0b013e31821a23d0] [PMID: 22197856]

11. Husby S, Koletzko S, Korponay-Szabó I, Kurppa K, Mearin ML, Ribes-Koninckx C, et al. European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020. J Pediatr Gastroenterol Nutr. 2020;70(1):141–56. [DOI: 10.1097/MPG.0000000000002497] [PMID: 31568151]
12. Pascual V, Dieli-Crimi R, López-Palacios N, Bodas A, Medrano LM, Núñez C. Inflammatory bowel disease and celiac disease: overlaps and differences. World J Gastroenterol. 2014;20(17):4846–56. [DOI: 10.3748/wjg.v20.i17.4846] [PMID: 24803796]
13. Mubarak A, Wolters VM, Gmelig-Meyling FH, Ten Kate FJ, Houwen RH. Tissue transglutaminase levels above 100 U/mL and celiac disease: a prospective study. World J Gastroenterol. 2012;18(32):4399–403. [DOI: 10.3748/wjg.v18.i32.4399] [PMID: 22969205]
14. Saito PK, Yamakawa RH, Pereira LC, da Silva WV Jr, Borelli SD. Complement-dependent cytotoxicity (CDC) to detect Anti-HLA antibodies: old but gold. J Clin Lab Anal. 2014;28(4):275–80. [DOI: 10.1002/jcla.21678] [PMID: 24578044]
15. Arshi J, Huber AR. Celiac sprue. Pathology Outlines, Inc 2022. [Available at: www.pathologyoutlines.com/topic/smallbowelceliacsprue.html]
16. Oberhuber G. Histopathology of celiac disease. Biomed Pharmacother. 2000;54(7):368–72. [DOI: 10.1016/S0753-3322(01)80003-2] [PMID: 10989975]
17. Catassi GN, Pulvirenti A, Monachesi C, Catassi C, Lionetti E. Diagnostic Accuracy of IgA Anti-Transglutaminase and IgG Anti-Deamidated Gliadin for Diagnosis of Celiac Disease in Children under Two Years of Age: A Systematic Review and Meta-Analysis. Nutrients. 2021;14(1):7. [DOI: 10.3390/nu14010007] [PMID: 35010880]
18. Krini M, Chouliaras G, Kanariou M, Varela I, Spanou K, Panayiotou J, et al. HLA class II high-resolution genotyping in Greek children with celiac disease and impact on disease susceptibility. Pediatr Res. 2012;72(6):625–30. [DOI: 10.1038/pr.2012.133] [PMID: 23041663]
19. Castro-Antunes MM, Crovella S, Brandão LA, Guimaraes RL, Motta ME, Silva GA. Frequency distribution of HLA DQ2 and DQ8 in celiac patients and first-degree relatives in Recife, northeastern Brazil. Clinics (Sao Paulo). 2011;66(2):227–31. [DOI: 10.1590/s1807-59322011000200008] [PMID: 21484038]
20. Potter K, de Koning L, Butzner JD, Gidrewicz D. Survey of the initial management of celiac disease antibody tests by ordering physicians. BMC Pediatr. 2019;19(1):243. [DOI: 10.1186/s12887-019-1621-5] [PMID: 31324159]
21. Ma MX, John M, Forbes GM. Diagnostic dilemmas in celiac disease. Expert Rev Gastroenterol Hepatol. 2013;7(7):643–55. [DOI: 10.1586/17474124.2013.834125] [PMID: 24070155]
22. Pinto-Sanchez MI, Seiler CL, Santesso N, Alaedini A, Semrad C, Lee AR, et al. Association Between Inflammatory Bowel Diseases and Celiac Disease: A Systematic Review and Meta-Analysis. Gastroenterology. 2020;159(3):884–903.e31. [DOI: 10.1053/j.gastro.2020.05.016] [PMID: 32416141]
23. Tursi A, Giorgetti GM, Brandimarte G, Elisei W. Crohn's disease and celiac disease: association or epiphenomenon? Eur Rev Med Pharmacol Sci. 2006;10(3):127–30. [PMID: 16875046]
24. Amir M, Parekh SM. Classic Autoimmune Liver Disorders and Celiac Hepatitis. Clin Liver Dis (Hoboken). 2021;17(5):347–52. [DOI: 10.1002/cld.1056] [PMID: 34136140]
25. Haggård L, Glimberg I, Lebwohl B, Sharma R, Verna EC, Green PHR, et al. High prevalence of celiac disease in autoimmune hepatitis: Systematic review and meta-analysis. Liver Int. 2021;41(11):2693–702. [DOI: 10.1111/liv.15000] [PMID: 34219350]

Процена дијагностичке вредности *HLA-DQ2/DQ8* типизирања и антитела на ткивну трансглутаминазу као алтернативе дуоденалној биопсији код целијачне болести деце

Драган Прокић[1], Славиша Ђуричић[2,3], Ивана Китић[1,4], Марија Коцић[1], Срђан Пашић[4,5], Биљана Вулетић[6]

[1]Институт за здравствену заштиту мајке и детета Србије „Др Вукан Чупић", Одељење гастроентерологије, Београд, Србија;
[2]Институт за здравствену заштиту мајке и детета Србије „Др Вукан Чупић", Одељење за клиничку патологију, Београд, Србија;
[3]Универзитет у Бањој Луци, Медицински факултет, Бања Лука, Република Српска, Босна и Херцеговина;
[4]Универзитет у Београду, Медицински факултет, Београд, Србија;
[5]Институт за здравствену заштиту мајке и детета Србије „Др Вукан Чупић", Одељење за имунологију, Београд, Србија;
[6]Универзитет у Крагујевцу, Факултет медицинских наука, Одељење за педијатрију, Крагујевац, Србија

САЖЕТАК

Увод/Циљ Циљ рада је да се процени применљивост серумских антиткивних трансглутаминаза (*tTG*) концентрације антитела *IgA* и *IgG* и *HLA-DQ2/DQ8* типизације, као неинвазивне алтернативе биопсији дуоденума у дијагностици целијачне болести (ЦБ) у педијатријској популацији.

Методе Проспективна кохортна студија обухватила је укупно 179 педијатријских болесника узраста 1–18 година. Код свих болесника одређена су антитела *tTG IgA* и *tTG IgG* и извршена је типизација хуманог леукоцитног антигена (*HLA*) *DQ2*/*DQ8*, као и биопсија дуоденума. Хистопатологија биопсије дуоденума је интерпретирана модификованим Маршовим системом бодовања.

Резултати Дијагноза ЦБ је потврђена код 101 (56%) болесника, док је *HLA-DQ2/DQ8* био позитиван код 100 болесника (99%). Антитела на *tTG IgA* у концентрацији већој од 100 *J/ml* откривена су код 77 (76,2%) болесника са ЦД и у значајно мањем броју за *tTG IgG* 29 (28,7%) ($p < 0,001$). Утврђена је статистички високо значајна повезаност атрофије дуоденума (Маршовог степена 3 *a*, *b*, *c*), са концентрацијом *tTG IgA* 10 пута већом од горњег нивоа нормале ($p < 0,001$).

Закључак Концентрација *tTG IgA* 10 пута већа од горњег нивоа нормале је у значајној позитивној корелацији са хистопатолошким налазима Маршовог степена 3. Одређивање ових специфичних антитела у комбинацији са *HLA-DQ2/DQ8* типизацијом показало се довољним за дијагнозу ЦБ, што говори у прилог чињеници да се биопсија дуоденума може избећи у значајној већини болесника – 75%.

Кључне речи: целијакија; антитела на ткивну трансглутаминазу; *HLA-DQ2/DQ8* типизација; неинвазивна дијагностика