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Original Research Article

The role of serological tests and biopsy in the diagnosis of celiac disease: retrospective review of 1137 duodenal biopsies

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ABSTRACT

Background: The aim of this study is to evaluate gluten sensitivity and/or celiac disease (CD) on the basis of serological tests and duodenal biopsy and to draw attention to the prevalence in the population and the correlation between serological tests and biopsy results.
Methods: Patients who applied to Health Sciences University Bursa High Specialization Training and Research Hospital between 2015-2019 and who underwent serological tests and duodenal biopsies with a diagnosis of CD or gluten sensitivity were retrospectively analyzed.
Results: The study was conducted with a total of 1137 cases, 61.2% (n = 696) of who were women and 38.8% (n = 441) were men. Their ages range from 17 to 91, with a mean of 40.16 ± 16.18 years. Of the 178 patients with gluten sensitivity, 122 (68%) were female and 56 (32%) were male. According to the results of duodenal biopsy, an average of 8% Marsh 3, 5% Marsh 1-2 was detected in the last five years. For the whole study, a significant difference was found between celiac autoantibody positivity rates according to the biopsy results ($p = 0.001$; $p < 0.01$). The rate of serological test positivity was higher in patients with biopsy result Marsh 3 than those with normal biopsy result, peptic duodenitis and Marsh 1 and 2. No statistically significant difference was found between the rates of Marsh 3 biopsy results and serological test positivity by years ($p > 0.05$).
Conclusions: The number of patients applied with a diagnosis of CD in the last five years has gradually increased (3.4-33.7%). Of the patients with Marsh 3 and Marsh 1-2 biopsy results, 78% were under 50 years old. This suggests that gluten enteropathy in young female patients having digestive system complaints should not be ignored during the diagnosis. Serological test results were highly correlated with the biopsy results in patients with Marsh 3 biopsy results. We think that if clinical findings are supported with serological tests and directed for biopsy in the diagnosis of celiac disease, it will be more cost effective and the workload and time loss will be prevented.

Keywords: Biopsy, Celiac disease, Diagnosis, Serologic tests

INTRODUCTION

Celiac disease (CD) or celiac sprue also known as gluten hypersensitivity is an immune-mediated inflammatory disease of the small intestine and it is caused by sensitivity to dietary gluten and related proteins. CD is seen in patients having genetic sensitivity. There are publications that CD is caused by human T cell mediated autoimmune mechanisms.[1] According to serological studies, the global prevalence of CD is approximately 1%. [2] However, in some studies where biopsy and serological tests were used together, the prevalence was ranged between 1:70 and 1: 300.[3]

In the Turkish adult population, the seroprevalence of CD was 0.77% and the prevalence of CD by biopsy was 0.39%.[4] Studies conducted in the last 25 years show an increase in the prevalence of CD.[5,6]

Nowadays, CD occurs between the ages of 10 and 40 years. CD can accompany to dermatitis herpetiformis, selective IgA deficiency, type I diabetes mellitus, autoimmune thyroiditis and other autoimmune diseases.

Some individuals have symptoms without the characteristic serological or histological findings of CD. The etiology and mechanism of these symptoms are unknown and no biomarkers have been identified. In non-celiac disease cases, it is unknown whether sensitivity to wheat causes an enteropathy associated with systemic immune activation. It is also necessary to distinguish between gluten hypersensitivity and CD without entropathy for management of disease.[7]

Anti-tisue transglutaminase (Anti tTG), anti-endomysium (EMA), anti-gliadin (AGA) antibodies and the combination of the HLA-DQ2 and/or DQ8 gene use to diagnose CD in patients with suspected and specific clinical signs. Differences from lymphocytic infiltration of the epithelium to complete villous atrophy are observed in small intestine biopsy in these patients.

The aim of our study is to evaluate the mucosal biopsies and serological tests of the patients in the last 5 years and to review the change in the prevalence of CD and between compatibility of serology and pathology.

METHODS

Patients who applied to Health Sciences University Bursa High Specialization Training and Research Hospital between 2015-2019 and who underwent serological tests and duodenal biopsies with a diagnosis of CD or gluten sensitivity were retrospectively analyzed in this study. We performed a retrospective review of pathology reports from 1137 duodenal biopsies submitted for pathologic assessment and correlated biopsy results with results for concurrent serological testing for celiac autoantibodies.

Serology and histology

AGA IgA, AGA IgG, EMA IgA, Anti tTG IgA, Anti tTG IgG tests were performed with ELISA Immunocap method using Chorus ELISA kits (Diesse Diagnostica Senese Spa, Siena, Italy) and BN II System - Siemens Healthineers (Siemens Healthineers, Erlangen, Germany). EMA IgA and EMA IgG tests were performed with IFA method using Aescu kits (Aescu Group, Wendesheim, Germany) and Helmed device (Aescu Group, Wendesheim, Germany), and Total IgA tests were performed with ELISA immunocap method and using Aescu IgA kits and Helmed device.

In our pathology laboratory, duodenal biopsy samples have been examined by staining with hematoxylin-eosin in accordance with the standard methods.

If there were changes suggestive of celiac disease in a biopsy specimen, it was graded according to the modified Marsh criteria: Marsh 0, normal appearance; Marsh 1, normal morphology with elevated intraepithelial lymphocytes; Marsh 2, elevated intraepithelial lymphocytes with crypt hyperplasia; Marsh 3 villous atrophy.[8,9]

This study was approved by the ethics committee of Health Sciences University Bursa High Specialization Training and Research Hospital. The study was conducted retrospectively by taking patient archives into consideration.

Statistical analysis

NCSS (Number Cruncher Statistical System) (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used while evaluating the study data. Pearson Chi-Square test and Fisher-Freeman-Halton Exact test were used to compare qualitative data. Significance was assessed at least at the $p < 0.05$ level.

RESULTS

In our study, the data of a total of 1137 cases, 61.2% (n = 696) females and 38.8% (n = 441) males, who applied to Bursa High Specialization Training and Research Hospital between 2015-2019 and underwent duodenal biopsy due to gluten enteropathy, were retrospectively evaluated. The ages of the cases were ranged from 17 to 91, with a mean of 40.16 ± 16.18 years. Distribution of descriptive features were shown in Table 1.

Evaluation of biopsy results and autoantibody and IGA results according to years was shown in Table 2.

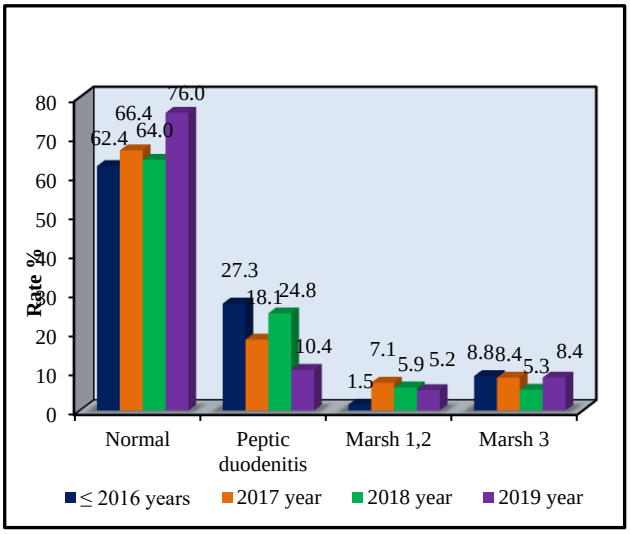

Figure 1: According to years duodenal biopsies results.

A statistically significant difference was found between the biopsy results by years (p=0.001; p <0.01). There was no statistically significant correlation between biopsy results and lgA results according to the presence of celiac autoantibodies over the years (p>0.05).There was no statistically significant difference between the rates of high of lgA levels by years (p> 0.05).

Table 1: Distribution of descriptive features.

		N	%
Years	2015	39	3.4
	2016	155	13.6
	2017	238	20.9
	2018	322	28.3
	2019	383	33.7
Age (year)	*Min-Max (Median)*	17-91 (38)	
	Median±SD	40.16±16.18	
	< 30	349	30.7
	30-39	250	22.0
	40-49	227	20.0
	50-59	154	13.5
	≥ 60	157	13.8
Sex	Female	696	61.2
	Male	441	38.8
Biopsy results	Normal	776	68.2
	Peptic duodenitis	216	19.0
	Marsh Stage1,2	59	5.2
	Marsh Stage 3	86	7.6
AGA IgA (n=70)	Negative	56	80.0
	Positive	14	20.0
AGA IgG (n=69)	Negative	46	66.7
	Positive	23	33.3
EMA IgA (n=191)	Negative	156	81.7
	Positive	35	18.3
EMA IgG (n=158)	Negative	135	85.4
	Positive	23	14.6
Anti tTG IgA (n=193)	Negative	169	87.6
	Positive	24	12.4
Anti tTG IgG (n=155)	Negative	115	74.2
	Positive	40	25.8
IgA (n=91)	Normal	64	70.3
	High	27	29.7
Celiac Autoantibody (n=351)	Autoantibody (-)	256	72.9
	Autoantibody(+)	95	27.1

Anti-tisue transglutaminase (Anti tTG), anti-endomysium (EMA), anti-gliadin (AGA)

There was no statistically significant difference between the biopsy results of 6 cases with celiac autoantibody positivity and IgA elevation and the biopsy results of other cases (p> 0.05). There was no statistically significant difference between AGA IgA, AGA IgG, EMA IgA, EMA IgG, Anti tTG IgA, Anti tTG IgG and one or more of them being positive by years (p>0.05). According to years duodenal biopsies results were shown in Figure 1.

In our study, we observed that the frequency of gluten enteropathy is increasing every year. Of the 178 patients with gluten sensitivity, 122 (68%) were female and 56 (32%) were male. The frequency of gluten sensitivity in women is more than men. According to the results of duodenal biopsy, an average of 8% Marsh 3, 5% Marsh 1-2 was detected in the last five years.

While the rate of biopsy results accepted normal in 2019 was higher than 2016 and before and 2017 and 2018, but the incidence of peptic duodenitis is lower. The incidence

of peptic duodenitis in 2016 and before is also higher than in 2017. In addition, the ratio of biopsy results to Marsh stage 1 and 2 in 2017, 2018 and 2019 is higher than in 2016 and before. Evaluation of biopsy and autoantibody results by years was shown Table 3.

Table 2: Evaluation of biopsy results and autoantibody and IGA results according to years.

		Years					P value
		≤ 2016	2017	2018	2019	Toplam	
		N (%)	N (%)	N (%)	N (%)	N (%)	
Biopsy results	**N**	194	238	322	383	1137	
	Normal	121 (62.4)	158 (66.4)	206 (64)	291 (76)	776 (68.2)	[a]0.001**
	Peptic duodenitis	53 (27.3)	43 (18.1)	80 (24.8)	40 (10.4)	216 (19.0)	
	Marsh Stage 1,2	3 (1.5)	17 (7.1)	19 (5.9)	20 (5.2)	59 (5.2)	
	Marsh Stage 3	17 (8.8)	20 (8.4)	17 (5.3)	32 (8.4)	86 (7.6)	
AGA IgA	**N**	28	31	2	9	70	
	Negative	24 (85.7)	24 (77.4)	1 (50)	7 (77.8)	56 (80)	[b]0.504
	Positive	4 (14.3)	7 (22.6)	1 (50)	2 (22.2)	14 (20)	
AGA IgG	**N**	28	29	1	11	69	
	Negative	22 (78.6)	18 (62.1)	1 (100)	5 (45.5)	46 (66.7)	[b]0.168
	Positive	6 (21.4)	11 (37.9)	0 (0)	6 (54.5)	23 (33.3)	
EMA IgA	**N**	44	57	27	63	191	
	Negative	37 (84.1)	49 (86)	23 (85.2)	47 (74.6)	156 (81.7)	[a]0.362
	Positive	7 (15.9)	8 (14)	4 (14.8)	16 (25.4)	35 (18.3)	
EMA IgG	**N**	27	52	23	56	158	
	Negative	25 (92.6)	47 (90.4)	19 (82.6)	44 (78.6)	135 (85.4)	[b]0.229
	Positive	2 (7.4)	5 (9.6)	4 (17.4)	12 (21.4)	23 (14.6)	
Anti tTG IgA	**N**	5	22	90	76	193	
	Negative	4 (80)	16 (72.7)	81 (90)	68 (89.5)	169 (87.6)	[b]0.120
	Positive	1 (20)	6 (27.3)	9 (10)	8 (10.5)	24 (12.4)	
Anti tTG IgG	**N**	5	18	77	55	155	
	Negative	4 (80)	15 (83.3)	52 (67.5)	44 (80)	115 (74.2)	[b]0.326
	Positive	1 (20)	3 (16.7)	25 (32.5)	11 (20)	40 (25.8)	
Celiac Auto-antibody	**N**	53	67	109	122	351	
	Autoantibody (-)	42 (79.2)	46 (68.7)	80 (73.4)	88 (72.1)	256 (72.9)	[b]0.628
	Autoantibody(+)	11 (20.8)	21 (31.3)	29 (26.6)	34 (27.9)	95 (27.1)	
lgA	**N**	11	17	31	32	91	
	Normal	8 (72.7)	13 (76.5)	22 (71.0)	21 (65.6)	64 (70.3)	[a]0.877
	High	3 (27.3)	4 (23.5)	9 (29.0)	11 (34.4)	27 (29.7)	

aPearson Ki-kare Test, bFisher Freeman Halton Exact Test **p<0.01, Anti-tisue transglutaminase (Anti tTG), anti-endomysium (EMA), anti-gliadin (AGA)

There was not any significant difference (p> 0.05) between celiac autoantibody positivity rates of the cases in 2016 and before and in 2017 according to the biopsy results.

In 2018, a significant difference was found between the autoantibody positivity rates according to the biopsy results of the cases (p=0.007; p<0.01) and autoantibody positivity rates were higher in patients with Marsh stage 3 biopsy results than who have peptic duodenitis, Marsh 1, 2 and normal biopsy findings.

In 2019, a significant difference was found between the celiac autoantibody positivity rates according to the biopsy results of the cases (p=0.001; p<0.01). Celiac autoantibody positivity rates were higher in patients with Marsh stage 3 biopsy results than who have peptic duodenitis, Marsh 1, 2 and normal. The rate of serological test positivity was higher in patients with biopsy results Marsh 3 than in patients with normal biopsy, peptic duodenitis and Marsh 1, 2. No statistically significant difference was found between the rates of Marsh 3 biopsy results and serological test positivity by years (p>0.05). The relationship between serological tests and biopsy results were shown Figure 2.

Table 3: Evaluation of biopsy and autoantibody results by years.

Years	Celiac Autoantibody	Biopsy Results					P value
		Normal	Peptic duodenitis	Marsh stage1+2	Marsh stage 3	Total	
		N (%)	N (%)	N (%)	N (%)	N (%)	
≤ 2016	**N**	**25**	**14**	**3**	**11**	**53**	
	Autoantibody (-)	22 (88)	10 (71.4)	3 (100)	7 (63.6)	42 (79.2)	[b]0.269
	Autoantibody(+)	3 (12)	4 (28.6)	0 (0)	4 (36.4)	11 (20.8)	
2017	**N**	39	6	9	13	67	
	Autoantibody (-)	29 (74.4)	5 (83.3)	7 (77.8)	5 (38.5)	46 (68.7)	[b]0.085
	Autoantibody(+)	10 (25.6)	1 (16.7)	2 (22.2)	8 (61.5)	21 (31.3)	
2018	**N**	63	23	11	12	109	
	Autoantibody (-)	52 (82.5)	16 (69.6)	8 (72.7)	4 (33.3)	80 (73.4)	[b]0.007**
	Autoantibody (+)	11 (17.5)	7 (30.4)	3 (27.3)	8 (66.7)	29 (26.6)	
2019	**N**	78	12	11	21	122	
	Autoantibody (-)	64 (82.1)	12 (100)	9 (81.8)	3 (14.3)	88 (72.1)	[b]0.001**
	Autoantibody (+)	14 (17.9)	0 (0)	2 (18.2)	18 (85.7)	34 (27.9)	
Total	**N**	205	55	34	57	351	
	Autoantibody (-)	167 (81.5)	43 (78.2)	27 (79.4)	19 (33.3)	256 (72.9)	[a]0.001**
	Autoantibody (+)	38 (18.5)	12 (21.8)	7 (20.6)	38 (66.7)	95 (27.1)	

aPearson Ki-kare Test, bFisher Freeman Halton Exact Test, **p<0.01

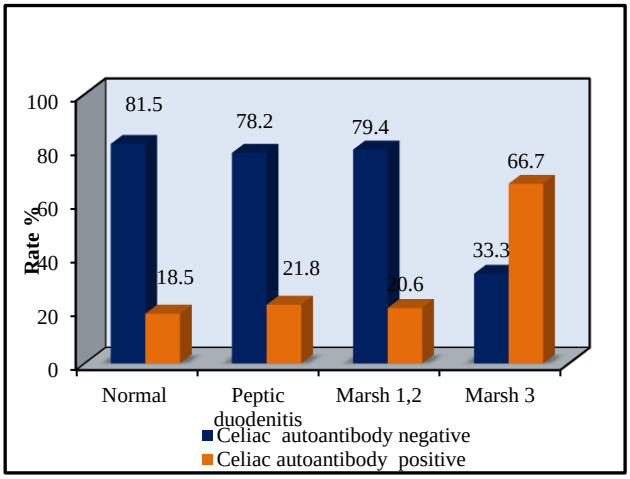

Figure 2: The relationship between serological tests and biopsy results.

For the whole study, a significant difference was found between celiac autoantibody positivity rates according to the biopsy results (p=0.001; p<0.01). Autoantibody positivity rates were higher in patients have Marsh stage 3 biopsy results than who have peptic duodenitis, Marsh 1,2 and normal.

DISCUSSION

The widespread use of a carbohydrate-rich diet has also made gluten sensitivity a more common public health problem. In our study, we observed that the prevalance of gluten enteropathy is increasing every year. The leading reason for this can be attributed to the advanced diagnostics methods, easy access of patients to diagnostic methods and the presence of newly developed serological tests.

In our study, we observed that the frequency of gluten enteropathy is increasing every year. Of the 178 patients with gluten sensitivity, 122 (68%) were female and 56 (32%) were male. The frequency of gluten sensitivity in women is more than men. According to the results of duodenal biopsy, an average of 8% Marsh 3 gluten sensitivity was detected in the last five years.

While the rate of biopsy results accepted normal in 2019 was higher than 2016 and before and 2017 and 2018, but the incidence of peptic duodenitis was lower. The incidence of peptic duodenitis in 2016 and before was also higher than in 2017. In addition, the ratio of biopsy results to Marsh stage 1 and 2 in 2017, 2018 and 2019 was higher than in 2016 and before.

In this study, we evaluated the change of CD taking into account the results of serological tests and duodenal biopsy in our region over the years. All of the patients who applied with gastrointestinal complaints had duodenal biopsy because they are thought to have CD and / or gluten sensitivity. There was no correlation between the complaints and the results of the biopsy, which was also consistent with the literature. We also evaluated the correlation of biopsy results with serological tests in patients who had AGA IgA, AGA IgG, EMA IgA, EMA IgG, Anti tTG IgA, Anti tTG IgG as celiac autoantibody tests. Total IgA levels of our patients were generally normal in the patients who were examined and it was high in only six patients. This can be seen as a parameter that shows the accuracy of our serological tests in patients.

There was not a significant difference (p>0.05) between celiac autoantibody positivity rates of the cases in 2016 and before and in 2017 according to the biopsy results.

Of the 178 patients with gluten sensitivity, 122 (68%) were female and 56 (32%) were male. The rate of occurrence of gluten sensitivity in women is more than men. According to the results of duodenal biopsy, an average of 8% Marsh 3, 5% Marsh 1-2 was detected in the last five years. Of the patients with Marsh 3 and Marsh 1-2 biopsy results, 78% were under 50 years old. This suggests that gluten enteropathy in young female patients having with digestive system complaints should not be ignored during the diagnosis.

Serological test results were highly correlated with the biopsy results in patients with Marsh 3 biopsy results.

There may not be a correlation between the severity of clinical symptoms and the degree of mucosal damage in CD. There is also a lot of evidence in the literature on this subject.[10-12]

It is important for the clinician to be know about the histopathologic feature of the mucosa in order to apply serology and other laboratory findings to the clinic of patient. The pathology report is important in order to explain mucosal pathology in a descriptive way.

One of the most common indications for duodenal biopsy is CD. Although autoantibody screening tests associated with the disease are widely used, positive findings in duodenal biopsies are relatively rare. This is because some of the duodenal biopsy samples sent to exclude the disease are not biopsies based on positive serological results. This can be seen as a limitation of our retrospective study. However, these patients may also have applied celiac serology tests before being referred to our hospital.

Serological tests performed in patients with CD should be considered as a possible indicator of the disease in biopsy findings. Serological tests in our study had also been performed before or after biopsy, but within the same time frame.

Both clinical and serological tests are important in making a biopsy decision in patients with suspected CD. There is a high risk in patients with diarrhea and anemia, and biopsy is necessary.[13] According to some authors, gastroesophageal reflux disease is also an indication for duodenal biopsy.[14] It is important to perform serological testing before biopsy in patients with low risk of CD.[15]

İncreasing the use of serological tests can reduce the time and economic losses in patients referred for endoscopy. As a result, the diagnosis and treatment costs of the patients will decrease. The data in our study also suggest that this approach was generally not applied in patients referred for duodenal biopsy.

CONCLUSION

The number of patients who applied with a diagnosis of gluten disease in the last five years has gradually increased (3.4-33.7%). The rate of serological test positivity was higher in patients whose biopsy result is Marsh 3 than those with normal biopsy result, peptic duodenitis and Marsh 1 and 2. Although the increase in Marsh 1 and 2 biopsy results over the years is noteworthy, there was no such increase for Marsh 3. Of the patients with Marsh 3 and Marsh 1-2 biopsy results, 78% were under 50 years old and %68 were women. This suggests that gluten enteropathy in young female patients having digestive system complaints should not be ignored during the diagnosis.

Serological test results were highly correlated with the biopsy results in patients with Marsh 3 biopsy results,

We think that if clinical findings are supported with serological tests and directed for biopsy in the diagnosis of CD, it will be more cost effective and the workload and time loss will be prevented.

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Ethical approval: The study was approved by ethics committee of Health Sciences University, Bursa High Specialization Training and Research Hospital. (Ethics committee decision dated 11.12.2019 and numbered 2011-KAEK-25 2019/12-20) It conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000).The study was conducted retrospectively by taking patient archives into consideration

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