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Original Scientific Article

The association of serological tests and anemia in celiac disease

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ABSTRACT

***Aim**:* Celiac disease (CD) is a common immune-mediated enteropathy caused by gluten. These patients may apply with many different clinical forms. The aim of this study is to determine the association of serological tests and type of anemia in CD.

***Methods**:* Totally117 biopsy proven CD patients aged between 1-17 years were included. Serological and hematological parameters of all patients were studied.

***Results**:* Anemia was identified in 71 (60.7%) cases. Patients with anemia were diagnosed earlier than other patients (5.2±4.5 vs. 15.3±33.8 years, p=0.012). Among CD patients with anemia 39 (54.9%) were having iron deficiency, 22 (30.9%) were having folate deficiency and 10 (14%) were having vitamin B 12 deficiency. In patients with tissue transglutaminase (tTG) seropositivity serum iron levels and ferritin levels were significantly lower compared to anti-gliadin antibody (AGA) or anti-endomysium antibody (EMA) seropositivity (35±23.5 vs. 57.5±33.3, p=0.007 and 12.4±21.9 vs. 24.2±18.5, p=0.026, respectively). Low serum folate levels were more frequent in the presence of tTG seropositivity compared with AGA+EMA seropositivity (81.8% vs. 25%, p=0.015).

***Conclusions**:* Anemia is an important cause of admission in CD. These patients are diagnosed earlier as a result of anemia. Alone tTG seropositivity is more valuable to demonstrate anemia associated with iron or folate deficiencies.

Key words: Celiac disease, serological tests, anemia, child.

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Introduction

Celiac disease (CD) is a systemic chronic inflammatory, immune-mediated enteropathy caused by permanent intolerance to gluten in genetically susceptible individuals. The characteristic of this disease is the mucosal damage in the small intestine after ingestion of gluten-containing foods. The prevalence of CD has been estimated to be 0.5–1% [1]. Serological tests are mostly used for screening purpose. A definite diagnosis is based on duodenal biopsy. Characteristic histologic abnormalities identified on the mucosa are

intraepithelial lymphocyte infiltration, mononuclear cell infiltration of the lamina propria, crypt hyperplasia and varying degrees of villous atrophy [2].

CD can show many different clinical forms. Chronic diarrhea, vomiting, weight loss, abdominal pain and abdominal distension are present in typical form of CD. The term of atypical CD is used for patients who present with extraintestinal symptoms like dermatological lesions, dental enamel hypoplasia, osteoporosis, delayed puberty and rickets. Serological positive patients without any symptoms is considered as asymptomatic form. Latent form of CD covers the subjects with genetic predisposition who have initially a normal histology despite a gluten-containing diet [3]. Among those factors of genetic predisposition the most important ones are HLA DQ2 and DQ8, which are present in more than 95% of CD patients [4]. Early diagnosis and treatment of CD prevents the development of autoimmune diseases [5] and malignancies [6].

Anemia may be defined as a reduction in blood hemoglobin concentration according to age [7], and it is a frequent finding in patients with CD that usually occurs due to impaired absorption of iron, folate, and vitamin B12 caused by mucosal damage [8]. These reduced hemoglobin levels lead to diminished oxygen-carrying capacity. This effect of anemia is harmful for infants and children since it causes delay in psychomotor development and impaired cognitive performance. Also, it increases the morbidity and mortality in these age groups [9].

The diagnosis of anemia in patients with classical CD, who were histologically confirmed, is easy. However, publications, indicating that biopsy may not be necessary in the diagnosis of CD, are increasing in recent years [10]. In the absence of typical diarrheal presentation, both diagnosis of CD and anemia may be delayed. We could not identify any study about the relationship between CD serology and anemia in the literature. In this study, we aimed to investigate the relationship between hematologic and serological tests to gain early diagnosis of anemia in biopsy-proven CD patients.

Methods

The records of all children who were followed up with the diagnosis of CD between 2007 and 2012 in our hospitals were retrospectively investigated. The diagnosis of CD was based on the criteria defined by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. Genetic assessment (HLA-DQ2/DQ8) was not performed. Serologic tests were investigated in all cases. Biopsies of the small intestine were performed for all seropositive patients and biopsy specimens were evaluated according to Marsh criteria [11]. Patients less than 1 year or more than 17 years of ages or Marsh type 1 were excluded. Demographic characteristics of the patients, results of laboratory parameters (complete blood count, serum iron, ferritin, iron binding capacity, folate and vitamin B 12 levels), serological tests (anti-gliadin antibody (AGA Ig A, IgG), anti-endomysium antibody (EMA Ig A, IgG), tissue transglutaminase antibody (tTG Ig A, IgG) positivities) were recorded. AGA and tTG were checked using an enzyme-linked immunosorbent assay, whereas EMA was evaluated using the immunofluorescent method. Serum ferritin, serum folate and serum vitamin B 12 levels were studied with chemiluminescence assay in all patients. Serum iron and serum iron binding capacity were studied with the colorimetric method. Hemoglobin level <11 g/dL in children aged 6-

59 months, <11.5 g/dL in children aged 5-11 years and <12 g/dL in older children were considered as anemia.[7] The patients with iron deficiency anemia (IDA) were having low serum iron levels, elevated total iron-binding capacity and low ferritin levels [12]. Firstly, ferritin level decreases, then total iron binding capacity increases when serum iron levels decreases and finally serum hemoglobin level decreases in IDA [13]. The serum iron levels <25 µg/dL in patients younger than 3 years, <15 µg/dl in patients between 4–10 years, and <32 µg/dL in patients older than 11 years of age for males and <55 µg/dl in patients younger than 3 years, <28 µg/dL in patients between 4–10 years, and <25 µg/dl in patients older than 11 years of age for females were considered as low [14]. The minimum limits for serum ferritin levels were considered as 12 µg/l for patients younger than 5 years of age and 15 µg/l for older patients [15]. The minimum limit for serum folate levels was considered as 3 ng/ml [15]. The minimum limit for serum vitamin B12 levels was considered as 200 ng/L [16].

The statistical analysis was conducted using SPSS 15.0 software (SPSS, Inc., Chicago, IL, USA). The Student's t-test, Mann–Whitney U-test, One-way ANOVA and Kruskal-Wallis test were used for the comparisons. $p < 0.05$ was considered as significant.

Results

117 cases were included in this study. Anemia was identified in 71 (60.8%) cases. Forty cases were female (56.3%). Mean age was 8.5 ± 5 years (range, 1–17 years). Forty-five (63.3%) were classical form. Twenty-four (33.8%) were atypical form. Two (2.8%) were asymptomatic.

A total of 22 of 26 (84.6%) cases were positive for AGA Ig A, 21 of 25 (80.7%) cases were positive for AGA Ig G; 22 of 24 (91.6%) cases were positive for EMA IgA, 26 of 28 (92.8%) cases were positive for EMA IgG and 53 of 54 (98.1%) cases were positive for tTG IgA, while 50 of 51 (98%) cases were positive for tTG IgG [Table1].

Table 1. Distribution of serologic tests.

Serological test	Situation	n	%
AGA IgA	Positive	22	84.6
	Negative	4	15.3
AGA IgG	Positive	21	80.7
	Negative	4	19.2
EMA IgA	Positive	22	91.6
	Negative	2	8.3
EMA IgG	Positive	26	92.8
	Negative	2	7.1
tTG IgA	Positive	53	98.1
	Negative	1	1.8
tTG IgG	Positive	50	98
	Negative	1	1.9

AGA: Anti-gliadin antibody, EMA: Anti-endomysium antibody, tTG: Tissue transglutaminase antibody.

Anemia was identified in 71 (60.7%) cases. Hematologic data of all patients are given in table 2. Patients with anemia were diagnosed earlier (5.2±4.5 vs. 15.3±33.8 years, p=0.012). In these patients serum ferritin and serum vitamin B 12 levels were significantly lower

(13.6±20 vs. 21.4±17, p=0.032 and 343±268 vs. 446±278, p=0.049, respectively).

Anemia was found in 50 (59.5%) children and 21 (63.6%) adolescents with CD, but the difference was not statistically significant (p=0.68).

Among CD patients with anemia 39 (54.9%) were having iron deficiency, 22 (30.9%) were having folate deficiency and 10 (14%) were having vitamin B 12 deficiency.

Table 2. Hematological parameters of CD patients.

Specifications	Mean±SD	Min	Max
Hemoglobin (g/dl)	10.4±1.5	7	14
Hematocrit (%)	31.7±4.7	21	42
Serum iron (µg/dl)	41.2±30.3	6	130
Iron binding capacity	405±108	132	626
Serum ferritin (µg/l)	16.7±19.2	1	127
Serum folate (ng/ml)	7.8±5.8	1	26
Serum vitamini B 12 (ng/l)	383±275	60	1628

IDA was found in 28 (62.2%) of the patients with classical form, in 9 (37.5%) of the patients with atypical form and in 2 (100%) patients with asymptomatic form.

Folate deficiency anemia was found in 16 (35.5%) of the patients with classical form and in 6 (25%) of the patients with atypical form. However, there was no statistically significant difference between groups regarding presence of folate deficiency (p=0.48).

Vitamin B12 deficiency anemia was found in 7 (15.5%) of the patients with classical form and in 3 (12.5%) of the patients with atypical form. However, there was not any statistically significant difference between groups regarding presence of vitamin B12 deficiency (p=0.2).

Hemoglobin and hematocrit values of these patients according to type of anemia was not significantly different (p=0.3 and p=0.19, respectively). MCV was significantly lower in patients with IDA (71.7±5.9 vs. 74.7±7 fl, p=0.027), but it was not significantly different in patients with folate deficiency (73.4±6.2 vs. 72.9±6.7 fl, p=0.7) and vitamin B12 deficiency (75.5±2.3 vs. 72.9±6.8 fl, p=0.19). Thirteen (%32.5) of the patients with folic acid and/or vitamin B12 deficiency anemia had also IDA.

In comparison of patients with positive or negative results for EMA IgG; serum hemoglobin and hematocrit levels of patients with EMA IgG positivity were lower (respectively 10.2±1.6 vs. 12.3±2 , p=0.035 and 31.2±4.9 vs.37.4±5.8 , p=0.038) while iron binding capacity was higher (398±104 vs. 336±19 , p=0.004) compared with EMA IgG negative cases.

In comparison of patients with positive or negative tTG IgG; serum ferritin level of patients with tTG IgG positivity was lower (13±18.7 vs. 30.1±19.1, p=0.044).

Serum iron was higher in classical form of CD compared to asymptomatic form (43±30.9 vs. 15.8±12.6, p=0.049). Likewise, serum ferritin was lower in classical form compared to atypical form (14.9±15.8 vs. 28.1±32.9, p=0.011).

When serological tests were analyzed, just AGA positivity in 8 patients, just EMA positivity in 16 patients, just tTG positivity in 33 patients, AGA+EMA positivity in 4 patients, AGA + tTG positivity in 13 patients, EMA + tTG positivity in 7 patients and AGA + EMA + tTG positivity in 1 patients were detected.

Serum hemoglobin and hematocrit levels were higher in patients with AGA seropositivity

compared to patients with EMA+tTG seropositivity (11.3±1.2 vs. 9.9±1.6, p=0.026 and 35±4.2 vs. 30.5±5.1, p=0.018, respectively). In patients with tTG seropositivity serum iron levels and ferritin levels were significantly lower compared to patients with AGA+EMA seropositivity (35±23.5 vs. 57.5±33.3, p=0.007 and 12.4±21.9 vs. 24.2±18.5, p=0.026, respectively).

Table 3. Comparison of serological tests and hematological parameters.

Specifications	Serological tests	Mean±SD	p
Hemoglobin (g/dl)	AGA	11.3±1.2	0.026
	EMA+tTG	9.9±1.6	
Hematocrit (%)	AGA	35±4.2	0.018
	EMA+tTG	30.5±5.1	
Serum iron (µg/dl)	tTG	35±23.5	0.007
	AGA+EMA	57.5±33.3	
Ferritin (µg/l)	tTG	12.4±21.9	0.026
	AGA+EMA	24.2±18.5	
Serum folate (ng/ml)	tTG	5.5±5.1	0.007
	AGA+tTG	10.6±6.5	
Serum vitamin B 12 (ng/l)	tTG	279±210	0.002
	AGA+tTG	552±418	
Serum vitamin B 12 under 200 ng/l	tTG	16/33 (48.4%)	0.025
	AGA+tTG	1/13 (7.6%)	
Serum folate below 3 ng/ml	tTG	27/33 (81.8%)	0.015
	AGA	2/8 (25%)	

AGA: Anti-gliadin antibody, EMA: Anti-endomysium antibody, tTG: Tissue transglutaminase antibody.

In addition, in patients with tTG seropositivity serum folate and vitamin B12 levels were significantly lower compared to patients with AGA+tTG seropositivity (5.5±5.1 vs. 10.6±6.5, p=0.007 and 279±210 vs. 552±418, p=0.002 , respectively). Having serum folate level below 3 ng/ml was more frequent in patients with tTG seropositivity compared to patients with AGA + EMA seropositivity (81.8% vs. 25%, p=0.015). Having serum vitamin B 12 level below 200 ng/ml was more frequent in patients with tTG seropositivity compared to patients with AGA + tTG seropositivity (48.4% vs. 7.6%, p=0.025) [Table 3].

Discussion

CD is a major public health problem worldwide in children and adolescents. CD is diagnosed usually around 2 years of age [17]. The timing of introduction of gluten into the diet is an important factor in initiation of complaints of the disease. However, CD is diagnosed to any further extent at a later age in recent years. It is suggested probably due to the longer usage of breast milk and later introduction with gluten [18]. Depending on these features, delay in diagnosing CD can be more than a decade [19]. In our study, about 1/3 patients were adolescents. Similar to the literature, we found that CD was seen usually in females [17,20,21].

The diagnosis of classical CD is easy. However, CD patients may apply with atypical or asymptomatic presentations and diagnosis in this group is relatively difficult. Therefore, it is thought that more patients may be undiagnosed [22]. According to the literature, classical CD was diagnosed in 51.3-79% of cases, while atypical form was diagnosed in 21-37.6% of cases and asymptomatic form was diagnosed in 15.4% of cases [20,23,24].

Classical CD was also most frequently diagnosed in our study while atypical form in about 1/3 of cases and asymptomatic form was diagnosed in 2.8% of patients. The rate of diagnosis of atypical and silent forms of CD increased due to the increase in use of serologic tests such as the EMA and tTG in recent years [20].

AGA is unsuitable for diagnosis of CD due to low sensitivity and specificity [24] and it is used only in under 2 years of age, but the other serological tests are used for screening of CD in all age groups with high sensitivity [25-28]. The tests, except AGA, have sensitivities greater than 90% and were considered to correlate with the degree of mucosal damage [10]. We found AGA seropositivity in 84.6% patients, EMA seropositivity in 92.8% patients and tTG seropositivity in 98.1% patients in our study.

Anemia in CD patients is diagnosed earlier. This is because of failure to thrive due to low serum ferritin and vitamin B 12 levels in our patients.

Hematological manifestations of CD are being recognized increasingly. The most important cause of these disorders is destruction of the small intestinal mucosa. Anemia, one of the most important manifestations, has been determined in 12-69% of CD patients at the time of diagnosis [29-31]. Sixty point seven percentages of anemia cases that we found in our study is consistent with the literature.

Iron is the essential element for hemoglobin to bind oxygen, normal functioning of enzymes and immune system. Anemia can lead to hypoxemia, failure to thrive and infections [32]. Iron is absorbed in the proximal small intestine.

In celiac disease, the mucosal integrity deteriorates. So, IDA is usually due to increased iron loss or impaired absorption of iron in these cases [33]. IDA is a microcytic, hypochromic anemia and patients have low serum iron levels, elevated total iron-binding capacity, and low ferritin levels [12]. IDA is common in CD and it is diagnosed in 19-81.6% cases [23,24,34]. We found IDA in 54.9% of CD cases in our study.

Folic acid is an essential element for nucleic acid metabolism. Inadequate folic acid intake leads to impairment hematopoiesis and development of the nervous system. It is absorbed in the jejunum. Deficiency of folic acid usually presents with macrocytic anemia. Concomitant iron deficiency can be seen in patients with deficiencies of folate and vitamin B12 and characteristic macrocytosis may not be detected in these cases as in our study [35]. Folate deficiency anemia is reported in 10-42% of CD patients [21,23,36,37]. Thirty point nine percentage of folate deficiency anemia that we found in our study is consistent with the literature.

Vitamin B12 is another essential element for nucleic acid metabolism. This type of anemia shows that distal small intestine where is the only absorption place of vitamin B12 is affected in these patients [38]. Laboratory findings similar to folate deficiency except for normal serum folate and low serum B 12 vitamin levels. Vitamin B 12 deficiency anemia is diagnosed in 5-41% of CD patients [21,23,36,37]. Fourteen percentage of vitamin B 12 deficiency anemia that we found in our study is consistent with the literature.

The anemia can also be seen due to malabsorption of some micronutrients like copper or zinc in CD [39].

Frequency of diagnosis of IDA can vary according to the form of CD. IDA was more frequently reported in children with classical CD when compared with atypical form [20]. We found similar results. However, the

incidence of other types of anemia did not differ according to the form of CD.

Kuloglu et al [22] reported iron-deficiency anemia in 89%, folate deficiency anemia in 19.6% and vitamin B 12 deficiency anemia in 7.6% of patients with classical CD. These rates were 62.2%, 35.5% and 15.5% in our study.

Kuloglu et al [23] reported iron-deficiency anemia in 67.6%, folate deficiency anemia in 16.6% and vitamin B 12 deficiency anemia in 9.5% of patients with atypical form of CD. These rates were 37.5%, 25% and 12.5% in our study.

Delay in the diagnosis of CD causes worsening of anemia. Iwanczak et al [20] reported anemia more frequently in adults than in children. We found similar result in our study, but it was not statistically significant.

Serum hemoglobin and hematocrit values were found to be lower in patients with AGA seropositivity than patients with EMA+tTG seropositivity. These results were regarded as quite interesting by us due to the less sensitivity of AGA seropositivity in the diagnosis of CD in recent years.

We found a significant relationship between EMA IgG or tTG IgG and IDA. Particularly, patients positive for these parameters should be monitored more closely for the presence of IDA.

We found IDA more frequently than megaloblastic anemia due to vitamin B 12 or folate deficiencies in patients with tTG seropositivity. Particularly, patients positive for this parameters should be monitored more closely for the presence of vitamin B 12 or folate deficiencies.

In conclusion, anemia is an important cause of admission in CD. These patients are diagnosed earlier as a result of anemia. Alone tTG seropositivity is more valuable to demonstrate anemia associated with iron, folate or vitamin B 12 deficiencies than the single or combined use of other serological tests.

Compliance with ethical statements

Conflicts of Interest: None.

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