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The hematologic manifestations of pediatric celiac disease at the time of diagnosis and efficiency of gluten-free diet

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Background/aim: To determine the hematologic manifestations at the time of diagnosis of celiac disease in children and the effects of a gluten-free diet on hematologic signs upon follow-up.

Materials and methods: The records of patients with celiac disease who received a follow up examination at the Pediatric Gastroenterology Clinic between June 2006 and June 2013 were retrospectively examined.

Results: Ninety-one patients were included in the study. The mean age at diagnosis was 8.1 ± 4.21 years and 59 patients (64.8%) were female. Thirty-two patients (35.2%) had hematologic signs at the time of diagnosis. Anemia (24.2%) was the most common hematologic sign, followed by thrombocytosis (16.5%) and leukopenia (4.4%). The tTG IgA titers were screened in 80 of the 91 patients during diagnosis. Follow-up examinations found that remission for anemia (P = 0.017), thrombocytosis (P = 0.039), and decreases in tTG IgA titers (P = 0.034) were more prominent in patients who had followed a strict gluten-free diet.

Conclusion: Approximately one-third of the celiac disease patients had hematologic manifestations at the time of diagnosis. Remission in hematologic signs and decrease in tTG IgA titers were more prominent in patients who had adhered to a gluten-free diet.

Key words: Anemia, celiac, leukopenia, thrombocytosis, tTG IgA

1. Introduction

Celiac disease (CD) is a chronic immune-mediated disease that specifically affects the proximal small intestines (1). The pathophysiology of the disease involves autoimmune mechanisms playing a role in intestinal mucosal injuries due to a hypersensitivity against gluten in genetically predisposed individuals resulting in malabsorption. The diagnosis of CD is made with the aid of a small-bowel biopsy, which is still considered the gold standard (2,3). Serologic testing is based on identifying immunoglobulin A (IgA) antibodies against gliadin, endomysium, and tissue transglutaminase. Antiendomysium antibodies (EMAs) and antitissue transglutaminase antibodies (anti-tTGAs) have been shown to be highly sensitive and specific (4–8). Anti-tTGAs are now widely used for the diagnosis of CD and for monitoring gluten-free diet adherence. The clinical presentation of CD is extremely heterogeneous. Typical symptoms include chronic diarrhea, abdominal distension, and a failure to thrive (9,10). However, patient presentations with extraintestinal signs are becoming more common in CD. The hematologic system is one of the most affected extraintestinal systems, with anemia being the most presented sign (11). Anemia in CD is usually due to a malabsorption of micronutrients, such as iron, folic acid, and vitamin B12 (11). Thrombocytopenia, thrombocytosis, neutropenia, and a predisposition to thrombosis are also observed (11). Gluten-free diets, the main treatment of the disease, reduce ailments, prevent complications, and also improve hematologic signs. This study was aimed to determine the hematologic signs of CD at the time of diagnosis and to examine the effects of a gluten-free diet on hematologic signs and tTG IgA titers.

2. Materials and methods

The records of patients with a CD diagnosis, who were followed up in the Pediatric Gastroenterology Clinic between June 2006 and June 2013, were investigated retrospectively. Therefore, this study is a retrospective chart review study. The patients' demographic features, complaints at presentation, celiac disease serology (tTG

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IgA and EMA IgA), duodenal biopsy findings according to Marsh classification, complete blood count results at diagnosis, treatment provided, diet adherence, period of follow-up, complete blood count results at the last visit, and whether or not the patient came for regular checkups were noted for each patient. The diagnosis of celiac disease was done according to the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) guidelines (12) in our clinic. The serologic screening included tTGA IgA and EMA IgA. Serum tTGA IgA values were measured using the ELiA Celikey IgA kit (Phadia AB, Uppsala, Sweden). As recommended by the manufacturer, serum samples containing an antibody titer greater than 10 U/mL were considered positive. IgA EMA values were detected by indirect immunofluorescence using sections of distal monkey esophagus mounted on glass slides (EUROIMMUN, Lübeck, Germany). The histological examinations of biopsy specimens were performed by an experienced pathologist using the Marsh classification as modified by Oberhuber (3,14). According to this classification, an increased number of intraepithelial lymphocytes (Marsh I) were considered not to be diagnostic for CD. In contrast, Marsh I combined with crypt hyperplasia (Marsh II) or findings with villous atrophy (Marsh III) were considered to be diagnostic for CD. All the patients were given a gluten-free diet for their treatment and were required to come for a regular checkup at 3-month intervals. Anti-tTGA IgA antibodies were screened to evaluate the patients at diagnosis and to monitor their adherence to the diet. Patients with hemoglobin values of less than 10.5 mg/dL in those younger than 6 years old, 11 mg/dL in those 6–11 years of age, 12 mg/dL in females older than 12 years of age, and 13 mg/dL in males older than 12 years of age were considered anemic (15). Iron deficiency anemia was defined as microcytic anemia with a low mean corpuscular volume and a high red cell distribution width (16). Leukopenia was defined as a white blood cell counts of less than 4000 mm^3 in the complete blood count and neutropenia as an absolute neutrophil count of less than 1500 mm^3. Thrombocytosis (17) was defined as a platelet count of more than 450×10^6.

Patients with obvious blood loss, such as those with a history of melena, hematochezia, hemoptysis, recurrent epistaxis, hematuria, and trauma; those with chronic diseases (e.g., chronic liver disease, chronic renal failure, heart failure, etc.) or hematologic diseases; and those with IgA deficiency were excluded from the study.

This study was approved by the Ethics Committee of the Turgut Özal Medical Center of İnönü University (approval number 101 /2013).

3. Results

3.1. Demographic features

Ninety-one patients with celiac disease as indicated by duodenal biopsy, and who met the study criteria, were included in the study. Fifty-nine (64.8%) patients were girls and the mean age at diagnosis for all patients was 8.1 ± 4.21 years. The median follow-up time of the patients after diagnosis was 48 months, varying between 12 months and 84 months. The patients mostly presented with gastrointestinal complaints. Abdominal pain was the most common complaint among the gastrointestinal symptoms (Table 1). Seven (7.7%) of the patients had diabetes mellitus, five (5.5%) had gastritis, and one (1.1%) had gallstones at the same time. At diagnosis, of the 91 patients, 80 had their tTG IgA titers screened and 35 had their EMA IgA antibodies screened. While all of the 80 patients who had their tTG IgA titers screened were positive, 20 (57.1%) of the 35 patients who had their EMA IgA antibodies screened were found to be positive. Ten patients (12.5%) had tTG IgA levels of <100 U/mL and 70 patients (87.5%) had tTG IgA levels of ≥100 U/mL. In the histopathologic examination of the duodenal biopsy specimen, six (6.6%) of the patients who were screened for tTG IgA had a Marsh II lesion and 85 patients (93.4%) had a Marsh III lesion. Sixty-eight (97.1%) of the patients who had tTG IgA levels of ≥100 U/mL had Marsh III lesions in the pathologic examination of the biopsy specimen. Despite all the patients being advised to follow a gluten-free diet, only 52 (57.1%) of them adhered to the treatment completely and 34 (37.4%) returned for a regular checkup. During the follow-up examination, the last tTG IgA titers were significantly lower in patients who adhered completely to the gluten-free diet compared to those who did not adhere completely to the diet (P = 0.034) (Table 2).

Table 1. Symptoms of patients with celiac disease at the time of diagnosis (n = 91).

Symptoms and signs	n (%)
Gastrointestinal system symptoms/signs	67 (73.6)
Abdominal pain	57 (62.6)
Diarrhea	17 (18.7)
Anorexia	16 (17.6)
Abdominal distention	13 (14.3)
Constipation	9 (9.9)
Vomiting	6 (6.6)
Extraintestinal signs/symptoms	
Failure to thrive	52 (57.1)
Arthralgia	1 (1)
Asymptomatic	4 (4.4)

Table 2. The effect of strict gluten-free diet on the hematologic manifestation and tTG Ig A* antibody.

Variable	At the time of diagnosis n (%)	After gluten-free diet		
		Did not adhere to gluten-free diet n (%)	Adhered to gluten-free diet n (%)	P-value
Hematologic manifestation				
Anemia	22 (24.2)	10/39 (25.6)	3/52 (5.8)	0.017
Microcytic	22	10	3	
Normocytic	-	-	-	
Leukopenia	4 (4.4)	-	-	
Neutropenia	3 (3.3)	-	-	
Thrombocytosis	15 (16.5)	6/39 (15.4)	1/52 (3.8)	0.039
Celiac serology				
tTG Ig A antibody, median (min-max)	207 (15–300)	20.8 (0–300)	8.1 (0–146)	0.034

*tTG IgA: tissue transglutaminase IgA.

3.2. Hematologic manifestations at the time of diagnosis and the effect of a gluten-free diet on the hematologic parameters

Thirty-two (35.2%) of the CD patients had hematologic manifestations at the time of diagnosis, with anemia being the most commonly presented hematologic sign (24.2%). All of the anemic patients had microcytic anemia due to iron deficiency. All of the patients were given a gluten-free diet to follow and those with anemia were also given iron treatment. The last screened complete blood count was also examined from the patients' records. Anemia persisted in 13 patients (14.3%) and thrombocytosis persisted in seven patients (7.7%). When remission of hematologic signs was compared in patients who maintained a strict gluten-free diet versus those who did not, anemia (P = 0.017) and thrombocytosis (P = 0.039) were less persistent in patients who had adhered completely to the diet (Table 2).

4. Discussion

Our study showed that one-third of CD patients of childhood age had hematologic manifestations at the time of diagnosis, and microcytic anemia was the most commonly presented hematologic sign, followed by thrombocytosis and leukopenia. Moreover, all of our patients had positive tTG IgA at the time of diagnosis. An improvement in hematologic signs and a definite decrease in tTG IgA titer levels were observed in patients who adhered to a strict gluten-free diet.

Hematologic manifestations are one of the most presented extraintestinal signs of CD. Anemia is the most common hematologic sign with a prevalence varying between 12% and 69% (18–22). Deficiencies in iron, vitamin B12, and other microelements are thought to play a role in the etiology of anemia (11,23). At the same time, anemia could occur as a result of the chronic inflammation that occurs with CD (24). Anemia was the most common hematologic sign in our study, being present in one-fourth of the patients. All those with anemia were microcytic and linked to an iron deficiency. Only 5.8% of patients with strict gluten-free diet adherence had anemia persisting at follow-up.

Thrombocytopenia rarely develops in CD and is generally a result of autoimmune mechanisms (25–27). Thrombocytosis is more commonly seen than thrombocytopenia with a prevalence of up to 60% in CD patients (11,28,29). Even though its etiology is not well known, it is thought to be due to inflammatory mediators, iron deficiency anemia, or functional hyposplenism. Thrombocytosis has been shown to improve with a gluten-free diet (28). In our study, 16.5% of patients had thrombocytosis at the time of diagnosis; however, only 3.8% of patients who adhered to a gluten-free diet had persisting thrombocytosis at follow up.

Leukopenia has been reported in some CD patients (25) and is thought to be due to folic acid and copper deficiencies. Therefore, it is advised that patients with leukopenia who have folic acid or copper deficiencies be supplemented with these minerals. Leukopenia was the least commonly seen hematologic sign in our study and folic acid levels were normal in those patients. Leukopenia was improved in all patients after following a gluten-free diet.

The only treatment for CD is a lifelong exclusion of gluten. This requires a wheat-, barley-, and rye-free diet. After gluten withdrawal, there is a rapid remission of symptoms, improved bone mineralization, and reversal of growth failure and nutritional deficiencies. After the diagnosis of CD, children with CD should be monitored with periodic assessments of symptoms, growth,

physical examinations, and adherence to a gluten-free diet. Measuring tTGA titers after a gluten-free diet can be helpful in evaluating adherence to the diet. Gluten withdrawal leads to a reduction of tTGA titers (15). In our study, patients who strictly adhered to a gluten-free diet had improved hematologic signs and a reduction in tTG IgA levels that were more evident compared to patients without strict adherence to a gluten-free diet.

The retrospective nature of our study is the main limitation that might affect our results due to a lack of data for some parameters, such as tTGA (in one of the nine cases) and EMA (in one-third of the cases).

In conclusion, approximately one-third of our patients had hematologic involvement signs at diagnosis, with anemia being the most and leukopenia the least commonly presented sign. Almost all of the patients had tTGA titers of over 100 U/mL. Improvements in hematologic signs and decreases in tTGA titers were evident in patients who strictly adhered to a gluten-free diet.

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