Liver Involvement in Children during the Diagnosis of Celiac Disease: A Single-Center Experience from Turkey

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ABSTRACT

BACKGROUND:
Liver abnormalities in Celiac disease (CD) are common. The aim of this study was to investigate the children with CD who were followed up in our clinic presenting with elevated aminotransferase levels.

METHODS:
In this study, the data of 419 pediatric patients with CD were retrospectively analyzed, and those with elevated aminotransferase levels during the diagnosis of CD were assessed.

RESULTS:
Elevation of aminotransferase levels was found in 66 (15.7%) patients among the 419 patients during the diagnosis of CD. The mean age of these patients was 7.33±3.96 years. Liver enzymes were mildly elevated in 63 (95.4%) patients. However, half of the patients with elevated liver enzymes had a 1.25-fold increase in aminotransferase levels. Patients with hypertransaminasemia had higher weight loss and lower folic acid values compared with patients with normal liver enzymes. Patients' liver tests were reverted to normal, except for two patients with chronic liver disease, after 9.27±3.16 months of administering a gluten-free diet.

CONCLUSION:
Patients with liver involvement should be investigated for CD. Especially, mildly elevation of aminotransferase levels should be taken into account by pediatricians for Celiac hepatitis.

KEYWORDS:
Aminotransferase levels, Celiac disease, Pediatric

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INTRODUCTION

Celiac disease (CD) is a chronic, immune-mediated enteropathy of the small intestines, which is induced by exposure to dietary gluten in susceptible pediatric patients.[1] The diagnosis of CD is easier in the presence of gastrointestinal symptoms, such as diarrhea, abdominal pain, vomiting, constipation, and abdominal distension with failure to thrive than in the presence of non-gastrointestinal symptoms. In children, the classical form of CD includes gastrointestinal symptoms at 6 months of age after the introduction of gluten into the diet.[2] Although this disease is known as an enteropathy, it appears as a systemic disease, as extraintestinal manifestations have become increasingly evident in

recent years. Many symptomatic patients diagnosed with CD have initially presented with extraintestinal manifestations. These extraintestinal findings include short stature, iron deficiency anemia, osteopenia/osteoporosis, elevation of liver enzymes, and neurological problems. Elevation of aminotransferase levels is the most common hepatic manifestation of CD, with a prevalence of approximately 9%-14%. Liver involvement in CD is mostly mild and reversible. However, liver failure may rarely develop in patients with hepatic involvement. Elevation of aminotransferase levels is directly proportional to duodenal mucosal damage, malabsorption, and elevation of serum tissue transglutaminase (tTG).[3] As a result of alterations in intestinal permeability, hepatotoxins reach the liver via portal circulation and cause inflammation in the liver.[4] With the introduction of a gluten-free diet, aminotransferase levels usually return to normal within approximately one year.[3] In this study, data of the patients diagnosed with CD were screened retrospectively, and the aminotransferase levels at the time of diagnosis were evaluated.

MATERIALS AND METHODS

Elazığ is an Eastern Anatolian city located in the upper Fırat section of the Fırat Basin. Fırat University Faculty of Medicine, located in Elazığ, is an important regional hospital providing tertiary healthcare for many patients from the surrounding provinces. The medical records of 419 patients with CD who were followed up by the Pediatric Gastroenterology Department of the Faculty of Medicine in Fırat University were screened retrospectively.

Data regarding the age at presentation, presenting complaints, z scores for weight and height, serum anti-tTG IgA levels, serum IgA levels, upper gastrointestinal endoscopic findings for duodenum and histopathological findings, serum hemoglobin, ferritin, folic acid, vitamin B_{12}, lipid profile, thyroid function tests, and bone mineral densitometry results were extracted from the patients' files.

The endoscopic procedure was performed with an Olympus Evis Lucera CLV-260SL. The diagnosis of CD was made according to the diagnostic criteria established by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN).[1] Upper gastrointestinal endoscopy was performed in patients with elevated anti-tTG IgA antibody levels regardless of the presence of typical or atypical symptoms. CD was diagnosed in patients with Marsh scores ≥ 2 in the histopathological examination of their duodenal biopsy samples. Patients with CD were divided into two groups: those presenting with hypertransaminasemia and those with normal liver enzymes.

Serum alanine aminotransferase (ALT) levels obtained just before diagnosis were recorded as well. Patients with ALT levels higher than 40 U/L (the upper limit of normal) were included in the study; in other words, the upper limit for serum ALT values in our biochemistry laboratory was 40 U/L. Degrees of aminotransferase elevations were grouped as mild (<5 times the upper limit of normal), moderate (5-10 times the upper limit of normal), and severe (>10 times the upper limit of normal). All patients were assessed for comorbid liver diseases through a review of their file records. Using these data, we investigated the frequency of patients who presented with elevated aminotransferase levels at the time of diagnosis with CD. In addition, the amount of time that passed from the initiation of a gluten-free diet to the resolution of liver enzymes was also evaluated.

The serum hemoglobin, ferritin, folic acid, and vitamin B12 levels of the patients at diagnosis were analyzed retrospectively. Anemia was defined as hemoglobin levels lower than 10.5 g/dL for children aged 6 months to 2 years, 11.5 g/dL for children aged 2-12 years, 12 g/dL for females, and 13 g/dL for males aged 12-18 years. Reference values were 12 ng/dL for ferritin, 3 ng/mL for folic acid, and 175 pg/mL for vitamin B_{12}. The reference value for serum anti-tTG IgA was 18 U/mL.

Bone mineral density (BMD) values were obtained from the patients and examined at the time of diagnosis with CD. BMD was measured by dual-energy X-ray absorptiometry (DEXA) of the L1-L4 lumbar region. BMD z scores were calculated using the following formula[5]:

z score = (patient's BMD - mean BMD of age- and sex-matched normals)/(standard deviation (SD) of BMD of age- and sex-matched normals)

Osteoporosis was present when a patient's z-score

was less than -2, and osteopenia was present when a patient's z-score ranged from -1 to -2.[6]

Statistical Analysis

All data were analyzed by using SPSS software for Windows version 22.0 (SPSS Inc., Chicago, IL, USA). The distributions of all the parameters were determined using a Shapiro-Wilk test. Parameters with abnormal distributions were expressed as median (25^{th}-75^{th} percentile) values, and parameters with normal distribution were expressed as mean ± standard deviation (SD) values. Parameters were compared for baseline variables using a Student's *t* test or a Mann-Whitney U test. A Pearson's chi-square test was used to assess differences in frequency among categorical variables. The accepted limit of significance was $P < 0.05$.

RESULTS

In a retrospective screening of the medical records of 419 patients with CD who were followed up in our department, elevated aminotransferase levels at the time of diagnosis with CD were detected in 66 patients (15.7%; 53% female). The mean age of the patients with elevated aminotransferase levels was 7.33±3.96 years (range: 2-17 years). The mean age of the patients with normal liver enzymes was 8.12±4.25 years (range: 2-17 years; $P > 0.05$). The most frequent presenting complaint was failure to thrive, followed by abdominal pain and diarrhea, as can be seen in all patients with CD. Only four patients (6%) were referred to our department with elevated aminotransferase levels from other pediatric departments and diagnosed with CD. The serum lipid profile and thyroid function tests of the patients included in the study were normal. The complaints of the patients with CD and elevated aminotransferase levels as well as those with normal aminotransferase levels are shown in Table 1 ($P > 0.05$).

Mean z-scores for weight and height were -1.36±1.31 and -1.27±1.60, respectively, in patients with elevated aminotransferase levels. The weight and height z-scores of the patients with CD and normal aminotransferase levels were -1.57±1.42 and -1.38±1.29, respectively. The *P* value for weight z-scores between the groups was 0.004, and the *P* value for height z-scores between the groups was 0.64.

When the cases were assessed for aminotransferase levels, it was found that the mean ALT level was 73.27±85.05 U/L (range 41-533 U/L). It was also found that ALT levels were within a range of 40-50 U/L (up to 1.25 times of normal limit) in 33 cases (50%).

The endoscopic findings showed irregularity of the duodenal mucosa in 51 patients (77.3%) and marked scalloping in seven patients (10.6%), while the duodenal mucosa appeared normal in eight patients (12.1%) with elevated aminotransferase levels. In the patients with CD and normal liver enzymes, the rates of irregular duodenal mucosa, marked scalloping, and normal duodenal mucosa were 65.3%, 13.9%, and 20.8%, respectively ($P > 0.05$).

The histopathological examination showed grade 2 disease in 10 patients (15.1%), grade 3b disease in 51 patients (77.3%), and grade 3c disease in five patients (7.6%) according to the Marsh scores of the patients with hypertransaminasemia. The rates of grade 2, grade 3b, and grade 3c disease in patients with CD and normal aminotransferase levels were 16.4%, 71.2%, and 12.4%, respectively ($P > 0.05$).

Of all 66 cases, aminotransferase levels were mildly elevated in 63 cases (95.4%). Two patients (aged 5 and 6 years) presented with unexplained liver cirrhosis and were diagnosed with CD. A liver biopsy was performed in one of the patients with elevated liver enzymes, which showed non-specific, chronic inflammatory changes in the liver. In these two

Table 1. Comparison of the complaints of the patient groups at the time of admission

	CD with elevated aminotransferases (n=66)	CD with normal aminotransferases (n=353)
Failure to thrive	38 (57.6%)	145 (41.0%)
Abdominal pain	15 (22.7%)	86 (24.3%)
Diarrhea	9 (13.6%)	63 (17.8%)
Constipation	1 (1.5%)	24 (6.7%)
Anemia	1 (1.5%)	9 (2.5[%)
Asymptomatic for CD	2 (3%)	26 (7.3%)

$P > 0.05$

patients, CD was diagnosed during the investigation of the etiology of portal hypertension. In a patient aged 6 years, esophageal band ligation was performed due to grade 3 esophageal varices. Apart from these two patients, type 1 diabetes mellitus was found in one patient, and chronic hepatitis B infection was found in another patient accompanying CD.

No statistically significant differences were found in serum hemoglobin, ferritin, or vitamin B_{12} values between patients with elevated liver enzymes and normal liver enzymes. Considering that the anemia limit according to the average age of the patients was 11.5 g/dL, the group with elevated liver enzymes was more anemic than the group with normal liver enzymes. In addition, folic acid values were significantly lower in the group with elevated liver enzymes than in the group with normal liver enzymes. BMD levels were also significantly lower in the group with elevated liver enzymes compared with the group with normal liver enzymes, but there was no difference between the groups in terms of BMD z-scores. There was also no difference between the groups in terms of anti-tTG IgA values. The serum IgA levels of the patients with CD included in this study fell within the normal range according to their age groups. A comparison of the laboratory results is shown in Table 2.

Finally, it was found that aminotransferase levels returned to normal within 9.27±3.16 months after the implementation of a gluten-free diet in cases without comorbid liver disease.

DISCUSSION

CD is an immune-mediated enteropathy caused by gluten intolerance. In population-based studies, its prevalence has been reported as 1%.[7] In a study by Dalgic and colleagues[8] the prevalence of CD was reported to be 0.47% among school-age children in Turkey. The clinical presentation of CD can vary from classical malabsorption syndrome to extraintestinal symptoms, such as iron deficiency anemia or osteoporosis.[9] In the present study, the most common complaints presented by patients with elevated aminotransferase levels at the time of diagnosis with CD were failure to thrive, abdominal pain, and diarrhea, representing the classical complaints of malabsorption.

Hepatic manifestations of CD range from asymptomatic elevation of aminotransferase levels to autoimmune hepatitis, non-alcoholic fatty liver disease, and cholestatic liver disease. The liver can be affected at varying degrees in patients with CD.[10] Liver damage in patients with CD usually occurs in the form of non-specific hypertransaminasemia (Celiac hepatitis). Although the pathogenesis of liver damage is not clear in CD, it is believed that increased intestinal permeability, alterations in intestinal microbiota, chronic intestinal inflammation, and genetic predisposition may contribute to liver damage. Given that three-fourths of the blood supply to the liver comes from the small intestine, the liver is exposed to toxic substances with intestinal origins. Increased intestinal permeability accelerates the passage of toxins, antigens, and inflammatory substances to portal circulation, resulting in liver damage mediated by these substances. Enterohepatic T lymphocyte circulation via the portal vein also contributes to liver damage.[8,11] Impaired liver function has been reported in 40% of adults and 54% of children presented with typical symptoms of CD.[12] Further, several studies have found CD to be present in 9% of patients with chronic, unexplained hypertransaminasemia.[13-15] Benelli and others [16] found the rate of hypertransaminasemia to be 3.9% in their study and stated that hypertransaminasemia

Table 2. Comparison of the laboratory results of the patient groups

	CD with elevated aminotransferases (n=66)	CD with normal aminotransferases (n=353)	*P*
Hemoglobin g/dL, median (IQR)	11.1 (9.9-12.3)	11.6 (10.1-12.9)	0.28
Ferritin ng/dL, median (IQR)	6.2 (3.2-11.5)	8.9 (3.5-17)	0.23
Folic acid ng/mL, median (IQR)	4.4 (2.4-6.1)	6.5 (3.3-10.2)	**0.01**
Vitamin B_{12} pg/mL, median (IQR)	301 (234.5-425.2)	274 (210.7-374.2)	0.65
BMD g/cm^2, median (IQR)	0.39 (0.25-0.54)	0.52 (0.44-0.61)	**0.006**
BMD z score, median (IQR)	-1.37 (-2.29-(-1.77))	-0.94 (-1.93-(-1.10))	0.74
Anti-tTG IgA U/mL, median (IQR)	200 (200-335)	230 (200-342)	0.51

was higher in younger children. CD-related liver damage was detected in 15.7% of the participants in the present study, but the ages of the patients with hypertransaminasemia were close to those of the patients with CD and normal liver enzymes. There was a mild elevation in aminotransferases in most of the patients. Routine liver biopsy is not indicated; however, Kupffer cell hyperplasia, mononuclear cell infiltration, steatosis, and mild fibrosis can be detected through histopathological examination of liver biopsies.[17,18] Non-specific, chronic inflammatory changes were detected in the liver biopsy of a patient with severely elevated aminotransferase enzymes. In two cases, CD was diagnosed as a result of the endoscopic and histopathological evaluation, which was conducted due to the discovery of positive anti-tTG IgA antibodies during the investigation of the etiology of portal hypertension. CD rarely causes severe liver disease. However, there are some reports of cases of CD and severe liver disease requiring liver transplantation in the literature.[10,19]

Sima and colleagues[20] showed that anti-tTG IgA antibodies were positive in 9% of cases with chronic hepatitis B infection. It was suggested that the use of interferon-α for the treatment of hepatitis B predisposed patients to CD by altering immune responses. In a study by Leonardi and co-workers.[21] CD was not detected in a screening of 60 patients with chronic hepatitis B infections acquired during childhood. In the present study, only one patient had chronic hepatitis B infection, and serology markers for CD were positive in this patient. It was discovered that this patient had received interferon and lamivudine therapies, and the serological markers for CD were investigated due to the discovery of mildly elevated aminotransferase levels at the follow-up. Subsequently, the patient underwent endoscopic evaluation due to increased anti-tTG IgA and was diagnosed with CD.

CD was shown to be associated with autoimmune liver diseases, such as autoimmune hepatitis, primary sclerosing cholangitis, and primary biliary cirrhosis .[22] Given that the human leukocyte antigen (HLA) Class II region on chromosome 6 is responsible for CD and autoimmune liver disease, both diseases are likely to coexist.[23] However, there were no patients with autoimmune liver disease among the patients with CD and hypertransaminasemia in the present study.

In addition, patients with type 1 diabetes mellitus are known to have an increased predisposition to CD.[24] This relationship is closely related to HLA-related autoimmune endocrinopathies, such as CD, type 1 diabetes, and hypothyroidism. Alaswad et al[25] presented a pediatric case with CD, type 1 diabetes, hypothyroidism, chronic liver disease, and selective IgA deficiency. Among the present cases, there was only one patient with type 1 diabetes mellitus in addition to hypertransaminasemia.

Extraintestinal manifestations of CD are more common than the typical symptoms of CD. Short stature is one of the most common extraintestinal manifestations of pediatric CD. Malabsorption of nutrients and dysregulation of the growth hormone-insulin-like growth factor axis play major roles in the pathogenesis of short stature. In the present study, there was no significant difference between the group with elevated liver enzymes and the patients with normal enzymes in terms of short stature. However, weight loss was higher in the group with elevated liver enzymes. While weight loss is at the forefront of the acute phase of malnutrition, short stature accompanies the chronic period. Notably, weight loss was more prominent in patients with CD and elevated liver enzymes. Hypertransaminasemia is known to be directly proportional to duodenal mucosal damage and serum anti-tTG IgA levels. In the present study, no difference was found between the groups in terms of serum anti-tTG IgA levels. However, there were also no differences between the groups in terms of endoscopic findings or Marsh scores.

Anemia is another common extraintestinal finding that is directly proportional to the severity of CD. Although iron deficiency anemia is most commonly seen, folic acid deficiency and vitamin B12 deficiency can also be seen in patients with CD. In the present study, there were no differences between the cases in terms of ferritin or vitamin B_{12} levels, but folic acid levels were significantly lower in the group with hypertransaminasemia. Folic acid is a vitamin absorbed from jejunum, and in cases of hypertransaminasemia, low folic acid is associated with malabsorption.

Low BMD is defined as osteopenia, is seen as a result of malabsorption of calcium and vitamin D, and

may occur even before enteropathy progresses. In the present study, BMD values were found to be lower in the group with hypertransaminasemia, but there was no difference between the two groups in terms of BMD z-scores. BMD z-scores are more accurate for the evaluation of osteopenia or osteoporosis and are therefore used in clinical practice for pediatric patients in place of BMD values.

In the present study, 15.7% of patients with CD had hypertransaminasemia. ALT values fell between 40-50 U/L in half of the patients with hypertransaminasemia. Patients with elevated liver enzymes experienced more weight loss and had lower folic acid and BMD values. For the early diagnosis and treatment of CD, it is important to take into account even the slightest elevations in ALT values, which often result in frequent admission to general pediatric outpatient clinics.

Celiac hepatitis responds well to a gluten-free diet. Hepatic dysfunction returns to normal within 6-12 months after commencing a gluten-free diet.[26,27] In the present cases, aminotransferase levels returned to a normal range approximately 9 months after commencing a gluten-free diet. However, abnormal hepatic function tests persisted in two cases with portal hypertension.

The present study had some limitations. The first limitation was that the study was retrospective, and therefore there were difficulties in medical data collection. Secondly, liver involvement in patients with CD in their first-degree relatives was not evaluated. Another limitation of the study was that liver autoantibody screening and magnetic resonance cholangiography were not performed for the differentiation of celiac hepatitis and autoimmune hepatitis. However, the presence of mild transaminase elevation in most of the cases and the normalization of liver enzymes within months with a gluten-free diet suggested celiac hepatitis.

CD is increasingly diagnosed in asymptomatic children and those with atypical symptoms. Hepatic findings are common in CD, ranging from mild disease to severe liver failure. However, CD rarely causes hepatic damage requiring liver transplantation. Early diagnosis and timely treatment of CD-related hepatic disorder are important in terms of prognosis. In conclusion, children with abnormal liver test results should be screened for CD and vice versa.

ETHICAL APPROVAL

This study was approved by the Ethics Committee of Fırat University (date: 01.08.2019, decision number: 12/11).

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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