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Original Article

Study of Liver Effect in Children with Celiac Disease

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ABSTRACT

Objective: It is well known that there are different rates of liver damage in celiac disease (CD). A wide spectrum of cases has been reported, ranging from asymptomatic transaminase elevation to cirrhosis. In this study, we investigated the frequency and clinical features of liver stress in children diagnosed with CD in our department.

Methods: Patients who were aged 1-18, serologically and histologically diagnosed as having CD and followed up were retrospectively included. Medical history, physical examination, serum anti-tissue transglutaminase and anti-endomysium antibodies, duodenal histology, liver function tests and imaging findings were evaluated.

Results: One hundred and eleven patients were included in the study. Of the patients, 74 were girls (64%) and 40 were boys (36%), and the mean age of admission was 7.1±4.3 years (1-18 years). The follow-up period was 3.5±4.4 (1-16) years. At diagnosis, alanine aminotransferase (ALT) was elevated in 5 (4.5%) of the 111 patients, and at follow-up, 3 patients were found to have lower levels that returned to the normal range. Elevation of gamma-glutamyl transferase (GGT) (3.7%) was found in 4 patients. Sclerosing cholangitis was diagnosed by liver biopsy in 2 patients with elevated GGT. Abdominal ultrasonography (USG) was performed in 50 (45%) patients. Hepatomegaly was found in 4 (3.6%) of these 50 patients and biliar dilatation in 2 (1.8%) patients. Abdominal USG also revealed hepatomegaly in 4 patients, without elevation in GGT and ALT levels.

Conclusion: We found 8% liver-related findings at the time of diagnosis in children with CD. No new liver effects were observed in 29% of patients followed up for five years.

Key words: Celiac disease, liver, child, transaminase levels

INTRODUCTION

Celiac disease (CD) is a disease that predominantly affects the proximal small intestine and is characterized by persistent intolerance to the gluten in wheat and other gluten-like grain proteins found in grains such as barley, rye and oats. Although CD is known as an enteropathy, it is a disease that affects many organs, and findings outside the gastrointestinal tract are common[1].

The association between CD and the liver was first demonstrated in 1977 by Hagander et al.[2] This association has been demonstrated in many studies over the past 40 years. Studies have reported that 9-42% of adults with CD and 24-40% of children with CD have elevated transaminase levels[3,4]. In addition, the prevalence in patients with unknown transaminase elevation is reported to be 4% in adults and 1.8% in children[5,6]. In CD, the only finding may be elevated liver enzymes; it may occur together with non-specific hepatitis, non-alcoholic fatty liver disease (NAFLD), autoimmune disease, and cholestatic liver disease. For this reason, it is recommended that liver functions be measured in children newly diagnosed with CD[7]. Elevated transaminases due to CD are defined as liver abnormalities caused by gluten that usually return to normal after 12 months of a strict gluten-free diet[8-10]. Changes in liver histology have been reported to improve with diet[11].

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The mechanisms of transaminase elevation associated with CD are not fully understood[12]. It is suggested that increased intestinal permeability in CD with elevated transaminase levels may facilitate the entry of toxins, microbial and other antigens, cytokines, and other mediators of liver injury into the portal circulation (and subsequently into the liver)[13,14]. However, in the presence of chronic liver disease and transaminase levels higher than five times the upper normal limit, detailed testing for other liver diseases should be performed at the time of diagnosis[13-15].

In addition to elevated transaminases due to CD, sclerosing cholangitis and autoimmune hepatitis may also be associated with CD. In studies of adults, the association of CD with sclerosing cholangitis has been reported at a rate of 0.1%-3%[16]. This association is an autoimmunity caused by a common genetic predisposition and resulting immune-related damage to the epithelium of the bile ducts and small intestine. Tissue HLA-DQ2 positivity poses a risk, especially in patients with primary sclerosing cholangitis and CD[16].

This study investigated liver disease in CD in childhood and clinical and laboratory findings that might be effective in patients diagnosed with CD and followed up in our department.

MATERIALS AND METHODS

The data of 111 patients, 71 girls and 40 boys, aged 1-18 years, diagnosed clinically, serologically and endoscopically with CD in Dokuz Eylül University Faculty of Medicine, Department of Pediatric Gastroenterology, Hepatology, and Nutrition, were retrospectively retrieved from the Hospital Information System database.

Ethical approval for this study was obtained from Dokuz Eylül University Non-Interventional Research Ethics Committee (approval no: 2019/28-14, date: 18.11.2019).

The diagnosis of CD is based on a combination of clinical, serological and histopathological data. Anti-endomysium immunoglobulin A antibody [Euroimmun, EUROPLUS liver (monkey)] and anti-tissue transglutaminase immunoglobulin A antibody (anti-TgA) (Euroimmune, ELISA method negative: <20 RU/mL, positive: ≥20 RU/mL) measurements were made. With regard to selective immunoglobulin A (IgA) deficiency, serum IgA levels (normal reference range: 70-400 mg/dL) were determined. The examination was performed with a Fujinon EG-590 WR (Japan) gastroscope device. In children with positive antibody, at least 4 biopsies were taken from the distal duodenum and at least 1 from the bulb. Histologic features of CD in the small intestine range from a mild change characterized only by increased intraepithelial lymphocytes to a severely atrophic mucosa with complete loss of villi, increased epithelial apoptosis, and hyperplasia of the crypt. The histologic severity of intestinal lesions in CD is graded using the Marsh-Oberhuber classification. The presence of Marsh type 2 and 3 lesions support the diagnosis[17]. Endoscopic duodenal biopsies of Marsh type-2 and Marsh type-3 were included in the study.

Serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase, alkaline phosphatase, albumin, total bilirubin, direct bilirubin, total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol of the patients were recorded. The upper normal limit for AST and ALT was 45 U/L. The abdominal ultrasonography (USG) records of the patients were examined. Abdominal USG was performed to evaluate for liver parenchyma as well as gallbladder stones and sludge that might accompany them. In 2 patients, the bile ducts were examined by using magnetic resonance cholangiopancreatography (MRCP).

Records of other causes (viral hepatitis, toxic causes) that might increase AST and ALT levels in the patients were reviewed. Body weight and height were recorded. Body mass index (BMI) and standard deviation score (SDS) were calculated.

Statistical Analysis

It was performed using SPSS 19.0 for Windows (SPSS, Inc.; Chicago, USA). Descriptive statistics were expressed as number (n), percentage (%), mean, SD. The Pearson chi-square test was used to search for the relationship between two categorical variables. A p-value of less than 0.05 was set for statistical significance.

RESULTS

One hundred and eleven patients that met the inclusion criteria were included in the study. Of the 111 patients, 71 (64%) were girls and 40 were boys (36%). The mean age at inclusion was 7.1±4.3 months (range, 1-18 years). The follow-up time of patients was 3.5 ±4.4 (range 1-16) years, and the number of patients followed up for 5 years or more was 32 (29%).

At the time of diagnosis, 5 (4.5%) patients were found to have elevated ALT levels. It was observed that ALT levels returned to the normal range in 3 (2.7%) of these patients with diet therapy. An elevated GGT level was observed in 4 patients (3.7%). Liver biopsy was performed in 2 patients in which ALT and GGT elevations were observed together. Liver biopsy was found to be compatible with sclerosing cholangitis. In these 2 patients, dilatation of the intrahepatic and extrahepatic bile ducts was observed on MRCP. Cholestasis was not observed in any of our patients. One of our patients was diagnosed with ulcerative colitis two months after the diagnosis of CD. Our patient was monitored in remission for 4 years with azathioprine therapy and a gluten-free diet. Elevations of ALT and GGT levels were never observed again. Another patient with CD and sclerosing cholangitis was not followed up after liver biopsy.

Abdominal USG was performed in 50 (45%) of the patients. Hepatomegaly was found in 4 (3.6%) of these patients and dilatation of the bile ducts in 2 (1.8%) patients. Hepatosteatosis was not detected in USG. In 4 patients with hepatomegaly, no elevation of ALT and GGT levels was detected in USG. In addition, gallbladder stones and sludge were examined by using USG.

Wool above BMI SDS 2 was detected in 4 of the 11 patients (3.6%). In these patients, elevated ALT and GGT levels were detected and no hepatosteatosis was detected in USG (Table 1). No liver involvement was observed in patients with a follow-up of 5 years or more.

DISCUSSION

In CD, the liver is affected to varying degrees. Because elevated liver enzymes are relatively common at the time of diagnosis of CD, it is recommended that all newly diagnosed patients with CD be tested for hypertransaminemia[18,19]. This approach was recently validated in the only population-based study of liver involvement in adults with CD in the USA[4].

In our study, ALT was found to be elevated in 5 (4.5%) of 111 patients. Compared with the literature, a lower rate of elevated ALT level was observed. It was observed that ALT levels returned to the normal range in 3 (2.7%) of these patients when treated with a gluten-free diet. When transaminases normalize on gluten-free diet therapy, annual follow-up is recommended[3]. In both patients, elevations in both ALT and GGT levels were observed, which were evaluated as sclerosing cholangitis after liver biopsy. The frequency of sclerosing cholangitis in patients with CD was 0.1-3% in the literature[16] and our frequency (1.88%) was in accordance with the literature. Patients with CD and sclerosing cholangitis should be evaluated in terms of inflammatory bowel disease (IBD), which may accompany them. Recognition of the coexistence of sclerosing cholangitis and CD is also important in terms of treatment options. In one of our patients, CD, sclerosing cholangitis, and ulcerative colitis were observed together. We were unable to complete the study of our other patient on this issue. In our study, coexistence of CD, PSC, and IBD was noted in 1 (0.9%) of 111 patients. IBD was significantly more common (3.2%) in the adults with CD than in the general population according to the literature[20]. There was an association between CD and gallstones, but gallstones were not found in this study using USG.

Table 1. Clinical and laboratory findings of the patients

Gender	
Female	74 (64%)
Male	40 (36%)
Age (mean)	7.1±4.3 years (1-18 years)
Follow-up time (mean)	3.5±4.4 (1-16) years
Reason for admission (n)	
Growth retardation	27
Diarrhea	19
Abdominal pain	25
Constipation	11
Screening (type I diabetes, family history of celiac disease)	29
Laboratory	
ALT (10-46 U/L)	5 (4.5%)
GGT (10-20 U/L)	4 (3.7%)
ALT and GGT (combined elevation)	2 (1.8%)
Radiology (USG) (n)	
Hepatomegaly	4
Hepatosteatosis	0
Bile duct anomalies	2
Liver biopsy	2
Sclerosing cholangitis	2 (1.8%)

ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, USG: Ultrasonography

Liver biopsy is not required in newly diagnosed CD with isolated hypertransaminasemia. However, it is recommended in selected patients with suspected chronic cholestatic liver disease that cannot be diagnosed by using non-invasive methods. There are no pathognomonic findings in liver histopathology and mild or non-specific changes are observed. Severe fibrosis or cirrhosis is rare. Liver histology is preserved, and mild mononuclear infiltrates in portal and lobular areas, and mild hyperplasia of Kupffer cells may be observed[21].

Other causes of transaminase elevation (viral hepatitis, toxic causes) were investigated in the patients. Hepatitis B and C were not detected in our pediatric patients.

NAFLD is the most common cause of chronic liver disease in children and adolescents in Western countries and is estimated to occur in 20% of the population[22,23]. Obesity and metabolic syndrome are the main causes of NAFLD[24]. However, not all patients with NAFLD are obese[25]. The prevalence of CD in adult NAFLD patients was reported to be 2.2-7.9%, and BMI was often within the normal range in these patients[26,27]. In the study by Reilly et al.[23], individuals diagnosed with CD in childhood were found to have a relative risk of NAFLD of 4.6%. In their studies of adults, Bakhshipour et al.[25] found that fatty liver was more common in CD, and CD was more common in patients with fatty liver.

In our study, 4 patients (3.6%) out of 111 patients with BMI SDS of 2 and >2 were observed. In these 4 patients, no hepatosteatosis was detected in USG, and no elevation in ALT and GGT levels were observed in the laboratory.

Moreover, in patients in whom CD and NAFLD coexist, a low gluten diet also reduces liver fat in these patients[28]. However, in the study by Reilly et al.[23], the increase in hepatosteatosis in patients with CD was higher than in the normal population, and this increase was not only in the first year but also continued for 15 years after diagnosis.

In our study, the number of patients with more than 5 years of follow-up was 32 (29%). During the follow-up period, NAFLD and non-alcoholic steatohepatitis were not encountered.

Study Limitations

The major limitation of our study was that it was a retrospective study and we primarily attempted to search for liver pathologies using ALT and USG based on the literature in the screening program. Although the use of USG in routine screening programs for NAFLD was not supported, it was preferred because it was non-invasive, simple, and inexpensive. Studies in adults observed in the literature were evaluated with the gold standard liver biopsy in suspicious patients after screening with USG and with ALT measure.[29,30]

CONCLUSION

As a result, elevation of transaminase levels in newly diagnosed celiac patients, apart from other specific liver diseases, may be due to CD and is common. Patients respond to a gluten-free diet. Intestinal barrier dysfunction, dysbiosis, and bacterial translocation are characteristic of CD and liver disease. Early diagnosis and treatment of CD is critical because a gluten-free diet can both relieve symptoms and prevent more serious celiac-related liver damage. If elevation of liver enzymes persists for 1 year despite a strict diet, further investigation for the etiology should be planned. Although autoimmune liver diseases are less associated with CD, their diagnosis is important in treatment of patients with severe clinical findings. Therefore, liver enzymes should be checked in newly diagnosed celiac patients. As the relationship between gluten-related immunity and liver damage becomes better understood, new opportunities for both prevention and treatment will emerge.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from Dokuz Eylül University Non-Interventional Research Ethics Committee (approval no: 2019/28-14, date: 18.11.2019).

Informed Consent: Retrospective study.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Concept: Y.Ö., Design: Y.Ö., Data Collection or Processing: G.Ş., Analysis or Interpretation: G.Ş., S.K.Ç., Literature Search: G.Ş., S.K.Ç., Y.Ö., Writing: G.Ş.

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