

## Fluctuation of liver transaminases with gluten-free diet compliance of a patient with celiac disease and autoimmune hepatitis; a case report

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### Abstract

Although the association of celiac disease with autoimmune hepatitis is well-known, the effect of gluten-free diet on autoimmune hepatitis progression is poorly defined. We described a patient with celiac disease coexisting with autoimmune hepatitis and effectiveness of gluten-free diet on both diseases.

A young patient with elevated serum liver transaminases was diagnosed as celiac disease and autoimmune hepatitis according to clinical, laboratory and pathological findings. Clinical complaints and laboratory findings of patients resolved exactly after gluten-free diet. However, liver transaminases elevated and clinical manifestations re-emerged when he left the diet.

Clinicians should consider that other autoimmune diseases may occur in the course celiac disease and gluten-free diet may improve also extra-intestinal manifestations of celiac disease.

**Keywords:** Celiac Disease; Hepatitis, Autoimmune; Diet, Gluten-Free.

## INTRODUCTION

Celiac disease (CD) is an autoimmune disorder of the small intestine characterized by the clinical features of malabsorption that manifests in genetically susceptible individuals when exposed to dietary gluten (1). The prevalence of CD in European countries is nearly 1% (2). Ingestion of gluten starts inflammatory reaction in the intestine and various cytokines are released from the T cells with subsequent production of anti-gliadin and anti-transglutaminase antibodies in genetically predisposed individuals (3). Elevation of liver transaminases and normalization of them with gluten-free diet and also liver changes in CD patients have been known since 1977 (4). Serum aminotransferase elevation can be seen in 15 to 55% of patients with untreated CD and CD can be found in up to 10% of patients with unexplained abnormal liver function tests (5). Due to autoimmune basis of both diseases, there are studies which investigate the relation between CD and autoimmune liver diseases recently (6).

Autoimmune hepatitis (AIH), primary biliary cirrhosis and primary sclerosing cholangitis are autoimmune liver disorders that may be associated with CD (6). Mirzaagha et al. investigated the prevalence of CD among autoimmune liver diseases and found that it was high in patients with AIH (7). Herein we aimed to present a patient with elevated liver enzymes who was diagnosed as CD and AIH in his follow-up.

## CASE REPORT

### Case presentation

26 year old male patient working as labourer in a private company was admitted to our hospital with complaint of weight loss. Patient's general physical examination was normal and in laboratory tests Aspartate aminotransferase (AST; 53 U/L) and Alanine aminotransferase (ALT; 98 U/L) were elevated. Alkaline phosphatase (ALP), Gamma-Glutamyltransferase (GGT), Lactate dehydrogenase (LDH) and albumin had been found in normal range. Although complete blood count (CBC) was normal he had low levels of serum iron and ferritine. Because of the high levels of serum transaminases detailed assessment was made; erythrocyte sedimentation rate (ESR) was 5 mm/h, C-reactive protein (CRP) was 3 mg/dL, and acute and chronic viral markers were negative. IgG, IgA and IgM levels were normal.

Anti Ro-52 and Anti-SLA/LP were detected 3 positive (Table 1).

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**Table 1.** Serum antibody levels of patient.

Serum antibodies	Laboratory results
ANA	Negative
Anti-dsDNA	Negative
AMA	Negative
AMA-M2	Negative
ASMA	Negative
ANCA	Negative
Anti-LKM-1	Negative
Anti-LC-1	Negative
<b>Anti-Ro-52</b>	<b>+++ (1/320)</b>
<b>Anti-SLA/LP</b>	<b>+++ (1/320)</b>

During follow up period of 6 months, elevation in liver enzymes were observed up to 2 times, that's why liver biopsy was planned. Patient was hospitalized and liver biopsy was done. Presence of portal inflammation, interface hepatitis, confluent necrosis around central vein, mononuclear inflammation of parenchyma, hydropic degeneration of hepatocytes, vacuolar changes and rosette formation were reported in pathological evaluation of liver biopsy specimen. These findings were in favor of AIH. As he had low serum ferritine and iron levels and unable to gain weight, CD was thought as co-morbidity. Anti-endomysium (EMA) and anti-gliadin (AGA) antibodies were detected as positive and atrophic appearance and scalloping of intestinal folds were seen in second part of duodenum by upper gastrointestinal endoscopy. Lymphocytic infiltration, blunting of villi and crypt hyperplasia were detected in microscopic evaluation of duodenum (Marsh 3a) and according to these pathological findings patient was diagnosed as CD.

Revised scoring system for the diagnosis of AIH of the patient was calculated 17 (Table 2) (8) and simplified scoring was 6 (Table 3) (9). Patient was asymptomatic and the disease was not progressed in course, therefore drug therapy was not started (10). Gluten free diet (GFD) was suggested to the patient and outpatient clinic follow up was planned. After 4 months, AST and ALT levels were decreased to normal range ferritine level was increased. EMA and AGA antibodies were detected as negative and also patient had gained 5 kg weight in this period. Because of reducing of his complaint patient left the diet after 1 year of regular follow-up. Aproximately 2 years later he re-admitted to our clinic with weight loss again. AST level was 56 U/L and ALT level was 70 U/L in his laboratory tests. Tissue transglutaminase (tTGA) IgA, EMA IgA and AGA IgA antibodies were also positive. GFD was started again and after 5 months liver transaminase were decreased to normal range (Figure 1). tTGA IgA and EMA IgA were still positive at the end of 5 months of follow-up but with low titers. Liver transaminases were in normal range and both antibodies were negative at the end of 1 year with GFD.

**Table 2.** Revised original scoring system for the diagnosis of autoimmune hepatitis of patient.

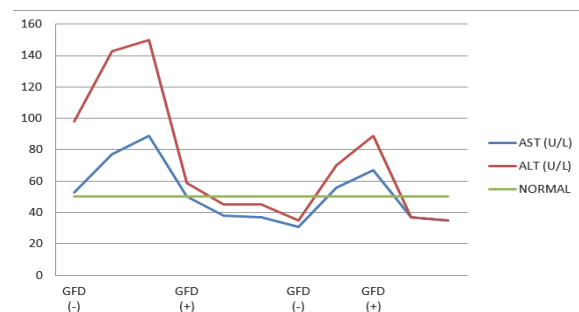
Category	Score
ALP/AST <1.5	+2
Anti-SLA (+)	+2
Viral markers (-)	+3
Drug usage (-)	+1
Alcohol consumption (-)	+2
Presence of another autoimmune disease (Celiac disease (+))	+2
Interface hepatitis	+3
Lymphocytic infiltration	+1
Rosette formation	+1
<b>TOTAL</b>	<b>17*</b>

*\*Definite diagnosis for AIH*

**Table 3.** Simplified scoring system for the diagnosis of autoimmune hepatitis of patient.

Category	Score
Anti-SLA (+)	+2
Typical histological features of autoimmune hepatitis	+2
Viral markers (-)	+2
<b>TOTAL</b>	<b>6*</b>

*\*Probable diagnosis for AIH*



**Figure 1.** Changes of AST-ALT levels of patients with gluten free diet compliance.

## DISCUSSION

The serum aminotransferases are the most sensitive laboratory markers used for the diagnosis of acute hepatic injury (11). All forms of liver injury may elevate aminotransferases and mild elevations ( $\leq 5$ -fold) of these tests are not spesific for a diagnosis. Patients with high serum aminotransferases are usually asymptomatic and detected during routine screening. All patient's medications including legal or illegal drugs and herbal medicine have to be queried firstly and detailed physical examination have to be performed for slightly elevated serum aminotransferases. If the etiology can not be found, more common and treatable causes of liver diseases should be investigated. Hepatic viruses including B and C, genetic disorders of liver such as hemochromatosis and Wilson disease, AIH and non-alcoholic fatty liver disease are the leading of this diseases. Finally, if the diagnosis is still unclear, the less

common liver diseases should be considered, such as  $\alpha$ 1-antitrypsin deficiency and CD (12).

Many organs or systems such as cardiac, neurological, bone, skin, liver, and endocrin may be involved in the course of CD (13-19). Although it is an intestinal autoimmune disease, as the diagnostic age of CD getting older, the disease presents itself with complaints that not directed to gastrointestinal tract. Volta et al. stated that 9% of patients with cryptogenic hypertransaminasaemia are affected by symptom-free CD (20). On the other hand, elevated levels of serum transaminases have been reported in about 40% of adult celiac patients (21). A meta-analysis of 11 studies has shown that, undetected celiac disease can be the potential cause of unexplained elevated serum aminotransferase levels in 3% to 4% of the cases (22). Increased intestinal permeability and alterations in gut microbiota may be assumed as the cause of hypertransaminasaemia in CD patients as the normalization of transaminases with GFD supports (23).

AIH and CD may be seen together because both diseases are associated with specific HLA class-II molecules (23). Volta et al. was one of the first to report the association of CD and AIH (type I and type II AIH) (24). Other several studies were established subsequently about this relationship (7). The effect of GFD on natural history of AIH is not clear but GFD is necessary to improve the symptoms of CD (25).

In our case, ANA, ASMA and anti-LKM were negative but anti- SLA/LP antibody was positive. Since pathological evaluation of liver biopsy was compatible with AIH and revised original scoring system was 17 and simplified scoring system was 6, in accordance with these patient was diagnosed as AIH. Thirteen percent of AIH in adults may not have ANA, ASMA, and anti-LKM-1 antibodies and it is called autoantibody-negative AIH. These patients may express pANCA and anti-SLA antibodies. Liver diseases such as Wilson disease, celiac-related liver disease, and drug-induced liver disease may closely resemble autoantibody-negative AIH and must be excluded by appropriate clinical history, laboratory tests, and histologic assessment (26). In our case, we diagnosed AIH and concomitant CD while investigating the etiology of progressively elevating liver transaminases. After precise diagnosis of both autoimmune diseases, we suggested GFD to patient, because drug therapy indication was not present for AIH. After GFD serum AST and ALT levels were decreased and antibodies for CD were negative in a four month period. In outpatient follow-up patient did not complied GFD diet exactly, so liver transaminase levels showed a fluctuating trend (Figure 1). which shows us that the compliance of GFD is substantial in the treatment of AIH as it is in the course of CD.

## CONCLUSION

Because of similar underlying mechanisms, different autoimmune diseases can occur in their course. Early diagnosis would improve patient's quality of life and may delay disease progression. So, clinicians should consider

that other autoimmune diseases may occur in CD patients and GFD may improve extra-intestinal manifestations of CD.

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