Original Article

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Prevalence of Celiac Disease in Children with Autoimmune Hepatitis and *vice versa*

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Abstract

Objective: Celiac disease is an autoimmune disorder in which the risk of autoimmune liver disease is high. Autoimmune hepatitis is a chronic and progressive entity and the risk of its being associated with other autoimmune disorders such as celiac disease is high also. The aim of this study was to determine the prevalence of celiac disease in patients with autoimmune hepatitis and vice versa.

Methods: In a cross-sectional study children with autoimmune hepatitis underwent serological screening and endoscopy for celiac disease. In patients with celiac disease, serum aminotransferases were measured and, if abnormal, autoantibodies related to autoimmune hepatitis were checked and needle liver biopsy was performed.

Findings: Of the 96 patients, 64 had autoimmune hepatitis and 32 celiac disease. Among patients with autoimmune hepatitis only three (4.7%) were compatible with celiac disease. In the group of patients with celiac disease, autoimmune hepatitis was confirmed in four (12.5%) cases. We consider important to state that 3.1% of this group had celiac hepatitis.

Conclusion: Autoimmune liver disease is sometimes associated with latent celiac disease. Serological screening for celiac disease should be routinely done in patients with abnormal serum aminotransferases, particularly those with chronic liver disease. On the other hand, celiac disease is often accompanied by other autoimmune diseases, including autoimmune hepatitis.

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Introduction

Celiac disease (CD) is an autoimmune disorder in pathogenesis of which environmental factors including gluten containing foods have a critical role, especially in genetically susceptible individuals[1]. It has gastrointestinal and extraintestinal symptoms and is characterized by chronic inflammation of the small intestine[1]. Its prevalence is 1%[1]. In these patients, the risk of autoimmune liver disease is especially high[2]. The most common form of liver abnormality associated with CD presents without symptoms but only a moderate increase in liver enzymes with mild lobular and portal inflammation, which is called "celiac hepatitis"[3]. The rare form presents with a marked increase in liver enzymes accompanied by severe and progressive liver injury. Liver biopsies usually show severe inflammation compatible with specific

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autoimmune changes, which is called "autoimmune hepatitis"[3]. Gluten-free diet (GFD) can correct mild but not severe involvement of liver[4]. In untreated celiac disease, the risk of malignancy is raised[5].

Autoimmune hepatitis (AIH) is a chronic and progressive hepatitis of immune etiology. In this disease, extrahepatic syndromes are more common[6]. The prevalence of AIH in Europe is 16.9 per 100,000[7] and in Iran 5.6% of childhood liver disease[8]. It has two main types: Type 1, the most common, is associated with a positive anti-nuclear antibody (ANA) and anti-smooth muscle antibody (ASMA), type 2, the less common. is associated with a positive anti liver–kidney microsome type 1 antibody (LKM_1)[9].One of the clues to identify an autoimmune hepatitis is the existence of other autoimmune disorders[6,9].

The aim of this study was to determine the prevalence of celiac disease in patients with autoimmune hepatitis or vice versa and whether routine screening for this disease is reasonable or not. If yes, when to screen?

Subjects and Methods

This was a prospective and cross-sectional study on patients with celiac disease or autoimmune hepatitis during the period of 1 year (2011-2012) in children between 6 months and 18 years old who were referred to the Gastroenterology clinic in Children's Medical Center. At first the need to check a second condition was explained to the patients and their parents. All patients included in the study, received a questionnaire for collection of clinical, biochemical, serological and histological data. In cases where a biopsy was required, written informed consent was obtained. The Ethical Committee of Tehran University of Medical Sciences approved this study.

Inclusion criteria:

1. Celiac disease with positive tissue trans-glutaminase antibodies (tTG-IgA) and specific histopathological findings in duodenal biopsy.
2. Autoimmune hepatitis diagnosed according to the grading system of the International Autoimmune Hepatitis Group Score (IAHGS)[10] and specific histopathological findings in biopsy of liver and positive auto antibodies.

Exclusion criteria:

1. In patients with CD: self-limiting enteritis, acute gastroenteritis, IBD and food intolerances.
2. In those with AIH, other known causes of chronic liver damage like viral, drug or toxin-related, as well as metabolic diseases (Wilson disease, alpha one antitrypsin deficiency and non-alcoholic steatohepatitis).

For all children with AIH, serologic screening tests of CD including tissue transglutaminase antibody (tTG-IgA) with ELISA method and serum IgA levels by Nephlometry method were performed. A tTG-IgA titer greater than 10 U/mL was interpreted as positive and serum IgA levels higher than 40 mg/dl were considered normal. Patients with positive or suspected serologic tests underwent upper gastrointestinal (GI) endoscopy by the same pediatric gastroenterologist using pediatric video endoscope model PENTAX EG 2490 K with outer shaft diameter 8 mm and length 105 cm. Four-piece biopsies were taken from the proximal small intestine (second part of duodenum) and analyzed by the pathology department of the Center. These pieces were stained by H&E and reported by the same pathologist using light microscopy, based on the MARSH classification[11].

In patients with CD, serum aminotransferases were measured. In cases of increased aminotrans-ferase levels less than 5 times the upper normal limit (UNL), gluten-free diet was started and the patient followed up for 6 months. If this diet had no effect on the aminotransferase levels, further evaluation was carried out. In patients with higher levels of aminotransferases (>5 times UNL) causes of chronic liver disease were assessed (including viral, drug or toxin-related, metabolic disorders and non-alcoholic steatohepatitis). Anti-smooth muscle antibody (ASMA), anti-nuclear antibody (ANA) and anti-liver–kidney microsome type 1 antibody (LKM_1) were measured by ELISA method. Antibody titers higher than 1/10 were considered as positive. Ultimately, the liver needle biopsy was done and samples sent to pathology. They were reported by same pathologist according to the International Hepatitis Group IAHGS criteria[10].

Fig. 1 depicts the steps followed in order to identify patients with both celiac disease and autoimmune hepatitis.

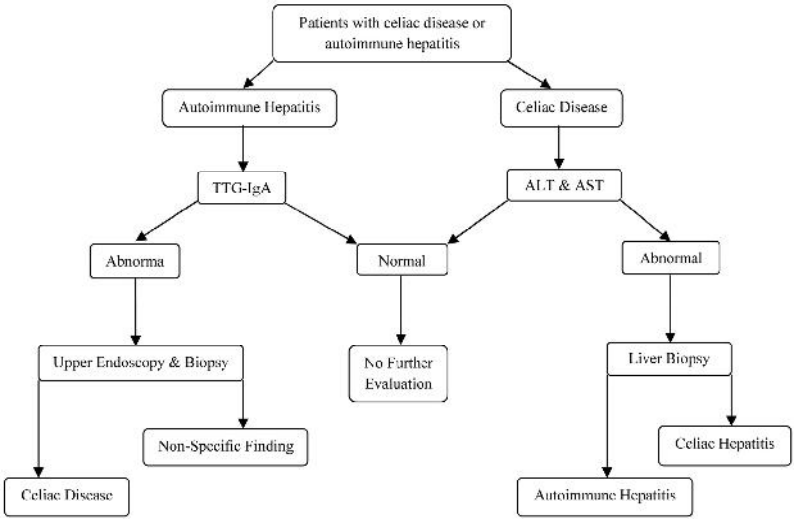

Fig. 1: Steps to follow patients with both celiac disease and autoimmune hepatitis
TTG: tissue transglutaminase antibody; AST: aspartate aminotransferase; ALT: alanine aminotransferase

Findings

In our study, 96 patients were enrolled. 64 had AIH and 32 CD. AIH group age ranged 2.5 to 14 (mean 8.39) years consisting of 56 (87.5%) females and 8 (12.5%) males. All patients had normal IgA serum levels. Three patients had elevated tTG antibody. (18.5, 21, 100, with upper limit of normal 10) and underwent upper GI endoscopy with biopsy of the upper small intestine (D2). None had severe bleeding, so there was no hindrance for endoscopy and biopsies; therefore no patient was excluded from the study. Histopathological findings were consistent with MARSH III (subtotal or total villous atrophy with crypt hyperplasia). (4.7%) These patients were diagnosed CD associated with AIH and GFD was given (in addition to the AIH treatments) (Table 1).

Eighteen out of 32 (56.3%) patients with CD were females and 14 (43.7%) males. Average age of these patients was 6.75 years. In all patients, serum aminotransferase levels (AST: aspartate aminotransferase and ALT: alanine amino-transferase) were measured. In five, these levels were increased (15.6%). Only one patient had an increase 3 fold above normal levels and four patients more than 5 fold. All these patients were girls. ASMA level in three (9.4%) girls was abnormal. ANA level was abnormal in only one (3.1%) patient. None of these patients had simultaneously abnormal ASMA and ANA. Overall 12.5% of subjects had positive serology for AIH. All patients were negative for antibodies LKM_1, in whom needle biopsy of the liver was performed. In four patients, IAHG tissue diagnostic criteria were fulfilled (interface hepatitis and bridging necrosis in all patients, with several degrees of fibrosis) (12.5%). All these cases had positive ANA or ASMA. In one (3.1%) child, there was mild inflammation. This patient did not have any autoantibodies (Table 2).

Discussion

According to our search, we can state that this study was launched for the first time in Iranian

Table 1: Incidence of celiac disease in AIH

AIH	n (%)	Type I	Type II	TTG-IgA	Intestinal biopsy
Male	8(12.5)	7(10.9)	1(1.55)	1(1.6)	Celiac (Marsh III)
Female	56(87.5)	55(86)	1(1.55)	2(3.1)	Celiac (Marsh III)
Total	64(100)	62(96.9)	2(3.1)	3(4.7)	Celiac (Marsh III)

AIH: autoimmune hepatitis; TTG: tissue transglutaminase antibody

Table 2: Incidence of AIH in celiac disease

Celiac Disease		AST & ALT	n (%)	ANA	ASMA	LKM_1	Liver biopsy
Male	14 (43.75)	≤ 3 fold	0	0	0	0	-
		≥ 5 fold	0	0	0	0	-
Female	18 (56.25)	≤ 3 fold	1(3.12)	0	0	0	Celiac hepatitis
		≥ 5 fold	4(12.5)	1(3.12)	3(9.37)	0	AIH
Total	32 (100)		5(15.6)	1(3.12)	3(9.37)	0	

AST: aspartate aminotransferase; ALT: alanine aminotransferase; ANA: antinuclear antibodies; SMA: smooth muscle antibodies; LKM_1: anti liver kidney microsome type 1antibodies

children. Our hospital is one of the national referral centers for chronic liver diseases but not for CD. Each center has its own statistics for CD and the patients are not referred to us. That is why the number of cases of AIH is higher. Most of the studies were conducted on adult population.

In our study, there were 64 children with AIH. Of whom 87.5% were females and 12.5% males. This ratio was consistent with gender prevalence of autoimmune hepatitis. 62 out of 64 patients had type 1 autoimmune hepatitis and two patients had type 2, which reconfirms type 1 being as the most common type[9]. Contrary to previous reports[12], in our study none of the patients had IgA deficiency. Three children of 64 had rising tTG-IgA and histopathological findings compatible with celiac disease (MARSH III). This shows that even an increase of less than two fold normal tTG levels in patients with autoimmune hepatitis is important.

In Finland, the prevalence of celiac disease was 1.5%[13] and in Sweden 3%[14]. In Iran, according to reports of Healthy Adult's Blood Donor Organization, the prevalence of celiac disease was about 0.6-1%[15,16]. In our study, the prevalence of celiac disease in autoimmune hepatitis was higher (4.7%) than in general population.

Emami[17] and Crete[18] reported a prevalence of positive tTG in patients with liver involvement of about 4.4% and a prevalence in confirmed celiac disease of 3.4%, but Akbari's[16] result was 0.96%. In other study by Volta et al[19] the prevalence of CD in AIH was reported in about 2.8%, which was less (4.7%) than our findings. Sifford reported this prevalence in 3-6%[20] and in another study[21] it was between 4-6.4%, similar to ours. However, recent studies indicate that both types I and II autoimmune hepatitis can be seen in celiac disease, but all our celiac patients were from type I and none of type II.

None of the patients with AIH had the classic symptoms (chronic diarrhea, steatorrhea, and abdominal distention) of CD. Therefore, the absence of classic symptoms of CD should not prevent screening of this disease in patients with AIH. On the other hand, one of the most common symptoms of extraintestinal CD is short stature; this disorder in patients with AIH is frequently seen due to chronic diseases and medications, thus in the patients with CD, medications like corticosteroids ought to be avoided because the main treatment of celiac hepatitis is a GFD.

We observed 32 patients with CD, 56.3% were female. Five (15.6%) patients had increased AST and ALT. In three girls, ASMA was detected, and only one patient had ANA. Because healthy children do not have autoantibodies in circulation, relatively low amounts are significant[9].

Lo Iacono et al reported 15-55%[22] increase of liver enzymes in patients with untreated CD. Our rate was also 15.6%. In a large group of children with CD, the prevalence of AIH was 1.1%[23]. Di Biase's was 2%. In our study, prevalence of AIH in patients with CD was 12.5%, much higher than previously recorded. In order to explain the difference, it should be considered that some patients with autoimmune hepatitis without autoantibodies are identifiable. These patients are considered as having cryptogenic autoimmune hepatitis and the evaluation of anti-SLA can be helpful[9,12]. Another reason for this finding could be that most of our patients had an illness for a long time and did not use GFD. Continued use of gluten in the patients may lead to increased intestinal permeability. This can increase the entering of cytotoxins and other inflammatory components to the portal circulation, which may have a role in liver inflammation[24]. On the other hand, the presence of autoantibodies (tTG) in circulation for a long-time can trigger autoimmune process in liver[25]. However, in order to obtain the actual prevalence of autoimmune hepatitis in

these patients further specimens are needed. Several studies reported isolated hypertransaminasemia elevation of 40%[26], which is much higher (3.1%) than our results. In our study, 3.1% of patients with CD had an increase of non-immune liver enzymes without serious liver damage (Celiac hepatitis) and 12.5% of them had AIH. In various studies, different values from 2 to 11.5% were reported[27]. However, a large Swedish study[28] reported 2-6 fold increased risk of liver disease in patients with celiac disease (in our study it was 4 fold) and 4-6 fold increased risk of CD in patients with chronic liver disease.

Most studies such as Ventura's[23] were focused on the efficacy of GFD in patients with CD and its ability to prevent progression of liver disease. The study by Cosnes[29] expressed a strong relationship between the GFD and reduction of the risk of autoimmune disease in future. Therefore, early onset of GFD improves gut damage and intestinal permeability. Also it may help prevent a process of immune inflammation secondary to contact by various antigens. Delay in the onset of this regime would have no effect as the immunity process has already started[26]. In patients with autoimmune liver disease, immunosuppressive therapy can improve intestinal mucosal lesions[30] leading to false negative results in celiac screen, resulting in delayed treatment and increasing the complications of CD.

Conclusion

Coexistence of autoimmune disease should be taken seriously. When an autoimmune disorder occurs, consideration should be given to the risk of other autoimmune diseases and ruled out. Our study showed that the prevalence of AIH in CD is very high (12.5%), as a result, all patients with CD should be evaluated for hepatitis, even if there is no clinical evidence. The prevalence of CD in AIH was also much higher (4.7%) than in general population and due to the many complications and risks of lifetime, it is suggested that all patients with AIH should be carefully evaluated for CD. Also a routine screening should be carried out regardless of the symptoms of each disease because most cases are asymptomatic and silent. It is advisable to perform more studies in a larger scale in future.

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Authors' Contribution

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Critical Revision of the Manuscript: M. Najafi, K. Eftekhari
All authors approved final version of the paper

Conflict of Interest: None

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