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Does chronic delta hepatitis increase risk of celiac disease?

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Abstract

Celiac disease is a small intestinal malabsorption syndrome whose importance remains underappreciated. This is underestimated by the fact that it remains under recognized in almost 90% of patients. Hepatitis D virus (HDV) infection is a serious health problem leading to cirrhosis and hepatocellular carcinoma. Furthermore, the impact of on the clinical picture in patients with chronic HDV infection, with regards to laboratory parameters is not clear. So, we examined this relationship using recent hospital-based data. We analyzed data from 50 delta hepatitis patients (mean age 52.5 ± 12.8 years; 30 male). 21 of them had cirrhosis. Both groups were screened for serum tissue transglutaminase antibodies and immunoglobulin A, and those antibody-positive were further investigated by intestinal biopsy. Histopathological examination was performed according to Marsh classification. Demographic features and laboratory data were compared between groups. There were six (28.5%) seropositivity of TTG IgG among patients with delta hepatitis related cirrhosis. No patient tested positive for TTG IgA in cirrhotic group whereas, there were no positive results for both TTG IgA and G among non-cirrhotic delta hepatitis group. In cirrhotic group, the rate of TTG IgG seropositivity was higher than those without cirrhosis (p=0.036). Seropositivity of TTG IgG was correlated with higher MELD scores (p<0.05). Higher rate of seropositivity of TTG IgG antibodies and CD among patients with chronic HDV-related cirrhosis may reflect a unique phenomenon that requires further investigation to determine underlying causative factors.

Keywords: Celiac disease, Chronic delta hepatitis, Turkey.

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Introduction

Hepatitis D Virus (HDV) is a small, defective hepatotropic RNA virus which requires Hepatitis B Virus (HBV) for replication. It has been showed that chronic HBV and HDV co-infection causes more severe liver damage than those with chronic HBV infection alone [1]. Highest HDV prevalence is seen in the Mediterranean basin, parts of Southern America and Eastern Europe [2,3]. Chronic Hepatitis D Virus (C-HDV) infection affects approximately 20% of individuals with HBV infection in the Eastern part of Turkey, ultimately leading to fibrosis, cirrhosis and hepatocellular carcinoma [4]. Celiac disease (CD) is a small intestinal malabsorption syndrome and is caused by hypersensitivity to gluten in subjects who carry HLA haplotypes HLA DQ2 and DQ8. This hypersensitivity reactions result in chronic inflammatory reaction in the small intestine and lead to a broad spectrum of symptoms and findings including chronic diarrhoea, failure to thrive, anemia, arthritis, osteopenia, elevated liver enzymes and lower albumin levels [5]. The prevalence of the CD in the population is estimated at about 1% worldwide [6,7] with significant regional differences, higher prevalence up to 6% in case autoimmune diseases coexist [8,9].

Moreover, CD may be more frequent than the number of diagnosed among subjects who live in rural areas of near East [10]. On the other hand, there is a close association between CD and autoimmune disorders, including type-1 diabetes mellitus and autoimmune thyroid disorder [11]. Patients with chronic HDV infection can be treated with an interferon alpha based therapy if severe liver cirrhosis has been excluded. Concomitant autoimmune disorders are also believed to hasten IFN-related side effects, but the role of CD is unclear [12]. There is a growing body of literature describing false seropositivity of CD markers such as TTG IgA and IgG in patients without CD [13]. However, frequency of CD which is also autoimmune disorder has not been investigated yet in patients with chronic HDV infection. Therefore, the main objective of this study was to examine the rate of CD among subjects with chronic HDV infection. The other aim of this

study was also to investigate laboratory parameters of the patients with CD in the setting of chronic HDV infection as well as HDV-related liver cirrhosis.

Materials and Methods

We analyzed data from adult delta hepatitis patients who admitted to our gastroenterology clinic from June 2013-2014. Baseline characteristics of the patients are seen in Table 1. There were 50 patients (mean age 52.5 ± 12.8 y; 30 male) with HDV of whom 21 (35%) had biopsy-proven cirrhosis. Cirrhotic patients were also classified according to their The Model for End-Stage Liver Disease (MELD) scores. Exclusion criteria included the prior liver transplantation, presence of hepatocellular carcinoma, chronic renal insufficiency, (creatinine level>2.0 mg per deciliter), selective IgA deficiency and prior diagnosis of CD. Data extraction was performed retrospectively. Demographics, laboratory data, MELD scores, ultrasonographic examination of the liver and tissue transglutaminase antibodies (TTG IgA and IgG) were examined among study population. Patients who tested positive for TTG antibodies also underwent upper gastrointestinal tract endoscopy with histopathological examination. All patients or their legally authorized representatives provided written informed consent. The study was approved by the ethics committees of Clinical investigations of the faculty of medicina of Yuzuncu Yıl University with the understanding that all data would be coded and patient anonymity was guaranteed.

Table 1. *Baseline characteristics of the patients.*

Parameters	Cirrhotic patients (n:52)	Non-Cirrhotic patients (n:44)
Age (y)	53.2	51.7
Brucella titers	97.6	30.0
White blood cells (103/μL)	6869	7329
Hemoglobin (gr/dl)	14.5	14.7
Platelet (103/microL)	122	200
Aspartate aminotransferase (units/L)	72	51
Alanine aminotransferase (units/L)	70	60
Albumin (g/dl)	3.7	3.9
Globulin (g/dl)	3.7	3.5
MELD	9.4	

Serologic studies

Results of the samples that have HBsAg reactive anti-HDV antibodies micro-ELISA (Enzyme-Linked Immuno Sorbent Assay) (Triturus ELISA) with Dia. Pro Diagnostic Bioprobes anti-HDV IgG, Italy) kits were determined. Sera from study patients were also analyzed for IgA, IgG, with ELISA using human recombinant tTG (AESKULİSA, Aesku. Diagnostic, Germany). Aeskulisa tTg-A and tTg-G are a solid phase enzyme immunoassay quantitative and qualitative detection of IgA-IgG antibodies against neo-epitopes of tTG in human serum. The assay employing human recombinant transglutaminase cross-linked with gliadin-specific peptides displays neo-epitopes of tTg which ensures a significantly increased sensitivity and specificity of the test. The assay is a tool for the diagnosis and monitoring of celiac diseases (gluten-sensitive enteropathy).

Statistical analysis

As descriptive statistics average, standard deviation, minimum, maximum values were used for continuous variables while number and percentage were used for categorical variables. Wilcoxon test was used to compare variables and the Pearson's chi-square and Fisher's exact test were used to compare categorical variables. Variables with normal distribution in the two groups were compared by t-test for independent samples comparison. In comparing the average group in terms of continuous variables were made one-way variance analysis. Pearson correlation coefficients were calculated to determine the relationship between these variables. Chi-square test was performed in determining the relationship between categorical variables and groups. Significance limit was taken as $P<0.05$ and duplex. Analyses were performed using SPSS 21 software.

Results

Table 1 provides demographics and clinical-pathological data for all the patients. At the time of evaluation, the mean MELD score was 11.3 ± 4.8, in cirrhotic group. On the other hand, there was no statistical difference between the groups in respect to age and gender ($p>0.05$). Also mean globulin levels were similar between two groups. Two patients (9.5%) tested positive for TTG IgA in cirrhotic group whereas, there was one positive result (3.4%) for TTG IgA among non-cirrhotic delta hepatitis group. There was no significant difference between cirrhotic and non-cirrhotic groups in terms of TTG IgA seropositivity ($p=0.37$).

There were three (14.3%) seropositivity of TTG IgG among patients with delta hepatitis related cirrhosis. No patients had positivity for TTG IgG in non-cirrhotic group. In cirrhotic group, the rate of TTG IgG seropositivity was higher than those without cirrhosis ($p=0.036$). In Pearson analysis, seropositivity of TTG IgG was also correlated with higher MELD scores ($p<0.05$). In further investigation, two (9.5%) cirrhotic patients had histopathologically confirmed CD according to Marsh classification (one had Marsh II and other had Mars IIIa disease). Furthermore, we also showed that patients tested positive for both TTG IgA and TTG IgG have also significantly lower levels of haemoglobin, albumin and calcium than those without TTG IgG.

Discussion

CHD is a progressive liver disease caused by a defective virus HDV which is a prevalent problem inside the Middle-East [10]. HDV prevalence in general Turkish population is 1.6%, but data in Turkey is limited. However, in Turkey, there are few nationally representative data on the contribution of HDV infection to cirrhosis. On the other hand, Eastern part of the country is still home to one of the world largest delta hepatitis populations. It is currently estimated that twenty percent of hepatitis B patients in the Eastern part of Turkey are complicated by HDV infection, corresponding to approximately 400.000 patients [12]. CHDV is also a major risk factor for the liver cirrhosis development. The current treatment of chronic HDV is subcutaneous injections of pegylated interferon every week for at least 48 weeks, if decompensated cirrhosis has been excluded [11].

Early detection of cirrhosis with non-invasive methods is traditionally considered to be component of diagnostic work-up. Early identification of cirrhosis is also important to obtain better outcomes and prolonged survival. Liver biopsy remains to be the gold standard in investigating the presence and severity of cirrhosis, but it has many risks including bleeding particularly in advanced stages of the cirrhosis [14]. CD is a wheat-related gluten sensitivity of proximal part of small intestine. CD has roots in both genetic and environmental factors. There is a close association between HLA haplotypes (HLA-DQ2 and DQ8) and CD. In the past, diarrhoea is predominated the clinical picture; today, an increasing association with other diseases and symptoms is detected [15]. The prevalence of CD in population-based studies has been reportedly estimated at about 1% worldwide, depending on the size of the population studied and the nature of the laboratory techniques performed for screening. Other hand, this is underscored by the fact that it remains unrecognized in as high as 90% of patients [16]. Even in Asia, especially in Turkey, where CD was long considered a rarity, recent surveys estimate a prevalence of about 1% [17]. Recently, there has been some literature published regarding association between false seropositivity of celiac antibodies and different diseases including febril illnesses and connective tissue disorders [18,19].

HCV and HDV viruses are one of the most important RNA viruses causing chronic hepatitis. In contrast to infections with DNA viruses both RNA viruses are strongly associated with autoimmune manifestations. A link between infection and autoimmunity is particularly well documented for the HCV infection. It has been also reported that endomysial antibodies have often produced during infection with chronic HCV, but it remains obscure whether they affect the treatment modalities and histological features of the disease [20-22]. It has been reported that non-organ-specific autoantibodies (antinuclear, anti-smooth muscle, anti-gastric parietal cell and anti-liver-kidney microsomal type 1) were detected in 22% of patients with C-HDV infection and did not correlate with histological severity [23]. On the other hand, autoantibodies directed against antigens of the endoplasmic reticulum (LKM-3) are also common in CHDV [24]. Anti-BCLA (Basal cell layer antibody) is also present in a variable proportion of patients with HDV infection. Despite its high specificity with HDV infection, its clinical importance remains to be documented [25]. Interestingly, the rate of anticardiolipin antibodies (ACAs) among patients with chronic HDV infections has been found as 13.3%. Although the data of this study revealed a statistically significant positive correlation between chronic HDV infection and anticardiolipin antibodies, the mechanism of this phenomenon is not well understood [26]. In cases with cryptogenic liver cirrhosis, CD has been diagnosed in 1-4%, the diagnosis is important because of some patients respond to gluten restriction within 6-12 months [27].

An increased prevalence of celiac disease was also observed among hepatitis B patient. It has been postulated that its coexistence may be due to triggering effect of hepatitis B virus on CD [28]. Additionally, patients with advanced stages of the liver diseases frequently have hypergammaglobulinemia particularly of the IgG class that might cause false positive results for IgG-related serological markers [29]. Currently, there is still no information in the English literature regarding the impact and rate of CD antibodies in patients with delta hepatitis. In the current study, the rate of TTG IgG seropositivity was high among HDV related cirrhotic patients overall (14.3%) especially in comparison to non-cirrhotic delta hepatitis patients, but even higher for those with higher MELD scores. In TTG IgA and IgG positive cirrhotic patients, lower levels of haemoglobin, albumin and calcium may be related to both higher MELD scores as well as underlying CD. An association of low socioeconomic status with CD has already been reported in many studies [30]. Although limited by small numbers, our results suggest the presence of CD, mainly related to the chronic HDV-related cirrhosis. This unique phenomenon may be due to residential areas of the patients where CD is prevalent. There were several limitations of this study. First, the number of patients in study and control groups was relatively low. Second, data does not reflect data from all regions.

Conclusion

Both seropositivity of TTG IgG and the rate of true celiac disease are extraordinarily high among delta hepatitis related cirrhosis, especially in patients with higher MELD scores. Targeted efforts using celiac seromarkers may increase the rate of early identification of advanced cirrhosis. Furthermore, celiac testing in high-risk populations can identify individuals in the earliest stages of infection. We believe that all patients with delta hepatitis related cirrhosis should be investigated for celiac disease, even in case if no symptoms indicate CD.

Ethics Approval

The study was approved by the ethics committees of Clinical investigations of the faculty of medicine of Yuzuncu Yil University.

References

1. Hughes SA, Wedemeyer H, Harrison PM. Hepatitis delta virus. Lancet 2011; 378: 73-85.
2. Sagnelli E, Stroffolini T, Ascione A, Chiaramonte M, Craxì A, Giusti G, Piccinino F. Decrease in HDV endemicity in Italy. J Hepatol 1997; 26: 20-24.
3. Rosina F, Conoscitore P, Cuppone R, Rocca G, Giuliani A, Cozzolongo R, Niro G, Smedile A, Saracco G, Andriulli A, Manghisi OG, Rizzetto M. Changing pattern of chronic hepatitis D in Southern Europe. Gastroenterology 1999; 117: 161-166.
4. Tukdogan MK, Bozkurt H, Uygan I, Tuncer I, Irmak H, Buzgan T, Akdeniz H. Chronic hepatitis delta virus infection in Van region of eastern Turkey. Turk J Gastroenterol 2005; 16: 17-20.
5. Green PH, Cellier C. Celiac disease. N Engl J Med 2007; 357: 1731-1743.
6. West J, Logan RFA, Hill PG, Lloyd A, Lewis S, Hubbard R. Seroprevalence, correlates, and characteristics of undetected coeliac disease in England. Gut 2003; 52: 960-965.
7. Rubio-Tapia A, Ludvigsson JF, Brantner TL, Murray JA, Everhart JE. The prevalence of celiac disease in the United States. Am J Gastroenterol 2012; 107: 1538-1544.
8. Güvenç S, Kaymakoglu S, Gürel N, Karsidag K, Demir K, Dinçer D, Kekik C, Salman S, Yilmaz T, Besisik F. The prevalence of manifest and latent celiac disease in type 1 diabetes mellitus. Turk J Gastroenterol 2002; 13: 103-107.
9. Guliter S, Yakaryilmaz F, Ozkurt Z, Ersoy R, Ucardag D, Caglayan O, Atasoy P. Prevalence of coeliac disease in patients with autoimmune thyroiditis in a Turkish population. World J Gastroenterol 2007; 13: 1599-1601.
10. Cummins AG, Roberts-Thomson IC. Prevalence of celiac disease in the Asia-Pacific region. J Gastroenterol Hepatol 2009; 24: 1347-1351.
11. Fasano A, Catassi C. Clinical practice. Celiac disease. N Engl J Med 2012; 367: 2419-2426.
12. Rizzetto M, Smedile A. Pegylated interferon therapy of chronic hepatitis D: in need of revision. Hepatology 2015; 61: 1109-1111.
13. Drastich P. Celiac disease markers in patients with liver diseases: A single center large scale screening study. World J Gastroenterol 2012; 18: 6255-6262.
14. Ginès P, Cárdenas A, Arroyo V, Rodés J. Management of cirrhosis and ascites. N Engl J Med. 2004; 350: 1646-1654.
15. Tovoli F, Masi C, Guidetti E, Negrini G, Paterini P, Bolondi L. Clinical and diagnostic aspects of gluten related disorders. World J Clin Cases 2015; 3: 275-284.
16. Kratzer W, Kibele M, Akinli A, Porzner M, Boehm BO, Koenig W, Oeztuerk S, Mason RA, Mao R, Haenle MH. Prevalence of celiac disease in Germany: a prospective follow-up study. World J Gastroenterol 2013; 19: 2612-2620.
17. Gursoy S, Guven K, Simsek T, Yurci A, Torun E, Koc N, Patiroglu TE, Ozbakir O, Yucesoy M. The prevalence of unrecognized adult celiac disease in Central Anatolia. J Clin Gastroenterol 2005; 39: 508-511.
18. De Leo L, Quaglia S, Ziberna F, Vatta S, Martelossi S, Maschio M, Not T. Serum anti-tissue transglutaminase antibodies detected during febrile illness may not be produced by the intestinal mucosa. J Pediatr 2015; 166: 761-763.
19. Rodríguez GR, Zazzetti F, da Representaçao SR, Lencina MV, Barreira JC, Álvarez KE. Serum anti endomysial and anti transglutaminase antibodies in patients with connective tissue diseases. Rev Med Chil 2014; 142: 1510-1516.
20. Obermayer-Straub P, Manns MP. Hepatitis C and D, retroviruses and autoimmune manifestations. J Autoimmun 2001; 16: 275-285.
21. Strassburg CP, Vogel A, Manns MP. Autoimmunity and hepatitis C. Autoimmun Rev 2003; 2: 322-331.
22. Marconcini ML, Fayad L, Shiozawa MB, Dantas-Correa EB, Lucca Schiavon Ld, Narciso-Schiavon JL. Autoantibody profile in individuals with chronic hepatitis C. Rev Soc Bras Med Trop 2013; 46: 147-153.
23. McFarlane BM, Bridger CB, Smith HM, Antonov KA, Naoumov N, Williams R, McFarlane IG. Autoimmune mechanisms in chronic hepatitis B and delta virus infections. Eur J Gastroenterol Hepatol 1995; 7: 615-621.
24. Philipp T, Obermayer-Straub P, Manns MP. Autoantibodies in hepatitis delta. Biomed Pharmacother 1995; 49: 344-349.
25. Vergani D, Mieli-Vergani G. Autoimmune manifestations in viral hepatitis. Semin Immunopathol 2013; 35: 73-85.
26. MeÅŸe S, Ozekinci T, Atmaca S, Arikan E, Akin D. Investigation of anticardiolipin antibodies in chronic hepatitis B infection together with total anti-delta positivity. Mikrobiyol Bul 2008; 42: 483-487.
27. Czaja AJ. Cryptogenic chronic hepatitis and its changing guise in adults. Dig Dis Sci 2011; 56: 3421-3438.
28. Nau AL, Fayad L, Lazzarotto C, Shiozawa MB, Dantas-Corrêa EB, Schiavon Lde L, Narciso-Schiavon JL. Prevalence and clinical features of celiac disease in patients with hepatitis B virus infection in Southern Brazil. Rev Soc Bras Med Trop 2013; 46: 397-402.
29. Gatselis NK, Zachou K, Norman GL, Tzellas G, Speletas M, Gabeta S, Germenis A, Koukoulis GK, Dalekos GN. IgA antibodies against deamidated gliadin peptides in patients with chronic liver diseases. Clin Chim Acta 2012; 413: 1683-1688.
30. Cummins AG, Roberts-Thomson IC. Prevalence of celiac disease in the Asia-Pacific region. J Gastroenterol Hepatol 2009; 24: 1347-1351.

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