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Research Article

How Often do we Find Celiac Hepatitis?

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Abstract

Aim: To determine the prevalence of patients with hepatic injury related to celiac disease.

Method: Retrospective analysis of patients' records from Hepatology Outpatient Clinic in the period of 18 months was done. Data regarding referral and final diagnosis as well as hepatic injury profile were analysed.

Results: There were 1207 exams performed in 684 patients, and only 446 of them with initial diagnosis suggesting liver disease. Elevated liver enzymes had 299/446 patients (67%), and only in 30% of them (89/299) proper screening for metabolic, viral, and autoimmune diseases was done. None of referred (0%) patients was screened for celiac disease. Finally, in 248 patients diagnosis of either viral hepatitis, NAFLD/NASH, ALD, haemochromatosis, autoimmune liver disease, Gilbert syndrome, toxic liver injury and even primary aceruloplasminemia, was established. In five patients celiac disease was already established, but additional liver disease was suspected and confirmed, but there were still 52 patients with no diagnosis. In 9 of those 52 patients (17%), celiac disease was diagnosed with positive tissue transglutaminase antibodies and confirmed with duodenal mucosa biopsy.

Conclusion: Our data suggest that the prevalence of celiac disease in adult population with hepatic injury is up to 17%. Celiac disease can be the sole cause of hepatic injury, meaning celiac hepatitis, but can also be combined with other autoimmune diseases of the liver as well as with steatohepatitis. High level of suspicion is necessary to recognize disease early, and that is the reason why serology testing for celiac disease should be positioned high in the algorithm of liver injury workup.

Keywords: *Celiac Disease; Celiac Hepatitis; Screening; Liver Injury Workup*

Abbreviations

CD: Celiac Disease; HLA: Human Leukocyte Antigens; Ttg: Tissue Transglutaminase; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; AILD: Autoimmune Liver Disease; PBC: Primary Biliary Cholangitis; PSC: Primary Sclerosing Cholangitis; GFD: Gluten Free Diet; NAFLD: Non- Alcoholic Fatty Liver Disease; NASH: Non-Alcoholic Steato-Hepatitis; GGT: Gamma Glutamyl Transferase; AP: Alkaline Phosphatase; ANA: Anti-Nuclear Antibody; ANCA: Anti-Neutrophil Cytoplasmic Antibodies; AMHA: Antimitochondrial Antibodies; SMA: Smooth Muscle Antibodies; SLA/LP: Anti-Soluble Liver Antigen/Liver-Pancreas Antibodies

Introduction

Celiac disease (CD) is a common disorder recently defined as multiple-organ autoimmune disease provoked by the ingestion of gluten from wheat, rye and barley. It can affect people in every age, at least 1% of Caucasian population, who are genetically predisposed [1,2].

Celiac patients (pts) have obligatory genetic changes as HLA-DQ2 and/or HLA-DQ8 haplotypes or some variations in other non-HLA genes [3-5]. Regarding this fact, DQ2/DQ8 testing is very useful in the diagnostic algorithm for exclusion of the diagnosis [1,6].

Clinical manifestations, in adult population, may range from a typical malabsorption syndrome to a silent disease with various, apparently unrelated symptoms, including unexplained liver enzyme elevation. The diagnosis of CD, especially early and prompt diagnosis in patients without evident, classic clinical manifestation, could represent a challenge [2]. A first-line test for all adult patients, guidelines suggest anti-tissue transglutaminase (anti-tTG) IgA, combined with total IgA [1,7-9]. This testing approach has high sensitivity and specificity (in absence of IgA deficiency) and has been recommended as the most efficient single test for screening of CD [10]. In the adult population cut-offs are not so clear as in paediatrics, and the differential diagnosis is much more heterogeneous so small bowel biopsy is obligatory to confirm diagnosis [11]. Duodenal biopsies must be taken when patients are on a gluten-containing diet [1,12].

In spite of the fact that gluten causes primarily enteropathy, the disease can present as a wide diversity of signs and symptoms. Celiac can have classic, nonclassical or asymptomatic disease. Nonclassical clinical signs and symptoms includes hepatic injury as one of the important extraintestinal manifestations of CD [13,14]. Celiac hepatitis, also addressed as "cryptogenic hepatitis" can be defined as isolated elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in the presence of active celiac disease, and no other reason for their elevation, as well as resolution of it upon introduction of strict gluten-free diet. According to the published data, the prevalence of elevated transaminases in patients with active celiac disease is from 10 - 60% [14-19]. There is also a variety of liver diseases that can be associated with or coexist with CD. Autoimmune liver diseases (AILD) can be associated with CD, and even though association is not so common it is well demonstrated with the prevalence of CD in autoimmune hepatitis (AIH) of 4 - 6%, primary biliary cholangitis (PBC) 1-7% and primary sclerosing cholangitis (PSC) 2 - 3% in adult population. It is known that liver injury in those patients is not driven only or dominantly by gluten but gluten free diet (GFD) does improve symptoms related to the CD and there are some data that GFD can be the reason of improving liver function in patients with liver failure due to AILD combined with CD [20].

Non-Alcoholic Fatty Liver Disease (NAFLD) which is becoming the leading cause of chronic liver disease, has reported prevalence of CD up to 14%, and that is rather coincidence than a true relationship, since both of the diseases have rather high prevalence in population. On the other hand, patients with established CD, have higher risk of developing NAFLD [20].

The treatment of CD is actually limited to the lifelong, strict gluten-free diet, but if the disease is detected later during the life we can expect complications. That is the reason to raise awareness about possibility of celiac hepatitis as a sole, manifestation of CD, as well as in combination with other autoimmune and metabolic diseases [7,21,22].

Patients/Materials and Methods

In order to determine the prevalence of patients with celiac hepatitis we have done retrospective analysis of patients' records from Hepatology Outpatient Clinic in University Hospital Centre Zagreb which serves as a tertiary referral centre for chronic liver diseases, in period of 18 months. Records of 1207 exams in 684 patients were analysed. Data regarding referral and final diagnosis as well as liver injury profile and the extent of workup done before referring to the tertiary centre, were analysed. Liver injury was classified as: mild (up to five times upper limit of normal), or severe (more than five times upper limit of normal). It was also classified as: predominantly cellular (elevation of AST and ALT), predominantly cholestatic (elevation of γ-glutamyl transferase (GGT) and alkaline phosphatase (AP) or mixed.

Patients determined as correctly screened for metabolic liver diseases were patients with findings of serum copper, ceruloplasmin, iron and ferritin levels. Serological markers for hepatitis B and C were considered as a proper screening for viral diseases, and serological markers of autoimmune diseases, meaning anti-nuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), antimitochondrial antibodies (AMHA), smooth muscle antibodies (SMA), anti-soluble liver antigen/liver-pancreas antibodies (SLA/LP) together with immunoelectrophoresis of serum proteins as a proper screening for autoimmune liver diseases.

Results

Out of 684 patients examined there were 313 male and 391 female patients, from 21 to 94 years old. Only 446 of 684 (65%) patients (pts) were referred to hepatologist with initial diagnosis suggesting liver disease. Elevated liver enzyme tests had 299/446 pts (67%), and only 30% of them (89/299 pts) had correct screening for metabolic, viral, and autoimmune diseases performed prior to referring to the tertiary centre. None (0%) of the referred pts was screened for celiac disease.

Finally, 53 of 299 pts with elevated liver enzyme tests were diagnosed with viral hepatitis, 109 with NAFLD/NASH (non-alcoholic fatty liver disease/non-alcoholic steatohepatitis), 30 with ALD (alcoholic liver disease), 15 with haemochromatosis, 21 with autoimmune liver disease (AIH or PBC), 6 with Gilbert syndrome, 7 with toxic liver injury, and one with primary aceruloplasminemia. In 5 pts celiac disease was previously established, but additional liver disease was diagnosed, in two of them NASH, in one AIH, and in two PBC. Both NASH patients were male, and other three patients were female.

There were still 52 pts with no diagnosis. In 9/52 pts (17%), CD was diagnosed with anti-tTg IgA and biopsy of duodenal mucosa. Among those patients there were 5 female and 4 male patients 36 to 55 years old. In 2 of 21 (9%) of patients with autoimmune diseases we found simultaneous celiac disease, both diseases not known before, and both pts had PBC and CD. Both patients were female, age 65 and 48. That is all together 11 pts with newly diagnosed celiac disease in a pool of 299 pts or 3% of all our patients with altered liver enzymes tests.

All patients with diagnosed isolated CD had mild, cellular liver injury. Patients with newly diagnosed combined PBC and CD had mixed liver injury with mild cellular component and severe cholestatic injury without elevation of serum bilirubin.

Patients with previously established CD, and additional liver injury had liver enzymes elevated according to the additional diagnosis: GGT and ALT were elevated in NASH; AST, ALT and IgG were elevated in AIH; GGT and AP were elevated in PBC. All of the patients with previously established CD were on strict gluten-free diet. Patients with previously diagnosed CD and additional diagnosis of AIH and PBC didn't' have normalization of liver enzymes in spite of strict gluten free diet, until correctly treated with corticosteroids and ursodeoxycholic acid, respectively. Strict gluten-free diet was continued. In two patients with NASH/CD we introduced strict dietary regime with recommendation of weight loss in range of 7 - 10%. Gluten-free diet was continued.

Discussion

Although celiac disease is known from ancient Greece, knowledge of the disease has undergone extensive reviews in recent years [23-25]. First, until the end of the last century, celiac disease was considered to be exclusively a disease of children and that the need for further gluten-free diet wasn't recommended by the recovery of the mucosa. The discovery of sensitive serological tests that have proven the existence of the disease in the adult population revised the definition of diagnosis into a chronic, incurable disease that can occur at any age [1,7]. Second, adults have been found to have only in a minority of cases a classic picture of malabsorption, chronic diarrhea, steatorrhea, sideropenic anemia, and weight loss. In the adult population, patients may have also non-classical symptoms - nonspecific abdominal difficulties without malabsorption (dyspepsia, early satiety, bloating, abdominal pain, constipation) or extraintestinal symptoms. Among the possible many extraintestinal symptoms (migraine, skin changes, peripheral neuropathy, infertility, miscarriages, late

menarche, early menopause, dental enamel defects, depression, anxiety) is a hepatic injury [1,3,7,19,26].

Celiac related liver injury in paediatric and adult population has a rather high prevalence [27-30]. According to our data, in our cohort of pts, the prevalence of celiac hepatitis was 17%, the definition of celiac hepatitis being: isolated elevation of ALT and AST in the presence of active celiac disease, and no other reason for their elevation, as well as resolution of it upon introduction of strict gluten-free diet. If we look at the whole cohort of the patients with elevated liver enzymes, 3% of them will have celiac disease which should be a reason to think about it every time we evaluate a patient with elevated liver enzymes. Contrary to this fact, the awareness of the celiac disease in routine clinical practice obviously doesn't exist or it is very low. According to our data we conclude that celiac disease is not recognized as a possible cause of liver damage outside of tertiary centres. No one of the patients send to us for evaluation of elevated liver enzymes, was screened for celiac disease. We also encountered some other problems. First one is that a large proportion of patients, 35% in our cohort, were send to hepatologist with no evident reason for it, and a second one is that just a minor proportion of patients, 30% in our cohort, got an adequate screening for liver diseases before being sent to a tertiary centre. According to those data, a large amount of work should be done to increase an awareness of the existence of celiac-related liver injury. Celiac hepatitis, can be the sole manifestation of CD in adult population, furthermore it is the fairly common liver manifestation of CD [19]. Hypertransaminasaemia is usually mild, with values greater than 5-time upper limit of normal seen in minority of patients. Celiac hepatitis is usually clinically silent but left untreated can lead to chronic hepatitis with consequent liver cirrhosis and rarely end stage liver disease. Very rarely, hepatic injury can lead to liver failure [31]. There is no pathognomonic pathohistological finding for celiac hepatitis. Most often it is described as non-specific reactive hepatitis, but it is not unusual to find normal liver architecture as well as advanced fibrosis or cirrhosis. Alterations of the bile ducts are not present. The time needed for resolution of hypertransaminasaemia after introduction of strict gluten-free diet, usually does not exceed 12 months, which is also the time needed in most patients for complete intestinal mucosa restoration. That implicates that gluten intake drives the pathogenesis of celiac hepatitis [19,32]. IgA antibodies targeted against tTg, have been found in liver biopsy specimens from patients having an active CD and elevated liver enzymes. Vitamin D deficiency is commonly found in patients with active celiac disease, and knowing of its anti-inflammatory effect on immune cells, it could also contribute to proinflammatory state in the liver [32]. In our cohort of patients, since we did retrospective analysis, there was not sufficient data about Vitamin D deficiency, but it certainly should be investigated in al CD patients as well as in celiac-related hepatitis.

As we mentioned earlier, CD can also be combined with other autoimmune liver diseases (AILD). In our cohort three patients previously known to have CD, were found to have autoimmune liver disease, one AIH and two PBC. We also found two patients with newly simultaneously diagnosed CD and PBC. These associations found in our cohort were previously described in the literature but the mechanisms responsible for association of CD and AILD have not yet been clarified. It is likely that they share genetic predisposition to autoimmunity, but epigenetics, microbiota, and intestinal barrier dysfunction have to be considered as potential modulating factors [32].

Although NAFLD has reported prevalence of CD up to 14%, we have found only two patients in our cohort with developed NAFLD and previously known CD, on a strict gluten-free diet [32].

There are two main concerns in patients with combined NAFLD and CD, first one being risk of delayed diagnosis of CD in patients with established NAFLD. In situations when there are no other signs of metabolic syndrome in patients with NAFLD, they should early in the course of the disease be screened for CD. It does not mean that patients with developed metabolic syndrome, including NAFLD, cannot also have CD, and if there is hypertransaminasaemia present, they should also be screened.

Conclusion

In conclusion, several points on the topic of hepatic injury in CED should be emphasized.

First, a rather often simultaneous presentation of CD with numerous other liver diseases should be a trigger to implement screening for CD into a routine workup of liver lesion [1,7,8,9,22]. In AILD screening should be done before starting of immunosuppressive therapy and in end stage liver disease before transplantation. Screening should also be done in all cases of unexplained hypertransaminasaemia, chronic hepatitis or cryptogenic cirrhosis, as well as in patients with NAFLD especially without metabolic syndrome.

Second, celiac disease, as well as celiac related hepatitis should be recognized as early as possible to prevent further damage to the organs. Regarding that, celiac serology testing should be done as a part of liver injury work-up. Strict GFD should be started in all cases of established celiac hepatic injury and lifelong monitoring of patients is required to achieve the best outcome [33].

Third, the pathogenesis of hepatic injury in CD has been unclear for years, but recently the solution seems to be insight. New data on disturbances in gut-liver axis, demonstrated in impaired intestinal barrier, dysbiosis and changed intestinal microbiome with bacterial antigens dislocation, inhibition of liver tTg2, vitamin D deficiency, and mitochondrial dysfunction due to malnutrition, start to elucidate a complex nature of relationship between liver lesion and CD [32,34,35]. The common genetic risk and increased intestinal permeability could be the most important factors in the pathogenesis of hepatic injury in CD [19,32].

Bibliography

1. Bai JC and Ciacci C. "WGO Global Guidelines. Celiac Disease". *Journal of Clinical Gastroenterology* 51.9 (2017): 755-768.

2. Tack GJ., *et al*. "The spectrum of celiac disease: epidemiology, clinical aspects and treatment". *Nature Reviews Gastroenterology and Hepatology* 7.4 (2010): 204-213.

3. Lauret E and Rodrigo L. "Celiac disease and autoimmune-associated conditions". *BioMed Research International* (2013): 127-589.

4. Van Belzen MJ., *et al*. "Defining the contribution of the HLA region to cisDQ2-positive coeliac disease patients". *Genes and Immunity* 5 (2004): 215-220.

5. Karell K., *et al*. "HLA types in celiac disease patients not carrying the DQA1*05-DQB1*02 (DQ2) heterodimer: results from the European Genetics Cluster on Celiac Disease". *Human Immunology* 64 (2003): 469-477.

6. Rostami-Nejad M., *et al*. "Allele and haplotype frequencies for HLA-DQ in Iranian celiac disease patients". *World Journal of Gastroenterology* 20.20 (2014): 6302-6308.

7. Al-Toma A., *et al*. "European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders". *United European Gastroenterology Journal* 7.5 (2019): 583-613.

8. Ludvigsson JF., *et al*. "Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology". *Gut* 63.8 (2014): 1210-1228.

9. Rubio-Tapia A., *et al*. "American College of Gastroenterology. ACG Clinical Guidelines: Diagnosis and Management of Celiac Disease". *The American Journal of Gastroenterology* 108.5 (2013): 656-676.

10. Leffler DA and Schuppan D. "Update on serologic testing in celiac disease". *The American Journal of Gastroenterology* 105.12 (2010): 2520-2524.

11. Werkstetter KJ., *et al*. "Accuracy in diagnosis of celiac disease without biopsies in clinical practice". *Gastroenterology* 153.4 (2017): 924-935.

12. Leffler D., *et al*. "Kinetics of the histological, serological and symptomatic responses to gluten challenge in adults with coeliac disease". *Gut* 62.7 (2013): 996-1004.

13. Ludvigsson JF., *et al*. "The Oslo definitions for coeliac disease and related terms". *Gut* 62.1 (2013): 43-52.

14. Sainsbury A., *et al*. "Meta-analysis: coeliac disease and hypertransaminasaemia". *Alimentary Pharmacology and Therapeutics* 34.1 (2011): 33-40.

15. Hagander B., *et al*. "Hepatic injury in adult coeliac disease". *Lancet* 2.8032 (1977): 270-272.

16. Bardella MT., *et al*. "Prevalence of hypertransaminasemia in adult celiac patients and effect of gluten-free diet". *Hepatology* 22.3 (1995): 833-836.

17. Volta U., *et al*. "Coeliac disease hidden by cryptogenic hypertransaminasaemia". *Lancet* 352.9121 (1998): 26-29.

18. Ludvigsson JF., *et al*. "Celiac disease and risk of liver disease: a general population-based study". *Clinical Gastroenterology and Hepatology* 5.1 (2007): 63-69.

19. Rubio-Tapia A and Murray JA. "The liver and Celiac Disease". *Clinical Liver Disease* 23.2 (2019): 167-176.

20. Marciano F., *et al*. "Celiac disease-related hepatic injury: Insights into associated conditions and underlying pathomechanisms". *Digestive and Liver Disease* 48.2 (2016): 112-119.

21. Narciso-Schiavon JL and Schiavon LL. "To screen or not to screen? Celiac antibodies in liver diseases". *World Journal of Gastroenterology* 23.5 (2017): 776-791.

22. Catassi C and Fasano A. "Coeliac disease. The debate on coeliac disease screening - are we there yet?" *Nature Reviews Gastroenterology and Hepatology* 11.8 (2014): 457-458.

23. Dowd B and Walker-Smith J. "Samuel Gee, Aretaeus, and the Coeliac Affection". *British Medical Journal* 2 (1974): 45-47.

24. Čuković-Čavka S., *et al*. *Medicus* 21.2 (2012): 179-186.

25. Farrell RJ and Kelly CP. "Celiac sprue". *The New England Journal of Medicine* 346.3 (2002): 180-188.

26. Santonicola A., *et al*. "From menarche to menopause: the fertile life span of celiac women". *Menopause* 18.10 (2011): 1125-1130.

27. Aarela L., *et al*. "Prevalence and associated factors of abnormal liver values in children with celiac disease". *Digestive and Liver Disease* 48 (2016): 1023-1029.

28. Anania C., *et al*. "Liver involvement in pediatric celiac disease". *World Journal of Gastroenterology* 21 (2015): 5813-5822.

29. Lee GJ., *et al*. "Hypertransaminasemia in newly diagnosed pediatric patients with celiac disease". *Journal of Pediatric Gastroenterology and Nutrition* 63 (2016): 340-343.

30. Korpimäki S., *et al*. "Gluten-sensitive hypertransaminasemia in celiac disease: an infrequent and often subclinical finding". *The American Journal of Gastroenterology* 106.9 (2011): 1689-1696.

31. Kaukinen K., *et al*. "Celiac disease in patients with severe liver disease: gluten-free diet may reverse hepatic failure". *Gastroenterology* 122 (2002): 881-888.

32. Hoffmanová I., *et al*. "Review Celiac Disease and Liver Disorders: From Putative Pathogenesis to Clinical Implications". *Nutrients* 10 (2018): 892.

33. Husby S and Bai JC. "Follow-up of Celiac Disease". *Gastroenterology Clinics of North America* 48.1 (2019): 127-136.

34. Hagander B., *et al*. "Hepatic injury in adult coeliac disease". *Lancet* 2 (1977): 270-272.

35. Koning F., *et al*. "Pathomechanisms in celiac disease. Best practice and research". *Clinical Gastroenterology* 19.3 (2005): 373-387.

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