

Too Few Studies Provided a Link between Viral Infections and Celiac Disease

Iulian Diaconescu^{1,*}, Giulia Alexandru¹, Rahela Carpa¹, Iulia Lupan², Corina Crisan³,
Lucia Sur⁴, Genel Sur⁵, Anamaria Girbovan⁶

¹Department of Microbiology, Babes Bolyai University, Cluj-Napoca, Romania

²Department of Molecular Biology, Babes Bolyai University, Cluj-Napoca, Romania

³Emergency Hospital for Children, Cluj-Napoca, Romania

⁴Department of Pediatrics I, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

⁵Department of Pediatrics II, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

⁶Department of Immunology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

*Corresponding author: mac_master_02@yahoo.com

Abstract *Introduction.* Celiac disease has a prevalence of 1% of the global population and it is increasing every year. Viral infections such as hepatitis C and hepatitis B are the most common liver diseases and studies show that may be a link between them and celiac disease. Recent studies show attempts to find a link between viral infections and celiac disease. We focused our study on the association between viral infections and celiac disease. *Material and Method.* We studied 63 articles from the Pub Med Database that revealed a possible connection between viral infections and celiac disease. *Results.* Since it is more frequent, hepatitis C is associated with the development of celiac disease, but celiac disease is not the autoimmune manifestation of hepatitis C. Patients with celiac disease have a significantly decreased response to hepatitis B vaccine. Other viruses that are associated with celiac disease are: rotavirus, adenovirus, enterovirus and Epstein-Barr virus. *Conclusions.* The serological screening for celiac disease at hepatitis C patients, after starting treatment with interferon, is necessary. Also, it is justified the serological screening for celiac disease among adults infected with hepatitis B. Further studies are still needed to show the possible association of viral infections in the pathogenesis of celiac disease.

Keywords: celiac disease, viral infection, possible connection

Cite This Article: Iulian Diaconescu, Giulia Alexandru, Rahela Carpa, Iulia Lupan, Corina Crisan, Lucia Sur, Genel Sur, and Anamaria Girbovan, "Too Few Studies Provided a Link between Viral Infections and Celiac Disease." *International Journal of Celiac Disease*, vol. 4, no. 4 (2016): 135-137. doi: 10.12691/ijcd-4-4-9.

1. Introduction

Anti-tissue transglutaminase antibodies (tTG) may occur during infections with hepatitis [1]. Environmental factors may also be involved in the pathogenesis of celiac disease (CD) [2]. The major pathogenic factors can be categorized into environmental effects and genetic variations. According to some studies, mostly are caused by hepatitis B virus or hepatitis C virus (3). Therefore, it is also important to identify the cellular reactions as response to the environmental factors that are capable of inducing an immune response associated with human leukocyte antigen (HLA) [4,5]. Our goal was to make a theoretical study of literature to find out the current state of knowledge about the possible association of CD with viral infections.

2. Materials and Methods

We used the keywords „celiac disease” and “viral infections” in the PubMed database. We found 63 articles, of which we studied just those articles that revealed a possible connection between viral infections and CD.

3. Results

3.1. Celiac Disease and Viral Hepatitis C

CD was associated with viral hepatitis C (HCV) and with chronic autoimmune liver disease. Given the fact that HCV was more frequent than autoimmune liver diseases, HCV seems to be the most common liver disease associated with the development of CD [6].

CD is not an autoimmune manifestation of HCV. That is why some researchers did not recommend screening for CD in patients with HCV [7]. Other researchers have argued that silent CD activation occurs during treatment with interferon in patients with HCV and CD should be suspected [8]. The prevalence of CD in patients with positive HCV was 0% (95% confidence interval: 0-0.59%); the IgA antiendomysium antibodies (EMA) were positive for 0.16% of patients, but histopathological examinations of intestinal biopsies were negative [9]. It was proposed that the serological screening of CD should be performed before and after starting treatment with interferon [10]. Later, a series of four CD patients with HCV associated have been described. It was showed that HCV infection

and CD may occur together. The conclusion was that chronic HCV and CD are not causally related [11].

Inflammatory non-intestinal diseases can trigger intolerance to gluten at sensitive people and HCV was considered as a suitable candidate. Interferon therapy could accelerate the symptoms in patients with silent CD. Symptoms that may occur are diarrhea, anemia, weight loss during therapy with interferon and positive tTG. As such, serology for CD should be considered in patients who develop diarrhea and / or weight loss during therapy with interferon [12].

3.2. Celiac Disease and Viral Hepatitis B

Some researchers have postulated that patients with CD may have a significant predisposition for lack of response to viral hepatitis B (HBV) vaccine. Patients with CD may have failed to induce humoral immune response necessary for long-term development of immunity; however, the responsible mechanism is still uncertain [13]. One of the theories claims that there is a relationship between the lack of response to HBV vaccine and certain genotypes of HLA. The response to HBV vaccine in children who have CD and gluten-free diet was not different from a healthy population [14]. An association between CD and HBV was not found in the pediatric population, however, the researchers acknowledged that further studies are needed in larger populations [15]. Some studies have focused on the possible pathogenic causes for no response at HBV vaccine in patients with CD [16]. Previous studies have suggested that vaccines for HBV may be less immunogenic in CD patients [17]. Recent studies showed that unprotected antibodies responses occurred more often in CD patients than in the unaffected population [18]. Other studies showed an increased prevalence of CD among patients with HBV. These patients were symptomatic and had significant changes in laboratory tests [19].

Despite major advances over the past decades, future studies are still needed to define the prevalence of CD in different etiologies of liver diseases and to prove any alleged association [20].

3.3. Celiac Disease and Rotavirus Viral Infection

Some prospective studies have shown that a high frequency of rotavirus infections can increase the risk of childhood CD in genetically predisposed people [21]. Gene-array analysis revealed that VP7 anti-rotavirus purified antibody modulates genes that are involved in modulating apoptosis, inflammation and alterations in the integrity of the epithelial barrier in the intestinal epithelial cells, resulting in all the typical characteristics of CD [22]. It was rumored the hypothesis about the involvement of rotavirus in triggering CD through molecular mimicry between human protein transglutaminase and dodecapeptide from VP7 protein of rotavirus, but current studies have shown that children with CD have immune reactivity to rotavirus [23].

3.4. Other Possible Viral Infections Associated with Celiac Disease

Serological IgA anti-adenovirus antibodies were detected in children with CD being in close relationship

with CD regression [24]. Enterovirus infection was the first viral infection reported to be associated with CD. Some studies have shown that enterovirus infection during pregnancy was associated with CD development during childhood. Among the mothers whose children developed CD, 4% had IgA EMA, which may show a silent CD [25]. Respiratory syncytial virus infection was observed in children under two years diagnosed with CD before hospital admission [26]. Epstein-Barr virus has been detected in inflammatory cells and enterocytes of patients with refractory CD. Further studies are necessary to find if infection with Epstein-Barr virus contributes to the pathogenesis of refractory CD [27].

4. Conclusions

The serological screening of CD at HCV patients, after starting treatment with interferon, is necessary. Also, it is justified the serologic screening for CD among adults infected with HBV. Other viruses like rotavirus, adenovirus, enterovirus and Epstein-Barr virus could be associated with CD but few studies have reported the association of viral infections with CD.

Acknowledgements

Anamaria Girbovan received a grant from the University of Medicine and Pharmacy "Iuliu Hațieganu" Cluj-Napoca 2016, project no. 4995/21/08.03.2016.

References

- [1] Sarmiento L, Galvan JA, Cabrera-Rode E, Aira L, Correa C, Sariego S, Fonseca M, Cubas-Dueñas I, Hung LH, Resik S, Cilio, CM. Type 1 diabetes associated and tissue transglutaminase autoantibodies in patients without type 1 diabetes and coeliac disease with confirmed viral infections. *J Med Virol* 2012; 84: 1049-1053.
- [2] Capriati T, Francavilla R, Castellana S, Ferretti F, Diamanti A. Impact of the birth's season on the development of celiac disease in Italy. *Eur J Pediatr* 2015; 174: 1657-1663.
- [3] Zhu H, Wu J, Shen X. Genome-wide association study: new genetic insights into HBV/HCV-related hepatocellular carcinoma genomes. *Scand J Gastroenterol* 2016; 31: 1-7.
- [4] Lernmark A. Environmental factors in the etiology of type 1 diabetes, celiac disease, and narcolepsy. *Pediatr Diabetes* 2016; 17: 65-72.
- [5] Samasca G, Sur G, Lupan I. Current trends and investigative developments in celiac disease. *Immunol Invest* 2013; 42: 273-284.
- [6] Fine KD, Ogunji F, Saloum Y, Beharry S, Crippin J, Weinstein J. Celiac sprue: another autoimmune syndrome associated with hepatitis C. *Am J Gastroenterol* 2001; 96: 138-145.
- [7] Vivas S, Ruiz de Morales JM, Martínez J, González MC, Martín S, Martín J, Cechini C, Olcoz JL. Human recombinant anti-transglutaminase antibody testing is useful in the diagnosis of silent coeliac disease in a selected group of at-risk patients. *Eur J Gastroenterol Hepatol* 2003; 15: 479-483.
- [8] Durante-Mangoni E, Iardino P, Resse M, Cesaro G, Sica A, Farzati B, Ruggiero G, Adinolfi LE. Silent celiac disease in chronic hepatitis C: impact of interferon treatment on the disease onset and clinical outcome. *J Clin Gastroenterol* 2004; 38: 901-905.
- [9] Thevenot T, Denis J, Jouannaud V, Monnet E, Renou C, Labadie H, Abdelli N, Nguyen-Khac E, Dumouchel B, Bresson-Hadni S, Chousterman M, Di Martino V, Cadranet JF. Coeliac disease in chronic hepatitis C: a French multicentre prospective study. *Aliment Pharmacol Ther* 2007; 26: 1209-1216.

- [10] Samaşca G, Burac L, Farcău D, Dejica D. Celiac disease screening in chronic viral hepatitis C. *Ro J Pediatr* 2010; 9: 49-50.
- [11] Garg A, Reddy C, Duseja A, Chawla Y, Dhiman RK. Association between Celiac Disease and Chronic Hepatitis C Virus Infection. *J Clin Exp Hepatol* 2011; 1: 41-44.
- [12] Casella G, Viganò D, Romano Settanni C, Morelli O, Villanacci V, Baldini V, Bassotti G. Association between celiac disease and chronic hepatitis C. *Gastroenterol Hepatol Bed Bench* 2016; 9: 153-157.
- [13] Noh KW, Poland GA, Murray JA. Hepatitis B vaccine nonresponse and celiac disease. *Am J Gastroenterol* 2003; 98: 2289-2292.
- [14] Ertem D, Gonen I, Tanidir C, Ugras M, Yildiz A, Pehlivanoğlu E, Eksioğlu-Demiralp E. The response to hepatitis B vaccine: does it differ in celiac disease? *Eur J Gastroenterol Hepatol* 2010; 22: 787-793.
- [15] Leonardi S, La Rosa M. Are hepatitis B virus and celiac disease linked? *Hepat Mon* 2010; 10: 173-175.
- [16] Vitaliti G, Praticò AD, Cimino C, Di Dio G, Lionetti E, La Rosa M, Leonardi S. Hepatitis B vaccine in celiac disease: yesterday, today and tomorrow. *World J Gastroenterol* 2013; 19: 838-845.
- [17] Heshin-Bekenstein M, Turner D, Shamir R, Bar-Meir M, Dagan R, Zevit N, Silbermintz A. Hepatitis B Virus Revaccination With Standard Versus Pre-S Vaccine in Previously Immunized Patients With Celiac Disease. *J Pediatr Gastroenterol Nutr* 2015; 61: 400-403.
- [18] Opri R, Veneri D, Mengoli C, Zaroni G. Immune response to Hepatitis B vaccine in patients with celiac disease: A systematic review and meta-analysis. *Hum Vaccin Immunother* 2015; 11: 2800-2805.
- [19] Nau AL, Fayad L, Lazzarotto C, Shiozawa MB, Dantas-Corrêa EB, Schiavon L de 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.
- [20] Narciso-Schiavon JL, Schiavon LL. Is screening for Celiac Disease Needed in Patients with Liver Disease? *International Journal of Celiac Disease* 2015; 3: 91-94.
- [21] Stene LC, Honeyman MC, Hoffenberg EJ, Haas JE, Sokol RJ, Emery L, Taki I, Norris JM, Erlich HA, Eisenbarth GS, Rewers M. Rotavirus infection frequency and risk of celiac disease autoimmunity in early childhood: a longitudinal study. *Am J Gastroenterol* 2006; 101: 2333-2340.
- [22] Dolcino M, Zaroni G, Bason C, Tinazzi E, Boccola E, Valletta E, Contreas G, Lunardi C, Puccetti A. A subset of anti-rotavirus antibodies directed against the viral protein VP7 predicts the onset of celiac disease and induces typical features of the disease in the intestinal epithelial cell line T84. *Immunol Res* 2013; 56: 465-476.
- [23] Zibera F, De Lorenzo G, Schiavon V, Arnoldi F, Quaglia S, De Leo L, Vatta S, Martellosi S, Burrone OR, Ventura A, Not T. Lack of evidence of rotavirus-dependent molecular mimicry as a trigger of coeliac disease. *Clin Exp Immunol* 2016.
- [24] Samaşca G, Pîrvan A, Miu N, Andreica M, Cristea V, Dejica D. Adenoviruses in celiac disease in children. *Ro J Infect Dis* 2014; 14: 5-9.
- [25] Carlsson AK, Lindberg BA, Bredberg AC, Hyöty H, Ivarsson SA. Enterovirus infection during pregnancy is not a risk factor for celiac disease in the offspring. *J Pediatr Gastroenterol Nutr* 2002; 35: 649-652.
- [26] Tjernberg AR, Ludvigsson JF. Children with celiac disease are more likely to have attended hospital for prior respiratory syncytial virus infection. *Dig Dis Sci* 2014; 59: 1502-1508.
- [27] Perfetti V, Baldanti F, Lenti MV, Vanoli A, Biagi F, Gatti M, Riboni R, Dallera E, Paulli M, Pedrazzoli P, Corazza GR. Detection of Active Epstein-Barr Virus Infection in Duodenal Mucosa of Patients With Refractory Celiac Disease. *Clin Gastroenterol Hepatol* 2016; 14: 1216-1220.