International Journal of Celiac Disease, 2016, Vol. 4, No. 2, 68-70
Available online at http://pubs.sciepub.com/ijcd/4/2/1

DOI:10.12691/ijcd-4-2-1

The Gut-gut Axis: Cohabitation of Celiac, Crohn's Disease and IgA Deficiency

Aaron Lerner[1,*], Sandra Neidhöfer[2], Torsten Matthias[2]

[1]B. Rappaport School of Medicine, Technion-Israel Institute of Technology, Haifa, Israel
[2]AESKU.KIPP Institute, Wendelsheim, Germany
*Corresponding author: aaronlerner1948@gmail.com

Abstract An adult patient with IgA deficiency, celiac and Crohn's disease is described. In addition to the rare association, he developed an unusual proximal Crohn's disease. Unbalanced microbiome, increased intestinal permeability, susceptibility to infections that might initiate post translational modification of naïve protein and the genetic background, are shared between the three entities. It is speculated that the IgA immune deficiency and its consequences are the early factors that set the stage for the progression of the other two diseases. Based on recent knowledge, special nutritional therapies should be considered, in addition to the gluten free diet.

Keywords: *celiac disease, Crohn's disease, IgA deficiency, association, small bowel, case report*

Cite This Article: Aaron Lerner, Sandra Neidhöfer, and Torsten Matthias, "The Gut-gut Axis: Cohabitation of Celiac, Crohn's Disease and IgA Deficiency." *International Journal of Celiac Disease*, vol. 4, no. 2 (2016): 68-70. doi: 10.12691/ijcd-4-2-1.

1. Introduction

The association of celiac disease (CeD), Crohn's disease (CD) and selective immunoglobulin A deficiency (IgAD) is rare but, based on the current knowledge, it brings up interesting and stimulating thoughts. We congratulate Tankova L et al. for reporting such a rare association [1].

Several shared aspects can be delineated between the 3 conditions:

1. The intestinal ecosystem. It is apparent that the microbiota and its products have a profound effect on the development and maintenance of the immune system. The dysbiotic populations, despite not being well identified, confer the susceptibility to immune-mediated diseases, including autoimmune disease [2]. Changing a single bacterial species and/or the entire commensal community can alter the outcome of a specific AD due to the imbalance of pathological/protective immune responses. In IBD, reduction of Firmicutes+Bacteroides and overgrowth of Proteobacteria, were described. In CD, increased diversity of Lachnoanaerobaculum, Prevotella, Actinomycetes, and Lachnoanaerobaculum umeaense was reported [2]. The third condition, IgAD is a luminal immunodeficiency state where the normal microbiome is at risk of pathogenic bacteria invasion. In all of those states, the luminal microbial enzymes act as post-translational modifiers of proteins thus turning naïve/self-proteins to neo-peptides/non-self-protein, which drives the autoimmune cascade [2].

2. Breached tight-junction integrity. Only a single layer of epithelial cells separates the luminal contents from effector immune cells in the lamina propria and the internal milieu of the body. Breaching this single layer of epithelium can lead to pathological exposure of the highly immunoreactive subepithelium to the vast number of foreign antigens in the lumen. In fact, tight-junction dysfunction seems to be a primary defect in AD and intestinal permeability is increased in many autoimmune diseases, including: CD, CeD and IgAD [3,4,5].

3. Infections are drivers of autoimmunity. All three conditions are associated with infections. Multiple microbes and viruses are associated with CeD [6]. In CD, deregulated immune response toward the microbiome is the leading hypothesis and IgAD is related to bacterial overgrowth and susceptibility to infections.

4. The hygiene hypothesis. Epidemiologically, CeD and CD are more prevalent in high socioeconomic societies and the IgAD in the presently described patient put him in a higher risk of autoimmunogenesis.

5. Shared genes. As many as 14 susceptibility loci are shared between IBD and celiac disease, indicating significant overlap in pathophysiology [7].

The ability to respond to an antigen, whether foreign or self, and the nature of that response are determined to a large extent by the unique amino acid sequences of HLA alleles. More than 100 diseases, many of which are autoimmune, have been associated with HLA genes. DQB1*0201 is shared between CD and IgAD [8] and multiple associations were described between CeD and CD [9,10] as well as between CeD and IgAD [11,12]. In fact, genetic factors are important for the development of both IgAD and various autoimmune disorders, including CD, CeD, and a strong association with the major histocompatibility complex region has been reported [11].

After detailing the shared aspects between the 3 entities, several theoretical and more practical questions arise concerning the case reported patient:

2. Why did the CD Manifest, unusually, in His Proximal Intestine?

Since CeD is a proximal mucosal inflammatory disease, it can be speculated that the immune activation, the proinflammatory local cytokines, the breach in tight junction integrity, the misbalanced microbiome and the IgAD mediated proximal bacterial overgrowth or infection, predisposed the jejunum for the CD pathological events.

3. What was the Initiating Factor or the Driving Force for the Patient's Late Clinical Presentation?

As in many autoimmune diseases, there are genetic and environmental factors that initiate and drive the autoimmune process. No one can argue against the importance of the genetics that the patient carries from birth but most probably, a combination of environmental events that occurred later in his life impacted the clinical manifestations in the long run. IgA has many functions, serving as a first-line barrier that protects the mucosal epithelium from pathogens, toxins and food antigens, shaping the intestinal microbiota, and regulating host-commensal homeostasis. Signals induced by commensal colonization are central for regulating IgA induction, maintenance, positioning and function [13]. Between the 3 conditions IgAD appears early in life and it is speculated that the resulting changes in the microbial luminal compartmental composition, like bacterial overgrowth, recurrent infections, dysbiotic post translational modification of proteins, increased gut permeability, merged together and predisposed the patient for hyposymptomatic CeD and late onset CD.

4. Is there a Place for Therapeutic or Preventive Nutrition in the Reported Case?

Unquestionably, having CeD, the patient needs to follow a life-long gluten free diet. Recent observations are accumulating on the deleterious effects of gluten on non-celiac human health. It appears that gluten opens the tight junction, induces inflammation, decreases viability of cells, is immunogenic, induces oxidative stress, and affects microbiome, epigenetics and cellular metabolism. (Personal communication). More so, a gluten free diet was beneficial to certain patients with non-celiac autoimmune diseases like type 1 diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, autoimmune thyroiditis and hepatitis [14,15]. The question arises if other special or restrictive diets could benefit his health status. Industrial food additives, heavily used in processing food were suggested most recently to induce autoimmunity [4]. One of them, the microbial transglutaminase was offered as a potential new environmental inducer of CD [5,16,17]. Not less interesting is the suggestion to consume high fiber diet for rehabilitation of the physiological intestinal flora or the enhancement of the microbiome that produce regulatory and anti-inflammatory metabolome [18].

5. Conclusions

Sometimes publishing a case report, even a rare one, can increase our understanding of the pathophysiology, risk factors and evolution of human disease, mainly autoimmune diseases, as is the present case. It is suggested that multiple aspects are shared between CD, CeD and IgAD and comparing the three, most probably the IgAD was the earliest to impact the two other disease progressions. Several pathophysiological avenues are hypothesized to explain the proximal CeD and several therapeutic and preventive diets may benefit the present patient.

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