Volume 11, No. 1, 2022, pp. 74-80
Academy of Romanian Scientists Online ISSN 2285 – 4177
Annals Series on Biological Sciences ORIGINAL PAPERS

The Link Between the Altered gut Microbiota and Chronic Spontaneous Urticaria

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Background: *Nowadays, regulation of the immune system through gut microbiota is supposed to affect the chronic spontaneous urticaria. Unfortunately, the whole intestinal microbiome in chronic spontaneous urticaria patients is rarely being clarified. Lactobacillus in the prevention and treatment of the allergic and inflammatory diseases was reported.*
Objectives: *The gut microbiota may be a target for improving outcomes in subjects affected or at risk for chronic spontaneous urticaria.*
Materials and methods: The evaluation of the patients was based on history and physical examination. Specific bacterial genera including Lactobacillus and Bacteroides as well as their microbial metabolites, i.e., short-chain fatty acids, confer protection against chronic spontaneous urticaria.
Results: *Chronic spontaneous urticaria is a spontaneous disorder defined as persistent urticaria longer than 6 weeks in duration and without an identifiable cause. Imbalanced microbiota diversity should be considered as one of the most important underlying causes of chronic spontaneous urticaria. Although the mechanism of decreased microbiota diversity associated with the etiology of chronic spontaneous urticaria is not clear, alterations in gut bacterial diversity could disrupt mucosal immunological tolerance by promoting regulatory T cells reacting to dietary antigens.*
Conclusion: *This is the first study, to our knowledge, to show the change of microbiota composition in patients with chronic spontaneous urticaria. Our results demonstrated that the microbial composition was significantly different between patients with chronic spontaneous urticaria and the healthy individual, which may be the reason leading to the various outcomes of probiotic treatment. This study suggests that disturbances in the gut microbiome composition and metabolites and their crosstalk or interaction may participate in the pathogenesis of chronic spontaneous urticaria.*

Key words: microbiome, chronic spontaneous urticaria, probiotics

DOI https://doi.org/10.56082/annalsarscibio.2022.1.75

The pathogenesis of chronic urticaria is closely related to imbalances in immunity. Regulation of the immune system is one of the important roles of the gut microbiota. Nowadays, regulation of the immune system through gut microbiota is supposed to affect the chronic urticaria. Therefore, gut microbiota plays an important role in the evolution and regulation of the immune system. Cumulative evidence has demonstrated an intimate, bidirectional connection between the gut and skin. Gastrointestinal disorders are often accompanied by cutaneous manifestations and the gastrointestinal system, particularly the gut microbiome, appears to participate in the pathophysiology of many inflammatory disorders.

The latest study revealed that disturbances in gut microbiota composition and/or activity (dysbiosis) might contribute to the pathogenesis of allergic diseases. Intestinal microbiome in the different populations may be diverse and individually specific, which related to race genetics, lifestyle, diet habit, antibiotics, etc (1).

The prevalence is 1%, and two thirds of these cases are “chronic spontaneous urticaria.” Unfortunately, the whole intestinal microbiome in patients with chronic urticaria is rarely being clarified. Drugs, food, infections, and systemic diseases may be etiologic factors for chronic spontaneous urticaria, although it may be idiopathic. The evaluation of the patients was based on history and physical examination. Most cases of acute urticaria resolve-less than 8% will continue to chronic spontaneous urticaria (2).

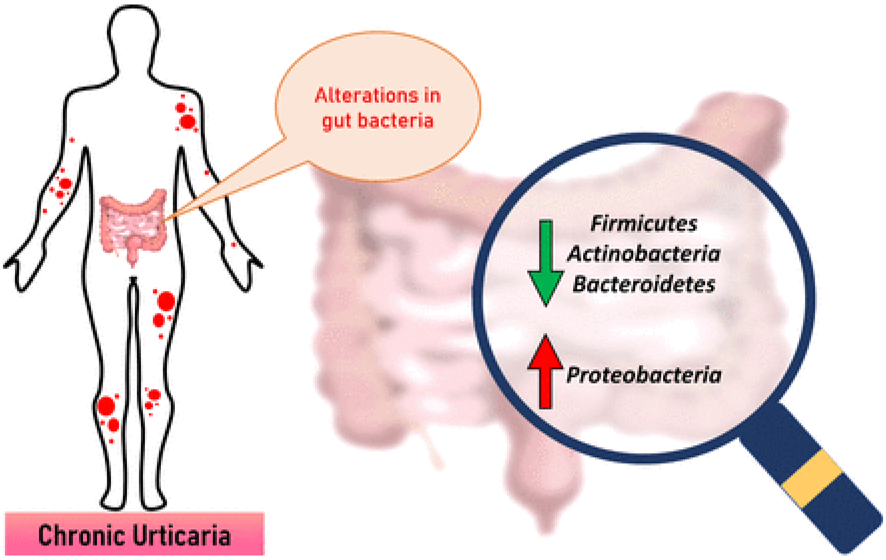

Fig. 1 Altered gut microbiome is associated with development of chronic urticaria (2)

The skin is the largest organ of the human body that harbors several hundreds of resident microorganisms. These microbes are collectively referred to as the skin microbiota that is fundamental to skin physiology and immunity. Studies have shown that shifts in the skin microbiota are associated with skin diseases.

Chronic spontaneous urticaria is more frequent in females with a male to female ratio varying between 1.5:1 to 2:1. Chronic spontaneous urticaria is frequently associated with autoimmunity and is often exacerbated by several factors. These include stress, infections, colourings and preservatives in pre-packaged foods, as well as deficiency of vitamin D3 and iron. While chronic underlying infection and mental and emotional stress have been known to precede the onset of chronic spontaneous urticaria, it is now clear that they can also aggravate the severity of the symptoms and perpetuate the condition (3).

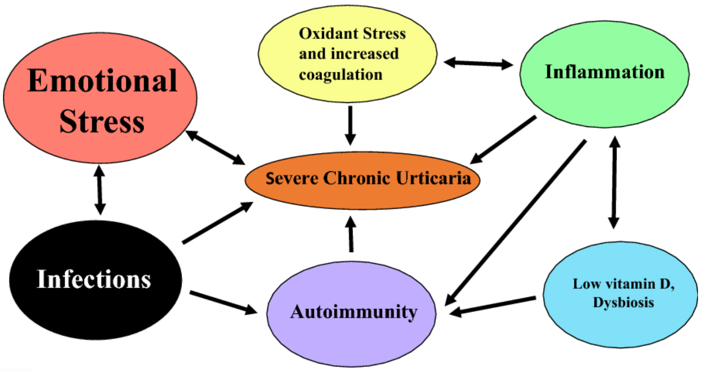

Fig 2. Interaction of different factors in chronic spontaneous urticaria (3)

It is unclear how gastrointestinal dysbiosis affects chronic spontaneous urticaria. Vitamin D3, however, can increase T regulatory function which can control a tendency to autoimmunity and inflammation. (4)

Chronic spontaneous urticaria is a histamine-mediated inflammatory skin disease, and second-generation non-sedating H1-antihistamines at licensed doses have long been the first-line therapy in chronic spontaneous urticaria (5).

The objective of this study was to explore the relationship between gut microbiota and the efficacy of antihistamines in people with chronic spontaneous urticaria. The aim of this study was to compare the diversity and distribution of the intestinal microbiome in patients with chronic spontaneous urticaria with that of healthy individuals. The hypothesis was to determine the probable association of intestinal microbiome with chronic spontaneous urticaria. The gut microbiota of patients with chronic spontaneous urticaria and healthy individuals were obtained by 16s rRNA massive sequencing.

In this review, we discuss the different factors that can exacerbate established chronic spontaneous urticaria, prolong the duration of the condition and encourage the need for second and third line therapy.

However, about 50% of patients are resistant to second-generation non-sedating H1-antihistamines, and the precise pathogenesis remains largely unknown but seems to be associated with low-level systemic or intestinal inflammation (6).

The gastrointestinal microbiota provides a vast and continuous stimulation for the immune system. Chronic spontaneous urticaria seems to be associated with low-level systemic or intestinal inflammation (7,8).

Intestinal permeability was reported to be increased in chronic spontaneous urticaria and this was partly reversed by 24 days on a reduced pseudoallergen diet.

Increasing evidence suggests that the gut microbiome plays a role in the pathogenesis of allergy and autoimmunity (9).

The association between abnormalities in the gut microbiota and chronic spontaneous urticaria remains largely undefined. Collectively, these results suggest that chronic spontaneous urticaria may in some people be due to a temporary sensitivity to pseudoallergens and natural low molecular weight compounds which enter the body across a leaky gut epithelium. The ability of pseudoallergens, infections and stress to initiate and/or aggravate chronic spontaneous urticaria suggests that a common pathway may be involved (10).

Certain infections and stress may be linked to an increase susceptibility to chronic spontaneous urticaria by perturbation of the immune system (11).

The urticaria associated with raised stress levels may then perpetuate the chronic spontaneous urticaria even when the original infection has been eliminated and there has been an improvement in the diet (12).

Therefore, the role of microbial diversity in allergy or chronic spontaneous urticaria remains a subject of debate requiring further investigation. Thus, intestinal abundance of Lactobacillus species and their function in the pathogenesis of chronic spontaneous urticaria and allergy need further exploration.

The intestinal microbiome was detected by 16Sr RNA sequencing.

Gut microbiota diversity and composition were compared, and bioinformatics analysis of the differences was performed.

Our data revealed disordered gut microbial constitution and metabolites using high-throughput molecular techniques, which provided potential clues for studying the pathogenesis of chronic spontaneous urticaria.

Chronic spontaneous urticaria is a disease involving allergy and autoimmunity, and there is no report detailing the role of microbiota alterations in its development (13).

Our results demonstrated that the microbial composition was significantly different between patients with chronic urticaria and the healthy individual, which may be the reason leading to the various outcomes of probiotic treatment.

The gastrointestinal microflora provides a vast and continuous stimulation for the immune system. However, the composition and diversity of gut microbiota in chronic urticaria patients are rarely reported. Chronic spontaneous urticaria is often associated with organ specific autoimmunity but is rarely caused by food allergy. In this study, decreased diversity was observed in patients with chronic urticaria (14,15). Although the mechanism of decreased microbiota diversity associated with the etiology of chronic urticaria is not clear, alterations in gut bacterial diversity could disrupt mucosal immunological tolerance by promoting Treg cells reacting to dietary antigens (16).

Our results indicated chronic spontaneous urticaria is associated with gut microbiota dysbiosis and pointed out that the bacterial taxa increased in patients with chronic spontaneous urticaria, which might be involved in the pathogenesis of chronic spontaneous urticaria. These results provided clues for future microbial-based therapies on chronic spontaneous urticaria.

Alergiplant tea from Deniplant is a natural immunomodulator of the intestinal and skin microbiota.

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In 2019 it was established the Center for Biomedicine (www.deniplant.ro/biomedicina) to combine the two sciences, biology and medicine, where we try to find the link between autoimmune diseases, metabolic, neurological, genetic and human microbiome. Here we try to elucidate the causes of disease and to find new ways to diagnose and fix them by modulating natural microbiome. One of the issues studied was the relationship between hives and microbiome, we presented it in the paper.

Studies in Biomedicine Center were presented at the 45th international conferences in Turkey, Cyprus, Spain, Portugal, England, Colombia, Mexic, Canada, USA (www.deniplant.ro/conferinte) and the programs that are running weekly music therapy on two online radio stations, one with headquarters in Italy and one's own Radio Deniplant
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Conclusions

Imbalanced microbiota diversity should be considered as one of the most important underlying causes of allergic disease Therefore, understanding the composition and overall structure of gut microbiota in patients with chronic urticaria before therapeutic protocol enactment is crucial for the therapeutic efficacy. This study suggests that disturbances in the gut microbiome composition and metabolites and their crosstalk or interaction may participate in the pathogenesis of chronic spontaneous urticaria. The alteration in the intestinal microbiota (dysbiosis) may be an essential factor for chronic spontaneous urticaria development and may explain idiopathic cases. Our results demonstrated that the microbial composition was significantly different between patients with chronic urticaria and the healthy individual, which may be the reason leading to the various outcomes of probiotic treatment. Alergiplant is the first study, to our knowledge, to show the change of gut microbiota composition in patients with chronic spontaneous urticaria.

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