Chapter 2

ROLE OF MICROBIOTA IN ANXIETY DISORDERS

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INTRODUCTION

Recent studies show that the prevalence of anxiety, which is one of the most common mental disorders worldwide, is 7.3% (1). Anxiety that starts at an early age develops in later periods and becomes chronic. Since it is the beginning of many psychiatric mental disorders, it is vital to record the onset of anxiety for subsequent processes (2,3).

According to a study published by the World Health Organization in 2008, major depressive disorder due to anxiety has been shown that it is the 3rd most common disease worldwide in 2030 (4).

As a matter of fact, it is among the findings obtained as a result of studies that individuals with depression and this disorder have suicide attempts in their later life cycles. According to a study published by Global Burden of Disease in 2010, it was revealed that disability ranks sixth among the leading causes of the condition, and it also revealed that this situation mostly occurs in the 15-34 age group in women (5,6).

Anxiety disorder is defined as a new disease spectrum that is formed by the combination of more than one disease, and the burden of the disorder varies between its limit and severity. The category of anxiety disorder began to appeal to a very wide class Although many factors are known to play a role in anxiety disorder, a clear cause is not yet clear among environmental and biological factors. On the other hand, clinical studies conducted in recent decades have revealed that the biological factors of this disorder are related to neuroanatomical abnormalities, norepinephrine, serotonin, and neuroendocrine abnormalities, hypothalamic-pituitary-adrenal (HPA) axis abnormalities (7).

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The causes of many mental and psychiatric disorders, especially anxiety and depression, and their treatment have been dealt with in the gut-brain axis in recent studies, and it has been seen that anxiety disorder can be controlled and explained in this context. The gut microbiota (also called gut microbial flora), which has started to develop since birth and has serious effects on the body at every step of life, has features such as fermentation, providing energy and nutrients, and balancing the immune system (8). The intestinal microflora is directly related to the central nervous system and also has a vital role in the human microbiome, interacting with organs. Recent studies have revealed that the intestinal microflora not only has features such as energy, nutrients, and immune system effects but also has various effects on the emotions and even behaviors of the individual. In this context, a bidirectional interaction and community concept called the microbiota-gut-brain axis has developed. From this point of view, the relationship between mental mood disorders and these in the brain-gut microbiota axis has been investigated, and as a result of these studies, it has been observed that there is a direct relationship with mental disorders such as schizophrenia, anxiety, and autism.

In this study, research and results revealing the connection between anxiety disorders in the gut microflora-brain axis were compiled.

MICROBIOTA-GUT-BRAIN AXIS DEVELOPMENT

The intestinal microflora, which constitutes an important part of the human microbiome, is formed by the combination of various microorganisms such as fungi, viruses, archaea, and bacteria, and is in a symbiotic relationship with the human gastrointestinal system (9). In addition, studies have revealed that the intestinal microflora has a very complex system and contains more than 40,000 bacterial species (10). Bacteria in the intestinal microflora play important roles in the body, such as the secretion of short-chain fatty acids and the regulation of the immune system.

Recent studies on the intestinal microbiota have shown that there are three basic entropies among the microorganisms that make up the microbiota, namely Bacteroides, Prevotella, and Ruminococcus (11). Although the microbiota that begins to form in the human body at birth is also affected by environmental factors, there are factors such as genetic predisposition, physical activity, stress, infection, diseases, and antibiotic use among the factors that play an important

role in the development of microbiota (8). In addition, these findings vary according to the type and genus of maternal microorganisms that come with the birth of the human microbiota. Maternal microbiota undergoes various changes during pregnancy and birth, which then significantly affects the microbiota community in offspring (12). In addition, as a result of a recent study, it was determined that the microbiota and maternal microorganisms have a serious role in the good progress of the offspring's behavior and neurodevelopmental process (13).

Vaginally, newborn babies are exposed to *Lactobacillus* and *Provotella* microorganisms, which are the most important elements of the microbiota. As a matter of fact, these bacteria and the *Bifidobacterium species* that come right after them are quite dominant in the microflora of newborns (14). In addition, babies born by cesarean section have Staphylococcus and Corynebacterium species, which are important elements of the skin flora (15). From this point of view, it is thought that the health, development, mood, nerve, and other changes of newborn babies are related to the microorganisms they acquire as soon as they are born (16).

ANXIETY – IMMUNE SYSTEM RELATIONSHIPS

Studies have shown that more than 50% of patients with IBS (irritable bowel syndrome), which is directly related to stress-related mental and psychological syndromes, have anxiety disorders and depression (17). When evaluated accordingly, it is concluded that the microbiota, the key element of the gut-brain axis, has an important role in anxiety disorder.

A study by Mikocka-Walus et al. revealed that individuals with IBD (inflammatory bowel disease) experience anxiety and depression disorders more frequently than healthy individuals. As a result of this study, the severity of IBD is directly related to the severity of anxiety and depression disorders (18). IBD patients experiencing depressive symptoms were treated with TNF (anti-tumor necrosis factor) alpha or immunomodulatory therapy in previous studies (19).

Findings from this and similar studies have shown that the immune system and inflammatory responses are directly related to the interaction that occurs in the gut microbiota-brain axis (20). The underlying reason why changes in the intestinal microbiota affect this phenomenon is the brain plasticity relationship,

which changes anxiety symptoms and social behaviors by affecting the motor functions of microbial metabolic activities.

The direct relationship between congenital activation of microorganisms in the microbiota, disruption of the immune system, and anxiety has also been associated with the vagus nerve. According to this hypothesis, there is a direct relationship between the vagus nerve and brain signals and the peripheral system (21). In this context, the vagus nerve acts as an emotional pathway between the gut and the brain. In a study conducted by Goehler et al on a mouse infected with *Campylobacter jejuni* (a foodborne pathogen), they stimulated the brain via the vagus nerve and observed that symptoms similar to anxiety appeared (22).

From this point of view, the increase or decrease of a bacterial group with inflammatory effects such as Ruminococcus gnavus, Fusobacteria, or Escherichia-Shigella in General Anxiety Disorder (GAD) also causes an increase or decrease in SCFA-producing strains, which causes dysfunction in the intestinal barrier (23). Therefore, the increase in pathogens that have the ability to break down gastrointestinal mucins, and produce exotoxins and inflammation can cause an inflammatory effect on the microbiota, causing severe symptoms in individuals with anxiety (24).

Similar studies have also been conducted on Obsessive-Compulsive (OCD), one of the most common anxiety disorders. In this context, various microbial differences were obtained in stool samples taken from patients with general anxiety problems and normal individuals. From this point of view, low bacterial-alpha diversity was observed in stool samples of patients with general anxiety problems. Firmicutes and Tenericutes ratios were found to be extremely low in the microbiota of anxious patients compared to normal individuals, and at the same time, Eubacterium coprostanoligenes, Ruminococcaceae UCG-014 and Prevotella 9 ratios were found to be negatively correlated with anxiety status (24). In addition, it has been revealed that the intestinal microflora of individuals with the obsessive-compulsive disorder has a very low diversity of microflora, especially Oscillospira, Odoribacter, and Anaerostipes species (25).

In another study, F. prausnitzii, which has a very important role in the intestinal microbiota and is abundant, caused an increase in the levels of SCFA and IL-10 in mice under mild stress, while it also caused a decrease in the levels of corticosterone and IL-6. Therefore, the decrease or depletion of F prausnitzii

level causes an increase in anxiety in the last body (26). Although natural microbiota diversity and health have an important role as a result of research conducted in general anxiety disorder patients, microbiota health has been improved with certain drug treatments. Accordingly, it was observed that the severity of symptoms decreased in patients with general anxiety disorder (27).

Studies also show that the diet of the individual has effects on regulating the intestinal microbiota (28). Correspondingly, microbiota activity has also been shown to play a key role in weight and energy intake through food (29). Studies based on these studies have revealed that imbalances in the human microbiota have effects on the mind, spirit, and nerves depending on diet and are especially associated with anxiety disorders (29). For this reason, recent studies have focused directly on the gut microbiota in individuals with anxiety and psychological disorders.

According to a study by Jiang et al. in 2015, stool samples of depressed and normal individuals were investigated. The study also found that the microbial community found in the stools of normal individuals was more diverse than that of depressed individuals (30). In this context, various studies have been carried out on animal models and it has been concluded that enteric microbes can play a key role in determining the effects on mental disorders. In animal studies, it was observed that when the fecal microbiota obtained from depressed patients was transplanted to rats that were depleted in terms of microbiota diversity, behaviors similar to depression were observed in rats (31).

While increased peripheral proinflammatory cytokine levels and low cortisol are known to predispose individuals to develop PTSD after a traumatic event, there are reports that CBT alone can reduce the proinflammatory profile, particularly an inflammatory profile associated with leaky gut (32,33)

CONCLUSIONS

Today, many people are faced with anxiety problems both due to environmental factors and biological factors, but the clear reason for this situation is not known. In this study, anxiety diseases, which are common mental-nervous disorders, are discussed on the axis of the brain-microbiota, and the studies conducted at this point are compiled. Studies in recent decades have shown that metabolic events occurring in the intestinal microflora are directly or indirectly related to brain signals. In addition, in studies conducted between patients suffering from

anxiety disorders and normal individuals, it has been observed that there is a significant difference in the intestinal microflora, and it has been observed that the microbiota diversity is relatively less in individuals with anxiety.

The intestinal microbiota is a condition that develops as soon as the baby is born, and babies born vaginally are exposed to *Lactobacillus*, *Bifidobacterium*, and *Provotella* microorganism species, while those born by cesarean section are exposed to skin phyla microorganisms called *Staphylococcus* and *Corynebacterium*. These microorganisms, to which the newborn is first exposed, affect the developmental periods and mental health. Although these species are predominantly in the newborn phylum, the development of different species and the ratio of these species vary in subsequent developmental periods.

Most of the recent research on the microbiota has focused on its relationship with the immune system. Studies conducted in this context have shown that the microbiota interacts with neurotransmitters and the neuroendocrine system. It has been reported that many metabolic systems, including the immune system of the body, are indirectly affected when irregularities occur in the microbiota–brain axis, which is explained by the neuroendocrine system. However, not only anxiety disorders but also mental and behavioral conditions such as neurodevelopmental and depressive disorders are among the factors affected by the microbiota-brain axis.

In this review study, it is aimed to combine the results of the researches that serve as a guide for future studies under a single roof. The results obtained from the findings of the studies, the causes and treatments of anxiety disorders were evaluated on the brain-anxiety axis. It has been observed that there is a direct connection between the metabolic activities in the intestinal microbiota and the activities of neurotransmitter molecules produced depending on the individual's nutrition and mental - nerve disorders. As a matter of fact, a study based on Randomized Clinical Trials showed that when the microbiota of individuals with anxiety symptoms was examined, single-strain probiotics were not significantly effective than multi-strain probiotics (34).

In future studies, microbiota-brain microorganism studies may offer promising results in the treatment of serious mental conditions such as anxiety disorders.

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