International Journal of Family & Community Medicine

Mini Review

Gut-brain axis as a key aspect of clinical conditions

Abstract

The brain-gut axis evidences the interactions between the gastrointestinal system and the brain in a general context. This physiological system is a mutual balance connection between two individual organs of the body in response to internal and external changes. It is extremely important to appreciate the current concepts that involve this system to understand brain-gut interaction, as well as to highlight the insertion of the axis today, using clinical conditions, neuropsychiatric disorders, intestinal microbiota, immunomodulators, and scientific evidence to verify and highlight axis activity in the human body. In this sense, there is a consistent background in literature supporting the physiological development and shaping of the gut in brain disorders by a constant interplay mediated by the several products originating from the microbiota.

Keywords: mental disorders, intestinal tract, microbiota, probiotics, fecal transplant

Volume 6 Issue 5 - 2022

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Received: September 30, 2022 | **Published:** October 18, 2022

Introduction

The concept of gut-brain axis, definable as a bidirectional channel of communication between two organs that perform functions of full importance for the functioning of the organism,[1] is a term that correlates changes in the intestinal scope with neurological biochemical changes, refuting previous studies that mitigated the correlation between organs. In consequence, changing paradigms of neuroscience nowadays.[2] Throughout the development of the axis, a pattern of biochemical change is repeated: The microbiota is one of the major factors active in the axis, and can considerably modify certain neural behaviors. Cross-talk between the gut microbiota and the brain can have a crucial impact on basic neuroactive processes and neurodegenerative disorders.[3] It is known that the intestine and brain communicate with each other. Central Nervous System (CNS) stimuli can modify intestinal functions, as well as stimuli from the gut to the CNS, can cause specific symptoms. Also, the Blood Brain Barrier plays an important role in the exchange of molecules and nutrients between the brain and blood, as well as in allowing the normal functioning of neurons. In view, the axis is a theme of full importance nowadays, even with its diversity of substantial applicability, the present study highlights essential points about the axis, as well as its evidence in practice.

Methodology

This present study has a descriptive-discursive character, emphasizing as a priority the concept of the "gut-brain axis" applied in a perspective of evidence of the concept in the human body, in addition, to pathologies and clinical conditions that highlight its action. Thus, objective searches were performed using the databases: PUBMED, SCIELO, and Google Scholar. In the search for the articles used in this bibliographic research, the terms "Gut-brain-axis" and "microbiota" were used, without exclusion criteria, but greater attention was paid to the most recent articles due to their applicability to the theme.

Results and discussion

Neurological clinical conditions and psychiatric disorders

Several neurobiological conditions, whether mental disorders are possibly affected by the gut microbiota. Moreover, the concept is evidenced in clinical conditions and mental disorders that can be directly emphasized by the axis, such as Schizophrenia, Alzheimer's, Parkinson's, Irritable Bowel Syndrome, and Epilepsy, being one of the possible causes of triggering or developing them.

Schizophrenia

Schizophrenia can have several causes, such as before and after birth risk factors. However, specific factors may increase the risk of developing or triggering the disorder, including a combination of molecular biology, brain chemistry, and the environment, emphasizing the action of the brain-gut axis in the disorder.[4] The development of schizophrenia may be linked to a common pathway in the intestinal tract. The change of composition in the gut microbiota has a possible effect through the process of symptoms and worsening of hallucinations. One of the theme mechanisms by which changes in the microbiota can lead to neuropsychiatric disease is through bacterial production of harmful products that compromise the integrity of the epithelial barrier of the intestine, allowing the entry of bacterial products with neuroactive properties in the circulation.[5] In addition, damage to the intestines wall may also be present in patients with schizophrenia.

Epilepsy

It is well established in the literature that gut dysfunction/dysbiosis has a hand in a variety of neurological diseases, such as epilepsy. Pre-existing inflammatory responses promote the onset of epilepsy, which conversely triggers an inflammatory cascade, producing a downstream effect and accelerating the progression of the disease.[6] In this sense, unhealthy signals will be sent to the brain when a microbial population is out of balance, which will then lead to substandard conditions including greater oxidative stress, imbalanced energy homeostasis, and cellular deterioration.[7] Numerous studies have shown that intestinal inflammation can cause epileptic events in susceptible patients and may also explain why antiepileptic medications are less effective.[8] Because of this, intestinal inflammation has become a promising target for antiepileptic drugs like sodium butyrate and alpha-lactoalbumin (a whey protein commonly used in animal models). In addition, several experiments using targeted drugs have established that vagal effects can be observed regarding the use of certain antidepressants and anxiolytics.[9,10] Vagus nerve (VN) stimulation has also been used as an alternative therapy for people with epilepsy since it has been found to have anti-inflammatory effects.[11] Nevertheless, vagotomy was unable to reverse these behavioral advantages, indicating that this bacterial impact may originate from the higher system of vagal stimulation.[12]

Irritable bowel syndrome

Irritable bowel syndrome is a gastrointestinal disorder that encompasses of various symptoms, such as; headache, lack of sleep, dyspepsia, fatigue, and depression. With its difficult diagnosis, the syndrome is not yet fully known by medicine, however, there is proof that irritability of the intestine may be correlated with changes in the microbiota.[13] Certain factors of bacterial diversity in the small intestine are commonly found in patients with **IBS**, in addition, certain types of non-systemic probiotics are also presented with some constancy in people who have developed the syndrome. There are biologically plausible mechanisms through which the gut microbiome can influence both cardinal symptoms and other prominent features of **ISI**, however, the syndrome may also be fully affected by emotional and social factors.[14] The role of the intestinal microbiota in bidirectional communication along the gut-brain axis and subsequent behavior changes were demystified over time. In short, stress and the gut microbiota may interact through complementary or opposite factors to influence visceral nociceptive behaviors, causing correlation factors between the brain and the intestine itself.[15]

Alzheimer's and parkinson's diseases

Gastrointestinal dysfunction often precedes the onset of motor symptoms in patients with Parkinson's disease (PD), and previous studies of the human microbiome had shown that patients with PD harbor distinct microbial communities in their gut. Moreover, understanding the specific contributions of different strains of gut bacteria in PD could eventually lead to targeted antibiotic therapy or modification of the gut microbiota with dietary interventions. Although eradication of the gut microbiota is not feasible in humans, the findings open a novel avenue for understanding and potentially intervening in the development of PD.[16] The pursuit of biomarkers for this neurological condition also includes a variety of non-motor symptoms (NMS), which are less recognizable but highly prevalent.[17] Since mobility impairment and its eventual development often tend to be the most obvious PD symptoms, they are frequently overlooked during patient screening. However, the disease's non-motor symptoms, such as hyposmia and constipation, have been able to provide light on its potential etiology.[18] As stated by Nowak et al.[17] faster diagnoses might be made by identifying specific PD risk biomarkers, ideally, before the motor phase of the illness emerges in these individuals. This could open the possibility for early medical monitoring and a more comprehensive approach to mitigating the symptoms of prodromal Parkinson's disease.

In addition, pathologic and epidemiologic studies suggest that PD may start in the enteric nervous system and spread via the vagal nerve to the brainstem. Hopfner et al.[19] analyzed the gut microbiome in 29 PD cases and 29 age-matched controls by next-generation-sequencing of the 16S rRNA gene and compared diversity indices and bacterial abundances between cases and controls, with a predominance of *Lactobacillaceae*, *Barnesiellaceae* and *Enterococaceae* associated genera with PD, exhibiting association of several biomarkers. Thus, dysbiosis of intestinal microbial function has been associated with behavioral and neurophysical deficits. A neurobiological disorder known as Alzheimer's disease (AD) is characterized by the accumulation of proteinaceous misfolded amyloid-β (Aβ) fibrils and oligomers as well as neurofibrillary modifications made of hyperphosphorylated tau protein in the cerebral cortex and other parts of the brain, causing a progressive neurodegenerative condition.[20] Changes in the gut microbiota, in particular, have been linked to AD, by triggering proinflammatory cytokines and increasing intestinal permeability. Furthermore, it is well recognized that the bacteria that constitute the gut microbiome release immunogenic combinations of amyloids, lipopolysaccharides (LPSs), and other microbial exudates into the environment.[21]

In this sense, there is a consistent background in literature supporting the physiological development and shaping of the gut in brain disorders by a constant interplay mediated by the several products originating from the microbiota.[22] It also can be seen the participation of the axis in AD during co-infections in gastrointestinal tract, such as *Helicobacter pylori* gastritis, promoting chronic inflammation, thus possibly influencing both occurrence and evolution of AD.[23] Besides, when exposed to pathological stimuli from the main microbiota products, neural cell types can also trigger the development of neuroinflammation and cause degeneration by changing the activation patterns of astrocytes and microglia from a healthy to a pathogenic state.[24] Thus, as can be seen in both Alzheimer's and Parkinson's diseases, the role of microbiota-gut-brain axis is a significant aspect to be considered in mitigating and preventing the classical neurological symptomatology.

Microbiota

Influence of the microbiota at the moment of delivery

Colonization of the intestinal microbiota begins at birth and has essential functions for the full functioning of the human organism, such as the modulation of the immune system and the link between the gut-brain axis, being of vital importance for the prevention and development of psychological disorders, allergies and other relevant pathologies.[25] In vaginal delivery, the microbiological transfer occurs vertically, in which the neonate establishes contact with the mother's vaginal and intestinal microbiota, especially with bacteria of the genus *Bifidobacterium*, which act as a probiotic, bringing benefits to the health of its host, and which are the most common colonizers in the intestinal region of stillbirths from this type of delivery.[26] On the other hand, neonates born of cesarean procedure are initially colonized by the skin microbiota, through the environment that surrounds it, and are colonized mainly by bacteria of the genus *Clostridium.* Cesarean surgery causes late colonization of the phylum *Bacteroides* and a lower microbiological diversity until two years of age, besides causing delays in the modulation of the immune system, since the immune responses sent during vaginal labor will not be present in elective cesarean sections.[25]

Therefore, such a situation is of great relevance, since children with low intestinal microbial diversity are prone to develop allergies caused by the delay in the development of the immune system, which alters the microbial community in a way that predisposes the host to diseases. However, the patterns of intestinal microbial colonization are still uncertain, since several studies present conflicting results.[25,26] In addition, intestinal dysbiosis is linked to several factors, such as perinatal exposure to antibiotics, use of formula in breastfeeding regarding exclusive breastfeeding, and especially cesarean delivery. Recent studies indicate some eligible solutions for the correction of intestinal dysbiosis in newborns, such as oral postnatal fecal microbiota transplantation, in which a fecal sample of the mother is diluted and offered to the neonate to perform microbial transfer that will not be obtained vertically in cesarean delivery. The results obtained through the use of this method were satisfactory, demonstrating that the intestinal microbiota of neonates resembled the microbiological environment of a baby born vaginally, even if they did not come from this mode of delivery.[27] A method called *Vaginal seeding* is known for the transference of the vaginal fluids of the parturient to the mouth,

Citation: Rodrigues SO, Pádua AG, Lima CMG, et al. Gut-brain axis as a key aspect of clinical conditions. *Int J Fam Commun Med.* 2022;6(5):285‒289.
DOI: 10.15406/ijfcm.2022.06.00291

nose, and skin of the newborn using a gauze, shortly after cesarean section, instituting the contact between the baby and the mother's vaginal microbiota.[28,29] In both methods it is necessary to perform clinical and microbiological screenings, ensuring the safety of the newborn and valuing the principles of biosafety.

Influence of food on the gut-brain axis

The modulation of the intestinal microbiota has become a trending and current topic in the research for the treatment of mental disorders.[30–33] In addition to strong evidence of the role of the intestinal microbiota in brain behavior, potential food-related pathways, immunological mechanisms, vagal nerve involvement, and production of microbial neurometabolites are involved in this bidirectional communication. In this sense, studies related to the development of new therapeutic strategies to treat psychiatric disorders aimed at the intestinal microbiota are growing rapidly. It is known that numerous factors can influence the composition of the intestinal microbiota, such as health status and genetics, but food intake is considered one of the most crucial factors affecting the human intestinal microbiota throughout the individual's life. Thus, dietary interventions may have the potential to modulate psychiatric symptoms associated with bowel-brain axis dysfunction.[34] Neuroactive compounds are synthesized by certain plants and microorganisms performing different tasks, especially as a stress response. The most common neuroactive compounds in food are gamma-aminobutyric acid (GABA), serotonin, melatonin, kynurenine, quinolinic acid, dopamine, norepinephrine, histamine, tryptamine, tyramine, and β-phenylethylamine. Fermented foods contain some of these compounds, which can affect people's health and mood. The discovery of the microbiota-intestine-brain axis requires the investigation of the effects of diet on the formation of neuroactive compounds in the intestine.[35] The components of the diet can influence the gut-brain axis by altering the composition of the microbiota or affecting neuronal functioning in both the enteric nervous system and the central nervous system.[36] Thus, the knowledge of probiotic, prebiotic, and symbiotic foods is indispensable for a better understanding of the food relationship and neurological disorders.

Types of microbiota in clinical conditions *versus* normal individuals

Intestinal microorganisms are constantly related to clinical conditions, especially diseases that coexist with them, and have determining factors, such as psychological stress and inflammation present in individuals who have depression, schizophrenia, autism spectrum disorder, epilepsy, migraine, and Parkinson's disease. The intestinal microbiota can influence the synthesis and metabolism of neurotransmitters and is also able to produce these substances on their own, which are not able to reach the brain due to the blood-brain barrier but can be used through the central nervous system.[37] The intestinal microbiota begins its colonization at the time of delivery and after being instituted, accompanies human development, being more dynamic and vulnerable during the periods of childhood and adolescence. As human aging occurs, there is a decline in microbiological complexity, in parallel with the decline of neural complexity, increasing the susceptibility to neurological diseases.[38,39]

Currently, studies are used by germ-free animals, however, there are predictions of future studies focusing on the regulation and treatment of such diseases through the intestinal microbiota, as well as research by biomarkers capable of assisting in the diagnosis and treatment of them.[37,38] Because of its connection with the brain, the gut microbiota becomes a viable option for the treatment of clinical conditions related to it, since it is more accessible and modifiable than the human genome, according to recent studies (39). Moreover, dietary supplements such as prebiotics or probiotics, as well as molecules that reproduce intestinal microbial signals are considered an auxiliary treatment for psychological diseases.[40] From the above, it is possible to conclude the interference of the intestinal microbiota in various clinical conditions, such as obesity, irritable bowel syndrome, diabetes, cancer, and other pathologies, through studies that demonstrate intestinal dysbiosis present in these individuals, caused by abnormal amounts of microorganisms and the presence of bacteria unusual to the colonization of the intestine.[41,42]

Fecal transplant

The first application of stool material dates back to the 4th century, which they called "yellow soup", had been administered orally for the treatment of a patient with severe diarrhea, by the Chinese physician Ge Hong.[43] Currently, new studies highlight the impact caused by fecal transplantation, as well as new techniques that can help in new treatments that use as a basis the concept of gut microbiota. Microbiota transplantation suggests a treatment option for inflammatory bowel disease. An experiment performed in Nanjing, China, demonstrated in 30 patients with Crohn's Disease (CD), 76.7% had significant improvement in abdominal pain and weight gain after 15 months of treatment. In this sense, fecal transplantation consists of an infusion of fecal suspension from a healthy donor into the gastrointestinal tract of a CD patient to restore natural microorganisms. Current therapeutic measures for CD aim at the suppression of the immune system. In contrast, fecal transplantation aims to trigger immune dysregulation, alter the microbiome, decrease "dysbiotic" bacteria, make the environment more pro-inflammatory, and increase bacteria that suppress the pathological mechanism.[44]

In addition, another study points out that a total of 15 of the 16 (93.8%) patients affected by a recurrent *Clostridium difficile* infection had their health condition improved using fecal transplant. In the control groups, patients receiving only vancomycin (antibiotic) obtained resolution of the infection for 4 of the 13 patients (30.8%), and the group receiving vancomycin followed by gastric lavage obtained resolution for 3 of the 13 patients (23.1%). It was concluded that the infusion of feces from a giver was considerably more effective for the treatment of recurrent *C. difficile* infection than standard antibiotic therapies, in this particular case, vancomycin.[45] In conclusion, fecal microbiota transplantation may be administered via the upper gastrointestinal tract (nasogastric tube, nasoduodenal, esophagogastroduodenoscopy, or oral capsules) or from the lower gastrointestinal tract (colonoscopy, sigmoidoscopy, or retention enema). However, it should be considered the risks and benefits of each route, as well as, the patient's health status regarding the Food and Drug Administration definition of the fecal microbiota transplantation as a biological product and classifying it as an experimental drug.[46]

Conclusion

The gut-brain axis exhibits a trending applicability and suitable role of action in clinical conditions in general, being evidenced by the change in microbial behavior of the intestinal microbiota. In addition, it can be fully influenced by ingested food, and consequently, modifying biochemical reactions in the human body. Moreover, the clinical conditions highlighted by the axis are diverse, altering the functioning of the disease or disorder itself, as well as its action on the body, causing full changes in action, behavior, and perpetuation. In addition, fecal transplantation can be a form of natural treatment for certain diseases that imply the axis, aiding in the process of recovery and repair of the intestinal microbiota.

Citation: Rodrigues SO, Pádua AG, Lima CMG, et al. Gut-brain axis as a key aspect of clinical conditions. *Int J Fam Commun Med.* 2022;6(5):285–289.
DOI: 10.15406/ijfcm.2022.06.00291

Acknowledgments

None.

Conflicts of interest

The author declares there is no conflict of interest.

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DOI: 10.15406/ijfcm.2022.06.00291