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The Brain-Gut-Microbiome Axis

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ABSTRACT

Introduction: *The presence of neurons in the gut, although in smaller amount than in the brain, is sufficient for the formation of a proper and autonomous nervous system, independent of the central nervous system called Enteric Nervous System (ENS). Through the production of substances such as serotonin, capable of transmitting impulses throughout the body, an efficient communication is created between the intestine and the brain through the vagus nerve (VN). The third element in this connection is the microbiome or intestinal flora, important in digestion and protection of the organism from infections. Here we describe the complex system of mediators of the brain-gut-microbiome-immune-neural-endocrine connection.*

Discussion: *The brain-gut-microbiome axis has several types of well-established connections. Alteration in any of those connections systems immediately will reflect in the axis, generating alterations in the gut system, in the brain function or in the microbiome. The disruption of the brain-gut-microbiome axis is related to several diseases.*

Conclusion: *Some measures can be taken prophylactically to prevent the establishment of diseases in the gut system and in the microbiome, such as exclusive breastfeeding and to avoid excessive hygiene and cow's milk early in life. The protection of neurons must be done to avoid inflammations that transform the neuron as the target organ to start immune reactions in the brain.*

Keywords

Microbiome, Brain, Neurons, Gut, Enteric Nervous System.

Introduction

The perfect interaction between the gastrointestinal enteric nervous system (ENS) and the central nervous system (CNS) is essential to preserve the normal function and activities of the gastrointestinal tract and the brain [1]. Microbiome and their metabolites have an important participation in this interaction between the brain and the gut creating a connection known as the brain-gut-microbiome axis.

Several different connections between those systems have been described such as: 1- connections by the nerves; 2- connections by the immune system; 3- connections by the hipotalamic-hipofisis-adrenal axis; 4- connections by the metabolites of the microbiome; 5- connections by the enteroendocrine cells and mast cells and 6- connections by the microglia and mast cells. A complex system of mediators of the brain-gut-microbiome-immune-neural-endocrine connection will be described. Here we will update and review the connections among the Brain and the Gut with basis on the literature.

Direct Connection Between the Brain and The Gut Via Neurons from Enteric Nervous System and Vagus Nerve (VN) To the Neurons of The Central Nervous System

In addition to sharing the same ectodermal embryonic origin, the central nervous system (CNS) and the gastrointestinal tract (TGI) are connected by approximately 3,000 neurons. It is not such an expressive number when compared to 100 million neurons that make up the enteric nervous system (SNE), but it represents a direct link between the SNE and the CNS [2].

The VN is the other direct link from the ENS and the CNS. Our gut is directly connected to our brain by the neuron circuit of the VN. Sensory neurons inside the gut inform the VN how our Gastrointestinal Tract (GI) is doing from the stomach to the intestines. Besides its participation in the direct communication with the CNS the VN represents the main component of the parasympathetic nervous system and a key route of neural communication between CNS and gut microbiota [3-5]. The VN actively participates in the bidirectional interactions between gut microbiota-brain to maintain homeostasis in both cerebrum and gut [6]. For example, nerve disorders can cause either CNS dysfunction, e.g., mood disorders or neurodegenerative diseases, or gastrointestinal pathologies, such as inflammatory bowel disease and irritable bowel syndrome [7-9].

The Vagus afferent fibers are distributed to all the layers of the digestive wall but do not cross the epithelial layer so that they are not in direct contact with the gut luminal microbiota. Consequently, these fibers can only receive signals from the microbiota indirectly, through the diffusion of bacterial compounds or metabolites, or through other cells located in the epithelium, especially enteroendocrine cells, which transmit luminal signals [10].

Vagus efferent fibers regulate the responses to environmental or pathophysiological conditions in gastrointestinal system via the release of neurotransmitters [11,12] thereby impairing the digestive process and influencing gastric motility [13] by immune regulatory effects on local immunity and intestinal permeability. The VN stimulation can alleviate the production of macrofages and proinflammatory cytokines which might relieve inflammatory reactions [14] and promotes the expression and proper localization of tight junction proteins, thus decreasing intestinal permeability and exerting protective effects in intestinal epithelium barrier [15,16]. Due to their anatomical position, located in the epithelium, and function, secreting various factors in metabolic process, [17,18]. The enteroendocrine cell (EEC) [19] communicate with gut microbiota to send output signals in forms of hormones, such as 5-hydroxytryptamine (5-HT), cholecystokinin (CCK), and peptide YY (PYY), to afferent neurons [20-22], to transmit physiological signals from gut to brain, and also activating neural afferent fibers by binding to chemoreceptors [23, 24]. This neuroepithelial circuit between the CNS and the intestinal lumen is completed by functional synapses with their neurotransmitter glutamate, which transduce signals from vagus neurons to EEC and vice-versa [25,26].

Direct Connection between the CNS and the ENS via Lymphatic's: From the Galt System to the Brain

There is a complex interdependent relationship between the gut immune system, the ENS and the brain. The human enteric microbiome system is developed at birth and is colonized by populations of cells that will change continuously in response to luminal conditions. Colonized by the breast milk or colonized by cow's milk, that two different colonization will play a role in pathophysiological states throughout the individual's lifetime. Lymphocytes are present in our body systems and in the digestive tract they are organized under the same name "gastrointestinal associated lymphoid tissue" (GALT). The GALT system is the largest reservoir of lymphocytes of the human body. They are located all over GI tract, associated particularly with mucosa of the intestines, and its location prevails in the terminal ileum, where they are concentrated in the lymphoid nodules, which in turn are organized in the Peyer patches (PP) [2].

The prevalence of the location in the terminal ileum of this immune system appears to be purposeful so that only to this terminal portion of the digestive tube reaches molecules of proteins and particles or microorganisms that have escaped the digestive and absorptive process that occur in the anterior portions of the digestive tract. The enteric immune system is positioned between the interior of the body and the outside world, to provide security at one of the most contaminated borders constituted by microorganisms including bacteria, archaea, fungi and virus collectively referred as gut "microbiota" and the dietary fibers, antigens, mostly proteins, parasites and toxins as they appear in the warm-dark-moist-anaerobic environment of the intestinal lumen of particular importance for this relationship between the intestines and the central nervous system is the recent knowledge that these lymphatic systems, from intestines and from other systems, travel via the spineal cord to the central nervous system [27]. One important role of these lymphatic systems associated with the intestines lies in their action to monitor allergic attacks of proteins from the diet. When a food allergen passes through the M cell, present this antigen to the T lymphocytes of the PP. The T lymphocytes thus sensitized by this allergen takes two paths: either aided by dendritic cells, responds with the production of regulatory T cells, the regulatory T cell (Treg) and ends with the allergic reaction, or start to recognize the antigen and informs B lymphocytes the need to produce antibodies against the antigen, initiating the allergic reaction. This responsive system moves to the lymphatic system and from there to the brain [2].

This type of allergic response that begins with inflammation in the intestinal wall starts the food allergic response, with the immunological production of immunoglobulins IgE, IgA, IgM, IgG by the B lymphocytes. This lymphocyte load, with the CD4 T cells, moves across the lymphatic system to the central nervous system, as long as the neurons of the CNS have any inflammatory focus, acting as "target organ" in the CNS. In this way, a connection is established between the intestines and the brain, which will last for as long as the food allergic reaction and inflammation in the central nervous system lasts [2].

Signaling from the cells of the enteric immune system to the ENS establishes the first line of defense against foreign invasion at the vulnerable interface of a single epithelial cell barrier between the body and the outside environment. In inflammatory states, the neurons of the ENS among others secrete the neurotransmitter glutamate, a modulator of the brain-gut axis. Normal secretion or dysfunctions of the enteric glutamatergic transmission are involved in health and disease [25]. Inflammation in the ENS drives the inflammation to the neurons of the CNS [2].

Chronic Inflammation and Brain-Gut connection

An inflammatory response can be acute, lasting no more than hours, usually beneficial or could last a longer duration, referred to as chronic inflammation, that in this case may result in tissue destruction caused by defective mechanisms of the inflammatory response or consequent to an inappropriate immune response with prolonged inflammation [28]. Neuroinflammation in the CNS when chronic and prolonged can be particularly injurious to the microglia [29,30]. Microglia is the principal immune effector cell of the brain, responsible for the immunosurveillance. This chronic inflammation induces the microglia to act as antigen presenting cell or the release of cytokines, this will provide cells with the ability to communicate with one another and orchestrate a complex multicellular behavior [31,32].

Microglia as antigen-presenting cells, in presence of type class I and II major histocompatibility complex molecules, present the antigen to the T cell, respective, to T $CD4^+$ and T $CD8^+$ cells, activating the humoral or cellular immune response. This constitutes a major antigen-dependent interaction between mast cells and T cells, inducing the T cell to activation, proliferation, and cytokine secretion [33,34]. The concept of immunological synapse is based in the dendritic cells or mast cells, as antigen presenting cells, to present the antigen to the T cells [35,36].

The contribution of mast cells and microglia to neuroinflammation is strongly influenced by their potential for mutual interaction, since these cell types are often found near each other, facilitating cell-to-cell communication. Once microglia call for the recruitment of immune system cells, such as mast cells, lymphocytes and immunoglobulins, both peripheral and central nervous system will start diseases of the neurons that could be neuroinflammatory or neurodegenerative [37,38]. Aberrant activation of the innate immune system, in particular involving mast cells and microglia, may occur in either a context-specific fashion or because of the body's inability to resolve a state of protracted inflammation [39-42].

Several mediators derived from mast cells have neuropharmacological actions in the electrical and synaptic behavior of neurons in the SNE. After activated mast cells secrete numerous vasoactive, neurosensitizing and pro-inflammatory mediators, inducing neuroinflammation, which include biogenic amines (5-hydroxytryptamine, histamine), cytokines (IL6, interlleukin-1p), mast cell proteases (chymase, tryptase, acid hydrolases, among others), lipid metabolites (prostaglandin D2, leukotriene C4, platelet-activating factor), ATP, neuropeptides, nerve growth factor (NGF), adenosine, vascular endothelial growth factor and nitric oxide [43-45]. On the other hand, amide fatty acid can modulate the mast cell and microglia activity contributing to the resolution of neuroinflamation [46].

Immuno-Neural Signals: The Connection by Gluten-Purkinje Molecular Mimicry Cells

Recent studies have shown that the cerebellum, in addition to participating in motor coordination, also plays an important role in motricity, cognition and emotional processes. Motor, cognitive and emotional abnormalities can result in damage to parts of the cerebellum, which extend to motor areas, prefrontal cortex and limbic system, respectively. There is also evidence that the cerebellum is related to several cognitive abnormalities and psychopathological manifestations. There is a strong association between abnormalities in the cerebellum and psychiatric diseases, such as schizophrenia, bipolar disorder, depression, anxiety disorders, attention deficit and hyperactivity disorder (ADHD) and autistic spectrum disorder [47-53] and also a strong association between allergic diseases (allergic rhinitis, atopic eczema and asthma) with ADHD and other psychiatric diseases, such as separation anxiety disorder, obsessive-compulsive disorder and Tourette's syndrome [54-56].

Currently, there are three known cerebellar abnormalities in patients with autism: reduction of Purkinje cells, reduction of cerebellum volume and interruption of feedback between the cerebellum and the cerebral cortex. Purkinje cells are inhibitory in nature and their lack would reduce the inhibition projected by the cerebellum in the cortical and subcortical areas, causing hyper-sensitivity in these brain regions found in most patients with autism [57-60]. The Gliadin proteins and brain Purkinje cells share common epitopes. In some patients with autism, we have identified these antibodies against Purkinje cells and gliadin peptides, which may be related to the genesis or exacerbation of autism. This cross-reactivity exists, probably between gluten and Purkinje cells, although antigliadin antibodies are not the only ones that react with the epitopes of these cells. Immunohistochemistry shows that the removal of antibodies against gliadin from the serum of patients does not interrupt the total reactivity with the epitopes of Purkinje cells [61,62].

In patients with Gluten Ataxia, in addition to anti-gliadin, oligoclonal bands occur in cerebrospinal fluid, inflammation of the cerebellum and antibodies to Purkinje cells. Considering the fact that, the withdrawal of anti-gliadin does not prevent immune-mediated inflammation in the cerebellum, the arbitrary restriction of gluten in the diet of all patients with autism, who usually have this inflammation, is not justified [63].

Therefore, there is a need for a thorough investigation of food allergy to understand the type of immune response involved and which allergens are participating in the lesion [65].

Enteric Mast Cells and Brain-Gut Connection: Antigen or Psychological Stimuli

Enteric mast cells are packed with granules that are sites of storage for a broad mix of preformed chemical mediators.

Antigens stimulate the mast cells to release the mediators, which then diffuse into the extracellular space inside the ENS. Enteric mast cells express high affinity receptors for IgE antibodies or other immunoglobulins on their surfaces. A deluge of multiple mediators is released from the mast cells when antibodies to a sensitizing antigen occupy the receptors and cross-linking occurs by interaction of the sensitizing antigen with the bound antibody. Inflammation in the ENC occurs and CNS is affected [2].

The degranulation of mast cells caused by psychological stress activates the ENS "defense program" to produce the same symptoms of diarrhea and abdominal discomfort as the degranulation caused by the antigens. The link between brain cells and mast cells is significant, because the gastrointestinal symptoms associated with mast cell degranulation are expected to be the same, whether mast cells are degranulated by antigen-antibody cross-linking in allergic reactions or are degranulated by brain action during stress [65,66].

Mast Cells and Signaling Substances

Several mediators derived from mast cells have neuropharmacological actions in the electrical and synaptic behavior of neurons in the ENS. After activated mast cells secrete numerous vasoactive, neurosensitizing and pro-inflammatory mediators, inducing neuroinflammation, which include biogenic amines (5-hydroxytryptamine, histamine), cytokines (IL6, interlleukin-1p), mast cell proteases (chymase, tryptase, acid hydrolases, among others), lipid metabolites (prostaglandin D2, leukotriene C4, platelet-activating factor), ATP, neuropeptides, nerve growth factor (NGF), adenosine, vascular endothelial growth factor and nitric oxide [67,68]. We will focus only on the functions of the main mediators, histamine and serotonin [69].

Histamine

Histamine is not synthesized by enteric neurons and is not considered a neurotransmitter in ENS. Mast cells and neutrophils are sources of histamine in the intestine. The knowledge of histaminergic actions on ENS neurons comes from results obtained from electrophysiological and immunohistochemical studies on unique enteric neurons in animals.

Mast cells observed in biopsies of the colonic mucosa of patients with Irritable Bowel Syndrome, with a predominance of diarrhea, release more histamine than normal individuals and can increase intestinal secretion leading to secretory diarrheal symptoms such as those associated with infectious agents and food allergies [69].

Serotonin

5-hydroxytryptamine is another preformed mediator that is known to be released during degranulation of enteric mast cells and mucosal enterochromaffin cells to form a neuromodulator overlap in man's ENS. It has been estimated that about 95% of serotonin is found in the GI tract [70] Both histamine and 5-HT act on inhibitory presynaptic receptors on cholinergic axons to suppress rapid neurotransmission, on nicotinic synapses, on enteric neural networks. Presynaptic inhibition by both neuromodulators is mediated by a different receptor subtype than that which evokes excitatory responses in neuronal cell bodies.

The immuno-neurophysiological evidence reinforces the hypothesis that the moment-to-moment behavior of the intestine, whether normal or pathological, is mainly determined by the integrative functions of ENS. The "intestinal brain" processes input signals, derived from immune / inflammatory cells (for example, mast cells), sensory and CNS receptors [71,72]

The Microbiome and the Brain-Gut Connection

The communication between the brain, the gut and the microbiota is bidirectional, through multiple pathways. From the brain side to the gut by the neurons of the spinal cord, by the endocrine system through the hypophisis- hypothalamic-adrenal axis (HHAA) and by the microglia-mast cells immune pathway. From the gut side to the brain by the ENS and VN and by the immune system. From the microbiota to the brain by the neuroactive metabolites released by bacteria such as γ-aminobutyric acid (GABA), serotonin, dopamine, acetylcholine (ACh), short chain fatty acids, (SCFAs) and tryptophan [73-77]. From the microbiota to the gut through the EEC, acting locally on the enteric nervous system i.e., the gut brain [78,79]. Some of these compounds reach directly the brain via blood and circumventricular organs or through the VN, or spinal cord neurons or via lymphatics [80].

The diverse microbial communities that coexist and reside in human's gastrointestinal tract are microorganisms including bacteria, archaea, fungi and virus collectively referred as gut "microbiota" [81]. By associating the diet with the gut flora and examining the stool samples was found that Bacteroides were mainly associated with a diet that was high in animal fat and proteins, whereas Prevotella was mainly associated with a high-carbohydrate diet [82]. Small bowel contamination, infections in the GI tract and inflammatory bowel diseases induce an adverse effect on the normal microbiota. The disruption of the gut flora, the dysbiosis, cause deleterious effects on GI tract, inducing complication of the organic disorders or start a visceral disorder such as irritable bowel syndrome [83].

Distinct microbial flora, which is inherited maternally at birth, changes due to our dietary habits and environmental signals [84-86]. Children breast-fed has a microbiota prevalent in *Lactobacilus sp* and *Biffidobacteria sp*, comparing with children formula fed that develop a microbiota prevalent in coliform [2]. The role of microbiota in various physiological activities, including in immune system, has been well established previously [87]. In addition, alterations in gut microbes in response to critical immune signaling contribute to the illnesses in intestine and distal organs, such as allergy, inflammatory bowel disease, autoimmune disease, and various types of cancer [88,89]. Commensal lactic acid bacteria have been shown to trigger TLR3-mediated INF-β secretion by DCs in the intestine [90-92]. The role of IFN-I in modulation of microbiota has been studied [93-95].

Microbial metabolites have been well documented as activators of immune cells [96]. SCFAs produced in large-scale by the intestinal microbiota, as butyrate and propionic acid, exhibits a protective effect in inflammatory reactions, acting with suppressive

functions in colitis. SCFAs induce differentiation of suppressive Tregs [97,98], and induce proliferation of Foxp3$^+$ Tregs [99], with increased Tregs through Foxp3 promoter modification [100,101]. Two major metabolic effects of the SCFAs are the stimulation of the production of Tregs and retinoic acid in intestine. The retinoic acid inhibits Th17 cell differentiation and promotes Treg proliferation, thus contributing to the beneficial effects in neuroinflammation [102].

Long-chain fatty acids (LCFAs), on the contrary, enhanced differentiation and proliferation of cellular immune stimulation with the production of Th1 and Th17 cells, with increased expression of pro-inflammatory factors, e.g., TNF-α and IFN-γ [103]. Since the blood brain barrier allows the transport of these molecules in bidirectional way, all immune-endocrine-secretory metabolites can flow from the microbiome to the gut and to the brain, playing an important participation in physiology and pathology of the brain and the gut.

The Importance of Microglia and Astrocytes

Microglia protect brain against various pathological conditions, through the involvement in immune response activation, phagocytosis, and cytokine production [104,105]. In addition, microglia regulate synaptic transmission, synaptic pruning, and neuronal circuit formation, which are involved in brain development and homeostasis [106-108].

Microglia originate from yolk sac-derived erythromyeloid progenitors, migrate to the brain during development, and maintain until adulthood through local self-renewal. Microbiota species can drive the maturation of microglia and maintain their homeostasis [109]. Studies have shown that microbiome impacts the properties and function of microglia [110].

The immune system plays an important role in maintaining health by gut homeostasis. The elderly has a state of immune senescence, with decreased immune function, resulting in a change in the microbiota-brain connection and subsequent behavioral change. Microglia are immune cells in the CNS, and studies have found that the metabolism of gut microorganisms can regulate the maturation and function of microglia, thereby affecting CNS function [111]. Astrocytes have multiple essential functions to keep the CNS normal function: 1- control of the brain–blood barrier (BBB) stability; 2- control of the blood perfusion in cerebrum; 3- regulation of ion gradient balance and nutrients across the membranes and 4- modulation of neuron transmission [112]. Astrocytes are the most abundant cell population in CNS and they outnumber neurons by almost fivefold [113], and excessive activation of astrocytes induce the production of neural cytotoxic or immune inflammatory substances, leading to CNS dysfunction and neurological disorders.

The microbiota and central nervous system interact in a bidirectional relationship bridged by the gut-brain axis. This axis is also influenced by the gut Immune system, enteric nervous system, vagal nerve and by the CNS, hypothalamic-hipofisis-adrenal axis, and entero-endocrine cells [2].

It has been accepted that human cells are outnumbered by microorganisms, in our body, mainly by the microbiota population, for a ratio of 1:10. Recent literature shows that the proportion is closer to 1: 1 [2].

The composition of the microbiome differs in number and species between individuals. Each one of us has his own "microbiome-microbiota signature". The normal equilibrium and harmony of the microbiota with the connected systems is essencial to the homeostasis and normal development of the microbioma-gut-brain axis for all humans [2].

The intestinal microbiota has played an important participation in digestion, in immunity, in protecting against inflammation, in keeping the normal flora whithout pathogenic microorganisms and in maintaining the integrity of the neurons of the ENS and CNS. This multiple function and the connections of the microbiota related to the gut and to the brain extend the old concept of "gut-brain axis" to new correlations, leading to the term "microbiota-gut-brain axis". The interaction of this axis is bidirectional, which means that the metabolites of the altered microbiota (dysbiosis) can affect the brain, the gut and vice versa Figure 1.

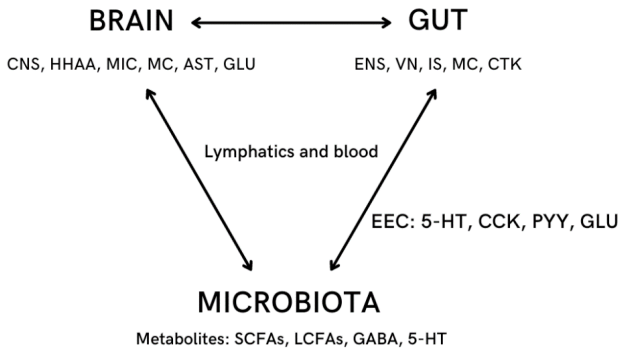

Figure 1: Microbiota-Gut-BrainAxis

BRAIN: CNS (central nervous system); **HHAA** (hipotalamic-hipofisis-adrenal axis); **MIC (**microglia); **MC** (mast cells); **AST** (astrocytes); **GLU** (glutamine)

GUT: ENS (enteric nervous system); **VN** (vagal nerve); **IS** (immune system); **MC** (mast cells); **CTK** (cytokines)

EEC (entero-endocrine cells):**5-HT** (5-hydroxytryptamine); **CCK** cholecystokinin; **PYY** (peptideYY); **GLU** (glutamine)

MICROBIOTA: metabolites: **SCFAs** (Short chain fatty acids); **LCFAs** (Long chain fatty acids); **GABA** (Gamma-AminoButyric Acid); **5-HT** (5-hydroxytryptamine); **CCK** (cholecystokinin), and **PYY** (peptide YY).

Dysbiosis

The human community of microorganisms develops early in life and remains stable for life. Modifications can occur influenced by breast milk or formula, by the diet, by environmental factors,

by leaving in urban or rural areas, by GI infections, parasites or by the use of antibiotics. The alteration in the composition of the microbiota is called dysbiosis [2].

Dysbiosis is seen in several GI diseases such as diarrhea, small bowel contamination, celiac disease, irritable bowel syndrome, inflammatory bowel disease, chronic colitis, malnutrition and food allergy. Although dysbiosis seems to be an important denominator in those diseases, no specific modification of the intestinal flora has been identified. In dysbiosis the metabolites from the altered microbiota such as SCFAs and LCFAs, seems to influence the microbiome-gut-brain axis by modulating neuroendocrine reaction (HHAA), neuroimmune (Microglia, Lymphocytes), mucosa secretions **(5-HT and Histamine) and intestinal sensory system (ENS-CNS) [121].**

Conclusion

The brain-gut-microbiome axis has several types of well-established connections: 1- the direct connections through the SNE and the vagus nerve; 2- the direct connection by the lymphatic system; 3- the connection after chronic inflammation in the brain; 4- through gluten-Purkinje molecular mimicry; 5- through immuno-mediators such as mast cells; 6- through the enteric microbiota and their metabolites.

Importance of the SNC axis

With this knowledge of the close relationship between the ENC, the CNS and the microbiome through several mechanisms of interaction, we must be extremely careful in producing any alteration in any of those systems that immediately will reflect in the axis, generating alterations in the gut system, in the brain function or in the microbiome.

The Disruption of the Brain-Gut-Microbiome Axis is Related to Several Diseases.

FA in the gut and inflammation in the brain are in the burden of the immune response, which promote the lymphatic circulation of immune lymphocytes that will circulate throughout the body in search of inflamed organs. Finding this inflammation in the neurons of the CNS, the immune response will focus on them and transform them into the “target organ” of the immune response, leading to chronic inflammation in those neurons of the CNS, therefore being able to place the individual inside the autism spectrum disorder, clinically changing its spectrum according to the affected area and the extent of allergic aggression.

Some measures can be taken prophylactically to prevent the establishment of FA, such as exclusive breastfeeding and to avoid excessive hygiene. If the patient still develops FA, we must avoid GI disease and concomitant CNS disease, eliminating all causes of antigens or antibodies circulating in these systems.

The protection of neurons must be done through a restrictive diet that ceases the immune action of FA in these systems. With the cure by the diet of the FA, the digestive disease and consequent aggression to the ENS will disappear. In this way, the aggression to the CNS ceases and the ASD goes into remission.

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