The Brain-Gut Connection and the Autistic Spectrum Disorder

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Abstract: The autism spectrum disorder (ASD) occurs in one out of every 68 individuals and can affect any child regardless of sex, race or socioeconomic status. This study enrolled all patients with the diagnosis of ASD attended the Unit of Gastroenterology, Food Allergy and Autism at the Unigranrio University. All of these patients were investigated for food allergy (FA). The gastrointestinal tract of patients with ASD has been extensively studied in recent decades and reveals indistinguishable findings from those found in FA. It is observed that autism often establishes itself as a disease in patients with adequate psychomotor development and without previous neurological conditions, but with FA preceding the neurological deficits. We hypothesized that FA is one of the foregoing factors in patients who develop ASD, if they suffer from inflammation of the central nervous system (CNS). This inflammatory injury may turn neurons the target organ or the FA homing site, once the brain-gut connection is established by different mechanisms.

Keywords: brain-gut connection, GALT disease, food allergy and ASD, neurons inflammation, CNS immune target organ

1. Introduction

Autism spectrum disorder (ASD) is characterized by disorders of the neurological development, typically diagnosed in the first 4 years of life, which presents clinically with compromised social interaction, deficits in verbal and non-verbal communication and stereotypes behaviors with repetitive non-purposive finality. (1-3) Occurs in one in 68 individuals and can affect any child regardless of gender, race or socioeconomic condition, being four to five times more frequent in sex masculine. (4)

In the literature indexed so far, ASD does not have a defined etiology and the pathophysiological mechanisms involved remain unknown. Current studies in search of these mechanisms and etiopathogenesis investigated the genetic, environmental and immunization causes. For this shortage of information on ASD, its treatment takes unpredictable and being a fallacy. (5) The lack of understanding about the disease is particularly of worse, because of the increase in prevalence, since ASD has already at epidemics levels. (6)

By studying patients with food allergy (FA) it is possible to observe that genetic factors, environmental factors and immunizations are also present in different moments, in expressive numbers. Genetic predisposition, which in this case determines the ability to respond with allergy to non-pathogens antigens, is fundamental to the genesis of allergic disease and also is present in the ASD. Children of both allergic parents have 80% of chance to be allergic and we observed that in more than 85% of the patients with ASD, there was a family history of respiratory and food allergies. (7)

Since 1998, with our publication of a prior notice in “The Lancet” signaling that patients with FA presented endoscopic alterations and in the biopsies of the terminal ileus show similar aspects to those described in patients with ASD (8,9), we start extensively research in the link of FA and ASD. Surprisingly we found that 100% of the patients with ASD were diagnosed also with FA, being the GI tract, more specifically the GALT system (gastrointestinal associated lymphoid tissue), the mucosal-associated lymphoid tissue (MALT) of higher prevalence of involvement before the onset of the neurological disturbance that makes up the development of ASD.

2. Material and Methods

We included in this study all patients with previous diagnosis of ASD, attended at the outpatient clinic Unit of Gastroenterology, Food Allergy and Autism of the University Unigranrio (UGAA). The diagnosis of FA was made through the Score for the Diagnosis of FA (10), through physical examination focused on the identification of clinical multisystemic involvement and with the laboratory investigation that identifies the immune mediation present in each patients with ASD and FA.

We collect information by reviewing the medical records, characterizing this study as a retrospective cross-sectional study. Some figures do not present the same total of patients, because over the years, we added new data to the anamnesis, according to the progress of the literature in this area. The UNIGRANRIO Ethics and Research Committee approved this research project under number CAAE 66813917.0.0000.5283. The Free and Informed Consent Term is in accordance with resolution number 466 of December 12, 2012, of National Health Council, on research involving human beings.

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3. Results

A total of 86 patients previously diagnosed within the spectrum of autism were studied and in 100% of these ASD patients the diagnosis of FA was present in 100% of them. In order to identify which of the two pathologies, ASD or FA, was established first in each individual, the number of MALTs affected before the start of the ASD was measured. Only two of the 86 ASD patients studied did not contain this information, belonging to a study conducted 20 years ago. It is clear that FA is a pre-existing condition, since that 98.8% patients had at least one MALT affected before the onset of ASD. (Figure 1) and only one patient (1.2%) enters in the spectrum of ASD involvement at the same time of interrupting breastfeeding.

In 84%, there was GALT involvement preceding ASD (Figure 2), others lymphoid tissues were also affected previously, but not so expressively. Immune mediators varied, 34% had mixed mediation, secondly with 32% the mediation was Th2, followed by 23% who presented Th1 mediation and 11% with other immune mediators such as NK cells involvement.

4. Discussion

Food allergy is a multifactorial disease that develops in the presence of factors such as inadequate breastfeeding, the health of the mother and her GI tract disease, during pregnancy and breastfeeding, complications and sterile (cesarean) deliveries and early exposure to cow's milk and, to a lesser extent, wheat and soybean (11). Once sensitized to a particular antigen, the individual may respond with food allergy in case that this conjuncture of factors is present. After immune activation in the Peyer patches (PP) of the GALT system, the antigens, lymphocytes and immunoglobulins, continue to search for their "homing" clinical response. The "homing" chosen may be in the BALT (bronchial associated lymphoid tissue), the NALT (nasal associated lymphoid tissue), in the SALT (skin associated lymphoid tissue), or can come back to GALT itself or go to the CNSALT (central nervous system associated lymphoid tissue), involved in ASD. The definition of which body system will be affected is influenced by the genetic inheritance, environmental factors and other inflammatory factors that function as triggers for the involvement of lymphoid tissues. (12-14)

Inflammation, physical and psychic trauma, infections and vaccine with neurotrophic agents (mainly measles, sabin and pertussis) has the potential to directly the inflammation to the neurons and make the central nervous system (CNS) the homing for the immune system affected in FA, attracting the circulating lymphocytes and the immunoglobulins that participate in the process of FA, to the CNS. (5) The clinical manifestations of the aggression to the CNS can thus cause the individual to develop the autism spectrum, varying clinically according to the affected area and the degree of allergic aggression to the CNS.

In addition to sharing the same embryonic ectodermal origin, the CNS, the Skin and GI tract are connected by about 3,000 neurons. The number is few but expressive, when compared to the 100 million neurons that make up the intestinal nerve plexus. (14) This abundance of neurons in the presence of FA, a condition that generates inflammation, favors homing to local neurons, causing alteration of the gastrointestinal tract, and probably for the CNS as well. It is often observed constipation, as a pattern of bowel movements in ASD. But those with the disorder have various forms of dysmotility other than diarrhea and constipation, (5,15-18), often misinterpreted as behavioral issues (19-22)

There is concrete evidence of immune activation in ASD, which is the finding of nodular lymphoid hyperplasia in the ileal-colonic area (INLH). (8) Since 1998, it has been described the association between ASD and this activation of peyer's patches (PP). This fact corroborates the finding of FA throughout all of this population.

One of the most important signal of FA with GALT involvement is the dysmotility, secondary to gastroparesis, that can be presenting as gastroesophageal reflux in the newborn or dyspepsia in older children, such as in schoolchildren the verification of gastric emptying time with Tc99 we are able to diagnosis and assess the dysmotility. (23-25) The change in peristalsis found in ASD patients occurs due to defective transmission of the nerve impulse, due to defects transmission between the neurons of the intestinal plexuses and the smooth muscle, probably due to the inflammation capable of altering the physiology of the neural cell.(26,27)

The GALT system was the most affected MALT (84%) preceding the onset of neurodevelopmental disorders that composed of ASD. (28-48) This fact supports the hypothesis of inflammation in the enteric nervous system favor the homing for both local neurons and the neurons of the CNS, since the lymphatic pathways has recently been recognized by immunological surveillance of both. (17) The inflammatory process from FA has continued exposure to antigens of the diet against which patients react on both GI tract and CNS, thus evolving into GALT and CNSALT disease. The interruption of this exposure, with the restrictive diet for FA antigens, is therefore justified, causing inflammation to cease in these systems affected. (16)

In October 2015, in the journal Nature, the brain-gut connection goes into because a growing set of data, mostly in mice, demonstrates that the intestinal microbiota influences behavior and can change the physiology of the brain and neurochemistry. (49,50) However, it follows the question whether the microbial differences associated with diseases are causes or only consequences. It is postulated that there is more speculation than data to date. Also in mice, it was possible to shown that the metabolites produced by their microbiota are capable of to change the blood-brain barrier, such as butyrate (short fatty acid) approaching the intercellular junctions of the barrier. (43)

Recent studies have shown that the cerebellum, besides participating in the motor coordination, it also plays an important role in the motor, cognition and emotional processes. (51) Motor abnormalities, cognitive and emotional problems, may result from damage to portions of

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the cerebellum projecting to motor areas, prefrontal cortex and limbic, respectively. (52,53) There is also evidence that the cerebellum is related to various cognitive abnormalities and psychopathological manifestations. (54-57) There is a strong association between abnormalities in the cerebellum and psychiatric illnesses such as schizophrenia, bipolar disorder, depression, anxiety disorders, ADHD and ASD. (58-71) It should be noted that there is a strong association between allergic diseases (allergic rhinitis, atopic eczema and asthma) with ADHD and that other psychiatric disorders such as anxiety disorder disorder, obsessive-compulsive disorder and Tourette's syndrome are also found more frequently in atopic patients. (72-77) Currently, three cerebellar abnormalities are recognized in patients with ASD: (71) decreased number of Purkinje cells, cerebellar volume reduction and interruption of feedback between the cerebellum pathway and the cortex. The cells of Purkinje area of an inhibitory nature and their lack would diminish the inhibition that the cerebellum projects in the cortical and subcortical areas, leading to hypersensitivity of these regions in the brain found in most patients with ASD. (78-81)

In 2002, it was reported in Neurology that gliadin proteins and the cells of Purkinje of the cerebellum share common epitopes. (78) In some patients with ASD have already been identified antibody against cells of Purkinje and against the peptides of gliadin, which may be related to the genesis or the exacerbation of autism. (79) Probably there is this reactivity between gluten and Purkinje cells, although the antigliadin antibodies are not the only ones that react with the epitopes of these cells. The Immunohistochemistry demonstrates that the removal of antibodies against gliadin of the patient's serum does not brake all the reactivity to the epitopes of the Purkinje cells. In patients with gluten Ataxia, in addition to anti-gliadin, we have oligoclonal bands in the cerebrospinal fluid, inflammation in the cerebellum and Purkinje anti-cell antibodies. (80)

In view of the fact that anti-gliadin withdrawal does not originate in the cerebellum, the arbitrary withdrawal of gluten from the diet of all patients with ASD, who usually present with this inflammation, are not justified. We therefore stress the need for FA in order to understand the type of immune response involved and which allergens that are participating in the aggression.

5. Conclusion

The brain-gut connection is established in several ways, from indirectly through the microbiota and the metabolites that it produces even directly as the gluten-Purkinje molecular mimicry or the homing for the enteric and CNS neurons. The clinical manifestations of AA in the CNS can thus cause the individual to enter the spectrum of autism, varying clinically according to the affected area and the degree of allergic aggression.

Some conducts can be adopted prophylactically to avoid establishment of FA (82-87), and if the patient develops FA, we should avoid GI disease and concomitant CNS aggression, cause of inflammation in these systems. The protection of neurons will be through the restrictive diet, which ceases inflammation in these affected systems, until the resolution of FA, digestive disease and the consequent aggression to the SNC. (88)

References


[79] Jackson JR, Eaton WW, Cascella NG, Fasano A, Kelly DL. Neurologic and Psychiatric Manifestations of