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Review

Autism: Etiology, Epidemiology, Pathology, Clinical Aspects and Treatment

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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 at our Unit of Gastroenterology, Food Allergy and Autism (UGAAA). All of these patients were investigated for food allergy (FA). The gastrointestinal tract, the upper and lower airway tract, the skin and the central nervous system of our patients with ASD where extensively studied regards of the epidemiology, pathology, clinical aspects and treatment. 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. With those new data we were able to develope the concept of the etiology, pathology, clinical aspects and treatment of ASD.

Keywords: Brain-gut connection in ASD; GALT; BALT; SALT diseases; Food allergy and ASD; Neurons inflammation; CNS target organ

INTRODUCTION

The autistic spectrum disorder (ASD) is a neurodevelopmental brain disorder presenting clinically with restricted, repetitive patterns of behaviors, interests, and activities, with deficits in social communication and social interaction, with persistent verbal and non-verbal communication, typically diagnosed within the first 4 years of life [1-3].It occurs in one out of 68 individuals and can affect any child regardless of sex, race or socioeconomic status and is four to five times more frequent in males [4].

Genetic, environmental and immunizations causes have been investigated, but ASD does not have a defined etiology and the pathological mechanisms involved remain unknown [5]. The lack of understanding about the disease is particularly worrying because, due to the increase in prevalence, the ASD has already reached epidemic levels [6].

Patients with food allergy (FA) have endoscopic alterations and terminal ileum biopsies similar to those described in patients with ASD [7,8]. The alterations in their immune responses identified in the peripheral blood, the immune-histochemical alterations in their biopsies, in addition to the findings of endoscopy found in over a hundred ASD patients were identical to those found in patients with FA [9]. Gastrointestinal symptoms identified in most patients with ASD, which lead these patients to present the stereotypical reactions of their illness, are also compatible with FA [10-12]. Aiming to understand the etiology and the pathological mechanisms involved in ASD, we collect the data from 499 patients with this disorder assisted at our service in the last years.

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

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to the progress of the literature in this area. The national 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.

ETIOLOGY AND PATHOLOGY

A The literature shows the etiology of ASD related to genetic, biological and environmental influences and all studies end up stating that their etiology is unknown. Much of the literature relates ASD to genetic factors, due to neurobiological disorders such as seizures, mental deficiency, decreased neurons and synapses in the amygdala, hippocampus and cerebellum, increased encephalon size and increased glutamine/glutamate concentration in these synapses. The findings of genetic mutations associated with ASD reinforce this genetic hypothesis. However, the genetic as the cause of ASD have not yet be scientifically proven to date [1-6].

Another group of researchers linked the ASD to biochemically unbalanced organisms. Until the mid-1970s, theories appeared that this disease originated from problematic affective relationships between mother and child. Other articles link to environmental factors such as maternal exposure in prenatal or postnatal period to viral infections and medications, as well as the exposure of children to pox virus, rubella, mumps and MMR. Studies also point out that maternal vitamin D deficiency is a risk factor for ASD. However, the etiologies cited have not yet been scientifically proven to date [1-5,13].

The disorder comprises a variety of different clinical endophenotypes and is potentially linked with certain comorbidities. According to current recommendations, children with ASD are at risk of having alimentary tract disorders i.e., they are at a greater risk of general gastrointestinal (GI) concerns, constipation, diarrhea, and abdominal pain. GI symptoms may overlap with ASD core symptoms through different mechanisms [1-5].

These mechanisms include multilevel pathways in the gut–brain axis contributing to alterations in behavior and cognition. Shared pathogenetic factors and pathophysiological mechanisms possibly linking ASD and GI disturbances, have been shown by most recent studies, that include intestinal inflammation with or without autoimmunity, immunoglobulin E-mediated and/or cell-mediated GI food allergies as well as gluten-related disorders (Celiac disease, Wheat allergy, Non-celiac gluten sensitivity), visceral hypersensitivity linked with functional abdominal pain, and dysautonomia linked with GI dysmotility and gastroesophageal reflux. Dysregulation of the gut microbiome has also been shown to be involved in modulating GI functions with the ability to affect intestinal permeability, mucosal immune function, and intestinal motility and sensitivity [14,15].

All the above-listed GI factors may contribute to brain dysfunction and neuroinflammation depending upon an individual patient's genetic vulnerability. Due to a possible clinical endophenotype presenting as comorbidity of ASD and GI disorders, we have been treating this situation as an "overlap syndrome". Practical use of the concept of an overlap syndrome of ASD and GI disorders may help in identifying those children with ASD who suffer from an alimentary tract disease as FA [16].

Based upon these data we propose the central hypothesis that a examination of the association of food allergy and other allergic conditions with ASD will offer new therapeutic opportunities within the field of the allergic and neurodevelopmental brain disorders. The immunomodulatory role of food allergy and neuroinflammation is the basic process in the pathogenesis of the clinicalsymptomatology of ASD in children [17-19].

A new paradigm emerges from our studies, weaving ASD to food allergy (FA). We found that FA precedes ASD and that the immune disorders of FA reach through the lymphatics to the central nervous system and compromise the neuronal functions that lead to ASD [5,20].

BRAIN-GUT CONNECTION

Besides sharing the same ectodermal embryonic origin, the CNS and the enteric nervous system (ENS) of the gastrointestinal tract are connected by approximately 3,000 neurons. This number is not expressive when compared to the 100 million neurons that compose the intestinal neural plexus [21,22]. This abundance of neurons in the presence of FA, a condition that leads to inflammation, promotes homing to local neurons, changing the peristalsis of the gut and probably to the CNS too. It is often observed variations in the peristalsis in autistic patients who usually have constipation and less frequently there are the patients that present diarrhea [23]. But those with ASD have various forms of intestinal dismotility besides diarrhea and constipation not often misinterpreted as behavioral issues, rather than a medical condition [23-30].

There is concrete evidence of the immune activation in ASD, which is the finding of ileocolonic lymphoid nodular hyperplasia [31-33]. Since 1998 it is described the association between ASD and this activation in Payer's patches which corroborates with the FA findings throughout this population [34,35]. One of the earliest signs of FA with GALT involvement is dysmotility that may present as gastroesophageal reflux in the newborn or dyspepsia with secondary glutting due to gastroparesis in children and adolescents or as constipation due to colonparesia at any age or as abdominal distension consequence of enteroparesia [36-46]. Using the gastric emptying scintigraphy with Tc99m, it is possible to evaluate the gastric dysmotility, [47]. The alteration in the peristalsis in ASD is caused by a transmission failure of the nervous impulse, due to a defect in the nitric oxide local metabolism, among the neurons of the intestinal plexuses and the smooth muscles, probably derived from inflammation capable of altering the physiology of the neural cell [27,48].

The GALT was the most affected MALT (88%) preceding the beginning of the neurodevelopment impairments that compose the ASD. This fact supports the hypothesis that inflammation in the neurons of the enteric nervous system promotes homing to local neurons as well as CNS neurons, once the lymphatic pathway was recently recognized for carrying out the

immunological surveillance of both [14]. The inflammatory process arising from FA has permanence in the gut and in the CNS thanks to continuous exposure to dietary antigens against which patients react, thereby progressing to disease of the GALT and CNSALT. The interruption of this exposure with the restrictive diet for the antigens that cause the FA is therefore justified and ceases inflammation in these affected systems.

In October 2015, in the journal Nature, the brain-gut connection is mentioned for a growing set of data, most in mice, showing that the gut microbioma influences behavior and can alter brain physiology and neurochemistry. However the questions remais if the microbial differences associated with diseases are causes or consequences only [49]. Also in mice, it was possible to prove that the metabolites produced by their microbiota can alter the blood-brain barrier, such as butyrate (short chain fatty acid) that approximates the intercellular junctions of the barrier [50].

Recent studies have shown that the cerebellum, besides participating in the motor coordination also performs an important role in motricity, cognition and in the emotional processes [51]. Motor, cognitive and emotional abnormalities can result from damage to some areas of the cerebellum which project to motor areas, prefrontal cortex and limbic system, respectively [52-54]. There is also evidence that the cerebellum is related to several cognitive abnormalities and psychopathological manifestations [55]. There is a strong association between abnormalities in the cerebellum and psychiatric diseases such as schizophrenia, bipolar disorder, depression, anxiety disorders, ADHD and ASD [56-71].

It stands out that there is a strong association between allergic diseases (allergic rhinitis, atopic eczema and asthma) with ADHD and other psychiatric disorders such as separation anxiety disorder, obsessive-compulsive disorder and Tourette's syndrome which are also found more frequently in atopic patients [72-75].Interestingly, it was discovered that the cerebellar damage in children can predict the occurrence of autism in older age, and this is another possible trigger mechanism for homing [76]. Presently, there are three known cerebellar abnormalities in patients with ASD: Reduction of the number of purkinje cells, reduced cerebellum volume and interruption of the feedback pathway between the cerebellum and the cortex. The purkinje cells are of inhibitory nature and their lack would decrease the inhibition projected by the cerebellum in cortical and sub cortical areas, causing hypersensitivity in these brain regions found in most patients with ASD [77].

In 2002, it was published in the journal Neurology that the gliadin proteins and the purkinje cells of the cerebellum share common epitopes [78]. In some patients with ASD, antibodies against purkinje cells and peptides of gliadin have been identified and these may be related to the genesis or exacerbation of autism [79]. Probably there is this cross reactivity between gluten and purkinje cells, although anti-gliadin antibodies are not the only ones that react with epitopes of these cells. Immunohistochemistry shows that the removal of antibodies against gliadin from the serum of patients does not stop the whole reactivity to epitopes of the purkinje cells [80-82].

The arbitrary removal of gluten from the diet of all patients with ASD, which generally have this inflammation, is not justified considering the fact that the withdrawal of the anti-gliadin does not stop the inflammation of immune origin in the cerebellum. We emphasize, therefore, the need for more careful investigation of FA in order to understand the type of immune response involved and which allergens are participating in the process [82].

EPIDEMIOLOGICAL ASPECTS

A retrospective cross-sectional study was performed in 499 patients of both sexes, 432 males and 67 females, diagnosed with ASD, who previously presented FA, with ages varying from 3 to 30 years, who were attended from January 2015 to December 2017 at our UGAAA.

As to the predisposing factors of FA, 499 patients had genetics in their parents and siblings at a level of 87% for allergy development (24% in the general population). The disease of the enteromammary cycle (DCEM) was present in 74 patients and did not occur in another 313. In 112, nothing was reported. Regarding the precipitating factors of FA, we found that, in 167 patients, the type of delivery was not reported, but in 32 patients the delivery was vaginal and in the other 300 it was cesarean.

The use of cow's milk formula before breast milk was present in the nursery in 261 children. The rest of the 148 were correctly breastfed and another 90 children did not have the information (96% of non-allergic children are correctly breastfed). As for gender, the male prevailed over the female, with a ratio of 6.5:1. The prevalence of age for ASD was 18 to 48 months in 89% of the patients.

FA is a disease that is influenced not only by predisposing factors such as genetic factors and DCEM, but also environmental factors such as type of birth, inadequate use of cow's milk before breastfeeding, age and sex.

IMMUNE MEDIATIONS AND "HOMING" IN ASD AND FA

After immune activation in Payer's patches (PP) of the GALT system, antigens, lymphocytes and immunoglobulin's, go through the lymphatic system searching for their homing at a target organ. The homing site could be the BALT, GALT, SALT, CNSALT or back to GALT itself. The definition of which target organ will be affected is influenced by genetic inheritance, environmental factors and other inflammatory factors that act as triggers [83-84].

Although it is accepted that central nervous system (CNS) receives constant immune surveillance, only in June 2015 it was discovered the presence of lymphatic vessels in the CNS going through the meninges. The confirmation of existence of the lymphatic system in the CNS requires a reassessment of the basic assumptions of the neuroimmunology and sheds new light on the etiology of neurodegenerative diseases and neuroinflammatory such as ASD, possibly mediated by the immune system [84-87].

Inflammation, physical and psychological trauma and infections of the CNS cause inflammation in neurons and have the potential to make the CNS the "homing" site or target organ, attracting the circulating lymphocytes and immunoglobulins involved in the process [88]. The clinical manifestations of FA in the CNS may therefore cause the individual to present within the autism spectrum, clinically varying according to the affected area and the extent of allergic aggression towards this system.

FA is pre-existing condition, since 98% had at least one MALT affected before the onset of signs and symptoms of ASD. Autism often established as disease in patients with adequate psychomotor development and neurological past without alterations, but with FA. We developed our hypothesis about the FA being one of the foregoing factors in patients who develop ASD, as long as these patients with FA suffer an inflammation of the CNS making neurons the target organ [5,83].

IMMUNE MEDIATIONS

The prevalence of immune mediation has been shown to be almost similar in the two populations studied: FA and ASD patients. The major difference occurred in one of the affected systems, where in the allergic population with ASD, the gastrointestinal impairment prevailed. In the population of FA without ASD the systems are affected without GALT prevalence.

Of the charts analyzed in 84,2%, there was involvement of GALT (lymphoid tissue associated to the gastrointestinal tract), in 42.2% of SALT (lymphoid tissue associated with the skin), in 36.8% of NALT (Lymphoid tissue associated to nasopharynx) and in 20.8% presented the BALT involvement (bronchial associated lymphoid tissue).

Immune mediations are similar in FA and ASD, which may have humoral mediation (IgE-mediated), cellular mediation (CD4 / CD8) with increased CD8 and mixed mediation (humoral and cellular), as well as other medications such as increased Natural Killer cells, eosinophils, IgG4 or marked reduction of CD8 T lymphocytes. In 37% of the patients, there was humoral mediation due to IgE, followed by mixed mediation allergies (35%)and by 17% presenting with cellular mediation and 11% with other known immune mediations (increase in NK cells (3%).

The antigen present in the allergic process was detected by Skin Prick Test (SPT): milk was positive in (84%) of the patients, eggs in (50%), wheat in (44%), also beef in (44%), chicken in (41%) and soy in (41%) and oilseeds in 32% of the patients. The diet was based in exclusion of the SPT positive allergens.

MALT´S AFFECTEDS IN ASD AND FA

Mucosal associated lymphoid tissues (MALTs) play an important role in the regulation of local immunity and are affected in food allergy (FA) as well as in autistic spectrum disorders (ASD).

Once sensitized to a given food antigen the individual responds with an immune response, starting a clinical alteration that we call FA. The immune system reaction include the T and B cells generated in the immune activity, after the food allergen is presented to the T cell by the dendritic cells in the area of the Mcells of the terminal ileum. After this presentation the T cells generate information to the B cells to start the production of antibody against the food allergen. This complex of cells travel in the lymphatic system in order to find the target organ, calling this process of "homing" to the target organ. The "homing" chosen depends on genetic influences, environmental or local factors, such as inflammation, which act as triggers for the involvement of the associated lymphoid tissues.

The central nervous system (CNS) involvement in the systemic immune response appears for the first time in the medical literature in the journal Nature on June 1, 2015, a finding made by researchers at Columbia University who demonstrated that lymphatic of the CNS; lead the systemic immune response to the CNS, when the central nervous system is inflamed.

FOOD ALLERGY IS A PRE-EXISTING CONDITION FOR ASD?

The diagnosis of FA was made in 100% of our patients with ASD and in order to identify which of the two pathologies was established first in each individual, the number of MALTs (mucosal associated lymphoid tissues) affected prior to the onset of ASD was measured. All had at least one MALT affected before the onset of signs and symptoms of ASD signaling FA as a pre-existing condition. Only 5 patients had one system affected before the onset of the disease and the other 95 had two or more systems.

It was evident that FA is a pre-existing condition, since 99.3% of the patients studied had at least one MALT affected before the onset of signs and symptoms of ASD. Only 2 patients (0.7%) were previously asymptomatic and one of them entered the spectrum simultaneously with multisystem FA involvement, coinciding with the interruption of breastfeeding.

PREVALENCE OF CLINICAL MANIFESTATIONS OF FOOD ALLERGY IN PATIENTS WITH AUTISTIC SPECTRUM DISORDER

A retrospective cross-sectional study using 499 patients of both sexes presenting ASD, with ages varying from 3 to 30 years, who were attended in our clinic between January 2015 and December 2017 where studied of the prevalence of the clinical manifestation of food allergy at the moment of their presentation at our clinic.

All patients analyzed in this study had ASD, therefore, 100% of the patients investigated had CNSALT involvement. Clinical changes due to FA in each mucosal associated lymphoid system (MALT), gastrointestinal tract (GALT), skin (SALT), upper airway (NALT) and bronchi (BALT) were observed.

In addition, we individually analyze the complaints related to each of these systems. The symptoms of the GALT system was constipation (162 patients), diarrhea (158 patients), abdominal pain (122 patients), reflux (116 patients), abdominal distension (87 patients), hematochezia (56 patients) and bulky stools (48 patients).

As for the skin affections, we noticed a higher incidence of facial pallor (222 patients), dark circles (145 patients), andxeroderma in 102 patients. Other dermatitis in 91 patients (pruritus in 55 patients, eczema in 46 patients and urticaria in 36 patients).

The respiratory system of these patients was the least affected, regards the NALT or BALT system. To the upper airway tract symptoms the NALT presenting allergy was present in 200 patients (rhinitis in 106 patients, coryza in 96, sinusitis in 46 and and otitis media in 24 patients). To the lower airway tract symptoms the BALT allergy was present in 106 patients with recurrent bronchitis in 90 patients and asthma in 63 patients and acute respiratory failure and bronchospasm in 44 patients.

In a typical patients with ASD, we noticed that the clinical aspects, related to the other systems, at the moment of the first contact with us, has multi-systemic presentation,characterized by the presence of constipation or diarrhea, facial pallor, dark circles and dermatitis.

We found that the digestive disease was similar to that of patients with FA without ASD: diarrhea, constipation, reflux, abdominal pain and abdominal distension. The same with regards to the respiratory disease with rhinitis, coryza, secretion, bronchitis or asthma and also the same in relation to your skin disease as dermatitis, eczema or urticaria.

HOW WE TREAT OUR PATIENTS

With these findings in our hands we postulate that FA occurred in patients with ASD, which allowed us to treat them for their food allergies, with strict diet modulated individually by the tests performed.

The treatment regimen that was used in our experience consists of identification of the offending food allergen followed by an elimination diet for a period of time until the immunological disturbance, present in ASD patients with FA, diagnosed at the moment of initiation of the study, will be abated with treatment. The elimination diet was based in the "skin prick test" (SPT) which was repeated every 3 months for establishment of the dietary intervention. All positive proteins identified by diagnostic testing were eliminated from the diet until the test becomes negative at which time the offending food allergen can be reintroduced. If some allergic symptoms become active once again, it may be necessary to re-introduce the dietary elimination regimen.

The type of the elimination diet was different depending on the typeimmunological mediation in each ASD patients:

- For ASD patients with IgE mediated FA the treatment consists of an elimination diet with restrictions made not only in food ingestion, but also by avoidance of skin and olfactory contact restriction;
- For ASD patients with other allergy-mediated FA, as those with cellular or mixed immunological mediated FA, i.e., the classical "non-IgE FA", the elimination diet was adopted, but the avoidance has a different strategy using a non-repetitive, seven-day elimination course, added to the regular food restrictions. A different diet for each day of the week was utilized referred to the patients as a rotatory diet. All restrictions were guided by the SPT, as well as a complete immunological blood examination that will identify other FA mediated mechanisms.

FIRST PUBLISHED EVIDENCE TO SUPPORT OUR TREATMENT

The first published evidence to support our treatment was obtained with the treatment of100 patients with ASD and FA, the results of which were first presented in poster format at the Congress of LASPGHAN (Latino American Society of Pediatric Gastroenterology, Hepathology and Nutrition) in 2017 (Porto, Portugal).

The study evaluated 100 patients with ASD with FA, treated for seven months for their food allergy by elimination diet. The sample consisted of 83 males and 17 females. The average age was 5 years and 1 month (ranging from 1 year and 11 months to 12 years and 3 months) and the ratio between male and female was 5:1, similar to that found in the literature.

The 100 patients diagnosed with ASD were treated at our outpatient clinic, at the UGAAA Unit. All ASD patients were diagnosed with food allergy. This evolutionary report aims to evaluate the clinical progression of 100 patients with ASD and FA, submitted to FA treatment. We evaluated after seven months of treatment the six of their most predictable dysfunction in ASD patients: verbal communication, eye contact, social interaction, sleep, stereotypic behavior and neurological development.

RESULTS FOR VERBAL COMMUNICATION

The first evaluation carried out prior to the treatment of FA, revealed that of the 100 who participated in this study, 46 children did not speak or babble words and 34 spoke words out of context; a total of 80 children could not establish verbal communication. Of the 20 children who were able to communicate verbally, only one was able to form sentences [89].

In the second evaluation, after seven months of treatment of their FA, the number of children who did not have verbal communication dropped from 80 to 27 and of the 73 patients who were able to communicate verbally, 44 could form sentences.

RESULTS FOR EYE CONTACT

Patients with ASD tend to avoid eye contact Prior to the FA treatment 28 patients failed make eye contact, 40 did so sporadically, 19 after tactile, visual or auditory stimulation, and only 13 had frequent and spontaneous eye contact [90-92].

In the second evaluation, after seven months of treatment of their FA, all patients with ASD showed eye contact, 6 patients occasionally, 36 after the previously mentioned stimuli and 58 normalized visual contacts that became frequent and spontaneous.

RESULTS FOR SOCIAL INTERACTION

Deficits in communication and impairments in social interaction are main characteristics of children and adolescents with ASD. Children with ASD have less social skills, are more often victims of bullying and spend less time interacting with others [93-99].

In the first evaluation 34 patients with ASD displayed no social interaction, 41 were able to interact only with family members, 16 could interact with strangers, and only 9 had good social interaction with others.

In the second evaluation, after seven month of treatment of their FA, only 3 of the 34 were still unable to interact socially, 17 interacted only with relatives, 33 were able to establish social contact with strangers and 47 presented good interaction with everyone.

RESULTS IN SLEEP

In healthy children between 2 and 3 years of age there are long periods of nocturnal of nocturnal sleep followed by one or two daytime naps not exceeding a total of 2 hours. At age 3, usually only an afternoon nap takes place. At 5 years of age, nocturnal sleep should already be fully consolidated, with no more nocturnal awakenings or need for daytime naps [12-14]. Only between 5 and 10 years of age does a gradual decrease of the total time in nocturnal sleep occur. In adolescence, nocturnal sleep reduction (mean of 7 hours) tends to occur, ranging from 8.6 to 6.4 hours from 14 to 16 years of age26. Children 3 to 5 years of age should sleep from 10 to 13 hours for 24 hours (including naps), children from 6 to 12 years of age should sleep from 9 to 12 hours for 24 hours and adolescents from 13 to 18 years of age should sleep 8 to 10 hours for 24 hours [100-104].

In the first evaluation of 100 patients, 13 slept less than 4h a day, 17 slept less than 7h per night and had sleep interruptions, 33 slept more than 7h per night also with interruptions and 37 could sleep more than 7h of continuous sleep, despite of large portion of patients making use of hypnotics, sleep inducers, anxiolytics and sedatives.

In the second evaluation, after seven months of treatment of their FA only one patient slept less than 4 h per day, 4 slept less than 7h per night with interruptions, 15 slept more than 7h per night with interruptions and 80 were sleeping more than 7h of continuous sleep.

RESULTS FOR STEREOTYPIC BEHAVIOR

Although considerable progress has been made in understanding the underlying mechanisms of social and communicative impairments in ASD, the neurofunctional architecture of repetitive and stereotyped behaviors as well as other cognitive conditions related to response and action control remain poorly understood [105].

Before treatment, 57 patients had constantly restrictive and repetitive behaviors, 24 occasionally, 13 rarely and 6 did not present this behavior.

In the second evaluation, after seven months of treatment of their FA, the number of ASD patients who presented restrictive and repetitive behaviors constantly dropped to 15, 24 occasionally, in 43 these behaviors were rare and 18 did not present them.

RESULTS IN LEVEL OF ACTIVITY

Autism and catatonia have common symptoms such as mutism, echolalia, stereotyped speech and repetitive behaviors, postures, facial mimics, stiffness, mannerisms, and purposeless agitation.

Of the patients previously diagnosed within the spectrum, 4 were at this extreme of the activity level in the first assessment, 18 were hypoactive, 70 hyperactive and 8 had regular activity level. Comorbidities such as hyperactivity, impulsivity and attention deficit occur in 41% to 78% of children with ASD [106-108].

After about 7 months of DRI, no patient was in a catatonic state, only 3 were hypoactive, 45 were hyperactive and 52 reached a regular activity level.

SECOND PUBLISHED EVIDENCE TO SUPPORT OUR TREATMENT

The second published evidence to support our treatment was obtained with the treatment of852 patients with ASD and FA, the results of which were first presented in poster format at the International Congress of Autism, held in Nice, France, September 2019.

After our first presentation of the evolution of 100 patients with autism spectrum disorder (ASD) treated of their food allergy (FA) for seven months, with evolution to partial remission in their neurological disorder (LASPGHAN 2017 Porto, Portugal), we were now able to present a follow-up of 852 patients with ASD and FA, treated after 3 years of their FA, with total remission in all cases as soon as each case completed 30 months of treatment.

The clinical evidence of total remission of patients with FA and ASD, after the treatment of their food allergy, with a restrict diet, for a period of time; open a new avenue for the future of patients with ASD.

TREATMENT AND PREVENTION OF ASD

There was no cure or specific preventive practices until now, however there are medications, supplements and therapies that could bring benefits to patients with ASD when implemented early. The NIH, the Centers for Disease Control and Prevention and the consensus so far do not recommend dietary restriction as a primary treatment for the disorder due to the lack of scientific data to justify and prove this practice, even so many children with ASD go on a diet with restriction of gluten and casein and some also restrict soy [82]. This inadequate conduct is globally practiced and benefits some patients with ASD but does not work in many others.

The treatment for ASD and FA after our findings should be established as soon as possible with a diet free from allergens

(amino acid formulas), until investigation of immune mediation and analysis of food allergens involved in the allergic response (prick test) is done. It is also necessary to evaluate the extent of brain damage and the staging of motor development, cognitive and socio-affective abilities. With all this information we apply an individualized diet for each patient based in the immunological personal involvement and periodically follow up the progress on development and the clinical features improvements.

The restrictive diet should be extended until clinical features and laboratory indicators of FA disappear. It is necessary to follow up the healing of FA because it will always be capable of causing inflammation in those patients who already have neurotropism for allergic response and that can relapse the clinical features. With the cure of FA, the neurotropic inflammatory mediators disappear and with them, the possibility of new immune aggressions on the CNS.

Newborns have predominance of the Th2 immune response and will respond by this pathway until the conversion from Th2 to Th1 which usually occurs around 8 months and is promoted by exclusive breastfeeding. Early exposure to cow's milk promotes a Th2 immune response polarization and has the potential to induce allergy to cow's milk but some measures can be taken prophylactic to prevent FA. As the cow's milk is the antigen with higher frequency of sensitization in the studied patients with ASD, we emphasize the importance of encouraging exclusive breastfeeding, curb exposure to non-hypoallergenic amino-acid based formulas for all newborns, stimulate vaginal delivery, avoid excessive hygiene and indiscriminate use of antibiotics and anti-acids, thereby reducing the risk factors for the development of FA [109-113].

CONCLUSION

Surprisingly FA was diagnosed in 100% of patients with ASD that were attended at UGAAA and is a pre-existing condition in most cases, since 98% had at least one MALT affected before the onset of signs and symptoms of ASD. Of these, 88% had involvement of the GALT that besides sharing the same embryonic origin and being connected by about 3,000 neurons to the CNS, it is also the organ with the highest number of neurons after CNS.

The report that these children diagnosed with ASD had a neurological past without alterations and appropriate psychomotor development is often, in many cases it is observed regression in skills that were previously present. It is possible to identify that many autistic patients were not born with ASD, showing that the disorder was acquired.

The fact that some children were not born with the disorder and that they were allergic previously corroborates with the hypothesis that FA is one of the foregoing factors in patients who develop ASD. If these patients with FA suffer an inflammation of the CNS, it could trigger the homing to neurons and clinically present as ASD [5,16,109].

The family history of skin and respiratory allergies and FA suggests that genetic factors involved in the pathogenesis of allergies may be influencing the development of the ASD (15) and the family history of ASD, ADHD and Asperger's syndrome is not expressive (9%) when compared to allergies (88%), which reinforces this link between the two pathologies. The clinical presentation of FA in the CNS could be the ASD which may vary clinically according to the affected area and the degree of allergic aggression.

Some measures can be taken prophylactic to prevent the establishment of FA (15) and if the patient develops FA the gut disease and the concomitant attack on the CNS must be avoided by removing all possible triggers for inflammation in these systems. The protection of neurons will be made by an individual restrictive diet which stops inflammation in these affected systems until the healing of the FA, digestive disease and aggression to the CNS. The result is the remission of the ASD.

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