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Original Article

Relationship and Therapeutic Evolution of Food Allergy in Children with Autism Spectrum Disorder: treating the "Overlap Syndrome"

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ABSTRACT

Introduction: The autism spectrum disorder (ASD) occurs in one out of every 54 individuals, it is characterized by disorders of neurological development and can affect any child regardless of sex, race, or socioeconomic status.

Methods: The goal of this work was to evaluate the clinical progression of ASD in 100 patients with ASD and food allergy (FA) submitted to FA treatment, the study group, compared to the 100 patients of a control group, with no diet. All ASD patients were diagnosed with food allergy and attended at the Unit of Pediatric Gastroenterology, Food Allergy and Autism at UNIGRANRIO University School of Medicine, Rio de Janeiro Brazil. All patients from the study were submitted to FA treatment of the "overlap syndrome" and the clinical progression of ASD was evaluated. After identification of the food allergens involved, treatment was performed with hypoallergenic diet followed by clinical and laboratorial reevaluation after seven months of treatment using Autism Treatment Evaluation Checklist (ATEC).

Results: Upon comparison of the evaluation performed before and after the FA treatment based in the 6 most frequent complaints: visual contact, speech, sleep, restrictive and repetitive behaviors, activity level and social interaction, all patients with ASD and FA of the study group had a significant evolution to partial remission after the FA treatment (*p-value* < 0,05). For control group, no significant improvement was observed in the.

Conclusion: Our data suggest that FA may be one of the preceding factors for the development of ASD. The FA turns neurons into the target organ and immune system homing site, making the patients suffer inflammation in the brain. Treating FA for seven months, ASD patients had evolution to partial remission.

Keywords: Autism Spectrum Disorder; Overlap Syndrome; Central Nervous System; Immunology; Gastroenterology; Food Allergy; Neurological Development; ASD; FA

INTRODUCTION

The autism spectrum disorder (ASD) is a genetically determined neurodevelopmental brain disorder presenting with restricted, repetitive patterns of behaviors, interests, and activities, or persistent deficits in social communication and social interaction. The disorder is comprising of 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 including multilevel pathways in the gut–brain axis contributing to alterations in behavior and cognition [1-5].

Shared pathogenetic factors and pathophysiological mechanisms possibly linking ASD and GI disturbances, have been shown in recent literature 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

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intestinal permeability, mucosal immune function, and intestinal motility and sensitivity [5-7].

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 [8].

METHODS

Patients

All procedures for enrollment and conduction of this research project was reviewed and approved by the Institutional Review Board of the UNIGRANRIO University under number CAAE 66813917.0.0000.5283.

In this study, we analyzed the progression of 100 patients, with a prior diagnosis of ASD that attended our outpatient clinic, from March 2012 to March 2017, and 100 patients of a control group with ASD, during the same period, matching with age and gender the study group.

ASD and FA diagnosis

For the diagnosis of ASD, we used the Childhood Autism Rating Scale (CARS). This scale is a behavior rating scale intended to help diagnose ASD. CARS were designed to help differentiate children with autism from those with other developmental delays, such as intellectual disability. Although there is no "gold standard" among rating scales in detecting autism, CARS is frequently used as part of the diagnostic process. The punctuation in the scale varies from 15 to 60. We select ASD patients to our study with a rating punctuation in the CARS over 30. Besides the selection of the patients by the CARS rating we confirmed the diagnosis of ASD by the DSM-5 criteria, made by two doctors' specialists in the diagnosis and treatment of patients with ASD [9].

Diagnosis of FA in both groups was made by anamnesis and immunological investigation [7]. FA was treated with a diet with the exclusion of the foods positive in the skin prick test done to identify the food allergens involved. These children were periodically reevaluated laboratorial and clinically for adjustments in diet and analysis of clinical evolution. The control group was submitted to the classic treatment of ASD with no special diet. Both groups received the classic treatment for ASD such as Phonotherapy and Occupational therapy [6,7].

Treatment Monitoring and Assessment

All patients of the study group were in the diet during all the seven months period of this study and the diet was monitored by one of us every month by questioning the parents involved in the study. As much the families noticed the improvement of their children, they became more collaborative and adjusted to the program. The control group was in a free diet.

To validate our treatment, we used the classic ATEC. Here we report the ATEC observational results pointed by the parents before and over the follow-up period of seven months of treatment. All parents completed the ATEC every three months during the seven months of treatment [10,11].

To evaluate the response to the treatment of these two groups of ASD patients (study group and control group) we analyzed the 6 most frequent complaints presents in ASD patients: visual contact, speech, sleep, restrictive and repetitive behaviors, activity level and social interaction. The evaluation was performed before the treatment of their FA with the diet in all patients and was repeated on average of 7 months after starting the treatment, according to the availability of return of the patients who undergo ambulatory follow-up.

Treatment Procedure

The treatment regimen used in our experience consists of identification of the offending food allergen followed by an elimination diet for the period of the study. 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 [6].

The type of the elimination diet was different depending on the type of immunological mediation in each ASD patient: 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 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 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.

RESULTS AND DISCUSSION

We evaluated 100 previously diagnosed patients within ASD, being 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, corroborating the literature data [1].

Immune Mediations

Data from the immunological investigation routine of all the 200 patients showed varied immune mediations.

In 37% of patients, there were mixed-mediated food allergy, with abnormal levels of Th2 (humoral) and Th1 (cellular), with elevated IgE and abnormal CD4/CD8 ratio.

In 34% of patients we found IgE mediated food allergy with IgE over the normal ratio for the age of the patients.

In 16% of patients we had cellular mediation with abnormal CD4/CD8 ratio and in the 13% remaining patients we found other type of immune mediations, with normal IgE and normal CD4/CD8 ratio, such as pathological increase in NK (Natural Killer cells), or a marked reduction in the lymphocytes TCD4/TCD8 ratio.

Regarding the IgE mediations in our group of patients, with humoral (Th2) or mixed (Th2 and Th1) mediations, its incidence occurs in 71% of the cases.

Number of MALTS affected before the ASD treatment

The diagnosis of FA was made in all cases to identify which of the two pathologies was established first in everyone. The number of MALTs (mucosal associated lymphoid tissues) affected prior to the onset of ASD was measured. All patients 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 195 had two or more systems affected.

MALTs affected in ASD

The gut-associated lymphoid tissue (GALT) system was the most frequently affected MALT at the time of the diagnosis of FA, out of the 200 patients 190 presented homing to this associated lymphoid tissue. In 148 patients the Nasal-associated lymphoid tissue (NALT) system was affected, in 122 the skin-associated lymphoid tissues (SALT) system was affected and 68 patients had the Bronchus-associated lymphoid tissue (BALT) system affected.

All ASD patients were diagnosed with food allergy. The clinical progression of 100 patients with ASD and FA, submitted to FA treatment, the study group, was evaluated compared to the 100 patients of the control group, with no diet. We evaluated after seven months of treatment the six of their most predictable dysfunctions 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 out of 100 patients, 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 [12].

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. The improvement of verbal communication was significant ($\chi 2$= 36,99, *p-value*<0.001) (Figure 1a).

The control group had no improvement in verbal communication.

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 [13-15].

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. ($\chi 2$=32.39, *p-value*<0.001), (Figure 1b).

The control group had no significant improvement in eye contact.

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 [16-22].

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. ($\chi 2$=31.7093, *p-value*<0.001) (Figure 1c).

The control group had no significant improvement in social interaction.

Results in Sleep

In healthy children between 2 and 3 years of age there are long periods 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 to 10 years of age a gradual decrease of the total time in nocturnal sleep occur. In adolescence, nocturnal sleep reduction (mean of 7 hours) tends to occur,

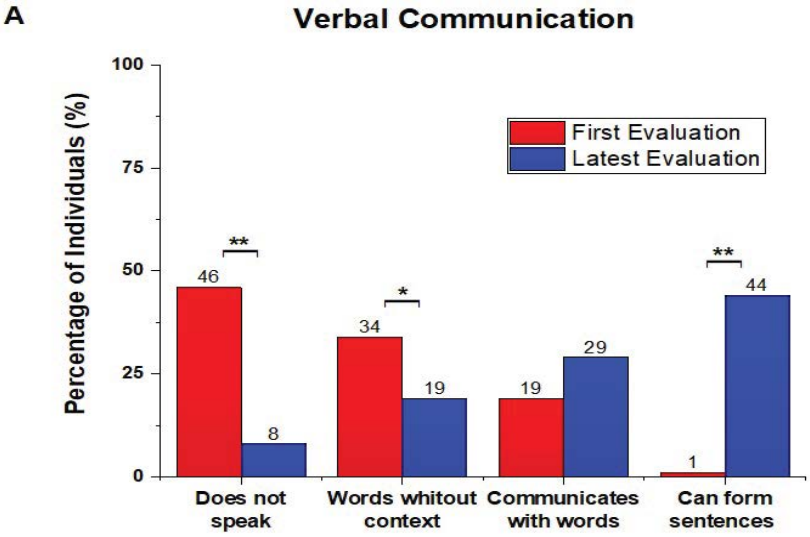

Figure 1(a): Comparative analysis of verbal communication of patients with ASD and FA before starting treatment of food allergy and about seven months after.

** *p value* <0.001, *p value <0.05

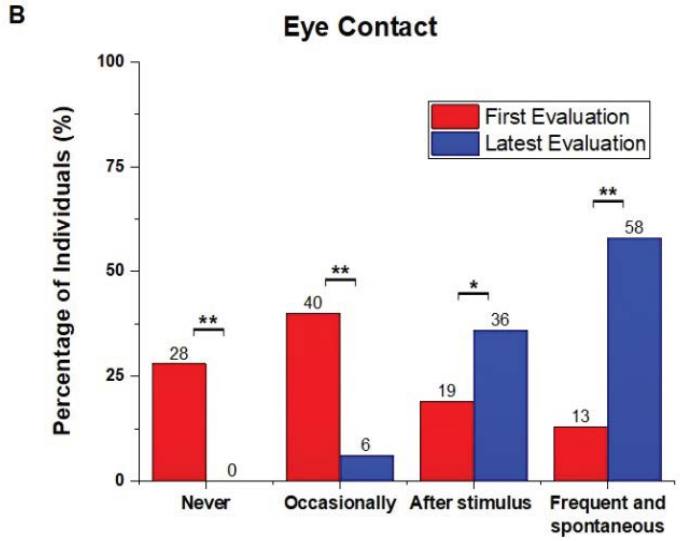

Figure 1(b): Comparative analysis of eye contact of patients with ASD and FA before starting treatment of food allergy and about seven months after.

** *p value* <0.001, *p value* <0.05

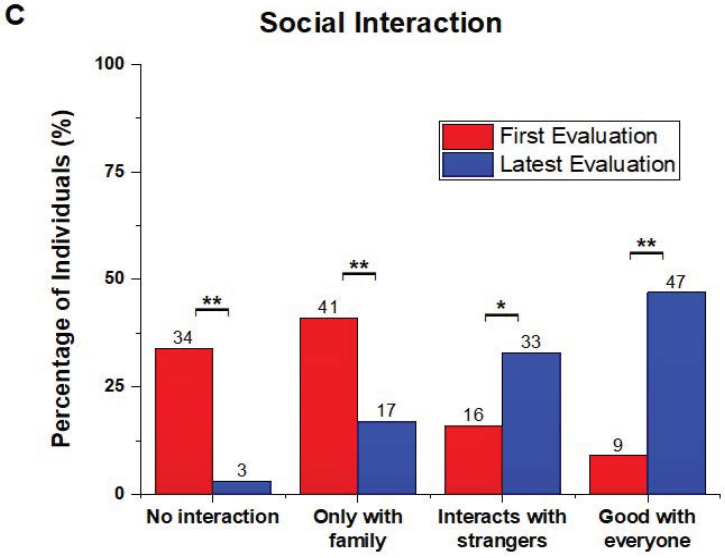

Figure 1(c): Comparative analysis of social interaction of patients with ASD and FA before starting treatment of food allergy and about seven months after.

** *p value* <0.001, *p value* <0.05

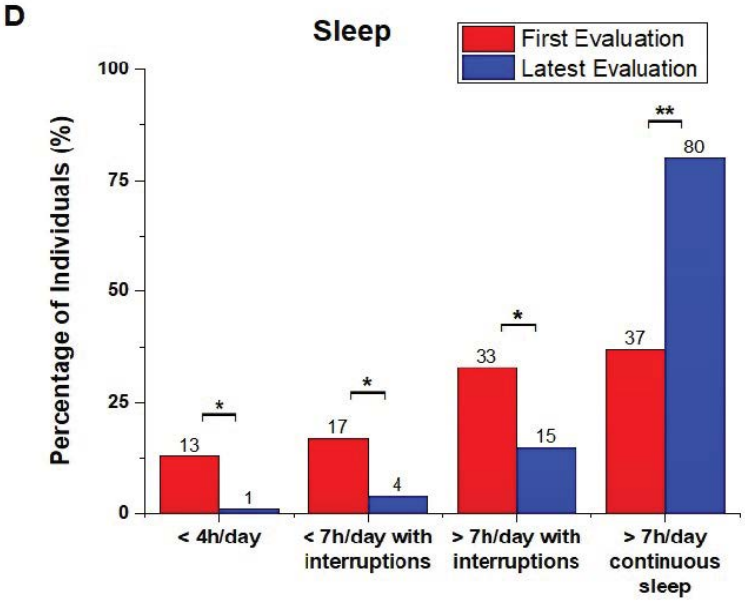

Figure 1(d): Comparative analysis of sleep of patients with ASD and FA before starting treatment of food allergy and about seven months after.

** *p value* <0.001, *p value* <0.05

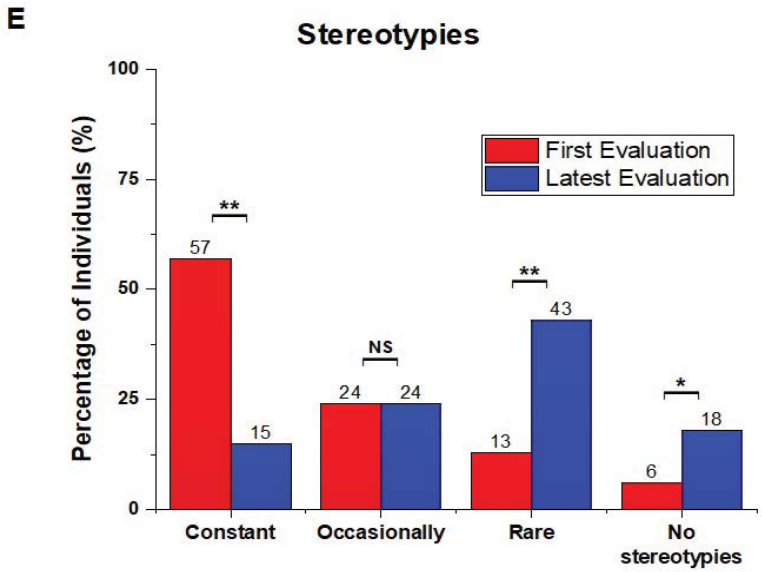

Figure 1(e): Comparative analysis of stereotypes of patients with ASD and FA before starting treatment of food allergy and about seven months after. ** *p value* <0.001, **p value* <0.05, NS = Not Significant

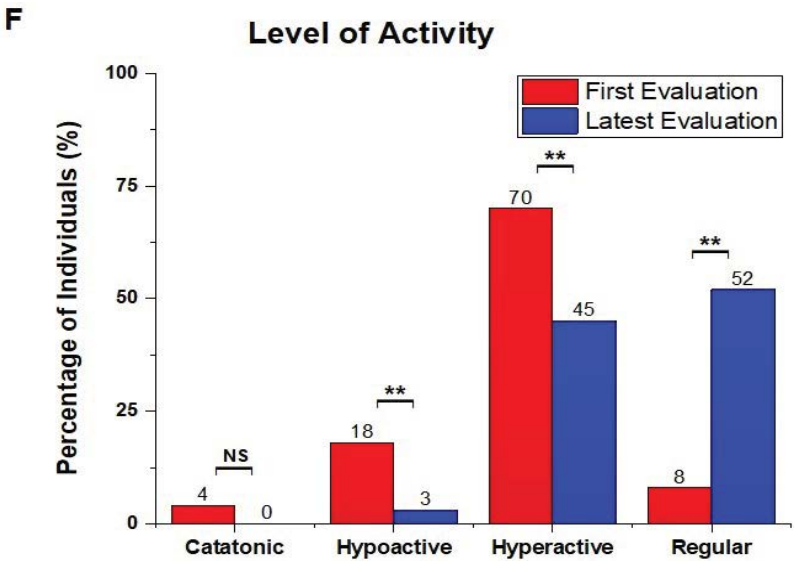

Figure 1(f): Comparative analysis of level of activity of patients with ASD and FA before starting treatment of food allergy and about seven months after. ** *p value* <0.001, **p value* <0.05, NS = Not Significant

ranging from 8.6 to 6.4 hours from 14 to 16 years of age. 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, adolescents from 13 to 18 years of age should sleep 8 to 10 hours for 24 hours [23-27].

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 hours 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. (Figure 1d)

The control group had no significant improvement in 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 [28].

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 ($\chi 2$= 38,08, *p-value*<0.0001) (Figure 1e).

The control group had no significant improvement in stereotypic behavior

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, and 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 [29-34].

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 ($\chi 2$= 4.0612, *p-value*=0.04) (Figure 1f).

The control group had no significant improvement in the level of activities.

CONCLUSION

Since the brain-gut connection is now well established in several studies, the hypothesis that was tested was that manifestations of FA and CNS dysfunction can in the CNS influence the clinical manifestations of the autism spectrum disorder that may vary clinically according to the brain area affected and the severity of allergic aggression. The clinical improvement of the mucosal associated lymphoid tissues (MALTs) affected usually precedes the clinical improvement of ASD (CNSALT). The clinical manifestations and laboratory abnormalities of FA was systematically evaluated in the proposed treatment to test our hypothesis that neuroinflammation is playing a mechanistic role in the pathogenesis of disease symptoms triggered by an allergic reaction to foods. Even with normality of neuronal function, the role of neuroinflammation in compromised by their allergic disease which therefore may contribute to the relapsing nature of the clinical manifestations of ASD.

All of our patients received nutrological monitoring and despite dietary restrictions had their growth curves monitored and received when necessary, aminoacid-based formula supplementation.

Based in the excellence of the improvement of the clinical spectrum of our 100 patients with ASD, treated for seven months of their FA, we predict that better results will be seen keeping the treatment regimen for more months. At the same time the control group had no improvement in the studied clinical manifestation of ASD.

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