



EVOLUTION OF CHILDREN WITH AUTISM SPECTRUM DISORDER WITH THE TREATMENT OF THEIR FOOD ALLERGY

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ABSTRACT

Autism spectrum disorder (ASD) is characterized by disorders of neurological development, typically diagnosed within the first 4 years of life, clinically presents with impairment in social interaction, deficits in verbal and non-verbal communication, and repetitive and purposeless stereotypic behaviors. All pre-diagnosed ASD patients that attended at the Department of Gastroenterology and Food Allergy at Unigranrio University were diagnosed with food allergy (FA) until the closing of this research. This evolutionary report aims to evaluate the clinical progression of ASD in 100 patients submitted to FA treatment.

Key-words: autism spectrum disorder, immunology, gastroenterology, food allergy, eye contact, social interaction, speech, sleep, stereotypic behavior, neurological development.

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We collect information by reviewing the medical records, characterizing this study as a retrospective cross-sectional study. Some figures do not have 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.

INTRODUCTION

The autistic spectrum disorder (ASD) is a neurodevelopment disorder, typically diagnosed within the first 4 years of life, which clinically presents with persistent impairment in social interaction, deficits in verbal and non-verbal communication and repetitive purposeless behavior¹⁻⁴. 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 males⁵.

Genetic genesis of food allergy predisposes the individual to respond with allergy to food antigens and is also present in ASD. Children with both atopic parents have 80% probability of being allergic too. Aiming to understand how genetic factors may be contributing to the genesis of the disorder we analyzed the family history of respiratory and food allergy of patients with ASD and it was present in over 89%⁶.

Once sensitized to a particular antigen, the individual may respond with allergy through the pathway of T helper lymphocyte type 2 (Th2 or humoral) and/or T helper lymphocyte type 1 (Th1 or cellular). After the immune activation in Payer's Patches of GALT system (gastrointestinal associated lymphoid tissue), antigens, lymphocytes and immunoglobulin are directed towards their homing of clinical response. Homing may occur in BALT (bronchial associated lymphoid tissue), NALT (nasopharynx associated lymphoid tissue), SALT (skin associated lymphoid tissue), back to GALT itself or CNSALT (central nervous system associated lymphoid tissue) which is affected in ASD. The definition of which target organ will be affected is influenced by genetic inheritance, environmental factors and inflammatory conditions that can act as triggers for the involvement of lymphoid tissues⁷.

Patients pre-diagnosed with ASD undergo anamnesis, clinical examination, laboratory investigation and identification of the sensitization profile to the most common allergens. We implemented an individualized restrictive diet (IRD) with nutritional monitoring, which stops inflammation in the affected systems, until the resolution of food allergy (FA) and consequent CNS aggression. This evolutionary report aims to evaluate the clinical progression of ASD in patients undergoing food allergy treatment and structures a new clinical evaluation that serves as a tool to quantify the progress achieved.

MATERIAL AND METHODS

All patients with ASD who had already been treated at the Unit of Pediatric Gastroenterology, Food Allergy and Autism, at Unigranrio University (UGAAA) were diagnosed with FA until the occasion of this study, of which we randomly selected 100 patients with previous diagnosis of ASD. In addition to the immunological investigation, physical examination and anamnesis, all were submitted to the skin prick test to identify the food allergens involved. The FA diagnosed was treated with hypoallergenic diet with the exclusion of the foods positive in the skin prick test. These children were periodically reevaluated clinically and laboratorially for adjustments in diet and analysis of clinical evolution.

Existing forms for evaluation of ASD treatment are too extensive to be filled by the physician at the time of a medical appointment. And due to the need to evaluate the progress achieved in ASD with FA treatment, we structured in a meeting at the Brazilian Society of Food Allergy a table for objective evaluation. It was based on the existing ones and including the most frequent complaints on the occasion of the first medical appointment by over 1000 patients with the disorder treated at UGAAA. (Fig 1).

The 6 most frequent complaints were: 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 hypoallergenic diet in all patients and was repeated on average 7 months after starting the IRD, according to the availability of return of the patients who undergo ambulatory follow-up.

RESULTS/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, similar to that found in the literature.

IMMUNE MEDIATIONS

We requested the immunological investigation routine of all 100 patients and in these the immune mediations were varied. In 37 patients, there were mixed-mediated allergies, secondly IgE mediation with

34, followed by 16 who had cellular mediation and 13 with other immune mediations, such as pathological increase in NK (Natural Killer cells) and eosinophil cells, or a marked reduction in the lymphocytes TCD4/TCD8 ratio. Verifying all IgE participations in exclusively humoral (Th2: T helper type 2) and mixed (Th2 and Th1: helper T lymphocytes type 1) mediations, its incidence occurs in 71% of the cases.

Number of MALTS affected before the ASD treatment

The diagnosis of FA was made in 100% 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.

MALTS AFFECTED IN ASD

GALT was the most frequently affected MALT at the time of the diagnosis of FA, out of the 100 patients 95 presented homing to this associated lymphoid tissue. In 74 patients NALT was affected, in 61 SALT and 34 had BALT affected.

VERBAL COMUNICATION

Individuals with ASD tend to have unique and atypical acoustic patterns in speech. These behaviors affect social interactions and social development and may represent a non-invasive marker of ASD. Functional neuroimaging and electroencephalography recent studies demonstrate that aberrant voice processing could be a promising marker to identify ASD early¹².

The first evaluation was carried out prior to the treatment of FA, it reveals that out of the 100 who participated in this study, 46 children did not speak or babble words and 34 spoke words out of context, totalizing 80 children who could not establish verbal communication. Of the 20 children who were able to communicate verbally, only one was able to form sentences. In the second evaluation, after 7 months of FA treatment, 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. (Fig 2)

EYE CONTACT

Patients with ASD tend to avoid eye contact¹³⁻¹⁵ and before the FA treatment 28 patients didn't make eye contact, 40 did so sporadically, 19 after tactile, visual or auditory stimulation, and only 13 had frequent and spontaneous eye contact. In the second evaluation after 7 months of the FA treatment, all patients with ASD showed eye contact, 6 patients occasionally, 36 after the previously mentioned stimuli and 58 normalized visual contact that became frequent and spontaneous. (Fig 2)

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 skills¹⁷, are more often victims of bullying¹⁸ and spend less time interacting with others¹⁹⁻²².

In the first evaluation 34 patients with ASD presented 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 everyone. After the second evaluation, after 7 months of the FA treatment 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 all. (Fig 2)

SLEEP

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 the afternoon siesta 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)²³⁻²⁵. Only between 5 and 10 years of age a gradual decrease of the total time in nocturnal sleep occurs. 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, adolescents from 13 to 18 years of age should sleep 8 to 10 hours for 24 hours²⁷.

In the first evaluation of the 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 7 months of the FA treatment 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. (Fig 3)

RESTRICTIVE AND REPETITIVE BEHAVIOURS

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 understood²⁸.

Before the treatment 57 patients had constantly restrictive and repetitive behaviors, 24 occasionally, 13 rarely and 6 did not present that kind of behavior. In the second evaluation, after 7 months of the FA treatment 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. (Fig 3)

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 agitation²⁹. 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^{30,31}. After about 7 months of the FA treatment, no patient was in a catatonic state, only 3 were hypoactive, 45 were hyperactive and 52 reached a regular activity level. (Fig 3)

CONCLUSION

The brain-gut connection is established by several pathways and the clinical manifestations of FA in the CNS can influence the autism spectrum, varying clinically according to the affected area and the extension of allergic aggression³²⁻³⁴. The clinical improvement of the MALTs affected usually precedes the clinical improvement of ASD (CNSALT). It is necessary to follow up the clinical manifestations and laboratory abnormalities of FA, even if there is normality of the neuronal function, because this may cause inflammation in these patients who already present neurotropism for allergic response, thereafter relapsing the clinical manifestations of ASD. The patients underwent nutrological monitoring and despite dietary restrictions were able to follow the growth curves using, when necessary, amino acid based formulas.

Based on the six most frequent complaints of about 1,000 patients previously included in the ASD who were treated in the UGAAA, the table for treatment evaluation is a tool for comparative analysis of progress in ASD. Useful to follow up the clinical evolution of patients with ASD in visual contact, speech, sleep, restrictive and repetitive behaviors, level of activity and social interaction. With seven months of IRD all the most frequent complaints evaluated improved significantly in treatment with the hypoallergenic diet.

We postulate that this diet has stopped the inflammation in the neurons of the CNSALT and also in other systems affected by the FA, in different MALTs of the immune system. It is fundamental to follow up the IRD and the clinical condition of the patients with ASD until we had clinical and laboratory cure of FA. The remission of ASD started after the FA treatment as we can see in figures 2 and 3.

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ANNEX

TABLE FOR EVALUATION OF ASD TREATMENT

SPEECH	DO NOT SPEAK OR BABBLE WORDS	ECHOLALIA OR WORDS OUT OF CONTEXT	BABBLE OR SPEAK WORDS WITH CONTEXT	SPEAK SENTENCES
SOCIAL INTERACTION	NO INTERACTION	INTERACTS WITH FAMILY ONLY	INTERACTS WITH STRANGERS	GOOD INTERACTION WITH EVERYONE
EYE CONTACT	NEVER	OCCASIONALLY	AFTER TACTILE, VISUAL OR AUDITORY STIMULATION	FREQUENT AND SPONTANEOUS
LEVEL OF ACTIVITY	CATATONIC	HYPOACTIVE	HYPERACTIVE	REGULAR
SLEEP	<4h/DAY	<7h/DAY WITH INTERRUPTIONS	>7h/DAY WITH INTERRUPTIONS	>7h/DAY CONTINUOUS SLEEP
RESTRICTED AND REPETITIVE BEHAVIOURS	CONSTANT	OCCASIONALLY	RARE	NO STEREOTYPIC BEHAVIORS

FIGURE 01: Table for evolutionary analysis of patients with ASD when they underwent FA treatment, to be completed by the physician at the time of the outpatient visit. Based on the existing assessments and focusing on the six most frequent complaints of patients with the disorder.



FIGURE 02: Comparative analysis of verbal communication, visual contact and social interaction of carriers of ASD before the start of treatment of food allergy and about seven months after.

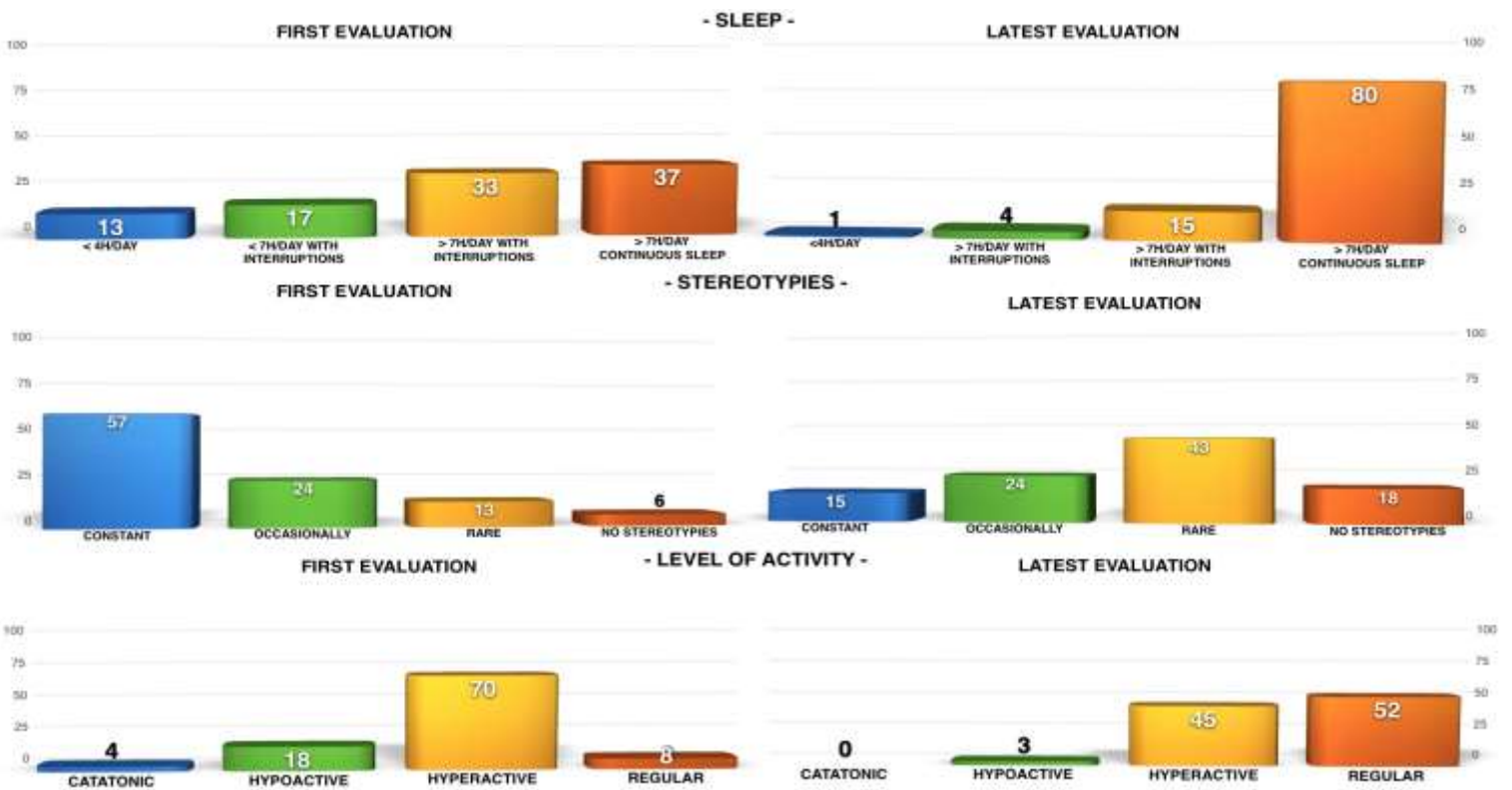


FIGURE 03: Comparative analysis of sleep, stereotypies and level of activity of carriers of ASD before the start of treatment of food allergy and about seven months after.

