

## Screening For Autism Spectrum Disorder in Children with Food Allergy

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### Abstract:

**Objective:** To apply the M-CHAT questionnaire (Modified Checklist for Autism in Toddlers) to children diagnosed with food allergy, analyzing the prevalence of symptoms of autism in children with food allergy.

**Methods:** Descriptive, exploratory and cross-sectional study conducted by applying the M-CHAT questionnaire to the guardians of children aged 16 months to 4 old-years, diagnosed with food allergy, who has received special diet at municipal specialized out-patient clinic care of these children, from April/2019 to July/2020. The selection of voluntary participants was by convenience and Parental Written Informed Consent form were obtained for subsequent completion of the M-CHAT, in addition to this, the variables sex and age were analyzed, further the statistical analysis of the results.

**Results:** 77 M-CHAT questionnaires were applied, 15 were excluded because they did not fit the age group or because they had associated neurological comorbidities. The sample consisted of 62 children, all diagnosed with food allergy, 33 (53%) were male and 29 (47%) were female. Two (3.2%) girls had critical items on the M-CHAT, in addition to moderate risk for autism. Age ranged from 18 months to 4 old-years (mean: 2.5 years  $\pm$  0.9 years).

**Conclusion:** Girls with food allergy were more at risk for developing autism spectrum disorder, which goes against the literature.

**Key words:** autism spectrum disorder, food allergy, child, gut microbiome

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### I. Introduction

Autism Spectrum Disorder (ASD) is characterized by impairments in social interaction, verbal and non-verbal communication, stereotyped behaviors, and by restricted interests. Genetic and environmental factors and their interactivity contribute to the autism phenotype, however the causal mechanisms are not yet precise [1, 2].

The incidence of ASD has increased exponentially in recent years in the United States of America; for example, in 2000 and 2002 it was one in 150 children at age 8 years, compared to 2010 and 2012, when the prevalence of ASD increased to one in 68 children, and finally, reaching the prevalence of one in 58 in 2014. In Brazil, there are no broad-spectrum studies that demonstrate the prevalence of ASD. The increase in prevalence coincided with the expansion of diagnostic criteria and greater knowledge of this disease by the general population, leading parents to seek medical care at the first signs of autism. Currently, it is questioned why some populations are more affected than others and if there are specific factors that can increase the incidence of ASD in the population [3].

The suspicion that food allergy and ASD could be related is due to the fact that allergic (respiratory and/or food) and autoimmune manifestations are highly prevalent in patients with ASD, in addition to gastrointestinal symptoms, such as diarrhea, constipation and abdominal distention [4-5].

There are questionnaires that aim the early screening for autism. In this regard, the American Academy of Pediatrics recommends that all children must be screened for ASD at 18 and 24 months of age. Among the screening methods, the M-CHAT (Modified Checklist for Autism in Toddlers) is one of the most frequently used, which aims to identify the early symptoms of ASD from 18 months of age and has high sensitivity and specificity. However, as a screening method, the diagnosis needs to be confirmed by clinical evaluation by mental health professionals [6, 7, 8].

Since the relationship between autism and food allergy has not yet been proven, the purpose of this study was to perform autism screening in children diagnosed with food allergy.

## II. Methods

It was descriptive study of exploratory nature, with cross-sectional design that included children aged from 18 months to 4 years with food allergy diagnosis (in this study, food allergy was considered to be any food-related allergic reaction that was diagnosed and treated by a pediatric gastroenterologist) attended at a municipal unit specialized in the care of these children (Specialized Center for Health Care of Neonates, Children and Adolescents - *CEACRI*), from April 2019 to July 2020. Before the beginning of the research, the parents or guardians signed the Free and Informed Consent Form for the children who were participating in the study.

Children of an age compatible with the study and who were diagnosed with food allergy were included through selection by convenience (specific food allergy outpatient clinic). When the child was over 30 months old, the questionnaire was filled out retroactively (before the child completed the age of 30 months or more).

The questionnaire used to autism screening in this population was the M-CHAT, Brazilian Version, a useful method in screening for ASD in toddlers between 18 months to 30 months old. This questionnaire consists of 23 questions with objective answers, each question worth 1 point, consequently, the score ranges from 0 to 23 and the total score is calculated from the sum of the points. Except for questions 11, 18, 20 and 22, all must be answered affirmatively in order not to score. The risk classification of autism was based on Diana Robins (creator of the questionnaire) recommended, as follows: low risk for autism (total score from 0 to 2), moderate risk (total score from 3 to 7) and high risk (score above 8). The analysis of critical items, which are questions 2, 7, 9, 13, 14 and 15, was also considered.

Individuals under 18 months old and over 4 years old, as well as children with neurological or muscular comorbidities, were excluded from the research.

The following variables were analyzed: gender, age, presence of food allergy (mandatory), M-CHAT score, risk of autism (low, moderate or high) and score of critical items greater than 2. Fisher's exact test was used to evaluate the association between gender and risk for developing ASD with the number of critical items. P values smaller than 0.05 was considered statistically significant.

This study was approved by the Research Ethics Committee of Western Paraná State University from Cascavel, PR, Brazil, under legal opinion 3.142.884/February 2019.

## III. Results

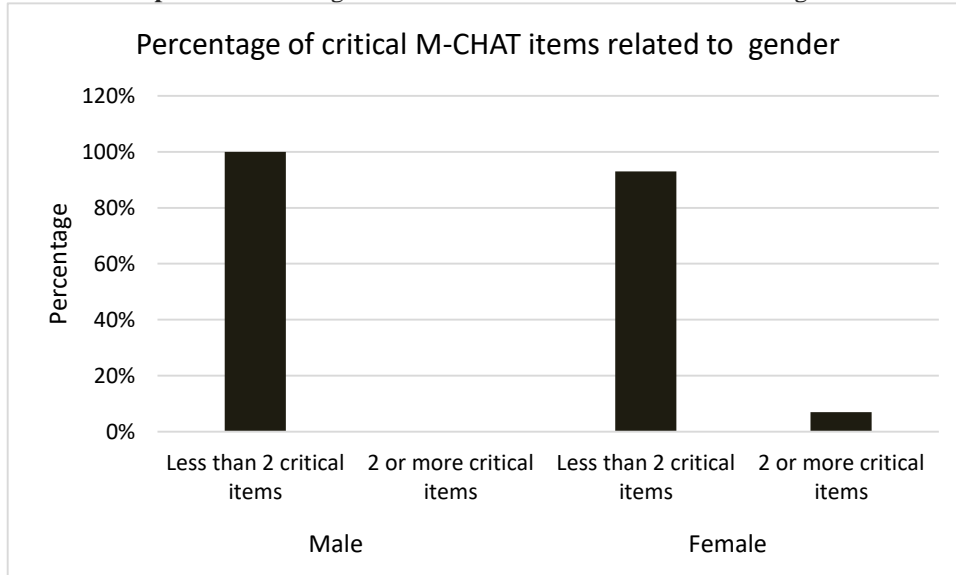
In this study, 77 questionnaires were applied, among which, 15 were excluded for not meeting the inclusion criteria. The sample was consisted of 62 children diagnosed with food allergy, 33 (53%) were male and 29 (47%) were female. The average age of the participants was 2.5 years old with a standard deviation of  $\pm 0.9$  years. Table 1 shows the relationship between gender and number of critical items in the M-CHAT, and between risk for developing ASD and the number of critical items. When the frequency of low and moderate risk was analyzed, there was no statistical significance. Graphic 1 shows the percentage of critical M-CHAT items in relation to the gender.

**Table 1:** Analysis of the relationship between gender and the number of critical M-CHAT items, and between risk for developing ASD and the number of critical items (more than 2 critical items is considered high risk to develop ASD).

Critical items	Gender				P value
	Male		Female		
	n	%	n	%	
Less than 2	33	100%	27	93%	0.215
2 or more	0	0%	2	7%	
Total	33	100%	29	100%	

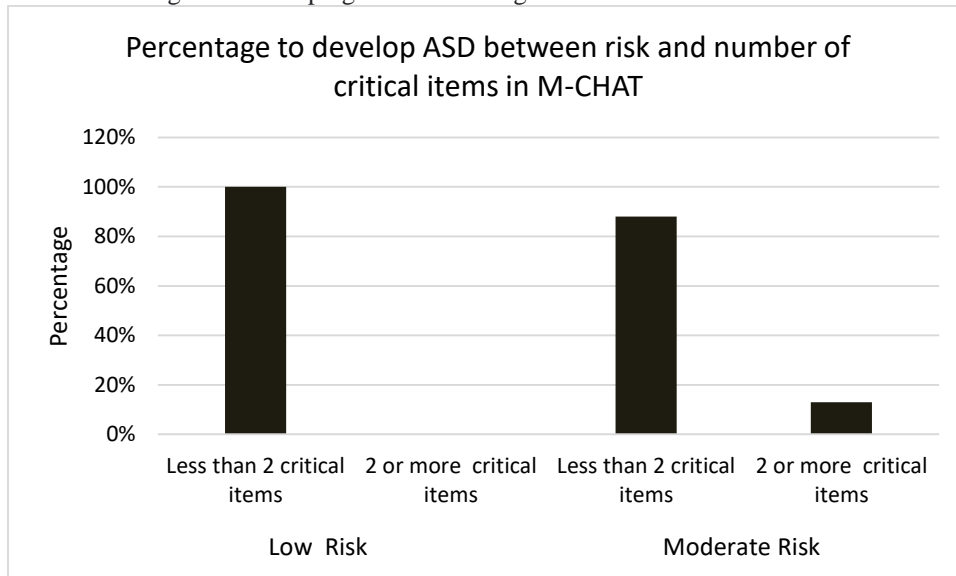
Critical items	Risk				0.215
	Low		Moderate		
	n	%	n	%	
Less than 2	33	100%	27	93%	
2 or more	0	0%	2	7%	
Total	33	100%	29	100%	

**Graphic 1:** Percentage of critical M-CHAT items related to the gender



Graphic 2 shows the percentage of developing ASD according to the risk (low and moderate) and the number of critical items in M-CHAT.

**Graphic 2:** Percentage for developing ASD according to the risk and number of critical items in M-CHAT.



#### IV. Discussion

The etiology of autism remains uncertain, but there are studies that correlate allergic diseases and ASD [9], in addition, children with autism spectrum disorder present a greater number of digestive tract disorders, such as constipation, diarrhea and abdominal pain [10]. Food allergy can be defined as an immune hypersensitivity reaction against food proteins. Although different immunological mechanisms may be underlying at the disease, it is usually characterized by the distortion of the immune system of the Th2 auxiliary lymphocyte (T Helper)

[11]. The activated immune system produces cytokines that stimulate the microglia and macrophages to indirectly activate the mammalian Target of Rapamycin (mTOR). This enzyme, when activated in neurons, is responsible for inhibiting autophagy, so the suspension of redundant synapses is impaired, favoring the development of ASD [12]. In this study, no relationship was found between food allergy and development of ASD.

The higher incidence of ASD in the last decade can be justified by better screening methods, the American Academy of Pediatrics proposes universal screening for all children aged between 18 and 24 months who are followed up in child care consultations. There is evidence that the early diagnosis of autism improves the prognosis of these patients due to interventions, such as cognitive therapy, individualized and multidisciplinary treatments. Among the screening tools used, M-CHAT proved to be effective, being translated and validated in several countries, including Brazil. The sensitivity of this method is close to 95%, being a reliable method for screening of ASD [13-17]. Therefore, in this study, the application of M-CHAT proved to be an effective method of screening because it indicated children with two or more critical items in M-CHAT, who had not yet been evaluated by a mental health professional.

ASD is more prevalent in boys. Studies that analyzed the prevalence of ASD in several populations (Spain, Israel, United States and Denmark) showed that the prevalence is up to four times higher in males [18-21]. In contrast, Loomes *et al.*, in a meta-analysis of 54 studies, found a lower prevalence (close to 3:1) and considered that there could be a gender bias in the diagnosis; therefore, girls who meet criteria for ASD may not be diagnosed [22]. Other studies suggest the existence of a protective effect that would be responsible for the lower incidence in females, although this mechanism is still unknown, so the hypothesis that ASD would be in an X-linked genetic locus is suggested [23]. In our study, girls were at higher risk for developing ASD, which is contrary to the literature. There are no studies showing the incidence of ASD higher in females, regardless of age. Some studies have demonstrated the possibility of underdiagnoses of ASD in girls, the probable explanation would be that in the current questionnaires, females would be more prone to bias in individual characteristics, and this factor connotes the indication of specific tests for ASD diagnosis in females, mainly in those with low intelligence quotient [24]. Those with high-functioning autism could also be underdiagnosed due to behavioral bias, even though they had varying levels of cognition, communication and adaptive ability, and emotional and behavioral dysfunction. Girls requires more severe autistic symptoms than boys and greater cognitive and behavioral problems in order to meet the diagnostic criteria for ASD [25], this factor confirm the data in our study, in which girls presented a higher percentage of critical items.

## V. Conclusion

There was a predominance of autism symptoms in girls diagnosed with food allergy. It is suggested that further studies relating food allergy and autism be performed, since there isn't still evidence of this relationship.

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