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FOOD INTOLERANCE IN AUTISM SPECTRUM DISORDERS

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ABSTRACT

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder with a rising prevalence worldwide. While its etiology remains multifaceted, emerging research has suggested a potential link between food intolerance and the manifestation of ASD symptoms. This study aimed to investigate the prevalence of food intolerance in individuals with ASD and compare it to a control group, shedding light on the role of dietary factors in the disorder.

A total of 105 participants with ASD and 105 age- and gender-matched controls were enrolled in this study. Food intolerance was assessed by measuring IgG4 antibody levels in response to various food items. Statistical analyses, including unpaired t-tests and Pearson correlations, were employed to examine the data.

Our findings revealed that a remarkable percentage of individuals with ASD exhibited elevated IgG4 responses to specific foods, including cow's milk, casein, egg yellow, egg white, sheep's milk, wheat, and gluten. These results indicate a significant association between food intolerance and ASD ($p < 0.05$). Notably, while food intolerance was also observed in the control group, its prevalence was significantly higher in the ASD group, suggesting its potential role in ASD etiology.

This study provides compelling evidence of a link between food intolerance, particularly elevated IgG4 antibody levels, and Autism Spectrum Disorder. While food intolerance alone cannot account for the complexity of ASD, our results underscore the importance of dietary considerations in managing ASD symptoms. Further research is needed to unravel the precise mechanisms underlying this relationship and its implications for autism treatment and management, aiming to improve the quality of life for individuals with ASD.

KEY WORDS: autism spectrum disorder, food intolerance, IgG4 antibodies, dietary factors, gastrointestinal symptoms.

1. INTRODUCTION

Autism Spectrum Disorder (ASD) is a complex neurodevelopment condition characterized by deficits in communication, social interaction, and a range of behavioral patterns (American Psychiatric Association 2013). While its precise etiology remains elusive, researchers have explored a multifactorial model, encompassing genetic, environmental, and biological factors (Adams et al., 2006). Among the myriad challenges faced by individuals with ASD, the often-overlooked connection between ASD and gastrointestinal (GI) symptoms has gained prominence (Silva, 2011).

ASD is marked by diverse characteristics, including difficulties in communication and social interaction, sensory sensitivities, repetitive behaviors, and resistance to routine changes (Newschaffer et al., 2007). Communication deficits extend to non-verbal aspects, affecting individuals' ability to predict and engage in conversations, leading to social isolation. Sensory sensitivities often manifest as heightened reactions to sensory stimuli and selective food preferences, known as health neophobia (Rutter, 2015). These dietary selectivity patterns can lead to limited diets, potentially impacting nutrition and overall health (Gaugler et al., 2014).

Diagnosis of ASD relies on clinical evaluation using the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), updated in 2013, which identifies deficits in reciprocal social interaction and communication as key diagnostic criteria (American Psychiatric Association 2013). The heterogeneity of ASD symptoms necessitates individualized care and intervention strategies.

The origins of ASD are multifaceted, with genetic, environmental, and biological factors interplaying (Huguet et al., 2013). Heredity is a significant contributor, with genetic involvement estimated at 60% to over 80% (Sandin et al., 2017). Mutations and splicing of genes like SHANK3 have been associated with ASD (Durand et al. 2007; Guilmatre et al. 2014). Environmental factors, including air pollution, maternal infections, stress, and medications during pregnancy, have also been linked to increased ASD risk (Raz et al., 2015; Herbert 2010).

Moreover, an intriguing link between ASD and the gut micro biota has emerged. Research suggests altered gut microbial profiles in individuals with ASD compared to healthy controls (Paula Krakowiak et al., 2011). This alteration may affect not only gastrointestinal tract (GIT) with a variety of symptoms, but also potentially influence the central nervous system (CNS) through the passage of gut-derived molecules into the bloodstream (Kang et al., 2019).

ASD's primary focus on neurological and behavioral aspects has, at times, overshadowed its connection to GIT symptoms. However, research indicates that a substantial proportion of individuals with ASD experience GIT issues, with symptoms ranging from abdominal pain to constipation and diarrhea (Nikolov et al., 2009). These symptoms, along with dietary selectivity, create a clinical phenotype characterized by problem behaviors like anxiety and aggression (Fulceri et al., 2016). An association between specific behavioral problems, such as anxiety and aggression, and an increased degree of GIT disorders has been observed (Fulceri et al., 2016).

Notably, research suggests that altered gut micro biota composition may underlie some GIT symptoms in ASD. Reduced levels of essential intestinal bacteria have been noted in children with ASD compared to healthy controls (Wang et al., 2011).

Dietary interventions and specialized diets have garnered attention as potential tools to alleviate ASD symptoms and enhance the quality of life for affected individuals. Among these diets, the gluten-free/casein-free diet (GF/CFD) stands out, aiming to eliminate gluten and dairy products. While some studies suggest potential benefits, others question its universal efficacy and its impact on nutrient intake and GI symptoms (Ghalichi et al., 2016). In addition to the GF/CFD, other dietary approaches, such as the ketogenic diet (KD), specific carbohydrate diet, and Mediterranean diet, have been explored.

Before implementing specific diets, it is crucial to assess potential food intolerances, which are more prevalent in individuals with ASD (American Psychiatric Association 1994). Detection of food intolerance often involves tests for immunoglobulin G (IgG) antibodies (World Health Organization 2016) especially using the IgG4 subclass, which is the most effective and accurate intolerance indicator, especially in connection with ASD subjects.

Our further study will be focused on implementing GF/CFD in ASD subjects within 1 year period and the impact of this diet on ASD GIT and behavioral symptoms.

2. MATERIAL AND METHODS

2.1. Study design

This was a cross-sectional study, approved by University "St. Kliment Ohridski"-Bitola, Faculty of Technology and Technical Sciences, Veles. This part of the research was focused on searching the incidence of Food Intolerance in autism during one year. Individuals were divided in 2 groups, an investigated group - ASD individuals and Control group -normal neurodevelopment category individuals.

The study, included 210 patients in total, each group had 105 participants, who attended Olive Medical Laboratory in Kosovo, in the period from July 2020 to July 2021 and underwent the food intolerance test. The participants performed the test using the IgG4 subclasses, which is the most effective and accurate intolerance indicator, especially of the connection with ASD subjects.

The first pre-analytical and pre-testing rule was that the participants do not stop the food consumption for 3 weeks because the half plasmatic life of IgG4 is 18-21 days. The reagent was taken out of the refrigerator and left out in room temperature for 30 minutes before testing, 30 micro-liters of capillary blood was taken from the participants and after 50 minutes results were obtained (Haskå et al., 2011). Food intolerance form that has been used is presented in Table 1.

Table 1. The form of food intolerance IgG4 by Olive Medical & Laboratory



Olive
medical & laboratory

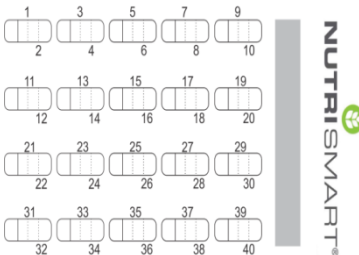
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Adresa/Rr: Fadil Hoxha, Lagja Kalabria - Prishtinë 10000

**NUTRISMART-
Level**

INTOLERANCË USHQIMORE			Code	Food	I	II	III	Code	Food	I	II
	1	f4.	Wheat (Grurë)					f1	Egg white		
	2	f5	Rye (Thekër)					f75	Egg yellow		
	3	f6	Barley (Elb)					f78	Casein (Kazeinë)		
	4	f7	Oat(tërshërë)					f199	Cow's milk		
	5	fx87	Grain Mix A					f300	Goat's milk		
	6	fx602	Grain Mix B					f325	Sheep's milk		
7	f35	Potato (Patate)					f3	Cod (Merluc)			
8	f14	Soy (Soja)					fx97	Fish Mix			
9	fx451	Yeast Mix (Majë)					f40	Tuna (Ton)			
10	f79	Gluten					fx81	Seafood Mix			
11	f13	Peanut (Kikirikë)					f25	Tomato (Domate)			
12	f17	Hazelnut (Lajthi)					fx144	Legume Mix			
13	f20	Almond (Bajame)					fx98	Veg.Mix A			
14	f29	Banana (Banane)					fx99	Veg.Mix B			
15	fx88	Fruit Mix A					fx96	Leek Mix			
16	fx90	Fruit mix B					f88	Lamb/Mutton			
17	f49	Apple (Mollë)					fx91	Meat Mix A			
18	f52	Pineapple (Ananas)					fx92	Meat Mix B			
19	f84	Kiwi fruit (Kivi)					f955	Coffee (Kafe)			
20	f97	Cacao (Kakao)					f89	Mustard			

NUTRISMART – Level	slgG4 Concentration
1	I ulët/Low
2	Mesatar/Mean
3	I lartë /High

Name/Emri:	
Surname/Mbiemri:	
Date of birth/Data e lindjes:	
Residence/Vendbanimi:	
worked by/punoi:	

2.2. Statistical analysis

t-test. It is based on two independent samples. To make this statement, the mean of the two samples is compared. If the difference in means is large enough, it is assumed that the two groups are significantly different. $p < 0.05$ is considered statistically significant.

Pearson's test was used to determine the correlation between the two groups.

The results of the food intolerance test, the characteristics of the group, and the breakdown by gender and age was processed and analyzed with data analysis in Microsoft Excel. The obtained

results are presented in tabular and graphical formats.

3. RESULTS AND DISCUSSION

A higher number of ASD males (64) or 60.95 % was present compared to females (171) or 39.05 %). The mean age of the studied subjects was 24 years, and the age range was 1,5 -75 years (Table 9), while the control group (CG) consisted of 57 females (54.29%) and 48 males (45.71%). The mean age was 29 years and the age range was 2-66 years. In the control group, on contrary, females dominated over the males (57- 39.05% vs. 48-45.71%)

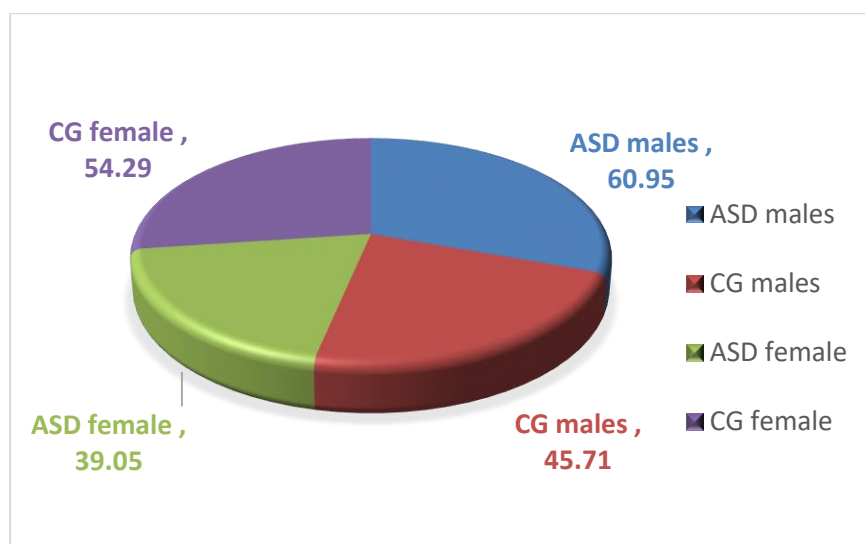


Figure 1. Gender percentage in ASD group and Control group

In terms of geographical position, all the participants were from Kosovo, with the exception of one participant (male) who lived in Germany and was born in Pristina. The vast majority were from Pristina 54% and the rest from other towns such as: Peja, Ferizaj, Vushtri, Gjakove etc.

They also lived in different regions of Kosovo where 58% of ASD members lived in urban areas and 52% in rural areas (Figure 2).

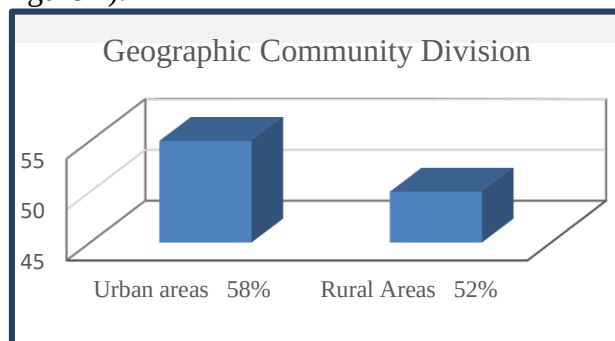


Figure 2. Division according to geographic community

Both groups belonged to different economic and intellectual levels. Some of the members of the ASD group, had lost their parents in various circumstances and reasons. (Example: the autistic member male 1972 had lost both of his parents due to their age, as well as member male 1969 etc.) Thus, a total of 100 fathers and 102 mothers completed the study.

According to educational level, a higher number of fathers had university diploma compared with mothers (59 vs 39). Mothers had more often a high school diploma compared to fathers (63 vs 41)., Some of the mothers declared that they could do some basically manual skills that were uncertified as professional degree (knitting, handmade crafts etc.). As they dedicated their time to their autistic children, only 28% of them had a job, so so other family members took care for the autistic child. Other women (77%) were unemployed, even though they had a university degree but they couldn't work because of the dedication to child needs.

Therefore males were more educated (59%) and employed (83%). They were, in most cases the one that supported the family financially. 6 cases of families reported that they received social/economic assistance and support from the government, because none of the parents had a job, other parents were diagnosed with congenital diseases. These categories refused also to be part of the ASD treatment group as they hadn't possibility to afford the costs of the study. Among these 105 autistic subjects only 39 accepted and agreed to be part of the clinical trial as the so-called "nutritional treatment group", to undergo strict diet and supplements intake, 42 subjects remained as "the non-treatment group" and 24 autistic subjects refused totally to be part of this trial, to undergo controls, medical examinations, routines etc.

The total information about the results of food intolerance test in ASD group, with detections of all three degrees of IgG4 is presented on Figure 3 below. The form contains 40 products belonging to different food categories such as fruits, meat, fish, egg, vegetable, grain and dairy products. However, the high range of IgG4, which has a diagnostic value was important to detect in our ASD group. The results are presented in Figure 3 below.

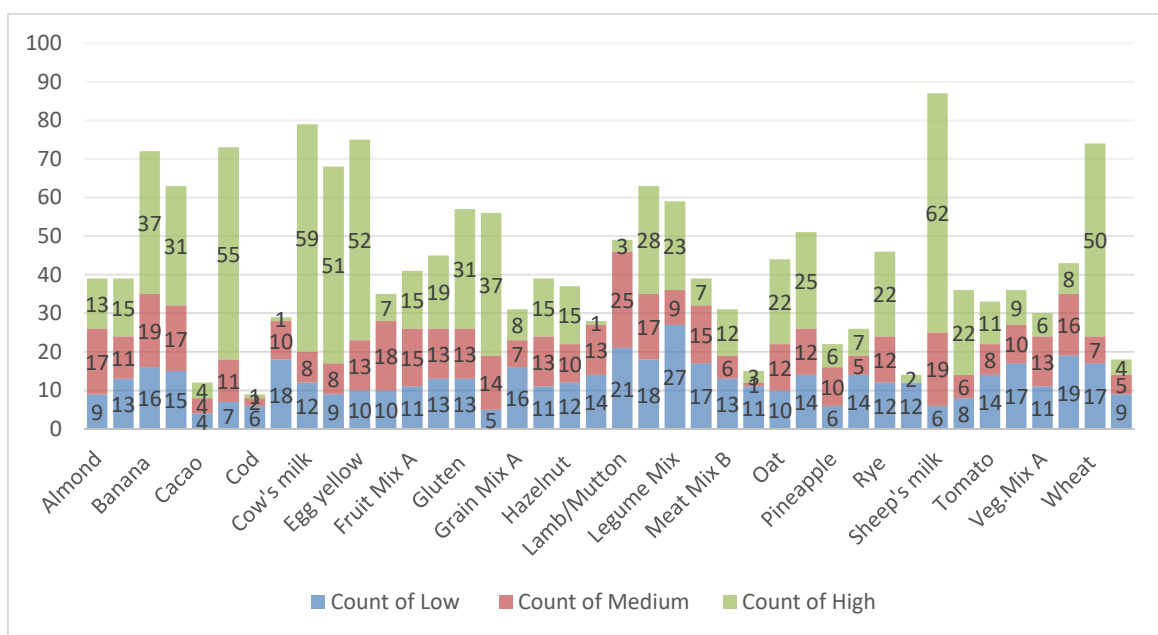


Figure 3. The total profile of food intolerance test of 105 ASD subjects

In one research, about 33% of individuals with autism have been found to have high total values of IgE (Lucarelli et al., 1995). In our study, results revealed that highest values of IgG4 have been found in remarkable number of ASD patients when testing for the following food: Cow's milk detected in 59 autistic members with high value of IgG4, with a total percentage of 56%, Casein founded out in 55 autistic subjects, with a percentage of 52%, Egg yellow detected in 52 autistic members with high value of IgG4, with a total percentage of 50%, Egg white reported in 51 autistic subjects, with 49%, Sheep's milk detected in 62 ASD subjects with 59% of participants, Wheat reported 50 subjects with high value of IgG4 with a percentage of 48%, Gluten reported in 31 autistic members with a percentage of 30%.

The results indicate that a significant percentage of individuals with autism spectrum disorder exhibited elevated values of IgG4 antibodies in response to specific food items. These findings suggest a potential link between food intolerances and ASD. Notably, the Control Group also displayed subjects with elevated rates of intolerance to various food products, indicating that food sensitivities may not be exclusive to individuals with ASD.

Meanwhile the data of the Control Group are reported below, Figure 4, calculated as a percentage. As noted, this group also has subjects with high rates of intolerance related to various food products.

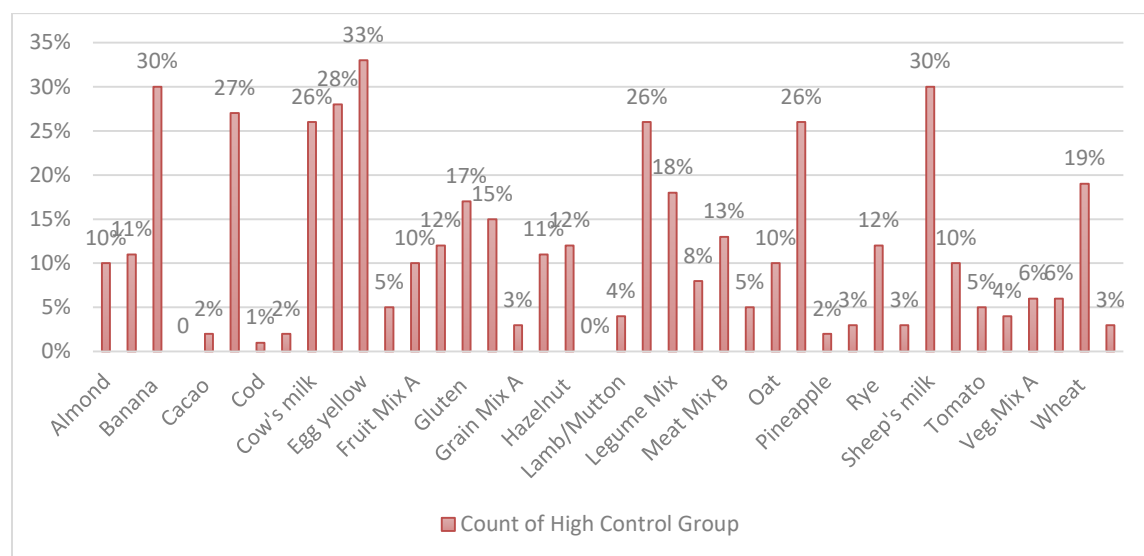


Figure 4. Food intolerance test in Control Group

As our principal focus is to determine the hypothesis about the food intolerance comparing these two groups, which are unrelated between them, so independent samples from each other and the data from each group are normally distributed, unpaired t-test (or independent t-test) is used to calculate the p-value(2-tailed).

The unpaired t-test is used to make a statement about the population based on two independent samples. To make this statement, the mean value of the two samples is compared. If the difference in means is large enough, it is assumed that the two groups differ. First an assessment

of the significance between the two groups was made, based on all the foods tested, and the p-value was calculated (Table 2).

Table 2. P (T<=t) two-tail calculation with alpha 0.05

t-Test: Two-Sample Assuming Unequal Variances	<i>Count of High ASD Group</i>	<i>Count of High Control Group</i>
Mean	19.975	12.5
Variance	318.5891026	99.8974359
Observations	40	40
Hypothesized Mean Difference	0	
df	61	
t Stat	2.311002666	
P(T<=t) one-tail	0.012113939	
t Critical one-tail	1.670219484	
P(T<=t) two-tail	0.024227877	
t Critical two-tail	1.999623585	

t-Test calculations P=0.024227877

The P-value is approximately 2%, lower than 5%, which serves as an indicator that the Null Hypothesis is rejected, thus the link between specific food intolerances and autism spectrum disorders, is significant. ($p < 0.02$).

Then, specific food with the highest IgG4 value were collected to specify the significance in certain food, to be able to determine the type of diet they should undergo, based on Food Intolerance results (Figure 5).

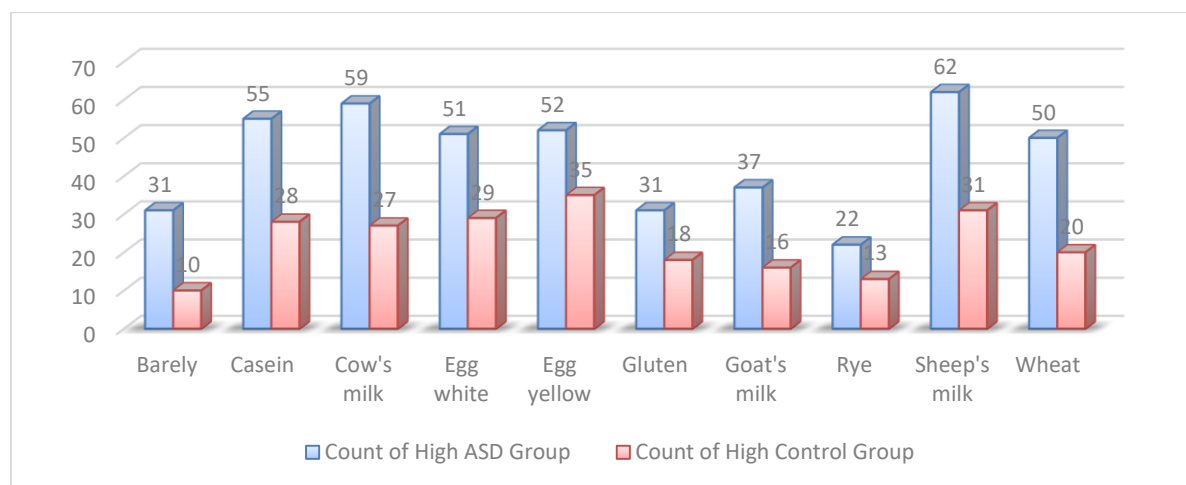


Figure 5. Highest value of IgG4 reported to specific food in ASD and Control group

In 2004, the research of Vojdani, O'Bryan, et al., found significantly higher levels of both gluten and cerebellar peptide antibodies in more than 80% of the cases with autistic disorder.

In our study, there was a statistically significant difference ($p=0.0005$) between the number of ASD patient's and Control group intolerant to certain food, such as: to casein (55 vs. 28); to egg yellow (52 vs. 35); to egg white (49 vs. 28); to wheat (50 vs. 20), to gluten (31 vs. 18); to rye (23 vs. 13); to barely (31 vs. 10); to cow's milk (59 vs. 27); to sheep's milk (62 vs. 31). The results are presented in Table 3. below.

Table3. $P(T \leq t)$ two-tail calculation with alpha 0.05

	Count of High ASD Group	Count of High Control Group
Mean	45	22.7
Variance	186.6666667	70.67777778
Observations	10	10
Hypothesized Mean Difference	0	
df	15	
t Stat	4.39589656	
$P(T \leq t)$ one-tail	0.000260587	
t Critical one-tail	1.753050356	
$P(T \leq t)$ two-tail	0.000521173	
t Critical two-tail	2.131449546	

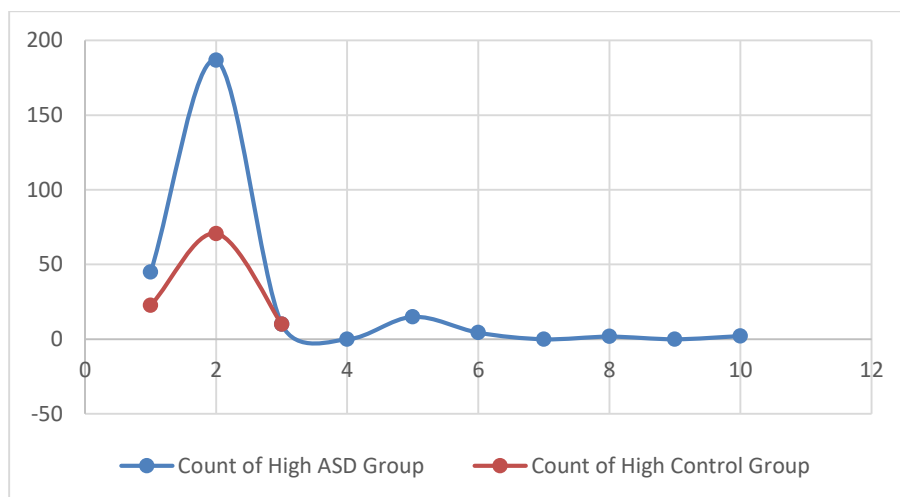


Figure 6. Two-Sample Assuming Unequal Variances

After the very strong significance of the p-value result to specific food, we wanted to find out if there is a correlation between the two groups, using the Pearson test of correlations, using the Data Analyses Tool pack in Microsoft Excel, and significant correlation was reported ($p=0.001$).

Table 4. Statistical summary output

SUMMARY OUTPUT					
Regression Statistics					
Multiple R	0.856102829				
R Square	0.732912053				
Adjusted R Square	0.69952606				
Standard Error	4.608343559				
Observations	10				
ANOVA	0.001 <0.05				
	<i>df</i>	<i>SS</i>	<i>MS</i>	<i>F</i>	<i>Significance F</i>
Regression	1	466.2053571	466.2054	21.95268076	0.001570917
Residual	8	169.8946429	21.23683		
Total	9	636.1			
	<i>Coefficients</i>	<i>Standard Error</i>	<i>t Stat</i>	<i>P-value</i>	<i>Lower 95%</i>
Intercept	-1.005357143	5.265135155	-0.19095	0.853324675	-13.14678058
Count of High ASD Group	0.526785714	0.11243207	4.685369	0.001570917	0.267516895

The decision rule is as follows: If our p-value is given by the significance F or p-value, and if it is less than 0.5 than the correlation is statistically correct, and since 0.001 is less than 0.05, that indicates that the correlation is in fact significant. So, there is a significant positive correlation between the highest value of IgG4 in the ASD Group as well as in the Control Group.

Once we obtained the result that there is a significant statistical connection and correlation between autism and food intolerance, it was time to intervene professionally as a nutritionist, modifying, eliminating, and replacing food products.

Initially, we tried to figure out which food was considered as a risk factor for autistic children. To fulfill the second goal of our study, namely the modification of the food diet, we had to understand which food exactly, have a high prevalence to cause food intolerance in ASD category. So, we divided the food products into small groups, based on categories and nutritional values.

The five food groups are Fruits, Vegetables, Grains, Protein Foods, and Dairy. The *2015-2020 Dietary Guidelines for Americans* emphasizes the importance of an overall healthy eating pattern with all five groups as key building blocks, plus oils. Each food group includes a variety of foods that are similar in nutritional makeup, and each group plays an important role in an overall healthy eating pattern (Table 5.).

Table 5. Food categories based on categories and nutritional values

Food Group	Subgroups	Sample of Foods tested
Fruits	Whole Fruit	Apple, Banana, Kiwi, Fruit Mix A, Fruit Mix Pineapple
	Fruit Juice	
Vegetables	Dark Green Vegetables	Potato, Tomato, Leek Mix, Veg. Mix A, Veg.Mix B, Mustard
	Red and Orange Vegetables	
	Beans and Peas	
	Starchy Vegetables	
	Other Vegetables	
Grains	Whole Grains	Barley, Grain Mix A, Grain Mix B, Oat, Rye, Wheat, Gluten
	Refined Grains	
Protein Foods	Seafood	Meat Mix A, Meat Mix B, Lamb/Mutton, Fish Mix, Tuna, Cod, Egg white, Egg yellow, Peanut, Almond, Hazelnut, Soy, Legume Mix
	Meat,Poultry and Eggs	
	Nuts,Seeds and Soy,	
Diary	Milk and Yogurt	Cow's milk, Goat's milk, Casein, Sheep's milk
	Cheese	

Table.6. A count of food category data, based on t-test

Nutrient division category	<i>p-value</i>
Fruits	0.28
Vegetables	0.36
Grains*	0.04
Dairy /Milk products*	0.01
Protein foods	0.09
Other	0.46

P < 0.05*

Our statistical and clinical data obtained, strongly suggest that children with ASD have abnormal immune response to certain food, especially gluten (in wheat, rye, barley, oats) and casein (in dairy products), (Figure 7). They have food sensitivities and all the data collected report that the link between food intolerance and ASD is significant (p-value=0.03), which probably is based on the link with the use of dairy products and grains.

Based on the results of this study, we suggest that food intolerance is a probable risk factor in autistic children which can initiate more severe form of GIT and behavioral symptoms. Taking into consideration that autism is a multi-factorial disorder, intolerance cannot be the only

etiological factor responsible for its increased prevalence in the past 20-30 years. Further investigation studies are needed.

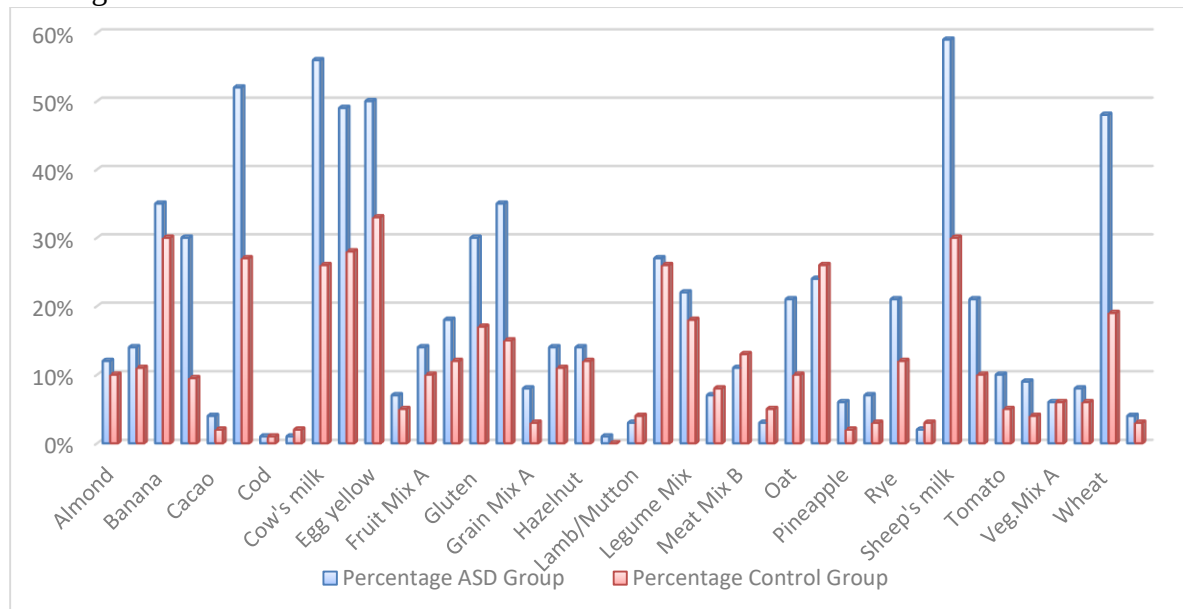


Figure 7. The percentage of subjects in ASD and Control Group who manifested food intolerance to certain food

Our results are compatible with other four studies (Jyonouchi et al., 2005, Jyonouchi et al., 2002, De Magistris et al., 2013, Iovene et al., 2016) where it was found that children with ASD had higher incidence of food intolerance than did typical children, and that may be related to increased intestinal permeability (Iovene et al., 2016, Cade et al., 2000). A large study of 150 children with ASD found that 87% had IgG antibodies and sensitivity to gluten, vs. 1% of the age and gender-matched controls, and 90% had IgG antibodies to casein, vs. 7% of the controls (Lucarelli et al., 1995).

4. CONCLUSION

Our findings revealed a significant association between food intolerance, specifically elevated IgG4 antibody levels, and ASD. Notably, a substantial percentage of individuals with ASD exhibited heightened IgG4 responses to various food items, including cow's milk, casein, egg yellow, egg white, sheep's milk, wheat, and gluten. These results suggest a potential link between food intolerance and the severity of ASD symptoms.

It is important to highlight that food intolerance was not exclusive to the ASD group, as the control group also exhibited subjects with elevated intolerance to certain food. However, the prevalence of food intolerance was significantly higher in the ASD group compared to Control Group, indicating that it may be a contributing factor to the disorder.

Our study underscores the need for further research to comprehensively understand the complex relationship between food intolerance and autism. While our findings suggest a connection, it is essential to acknowledge that autism is a multifactorial disorder with various contributing

factors. Food intolerance alone cannot account for the increased prevalence of autism observed in recent years.

In conclusion, our results provide valuable insights into the potential role of food intolerance in individuals with ASD. This knowledge can initiate implementation of dietary interventions and therapeutic strategies for managing ASD symptoms. However, continued investigation is required to elucidate the precise mechanisms underlying this relationship and its implications for autism treatment and management.

We hope that this study contributes to the growing body of research aimed at improving the quality of life for individuals with Autism Spectrum Disorder and provides a foundation for future studies in this field.

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