IMPACT OF SELECTIVE DIET ELIMINATION ON PSYCHO-BEHAVIORAL OUTCOME IN CHILDREN WITH FOOD ALLERGIES

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ABSTRACT

Introduction: Current trends in gut–brain axis science recognize the role of the gut microbiome interacting with the brain. Psycho-biotics have been recently defined as "any substance that exerts a microbiome-mediated psychological effect" and are thus not limited to probiotics and prebiotics. Considering this, it is worthy to imagine food selected to act as a psycho-biotic, which may be enriched with prebiotic fiber or probiotics with a recognized effect on human behavior.

Aim Of The study: We aim to evaluate the effect of food elimination interventions in psycho-behavioral disorders treatment in food allergic patients and identify the effect of selective diet elimination on treatment of psycho-behavioral disorders in children with non-IgE mediated gastrointestinal food allergy

Patient and methods: This is an interventional study that was carried out on 50 children aged 3 to 18 years presenting to pediatric outpatient and Gastroenterology and Neuropsychiatry clinics during the period from April 2019 to December 2022. They were selected using open random selection technique. They were having psycho-behavioral disorders plus non IgE-mediated food allergy. Food elimination diet was introduced, and Conner's, CARS "Childhood Autism Rating Scale", and Intelligent Quotient "IQ" tests were done before and six weeks after diet elimination.

Results: There was statistically significant difference between Conners, CARS, and IQ tests before and six weeks after food elimination. However, this difference was not clinically significant as the patients were still in the same diagnostic subcategories of each test. There was no difference in speech delay before and after food elimination therapy.

Conclusion: *Food elimination diet has no clinically significant effect on psycho-behavioral disorders, but showed statistical significance, in patients with food allergies.*

Keywords: *food elimination, food allergy, autism, ADHD, psycho behavioral.*

INTRODUCTION

There is considerable and growing evidence implicating the gut microbiome not only in the normal development and function of the nervous system but also in a range of acute and chronic diseases affecting the gut, as well as the nervous system throughout life. It remains to be determined if the gut microbiota play a causal role, but its facilitation of pathogenesis and potentiation of severity in disease models suggests that it is not merely a secondary effect of the underlying etiology (**Rogers et al., 2019**).

The diet plays a fundamental role in shaping microbiome composition and function. The way food is selected is a key factor determining the amount and type of material reaching the gut bacteria and influencing their growth and the production of microbiota metabolites. In this perspective, the current possibilities to address food selection toward a better feeding of gut microbiota are suggested (**Ercolini & Fogliano, 2018**). Current trends in gut–brain axis science recognize the role of the gut microbiome interacting with the brain. Psycho-biotics have been recently defined as "any substance that exerts a microbiome-mediated psychological effect" and are thus not limited to probiotics and prebiotics. Considering this, it is worthy to imagine food selected to act as a psycho-biotic, which may be enriched with prebiotic fiber or probiotics with a recognized effect on human behavior. The efficacy of diet treatments in psycho-behavioral disorders as Attention Deficit Hyperactivity Disorder "ADHD" and Autism Spectrum Disorder "ASD" was recently evaluated in three reviews, reporting divergent and confusing conclusions based on heterogeneous studies and subjects (**Ercolini & Fogliano, 2018**).

Food allergies, defined as an immune response to food proteins, affect as many as 8% of young children and 2% of adults in westernized countries, and their prevalence appears to be rising like all allergic diseases. In addition to well-recognized urticaria and anaphylaxis triggered by IgE antibody-mediated immune responses, there is an increasing recognition of cell-mediated

disorders such as eosinophilic esophagitis and food protein-induced enterocolitis **(Cianferoni & Spergel, 2009)**.

No known studies till now did evaluate the efficacy of diet elimination in treatment of psycho behavioral disorders in gastrointestinal food allergic patients, which may be more rational; as the food who affects the GIT more likely play role in affecting also the nervous system.

AIM OF THE STUDY

We aim to evaluate the effect of food elimination interventions in psycho-behavioral disorders treatment in food allergic patients and identify the effect of selective diet elimination on treatment of psycho-behavioral disorders in children with non-IgE mediated gastrointestinal food allergy.

Sample size calculation:

The sample size was calculated using Epi-Info 7. The criteria used for sample size calculation were as follows: confidence limit of 95%, and precision of 80%. The calculated sample size was N=47 children. The sample size was increased to 50 to compensate for non-responses and missed data.

Ethical considerations:

The study was approved by internal review board of Faculty of Medicine, Al-Azhar University in May 2019.

1. A written informed consent was obtained from patients or their legal guardians.

2. An approval by the local ethical committee was obtained before the study.

3. The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

4. All the data of the patients and results of the study are confidential, and the patients have the right to keep it.

5. The patient has the right to withdraw from the study at any time.

6. The researcher explained the aim of the study to each patient.

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Inclusion criteria:

1. Children with proven non IgE-mediated gastrointestinal food allergy, diagnosed with food elimination and challenge.

2. Children with proven psycho behavioral disorders (ASD,

ADHD, low IQ), diagnosed by validated diagnostic tests.

3. Age between 3-18 years old.

Exclusion criteria:

1. Any child with IgE mediated food Allergy

2. Any child with organic brain lesion. e.g., CP, HIE

3. Any child with organic gastrointestinal disease. e.g., Celiac, Hirschsprung

4. Age below 2 and above 18 years old.

Statistical analysis:

It was performed using IBM SPSS statistical software, version 25 "2017". Categorical data were reported as count and percentage. Numerical data were reported as mean and standard deviation. Paired Samples t-test, and Pearson's Chi square test for independence were used to compare numerical and categorical data, respectively. Significance was adopted at < 0.05 for interpretation of statistical tests' result.

PATIENTS AND METHODS

Study design:

This is an open non-blinded prospective interventional study on a group of 50 patients, 25 of them were selected from Al-Hussien and Sayed-Galal, Al-Azhar University Hospitals, and the other 25 were selected from University Hospitals, Rainbow Babies and Children Hospital, Cleveland, Ohio, United States of America from where we included the other 25 patients. Age of participating patients ranged from 3 to 18 years. They presented to pediatric outpatient and Gastroenterology and neuropsychiatric clinics having psycho behavioral disorders plus non IgE-mediated food allergy.

All the study children were subjected to:

I. Complete history and physical examination with details on gastrointestinal symptoms such as constipation, vomiting, diarrhea, abdominal pain, and psycho-behavioral symptoms such as ASD, ADHD, or developmental delay.

II. Thorough medical examination with focus on anthropometric measures, allergic signs such as hives, wheels, flares, and gastrointestinal signs as abdominal guarding, dehydration.

III. Laboratory investigation and evaluation of non-IgE mediated food allergy including total IgE serum level, food specific IgE serum level, Conners, CARS, and IQ tests before intervention.

IV.   Diet elimination in the form of cow milk and dairy products elimination.

V. Conners, CARS, IQ tests six weeks after food elimination.

RESULTS

Our results will be demonstrated in the following tables:

Table (1): Demographics and anthropometric measures of study participants

n=50	Mean±SD, n (%)	Range
Sex		
Males	36 (72.0%)	
Females	14 (28.0%)	
Age (years)	6.9±3.1	3.0-18.0
Height for age (% of median)	98.5±7	88.0-113.0
Weight for height (% of median)	100.1±5.8	91.0-112.0
Head circumference for age (% of median)	99.2±8.3	76.0-117.0
Body Mass Index "BMI"	16.1±2.5	13.1-23.0

Males represented 36 patients (72.0%) of the study patients. Mean age was 6.9±3.1 years and mean BMI was 16.1±2.5. Percentage of median was 98.5±7 for height for age, 100.1±5.8 for weight for height, and 99.2±8.3 for head circumference for age.

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Table (2):   Gastrointestinal symptoms of study participants

n=50	N	%
Abdominal pain	30	60.0
Abdominal distention	20	40.0
Diarrhea	4	8.0
Constipation	46	92.0
Anorexia	20	40.0
Nausea	8	16.0
Vomiting	2	4.0
GI bleeding	0	0.0
Rumination	0	0.0
Allergy to:		
Cow milk	50	100.0
Soy	8	16.0
Egg	12	24.0
Wheat	6	12.0
Nuts	2	4.0
Fish	2	4.0

The most common gastrointestinal symptom at presentation was constipation in 46 patients (92.0%), followed by abdominal pain in 30 patients (60.0%), abdominal distention in 20 patients (40.0%), and anorexia in 20 patients (40.0%). All study patients had cow milk allergy, 12 (24.0%) had egg allergy, 8 (16.0%) had soy allergy, and 6 (12.0%) had wheat allergy.

Table (3): Psycho-behavioral symptoms of study participants

n=50	N	%
Mental delay	38	76.0
Speech delay		
No (>200 words)	24	48.0
50-200 words	24	48.0
<50 words	2	4.0
Sentence formation problems	30	60.0
ADHD		
No ADHD	4	8.0
Inattentive	2	4.0
Hyperactive	44	88.0
ASD	30	60.0
Others "Aggressive"	10	20.0
Psychotherapy	6	12.0
Receiving medications	12	24.0

Thirty-eight (76.0%) of the study patients had mental delay with IQ lower than 80, 24 (48.0%) had speech delay with a vocabulary of 50-200 words, 30 (60.0%) had problems in sentence formation, 44 (88.0%) had hyperactive subtype of ADHD, 30 (60.0%) had ASD. Only 6 patients (12.0%) were having psychotherapy and 12 (24.0%) were receiving medications.

Table (4): Lab findings of study participants

n=50	N	%
CBC abnormalities		
Anemia	8	16.0
Eosinophilia	4	8.0
Total serum IgE		
Mean±SD.	224±28	

CBC showed that 16.0% of the children had anemia and 8.0% had eosinophilia. None of study patients had abnormalities in total IgE, food specific IgE, or basal metabolic abnormalities.

Table (5): **Comparison of GI symptoms between Egyptian and American children**

n=50	Egyptian		American		P
	N	%	N	%	
Abdominal pain	13	43.3	17	56.7	
Abdominal distention	9	45.0	11	55.0	
Diarrhea	3	75.0	1	25.0	
Constipation	22	47.8	24	52.2	
Anorexia	12	60.0	8	40.0	**0.556**
Nausea	3	37.5	5	62.5	
Vomiting	2	100.0	0	0.0	
GI bleeding	0	0.0	0	0.0	
Rumination	0	0.0	0	0.0	
Allergy to:					
Cow milk	25	50.0	25	50.0	
Soy	5	62.5	3	37.5	
Egg	6	50.0	6	50.0	**0.892**
Wheat	4	66.7	2	33.3	
Nuts	0	0.0	2	100.0	
Fish	2	100.0	0	0.0	
P: Exact Fischer test					

Table (6): **Comparison of psycho-behavioral symptoms between Egyptian and American children**

n=50	Egyptian		American		P
	N	%	N	%	
Mental delay	18	47.4	20	52.6	
Speech delay					
No (>200 words)	13	54.2	11	45.8	
50-200 words	14	58.3	10	41.7	
<50 words	2	100.0	0	0.0	
Sentence formation problems	17	56.7	13	43.3	
ADHD					
No ADHD	2	50.0	2	50.0	0.742
Inattentive	2	100.0	0	0.0	
Hyperactive	25	56.8	19	43.2	
ASD	16	53.3	14	46.7	
Others "Aggressive"	4	40.0	6	60.0	
Psychotherapy	0	0.0	6	100.0	
Receiving medications	3	25.0	9	75.0	
P: Exact Fischer test					

Table (5) and **table (6)** show the difference in gastrointestinal symptoms, food allergies, and psycho-behavioral symptoms between the Egyptian group of children and the American group. Both groups were similar to each other in most of the symptoms with no statistical significance between them, p value was 0.556, 0.892, and 0.742, respectively.

Table (7): Results of psycho-behavioral tests before and after food elimination

n=50	Before	After	*P*
Conners	74.2±3.9	71.4±5.1	**0.001***
CARS	31.8±7.9	30.4±8.2	**0.015***
IQ	67.6±16.9	70.3±16.8	**0.001***
Speech delay before No (>200 words) 50-200 words <50 words	24 (48.0%) 24 (48.0%) 2 (4.0%)	24 (48.0%) 24 (48.0%) 2 (4.0%)	**1.000ᵃ**
*P: Paired Samples t-test, *: Statistically significant, a: Chi-Square test*			

Differences in Conners, CARS, and IQ tests before and six weeks after food elimination were statistically significant with p values of 0.001, 0.015, and 0.001, respectively. However, these differences were not clinically significant as the patients were still in the same diagnostic subcategories of each test. There was no difference in speech delay before and after food elimination therapy.

DISCUSSION

Relationship between gastrointestinal tract and some psycho-behavioral disorders are not well established yet. Several studies have been investigating the effect of food elimination diet on ASD, ADHD, and other developmental delays but most of them were not blinded, not randomized, or observational. They studied the effect of food elimination diet on different outcomes as symptoms reported by physicians, parents, or teachers, Diagnostic and Statistical Manual "DSM"-based diagnosis of ASD, severity of symptoms, CARS, the Autism Treatment Evaluation Checklist Scale "ATEC", Ecological Communication Orientation "ECO" scale, neurocognitive skills, social skills, and psychometric tests of attention

(**Keller et al., 2021**). In our study we introduced food elimination and defined speech delay, Conners test, CARS test, and IQ test as our desirable primary outcomes.

Population included in previous studies was mostly children and adolescents diagnosed with psycho-behavioral disorders (**Nigg et al., 2012**). To our knowledge, there are no previous studies that included patients with psycho-behavioral disorders and food allergy.

In our study we used cow milk and dairy products elimination for all patients since we only included patients with food allergies and all of them had cow milk food allergies. Some of our patients were restricted from soy, eggs, wheat, nuts, or fish according to the previously diagnosed non-IgE mediated food allergy, While in **Nigg et al. study 2012**, they eliminate only gluten or casein.

This study showed that the mean age of patients was 6.9±3.1 years, which was comparable with Killer study in which age ranged from 7.3-8.9 years. Duration of food elimination ranged from four weeks to one year in his study and six months period was considered the minimum duration, based on clinical experience, to assess the desired effects. Follow up in his study was six weeks which was average among other studies (**Keller et al., 2021**).

Regarding Psychological evaluation, Conners, CARS, IQ tests and speech delay were not affected by elimination of allergy-causing foods in our populations. This was in line with one systematic review and metanalysis that concluded there is no benefit of food elimination on core symptoms of ASD., While in other studies the outcomes were controversial (**Keller et al., 2021**). Other systematic review agreed with the same findings, and positive effects were only reported in studies with low quality (**Sathe et al., 2017**).

Regarding gastrointestinal symptoms we founded that the abdominal pain followed by abdominal distension were the most prominent symptoms reported (**Table 1**). To our knowledge no other studies reported these items.

Regarding gastorintestinal and psychological manifestations in both Egyptian and American children, our study showed no significant difference.

Also, our study is the first one to test the effect of food elimination diet in patients with psycho-behavioral disorders and food allergies.

LIMITATIONS

The study included only one group, small sample size, no blindness or randomization.

CONCLUSIONS

Food elimination diet has no clinically significant effect on psycho-behavioral disorders in patients with food allergies.

RECOMMENDATIONS

Larger randomized controlled studies are needed to assess the efficacy and safety of the intervention and the sufficient follow up duration to evaluate this effect.

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