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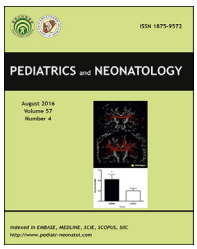

Original Article

Evaluation of emotional, Behavioral, and clinical characteristics of children aged 1–5 with a history of food-related anaphylaxis

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Key Words
anaphylaxis;
children;
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Background: Our study aimed to investigate emotional, behavioral, and social characteristics assessed with internationally validated psychometric scales and their relationship with demographic, clinical, and laboratory data in children with a history of food-related anaphylaxis.
Method: The study included patients aged 1–5 who were followed up in the pediatric allergy outpatient clinic with a diagnosis of food-related anaphylaxis. All participants were evaluated during admission to the clinic using a study questionnaire, which was prepared by the authors, consisting of three parts: a sociodemographic information form, a clinical evaluation form, and the Aberrant Behavior Checklist (ABC) for psychiatric evaluation. Parents answered the questionnaires regarding the patients' emotional and behavioral health.
Results: Thirty patients aged between 12 and 62 months were included in the study. The data were compared with 30 healthy controls with similar age and gender distribution. The total ABC score ($p = 0.015$), and the stereotypic behavior ($p = 0.003$) and hyperactivity ($p = 0.002$) subscale scores were significantly higher in patients with anaphylaxis history compared to the controls.
Conclusion: Emotional and behavioral status assessments and the clinical follow-up of food allergies of patients who experienced anaphylaxis in early childhood are useful for the holistic management and early recognition of possible pathologies.

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1. Introduction

Food allergy is an adverse immune response against food proteins. It is an important health problem with increasing prevalence in developed countries that negatively affects the lives of both children and parents.[1] In immunoglobulin E-mediated food allergies, symptoms usually occur immediately after exposure to the food containing the allergen. Although most reactions (e.g., urticaria) are mild, severe and life-threatening reactions, such as anaphylaxis, may occur.[2]

The effects of food allergies on the quality of life and mental health of patients and their families have been investigated in recent years.[3] The early onset of food allergies, the delay in the development of tolerance until school age or even adolescence, and the presence of accompanying allergies, such as atopic dermatitis, allergic rhinitis, and asthma, enhance the negative impact.[4]

Although psychiatric diseases, such as behavioral disorders, anxiety, depression, autism spectrum disorders (ASD), and attention deficit hyperactivity disorder (ADHD), have been investigated in children with allergies, the mental and behavioral evaluation of patients experiencing severe life-threatening allergic reactions, such as anaphylaxis, in early childhood are limited in the literature.[5,6]

Our study aimed to investigate emotional, behavioral, and social factors assessed by an internationally validated psychometric scale and their relationship with demographic, clinical, and laboratory characteristics in children aged 1—5 with a history of food-related anaphylaxis.

2. Methods

The study was conducted from January to July 2021 at a tertiary care children's hospital, at the Pediatric Immunology and Allergy Diseases Outpatient Clinic. The approval of the Ethics Committee for Clinical Studies was obtained for this study, and a signed informed consent form was obtained from all participants' caregivers before inclusion in the study. The study was carried out in accordance with the principles of the Declaration of Helsinki.

2.1. Participant selection and diagnosis of anaphylaxis

The study included patients aged 1—5 who were followed up in the pediatric allergy outpatient clinic with a diagnosis of food-related anaphylaxis. Anaphylaxis was clinically diagnosed by pediatric allergy and immunology experts, following the update by the European Academy of Allergy and Clinical Immunology, Food Allergy, and Anaphylaxis Guidelines Group, in 2021.[7] Food allergy was confirmed with *in vivo* and/or *in vitro* diagnostic tests in the presence of a compatible clinical history. Participants presenting a non-allergic chronic disease were excluded from the study.

2.2. Data collection tools

All participants were evaluated during their admission to the clinic using a study questionnaire, which was prepared by the authors, consisting of three parts: a sociodemographic information form, a clinical evaluation form, and a psychiatric assessment with a standardized scale.

1) *Sociodemographic Information Form*: It includes sociodemographic information, such as age, gender, duration of breastfeeding, age at which supplementary food intake was initiated, concomitant allergic disease, family history of atopy, parental education level, and monthly income.
2) *Clinical Evaluation Form*: It includes clinical data, such as the number of allergenic foods, number of severe allergic reactions, systems involved in the reaction, the application of an elimination diet, and the tolerance state associated with food allergy. Results of provocation tests, if performed, were documented in a standard form.
3) *Psychiatric Assessment:* The Aberrant Behavior Checklist (ABC) was administered to parents for the evaluation of emotional and behavioral health. Various tools have been developed for assessing emotions and behavior in childhood. ABC is useful in assessing inappropriate and non-compliant behaviors.[8] The subscales of the test are the following: 1) irritability, agitation, and crying, 2) lethargy and social withdrawal, 3) stereotypic behavior, 4) hyperactivity and noncompliance, and 5) inappropriate speech. They assess the severity of psychiatric conditions in early childhood, especially destructive behavioral disorders and common developmental disorders. ABC's validity and reliability in Turkish were evaluated by Karabekiroğlu et al.[9]

3. Results

3.1. Sociodemographic data and clinical characteristics of food allergies

Of the 30 patients included in the study, 15 (50%) were male. The median age of the patients was 19 months, and the age ranged from 12 to 62 months (interquartile range [IQR]: 15—31.50). The youngest age of an anaphylactic event was 1 month, and the oldest was 48 months (median: 8 months; IQR: 4.75—18.50). Although the majority of patients had experienced anaphylaxis once, nine patients (30%) had a history of anaphylaxis caused by the same food more than once. The sociodemographic data and the food allergy clinical data are summarized in Tables 1 and 2, respectively.

3.2. Psychiatric Assessment

The ABC patients' results were evaluated as total scores and subscale scores (irritability, lethargy and social withdrawal, stereotypic behavior, hyperactivity, and inappropriate speech). No significant differences in the scores were found between male and female patients. Furthermore, the number of anaphylactic events did not relate to the ABC scores.

The data were also compared with 30 healthy controls with similar age and gender distribution who did not have chronic diseases and underwent routine examinations at the children's health and disease outpatient clinics. The

Table 1 Characteristics of the study population, n = 30.

Parameter	n (%)
Gender	
Female	15 (50)
Male	15 (50)
Gestational age	
<37 week	5 (16.7)
37–42 week	24 (80)
>42 week	1 (3.3)
Type of birth	
Vaginal delivery	17 (56.7)
C/S	13 (43.3)
Presence of allergic diseases	
Another food sensitization other than the food that caused anaphylaxis	8(26.6)
Mild atopic dermatitis	6 (20)
Symptoms of allergic rhinitis	2 (6.6)
Family history of atopy	17 (56.7)
Family history of psychiatric disease	4 (13.3)
Family type	
Nuclear	25 (83.3)
Extended	5 (16.7)
Socioeconomic level	
Low	4 (13.3)
Middle	22 (73.3)
High	4 (13.3)
Consanguinity	6 (20)
Infantile colic history	16(53.3)
Age of the introduction of complementary feding (month),(median, IQR)	6 (6–6)

total ABC ($p = 0.015$), stereotypic behavior ($p = 0.003$), and hyperactivity ($p = 0.002$) scores were significantly higher in patients with anaphylaxis history compared with the controls. The data are summarized in Table 3.

4. Discussion

Apart from the impact on general health, food allergies negatively affect mental health and quality of life as shown in recent investigations. Our study aimed to evaluate emotional and behavioral well-being, apart from the clinical features of life-threatening severe allergic reactions, in early childhood, a developmental period lacking relevant studies. Thus, patients of this age group with a history of anaphylaxis were evaluated and presented significantly higher scores on the total ABC scale and the stereotypic behavior and hyperactivity subscales than the control group.

Palloni et al.[10] studied 232 adolescents and found that the internalization scores, related to emotional and relational problems, were higher in the group with food allergies than in healthy controls, emphasizing the negative impact of food allergies on everyday life (home life, friendships, classroom activities, leisure activities, and general troubles). Another study found that experiencing severe allergic reactions in childhood causes nutritional disorders, retreat, fear, depression, and social difficulties.[11] Moreover, parents with children who experienced

Table 2 Characteristics of the patients regarding anaphylaxis clinic and status of tolerance or persistence of the culprit allergen.

Parameter	n (%)
Data of anaphylaxis clinic	
Age at which anaphylaxis occur (month), median, IQR	8 (4.75–18.50)
Culprit food allergen causing anaphylaxis	
dairy products	15 (50)
nuts (peanuts, cashews, and nuts)	8 (26.7)
Egg	6 (20)
Lentil	1 (3.3)
Number of anaphylaxis episodes	
One	21 (70)
Two	4 (13.3)
Three or more	5 (16.7)
Clinical presentation of anaphylaxis	
Skin symptoms	29 (96.6)
Respiratory symptoms	18 (60)
Gastrointestinal symptoms	22 (73.3)
Administration af adrenaline for the treatment of anaphylaxis	
Yes	18 (60)
Follow-up time for anaphylaxis	
<24 h	20 (66.7)
>24 h	10 (33.3)
Patients receiving dietitian consultation	13 (43.3)
Patients who used amino-acid based formula	6 (20)
Patients who were prescribed adrenaline auto-injecteur	24 (80)
Patients who were prescribed adrenaline auto-injecteur	3 (12.5)
Data of tolerance status	
Patients who underwent oral food cahallenge	10 (33.3)
Time between diagnosis and oral food cahallenge (months) Median, IQR	10.5 (5.75–19.75)
Age at oral food cahallenge (months),Median, IQR	20 (15.25–35.25)
Result of oral food cahallenge (n:10)	
Positive	3 (30)
Patients who developed tolerance to the food that caused anaphylaxis (n:30)	2 (6.7)

Table 3 Data of psychiatric assessment scale.

Parameter	Study group n:30	Control group n:30	p
ABC Total Score	9 (2–20.25)	5.5 (2.75–7.25)	0.015*
Irritability	2(0–8)	2 (1–3)	0.533
Lethargy/Social withdrawal	1 (0–2)	0.5 (0–1)	0.488
Stereotypic Behavior	1 (0–2)	0 (0–0.25)	0.003*
Hyperactivity	3.5 (1–7.25)	1 (0–2)	0.002*
Inappropriate Speech	1 (0–2)	1 (0.75–1)	0.479

*P < 0.05.

anaphylaxis may be stressed with consequent physiological reactions in the follow-up period, and gradually, this anxiety is transferred from parents to children. Walkner[12] assessed anaphylaxis as trauma and stated that it could cause posttraumatic stress disorder. In many studies conducted in pediatric and adolescent populations, food allergies were associated with higher levels of stress and anxiety and lower life quality indices compared with the control group.[13] Laurens[14] found that anaphylaxis and allergy caused an increase, albeit slight, in emotional, behavioral, and social problems in middle childhood. Another study emphasized that children with food allergies experience more bullying than their peers and adverse effects on social functionality, academic functioning, and mental health.[15]

The literature on the impact of food allergies on mental health in early childhood is scarce compared with that in adolescents and school-age groups. A meta-analysis of longitudinal studies showed that allergic diseases, such as asthma, atopic dermatitis, and allergic rhinitis, were independently associated with ADHD, whose rate was 30%—50% in children with atopy.[16] In another study that evaluated the frequency and severity of psychiatric disorders in preschool children with milk allergy, the scores of ADHD, oppositional defiant disorder, and bonding disorder were higher in children with this allergy compared to the control group.[4] Similarly, in our study, hyperactivity scores of the atopy subgroup with a history of food-related anaphylaxis in early childhood were higher than the control group, as reported by parents. This implies the presence of shared risk factors, such as genetic factors and perinatal stress, for both groups of diseases.

The underlying common mechanism probably causes an increase in the release of allergic inflammatory cytokines during the perinatal period, affecting certain neurotransmitter systems and brain regions, for example, the prefrontal cortex, which plays a role in ADHD pathophysiology.[17] Hence, although the clinical characteristics and severity of ADHD and allergic diseases in children vary, their symptoms can occur anytime from the neonatal period onwards.

ADHD has different subtypes in terms of etiology due to the clinical characteristics and heterogeneous nature of its course.[18] In this context, as some children with ADHD benefit from a diet based on food restriction, ADHD accompanied by allergic diseases could be considered a separate etiological subtype in the future.[19] As these patients need specific diagnostic markers and etiology-based interventions are needed for treatment, the findings that we obtained from the atopy sample serve as a foundation for future studies.

Meldrum et al.[20] found that food allergies in the infantile period adversely affect motor neurodevelopment and are associated with internalization and social/emotional problems. Another study mentioned that intense anxiety in patients who experienced anaphylaxis during the infantile period is transformed into phobia through negative reinforcement by avoiding behavior of themselves and their parents.[21]

Our study did not demonstrate any significant differences in other areas such as irritability, lethargy and social withdrawal, and speech problems. This may be associated with the sample's characteristics, in that it consisted of early childhood patients. According to Beck's[22] cognitive model, early life experiences form the fundamental beliefs and conditional assumptions about oneself, the outside world, and the future, reinforced by experiences in later stages of life. During this process, negative thoughts can be learned, and their reflection in the clinic can be in the form of emotional and behavioral problems. As children of this age group are still in their early childhood, these symptoms may be difficult to observe. However, internalization can be observed with longitudinal follow-up. Chen et al.[23] found that atopic diathesis at the age of 0—3 increases the risk of developing ADHD and ASD in the future.

Our study revealed that the study sample exhibited stereotypic behavior, one of the most important diagnostic features of autism. Stereotypic behavior is observed at significantly higher levels in children with ASD in early childhood compared with those without ASD.[24] It is also known that the prevalence of food allergies in children with ASD is higher than in healthy controls.[5] In a meta-analysis including twelve studies, a significant correlation between food allergy and ASD risk was observed.[25]

In atopic diseases, such as food allergies, mast cells are activated and release inflammatory and vasoactive mediators, which are also found perivascularly in brain regions, such as the thalamus and hypothalamus, increasing the permeability of the blood—brain barrier. Although not specific to the disorder, some patients with ASD have increased expression of inflammatory cytokines in the brain, cerebrospinal fluid, and peripheral circulation. Inflammatory cascades stimulate the proliferation and activation of microglia, leading to neuronal linkage disruption.[26] As a result, atopic diseases, such as food allergies, can form an ASD-sensitive phenotype, which can be identified as a separate etiological subgroup of ASD. Future cell therapies specifically targeting brain inflammation may reduce stereotypic behaviors in this group of patients.

The small sample size and the cross-sectional design of our study can be considered limitations. However, one of the strengths of our study is that it provides real-life data that reflect a single-center experience and, unlike other studies, data related to life-threatening reactions, such as anaphylaxis, in early childhood. To the best of our knowledge, this is the first study in this age group. There is a need for large-scale and multicenter studies involving long-term follow-up to confirm these findings.

In the management of food allergies, after emergency intervention for acute reactions, a long-term follow-up period, involving the elimination of foods, begins. At this stage, the patient should be referred to the pediatric allergy and immunology department, a dietitian should be consulted for the long-term application of the diet, and the child should be closely examined for growth and development parameters. Patients and their relatives should be trained on cross-reactivity, label-reading of food containers to avoid allergenic proteins, risk of contamination during food preparation, and auto-injector application in emergencies. Oral food provocation tests assess the tolerance status, in an attempt to include the tolerable form of the food in the diet.[27] In this follow-up process, frequent visits to the polyclinic, special diets, emergency department admissions, social isolation due to parental fears, a

necessity to constantly carry medications, and the inability to find a suitable school/nursery can cause emotional and behavioral pathologies in both parents and patients.[28]

The early childhood period is important in the psychosocial development of the central nervous system. Therefore, early recognition and early intervention in children with social, emotional, and behavioral problems are becoming increasingly important. In this context, we recommend the assessment of the emotional and behavioral status and the clinical follow-up of food allergies in patients who experienced anaphylaxis in early childhood for holistic management and early recognition of possible pathologies. Clinicians who follow patients with childhood food allergies should be aware of the adverse psychological effects that are not often part of the follow-up and treatment strategies in daily practice. If necessary, they should cooperate with a psychiatrist to provide appropriate care.

Conflict of interest

The authors have no conflicts of interest to declare.

Ethics

The approval of the Ethics Committee for Clinical Studies (E—20/12—61) was obtained for our study, and a written informed consent form was obtained from all participants before inclusion in the study.

Author contributions

Zeynep Şengül Emeksiz: Data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), resources (equal), writing-original draft (equal), writing-review and editing (equal); **Aysegül Ertugrul**: Data curation (equal), formal analysis (equal), resources (equal); **Sabide Duygu Uygun:** Data curation (equal), formal analysis (equal) resources (equal); **Serap Ozmen:** Project administration (equal), data curation (equal), methodology (equal), formal analysis (equal) writing-original draft (equal), writing-review and editing (equal).

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