











Food Allergy Management Has Been Negatively Impacted During the COVID-19 Pandemic

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ABSTRACT

Objective: The coronavirus disease 2019 (COVID-19) pandemic creates secondary problems for the health care system, and understanding specific issues can guide the management of the pandemic and its future consequences. We aimed to characterize the problems and related risk factors experienced with outpatient compliance and dietary compliance of children with food allergies during the COVID-19 pandemic.

Materials and Methods: A cross-sectional survey was conducted on the mothers of children with ongoing food allergies, eight months after Turkey's first confirmed case of COVID 19.

Results: Of the 288 patients, 76.3% and 40.2% were non-adherent to their scheduled appointments and oral food challenge, respectively, during the pandemic. The group non-adherent to their scheduled visit was significantly older ($p=0.005$), had more frequent home food trials without the consent of their physicians ($p<0.001$), and had less usable epinephrine auto-injectors (EAI) available compared with the adherent group ($p<0.001$). Eighty-nine patients (30.9%) with home food trial experience had more essential food allergies ($p<0.001$) and experienced more allergic reactions ($p=0.002$), compared with patients who adhered to dietary elimination. Thirty parents (10.4%) eliminated some foods from their children's diet because of the suspected reactions.

Conclusion: The COVID-19 pandemic, significantly reduces adherence with scheduled appointments and OFC, and increases home food trials and food eliminations without physician approval.

Keywords: The COVID-19 pandemic, food allergy, compliance, telemedicine, oral food challenge

INTRODUCTION

The coronavirus disease 2019 (COVID-19) has had a negative impact on the capacity of health care systems to maintain preventive and curative services. A thorough understanding of this period's dynamics is required for fast actions and solution developments, and has created the opportunity to prepare for potential future threats. Food allergy (FA) is a global health problem that affects up to 10% of children worldwide and causes high social burden and health care costs (1). It differs from many health problems, primarily because it affects young children, where nutrition is much more critical.

During the COVID-19 pandemic, all oral food challenges (OFC) are recommended to be delayed unless there is a critical acute nutritional need for introduction of a key nutrient (2). Besides, virtually supervised OFCs and oral immunotherapy were offered to the patients with the low risk food allergy procedures (3). With the understanding that the pandemic will last longer, we implemented a telemedicine application as used in many health services, where we informed our patients and their caregivers about FA and allergen elimination, determined their needs such as epinephrine auto-injector (EAI) prescription and dietary advice, and made a new appointment if necessary. During this procedure, we aimed to document the impact of COVID-19 on FA management using a questionnaire.

MATERIALS and METHODS

Study Population

This cross-sectional survey was conducted almost eight months after the first confirmed case of COVID-19 during telemedicine activity in the Pediatric Allergy Division of Hacettepe University Ihsan Doğramacı Children's Hospital in November 2020, which is a referral center for the whole of Turkey. Patients who were followed up regularly with immunoglobulin (Ig)-E and non-IgE mediated ongoing food allergies during the last year were included in the study. Infants who were diagnosed as having proctocolitis were excluded because they have no regular follow-up plan. Patients who could not be reached with three attempts or refused to participate in the questionnaire-based study during telephone-based telemedicine visits were excluded. Outpatient non-adherence was defined if the appointment was postponed ≥ 2 weeks. A 60-item questionnaire in open-label and multiple-choice formats was developed and used to conduct the telephone survey with the mother, who is the primary caregiver in our culture, unless stated otherwise.

After the questionnaire survey, a telemedicine visit was performed where parents were informed about their child's FA and comorbidities, dietary advice was given, questions were answered, and outpatient appointments were made for those who requested them. Caregivers were questioned about the clinical and demographic features of the patients; changes in diet, and allergic reactions during the COVID-19 pandemic; the mother's education level and employment status, the parents' opinions about the impact of the COVID-19 pandemic on FA, and the use of EAIs.

Statistical Analysis

Statistical analyses were performed using the SPSS version 22.0 statistical software package (IBM SPSS Statistics, USA). The results were given as median [interquartile range (IQR)] because the continuous variables were distributed non-normally. The Chi-square and Mann-Whitney U tests were used to compare nonparametric values. For the risk analysis of drop-outs, variables were selected if the p-value was less than 0.20 in the univariate analysis and were then included in multivariate analysis. Odds ratios (ORs) with relevant 95% confidence intervals (CIs) were calculated to evaluate potential associations. P-values of <0.05 were accepted as significant.

Statement of Ethics

The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki, and the use of data for this study was approved by the local Ethics Committee of Hacettepe University, Ankara Turkey (6020/951, 2020/18-06). As written informed consent is not possible in telephone interviews, the ethical committee requested verbal informed consent from the study participants. Verbal informed consent of all the subjects' parents was obtained just before the telephone survey.

RESULTS

Study Group

In the year before the first reported case of the pandemic, 392 patients were followed in the outpatient clinic due to FA, and 288 (73.4%) were included with a median age of 3.6 (0.7-18.3) years and male predominance (67.7%). Two hundred twenty (76.3%) and 68 (23.7%) patients were considered non-adherent and adherent, respectively, depending on their scheduled visits. Twenty-nine (29.8%) and 75 patients (25.4%) from the non-adherent and adherent groups, respectively, could not be reached (n=94) or refused to participate (n=10). There were no significant differences in terms of age, gender and multiple FA between the patients who were included the study, and those who were not. All phone surveys were conducted with the mothers. The most frequent initial FA symptoms/diagnosis were atopic dermatitis (63.9%), followed by urticaria (19.4%), anaphylaxis (11.8%), angioedema (2.4%), and food protein-induced enterocolitis syndrome (FPIES) (2.4%). Tree nuts were the most common FA etiology (50.3%), followed by cow's milk (45.5%), hen's egg (44.4%), seeds (27.4%), and peanut (26%). A scheduled OFC was planned for 155 (53.8%) patients, whereas it was only performed for 39 patients (13.1%) on time and 29 patients with a delay (10%).

Non-Adherent vs. Adherent Study Groups

Of the patients who were non-adherent during the COVID-19 pandemic, the median time of delay was 5.7 (0.8-9.3) months. The median age of the non-adherent group was 3.7 (2.3-5.8) years, and it was significantly higher compared with the adherent group [3.0 (1.7-5.1) years, $p=0.005$] (Table I).

Tree nuts were the most frequent culprit foods in the non-adherent group (52.2%), followed by hen's egg (45.4%), cow's milk (38.1%), peanut (25.4%), and seeds (25.0%). However, in the adherent group, cow's milk (69.1%) was the most frequent culprit food followed by tree nut (44.1%), hen's egg (41.1%), and seeds (35.2%). Cow's milk allergy was significantly more frequent in the adherent group when compared with the non-adherent group ($p < 0.001$). In the non-adherent group, OFC was planned for 112 patients (50.9%) but performed only in 29 patients (13.2%) with a delay. In the adherent group, OFC was planned for 43 patients (63.2%) and performed

for 39 patients (57.3%). There was a higher frequency of scheduled OFCs with cow's milk (58.1% vs. 29.2%, $p = 0.001$) and lower frequency with hen's egg (16.3% vs. 40.7%, $p = 0.004$) and tree nuts (9.3% vs. 23.0%, $p = 0.052$) in the adherent group, compared with the non-adherent group.

In the adherent group, 57 patients (83.7%) had at least one FA to the essential nutrition sources in our culture (cow's milk, hen's egg, wheat, and red meat) compared with the non-adherent group (66.8%) ($p = 0.007$).

Table I. Demographic and clinical characteristics of the study population according to adherence in the outpatient setting.

	All (n=288)	Non-adherent group (n=220)	Adherent group (n=68)	p
Gender, male, n (%)	195 (67.7)	144 (65.4)	51 (75.0)	0.14
Age (years)*	3.6 (2.3-5.8)	3.7 (2.4-5.9)	3.0 (1.7-5.1)	0.005
Age at symptom onset (months)*	3 (2-6)	3 (2-6)	3 (2-6)	0.080
Age at admission (months)*	6 (4-7.25)	6 (4-8)	5 (4-6)	0.012
Family history of atopy, n (%)	156 (54.1)	123 (55.9)	33 (48.5)	0.35
Patients who reported food trials at home by families, n (%)	89 (30.9)	79 (35.9)	10 (14.7)	.001
Having a scheduled OFC plan before the pandemic, n (%)	155 (53.8)	112 (50.9)	43 (63.2)	0.07
Ongoing food desensitization plan, n (%)	31 (10.7)	24 (10.9)	7 (10.2)	0.88
Eliminating a food without the doctor's consent, n (%)	30 (10.4)	27 (12.2)	3 (4.4)	0.07
Experiencing an allergic reaction at home, n (%)	89 (30.9)	70 (31.8)	19 (27.9)	0.59
Food allergy, n (%)				
Cow's milk	131 (45.4)	84 (38.1)	47 (69.1)	0.001
Hen's egg	128 (44.4)	100 (45.4)	28 (41.1)	0.51
Tree nuts	145 (50.3)	115 (52.2)	30 (44)	0.24
Legume	27 (9.3)	19 (8.6)	8 (11.7)	0.43
Seed	79 (27.4)	55 (25.0)	24 (35)	0.09
Peanut	75 (26.0)	56 (25.4)	19 (27.9)	0.68
Number of allergies	2 (1-5)	2 (1-5)	2 (1-6)	0.727
Having an essential food allergy	204 (70.8)	147 (66.8)	57 (83.8)	0.007
Prescription of an EAI	175 (60.7)	137 (62.2)	38 (55.8)	0.32
Having a proper EAI	122 (42.3)	86 (39)	36 (52.9)	<0.001
Mother's view on how covid-19 impacted overall on food allergy management, n (%)				
Neutral	176 (61.1)	126 (57.3)	50 (73.5)	
Positive	29 (10.1)	22 (10.0)	7 (10.3)	0.027
Negative	83 (28.8)	72 (32.7)	11 (16.2)	

*Median, (interquartile range), **EAI**: Epinephrine auto injector, **OFC**: Oral food challenge.

During the COVID-19 pandemic period, 89 patients (30.9%) experienced 94 food-related allergic reactions at home. Among these allergic reactions, 54 (57.4%) were urticaria and 31 (32.9%) were anaphylaxis episodes. Only 4 patients who experienced anaphylaxis used EAI. Although the allergic reactions were more frequent in non-adherent patients (31.8%), there was no significant difference between the groups (27.9%, $p=0.59$). The most frequent reason for an allergic reaction was accidental consumption of allergen food (50.0%), followed by a home trial of allergen food (29.8%), and consuming food that was not a known allergen before (20.2%).

In the non-adherent group, 79 patients (35.9%) had made 118 food trials at home without the encouragement of their physician, and the number was significantly higher compared with the adherent group [10 patients (14.7%) and 13 trials] ($p=0.001$). Among all these 131 home food trials, hen's egg was the most frequent (38.9%), followed by cow's milk (21.3%), tree nuts (12.2%), peanut (5.3%), and legumes (5.3%). Ninety-nine home food trials (75.6%) were tolerated well by patients, but a positive reaction was experienced in 32 trials (24.4%). Urticaria (53.1%) and anaphylaxis (31.2%) were the most frequent reactions. None of the patients who experienced anaphylaxis used EAI, and only two patients presented to the emergency department.

Epinephrine auto-injectors had been prescribed previously to 137 patients (62.2%) in the non-adherent group and 35 patients (55.8%) in the adherent group. Non-adherent patients (39.0%) had significantly less EAIs available for use (52.9%, $p<0.001$), and the most common reason was that the EAIs had expired (32.1%).

Thirty patients eliminated some foods, because of suspected reactions, without their physicians' approval, and this was more common in the non-adherent group (12.2%) compared with the adherent group (4.4%, $p=0.07$). Tree nuts were the most commonly eliminated food, followed by seeds and hen's egg (41%, 18%, 18%, respectively).

Seventy-two mothers (32.7%) in the non-adherent group stated that the COVID-19 pandemic had a negative impact on overall FA management, and 126 (57.3%) and 22 mothers (10%) reported neutral or positive views, respectively. In the adherent group, negative views were less frequent (5%), and neutral views (73.5%) were more frequent ($p=0.02$) compared with the non-adherent group.

We further evaluated the potential risk factors for outpatient non-adherence during the COVID-19 pandemic. Home food trial (OR: 4.468, 95% CI: [2.048-9.748]; $p=0.004$), and older age (OR: 1.169, 95% CI: [1.039-1.315]; $p=0.004$) were found to be independent risk factors for being non-adherent, whereas presence of cow's milk allergy (OR: 0.270, 95% CI: [0.146-0.498]; $P<0.001$) was a protective factor for non-adherence (Table IIA).

Home Food Trial vs. No Home food Trial

When the patients were divided into two groups according to food elimination compliance, those who tried the food at home (median age: 2.4 (2.1-3.3) years) were younger than those who did not (median age: 4.4 (2.9-6.6) years) ($p<0.001$) (Table III). Hen's egg (17.7%) was the most commonly tried food, followed by cow's milk (9.7%) and tree nuts (5.5%). There was a higher frequency of a scheduled OFC in patients who had a trial at home (64.0% vs. 49.2%, respectively, $p=0.02$) (Table III). Hen's egg allergy and having a basic food source allergy were more frequent in patients who had a home food trial than patients who did not (73.0% vs. 31.6%, $p<0.001$; 87.6% vs. 63.6%, $p<0.001$, respectively). In addition, the number of mothers who are housewives was higher in the home food trial group compared to those who did not.

When risk factor analysis was performed for a home food trial without the encouragement of physicians, the presence of egg allergy increased the risk of home food trials (OR: 4.223, 95% CI: [2.290-7.787]; $p<0.001$), whereas older age decreased the risk (OR: 0.750, 95% CI: [0.646-0.870], $p<0.001$) (Table IIB).

DISCUSSION

This is the first study to document the impact of COVID-19 on FA management. Approximately three-quarters of the patients were non-adherent to their scheduled visits and half of the patients were non-adherent to OFCs during the COVID-19 pandemic. Older age and having FA to less essential food were associated with this. In addition, non-adherent patients were less compliant with their dietary elimination and had less available EAIs. One in three patients underwent a home food trial without the physician's consent; these patients were significantly younger, had a scheduled OFC plan before the pandemic, and experienced more reactions at home.

Table II. A) Univariate and multivariate regression analysis for risk factors of outpatient non-adherence. B) Univariate and multivariate regression analysis for risk factors of home food trial.

A	Univariate analysis			Multivariate analysis			
	Variable	OR	CI (95%)	p	OR	CI (95%)	p
	Age (year)	1.110	1.004-1.228	0.042	1.169	1.039-1.315	0.004
	Cow's milk allergy	0.276	0.154-0.494	<0.001	0.270	0.146-0.498	<0.001
	Seed allergy	0.611	0.341-1.095	0.098	0.575	0.303-1.094	0.093
	Scheduled OFC before pandemic	0.603	1.573-6.713	0.076			
	OFC at home by families	3.250	0.345-1.055	0.001	4.468	2.048-9.748	<0.001
B	Univariate analysis			Multivariate analysis			
	Variable	OR	CI (95%)	p	OR	CI (95%)	p
	Age (year)	0.723	0.631-0.829	<0.001	0.723	0.631-0.829	<0.001
	Egg allergy	5.804	3.3300-10.115	<0.001	5.804	3.3300-10.115	<0.001
	Oral desensitization	0.396	0.147-1.068	0.067	0.396	0.147-1.068	
	Scheduled OFC before pandemic	1.836	1.097-3.071	0.021	1.836	1.097-3.071	
	Mother's employment status	0.617	0.441-0.864	0.005	0.617	0.441-0.864	

Table III. Demographic and clinical characteristics of the patients according to allergen avoidance.

	Patients who made Home food trial (n=89)	Patients who complied food elimination (n=199)	P
Gender, male, n (%)	61 (68.5)	134 (67.3)	0.84
Age (years)*	2.4 (2.1-3.3)	4.4 (2.9-6.6)	<0.001
Having an essential food allergy, n (%)	78 (87.6)	126 (63.3)	<0.001
Food allergy, n (%)			
Cow's milk	38 (42.6)	93 (46.7)	0.52
Hen's egg	65 (73.0)	63 (31.6)	<0.001
Tree nuts	47 (52.8)	96 (48.2)	0.47
Legume	12 (13.4)	15 (7.5)	0.11
Cereal	3 (3.3)	4 (2)	0.68
Seed	42 (47.1)	57 (28.6)	0.49
Peanut	25 (28.0)	50 (25.1)	0.59
Food desensitization, n (%)	5 (5.6)	26 (13.0)	0.06
Having a scheduled OFC before the pandemic, n (%)	57 (64.0)	98 (49.2)	0.02
Experiencing an allergic reaction at home, n (%)	39 (43.8)	50 (25.1)	0.002
Mother's employment status, n (%)	28 (31.5)	99 (49.7)	0.003
Mother's view on how covid-19 impacted overall on food allergy management, n (%)			
Neutral	45 (50.6)	131 (65.8)	
Positive	16 (18)	13 (6.5)	0.005
Negative	28 (31.4)	55 (27.7)	

*Median, (interquartile range), EAI: Epinephrine auto injector, OFC: Oral food challenge.

In the present study, two structural factors were associated with a better outpatient adherence: Cow's milk allergy and younger age. Dietary elimination of essential foods in children results in nutritional deficiency and reduced quality of life in families (4). Cow's milk is the second most common cause of IgE-mediated FA during the first two years of life (5). However, it provides one of the major contributions to human nutrition as an easily accessible and affordable source of protein and calcium. We believe that this may explain why patients with milk allergy adhered to their outpatient appointments. Besides, cow's milk allergy develops in early infancy, rarely after 12 months of age, and that may be the reason why adherent patients had younger age (6).

During the COVID-19 pandemic, skin tests, blood tests, and OFCs were discontinued in some allergy clinics (7). In our clinic, the majority of patients had a scheduled OFC, mostly with cow's milk and hen's egg. It is known that the duration of allergy to cow's milk or hen's egg may be shortened by consuming baked forms after an OFC (8), so it can be predicted that the development of tolerance may be delayed due to the COVID-19 pandemic. Besides, we observed that patients with a scheduled OFC were more likely to perform home food trials and were more frequently adherent to outpatient appointments. We concluded that having a scheduled OFC made families believe that the culprit food could be tolerated, increased outpatient compliance, and encouraged families to conduct home food trials.

Performing OFCs at a clinic is recommended for IgE mediated FA, and careful observation is required by the physician due to the risk of anaphylaxis. However, in our cohort, one-third of the patients were exposed to a home food trial by caregivers. The risk factors for performing home food trials were younger age, having an essential FA, hen's egg allergy, and a plan for scheduled OFC. In a study from Australia, Allen et al. found that 32% of children with hen's egg allergy were not adherent to dietary advice (9). We speculate that hen's egg allergy might be perceived more tolerable by the caregivers. In infants, extensive skin prick test (SPT) panels can lead to over-diagnosis of FA (10). When there is high sensitization, elimination is required due to the risk of anaphylaxis until an OFC is performed, even though patients may not have an allergic reaction (10, 11). In addition, this may explain the low number of positive reactions in home food trials, and why caregivers were more courageous.

Having an OFC plan may cause caregivers to think that an allergic reaction risk is low. In the present study, we observed that some caregivers made dietary restrictions without their physicians' consent. During the COVID-19 pandemic, social restrictions increased the time spent at home. In addition, it has been reported in multiple studies that depression, anxiety, stress, and phobia has increased (12). Mothers with prominent protective behavior might eliminate foods in case of suspicion of an allergic reaction to avoid an adverse reaction.

Although, the cost of EAI is covered by the social security system, and along with the pandemic, EAIs can be obtained without a prescription in Turkey; non-adherent patients had significantly less usable EAIs available mostly because they had expired. We may think that some mothers were either unaware of this bypass or were not aware that the expiration date had passed. Besides, none of the caregivers experiencing anaphylaxis after the home food trial used an EAI. Consistent with this finding, as it has been shown before that only 30% of patients requiring EAIs tended to use them (13). It is noteworthy that one in three patients on an EAI prescription did not have an appropriate EAI during the COVID-19 pandemic, and most hesitated to use it in the event of anaphylaxis, which requires medical attention.

Our study has several limitations. First, the questionnaire was administered during a telephone-based telemedicine visit, and it may be associated with recall bias. Secondly, the levels of anxiety of mothers, which may be strongly associated with the patients' dietary and outpatient adherence, were not addressed. However, the strength of this study is in its being the first of its kind, the relatively high number of allocations, the reflection of real-life experiences, and being conducted in the largest referral center of the country. The finding of this study illustrates a high prevalence of home food trials and increased reaction risks during the COVID-19 pandemic. It will also contribute to the management of food allergies and the development of telephone-based telemedicine.

Finally, we think that a significant part of our patients' problems would not have been experienced if telephone-based telemedicine had been put into use earlier. In addition to reducing the burden of healthcare costs, it could even contribute to some degree of prevention of home food trials, proper management of potential reactions, and the application of unnecessary dietary eliminations.

This is the first study to evaluate the impact of the COVID-19 pandemic on FA management. We concluded that the COVID-19 pandemic significantly reduced adherence with scheduled appointments and OFC, and increased food trials at home and food eliminations without physician approval. With the understanding that the pandemic will last longer, telephone-based telemedicine could positively influence the prevention of future potential threats. In telemedicine applications, priority should be given to young children, and those who are allergic to essential foods, and an EAI supply should be provided without the need for a prescription.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Author Contributions

ESA collected data, contributed to data analysis, participated in the review of the files, and prepared the manuscript. STD, HU, AA and MO collected data and participated in the review of the files. UMS and OS contributed to data analysis and preparation of the manuscript. BES planned the study and supervised the whole manuscript.

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