ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALERJİ İMMÜNOLOJİ

doi: 10.21911/aai.602
Asthma Allergy Immunol 2022;20:71-76

RESEARCH ARTICLE

Received: 10.12.2020 • Accepted: 27.12.2021
Online Published: 21.01.2022

The Attitudes of Patients' Parents Receiving Allergen-Specific Immunotherapy Against Anaphylaxis

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ABSTRACT

Objective: Allergen immunotherapy (AIT) employs incremental amounts of an antigen to selected patients to promote clinical tolerance towards the offending allergen. The adverse reactions to AIT include local side effects such as induration in the field of application, itching and hyperemia, or systemic side effects such as shortness of breath, urticaria, hypotension, abdominal pain, vomiting and anaphylaxis. It is important that patients receiving AIT and their parents know about possible adverse reactions and can intervene when necessary. We aimed to assess the knowledge and attitudes towards anaphylaxis of the caregivers/parents of allergic children who receive subcutaneous immunotherapy (SCIT).

Materials and Methods: We gathered information using a structured questionnaire on the subject demographics and clinical information as regards the type of allergies and symptoms; and employed specific questions to capture information on the knowledge and attitudes of the patients' parents about the symptoms and management strategies of anaphylaxis and the use of an epinephrine autoinjector. All pediatric allergy patients' parents who were received SCIT between 2016 and 2019 at the Yeditepe University Hospital's pediatric allergy clinic were included in the study.

Results: We studied 101 participants who completed the questionnaire. The median age of the patients receiving SCIT was 12.0 (min-max, 5.0-17.0) years, and 52.5% of the study group were boys. Only less than half of the subjects had some idea about anaphylaxis. Seventy-eight percent had no idea that food might lead to anaphylaxis. Seventy percent of the participants did not expect SCIT to cause anaphylaxis; 6% had no idea about this anaphylaxis at all. Most of the parents did not know how to react to anaphylaxis and the majority had no clue about the epinephrine autoinjector.

Conclusion: We identified important knowledge gaps among the parents of children receiving SCIT about anaphylaxis or its management. We emphasize the necessity of educating the parents of children receiving SCIT on anaphylaxis as well as the application of epinephrine autoinjectors when indicated.

Keywords: Parent attitude, anaphylaxis, immunotherapy, SCIT, children

INTRODUCTION

Allergen immunotherapy (AAIT) employs incremental amounts of an antigen to selected patients to promote clinical tolerance towards the offending allergen. Allergen immunotherapy has been used with success in allergic rhinitis, atopic dermatitis, and asthma (1). Allergen immunotherapy can be generally applied in two distinct forms: i. the patient receives a subcutaneous injection (subcutaneous immunotherapy = SCIT), given at a clinical site, or ii. sublingual or oral ingestion of an AIT in an outpatient setting (1,2). The adverse reactions to AIT include local side effects such as induration in the field of application, itching and hyperemia, or systemic side effects such as shortness of breath, urticaria, hypotension, abdominal pain, and vomiting (1-4). Anaphylaxis occurs in an allergic subject upon inadvertent exposure to the offending allergen, to which the patient had been previously sensitized to. Unsurprisingly, immunotherapy can lead to anaphylaxis, since the allergen is directly administered to the patient (1,3-5). Given this compromise, SCIT is

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implemented only in tertiary care units well-prepared with the emergency care resources; patients are maintained under observation for a certain time following injection to watch for any possible reactions (1,6). There are anecdotal descriptions of anaphylaxis following SCIT occurring even after discharge from the facility, or with oral AIT, when subjects are outside a clinical environment (3,7-9). Previous research has established certain risk factors that predispose subjects to such incidents: uncontrolled asthma, history of systemic reactions after application of SCIT, insufficient observation time after the dose, late-onset reactions, beta-blocker use during SCIT, and the presence of grass-pollen allergy in term of the pollen season (3,7,8,10-12). General practice demands that allergic subjects and/or caretakers, if the patient is a minor, be educated for anaphylaxis and its management before prescription of SCIT. We are not familiar with a publication in the English language that reports on the competence of patients and/or parents to deal with anaphylaxis outside the hospital. In the present study, we sought information to capture the knowledge and attitudes of the patients and caregivers/parents who receive SCIT regarding the most dangerous side effect of immunotherapy, namely anaphylaxis.

MATERIALS and METHODS

A questionnaire assessing the knowledge of participants on anaphylaxis and the emergency treatment facilities was handed over to the patients receiving SCIT and/or their parents.. We included the parents of all pediatric allergy patients who received SCIT between 2016 and 2019 at the Yeditepe University Hospital pediatric allergy clinic. Patients who did not sign the consent form were excluded from the study. All the patients in this study continued to receive SCIT at our clinic. Before SCIT. all the patients and their parents have been educated about anaphylaxis and a consent form that included anaphylaxis and other risks of SCIT was obtained. In addition, an epinephrine autoinjector was prescribed to patients who have venom allergy and the method of use was explained for home use if necessary. This questionnaire was formerly used for evaluating primary school teachers' knowledge and perspectives towards anaphylaxis, and was revised for the present study (13). The questions included: i. What are the potential causes of anaphylaxis, ii. What alterations happen in the body during anaphylaxis, iii. How would you react to anaphylaxis, iv. What medications that can be used during anaphylaxis are you aware of? The questionnaire is presented in Supplementary Table. We received IRB approval from the Local Ethics Committee and informed consent from the research participants under the Helsinki principles for the enrollment of human subjects (decision no: 63/519).

Statistical Analysis

Demographical data is given as median, mean ± standard deviation, and the number and percentage of children as appropriate. Data was analyzed by using IBM SPSS 22.0 (Chicago, IL, USA).

RESULTS

We studied 101 participants who completed the questionnaire. Table I presents the demographic features of the patients who had been on immunotherapy. The mean age of patients receiving SCIT was 12.0 (5.0-17.0) years, and 52.5% of the study group were boys. The mean age at disease onset was 4.0 (1.0-15.0) years. As of the time

Table I: The demographic features of the patients receiving immunotherapy.

	n (%)
Age (years)	12.0 (5-17)
Sex	
Male	53 (52.5)
Female	48 (47.5)
Disease onset age (years)	4.0 (1.0-15.0)
Atopy to	
Mite	47 (46.5)
Pollen	3 (3.0)
Mite+pollen	45 (44.6)
Venom	6 (5.9)
Actual Disease	
Asthma	47 (46.5)
Allergic Rhinitis (AR)	20 (19.8)
Asthma+AR	26 (25.7)
Atopic Dermatitis (AD)	2 (2.0)
Anaphylaxis (venom)	6 (6.0)
Are you aware of the symptoms of a severe allergic reaction?	
Yes	37 (36.6)
No	64 (63.4)
Have you been informed about anaphylaxis before?	
Yes	44 (43.6)
How were you informed?	34 (77.3)
Doctor booklet	6(13.6)
Booklet	4 (9.1)
Internet-Media	

we completed the questionnaire, 36.7% of the patients had experienced a severe allergic reaction, and 43.6% of the parents had some knowledge about anaphylaxis. When we asked how that knowledge was gained, the source that trained the participants about anaphylaxis was a physician in 77.3% of the cases.

We present data on the parents' knowledge about the symptoms and causes of anaphylaxis in Table II. When asking about the potential causes of anaphylaxis, 75% of the participants thought that anaphylaxis can be caused by house dust mites; followed by pollens (43%), medications (5%), food (6%), and venom (3%). Interestingly, 38% of the participants believed that tobacco smoke could cause anaphylaxis. Seventy-eight percent stated they were unaware that foods might cause anaphylaxis. Thirty-three percent of them thought exercise or rubber could cause anaphylaxis. Although 70% of the participants did not think the SCIT treatment could cause anaphylaxis, and 6% did not understand about this situation. The remaining 24% thought SCIT may cause anaphylaxis.

The families' answers about the questions of anaphylaxis management are shown in Table III.

Table II: Parents' knowledge about symptoms and causes of anaphylaxis.

	n (%)
What type of substances can cause a severe allergic reaction?	
Pollen	43 (42.6)
Food	6 (5.9)
Mite	76 (75.2)
Medications	5 (4.9)
Mold	2 (1.9)
Cigarettes	38 (37.6)
Venom	3 (2.9)
Is exercise one of the causes of severe allergic reactions ?	
Yes	33 (32.7)
No	55 (54.5)
No idea	13 (12.8)
Can your immunotherapy cause severe allergic reactions?	
Yes	24 (23.8)
No	71 (70.3)
No idea	6 (5.9)
Is rubber one of the causes of severe allergic reactions ?	
Yes	32 (31.7)
No	63 (62.4)
No idea	6 (5.9)
What type of foods can cause a severe allergic reaction?	
Egg	14 (13.9)
Strawberry	7 (6.9)
Nuts	2 (2.0)
Chocolate	4 (4.0)
No idea	74 (73.2)

Table III: Parents' knowledge about management of anaphylaxis.

		n (%)
What is the initial action in the event of a severe allergic reaction?	I place him/her on a flat surface and perform the first intervention.	7 (7.0)
	I call the 112 emergency service	47 (46.5)
	I take him/her to a hospital immediately	47 (46.5
Should children with severe allergies carry something alerting others to their allergy ?	yes	49 (48.5)
What is the initial drug to be used in the event of a life-threatening allergic reaction?	no idea	71 (70.3)
	antihistamines	8 (7.9)
	Salbutamol inhalation	21 (20.8)
	epinephrine	1 (1.0)
Have you ever heard of epinephrine as a drug?	yes	31 (30.7)
Have you ever heard of an autoinjector?	yes	5 (5.0)
If Your answer is ''yes'', Do you know how to use an autoinjector?	yes	1 (20.0)
How should epinephrine be administered?	No idea	99 (98.0)
	Intramuscular	2 (2.0)
Is there an action plan to be used in the event of a severe allergic reaction?	yes	9 (8.9)
	no	92 (91.1)
What is the correct order of actions to take in the event of a life-threatening allergic reaction?	He/she could make the correct order	11 (10.9)
	He/she could not make an order at all	32 (31.7)
	He/she could make the order without the administration of epinephrine	58 (57.4)

Forty-eight and a half percent of families thought that the patient should carry a notification label on his/her clothing that shows the subject is allergic to an agent. Only 7% of them reported confidence in their ability to perform emergency treatment during anaphylaxis on their own. About half of the participants (46.5%) stated that they would call 112 (Turkish emergency), while the rest of the participants believed they should refer the subject to a hospital. Seventy percent of the participants stated they were not knowledgeable about the first-line medication during anaphylaxis, while 20% responded that they would use salbutamol inhalation and another 8% were in favor of antihistamine use as the first-line treatment. Only a single participant (1.0%) responded that he would immediately use epinephrine for anaphylaxis treatment. When we asked if the subjects had ever heard of Epinephrine, 31% stated they heard about this medication and 5% knew specifically about the epinephrine autoinjector. Only one subject (a parent of a venom allergic child) reported that he knew the application of epinephrine autoinjector (and he was not a healthcare worker). Among the subjects, 9% thought they had an action plan for severe allergic reactions. Only 11% of the caregivers could develop a correct algorithm for lifesaving management.

DISCUSSION

Our findings show that the parents of children who are on SCIT have major knowledge gaps about the recognition and treatment of anaphylaxis: they appear to be unaware of the causes of anaphylaxis, they did not even know that SCIT carries an anaphylaxis risk, and they were unaware of epinephrine as a medication or an epinephrine autoinjector to use in the emergency treatment of anaphylaxis. Even in the case of parents of children with a venom allergy, only a single subject was knowledgeable and confident about administering an epinephrine autoinjector. The common causes of anaphylaxis in childhood include foods, drugs, and insect venoms; however, most of the parents did not assume foods or drugs can cause anaphylaxis during childhood (1,2,10). Intriguingly, when testing the answers given by each parent, there was a perception by the parents that the most important factor that causes an allergy is the one that his/her child is allergic to. Importantly, 70% of the participants did not think SCIT itself is a cause of anaphylaxis while 6% had no comment on this association. Previous reports show that among patients who receive SCIT, anaphylaxis can be seen during or after the injection (1,11,12,14,15). Thus, the common practice states that patients should be given SCIT shots in well-equipped clinics that can handle anaphylaxis management; patients should also be kept at the hospital or clinics for some time following injections to watch for side effects (1,6,15). Not with standing these precautions, there is still a risk that anaphylaxis develops after the patient leaves the health care facility (7,8,15). Therefore, both the patients receiving SCIT and their caregivers must be trained about recognizing and managing anaphylaxis, including the application of epinephrine autoinjector in the event of anaphylaxis (1). Previous reports show that patients with allergic asthma whose disease is not well-controlled are at an increased risk of anaphylaxis, and when it happens, it is more severe (1,7,8,15). For that reason, an outline should be given to the patients who are planned to receive immunotherapy -particularly those with asthma- training them about anaphylaxis, including the potential causative factors, symptoms, and first-line treatment. In the present study, 37% of patients described severe allergic reactions; 44% reported that they had information about anaphylaxis, among which 77% had gained that information from their physicians. Among all participants, only 7% stated that they could perform first aid during anaphylaxis. Only one-third of the participants stated they heard about epinephrine, and only 5% knew about an autoinjector. Nine percent of the participants had an action plan for a severe allergic reaction. Only 11% of the parents could list what they should do during a life-threatening allergic reaction correctly. Taken together, our data indicate that although parents believe they have enough knowledge, they are devoid of the basic knowledge and intervention skills. Even if the physicians have trained the participants, we believe that this training has not been systematic. As part of general practice, each patient and/or parent is supposed to receive training about the facts of SCIT and all potential side effects, including anaphylaxis. Indeed, it is a legal obligation to obtain signed informed consent from the subjects/guardians before starting SCIT. Our data show that this process has not met with success as regards obtaining the desired awareness and skills. We emphasize that these flaws might lead to significant adverse events, including death; therefore, an allergist should consider the risks and spend every effort to ensure that the training is delivered and well-understood by the patients/caregivers. We also propose that the prescription of epinephrine autoinjectors should be considered for high-risk subjects. It is probably an important action that physicians keep monitoring their patients regarding awareness about anaphylaxis and periodically check if they are appropriately trained. We also favor wearing medical alert tags that contain information about the patient's allergies and instructions for an emergency action plan.

This is in line with recommendations of various Allergy Societies from Europe and USA, and a recently published Turkish national guideline (16-18).

A potential limitation of our present study is the relatively small sample size and the lack of a control group. In a previous study on teachers, we showed that the teachers lacked sufficient knowledge about anaphylaxis although there were allergic children in their classrooms (13).

In conclusion, SCIT has been considered a risk factor for anaphylaxis in recent years, but guidelines have not specified the need for routinely prescribing an epinephrine autoinjector. Those patients may be at a higher risk of anaphylaxis because of SCIT or pre-existing asthma. We draw attention to the importance of knowledge gaps towards anaphylaxis in a vulnerable group of patients and their families. These findings should lead to implementing strategies towards avoiding poor outcomes of SCIT-related anaphylaxis.

Acknowledgement

None.

Conflict of Interest

The authors declare that they have no conflict of interest.

Authorship Contributions

Concept: **Hülya Ercan Sarıçoban,** Design: **Hülya Ercan Sarıçoban,** Data collection or processing: **Mustafa Berber, Hülya Ercan Sarıçoban,** Analysis or Interpretation: **Ahmet Özen,** Literature search: **Mustafa Berber,** Writing: **Mustafa Berber, Meltem Uğraş,** Approval: **Mustafa Berber.**

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Supplementary Table: Questionnaire: The patient's knowledge about and attitudes towards anaphylaxis.

1. Age..... Sex: M/F
2. The age of the beginning of the illness?
3. What are you allergic to? ☐ Mites ☐ venom ☐ other
4. Type of Immunotheraphy ☐ subcutan ☐ sublingual
5. Are you aware of the symptoms of a serious allergic reaction? ☐ yes ☐ no
6. Do you think that immunotherapy may cause severe allergic reaction? ☐ yes ☐ no
7. Have you been informed about anaphylaxis before? ☐ yes ☐ no
8. If yes for question 7;
   How were you informed? ☐ booklet ☐ internet ☐ seminars ☐ media
9. What type of substances can cause a serious allergic reaction? ☐ Pollens ☐ Foods ☐ Mites
   ☐ Medications ☐ cigarette smoking ☐ close contact to animals ☐ mold
10. Is exercise one of the causes of serious allergic reactions ? ☐ yes ☐ no ☐ no idea
11. Is rubber one of the causes of serious allergic reactions ? ☐ yes ☐ no ☐ no idea
12. What type of foods can cause a serious allergic reaction?.....
13. What is the intial action to do in the event of a serious allergic reaction ?
    ☐ I place him/her on a flat surface and perform the first intervention.
    ☐ I call 112 emergency service
    ☐ I take him/her to a hospital immediately
14. Should children with serious allergies wear something allerting others to their allergy ? ☐ yes ☐ no
15. What is the initial drug to be used in the event of a life threatening allergic reaction?
    ☐
    ☐ no idea
16. Have you ever heard of epinephrine as a drug ? ☐ yes ☐ no
17. Have you ever heard of an autoinjector? ☐ yes ☐ no
18. If yes for 17;
    Do you know how to use an autoinjector? ☐ yes ☐ no
19. How should adrenaline be administered? ☐ I don't know ☐ Subcutaneous ☐ Intramuscular ☐ Intravenous
20. Is there an action plan to be used in the event of a a serious allergic reaction?
    ☐ yes ☐ no ☐ no idea
21. What is the order of actions to take in the event of a life threatening allergic reaction?
    ☐ placed him/her on a hard surface
    ☐ make sure that airway is patent
    ☐ elevate his/her legs
    ☐ apply epinephrine autoinjector
    ☐ call 112
    ☐ take a Picture of the child if available
22. Are the emergency medications to be used in the event of a serious allergic reaction available?
    ☐ yes ☐ no ☐ no idea