Original Research Article

The Egyptian Journal of Immunology
Volume 30 (4), 2023: 134–144.
www.Ejimmunology.org

Incidence of Food allergy among patients with allergic conjunctivitis

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Abstract

The prevalence of ocular allergy is increasing worldwide. Skin prick test is widely recognized as the most reliable method for diagnosing the incriminating allergen as regards type I hypersensitivity reactions. Food allergy results as immunological response to food protein which leads to occurrence of allergic conjunctivitis (AC), allergic rhinitis, asthma, atopic dermatitis, and eosinophilic esophagitis. There is a scarcity of research investigating the association between food allergy and AC. This retrospective cohort study aimed to determine the incidence of food allergy within AC patients and its linkage to disease intensity and to compare the response to sublingual immunotherapy after 4 months of therapy. The study included 240 individuals diagnosed with AC. Of these patients, only 214 (89.16%) cases exhibited positive skin prick test results and showed incidence of food allergy of 29.6 %. After 4 months of sublingual allergen immunotherapy, the total serum IgE level and the grades of severity decreased significantly (p <0.001 for each). On comparing patients with food allergy on sublingual immunotherapy and patients without food allergy and on sublingual immunotherapy, the change in total serum IgE concentration and the grade of severity did not differ among the two groups (p value was 0.63 and 1.00 respectively). In conclusion, food allergies can contribute to the development of AC. Sublingual allergen immunotherapy can be proposed as a promising therapeutic option for AC patients.

Keywords: Allergic conjunctivitis; Allergen Immunotherapy; Desensitization; IgE.

Date received: 04 June 2023; **accepted:** 23 September 2023

Introduction

Allergic conjunctivitis (AC) refers to a set of conditions explained by an eye allergic reaction to environmental irritants. It is estimated to impact 10-20% of people worldwide.[1] Many patients suffer from concomitant atopic conditions, including allergic rhinitis, food

allergy, atopic dermatitis, asthma, and eosinophilic esophagitis. However, 6% of atopic patients experience exclusive eye symptoms.[2-4]

AC can also be categorized into seasonal (SAC) and perennial (PAC) depending on whether the symptoms follow a seasonal pattern or are chronic throughout the year, in which seasonal AC is more common. The type of sensitized allergen is the main reason for the periodicity and chronicity of symptoms. Seasonal AC is sparked by temporary allergens including pollens from trees or grasses. Relapse is reported at the same time every year. Perineal AC is triggered or caused by indoor allergens including animal dander, mould, certain food types like vegetables, fruit, fish, nuts and legumes, cockroach, or rodents.[5,8,10]

A thorough history, clinical inspection of the eye and adnexa, nose and skin and inspection using by slit-lamp bio-microscopy are required to affirm the diagnosis and to excluded other ophthalmological diseases necessitating different treatments. Allergy testing is also recommended when AC is considered as the cause of symptoms.[11]

AC involves purely a type I allergic reaction, in which Th2 cells produce pro-inflammatory cytokines (Interleukin-3, 4, 5, and 13), trigger production of immunoglobulin E (IgE) by the B cells in sensitized patients.[6] This IgE binds to the mast cell membrane and subsequently cross-links with other respective allergens resulting in degranulation of mast cell and release of many mediators (histamine, leukotrienes, prostaglandins, and tryptase).[7]

The presence of allergen-specific immunoglobulin E (sIgE) response explains allergic sensitization, which can be detected through skin prick test (SPT) in vivo and by measuring serum sIgE in vitro (8). SPT remains an authorized approach for testing allergic sensitization in individuals with atopic conditions. It is a simpler, safer, more accurate, and less expensive method of diagnosis compared to sIgE quantification.[8] The incidence of adverse reactions in SPTs is very low, estimated to be under 0.04%. When such reactions do occur, they tend to be mild.[8-10]

Treatment of AC aims at stopping or minimizing the inflammatory immune response, relieving symptoms, and stopping complications. Specific allergen immunotherapy (SIT) is the sole treatment available that can modify disease course of allergic conditions like AC. It provides ongoing benefits even after completing the desensitization process.[9,11] SIT includes administering progressively higher doses of the allergen causing the allergic reaction. It results in clinical and immunologic tolerance by developing a normal immune response to the allergen instead of the extreme adverse reactions that occur upon exposure to this allergen. These allergic reactions can involve redness, burning, intense itching, and watery eyes.[11,13]

Food allergy prevalence is rapidly escalating worldwide. It results in immunological response to food protein which leads to occurrence of AC, allergic rhinitis, asthma, atopic dermatitis, and eosinophilic esophagitis.[12] Limited studies were performed to determine the correlation between food allergy and AC.[15-17] The current study was performed to assess the incidence of food allergy among patients with AC and its correlation with disease severity and to compare the response to 4 months sublingual immunotherapy.

Patients and Methods

This retrospective cohort study included 240 individuals with AC attending the ophthalmology clinic at Zagazig University and at Sohag Ophthalmology Hospital. Skin prick test and sublingual allergen immunotherapy were done at the Allergy and Clinical Immunology clinic at Ain Shams University hospitals and at Zagazig University Hospitals.

The study included patients with atopic AC aged between 6 years and 50 years, exhibited positive skin prick test and high serum IgE. These patients were on allergen immunotherapy for a duration of four months. The exclusion criteria included other causes of conjunctivitis, pregnancy, and patients with negative skin prick test.

Methods

The patient's hospital records were thoroughly examined to gather comprehensive medical

history and conduct examinations aimed at ruling out any comorbidities that could potentially impact the study results. Detailed allergic history was also obtained for each patient. Additionally, total serum IgE levels were measured using an enzyme-linked immunosorbent assay (ELISA) both before and 4 months after the initiation of immunotherapy. Confirmation of food allergy was achieved through multiple methods, including the maintenance of a food diary, skin prick tests (SPT) using standardized allergen extracts prepared at the Allergy and Clinical Immunology Unit laboratory, and diet elimination and oral food challenge tests. The severity and control of AC were assessed using the criteria outlined in the Spanish consensus document on AC (DECA). Finally, sublingual allergen immunotherapy was administered as part of the treatment plan. These comprehensive records formed the basis of the methodology for the study.

The criteria from the Spanish consensus document on AC (DECA) include a) Criteria for severity and b) Criteria for control.[14] For AC severity evaluation, patients were categorized as having an intermittent course if symptoms occurred for less than or equal to 4 days per week or less than or equal to 4 consecutive weeks. Persistent symptoms were defined as symptoms present for more than 4 days per week or more than 4 consecutive weeks. The grading of severity of ocular symptoms included mild, moderate, and severe. Where mild signs and symptoms were not bothersome and had no impact on vision, school/work tasks, or activities. The moderate shows bothersome signs and symptoms affecting vision, school/work tasks, and activities (1-3 points). While in the severe all items were present, causing bothersome signs and symptoms, impacting vision, school/work tasks, and activities. Controlled AC was determined based on the following criteria: controlled if there were no symptoms, no bothersome symptoms or symptoms occurring on ≤2 days per week, a visual analogue scale of ≤5 cm, and hyperemia (Efron Scale) of 0-1. While uncontrolled was considered with any intensity of symptoms present on ≥2 days per week, a visual analogue scale of ≥5 cm, or hyperemia (Efron Scale) of 2-4.[14]

Skin testing

This was done according to the method described by Bernstein et al., 2008.[15] We used standardized allergen extracts (Allergy products, Omega, Montréal, Canada) and stored at 4 °C. The test included the following antigens: Aeroallergens included mixed pollens; *Dermatophagoides pteronyssinus* (American house dust mite) and *Dermatophagoides farinae* mites; hay dust, mixed molds, grass, cotton, tobacco, cockroach, wool. Food allergens included milk, fish, egg, banana, strawberry, *Solanaceae*, wheat, mango, aspirin, and maize. For the positive and negative controls, histamine dihydrochloride (10 mg/ml) and saline were used, respectively. Patients were required to discontinue taking antihistamines 7 days prior to skin testing. The wheals diameter was determined, with a wheal of 3 mm or larger interpreted as a positive reaction.

Sublingual Allergen Immunotherapy

Glycerinated solutions of immunotherapy extracts were prepared using the weight/volume method with ratio 1:50,000, 1:5000, 1:500 and 1:50. Oral antihistamines were administered to patients 2 h prior to the immunotherapy to avoid any systemic reactions.[30,31]

The immunotherapy was self-administered taken on an empty stomach. Patients were asked to keep the sublingual under their tongue for 2 min before swallowing it. No food or drink was allowed for 5 minutes after swallowing. Patients were instructed not to consume any food or drinks for 5 min following swallowing the drops.

Blood sample collection

Venous blood samples (5 ml) were collected from study participants under aseptic conditions. Samples were allowed to clot then centrifuged for 15 minutes at 1000 xg. After centrifugation, the serum was isolated and kept at -20°C until used.

Serum level of total IgE

The concentration of serum total IgE was quantified using a commercially available sandwich enzyme-linked immunosorbent assay (ELISA) Kits (Cat No.10602, Chemux Bioscience, Inc., CA, USA,), according to the manufacturer's instructions. The absorbance of standards and samples were obtained at 450 nm utilizing a microtiter plate ELISA reader (Biotek, USA). The results were reported as IU/ml. This ELISA assay can detect IgE at minimum concentrations around 5.0 IU/ml. In allergy-free adults, the normal serum total IgE levels are under 100 IU/ml.

Ethical considerations

The protocol of the study was reviewed and approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University (approval #: ZU-IRB #: 10164 12 /2022). All participants or their first-degree relatives provided written informed consents after been informed of the study objectives and procedures.

Statistical Analysis

We used the Statistical Package for the Social Sciences (SPSS) program (V. 26.0, IBM Corp., USA, 2019). Non-parametric quantitative data were described as medians and percentiles. Besides, categorical data were described as numbers and percentages. For non-parametric data, the Wilcoxon Rank Sum test was employed to compare two independent groups. The Chi-squared test was used to examine the relation between two qualitative variables. To examine the significance between means of two groups, the student T test was used. The Mann-Whitney U test was used in nonparametric data to compare two independent groups. A $p \leq 0.05$ was considered statistically significant.

Results

The present study involved 240 AC patients with mean age of 20.91 ± 9.17 years and slight female predominance 55.4% (133 females). Perineal AC represented 74.2 % (178 patients) and seasonal AC represented 25.8% (62 patients). The most prevalent concomitant allergic condition was allergic rhinitis (5%) followed by bronchial asthma (3.8%). The proportion of patients who had atopic dermatitis and those with chronic urticaria was comparable to 1.3%. The mean of total serum IgE was 218.90 ± 117.18 IU/ml, as shown in Table 1.

Among the 240 patients, 214 had positive skin prick test results. Among these 214 patients, the incidence of food allergy was 29.6% (71 patients). Of the patients with food allergy, 67.6% (48 patients) tested positive on the diet elimination challenge test, as shown in Table 1. The most prevalent food allergen was milk (11.7%), followed by egg (6.3%), and fish and shellfish at a comparable rate of 5.8%. Wheat was the least common food allergen at 1.7%, as illustrated in Table 2. As regards animal dander allergens, rabbit epithelium allergy was the most common 22.1% followed by dog epithelium (15.0 %), then cat epithelium (14.6 %). Concerning other aeroallergens, the most prevalent allergen was mixed pollens (30.8%), followed by mites (26.3%), then a mix of grass (18.8 %). The least common was rubber latex (1.7%), as shown in Table 2.

Perennial AC was diagnosed in 62 patients, while seasonal AC was observed in 9 patients, as displayed in Table 3. The highest proportion of patients with food allergy was found among those with concomitant asthma (66.7%) and atopic dermatitis (66.7%), followed by allergic rhinitis (41.7%) and chronic urticaria (33.3%), as shown in Table 3.

Table 1. Description of the baseline data of the 240 studied patients.

		Min.	Max.	Mean±SD
Age		6.00	55.00	20.91±9.17
Baseline Serum IgE IU/ml		24.00	780.00	218.90±117.18
		N		%
Sex	Female	133		55.4%
	Male	107		44.6%
Allergic rhinitis	Positive	12		5.0%
	Negative	228		95.0%
Bronchial Asthma	Positive	9		3.8%
	Negative	231		96.3%
Atopic dermatitis	Positive	3		1.3%
	Negative	237		98.8%
Chronic urticaria	Positive	3		1.3%
	Negative	237		98.8%
Baseline grade	Mild	108		45.0%
	Moderate	104		43.3%
	Severe	28		11.7%
Type of allergic conjunctivitis	PAC	178		74.2%
	SAC	62		25.8%
Food allergy	Yes	71		29.6%
	No	169		70.4%
Open challenge test	Positive	48		67.6%
	Negative	23		32.4%

PAC: Perennial allergic conjunctivitis, SAC: Seasonal allergic conjunctivitis.

Table 2. Skin prick test results.

	Positive		Negative	
	N	%	N	%
Milk	28	11.7%	212	88.3%
Fish	14	5.8%	226	94.2%
Egg	15	6.3%	225	93.8%
Banana	12	5.0%	228	95.0%
Strawberry	9	3.8%	231	96.3%
Salonacae	14	5.8%	226	94.2%
Wheat	4	1.7%	236	98.3%
Mango	5	2.1%	235	97.9%
Aspirin	18	7.5%	222	92.5%
Maize	9	3.8%	231	96.3%
Cat ep	35	14.6%	205	85.4%
Dog ep	36	15.0%	204	85.0%
Rabbit ep	53	22.1%	187	77.9%
Pigeon f	33	13.8%	207	86.3%
Horse ep	21	8.8%	219	91.3%
Mites	63	26.3%	177	73.8%
Candida	20	8.3%	220	91.7%
M molds	37	15.4%	203	84.6%
M pollens	74	30.8%	166	69.2%
Alternaria	37	15.4%	203	84.6%

Table 2. Continued.

	Positive		Negative	
	N	%	N	%
Aspergillus	36	15.0%	204	85.0%
Rhizopus	25	10.4%	215	89.6%
Strow dust	35	14.6%	205	85.4%
Dust	33	13.8%	207	86.3%
Hay dust	35	14.6%	205	85.4%
House dust	37	15.4%	203	84.6%
Tobacco	14	5.8%	226	94.2%
Latex	4	1.7%	236	98.3%
Ragweed	21	8.8%	219	91.3%
Penicillium	5	2.1%	235	97.9%
Cockroaches	24	10.0%	216	90.0%
Mix grasses	45	18.8%	195	81.3%
Skin prick test	214	89.2%	26	10.8%

Table 3. Characteristics of patients with food allergy.

Type of allergic conjunctivitis		Food allergy				*p value
		Yes		No		
		N	%	N	%	
Type of allergic conjunctivitis	PAC	62	34.8%	116	65.2%	0.003
	SAC	9	14.5%	53	85.5%	
Presence of allergic co-morbid conditions						
Allergic rhinitis	Positive	5	41.7%	7	58.3%	NS
	Negative	66	28.9%	162	71.1%	
Bronchial Asthma	Positive	6	66.7%	3	33.3%	0.02
	Negative	65	28.1%	166	71.9%	
Atopic dermatitis	Positive	2	66.7%	1	33.3%	NS
	Negative	69	29.1%	168	70.9%	
Chronic urticaria	Positive	1	33.3%	2	66.7%	NS
	Negative	70	29.5%	167	70.5%	

*Chi square test (FE: Fisher Exact). $P > 0.05$ is not significant (NS).

All 214 patients with positive skin prick test results received sublingual allergen immunotherapy. There was a significant reduction in the mean value of total serum IgE after 12 months of immunotherapy ($p < 0.001$). The baseline mean value of total serum IgE was 220.93 ± 119.48 IU/ml, which decreased to 53.34 ± 35.41 IU/ml after 4 months. Moreover, there was a significant improvement in the grade of severity after 4 months ($p < 0.001$), as presented in Table 4 and Figure 2. At the beginning of the study, all patients were symptomatic: 24 patients (11%) had severe AC, 92 patients (43%) had moderate AC, and 98 patients had mild AC. After 4 months of immunotherapy, 128 patients were symptom-free, while none had severe AC. Seventy-nine patients had mild AC, and 7 patients had moderate AC, as shown in Table 4.

Table 4. Change in serum IgE levels and Grades of Severity after 4 months among patients with positive skin prick test.

Serum IgE		Mean±SD		*p value
Baseline Serum IgE IU/ml		220.93±119.48		<0.001
Serum IgE IU/ml after 12 months		53.34±35.41		
Grade of severity		N	%	p value**
Baseline Grade	No symptoms	0	0.0%	<0.001
	Mild	98	45.8%	
	Moderate	92	43.0%	
	Severe	24	11.2%	
Grade after 4 months	No symptoms	128	59.8%	
	Mild	79	36.9%	
	Moderate	7	3.3%	
	Severe	0	0.0%	

* t test of paired samples. **Marginal Homogeneity test. $P \leq 0.05$ is significant.

When comparing the change in total serum IgE levels and the grades of severity after 4 months in the 214 patients who received 4 months of sublingual allergen immunotherapy with the 16 patients who tested negative on the skin prick test and received only medical treatment, there was a statistically significant difference between the two groups (p<0.001 for both), as shown in Table 5.

Table 5. Comparison of the change in serum IgE levels and grade of Severity after 4 months between patients on immunotherapy and patients not on immunotherapy.

		Change in IgE level				*p value
		Median	IQR			
Immunotherapy	Yes (n=214)	-149.50	(-212.00) – (-87.00)			<0.001
	No (n=16)	-49.00	(-100.00) – (11.00 0)			
Regarding grade of severity		Immunotherapy				**p value
		Yes		No		
		N	%	N	%	
Grade after 4 months	No symptoms	128	59.8%	4	15.4%	<0.001
	Mild	79	36.9%	14	53.8%	
	Moderate	7	3.3%	6	23.1%	
	Severe	0	0.0%	2	7.7%	

$P \leq 0.05$ is significant. *Z: *Wilcoxon Rank sum test*, **X^2: *Chi square test*(FE: Fisher Exact).

Moreover, Table 6 compares patients undergoing sublingual immunotherapy with food allergy and patients without food allergy undergoing sublingual immunotherapy in terms of the change in total serum IgE levels and the grade of severity. There was no significant difference between the two groups (p=0.63 and p=1.00, respectively).

Table 6. Comparison of the change in serum IgE levels and symptoms of food allergy between patients with food allergy and patients without food allergy after 4 months of Immunotherapy

			Change in IgE level				*p value
			Median		IQR		
Food allergy	Yes		-129.00		(-189.00) – (-87.00)		NS
	No		-137.00		(-204.00) – (-74.00)		
			Food allergy				**p value
			Yes		No		
			N	%	N	%	
Grade after 4 months		No symptoms	37	52.1%	95	56.2%	NS
		Mild	31	43.7%	62	36.7%	
		Moderate	3	4.2%	10	5.9%	
		Severe	0	0.0%	2	1.2%	

P > 0.05 is not significant (NS). **Z:* Mann Whitney U test*, **X^2: Chi square test* (FE: Fisher Exact).

Discussion

The current study aimed to determine the incidence of food allergy among patients with AC and its correlation with the disease severity. Additionally, the study sought to compare such findings to those observed after sublingual immunotherapy for four months. Among the 240 AC patients included in the study, females represented 55.4% of the study cohorts. The influence of gender on allergy predisposition was examined in previous studies, some of which have suggested that males may have a higher incidence of allergy during childhood, with a reversal of this trend after puberty. This difference has been attributed to the effects of sex hormones on the activation of dendritic cells, naïve T cells, and B cells.[19] Additionally, female sex hormones were found to influence the immunological recall response, potentially leading to more severe allergic diseases.[19] These findings may explain the slight predominance of females observed in the current study.

Regarding the observed increase in serum total IgE in the current study, several previous studies have reported similar results. Studies by Arej, et al., 2018, Bao, et al., 2022 and Kırıkkaya, et al., 2022 all observed the rise in serum total IgE in AC patients relative to apparently healthy controls.[20-22]

In the current study, the skin prick test results indicated that among the aeroallergens tested, animal dander allergen sensitivities were commonly observed, specifically rabbit epithelium allergy (22.1%), followed by dog epithelium allergy (15.0%). Regarding other aeroallergens, the most prevalent allergen was a mix of pollens (30.8%), followed by mites (26.3%) and a mix of grass (18.8%), while the latex allergy was the least common (1.7%). The specific allergen sensitivities observed in the study population can be attributed to the high proportion of patients engaged in farming and animal raising activities. Our study results align with findings of a previous study conducted by Sayed, et al., 2019, which reported pollen (40%), house dust (30%), house dust mites (28%), and hay dust (24%) as the most prevalent aeroallergens among AC patients.[23] Additionally, a study conducted by Navarro et al., 2009, in Spain on patients with allergic rhino-conjunctivitis found that pollen was the most frequent allergen (51%), followed by dust mites (42%).[24] These results are consistent with the findings of the current study, further supporting the prevalence of specific aeroallergens among patients with AC.

It is worth noting that there is a limited number of studies assessing the role of food allergy among patients with ocular allergies worldwide. However, a study by Sayed and Ali, 2022, examined the proportion of wheat allergy in AC patients and found that 1% of patients had a positive wheat allergy.[25] In their study, only 10% of patients had ocular allergy alone, while 60% had concomitant AC and bronchial

asthma. However, their evaluation was limited to a single food allergen and a smaller number of subjects. Another study by Yamana et al., 2022, examined IgE levels in patients with pollen-induced AC and found that 32 cases reported a positive serum specific IgE for food, primarily plant-derived food-specific IgE.[26]

In terms of treatment options for AC, topical treatments such as mast cell stabilizers, antihistamines, and topical steroids are commonly used. Prolonged use of topical steroids can lead to side effects such as cataracts and glaucoma.[27] Allergen immunotherapy is considered a beneficial treatment option as it induces sustained benefits. This approach involves the introduction of allergens to dampen the Th2 immune response and promote the activity of regulatory T cells, which produce immunosuppressive cytokines.[28,30, 31]

In the current study, 214 patients with positive skin prick test results received sublingual allergen immunotherapy. Following four months of treatment, there was a significant decrease in mean total serum IgE levels (p<0.001) and a significant improvement in the disease severity grade (p<0.001). Initially, all patients were symptomatic, with 11% classified as severe, 43% as moderate, and 46% as mild. After four months of immunotherapy, 60% of patients were symptom-free, and none had severe AC. The majority of patients (79%) had mild AC, and a small proportion (3%) had moderate AC. When comparing patients with and without food allergy who received sublingual immunotherapy, no significant differences were observed in terms of the change in total serum IgE levels or disease severity grade (p=0.63 and p=1.00, respectively). Furthermore, when comparing the 214 patients who received four months of sublingual allergen immunotherapy with the 16 patients who had a negative response to the skin prick test and received only medical treatment, the change in total serum IgE levels and disease severity grade after four months differed significantly (p<0.001 for both). These findings are consistent with data of previous studies that showed the efficacy of allergen immunotherapy in reducing ocular symptoms and improving disease severity in AC patients.[29,30]

Furthermore, meta-analyses studies demonstrated the benefits of immunotherapy in pollen-induced AC, house dust mites, weeds and cat extract, with a significant reduction in total ocular symptom scores compared to placebo.[28,29] Additionally, sublingual immunotherapy showed significant improvements in the overall ocular symptom scores, as well as reductions in ocular redness, itching, and tearing.[28,29] However, the effectiveness of immunotherapy to mite-induced AC was found to be limited.

Moreover, a study by Sayed & Ali, 2022, evaluated the efficacy of allergen immunotherapy in AC patients over one year found that sublingual immunotherapy led to a significant reduction in ocular symptoms, as well as a decrease in the use of rescue medications.[25] Other studies also reported a sustained effect of immunotherapy even after discontinuation, with a lower recurrence rate of ocular symptoms compared to the control group.[24,29] Additionally, a systemic review and metanalysis, involved 25 randomized controlled trials on the role of immunotherapy in food allergy demonstrated significant effect as regards desensitization and some of these studies demonstrated sustained unresponsiveness after discontinuing immunotherapy.[32]

In summary, the current study explored the incidence of food allergy among patients with AC and its correlation with the disease severity. While the study found a slight predominance of females in the cohort, no significant correlation was observed between food allergy and disease severity. However, four months of sublingual immunotherapy resulted in a significant improvement in disease severity and a decrease in serum total IgE levels among AC patients. These findings support the proposal of allergen immunotherapy as a treatment option for AC. Finally, in conclusion, food allergy contributes significantly to the pathogenicity underlying AC. Sublingual allergen immunotherapy could be proposed as a promising treatment approach for AC patients.

Author Contributions

The study design was done by all authors. SHF, SAB and SWR did the investigations. SHF, SAB, OFMZ, AE and SWR shared in sample collection. SHF and SWR wrote the manuscript. All authors reviewed the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) denies receipt of any financial support for the research, authorship, and/or publication of this article.

Ethical approval

The protocol of the study was reviewed and approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University (approval #: ZU-IRB #: 10164 12 /2022).

Informed consent

All participants or their first-degree relatives provided written informed consents after been informed of the study objectives and procedures.

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