The role of immunotherapy in cases with both allergic rhinitis and migraine; a Randomized Controlled Trial

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Background: The current study aimed to determine the efficacy immunotherapy versus the medical treatment in cases of allergic rhinitis-associated migraine.

Patients and Methods: This randomized-controlled study was conducted in Banha Medical University Hospitals, Egypt in the period 2014-2015. Eligible patients having both allergic rhinitis and migraine were randomly allocated to the study group and the control group. For the study group, immunotherapy was used, and for the control group medical treatment was used. The primary outcome measure was the IgE level in both groups after the treatment period.

Results: A Forty-one patients were included in the analysis, 20 in the study group and 21 in the control group. The two groups were comparable regarding the baseline characteristics.

At the end of the study, there was no significant difference in the IgE level between groups (p-value 0.288) where it was 18.3 (6.0) & 16.5 (5.1) in the study group and the control group, respectively. Also, there was no significant difference in the number of migraine attacks between groups (p-value 0.756) where it was 1.9 (0.7) & 1.8 (0.7) in the study group and the control group, respectively. However, within-group analysis revealed a highly significant reduction in IgE level and number of migraine attacks in both groups (p-values < 0.0001).

Conclusions: In conclusion, immunotherapy is as effective as medical treatment for cases of migraine associated with allergic rhinitis.

Keywords: Allergic rhinitis; migraine; immunotherapy; anti-allergic.

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Background

The prevalences of allergic rhinitis (AR) and migraine are high in the populations. Therefore, of course, a considerable proportion of cases suffer from both conditions at the same time. [1-3]

Many research studies proposed different mediators like immunoglobulin E (IgE), histamine, vasoactive intestinal peptide (VIP), tumor necrosis factor-α (TNF-α), interleukin–1 (IL-1) and other mediators in both conditions as a pathophysiological basis for this association.[4-9]

Different lines of treatment were investigated in each condition separately using anti-allergic, antileukotriens, other medical treatment and immunotherapy. However, the literature about the management of allergic rhinitis associated with migraine is scarce. [3,10,11]

Therefore, in the current randomized controlled study, we aimed to compare the effectiveness of immunotherapy and medical treatment in the treatment of allergic rhinitis and migraine.

Patients and Methods

This prospective parallel randomized controlled trial was conducted in Banha University hospital, Egypt, during the period from December 2014 to December 2015. This study followed the principles of the Declaration of Helsinki and following the Medical Research Involving Human Subjects Act (WMO), and was approved by Institutional Review Board. The purpose of this study was clearly explained in the Arabic language to all parents of the subjects before their enrolment to the study, and an informed consent form was signed by and obtained from all of those enrolled.

We recruited male and female patients with age from 18-55 years old attending Banha University hospital Egypt having both allergic rhinitis and migraine.

Full history was taken; present history of allergic rhinitis (sneezing, rhinorrhea, nasal obstruction, sinusitis, lacrimation and eye congestion) migraine (± aura, headache attack lasts for 4 hours two-three days, unilateral, pulsating pain, nausea, vomiting, photophobia, phonophobia, hemiparaesthetic, hemiplegic, aphasic) according to the ICHD-3. [12-13]

Randomization and blinding:

Random numbers list was generated by the computer to be used for the allocation of the participants. Block randomization with a block size of two was used with 1:1 ratio of immunotherapy (study) group and traditional treatment (Control) group. The allocation sequence was concealed from the researchers enrolling and assessing participants. The study was assessor blinded.

Participants were randomly allocated to the study group and the control group. Patients of the study group were treated by immunotherapy. On the other hand, patients of the control group were treated by the traditional treatment.

Neither the researcher allocating the participants nor the assessing person knew the decoding of the groups in its relation to the allocation sequence. Data were collected by a junior pain resident who was blinded to the study.

Procedures:
For all patients, comprehensive information about the participants was collected, including age, gender, and medical history. Conventional examinations were performed.

Before randomization, the same procedures were applied to both groups. Blood samples were taken from all patients to measure the level of the IgE, and skin tests were performed for all patients to detect allergens (the grading scale is the agreement of the wheal in mm) less than 4 mm is negative , from 5 to 10 mm mildly sensitive, from 10 to 15 mm moderately sensitive, and over 15 mm very sensitive. Patients were asked to stop any anti-allergic for 72 hours. Patients were asked for any precipitating factors and seasonal variation. Patients were asked for the number of migraine attacks per month.

After randomization, patients in the study group received immunotherapy scheduled as twice a week. First bottle was 1/1000 concentration, second bottle 1/500, third bottle 1/250, and the forth bottle 1/125 concentration. The bottle contained not more than two types of allergen. Aspergillus was given alone. On the other hand, patients of the control group received medical treatment in the form of anti-allergic oral fexofenadine 180 once daily before seasons and during attacks ((Telfast, Sanofi-aventis), for severe cases corticosteroids oral prednisolone 20 mg tab, 100 mg per day for 3 days, reducing the dose by 20 mg every three days (Sloupred, Sanofi-Aventis) , anti-allergic nasal spray mometasone furoate monohydrate 50 mcg twice daily (Nasonix, Merck Sharp & Dohme Corp), and alkaline nasal wash 3-5 times per day.

All patients of both groups were followed up until 6 months. At the end of the study, all patients were asked for number of migraine attacks per last month as well as other symptoms of allergic rhinitis and migraine. Moreover, blood samples were taken from all patients and IgE levels were measured.

Outcome measures:
The primary outcome measure was the IgE level in both groups after the treatment period.

Secondary outcome measures were: the number of migraine attacks on the last month, improvement of symptoms and signs after the treatment period in both groups as well as the incidence of any adverse events in both groups.

Statistical analysis and sample size justification:
Taking type I or α error of 5%, type II or β error of 20%, sample size calculation suggested that a minimum of 16 subjects per group is required to detect two point differences of 5.1 and 7.3 ng/mL in IgE level with standard deviation of 2.2. . These numbers were based on a pilot study on 10 participants, five in each group. We decided to include 25 patients per group to allow for dropouts.

All statistical tests were made using a significance level of 95%. SPSS software (Statistical Package for the Social Sciences, version 20.0, SSPS Inc, Chicago, IL, USA) was used for the statistical analyses. Data were summarized by mean & standard deviation or median & interquartile range in the numerical data according to their distribution and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were made using the student t-test and the non-parametric Mann-Whitney test. For comparing categorical data, Chi-square test was performed. The Exact test was used instead when the expected frequency is less than five. P-values less than 0.05 were considered as statistically significant.

Results
All patients (64 subjects) who came to the center with the presentation of allergic rhinitis plus migraine were asked to participate in the study. Sixteen subjects refused to participate. Enrolled subjects (50) were randomized to the study (immunotherapy) group and the control (traditional treatment) group, 25 in each group. Eight patients were excluded after randomization, four in each group due to lost follow up. The dispositions of these subjects are shown **(Fig. 1)**.

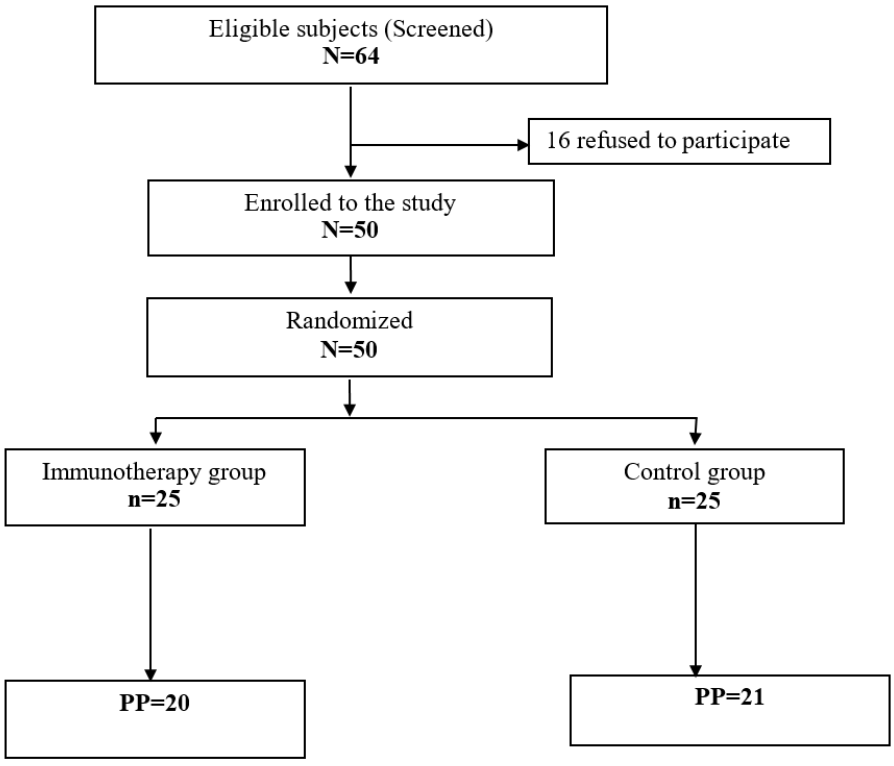

Fig 1 Consort diagram of statistical analysis of patients

Baseline characteristics:
Forty-one patients were included in the analysis, 20 in the study group and 21 in the control group. There was no significant difference (p-value > 0.05) between the two groups regarding the age, gender, seasonal variation, the presence of aura, occupation, family history or the presence of precipitating factors. The average age was 39.9 (SD=10.1) years in the study group and 33.0 (9.5) years in the control group (p-value 0.63). The majority of patients in both were females 60% & 71.4%, for the study group and the control group, respectively (p-value = 0.333), as shown in **Table 1**.

Table 1 Baseline characteristics

		Study group N = 20		Control group N = 21		p-value
Gender		**Number**	**%**	**Number**	**%**	
	Female	12	60%	15	71.4%	0.333
	Male	8	40%	6	28.6%	
Occupation						
	Employee	10	50%	8	38.1%	0.644
	Housewife	2	10%	4	19.0%	
	Student	5	25%	7	33.3%	
	Worker	3	15%	2	9.5%	
Family history						
	Allergy	17	85%	16	76.2%	0.51
	Migraine	18	90%	19	90.5%	0.696
Aura		12	60%	10	47.6%	0.533
Seasonal variation		19	95%	18	85.7%	0.51
Precipitating factors						
	INFECTION	7	35%	10	47.6%	0.344
	EXERCISE	11	55%	10	47.6%	0.756
	DUST	13	65%	13	61.9%	0.95
	HYPOGLASEMA	13	65%	13	61.9%	1
	SLEEP	14	70%	13	61.9%	0.746
		Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Age, year		39.9 (10.1)	40 (20)	33.0 (9.5)	35 (20)	0.63

Allergy skin test:
There was insignificant difference between the study group and the control group with regard the type of allergen detected (p = 0.967). Pollen and dust were the most prevalent allergen in both groups (more than 70%) followed by rice straw, wool and aspergillus, as shown in **Table 2**.

Table 2 Allergic skin test

	Study group N = 20		Control group N = 21		p-value
	Number	%	Number	%	
Pollen	15	75%	16	76.2%	0.967
Dust	16	80%	15	71.4%	
Rice straw	12	60%	12	57.1%	
Wool	12	60%	11	52.4%	
Asprigillus	4	20%	5	23.8%	

IgE test and number of migraine attacks before and after treatment:

At the start of the study and before treatment, there was no significant difference in the the level of IgE between groups (p-value 0.957), where it was 23.3 (4.6) & 23.2 (4.6) in the study group and the control group, respectively. Also, at the start of the study and before treatment, there was no significant difference in the number of migraine attacks between groups (p-value 0.221) where it was 4.7 (1.2) & 4.9 (1.3) in the study group and the control group, respectively.

At the end of the study and after treatment period, also, there was no significant difference in the level of IgE between groups (p-value 0.288), where it was 18.3 (6.0) & 16.5 (5.1) in the study group and the control group, respectively. Also, there was no significant difference in the number of migraine attacks between groups (p-value 756) where it was 1.9 (0.7) & 1.8 (0.7) in the study group and the control group, respectively.

However, within-group analysis revealed a highly significant reduction in IgE level and number of migraine attacks in both groups (p-values < 0.0001), as shown in **Table 3**.

Table 3A IgE and migraine attacks between groups analysis

	Study group N = 20		Control group N = 21		p-value
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
IgE before treatment ng/mL	23.3 (4.6)	22.7 (6.4)	23.2 (4.6)	22 (6.4)	0.957
IgE after treatment	18.3 (6.0)	18.6 (7.25)	16.5 (5.1)	17.9 (6.85)	0.288
Number of migraine attacks per month before treatment	4.7 (1.2)	4 (2)	4.9 (1.3)	5 (2)	0.221
Number of migraine attacks per month after treatment	1.9 (0.7)	2 (1)	1.8 (0.7)	2 (1.3)	0.756

Table 3B IgE and migraine attacks within group analysis

	Mean difference (SD)	95% Confidence Interval of the Difference	p-value
Immunotherapy group			
IgE, ng/mL	4.94 (2.66)	3.73-6.15	< 0.001
Migraine attacks, number per month	2.81 (0.91)	2.39-2.32	< 0.001
Medical treatment group			
IgE, ng/mL	6.72 (4.38)	4.73-8.71	< 0.001
Migraine attacks	3.07 (1.06)	2.59-3.56	< 0.001

Discussion

This randomized placebo-controlled trial was conducted to compare the immunotherapy to traditional medical treatment as alternative ways for the management of allergic rhinitis with migraine cases. The results if our study showed that there was no significant difference in the level of IgE between both groups. Also, at the end of the study there was no significant difference in the number of migraine attacks between groups. However, within-group analysis revealed a highly significant reduction in IgE level and number of migraine attacks in both groups.

In consistence with the results of our study, many researchers showed that immunotherapy decreases the frequency of the headache attacks in those patients with an atopic headache. [11,14-16] Mansfield et al. reported that 40% of migraineurs were atopic for specific food allergens as proved by skin prick tests. After avoidance of the identified foods, 69% of those cases had at least a 66% reduction in the frequency of the headache attacks compared with baseline. [17]

Immunotherapy (e.g., allergy injections) can produce tolerance to specific allergens by modifying the cytokine responses of T-helper cells, and the induction of IgG and IgA antibodies that can block IgE binding to mast cells. [18]

In our study, all cases received immunotherapy have more frequent migraine attacks at the first month, however, after the first month the number of attacks decreased significantly.

The results of our study showed that the medical treatment was as effective as the immunotherapy in management of allergic rhinitis with migraine. The role of anti-allergic therapy in migraine was proposed by Manfield in 1990. [19] However, no documented benefit from H1 or H2 blockers in preventing migraine headaches was established. The authors reported that anti-allergic might potentiate the pain relief when combined with a narcotic agent. [19] Thus, cinnarizine, an L-type calcium channel blocker with anti-allergic properties, has shown promise in the prophylaxis for migraine. [20] Furthermore, montelukast has been studied in those cases by Carvalho et al. [21] who reported that 24-week treatment decreased reported asthma attacks and significantly decreased the headache frequency in patients

with asthma and migraine. Another open-label study showed a promise in using montelukast in prevention. [22] However, further studies have failed to show a benefit. [23]

Conclusions

In conclusion, immunotherapy is as effective as medical treatment for cases of migraine associated with allergic rhinitis. Further multicentre randomized controlled study with large sample size is recommended to emphasize the results of this study.

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