Level of total and specific fungus IgE in allergic fungal sinusitis: how it affects management and follow-up

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Objective
The aim of this study was to evaluate the relationship between the level of total serum IgE and the prognosis of allergic fungal sinusitis, possibility of recurrence and level of aggressiveness.

Type of the study
This study was a prospective controlled one.

Patients and methods
Forty patients who were diagnosed as having allergic fungal sinusitis were randomly divided into two equal groups. One group (group A) received postoperative systemic steroids, whereas the other group (group B) received postoperative local steroids only. The patients were followed up for 6 months with endoscopy and IgE level evaluation.

Results
The total number of patients who had recurrence of the disease 6 months postoperatively was 17. Six of them were from group A (systemic steroids) and 11 were from group B (local steroids only).

Conclusion
Allergic fungal sinusitis should be treated with minimal surgical or endoscopic procedures, followed by local and more important systemic steroids for a prolonged period. Patients should be followed up at close intervals postoperatively using nasal endoscopy and more importantly serum IgE (total and if available fungus specific) as it is a good indicator to the future possibility of recurrence and thus the possibility of resurgery or further medical treatment.

Keywords:
algorithm, allergic, fungal, IgE, sinusitis

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Introduction

Allergic fungal sinusitis (AFS) is characterized by chronic hypertrophic rhinosinusitis with fungal hyphae growing within inspissated allergic mucin obstructing the sinus cavities. The fungal process involved in allergic fungal sinusitis is nontissue-invasive, representing an allergic, not infectious, disorder. Dematiaceous fungi are the most common offending organisms, with *Bipolaris spicifera* found most often [1].

The immunologic basis for AFS is thought to involve a fungal-specific immediate hypersensitivity (IgE) reaction as well as other antibody responses to the fungus. AFS serologies have been suggested to be partly analogous to allergic bronchopulmonary aspergillosis and include fungal-specific IgG and fungal-specific IgE [2].

The past two decades have been momentous in advancing our understanding of the role of antibody-mediated immunity (AMI) in host defence against fungi, and they have brought about a paradigm shift in our thinking on this question. Before the 1990s, AMI was considered to be irrelevant in host defence against fungi, as the experimental methods that were in use at the time were not able to consistently establish a role for AMI [3].

Only two decades ago, antibodies to fungi were thought to have little or no role in protection against fungal diseases. However, subsequent research has provided convincing evidence that certain antibodies can modify the course of fungal infection to the benefit or detriment of the host. Hybridoma technology was the breakthrough that enabled the characterization of antibodies to fungi, illuminating some of the requirements for antibody efficacy [4].

In this study, our aim was to evaluate the relationship between the level of total serum IgE and the prognosis of allergic fungal sinusitis, possibility of recurrence and level of aggressiveness, as well as the effect of steroid therapy on the level of IgE and its impact on recurrence rates and aggression.

Patients and methods

This prospective study (randomized control study) was performed in the Otorhinolaryngology Department, Kasr El-Aini Hospital, Cairo University (Cairo, Egypt), during the period from July 2013 to January 2015. This study has been approved by the ethical committee. It included 40 patients who were diagnosed at the outpatient clinic as having AFS.

These patients were diagnosed as having AFS according to the major and minor criteria. Two major with two minor criteria were sufficient for diagnosis.

Major criteria

- Presence of nasal polyps with allergic mucin
- IgE-mediated hypersensitivity
- Characteristic computerized tomographic scan features
- Eosinophilic nasal mucosa
- Noninvasive fungal colonies on smear, culture, or histopathology.

Minor criteria

- History of bronchial asthma
- Unilateral predominance of polyps
- Eosinophilia in peripheral smear
- Charcot–leyden crystals on histopathology
- Radiographic bone erosion.

All patients with allergic fungal sinusitis (denovo or recurrent) and patients of all age groups and geographic and demographic distributions were included. Only patients with immunocompromised state and patients who were found to have tissue invasion were excluded.

The 40 patients who were included in this study were randomly divided into two groups (20 patients in each group). Patients in the first group (group A) received systemic steroid therapy postoperatively, whereas patients in the other group (group B) did not receive systemic steroids and were only given local steroids as postoperative therapy.

All patients were subjected to clinical assessment, including a thorough physical examination, nasoendoscopy (Fig. 1), routine preoperative laboratory investigations, preoperative anaesthetist consultation and full history taking from patient. All patients were counselled about the plan of management and procedure, and a signed written consent form of approval was obtained from patients.

Level of IgE (total) was evaluated in serum. Patients were managed accordingly. All patients needed surgical intervention ranging from middle meatal antrostomy to ethmoidectomy and sphenoidotmy. All procedures were performed by the same surgeon. All procedures were performed endoscopically under general anaesthesia.

Patients stayed at the department for 2 days postoperatively. Non-narcotic pain killers were administered in the postoperative period. The nasal packs were removed and the patients were discharged on medical treatment according to the grouping.

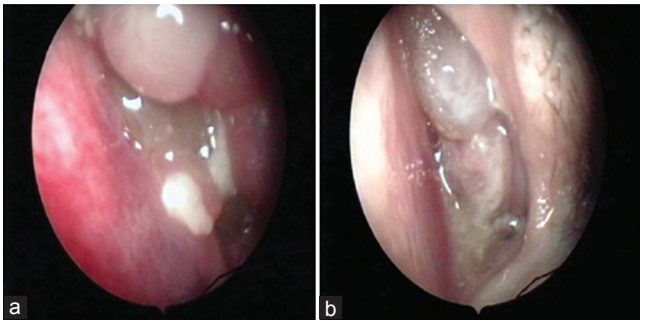
Patients in group A who received oral steroid therapy were administered oral prednisolone at a dose of 80 mg daily for 2 weeks, which was tapered over a further period of 2 weeks. All patients received oral ranitidine 150 mg once daily with the systemic steroid, and fluticasone propionate nasal spray at a dose of two puffs once daily. Patients in group B received fluticasone propionate nasal spray only at the same dose as group A.

At the time of recruitment, enquiry was made as regards the presence of nasal obstruction, nasal discharge, sneezing, hyposmia or anosmia, headache, facial pain, visual disturbances and change in facial features. At 3 months and again at 6 months following recruitment, enquiry was made again as regards these symptoms.

Patients were followed up postoperatively at 3 and 6 months. In the outpatient clinic, patients were examined by means of anterior rhinoscopy and nasal endoscopy, searching for polypi, allergic mucin or fungal masses. Moreover, new computed tomography (CT) scans were performed to evaluate the current state of the nose and sinuses radiologically.

Kupferberg's prognostic endoscopic mucosal staging system for diagnosing recurrence of AFS has been followed as the standard parameter in the follow-up care of postoperative AFS patients [5]. This staging system comprises of the following:

Figure 1



Endoscopic picture of allergic fungal sinusitis patients showing (b) polyps and (a) allergic mucin.

Stage 0: No evidence of disease.
Stage 1: Oedematous mucosa with allergic mucin.
Stage 2: Polypoidal mucosa with allergic mucin.
Stage 3: Polyps with allergic mucin and fungal debris.

This last stage signals the recurrence of disease and necessitates surgical reintervention.

The levels of serum IgE (total) were also evaluated at 3 and 6 months postoperatively. The prognosis of the patients was evaluated at 3 and 6 months to screen for recurrence and evaluate aggressiveness and its relation with the level of IgE and systemic steroid therapy.

All data were collected and statistical analysis was performed on an intention-to-treat basis. Comparison of the two groups was made in terms of levels of total serum IgE, presence of recurrence and aggression of recurrence.

Results

Forty patients of those diagnosed as having AFS accepted our plan of management and were recruited in our study. Those were randomly divided into two groups. Group A (20 patients) received local and systemic steroids, whereas group B (20 patients) received local steroid therapy only. Of the 40 patients, 25 were female and 15 were male. All patients were within the age group of 20–50 years, except for seven patients (five teenagers and two patients above 50 years of age).

The total number of patients who had recurrence of the disease after 6 months postoperatively was 17 patients. Six of them were from group A (systemic steroids) and 11 were from group B (local steroids only). As regards the severity and aggression of recurrence, 12 patients had mild recurrence (five from group A and seven from group B), four patients had moderate recurrence (one from group A and 3 from group B) and one patient was considered to have severe recurrence (group B).

The mere values of the serum IgE varied from one patient to another and from one laboratory to another. Therefore, the increase in the level of serum IgE from 3 to 6 months postoperatively was calculated, and the percentage increase from the first value obtained postoperatively (at 3 months) was obtained.

On obtaining the percentage increase in serum IgE, it was found that patients with less than 10% increase in serum IgE had no recurrence, whereas those who had more than 10% increase in serum IgE had some sort of recurrence of the disease.

Furthermore, patients with more than 10% increase in serum IgE could be divided according to the aggression of the recurrence as follows: (i) 10–30%, mild recurrence, (ii) 30–50%, moderate recurrence and (iii) more than 50%, severe recurrence of the disease.

The results obtained were statistically analysed as follows: descriptive output (group A, Tables 1 and 2; group B, Tables 3 and 4) and relations output (Tables 5–10).

From the previous statistical analysis we can find that there is a significant relation between the administration of systemic steroids and the percentage increase in the serum IgE. The percentage increase in total serum IgE was lower in the group receiving systemic steroids (sometimes there was a decrease in serum IgE).

Table 1 Recurrence aggressiveness

Valid	Frequency (*n* (%))
None	14 (70.0)
Mild	5 (25.0)
Moderate	1 (5.0)
Total	20 (100.0)

Table 2 Recurrence possibility

Valid	Frequency (*n* (%))
No recurrence	14 (70.0)
Recurrence	6 (30.0)
Total	20 (100.0)

Table 3 Recurrence aggressiveness

Valid	Frequency (*n* (%))
None	9 (45.0)
Mild	7 (35.0)
Moderate	3 (15.0)
Severe	1 (5.0)
Total	20 (100.0)

Table 4 Recurrence possibility

Valid	Frequency (*n* (%))
No recurrence	9 (45.0)
Recurrence	11 (55.0)
Total	20 (100.0)

Table 5 Relation between IgE and recurrence possibility

	Recurrence possibility	*N*	Mean	SD
IgE preoperative	No recurrence	23	1143.48	558.196
	Recurrence	17	1621.41	781.794
IgE 3 months	No recurrence	23	490.57	357.612
	Recurrence	17	971.00	503.605
IgE 6 months	No recurrence	23	466.65	387.575
	Recurrence	17	1240.76	717.399

Table 6 Relation between IgE and the steroid groups

	Groups	*N*	Mean	SD
IgE preoperative	Group A receiving systemic steroids	20	1468.30	789.640
	Group B receiving local steroids	20	1224.90	581.618
IgE 3 months	Group A receiving systemic steroids	20	590.35	512.450
	Group B receiving local steroids	20	799.15	441.419
IgE 6 months	Group A receiving systemic steroids	20	622.00	641.899
	Group B receiving local steroids	20	969.30	663.410

Table 7 Relation between increase in IgE in percent and steroid groups

	Group	*N*	Mean	SD
Increase in IgE in percent	Group A receiving systemic steroids	20	−8.15	40.056
	Group B receiving local steroids	20	15.35	18.715

Table 8 Relation between increase in IgE in percent and recurrence possibility

	Recurrence possibility	*N*	Mean	SD
Increase in IgE in percent	No recurrence	23	−12.74	33.632
	Recurrence	17	25.71	14.426

Table 9 Relation between IgE and recurrence aggressiveness

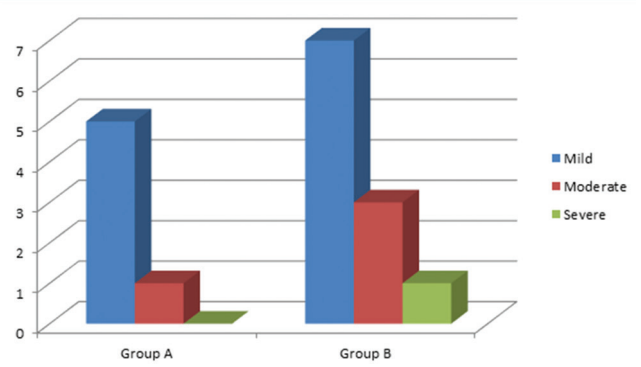
	ANOVA	Significance
IgE preoperative	Between groups	0.175
IgE 3 months	Between groups	0.004
IgE 6 months	Between groups	0.000

ANOVA, analysis of variance.

It was also found that there is a significant relation between administration of systemic steroids and the possibility of recurrence, whereas the relation with the degree of recurrence was not so significant.

Furthermore, it was found that there is a significant relation between the % increase in serum IgE and the possibility and severity of recurrence. The higher the % increase in serum IgE, between 3 and 6 months, the higher the possibility of recurrence and the more the aggression of the recurrence (Fig. 2).

Figure 2



Group recurrence.

Discussion

Recent evidence supports the theory that allergic fungal rhinosinusitis (AFRS) represents an immunologic, rather than a infectious, disease process. An improved understanding of this underlying disease process has led to an evolution in the treatment of AFRS [6].

Medical therapy has begun to shift from an emphasis on systemic antifungal therapy to various forms of topical treatment and immunomodulation. Likewise, surgical treatment of AFRS, still a crucial component of the overall treatment plan of the patient, has shifted from radical to a more conservative, yet complete, approach. In our series, all patients underwent endoscopically by the same surgeon. Although important, surgery alone does not lead to a long-term, disease-free state. A comprehensive management plan incorporating both medical and surgical care remains the most likely way to provide long-term disease control for AFRS [6] and this is the management plan we followed in our study.

Waxman *et al.* [7] were one of the first researchers to suggest that oral steroid therapy should be initiated in the immediate postoperative period after complete surgical extirpation of the disease. The role of surgery was to decrease the antigen load by removing the fungus entrapped in allergic mucin and improve drainage of the sinuses, whereas that of steroid was to decrease the inflammatory response and polyposis. They described a good response in seven patients who were administered this therapy. Soon similar reports followed. Our results also showed good response in patients of group A. Out of 20 patients, only six patients had recurrence on follow-up, compared with 11 in group B.

Kupferberg *et al.* [5] recommended oral prednisolone at a dose of 40 mg/day for 4 days, 30 mg/day for 4 days and 20 mg/day for 1 month. The dose was then adjusted to the lowest possible dose at which the patient could be maintained at stage 0. Using this protocol, the authors studied 26 adult patients with AFS, of whom 12 received oral steroid. Six (50%) of these patients were maintained at stages 0 and 1, whereas only one out of 14 others who had not received oral steroid was at stage 0. The beneficial effect of oral steroid was found

Table 10 Relation between increase in IgE in percent and recurrence aggressiveness

ANOVA	Significance
Between groups	0.000

ANOVA, analysis of variance.

to be statistically significant ($P = 0.04$). Dosages of less than 15 mg/day on alternate days led to recurrence, suggesting that prolonged maintenance steroid therapy was essential. In our study, patients who received oral steroid therapy were administered oral prednisolone at a dose of 80 mg daily for 2 weeks, which was tapered over a further period of 2 weeks. In all, 14 of those patients were maintained disease free after 6 months postoperatively ($P < 0.01$).

Kupferberg *et al.* [5] also suggested a prolonged maintenance dose of oral steroid to prevent recurrence. In a recent study, after the initial course of oral steroid, maintenance of sinus mucosa at stage 0 was possible with inhaled steroid alone. However, two patients in the oral steroid group with a follow-up of 9 months and 1 year developed recurrence (endoscopic stage 3) when they stopped all therapy for 2 months before presentation. This suggests the need for prolonged surveillance and maintenance with inhaled steroid even in those who have responded completely initially, which is similar to our recommendations when comparing our results with other studies covering a longer postoperative period of time.

Rupa *et al.* [8] suggest that oral steroid therapy with inhaled steroids administered for at least 3 months following successful sinus surgery is effective in controlling disease and preventing early recurrence in patients with AFS. Recurrence of disease could occur in those who do not continue prolonged maintenance therapy with oral and/or inhaled steroid. The speed of recurrence is, however, variable and needs further study.

A comprehensive management plan incorporating both medical and surgical arms remains the most likely way to provide long-term disease control of AFS [1]. This was the plan of management in our study too, surgical and medical treatment together with frequent nasal douches.

In our series, all 40 patients were essentially treated surgically. Only endoscopic approaches were used, ranging from middle meatal antrostomy to ethmoidectomies and sphenoidotomy, depending mainly on the extent of the disease. Moreover, the surgeon's preference was the deciding factor. All procedures were performed under general anaesthesia.

AFS tends to be recurrent and resistant to antimicrobial treatment with numerous surgical procedures being the rule. No treatment modality has proved to be consistently effective. Kupferberg and Bent [9] recommended that patients should be examined monthly for an indefinite period. Physical signs usually appear before clinical symptoms. In our study, patients were followed up every 3 months with serum IgE and nasal endoscopy. If any physical findings or elevated levels of total serum IgE were encountered, noncontrast CT scans were performed.

The main reasons for recurrence are inadequate initial debridement, irregular follow-up and not cleaning the postoperative cavities. Careful follow-up and early treatment of the recurrent disease may salvage some patients from revision surgery. In a similar study, the only significant factors that are responsible for the recurrence were found to be the complete opacification of the sphenoid and the frontal sinus preoperatively [10]. In our study, there were 17 recurrences out of 40 patients (i.e. a recurrence rate of 42.5%). All these recurrences were within the 6 months of the surgery. Both groups, topical steroids and systemic steroids, had recurrences.

In our study, however, we had several similar results to previous studies and what has been reported in the literature, as well as some disagreeing results. There is a statistically significant relation between the administration of systemic steroids for a prolonged period of time postoperatively and the level of total serum IgE ($P < 0.001$). The percentage increase in the level of total serum IgE was found to be much less in patients receiving systemic steroids; in fact, in several patients the level of serum IgE fell between 3 and 6 months, which means that systemic steroids postoperatively lowers the levels of serum IgE.

Another significant finding was that there is a significant relation between the % increase in serum IgE levels and the possibility of recurrence and its degree. When there was no or mild percentage increase in serum levels of IgE, there was no recurrence at all. The higher this, the greater the incidence of recurrence. Moreover, the higher the percentage increase, the more aggressive the recurrence. This means that the follow-up of the levels of serum IgE and the calculation of this percentage increase over the period of follow-up is a very useful and reliable method for predicting the possibility of recurrence and, if present, its aggression.

Conclusion

AFS should be treated with endoscopic procedures, followed by local and more important systemic

steroids for a prolonged period of time. This might be followed by long-term maintenance on local steroids alone. Patients should be followed up at close intervals (4 weeks) postoperatively using nasal endoscopy and more importantly serum IgE (total and if available fungus specific) as it is a good indicator of the future possibility of recurrence. If recurrence is highly suspected, CT scan is performed. Decision could be taken accordingly on whether resurgery or another course of systemic steroids is needed.

We also recommend further studies on immunotherapy in AFS, prolonged study periods for longer follow-up of patients in the future, and fungus-specific serum IgE evaluation to avoid fallacies that might occur from total IgE that might be elevated in some patients due to other atopic conditions.

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Conflicts of interest
There are no conflicts of interest.

References

1 Chakrabarti A, Denning DW, Ferguson B, Ponikau J, Buzina W, Kita H, *et al*. Fungal rhinosinusitis: a categorization and definitional schema addressing current controversies. Laryngoscope 2009; 119:1809–1818.

2 Wickern GM. Pediatric allergic fungai sinusitis: another 'great masquerader'. Pediatr Asthma Allergy Immunol 1993; 7:147–156.

3 Casadevall A. Antibody immunity and invasive fungal infections. Infect Immun 1995; 63:4211–4218.

4 Casadevall A Pirofski LA. A new synthesis for antibody-mediated immunity. Nat Immunol 2012; 13:21–28.

5 Kupferberg SB, Bent JP III, Kuhn FA. Prognosis for allergic fungal sinusitis. Otolaryngol Head Neck Surg 1997; 117:35–41.

6 Luong A, Marple BF. Allergic fungal rhinosinusitis. Curr Allergy Asthma Rep 2004; 4:465–470.

7 Waxman JE, Spector JG, Sale SR, Katzenstein AA. Allergic aspergillus sinusitis: concepts in diagnosis and treatment of a new clinical entity. Laryngoscope 1987; 97:261–266.

8 Rupa V, M Jacob, MS Mathews, MS Seshadri. A prospective, randomised, placebo-controlled trial of postoperative oral steroid in allergic fungal sinusitis. Eur Arch Otorhinolaryngol 2010; 267:233–238.

9 Kupferberg SB, Bent JP. Allergic fungal sinusitis in the pediatric population. Arch Otolaryngol Head Neck Surg 1996; 122:1381–1384.

10 Quraishi JA, Ramadan HH. Endoscopic treatment of allergic fungal sinusitis. Otolaryngol Head Neck Surg 1997; 117:29–34.