MANAGEMENT PROTOCOLS OF ALLERGIC FUNGAL SINUSITIS

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Abstract : Controversy surrounds the appropriate surgical approach and the appropriate medical therapy for Allergic Fungal Sinusitis. The present prospective study aims to assess the impact of these factors on the treatment outcome of Allergic Fungal Sinusitis. In the present study 34 cases with AFS were randomized into one of 3 methods of post operative therapy i.e. systemic itraconazole (group A, n=11), topical steroids (group B, n=12) and nasal alkaline douches only (group C, n=11). Outcome was assessed at 6 months post-operative by the Kupferberg grading system for assessment of nasal and sinus mucosa. Grade '3' mucosal disease was defined as recurrence.

Complete pre-operative opacification of sphenoid and frontal sinus was a predictor of poorer outcome. Postoperative systemic itraconazole therapy demonstrated a trend towards a better outcome but was not statistically significant. Larger trials are required to conclusively evaluate the merit of various post-operative treatment regimens for AFS.

Keywords: Aspergillosis, paranasal sinus, itraconazole, endoscopic sinus surgery.

INTRODUCTION

“Fungal sinusitis” is an umbrella term which encompasses a bewildering range of diseases caused by different fungi. The type of infection depends upon the immune status of the host. Allergic fungal sinusitis (AFS) is a recently described clinical entity that has gained attention as a cause of chronic sinusitis. The fungus colonizes the sinus of an atopic and immunocompetent patient and act as an allergen, eliciting an immune response. Typically this develops in a young immunocompetent patient. AFS is a persistent disease with frequent recurrences. The treatment of AFS has been surgery, either by external or by endoscopic routes. However, recurrence of disease following surgical excision is not infrequent, and adjunctive medical therapy is therefore often used in order to minimize recurrences. But there are lacunae in literature regarding the appropriate post surgical therapy, which varies from oral steroids, topical steroids, no medical therapy to systemic antifungals. Also, the extent of surgery has not been clearly defined.

The aims and objectives of the present study are:-

1. To define the extent of surgery on the basis of clinical and radiological findings.
2. To compare the various post surgical protocols for AFS.
3. To establish whether antifungals have a role in the postoperative management of AFS.

MATERIALS AND METHODS

The present study prospectively followed 34 cases of biopsy proven cases of Allergic Fungal Sinusitis (AFS), seen during June 2000 to June 2002 at the All India Institute of Medical Sciences, New Delhi. All the patients satisfied the following criteria for Allergic Fungal Sinusitis. (Bent & Kuhn-94)

1. Type I hypersensitivity as confirmed by either history, serology or examination.
2. Nasal polypi.

3. Characteristic CT scan signs i.e hyperattenuation, bony expansion with or without erosion.
4. Allergic mucin without fungal invasion of mucosa, on histopathological examination.
5. Positive fungal identification in the sinus contents removed during surgery, on special stains in tissue sections.

The diagnostic histopathological criteria for AFS used in our study were:

1. Sinonasal mass called “allergic mucin” revealed sheets of eosinophilis, degranulating eosinophilis and cellular debris within an amorphous stroma.
2. High power examination revealed Charcot-leyden (CL) crystals with a hexagonal cross-section and a bipyramidal longitudinal section. CL crystals are suggestive but not diagnostic of AFS.
3. Fungal hyphae which can be seen on methenamine silver and KOH preparations. These fungal hyphae are extra mucosal are not seen in non-allergic mucin. The hyphae of aspergillus are septate and acute angle branching.
4. Nasal polypi showing inflammatory infiltrate without fungal hyphae.

EXCLUSION CRITERIA

1. Patients already operated earlier or those who had received any treatment previously were excluded from the study. Patients were treated on either OPD basis or admitted in the ward and a detailed work up was done for each patient, which had the following parameters.
 - a. Detailed history of clinical symptoms.
 - b. Detailed otolaryngological and systemic examination (especially to rule out immunosuppression)
 - c. Radiological examination - An NCCT of paranasal sinuses was done and the features looked for were: soft tissue densities, hyperattenuation, bony expansion, bony erosion,

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intracranial extension and intra-orbital extension. The disease extent was quantitatively scored as per the "Lund and Kennedy 1995" radiological scoring system.¹⁷ Each sinus was scored individually (0,1,2) and a composite result for each nasal side computed by summing the individual scores of all sinuses (0-12). Bilateral scores (0-24) were computed by summing the scores of each side.

Blood tests: they were done in each patient:

1. Total eosinophil count = level $> 400/\text{mm}^3$ was considered as elevated.
2. Total IgE level (RAST) = value $> 35\text{IU/l}$ was abnormal.
3. Sp IgE level (against aspergillus).

The preoperative diagnosis was made on the triad of nasal polyposis, hyperattenuation witnessed on CT and positive serology. Each patient was taken up for surgery. The type of surgery and anaesthesia depended upon the extent of the disease. Surgery would consist of either endoscopic approach or an external approach. The external approaches used were the following:

1. External ethmoidectomy
2. Fronto ethmoidectomy
3. Horgan's procedure

During surgery all caseous material and polyps were removed from the sinuses and were sent as separate specimens. The normal mucosa was preserved as much as possible and the ventilation and drainage of the sinuses was established.

Histopathological examination: The specimens were reviewed by a single pathologist. The sinus luminal contents and the polyps were evaluated separately. The specimens were fixed in 10% buffered formalin and following things were looked for:-

1. Inflammatory polyp
2. Allergic mucin in the form of an eosinophilic background with degranulating eosinophils.
3. Special stains for fungal hyphae.

All the specimens were routinely processed and paraffin embedded. Five micron thick sections were cut and stained with hematoxylin and eosin (H&E) stains. PAS and methanamine silver stains were used for fungus. Fungal smear/ culture All the surgical specimens were subjected to:

- (i) KOH wet mount (to observe fungal hyphae).
- (ii) Fungal culture

The culture medium was Sabouraud's Dextrose Agar (SDA). It was incubated at 25°C and 37°C for 4 weeks. The medium was examined daily, and further identification of any growth undertaken by microscopic morphology on a lactophenol cotton blue (LCB) mount. Negative cultures were documented after 4 weeks of incubation.

Following surgery and pack removal patients were advised alkaline nasal douches. Subsequent adjunctive medical therapy was as per randomization into three different groups.

Group "A":- (n=11) Systemic itraconazole therapy for 2 months + nasal alkaline douches after surgery. The liver function tests were done in each patient before treatment. The dose varied according to age. The standard adult dose was 200mg BD for 2 months. Group "B":- (n=12) Topical steroids for 4 months + nasal alkaline douches. The compound used was budesonide 100 microgram BD in each nostril. Sprays were used after the nose was cleaned by nasal douches. Group "C":- (n=11) alkaline nasal douches for 6 months.

Patients were followed on weekly basis for first month and then on monthly basis for minimum of six months. Regular endoscopic cleaning of the operated cavities was done and all the crusts were removed. Nasal endoscopy was carried out under topical anaesthesia. The mucosal condition was staged as per the following system (Kupferberg et al 1997):-

Gd 0 - No evidence of disease.

Gd 1 - Edematous mucosa.

Gd 2 - Polypoidal mucosa.

Gd 3 - Frank polyps or caseous debris

A repeat CT scan was done for the grade 3 recurrence to confirm the disease status. But no alteration in the original protocol was made. The patients in which disease recurred as confirmed by radiology and endoscopy, were taken up for the revision surgery. Statistical analysis was undertaken to identify factors which may have an impact on the final outcome. The Kupferberg score (grade) as at 6 months post surgery was used as the final outcome measure. The variables that were assessed statistically are:

1. Age and Sex.
2. The surgical approach i.e. endoscopic versus external approach.
3. The nature of postoperative medical treatment.
4. The extent of preoperative involvement of paranasal sinuses.

Since each patient had bilateral disease, analysis was done for 68 sites (34 patients).

RESULTS AND ANALYSIS

The demographic characteristics of the study patients is listed in Table 1.

A significant proportion of patients had atopy i.e. drug hypersensitivity to aspirin (25%) or associated bronchial asthma (25%). Systemic eosinophilia was found in 20/34 (i.e. 59% patients). Total IgE was elevated in 19/21 (90%) and sp. IgE against aspergillus was elevated in 15/17 (88%) of the patients. On radiology all patients showed hyperattenuation and bony expansion of paranasal sinuses, 7 patients (20.5%) had an evidence of the intraorbital extension out of which 2 had bilateral intraorbital extension. Intracranial extension was found in 6 patients i.e. 17.6%. All the patients with intracranial extension had the intraorbital extension also. The radiological score varied from 16 to 24 (bilateral score) with an average of 20.5 [standard deviation 1.5]. All the patients had histopathology consistent with AFS. The mycology showed aspergillus flavus in 22 patients, aspergillus fumigatus in 5 patients, branching hyphae in 1 patient and in 6 cases the culture was negative.

Final outcome in each of the three post op randomized groups was as such

Group A : Itraconazole group (n=11), average radiological score was 22.5. The surgical technique employed was endoscopic (FESS) in 3 patients, B/L frontoethmoidectomy [FE] in 5 patients and combined FESS and FE in 3 patients. There were 2 recurrences as seen clinically and confirmed radiologically, both were reoperated with an endoscopic technique.

Group B : Topical steroids group (n=12), average radiological score was 21.6. Surgery employed was B/L FESS in 10 patients and B/L FE in 2 patients. There were 3 recurrences, which were reoperated by endoscopic approach.

Group C : Nasal douches only group (n=11), avg. radiological score was 18.4. FESS was employed in 9 patients, FESS + FE in 2 patients. There were 3 recurrences, which were reoperated by endoscopic approach. These 3 groups evenly matched regarding age (p=0.832) and sex (p=0.978) profile. Regarding the extent of the disease the avg. radiological score in group 'C' was significantly lower than other two groups (p=0.0123). Also in group 'A' (itraconazole group) more procedures were done by external approach as compared to the other two groups (p=0.02). In group 'A' relatively more procedures were done under GA as compared to other 2 groups (p=0.064).

On analysis it was noted that:

1. Age and Sex do not influence the outcome significantly.
2. Effect of type of surgery. (Table 2 , Figure 1)

We observed that both groups (endoscopic/external) had disease free state and both had recurrences. In 49 endoscopic procedure, 18 i.e. 36.7% were grade '0' and 7 i.e. 14.3% were grade 3 at the end. In 19 external procedures, 8 i.e. 42.1% were grade '0' and 2 (10.5%) were grade 3 at the end.

But the difference was not significant [p=0.315]. The external approach was used in patients with more extensive disease (avg. radiological score 11.37) as compared to the endoscopic group where the avg. radiological score for individual site was lower (i.e. 10.22).

3. Effect of the post operative therapy (Table 1, Figure 2)

We observed that 59% (13/22) sites in group A are in grade '0' and only 9% (2/22) recurred. Similarly in group B, 16% (4/24) procedures recurred and in group C 14% (3/22) procedures recurred. The difference in the three groups is not statistically significant, (p=0.22) but there is favourable trend towards group 'A' i.e. itraconazole group.

4. The effect of extent of preoperative involvement of each paranasal sinus as a predictor of a final outcome (Table 3)

Complete preoperative opacification of the sphenoid sinus was associated with higher risk of post operative recurrence (p=0.08) Similarly complete opacification of the frontal sinus was associated with recurrence. The effect of maxillary and ethmoid sinus involvement was not significant.

DISCUSSION

Allergic fungal sinusitis [AFS] is a relatively newly characterized disease entity, whose pathophysiology is similar to allergic bronchopulmonary aspergillosis [ABPA]. AFS is typically found in atopic, immunocompetent patients with chronic sinusitis and nasal polyps, who develop an allergic immuneresponse to extramucosal fungal hyphae, depicted histologically as allergic mucin ¹. The average age of AFS patients is the 3rd and the 4th decade of life. ² It is usually a bilateral disease. In our study of 34 patients, the mean age was 30.6 years (12 years -56 years) and all patients had a bilateral disease.

Table 1: Comparative Preoperative profile, surgical intervention, and final outcome in 3 groups

	Group A(n=11) Itraconazole 22 Sites	Group B (n=12) Topical steroids 24 Sites	Group C (n=11) Nasal douches 22 Sites	Total
Age	31.1 years	27.9 years	33 years	
Sex	6M/7F	7M/5F	6M/5F	34
Average radiological score	22.5	21.6	18.4	
Surgical procedure				
Endoscopic	9	20	20	49
External	13	4	2	19
Anaesthesia				
LA	4	14	14	32
GA	18	10	8	36
Outcome assessed at 6 months following surgery				
Kupferberg grade 0	13	7	6	26
Kupferberg grade 1	7	9	10	26
Kupferberg grade 2	0	4	3	7
Kupferberg grade 3	2	4	3	9

Table 2 Effect of the type of surgery on individual sites (n=68).

Surgical approach	Follow-up grade				Total	
	Average radiological score	0	1	2	3	
Endoscopic	11.37	18	17	7	7	49
External	10.22	8	9	0	2	19

Table 3 Impact of individual sinus radiological score on final outcome

	Follow-up grade				
	0	1	2	3	
Sphenoid Sinus					
Partial Opacification	10	8	4	0	22
Complete Opacification	16	18	3	9	46
Frontal sinus					
Partial Opacification	11	11	5	0	27
Complete Opacification	15	15	2	9	41

AFS represents a type I and type III hypersensitivity reaction to the fungal hyphae³. The various presenting features are nasal obstruction associated rhinorrhoea, telecanthus and proptosis. Almost all our patients had nasal obstruction, headache and rhinorrhoea. Telecanthus and proptosis was found in 20% and 10% of the patients respectively. Nasal polyps is the most consistent clinical finding. Various diagnostic criteria have been proposed from time to time^{4,5,16}. The criteria given by Bent and Kuhn are the most accepted one and thus were used in our study.

AFS is associated with other atopic disorders like asthma, drug hypersensitivity and skin reactions.⁶ In our study 25% patients had symptoms of bronchial asthma and another 25% had drug hypersensitivity especially to aspirin. 50-70 % of the AFS patients have eosinophilia. Various authors have reported various percentages. In our study 59% had eosinophilia. Similarly total IgE and sp.IgE have been found to be elevated in AFS patients⁴. In our series, total IgE was elevated in 90% and specific IgE against aspergillus was elevated in 88% of the patients.

Hyperattenuation is a universal feature in AFS². Such hyperdensities are due to calcium phosphate and calcium sulphate deposits in the necrotic areas of the disease. Long standing disease causes the bony expansion and bony erosion^{7,8}. In our series all patients had hyperattenuation and bony expansion. 20.5% patients had intraorbital extension and 17.6% had intracranial extension.

Histopathology is the cornerstone of diagnosis. Allergic mucin which is the characteristic finding of this disease reveals eosinophils, cellular debris within an amorphous stroma. Fungal hyphae can be seen which are extramucosal^{4,9}. In the present series, all polyps showed inflammatory changes. Allergic mucin was picked up in all the patients along with the fungal hyphae. Methenamine silver revealed typical septate hyphae, acutely branching, characteristic of aspergillus.

The mycology showed aspergillus flavus to be the most common organism followed by aspergillus fumigatus. 17.7% had negative fungal cultures. Improved understanding of the pathophysiology of AFS had led to the evolution of its treatment. The surgical treatment of AFS, a crucial component of the overall treatment plan of the patient, has shifted from radical to a more conservative but complete approach¹⁰.

Similarly medical treatments which are based on the presumed etiology have been proposed and these include systemic treatments, topical treatments and immunomodulation. A comprehensive management plan incorporating both medical and surgical arms remains the most likely way to provide long term disease control of AFS.

Traditional surgical therapy was accomplished frequently through the use of open antrostomies, with radical removal of mucosa, intranasal sphenoethmoidectomies and Lynch frontoethmoidectomies. Despite such aggressive therapy, recidivism remained high¹¹ and most patients required multiple surgical procedures¹¹. Also these external approaches led to the problem of external visible scar and these procedures almost always required general anaesthesia.

Surgery should be done to achieve 3 goals¹².

1. Complete extirpation of all allergic mucin and fungal debris.
2. To impart permanent drainage and ventilation of the affected sinuses.
3. Postoperative access to the previously diseased area.

Endoscopic sinus surgery has been extremely useful for this disease especially with the recent advent of tissue sparing instrumentation. The nasal polyposis and expansile behaviour of the disease expands the paranasal sinuses as well as the surgical route to the involved sinuses.

Fig 1 : Bar diagram showing the follow-up grades in two different surgical approaches.

Even in the setting of significant dissolution of fovea ethmoidalis, lamina papyracea, wide marsupialization of the diseased area can be done without causing trauma to underlying mucosa, which ensures that underlying periosteum, dura or periorbita remain free of penetrating injury¹⁰.

We treated all the 34 patients with surgery. Both endoscopic and external approaches were used, depending mainly on the extent of the disease. Also the surgeon's preference was the deciding factor. All the external approaches were done under general anaesthesia, while in endoscopic group both type of anaesthesia was used.

We were able to clear out the disease as much as possible by both the methods. We had an overall recurrence rate of 20.5% i.e. 7 patients recurred. Classifying each side separately, a total of 68 sides [34 pts] were operated and 9 recurred [2 patients had bilateral recurrence]. A recurrence was defined as grade 3 sinonasal mucosa which is supported by radiology in the form of NCCT PNS.

Various authors have advocated different recurrence rates varying from 25 to 80% with either approach but the determining factors or the prognostic criteria for the recurrences are not well demarcated. We made an attempt to determine the prognostic factor by doing a univariate analysis for the different variables like age, sex, type of surgical approach, postoperative medical therapy and preoperative extent of the disease. We used Lund and Kennedy 1995 system to stage the disease which gives the radiological score for each sinus involvement. In endoscopic group total 49 procedures were done out of which 7 recurred i.e. 14.2%. In external group total 19 procedures were done of which 2 recurred i.e. 10.5%. We concluded that the difference between these two groups is not statistically significant ($p=0.315$).

Similarly there were recurrences in both GA and LA groups and the difference in these groups were not significant ($p=0.45$). We found the preoperative complete opacification of sphenoids ($p=.08$) and frontal sinus ($p=.02$) was a predictor of an increased chance of disease recurrence whatever therapy is used. The role of antifungals had been controversial and one view is that these are too expensive and toxic for routine use, but recently some studies^{13, 14} however report good result with the use of systemic itraconazole therapy. The appropriate dose and duration of this therapy is not yet well established. We used postoperative systemic itraconazole therapy in the dosage of 200mg BD for 2

Fig 2: Bar diagram showing the effect of the postoperative therapy on the follow-up grades in three groups

months, in 11 patients. These patients had extensive disease and were operated by external methods mostly. There were 2 recurrences which were reoperated. We saw a favourable outcome in itraconazole groups as compared to other groups in the form of the follow up grades. This difference was however was not statistically significant to reach any conclusion.

Larger trials are needed to determine the appropriate dose and duration of this drug in the management of AFRS. This therapy in our set up currently costs around Rs.3000/- per month and thus cannot be given to each patient, in a developing country like ours.

One view, with which most of the authors would agree is that regular alkaline nasal douching of the post operative cavity is very important for maintaining a disease free state. It is proposed that by avoiding prolonged contact between fungus and mucosa, as is achieved by nasal douching, an allergic response is avoided. Long standing disease can cause the erosion of lamina papyracea. But the literature is silent about the approach of surgery if lamina papyracea is eroded. Though most of the old authors advocated external approach, now a days with powered instrumentation disease can be adequately cleared from the area. In our study 7 patients [9 sites] had intraorbital (extraperiosteal) extension. Out of 9 sites 7 were operated by external approach under GA, out of which 2 recurred. 2 sites were operated by endoscopic route out of which 1 recurred. But on the basis of this small data we are unable to comment about the surgical approach to be used in a case of AFS with intraorbital extension.

The clinical presentation in paediatric population is same as in adult population i.e. nasal polyposis, headache, rhinorrhoea and telecanthus. We used endoscopic techniques in younger patients. There were six patients less than 20 years of age out of which five were operated by FESS and one was operated by bilateral frontoethmoidectomy. All these patients were doing well i.e. disease free at the minimum six months of follow up. So we recommend FESS in younger age groups, as it has good results in the competent hands. It prevents the external scar, an issue of much concern in the younger age group.

RECURRENCES:

AFS tends to be recurrent and resistant to antimicrobial treatment with numerous surgical procedures being the rule⁹. No treatment

modality has proved to be consistently effective. Kupferberg [1996] recommended that patients should be examined monthly for an indefinite period¹⁵. Physical signs usually appear before clinical symptoms.

Patients can be followed up by either nasal endoscopy or by serum IgE levels. Nasal endoscopy is one of the most reliable technique to follow up^{3, 15}. It is an objective method and recurrence can be picked up early and appropriate action can be taken accordingly. Patients should undergo nasal endoscopy every 4 to 6 weeks to look for the return of disease.

The main reasons for recurrence are inadequate initial debridement, irregular follow up and not cleaning the postoperative cavities². Careful follow up and early treatment of the recurrent disease may salvage some patients from revision surgery. In our study there were 7 recurrences out of 34 patients i.e. recurrence rate of 20.5%. All these recurrences were within the six months of the surgery. All the three groups i.e. itraconazole, topical steroids, nasal douches had recurrences. The only significant factors which are responsible for the recurrence were found to be the complete opacification of sphenoid and frontal sinus preoperatively.

SUMMARY AND CONCLUSIONS

This prospective study of 34 patients of Allergic Fungal Sinusitis assessed the impact of various factors on the treatment outcome of AFS. Age and sex were not found to influence outcome significantly. The type of anaesthesia (LA vs GA), and the type of surgical approach (endoscopic vs external) also did not significantly impact on the outcome. ($p > .05$). It was however noted that postoperative medical with itraconazole had a favourable but not statistically significant trend. Complete opacification of frontal and sphenoid was a predictor of poor outcome, with both external and endoscopic approach. Good and nearly comparable results were obtained by both external and endoscopic techniques.

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