



## Prevalence of Allergic Fungal Rhinosinusitis in Patients with Sinonasal Polyposis: A Prospective Cross-Sectional Study.

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### Abstract

**Background:** Sinonasal polyposis is a common clinical condition with multiple underlying etiologies. Allergic fungal rhinosinusitis (AFRS) represents an important association and is characterized by an allergic response to fungal antigens with accumulation of allergic mucin containing fungal elements without tissue invasion. Differentiation of AFRS from conventional sinonasal polyposis is clinically important because the diagnosis may influence surgical planning and postoperative medical management. **Methods:** A prospective cross-sectional study was conducted among patients with sinonasal polyposis who were candidates for surgical treatment at KMCRI hospital, Hubli. Patients underwent detailed clinical evaluation, computed tomography of the nose and paranasal sinuses, absolute eosinophil count and estimation of total serum immunoglobulin E (IgE). All patients underwent surgery, and surgical specimens consisting of nasal polyps and/or allergic mucin were subjected to histopathological examination and fungal culture. Histological evaluation included hematoxylin and eosin, periodic acid-Schiff and Gomori methenamine silver staining. Fungal culture was performed using Sabouraud dextrose agar. **Results:** Among 42 patients with sinonasal polyposis, 4 patients (9.5%) fulfilled the clinical, radiological, histopathological and mycological criteria for AFRS. All four patients with AFRS had positive fungal cultures for *Aspergillus* species. Three of the four patients (75%) demonstrated unilateral predominance of sinonasal disease. A history of previous nasal surgery was present in three patients (75%) with AFRS compared with four patients among the 38 patients without AFRS; this difference was statistically significant ( $p < 0.000$ ). Total serum IgE levels were significantly higher in patients with AFRS-associated sinonasal polyposis than in patients without an underlying fungal etiology ( $p < 0.000$ ). **Conclusion:** AFRS was identified in 9.5% of patients with sinonasal polyposis in this study. Histopathological examination and fungal culture of surgical specimens, together with clinical, radiological and immunological evaluation, are important for identifying AFRS among patients presenting with sinonasal polyposis.

**Keywords:** Allergic Fungal Rhinosinusitis, Sinonasal Polyposis, Nasal Polyps, Fungal Sinusitis, *Aspergillus*, Serum IgE.



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### INTRODUCTION

Allergic fungal rhinosinusitis is a distinct non-invasive form of fungal rhinosinusitis characterized by an exaggerated host response to fungal antigens rather than tissue invasion. The entity was described by Robson and colleagues in 1989 and subsequently became increasingly recognized as a clinicopathological disorder occurring in immunocompetent patients, often in association with nasal polyposis and atopy.[1,2]

Bent and Kuhn proposed a widely used diagnostic framework in 1994 that incorporated type I hypersensitivity, nasal polyposis, characteristic computed tomography findings, positive fungal staining or culture without tissue invasion, and allergic mucin containing fungal elements.[3] Subsequent studies have emphasized that fungi may be difficult to demonstrate preoperatively and that histopathological assessment of surgical material is particularly important.[4,5]

The reported prevalence of AFRS varies considerably according to geographic region, patient selection and diagnostic criteria. Published series have generally reported AFRS in approximately 5–10% of patients with chronic rhinosinusitis undergoing surgery, while studies from different regions have produced differing estimates.[6–8] In the Indian subcontinent, *Aspergillus* species, particularly *Aspergillus flavus*, have been frequently reported among fungal isolates.[9–11]

The present study was undertaken to determine the prevalence of AFRS among patients with sinonasal polyposis and to assess the clinical, radiological, immunological, histopathological and mycological features that may help distinguish AFRS from non-AFRS polyposis.

### Objectives

1. To detect the co-existence of fungal elements in patients presenting with sinonasal polyposis and establish the diagnosis of AFRS.
2. To evaluate the prevalence of AFRS among patients with sinonasal polyposis.

### MATERIALS AND METHODS

This was a prospective, time-bound cross-sectional study conducted in patients attending the ENT outpatient departments of Karnataka medical college and research institute (KMCRI) Hubli, Karnataka, India. The study period was from October 2014 to August 2016.

#### Inclusion Criteria

1. Patients between 20 to 70 years of age and of either sex.
2. Patient presenting with Symptoms of nasal obstruction, headache, mass in the nose, hyposmia/anosmia.
3. On Anterior rhinoscopic examination - nasal cavity showing polypoidal glistening mass in either or both sides, which were soft and insensitive to probing.
4. Patients with ability to understand and sign the informed consent.

#### Exclusion Criteria

1. Pregnant, lactating mother
2. Patients <15 years of age
3. Presence of nasal or sinus tumor
4. Known case of immunodeficiency

#### Clinical and Laboratory Evaluation

A structured clinical history and otorhinolaryngological examination were performed. Diagnostic nasal endoscopy documented laterality of polyposis and the presence of discharge. All patients underwent non-contrast CT of the nose and paranasal sinuses. Absolute eosinophil count and total serum IgE were measured as indicators of the allergic/immunological profile.

#### Surgical and Mycological Evaluation

All patients underwent surgery at the study institution. Surgical specimens, including nasal polyps and allergic mucin or caseous material when present, were submitted separately for histopathological and mycological evaluation. Histological sections were stained with hematoxylin and eosin, periodic acid–Schiff and Gomori methenamine silver stains. For fungal evaluation, specimens were processed for direct 20% potassium hydroxide examination and cultured on Sabouraud's dextrose agar with antibiotics at 25°C and 37°C for up to four weeks. Isolates were identified using colony morphology and lactophenol cotton blue preparation.[12]

#### Diagnostic Approach

AFRS was diagnosed using the combined clinical, radiological, histopathological and mycological findings in the study, consistent with the diagnostic principles described by Bent and Kuhn.[3] Particular attention was given to allergic mucin with fungal hyphae, absence of invasive fungal disease, characteristic CT abnormalities, elevated allergic markers and fungal culture.

### RESULTS

No. of patients: 42

**Table 1: Age Distribution**

| Age       | Frequency   | Percent |
|-----------|-------------|---------|
| 20-29     | 6           | 14.3    |
| 30-39     | 14          | 33.3    |
| 40-49     | 12          | 28.6    |
| 50-59     | 6           | 14.3    |
| 60-69     | 4           | 9.5     |
| Total     | 42          | 100.0   |
| Mean & Sd | 40.6 ± 17.3 |         |

In this study, the youngest was 20 years and eldest was 68 years old patient. Maximum number of cases were found to be of the age group 30-39 years (33.3%) followed by 40-49 years (28.6%). The mean age was  $40.6 \pm 17.3$ .

**Table 2: Sex Distribution**

| Sex    | Frequency | Percent |
|--------|-----------|---------|
| Male   | 26        | 61.9    |
| Female | 16        | 38.1    |
| Total  | 42        | 100.0   |

In this study number of male patients were 26 (61.9%) and female patients were 16 (38.1%). Male to female ratio was 1.62:1.

**Table 3: Nasal Symptoms**

| Nasal Symptoms    | Frequency | Percent |
|-------------------|-----------|---------|
| Nasal obstruction | 42        | 100.0   |
| Nasal discharge   | 42        | 100.0   |
| Smell             | 36        | 85.7    |
| Headache          | 22        | 52.4    |
| Sneezing          | 34        | 81.0    |

In this study, all the 42 patients presented with the complaints of nasal obstruction and nasal discharge (100%), followed by smell abnormality (85.7%) and sneezing (81%).

**Table 4a: Other Variables**

| Other Variables             | Frequency | Percent |
|-----------------------------|-----------|---------|
| H/o allergy (aspirin)       | 1         | 2.4     |
| H/o asthma                  | 4         | 9.5     |
| H/o recurrent nasal surgery | 7         | 16.7    |

In this study, 4 (9.5%) out of 42 patients were asthmatics and the remaining 38 patients (90.5%) were non-asthmatic.

7 patients (16.7%) underwent repeated nasal surgery. Only one patient (2.4%) in this study had a history of aspirin sensitivity.

**Table 4b**

| Other variables   |      |          |                     |
|-------------------|------|----------|---------------------|
| Recurrent Surgery | HPE  |          | Fisher's Exact Test |
|                   | AFRS | Non-AFRS |                     |
| Present           | 3    | 4        | P<0.000             |
| Absent            | 1    | 34       |                     |

7 (16.7%) out of 42 patients had history of recurrent nasal surgery (polypectomy). 3 out of 4 patients of AFRS had history of previous nasal surgery. This difference was statistically highly significant ( $p < 0.000$ ) when compared to non-AFRS patients.

**Table 5: Signs**

| Signs                          | Frequency | Percent |
|--------------------------------|-----------|---------|
| Septal deviation               | 18        | 42.9    |
| Discharge                      | 28        | 66.7    |
| Inferior turbinate hypertrophy | 13        | 31      |
| Mucosa Normal                  | 23        | 54.8    |
| Mucosa pale                    | 19        | 45.2    |

In this study on patients with sinonasal polyposis, apart from nasal polyp which was present in all the 42 patients (100%), the next commonest sign was nasal discharge which was present in 28 patients (66.7%), normal mucosa (54.8%).

**Table 6: Diagnostic Nasal Endoscopy**

| Diagnostic Nasal Endoscopy |            | Frequency | Percent |
|----------------------------|------------|-----------|---------|
| Polyp on DNE               | Unilateral | 8         | 19.0    |
|                            | Bilateral  | 34        | 81.0    |
| Discharge                  | Present    | 12        | 28.6    |
|                            | Absent     | 30        | 71.4    |

In this study, on DNE, nasal polyps were present unilaterally in 8 cases (19%) and bilateral in 34 (81%). Nasal discharge was present in 12 cases (28.6%) and absent in 30 (71.4%).

**Table 7a: CT PNS**

| CT-PNS       | Frequency | Percent |
|--------------|-----------|---------|
| Unilateral   | 8         | 19      |
| Bilateral    | 34        | 81      |
| Hyperdensity | 8         | 19      |
| Bone erosion | 4         | 9.5     |

On CT scan of PNS, sinonasal disease was unilateral in 8 (19%) out of 42 patients and bilateral in 34 patients (81%). Hyperdensity was present in 8 cases (19%) and bone erosion in 4 cases (9.5%).

**Table 7b**

| CT-PNS     |      |          |                     |
|------------|------|----------|---------------------|
| Laterality | HPE  |          | Fisher's Exact Test |
|            | AFRS | Non-AFRS |                     |
| Bilateral  | 1    | 33       | P<0.01              |
| Unilateral | 3    | 5        |                     |
| Total      | 4    | 38       | 42                  |

In this study, on CT scan of PNS, 33 out of 38 non-AFRS patients had bilateral sinonasal disease, whereas among 4 AFRS patients, 3 patients had unilateral predominance of the disease and 1 patient had bilateral sinonasal involvement. This unilateral predominance of sinonasal disease among AFRS patients was statistically significant. (p<0.01).

**Table 7c**

| CT-PNS       |      |          |                     |
|--------------|------|----------|---------------------|
| Bone erosion | HPE  |          | Fisher's Exact Test |
|              | AFRS | Non-AFRS |                     |
| Present      | 4    | 0        | P<0.000             |
| Absent       | 0    | 38       |                     |

In this study, on CT of PNS, bone erosion was present in all the 4 cases of AFRS. None of the patients of non-AFRS had bony erosion on CT scan of PNS. This difference was found to be statistically significant (p<0,000).

**Table 8a**

|                | AEC    | Total S.IgE |
|----------------|--------|-------------|
| Mean           | 509.93 | 603.86      |
| Std. Deviation | 203.49 | 697.92      |
| Range          | 862.00 | 2937.10     |
| Minimum        | 106.00 | 62.90       |
| Maximum        | 968.00 | 3000.00     |

In this study, the mean AEC among all the 42 patients was 509.93 cells/cumm and the total serum IgE was 603.86 IU/ml.

**Table 8b**

| Parameters  | HPE     |                |         |                | Unpaired t test |         |
|-------------|---------|----------------|---------|----------------|-----------------|---------|
|             | AFS     |                | Non-AFS |                |                 |         |
|             | Mean    | Std. Deviation | Mean    | Std. Deviation | t value         | P value |
| AEC         | 909.00  | 42.03          | 467.92  | 163.43         | 5.32            | P<0.000 |
| Total S.IgE | 2413.05 | 406.73         | 413.42  | 367.73         | 10.26           | P<0.000 |

In this study, mean AEC among AFRS patients was 909 cells/cumm and mean total S.IgE was 2413.05 IU/ml. the mean AEC among non-AFRS patients was 467.92 cells/cumm and total S.IgE was 413.42 IU/ml. this difference in AEC and total S.IgE level was found be statistically highly significant ( $p < 0.000$ ).

**Table 9**

| HPE                                  | Frequency | Percent |
|--------------------------------------|-----------|---------|
| Inflammatory polyp                   | 37        | 88.1    |
| Allergic mucin with fungal hyphae    | 4         | 9.5     |
| Allergic mucin without fungal hyphae | 1         | 2.4     |

In this study, all the 42 patients with sinonasal polyposis were operated at our institution. Surgical specimen was sent to Histopathological and mycological examination.

On HPE, 37 patients (88.1%) showed inflammatory polyp and 4 patients (9.5%) showed typical characteristics of allergic mucin with fungal hyphae. However in 1 case (2.4%), all though classic allergic mucin was present on HPE, fungal hyphae could not be identified.

**Table 10**

| Fungal Culture | Frequency | Percent |
|----------------|-----------|---------|
| Positive       | 4         | 9.5     |
| Negative       | 38        | 90.5    |
| Total          | 42        | 100.0   |

In this study, on fungal culture, growth was identified on fungal culture in 4 out of 42 patients (9.5%) and no growth was seen in the remaining 38 patients (90.5%).

**Table 11: Principal findings of the study**

| Variable                   | Finding                             | Interpretation                                       |
|----------------------------|-------------------------------------|------------------------------------------------------|
| Study population           | 42 patients                         | Sinonasal polyposis requiring surgery                |
| AFRS prevalence            | 4/42 (9.5%)                         | AFRS identified in approximately one in ten patients |
| AFRS fungal culture        | 4/4 positive                        | All grew <i>Aspergillus</i> species                  |
| Unilateral disease in AFRS | 3/4 (75%)                           | Significant unilateral predominance; $p < 0.01$      |
| Bone erosion in AFRS       | 4/4 (100%)                          | Absent in non-AFRS; $p < 0.000$                      |
| Previous nasal surgery     | 3/4 AFRS vs 4/38 non-AFRS           | Significant association; $p < 0.000$                 |
| Mean AEC                   | 909 vs 467.92 cells/mm <sup>3</sup> | Higher in AFRS; $p < 0.000$                          |
| Mean total serum IgE       | 2413.05 vs 413.42 IU/mL             | Higher in AFRS; $p < 0.000$                          |

## DISCUSSION

AFRS represents an important subtype of chronic sinonasal disease in which fungal exposure is associated with an exaggerated allergic inflammatory response. The condition differs fundamentally from invasive fungal rhinosinusitis because fungal elements remain within allergic mucin and do not invade viable tissue.[3,13] Recognition is important because patients may have extensive disease, recurrent polyposis and characteristic radiological changes despite an apparently typical presentation of sinonasal polyposis.

In the present study, AFRS was identified in 4 of 42 patients, giving a prevalence of 9.5%. This finding is closely comparable with the 9.45% prevalence reported by Bakhshae and colleagues among patients with sinonasal polyposis in northeastern Iran.[14] It is also within the broad 5–10% range described in surgical chronic rhinosinusitis populations.[6,15,16] Telmesani reported a somewhat higher prevalence of 12.1% among patients with nasal polyps in the Middle East,[17] whereas Collins and colleagues reported an 8.6% prevalence of allergic fungal sinusitis in a South Australian surgical population with chronic rhinosinusitis.[18] The variation between studies may reflect differences in diagnostic criteria, geographic fungal exposure, referral patterns and methods of fungal detection.

The demographic profile of the present cohort showed a mean age of 40.6 years and male predominance. The thesis literature review notes that AFRS has often been described in younger patients and that sex distribution varies among published series, with some reporting approximately equal distribution and others a male predominance.[2,7] Because only four patients were classified as AFRS in the present study, the demographic characteristics of the AFRS subgroup should be interpreted cautiously.

The most frequent symptoms in the cohort were nasal obstruction and nasal discharge, followed by smell abnormality and sneezing. These findings are consistent with the nonspecific presentation of chronic sinonasal polyposis and reinforce the difficulty of diagnosing AFRS solely from symptoms. The thesis review notes that AFRS may resemble other forms of chronic rhinosinusitis and that a history of nasal polyposis, previous sinonasal surgery and atopy may provide useful clues.[6]

Previous nasal surgery showed a strong association with AFRS in this study: three of four AFRS patients had undergone previous nasal surgery compared with four of 38 non-AFRS patients ( $p < 0.000$ ). Recurrent disease and revision surgery are recognized features of AFRS, and historical series have documented multiple procedures in affected patients.[19] This finding may indicate that AFRS should be considered in patients with recurrent sinonasal polyposis, particularly when other characteristic features are present.

CT findings provided an important distinction between AFRS and non-AFRS polyposis. Three of four AFRS patients had unilateral disease, compared with five of 38 non-AFRS patients, and this difference was significant ( $p < 0.01$ ). All four AFRS patients had CT evidence of bone erosion, whereas no non-AFRS patient showed bone erosion. Characteristic CT abnormalities, including heterogeneous or hyperdense sinus contents and bony remodeling or erosion, have been described in AFRS.[20,21] The present observation supports the role of CT as an important component of the preoperative assessment, although CT findings alone are not sufficient to establish the diagnosis.

A marked difference in allergic markers was also observed. Mean AEC was 909 cells/mm<sup>3</sup> in AFRS compared with 467.92 cells/mm<sup>3</sup> in non-AFRS patients, and mean total serum IgE was 2413.05 IU/mL versus 413.42 IU/mL, respectively; both differences were highly significant ( $p < 0.000$ ). Elevated IgE and eosinophilic inflammation are consistent with the proposed hypersensitivity-mediated pathophysiology of AFRS.[2,22] The present findings therefore support the use of AEC and total serum IgE as supportive investigations rather than isolated diagnostic tests.

Histopathology was central to diagnosis. Allergic mucin with fungal hyphae was demonstrated in four patients, while one additional patient showed allergic mucin without demonstrable fungal hyphae. The latter finding illustrates an important limitation of relying on a single diagnostic modality: fungi may be difficult to demonstrate, and the literature has highlighted differences in the sensitivity of fungal detection methods.[4,5] Ponikau and colleagues also emphasized the importance of histopathological identification of allergic mucin in chronic rhinosinusitis.[5]

All four AFRS cases in the present study yielded *Aspergillus* species on culture. This observation is compatible with reports from India in which *Aspergillus*, particularly *A. flavus*, has been frequently identified.[9-11] In contrast, studies from other geographic regions have reported a substantial contribution from dematiaceous fungi such as *Bipolaris*, *Curvularia* and *Alternaria*. [7,23,24] Geographic and environmental factors may therefore influence the fungal profile of AFRS.

The study findings support a multimodal approach to AFRS diagnosis. Clinical history and endoscopy identify patients with sinonasal polyposis; CT can demonstrate characteristic distribution and bony changes; AEC and serum IgE provide evidence of an allergic phenotype; and histopathology and fungal culture provide direct evidence from surgical material. This combined approach is consistent with the diagnostic principles outlined by Bent and Kuhn.[3]

### **Clinical Implications**

- AFRS should be considered in patients with sinonasal polyposis, particularly when disease is recurrent, unilateral or associated with marked eosinophilia/elevated serum IgE.
- CT findings such as heterogeneous hyperdensity, unilateral predominance and bony remodeling or erosion may raise suspicion for AFRS.
- Surgical material should be systematically submitted for histopathological examination and fungal culture when AFRS is suspected.
- A negative fungal study on one modality does not necessarily exclude AFRS; clinicoradiological and histopathological findings should be interpreted together.
- Recognition of AFRS is relevant to postoperative care because recurrence is common and adjunctive anti-inflammatory strategies may be required.[25,26].

### **CONCLUSION**

The prevalence of allergic fungal rhinosinusitis among patients with sinonasal polyposis in the present study was 9.5%. All patients diagnosed with AFRS had positive fungal cultures for *Aspergillus* species. Unilateral predominance of disease was observed in 75% of AFRS patients. A history of previous nasal surgery and elevated total serum IgE were significantly associated with AFRS in this study.

AFRS should therefore be considered in patients presenting with sinonasal polyposis, particularly in those with recurrent disease, unilateral or asymmetric sinonasal involvement and elevated serum IgE. A combination of clinical assessment, CT imaging, histopathological examination of surgical material and fungal culture is useful for establishing the diagnosis.

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