

A Study to Determine Role of Fungus in Cases of Chronic Rhinosinusitis with or without Nasal Polyps in Indian Population

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ABSTRACT

Introduction

Chronic rhinosinusitis (CRS) with or without nasal polyps is a significant public health burden worldwide and owing to its multifactorial etiology, it is often encountered across various medical and surgical specialities. Role of fungus in etiology of CRS has been debated for decades altogether and there is plethora of researches on cellular, molecular and biochemical aspects of fungal presence in nasal cavity and paranasal sinuses and how it affects. Although, there is denial at large on fungal effects on development of CRS, but the question, that whether concomitant and demonstrable presence of fungus in cases of CRS aggravates classic symptoms and signs, largely remains unanswered.

Materials and Methods

This cohort study includes 121 subjects, which were divided in CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP) on basis of rigid nasal endoscopic findings. Severity of disease symptoms, among these groups was correlated with Lund-Mackay (LM) symptom scores and extent of disease with LM endoscopic staging scores and LM radiology scores. Histopathology samples for demonstrating presence of fungus were taken and cohort was further subdivided into Fungi positive CRS and Fungi negative CRS, and, LM scores were compared.

Results

In fungi positive CRS group, mean LM symptoms score was 7.09 with standard deviation (SD) ± 1.07 ; mean LM endoscopy score was 6.64 with SD ± 1.94 and LM radiological score was 14.58 with SD ± 2.96 . In Fungi negative group, mean LM symptoms score was 3.58 with SD ± 1.30 ; mean LM endoscopy score was 4.47 with SD ± 1.57 and LM radiological score was 12.20 with SD ± 2.98 .

Conclusion

Results of this study were statistically significant that fungi positive group was found to have more severe symptoms and larger extent of disease as compared to fungi negative group which indicate that fungal presence may have a role in escalation of symptoms, signs and radiological scores and it may aggravate pre-existing CRS.

Keywords

Rhinosinusitis, Chronic; Nasal Polyps; Fungi; Endoscopy; Radiology; Severity of Illness Index

Chronic rhinosinusitis (CRS) with or without nasal polyps encompasses a spectrum of disease encountered not only by Otorhinolaryngologists but owing to its multifactorial etiology, by multiple specialities like Physicians, Pulmonologists, Intensivists and even Neurosurgeons.¹ Although there are plethora of studies focussing on cellular and molecular aspects of fungus in development of Chronic rhinosinusitis, there seems to be a dearth of Indian researches concentrating on variations in symptomatology and signs in cases diagnosed as CRS with concomitant fungal presence, and,

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CRS remains a significant public health burden across the world and cause of suffering of 5-15% population in United States of America and European region.^{1,2} Known for decades, there have been many revisions in diagnostic criteria of CRS, most recent and accepted being European Position paper on Rhinosinusitis and nasal polyps 2020. It defines CRS as inflammation of the nose and the paranasal sinuses with two or more symptoms viz. nasal blockage or rhinorrhoea, with or without facial pain or hyposmia/ anosmia supported with either characteristic nasal endoscopic findings or Computed tomography Scan (CT Scan) changes.¹

Multidimensional etiology has been postulated and among these, role of allergy, viruses, bacteria, and fungi have been hypothesized and continue to be debated. Demonstrable and reproducible presence of fungi in nasal cavity and paranasal sinuses in cases of CRS have been well documented across literature but its direct causal relationship with CRS is still being researched and argued upon but still have not been outrightly refuted.^{1,3} Having established that, it would be pertinent to throw some light on clinical variations found in cases of CRS with concomitant fungal presence in order to usher further researches to find its role in etiology of this disease, especially in Indian scenario where such studies have been next to nil. This study aims to fill in this knowledge gap and try and find some objective evidence of clinical variations in symptoms and signs in cases of CRS with demonstrable concomitant fungal presence as compared to patients of CRS without it, in a cohort of Indian population.

Materials and methods

This prospective cohort study was conducted at a tertiary care hospital at Maharashtra (India) from June 2017 to December 2019 after taking due clearance from Institutional Ethics Committee. The sample size was calculated to test the null hypothesis that there is no difference in severity of symptoms and extent of disease among a group of CRS cases with evidence of fungal presence and group of CRS cases without fungal elements with 5% 2- sided level of significance and 80% power

of study. Based on the data from previous studies, a sample size of 55 adult patients in each group (i.e., total 110 numbers of adult patients) was calculated.

All patients, who presented or referred to Department of Otorhinolaryngology, Head and Neck Surgery of a tertiary care centre at Pune, Maharashtra (India), investigated and found to have been suffering from CRS, were included. Patients who were having concomitant immunodeficiency syndromes or taking immune suppression therapy, those with acute or chronic invasive or granulomatous fungal rhinosinusitis, allergic fungal rhinosinusitis, Antrochoanal polyp or patients with history of previous surgery for chronic rhinosinusitis were excluded. Written informed consent was taken and patients were made free to exit from study whenever they wish so, without interruption in their management protocols.

Aim of this study was to compare severity of symptoms and clinical signs and extent of disease in cases of CRS among a cohort of Indian population who have been found to harbour fungal elements with those who were not. Our objectives were -

- (a) Correlation of severity of disease symptoms with Lund-Mackay (LM) symptom scores, which assess five categories of CRS symptoms, each on a 10 point psychometric visual analogue scale (VAS), where 0 = No symptoms and 10 = very severe symptoms; and total score range being 0 – 50 (details are as per Supplement 1 of this article).
- (b) Correlation of extent of disease through –
 - (i) Lund and Mackay (LM) endoscopic staging scores, which, assess five rigid nasal endoscopic findings on 0-2 point scale, range of scores being 0 – 10 (details are as per Supplement 2 of this article).
 - (ii) Lund and Mackay (LM) radiological staging scores, which is based on Non- Contrast Computed Tomography (NCCT) Nose and paranasal sinuses (PNS), indirectly assess extent of disease bilaterally in maxillary, anterior ethmoidal, posterior ethmoidal, sphenoid and frontal sinuses on a 0 – 2 point scale, and in ostiomeatal complex on 0 or 2 points scale.

Range of scores being 0 – 24 (details are as per Supplement 3 of this article).

Total of 121 patients were recruited in study and subjected to complete Otorhinolaryngology examination. During clinical history taking, LM symptoms scores was administered to all subjects in form of a psychometric 10 point VAS. LM endoscopic staging scores were administered including during unsedated office based nasal endoscopy using a 0° 4 mm rigid nasal endoscope. All patients were then subjected to NCCT scan nose and PNS and LM radiology scores were derived; all findings were recorded on a Windows™ based computer for further data processing. Subjects were diagnosed as Chronic Rhinosinusitis without polyps (CRSsNP) in setting of typical history of nasal obstruction and bilateral rhinorrhoea with or without facial pain and hyposmia/anosmia of >12 weeks duration *with either* endoscopic signs of bilateral middle meatal mucopurulent discharge and mucosal obstruction/oedema *or* NCCT changes within osteomeatal complex and/or sinuses. Diagnosis of Chronic Rhinosinusitis with polyps (CRSwNP) was made when all the criterion of

CRSsNP were met in addition to endoscopic signs of nasal polyps or suggestive NCCT changes.

An endoscopic guided middle meatal swab was taken from all patients diagnosed with CRSsNP during their initial examination and sent for fungal staining and culture. All subjects diagnosed as CRSsNP were put on conservative treatment in form of intranasal Fluticasone propionate spray 50 µg twice a day in both nasal cavities for 3 months and followed up monthly for 3 months, and if significant improvement (i.e., decrease in Lund and Mackay endoscopic scores by half) is seen after 3 months, they were continued on conservative management and followed 3 monthly thereafter as institutional protocol. LM symptoms and endoscopy scores were measured during every follow up visit. 5 CRSsNP patients were either lost to follow up or exited from study.

Subjects diagnosed with CRSwNP were again divided into two groups on basis of LM endoscopy scores measured as per extent of disease for management purpose. CRSwNP cases having LM endoscopy scores ≤ 5 were put on similar conservative management,

i.e., intranasal Fluticasone propionate spray 50 µg twice a day both nasal cavities for 3 months with same follow up protocol as CRSsNP cases. Patients of CRSwNP having LM endoscopy scores > 5 and those cases of CRSsNP who showed no significant improvement after 3 months of conservative management were scheduled for Functional Endoscopic Sinus Surgery (FESS) under general anaesthesia. During FESS, tissue biopsy (with fungal and necrotic debris, if present) was taken from ostiomeatal complex and sent for fungal staining and culture. Postoperative period for all patients who underwent surgery was largely uneventful and all subjects were followed up monthly till 3 months and 3 monthly thereafter. 6 subjects diagnosed as CRSwNP and underwent FESS exited from study at this point. Endoscopic middle meatal swabs taken from CRSsNP cases and tissue biopsies taken from CRSwNP patients were subjected to fungal staining (stains used – Haematoxylin & Eosin and Gomori methenamine silver apart from Potassium hydroxide (KOH) wet mount) and fungal culture (culture media used - Sabouraud Dextrose Agar and Selective Agar). Based on either fungal staining or culture reports, cases were divided into Group A who were Fungi positive CRS (n = 55) and Group B who were Fungi negative CRS (n = 55). These groups were then compared in terms of LM symptoms, endoscopic staging and radiological scores measured initially as per study objectives (Fig. 1).

Later on, a subgroup analysis was performed in group of patients who were diagnosed as CRSsNP and correlation of LM Scores was made among those cases who showed no improvement and had to be operated with the rest. Similar analysis was performed in CRSwNP group and correlation done among cases having LM endoscopy staging scores d' 5 with cases having these scores > 5. Statistical analysis was done using IBM SPSS Statistics ver 27.0.

Results

In this study, total of 121 adult subjects participated and as discussed above, 11 subjects exited from study rendering effective study population as 110 (65 males

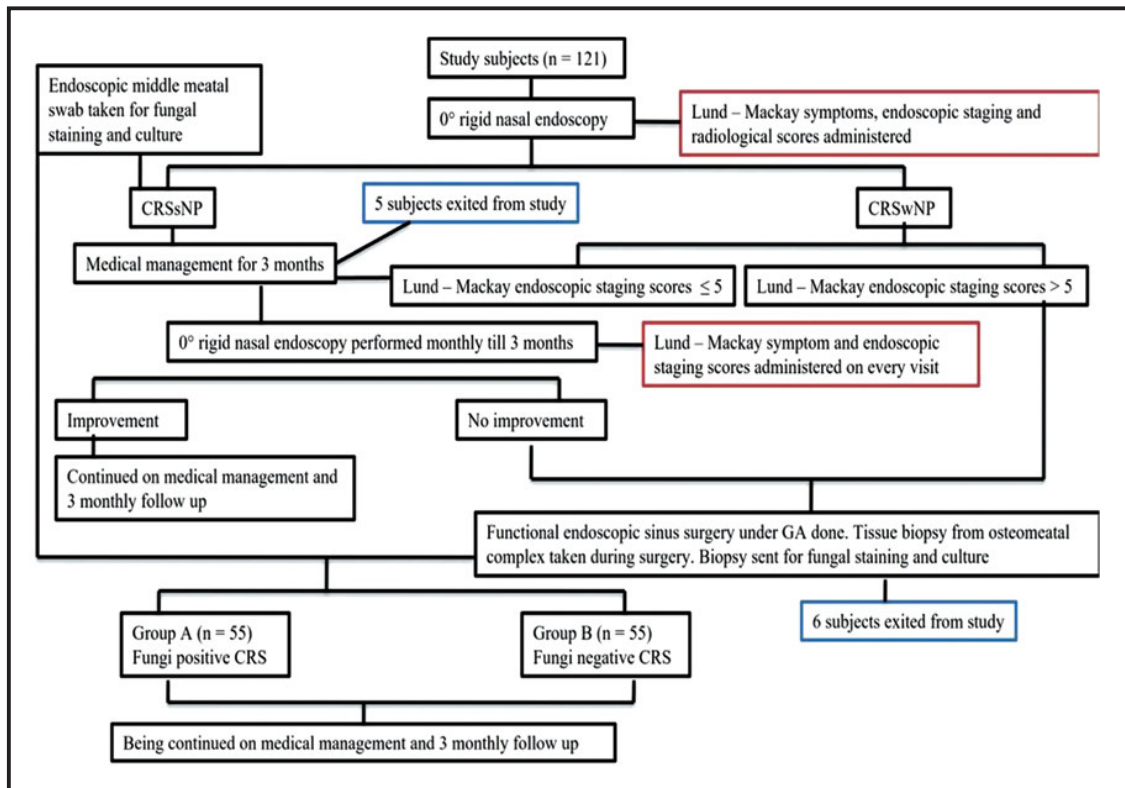


Fig. 1. Methodology of the study

and 45 females) with age ranging from 20 – 74 years (mean age – 48.07 years). Based on complete otorhinolaryngology examination including rigid nasal endoscopy and NCCT Nose and PNS, 62 subjects were diagnosed as CRSsNP and 48 as CRSwNP. Study progressed as per protocol and based on either fungal staining or culture results, study population was divided into two groups, Fungi positive CRS (n = 55) and Fungi negative CRS (n = 55).

Fungi positive vs Fungi Negative CRS

Among study population who were found to be Fungi positive CRS, there were 34 males and 21 females (Male:Female ratio being 1.62:1) of mean age 43.6 years (age range – 20 – 74 years). In this group, mean LM symptoms score was 7.09 with standard deviation (SD) ± 1.07 ; mean LM endoscopy score was 6.64 with SD ± 1.94 and LM radiological score was 14.58 with SD ± 2.96 (Fig. 2).

In Fungi negative group, there were 35 males and 20 females (Male:Female ratio being 1.75:1) of mean age 49.07 years (age range – 20 – 73 years). Among study population of this group, mean LM symptoms score was 3.58 with SD ± 1.30 ; mean LM endoscopy score was 4.47 with SD ± 1.57 and LM radiological score was 12.20 with SD ± 2.98 (Figure II).

Statistical analysis

Intermediate values used in comparison of LM scores among two groups were :-

- LM Symptoms scores :- $t = 14.1783$, degree of freedom (df) = 108, standard error of difference = 0.247
- LM Endoscopy scores :- $t = 6.3720$, df = 108, standard error of difference = 0.340
- LM Radiology scores :- $t = 4.1717$, df = 108, standard error of difference = 0.571 Student's

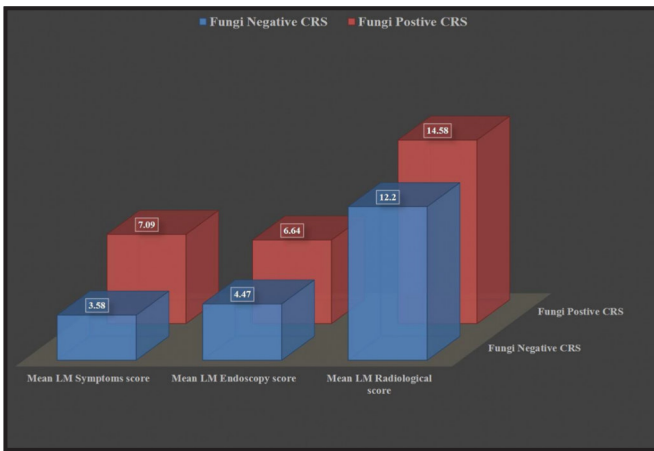


Fig. 2. Fungi Negative vs Fungi Positive CRS – Comparison of Lund-Mackay Scores

unpaired t test was applied with 95% confidence interval, and the two tailed P value in all comparison of all three scores was 0.0001, which was extremely statistically significant.

Subgroup analysis

CRSSNP :- Among cohort of cases diagnosed as CRSSNP

(n = 62), 64.5% cases showed improvement; out of these cases 01 subject was found to have been harbouring fungal elements while rest 39 were Fungus negative. On the other hand, rest 35.5% cases showed no improvement after 3 months of conservative management; out of these cases 16 were found to be positive for fungal elements and 25 were reported fungus negative (Table I).

Statistical analysis was using Chi Square test on a 2 X 2 contingency table, results were :- $\chi^2 (1, N = 62) = 10.8559, p < 0.05$.

Test was repeated using Fisher exact test using same intermediary values and p value was statistically significant at <0.05.

CRSwNP :- Among cases diagnosed as CRSwNP (n = 48), LM Endoscopy scores of 14.6% cases were found to be d” 5 and they were given a trial of conservative management; out of these cases 06 cases were found to be fungus positive and 01 fungus negative. LM Endoscopy scores of rest 85.4% cases were recorded to be > 5; out of these cases 16 were found to be fungus positive and 25 fungus negative. Statistical analysis was done using Fisher exact test and p value was statistically significant at < 0.05 (Table I).

Table I: Subgroup analysis of cases diagnosed as CRSSNP and CRSwNP

CRSSNP	IMPROVEMENT	NO IMPROVEMENT	P VALUE
(n = 62)	40	22	0.001*
<i>Fungi Positive CRS</i>	01	07	
<i>Fungi Negative CRS</i>	39	15	
CRSwNP	<i>LM Endoscopy Scores ≤ 5</i>	<i>LM Endoscopy Scores > 5</i>	0.03**
(n = 48)	7	41	
<i>Fungi Positive CRS</i>	6	16	
<i>Fungi Negative CRS</i>	1	25	

* Chi Square test and Fisher exact test

** Fisher exact test

Discussion

Fungal presence and its causal relationship with chronic rhinosinusitis have been known for decades and continuously being researched. Katzenstein et al opened this Pandora's box in 1983 when he isolated *Aspergillus* from mucous of paranasal sinuses in cases of CRSsNP and coined the term "Allergic *Aspergillus* Sinusitis".⁴ However, the term was modified as "Allergic Fungal Sinusitis" (AFS) in 1989 when similar clinicopathological picture was demonstrated with other fungi as well.⁵ In 1994, Bent & Kuhn designed and proposed five-point criteria for AFS which presently stands as standard diagnostic criteria for allergic fungal rhinosinusitis.⁶ Right when the Rhinologists all over the world were drawn and invested in finding clinicopathology of AFS, Ponikau et al objected to the existing theory of Type I hypersensitivity and IgE mediated response and proposed that the term AFS should be replaced by 'Eosinophilic Fungal Rhinosinusitis' (EFRS). They demonstrated ubiquitous presence of fungi in cases of CRS and healthy controls alike by using special sample collection (nasal irrigation) and culturing methods.⁷⁻⁹

There is plethora of literature on different types of research focussing and debating on clinicopathology of AFS/EFRS at cellular and molecular level (and still are unclear about it) but few studies support the fact that fungal existence in nasal cavity and paranasal sinuses can further cause worsening of symptoms and signs in susceptible cases of CRS.¹⁰ Our study was aimed at finding objective evidence to it and has done successfully so.

This study has proven that symptoms developed in cases of CRS with concomitant fungal infection are of greater magnitude than those cases who are free of it; and it is a proven fact that sharp clinical acumen is required to assess severity of symptoms and in that case, an Otorhinolaryngologist should always keep in mind the possibility of fungal rhinosinusitis in patients who may be otherwise diagnosed as CRS.^{1,11,12}

Results from our study have shown that LM Endoscopy scores of fungi positive CRS were way higher than cases of CRS who were fungi negative. Nasal

endoscopy, being vital in diagnosis of fungal rhinosinusitis, can detect signs out of proportion to symptoms and thus, should always arouse a clinician's suspicion of fungal rhinosinusitis.^{6,10,13-15}

Similarly, in our study, LM Radiology scores were also found significantly higher in cases of fungi positive CRS when compared to cases of fungi negative CRS. Although, classic radiology features as explained by Bent and Kuhn in their classic research⁶ were not found in many fungi positive CRS patients. But there is literature existing which stresses upon the fact that radiological studies of cases of CRS may depict CT signs which support diagnosis of fungal rhinosinusitis.¹⁶⁻¹⁸

Subgroup analysis in our study has pointed us to a finding that surgical intervention is required for patients of CRS with nasal polyps with or without fungal presence, and, it is difficult to ascertain that fungus alone, is responsible for their symptoms, signs and CT features.

Conclusions

Role of fungus in development of Chronic Rhinosinusitis with or without nasal polyps has always been a point of debate and conflict and has never been successfully proven. There have been multitude of studies focussing on cellular, immunological and molecular aspects of fungus and concluded that fungal presence is ubiquitous and has no role in development of CRS. Our study just indicates at the tip of iceberg that fungal presence may have a role in escalation of symptoms, signs and radiological scores and it may aggravate pre-existing CRS, and, for which, sharp clinical acumen and a bent of mind is required that these patients can be adequately diagnosed and managed.

Limitations

Although, our study could point over the fact that concomitant presence of fungus in cases of CRS may exaggerate symptoms and signs of disease but due to cohort design and lesser sample size, definitive conclusions could not be drawn. There remains a felt need for large scaled multicentric randomised controlled

trials/meta-analyses to reach concrete conclusions and to form guidelines for management of such cases in larger applicability.

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SUPPLEMENT I

Symptoms	Scores (0-10)
Nasal blockage/congestion /pressure	
Headache	
Facial Pain	
Nasal discharge	
Problems of smell	
Overall	

Supplement I: Lund-Mackay symptoms scores: Measurement is done subjectively by patients on a psychometric 10-point Visual Analogue Scale, where 0 = no symptoms and 10 = most severe symptoms. Scores range from 0 – 50.

Reference: Lund VJ, Mackay IS. Staging in rhinosinusitis. *Rhinology.* 1993 Dec 1;31:183

SUPPLEMENT II

Endoscopic appearances	Scores (0-2)
Polyp	
Discharge	
Oedema	
Scars or adhesions	
Crusting	
Overall	

Supplement II: Lund-Mackay Endoscopic staging scores: Quantified subjectively on a 0 – 2-point scale by clinician for extent of polyps (0 = none; 1 = confined to middle meatus; 2 = beyond middle meatus); discharge (0 = none, 1 = clear and thin; 2 = thick and purulent), oedema, scarring or adhesions and crusting. Overall scores may range from 0 – 10.

Reference: Lund VJ, Mackay IS. Staging in rhinosinusitis. *Rhinology*. 1993 Dec 1;31:183

SUPPLEMENT III

Sinus systems - Scores (0-2)	Right	Left
Maxillary		
Anterior ethmoids		
Posterior ethmoids		
Sphenoid		
Frontal		
Ostiomeatal complex (0 or		
Overall		

Supplement III: Lund-Mackay Radiology scores: Quantified on basis of NCCT Nose and PNS, each sinus group can be scored on a 0 – 2 point scale by clinician. (0 = no abnormality; 1 = partial opacification; 2 = total opacification). Ostiomeatal complex is scored as 0 = not obstructed or 2 = obstructed. Scoring is done for each side of PNS and can also be considered separately. Total scores may range from 0 – 24.

Reference: Lund VJ, Mackay IS. Staging in rhinosinusitis. *Rhinology*. 1993 Dec 1;31:183