A STUDY ON INCIDENCE AND CLINICAL PROFILE OF FUNGAL SINUSITIS IN PATIENTS DIAGNOSED WITH CHRONIC RHINOSINUSITIS

Dissertation submitted to

THE TAMIL NADU DR. M.G.R MEDICAL UNIVERSITY

In fulfillment of the regulations for the award of the degree

M.S. OTO-RHINO-LARYNGOLOGY

DEPARTMENT OF E.N.T.

PSG INSTITUTE OF MEDICAL SCIENCES & RESEARCH
THE TAMIL NADU DR. M.G.R MEDICAL UNIVERSITY
CHENNAI, TAMIL NADU

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GUIDE: DR. GEORGE ZACHARIAS, M.S., D.L.O.

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CERTIFICATE

This is to certify that the thesis entitled **"A STUDY ON INCIDENCE AND CLINICAL PROFILE OF FUNGAL SINUSITIS IN PATIENTS DIAGNOSED WITH CHRONIC RHINOSINUSITIS"** is a bonafide work of **Dr. Sandeep Suresh** done under the direct guidance and supervision of **Dr. GEORGE ZACHARIAS, MS, DLO** in the Department of E.N.T, PSG Institute of Medical Sciences and Research, Coimbatore in fulfillment of the regulations of DR. MGR Medical University for the award of M.S. Degree in Oto-Rhino-Laryngology.

DR. GEORGE ZACHARIAS
Professor and HOD,
Dept. of E.N.T.

DR. S. RAMALINGAM
Principal

DECLARATION

I hereby declare that this dissertation entitled **"A STUDY ON INCIDENCE AND CLINICAL PROFILE OF FUNGAL SINUSITIS IN PATIENTS DIAGNOSED WITH CHRONIC RHINOSINUSITIS"** was prepared by me under the direct guidance and supervision of Professor & HOD of E.N.T, **Dr. GEORGE ZACHARIAS, MS, DLO,** PSG Institute of Medical Sciences & Research, Coimbatore.

This dissertation is submitted to the Tamil Nadu DR. MGR Medical University in fulfillment of the University regulations for the award of M.S. degree in Oto-Rhino-Laryngology. This dissertation has not been submitted for the award of any other Degree or Diploma.

Dr. Sandeep Suresh

CERTIFICATE BY THE GUIDE

This is to certify that the thesis entitled **"A STUDY ON INCIDENCE AND CLINICAL PROFILE OF FUNGAL SINUSITIS IN PATIENTS DIAGNOSED WITH CHRONIC RHINOSINUSITIS"** is a bonafide work of **Dr. Sandeep Suresh** done under my direct guidance and supervision in the Department of E.N.T, PSG Institute of Medical Sciences and Research, Coimbatore in fulfillment of the regulations of DR. MGR Medical University for the award of M.S. degree in Oto-Rhino-Laryngology.

DR. GEORGE ZACHARIAS
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July 8, 2013

To
Dr Sandeep Suresh
Postgraduate
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Coimbatore

The Institutional Human Ethics Committee, PSG IMS & R, Coimbatore -4, has reviewed your proposal on 5th July, 2013 in its expedited review meeting held at IHEC Secretariat, PSG IMS&R, between 2.00 pm and 3.00 pm, and discussed your application to renew the study entitled:

"A study on incidence and clinical profile of fungal sinusitis in patients diagnosed with chronic rhinosinusitis"

The following documents were received for review:

1. Application for renewal
2. Status report of the study

After due consideration, the Committee has decided to renew the approval for the above study.

The members who attended the meeting held on at which your proposal was discussed, are listed below:

Name	Qualification	Responsibility in IHEC	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
Dr P Sathyan	DO, DNB	Clinician, Chairperson	Male	No	Yes
Dr S Bhuvaneshwari	M.D	Clinical Pharmacologist Member – Secretary	Female	Yes	Yes
Dr Sudha Ramalingam	M.D	Epidemiologist Alt. Member – Secretary	Female	Yes	Yes
Dr Y S Sivan	Ph D	Member – Social Scientist	Male	Yes	Yes
Dr D Vijaya	Ph D	Member – Basic Scientist	Female	Yes	Yes

The renewal is valid for one year (From 28.06.2013 to 27.06.2014).

This Ethics Committee is organized and operates according to Good Clinical Practice and Schedule Y requirements.

Non-adherence to the Standard Operating Procedures (SOP) of the Institutional Human Ethics Committee (IHEC) and national and international ethical guidelines shall result in withdrawal of approval (suspension or termination of the study). SOP will be revised from time to time and revisions are applicable prospectively to ongoing studies approved prior to such revisions.

Yours truly,

Dr S Bhuvaneshwari
Member - Secretary

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Proposal Number	:	**11/259**
Project Title	:	**A study on incidence and clinical profile of fungal sinusitis in patients diagnosed with chronic rhinosinusitis**
Investigator(s)	:	**Dr Sandeep Suresh**
institution	:	**PSGIMS & R**
Name of the Guide(s)	:	**Dr George Zacharias**
Institution	:	**PSGIMS & R**
Waiver of Consent	:	**No**
Review Type	:	**Exempt**
Date of the Meeting	:	**N/A**
Decision	:	**Approved**
Approval Date	:	**28.06.2012**
Validity of the Approval	:	**One year**

Approval for this study is given under the following terms and conditions:

1. Non-adherence to the Standard Operating Procedures (SOP) of the Institutional Human Ethics Committee (IHEC) and national and international ethical guidelines shall result in withdrawal of approval (suspension or termination of the study). SOP will be revised from time to time and revisions are applicable prospectively to ongoing studies approved prior to such revisions.
2. PIs are required to send progress reports (in the form of an extended abstract with publications if any) to the IHEC every six months (and a month before expiry of approval date, if renewal of approval is being sought).
3. Request for renewal must be made at least a month ahead of the expiry of validity along with a copy of the progress report.

28/06/2012

Dr Y S Sivan
Member - Secretary

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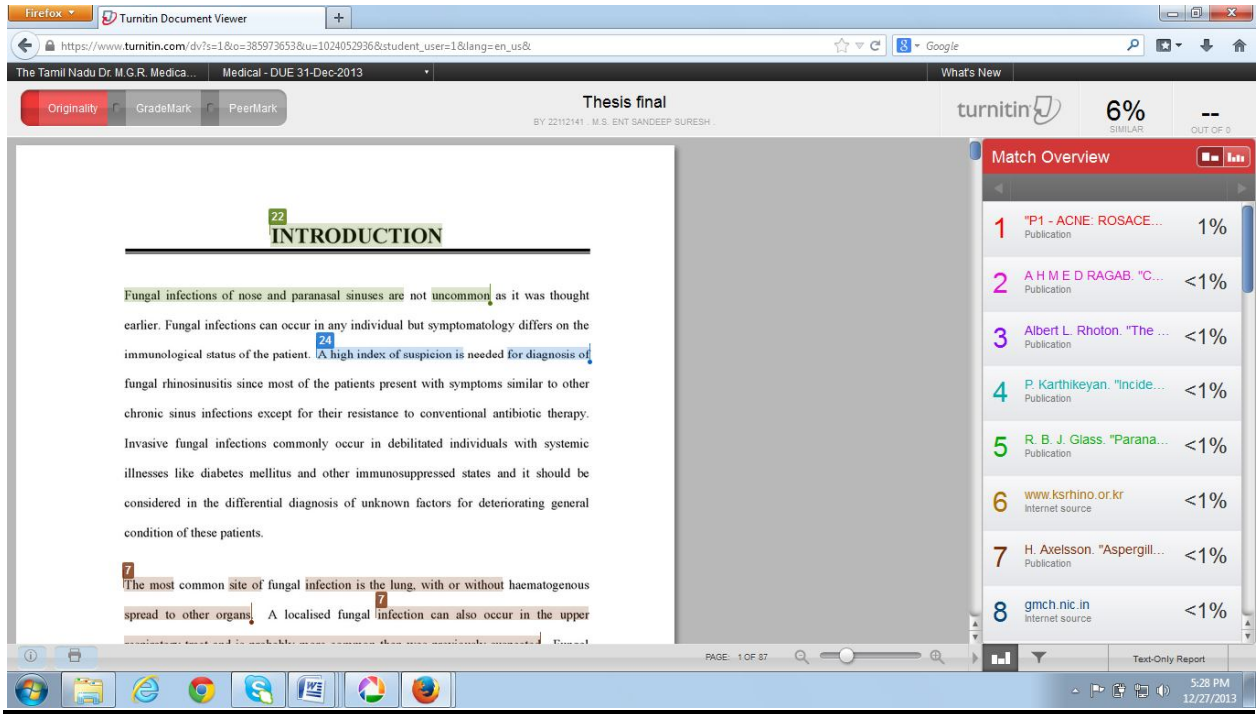
A STUDY ON INCIDENCE AND CLINICAL PROFILE OF FUNGAL SINUSITIS IN PATIENTS DIAGNOSED WITH CHRONIC RHINOSINUSITIS



ACKNOWLEDGEMENTS

It is my greatest pleasure to recall the people who have helped me in the completion of my dissertation.

It gives me immense pleasure to express my heartfelt gratitude and sincere thanks to my beloved teacher, Professor and HOD **Dr. George Zacharias**, Dept. of E.N.T, PSG IMS & R, Coimbatore for being an inspiration and for providing all the support during this study, without whose towering presence this study would not have been possible.

I thank my teacher, **Dr. S. Palaninathan**, Professor of E.N.T for his staunch support during the period of this study. His suggestions have helped me in improving the quality of this work.

I would like to express my sincere gratitude to **Dr. A. Dayanand**, Associate Professor who was instrumental in guiding me in selecting this topic and who provided valuable tips from time to time which helped me complete my work. My Associate Professor, **Dr. V. Ravishankar** has played a crucial role by helping me identify cases for my study. Without his support, my study would not have taken its present shape. I wish to express my sincere gratitude to **Dr. G. Sholai Selvan**, Assistant Professor who also played a significant role in this topic selection and guided me during the initial stages of my work.

I owe a great deal of respect and gratitude to **Dr. V. Venkat Raman** for his valuable academic inputs which have made a remarkable impact on the final outcome of my study and **Dr. S. Sathiyabama** for being a source of motivation during this study.

I am also grateful to **Dr. S. Shantakumari**, Professor, Department of Pathology for the valuable her valuable support in completion of my work.

I would like to thank the faculty of the department of Microbiology **Dr. B. Appala Raju**, Professor and HOD and **Dr. S. Parvathi**, Professor who took time off their busy schedules to help me in my dissertation. I cannot forget the hardwork **Mr. Baskkaran.A.C** provided me in gathering clinical photograghs for this work.

Words are not enough to express my gratitude to **Dr. S. Senthil**, **Dr. Girish Deepak** and **Dr. Jenit Osborn**, my colleagues and friends who gave me the confidence and guided me right throughout the publishing of this work. I sincerely thank **Dr. Deepthi Madhu** who helped me in completing my literature review.

I take this opportunity to thank **Dr. Anil Mathew**, Professor in Biostatistics whose inputs were very valuable in completion of this study.

I take this opportunity to recognize the efforts of all the individuals who have guided and supported me through this study period – **Mr. Kannan, Mr. Prabhu** and the entire IT Dept and E.N.T department staff, **Mrs. Chitra**, **Mrs. Anandhi** and E.N.T ward nursing staff for helping me collect all necessary patient details.

I am thankful to my family who were the real source of encouragement for me during my dissertation work. I thank my Post Graduate colleagues for their whole-hearted support.

At the outset I would like to sincerely thank **Dr. S. Ramalingam**, Principal and the Ethics Committee, PSG IMS &R for having consented to this study.

Finally my heartfelt appreciation & greatest thanks to all the **patients** enrolled in the study.

Lastly I dedicate this work to my Dad who is not with us anymore.

CONTENTS

ABSTRACT

Aim: To study the incidence and clinical profile of fungal sinusitis in diagnosed cases of chronic rhinosinusitis.

Materials and Methods: This was a prospective study in which 100 patients with chronic rhinosinusitis who underwent treatment in the department of E.N.T at a tertiary care centre over two years were randomized into the study. Diagnosis was confirmed by fungal culture and pathological examination of the excised specimen. The data collected from the patients was analysed by Pearson Chi- Square and Fisher's Exact tests. Patients underwent either endoscopic sinus surgery or medical line of management or a combination of both.

Results: Fungal rhinosinusitis was more common in the elderly age groups with involvement of maxillary sinus in most of the cases. Nasal discharge, nasal obstruction and headache were the most common presenting symptoms. Pathological examination had a higher sensitivity than microbiology examination in the diagnosis. Mucor was the most commonly isolated organism. Fungal sinusitis was comparatively more common among immunocompetent individuals. More than one-third of cases were invasive fungal rhinosinusitis. Complications were more in cases of mucormycosis. Surgery with chemotherapy offered better treatment outcome as compared to single modality.

Conclusion: Early detection and treatment of fungal rhinosinusitis is the key in tackling this clinical condition which can otherwise be fatal.

Key words: chronic rhinosinusitis, fungal sinusitis, immunocompromised state, mucormycosis, aspergillus

INTRODUCTION

Fungal infections of nose and paranasal sinuses are not uncommon as it was thought earlier. Fungal infections can occur in any individual but symptoms differ based on the immunity status of the patient. A high index of suspicion is needed for diagnosis of fungal rhinosinusitis since most of the patients present with symptoms similar to other chronic sinus infections except for their resistance to conventional antibiotic therapy. Invasive fungal infections commonly occur in debilitated individuals with systemic illnesses like diabetes mellitus and other immunosuppressed states and it should be considered in the differential diagnosis of unknown factors for deteriorating general condition of these patients.

The most common site of fungal infection is the lung, with or without haematogenous spread to other organs. A localized fungal infection can also occur in the upper respiratory tract and is probably more common than was previously suspected. Fungal infections of the paranasal sinuses most often include histoplasmosis, coccidiomycosis, candidiasis, phycomycosis and aspergillosis. Aspergillus is the most common fungal pathogen in sinus disease and is the most common primary fungal organism infecting the maxillary antrum. Aspergillus is a fungus of the Ascomycetes class that occurs worldwide and may appear as a saprophyte, parasite or frank pathogen in man. It is found in many of the moulds on food, fruits, grain seeds and plants. Its ubiquitous spores present in dust enter the respiratory system of man where under proper climatic conditions they become pathogenic.

The occurrence of fungal sinusitis in healthy individuals was first reported by Zarniko in 1891 when he isolated Aspergillus fumigatus from the antrum of a patient who presented with symptoms of chronic maxillary sinusitis. Since 1968 the number of reported cases of aspergillosis of the nose and paranasal sinuses has increased more than threefold. Most reports of mycotic infections of the maxillary sinus in healthy individuals have been solitary ones where the diagnosis was made either at surgery or post operatively in patients presenting with typical features of chronic bacterial sinusitis, resistant to conventional methods of therapy. It may be that aspergillosis of the maxillary sinus is much more common than reported.

This disease entity is being increasingly recognized, because of increased awareness, improved techniques of specimen collection, processing, fungal culture and special staining for pathological examination.

REVIEW OF LITERATURE

American Academy of Otolaryngology recommended that the term rhinosinusitis is more accurate over sinusitis to describe the disease involving nose and paranasal sinuses. Fungi are eukaryotic unicellular filamentous organisms of ubiquitous nature. Majority of fungi exist as soil saprophytes and few as parasites of humans and animals. Most of the human fungal infections are opportunistic. The incidence of fungal infections and especially the morbidity and mortality caused by them have been grossly under-estimated. Another major reason for the rapid increase in the number of fungal rhinosinusitis cases is higher prevalence of immunocompromised patients.

McGuirt and Harill[7] identified Aspergillus as the most commonly encountered pathogen in the nose and paranasal sinuses.

Plaignaud was the first to report a case of possible fungal sinusitis in a 22 year old soldier with maxillary pain.

Paultauf in 1884 was the first to describe a definite case of fungal sinusitis. In 1885, Schubert reported a case of non-invasive aspergillosis involving the paranasal sinuses.

Since 1968, the number of reported cases has increased more than three folds. In 1972, a review of world literature by Zinneman revealed 37 cases of fungal sinusitis, of which 17 were reported by Milosev and Magoub[3] from Sudan.

Mirsky and Cuttner in 1972 found severe fungal infection at autopsy in 28% of patients who died of acute leukemia.

In 1979, Jahrsdoefer et al in his review of world literature found 103 cases of fungal sinusitis most of which were solitary case reports.

Cho Choi in 1979 found fungal infection in 22% of patients who died of acute leukemia. Glass and Hertzanu in 1984, reviewed world literature and found 115 case reports of Aspergillus sinusitis.

Stammberger[15] in 1985 reported of having treated over 140 patients with massive fungal sinusitis in the period of 1976-1985.

Mayo clinic reported 12 cases of Aspergillus sinusitis over a period of 13 years from 1972 – 1985.

Hazarika et al[12] in 1984 reported three cases of rhinocerebral mucormycosis, all of them were elderly and diabetic.

Chakrabarti et al[40] in 1992 isolated fungi in 50 of 119 clinically suspected cases in North India over a two-year period.

The reported incidence of fungal sinusitis varies widely with very high rate appearing in the European countries. According to literature review highest incidence of allergic fungal rhinosinusitis (AFRS) was noted in Mumbai, India (Ferguson et al 2000).

ANATOMICAL CONSIDERATIONS:

The development of nose is from the structures surrounding the primitive stomodeum, namely the mesenchymal processes i,e…frontonasal process and maxillary processes.

Thickenings of ectoderm called olfactory placodes which appear above the stomodeum develop into olfactory pits. These olfactory pits at 5-7 weeks of gestation extend posteriorly to form nasal cavities. The fusion of maxillary process with the lateral nasal process occurs at the nasolacrimal groove which later develops into the nasolacrimal duct. The maxillary process also fuses with the median nasal process leading to formation of lateral part of the upper lip.

The Nasal septum and premaxilla are formed by the fronto-nasal process.

Evaginations of mucus membrane from nasal cavities on either side develop into various paranasal sinuses.

Maxillary sinus develops due to expansion of primitive ethmoidal infundibulum into the mass of maxilla and is the first sinus to appear at 7-10 wks of gestation. Maxillary sinus expands in childhood with development of maxilla & teeth and attains adult size in the latter part of the second decade of life.

Anterior and Posterior ethmoid sinuses develop as an outpouching of lateral nasal wall in the middle meatus region at third month of gestation. Posterior ethmoid cells develop from the region of the superior meatus. Ethmoid sinuses reach adult size by 12 years of age.

Frontal recess expands and further growth occurs superiorly to form frontal sinus which becomes radiologically visible by 7-12 years of age. They are asymmetrical since they develop separately.

Sphenoid sinus develops from the nasal capsule of the embryonic nose. It is underdeveloped till 3 years of age after which there is more rapid growth. Complete pneumatization of the sphenoid sinus occurs by 9-12 years of age.

The development of nasal cavities begin at the external nares and extends upto the posterior choanae. In adults the nasal cavities measure around 5-7 cm in length and 2-5cm in height. They are narrowed transversely.

Vestibule is skin-lined, dilated passage of the nasal cavity from external nares to the nasal fossa which contains sebaceous glands and sweat glands. Also contains hair follicles.

Floor of the nose: Palatal process of maxilla constitutes anterior three-fourths of the floor while the rest one-fourth is constituted and remaining part is formed by horizontal process of palatine bone.

Roof of the nose: Nasal bone and nasal part of the frontal bone forms the anterior part of the roof while the middle part is formed by the cribriform plate of the ethmoid bone. Part of body of sphenoid bone forms the posterior part of the roof.

Nasal septum or the medial wall is anteriorly formed by the quadrangular cartilage & premaxilla, posteriorly by the perpendicular plate of ethmoid & the sphenoidal crest. Inferior part of the nasal septum is constituted by crests of vomer, maxillary and palatine bones.

Lateral nasal wall is anatomically is more complex, receiving the openings of paranasal sinuses. The most prominent structures on the lateral wall are the three turbinates namely inferior, middle and superior. A fourth turbinate, supreme turbinate may be seen in 60% of cases. Air passages below and lateral to turbinates are called meati, named after the respective turbinate. The site of drainage of the sphenoid sinus is the sphenoethmoidal recess, which is the area that lies above the superior turbinate and below the body of sphenoid. The frontal, anterior & middle ethmoids and the maxillary sinuses which comprises of the anterior group of sinuses drain into the middle meatus, whereas the posterior ethmoid sinuses drain into the superior meatus. The Nasolacrimal duct opens just anterior to the junction of the anterior $1/3^{rd}$ and middle $1/3^{rd}$ of the inferior turbinate in the inferior meatus.

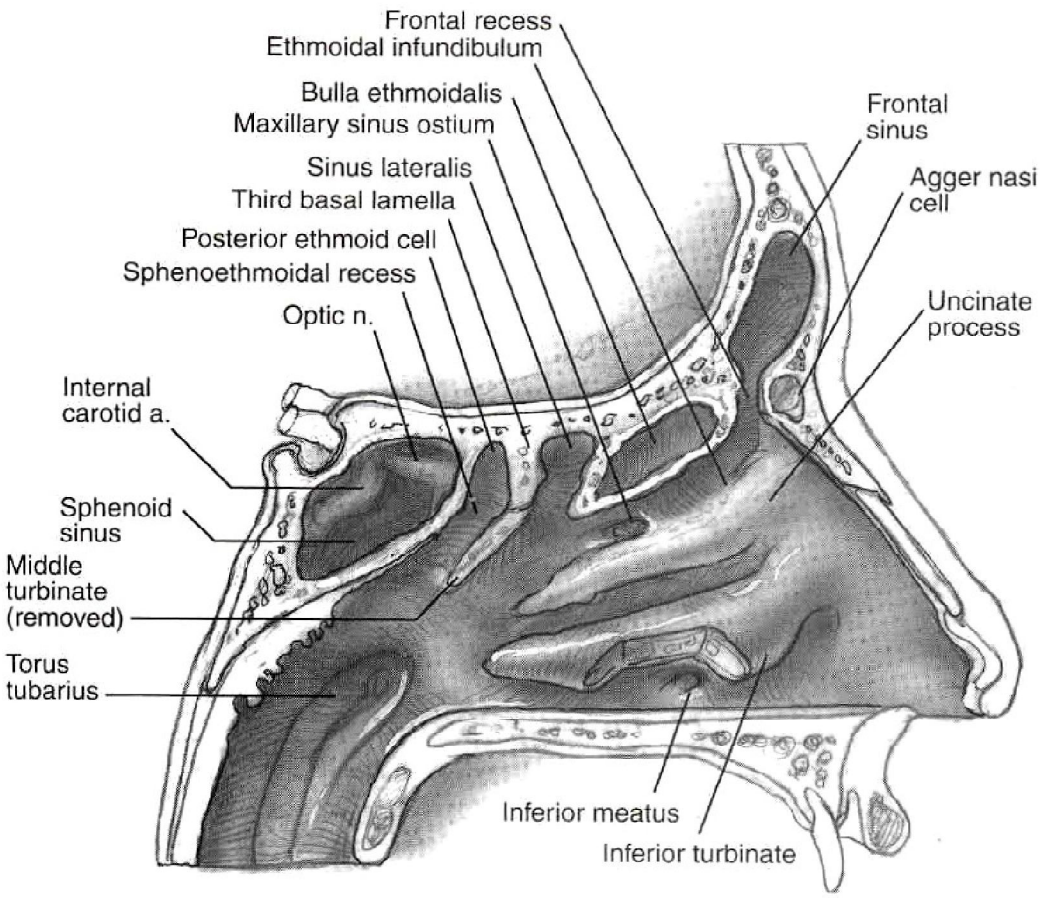


Fig.1 Lateral nasal wall

Inferior turbinate is composed of an independent bone covered with periosteum. It articulates with the inferior margin of the maxillary hiatus, ethmoid, palatine and lacrimal bones. Contains soft tissue with cavernous plexus with sinusoids submucosally which become engorged with blood in response to triggers or part of nasal cycle.

Agger nasi is part of the lateral nasal wall anterior to the middle turbinate insertion which is usually pneumatized. Agger nasi is part of the anterior ethmoid labyrinth.

The middle turbinate is a part of ethmoid labyrinth. The orientation is along 3 different planes. Anterior 1/3rd of the middle turbinate is along the sagittal plane and is attached superiorly to lateral nasal wall and cribriform plate. The middle 1/3rd of the middle turbinate has a coronal orientation, forming the basal lamella of the middle turbinate. Anterior to basal lamella, the ethmoid cells drain into middle meatus and posterior to it, the ethmoid cells drain into superior meatus. The posterior 1/3rd of the middle turbinate runs in the axial plane and gets inserted adjacent to sphenopalatine foramen.

Frontal recess is an important structure where the lateral margin is formed by the lamina papyracea, bounded medially by middle turbinate, agger nasi anteriorly and ethmoid bulla posteriorly.

The uncinate process, bulla ethmoidalis and hiatus semilunaris are the important structures in the middle meatus from anterior to posterior direction.

The uncinate process is a thin crest of bone, the free border of which is parallel with the anterior surface of bulla ethmoidalis. Ethmoid bulla is a rounded elevation formed by the middle ethmoidal cell. Hiatus semilunaris is a deep semi-circular sulcus below the ethmoid bulla. Opening of frontal sinus present in the infundibulum located at the anterior end of hiatus. Maxillary sinus opening is in the posterior part of hiatus. Anterior and middle ethmoidal sinuses open into the upper margin of bulla. Osteomeatal complex includes structures draining into middle meatus i,e…maxillary sinus ostium, anterior ethmoidal cells and frontal recess.

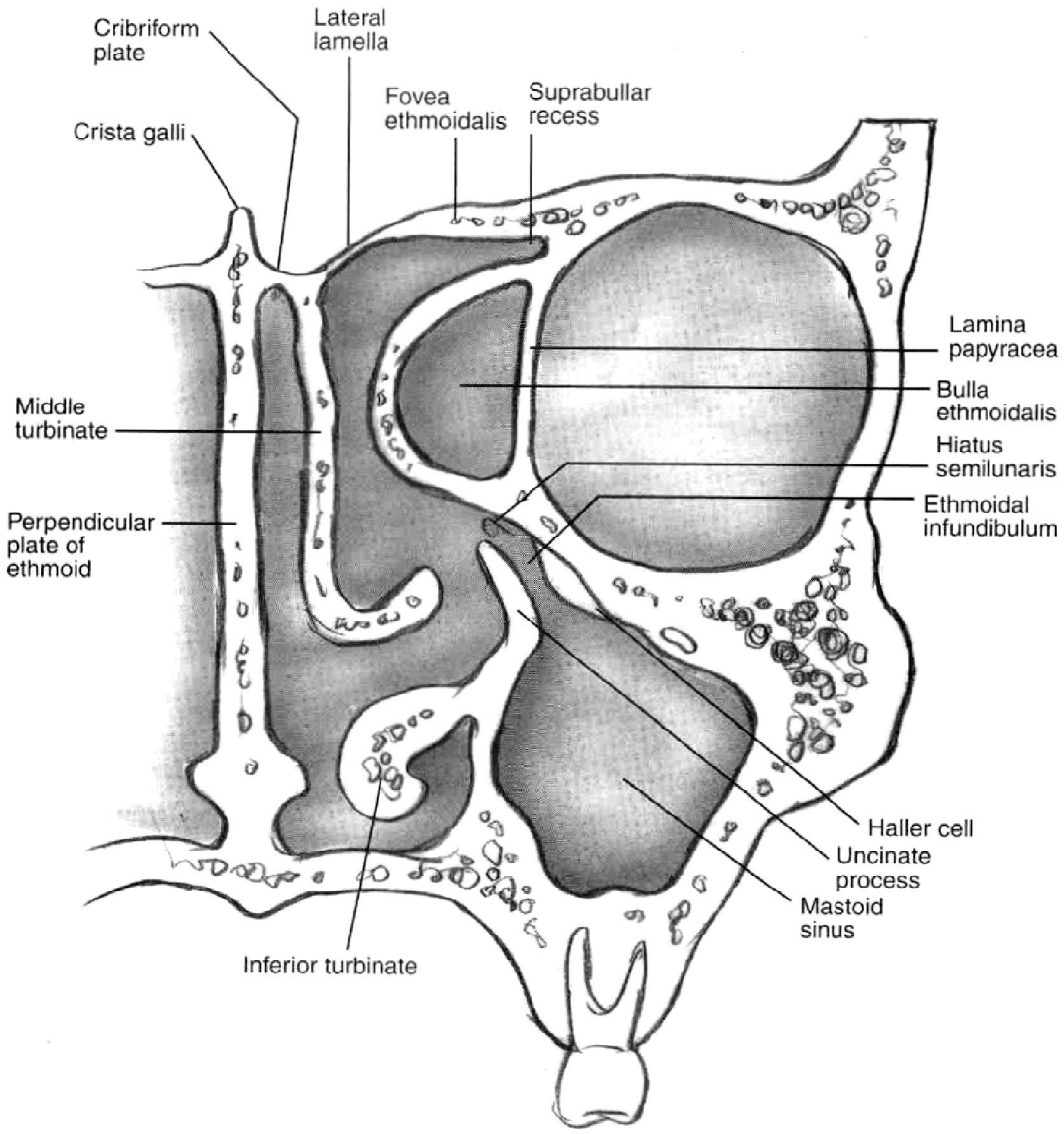


Figure.2

Maxillary sinus (Antrum of Highmore) occupies the body of maxilla and is pyramidal in shape, the base of which is at the lateral wall of the nose and the apex projecting into the zygomatic process. It is the largest among paranasal sinuses. Maxillary sinus is bounded anteriorly by the maxillary face, medially by the ascending process of the palatine bone

and posteriorly by the pterygomaxillary space. Maxillary ostium is in the anteromedial aspect of sinus near the roof of the sinus cavity hence mucociliary clearance is not gravity dependent and starts in a star-like pattern from the floor of the maxillary sinus towards the maxillary ostium.

Frontal sinus: They are asymmetrical in shape, situated between the inner and outer tables of the frontal bone draining into each other or draining separately. Formation of frontal sinus occurs by growth and pneumatization of the ethmoid labyrinth into the frontal bone. Frontal sinus drainage occurs through the infero-medial aspect through the frontal ostium into middle meatus via the frontal recess. Frontal recess has various shapes depending on pneumatization of the air cells at its base, also depending on the anatomy of structures surrounding it.

Ethmoid sinus: Located within the ethmoid labyrinth, the collection of cells is called ethmoid sinuses, which lies lateral to the nasal cavity and medial to the orbit. Ethmoid sinus is in the shape of a pyramid. Fovea ethmoidalis is the roof of the ethmoid labyrinth which is much thicker than the rest of the bony structures in the region. Lateral wall is formed anteriorly by frontal and lacrimal bones while it is constituted posteriorly by a paper thin bone called lamina papyracea which delineates the ethmoid sinus from the orbit per se.

Sphenoid sinus: Complete pneumatization of sphenoid sinus occurs only by 9 – 12 years of age and is quite variable in nature. The wall and roof of the sphenoid sinus are the

thinnest. Sphenoid sinus lies adjacent to vital structures like the internal carotid artery, optic nerve, vidian nerve, cavernous sinus and foramen rotundum.

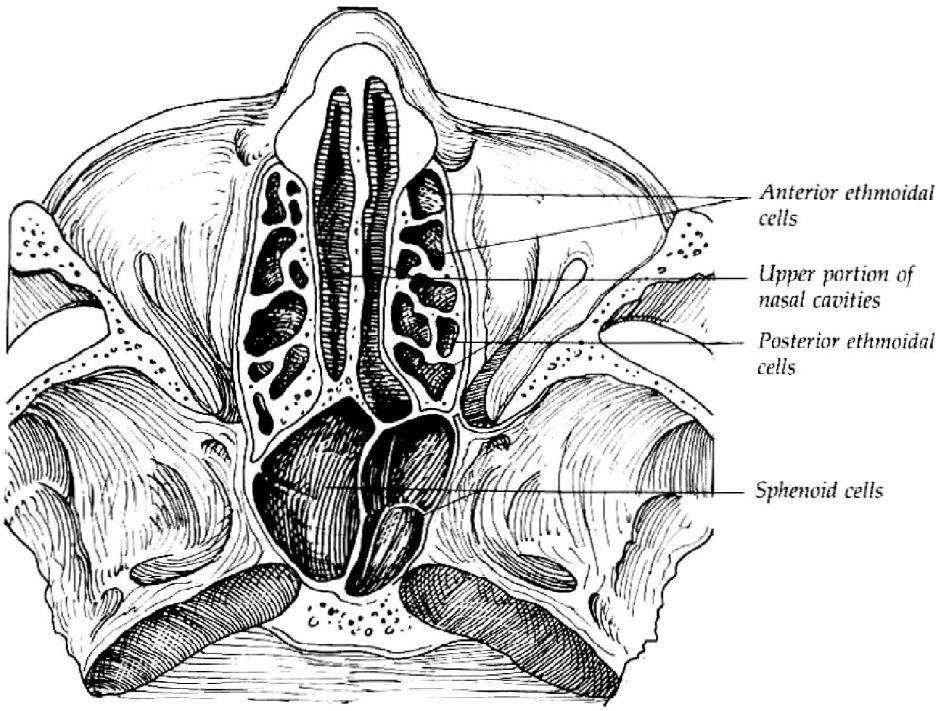


Fig.3 Coronal section showing ethmoid and sphenoid sinuses

Pseudostratified ciliated columnar epithelium lines the sinonasal cavity. Ciliated columnar epithelium lines most of the areas in the respiratory tract. The other cells present are basal cells which are pluripotent and secretory cells like goblet cells. The mucociliary flow is around 1 cm/min and is not gravity dependent.

Physiological importance of paranasal sinuses:

(a) Inspired air gets conditioned

(b) Voice resonance

(c) Acts as shock absorber to the head and reduces the weight of skull bones

(d) Moistens the nasal chambers

(e) Provide thermal insulation for the brain

(f) Plays a role in growth of facial skeleton

MYCOLOGY:

Fungi belong to the group of eukaryotic organisms. These organisms are characterized by a very rigid cell wall made up of polysaccharides like mannan and chitin which have high molecular weight. The cell membranes of these organisms contain sterols.

Growth cycle of fungi[23]:

Fungi usually have two phases of development namely vegetative phase and reproductive phase. Fungi undergo both these phases of life cycle or either one of these phases. Vegetative phase is usually the haploid phase wherein the fungi exist as yeast or mould forms. Reproduction in the case of fungi occurs by asexual or sexual means, namely mitotic or conjugative process. Telomorphs are the sexual forms while the asexual forms are anamorphs.

Classification of fungi is into four groups based on mode of sexual reproduction and morphology.

a) Ascomycetes eg. Histoplasma, Aspergillus

b) Zygomycetes eg. Rhizopus, Mucor

c) Dueteromycetes eg. Alternaria, Candida

d) Basidiomycetes eg. Cryptococcus

Mycosis[23] is generally defined as infection caused by fungi. Based on the mode of entry of the organism and site of entry, they are classified into:

- Superficial mycoses eg. Tinea corporis, Tinea pedis
- Sub-cutaneous mycoses eg. Mycetoma
- Systemic mycoses eg. Histoplasmosis, Coccidiomycosis,
- Opportunistic mycoses eg. Aspergillosis.

Diagnosis of fungal infections[23]:

Microscopic Examination:

Microscopic examination of specimens for fungi or fungal elements is important in the diagnosis where diagnosis can be obtained prior to culture. 10% potassium hydroxide (KOH) is the most commonly used medium, making fungal structures readily visible by dissolving the human tissues. Optical brighteners like Calcofluor white also aid in diagnosis.

Fungal Culture:

After collecting the clinical specimen for culture prior to antifungal therapy, multiple media are used for culturing the organisms. An appropriate temperature of 30^{o}Centrigrade must be maintained for an incubation period which varies from several days to weeks which again depends on the medium and fungi cultured.

Serological diagnosis:

When fungal cultures are nonproductive, immunological tests are used to confirm the diagnosis. Alteast a fourfold increase in antibody titre is needed for serological tests like Complement Fixation Test (CFT), Immuno-diffusion (ID), Enzyme Linked Immunosorbent Assay (ELISA), Latex Agglutination (LA) and Radioimmuno Assay (RIA) to be diagnostic. Detection of specific IgM antibody for a species of fungi is considered significant.

Histopathological examination[49]:

The gold standard investigation for invasive fungal rhinosinusitis is histology showing presence of fungal organisms. Though this process is more elaborate and time consuming, it is the only method to determine tissue invasion.

Hematoxylin and Eosin (H&E) staining is very useful but is unable to delineate the fungal cell wall. Silver staining is the most sensitive staining method, but however its disadvantage is that silver stains the cells too dark. A more specific but less sensitive method than silver stain is Periodic Acid Schiff (PAS) stain which allows the study of fungal morphology since it stains less dark than silver stain. When a mould is suspected in a tissue material, Fontana Masson (FM) stain for melanin can be used as a differential stain.

PATHOPHYSIOLOGY OF FUNGAL SINUSITIS:

A variety of causative factors play a major role in the development of fungal sinusitis. The common pathway is sinus obstruction causing impaired ventilation leading to

fungal organisms becoming pathogenic.

Environmental and Occupational factors:

A hot humid dusty low hygienic environment usually is a predisposing factor to development of mycotic infections of paranasal sinuses especially in people engaged in farming and in agriculture industries in tropical countries.

Host-factors[50]:

I. Barrier defense which comprises of intact lining epithelium forms the basic mode of defense mechanism against fungal organisms. Any breach in the lining epithelium which can be a result of wide range of factors including trauma and any surgical intervention can make the patient susceptible to fungal infection.

II. Antagonism by bacterial flora: The bacterial flora inhabiting the upper airway inhibits the colonization by fungi by competing with them for nutrient supply and by producing substances which inhibit their growth.

III. Non-immune host factors: Mucociliary clearance is the basic mechanism of elimination of fungal spores which get lodged in the upper airway. Factors like transferrins which are present in serum promote phagocytosis of fungal organisms.

IV. Cellular immunity: This modality forms the mainstay among host defense mechanisms by antigen processing, macrophage activation, monocyte-macrophage activity and secretion of interleukin-2 and γ-interferon.

V. Iatrogenic factors which predispose to fungal infection are:

- Patients who are on long-term antibacterial therapy
- Patients who are on steroid therapy for a long period of time, since corticosteroids depress leucotaxis
- Chemotherapy which leads to granulocytopenia leading to immunocompromised state.

Medical conditions[50] that confer susceptibility to fungal infections are:

Condition	Defect
AIDS	Cell mediated immunity
DiGeorge Syndrome, Thymic dysplasia	Cell mediated immunity
Hodgkin's disease	Cell mediated immunity
Diabetes mellitus	Depressed PMN function
Chronic granulomatous diseases & myeloperoxidase deficiency	Depressed PMN function
Leukemia	Depressed PMN function
Bronchitis	Depressed mucociliary action

Classification of fungal rhinosinusitis (FRS)[8,64]:

Fungal rhinosinusitis can be defined as a spectrum of diseases caused by fungal organisms. This entity is divided into two basic types based on course of the disease which in turn depends on the relationship of the fungal organisms to their hosts:

1. Invasive
2. Non-invasive

They are further divided into 5 distinct entities along the immunological spectrum[64].

Host defense	Immunocompromised	Immunocompetent			Atopy
Fungal form	1. Invasive	2. Granulomatous	3. Saprophytic	4. Fungal ball	5. AFRS

With change in the immunologic status of patient, the non-invasive form of FRS becomes invasive in nature[5]. Immunologic condition of the host plays a more important role than the type of fungal organism affecting the host[64]. Leucopenia in bone marrow transplant patients, organ transplant recipient on anti-rejection medication, AIDS patients and diabetics who are immunocompromised are susceptible to invasive disease.

Acute invasive fungal rhinosinusitis is less than 4 weeks duration where vascular invasion is prominent on histology[64].

Chronic invasive fungal rhinosinusitis is more than 4 weeks duration where vascular invasion is absent or minimal.

Paranasal Aspergillosis is categorized into two forms by McGuit and Harill[7]:

i) A localized form with no associated underlying disease

ii) An invasive form especially in immunocompromised individuals

ALLERGIC FUNGAL RHINOSINUSITIS (AFRS)[72]:

Allergic fungal rhinosinusitis (AFRS) is the most common type of fungal rhinosinusitis. The term allergic fungal rhinosinusitis was introduced by Robson et al in 1989. Ponikau[63] et al claimed that most patients with chronic rhinosinusitis satisfy the criteria for Allergic Fungal Sinusitis[81].

AFRS and allergic bronchopulmonary aspergillosis (ABPA) share the same aetiology (Miller's group; Katzenstain), mediated by both type-I (IgE mediated) and type-III (IgG antigen immune complexes).

Type-I (IgE mediated) sensitivity to Aspergillus fumigatus was first demonstrated by Miller. Alternaria, Curvularia, Bipolaris (Schubert & Goetz), Dreschslera, Exserohilum are the most common organisms associated with AFRS.

AFRS is now a more widely encountered type of FRS. Individuals belonging to the younger age groups on an average 23-42 years are more prone to AFRS. In the study conducted by Manning[37] & Holman, a male predominance was noted for AFRS. Warm

and humid climate favour the prevalence of AFRS. Cody et al[45] described that asthma and aspirin sensitivity are seen in one-third to half of AFRS patients.

Marple [70,14] has given a graphical representation of the event of AFRS.

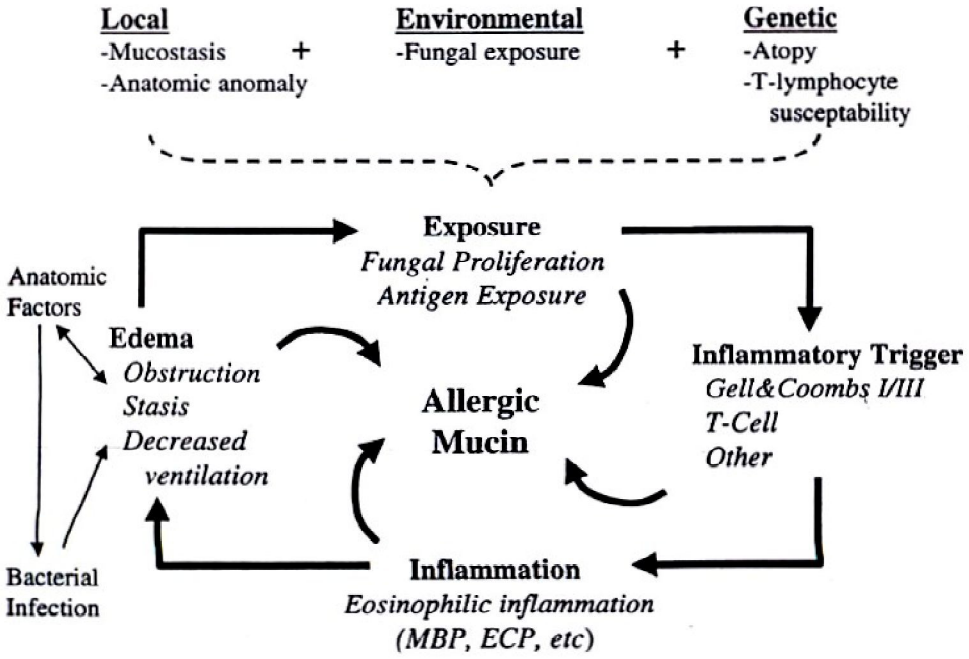


Fig.4

The pathophysiology of AFRS is initiated when inhaled fungi gets deposited in the sinuses triggering an immunologic reaction (type I along with possibly type III) takes place in an atopic individual. Mucosal edema caused by the immunologic reactions lead to stasis of secretions along with accumulation of inflammatory exudate leading onto obstruction of sinus ostia. This phenomenon may expand to adjacent sinuses producing expansion of the involved sinus.

Symptomatically AFRS is similar to other varieties of chronic rhinosinusitis with a history of nasal polyposis. Three quarter of AFRS patients give a typical history of

discharging dark rubbery nasal crusts containing tenacious allergic mucin containing fungal elements which appear as hyphal forms.

Bent & Kuhn[69,5] developed the following diagnostic criteria for AFRS:

- Major criteria:
  - Type – I hypersensitivity
  - Nasal polyposis
  - Characteristic CT scan findings
  - Positive fungal smear or culture
  - Allergic mucin with fungal elements with no evidence of tissue invasion

- Minor criteria:
  - Asthma
  - Unilateral disease
  - Radiographic evidence of bone erosion
  - Fungal culture positivity
  - Presence of Charcot - Leyden crystals
  - Serum eosinophilia

Marple[73,14] in his study excluded the necessity of having a positive fungal culture since a negative culture can be due to laboratory error and a positive culture may not always be accurate since it could be because of a saprophytic fungal growth.

The typical CT Scan finding noticed in AFRS is unilateral disease with hyper attenuated central areas within a sinus cavity. This CT finding corresponds to areas of hypointensity on T1 weighted MR images and signal void on T2 weighted MR images. The dura and periorbita are not breached[69].

AFRS usually produces tan to green, brown or black coloured mucus which is thick and tenaceous. Eosinophils, Charcot - Leyden crystals and fungal hyphae may be seen on H&E staining. However Charcot – Leyden crystals are well seen with Brown-Benn stain since they are made up of lysophospholipase. Fungal elements in allergic mucin are typically stained by GMS stain[69].

The work-up[69] for suspected AFRS should include:

- Total eosinophil count
- Total serum IgE and antigen-specific IgE antibody
- Mucin obtained intraoperatively is subjected to microscopic examination and fungal culture
- Antigen-specific IgG antibody
- Precipitating antibodies

The management of AFRS is exteriorization of sinuses followed by nasal irrigation along with administration of systemic steroids and topical steroids. Long term steroid usage in such cases can be avoided by resorting to antigen-specific immunotherapy along with

antifungal agents. Recurrence of the disease can also be avoided by the same modality of management.

Surgical management of AFRS:

McGuirt et al[7] in their study conducted in 1979 found that removal of the diseased sinus mucosa, allowing good aeration and hence maintaining satisfactory drainage is very crucial in the surgical outcome of AFRS. For AFRS, more conservative surgical approach is now preferred over traditionally radical procedures. In their paper published in 1998, Mabry et al[70,79] described this mode of surgery as conservative but complete.

Goals of surgical management of AFRS:

1. Removal of allergic mucin and fungal debris which usually has the highest antigenic load and hence reducing the same
2. Establish ventilation and permanent drainage to all involved sinuses
3. To establish a post-operative access to all involved sinuses for irrigation purpose

Post-operative care mainly involves nasal irrigation, endoscopic evaluation of post-operated sinonasal cavity and debridement of the operated cavity if necessary.

Endoscopic mucosal staging system in AFRS[71]:

A staging system was devised by the endoscopic follow-up based on mucosal response to medical management by Kupferberg et al[80].

Stage	Endoscopic findings
0	No mucosal edema or allergic mucin
I	Mucosal edema with or without allergic mucin
II	Polypoid edema with or without allergic mucin
III	Sinus polypi with fungal debris or allergic mucin

In the treatment protocol formulated by the Georgia nasal and sinus institute[26], AFRS patients undergo Endoscopic Sinus Surgery (ESS) followed by initiating oral prednisolone by second day of surgery at 0.4 mg/kg for 4 days, then is gradually tapered and continued till one month post-operatively. Dosage of prednisolone in the postoperative period is based on the maintenance of stage '0' according to the endoscopic mucosal staging system in AFRS. Oral prednisolone is tapered to a dose of 0.1 mg/kg if patient maintains in stage '0' for 4 consecutive months. This is followed by initiation of intranasal steroid spray which is continued for at least a year. If patient continues to be in stage '0' for an additional two months, oral prednisone can be stopped. After which regular follow-up is required upto 5 years with endoscopy and serum IgE levels.

Antifungal agents:

Kuhn[5] and colleagues in their study on the effectiveness of anti-fungal agents in AFRS revealed that Ketoconazole and Amphotericin-B were very beneficial drugs in preventing recurrence of the disease.

Immunotherapy:

Ferguson[64] reported that patients who received immunotherapy after initial control of disease with surgery responded well. For 12 index non-fungal pathogens and 11 common moulds allergic testing was done using intradermal titration methods and incorporated all positive reactors into treatment vial which were given on a weekly basis during the first year, on a biweekly basis in the second year and once in three weeks thereafter.

FUNGAL BALLS:

Fungal hyphae seen in a matted form is the major component of fungal balls seen in paranasal sinuses. In the spectrum of fungal sinusitis, this entity comes under the non-invasive category seen in immunocompetent individuals. The first case was reported in 1893 by Mackenzie. He described that this entity was more common among the individuals in older age groups with a female preponderance. According to the Mayo clinics[9] review, fungal balls had an incidence of 3.7% and AFRS had a higher incidence of 69%.

Pathogenesis:

Fungal spores which enter the nasal cavity further gain entry into sinuses and germinate leading to formation of fungal balls. Fungal ball in paranasal sinuses present with symptoms similar to chronic rhinosinusitis including nasal blockage, nasal discharge and facial pain, the usually involved sinuses being maxillary sinus and sphenoid sinus in that order.

Opacification of involved sinus which maybe total or subtotal may be seen on imaging studies. Calcification or dense hyphae may appear as radio-densities in central soft tissue in around 50% of cases.

Tangled hyphae with no evidence of tissue invasion is the typical histopathology in a case of fungal ball involving paranasal sinuses. In one-quarter to one-third of cases show positive fungal cultures. Most common organisms cultured are Aspergillus species, Alternaria and P.boydii.

Surgical removal is the gold standard modality of treatment for fungal ball involving paranasal sinuses. Endoscopic large middle meatal antrostomy is sufficient for adequate clearance of fungal balls from maxillary sinus, though Caldwell-Luc surgery offers best chances to avoid recurrence.

Only in immuno-compromised patients, fungal ball has a chance to become invasive FRS especially in cases of surgical trauma involving sphenoid sinus or lateral sphenoid body dehiscence.

CHRONIC INVASIVE FUNGAL RHINOSINUSITIS:

The classification of chronic invasive fungal rhinosinusitis into two entities namely granulomatous and non-granulomatous varieties was put forth by DeShazo et al[54]. Symptoms appear once there is erosion of bony margins occur, the most common bones involved being the orbit, the skull base and palatal bones. Due to bony involvement, the

symptoms appear after several months or years after onset of the disease. Symptoms include chronic headache and neurological symptoms like seizures, decreased mental status or focal neurological signs which are again due to erosion of the cribriform plate. In a study done in Sudan[3], it was found that among patients who presented with granulomatous invasive fungal sinusitis, proptosis was the most common presenting feature.

In cases of chronic invasive fungal rhinosinusitis, complications like cranial nerve deficits, cavernous sinus thrombosis, mycotic aneurysms and internal carotid artery rupture have been documented in rare instances.

Severe congestion of nasal mucosa with polypoidal changes is usually seen on intranasal examination. Soft tissue with or without ulceration and slough may be seen.

CT Scan of nose and paranasal sinuses show mucosal thickening, hyper-attenuated areas within the sinus cavity which maybe focal or diffuse, erosion of bony margins or expansion of the bony sinus cavity. Silverman and Mancuso in their study conducted on cases of chronic invasive fungal rhinosinusitis noted that infiltration of periantral fat planes around the maxillary sinus is one of the earliest evidence of invasive fungal disease. Neoplasms both benign or malignant and granulomatous lesions like syphilis and sarcoidosis are part of differential diagnosis. Ultimate distinction between invasive, non-invasive forms and neoplasia is best made on histology and is regarded as the best means to distinguish the two forms of FRS. Examples of fungal organisms associated with

invasive form of fungal rhinosinusitis are Aspergillus species, Alternaria, Bipolaris, Candida, Curvularia, Drechsclera, Mucor, Sporothrix schenckii and Psedoallescheria boydii.

Pathological examination shows typical periarterial inflammation without evidence of fungal elements or invasion of blood vessels. Veress described three types of invasive fungal rhinosinusitis, namely proliferative, exudative necrotizing and mixed forms.

The management includes both surgery and anti-fungal therapy including agents like amphotericin-B or itraconazole though the use of steroids is contraindicated.

SINONASAL MUCORMYCOSIS:

Amongst fungal infections affecting man, the most fatal is sinonasal mucormycosis. Diabetics are more prone to acquire mucormycosis and in such cases diabetes becomes difficult to treat since it triggers further growth of fungus. This infection can occur in an individual in any immunocompromised state or in a normal individual. Platauf in 1885 first reported the first case of mucormycosis involving the upper airway and coined the term ‘mycosis mucorina’. A case report of mucormycosis being successfully managed was first reported by Haris in 1955. The pathogenic species in this group are members of the family mucoraceae the most usual pathogen encountered being Rhizopus oryzae which contributes to 60% of all forms of mucormycosis reported and more significantly 90% of all cases of rhinocerebral mucormycosis.

The factors which make an individual susceptible to mucormycosis include type-2 diabetes mellitus, immunocompromised state during organ transplantation, haematological malignancies, immunodeficiency neutropenia, intravenous drug abusers and patients on long term steroids. This disease entity has a rapid progressive fulminant course when the host is severely immunocompromised.

It takes 72 hours for the symptoms to manifest even in the case of an acute fulminant sinonasal mucormycosis. The most common symptoms seen among patients are fever, ulceration or necrosis of sinonasal mucosa and sometimes even periorbital or facial swelling which may be associated with reduced vision showing early signs of orbital cellulitis. Numbness over the face may be seen as an early symptom in a small percentage of cases. Infiltration of perisinus fat planes and bony erosion as seen in cases of chronic fungal rhinosinusitis is seen in radiographic imaging studies.

Surgical modality of treatment without reversing the immunocompromised state of the individual is not beneficial. Systemic antifungal therapy and surgical debridement together form the pillars in management of this condition.

ACUTE FULMINANT INVASIVE FUNGAL RHINOSINUSITIS[80]:

Acute fulminant invasive fungal rhinosinusitis occurs due to tissue infiltration of sinonasal mucosa by the fungal organisms. The main objective of an otolaryngologist is to identify a case of invasive FRS at the earliest and to start treatment as soon as possible since this condition is fatal in 50-80% of cases, especially in those cases where it is

complicated by orbital and intracranial complications. Usually occurs in patients in whom the neutrophilic response is impaired and in susceptible individuals within 2-3 weeks post bone marrow transplantation. Absolute neutrophil count is usually less than 500 cells/ml.

Immunologic status of the individual and prominent vascular invasion on histology are the main prognostic factors. Acute fulminant invasive fungal rhinosinusitis usually begins with subtle symptoms. The commonest symptom is persisting fever of unknown origin (FUO) not responding to intravenous antibiotic therapy. Around 50% of patients have symptoms of facial and periorbital pain, nasal discharge, nasal blockage and headache. In the later stages, the manifestations include proptosis, ophthalmoplegia, loss of visual acuity, seizures, change in mental status and focal neurological signs.

Diagnostic nasal examination include nasal mucosa discolouration which is due to ischemia or necrosis. Anatomical structures in the order of involvement are the middle turbinate in 67% of cases, followed by nasal septum (24%), palate (19%) and inferior turbinate (10%). Diminished sensation of the nasal mucosa and bleeding is suggestive of tissue invasion by fungal organisms.

CT imaging helps in diagnosis, however the diagnosis is confirmed by histopathology examination. But before taking a biopsy, correction of thrombocytopenia (platelet count less than 60×10^9 /L) is mandatory.

Invasive fungal disease has histopathological diagnostic criteria which include:

1. Submucosa shows presence of fungal hyphae which may or may not be associated with angiocentric invasion.
2. Evidence of tissue necrosis with minimal host inflammatory response.

The primary modality of treatment like in the previously described conditions is a combination of antifungal agents along with aggressive surgical debridement. Adequate surgical debridement is ensured when clear bleeding margins are obtained. Studies have proved that debridement slows down the progression of disease by reducing the fungal load and hence improving the efficacy of antifungal agents administered. Surgical debridement also provides specimen for fungal culture and histopathology examination.

Prevention of Invasive Fungal rhinosinusitis:

Prevention of invasive FRS in high-risk groups can be accomplished by nursing such patients in rooms with laminar airflow and by using high efficiency particulate air (HEPA) filters. Use of amphotericin nasal spray in patients who have undergone bone marrow transplantation has reduced the incidence of invasive FRS. Secondary prophylaxis is recommended for patients with a past history of invasive fungal disease and intravenous Amphotericin-B is the drug of choice.

Algorithm for diagnosis and management of invasive fungal rhinosinusitis[75]:

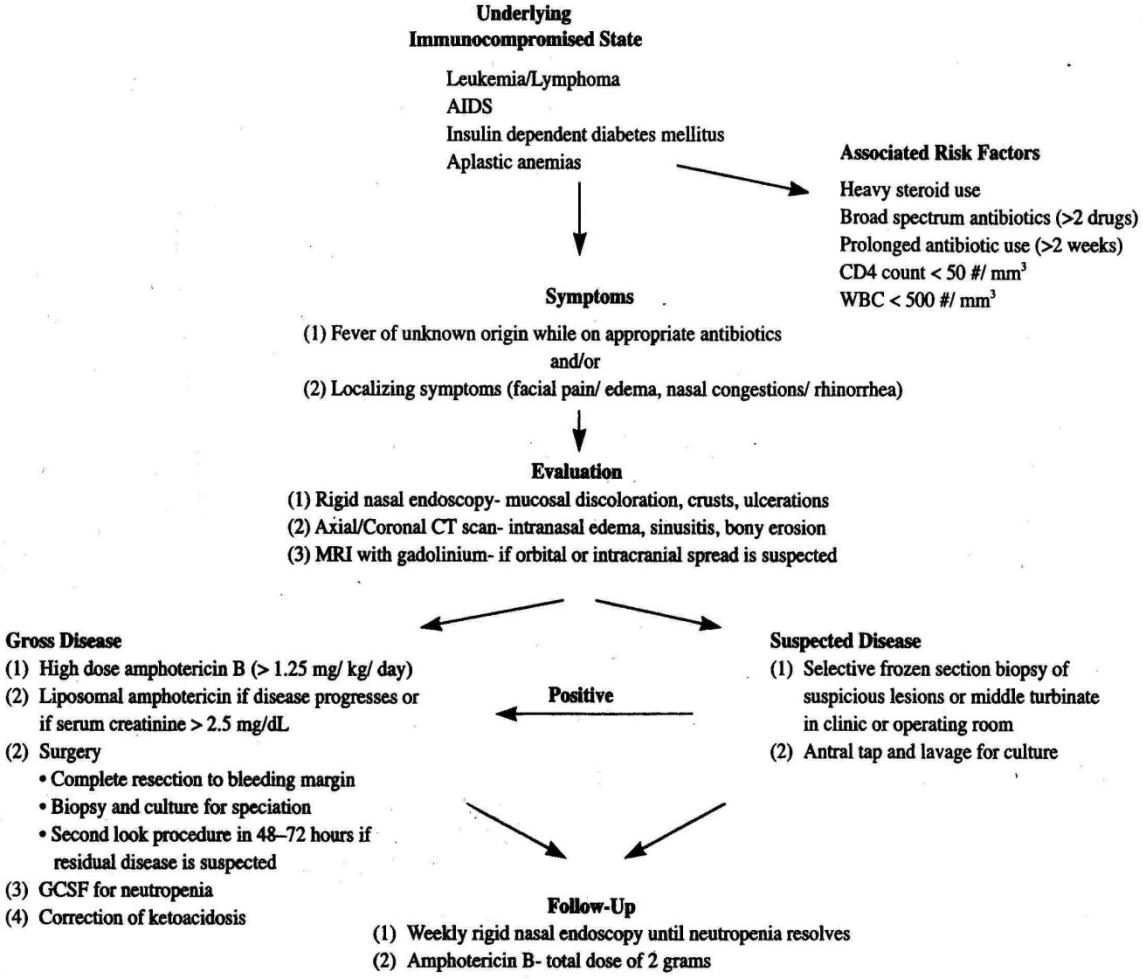


Figure. 5

RATIONALE FOR STUDY

Our institution, PSG Institute of Medical Sciences & Research at Coimbatore serves as a referral centre for the three southern states of India namely Tamil Nadu, Kerala and Andhra Pradesh which have an agricultural economy. The warm moist climate with its attendant high rate of allergic, hypertrophic, vasomotor and infectious rhinosinusitis provides one of the pre-requisites for fungal sinonasal infections due to the altered physiology of upper airway. The presentation of patients with chronic fungal rhinosinsusitis can be varied causing dilemma in managing such a disease entity.

Reviewing the available literature we realized that all the landmark studies on fungal rhinosinusitis were done in Europe and American continents. The living conditions of the general population, the lifestyle of people, methods of farming and vegetation in these countries are very different from that of India. The lack of recognition of this disease entity and the scarcity of reports prompted us to undertake this study.

AIMS OF THE STUDY

1. To study the incidence of fungal sinusitis in diagnosed cases of chronic rhinosinusitis
2. To study the clinical, radiological & microscopic features of fungal rhinosinusitis
3. To study the aetiological basis of fungal rhinosinusitis
4. To evaluate the various treatment modalities available

MATERIALS AND METHODS

This is a prospective study in which evaluation of 100 patients with chronic rhinosinusitis who underwent treatment on an Out-Patient or In-Patient basis in department of E.N.T, PSG Institute of Medical Sciences & Research, Coimbatore, Tamil Nadu from July 2011 to July 2013 were considered.

History of every patient was taken in detail and importance was given to their presenting symptoms, both local and general. Any significant past history including type-2 diabetes mellitus, leukemia and tuberculosis was also elicited. History of organ transplant, nasal surgeries and treatment history for the present symptoms like antihistamines, steroids, antibiotics or history of administration of chemotherapeutic agents were also given importance.

All the patients were taken up for the study based on the clinical presentation namely nasal discharge, nasal obstruction, headache, facial pain, swelling over the face and sneezing and haziness of sinuses noted radiologically who did not respond satisfactorily to conventional antibiotic therapy.

Inclusion Criteria for cases considered in the study:

1. Age-group > 14 years
2. Both genders
3. Established diagnostic criteria for chronic rhinosinusitis

Exclusion Criteria for cases:

1. Age-group < 14 years
2. Patients unwilling to comply with the study
3. Systemic diseases preventing participation in the study
4. Patients diagnosed with underlying paranasal sinus malignancies

All patients underwent diagnostic nasal endoscopy to rule out any changes of the osteomeatal complex, and to obtain specimen for fungal culture and pathology examination. A nasal swab from the middle meatus was taken for fungal culture. CT scan of the nose and paranasal sinuses was done for all patients who could afford a scan.

Evaluation:

All 100 patients were worked up based on a proforma. The diagnosis was confirmed by fungal culture and histopathology examination of the excised specimen. The data collected from the patients was analysed by Pearson Chi- Square and Fisher's Exact tests. Patients underwent either endoscopic sinus surgery or medical line of management or a combination of both.

Follow-up:

All the patients were followed up in the outpatient department of E.N.T, PSG Institute of Medical Sciences & Research. During follow-up, all patients were assessed clinically for improvement in symptoms following treatment. All the patients were analysed for their

improvement in symptoms namely nasal obstruction, nasal discharge, swelling over the face, headache, cold and sneezing.

On follow-up also, repeat diagnostic nasal endoscopy was done, to evaluate the presence of nasal discharge, mass or any other pathology in the nose. The follow-up period usually ranges from two months to two years.

LABORATORY TECHNIQUES FOR SPECIMENS:

Specimen collection and transport for microscopic examination:

The material obtained during diagnostic nasal endoscopy or surgery is subjected for potassium hydroxide (KOH) preparation, Gram staining and microscopic examination with hematoxylin and eosin staining for eosinophils. Microscopy also reveals Charcot-Leyden crystals which is a characteristic feature of AFRS. Lactophenol Cotton Blue (LPCB) stain was used to identify the fungal species. Solid tissue specimens were fixed with 10% buffered formalin and embedded in paraffin in order to obtain tissue sections 5-6 micrometers in thickness. Hematoxylin and eosin staining of the sections were done for routine histologic evaluation. Representative sections were also stained with Gomori Methenamine Silver stain (GMS), Periodic Acid-Schiff stain (PAS) and Fontana – Masson stain which are special stains for fungal organisms.

For fungal culture the specimens obtained were transported in saline or moistened gauze and cultured on mould-inhibitory agar and Sabouraud's dextrose agar at 30°C. The

fungal moulds grew in 2 weeks and were brown and black in colour with a pigmented surface. Microslide culture technique was then used to identify the fungus.

Laboratory Techniques for Nasal Swab:

Two nasal swabs were taken from the middle meatus of the discharging nasal cavities in a sterile test tube. Nasal swabs in all cases were collected before administering any local medication.

One of the swabs was cultured on 2% blood agar aerobically and anaerobically at 37°C and examined for growth at the end of 24 hours and 48 hours. Morphology, colony and cultural characteristics and standard biochemical reactions were the basis of identification of the organisms (Cruickshank, 1965). Standard disc technique as recommended by W.H.O (1961) was used to test the antibiotic sensitivity of these strains that were obtained from the nasal swab cultures.

The other swab was used for the purpose of mycological examination. Direct demonstration of fungal elements was demonstrated in a potassium hydroxide preparation. Irrespective of the results of KOH preparation, the second nasal swab was cultured on Sabouraud's dextrose agar plates. Caution was taken at every step of inoculation to avoid aerial contamination. After inoculation, the culture tubes were incubated at 37°C for 10 days. Examination was done on a daily basis to assess the pattern of fungal growth at the site of inoculation. To suppress bacterial growth it was not necessary to add antibiotic to this medium since the medium had a low pH which was

sufficient to inhibit superadded growth of bacterial pathogens. Usually fungal growth was obtained after 3-5 days of incubation. As a routine practice, the culture tubes were retained for a period of four weeks before discarding them as negative.

Some of the most commonly seen species were identified by the typical microscopic features like Aspergillus species were identified by the presence of typical conidiophores, Mucor by the presence of right-angled aseptate hyphae and Candida species which appear as budding yeasts and occasionally with pseudohyphae.

RESULTS

In this study, analysis of 100 patients with chronic rhinosinusitis was done in the Department of E.N.T, PSG Institute of Medical Sciences & Research from July 2011 to July 2013 to determine the incidence of fungal sinusitis. Detailed evaluation of each case was done comprising of the history, clinical examination, investigations, histopathology and microbiology examination. Medical or surgical treatment or a combination of both and follow-up were done for all cases.

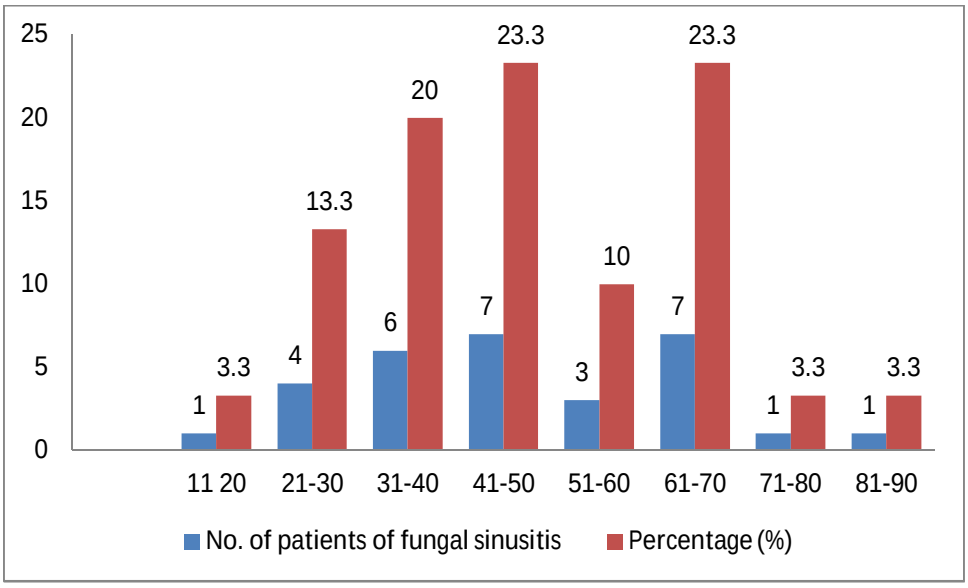
The clinical data was collected by means of a proforma and the observations made were analyzed with the Master Chart as shown in the Annexure.

The results have been evaluated primarily keeping in mind the aims of the study, namely to determine the incidence of fungal sinusitis, to study the clinical, radiological and microscopic features, to study the aetiological basis, to identify the type of fungus prevalent in these fungal infections and to evaluate the results of various treatment modalities.

In our study of 100 cases of chronic rhinosinusitis, 30% of cases turned out to have a fungal aetiology.

Age distribution of fungal rhinosinusitis cases:

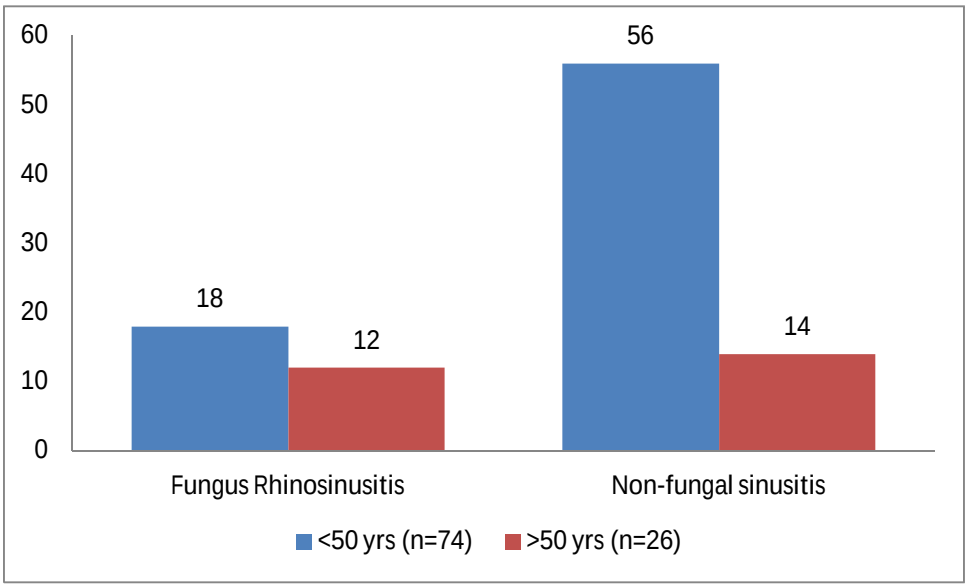
Age (years)	No. of fungal sinusitis patients	Percentage (%)
11-20	1	3.3
21-30	4	13.3
31-40	6	20
41-50	7	23.3
51-60	3	10
61-70	7	23.3
71-80	1	3.3
81-90	1	3.3
Total	30	100



From the table above it is evident that the maximum incidence of fungal rhinosinusitis (23.3%) was in the age group of 41-50 and 61-70 years followed by 20% in 31-40 years age groups. Majority of the patients i,e…76.6% were in the age group of 31-70 years.

Overall Age distribution in our study:

Age-wise distribution	Fungus Rhinosinusitis	Non-fungal sinusitis	p value
<50 yrs (n=74)	18	56	.037
>50 yrs (n=26)	12	14	



Age-group more than 50 years has got comparatively more number of fungal rhinosinusitis cases and the value is statistically significant ($p<0.05$).

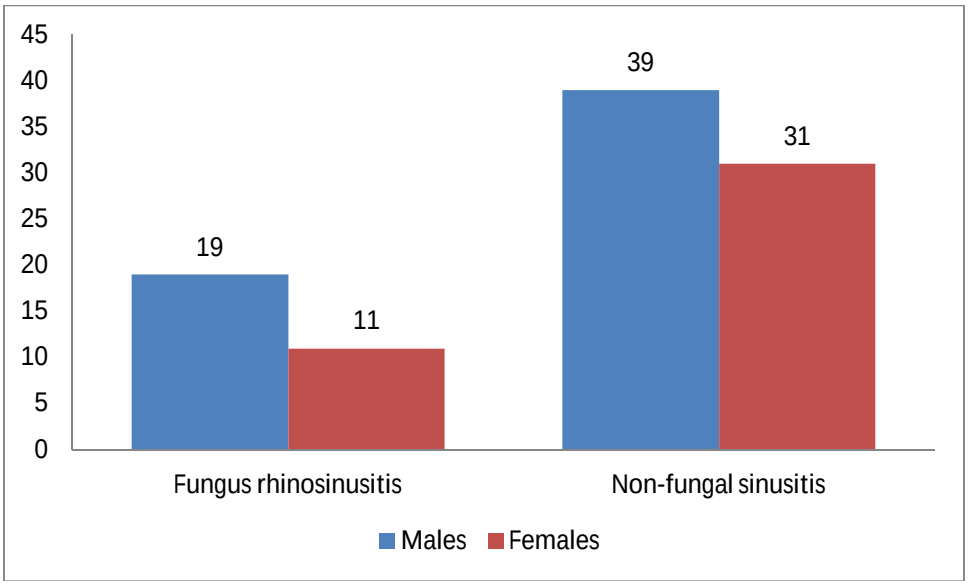
Sex distribution of fungal rhinosinusitis cases:

Sex	No. of cases	Percentage (%)
Male	19	63.3
Female	11	36.6
Total	30	100

In our study, the incidence of fungal rhinosinusitis amongst males was 63.3% (19 males) and 36.6% in females (11 females).

Overall Sex distribution in our study:

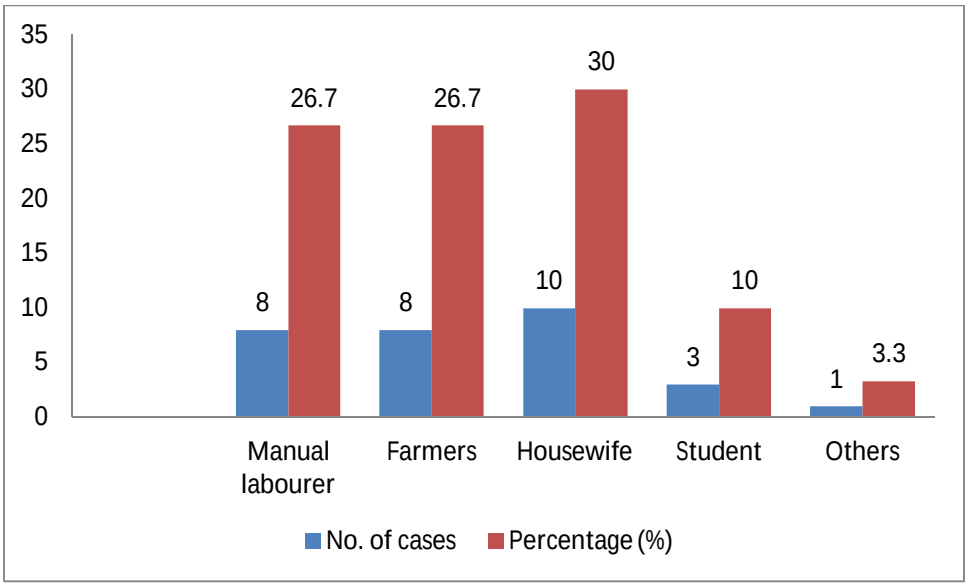
Sex	Fungus rhinosinusitis	Non-fungal sinusitis	p value
Males (n=58)	19	39	.479
Females (n=42)	11	31	



Hence sex of individual is not a statistically significant parameter (p>0.05) in our study.

Occupation distribution of fungal rhinosinusitis cases:

Occupation	No. of cases	Percentage(%)
Manual labourer	8	26.7
Farmers	8	26.7
Housewife	10	30
Student	3	10
Others	1	3.3
Total	30	100

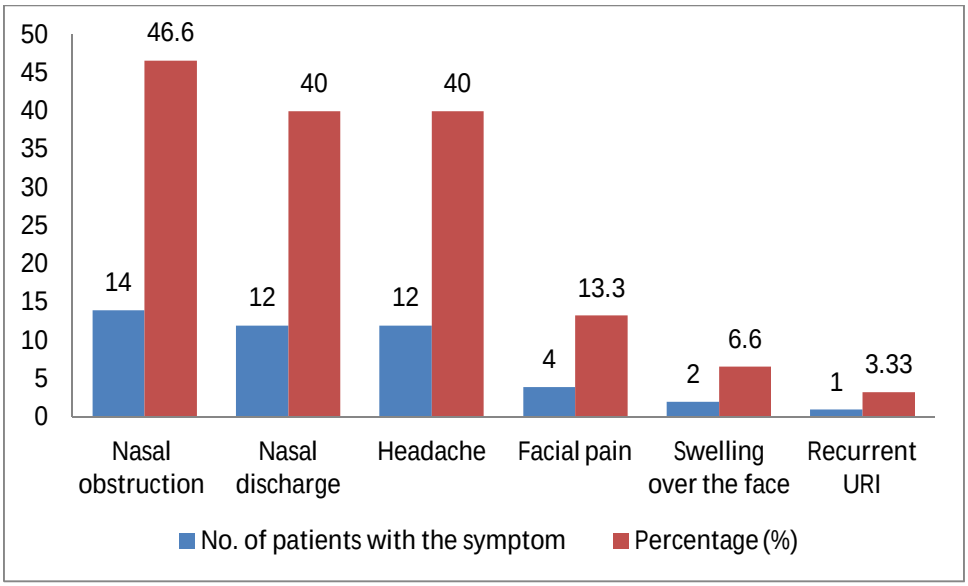


From the above table we conclude that in our study, maximum number of cases of fungal rhinosinusitis were amongst housewives (30%), followed by manual labourers (26.7%) and farmers (26.7%).

Clinical features of fungal rhinosinusitis:

Symptoms	Pre operative incidence	Percentage (%)
Nasal obstruction	14	46.6
Nasal discharge	12	40
Headache	12	40
Facial pain	4	13.3
Swelling over the face	4	13.3
Recurrent URI	1	3.33

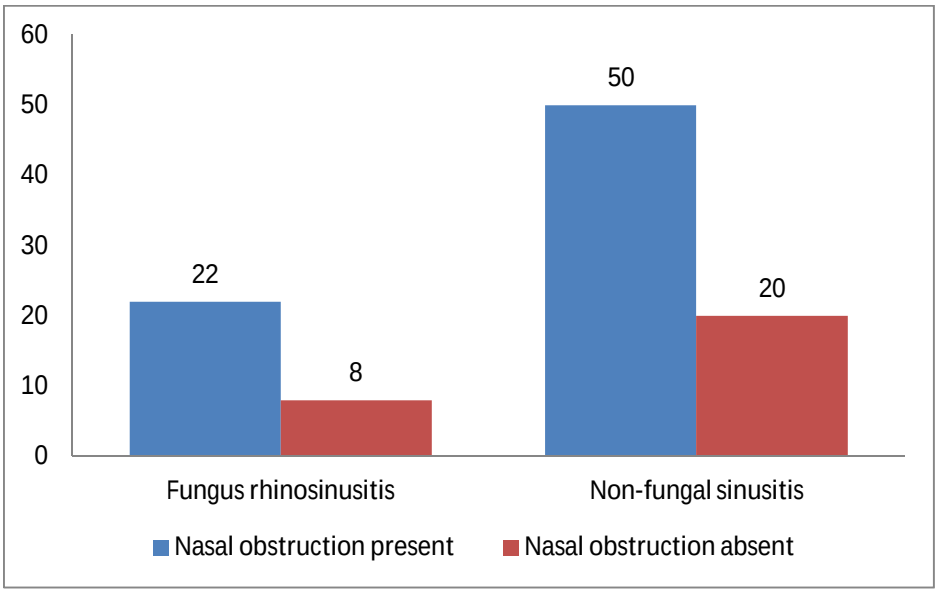
In our study, the incidence of most common symptoms at the time of presentation was nasal obstruction (46.6%), nasal discharge (40%) and headache (40%) respectively. The other symptoms included facial pain (13.3%), swelling over the face (6.6%) and recurrent respiratory tract infections (3.3%).



Overall distribution of symptoms in our study population:

Nasal Obstruction:

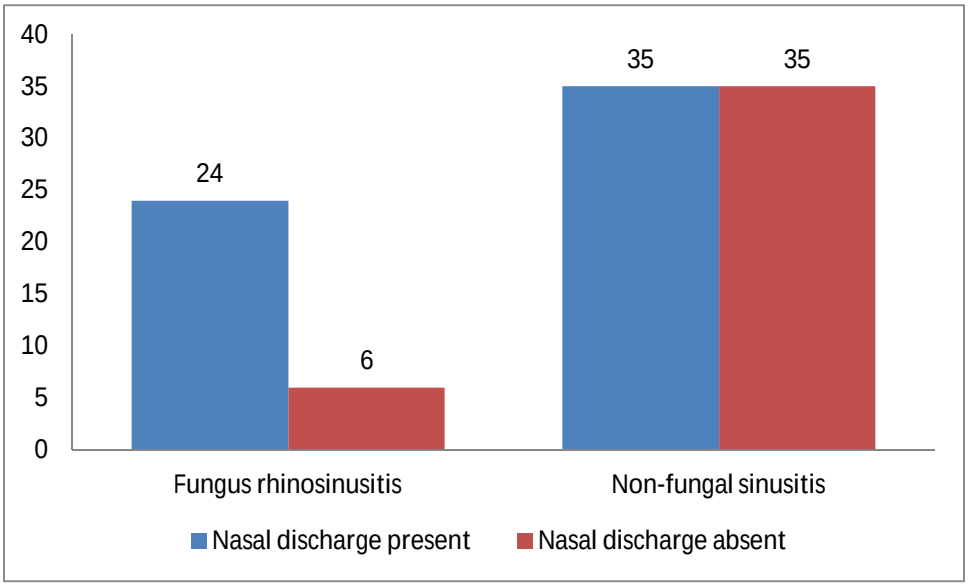
Nasal obstruction	Fungus rhinosinusitis	Non-fungal sinusitis	p value
Present (n=72)	22	50	.846
Absent (n=28)	8	20	



Hence nasal obstruction as a symptom of fungal rhinosinusitis is not statistically significant (p>0.05) in our study.

Nasal discharge:

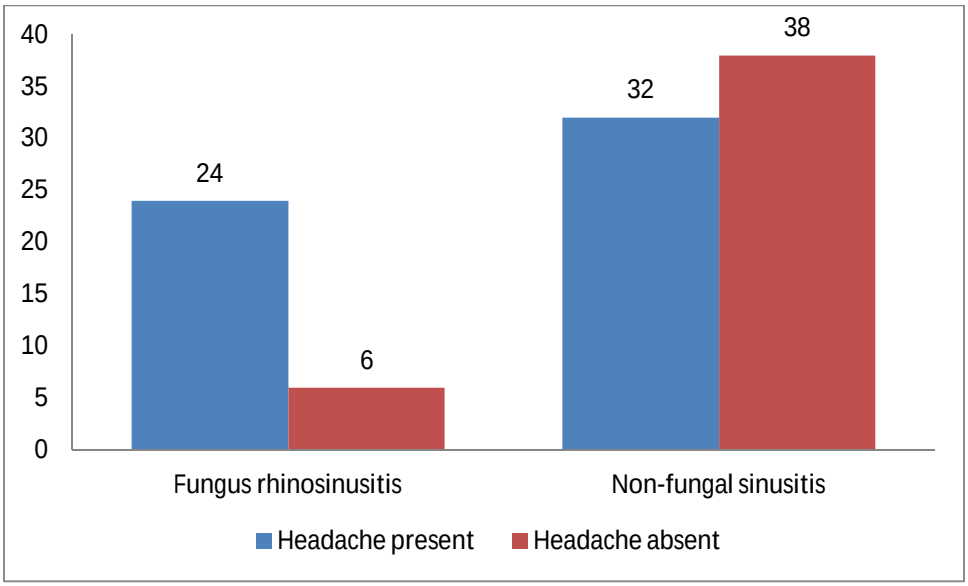
Nasal discharge	Fungus rhinosinusitis	Non-fungal sinusitis	p value
Present (n=59)	24	35	.005
Absent (n=41)	6	35	



Hence nasal discharge as a symptom of fungal rhinosinusitis is statistically significant (p<0.05).

Headache:

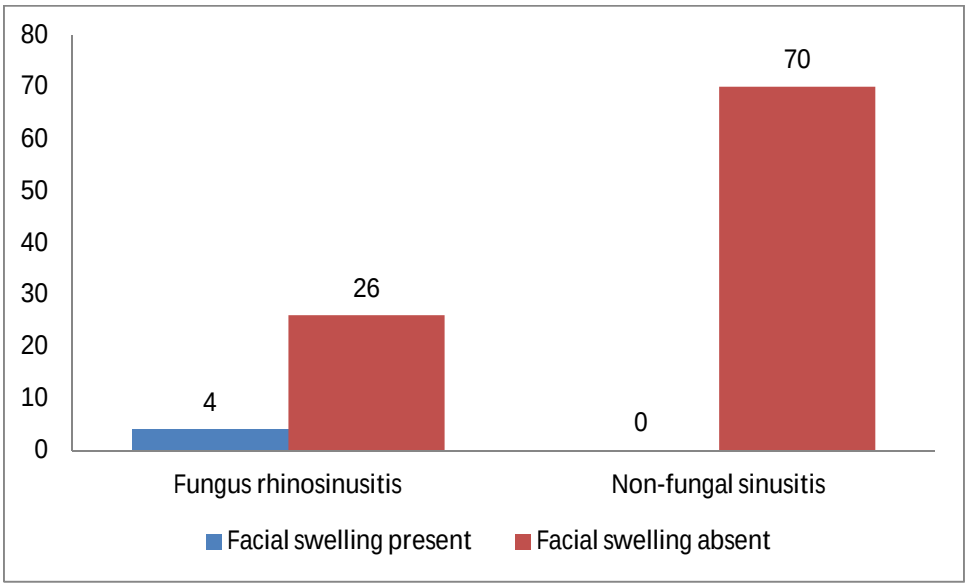
Headache	Fungus rhinosinusitis	Non-fungal sinusitis	p value
Present (n=56)	24	32	.002
Absent (n=44)	6	38	



Hence headache as a symptom of fungal rhinosinusitis is statistically significant ($p<0.05$).

Facial swelling:

Facial swelling	Fungus rhinosinusitis	Non-fungal sinusitis	p value
Present (n=4)	4	0	.003
Absent (n=96)	26	70	



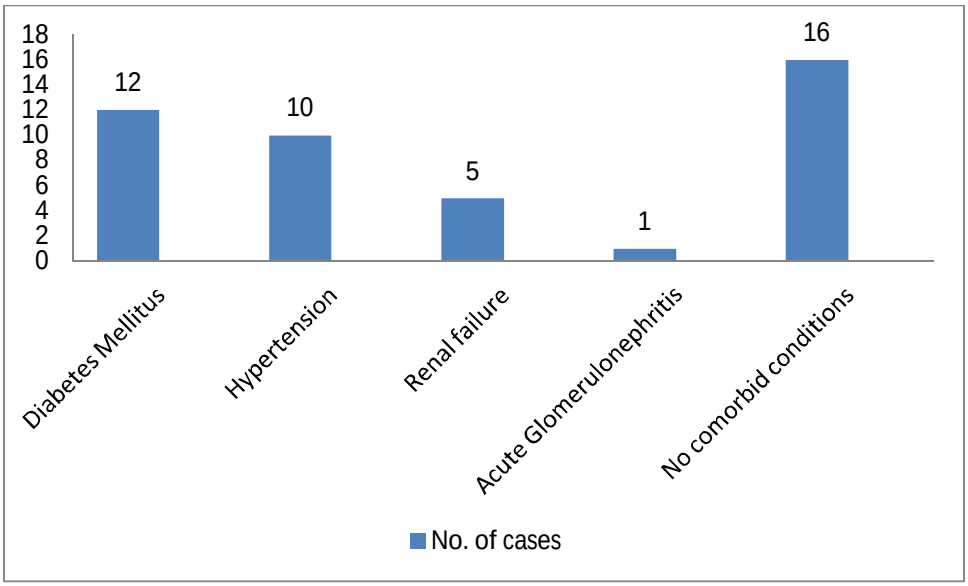
Hence facial swelling as a symptom of fungal rhinosinusitis is statistically significant ($p<0.05$).

Systemic diseases associated with fungal rhinosinusitis in relation to the number of cases studied:

Medical illness	No. of cases
Diabetes Mellitus	12
Hypertension	10
Renal failure	5
Acute Glomerulonephritis	1
No other illness	16

From our study, we could conclude that there were no systemic diseases associated with 16 cases of fungal rhinosinusistis which constitutes to 53.3% of the total number of fungal rhinosinusitis cases. Diabetes mellitus was seen associated with as many as 12 patients (40%). 10 patients (33.3%) were hypertensive. 5 patients (16.6%) were suffering from chronic renal failure and 1 patient (3.3%) was suffering from acute glomerulonephritis.

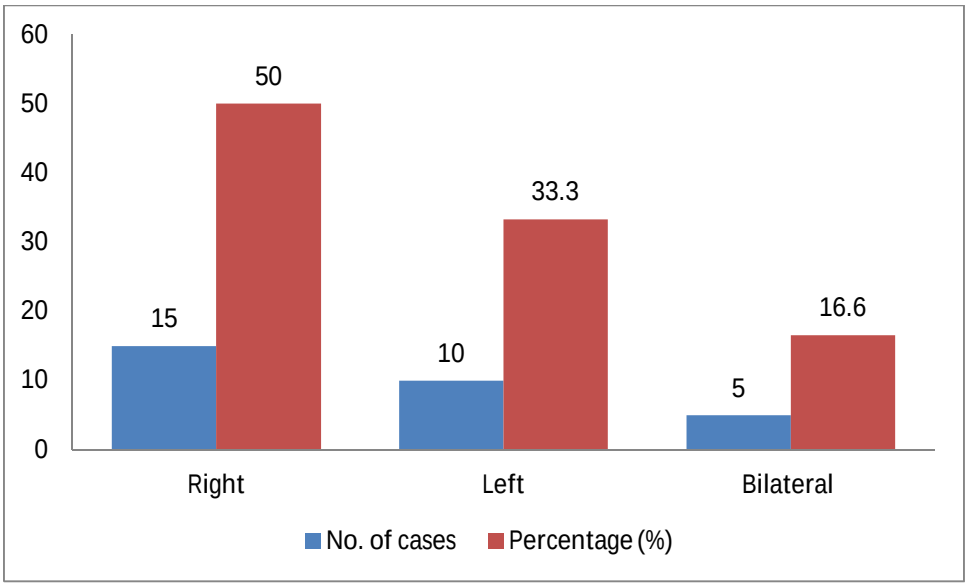
The results of our study can be compared with the study done by **Emmons** et al in 1963 who stated that Aspergillus infection of maxillary sinus can be found not just among debilitated individuals, but also among people in general good health and among nutritionally deprived persons.



Radiological findings in fungal rhinosinusitis cases:

Side affected	No. of cases	Percentage (%)
Right	15	50
Left	10	33.3
Bilateral	5	16.6
Total	30	100

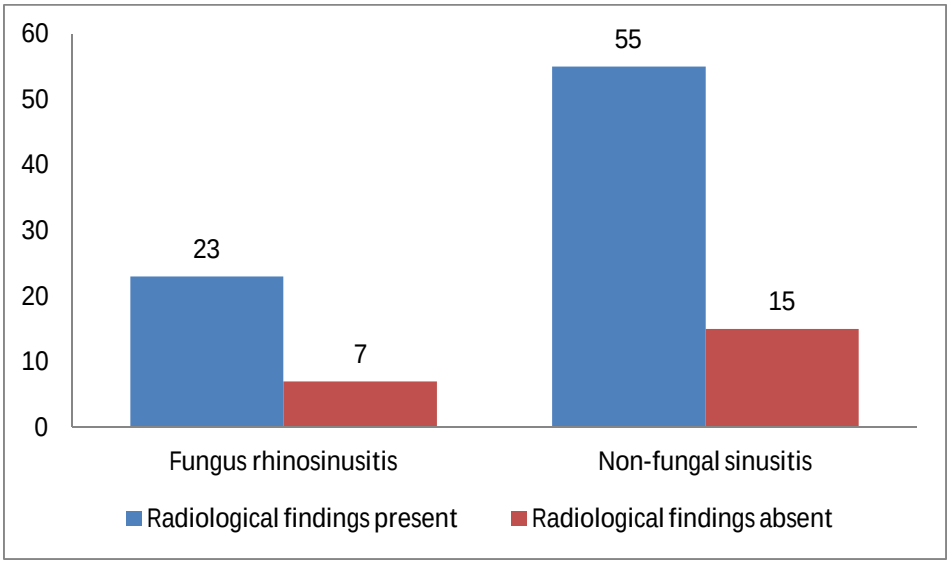
In this study, the right side paranasal sinuses are more affected (50%) when compared to the left side sinuses (33.3%) according to the radiological findings. Unilateral involvement of sinuses is seen in 25 cases (83.3%) of the cases and only 5 cases (16.6%) have bilateral involvement.



Overall comparison of radiological findings in our study:

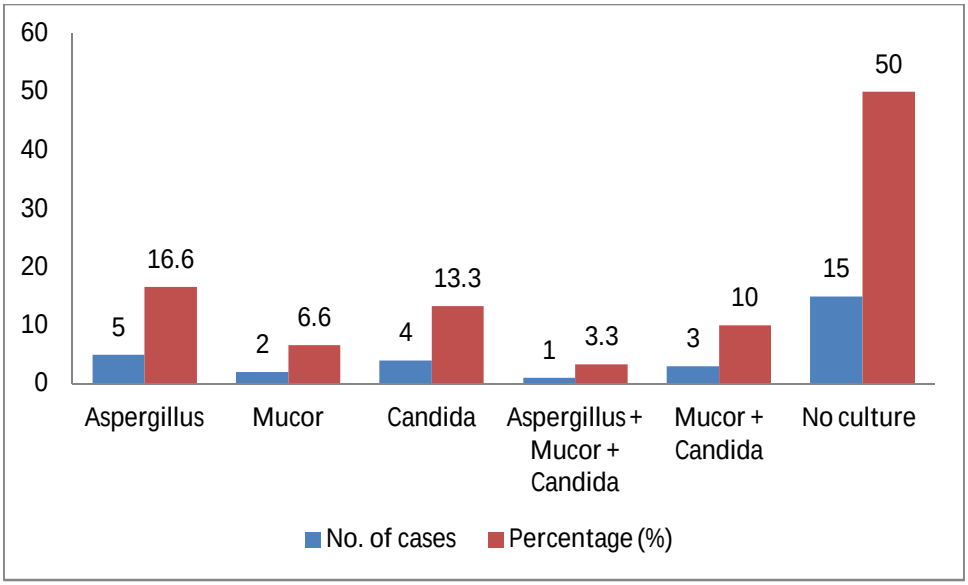
Radiological findings	Fungus rhinosinusitis	Non-fungal sinusitis	p value
Present (n=78)	23	55	.833
Absent (n=22)	7	15	

Hence the presence of radiological findings suggestive of fungal rhinosinusitis is not statistically significant (p>0.05) in our study.



Various fungi isolated during fungal culture from fungal rhinosinusitis cases:

Fungus	No. of cases	Percentage (%)
Aspergillus	05	16.6
Mucor	02	6.6
Candida	04	13.3
Aspergillus + Mucor + Candida	01	3.3
Mucor + Candida	03	10
No culture	15	50
Total	30	100

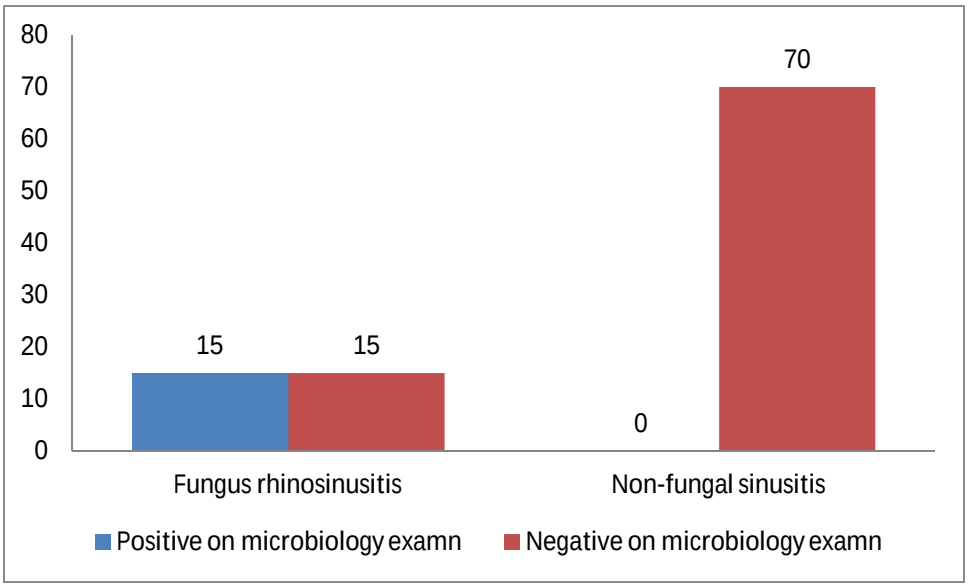


Aspergillus (in 5 cases, 16.6%) was the most common fungus isolated by microbiology examination followed by Candida (in 4 cases, 13.3%) and Mucor (in 2 cases, 6.6%). Cultures showing mixed growth of Aspergillus, Mucor and Candida were obtained in 3.3% of cases while a mixed growth of Mucor and Candida was obtained in 10% of cases. Negative culture was obtained in 15 cases (50%).

Microbiological examination of the study population:

Microbiology examination	Fungus rhinosinusitis	Non-fungal sinusitis	p value
Positive (n=15)	15	0	.000
Negative (n=85)	15	70	

Hence the correlation between microbiology examination in diagnosis of fungal sinusitis is statistically significant ($p<0.05$).



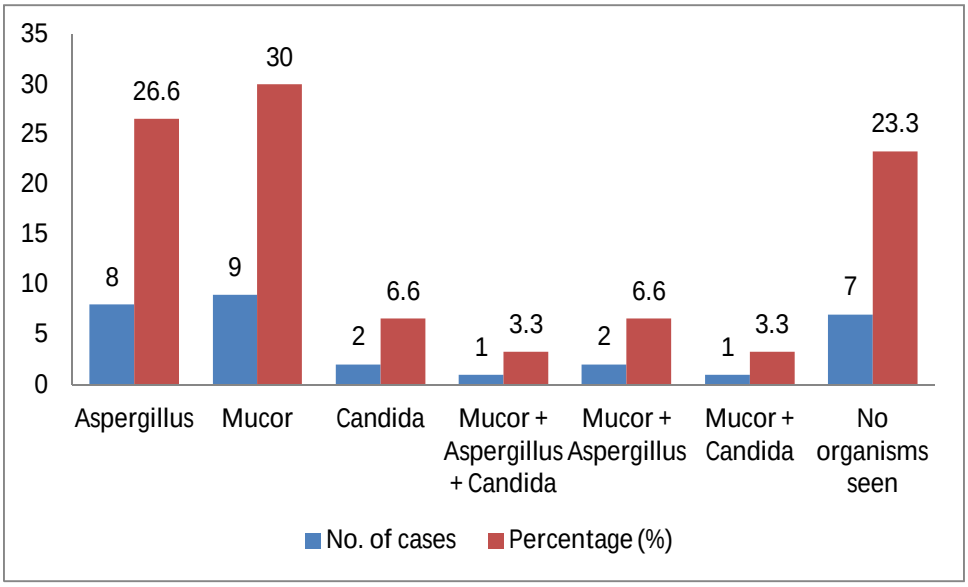
Microbiology vs Fungal Positivity Crosstabulation

			POSITIVITY		Total
			1	2	
MICRO	1	Count	15	0	15
		% within MICRO	100.0%	0.0%	100.0%
	2	Count	15	70	85
		% within MICRO	17.6%	82.4%	100.0%
Total		Count	30	70	100
		% within MICRO	30.0%	70.0%	100.0%

The sensitivity of microbiological examination in diagnosing fungal rhinosinusitis is 50%, but specificity is 100%.

Histopathology in fungal rhinosinusitis cases:

Fungus	No. of cases	Percentage (%)
Aspergillus	08	26.6
Mucor	09	30
Candida	02	6.6
Mucor + Aspergillus + Candida	01	3.3
Mucor + Aspergillus	02	6.6
Mucor + Candida	01	3.3
No organisms seen	07	23.3
Total	30	100

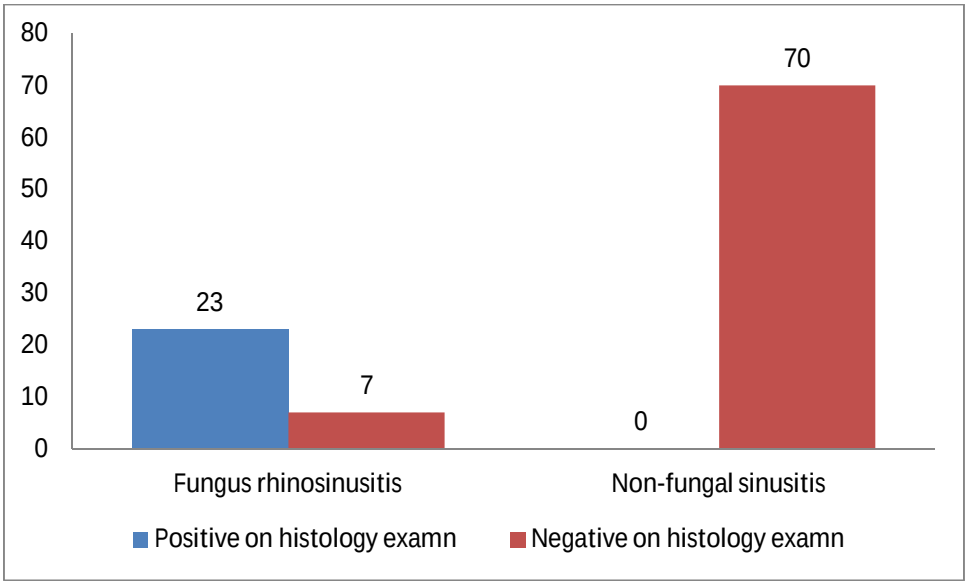


Histopathological examination of specimen from 23 cases showed the presence of fungal organisms with Mucor (9 cases, 30%) being the most commonly identified fungus on histology, followed by Aspergillus (8 cases, 26.6%) and Candida (2 cases, 6.6%). A

mixed growth comprising of Mucor, Aspergillus and Candida was seen in 1 case (3.3%). Whereas a mixed growth of Mucor and Aspergillus was seen in 2 cases (6.6%). A mixed growth of Mucor and Candida was seen in 1 case (3.3%). No mixed growth of Aspergillus and candida was noted in our study. No fungal organisms could be identified in 7 cases (23.3%).

Pathological examination of the study population:

Histopathology examination	Fungus rhinosinusitis	Non-fungal sinusitis	p value
Positive (n=23)	23	0	.000
Negative (n=77)	7	70	



The correlation between pathological examination in diagnosis of fungal sinusitis is statistically significant ($p<0.05$).

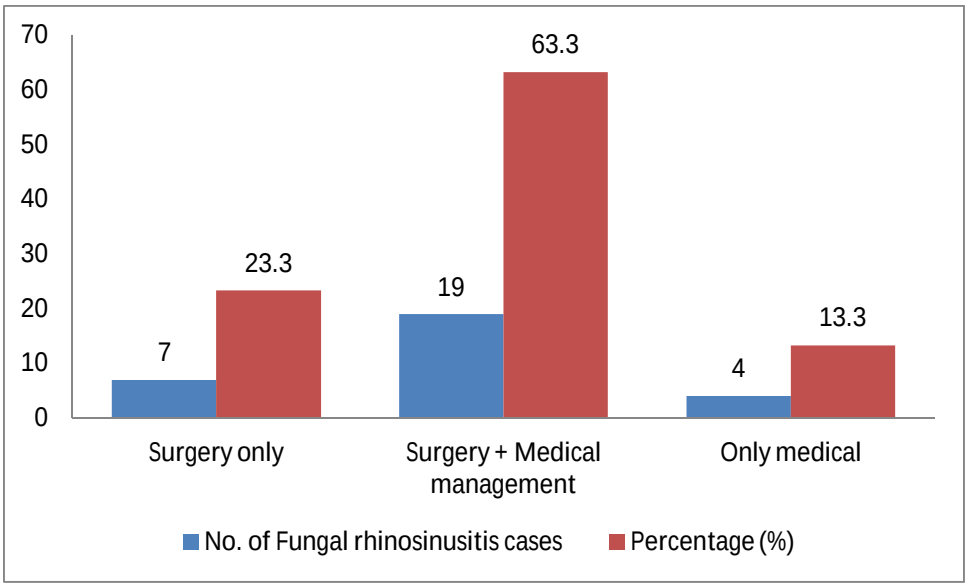
Pathology vs Fungal Positivity Crosstabulation

			POSITIVITY		Total
			1	2	
HISTO	1	Count	23	0	23
		% within HISTO	100.0%	0.0%	100.0%
	2	Count	7	70	77
		% within HISTO	9.1%	90.9%	100.0%
Total		Count	30	70	100
		% within HISTO	30.0%	70.0%	100.0%

The sensitivity of pathological examination in diagnosing fungal rhinosinusitis is 76.67%.

Modality of treatment for fungal rhinosinusitis:

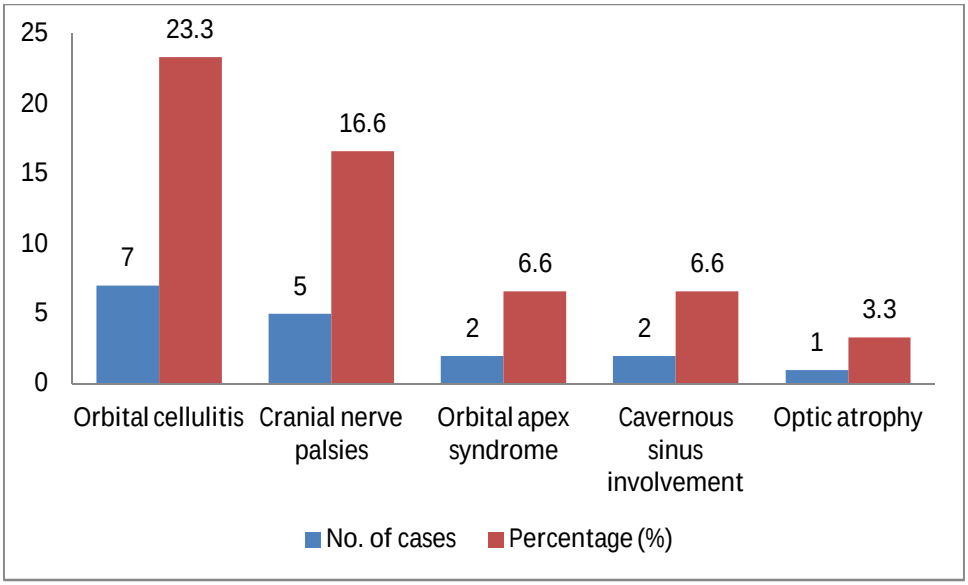
Treatment modality	No. of cases
Only Surgical	7
Surgery + Medical	19
Only Medical	4



Most of the cases (63.3%) were managed by a combination of surgical debridement followed by anti-fungal therapy. Whereas 23.3% of cases were managed by surgery alone and only 13.3% of cases were managed by anti-fungal therapy alone.

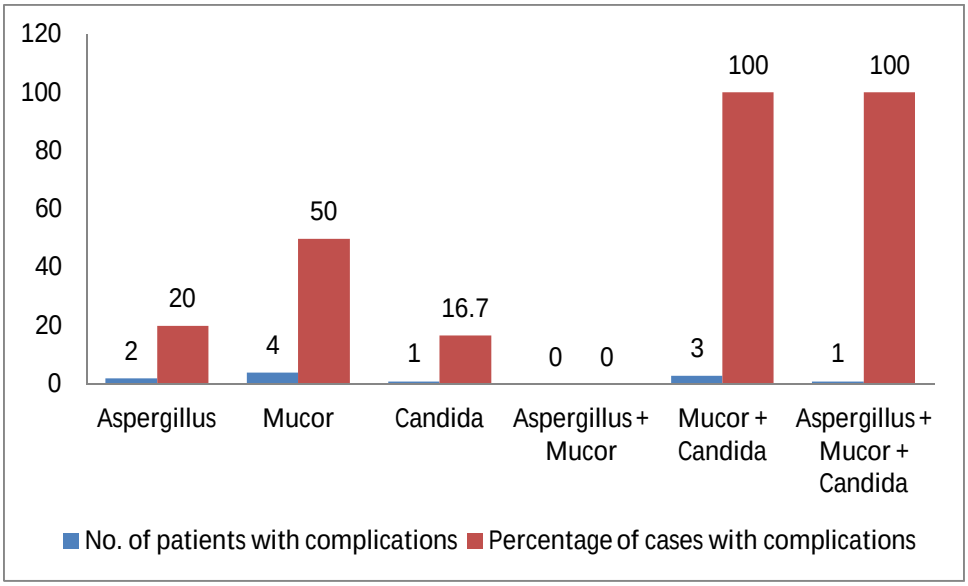
Complications of fungal rhinosinusistis:

Complications	No. of cases	Percentage (%)
Orbital cellulitis	07	23.3
Cranial nerve palsies	05	16.6
Orbital apex syndrome	02	6.6
Cavernous sinus involvement	02	6.6
Optic atrophy	01	3.3



In our study, orbital cellulitis was the most common complication of fungal rhinosinusitis (23.3%), followed by cranial nerve palsies (16.6%), orbital apex syndrome and cavernous sinus involvement contributing 6.6% each.

Association of complications and fungal species:



Fungal sinusitis vs Complications Crosstabulation

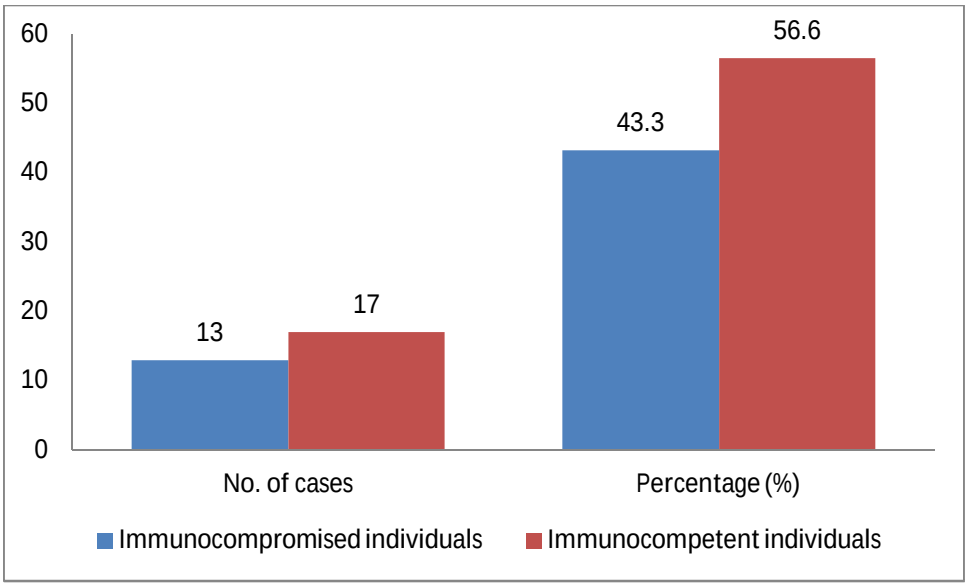
			COMPLICATION		Total
			1	2	
Fungal Sinusitis	1.00	Count	2	8	10
		% within Fungal Sinusitis	20.0%	80.0%	100.0%
	2.00	Count	4	4	8
		% within Fungal Sinusitis	50.0%	50.0%	100.0%
	3.00	Count	1	5	6
		% within Fungal Sinusitis	16.7%	83.3%	100.0%
	4.00	Count	0	2	2
		% within Fungal Sinusitis	0.0%	100.0%	100.0%
	5.00	Count	3	0	3
		% within Fungal Sinusitis	100.0%	0.0%	100.0%
	6.00	Count	1	0	1
		% within Fungal Sinusitis	100.0%	0.0%	100.0%
Total		Count	11	19	30
		% within Fungal Sinusitis	36.7%	63.3%	100.0%

1- Aspergillus
2- Mucor
3- Candida
4- Aspergillus + Mucor
5- Mucor + Candida
6- Aspergillus + Mucor + Candida

Hence complications in fungal rhinosinusitis were more associated with Mucor species.

Immunity status of fungal rhinosinusitis patients:

Immunity status	No. of cases	Percentage (%)
Immunocompromised individuals	13	43.3
Immunocompetent individuals	17	56.6
Total	30	100

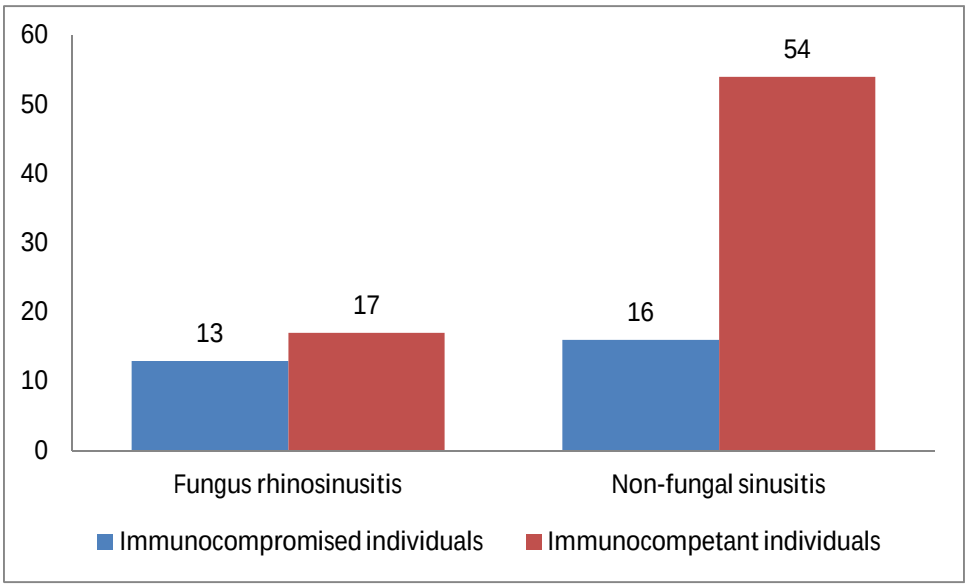


Of the total 30 cases of fungal rhinosinusitis worked up in our study, only 13 cases (43.3%) were immunocompromised, rest 17 cases (56.6%) were immunocompetent

individuals. Amongst the 13 immnocompromised cases, 11 cases were sinonasal mucormycosis (i,e...84.6% of immunocompromised cases). Amongst the immunocompetent cases, 4 cases were immunocompetent mucormycosis.

Overall immunity levels of the study population:

Immunity level of individuals	Fungus rhinosinusitis	Non-fungal sinusitis	p value
Immunocompromised (n=29)	13	16	.039
Immunocompetent (n=71)	17	54	



Hence immunity level of patients has got a statistical significance ($p<0.05$) to the prevalence of fungal rhinosinusitis.

Overall results among fungal rhinosinusitis patients:

Amongst the 30 cases of fungal rhinosinusitis, there were 5 cases (10%) of fungal ball and 2 cases (6.6%) of chronic indolent fungal sinusitis that are still on regular follow-up.

There were 4 cases (13.3%) of fungal rhinosinusitis which showed angioinvasion and tissue invasion on histopathology, the aetiology being Mucor and Aspergillus species.

In our study, there were 12 cases (40%) of invasive fungal sinusitis amongst which 4 cases (33.3% of invasive fungal rhinosinusitis) were invasive mucormycosis.

One case of invasive mucormycosis also had associated ileal mucormycosis for which he had undergone surgery.

One patient in our study who was on Itraconazole (following weaning of Amphotericin therapy) developed skin rashes which were proven to be itraconazole-induced and resolved after discontinuing the drug.

Follow up:

All the patients were followed up to the best possible extent. However 3 patients were lost to follow up. There were 3 patients who succumbed to the disease. All of them were cases of invasive mucormycosis who developed renal failure and succumbed to cardio-pulmonary arrest during the course of treatment with Amphotericin-B.

DISCUSSION

Allergic rhinitis, fungal ball, chronic indolent rhinosinusitis and invasive rhinosinusitis belong to the spectrum of sinonasal disorders caused by fungal organisms in human beings.

The predisposing factors for sinonasal fungal diseases are:

- Immune status of the host and underlying co-morbid conditions
- Environmental factors
- Local anatomical variations in nose and paranasal sinuses
- Virulence of fungi

Some parameters which lead to a high index of suspicion of sinonasal diseases are:

- Young adults
- Past history of poor response to medical management
- History of multiple surgical interventions in the past
- Recurrent sinonasal polyposis
- History of bronchial asthma and atopy
- Involvement of multiple sinuses
- Inspissated, viscid mucus in the sinonasal cavities

Sinonasal fungal disease may present in different forms as a fungus ball, slowly invasive sinonasal disease or in immunocompromised patients, as an acute fulminant infection with invasion of underlying tissues and vascular channels. Aspergillus species seem to be responsible for the more benign extramucosal sinonasal disease while the fulminant entity is usually due to Mucor species.

Usual presentation of FRS is similar to chronic rhinosinusitis which poorly responds to antibiotic therapy. There may also be a history of multiple surgeries in the past for his complaints. However in most cases, a fungal aetiology is only suspected during surgery based on intraoperative findings or sometimes only after pathological or microbiological evaluation.

Review of literature and our experience gained during the course of study indicate confusion in the presentation of patients with chronic fungal rhinosinsusitis and hence causing dilemma while managing such a disease entity. On the contrary, the management of acute fungal rhinosinusitis in immunocompromised individuals and paranasal mucormycosis is more clearly defined inspite of a poor prognosis. Some of the main reasons for the lack of understanding of this disease entity have been the infrequency in the incidence of this entity and the lack of long term follow-up of these patients in understanding the natural history of illness. However advances in imaging modality including computerized tomography and magnetic resonance imaging have contributed a great deal in better understanding of the spectrum of sinonasal diseases and even contributes to distinguishing one clinical entity from another. Still very little is known

about the pathogenesis of fungal rhinosinusistis. However at the end of our study we realize that logical treatment plans can be derived from our existing knowledge about the disease though there exists some lacunae in our understanding of the disease per se. The management protocol also depends on the exact identification of the fungal species and susceptibility of the organisms to antifungal agents.

Age:

Waxman et al[17] in 1987 described allergic fungal rhinosinusitis as mostly affecting individuals in younger age groups. **Milosev and Mahgoub**[3] in 1967 found that Aspergillus rhinosinusitis occurs more frequently in males in their teens and twenties. **Hartwick** and **Batsakis**[35] in 1991 reported 32 cases of AFRS caused by Aspergillus in the ages of 8-56 years. In 1982, **Bassiouny** et al[10] 1982 identified six different species of fungus from different cases and the individuals were all between 24-44 years.

In contrast to the results of the studies done by **Waxman** et al[17] and **Milosev** and **Mahgoub**[3], in our study majority of the patients (76.6%) were in the age group of 31-70 years. On further investigating the cause for a higher incidence in 3^{rd} – 7^{th} decade of life, we realized that type-2 diabetes mellitus could have played a major role in determining immunity status of such individuals. Out of 18 patients in this age group, 9 were diabetic individuals (maturity-onset diabetics) with relatively poor glycemic control. There was no past history of diabetes mellitus in any patient below the age of 30 years in our study.

From our study we conclude that there were proportionately more fungal rhinosinusitis cases among those who are in the age group more than 50 years when compared with those in the age group less than 50 yrs and this value is statistically significant ($p<0.05$).

In 1984, Hazarika et al[12] in his case series noted that incidence of fungal sinusitis was common in older age groups.

The younger generation taking to industrialization and the older members of the family becoming entitled to perform agricultural work is probably the reason for higher incidence of fungal rhinosinusitis in the older age group in our case series.

Sex:

In our study there were eleven females (36.6%) and nineteen males (63.3%). A higher incidence of fungal rhinosinusitis was noted among females in the study done by McGuirt and Harill[7] in 1976. In 1991, Hartwick and Batsakis[35] published a case study of 32 cases of allergic fungal rhinosinusitis (Aspergillus) with female predominance. In Mayo Clinic, Cody et al[45] conducted a study on 100 patients, in which 53% of patients were males showing a slight male predominance. In yet another study conducted by Manning et al[37] the reported incidence of allergic fungal rhinosinusitis had a female dominance.

From our study, we conclude that sex of an individual is not a statistically significant ($p>0.05$) parameter in considering the susceptibility to fungal rhinosinusitis.

Occupation:

A case series published from Sudan by Milosev and Mahagoub[3] in 1969 showed a higher incidence of fungal rhinosinusitis among farmers. In their case series seven patients were farmers. In yet another study done by Henderson[2] in 1968, five patients were associated with agriculture with a history suggestive of exposure to Aspergillus spores.

In our study, considering the cases of fungal rhinosinusitis, we found the number of farmland workers and manual labourers was eight each (26.7% each), whereas the number of housewives was 10 (30%) which was marginally higher. Thus from our study, we found that occupation has no significant role in contributing to the incidence of fungal rhinosinusitis. However we noted that patients from a low socio-economic status and those suffering from malnutrition and anaemia have a higher chance of acquiring the disease.

Symptoms and signs:

The anatomy of paranasal sinuses and adjacent structures contribute significantly to the symptoms with which the patients present. In our study, the major symptoms included nasal obstruction, nasal discharge, headache, facial pain, swelling over the face and frequent attacks of upper respiratory tract infections.

According to the study conducted by Prabhakar et al[39] in 1992, postnasal discharge and headache were the most common symptoms invariably noted in 100% of cases whereas

nasal obstruction as a symptom was noted only in 71% of cases, fullness over the cheek was the symptomatology in 57% of cases and sneezing in 43% of the patients.

Whereas in another study conducted by Axelsson et al[6] in 1978, reported pain over the cheek in 50%, cacosmia in 50%, epistaxis in 25% and nasal discharge in 5% of cases.

Morgan et al[13] noted nasal obstruction as the predominant symptom in 100% of cases, facial pain or headache in 50% and nasal discharge in 50% of individuals in his case series comprising of six cases done in 1984.

In another research paper which was quoted earlier as well, McGuirt and Harill[7] (1979) who published a case series of four cases described headache as the major symptom in three patients i,e…75% of the study population, nasal discharge as a symptom in two patients and postnasal discharge in two cases contributing 50% each.

In our study, the most common symptom encountered was nasal obstruction seen in 22 patients with fungal rhinosinusitis i,e…73.3% of the fungal rhinosinusitis cases included in our study. Our results are comparable with those of the study done by Prabhakar et al[39], which was yet another study undertaken in our country. However in our case series nasal obstruction as a symptom of fungal rhinosinusitis is not statistically significant ($p>0.05$).

The second most frequent symptom in our case series considering all cases of fungal rhinosinusitis was nasal discharge i.e., twenty four patients (80%). Our results are comparable to the previous studies done by Morgan et al[13] in 1984, Axelsson et al[6] in 1978 and McGuirt and Harill[7] in 1979. In all the above mentioned studies, nasal discharge was seen in 50% of the study population.

In our case series, the association of nasal discharge as a symptom in cases of fungal rhinosinusitis is statistically significant ($p<0.05$).

Headache was also an equally prevalent symptom as nasal discharge seen in as many as 24 patients of fungal rhinosinusitis i,e…80% of fungal rhinosinusitis cases. Our results are comparable to the observation made by Morgan et al[13] in his study in which 50% of the individuals presented with complaints of headache.

In our study, there is significant correlation between headache as a symptom and incidence of fungal rhinosinusitis. Prevalence of headache as a symptom of fungal rhinosinusitis is statistically significant ($p <0.05$).

In our study facial swelling was noted in four cases of fungal rhinosinusitis i,e…13.3% of cases. In all cases, the aetiology was found to be Mucor species. Our result was comparable to the results of the study done by Hazarika et al[12] in 1984 where he reported three cases of mucormycosis, with cheek swelling being a feature of all the cases. Other studies don't make a mention of facial swelling as a presenting symptom. Hence in any

chronic rhinosinusitis patient presenting with facial swelling, it is therefore important to consider the possibility of sinonasal mucormycosis.

Facial swelling as a symptom of fungal rhinosinusitis is statistically significant ($p<0.05$) in our study. But however, facial pain and recurrent upper respiratory tract infections as symptoms of fungal rhinosinusitis were not statistically significant ($p>0.05$).

Diagnostic nasal endoscopic findings:

Considering the diagnostic nasal endoscopic findings in our study there were thirteen patients who had nasal polyps (43.3%) at the time of presentation. Nine patients had purulent nasal discharge (30%) and four had black eschar (13.3%) formation when they presented to us.

From our review of literature, we realized there are no established criteria for diagnosing fungal rhinosinusitis based on diagnostic nasal endoscopy findings. Hence we hope the observations made during our study will help in formulating criteria for diagnosis of FRS by diagnostic nasal endoscopy.

Radiology:

Considering the radiology findings in our study, in majority of the cases of fungal rhinosinusistis the maxillary sinus was most commonly involved in as many as 14 cases (46.6%), followed by involvement of ethmoids in 12 cases i,e…in 40% of cases and

involvement of the sphenoid sinuses was noted in 36.6% cases. Frontal sinus was involved in only 2 cases (6.6%).

The results of our study are comparable to the case series of 22 patients of fungal rhinosinusitis published by Zinreich et al[23] in 1988 in which correlation with CT imaging revealed hyper-attenuation of sinuses suggestive of sinusitis. There was involvement of the maxillary sinus in 14 patients (63.6%), sphenoid sinus involvement in 10 patients (45.4%), ethmoid sinus involvement in seven patients (31.8%) and the frontal sinus was involved in three patients (13.6%).

In the study by Blitzer et al[8] (1980) in which nine cases of fungal sinusitis were evaluated, radiographs of eight patients (88.8%) revealed haziness of unilateral maxillary and ethmoid sinuses while haziness of frontal sinus (22.2%) and sphenoid sinus (11.1%) was noted only in two patients and one patient respectively.

Another study conducted by Morgan et al[13] in 1984 reported the radiological findings of X-ray paranasal sinuses of six cases of fungal sinusitis which showed haziness of unilateral maxillary sinus in five cases (83.3%) and of ethmoid sinus in two cases (22.2%).

The study previously quoted by McGuirt and Harill[7] assessed X-ray findings of four cases of fungal sinusitis which revealed involvement of unilateral maxillary sinus in three cases (75%) and involvement of sphenoid sinus in one case (25%).

From our review of literature it appears that the maxillary sinus appears to be the most commonly involved sinus in fungal rhinosinusitis. Like the above mentioned studies, in our case series too, we find that maxillary sinus is the most commonly involved sinus. This is probably because the maxillary sinus ostium is located lowest in the middle meatus as compared to other sinuses providing easy access to organisms. However the overall percentage of maxillary sinus involvement in our study is comparatively lower than the studies quoted.

We have observed in our case series that when there is an opacification of unilateral paranasal sinus, a high index of suspicion of fungal aetiology needs to be considered. This is probably because of the nasal septum acting as a barrier to the spread of infections to the contralateral side. However other conditions like chronic bacterial sinusitis, tumours involving paranasal sinuses, infections like tuberculosis and other granulomatous conditions like Wegeners granulomatosis need to be excluded before coming to a diagnosis of fungal rhinosinusitis.

A plain radiograph of paranasal sinuses may reveal a double density appearance of maxillary antrum due to deposition of calcium salts like calcium phosphate and calcium sulphate which is pathognomonic of fungal sinusitis. This was first described by Stammberger et al[77] in 1984.

Glan et al in 1984, according the results of his case series stated the importance of Computed Tomography scan images in diagnosis of sinonasal aspergillosis. In our study CT scan imaging of nose and paranasal sinuses was done for all patients to assess the patency of the ostiomeatal complex, except for those patients who could not afford the cost of the imaging modality. In some cases, the suspicion of fungal sinusitis was considered intraoperatively based on the on-table findings.

These are the results and interpretation when we analysed the radiological findings of all cases included in our study. We found that there were twenty three cases (76.7%) of fungal rhinosinusitis with positive radiology findings.

In our study we observe that positive radiological findings suggestive of fungal rhinosinusitis is not statistically significant ($p>0.05$).

Microbiology and Pathology:

In our study, the aetiological agent responsible for the infection was identified by fungal culture or pathology examination or a combination of both. Mucor was the most commonly reported fungus in as many as 15 cases (50%) followed by Aspergillus in 13 patients (43.3%) and Candida species in 9 cases (30%). This is contrary to the studies done earlier in this part of our country which revealed Aspergillus species to be the commonest cause of fungal rhinosinusitis.

Axellson and Carlsoo[6] in 1978 in his study confirmed the diagnosis by microscopic examination of specimen and from fungal culture.

Three cases of rhinocerebral mucormycosis were diagnosed in diabetic individuals in the case series reported by Hazarika et al[12] in 1984.

Another study done in our country was by Chakrabarti et al[40] (1992) in North India had results which were comparable to our study. He isolated fungi in as many as 50 out of 119 clinically suspected cases over a two-year period. The most common species isolated in his study was Aspergillus. Aspergillus flavus was isolated in as many as 40 cases.

From our study we observe that the correlation of microbiology examination in the diagnosis of FRS is statistically significant ($p<0.05$) and the sensitivity of microbiological examination in diagnosing fungal rhinosinusitis is 50%.

Similarly in our study the correlation between pathological examination and fungal positivity is statistically significant ($p<0.05$). The sensitivity of histopathological examination in diagnosing fungal rhinosinusitis is 76.67% whereas the specificity is 100%. Hence, comparing the overall sensitivity, we conclude that in our study pathological examination is a more sensitive investigation than microbiological examination.

In our study, we were able to diagnose the fungal organisms by means of histological examination in 23 out of the 30 cases diagnosed (76.6%). Whereas fungal culture was able to diagnose fungal organisms only in 15 cases (50%). Histological features of angioinvasion and tissue invasion were recorded in 4 out of 30 cases (13.3%).

On reviewing literature and comparing our study to the other mentioned studies, we realized that the most common fungal organisms identified in our study i,e…Mucor followed by Aspergillus is not in adherence with the results of the other studies, since in most of them the common species identified was Aspergillus species. Mucormycosis is an opportunistic infection and the presence of a high number of immunocompromised individuals in our study i,e…13 cases (43.3%) would have probably influenced the outcome of our study.

According to **McNulty and Blitzer**[10], stress factors favour propagation of a mucormycotic infection. In individual with ketoacidosis, the fungus derives much of its metabolic requirements from a ketone-reductase enzyme system thus it hereby explain our results. Aspergillus is abundantly found in the soil, decaying food, fruit, grain and plants.

On classifying the fungal sinusitis, it was found that there were three cases of fungal ball, two cases of chronic indolent fungal sinusitis and twelve cases (40%) of invasive fungal sinusitis among which four cases were invasive mucormycosis.

Immunity status of patients:

Of the 17 immunocompetant cases (56.6%), four cases were mucormycosis. Immunocompetant mucormycosis is a rare clinical condition and our review of literature revealed very few case series reporting this disease entity. In our study, the prevalence of fungal rhinosinusitis was more in immunocompetent than in immunocompromised individuals.

Complications of rhinosinusitis:

In our study, we noticed that as single agents, Aspergillus caused complications in 20% of patients, Mucor caused complications in as high as 50% and Candida caused complications only in 16.7% of cases. Whereas considering mixed infections, a combined infection of Mucor and Candida species and a combination of Aspergillus, Mucor and Candida had complications in 100% cases.

Treatment:

Georgia Nasal and Sinus institute formulated the treatment strategy for AFRS which comprised of FESS, tapering doses of oral steroids like prednisolone and intranasal steroid sprays.

Ferguson et al[64] obtained satisfactory results by combining immunotherapy after surgery. Immunotherapy decreases the necessity for corticosteroid therapy in preventing recurrences of the disease.

For the treatment of chronic invasive fungal sinusitis, Stringer and Ryan[67] suggested a combined modality approach including surgery and anti-fungal chemotherapy for 6 weeks. Use of steroids is strictly contraindicated.

Ferguson[64] proposed that fungal balls should be managed surgically, either endoscopic or Caldwell-Luc approach. Also stated that mainstay of treatment of mucormycosis includes reversal of immunocompromised state of the affected individual, systemic amphotericin-B and surgical debridement.

Twenty-six out of our thirty cases of fungal rhinosinusitis underwent debridement by functional endoscopic sinus surgery, to ensure drainage and ventilation of paranasal sinuses. Twelve patients were started on antifungal agent intravenous Amphotericin-B for a period of six weeks at 0.7mg/kg/day. Monitoring of renal parameters and serum electrolytes was done during administration of intravenous Amphotericin-B. Intravenous Amphotericin-B was gradually tapered and patients were started on Itraconazole for six weeks. Four patients did not undergo surgery due to financial constraints and were lost to further follow up.

Combined modality treatment offered a better treatment outcome as compared to those who were treated either medically or surgically.

There were two cases of invasive mucormycosis with intracranial extension. One case was associated with ileal mucormycosis. Three patients who had invasive mucormycosis later succumbed to cardiopulmonary arrest.

LIMITATIONS OF THE STUDY

1. Nasal obstruction as a symptom of fungal rhinosinusitis is not statistically significant according to our study. However this could have been probably because nasal obstruction was present in 71.4% of non-fungal sinusitis patients, hence influencing the outcome of our study.

2. Contrary to other studies, Mucor was the commonest aetiological agent in our study. This is probably because mucormycosis is an opportunistic infection and we had a large number of immunocompromised individuals in our study who were more susceptible to this infection.

3. The reason for a lower sensitivity of microbiological examination in diagnosis of fungal rhinosinusitis could have been due to inadequate sampling.

4. In few cases, fungal aetiology was suspected only during surgery based on intraoperative findings and at times, only after pathological or microbiology evaluation, so a complete pre-operative work-up for fungal rhinosinusitis including diagnostic nasal endoscopy could not be done in such cases.

CONCLUSIONS

1. The prevalence of fungal rhinosinusitis in our study is 30%
2. The prevalence of fungal rhinosinusitis was higher in the elderly age group.
3. Nasal discharge, nasal obstruction and headache were the most common symptoms of fungal rhinosinusitis found in more than 40% of cases of fungal rhinosinusitis.
4. Maxillary sinus was most commonly involved sinus in cases of fungal rhinosinusitis and unilateral involvement of paranansal sinuses was more in favour of fungal aetiology.
5. Mucor was the most common cause of fungal rhinosinusitis followed by Aspergillus species.
6. According to our study, pathological examination has a higher sensitivity (76.67%) as compared to microbiology examination (50%) in diagnosis of fungal rhinosinusitis.
7. In our study 40% of fungal rhinosinusitis were invasive fungal sinusitis. Amongst them 33.3% were invasive mucormycosis.
8. In our study the prevalence of fungal rhinosinusitis was more among immunocompetent than immunocompromised individuals. Amongst the immnocompromised cases, 84.6% cases were sinonasal mucormycosis.
9. There were four cases of immunocompetent mucormycosis which is a rare clinical entity since there are very few case reports in world literature.
10. Amongst the fungal species, complications were highest in cases of mucormycosis.
11. Functional endoscopic sinus surgery is an effective first line of management in fungal sinusitis. Antifungal chemotherapy combined with surgery offered better treatment outcome as compared to surgery or chemotherapy as a single modality of treatment.

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CLINICAL PHOTOGRAPHS

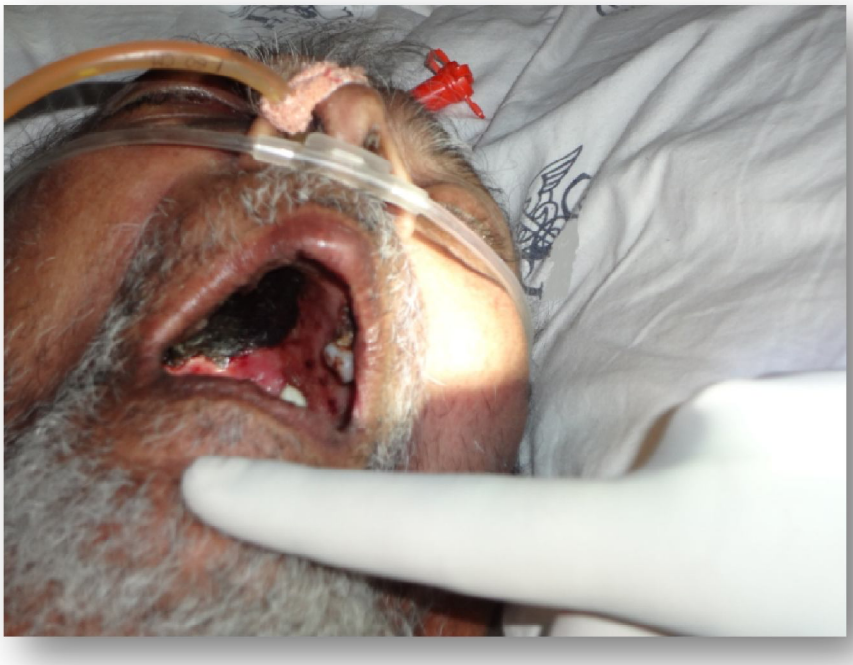
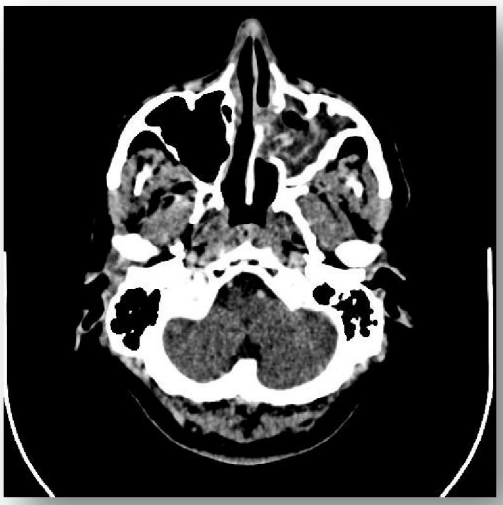


Figure 1: Eschar noted on the hard palate in a case of invasive sinonasal Mucormycosis



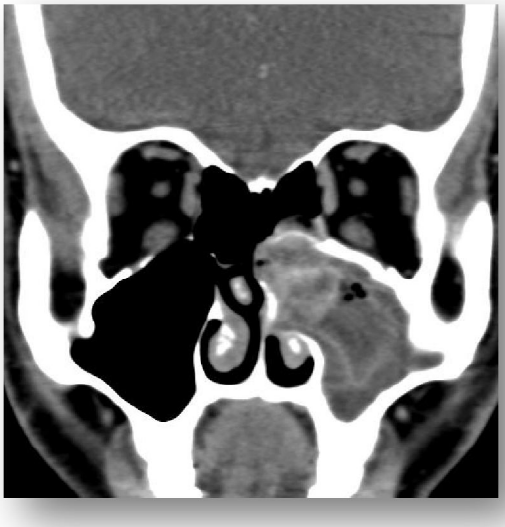


Fig. 2 & 3: Soft tissue density lesion with heterogenous hyperdensities in the Left maxillary sinus & posterior ethmoids in a case of fungal rhinosinusitis

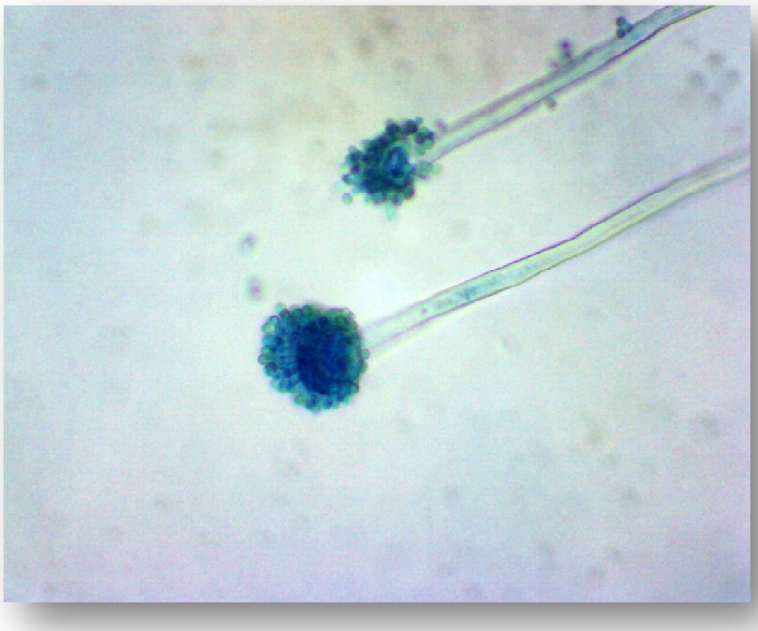


Figure 4: Aspergillus on LPCB staining showing septate hyphae and swollen vesicle giving rise to phialides from which chains of conidia arise

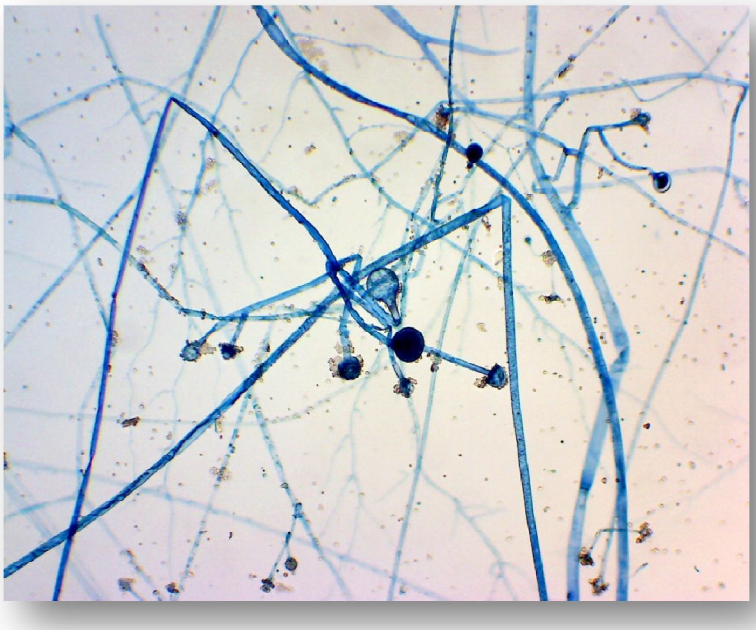


Figure 5: Mucor on LPCB staining showing aseptate hyphae branching at 90^{o} and absence of rhizoids

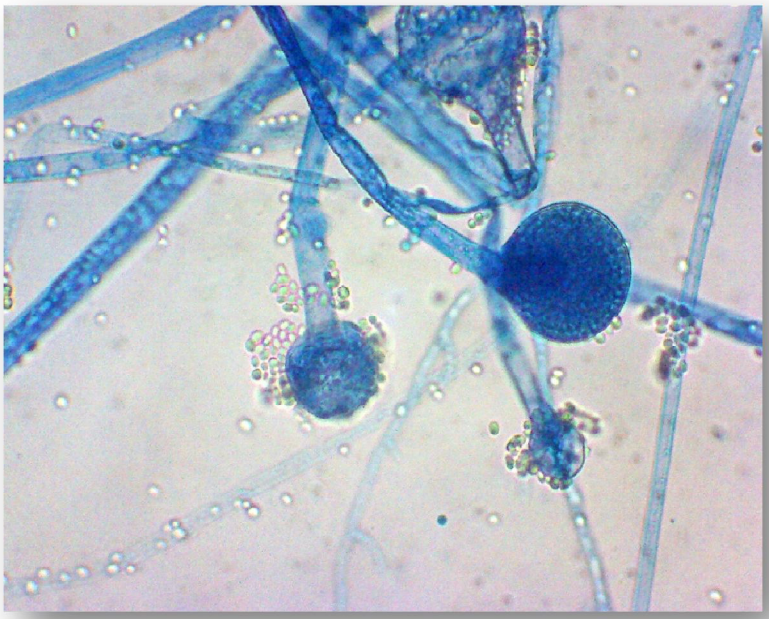


Figure 6: Mucor on LPCB staining showing broad aseptate hyphae with extension of columella into sporangium and aggregation of sporangiospores

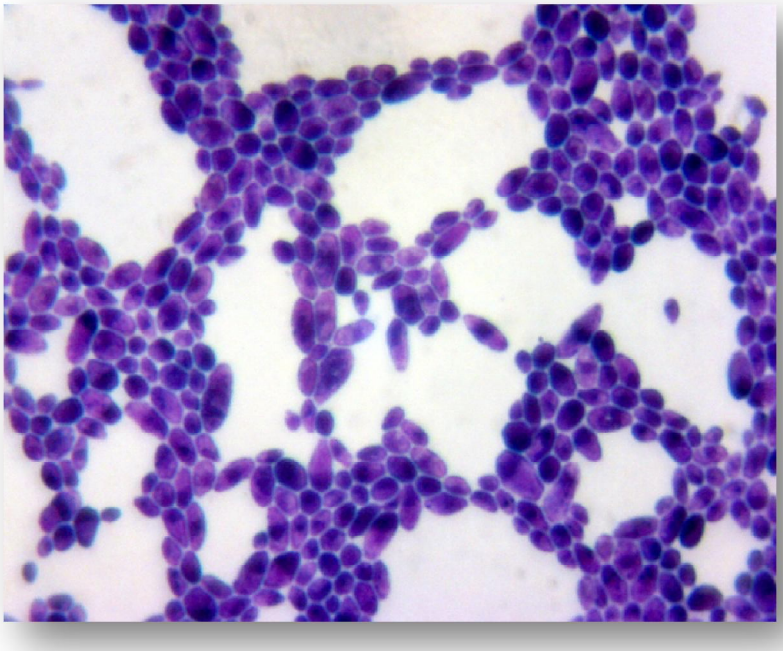


Figure 7: Candida on Gram staining showing pseudohyphae and budding blastoconidia

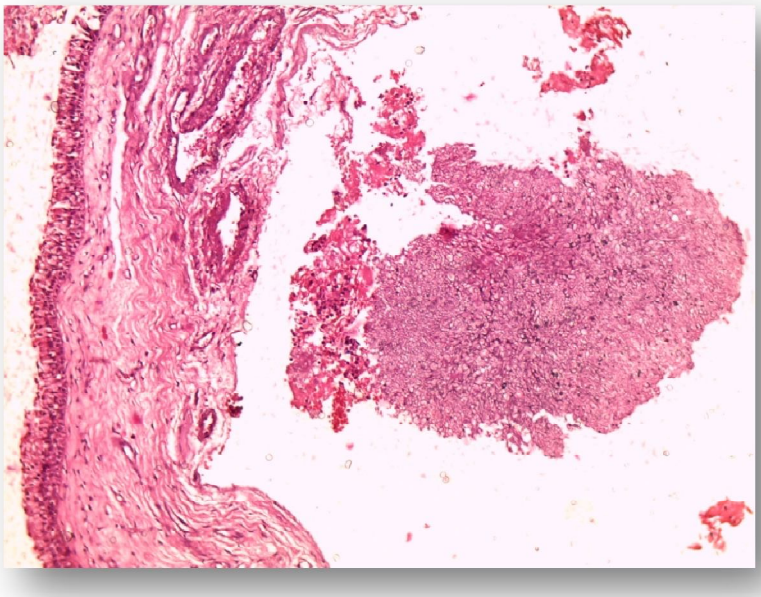


Figure 8: H&E stained tissue section showing polypoidal mucosa lined by respiratory epithelium with adjacent fungal ball (10X)

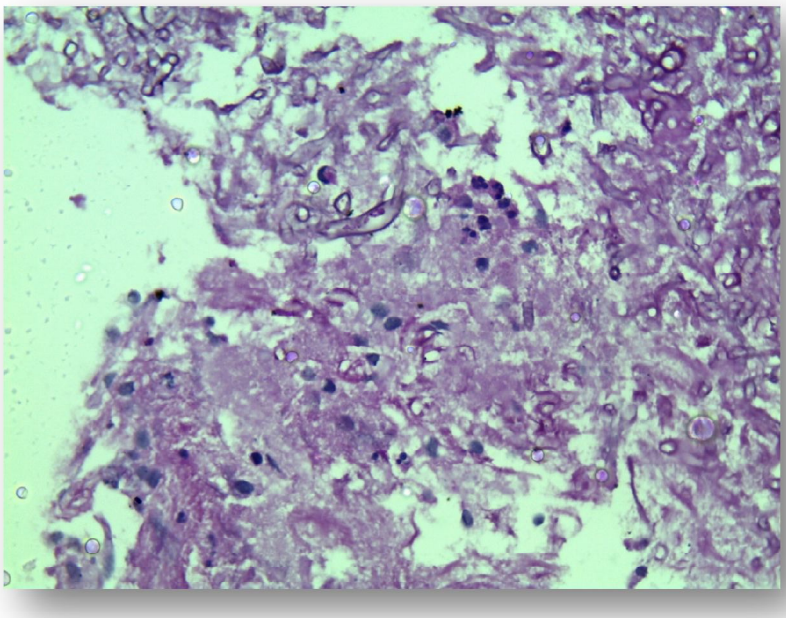


Figure 9: Mucor on PAS stain showing broad aseptate hyphae (400X)

ABBREVIATIONS

CRS – Chronic Rhinosinusitis

FRS – Fungal Rhinosinusitis

AFRS – Allergic Fungal Rhinosinusitis

ABPA – Allergic Bronchopulmonary Aspergillosis

FESS – Functional Endoscopic Sinus Surgery

ESS - Endoscopic Sinus Surgery

FUO – Fever of Unknown Origin

HEPA - High Efficiency Particulate Air

KOH – Potassium hydroxide

PAS – Periodic Acid Schiff

GMS - Gomori methenamine silver

H & E – Hematoxylin and Eosin

LPCB – Lactophenol Cotton Blue

ELISA – Enzyme linked Immunosorbent Assay

CFT – Complement Fixation Test

ID – Immuno-diffusion

LA – Latex Agglutination

RIA – Radio Immunosorbent Assay

FM – Fontana Masson

MASTER CHART

S. No	Agp	S	NO	ND	Ha	FP	FS	URI	Com	Imm	Imag	Mic	HP	F1	F2	F3	R
1	6	1	1	2	2	2	2	2	2	2	1	2	1	1	2	2	1
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3	6	1	1	1	1	2	2	2	1	1	1	1	1	2	2	1	1
4	4	1	1	1	1	2	1	2	1	1	1	1	1	1	1	1	1
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8	1	2	1	1	2	2	2	2	2	2	1	2	1	1	2	2	1
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12	6	1	2	1	1	1	2	2	2	1	2	2	1	1	1	2	1
13	3	2	1	1	2	2	2	2	2	2	2	1	2	2	2	1	1
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25	8	1	1	1	1	2	2	2	1	1	1	1	1	2	1	1	1
26	4	1	1	1	1	1	1	2	2	1	1	2	1	2	1	2	1
27	4	2	2	2	1	2	2	2	2	2	1	1	1	1	2	2	1
28	6	2	1	1	1	2	2	2	2	2	1	1	1	1	2	2	1
29	2	1	1	2	2	2	2	2	2	2	1	1	2	2	2	1	1
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34	3	2	2	1	1	2	2	2	2	2	1	2	2	2	2	2	2
35	4	1	1	2	2	2	2	1	2	2	2	2	2	2	2	2	2
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37	3	1	1	1	1	2	2	2	2	2	1	2	2	2	2	2	2
38	5	1	2	1	1	2	2	2	2	1	1	2	2	2	2	2	2
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44	4	1	1	2	2	2	2	1	2	2	1	2	2	2	2	2	2
45	6	1	1	1	1	2	2	2	2	1	1	2	2	2	2	2	2
46	5	2	1	1	2	1	2	2	2	2	2	2	2	2	2	2	2
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48	3	1	1	2	1	2	2	2	2	2	1	2	2	2	2	2	2
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56	3	1	1	2	2	2	2	2	2	2	1	2	2	2	2	2	2
57	4	1	1	2	2	2	2	2	2	1	2	2	2	2	2	2	2
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64	2	2	1	1	2	2	2	2	2	2	1	2	2	2	2	2	2
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77	5	1	2	1	2	2	2	2	2	2	1	2	2	2	2	2	2

78	3	1	2	2	1	2	2	2	2	2	1	2	2	2	2	2	2
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81	4	2	1	2	2	2	2	2	2	1	1	2	2	2	2	2	2
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83	3	1	1	1	2	2	2	1	2	2	1	2	2	2	2	2	2
84	2	2	1	2	2	1	2	2	2	2	1	2	2	2	2	2	2
85	4	1	1	2	2	2	2	2	2	1	1	2	2	2	2	2	2
86	4	2	1	2	1	2	2	1	2	2	1	2	2	2	2	2	2
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96	1	1	1	2	1	2	2	2	2	2	2	2	2	2	2	2	2
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98	5	1	2	1	1	2	2	2	2	2	2	2	2	2	2	2	2
99	4	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2
100	5	2	2	2	1	2	2	2	2	1	1	2	2	2	2	2	2

S. No – Serial No.

Ag gp – Age groups

Code	Age groups
1	11-20
2	21-30
3	31-40
4	41-50
5	51-60
6	61-70
7	71-80
8	81-90

S – Sex: Male - 1, Female - 2

Symptoms of the study: Present – 1, Absent - 2
NO – Nasal Obstruction
ND – Nasal Discharge

Ha – Headache
FP – Facial Pain
FS – Facial Swelling
URI – Upper Respiratory Tract Infection

Com – Complications: Present – 1, Absent – 2

Imm – Immunity level: Immunocompromised – 1, Immunocompetant - 2

Imag – Imaging findings positive for Fungal sinusitius: Present – 1, Absent – 2

Mic – Microbiology findings positive for Fungal sinusitius: Present – 1, Absent - 2
HP – Histopathology findings positive for Fungal sinusitius: Present – 1, Absent – 2

F1 – Aspergillus: Present – 1, Absent - 2
F2 – Mucor: Present – 1, Absent - 2
F3 – Candida: Present – 1, Absent – 2

R – Result: Fungal Sinusitis – 1, Non-fungal sinusitis – 2

CONSENT FORM

I, Dr. Sandeep Suresh, am carrying out a study on the Incidence and clinical profile of fungal sinusitis in patients diagnosed with chronic rhinosinusitis as a part of my research in the Department of E.N.T.

I am doing this study so that it is possible to detect early and treat the life threatening complications of fungal rhinosinusitis.

In this study, nasal discharge is collected for microbiological examination and biopsy of tissues is done as part of pathological examination and the sample will not be used for any other purpose and the results will be kept highly CONFIDENTIAL.

Having understood the above from my doctor,

I _____ aged _____ years diagnosed to have _____ have been explained the importance of testing for Fungal rhinosinusitis. It has also been explained to me that the test results will be included in the above mentioned study.

I hereby give full consent to proceed with the investigation.

Signature / Left Thumb Impression: Date:

PROFORMA

Name	:	Case No.	:
Age	:	Hosp No.	:
Sex	:	IP No.	:
Occupation	:	Date	:
Address	:	Culture/Biopsy No:	

Clinical Data:

Symptoms:

Nasal discharge:

- Onset and duration
- Appearance and colour
- Quantity
- Consistency
- Smell
- Precipitating factors if any
- Whether associated with upper respiratory tract infection
- If associated with epistaxis or not

Nasal obstruction:

- Side
- Onset and duration
- Progression - intermittent or constant
- Associated symptoms – relationship to cold
- History of drug intake
- History of trauma

Facial pain:

- Side
- Onset and duration
- Nature of pain
- Radiation
- Precipitating and relieving factors

Headache:

- Location
- Onset and duration
- Number of attacks per day or week or month
- Type - Intermittent / continuous
- Severity
- Radiation
- Precipitating and relieving factors
- Association with nausea / vomiting / giddiness / visual disturbances

Allergy:

- History of atopy
- Allergen - if patient can identify
- Seasonal or perennial
- Whether associated with other conditions like bronchial asthma or hay fever

Throat symptoms:

- Duration
- Onset and progression

Ear symptoms:

- Duration
- Onset and progression

Other Complaints:

- Nausea / vomiting / vertigo / fever / loss of weight / altered sensorium.

Treatment history:

- History of any previous surgery for the nose and paranasal sinuses
- Whether patient symptomatically improved following the procedure
- History of drug intake – including antibiotics / decongestants antihistamines / anti-inflammatory / immunosuppressant drugs.
- Whether patient has undergone treatment for pulmonary tuberculosis or diabetes mellitus.

Past history:

- History of diabetes / AIDS
- History of trauma over the face

Personal history:

- Occupation, personal hygiene
- Environment / living conditions
- Socioeconomic status
- Sleep, appetite, bowel and bladder habits

Family History:

- History of any similar illness had occurred in the family
- History of familial diabetes or bronchial asthma.

General physical examination:

Built & Nourishment	Level of sensorium
Anaemia	Jaundice
Cyanosis	Edema
Clubbing	Lymphadenopathy

Vital signs:

- Temperature
- Pulse
- Respiratory rate
- Blood pressure

Ears, Nose and Throat Examination:

Nose and paranasal sinuses:

- External nasal framework
- Vestibule
- Anterior Rhinoscopy:
  - Condition of the nasal mucosa
  - Nasal discharge
  - Deviation of Nasal Septum
  - Mucosa and size of the turbinates
  - Middle and Inferior meati
  - Presence of nasal polyp or any other mass
- Posterior Rhinoscopy:
  - Condition of nasopharyngeal mucosa
  - Eustachian tubal orifices
  - Any discharge in the nasopharynx
  - Presence of polyp / mass
  - Choanal patency
  - Posterior end of the nasal septum / turbinates
- Examination of paranasal sinus tenderness

Oral Cavity and Oropharynx:

- Lips, teeth and gums
- Buccal mucosa

- Hard and soft palate
- Condition of tonsils
- Any lymphoid aggregations on the posterior pharyngeal wall

Indirect Laryngoscopy:

- Assessment of laryngeal and hypopharyngeal mucosa
- Vocal cords - appearance and movements

Ears:

- Pinna, Pre- and Post-auricular areas
- Mastoid or tragal tenderness
- External auditory canal examination
- Tympanic membrane appearance
- Tuning fork tests

Systemic Examination:

- Cardiovascular system
- Respiratory system
- Central Nervous system
- Abdominal examination

Investigations:

- Routine Blood - Hb in gm%, PCV
- Total WBC count, Differential Count, AEC or Absolute Eosinophil Count
- Erythrocytic Sedimentation Rate
- Bleeding Time and Clotting Time
- Blood Sugar – fasting and post prandial
- Blood grouping and typing
- Serology for HIV and HBsAg
- Urine analysis – Albumin / Sugar / Microscopy

- Allergic test
- Diagnostic Nasal Endoscopy
- Radiological Examination:
    - X-ray paranasal sinuses - Water's view
    - CT Scan – Nose and paranasal sinuses
- Discharge for allergic mucin, Gram stain, KOH smear and fungal culture
- Histopathological examination of specimens

Treatment:

- Surgery, medical or both

Follow-up:

- Improvement in symptoms
- Endoscopic evaluation