



ISSN:2456-9739

Available Online at <http://www.bjbr.org>

BRITISH JOURNAL OF BIO-MEDICAL RESEARCH

Cross Ref DOI: <https://doi.org/10.24942/bjbr.2022.922> Volume 06, Issue 01, Jan - February 2022

Research Article

Rhino- Orbito-Cerebral Mucormycosis During Covid 19 Second Wave Our Experience

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ARTICLE INFO

Article History:

Received on 16th Jan 2022

Peer Reviewed on 28th Jan 2022

Revised on 15th February 2022

Published on 26th February 2022

Keywords:

Mucormycosis; Covid 19;
Second Wave

ABSTRACT

Aim and objectives- This analytical study aimed to present clinical presentation, microbiological and histopathological diagnostic variation, outcome of mucormycosis in correlation to HbA1C And random Blood sugar, management strategies, complications, mortality and morbidity of Rhino-orbito-cerebral Mucormycosis patients.

Material & Methods- This is a prospective interventional study where patients who presented with complains of blood stained nasal discharge, facial pain or swelling, ptosis, proptosis, loss of vision, loosening of teeth with or without history of Covid, prolonged oxygen mask use, steroid use and diabetes mellitus. In each patient CTScans and MRI Brain + orbit + paranasal sinuses was

performed .

Results- An interventional analytical study was undertaken on 90 patients to evaluate clinical presentation, extent of involvement on radio diagnostic studies, possible risk factors, management strategies, complications, mortality and morbidity of Rhino-orbito-cerebral Mucormycosis.

Conclusion- Despite of meticulous management by early diagnosis, radical and aggressive surgical debridement and antifungal therapy patients had permanent morbidity. In Rhinocerebral Mucormycosis, acute renal failure due to amphotericin B and uncontrolled diabetes continues to be associated with a fulminant course of the disease and with high mortality. The tissue of suspected cases were examined by KOH microscopy, histopathological and culture. Invasive fungal sinusitis were treated by sinus, orbital surgery and debridement depending on extension of disease.

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INTRODUCTION

Rhino-orbito-cerebral mucormycosis is an invasive, opportunistic fungal infection usually seen in immuno-compromised patients and particularly in the setting of diabetes or immune deficiency. It is assumed that the port of entry is colonization of the nasal mucosa, allowing the fungus to spread via the paranasal sinuses into the orbit. Involvement of the brain and cavernous sinus occurs by way of the orbital apex; therefore, spheno-ethmoidectomy with or without maxillectomy and orbital exenteration or enucleation to reduce bulk of fungal load along with antifungal treatment seems to be the definitive method to eradicate this infection.

India's resurgence in COVID infections began around mid-March 2021 and increased rapidly, reaching a peak of more than 414,000 daily cases on May 6, 2021. The daily death Toll rose to 3754 by May 9, 2021.¹ While the attack continued, another invisible foe entered in the form of COVID-19 associated Mucormycosis (CA-Rhino Orbito Cerebral). had been recognized during the first wave in India. By June 7, 2021, a deluge of 28,252 mucormycosis cases were reported, 86% having history of COVID-19.² Covid associated Rhino Orbito Cerebral has a world-wide distribution, the major chunk being contributed by India. In a systematic review of 101 cases of mucormycosis with COVID-19, 82 were from India and the remaining 19 from USA (9), Iran (3), UK (1), France (1), Italy (1), Brazil (1), Turkey (1), Mexico (1) and Austria (1).³

Recently, 15 more cases from 5 centres in Iran from April to September 2020 and 2826 cases from 98 centres between January 1, 2020 and May 26, 2021 in India have been reported, reflecting the magnitude of the disease burden.⁴

⁵ Most of the reports of Rhino Orbito Cerebral include the time period over 2020 till May 2021. There exists only one report of 70 cases of Rhino Orbito Cerebral exclusively in the severe, devastating second wave of COVID 19 starting in April 2021.⁶

Fungi are ubiquitous in nature, and exposure to the sinonasal and respiratory epithelium is thus unavoidable. Inhalation of these organisms can

cause both acute and chronic Rhinosinusitis, and the spectrum of disease ranges from non-invasive disease to acute and fulminant infection. The development of fungal rhinosinusitis is thus multifactorial, depending on the immune status of the patient, environment, the nature of fungus and the genetic factors. Acute invasive fungal rhinosinusitis (AIFRS) is a life-threatening disease, affecting mostly immune compromised patients with neutrophilic dysfunction^[7, 8, 9]. In these patients, saprophytic fungi, particularly Zygomycetes and Aspergillus, can invade the nasal mucosa and blood vessels, leading to rapid dissemination into the orbits, palate and the brain^[8, 9, 10]. For this reason, a systematic review states that the overall survival rate of AIFRS patients is as low as 50%^[8]. Early diagnosis and immediate treatment, including antifungal therapy and surgical debridement, are considered vital for better survival rates^[8]. A preliminary study was thus designed to document the presentation, clinical features, sensitivity and specificity of KOH mount in comparison with HPR, management strategies, complications, mortality and morbidity and possible risks to gain an insight into the triggering factors for the swarm of rhino-orbito-cerebral mucormycosis presented in the Dept. of ENT, at our tertiary care centre.

MATERIAL AND METHODS

This is a prospective interventional study conducted by us where patients who presented with complains of blood stained nasal discharge, facial pain or swelling, ptosis, proptosis, loss of vision, loosening of teeth with or without history of Covid, prolonged oxygen mask use, steroid use and diabetes mellitus. In each patient CT

Scans and MRI Brain + orbit + paranasal sinuses was performed at closest to symptom of onset suggestive of Invasive fungal sinusitis with or without intracranial and intra-orbital extension. Depending on radiological extent of disease patients are categorised as-

Grade 1: disease limited to nasal cavity, Grade 2: disease limited to para nasal sinuses, Grade 3: disease extended up to orbit, Grade 4: intracranial extension of disease. The tissue of suspected cases were processed and examined by KOH microscopy, histopathological and culture.

Invasive fungal sinusitis were operated for functional endoscopic sinus surgery and debridement depending on extension of disease and were started empirically on Amphotericin (Conventional/Liposomal): Conventional-0.5 to 1mg/kg, Liposomal Amphotericin 4 to 5mg/kg. Patients having aspergillosis on fungal culture/histopathology were started on a loading dose of Voriconazole of 400mg twice a day on the first day followed by 200mg twice a day on the remaining days for a period of 6-8 weeks. Patients who had mixed infections were started on Amphotericin and Voriconazole, and then discharged on Posaconazole and Voriconazole.

Patients with intra-orbital extension were managed with transcutaneous retroorbital injection of Amphotericin B, enucleation and exenteration of eyeball as per requirement by the Ophthalmology Department. Patients having dental loosening and alveolar or palatal involvement underwent dental extraction and debridement of necrotic bone with postoperative prosthesis placement.

Neurosurgical intervention in the form of intracranial abscess drainage done for required patients and for cavernous sinus thrombosis, major vessel thrombosis and pachymeningeal enhancement conservative management was the cornerstone in the treatments. After surgical debridement patients

were regularly assessed using nasal endoscopy and post operative CT and MRI, residual disease was removed. With completion of medical line of management and healthy mucosa on diagnostic nasal endoscopy, patients were subsequently discharged with strict follow up every three weeks with repeat scans to address residual disease at earliest to prevent further morbidity.

Permanent morbidity in the form of loss of vision, palatal perforation, chewing difficulty in edentulousness, facial deformity were noted. Mortality patients and underlying associated factor for fulminant course of illness were evaluated.

RESULTS

An interventional analytical study was undertaken on 90 patients to evaluate clinical presentation, extent of involvement on radio diagnostic studies, possible risk factors, management strategies, complications, mortality and morbidity of Rhino-orbito-cerebral Mucormycosis. The following observations were noted:

Demographic Profile and Risk Factors for Rhino OrbitoCerebral Mucormycosis

Patients were in age group of 18 to 77 years. The mean age of patients was 49.6 ± 12.6 years. Out of 90 cases, 69 (76.9%) were males, 21 (23.30%) were females. 45 (50%) patients had pre-existent Diabetes Mellitus (DM), while 45 (50%) patients had no history of DM previously. Out of 90 cases, 86 (95.55%) had history of COVID-19 infection, while 4 (4.44%) patients did not have history of COVID-19.

Table-1 and 2: Showing Demographic Profile and Risk Factors for Rhino OrbitoCerebral Mucormycosis

AGE DISTRIBUTION		
AGE (yrs)	NO. OF CASES	%
18-20	2	2.2
21-30	6	6.7
31-40	13	14.4
41-50	21	23.3
51-60	32	35.6
61-70	15	16.7
71-80	1	1.1
Total	90	100
GENDER		
MALE	69	76.9
FEMALE	21	23.3
DIABETES		
YES	45	50
NO	45	50
HISTORY OF COVID		
YES	86	95.55
NO	4	4.44
Mucor Grade ¹¹	No.of cases	%
1	2	2.2
2	29	32.2
3	35	38.9
4	24	26.7
Total	90	100

41 (45.6%) patients received Oxygen for their COVID-19 symptoms while 49 patients (54.4%) did not receive Oxygen. 54 (60%) patients received oral steroids (prednisolone/methylprednisolone), 36 (40%) patients did not receive any form of steroid treatment for COVID -19 infection. In study group majority of patients had grade 3 of Rhino Orbito Cerebral, wherein intraorbital

extension of disease along with sinuses involvement was seen followed by 29 (32.2%) cases had grade 2 Rhino Orbito Cerebral having involvement of nasal cavity & PNS without intraorbital and intracranial extension of disease, 24 (26.7%) patient had Grade 4 RCOM with intracranial extent of disease, only 2 (2.2%) patients had grade 1 RCOM with disease limited to nasal cavity.

The median duration between the first laboratory confirmation of COVID-19 and detection of CA-Rhino Orbito Cerebral was 8-97 days with mean 28.9 ± 15.3 .

Distribution of patients according to clinical features

Majority of patient were presented with isolated nasal symptoms (30%) in the form of nasal crusting, nasal obstruction, blood stained nasal discharge, facial pain, sinusitis; followed by isolated orbital symptoms (18.8%) in the form of decrease vision, loss of vision, cellulitis, chemosis of eye, ophthalmoplegia, ptosis;

followed by mixed nasal and palatal symptoms (16.6%), isolate palatal symptoms (11.1%) in the form of loosening of teeth, palatal ulcer, palatal erosion; combined nasal, palatal and orbital symptoms (6.6%), nasal and orbital presentation (4.4%); nasal, palatal, orbital and CNS symptoms (3.3%); combined palatal and orbital presentation (3.3%); 3.3% of patients had no complaints and found incidentally on radiological investigation, 2.2% were presented with combined palatal, orbital and presentation.

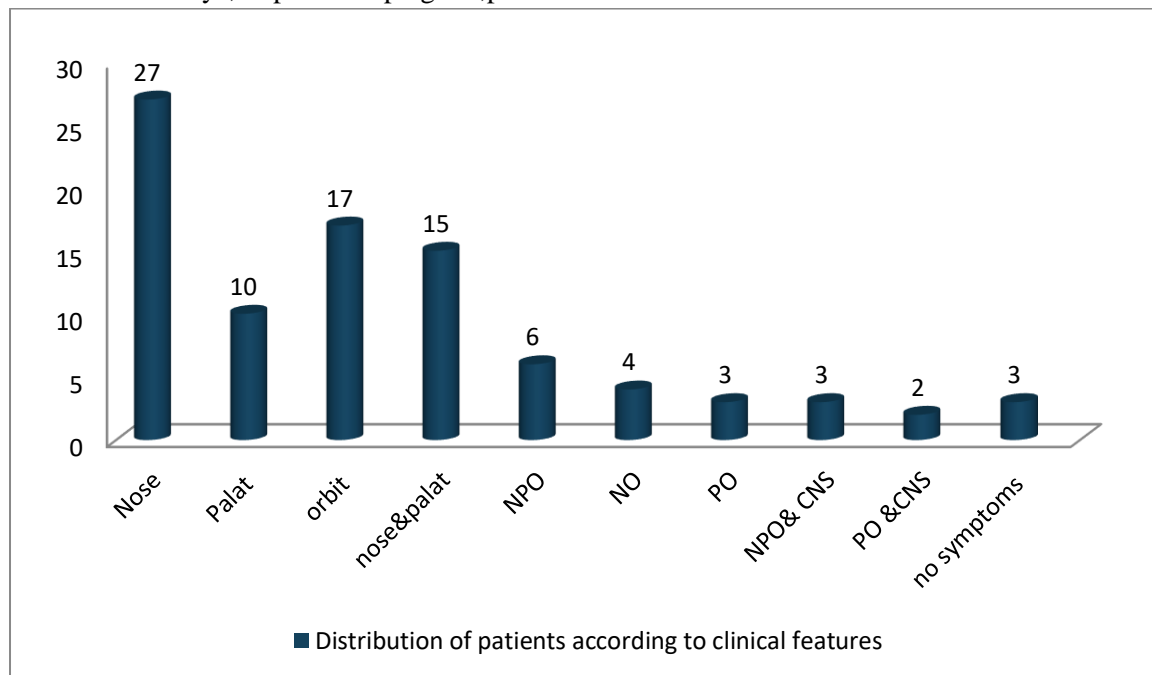


Table-3: Distribution of patients according to clinical features

DIAGNOSIS OF FUNGAL INFECTION ON KOH AND HPR

The sensitivity of KOH for diagnosis was 42.2% (38/90). Out of 38 cases diagnosed on KOH, 3 (7.9%) were mucormycosis, 2 (5.3%) were candida, 6 (15.8%) were Aspergillus and

27 (71.1%) were non-specific. Sensitivity of diagnosis of fungal infection by HPR was 82.2% (74/90). The false negative rate of fungal infection detected by KOH was 89.48% considering HPR gold standard test.

Table-4: diagnosis of fungal infection on KOH AND HPR

DIAGNOSIS OF FUNGAL INFECTION ON KOH		
KOH	No.of cases	%
M	3	7.9
C	2	5.3
A	6	15.8
NONSPECIFIC	27	71.1
MIXED	-	-
Total diagnosed cases by KOH	38	100%
DIAGNOSIS OF FUNGAL INFECTION ON HPR		
HPR	No.of cases	%
M	39	52.7
C	1	1.4
A	13	17.6
MIX	14	18.9
NON SPECIFIC	5	6.8
NOT REPORTED	2	2.7
TOTAL	74	100.0

Correlation of HbA1c, Blood sugar Levels and steroid use

In our study 45 patients were diabetic and rest 45 non diabetic, all non diabetic patients had history of covid, 27 patient received steroid treatment had RBS 243.5 ± 57.6 mg/dl and

HbA1c 10.20 ± 1.53 on investigation at time of mucor assessment, in rest 18 patients was not taken steroid in covid treatment had RBS 124.7 ± 26.7 and HbA1c 5.78 ± 0.87 . our study showed p value <0.001 highly significant association between steroid used and deranged sugar level.

	Steroid used (n=27)	Steroid not used (n=18)	t value	P value
Rbs (mg/dL)	243.5 ± 57.6	124.7 ± 26.7	9.80	< 0.001 , HS
HbA1c	10.20 ± 1.53	5.78 ± 0.87	12.75	< 0.001 , HS

Table-5: Correlation of HbA1c, Blood sugar Levels and steroid use

Distribution of patients according to Management strategies:

PNS		
PNS	No.of cases	%
Fess	49	54.4
fees+pd+te	21	23.3
fess +pd	4	4.4
fess+maxillectomy	6	6.7
fess+TE	8	8.9
septal de	2	2.2
Total	90	100.0

EYE		
Ophthalm	No.of cases	%
Tramp	52	57.8
Enucleation	5	5.6
-	33	36.7
Total	90	100.0

CNS		
Neurosurgery	No.of cases	%
Required	23	25.6
Not required	67	74.4
Total	90	100.0

Table-6 : Surgical Debridement

90 patients underwent surgical debridement followed by antifungal treatment. Out of 90 patients, only 23 patients required neurosurgical intervention. Out of 90 patients who had PNS involvement, 49 (54.4%) patients underwent FESS, while 41(45.6%) patients had

to undergo FESS along with either of the palatal debridement (PD), teeth extraction (TE), maxillectomy and septal debridement (SD). Out of 90 patients, 52 (57.8%) required intervention in the form of (TRAMB) and 5 (5.6%) patients required enucleation.

Distribution of patients according to morbidity

No of morbidity 48 Out Of 90 Sample				
	Type	No. of cases	%	% (n=48)
PALAT PRESENTATION	CP	6	30.0	41.7
	PF	6	30.0	
	PP	8	40.0	
Sub Total		20	100.0	
Edentulous Presentation	TE	27	-	56.3
CNS PRESENTATION	UMN FP	1	-	2.1
VISION	PROP	2	6.1	68.8
	ptosis	6	18.2	
	RTVL	6	18.2	
	RTDV	3	9.1	
	RT OP	1	3.0	
	BLOP	1	3.0	
	LTOP	5	15.2	
	LTVL	1	3.0	
	LTDV	2	6.1	
	RTLR PALSY	4	12.1	
	LTLR PALSY	2	6.1	
Sub Total		33	100.0	

Table-7 : Showing Distribution of patients according to morbidity

In our study, 20 (41.7%) had palatal involvement in the form of central palate perforation (CP) (n=6, 30%), palatal fistula (n=6, 30%) and partial palatal perforation (PP) (n=8, 40%). 27 (56.3%) patients had edentulous

presentation; while only 1 (2.1%) patient had CNS involvement in the form of Upper motor Neuron(UMN) facial palsy. 33 (68.8%) patients in our study had vision morbidity such as proptosis, ptosis, RTVL etc.

Distribution of patients according to mortality

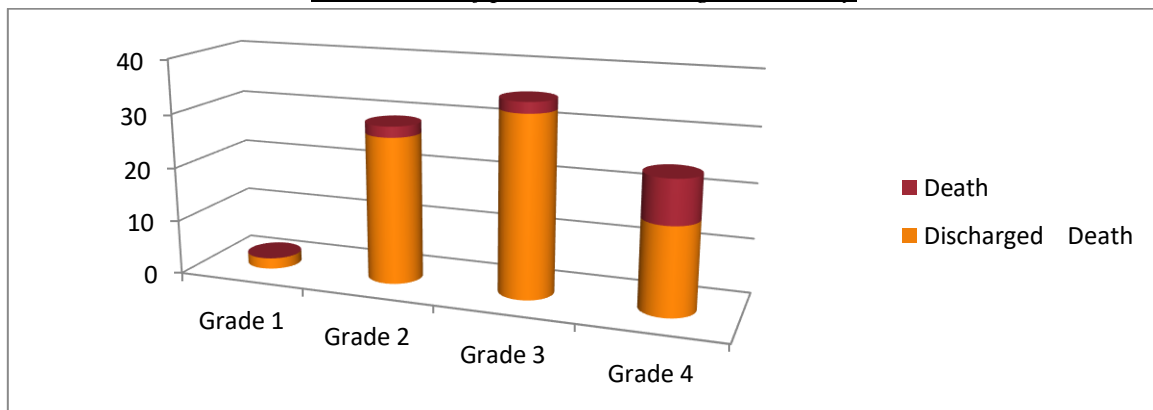


Table-8 : Showing Distribution of patients according to mortality

Out of the 90 patients, 78 (86.7%) patients were discharged while 12 (13.3%) patients died. Maximum

Mortality was seen in GRADE 4 (n = 8) Rhino Orbito Cerebral which account for 66.6% of total death

DISCUSSION

In our study ROCM which includes sino-nasal, rhino-orbital and rhino-orbital-cerebral disease, commonly has underlying uncontrolled diabetes and diabetic ketoacidosis (DKA).^{3, 13}. Susceptibility of COVID -19 patients to develop mucormycosis ascribed by presence of diabetes, use of steroid therapy in moderate to severe cases, ICU stay and oxygen therapy mechanical ventilation.^{8,13,14}

Out of 90 cases, 86 (95.55%) had history of COVID-19 infection, while 4 (4.44%) patients did not have history of COVID-19. majority of patients had grade 3 of Rhino Orbito Cerebralmucormycosis, wherein intraorbital extension of disease along with sinuses involvement was seen followed by 29 (32.2%) cases had grade 2 Rhino Orbito Cerebralmucormycosis, 24 (26.7%) patient had Grade 4 Rhino Orbito Cerebralmucormycosis, only 2(2.2%) patients had grade 1 Rhino Orbito Cerebralmucormycosis. The mean age of patients was 49.6±12.6 years. Out of 90 cases, 69 (76.9%) were males, 21(23.30%) were females which shows male to female ratio of CA- Rhino Orbito Cerebralmucormycosis 3.3:1, Factors Responsible for male at higher risk of getting mucormycosis are due to greater exposure to fungal spores due to prolonged out door exposure in males and protective mechanism of oestrogens in females.^{5,15}In study group 45 patients had pre existing diabetes in among rest 45 nondiabetic patients who received steroid treatment found to have deranged RBS124.7 ±26.7 and Hba1c5.78 ± 0.87 showing highly significant association between steroid used and deranged sugar level with p value <0.001 .In presence of hyperglycemia and low PH decrease phagocytic function with reduced chemotaxis,

elevated serum iron level possibly explain increase risk of mucor mycosis in steroid induced hyperglycemia¹².

The sensitivity of KOH for diagnosis was 42.2% (38/90). Sensitivity of diagnosis of fungal infection by HPR was 82.2% (74/90). The false negative rate of fungal infection detected by KOH was 89.48% considering HPR gold standard test, on kohlstudies 27 sample showed nonspecific fungal infection further diagnosis confirmed on HPR studies respectively received appropriate treatment .Aspergillus and Candida are the commonly reported fungi with COVID-19 infection¹⁶ In our series, mixed fungal infection was observed on histopathology in 14 of the 90patient,patients had to undergo FESS along with either of the palatal debridement (PD), tooth extraction (TE), maxillectomy and septal debridement (SD). Orbital intervention in the form of (TRAMB) and 5 enucleation ,neurosurgical intervention depending on extent of disease ,53 patients had intraorbital involvement of disease on radiological investigation out of which 15(28.3%) had visual disturbances , by early diagnosis and management in the rest 38 (71.7%) patients vision related morbidity in form of decrease vision, ophthalmoplegia, visual loss was prevented with p value <0.001 which is highly significant

In spite of aggressive multidisciplinary approach with early diagnosis, radical debridement and antifungal treatment 48 patients (53%) had morbidity in various forms including palatal defect, visual disturbance.78 (86.7%) patients were discharged while 12 (13.3%) patients died.

CONCLUSION

- Main pillars of management of invasive fungal sinusitis is surgical debridement and Antifungal therapy.
- Radio diagnostic test not only useful for diagnosis of mucormycosis but also helpful for surgical planning and subsequently

useful for preoperative counselling of patients.

- Though Deep nasal swab-KOH staining being used for microbiological diagnosis, HPR test is more appropriate test to prevent undertreatment of KOH false negative patient and overtreatment of false positive patients and to start appropriate antifungal agent as pertype of fungus.
- Despite of meticulous management by early diagnosis, radical and aggressive surgical debridement and antifungal therapy patient had permanent morbidity in the form of loss of vision, ophthalmoplegia, hyperesthesia or hypoesthesia along V1 distribution, palatal perforation, facial deformity, chewing difficulty in edentulous patient.
- In Rhinocerebral Mucormycosis, acute renal failure due to amphotericin B and uncontrolled diabetes continues to be associated with a fulminant course of the disease and with high mortality.

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How to cite this article:

Kamini Chavan, Nilam U Sathe, Rajat Magdum, Lal Pek Thangi *Rhino-Orbito-Cerebral Mucormycosis During Covid 19 Second Wave Our Experience* Br J Bio Med Res, Vol.06, Issue 01, Pg.1924 - 1934, January - February 2022. ISSN:2456-9739 Cross Ref DOI : <https://doi.org/10.24942/bjbmr.2022.922>

Source of Support: Nil

Conflict of Interest: None

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