International Journal of Health Sciences and Research
Volume 14; Issue: 3; March 2024
Website: www.ijhsr.org
Original Research Article *ISSN: 2249-9571*

Practice of Steam Inhalation at Home - A Major Contributory Risk Factor for Development of Rhino-Orbital Cerebral Mucormycosis (ROCM) in COVID-19 Patients

Dr. Nishant Agrawal[1], Dr. Rishu Garg[2], Dr. Rahul Jain[3], Dr. Kapil Telang[4], Dr. Ajoy Sodani[5]

[1,2,4]Senior Resident, Department of Neurology, Sri Aurobindo Institute of Medical Sciences, Indore.
[3]Professor & Head, Department of Neurology, Sri Aurobindo Institute of Medical Sciences, Indore.
[5]Professor, Department of Neurology, Sri Aurobindo Institute of Medical Sciences, Indore.

Corresponding Author: Dr. Nishant Agrawal

DOI: https://doi.org/10.52403/ijhsr.20240321

ABSTRACT

BACKGROUND: Coronavirus disease (COVID-19) outbreak has created a global health crisis. Amidst the pandemic, there was a massive surge of mucormycosis cases in COVID-19 patients. Uncertainties of pandemic times, accentuated by frequent changes in treatment guidelines, lead to widespread, often inadvertent, use of broad-spectrum antibiotics and immune-modulators. This has been implicated in the increased incidence of bacterial and fungal co-infections in COVID-19 patients.
METHODS: Rt-PCR positive SARS CoV-2 patients were recruited so as to populate two different verticals - ROCM (n=66) group and non-ROCM (n=132) group. The demographic profile, co-morbidities, vaccination status, treatment received, and other exposures were compared between the two groups. We aim to study the clinical profile of patients of SARS CoV-2 with rhino-orbital-cerebral mucormycosis (ROCM) and the predisposing factors.
RESULT: 66 ROCM and age matched 132 non-ROCM subjects were recruited in the study. The mean age of ROCM patients was 51.12±12.2 yr with male preponderance in ROCM group (81.8 vs 63.6, p= 0.008, 95% CI 4.7-29.5). Meantime to develop ROCM from the onset of initial symptoms of COVID-19 was 19.22±8.12 days. Headache was the most common symptom of ROCM, followed by peri-orbital discoloration and cranial nerve involvement. Uncontrolled blood sugar was the most important co-morbidity (91%). Steroids were received by 97% vs. 100% patients in ROCM and non ROCM groups (p=0.046).
CONCLUSION: Steam inhalation, uncontrolled blood sugar levels, and hyperferritinemia were found to be the major predisposing factors in the development of ROCM. Alarmingly, the use of steroids/immune-modulators in high doses and for prolonged duration did not predispose the patients of Covid-19 to the development of ROCM. The severity of COVID-19 infection, per se, did not increase the risk of developing ROCM.

KEYWORDS: Rhino orbital cerebral mucormycosis, Covid-19, steroids, diabetes mellitus, hyperferritinemia.

INTRODUCTION

The incidence of community and hospital acquired co-infection, bacterial as well as fungal, is known to be high in patients suffering from SARS CoV-2 [1]. Unexpected and alarming rise in the incidence of mucormycosis has been reported from India. According to systemic review done by Singh AK et al [2], out of total 101 cases of mucormycosis reported worldwide 81% were from India.

The fungus mucorales of zygomycetes family does not invade the immune-competent persons [3]. The reported prevalence, in pre-COVID times, of mucormycosis in India is 0.14/1000 population. It was more prevalent in persons either with malignancies, or uncontrolled diabetes or in organ-transplant recipients [4].

The uncertainties of pandemic times, accentuated by frequent changes in treatment guidelines, lead to widespread, often inadvertent, use of broad spectrum antibiotics and immune-modulators [1]. This has been implicated in increased incidence of bacterial and fungal co-infections in COVID-19 patients. In this context it is noteworthy that a case series of 23 patients of COVID with invasive mucormycosis reports uncontrolled diabetes in only 12 (52.17%) cases [5]. Similarly, in the systematic review of SARS CoV-2 with mucormycosis reported worldwide until May 2021 (Singh et al; 28 articles, 101 cases) only one was organ-transplant recipient and 20% cases were non-diabetic. Further, 17.82% (18 of 101) did not receive any immunosuppressant and 23.8% (24 of 101) did not receive steroids. It seems, therefore, that a sizable number of COVID patients develop invasive mucormycosis in absence of classical risk factors [2].

We therefore planned to systematically study the clinical profile of patients of SARS CoV-2 with rhino-orbital-cerebral mucormycosis (ROCM) and the predisposing factors thereof.

MATERIALS AND METHODS

The study was conducted between 15thApril 2021 to 15thJune 2021 in a dedicated COVID-care hospital, attached to a medical college. We recruited rt-PCR positive SARS CoV-2 patients so as to populate two different verticals - The ROCM group and non-ROCM group.

The ROCM group - Patients referred to us with suspected mucormycosis co-infection were recruited in this group. For inclusion they need to fulfill following criterion-

a) COVID-19 rt-PCR positive
b) At least one of more of following- headache, blackish nasal discharge, facial/periorbital discoloration and/or cranial nerve involvement
c) MRI/CT features suggestive of invasive fungal disease
d) Consent to participate in the study

These patients underwent history and examination at admission. The details of the treatment received and investigations done prior to the referral was extracted and entered in the study proforma. Following data was specifically sought for- a) age, gender, occupation, diabetes status, b) type of occupation with objective to identify those which lead to prolonged exposure to soil, c) COVID vaccine status, d) time lapse between first COVID symptom and appearance of symptoms suggestive of ROCM, e) number, dose, duration of immune-modulatory therapy received prior to the appearance of mucor-symptom, f) exposure to non-medical grade oxygen, steam inhalation, socioeconomic status, habitat g) hematological and biochemical lab parameters prior to the first symptom of mucormycosis, h) details of the pattern of the paranasal sinuses, orbit and brain involvement in MRI/CT and i) extent of the pulmonary parenchymal involvement of computed tomography (CT) chest.

The non-ROCM group- For every ROCM patient two age-matched non-ROCM cases was recruited. Criterions for inclusion were –

a) COVD rt-PCR positive
b) No clinical evidence of co-infection with mucormycosis
c) Moderately severe SARS CoV-2
d) Consent to participate in the study

Following data was extracted for this group- demographic including occupation, vaccine status, date of first COVID symptom, details of domiciliary treatment (if any), details of the therapy received, particularly of the immunosuppressant's, hematological and biochemical parameters, findings of CT chest. The non-ROCM patients were minutely observed during hospitalization for appearance of symptom/s suggestive of ROCM. Post discharge the surveillance continued through tele-medicine. Thus the, non-ROCM patients were observed for a minimum of 21 days from their first COVID symptom. Non-ROCM patients, who withdrew consent or died prior to the completion of the mandatory follow-up period, were excluded from the study.

Definitions:

1) COVID symptoms- fever, anosmia, cough, dyspnea, dysgeusia, loose motions, anorexia, lethargy
2) Exposure to soil- persons engaged in the work which leads to direct exposure to soil, viz. farmers and laborers.
3) Vaccinated- those who received one or both the dosages of any COVID-19 vaccine.
4) Non-medical grade oxygen- home based therapy through cylinders filled with commercial grade oxygen or use of oxygen concentrators filled with tape water at home
5) Diabetes (T2DM): A patient with history of diabetes or HbA1c value of >6.3% at admission.
6) Uncontrolled blood sugar: Individual with HbA1c >7% or random blood sugar (RBS) >250 mg/dl at admission.
7) Steam inhalation: taken at home, on hearsay, as a preventive measure for COVID infection using tape water.

The statistical analysis was done using Excel 2010 (ref) and SPSS version 26.0 (trial). Results of continuous data are presented as Mean ± Standard Deviation (SD) and the results of the categorical measurements are given as a frequency & percentage (%). As and when required, Pearson's Chi-Square test, two-tailed Fisher Exact test, and comparison of proportions z test were deployed to know the association between the variable. Mann-Whitney test used for comparison of two groups with skewed data sets. The probability value $p \leq 0.05$ and odd ration (OR) > 1 (at 95% CI) were considered significant.

The study was approved by the institutional ethical and research committee (SAIMS/IEC/2021/23)

RESULTS

The results are summarized in table 1 and 2.

Table-1: Comparison of exposures between ROCM Vs Non-ROCM

Parameters	ROCM (n=66)	Non-ROCM (n=132)	Significance & Confidence Interval (95%CI)
Age in years; (Mean ±SD)	51.12 (±12.2)	50.71 (±12.7)	MATCHED
Male	54 (81.8%)	84 (63.6%)	0.008 (4.7 to 29.5) [a]
COVID-19 Vaccinated	25 (37.9%)	59 (44.7%)	0.36 (-7.7 to 20.4) [a]
DM	60 (91%)	52 (39.4%)	<0.0001(38.9 to 60.8) [a]
Uncontrolled Blood Sugar	59 (89.4%)	36 (27.3%)	<0.0001(49.4 to 70.8) [a]
Steam inhalation at home	39 (59.1%)	42 (31.8%)	0.0002(12.6 to 40.5) [a]
Immunomodulator Therapy	64 (97%)	132 (100%)	0.046(-0.5 to 10.3) [a]
Steroids	64 (97%)	132 (100%)	0.046(-0.5 to 10.3) [a]
Steroid (total dose) in mg; mean (±SD)	1449.9mg (±1458.9)	1670.31 (±1017.8)	0.004 [b]
Duration of steroid therapy in days; mean (±SD)	14.1 (±6.74)	17.1 (±6.53)	0.001 [b]

a = comparison of proportions
b = Mann Whitney test

Table-2: Comparison of laboratory parameters between ROCM Vs Non-ROCM

Parameters	ROCM (n=66)	Non-ROCM (n=132)	Significance & Confidence Interval (95%CI)
N/L Ratio; Median (IQR)	8.60 (13.94)	8.9 (12.62)	0.482[b]
Ferritin; Median (IQR)	1026.50 (1105.75)	625.65 (766.50)	0.004[b]
LDH; Median (IQR)	313.00 (160.50)	499.50 (339.50)	0.001[b]
Lung involvement; Mean% (±SD)	48 (±23.7)	63.6 (±19.7)	<0.0001(9.3 to 21.8) [c]

b = Mann Whitney test
c = comparison of means

During the study period we recruited 66 ROCM and age matched 132 non-ROCM subjects. The mean age of ROCM patients was 51.12±12.2 yr. We noted male preponderance in ROCM group (81.8 vs 63.6, p= 0.008, 95% CI 4.7-29.5). History of diabetes and uncontrolled blood sugar was more frequent in patients with ROCM (91%) vs. non ROCM (39.4%) (Table1).

The two groups did not differ much in their covid vaccination status. Steam inhalation was significantly more common in ROCM patients (p= 0.0002, 95%CI 12.6-40.5; Table1).

Exposure to the non-medical grade oxygen was not common. Only 5 (7.5%) of the ROCM patients received home based industrial grade oxygen while none of the non-ROCM patient had similar exposure.

The symptom/s suggestive of ROCM were noted by the patients after mean 19.22 ± 8.12 days (range 3-43 days) post initial symptom of the COVID-19. Following symptoms of ROCM were reported by the patients: new onset headache (57 of 66; 86.4%), periorbital discoloration like chemosis or black areas of eschar (28 of 66; 42.4%), unilateral blindness (18 of 66; 27.3%), diplopia (46 of 66; 69.7%), facial pain/numbness (39 of 66; 59.1%), and facial asymmetry (10 of 66; 15.2%).

Out of 132 non-ROCM patients, 3 expired prior to the completion of the mandatory period of three weeks of the surveillance. One of them expired on 18th day while other two died on 19th and 20th day post initial symptom of COVID-19. Remaining 129 subjects were kept under close scrutiny for a mean 45.05±12.2 days (range 21-80, median 43 days). No non-ROCM patients, including those who died, developed any symptom/sign of invasive mucormycosis during the period of observation.

Amongst the ROCM group, 46 subjects (71.9%) received only steroids, while 15 (23.43%) and 3 patients (4.7%) received two and three immune-modulator agents, respectively.

It is interesting to note that significantly high numbers of non-ROCM patients received immunomodulatory treatment. They were treated, as per the institutional treatment protocol, with one or more immunomodulatory agent/s viz. steroid plus tocilizumab, thymosin alpha and/or immunoglobulin (IVIg). Thus every non-ROCM (n=132) patient received steroid therapy. In this group, 66 (50%) patients received only steroids. Remaining received one or more immuno-modulator, in addition to the steroids. Further, the total dose and duration of steroid therapy was significantly more in non-ROCM as compared to ROCM group (table 1).

Brain and PNS imaging could be performed in 81.8 % (54 of 66) ROCM patients. In Brain imaging, cavernous sinus involvement was most common finding (24.1%; 13 of 54). Supra-tentorial infarcts were found in 11 (20.1%), infra-tentorial infarcts in 5 (9.3%), subarachnoid hemorrhage and/or subdural hematoma in 5 (9.3%), meningeal enhancement in 4 (7.4%), optic nerve involvement in 9 (16.7%) of the imaging studies. In PNS imaging, Maxillary sinus involvement was found in every patient who underwent imaging while pan-sinusitis was detected in 31 of 54 scans (57.4%).

For histo-pathological evaluation samples were collected from nasal mucosa in 32(80%), sino-nasal sinuses in 8(20%), and eyeball in 1 (2.5%) from 41 (62.1%) patients. Microscopic examination was done using Hematoxylin-eosin and Periodic Acid Schiff stains. Presence of broad aseptate fungal hyphae branching at right angle was seen in all 32 of 41 cases (78.1%). 11 cases showed the presence of fungal spores with hyphae while two cases showed sporangio spores along with hyphae. Accompanying tissue necrosis was evident in 63.4% (26 of 41) subjects. Dense mixed inflammatory cell infiltrate was present in 82.9% (34 of 42) patients. While 9.7% (4 of 41) showed thick exudates.

DISCUSSION

India has the highest burden of mucormycosis in the world with an estimated prevalence of 140 cases per million populations [6]. Also, it has the second-largest number of adults with DM aged 20–79 years [7]. A recent nationwide multi-center study, prior to Covid-19, was conducted on 388 confirmed or suspected cases of mucormycosis in India by Prakash et al which revealed 57% of patients had uncontrolled diabetes mellitus [8].

In our study majority of ROCM patients were in the age range of 45-65 years with mean age of 51.12 years, making it concordant with other studies [9, 10]. Male preponderance (81.82%) was seen in the present study. Gupta et al also found males to be commonly affected in ROCM [9]. Similar finding has been reported by Vaughan et al in their review study of 175 patients of Sino–orbital mucormycosis where males were more commonly affected (68.5%) [11].

Present study showed the mean duration of 19.22 (±8.12) days between the first symptom of Covid-19 and development of mucormycosis symptoms. This result is in concordance with the study conducted by Sen et al who reported the mean duration between the diagnosis of COVID-19 and the development of symptoms of mucormycosis to be 15.6±9.6 days [12].

Headache was the most common presenting symptom of patients in our study followed by peri-orbital discoloration and unilateral blindness. III, IV, V, VI, VII cranial nerve involvement was also seen in proportionate number of cases. El-kholyet al in their recent work on invasive fungal sinusitis in post covid-19 patients reported similar clinical features. The most common presenting symptoms in their study were headache and facial pain (75%), facial numbness (66.7%), ophthalmoplegia and visual loss (63.9%) [13].

It has been promoted in printed media that covid vaccination offers protection against mucormycosis. This is in contrast to our study where 37.88% patients developed mucormycosis despite being vaccinated. Thus indicating no significant association between vaccination and prevention of mucormycosis (p=0.36).

John et al in April 2021 conducted a systematic review and reported the findings of 41 confirmed mucormycosis cases in people with COVID-19, whereby, DM was reported in 93% cases, while 88% were receiving corticosteroids [14]. These findings are in concordance with our findings of 66 mucormycosis cases in Covid-19 patients, where 90.91% cases had DM, and more than two-third (96.96%) received a course of corticosteroids. Collectively, these findings suggest a familiar relationship of mucormycosis with diabetes.

However, in context of corticosteroid intake, our results are in contrast to these studies as total steroid dose intake was higher in non ROCM group compared to ROCM group. Also, follow up of controls for minimum of 3 weeks did not reveal any sign and symptoms of ROCM. Interestingly, a kind of paradoxical association was noticed in two cases who developed mucormycosis without any treatment history with corticosteroids. Due to

lack of studies comparing patients of mucormycosis in non-diabetic COVID-19 who did not receive steroids versus COVID-19 patients who received steroids and developed mucormycosis, it is difficult to establish a causal effect relationship between COVID-19 and mucormycosis in relation to corticosteroids.

Steam inhalation is an age-old home remedy and a simple, non-pharmacological method often used to relieve nasal and sinus congestion, throat irritation and improve nasal mucociliary clearance in upper respiratory tract infections. But it can provide a warm and damp environment for the growth of fungus. Tap water used in steam inhalers tends to leave deposits in the water container which can provide a milieu for growth of microbes like fungi. Steam inhalation via such routes together with a warm and damp environment created by steam in the nasal passage can predispose to fungal infections especially in immuno compromised individuals or in patients on immune suppressive therapy or with high sugar and ferritin levels [15]. Our study data showed 59.09% cases to be on steam inhalation indicating it to be a significant predisposing factor in causing mucormycosis ($p<0.0002$).

Second wave of Covid-19 in India saw an unforeseen use of industrial oxygen, to address for the lack of oxygen supply. Medical oxygen compared to industrial oxygen is highly purified as it undergoes a range of processes such as compression, filtration and purification. Even its cylinders undergo disinfection and cleanliness processes [15]. Thus, in comparison, use of industrial oxygen along with its unhygienic delivery to Covid patients could be a potential root cause of mucormycosis. In our study population, non-medical grade oxygen was received only by 7.5% cases. It can thus be said that use of industrial (non-medical grade) oxygen does not appear to be a major predisposing exposure for mucormycosis.

Literature review shows many studies stating corticosteroid intake to be a significant risk factor for development of covid associated mucormycosis. [2,14] A systematic review by Singh et al on 101 cases of mucormycosis in COVID-19 patients identified corticosteroid therapy (76.3%) to be the most common risk factor [2]. Similarly, John et al reported COVID-19 associated mucormycosis in 87.8% patients who were on corticosteroid therapy [14]. Ravani et al in their retrospective study also found corticosteroid use (61.2%) to be a significant risk factor [16]. In our study results, 96.97% cases had treatment history with steroids and other immune-modulators (Tocilizumab and/ or Thymosin Alfa) for the treatment of COVID-19. Also, 100% non ROCM patients received steroids/immune-modulator therapies but did not develop any sign and symptom of ROCM during their entire observation and follow up period. As high percentage of patients received steroids/immune modulators in both the groups, we fail to find any association between development of mucormycosis due to steroid/immune-modulator therapy in Covid 19 population.

Evaluation of lung parenchymal involvement in cases showed no significant association between higher CT values (severe lung affection) and development of mucormycosis. Data showed that non ROCM patients despite having more significant lung parenchymal involvement [63.6(±19.7) in non ROCM group as compared to 48(±23.7) in ROCM group], did not develop any clinical features of mucormycosis during their hospital stay and in follow up period.

In our study, among laboratory parameters, hyperferritinemia was prominently observed in ROCM group compared from non ROCM group, median (IQR) value being 1026.50(1105.75) and 625.65(766.50) respectively ($p<0.004$). Which supported the concern raised in previous few studies that high ferritin levels provide an ideal

environment for germination of mucorales spores [17, 18].

It is now well known that Covid 19 can induce significant and sustained lymphopenia, which in turn can predispose to opportunistic infections [19]. Lymphocytes and macrophages are key components of immune system providing defense against large number of pathogens including fungal organisms. Our study data did not reveal any significant difference between the two groups with respect to lymphopenia (increased N/L ratio). Thus, it can be concluded that presence of lymphopenia is not a predisposing risk factor for the development of mucormycosis in Covid 19 patients ($p<0.482$). Also, we did not find any significant association between lactate dehydrogenase levels and risk of developing mucormycosis.

To the best of our knowledge, this is the first study taking into consideration the largest number of study participants (ROCM and non ROCM) to investigate predisposing risk factors for the development of ROCM in patients of Covid-19, and is the first study to have follow up of non ROCM patients.

We could not analyze certain laboratory parameters (D- Dimer, CRP) owing to availability of reports from different laboratories which used different methods for performing the test.

CONCLUSION

Uncontrolled blood sugar level, steam inhalation at home and hyperferritinemia were found to be the major predisposing factors for the development of ROCM in Covid 19 patients. Blood sugar and hyperferritinemia provides favorable environment for growth of fungi. Further inadvertent steam inhalation by producing moist environment in upper airway promotes to growth of fungus in paranasal sinuses. Surprisingly use of high doses and prolonged administration of steroids/ immuno-modulators did not predispose patients of Covid 19 to development of ROCM. Covid vaccination did not offer any protection in prevention of ROCM infection. Steam inhalation being an age old practice for allergic respiratory infection, but the safety of steam inhalation in immuno-compromised status like covid needs further evaluation.

Lessons learnt –

1. Blood sugar and hyperferritinemia provides favorable environment for growth of fungi.
2. Inadvertent steam inhalation by producing moist environment in upper airway promotes to growth of fungus in paranasal sinuses.
3. Uncontrolled blood sugar level, steam inhalation at home and hyperferritinemia were found to be the major predisposing factors for the development of ROCM in Covid 19 patients.
4. Use of high doses and prolonged administration of steroids/ immuno-modulators did not predispose patients of Covid 19 to development of ROCM.
5. Covid vaccination did not offer any protection in prevention of ROCM infection.

Declaration by Authors

Ethical Approval: Approved

Acknowledgement: None

Source of Funding: None

Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1. Kubin CJ, McConville TH, Dietz D, et al. Characterization of Bacterial and Fungal Infections in Hospitalized Patients with Coronavirus Disease 2019 and Factors Associated With Health Care-Associated Infections, Open Forum Infectious Diseases. 2021;8(6). https://doi.org/10.1093/ofid/ofab201
2. Singh AK, Singh R, Joshi SR, et al. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. Diabetes Metab Syndr.

2021;15(4):102146. doi: 10.1016/j.dsx.2021.05.019.
3. Sridhara SR, Paragache G, Panda NK, et al. Mucormycosis in immunocompetent individuals: an increasing trend. J Otolaryngol. 2005;34(6):402-6. doi: 10.2310/7070.2005.34607. PMID: 16343400.
4. Skiada A, Pavleas I, Drogari-Apiranthitou M. Epidemiology and Diagnosis of Mucormycosis: An Update. J Fungi (Basel). 2020;6(4):265. doi:10.3390/jof6040265.
5. Sharma S, Grover M, Bhargava S, et al. Post coronavirus disease mucormycosis: a deadly addition to the pandemic spectrum. J Laryngol Otol. 2021;135(5):442-7. doi:10.1017/S0022215121000992.
6. Prakash H, Chakrabarti A. Global Epidemiology of Mucormycosis. J Fungi (Basel). 2019;5(1):26. doi:10.3390/jof5010026.
7. Federation, International Diabetes. Idf Diabetes Atlas. [(accessed on 9 April 2021)];2019 Available online: https://diabetesatlas.org/en/resources/.
8. Prakash H, Ghosh AK, Rudramurthy SM, et al. A Prospective Multicenter Study on Mucormycosis in India: Epidemiology, Diagnosis, and Treatment. Med. Mycol. 2019; 57:395–402. doi: 10.1093/mmy/myy060.
9. Gupta S, Goyal R, Kaore NM. Rhino-Orbital-Cerebral Mucormycosis: Battle with the Deadly Enemy. Indian J Otolaryngol Head Neck Surg. 2020;72(1):104-11. doi:10.1007/s12070-019-01774-z.
10. Priya P, Ganesan V, Rajendran T, et al. Mucormycosis in a Tertiary Care Center in South India: A 4-Year Experience. Indian J Crit Care Med, 2020;24(3):168–71.
11. Vaughan C, Bartolo A, Vallabh N, et al. A meta-analysis of survival factors in rhino-orbital-cerebral mucormycosis - has anything changed in the past 20 years? ClinOtolaryngol. 2018;43(6):1454–64. doi: 10.1111/coa.13175.
12. Sen M, Lahane S, Lahane TP, et al. Mucor in a viral land: a tale of two pathogens. Indian J Ophthalmol. 2021; 69:244–52. 10.4103/ijo.IJO_3774_20.
13. El-Kholy NA, El-Fattah AMA, Khafagy YW et al. Invasive Fungal Sinusitis in Post COVID-19 Patients: A New Clinical Entity. The Laryngoscope. 2021. https://doi.org/10.1002/lary.29632
14. John TM, Jacob CN, Kontoyiannis DP. When uncontrolled diabetes mellitus and severe COVID-19 converge: the perfect storm for mucormycosis. J Fungi (Basel). 2021;7(4):298.
15. Banerjee M, Pal R, Bhadada SK. Intercepting the deadly trinity of mucormycosis, diabetes and COVID-19 in India Postgraduate Medical Journal Published Online First: 08 June 2021. doi: 10.1136/postgradmedj-2021-140537
16. Ravani SA, Agrawal GA, Leuva PA, et al. Rise of the phoenix: Mucormycosis in COVID-19 times. Indian J Ophthalmol. 2021; 69:1563-8.
17. Ibrahim AS, Spellberg B, Edwards J. Iron acquisition: a novel perspective on mucormycosis pathogenesis and treatment. Curr Opin Infect Dis. 2008;21(6): 620-5. doi: 10.1097/QCO.0b013e3283165fd1.
18. Habib HM, Ibrahim S, Zaim A, et al. The role of iron in the pathogenesis of COVID-19 and possible treatment with lactoferrin and other iron chelators. Biomed Pharmacother. 2021; 136:111228. doi: 10.1016/j.biopha.2021.111228. Epub 2021 Jan 13. PMID: 33454595; PMCID: PMC7836924.
19. Pasero D, Sanna S, Liperi C, et al. A challenging complication following SARS-CoV-2 infection: a case of pulmonary mucormycosis. Infection. 2021;49(5):1055-60. doi:10.1007/s15010-020-01561-x.

How to cite this article: Nishant Agrawal, Rishu Garg, Rahul Jain, Kapil Telang, Ajoy Sodani. Practice of steam inhalation at home - a major contributory risk factor for development of rhino-orbital cerebral mucormycosis (ROCM) in COVID-19 patients. *Int J Health Sci Res.* 2024; 14(3):143-150. DOI: *10.52403/ijhsr.20240321*

******