Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Infection and Public Health 15 (2022) 1265–1269

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: www.elsevier.com/locate/jiph

Determinants of stroke in patients with rhino cerebral mucormycosis seen during the second wave of COVID-19 pandemic: A prospective cohort study

Shweta Pandey [a,*], Hardeep Singh Malhotra [a], Ravindra Kumar Garg [a], Kamini Sharma [a], Imran Rizvi [a], Sukriti Kumar [b], Neeraj Kumar [a], Ravi Uniyal [a], Praveen Kumar Sharma [a], Prashant Gupta [c], Amita Jain [c], D. Himanshu Reddy [d]

[a] Department of neurology, King George's Medical University, Lucknow, Uttar Pradesh, India
[b] Department of Radiodiagnosis, King George's Medical University, Lucknow, Uttar Pradesh, India
[c] Department of Microbiology, King George's Medical University, Lucknow, Uttar Pradesh, India
[d] Department of Internal Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India

ARTICLE INFO

Article history:
Received 23 May 2022
Received in revised form 26 September 2022
Accepted 5 October 2022

Keywords:
SARS-COV-2
Mucormycosis
Stroke

ABSTRACT

Background: Rhino cerebral mucormycosis is an uncommon opportunistic infection of the nasal sinuses and brain, and a group of saprophytic fungi causes it. During the second wave of COVID-19, India witnessed an unprecedented number of patients with rhino cerebral mucormycosis. Invasion of the cavernous sinus and occlusion of the internal carotid artery in many cases resulted in a stroke. The study aimed to assess the clinical and neuroimaging predictors of stroke in patients with rhino cerebral mucormycosis. We also evaluated the predictors of death in these patients at 90 days.

Methods: A prospective study was performed at a tertiary care centre in India between July 2021 and September 2021. We enrolled consecutive microbiologically confirmed patients of rhino cerebral mucormycosis. All patients underwent neuroimaging of the brain. Treatment comprised of anti-fungal drugs and endoscopic nasal/sinus debridement. We followed the patients for 90 days and assessed the predictors of stroke and mortality

Results: Forty-four patients with rhino cerebral mucormycosis were enrolled. At inclusion, in 24 patients, the RT-PCR test for SARS-COV-2 was negative. Diabetes mellitus was the most frequent (72.7 %) underlying risk factor; in most, diabetes mellitus was recently discovered. At inclusion or subsequent follow-up, stroke was seen in 11 (25 %) patients. Only seven patients had hemiparesis. Imaging revealed internal carotid artery occlusion in 17 (38.6 %) patients. Hypertension, corticosteroid use, and cavernous sinus thrombosis were independent predictors of stroke. Nine (20.5 %) died during follow-up, and stroke was an independent predictor of death.

Conclusion: Stroke indicated poor prognosis among rhino cerebral mucormycosis patients encountered during the second wave of the COVID-19 epidemic.

Introduction

Rhino cerebral mucormycosis is generally considered a rare disease. During the second wave of the COVID-19 pandemic, India witnessed an unprecedented rise in cases of mucormycosis. SARS Cov-2 delta variant (B.1.617.2) outbreak resulted in most rhino cerebral mucormycosis cases. According to World Health Organization, the global incidence of mucormycosis varies from 0.005 to 1.7 per million. In India, the prevalence of mucormycosis is estimated to be

* Corresponding author.
E-mail addresses: shwetapandey@kgmcindia.edu (S. Pandey), drhsmalhotra@gmail.com (H.S. Malhotra), garg50@yahoo.com (R.K. Garg), windblow1386@gmail.com (K. Sharma), imranrizvi09@gmail.com (I. Rizvi), sukritikumar87@gmail.com (S. Kumar), drneeraj2903@gmail.com (N. Kumar), ravi.sun.uniyal@gmail.com (R. Uniyal), pspgimer@gmail.com (P.K. Sharma), prashantgupta46@hotmail.com (P. Gupta), amita602002@yahoo.com, amita60@gmail.com (A. Jain), dr.himanshu.reddy@gmail.com (D.H. Reddy).

https://doi.org/10.1016/j.jiph.2022.10.009

140 per million, almost 80 times higher than that in developed countries [1,2].

Mucormycosis is caused by saprophytic fungi of the order *Mucorales* and generally affects the immunocompromised population. Injudicious use of corticosteroids, other immunomodulating drugs, new-onset diabetes mellitus, SARS-COV-2- associated immune dysregulation, and industrial oxygen use was responsible for many mucormycosis cases in India.

Rhinocerebral mucormycosis predominantly involves nasal passages, sinuses, orbit, and the brain. Cavernous sinus thrombosis, internal carotid artery occlusion leading to stroke, and basi-frontal cerebritis are severe neurological complications [3]. Mucormycosis, if not promptly treated, is universally fatal. The mortality rate in rhino cerebral mucormycosis is high despite adequate anti-fungal treatment [4–6].

The study aimed to assess the clinical and neuroimaging predictors of stroke and mortality at 90 days in patients with rhino cerebral mucormycosis involving the brain.

Material and methods

Setting

This prospective cohort study was conducted at a tertiary care centre in North India. We included all consecutive patients with rhino cerebral mucormycosis admitted to the Neurology ward from July 2021 to September 2021. Our institutional ethics committee approved the study (Reference code-672/Ethics/2021). Before inclusion in the study, we obtained written informed consent from all the participants/caregivers.

Inclusion criteria and definitions

We enrolled microbiologically confirmed patients with rhino cerebral mucormycosis [7]. The fungus was demonstrated in the nasal mucosa and debrided or biopsied tissue, with evidence of intracranial structures' involvement in neuroimaging. Nasopharyngeal and oropharyngeal RT-PCR was done to diagnose SARS-COV-2 infection status in every patient. We labelled the patients as COVID-19-associated mucormycosis (CAM) who developed it within six weeks of COVID-19 disease. [8] We classified all the enrolled patients into two groups based on RT-PCR SARS-COV-2 test results (RT-PCR positive and RT-PCR negative).

Workup

All patients were subjected to a battery of blood tests, including haemoglobin, total leukocyte count, serum electrolytes, liver function tests, kidney function tests, C-reactive protein (CRP), and serum lactate dehydrogenase (LDH), serum ferritin, and D-Dimer levels. chest X-ray was done in all the patients. All patients with normal baseline renal functions were subjected to contrast-enhanced CT/MRI of the brain and CT/MR angiography.

Nasal swabs and tissue biopsies were obtained through diagnostic nasal endoscopy. Specimens were further tested for KOH staining, microscopy, histopathology, and culture on Sabouraud's dextrose agar media. The histopathological examination assessed Periodic acid-Schiff (PAS) stain status, tissue necrosis, inflammatory infiltrates, angioinvasion, and granuloma formation. MALDI-ToF (Matrix-Assisted Laser Desorption/Ionization-Time of Flight) mass spectrometry identified fungal species.

Treatment

A multispecialty team of experts from otolaryngology, ophthalmology, maxillofacial surgery, neurology, and neurosurgery were involved in the treatment of patients developing rhino cerebral mucormycosis. Intravenous liposomal amphotericin-B at dosage 5 mg/kg/day was the first line of treatment for 2–4 weeks. Oral extended-release posaconazole (300 mg 12 hourly on day 1, then 300 mg once a day) constituted the Step-down treatment in all patients. Patients continued taking posaconazole for the next 3–6 months. We extended intravenous liposomal amphotericin B treatment duration to 4–6 weeks if patients showed clinical deterioration. We could not administer amphotericin-B at a recommended dosage of 10 mg/kg [9] because of its acute crisis amid the mucormycosis epidemic in our country. Surgical treatment included endoscopic sinus/nasal debridement, orbital exenteration, palatal curettage, and debridement. In some patients, neurosurgeons performed craniotomy and evacuation of intracranial fungal abscesses or hematoma.

Follow up

We followed the patients for 90 days. Disability assessment was done using the modified Barthel Index: self-care assessment (MBI; 0–100 score) [10].

Statistical analysis

Statistical analysis was done using the IBM SPSS version 24.0. Categorical variables were presented as percentages, and continuous variables were presented as mean ± standard deviation (SD) and median and inter-quartile range (IQR).

The categorical variables were compared using the applicable Chi-square test/ Fisher exact test. The continuous variables were compared using the Mann-Whitney U test. Univariate odds ratios and 95 % confidence intervals were calculated for the categorical variables.

The multivariate analysis was done using binary logistic regression to identify the independent predictors of stroke and mortality. For binary logistic regression, outcome/ occurrence of stroke were taken as the dependent variable, and three discrete variables out of a total of five variables found significant on univariate analysis were taken as independent variables. For the second assessment, mortality was taken as the dependent variable while five discrete variable out of a total of six variables found significant of univariate analysis were taken as independent variables. The performance of the multivariate model was assessed using discrimination and calibration; the discrimination was assessed as the area under the receiver operating characteristic curve (AUC). The calibration was assessed using the calibration plots as well as the Hosmer and Lemeshow test.

Results

We enrolled 44 consecutive patients with rhino cerebral mucormycosis. The details of baseline demographic profile, biochemical parameters, clinical features, neuroimaging findings, drug treatment, surgical treatment, and clinical outcomes have been provided in Table 1.

The mean age of the study population was 50.14 years (range 32–75 years). Diabetes was present in 32/44 (72.7 %) cases; of these,15 patients (47 %) had new-onset diabetes. Ophthalmoplegia (91 %), ptosis (88.6 %), proptosis (79.5 %) and vision loss (79.5 %) were common clinical presentations. Other clinical features were facial sensory loss, headache, nerve palsy, palatal eschar, and hemiparesis. Seizures and meningitis were observed in 6.8 % and 4.5 % of patients (Table 1).

MRI of the brain revealed the involvement of the cavernous sinus in 28/44 (63.6 %) of patients. Internal carotid artery occlusion was seen in 17/44 (38.6 %) patients. Infarcts in the territory of a large

Table 1
Demographic, biochemical, drug treatment, surgical treatment, clinical features, neuroimaging findings and outcome parameters of rhino-orbito-cerebral mucormycosis.

Parameters	Total, n = 44 (%)	SARS-CoV-2 positive, n = 20	SARS-CoV-2 negative, n = 24	P value
Demographic profile				
Age (mean, range)	50.14 (32–75)	48.40 (35–62)	51.58 (32–75)	0.294
Sex (male %)	29(66)	12(60)	17(71)	0.450
Diabetes	32(72.7)	15 (46.9)	17 (53.1 %)	0.757
Long standing diabetes mellitus	17(38.6)	6(30)	11 (45.8)	0.282
New-onset diabetes mellitus	15(34)	9(45)	6(25)	0.601
HBA1C§ (mean)	10.29 ± 2.4	10.49 ± 2.6	10.04 ± 2.1	0.271
Hypertension	15(34)	7(35)	8(33.3)	0.908
Coronary Artery disease	2(4.5)	2(10)	0(0)	
Chronic kidney disease	1(2.2)	1(5)	0(0)	
Acute Renal impairment	6(13.6)	2(10)	4(16.6)	0.521
Diabetic ketoacidosis (DKA)	2(4.5)	2(10)	0(0)	
Latency of ROCM§ after COVID-19 disease mean (days)	12(5–30)	12(5–30)	NA	0.00
Steroid (n (dexamethasone means mg))	17(98 ± 49)	17(98 ± 49)	0(0)	0.00
Biochemical parameters				
C-reactive protein median (mg per dl)	66.50(4.84–168)	71.21(11.4–168)	69.36(4.84–141)	0.639
Serum Ferritin median (microgram per L)	550(88.2–2000)	522 (88–1164)	522(206–2000)	0.167
Serum Lactate dehydrogenase median (U/L)	537(304–4122)	613(357–1142)	478(304–4122)	0.194
D-Dimer median (mg per dl)	0.75(0.11–10.0)	0.63(0.11–10.0)	0.90(0.14–9.8)	0.613
Drug treatment				
Liposomal amphotericin B (mean dose (gm))	5.26 ± 1.94	5.78 ± 2.34	4.87 ± 1.44	0.133
Combination treatment (Liposomal amphotericin-B + Posaconazole)	15(34)	8(40)	7(29)	
Clinical features				
Ptosis	39(88.6)	20(100)	19(79)	0.030
Proptosis	35(79.5)	18(90)	17(71)	0.117
Ophthalmoplegia	40(91)	20(100)	20(83.3)	0.056
Vision impairment	35(79.5)	18(90)	17(71)	0.117
Facial sensory loss	27(61.3)	12(60)	15(62.5)	0.865
Facial pain	20(45.4)	12(60)	8(33.3)	0.076
Headache	20(45.4)	12(60)	8(33.3)	0.076
Facial palsy	13(29.5)	7(35)	6(25)	0.469
Hemiparesis	7(16)	4(20)	3(12.5)	0.498
Nasal discharge/bleeding	6(13.6)	3(15)	3(12.5)	0.809
Seizures	3(6.8)	2(10)	1(4.1)	0.356
Meningitis	2(4.5)	0 (0)	2(8.3)	
Palatal eschar	10(22.7)	3(15)	7(29)	0.264
Skin necrosis (eschar)	6(13.6)	2(10)	4(16.6)	0.521
Neuroimaging abnormalities				
Large vessel infarct	11(25)	6(30)	5(20.8)	0.484
Involvement of cavernous sinus	28 (63.6)	17 (85)	11(45.8)	0.011
ICA§ involvement	17(38.6)	11(55)	6(25)	0.042
Anterior temporal cerebritis/abscess	12 (27.3)	1(5)	11(45.8)	0.002
Basi-frontal cerebritis/abscess	5 (11.4)	3(15)	2(8.3)	0.487
Parieto-occipital abscess	1 (2.3)	1(5)	0(0)	
Dural thickening	36 (81.8)	16(8)	20(83.3)	0.775
Normal Brain parenchyma	8 (18)	4(20)	4((16.7)	0.775
Clinical outcome				
Death	9(20.5)	5(25)	4(16.7)	
Alive	32(72.7)	13(65)	19(79.2)	
Lost to follow up	3 (6.8)	2 (10)	1(4.1)	0.946

§ ROCM, rhino-orbito-cerebral mucormycosis; ICA, Internal carotid artery; HBA1C, glycated haemoglobin.
*CP angle, cerebellopontine angle; RMSO, retro mastoid suboccipital craniotomy.

cerebral vessel were observed in 11/44 (25 %) patients; 2/3rd of these patients had infarcts in the middle cerebral artery region. The other neuroimaging findings were anterior temporal cerebritis, basi-frontal cerebritis, and lacunar infarcts. (Table 1).

In 91 % (40/44) patients, KOH stain and microscopy detected Mucor hyphae in nasal swabs or biopsied tissue. Histopathology was positive in 34 % (15/44) of patients, and culture was positive in 22.7 % (10/44) patients. Species identification via MALDI-TOF PCR could be made in 13.6 % (6/44) of patients. We identified *Rhizopus oryzae* complex in five patients and *Rhizopus microsporus* in one patient. Interestingly, *Aspergillus* coinfection was noted in three patients.

We tried to compare clinical features, biochemical parameters, and mortality outcomes of positive RT-PCR cases with that of negative RT-PCR. We did not find a significant difference between the two groups except cavernous sinus thrombosis and internal carotid occlusion on neuroimaging were significantly more common RT-PCR positive cases.

We treated 45.45 % (20/44) of patients with liposomal amphotericin B for at least two weeks. Approximately 41 % (18/44) were treated for six weeks, and two patients (5 %) required liposomal amphotericin B for eight weeks. Four patients (9 %) could not receive an entire course of liposomal amphotericin B owing to the antifungal drug crisis. Nineteen (47.5 %) patients had Hypokalemia, which was corrected on potassium supplementation. Significant renal impairment necessitated liposomal amphotericin B withdrawal in one patient. Nine (20.5 %) patients died.

On univariate analysis, hemiparesis [Odds ratio, OR= 68.00, CI (6.02–767.69), P < 0.001], meningitis (P = 0.038), at least 2-week treatment with liposomal amphotericin B (OR=0.02, CI 0.002–0.255), P = 0.001), high lactate dehydrogenase (P = 0.011), interleukin-6 (P = 0.011), and C- reactive protein (P = 0.004) were significantly associated with mortality. However, in multivariate analysis using binary logistic regression analysis, only hemiparesis was an independent predictor of death [P = 0.011, OR= 83.23, 95 % CI 2.76–251.35).

Hypertension (OR=4.71; CI (1.24–17.97); P = 0.019), corticosteroids usage (OR=5.50; CI (1.44–20.96); P < 0.010)), cavernous sinus thrombosis (OR=17.31; CI (2.00–149.51); P = 0.003) internal carotid artery occlusion (OR=8.07; CI (2.01–32.39); P = 0.003), and vision loss (P = 0.016), on univariate analysis, were associated with stroke occurrence. In a multivariate model for stroke prediction using binary logistic regression, we found that hypertension (OR=6.35, 95 %CI 1.12–36.02, P = 0.037), corticosteroids usage (OR=5.34, 95 %CI 1.02–27.96, P = 0.048) and cavernous sinus thrombosis (OR=15.21, 95 %CI 1.45–159.35, P = 0.023) were independently associated with the stroke. The model showed good discrimination AUC = 87.2 % (95 % CI=75.2–99.1, P < 0.001), the model also showed good calibration Hosmer and Lemeshow test P value= 0.285.

Thirty-two patients were alive at day 90. Approximately 78 % (25/32) of patients had a unilateral and irreversible vision loss with no light perception. Vision loss was bilateral in one patient, and none of these patients showed visual recovery on follow-up. Twenty-three (72 %) patients had residual ophthalmoparesis.

At 90 days, 26 (81 %) patients were independent for activities of daily living, while 6 (18.75 %) patients were dependent on caregivers.

Discussion

In our series, 24 patients with rhino cerebral mucormycosis tested negative for the RT-PCR for SARS-COV-2. We believe these were patients of COVID-19 who turned negative by reaching us with mucormycosis. A similar observation was reported in several parts of India. In a series of 458 patients, Patel and colleagues noted that approximately one-fifth of the patients had no evidence of past or concurrent COVID-19 disease [11]. In another multicentric study involving 16 centres, out of 295, only 65 % (187/ 287) of mucormycosis cases had positive RT-PCR test for SARS-COV-2 [12]. Kumar and colleagues noted that 35 % (162/464) of mucormycosis patients had negative RT-PCR report for SARS-COV-2. However, 120 of these demonstrated SARS-COV-2 antibodies in serum [13].

We noted angiographic evidence of internal carotid artery occlusion in 17 patients with rhino cerebral mucormycosis, infarcts in the territory of a major cerebral artery were noted in 11 patients, and corresponding hemiparesis was present only in seven patients. Infarcts were in the watershed areas and in main territory of the middle cerebral artery. We further noted that pre-existing hypertension, corticosteroid usage and cavernous sinus thrombosis independently predicted cerebral vascular complications in patients with rhino cerebral mucormycosis. Six out of seven patients who had hemiparesis died. There are several routes through which fungus can invade the brain. Perineural invasion is one possible mechanism. The fungus also may spread directly into the anterior cranial fossa via perforating cribriform plate. Mucor has substantial angio-invasive property, and vascular invasion leads to thrombosis and tissue necrosis. While traversing through the cavernous sinus, the internal carotid artery is likely to get involved, resulting in occlusion and thrombus formation. In patients with rhino cerebral mucormycosis. Ischemic stroke was the most common cerebrovascular event. However, infrequently, fungal infiltration of arterial wall results in mycotic aneurysm formation and subsequent subarachnoid haemorrhage. We did not observe intracranial haemorrhage in our patients [14,15]. Diabetes mellitus, endothelial dysfunction, COVID-19 mediated cytokine storm, and hypercoagulable state might serve as underlying pathophysiological derangements triggering a stroke [16].

Ninety-day mortality in our study was approximately 21 %, and hemiparesis was an independent predictor of mortality. Mortality in mucormycosis, if there is pulmonary or cerebral involvement or if the disease is disseminated, is generally much higher and approaches 49 %. Most of the survivors are left with severe morbidities, like vision loss [17–19]. We could save many patients because of their timely treatment. We treated our patients aggressively with liposomal amphotericin B and surgical debridement, led by a multidisciplinary team. Treatment with amphotericin B has been reported to be an independent predictor of survival and may reduce mortality from 92 % to 41 %. [20,21] Combined treatment with amphotericin B and surgical debridement improve survival even further by 15–30 % compared to anti-fungal therapy alone [22,23].

There were several limitations to our study. The sample size was small, and a longer follow-up would have provided a better picture of mortality and disabilities. The results of binary logistic regression of our study may be confirmed in a larger sample size for a better level of confidence. We did not perform the serological evaluation for antibodies against SARS-COV-2 infection in our patients, who tested negative on the RT-PCR test.

In conclusion, stroke is frequent in rhino cerebral mucormycosis owing to fungal invasion and internal carotid artery occlusion in the cavernous sinus. COVID-19 disease-mediated thrombogenicity possibly enhances the risk. Stroke is an independent predictor of death, and aggressive treatment may improve survival.

Declaration of Competing Interest

None declared

References

[1] World Health Organization dashboard. Mucormycosis. Available from ⟨https://www.who.int/india/emergencies/coronavirus-disease-(covid-19)/mucormycosis⟩. Accessed on 20 January 2022.
[2] Muthu V, Rudramurthy SM, Chakrabarti A, Agarwal R. Epidemiology and pathophysiology of COVID-19-associated mucormycosis: india versus the rest of the world. Mycopathologia 2021;186:739–54.
[3] Chikley A, Ben-Ami R, Kontoyiannis DP. Mucormycosis of the central nervous system. J Fungi (Basel) 2019;5:59.
[4] Prakash H, Chakrabarti A. Epidemiology of mucormycosis in India. Microorganisms 2021;9:523.
[5] Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. Diabetes Metab Syndr 2021;15:102146.
[6] Sen M, Honavar SG, Bansal R, Sengupta S, Rao R, Kim U, et al. Epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbital-cerebral mucormycosis in 2826 patients in India - collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC), report 1. Indian J Ophthalmol 2021;69:1670–92.
[7] Honavar SG. Code Mucor: guidelines for the diagnosis, staging and management of rhino-orbito-cerebral mucormycosis in the setting of COVID-19. Indian J Ophthalmol 2021;69:1361–5.
[8] National Centre for Disease Control, Directorate General of Health Services, Government of India. Covid-19 Associated Mucormycosis. June 2021.Available from ⟨https://ncdc.gov.in/WriteReadData/l892s/22911839231625743853⟩. Accessed on 20 November 2021.
[9] Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SC, Dannaoui E, Hochhegger B, Hoenigl M, Jensen HE, Lagrou K, Lewis RE, Mellinghoff SC. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis 2019;19(12):e405–21.
[10] de Morton NA, Keating JL, Davidson M. Rasch analysis of the barthel index in the assessment of hospitalized older patients after admission for an acute medical condition. Arch Phys Med Rehabil 2008;89:641–7.
[11] Patel R, Jethva J, Bhagat PR, Prajapati V, Thakkar H, Prajapati K. Rhino-orbital-cerebral mucormycosis: an epidemiological study from a tertiary care referral center in Western India. Indian J Ophthalmol 2022;70(4):1371–5.
[12] Patel A, Agarwal R, Rudramurthy SM, Shevkani M, Xess I, Sharma R, et al. Emerg Infect Dis 2021;27:2349–59.
[13] Kumar S, Choudhary R, Pandey VP. "MuCovid-21" study: Mucormycosis at an Indian tertiary care centre during the COVID-19 pandemic. J R Coll Physicians Edinb 2021;51:352–8.
[14] Dubey S, Mukherjee D, Sarkar P, Mukhopadhyay P, Barman D, Bandopadhyay M, et al. COVID-19 associated rhino-orbital-cerebral mucormycosis: an observational study from Eastern India, with special emphasis on neurological spectrum. Diabetes Metab Syndr 2021;15:102267.
[15] Kulkarni R, Pujari SS, Gupta D, Ojha P, Dhamne M, Bolegave V, et al. Cerebrovascular involvement in mucormycosis in COVID-19 pandemic. J Stroke Cereb Dis 2022;31:106231.
[16] Ghasemiyeh P, Borhani-Haghighi A, Karimzadeh I, Mohammadi-Samani S, Vazin A, Safari A, et al. Major neurologic adverse drug reactions, potential drug-drug

interactions and pharmacokinetic aspects of drugs used in COVID-19 patients with stroke: a narrative review. Ther Clin Risk Manag 2020;16:595–605.
[17] Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, Kontoyiannis DP, Walsh TJ. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis 2005;41:634–53.
[18] Hussain S, Baxi H, Riad A, Klugarová J, Pokorná A, Slezáková S, et al. COVID-19-associated mucormycosis (CAM): an updated evidence mapping. Int J Environ Res Public Health 2021;18:10340.
[19] Hoenigl M, Seidel D, Carvalho A, Rudramurthy SM, Arastehfar A, Gangneux JP, et al. The emergence of COVID-19 associated mucormycosis: a review of cases from 18 countries. Lancet Microbe 2022. https://doi.org/10.1016/S2666-5247(21)00237-8. (Epub ahead of print).
[20] Yohai RA, Bullock JD, Aziz AA, Markert RJ. Survival factors in rhino-orbital-cerebral mucormycosis. Surv Ophthalmol 1994;39:3–22.
[21] Weprin BE, Hall WA, Goodman J, Adams GL. Long-term survival in rhinocerebral mucormycosis: case report. J Neurosurg 1998;88:570–5.
[22] Jeong W, Keighley C, Wolfe R, Lee WL, Slavin MA, Chen SC, et al. Contemporary management and clinical outcomes of mucormycosis: a systematic review and meta-analysis of case reports. Int J Antimicrob Agents 2019;53:589–97.
[23] Patel A, Kaur H, Xess I, Michael JS, Savio J, Rudramurthy S, et al. A multicentre observational study on the epidemiology, risk factors, management and outcomes of mucormycosis in India. Clin Microbiol Infect 2020;26:944.e9–944.e15.