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Neuro-mucormycosis: Lessons from COVID-19-associated cases

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Nahad Sedaghat[1], Masoud Etemadifar[2], Pouria Ghasemi[1], Mohammad Naghizadeh[1], Yousef Mokari[3], Mehri Salari[4], Bahar Golastani[5]

[1] Alzahra Research Institute, Alzahra University Hospital, Isfahan University of Medical Sciences, Isfahan, Iran
[2] Department of Neurosurgery, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[3] School of Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran
[4] Functional Neurosurgery Research Center, Shohada Tajrish Comprehensive Neurosurgical Center of Excellence, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[5] Department of Cell and Molecular Biology and Microbiology, School of Biological Science and Technology, University of Isfahan, Isfahan, Iran

Keywords
COVID-19; SARS-CoV-2; Mucormycosis; Neurological Manifestations; Case-Control Studies

Abstract

Background: Scarce data are available on the neurological presentations of coronavirus disease 2019 (COVID-19)-associated mucormycosis (CAM) and COVID-19-unrelated rhino-orbito-cerebral mucormycosis (ROCM). This study aimed to compare the neurological presentations and their associated outcomes in patients with CAM and COVID-19-unrelated ROCM.

Methods: In December 2021, a case-control analysis was conducted on the CAM (case group) and COVID-19-unrelated ROCM (control group) referrals of one center in Isfahan, Iran. Confirmed CAM patients from January 2020 to December 2021 constituted the case group, and patients with COVID-19-unrelated ROCM from 2016-2019 constituted the control group. Their data were then analyzed using proper (non) parametric tests and generalized linear models (GLM), therein P-value below 0.05 was considered as the criterion of statistical significance, and the SPSS software was used.

Results: After retrieving data on 177 patients with mucormycosis, 78 patients with CAM were included as the case group and 72 patients with COVID-19-unrelated ROCM were included as the control group. Neurological presentations suggestive of second, third, and eighth cranial nerve involvement were more prevalent in the CAM group (all with $P < 0.05$). The mortality rate in the CAM group was 1.9 times that of the controls ($P = 0.01$), being explained by higher extent of corticosteroid administration among them. Higher age and presentation with gait ataxia, ptosis, and mydriasis were considered to be predictive of poor prognosis in patients with CAM (all with $P < 0.05$).

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Corresponding Author: Nahad Sedaghat
Email: nahad.sedaghat@gmail.com

Conclusion: The neurological manifestations of CAM differ from COVID-19-unrelated ROCM based on the presented results, some of which are associated with poor prognosis. Further replication is warranted to confirm our retrospective analyses.

Introduction

Mucormycosis – a rare opportunistic entity with poor prognosis caused by the Mucorales spp. fungi[1] – is mostly seen in patients with immune dysfunction; diabetes mellitus (DM), hematological malignancies, and chronic corticosteroid therapy[2,3] are the main risk factors of mucor infection. Rhino-orbito-cerebral mucormycosis (ROCM) – its most common form – often starts with sinus congestion, headache, facial numbness, and vision impairments.[4-6] Early diagnosis and emergent antifungal therapy are the most crucial steps to prevent death in patients with ROCM.

Coronavirus disease 2019 (COVID-19)-associated mucormycosis (CAM) is a recently-recognized subtype of mucormycosis involving people recovering from COVID-19;[7] it mostly presents as ROCM.[8] Administration of corticosteroids in patients with COVID-19 has been suggested as the main cause of CAM, while other factors related to the viral immunopathological effects may also be involved.[7] Considering its fatal nature, early diagnosis and proper management is crucial for patients with CAM. Hence, many experts are currently occupied with providing an evidence-based knowledge on CAM's presentations, clinical course, and prognosis.[8-11] Our observations in the neurology clinic also indicated a difference in neurological courses of CAM and COVID-19-unrelated ROCM. Hence, in this study, we aimed to address the lack of evidence by comparing the CAM and ROCM from a neurological perspective. We hereby report it following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (available on: https://www.strobe-statement.org).

Materials and Methods

Study setting and samples: In December 2021, a case-control study was conducted on the clinical records of all ROCM referrals to the Alzahra University Hospital, Isfahan, Iran – one of the global hotspots of mucormycosis. Two researchers searched the entries of the hospital registry for cases with pathological evidence of mucormycosis from 2016, and screened all of them, selecting eligible cases for analysis.

Inclusion and exclusion criteria: Common inclusion criterion for all patients included definitive ROCM according to the criteria of the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSGERC)[12] with direct histopathological evidence of infection with the Mucorales spp. The additional inclusion criterion for the CAM group was having a history of confirmed COVID-19 based on World Health Organization (WHO) case definition,[13] and for the control group, was being admitted from 2016 to 2019. The control group was chosen from this timeframe, so that their COVID-19-naiivity could be guaranteed. The common exclusion criteria for both groups were: 1) having a fungal coinfection, and 2) inconclusive histopathological findings.

Variables and their stratification: After confirmation of eligibility based on the criteria put forth supra and subjects' or their next-of-kin's consent, all demographic and clinical characteristics of the patients, including their possible risk factors for mucor infection, their medications, underlying conditions, clinical courses, and presenting symptoms were gathered from the patients' clinical records.

Ethical considerations: The study was executed in accordance with the national ethical guidelines, and gained approval from the Research Ethics Committee of Isfahan University of Medical Sciences (approval ID: IR.ARI.MUI.REC.1400.120).

For the statistical analyses, (non) parametric tests were used to compare different findings between the case and control groups. Furthermore, a multivariable generalized linear model (GLM) accounting for age, sex, and other baseline variables showing significant difference between the groups was utilized to account for confounding. Another GLM was used to evaluate the prognostic value of different presentations of CAM. P-value equal or below 0.05 was used as the criterion of statistical significance. The SPSS software (version 26, IBM Corporation, Armonk, NY, USA) was used for the statistical analyses.

Results

177 records were found and retrieved from the hospital registry, of which 150 ROCM cases (80 men and 70 women, mean age: 54.14 ± 18.09) were included in the final analysis; the characteristics of the included cases are summarized in table 1.

Table 1. Characteristics of the participants

Variable	Case (n = 78)	Control (n = 72)	P
Sex [n (%)]			0.15
Male	34 (47.2)	46 (59.0)	
Female	38 (52.8)	32 (41.0)	
Age (year) (mean ± SD)	52.9 ± 19.5	55.6 ± 16.6	0.36
Hospital stay (day) [median (Range)]	6.0 (149), 7 missing	14.5 (59), 4 missing	0.09
Comorbidities [n (%)]			
Diabetes mellitus	41 (52.6)	31 (43.1)	0.24
Hypertension	33 (42.3)	21 (29.2)	0.09
Leukemia	7 (9.0)	17 (23.6)	**0.01**
Ischemic heart disease	15 (19.2)	10 (13.9)	0.38
Hyperlipidemia	11 (14.1)	11 (15.3)	0.84
Chronic kidney disease	3 (3.8)	7 (9.7)	0.15
Benign prostatic enlargement	1 (1.3)	3 (4.2)	0.27
Rheumatoid arthritis	2 (2.6)	1 (1.4)	0.61
Heart failure	2 (2.6)	0 (0)	0.17
Psoriasis	1 (1.3)	0 (0)	0.33
Prior drugs [n (%)]			
Corticosteroids	43 (55.1)	23 (31.9)	< 0.01
Remdesivir	15 (19.2)	0 (0)	< 0.01
Metoprolol	6 (7.7)	4 (5.6)	0.60
Losartan	6 (7.7)	4 (5.6)	0.60
Aspirin	9 (11.5)	4 (5.6)	0.19
Statins	15 (19.2)	5 (6.9)	0.03
Metformin	10 (12.8)	2 (2.8)	0.02
Insulin	15 (19.2)	6 (8.3)	0.05
Ceftriaxone	1 (1.3)	2 (2.8)	0.51
Levofloxacin	2 (2.6)	2 (2.8)	0.93
Prior ventilation support [n (%)]			0.33
No data	14 missing	17 missing	
None	34 (53.1)	35 (63.6)	
Oxygen mask/nasal cannula	6 (9.4)	2 (3.6)	
Ventilator	24 (37.5)	18 (32.7)	
Signs and symptoms of ROCM [n (%)]			
Headache	45 (57.7)	39 (54.2)	0.66
Convulsion	2 (2.6)	3 (4.2)	0.58
Sinus congestion	26 (33.3)	27 (37.5)	0.59
Gait ataxia	9 (11.5)	1 (1.4)	0.01
Hearing loss	6 (7.7)	0 (0)	0.02
Vertigo	22 (28.2)	5 (6.9)	< 0.01
Vision impairment	39 (50.0)	20 (27.8)	< 0.01
Ophthalmoplegia	22 (28.2)	23 (31.9)	0.62
Proptosis	34 (44.7)	11 (20.2)	< 0.01
Ptosis	19 (24.4)	17 (23.6)	0.92
Diplopia	9 (11.5)	11 (15.3)	0.50
Mydriasis	36 (46.2)	16 (22.2)	< 0.01
Facial numbness	39 (50.0)	31 (43.1)	0.39
Medical treatment for ROCM [n (%)]			0.06
Amphotericin B	56 (71.8)	41 (56.9)	
Other	22 (28.2)	31 (43.1)	
Surgical treatment for ROCM [n (%)]			
FESS	24 (41.4), 20 missing	23 (43.4), 19 missing	0.70
Oral resection	0 (0), 25 missing	1 (2.1), 24 missing	0.29
Maxillectomy	6 (10.7), 22 missing	8 (16.7), 24 missing	< 0.01
Final outcome [n (%)]			
Recovered and discharged	45 (57.7)	56 (77.8)	
Died	33 (42.3)	16 (22.2)	

SD: Standard deviation; ROCM: Rhino-orbito-cerebral mucormycosis; FESS: Functional endoscopic sinus surgery

As interpreted, the demographic characteristics of CAM and control groups were similar. Leukemia was more prevalent in the control group, while other comorbidities were similarly prevalent (Table 1). In addition to remdesivir and corticosteroids, the usage of statins, metformin, and insulin was more in the CAM group, indicating either better controlled hyperlipidemia and diabetes, or severer illnesses (Table 1). The more extensive usage of corticosteroids may also explain the more extensive medical treatments for hyperglycemia in the CAM group.

The neurological presentation and outcomes significantly differed between the CAM and control group (Table 1). Headache and facial numbness were the most common presentations in both groups, followed by vision impairment (50.0%), proptosis (44.7%), and mydriasis (46.2%) in the CAM group, in contrast to sinus congestion (37.5%), ophthalmoplegia (31.9%), and vision impairment (27.8%) in the control group.

Neurological presentations suggestive of optic, oculomotor, and vestibulocochlear nerve involvement were significantly more prevalent in the CAM group; while the prevalence of other presentations seemed to have been similar between the two groups (Table 1). The mortality rate was 1.9-folds [95% confidence interval (CI): 1.2-3.2, P = 0.01] higher in the CAM group, despite similar treatment strategies (Table 1); however, according to a multivariable GLM, higher mortality in the CAM group was due to the more extensive usage of corticosteroids among them (Table 2). In the CAM group, higher age and presenting with gait ataxia, ptosis, and mydriasis predicted a poor prognosis with statistical significance based on a multivariable GLM (Table 3).

Discussion

We ran a case-control analysis on the cases of CAM and COVID-19-unrelated ROCM of a single tertiary center in Isfahan – one of the hotspots of mucormycosis across the globe – focusing on their neurological presentations. Being among the first and largest outside Indian settings, this study could be of value for further understanding of CAM, future policy-makings, and management of patients with CAM.

The characteristics of our CAM group, including their neurological presentations and overall mortality, were comparable with the larger Indian studies.[8,14] Furthermore, the frequency of vision impairments in our CAM group was comparable to Muraleedharan et al. study in India[15] (both being around 50%), while the frequency of vision impairments differed significantly in the control groups of the two studies (27.8% in the present study vs. 73.8% in the Muraleedharan et al.'s). Considering that pre-pandemic studies demonstrated visual impairment to occur in around 20% of patients with ROCM upon diagnosis,[16] our results may be more relatable, according to which the frequency of vision impairment in patients with CAM is nearly two-folds the COVID-19-unrelated ROCM ones. Apart from vision impairments, our study further revealed that CAM might present more frequently with other neurological symptoms in comparison with COVID-19-urelated ROCM. Altogether, they mainly suggested involvement of the second, third, and eighth cranial nerves. Involvement of these nerves may be explainable by their close proximity to vascular structures, e.g., the cranial venous sinus structures, which are invaded by the vasotropic mucor hyphae. The pattern of presenting symptoms in the CAM group seemed to have involved less mucosal inflammation compared to the controls, but more damage to the deeper tissues such as cranial nervous structures.

Table 2. Results of multivariable generalized linear model (GLM) of the effect of possible confounders on final outcome of COVID-19-associated mucormycosis (CAM) or control groups

Variables in model (reference)	Multivariable GLM (n = 150, outcome: death)	
	B (SE)	P
Age (per year)	0.01 (0.01)	0.65
Male sex (female)	-0.22 (0.38)	0.57
Having leukemia (not having leukemia)	0.19 (0.61)	0.75
Receiving corticosteroids (not receiving corticosteroids)	1.08 (0.39)	< 0.01
Receiving remdesivir (not receiving remdesivir)	0.72 (0.62)	0.25
Receiving statins (not receiving statins)	0.05 (0.62)	0.94
Receiving metformin (not receiving metformin)	-0.36 (0.72)	0.61
Receiving insulin (not receiving insulin)	0.36 (0.64)	0.57
CAM group (control group)	0.55 (0.43)	0.20

GLM: Generalized linear model; CAM: COVID-19-associated mucormycosis; SE: Standard error

Table 3. Results of multivariable generalized linear model (GLM) of the predictive effect of the presenting symptoms of COVID-19-associated mucormycosis (CAM) on its final outcome

Variables in model (reference)	Multivariable GLM (n = 78, outcome: death)	
	B (SE)	P
Age (per year)	0.06 (0.03)	0.04
Male sex (female)	-0.29 (0.72)	0.69
Headache (no headache)	-0.38 (0.79)	0.63
Sinus congestion (no sinus congestion)	-0.47 (0.79)	0.56
Gait ataxia (no gait ataxia)	4.55 (1.68)	< 0.01
Hearing loss (no hearing loss)	-0.26 (1.28)	0.84
Vertigo (no vertigo)	0.73 (0.82)	0.37
Vision impairment (no vision impairment)	-1.26 (0.88)	0.28
Ophthalmoplegia (no ophthalmoplegia)	-0.98 (0.93)	0.29
Proptosis (no propstosis)	0.56 (0.74)	0.45
Ptosis (no ptosis)	2.90 (1.05)	< 0.01
Diplopia (no diplopia)	-1.54 (1.34)	0.25
Mydriasis (no mydriasis)	1.92 (0.74)	< 0.01
Facial numbness (no facial numbness)	0.03 (0.78)	0.97

GLM: Generalized linear model; SE: Standard error

Due to the retrospective nature of our study, we were unable to affirm this finding with imaging. Other studies which utilized imaging studies such as magnetic resonance imaging (MRI) showed no significant difference in the frequency and extents of cranial involvements in CAM and COVID-19-unrelated ROCM patients;[15,17,18] however, it should be emphasized that absence of findings in MRI – especially the conventional 1.5T studies and in early stages – could not rule out the involvement of deep cranial nervous structures.[16] Evaluation and comparison of neurological presentations – as done in the present study – may, therefore, bear greater potential for correct identification and comparison of the frequency and extent of intracranial invasion of the hyphae among CAM and COVID-19-unrelated ROCM patients. Nevertheless, subject to further replication and confirmation, our results may suggest disruption of mucosal barriers in the people recovering from COVID-19, the exact mechanisms of which – probably driven by corticosteroid administration – remain to be investigated.

Additionally, despite similar treatment strategies with controls, a nearly two-fold higher mortality rate was observed among people with CAM, which was dependent on the prior use of corticosteroids. This mainly indicates that patients with ROCM with prior use of corticosteroids are susceptible to a severer disease course – regardless of their COVID-19 status. Furthermore, apart from higher age, ataxic gait, ptosis, and mydriasis – presentations indicative of intracranial involvement – were shown to be predictors of poor prognosis in the CAM cases; this was an expected finding as intracranial involvement has always been associated with poor prognosis in ROCM even before the COVID-19 pandemic.[19] While also considering the crucial value of early diagnosis and aggressive treatment, physicians are encouraged to be advised of mucormycosis in patients recovering from COVID-19 developing the mentioned sequelae – especially in settings with limited paraclinical diagnosis equipment.

Limitations: Important limitations are applicable to this study due to its retrospective nature, which are encouraged to be accounted for in future replications. Although all participants went through imaging studies in their hospitalization course, the results were not recorded in the center's registry. Therefore, although the extent of the mucor invasion was speculated based on the neurological presentations, it was not affirmed by imaging; the conclusions of the study are, therefore, subject to confirmation by future studies and should be interpreted with caution. Furthermore, the cases of CAM in this study were enrolled during a short period of time in contrast to the COVID-19-unrelated ROCM cases. This higher frequency of ROCM cases during the COVID-19 pandemic could have been due to the so-called "Baader-Meinhof Phenomenon"; therefore, we refrained from conducting any analysis on the incidence or frequency of cases, and focused on comparing the neurological presentations of CAM and COVID-19-unrelated ROCM and their associated outcomes

in a case-control fashion. Finally, the comparison of CAM and COVID-19-unrelated ROCM cases could have been more justified if they were enrolled from the same period of time; however, ruling out of prior asymptomatic or non-documented COVID-19 could prove challenging in cases presenting with ROCM during a global pandemic of COVID-19 and an epidemic of CAM. Similarly, inclusion of the ROCM cases with prior suspected or probable COVID-19 could present bias as the diagnosis of COVID-19 and therefore, CAM, could not be established in a definitive manner in them. To prevent the mentioned biases, we decided to enroll only the definitive CAM patients to the case, and the definitive COVID-19-unrelated ROCM patients – from the pre-pandemic period – to the control group.

Conclusion

Our study highlights that the neurological manifestations of CAM differ from COVID-19-unrelated ROCM, with gait ataxia, vision and/or hearing impairment, proptosis, ptosis, and mydriasis being more common in CAM. Some of these manifestations, comprising gait ataxia, ptosis, and mydriasis, are associated with worse prognosis. While providing better insight on neurological manifestations of CAM in comparison to COVID-19-unrelated ROCM, our results are subject to further replication due to the retrospective nature of the analyses, and should be interpreted with caution.

Conflict of Interests

The authors declare no conflict of interest in this study.

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