



Fungal Central Nervous System Infections in Patients With COVID-19

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Dear Editor,

Recent studies have indicated that fungal co-infections have a major impact on the morbidity and mortality of patients with COVID-19. In these patients, the excessive production of inflammatory cytokines and the reduction in CD4 + T and CD8 + T cell count entails susceptibility to fungal infections.¹ In addition to impaired cell-mediated immunity, comorbidities and immunosuppressive medications have a significant role in the development of fungal infections and have serious impacts on clinical outcomes.¹⁻³

Fungal infections of the central nervous system (CNS) are presented in different clinical syndromes and compared to other CNS infections, have a higher risk of morbidity and mortality.^{4,5} In healthy individuals, CNS has functional and anatomical barriers to provide resistance against fungal infections and T lymphocytes play a key role in the immune surveillance of CNS.⁴ Common agents responsible for CNS fungal infections are mucormycete, *Cryptococcus*, *Aspergillus*, and *Candida* species.⁵ Certain host factors make patients susceptible to the development of a specific etiological agent.⁵ CNS infections caused by *Cryptococcus*, *Aspergillus*, and *Candida* species are associated with impaired cell mediated immunity and corticosteroids. In addition to these factors, hyperglycaemia makes patients vulnerable to CNS mucormycosis development.^{5,6} In some patients, these agents are able to affect the CNS by direct spread from paranasal sinuses, orbits, and retro-pharyngeal area. Furthermore, particularly in immunocompromised patients, the inhalation of aerosolized fungi initiates

infection in the lung, possibly resulting in hematogenous spread to CNS.^{4,5} During the COVID-19 pandemic, fungal co-infections have significantly increased and common agents responsible for fungal infections are from *Aspergillus* and *Candida* genera.⁷ Patients with impaired immune system are highly exposed to CNS abscesses in the presence of invasive pulmonary aspergillosis and disseminated candidiasis, which are the two most prevalent fungal co-infections reported in patients with COVID-19.^{5,7,8} Recently, CNS fungal infections are emerging in patients with COVID-19 with mucormycetes and *Cryptococcus* species.⁹⁻¹¹ Generally, CNS Cryptococcal infections presented with meningitis and meningoencephalitis in immunocompromised setting and in patients without any history of organ transplant or acquired immunodeficiency syndrome (AIDS) are associated with poorer prognosis.^{4,5} Common presentation of mucormycosis is rhino-orbital-cerebral invasion and, in absence of proper treatment infection, may result in infarction and necrosis of host tissues.⁵ Because of COVID-19, various clinical presentations, such as neurological complications and fungal co-infections might be missed or misdiagnosed.^{7,12} In addition to the direct effect of COVID-19 on immune system, high-dose corticosteroids used in COVID-19 therapeutic regimen, past history of immunodeficiencies, steroid induced hyperglycemia, and diabetes mellitus make COVID-19 patients highly vulnerable to the development of CNS fungal infections.^{4,5,13,14} Taken together, early diagnosis, appropriate antifungal therapy, controlling the underlying predisposing factors and, in some cases,



surgical intervention are crucial for reducing the high mortality rates of CNS fungal infections (Table 1).

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Table 1. Reported COVID-19 Cases Affected by CNS Fungal Infections

Study	Country	Clinical Presentation	Outcome	Genus/Class	Comorbidities	Steroid Use
Werthman-Ehrenreich et al ¹⁵	United States	ROCM	Death	Mucormycetes	None	NM
Buil et al ¹⁶	Netherlands	ROCM	Death	Mucormycetes	Diabetes mellitus	Yes
Sharma et al ¹⁷	India	ROCM	Alive	Mucormycetes	Diabetes mellitus	Yes
Moorthy et al ¹⁸	India	ROCM	44% Mortality rate ^a	Mucormycetes	Diabetes mellitus	Yes
Veisi et al ¹⁹	Iran	ROCM	Death	Mucormycetes	None	Yes
Alekseyev et al ²⁰	United States	RCM	Alive	Mucormycetes	Diabetes mellitus	Yes
Ashour et al ²¹	Egypt	Rhino sinusitis with invasion to trigeminal nerve	Alive	<i>Aspergillus</i>	Diabetes mellitus	NM
		ROCM	Alive	Mucormycetes	Diabetes mellitus	NM
		ROCM	Alive	Mucormycetes	Diabetes mellitus	NM
Nehara et al ²²	India	RCM	Death	Mucormycetes	Diabetes mellitus	Yes
Revannavar et al ²³	India	ROCM	Alive	Mucormycetes	Diabetes mellitus	NM
Bayram et al ²⁴	Turkey	ROCM	Death	Mucormycetes	Diabetes mellitus, Chronic renal failure	Yes
		ROCM	Death	Mucormycetes	Myelodysplastic syndrome	Yes
Fouad et al ²⁵	Egypt	ROCM	Alive	Mucormycetes	Diabetes mellitus	Yes
		ROCM	Death	Mucormycetes	Diabetes mellitus	Yes
		ROCM	Alive	Mucormycetes	Diabetes mellitus	Yes
Thota et al ²⁶	United States	Cryptococcal meningoenophalitis	Alive	<i>Cryptococcus</i>	None	Yes
Ghanem et al ¹¹	United States	Cryptococcal meningoenophalitis	Alive	<i>Cryptococcus</i>	None	Yes
Prandecki et al ²⁷	United States	Cryptococcal meningoenophalitis	NM	<i>Cryptococcus</i>	Diabetes mellitus	NM
Gullapalli et al ²⁸	United States	Cryptococcal meningitis	Alive	<i>Cryptococcus</i>	Latent tuberculosis	Yes

Abbreviations: ROCM, Rhino-orbital-cerebral mucormycosis; NM, Not mentioned; RCM, Rhino cerebral mucormycosis

^a Case series study.

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