



# 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.<sup>1</sup> 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.<sup>1-3</sup>

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.<sup>4,5</sup> 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.<sup>4</sup> Common agents responsible for CNS fungal infections are mucormycete, *Cryptococcus*, *Aspergillus*, and *Candida* species.<sup>5</sup> Certain host factors make patients susceptible to the development of a specific etiological agent.<sup>5</sup> 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.<sup>5,6</sup> 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.<sup>4,5</sup> During the COVID-19 pandemic, fungal co-infections have significantly increased and common agents responsible for fungal infections are from *Aspergillus* and *Candida* genera.<sup>7</sup> 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.<sup>5,7,8</sup> Recently, CNS fungal infections are emerging in patients with COVID-19 with mucormycetes and *Cryptococcus* species.<sup>9-11</sup> 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.<sup>4,5</sup> 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.<sup>5</sup> Because of COVID-19, various clinical presentations, such as neurological complications and fungal co-infections might be missed or misdiagnosed.<sup>7,12</sup> 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.<sup>4,5,13,14</sup> Taken together, early diagnosis, appropriate antifungal therapy, controlling the underlying predisposing factors and, in some cases,



**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 <sup>15</sup>	United States	ROCM	Death	Mucormycetes	None	NM
Buil et al <sup>16</sup>	Netherlands	ROCM	Death	Mucormycetes	Diabetes mellitus	Yes
Sharma et al <sup>17</sup>	India	ROCM	Alive	Mucormycetes	Diabetes mellitus	Yes
Moorthy et al <sup>18</sup>	India	ROCM	44% Mortality rate <sup>a</sup>	Mucormycetes	Diabetes mellitus	Yes
Veisi et al <sup>19</sup>	Iran	ROCM	Death	Mucormycetes	None	Yes
Alekseyev et al <sup>20</sup>	United States	RCM	Alive	Mucormycetes	Diabetes mellitus	Yes
Ashour et al <sup>21</sup>	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 <sup>22</sup>	India	RCM	Death	Mucormycetes	Diabetes mellitus	Yes
Revannavar et al <sup>23</sup>	India	ROCM	Alive	Mucormycetes	Diabetes mellitus	NM
Bayram et al <sup>24</sup>	Turkey	ROCM	Death	Mucormycetes	Diabetes mellitus, Chronic renal failure	Yes
		ROCM	Death	Mucormycetes	Myelodysplastic syndrome	Yes
Fouad et al <sup>25</sup>	Egypt	ROCM	Alive	Mucormycetes	Diabetes mellitus	Yes
		ROCM	Death	Mucormycetes	Diabetes mellitus	Yes
		ROCM	Alive	Mucormycetes	Diabetes mellitus	Yes
Thota et al <sup>26</sup>	United States	Cryptococcal meningoencephalitis	Alive	<i>Cryptococcus</i>	None	Yes
Ghanem et al <sup>11</sup>	United States	Cryptococcal meningoencephalitis	Alive	<i>Cryptococcus</i>	None	Yes
Prandecki et al <sup>27</sup>	United States	Cryptococcal meningoencephalitis	NM	<i>Cryptococcus</i>	Diabetes mellitus	NM
Gullapalli et al <sup>28</sup>	United States	Cryptococcal meningitis	Alive	<i>Cryptococcus</i>	Latent tuberculosis	Yes

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

<sup>a</sup> Case series study.

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

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