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. 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.

Fungal infections of the central nervous system (CNS) are present in different clinical syndromes and compared to other CNS infections, have a higher risk of morbidity and mortality. 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. Common agents responsible for CNS fungal infections are mucormycete, Cryptococcus, Aspergillus, and Candida species. Certain host factors make patients susceptible to the development of a specific etiological agent. 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. In some patients, these agents are able to affect the CNS by direct spread from paranasal sinuses, orbits, and retro-pharyngeal area. Furthermore, in immunocompromised patients, the inhalation of aerosolized fungi initiates infection in the lung, possibly resulting in hematogenous spread to CNS. During the COVID-19 pandemic, fungal co-infections have significantly increased and common agents responsible for fungal infections are from Aspergillus and Candida genera. 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. Recently, CNS fungal infections are emerging in patients with COVID-19 with mucormycetes and Cryptococcus species. Generally, CNS Cryptococcal infections presented with meningoencephalitis in immunocompromised setting and in patients without any history of organ transplant or acquired immunodeficiency syndrome (AIDS) are associated with poorer prognosis. 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. Because of COVID-19, various clinical presentations, such as neurological complications and fungal co-infections might be missed or misdiagnosed. 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. 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).

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Clinical Presentation</th>
<th>Outcome</th>
<th>Genus/Class</th>
<th>Comorbidities</th>
<th>Steroid Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Werthman-Ehrenreich et al15</td>
<td>United States</td>
<td>ROCM</td>
<td>Death</td>
<td>Mucormycetes</td>
<td>None</td>
<td>NM</td>
</tr>
<tr>
<td>Buil et al16</td>
<td>Netherlands</td>
<td>ROCM</td>
<td>Death</td>
<td>Mucormycetes</td>
<td>Diabetes mellitus</td>
<td>Yes</td>
</tr>
<tr>
<td>Sharma et al17</td>
<td>India</td>
<td>ROCM</td>
<td>Alive</td>
<td>Mucormycetes</td>
<td>Diabetes mellitus</td>
<td>Yes</td>
</tr>
<tr>
<td>Moorthy et al18</td>
<td>India</td>
<td>ROCM</td>
<td>Mortality ratea</td>
<td>Mucormycetes</td>
<td>Diabetes mellitus</td>
<td>Yes</td>
</tr>
<tr>
<td>Veisi et al19</td>
<td>Iran</td>
<td>ROCM</td>
<td>Death</td>
<td>Mucormycetes</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Alekseyev et al20</td>
<td>United States</td>
<td>ROCM</td>
<td>Alive</td>
<td>Mucormycetes</td>
<td>Diabetes mellitus</td>
<td>Yes</td>
</tr>
<tr>
<td>Ashour et al21</td>
<td>Egypt</td>
<td>Rhino sinusitis with invasion to trigeminal nerve</td>
<td>Alive</td>
<td>Aspergillus</td>
<td>Diabetes mellitus</td>
<td>NM</td>
</tr>
<tr>
<td>Nehara et al22</td>
<td>India</td>
<td>ROCM</td>
<td>Death</td>
<td>Mucormycetes</td>
<td>Diabetes mellitus</td>
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<tr>
<td>Revannavar et al23</td>
<td>India</td>
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<td>Alive</td>
<td>Mucormycetes</td>
<td>Diabetes mellitus</td>
<td>Yes</td>
</tr>
<tr>
<td>Bayram et al24</td>
<td>Turkey</td>
<td>ROCM</td>
<td>Death</td>
<td>Mucormycetes</td>
<td>Diabetes mellitus</td>
<td>Yes</td>
</tr>
<tr>
<td>Fouad et al25</td>
<td>Egypt</td>
<td>ROCM</td>
<td>Alive</td>
<td>Mucormycetes</td>
<td>Diabetes mellitus</td>
<td>Yes</td>
</tr>
<tr>
<td>Thota et al26</td>
<td>United States</td>
<td>Cryptococcal meningoencephalitis</td>
<td>Alive</td>
<td>Cryptococcus</td>
<td>None</td>
<td>Yes</td>
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<tr>
<td>Ghanem et al27</td>
<td>United States</td>
<td>Cryptococcal meningoencephalitis</td>
<td>Alive</td>
<td>Cryptococcus</td>
<td>None</td>
<td>Yes</td>
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<tr>
<td>Prandecki et al28</td>
<td>United States</td>
<td>Cryptococcal meningoencephalitis</td>
<td>NM</td>
<td>Cryptococcus</td>
<td>Diabetes mellitus</td>
<td>NM</td>
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<tr>
<td>Gullapalli et al29</td>
<td>United States</td>
<td>Cryptococcal meningitis</td>
<td>Alive</td>
<td>Cryptococcus</td>
<td>Latent tuberculosis</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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

a Case series study.

References


