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Letter to the Editor

COVID-19: Acanthamoeba Creeps into the Brain

Ruqaiyyah Siddiqui [1,2], *Maryam Niyyati [3], Mohamed Yehia Abouleish [1], Mustafa Khamis [1], Taleb Ibrahim [4], *Naveed Ahmed Khan [2,5]

1. *College of Arts and Sciences, American University of Sharjah, Sharjah, United Arab Emirates*
2. *Department of Medical Biology, Faculty of Medicine, Istinye University, Istanbul, 34010, Turkey*
3. *Department of Medical Parasitology and Mycology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
4. *College of Engineering, American University of Sharjah, Sharjah, United Arab Emirates*
5. *College of Medicine, University of Sharjah, Sharjah, United Arab Emirates*

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*Correspondence Email:
naveed5438@gmail.com;
maryamniyati@yahoo.com

Dear Editor-in-Chief

It is now evident that patients who are seriously affected by COVID-19 (often associated with weakened immune system) are more susceptible to the "black fungus". Given a weakened host immune system, ubiquitous *Acanthamoeba* can cause fatal brain infection with >90% mortality rate (1). We believe that there is a need to raise awareness among physicians of granulomatous amoebic encephalitis (GAE) caused by *Acanthamoeba* in COVID-19 patients.

In most COVID-19 cases (around 98% of cases), patients develop mild to moderate illness, that are typical of common cold such as fever, cough, breathing difficulties, and muscle-aches. In severe cases (~2% of cases), coronaviruses can cause infection in the lungs (pneumonia), kidney failure etc. resulting in death (2). Patients with weakened immune system/underlying diseases such as diabetes, asthma, heart disease are susceptible to develop severe COVID-19, and become vulnerable to opportunistic pathogens. Opportunistic fungal (e.g., *Rhizopus* spp.) and protozoan pathogens (e.g., *Acanthamoeba* spp.) are ubiquitous in the environment. Humans and animals are routinely exposed to them; but an effective immune response is able to neutralize them (3). However, a debilitated immune system followed by exposure to opportunistic pathogens can lead to serious infections with life-threatening consequences. COVID-19 patients with pre-

existing diabetes are highly susceptible to mucormycosis, i.e., infection of sinuses/lungs caused by fungi belonging to the order Mucorales with *Rhizopus* species (4-6). The link between diabetes, COVID-19 and mucormycosis is now well-recognized. Mucormycosis is a rare fungal infection, also referred to as "black fungus" that can result in sight-threatening consequences, and may invade the CNS resulting in death (4-6). With increased awareness, and over 463 million diabetic patients worldwide, and 77 million patients in India alone, it is expected that the number of cases due to COVID-19-associated mucormycosis will continue to rise. In the absence of urgent and aggressive treatment with liposomal-amphotericin B, the prognosis of mucormycosis is poor, and it can lead to permanent disability, and possibly death (up to 50% mortality rate).

Given access and weakened immune system, free-living *Acanthamoeba* can produce cutaneous lesions/sinus infection, blinding keratitis and life-threatening GAE. For CNS infection, the portal of entry for *Acanthamoeba* include nasal passage into the lungs, followed by parasite invasion of the alveolar blood vessels and haematogenous dissemination. Parasite entry into the CNS likely occurs at the sites of the blood-brain barrier (1, 3). Alternatively, amoebae may bypass the respiratory tract and invade the bloodstream via skin lesions. Other portals of entry may include sinuses, in which amoebae attach to the nasal epithelium and migrate along the neuroepithelial route to invade CNS via permeable cribriform plate. In the CNS, it is challenging to eradicate parasite effectively using clinically-available drugs, leading almost always to death. The number of GAE cases are very few, suggesting the requirement of underlying diseases and/or lack of awareness.

Here, we suggest that severely ill COVID-19 patients, especially with underlying diabetes are likely susceptible hosts to contract GAE. Recent report of *Acanthamoeba* encephalitis in a COVID-19 patient has confirmed this suspicion (7). As the mortality rate of GAE due to *Acanthamoeba* is >90%, it is surprising that prognosis was successful. This was likely attributed to early diagnosis and aggressive chemotherapy with miltefosine at 50mg 3X per day for four weeks (and intermittent treatment with liposomal amphotericin B, trimethoprim-sulfamethoxazole, fluconazole, albendazole, azithromycin, rifampicin, flucytosine, midazolam, caspofungin) (Fig. 1, Table 1), however there is a need for standardized therapeutic regimen. It is important to note that the patient had no apparent pre-disposing condition, but a family history of diabetes and showed a reduced CD4+ T-cell count of 299/μL and marginally reduced neutrophil oxidative index, but normal NK and B-cells count. With COVID-19, there is a large population that is susceptible to *Acanthamoeba* and it should be a major concern.

Table 1: List of possible compounds against Mucormycosis and Granulomatous amoebic encephalitis

Drug	***Mechanism of action***	***References***
Albendazole	Inhibition of tubulin polymerization	pubchem.ncbi.nlm.nih.gov
Azithromycin	Inhibition of bacterial protein synthesis	pubchem.ncbi.nlm.nih.gov
Caspofungin	Inhibits the synthesis of beta-(1,3)-D-glucan	pubchem.ncbi.nlm.nih.gov
Fluconazole	Inhibition of ergosterol biosynthesis	pubchem.ncbi.nlm.nih.gov
Flucytosine	Inhibits growth by competitive inhibition of purine and pyrimidine uptake	pubchem.ncbi.nlm.nih.gov
Liposomal amphotericin B	Inhibitor of ergosterol	pubchem.ncbi.nlm.nih.gov
Midazolam	Increases the activity of gamma-aminobutyric acid	pubchem.ncbi.nlm.nih.gov
Miltfosine	Inhibits synthesis of phosphatidylcholine and also affects the parasite mitochondrion, inhibiting cytochrome c oxidase	www.chemsrc.com
Rifampicin	Inhibit bacterial DNA-dependent RNA polymerase	pubchem.ncbi.nlm.nih.gov
Trimethoprim-sulfamethoxazole	Inhibit folic acid synthesis	www.chemsrc.com

(combination)

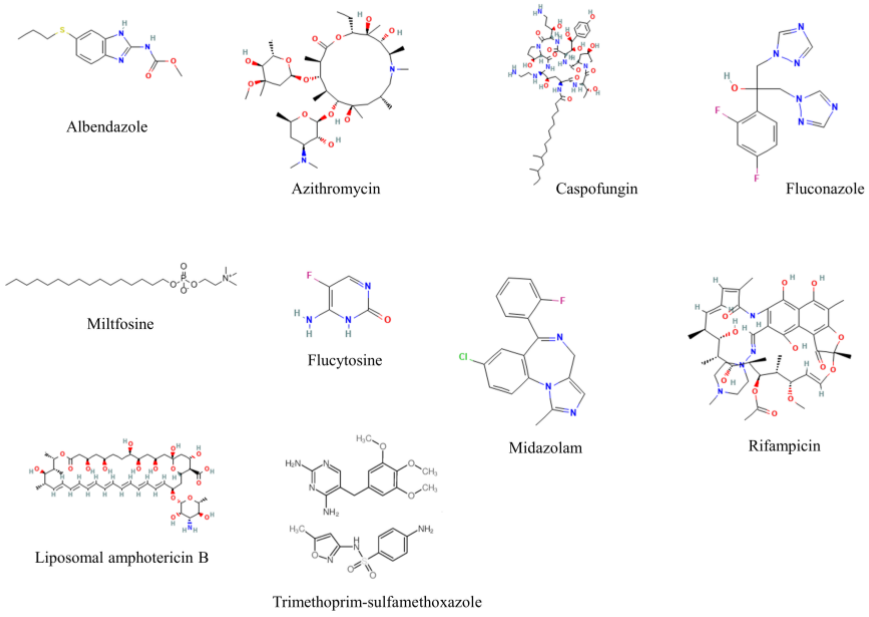

Fig. 1: Currently used anti-Acanthamoebic compounds that proved effective in the recent case of granulomatous amoebic encephalitis in a COVID-19 patient

As early diagnosis and aggressive treatment is a pre-requisite for successful prognosis, there is a need for awareness of this devastating infection, i.e., GAE, especially in developing countries among COVID-19 patients.

Conflict of Interest

The authors declare that there is no conflict of interests.

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