LETTER TO THE EDITOR

Does Long-term Oxygen Therapy and Noninvasive Ventilation Predispose Rhino-orbital-cerebral Mucormycosis in COVID-19 Patients?

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Keywords: Coronavirus disease-2019, High-flow nasal cannula, Mucormycosis, Noninvasive ventilation.
Indian Journal of Critical Care Medicine (2022): 10.5005/jp-journals-10071-24305

Coronavirus disease-2019 (COVID-19) is associated with a significant incidence of secondary infections, both bacterial and fungal, probably due to immune dysregulation. In recent times there are increased reports of invasive mucormycosis in COVID-19 patients in India. Rhino-orbital-cerebral mucormycosis is an uncommon infection caused by the angiotropic fungus belonging to the order Mucorales and has high morbidity and mortality despite treatment. There are a number of factors that can trigger mucormycosis in COVID-19 patients like uncontrolled hyperglycemia, acidosis, free iron, and COVID-19-induced immunological incompetence.[1] Moreover, COVID-19 often causes endothelialitis, endothelial damage, thrombosis, lymphopenia, and reduction in $CD4^+$ and $CD8^+$ level and thus predisposes to secondary or opportunistic fungal infection.[2] Additionally, the widespread use of steroids/monoclonal antibodies/broad-spectrum antibiotics as part of the armamentarium against COVID-19 may lead to the development/exacerbation of pre-existing fungal diseases.[3] Histopathology revealed evidence of angioinvasion and luminal thrombosis. Treatment of COVID-19-associated invasive fungal sinusitis (CAIFS) consists of reversal of predisposing state, surgical debridement, and antifungal therapy.[4]

Out of the 42 cases of CAIFS at our institute, we found that 35 of them were having a history of diabetes mellitus and steroid use. However, seven patients were not having any comorbidities at admission, and blood sugar was well-controlled during the course of hospitalization. These patients took steroids and immunomodulators as per COVID-19 institute's protocol. On retrospective analysis to determine the additional risk factors, we found a history of long-term oxygen therapy or noninvasive respiratory support in five of the seven noncomorbid patients.

In the second wave of the COVID-19 pandemic in India, a large number of critically ill patients were treated with immunosuppressive therapy in the form of steroids and immunomodulators like, tocilizumab and itolizumab. Current COVID-19 management guidelines in India recommend intravenous methylprednisolone 0.5–1 mg/kg/day for 3 days in moderate cases and 1–2 mg/kg/day in severe cases.[5] The National Institute of Health recommends the use of dexamethasone (6 mg per day for a maximum of 10 days) in patients who are ventilated or require supplemental oxygen, but not in milder cases.[6] The guidelines specifically mention the risk of developing a secondary infection.[7] Apart from rampant use of steroid therapy, the long-term oxygen therapy and noninvasive ventilation can be risk factors for CAIFS.

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How to cite this article: Kumar A, Kumar A, Kumar N, Kumar A, Sinha C, Singh PK. Does Long-term Oxygen Therapy and Noninvasive Ventilation Predispose Rhino-orbital-cerebral Mucormycosis in COVID-19 Patients? Indian J Crit Care Med 2022;26(9):1063–1064.
Source of support: Nil
Conflict of interest: None

High-flow nasal cannula (HFNC) delivers a high, humidified, and heated flow, this is not always an advantage. Too much pressure displeases and irritates the nostrils, and conditions like rhinitis, nasal mucosal damage, and epistaxis may be aggravated by its use.[8] In our case, all patients were on prolonged oxygen therapy in the form of HFNC or noninvasive ventilation (NIV). Paranasal sinuses provide fertile environment for rhino-orbital-cerebral mucormycosis. The spores of Mucorales that reach the respiratory tract adhere to the nasal mucus and are eliminated either by swallowing or sneezing. In the presence of any wound in the mucous membranes, the polymorphonuclear neutrophils phagocytose and destroy the fungal structures. Long-term use of high-flow nasal oxygen can damage the nasopharyngeal mucosa, making it susceptible to infection even after the patient is clinically cured. Another possible hypothesis of increased nasal mucosal damage in COVID-19 ARDS patients is owing to high minute ventilation. This high minute ventilation in NIV is beyond the humidification capacity of nasopharyngeal mucosa and can lead to mucosal damage. In the case of the presence of mucosal damage or wound, the neutrophils are the host defense against these infections.[9] As steroid use reduces the phagocytic activity of neutrophils (both first-line and second-line defense mechanism), causing impairment of bronchoalveolar macrophage migration, ingestion, and phagolysosome fusion, this can make these patients exceptionally vulnerable to fungal infection.[2]

Patients on long-term oxygen therapy and NIV should be observed vigilantly for mucormycosis as early identification of fungal co-infections may significantly reduce morbidity and mortality. Nasal high flow, NIV, and invasive ventilation with intubation should be carried out in a stepwise-treatment strategy, and unnecessary long-term use of NIV should be avoided. We propose here that the long-term oxygen therapy and NIV as a predisposing factor for CAIFS and formal investigation in this regard is warranted in the future.

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