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Correspondence

Letter: Spectrum of hospitalized NeuroCOVID diagnoses from a tertiary care neurology centre in Eastern India


Dear Editor,

We read with great interest the article published recently by Bhansali et al. [1] “Spectrum of hospitalized NeuroCOVID diagnoses from a tertiary care neurology centre in Eastern India”, where the authors investigated COVID-19 patients with neurological manifestations, showing that stroke and encephalopathy are the most frequently associated conditions in COVID-19 patients. Additionally, they found that neurological manifestations are independent of respiratory symptoms and fever [1]. We thank the authors for providing us with such valuable evidence, however, we would like to make a few comments on an invasive infectious condition of great importance, which can occur at different times of COVID-19 and which puts at risk the neurological integrity of the affected person: rhino-orbito-cerebral mucormycosis.

Currently, there are many questions about the pathophysiology of COVID-19. With respect to the neuroinflammation induced by SARS-Cov-2, it has been described that the manifestations and complications caused by this agent in the nervous system are mediated by immunologic (microglial activation, maladaptive expression of cytokines, and aggressive development of adaptive autoimmunity) and non-immunologic (hypoxia, micro/macrovacular thrombosis and hypotension) effects [2,3]; moreover, any of these two groups can trigger innumerable pathologic processes, some of those reported in the literature are: Guillain-Barré Syndrome, Septic Encephalopathy, Delirium, Acute Disseminated Encephalomyelitis, Acute Hemorrhagic Necrotizing Encephalitis, Acute Hemorrhagic Leukoencephalitis, Ischemic Stroke, among many others [2–5]. Recent publications that have characterized the pathobiology of SARS-Cov-2 neuroinvasion show that it is very difficult to control or prevent these mechanisms: transcriptional pathway, transsynaptic transfer, leukocyte infection and endothelial infection [2,3].

The natural history of NeuroCOVID shows that approximately 21 days after the onset of the acute phase of COVID-19 symptoms, the post-COVID-19 phase begins [6], which, if concentrated in sequelae or new neurological manifestations, is known as post-COVID-19 neurological syndrome [7–9]. It has been described that this is a risk period where the neuroinflammation caused by SARS-Cov-2 remains active and precipitates the development of complications due to neuroimmunological alterations, which may facilitate the appearance of co-infections [7–9]. This correlates with the invasion of fungal agents belonging to the genera *Mucor*, *Absidia* and *Rhizopus*, reported in different parts of the world [10–13], which produce mucormycosis; a condition that has a powerful destructive potential [10]. The most important thing to consider

about this disease is that it can go unnoticed and present in advanced stages, compromising a large number of organs and structures [13]. Interestingly, however, there are case reports and case series that show that this condition can develop even in those before 21 days (theoretically during the acute phase of COVID-19) [10–13]. But it should be clarified that there are still no precise cut-off scores for the time between the acute phase transition and post-COVID phase, which is a potential bias in the characterization of these patients [9].

The subtypes of mucormycosis with invasion to the central nervous system are cerebral or rhino-orbito-cerebral mucormycosis (even more extensive) [13]. In low- and middle-income Asian countries, where there are difficulties in the management of environmental sanitation, overcrowding and high rates of poverty, it has been reported an elevated risk of developing this condition in patients affected by COVID-19, especially in those groups that additionally have pathological antecedents such as Diabetes Mellitus and Cancer [11,13,14]. Taking into account the heterogeneity in the times of presentation of this condition, it is necessary to define whether rhino-orbito-cerebral mucormycosis is a manifestation of the acute phase of COVID-19, associated with the immune mechanisms involved in the neuroinflammation caused by the neurotropism of SARS-Cov-2, or typical of the post-COVID-19 neurological syndrome, where there is therapeutic remission and risk of complications. This discussion becomes relevant due to the new peaks of COVID-19 cases in the world in the last weeks (November–December 2021) [15], and the factors associated with the presentation of rhino-orbito-cerebral mucormycosis [16,17], such as the management of the acute phase of COVID-19 with corticosteroids and antibiotics, the high prevalence of diabetic patients or patients with endocrine disorders with off-target hyperglycemia [10–14,16,17], where an increase in the incidence of this complication, which entails high health costs during management and rehabilitation, morbidity and mortality, is expected.

We consider it essential to include cerebral and rhino-orbito-cerebral mucormycosis within the spectrum of NeuroCOVID-19, to propose prospective multicenter studies with large cohorts, which will allow us to determine associated factors, safe and effective management, prognosis and real prevalence. It is possible that some cases of bacterial or viral neuroinfection are confused with cerebral mucormycosis, and due to the public health calamity and the management of the flow of patients and deaths, the causes of deaths are not examined in detail. Other strategies, such as the creation of specialized public health units specifically for the strict surveillance of this disease, are not only necessary in those

countries where there have been a greater number of reports, but also in isolated cases that may cause an outbreak.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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