Impact of the second wave of covid 19 infection on neurosciences with reference to rhinocerebral mucormycosis: A narrative review

Nikhil A Kumar (M.D.)*; Rameshwar Nath Chaurasia (D.M.)**

Affiliation: *Senior Resident,**Professor, Department of Neurology, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005

Corresponding Author:

Dr. Rameshwar Nath Chaurasia,

Professor & Head,

Department of Neurology,

Institute of Medical Sciences, Banaras Hindu University,

Varanasi-221005

Phone No.:+91 9415353255

Email: goforrameshwar@gmail.com

Abstract:

Background: With COVID-19 becoming a major worldwide cause of concern, it is important to understand the various manifestations of the disease in order to fully manage it. Neurological manifestations of COVID-19 assume great importance because of considerable mortality and morbidity both during the disease and recovery. The following review aims to shed light on impact of COVID -19 on neurological system. Common neurological manifestations have been described. With more people surviving the disease, post-COVID syndrome has become a prominent ailment. A note is also made of the impact introduction of vaccines for COVID-19. Finally, the epidemic of -black fungus or Mucormycosis has also been touched upon.

Neurological manifestations: The most important neurological manifestations are stroke, encephalitis, encephalopathy and myelitis on the central nervous system and Guillain-Barre Syndrome (GBS) and chronic muscle fatigues on the peripheral nervous system.

Impact of second wave of COVID: The second wave of COVID has been particularly tragic for India because of the rapid spread which pressurized the health system and resources. With a record number of patients infected in this wave, patients with neurological symptoms have also increased. We must also be prepared for patients with Post-COVID Neurological Syndrome (PCNS). Vaccine associated adverse effects have also assumed importance.

Mucormycosis: With a decline in number of cases of COVID-19, the deadly epidemic of mucormycosis has resurged. It is characterized by involvement of sinuses, eye and brain. Early recognition and treatment can prevent many complications.

Keywords: Severe acute respiratory syndrome coronavirus-2 (SARS CoV-2), Mucormycosis, Neurosciences, Second Wave

Introduction

Corona Virus Disease 2019(Covid-19) is the deadliest pandemic in recent history due to severe acute respiratory syndrome coronavirus-2 (SARS CoV-2). No country is untouched by the scourge of this new disease which was first reported from Wuhan, China in December 2019. The rapid spread of this disease as well as the morbidity and mortality associated with this disease has led to unprecedented research into the various aspects of this disease. While respiratory manifestations are the most predominant feature of this disease, with time it has been found that the virus can involve almost any organ in the human body¹.

SARS-CoV-2, the causative agent of Covid-19, is a positive sense RNA virus from beta coronavirus family. This virus is taxonomically related to the SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). The virus gains entry into body by attaching to angiotensin converting enzyme 2 receptors (ACE2)^{2,3}. ACE2 receptors represent the primary but not the exclusive site of entry of the virus. SARS-CoV2 can cause neurological damage by various direct and indirect mechanisms. It can infect neurons directly using ACE2 receptors (or other receptors) or by axonal transport from periphery to central nervous system (CNS). Indirectly it may cause neurological effects by hematogenous dissemination to CNS or by effects of cytokine storm. Sepsis, hyperpyrexia and hypercoagulability may also contribute to neuronal injury. As such, SARS CoV2 can cause many neurological manifestations in both central and peripheral nervous system.

Literature search: The MEDLINE database was searched through PubMed using a search query constructed with the following medical subject heading terms: ("severe acute respiratory syndrome coronavirus 2" OR "COVID- 19") OR "coronavirus 2019" OR –sars cov-2|| AND "Neuroscience" as well as with addition of different keywords to increase the sensitivity and specificity of the search (e.g., "Signs and Symptoms, Neurological" OR "Nervous System" OR "CNS*" OR "PNS" "). A similar search was performed in Google Scholar engine and Google. The reference list of the papers, Websites of leading neurology journals, as well as WHO, and Centre for Disease Control and Prevention publications were reviewed manually by the authors.

CNS manifestations of covid-19 infection

In a case series of 219 patients of Covid-19 published from Wuhan, 36.4 % had CNS manifestations⁴.

Encephalitis: The first case of meningitis/meningo-encephalitis associated with SARS-CoV2 was described by Moriguchi et. al⁵. Since then, multiple case reports of encephalitis have been published. Rhombencephalitis and necrotizing encephalitis have also been described following COVID infection^{6, 7}. The most comprehensive study of neurological feature in COVID was done by Helms et al. In their case series involving a total of 58 patients, 7 patients underwent CSF analysis. Most patients had a normal CSF cytology and only 1 patient had elevated protein levels. All patients had negative CSF RTPCR for SARS-CoV 2 RNA⁸. Interestingly, CSF RTPCR was positive and nasopharyngeal swab RTPCR was negative in the first described case of meningo-encephalitis⁵. In the study by Helms et al, leptomeningeal enhancement and bilateral frontotemporal hypoperfusion were the most common radiological abnormalities on diffusion weighted MRI and MR perfusion studies respectively⁸. Acute necrotizing haemorrhagic encephalitis has also been recognized as a complication of COVID⁹. Opsoclonus and myoclonus which are suggestive of autoimmune encephalitis have been described in COVID patients by Paterson et al. They also described a case of limbic encephalitis¹⁰. Some case reports show that high dose methylprednisolone and IV immunoglobulin leads to faster recovery in severe COVID associated encephalitis¹¹.

Encephalopathy: Encephalopathy in COVID-19 infection ranges from subtle changes in personality and sensorium to coma. Delirium is a common and sometimes the only manifestation of COVID¹². It can also be seen in otherwise mild COVID-19 infection. Yin et al analysed 106 patients of COVID 19 in a single centre observational study and found that altered sensorium was seen in 5.7 % of the patients¹³. Seizures and coma have also been described in COVID-19 infection. In all these cases, sepsis with organ dysfunction plays an important role but radiological evaluation to rule out other causes like encephalitis, stroke, posterior reversible encephalopathy syndrome (PRES) is needed. Toxic, metabolic and drug-induced cerebral dysfunction should also be considered. Basal ganglia involvement with focal restriction, diffuse FLAIR changes on MRI, or discrete hypodensities on CT were common in patients with neurological involvement¹⁴. Myoclonus has also been described in a case series¹⁵.

Stroke: COVID 19 has been associated with high risk of thrombosis. High D-dimer levels have been associated with poor prognosis¹⁶. Yanan Li et al studied 219 patients of COVID-19 in April 2020 and concluded that incidence of ischaemic stroke was 4.6 % and that of haemorrhagic stroke was 0.5 %¹⁷. Thromboprophylaxis with prophylactic dose of low molecular weight heparin is advised in all latest guidelines to prevent these complications. The risk of bleeding associated with this dose is around 4 %¹⁸.

Guillain-Barre syndrome: There are multiple case reports of Guillain-Barre syndrome (GBS) following COVID infection. In one such case series Toscano et al, it was found that lower limb weakness and paraesthesia were the most common symptom. Axonal degeneration was the most common electrophysiological abnormality 19. However, no causal association can be made between COVID 19 and GBS based on these studies.

Differences between first and second wave of covid

On 31st December 2019, the WHO China Country Office was informed of cases of pneumonia of unknown etiology (unknown cause) detected in Wuhan City, Hubei Province of China. The causative agent, identified as a new type of coronavirus (novel coronavirus, nCoV), was isolated on 7 January 2020. Chinese doctors published the first case series of the original 41 patients reported from Wuhan on January 24, 2020 20. On January 13, 2020, Thailand reported the first case of COVID-19 outside China, thus heralding fears of a global pandemic which eventually turned out to be true. India reported the first case of COVID-19 on January 29, 2020 in Kerala 21. Since then there has been a relentless spread of the disease in the country. On March 11, WHO declared COVID to be a pandemic and called for nations to take appropriate steps to prevent spread of the disease. Based on the increasing cases in the country, a countrywide lockdown was announced on evening of March 24. The main aim of the lockdown was to prevent crowding and movement as well as to give time to build the necessary infrastructure and diagnostic facilities for the upcoming surge. The number of new cases rose slowed down a bit due to the lockdown and reached a peak in the middle of September with around 97000 cases per day, and then began a decline. However the trajectory was different in different states with Maharashtra which followed the national trend whereas Kerala started slowly but is had an unusually flat and extended peak 22. The number of active cases and death rate also followed a similar trend. Cases declined after mid- September. One important feature of the first wave of COVID was the relatively lower death rate per million population in India as compared to US, UK or Brazil.

India's second wave started in mid-February, 2021. In the beginning, it was centered around the smaller districts and towns of interior Maharashtra, including Akola and Amravati. Soon, an unusually large number of cases were reported from all over Maharashtra, Chhattisgarh and Delhi. Suddenly there was a huge surge in cases all over the country.

The second wave of COVID is characterized by variants and mutants of the original SARS-nCoV2. Whether these variants have differences in infectivity, clinical features or severity of the disease is an area of active investigation. There are very few studies which compare the two waves but the available ones show a difference. In a Spanish study, it was found that the second wave was characterized by a higher frequency of vomiting, asthenia, abdominal pain, rhinorrhoea and acute kidney failure, and less frequently a cough or chills ²³.

In a study done in Italy in 2021 which assessed the impact of first and second waves of COVID on migraine, it was found that the frequency and severity of headache and the number of symptomatic drugs were higher in the second wave as compared to the first wave in which there was a national lockdown. The patients who considered the risk of infection to be more in the second wave were more likely to have a severe headache. Presence of fear, anxiety or sadness due to the continuing pandemic had a positive correlation with the frequency and severity of headache²⁴.

The effect of COVID 19 on mental health is an area of immense interest due to its wide implications. A Polish study concluded that 21% experienced symptoms indicative of anxiety and more than 4% of depressive disorders. These symptoms rose in Poland when there were reports of new cases with a surge in COVID-19 associated deaths between November 10 and December 5, 2021²⁵. Other studies have also reiterated that COVID 19 can have adverse impact on mental health.

The changes in society due to COVID 19 can have adverse effect on people having prior neurological disease. For example, in Parkinson's disease (PD) social isolation carries risk equivalent to traditional factors²⁶. COVID 19 has been found to increase the motor and non-motor manifestations of Parkinson's disease²⁷. Similarly, people with dementia are also susceptible to negative effects of measures taken to control COVID 19²⁸.

With an increase in number of COVID 19 cases long COVID or post COVID-19 syndrome has risen to prominence. Post COVID-19 refers to people who still have symptoms 12 weeks or more after the start of acute infection²⁹. In a follow-up study of COVID patients for 6 months, Fatigue or muscle weakness was the most common symptom, which was found in 63 % of patients followed by sleep disturbances in 26 %. They were more common in severely ill patients³⁰.

With the rapid introduction of a plethora of vaccine options for COVID, vaccine associated adverse events also captured attention in many people during the second wave. In India, COVISHIELD and COVAXIN are 2 important vaccines. Headache and myalgia are common to both these vaccines but COVISHIELD has additional risk of venous thromboembolism due to vaccine-induced immune thrombotic thrombocytopenia. There have been isolated cases of stroke in young and cortical sinus thromboses after COVISHIELD but the overall incidence is rare³¹.

Mucormycosis: Mucormycosis is an angio-invasive saprophyte which is characterized by high morbidity and mortality. Characteristically found in post-transplant recipients, uncontrolled diabetes, patients on immunomodulators and deferoxamine, the disease has resurfaced due to its association with COVID. Mucormycosis has a distinct predilection for vascular invasion. Based on site of infection there are 6 types of Mucormycosis: (1) Rhino-cerebral, (2) Pulmonary, (3)

Cutaneous, (4) Gastrointestinal, (5) Disseminated, and (6) Uncommon rare forms, such as endocarditis, osteomyelitis, peritonitis, and renal infection³². Symptoms of the infection are varied and range from:

1. Purulent nasal discharge with or without epistaxis
2. Facial or periorbital pain
3. Diplopia or blindness

Nasal or palatine examination reveals a reddish mucosa which can progress to black eschar formation, hence the colloquial term –black fungus|. Further local spread can lead to complications including:

1. Eyelid abscess, vitritis, endophthalmitis, painful proptosis
2. Orbital apex syndrome
3. Superior orbital fissure syndrome
4. Cavernous sinus thrombosis

These complications may lead to varying degrees of ophthalmoplegia, pupillary abnormalities and blindness. Blindness with cavernous sinus thrombosis favours of fungal etiology rather than bacterial³³.

We should keep a high index of suspicion to diagnose the condition. Radiological investigations like CT, MRI helps in delineating the extent of the disease. CT with contrast is better to identify bony erosion and necrosis which is marker for poor prognosis whereas MRI is better to detect vascular spread and intracranial disease. However, etiological diagnosis is confirmed by fungal culture. Newer methods of detection of Mucorales like PCR and MALDI-TOF leads to faster results and are more sensitive than conventional culture.

Treatment of the disease is by a 3 pronged strategy:

1. Reversal of immunosuppression
2. Surgical debridement
3. Antifungals

Reversal of hyperglycaemia, ketosis or acidosis is the priority. Steroids may need to be discontinued.

IV Amphotericin is usually used for treatment of the disease. After achievement of clinical improvement, the therapy is stepped down to oral Posaconazole. Salvage therapy with IV or oral Posaconazole or Isavuconazole may be needed in patients not responding to amphotericin. The role of hyperbaric oxygen therapy in treatment is controversial.

Conclusion: COVID-19 is a novel coronavirus infection manifesting mostly as acute and chronic respiratory infection, with a variable rate of morbidity and mortality in different waves

of pandemic. COVID 19 infected patients also presenting with various neurological symptoms. During second wave of pandemic there is surge in cases of Mucormycosis which may involve paranasal sinuses, eyes and brain, if not diagnosed and treated promptly may lead to 100% mortality. So always keep high index of suspicion for these neurological manifestations in the COVID 19 infected patients. Why there is sudden surge in cases of Mucormycosis in second wave of pandemic in India is still unknown?

References:

1. AlSamman M, Caggiula A, Ganguli S, Misak M, Pourmand A. Non-respiratory presentations of COVID-19, a clinical review. *Am J Emerg Med*. 2020 Nov; 38 (11):2444–54.
2. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*. 2003 Nov; 426 (6965):450–4.
3. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020 Mar; 579(7798):270–3.
4. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurology*. 2020 Jun 1; 77(6):683–90.
5. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *International Journal of Infectious Diseases*. 2020 May 1; 94:55–8.
6. Wong PF, Craik S, Newman P, Makan A, Srinivasan K, Crawford E, et al. Lessons of the month 1: A case of rhombencephalitis as a rare complication of acute COVID-19 infection. *Clin Med (Lond)*. 2020 May; 20(3):293–4.
7. Kumar N, Kumar S, Kumar A, Pati BK, Kumar A, Singh C, et al. Acute Necrotizing Encephalitis as a Probable Association of COVID-19. *Indian J Crit Care Med*. 2020 Oct; 24(10):991–4.
8. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic Features in Severe SARS-CoV-2 Infection. *New England Journal of Medicine*. 2020 Jun 4; 382(23):2268–70.

9. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19–associated Acute Hemorrhagic Necrotizing Encephalopathy: Imaging Features. *Radiology*. 2020 Mar 31; 296(2):E119–20.
10. Paterson RW, Brown RL, Benjamin L, Nortley R, Wiethoff S, Bharucha T, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain*. 2020 Oct 1; 143(10):3104–20.
11. Delamarre L, Gollion C, Grouteau G, Rousset D, Jimena G, Roustan J, et al. COVID-19–associated acute necrotising encephalopathy successfully treated with steroids and polyvalent immunoglobulin with unusual IgG targeting the cerebral fibre network. *J Neurol Neurosurg Psychiatry*. 2020 Sep 1; 91(9):1004–6.
12. Pun BT, Badenes R, Heras La Calle G, Orun OM, Chen W, Raman R, et al. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. *Lancet Respir Med*. 2021 Mar; 9(3):239–50.
13. Yin R, Yang Z, Wei Y, Li Y, Chen H, Liu Z, et al. Clinical characteristics of 106 patients with neurological diseases and co-morbid coronavirus disease 2019: a retrospective study. *medRxiv*. 2020 May 10;2020.04.29.20085415.
14. Scullen T, Keen J, Mathkour M, Dumont AS, Kahn L. Coronavirus 2019 (COVID-19)–Associated Encephalopathies and Cerebrovascular Disease: The New Orleans Experience. *World Neurosurgery*. 2020 Sep 1; 141:e437–46.
15. Rábano-Suárez P, Bermejo-Guerrero L, Méndez-Guerrero A, Parra-Serrano J, Toledo-Alfocea D, Sánchez-Tejerina D, et al. Generalized myoclonus in COVID-19. *Neurology*. 2020 Aug 11; 95(6):e767–72.
16. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020 Apr; 18(4):844–7.
17. Li Y, Li M, Wang M, Zhou Y, Chang J, Xian Y, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Stroke Vasc Neurol*. 2020 Sep; 5(3):279–84.
18. Jiménez D, García-Sánchez A, Rali P, Muriel A, Bikdeli B, Ruiz-Artacho P, et al. Incidence of VTE and Bleeding Among Hospitalized Patients With Coronavirus Disease 2019. *Chest*. 2021 Mar; 159 (3):1182–96.

19. Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, et al. Guillain–Barré Syndrome Associated with SARS-CoV-2. *New England Journal of Medicine* [Internet]. 2020 Apr 17 [cited 2021 May 28]; Available from: <https://www.nejm.org/doi/10.1056/NEJMc2009191>
20. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*. 2020 Feb 15; 395(10223):497–506.
21. Andrews MA, Areekal B, Rajesh KR, Krishnan J, Suryakala R, Krishnan B, et al. First confirmed case of COVID-19 infection in India: A case report. *Indian J Med Res*. 2020 May; 151(5):490–2.
22. A year with Covid-19: peak behind India [Internet]. *The Indian Express*. 2021 [cited 2021 May 28]. Available from: <https://indianexpress.com/article/explained/a-year-with-covid-peak-behind-india-7167126/>
23. Iftimie S, López-Azcona AF, Vallverdú I, Hernández-Flix S, de Febrer G, Parra S, et al. First and second waves of coronavirus disease-19: A comparative study in hospitalized patients in Reus, Spain. *PLoS One* [Internet]. 2021 Mar 31 [cited 2021 May 28];16(3). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8011765/>
24. Gentile E, Delussi M, Abagnale C, Caponnetto V, De Cesaris F, Frattale I, et al. Migraine during COVID-19: Data from Second Wave Pandemic in an Italian Cohort. *Brain Sci* [Internet]. 2021 Apr 10 [cited 2021 May 28]; 11(4). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8070557/>
25. Chodkiewicz J, Miniszewska J, Krajewska E, Biliński P. Mental Health during the Second Wave of the COVID-19 Pandemic—Polish Studies. *IJERPH*. 2021 Mar 25; 18(7):3423.
26. Pantell M, Rehkopf D, Jutte D, Syme SL, Balmes J, Adler N. Social Isolation: A Predictor of Mortality Comparable to Traditional Clinical Risk Factors. *Am J Public Health*. 2013 Nov; 103(11):2056–62.
27. Brown EG, Chahine LM, Goldman SM, Korell M, Mann E, Kinel DR, et al. The Effect of the COVID-19 Pandemic on People with Parkinson’s Disease. *Journal of Parkinson’s Disease*. 2020 Jan 1; 10(4):1365–77.
28. Numbers K, Brodaty H. The effects of the COVID-19 pandemic on people with dementia. *Nature Reviews Neurology*. 2021 Feb; 17(2):69–70.

29. Venkatesan P. NICE guideline on long COVID. The Lancet Respiratory Medicine. 2021 Feb 1; 9(2):129.
30. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. The Lancet. 2021 Jan 16;397(10270):220–32.
31. Butcher L. Neurologists in India Face Off Against a New Devastating Surge of COVID-19. Neurology Today [Internet]. 2021 May 20 [cited 2021 May 28]; Available from: <https://journals.lww.com/neurotodayonline/blog/breakingnews/pages/post.aspx?PostID=1117>
32. Epidemiology and Clinical Manifestations of Mucormycosis | Clinical Infectious Diseases | Oxford Academic [Internet]. [cited 2021 May 31]. Available from: https://academic.oup.com/cid/article/54/suppl_1/S23/284492
33. Ak AK, Gupta V. Rhino-orbital Cerebral Mucormycosis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 [cited 2021 Jun 2]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK557429/>

How to Cite this article As: Nikhil A Kumar & Rameshwar Nath Chaurasia (2021). Impact of the second wave of covid 19 infection on neurosciences with reference to rhinocerebral mucormycosis: A narrative review National Medicos Organisation Journal (एन एम ओ जर्नल) (ISSN-2348-3806), 15 (1), 27-36. Retrieved from <https://nmojournal.org/index.php/nmojournal/index>