Original Article

Neurological Manifestations of Covid-19 Hospitalized Patients In the state of Punjab, India

Zahoor Ahmad Parry [1], Swapnil Sunil Bumb [2], Santosh Kumar [3], Rohan Bhatt [4], Mohammed Irfan [5], Pragya Bhatt [6].

Abstract

Introduction: *COVID 19 often presents with flu-like symptoms. Elderly patients with systemic comorbidities are more likely to have severe COVID 19 infections and deaths. Severe neurological complications are frequently reported in severely and critically ill patients. In COVID-19, both central and peripheral nervous systems can be affected. The study aims to overview the spectrum, characteristics, and outcomes of neurologic manifestations associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).*

Methods: *A total of 1000 confirmed CoVID-19 patients were enrolled for the study. Demographic features and initial clinical manifestations were noted, and patients were followed during the hospital stay to develop any new neurological signs and symptoms. For analytical purposes, neurological presentations were grouped into the central nervous system, peripheral nervous system, and musculoskeletal system manifestations. Appropriate laboratory testing was employed as required on a case-to-case basis.*

Results: *The mean age was 44.6 ± 14.3 years. 625 (62.5%) patients were male, while 375 (37.5%) were female. The neurological illness was a primary manifestation in 119 (11.9%) cases. These included encephalopathy (n=78), ischemic stroke (n=28), Guillain- Barre syndrome, (n=3), facial nerve palsy (n=4), and encephalitis (n=6). The most common neurological symptoms were headache 313 (31.3%) and hyposmia 52 (5.2%), followed by encephalopathy 78 (7.8%). More serious complications like seizures 18 (1.8%) and stroke 28 (2.8%) were also seen.*

Conclusion: *CoVID-19 can present with a neurological illness, and we should remain vigilant to the possibility of neurological presentation of COVID-19 that can be thrombo-embolic, inflammatory, or immune-mediated.*

Keywords: CNS, CoVID-19, Neurological, Pandemic, PNS, CoV-2

Bangladesh Journal of Medical Science, Special Issue on COVID-19. 2021. Page : 155-161
DOI: https://doi.org/10.3329/bjms.v20i5.55414

Introduction

Coronavirus disease 2019 (COVID-19), linked to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is a widely spread infectious disease, with the first cases reported in China in December 2019.[1,2] The virus has continued to spread since then. On Mar 11, 2020, the World Health Organization characterized COVID-19 as a pandemic. Common disease manifestations include respiratory tract and associated systemic manifestations, but neurologic manifestations, including headaches, dizziness, anosmia, encephalopathy, and stroke, have been reported in cohort studies.[3–5] Uncommon

1. Department of Neurology, Mogamedicity Superspeciality Hospital, Punjab, India Orcid ID: https://orcid.org/0000-0002-7157-9887.
2. Department of Public Health, ACPM Dental College, Dhule, Maharashtra, India Orcid ID: https://orcid.org/0000-0002-4009-0333
3. Professor, Department of Periodontology and Implantology, Karnavati University, Gandhinagar, Gujarat, India. Orcid ID: https://orcid.org/0000-0002-5117-7872
4. Department of Pedodontics, Karnavati University, Gandhinagar, Gujarat, India. Orcid ID: https://orcid.org/0000-0002-7962-3918
5. Department of Forensics, Federal University of Pelotas, Pelotas-RS, Brazil-96020-010, Orcid ID: https://orcid.org/0000-0003-0683-106X
6. Department of Human Anatomy, College of Physiotherapy, Janardhan Rai Nagar Vidyapeeth University, Udaipur, Rajasthan. Orcid ID: https://orcid.org/0000-0002-3928-8801.

Correspondence: Dr Santosh Kumar, Department of Periodontology and Implantology, Karnavati University, Gandhinagar, Gujarat, India. Email: drsantoshkumar2004@gmail.com

manifestations of COVID-19 include ischemic stroke, intracerebral hemorrhage, Guillain-Barré syndrome, and Bell's palsy.[6–8]

However, the potential pathogenesis of SARS CoV-2 in the central nervous system remains unclear,[9,10], and the range of neurologic disorders associated with COVID-19 are not fully defined.[11] The COVID-19 causative virus can cross the blood-brain barrier and invade the brain.[12] The SARS-CoV-2 virus enters the brain either via the olfactory system or the hematogenous route.[13] Endothelial cells on the cerebral vessels contain angiotensin-converting enzyme two receptors which are thought to be a possible viral entry point.[14] The most severe neurological manifestations, agitation, delirium, and coma, result from hypoxic and metabolic abnormalities.[15] A typical cytokine storm provokes several metabolic complications that lead to multiple organ failures.[16] Many a time, hemorrhagic or ischemic strokes occur due to profound coagulopathies.[17] A very few cases of SARS-CoV-2 virus encephalitis or acute disseminated encephalomyelitis, or acute necrotizing encephalopathy have been reported at present.[18] The most common neurological complication experienced is a nonspecific headache.[19] In a few recent studies, a new type of "personal protection equipment" related headache has been described.[20] A common peripheral nervous system manifestations are Complete or partial anosmia and ageusia.[21] Recently, many cases of Guillain-Barré syndrome were reported in COVID-19 patients, and a postinfectious immune-mediated inflammatory process was held responsible for this.[22,23] This syndrome often responds to immunoglobulin when administered intravenously.[24] Myalgia/fatigue is often seen, and raised creatine kinase levels point to injury of muscle.[25] Most of the neurological complications are currently reported from the Chinese population.[26] As the COVID-19 pandemic is spreading to different countries, the spectrum of neurological complications may extend further.

Materials and Methods

The present study aimed to provide a comprehensive overview of neurologic manifestations associated with SARS-CoV-2 infection and describe the clinical course and outcomes of COVID-19 patients with neurologic manifestations. This was a time-bound study conducted between November 2020 to April 2021. This multicenter prospective study was conducted during the coronavirus disease 2019(CoVID-19) pandemic from November 2020 to April 2021 at different hospitals in Punjab, India. The patients with de novo neurologic manifestations were eligible for this study. Thousand confirmed cases present during the study period were included (Figure 1). A confirmed case was defined after a positive result on real-time reverse transcriptase-polymerase chain reaction analysis of nasopharyngeal swabs. We excluded patients with no diagnosis of COVID-19, patients with neurologic signs that were not time-related to COVID-19, and patients with exacerbations of chronic neurologic diseases. The hospital's ethical committee (MMEC No. Rs/1020/1). Fully informed consent was obtained in all cases either from the patient or from next of kin if the patient himself was not considered capable of doing so because of impaired conscious level. Confidentiality was ensured, and the study was carried out according to "Declaration of Helsinki. Detailed data forms were filled by attending physicians. They were attending physicians who recorded and updated the demographics, history, examination findings, and complementary tests. A trained neurologist reviewed and confirmed the positive findings. Neurological manifestations were divided into the central nervous system, peripheral nervous system, and musculoskeletal manifestations for analytical purposes. Statistical analysis was performed by SPSS version 20 software.

Results

The study population comprised 1000 Covid-19 hospitalized patients. Baseline characteristics and comorbidities are given in table-I. The mean age was 44.6 ± 14.3 years and ranged from 22 to 71 years; 625 (62.5%) patients were male, whereas 375 (37.5%) were females. Most common comorbidities were hypertension 348 (34.8%), diabetes mellitus 188 (18.8%), ischemic heart disease 82 (8.2%) and cerebrovascular disease 52 (5.2%) (Table 1).

The most common presenting manifestations were fever 945 (94.5%), cough 643 (64.3%), and dyspnea 476 (47.6%). As many as 672 (67.2%) patients exhibited neurological symptoms (Table- 2 & Figure 2). The most common were headache 313 (31.3%) and dizziness 112 (11.2%). This was followed by hyposmia 52 (5.2%) and encephalopathy or altered sensorium 78 (7.8%). It is important to note that 36 (3.6%) of these patients presented with encephalopathy, whereas 78 (7.8%) developed encephalopathy during the hospital stay.

There were 28 cases of acute cerebrovascular events in our study population. Fourteen patients developed ischemic stroke during illness. All of them had at least

two comorbidities. Four patients, 42 years of age and 46 years of age, presented with ischemic stroke as index presentation. These two patients had noknown comorbidities or vascular risk factors. Besides, it is essential to note that they did not have any systemic manifestation of COVID-19 at the presentation time. However, a chest computed tomography scan showed a mild elevated bilateral ground-glass appearance with peripheral opacities in the lungs (CORADS 6) and C-reactive protein and LDH. D-dimers were raised in all cases with ischemic stroke (range of 0.5- 1.7mg/L), more so in cases who developed ischemic stroke during illness.

There were 6 cases of intracranial hemorrhage, all of which had at least two comorbidities and were on prophylactic anti-coagulation due to severe disease. The coagulation profile was mildly deranged in 4 cases (66% of the cases).

A total of 18 cases of seizures (1.8%) were seen in our study population. Seizures were the cause of presentation in 18 (1.8%) cases. Two patients were known cases of epilepsy, well- controlled on anti-epileptic drugs. They had breakthrough seizures despite good compliance. The other two were new-onset refractory status epilepticus. Two patients were diagnosed with encephalitis based on neuroimaging and CSF analysis. These five patients were diagnosed with COVID-19 on routine screening as they had no systemic disease manifestation. Peripheral nervous system manifestations were present in 64(6.4%) of the patients. The most frequent symptom was hyposmia 52 (5.2%), although it was revealed only directly. Four patients presented with isolated facial nerve palsy, and two with Guillain-Barre Syndrome. It was the presenting symptom in all patients with facial nerve palsy, and COVID was diagnosed later when they developed symptoms (Table 3 and Figure 3). However, the course of the disease was mild in all of them. The patients with GBS had been diagnosed with COVID two weeks back and had mild disease. Neuropsychiatric manifestations were found in 96 (11.8%) patients. The most common was anxiety, followed by insomnia, depression, and psychosis. These were not associated with anyother comorbidities.

Discussion

Our results highlight the broad spectrum of neurologic manifestations associated with SARS-CoV-2 infection. Our results showed that neurological manifestation was the presenting feature in 58 (5.8%) cases, and at least 42% of the patients develop neurological involvement during illness. This was less than the frequency of 53.4% (p=0.09) reported by Sanchez *et al.* [27] from Spain and higher than 37.4% reported by Mao *et al.* from Wuhan, China[3] (p=0.037). Three possible mechanisms are underlying the pathogenesis of neurological involvement. First is diffuse cerebral dysfunction due to systemic disturbances-namely cytokine storm, hypoxia, sepsis, and multi-organ dysfunction. Second is the immune-mediated mechanism that is also implicated in complications of many other viral illnesses. The third and most crucial factor is neuroinvasion or neurotropism that is well known with other human coronaviruses like 229E, OC43, and SARS- COV-1[9,28] and certain other respiratory viruses like measles.[29] Anosmia or hyposmia, which is an initial presentation in many cases of COVID-19, depicts the neuroinvasive potential of SARS- COV-2. The affinity of this virus to ACE-2 receptors can be a potential underlying mechanism, as ACE-2 receptors are expressed both in respiratory epithelium and neuronal cells.[30] As far as the central nervous system is concerned, the virus can reach there either by retrograde transfer through peripheral nerves[31,32] or by direct hematogenous spread after blood-brain barrier disruption by inflammatory mediators.[33] And, theoretically, if brainstem-mediated complications develop,[34] they can be devastating. This direct involvement of CNS has been proven by viral particles in frontal lobe neurons[35] and positive RT-PCR for SARS-COV 2 in cerebrospinal fluid.[36]

Now focusing on individual neurological manifestations in this cohort, about one-third (35%) of the patients complained of headaches that is significantly more than the frequency of 13.1% described by Mao *et al*.[3] Interestingly, the headache was the presenting complaint in 4 patients where it was so severe that they were immediately sent for Computed Tomography of Brain to rule out subarachnoid hemorrhage. It has been postulated that cytokines and chemokines released by macrophages trigger nociceptive sensory neurons resulting in headaches.[37] Apart from encephalitis, a preliminary report of patients with Posterior Reversible Encephalopathy Syndrome (PRES) like features on neuroimaging has emerged from Italy.[38] Poyiadji *et al.* [39] from Detroit also reported a case of Acute Necrotising Hemorrhagic Encephalopathy in a middle-aged female.

Skeletal muscle injury was found in 4 (0.4%) patients, which had significantly raised serum creatinine kinase levels, but as these patients had severe

respiratory disease, it cannot be reliably determined if it representeddirect or indirect injury.

We had two cases of encephalitis that presented with seizures and had bilateral temporal hyperintensities on Magnetic Resonance Imaging of the brain. The CSF examination revealed mild pleocytosis. However, it should be kept in mind that Magnetic Resonance Imaging and cerebrospinal fluid (CSF) analysis were not done in all patients with encephalopathy, especially where encephalopathy seemed to be secondary to severe disease or multi-organ dysfunction. Thus, there is a possibility that some cases of encephalitis might have been missed. Cases of encephalitis and optic neuritis have already been reported from other parts of the world as an inflammatory complication of COVID-19.[27]

Concerning ischemic stroke in patients with COVID-19, a frequency of 2.5% was reported from Italy[40], while a higher frequency of 5% has been reported from China.[41] We observed ischemic stroke in 2.2% of the patients in our study population. Lower incidence here could be the result of the overall younger age of the cohort. Although most of the ischemic strokes were seen in severely ill patients with multiple comorbidities, two cases of acute ischemic stroke are relatively young patients with no known comorbidities indicate that for a subset of patients, there is an actual neurological impact of COVID-19. A studyin New York has also reported stroke in COVID patients younger than 50 years of age.[42] Cases of acute ischemic strokes have also been previously reported with SARS-COV-1.[43] Underlying pathogenesis follows Virchow's triad as evidenced by direct endothelial damage by the virus resulting in endothelium and altered blood flow and hypercoagulability triggered by cytokine release.[44,45]

Limitations of the Study

This study has certain limitations. First, only 1000 patients were included. This could cause bias as the number of COVID-19 infections was huge. It would be advantageous to include more patients from different hospitals from different parts of the country. Second, all the data were obtained from the computerized record, so the patients with very mild neurologic manifestations, i.e., smell and taste impairment, might have missed out on diagnosis. Third, few of the included patients were still undergoing treatment. Hence clinical outcome data was unavailable. Lastly, the majority of the symptoms were the patient's subjective description. It could not be established whether these neurologic manifestations were caused by pulmonary disease, organ damage, or the virus directly.

Conclusion

Our study highlights the broad spectrum of neurologic manifestations associated with SARS-CoV-2 infection, probably related to different pathogenic pathways. We will also like to emphasize that many COVID patients who presented with vascular and inflammatory neurological diseases, like stroke, GBS, and facial nerve palsy, had mild or no respiratory symptoms. Thus we recommend that all patients presenting with acute neuro- logical illness be screened for COVID-19 during the pandemic.

Recommendation

Patients infected with severe COVID-19 should be constantly monitored for progression of neurological symptoms. Timely monitoring will indicate negative and positive progression of their condition. Secondly, the patients who present with new-onset focal neurology, with or without the presence of coryzal symptoms, should be reviewed and treated with the suspicion of SARS-CoV-2 infection. All this monitoring will allow the early detection of COVID-19 infection and, therefore, will lead to the prevention of deterioration of the disease.

Key Messages

- Patients with comorbidity, who are suffering from COVID-19, are at risk.
- Monitoring of neurological symptoms is of utmost importance.
- Timely monitoring will indicate negative and positive progression of their condition.
- This timely monitoring will prevent the worsening of the patients' health.

Acknowledgments

We thank Dr. Mainul Haque for his guidance in preparing this manuscript.

Conflict of Interest

We, the authors, declare they have no potential conflict of interest regarding this article.

Funding

The authors declare that we have not received any of the funding from any external agency.

Table 1 : Clinical characteristics of the patients with COVID-19.

Characteristics		**n (%)**
Age	<50	592 (59.2)
	>50	408 (40.8)
Gender	Male	625 (62.5)
	Female	375 (37.5)
CO-morbidities	Hypertension	348 (34.8)
	Diabetes Mellitus	188 (18.8)
	Ischemic Heart Disease	82 (8.2)
	Cerebrovascular disease	52 (5.2)
	Malignancy	10 (1)
	Chronic Kidney Disease	78 (7.8)
	Others	72 (7.2)

Table 2 : Central nervous system (CNS) Manifestations.

Clinical Features	n (%)
Headache	3 1 3 (31.3)
Dizziness	112 (11.2)
Encephalopathy	78 (7.8)
Ischemic stroke	28 (2.8)
Hemorrhagic stroke	11 (1.1)
Seizures	18 (1.8)
Encephalitis	6 (0.6)
Neuropsychiatric symptoms	1 0 6 (10.6)

Table 3 : Peripheral nervous system (PNS) and musculoskeletal manifestation.

Clinical Features	n (%)
Hyposmia	52 (5.2)
Neuropathy	5 (0.5)
Guillain-Barre Syndrome (GBS)	3 (0.3)
Myositis	4 (0.4)

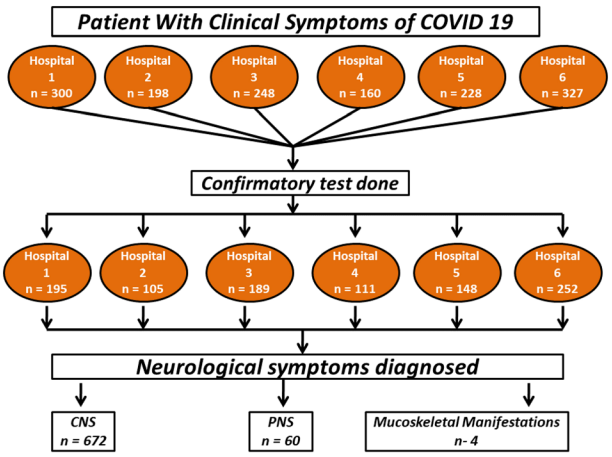

Figure 1: Flowchart of research methodology.

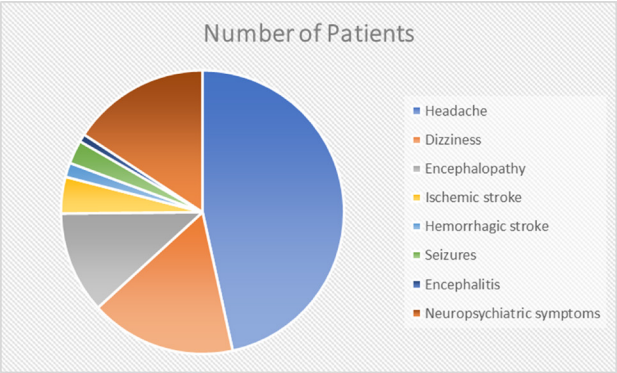

Figure 2: Number of patients suffering from different manifestations of the Central nervous system.

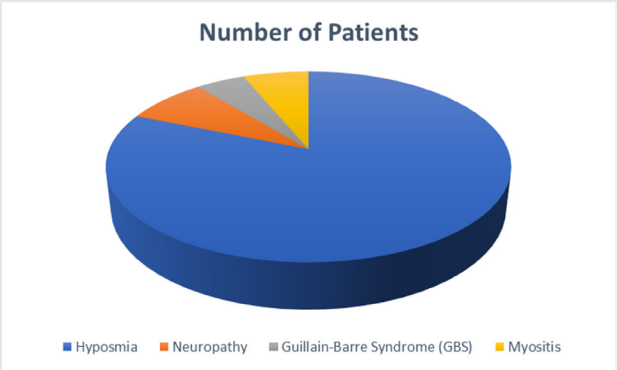

Figure 3: Number of patients suffering from different manifestations of the peripheral nervous system and Musculoskeletal manifestations.

References

1. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical Characteristics of Covid-19 in New York City. N Engl J Med. 2020 Jun 11;382(24):2372–4.
2. Shahzad F, Nasim MT. COVID-19: A natural phenomena or laboratory-based origin? Bangladesh J Med Sci [Internet]. 2020 Jul 20 [cited 2021 Aug 20]; Available from: https://www.banglajol.info/index.php/BJMS/article/view/48197
3. 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 Neurol. 2020 Jun 1;77(6):683–90.
4. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic Features in Severe SARS-CoV-2 Infection. N Engl J Med. 2020 Jun 4;382(23):2268–70.
5. Khan MG, Yezdani U, Chakravorty A, Shukla T. Efforts and Challenges paved by India to confront of Corona Virus (COVID-19). Bangladesh J Med Sci [Internet]. 2020 Jul 20 [cited 2021 Aug 20]; Available from: https://www.banglajol.info/index.php/BJMS/article/view/48198
6. Nepal G, Rehrig JH, Shrestha GS, Shing YK, Yadav JK, Ojha R, et al. Neurological manifestations of COVID-19: a systematic review. Crit Care Lond Engl. 2020 Jul 13;24(1):421.
7. Bastola A, Sah R, Nepal G, Gajurel BP, Rajbhandari SK, Chalise BS, et al. Bell's palsy as a possible neurological complication of COVID-19: A case report. Clin Case Rep. 2021 Feb;9(2):747–50.
8. Soltani S, Zakeri A, Rezayat S, Karimi M, Anbaji F, Tabibzadeh A, et al. A systematic literature review on COVID-19, clinical manifestation, laboratory, and radiologic features. Adv Hum Biol. 2021;11(1):26.
9. Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and Neurologic Manifestations of the Coronaviruses in the Age of Coronavirus Disease 2019 A Review. JAMA Neurol. 2020 Aug 1;77(8):1018–27.
10. Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection–a review of immune changes in patients with viral pneumonia. Emerg Microbes Infect. 2020 Mar 30;9(1):727–32.
11. Dhillon PS, Dineen RA, Morris H, Tanasescu R, Nikfekr E, Evans J, et al. Neurological Disorders Associated With COVID-19 Hospital Admissions: Experience of a Single Tertiary Healthcare Center. Front Neurol. 2021 Feb 19;12:640017.
12. Wang L, Ren Z, Ma L, Han Y, Wei W, Jiang E, et al. Progress in Research on SARS-CoV-2 Infection Causing Neurological Diseases and Its Infection Mechanism. Front Neurol. 2021 Jan 13;11:592888.
13. Jiao L, Yang Y, Yu W, Zhao Y, Long H, Gao J, et al. The olfactory route is a potential way for SARS-CoV-2 to invade the central nervous system of rhesus monkeys. Signal Transduct Target Ther. 2021 Dec;6(1):169.
14. Ni W, Yang X, Yang D, Bao J, Li R, Xiao Y, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. Crit Care. 2020 Dec;24(1):422.
15. Ahmad I, Rathore FA. Neurological manifestations and complications of COVID-19: A literature review. J Clin Neurosci. 2020 Jul;77:8–12.
16. Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R. The COVID-19 Cytokine Storm; What We Know So Far. Front Immunol. 2020 Jun 16;11:1446.
17. Unnithan AKA, Mehta P. Hemorrhagic Stroke. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 [cited 2021 Aug 18]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK559173/
18. Lazarte-Rantes C, Guevara-Castañón J, Romero L, Guillén-Pinto D. Acute Necrotizing Encephalopathy Associated With SARS-CoV-2 Exposure in a Pediatric Patient. Cureus. 13(5):e15018.
19. Garg RK. Spectrum of Neurological Manifestations in Covid-19: A Review. Neurol India. 2020 Jun;68(3):560–72.
20. Ong JJY, Bharatendu C, Goh Y, Tang JZY, Sooi KWX, Tan YL, et al. Headaches Associated With Personal Protective Equipment - A Cross-Sectional Study Among Frontline Healthcare Workers During COVID-19. Headache. 2020 May;60(5):864–77.
21. Khedr EM, Abo-Elfetoh N, Deaf E, Hassan HM, Amin MT, Soliman RK, et al. Surveillance Study of Acute Neurological Manifestations among 439 Egyptian Patients with COVID-19 in Assiut and Aswan University Hospitals. Neuroepidemiology. 2021;55(2):109–18.
22. Sedaghat Z, Karimi N. Guillain Barre syndrome associated with COVID-19 infection: A case report. J Clin Neurosci. 2020 Jun;76:233–5.
23. Razzaque M. COVID-19 pandemic: Can boosting immune responses by maintaining adequate nutritional balance reduce viral insults? Adv Hum Biol. 2020;10(3):99.
24. Al Hamdani S, Aljanabi FY, Abdulrasool MI, Salman AH. Child with Guillain-Barré Syndrome Responding to Plasmapheresis: A Case Report. Case Rep Acute Med. 2020 Feb 5;3(1):4–11.
25. Torres PA, Helmstetter JA, Kaye AM, Kaye AD. Rhabdomyolysis: Pathogenesis, Diagnosis, and Treatment. Ochsner J. 2015;15(1):58–69.
26. Chou SH-Y, Beghi E, Helbok R, Moro E, Sampson J, Altamirano V, et al. Global Incidence of Neurological Manifestations Among Patients Hospitalized With COVID-19—A Report for the GCS-NeuroCOVID Consortium and the ENERGY Consortium. JAMA Netw

Open. 2021 May 11;4(5):e2112131.

27. Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, Sánchez-Larsen Á, Layos-Romero A, García-García J, et al. Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. Neurology. 2020 Aug 25;95(8):e1060–70.

28. Lau K-K, Yu W-C, Chu C-M, Lau S-T, Sheng B, Yuen K-Y. Possible Central Nervous System Infection by SARS Coronavirus. Emerg Infect Dis. 2004 Feb;10(2):342–4.

29. Katow S, Shishido A, Kobune K, Uchida N. Growth of measles virus in nervous tissues. II. Neurotropic properties of a SSPE virus in hamsters. Jpn J Med Sci Biol. 1973 Dec;26(5):197–211.

30. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020 Apr 16;181(2):271-280.e8.

31. Dubé M, Le Coupanec A, Wong AHM, Rini JM, Desforges M, Talbot PJ. Axonal Transport Enables Neuron-to-Neuron Propagation of Human Coronavirus OC43. J Virol. 2018 Sep 1;92(17):e00404-18.

32. Li Y-C, Bai W-Z, Hirano N, Hayashida T, Taniguchi T, Sugita Y, et al. Neurotropic virus tracing suggests a membranous-coating-mediated mechanism for transsynaptic communication. J Comp Neurol. 2013 Jan 1;521(1):203–12.

33. Sankowski R, Mader S, Valdés-Ferrer SI. Systemic inflammation and the brain: novel roles of genetic, molecular, and environmental cues as drivers of neurodegeneration. Front Cell Neurosci. 2015;9:28.

34. Li Y-C, Bai W-Z, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol. 2020 Jun;92(6):552–5.

35. 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. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. 2020 May;94:55–8.

36. Paniz-Mondolfi A, Bryce C, Grimes Z, Gordon RE, Reidy J, Lednicky J, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). J Med Virol. 2020 Jul;92(7):699–702.

37. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect. 2020 Jun;80(6):607–13.

38. Anzalone N, Castellano A, Scotti R, Scandroglio AM, Filippi M, Ciceri F, et al. Multifocal laminar cortical brain lesions: a consistent MRI finding in neuro-COVID-19 patients. J Neurol. 2020 Jun 6;1–4.

39. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: Imaging Features. Radiology. 2020 Aug;296(2): E119–20.

40. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res. 2020 Jul;191:9–14.

41. 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.

42. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. N Engl J Med. 2020 May 14;382(20):e60.

43. Umapathi T, Kor AC, Venketasubramanian N, Lim CCT, Pang BC, Yeo TT, et al. Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). J Neurol. 2004 Oct;251(10):1227–31.

44. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet Lond Engl. 2020 Mar 28;395(10229):1054–62.

45. Becker RC. COVID-19 update: Covid-19-associated coagulopathy. J Thromb Thrombolysis. 2020 Jul;50(1):54–67.