NEUROLOGICAL MANIFESTATIONS OF COVID-19 IN PATIENTS ADMITTED AT A TERTIARY CARE HOSPITAL IN PUNJAB, PAKISTAN

Saima Shafait, Wasim Alamgir, Muhammad Ali Yousaf, Muhammad Adnan Manzar, Abdul Latif Khattak, Muhammad Javad Yousaf*

Pak Emirates Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan, *Army Medical College/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To determine the frequency of neurological manifestations and complications of SARS-COV-2. We were especially concerned with the cases where the primary presentation was neurological indicating the neuro-invasive potential of the virus.

Study Design: Prospective observational study.

Place and Duration of Study: Pak Emirates Military Hospital, Rawalpindi, from Apr to May 2020.

Methodology: A total of 405 confirmed COVID patients were enrolled for the study. Demographic features and initial clinical manifestations were noted and patients were followed during the hospital stay for the development of 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 case to case basis.

Results: In this study, the mean age was 46.6 ± 15.5 years. Two hundred and seventy one (66.9%) patients were male while one hundred and thirty four (33.1%) were female. The neurological illness was a primary manifesttation in twenty four (6%) cases. These included encephalopathy (n=15), ischemic stroke in young (n=2), Guillain-Barre syndrome, (n=1), facial nerve palsy (n=2), and encephalitis (n=1). The most common neurological symptoms were headache 142 (35%), and hyposmia 39 (9.6%) followed by encephalopathy 34 (8.3%). More serious complications like seizures 7 (0.7%) and stroke 9 (2.2%) were also seen.

Conclusion: Severe Acute Respiratory Syndrome-Coronavirus 2 can present with a neurological illness like its predecessors. We should remain vigilant to the possibility of neurological presentation of COVID-19 that can be thromboembolic, inflammatory or immune-mediated.

Keywords: Complications, Coronavirus, Neurological.

INTRODUCTION

An outbreak of pneumonia cases due to SARS-COV-2 was reported to WHO in December 2019 from Wuhan, China[1] and within a few weeks Coronavirus disease 2019, as it was designated, spread around the globe resulting in a wreaking pandemic[2]. As of 8 June 2020, there are 6.93 million confirmed cases and nearly 400,857 deaths worldwide[3]. Pakistan was during this time the 10th worst affected country with a rapid surge in new cases.

SARS COV-2 is a respiratory virus that bears a close homology to SARS-COV-1[4]. It presents with highly lethal pneumonia in addition to other general symptoms like fever, cough, and headache. However it does affect other organ systems of the body including the nervous system. Neurotropism, which is a known characteristic of many coronaviruses, seems to be the underlying mechanism in many cases and is being reflected by a high percentage of anosmia in COVID patients. Therefore, we can infer that neurological involvement can not only arise as a complication of a systemic disease but it can well be a primary presentation. A high index of suspicion especially by the emergency physicians is required for prompt diagnosis in such cases. We conducted a prospective observational study in Pak Emirates Military Hospital (PEMH), Rawalpindi to assess

Correspondence: Dr Saima Shafait, Resident Medical Officer, Pak Emirates Military Hospital, Rawalpindi Pakistan
Received: 15 Jun 2020; revised received: 13 Aug 2020; accepted: 21 Aug 2020

the pattern of neurological symptoms in our COVID-19 patients.

METHODOLOGY

It was a prospective observational study conducted in Pak Emirates Military Hospital, Rawalpindi, from 1st April 2020 to 22nd May 2020. It is a 1200 bedded tertiary care hospital designated to COVID-19 and having the largest cohort of COVID-19 patients in Pakistan. This study was done between 1st April 2020 to 22nd May 2020.

All confirmed cases presenting during the study period were included. A confirmed case was defined after a positive result on real-time reverse transcriptase-polymerase chain reaction analysis of nasopharyngeal swabs. Patients with AIDS and those on immunosuppression therapy for any cause were excluded from the study as immunosuppressed people tend to have distinct presentations and manifestations of any given illness, quite different from the general population.

Study design was reviewed and approved by ethics committee of the hospital (ERC no.A/28/161/EC). 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. Detailed data forms were filled by attending physicians. Demography, history, and examination findings and complementary tests were recorded and updated regularly by attending physicians. A trained neurologist reviewed and confirmed the positive findings. For analytical purposes, neurological manifestations were divided into 3 groups; the central nervous system, peripheral nervous system, and musculoskeletal manifestations. SPSS ver 20 was used for statistical analysis. Student t-test was used to compare this study with other similar studies done previously.

RESULTS

Between 1st April and 22th May 2020, 482 confirmed cases of COVID were admitted. Data could not be completed for 77 patients for various reasons. The final analysis was done for 405 patients. Baseline characteristics and co-morbidities are given in table-I. The mean age was 46.6 ± 15.5 years and ranged from 15 to 71 years, 271 (66.9%) patients were male whereas 134 (33.1%) were females. Most common comorbidities were hypertension 138 (34%), diabetes mellitus 63 (15.5%), ischemic heart disease 37 (9.1%) and cerebrovascular disease 18 (4.4%).

The most common presenting manifestations were fever 350 (86.4%), cough 298 (73.5%), and dyspnea 209 (51.6%). As many as 171 (42.2%) patients exhibited neurological symptoms (table-II & III). The most common were headache 142 (35%) and dizziness 46 (11.3%). This was followed by hyposmia (9.6%) and encephalopathy or altered sensorium 34 (8.3%). It is important to note that 15 (3.7%) of these patients presented with encephalopathy whereas 19 (4.6%) developed encephalopathy during the hospital stay.

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

Characteristics		n (%)
Age	<50	239 (59)
	>50	166 (40.9)
Gender	Male	271 (66.9)
	Female	134 (33.1)
CO-morbidities	Hypertension	138 (34.0)
	Diabetes Mellitus	63 (15.5)
	Ischemic Heart Disease	37 (9.1)
	Cerebrovascular disease	18 (4.4)
	Malignancy	4 (0.9)
	Chronic Kidney Disease	31 (7.6)
	Others	34 (8.3)

There were 9 cases of acute cerebrovascular events in our study population. Seven patients developed ischemic stroke during illness. All of them had at least 2 co-morbidities. Whereas 2 patients, one 42 years of age, and the other 46 years of age presented with ischemic stroke as index presentation. These two patients had no known co-morbidities or vascular risk factors. Besides it is important to note that they did not have any systemic manifestation of COVID-19

at the time of presentation, however, computed tomography scan of the chest showed bilateral ground-glass appearance with peripheral opacities in the lungs and C-reactive protein and LDH were mildly elevated. 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 the course of illness.

There were three cases of intracranial hemorrhage all of which had at least two co-morbidities and were on prophylactic anti-coagulation due to severe disease. The coagulation profile was mildly deranged in two cases (75% of the cases).

A total of seven cases of seizures (1.7%) were seen in our cohort. Seizures was the cause of presentation in three (0.7%) cases. One patient was a known case of epilepsy, well controlled on anti-epileptic drugs. He had breakthrough seizures despite good compliance. The other one was new-onset refractory status epilepticus. The third patient was diagnosed with encephalitis based on neuro-imaging and CSF analysis. These three patients were diagnosed with COVID-19 on routine screening as they had no systemic manifestation of the disease.

Table-II: Central nervous system (CNS) manifestaions.

Clinical Features	n (%)
Headache	142 (35)
Dizziness	46 (11.3)
Encephalopathy	34 (8.3)
Cerebrovascular Accident (CVA)/ischemic stroke	9 (2.2)
Cerebrovascular Accident (CVA)/hemorrhagic stroke	3 (0.7)
Seizures	7 (1.7)
Encephalitis	1 (0.2)
Neuropsychiatric symptoms	48 (11.8)

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

Clinical Features	n (%)
Hyposmia	39 (9.6)
Neuropathy	2 (0.4)
Guillain-Barre Syndrome (GBS)	1 (0.2)
Myositis	2 (0.4)

Peripheral nervous system manifestations were present in 5.9% of the patients. Most frequent symptom was hyposmia 21 (5.1%) although it was revealed only on direct questioning. Two patients presented with isolated facial nerve palsy, and one with Guillain-Barre Syndrome. In both patients with facial nerve palsy, it was the presenting symptom, and COVID was diagnosed later when they developed symptoms. However, the course of the disease was mild in both of them. The patient with GBS (AMAN variant) had been diagnosed with COVID two weeks back, had mild disease, and was self quarantined at home.

Neuropsychiatric manifestations were found in 48 (11.8%) patients. The most common was anxiety followed by insomnia, depression, and psychosis. These were not associated with any other comorbidities.

In 24 (6%) patients, neurological manifestation was the reason for the presentation. These included encephalopathy 15 (3.7%), seizures 3 (0.7%), facial nerve palsy 2 (0.4%), ischemic stroke 2 (0.4%), Headache 2 (0.4%), GBS 1 (0.2%) and encephalitis 1 (0.2%).

DISCUSSION

COVID-19 (Coronavirus disease 19) is an evolving epidemic and we are still in the process of understanding this new disease. This study was conducted in order to get an overview of the neurological aspects of the disease. Our results showed that neurological manifestation was the presenting feature in 24 (6%) cases and at least 42% of the patients develop neurological involvement during the course of illness. This was less than the frequency of 57.4% (p=0.09) reported by Sanchez *et al*[5] from Spain and higher than 37.4% reported by Mao *et al* from Wuhan, China[6] (p=0.037).

There are three possible mechanisms underlying the pathogenesis of neurological involvement. First is diffuse cerebral dysfunction as a consequence of 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 important factor is neuroinvasion or neurotropism that is well known with other human coronaviruses like 229E, OC43 and SARS-COV-1[7,8] and certain other respiratory viruses like measles[9]. Anosmia/hyposmia which is an initial presentation in many cases of COVID-19 depicts the neuroinvasive potential of SARS-COV-2. Affinity of this virus to ACE 2 receptor can be a potential underlying mechanism, as ACE 2 receptors are expressed both in respiratory epithelium and neuronal cells[10]. As far as the central nervous system is concerned, Virus can reach there either by retrograde transfer through peripheral nerves[11,12] or by direct hematogenous spread after blood-brain barrier disruption by inflammatory mediators[13]. And, theoretically, if brainstem-mediated complications develop[14], they can be devastating. This direct involvement of CNS has been proven by the presence of viral particles in frontal lobe neurons[15] and positive RT-PCR for SARS-COV 2 in cerebrospinal fluid[16].

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*. Interestingly, headache was the presenting complaint in 2 patients where it was so severe that they were immediately sent for Computed Tomography of Brain to rule out sub-arachnoid hemorrhage. It has been postulated that cytokines and chemokines released by macrophages trigger nociceptive sensory neurons resulting in headaches[17].

Skeletal muscle injury was found in two (0.4%) patients both of which had significantly raised serum creatinine kinase levels, but as these patients had a severe respiratory disease, it cannot be reliably determined if it represented direct or indirect injury.

We had one case of encephalitis that presented with seizures and had bilateral temporal hyperintensities on Magnetic Resonance Imaging of 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 inflammatory complication of COVID-19[5]. Apart of encephalitis, a preliminary report of patients with Posterior Reversible Encephalopathy Syndrome (PRES) like features on neuroimaging has emerged from Italy[18]. Poyiadji *et al*[19] from Detroit also reported a case of Acute Necrotising Hemorrhagic Encephalopathy in a middle aged female.

Concerning ischemic stroke in patients with COVID-19, a frequency of 2.5% was reported from Italy[20] while a higher frequency of 5% has been reported from China[21]. 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 co-morbidities, two cases of acute ischemic stroke in relatively young patients with no known co-morbidities indicate that for a subset of patients there is true neurological impact of COVID-19. A study in New York has also reported stroke in COVID patients younger than 50 years of age[22]. Cases of acute ischemic strokes have also been previously reported with SARS-COV-1[23]. Underlying pathogenesis follows Virchow's triad as evidenced by direct endothelial damage by the virus resulting in endothelitis and altered blood flow, and hypercoagulability triggered by cytokine release[24,25].

CONCLUSION

In conclusion, it can be said that although COVID-19 is a respiratory infection, a significant number of patients are developing neurological manifestations either through direct or indirect involvement of nervous system. Cases with indirect involvement are more common in our study

population but there is solid evidence of direct involvement. Therefore, we need to keep a close watch for long term neurological sequelae of this SARS COV 2 pandemic.

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 neurological illness should be screened for COVID-19 during the pandemic.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. World Health Organization.Pneumonia of unknown cause-China.Disease outbreak news. 2020. Available at: http://www.who.int/csr/don/05-January-20-pneumonia-of-unknown-cause-china/en/
2. WHO. Director-General's opening remarks at the media briefing on COVID-19. 2020. [Internet] Available at: http://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-COVID-19---11-march-2020
3. World Health Organisation. Coronavirus disease 2019 (COVID-19) Situation Report-140. Available at: http://www.who.int/docs/default-source/coronavirus/situation-reports/2020608-covid-19-sitrep-140.pdf
4. Zheng J. SARS-COV-2: an emerging coronavirus that causes a global threat. Int J Biol Sci 2020; 16(10): 1678-85.
5. 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. Neurol 2020; 1(1): 1-5.
6. 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. J Am Med Assoc Neurology 2020; 77(6): 683-90.
7. 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. J Am Med Assoc Neurology 2020; 77(8): 1018-27.
8. Lau KK, Yu WC, Chu CM, Lau ST, Sheng B, Yuen KY. Possible central nervous system infections by SARS Coronavirus. Emerg Infect Dis 2004; 10(2): 342-44.
9. Katow S, Shishido A, Kobune K, Uchida N. Growth of measles virus in nervous tissue. Jpn J Med Sci Biol 1973; 26(5): 197-211.
10. 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; 181(2): 271-80.
11. Dube M, Le Coupenac A, Wong AHM, Rini JM, Des Forges M, Talbot PJ. Axonal transport enables the neuron to neuron propagation of human coronavirus OC43. J Virol 2018; 92(17): e00404-18.
12. Li YC, Bai WZ, 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; 521(1): 203-12.
13. Sankowski R, Mader S, Valades-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): 1-4.
14. Li YC, Bai WZ, Hashikawa T. The Neuroinvasive potential of SARS-COV 2 may play a role in the respiratory failure of COVID-19 Patients. J Med Virol 2020; 10: 1002.
15. 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. 2020; 94(1): 55–58.
16. Mondolfi AP, 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; 92(7): 699-702.
17. Ye Q, Wang B, Mao J. The pathogenesis and treatment of theCytokine Storm'in COVID-19. J Infec 2020; 80(6): 607-13.
18. Anzalone N, Castellano A, Scotti R, Scandroglio AM, Filippi M, Ciceri F, et al. Multifocal transient cortical brain lesions: a consistent MRI finding in neuro-COVID-19 patients. Med Rxiv 2020; 1(1): 20103168.
19. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. Radiol 2020: 201187.
20. 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. Thrombosis Res 202; 191(2020): 9-14.
21. Li Y, Wang M, Zhou Y, Chang J, Xian Y, Mao L, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. Stroke Vas Neurol 2020; 000431.
22. 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. New England J Med 2020; 382(20): e60.
23. Umapathi T, Kor AC, Venketasubramanian N, Lim CT, Pang BC, Yeo TT, et al. Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). J Neurology 2004; 251(10): 1227-31.
24. 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 2020; 359; 5-11.
25. Becker RC. COVID-19 update: COVID-19 Associated coagulopathy. J Thromb Thrombolysis 2020; 50(1): 54-67.