DOI: https://doi.org/10.53350/pjmhs221621159

ORIGINAL ARTICLE

Neurological Manifestations and Its Outcome Due to Covid-19 Disease: An Observational Study

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ABSTRACT

Background: Corona virus has hit the world by the end of year 2019. Within few months it became pandemic and named as COVID-19 (SARS COV 2). Initially it was known as a disease of respiratory tract but with the advance study of clinical symptoms it has shown neurological manifestations, coagulopathies, diabetes mellitus and hypertension. The pathophysiology of disease showed that corona virus proteins bind to ACE receptors and effect multiple organ systems of body. The disease outcome is poor among those who develop such complications. The objective of this study was to determine the association of neurological manifestations with COVID 19 and to find out the health outcome of admitted patients.

Methods: A cross-sectional study was conducted on COVID 19 patients through convenient sampling. Patients were admitted to DHQ Hospital, Sargodha with clinical symptoms of disease and with neurological manifestations. Their comorbid factors were also identified along with laboratory investigations (CT- brain, D-dimers. Serum sugar level and base line investigations). Analysis was done on SPSS 20 and association was determined between neurological manifestations and COVID 19 disease by chi- square test of independence with $p<0.05$ taken as level of significance.

Results: Among 276 hospitalized patients male and female were of equal ratio with mean age of 59.22 (SD= 14.3). The death was more among 56-70 years (n=165) of patients with neurological manifestations and 100% in patients with age > 70 years with neurological manifestations. The outcome of disease is not significantly associated with age of patients (p=0.101). CT-scan findings showed 195(92.85%) patients' outcome was poor with thromboembolic phenomenon. Neurological manifestations of COVID 19 disease were also significantly associated with disease outcome (p=0.000). Only 30 (11.11%) patients with neurological manifestations recovered from disease and were discharged. The severity of disease was also significantly associated with neurological manifestations due to COVID 19 (p=0.000).

Conclusion: The neurological manifestations are associated with COVID 19 disease and its outcome is poor due to its neurological complications. The central nervous system involvement might be the result of invasion of virus. The COVID 19 disease is not only involving the respiratory system but it has its effects on multiple organs. The outcome of disease can be managed with early diagnosis and management of neurological manifestations.

Keywords: COVID 19, Neurological manifestations, Disease outcome, Severity of covid-19 disease.

INTRODUCTION

The history of corona virus disease begins with severe acute respiratory syndrome (SARS) in 2002 and middle east respiratory syndrome (MERS) in 2012.(1) It was considered to be a disease of respiratory system only. But with the outbreak of novel corona virus (COVID-19) disease it has presented with neurological manifestations along with respiratory symptoms.(2) The COVID 19 disease has been classified into mild, moderate and severe disease by WHO. The mild disease presents with fever, cough, malaise and flue like symptoms. The moderate disease presents with respiratory symptoms along with mild symptoms and severe disease leads to hospitalization and invasive or non-invasive ventilation.(3) SARS COV-2 may present with mild to severe neurological presentations like headache, dizziness, confusion, anosmia, ageusia to even stroke, coma, seizure, encephalitis and Guillain barre syndrome (GBS).(4)

As the pandemic has affected whole of the world with life-threatening effects also it has resulted in neuropsychological outcome of SARS-COV 2.(5) It can be seen with immediate and late effects during pandemic like depression, neurasthenia and neuritis.(6)

The heart, kidneys, lungs, brain, and coagulation system are all affected by the covid 19 disease. Myocarditis, cerebrovascular illness, encephalitis, and thromboembolic events are all possible side effects. Pneumonia, acute respiratory distress syndrome, acute liver injury, cardiac injury, prothrombic coagulopathy (resulting in venous and arterial thromboembolic events), acute kidney injury, and neurologic manifestations are the common complications.(3) Neurological complications includes meningitis and encephalitis. They may remain undiagnosed due to less or no symptoms.(7) Pathophysiology of neurological manifestations of covid-19 include ACE 2 inhibitors interact with covid-19 virus spike proteins.(8)

The neurological manifestations of covid 19 and its outcome in adult population has found to be important in order to determine its association while controlling the other factors that may also lead to same complications. Neurological symptoms were found to be the main cause of death among SARS COV 2 patients.(9)

The objective of this study was to determine the association of neurological manifestation and outcome of disease in COVID 19 patients who were hospitalized. It will provide future projections for early identification of condition of patients and control over outcome of disease.

MATERIAL AND METHODS

An observational study was conducted in DHQ Hospital, Sargodha and analyzed consecutive patients from 15th March 2021 to 30th September 2021, who were admitted to hospital with moderate to severe COVID 19 disease and had neurological involvement. Cases were confirmed on PCR testing of nasal swab, HRCT and CT brain. Laboratory investigations were done as required. As the study was conducted on admitted patients so according to protocol and requirement of time informed consent was taken at time of admission from attendants of patients.

Data was collected from the record sheets of each confirmed case of covid-19 patient. Data collected on age, gender, severity of disease (as classified by WHO)(10), neurological manifestations, D-dimer level, comorbid factors, CT brain findings, outcome of disease (death and discharge), type of anticoagulant therapy and oxygen delivery. The outcome of disease and severity of disease were taken as dependent variables.

Both male and female gender were included with age categorized into three groups (25-40,41-70 & 71-100 years).

Patients who required oxygen support were classified as moderate disease and patients who required invasive or non-invasive ventilatory support were label as with severe disease. The outcome of the disease was taken as death and discharge of

patients during the study period. The neurological manifestations on basis of symptoms and laboratory findings were included as patients with ischemic stroke, encephalitis, cerebral venous thrombosis, hemorrhagic stroke, posterior cerebellar infarct and Guillain-Barre syndrome. Patients with comorbid conditions like diabetes mellitus, hypertension, ischemic heart disease, diabetic ketoacidosis and limb ischemia were also included.

Analysis was done on SPSS version 20. Frequency of continuous variables was determined along with mean and standard deviation. The age, gender, neurological manifestations, comorbid conditions and CT-scan findings, outcome of disease and disease severity were taken as variables. The categorical variables were compared using chi square test of independence to determine association, with p-value <0.05 as level of significance.

RESULTS

Among the 276 hospitalized patients 136 were males and 136 were females with mean age of 59.22 (SD= 14.3). Age was categorized into three groups that is 30-55 years old patients were 51 (18.5%); 56-70 years were 183 (66.3%) and > 70 years old patients were 42 (15.2%). The characteristics of patients, D-dimer level, neurological presentation, comorbid factors and the CT-scan findings are shown in table 1.

Table 1: Clinical characteristics of patients with covid 19 disease.

Characteristics	Total (N=276) %	Moderate disease (n= 24)%	Severe disease (n=252)%
Age, mean,(SD)	59.22(14.3)		
Age, y			
30-55	51 (18.5)	7(13.72)	44(86.27)
56-70	183 (66.3)	15(8.19)	168(91.8)
>70	42 (15.2)	2(4.76)	40(95.23)
Gender			
Male	136(50)	13(9.55)	127(93.3)
Female	136 (50)	11(8.09)	125(91.91)
Comorbid factors			
No comorbidity	91 (33.7)	9(9.89)	82(90.11)
Diabetes	72 (26.1)	7(9.72)	65(90.3)
Ischemic heart disease	21 (7.6)	3(14.3)	18(85.7)
Hypertension	57 (20.7)	2(3.5)	55(96.5)
Diabetic ketoacidosis	24 (8.7)	2(8.3)	22(91.7)
Limb ischemia	9 (3.3)	1(11.1)	8(88.9)
D-dimers			
<500	18(6.5%)	16(88.9)	2(11.1)
500-5000	90(32.6%)	3(3.33)	87(96.7)
>5000	158(60.9%)	5(3.16)	153(96.8)
Neurological manifestations			
Ischemic stroke	186 (67.4)	10(5.37)	176(94.62)
Encephalitis	24 (8.7)	0	24
Cerebral venous thrombosis	21 (7.6)	0	21
Hemorrhagic stroke	6 (2.2)	0	6
Post cerebellar infarct	24 (8.7)	2(3.33)	22(91.7)
GBS	15 (5.4)	12(80)	3(20)
Outcome of disease			
Death	246(89.1)	3(1.22)	243(98.8)
Discharge	30 (10.9)	21(70)	9(30)

The table shows frequencies of all variables in relation to severity of disease. When comorbid conditions were analyzed, it showed that 93 (33.7%) patients were having no comorbid conditions associated with neurological presentation of COVID 19. Seventy-two (26.1%) with diabetes mellitus, 21 (7.6%) had ischemic heart disease, 57 (20.7%) had hypertension, 24(8.7%) diabetic ketoacidosis and 9 (3.3%) had limb ischemia. Among the admitted patients 18(6.5%) had D-dimers <500, 90(32.6%) had 500-5000 and 158(60.9%) had > 5000. All the patients were on anticoagulation therapy 165(59.8%) patients were given oral anticoagulants and 111(40.2%) were given unfractionated heparin.

The characteristics of patients with outcome of disease is shown in table 2. The death was more among 56-70 years (n=165) of patients and 100% in patients with age > 70 years. The outcome of disease is not significantly associated with age of patients (p=0.101). CT-scan findings showed 195(92.85%) patients' outcome was poor with thromboembolic phenomenon. Neurological manifestations of COVID 19 disease were also significantly associated with disease outcome (p=0.000). Only 30 (11.11%) patients with neurological manifestations recovered from disease and were discharged.

Table 2: characteristics of COVID 19 patients with outcome of disease.

Characteristics	Total (N=276) %	Death (n=246) %	Recovered & discharged (n= 30) %	p-value
Age ,y				0.101
30-55	51 (18.5)	39(76.4)	12(23.5)	
56-70	183 (66.3)	165(90.1)	18(9.83)	
>70	42 (15.2)	42(100)	0	
CT-brain				0.000
normal	18 (6.5)	6	12	
Thromboembolic phenomenon	210 (76.1)	195(92.85)	15(7.14)	
Venous infarct	27 (9.8)	24	3	
Hemorrhagic infarct	3 (1.1)	3	0	
Cerebral edema	18 (6.5)	18	0	
Neurological manifestations				0.000
Ischemic stroke	186 (67.4)	168(90.32)	18(9.67)	
Encephalitis	24 (8.7)	24	0	
Cerebral venous thrombosis	21 (7.6)	21	0	
Hemorrhagic stroke	6 (2.2)	6	0	
Posterior cerebellar infarct	24 (8.7)	24	0	
GBS	15 (5.4)	3	12	
Comorbidities				0.035
none	91 (33.7)	69	24	
Diabetes mellitus	72 (26.1)	69	3	
Ischemic heart disease	21 (7.6)	18	3	
Hypertension	57 (20.7)	57	0	
Diabetic ketoacidosis	24 (8.7)	24	0	
Limb ischemia	9 (3.3)	9	0	

DISCUSSION

276 patients were included in our study, 252(91.3%) had developed severe disease and 24(8.7%) had moderate disease. All these patients had various neurological manifestations including ischemic stroke, encephalitis, Cerebral venous thrombosis, stroke and GBS. Patients with severe disease were more in age group 51-70 years and had diabetes mellitus and hypertension, but fewer had mild symptoms. Either the disease is moderate or severe it requires hospital management for elderly population.[11] The reason might be that all patients who required medical management were admitted to hospital. Mortality among older people who were hospitalized was more in a study conducted in Indonesia.[12] Patients with severe disease were more likely to develop neurological conditions like ischemic stoke and encephalitis. Some patients with moderate symptoms developed Guillain barre syndrome, confirmed by clinical presentation and laboratory investigations. A study in Italy has shown cases presenting with GBS and weakness of lower limbs.[13] Most of the

neurological manifestations were diagnosed early during their hospital stay. All these patients require early diagnosis and management as neurological conditions has been found to be the main cause of death in COVID-19 patients.[13] Other comorbid conditions like hypertension, diabetes mellitus is also causing neurological manifestations, so physicians should make differential diagnosis of SARS-COV-2 in order to prevent poor outcome of disease. Further work is required to find out neurological manifestations and other co-morbid conditions.[14] the new emerging concept of long term impact of neurological manifestation of covid 19 is to be taken into account. It may lead to chronic covid syndrome.[15]

The pathophysiology of SARS-COV-2 infection determined the role of ACE 2 as it has functional receptor for the spike protein of corona virus.[16] These studies suggested that ACE-2 receptors have its mechanism of causing neurological manifestations in covid 19 disease. The pathophysiological condition may be resulted from invasion of virus into central nervous system as in case of SARS and MERS viruses.[17]

We have found in our study that patients with higher D-dimer levels developed severe disease with neurological symptoms and had poor outcome of disease. The impaired D-dimer levels may be the cause of cerebrovascular manifestations of the disease.[18] Ischemic stroke, encephalitis and cerebral venous thrombosis are the main cause of death among patients with neurological manifestations.

CONCLUSION

The neurological manifestations are associated with COVID 19 disease and its outcome is poor due to its neurological complications. The central nervous system involvement might be the result of invasion of virus. The COVID 19 disease is not only involving the respiratory system but it has its effects on multiple organs. This study may lead to new clinical information of high mortality of this disease due to its neurological manifestations. The outcome of disease can be managed with early diagnosis and management of neurological manifestations.

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