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Original Article

Prevalence of Neurological Symptoms Associated with COVID-19

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ABSTRACT

The COVID-19 pandemic caused by the SARS-CoV-2 virus has affected millions of individuals worldwide, leading to a broad spectrum of clinical manifestations. While primarily known for respiratory symptoms, emerging evidence suggests that COVID-19 can also have neurological implications. Understanding the prevalence and nature of neurological symptoms associated with the disease is crucial for effective management and resource allocation. **Objective:** To better understand the prevalence of neurological symptoms associated with COVID-19. Several factors such as age, gender, and comorbidity are explored to create a more holistic understanding of the impact of COVID-19. **Methods:** After meeting inclusion and exclusion criteria, 111 patients admitted to Ibne Sina Hospital were recruited between October 2021 and February 2022. A descriptive statistical analysis was conducted to summarize patients most often encountered signs and symptoms concerning the above parameters. **Results:** Out of 111 patients, a significant proportion of symptoms occurred in patients aged 40-60 years, with Dysgeusia being the most widespread (75.5%), followed by Encephalitis (45.9%), GBS (28.8%), Encephalopathy (18.9%), and Ischemic Stroke (6.3%). These were most prevalent in hypertensive individuals (46%) and Diabetes Mellitus (31%). In asthmatic individuals, they are the least prevalent (10.8%). **Conclusions:** Despite the predominance of neurological manifestations, the present scientific literature cannot demonstrate a definitive causal association between the symptoms and the virus. This study carefully ensures a link age, gender, and comorbidity along with the prevalence of neurological manifestations of COVID-19. For a comprehensive treatment plan, a holistic understanding of symptoms is critical.

INTRODUCTION

Coronavirus was first reported in Wuhan, China, in December 2019. It is also referred to as the severe acute respiratory syndrome (SARS) Coronavirus; as of April 24th, 2022, over 500 million confirmed cases and over six million deaths have been identified globally [1]. This disease can cause severe pneumonia with a high fatality rate. Every minute, extensive research is being undertaken to determine the best coronavirus management, diagnosis, and treatment methods. At the time of the disease's first outbreak, it was believed to have been spread by animals. Nonetheless, its human-to-human transmission was recognized later, and The WHO classified Covid-19 as a global pandemic (World Health Organization). To aid in the battle against this pandemic outbreak, numerous lines of study have been expedited to explore all characteristics of the unique COVID-19 virus while maintaining the highest degree of precaution and safety [2]. COVID-19 is most often associated with fever, a dry cough, and lethargy. Nonetheless, several practitioners in impacted regions noticed that some COVID-19 patients did not exhibit usual respiratory symptoms at the time of diagnosis, such as fever and coughing however, some infected individuals

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presented with only neurological issues, such as headache, languidness, unsteady walking, and malaise, which may be caused by non-specific presentations [3]. A recent study of 214 patients affected by COVID-19 showed that 78 (36.4%) had neurological symptoms such as headache, dizziness, acute cerebrovascular problems, and decreased cognition [3, 4]. Forty (18.7 %) of the 214 patients needed intensive care unit (ICU) treatments for severe neurological involvement. Despite several incidents of brain haemorrhages in COVID-19 individuals being reported, there is a paucity of comprehensive studies on this link. Consequently, the physiological mechanism through which COVID-19 causes cerebral bleeding is unclear [3]. There has been an increase in reports of neurological impairment of the central and peripheral nervous systems in patients infected with COVID-19. Some patients complain of headaches, and Dysgeusia, but a broader range of more serious neurological problems, particularly in hospitalized patients, including stroke, Encephalopathy, Encephalitis, and polyneuritis have been reported [5]. Coughing, sneezing, or touching unclean objects are how the virus spreads swiftly. It is more prevalent in the elderly, males, and those with diabetes, hypertension, cardiovascular disease, or cancer [6]. In order to better understand the disease's biology and transmission, researchers need to know where SARS-CoV-2 is located in the tissues of COVID-19 patients. This study examined samples from eight deceased SARS-CoV-2 patients in the United States using immunohistochemistry and electron microscopy. Upper and lower airway epithelium with extensive alveolar degeneration was the most common respiratory pathologyy in these individuals. SARS-CoV-2 was found in conducting airways, pneumocytes, alveolar macrophages, and a hilar lymph node, but not in other extrapulmonary tissues [7]. According to research, coronaviruses from the SARS family "hijack" the protein angiotensin-converting enzyme-2 (ACE2). It is an aminopeptidase that is membrane-bound and identified in a variety of human cells (respiratory tract, lung, heart, arteries, veins, kidney, brain, and intestines). A protein called SPIKE interacts with the ACE2 receptor, allowing the virus to enter the cell [8]. According to preclinical studies, coronavirus may propagate trans neuronally into the brain along olfactory pathways, compromising the integrity of the olfactory neuroepithelium. This is accomplished by the sustentacular cell's synthesis of TMPRSS2 and ACE2 [9-11]. Specific populations are more vulnerable to the consequences of COVID-19 than others. Children, the elderly, the disabled, those from rural regions, those with a lower socioeconomic standing, and those with pre-existing health problems are just a few examples [12].

METHODS

The prevalence of neurological COVID-19-related symptoms was determined using a quantitative research design in patients hospitalized at Ibne Sina Hospital, Multan. Five months of data collection occurred between October 2021 and February 2022. After meeting inclusion and exclusion criteria, a standardized questionnaire was utilized (that mentioned the biodata , history and physical exam , blood baselines, inflammatory markers Chest X-Ray, HRCT, neuro-imaging and Lumber puncture findings) to gather data from a sample of 111 individuals, conveniences sampling was used, and a descriptive statistical analysis was employed to summaries the findings. The sample size was not calculated based on statistical considerations or power calculations, as would be done in random or probability sampling methods. Instead, the sample size was determined by the number of participants who meet the inclusion and exclusion criteria and were available for recruitment within the study's timeframe. Various factors were used to identify participants from outpatient, inpatient, and previous medical records; informed consent was obtained by patients or guardians. The Criteria for inclusion are as below: Age groups over 15 years were employed, with subgroups of 15-30, 31-60, and greater than 60 years. All subjects were diagnosed with a neurological deficit apparent through the history and clinical examination. All participants had a history in which they were either clinically diagnosed with COVID-19 and had symptoms such as fever, cough, homogenous infiltrates bilaterally on lungs with lymphopenia and elevated inflammatory markers as baseline parameters, or had a positive PCR. The Criteria for exclusion are as below: Age less than 15 years. A history of substance abuse. Patients suffering from metabolic or septic encephalopathy, such as hepatic or uremic encephalopathy. Neuroimaging reveals the presence of any other disorder. It is worth mentioning that throughout the inclusion process, patients with clinically confirmed COVID-19 but a negative PCR were also included, suggesting that the PCR performed was less sensitive [13].

RESULTS

Our research involved 111 individuals, 45.9 % of whom were female and 54.1 % male. The majority of participants (50 %) in our research were between 40 and 69 years old. Hypertension was the most often reported comorbidity in our study participants (46.8). On Chest X-Rays, 91 % had bilateral lung infiltrates. COVID-19 PCR was positive in only 28.8 % of cases 19.8 % of patients had lung infiltrates on HRCT. All individuals included had a neurological impairment (Weakness in 5.4 %, Paraparesis in 24.3 %, Hemiplegia in 8.1 %, and Paraplegia in 19.8 %). Signs of

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meningeal irritation (Somi) were negative in 64.9 % of patients, hyporeflexia was present in 31.5 % of patients, and plantars were upgoing in 57.7 % of patients. GCS was worsening in 61.3 % of patients, and only 13.5 % of patients presented with an altered state of consciousness. 26.1 % exhibited elevated proteins, majority samples had normal glucose levels except for 6.3 % whom had reduced glucose, and 29.7 % had lymphocytosis on CSF testing. CT and MRI brain scans were available for only 83.8 % and 14.4 % of patients respectively. There were no abnormal imaging findings on CT Brain or MRI in all patients. Tables 1 and 2 below summaries the study population's characteristics.

Table 1: Baseline Clinical Features of study participants

Variable	Male	Female
N	60	51
Age, Years n (%)		
15-40	13(21.7)	4(7.8)
40-60	25(41.7)	31(60.8)
>60	22(36.7)	16(31.4)
Comorbidities		
Diabetes Mellitus	6(10)	29(56.9)
Hypertension	31(51.7)	21(41.2)
Asthma	12(20)	0(0)
History of Steroid Abuse	10(16.6)	4 (7.8)
Clinical Features		
Headache	41(68.3)	44(86.3)
Fever	60(100)	37(72.5)
Cough	45(75)	24(47.1)
Drowsiness	28(46.7)	36(70.6)
Irritability	15(25)	22(43.1)
Weakness	4(6.7)	2(3.9)
Paraparesis	15(25)	12(23.5)
Paraplegia	18(30)	4(7.8)
Hemiplegia	4(6.7)	5(9.8)
Agnosia	55(91.6)	27(52.9)
PCR		
N/A	16(26.7)	16(31.4)
Positive	15(25)	17(33.3)
Negative	29(48.3)	18(35.3)
X-Ray		
N/A	3(5)	2(3.9)
BL Infiltrates	52(86.7)	49(96.1)
Normal	5(8.3)	0(0)
HRCT Lungs		
N/A	41(68.3)	43(84.3)
Show Infiltrates	14(23.3)	8(15.7)
Normal	5(8.3)	0(0)
HRCT Lungs		
CBC(Lymphopenia)	47(78.3)	46(90.2)
Inflammatory Markers	55(91.7)	51(100)

N/A: not available; B/L: bilateral; CBC: completer blood count

Table 2: Neurological Evaluation of study participants

Variable	Male	Female
Neurological deficit		
Somi-ve,	37(61.7)	35(68.6)
Planters upping,	23(38.3)	41(81.4)
Deteriorating GCS	30(50)	38(74.5)
Decreased power,	36(60)	23(45.1)
Hyporeflexia	27(45)	8(15.7)
ASOC	7(11.7)	8(15.7)
CSF Findings		
Lymphocytosis		
Increased	14(23.3)	19(37.3)
Decreased	0(0)	0(0)
Normal	0(0)	1(2)
N/A	46(76.7)	31(60.8)
Proteins		
Increased	14(23.3)	15(29.4)
Decreased	1(1.7)	0(0)
Normal	9(15)	14(27.5)
N/A	36(60)	22(43.1)
Glucose		
Increased	0(0)	0(0)
Decreased	3(5)	4(7.8)
Normal	17(28.3)	30(58.8)
N/A	40(66.7)	17(33.3)
MRI Brain		
N/A	52(86.7)	43(84.3)
Normal	8(13.3)	8(15.7)
CT Scan Brain		
N/A	11(18.3)	7(13.7)
Normal	49(81.7)	44(86.3)
Neurological diagnosis		
GBS	27(45)	5(9.8)
Encephalopathy	6(10)	15(29.4)
Encephalitis	26(43.3)	25(49)
Ischemic Stroke	1(1.7)	6(11.8)
Dysgeusia	55(91.6)	27(52.9)

GCS: Glasgow coma scale; N/A: not available; ASOC: Altered state of consciousness

The patients diagnosed with Encephalitis and Encephalopathy mainly were from the 40-60 years of age group (56.9% and 71.4%, respectively. The diagnosis of ischemic stroke was made in only 6.3% of patients. The majority of the patients were from the 15-40- and 40-60-years age group (42.9% and 42.95%, respectively). The Prevalence of Neurological diagnosis in various age groups is summarized below in Table 3.

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Table 3: Prevalence of Neurological Manifestations in various Age groups

Neurological Manifestations	Age Groups	N (%)
Encephalitis	15-40	5(9.8)
	40-60	29(56.9)
	>60	17(33.3)
Encephalopathy	15-40	1(4.8)
	40-60	15(71.4)
	>60	5(23.8)
GBS	15-40	8(25)
	40-60	9(28.1)
	>60	15(46.9)
Ischemic Stroke	15-40	3(42.9)
	40-60	3(42.9)
	>60	1(14.3)
Dysgeusia	15-40	28(34.1)
	40-60	41(50)
	>60	13(15.8)

The prevalence of neurological manifestations with comorbidities (Diabetes Mellitus, Hypertension, Asthma) and Steroid Abuse is given below in Table 4. The neurological manifestation was most prevalent in hypertensive patients (46%), followed by Diabetes Mellitus (31%). The neurological diagnosis was least prevalent in asthma patients(10.8%).

Table 4: Prevalence of Neurological Manifestations in patients with various comorbidities

Comorbidities	Encephalitis	Encephalo-pathy	GBS	Ischemic Stroke	Agnosia
Diabetes	16 (31.4)	15 (71.4)	4 (12.5)	0(0)	26(23.4)
Hypertension	25(49)	8 (38.1)	18(56.3)	1(14.3)	56(68.2)
Asthma	5(9.8)	1(4.8)	6(18.8)	0(0)	0(0)
Steroid Abuse	5(9.8)	3(14.3)	6(18.8)	0(0)	0(0)

As in Figure 1, the most frequently reported presenting complaints were fever (87.4 %), headache (76.6 %), dysgeusia(75.5 %), cough(62.2 %), drowsiness(57.5 %), and irritability(33.3 %).

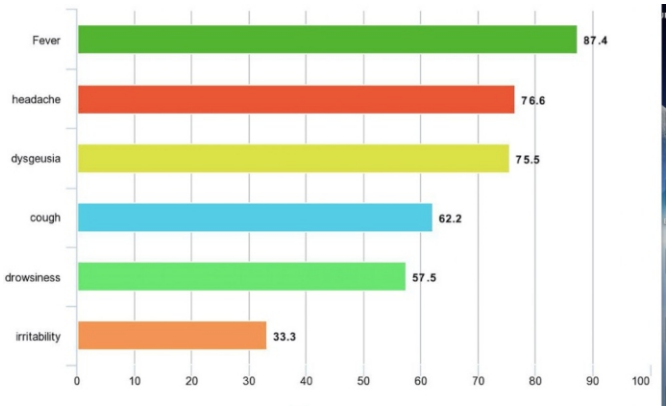

Figure 1: Prevalence of clinical features in study population

As in Figure 2, 75.5 % of patients were diagnosed with Dysgeusia, 45.9 % with Encephalitis, 28.8 % with GBS, 18.9 % with Encephalopathy, and 6.3 % with Ischemic Stroke.

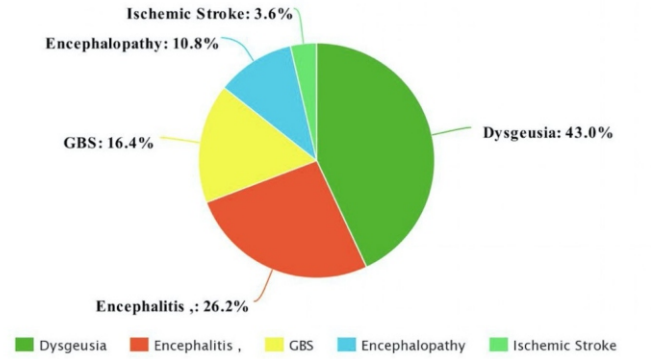

Figure 2: Prevalence of Neurological Associations amongst study population

DISCUSSION

SARS-CoV2 has neurological repercussions comparable to previous coronavirus outbreaks, Notably in 2003, SARS and the 2012 Middle East acute respiratory syndrome (MERS). Encephalopathy, Encephalitis, GBS, ischemic stroke, and hemorrhagic stroke were all recorded in those papers due to hypercoagulability, sepsis, and vasculitis [14]. A study from a Tertiary Care Hospital on the Frontline sampled 50 patients. Encephalopathy, cerebrovascular illness, cognitive impairment, seizures, hypoxic brain damage, Dysgeusia, and aberrant extraocular movement were neurological signs [15]. In a research conducted in Wuhan, 78 of 214 COVID-19 participants had neurological symptoms for four weeks. These patients were more seriously ill, older, and had a higher prevalence of comorbidities, particularly hypertension, and for some, the neurological symptom was the first indicator of COVID-19 infection. Apart from six patients (2.8%) who had a stroke, neurological symptoms might be caused by a viral infection (loss of smell and taste) or by the consequences of severe systemic illness in an intensive care unit, such as infection and hypoxia [16]. According to the Strasbourg group, 40/58 patients (69%) had agitation, whereas 26/40 (65%) had disorientation, and 39/59 had corticospinal tract symptoms (67%). MRI revealed meningeal enhancement, ischemic stroke, and perfusion abnormalities in 22 patients. Myoclonus and demyelination have been reported [17]. Coronavirus infections in the brain have previously been reported in patients with the severe acute respiratory syndrome (SARS), caused by the SARS-CoV virus, and Middle East Respiratory Syndrome (MERS), caused by the MERS-CoV virus. The severity and long-term consequences of these disorders vary significantly amongst people. SARS-CoV-2 infection of the cerebrospinal fluid (CSF) has been assessed only in a small number of cases, and positive findings are unusual. As per Lewis and colleagues' systematic review, 6% of patients

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who underwent cerebrospinal fluid (CSF) testing was positive for SARS-CoV-2. The CSF cell count was increased in 43% of fatal cases, 25.7 % of severe cases, and 29.4 % of non- severe cases, with lymphocytosis being the most prevalent. The great majority of those individuals suffer from neurological issues involving the central nervous system (CNS) [18]. According to another study by Tandon and colleagues that primarily focused on CSF protein levels, the most frequently encountered CSF finding was increased CSF proteins. They observed that patients who died with COVID-19 had significantly higher protein levels in their CSF (100%) and an average of 61.28 mg/dl than those who survived (65%) and had an average of 56.73 mg/dl. Similar increases in CSF protein levels were observed in 74.5 % of patients with mild COVID- 19 infection and 68.6 % of patients with severe COVID-19 illness [19]. The US Food and Drug Administration (USFDA) employs a methodical approach in combating COVID-19 and has approved only remdesivir medications for use in COVID-19 hospitalized patients. The Food and Drug Administration (FDA) of the United States granted an emergency use authorization (EUA) for antibodies neutralization (bamlanivimab + etesevimab and casirivimab/imdevimab), antiviral combination treatment (remdesivir + baricitinib), and COVID-19 convalescent plasma [20]. It is reasonable to expect that 80 % of patients who recovered from COVID-19 with minor symptoms will have no long-term consequences and will eventually make a full recovery. Patients with moderately severe symptoms who needed hospitalization but not mechanical ventilation had no long-term repercussions. Patients who need mechanical ventilation due to severe symptomatology are more likely to suffer long-term complications and delayed recovery as they age. Changes in SARS-CoV-2 pathophysiology, inflammatory damage, and immunologic abnormalities in COVID-19 might lead to post-COVID-19 sequelae. Numerous multiorgan systems may be compromised in severe COVID-19 survivors [21]. One of the purposes of this research was to investigate the association between age and neurological symptoms. However, the outcomes differed depending on the category. Those aged 40-60 had the most significant rates of Encephalitis and Encephalopathy (56.9 % and 71.4, respectively). In the case of Ischemic Stroke, both the age categories of 15-40 and 40-60 tied at 42.9 %. The research also looked at comorbidity. Hypertensive people (46 %) had the most significant neurological manifestations, followed by those with Diabetes Mellitus (31%). Asthmatic individuals had the lowest prevalence of neurological disorders (10.8%). While some patients may complain of headaches, anosmia, and Dysgeusia, studies have found that a broader range of more significant neurological issues, especially in hospitalized patients, may occur, including stroke, Encephalopathy, Encephalitis, and polyneuritis [21-23]. These results correspond to the study's findings and the incidence of neurological complaints reported by patients. As the findings show, the research has clinical implications by emphasizing the role of comorbidity for better prognosis. A study revealed that COVID-19-related deaths, cardiovascular diseases such as hypertension, and diabetes are highly significant ($p < 0.0001$). Similarly, deaths resulting from kidney diseases and neurological issues are also significantly higher than the total number of hospitalized patients for that particular health concern [24]. As a result, if comorbidities are not considered while developing a treatment plan, the illness prognosis may deteriorate dramatically. Contrary to common opinion, ACEI such as Valsartan has been shown in multiple studies to benefit and protect patients with hypertension thus, treatment should not be altered [25].

CONCLUSIONS

Evidence has been provided to indicate the likelihood of COVID-19-related CNS pathologies. This research relied heavily on many critical characteristics, including gender, comorbidity, and age. Between the ages of 40 and 60 years, neurological symptoms such as Encephalitis and Encephalopathy were most prevalent. In terms of gender and comorbidity, women had a significantly greater prevalence of diabetes (56.9 %), but males had a significantly higher prevalence of hypertension (51.7 %). Men were more likely to have fever, cough, paraparesis, and paraplegia, while women were more likely to experience headaches, sleepiness, irritability, and Hemiplegia. The study sheds vital light on the link between gender, comorbidity, age, and neurological symptoms for future research.

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Authors Contribution

Conceptualization: SHTR
Methodology: UAA, SZ, NI, NA
Formal Analysis: UAA, SZ, NI, NA
Writing-review and editing: SHTR, UAA, SZ, NI, NA

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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