Neurological Symptoms Associated with COVID-19

Syed Hassan Tanvir Ramzi*, Ubaidullah Ansari¹, Sana Manzoor², Namal Ilyas³ and Nabeel Ahmed⁴

¹Department of Pathology, Bakhtawar Amin Medical and Dental College, Multan, Pakistan
²Department of Neurology, Multan Medical and Dental College, Multan, Pakistan
³Department of Medicine, Multan Medical and Dental College, Multan, Pakistan
⁴Social Security Hospital, Faisalabad, Pakistan
⁵Department of Medicine, Recep Tayyip Erdogan Hospital, Muzaffargarh, Pakistan

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
Neurological Symptoms Associated with COVID-19

METHODS
The prevalence of neurological COVID-19-related symptoms was determined using a quantitative research design in patients hospitalized at Ibn-e 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. 18.8% 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...
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 summarises the study population’s characteristics.

### Table 1: Baseline Clinical Features of study participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>60</td>
<td>51</td>
</tr>
<tr>
<td>Age, Years n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-40</td>
<td>13(21.7)</td>
<td>4(7.8)</td>
</tr>
<tr>
<td>40-60</td>
<td>25(41.7)</td>
<td>31(60.8)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>22(36.7)</td>
<td>16(31.4)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>6(10)</td>
<td>23(56.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3(51.7)</td>
<td>2(4.2)</td>
</tr>
<tr>
<td>Asthma</td>
<td>12(20)</td>
<td>0(0)</td>
</tr>
<tr>
<td>History of Steroid Abuse</td>
<td>10(16.6)</td>
<td>4(7.8)</td>
</tr>
<tr>
<td>Clinical Features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>4(68.3)</td>
<td>4(86.3)</td>
</tr>
<tr>
<td>Fever</td>
<td>80(100)</td>
<td>3(72.5)</td>
</tr>
<tr>
<td>Cough</td>
<td>45(75)</td>
<td>2(4.2)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>28(46.7)</td>
<td>33(70.6)</td>
</tr>
<tr>
<td>Irritability</td>
<td>15(25)</td>
<td>2(3.9)</td>
</tr>
<tr>
<td>Weakness</td>
<td>4(6.7)</td>
<td>2(3.9)</td>
</tr>
<tr>
<td>Paraparesis</td>
<td>15(25)</td>
<td>12(23.5)</td>
</tr>
<tr>
<td>Paraplegia</td>
<td>18(30)</td>
<td>4(7.8)</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>4(6.7)</td>
<td>5(9.8)</td>
</tr>
<tr>
<td>Agnosia</td>
<td>55(91.6)</td>
<td>2(3.9)</td>
</tr>
<tr>
<td>PCR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>16(26.7)</td>
<td>16(31.4)</td>
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<tr>
<td>Positive</td>
<td>15(25)</td>
<td>17(33.3)</td>
</tr>
<tr>
<td>Negative</td>
<td>23(48.3)</td>
<td>18(35.3)</td>
</tr>
<tr>
<td>X-Ray</td>
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<tr>
<td>BL Infiltrates</td>
<td>52(86.7)</td>
<td>49(96.1)</td>
</tr>
<tr>
<td>Normal</td>
<td>5(8.3)</td>
<td>0(0)</td>
</tr>
<tr>
<td>HRCT Lungs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>4(68.3)</td>
<td>4(86.3)</td>
</tr>
<tr>
<td>Show Infiltrates</td>
<td>14(23.3)</td>
<td>8(15.7)</td>
</tr>
<tr>
<td>Normal</td>
<td>5(8.3)</td>
<td>0(0)</td>
</tr>
<tr>
<td>HRCT Lungs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC(Lymphopenia)</td>
<td>4(78.3)</td>
<td>4(80.2)</td>
</tr>
<tr>
<td>Inflammatory Markers</td>
<td>55(91.7)</td>
<td>5(100)</td>
</tr>
</tbody>
</table>

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

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### Table 2: Neurological Evaluation of study participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological deficit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somi-ve</td>
<td>37(61.7)</td>
<td>39(68.6)</td>
</tr>
<tr>
<td>Planters upping</td>
<td>23(38.3)</td>
<td>4(81.4)</td>
</tr>
<tr>
<td>Deterioring GCS</td>
<td>30(50)</td>
<td>38(74.5)</td>
</tr>
<tr>
<td>Decreased power</td>
<td>36(60)</td>
<td>23(46.1)</td>
</tr>
<tr>
<td>Hyporeflexia</td>
<td>27(45)</td>
<td>8(15.7)</td>
</tr>
<tr>
<td>ASOC</td>
<td>7(11.7)</td>
<td>8(15.7)</td>
</tr>
<tr>
<td>CSF Findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>14(23.3)</td>
<td>15(29.4)</td>
</tr>
<tr>
<td>Decreased</td>
<td>1(1.7)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Normal</td>
<td>9(15)</td>
<td>14(27.5)</td>
</tr>
<tr>
<td>N/A</td>
<td>36(60)</td>
<td>22(43.1)</td>
</tr>
<tr>
<td>Proteins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>0(0)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Decreased</td>
<td>3(5)</td>
<td>4(7.8)</td>
</tr>
<tr>
<td>Normal</td>
<td>17(28.3)</td>
<td>30(58.8)</td>
</tr>
<tr>
<td>N/A</td>
<td>4(6.7)</td>
<td>7(13.3)</td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>0(0)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Decreased</td>
<td>3(5)</td>
<td>4(7.8)</td>
</tr>
<tr>
<td>Normal</td>
<td>17(28.3)</td>
<td>30(58.8)</td>
</tr>
<tr>
<td>N/A</td>
<td>4(6.7)</td>
<td>7(13.3)</td>
</tr>
<tr>
<td>MRI Brain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>52(86.7)</td>
<td>4(8.3)</td>
</tr>
<tr>
<td>Normal</td>
<td>8(13.3)</td>
<td>8(15.7)</td>
</tr>
<tr>
<td>CT Scan Brain</td>
<td>1(1.7)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Normal</td>
<td>49(81.7)</td>
<td>4(8.3)</td>
</tr>
<tr>
<td>Neurological diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GBS</td>
<td>27(45)</td>
<td>5(9.8)</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>6(10)</td>
<td>15(29.4)</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>26(43.3)</td>
<td>2(3.9)</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>1(1.7)</td>
<td>6(11.8)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>55(91.6)</td>
<td>2(3.9)</td>
</tr>
</tbody>
</table>

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.
Table 3: Prevalence of Neurological Manifestations in various Age groups

<table>
<thead>
<tr>
<th>Neurological Manifestations</th>
<th>Age Groups</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalitis</td>
<td>15-40</td>
<td>5(9.8)</td>
</tr>
<tr>
<td></td>
<td>40-60</td>
<td>29(56.9)</td>
</tr>
<tr>
<td></td>
<td>&gt;60</td>
<td>17(33.3)</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>15-40</td>
<td>1(4.8)</td>
</tr>
<tr>
<td></td>
<td>40-60</td>
<td>15(71.4)</td>
</tr>
<tr>
<td></td>
<td>&gt;60</td>
<td>5(23.8)</td>
</tr>
<tr>
<td>GBS</td>
<td>15-40</td>
<td>8(25)</td>
</tr>
<tr>
<td></td>
<td>40-60</td>
<td>9(28.1)</td>
</tr>
<tr>
<td></td>
<td>&gt;60</td>
<td>15(46.9)</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>15-40</td>
<td>3(42.9)</td>
</tr>
<tr>
<td></td>
<td>40-60</td>
<td>3(42.9)</td>
</tr>
<tr>
<td></td>
<td>&gt;60</td>
<td>1(14.3)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>15-40</td>
<td>28(34.1)</td>
</tr>
<tr>
<td></td>
<td>40-60</td>
<td>4(50)</td>
</tr>
<tr>
<td></td>
<td>&gt;60</td>
<td>13(15.8)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Encephalitis</th>
<th>Encephalopathy</th>
<th>GBS</th>
<th>Ischemic Stroke</th>
<th>Agnosia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>16 (31.4)</td>
<td>15 (71.4)</td>
<td>4 (12.5)</td>
<td>0 (0)</td>
<td>26 (23.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25 (49)</td>
<td>8 (38.1)</td>
<td>18 (56.3)</td>
<td>1 (4.3)</td>
<td>56 (68.2)</td>
</tr>
<tr>
<td>Asthma</td>
<td>5 (9.8)</td>
<td>1 (4.8)</td>
<td>6 (18.8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Steroid Abuse</td>
<td>5 (9.8)</td>
<td>3 (41.3)</td>
<td>6 (18.8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

As in Figure 1, the most frequently reported presenting complaints were fever (87.4%), headache (78.6%), dysgeusia (75.5%), cough (62.2%), drowsiness (57.5%), and irritability (33.3%).

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 1: Prevalence of clinical features in study population

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 33/59 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...
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].

**C O N C L U S I O N S**

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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REFERENCES


