Prevalence of Neurological Manifestations and Complications of COVID-19 in Menoufia Governorate

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Recommended Citation
DOI: https://doi.org/10.59204/2314-6788.1007

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**ORIGINAL STUDY**

**Prevalence of Neurological Manifestations and Complications of Coronavirus Disease 2019 in Menoufia Governorate**

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**Abstract**

**Objectives:** To define any neurological manifestations and problems of definite coronavirus disease 2019 (COVID-19) infection patients, and its relation with onset and evolution of the infection.

**Background:** Spread of COVID-19 infections has been rapid in both low-income and high-income countries. Outbreak of respiratory disease took place in China in December 2019, and it later spread to other countries. Acute neurological insults are more likely in studied cases who are badly infected.

**Patients and methods:** This study is cross-sectional research. Data were obtained from the archived files of the selected COVID-19 patients, in addition to patients who were admitted at isolated ICU and inpatient rooms of Menoufia University Hospitals, Shebin El-Kom Teaching Hospital, El-Bajur General Hospital, Menoufia General Hospital, and Sirs-Ellian General Hospital. The duration of the recruiting period was from February to August 2021.

**Results:** In the multivariate logistic regression, the significant predictors of the neurological manifestations are female sex, obesity, diabetes mellitus, and any comorbidity.

**Conclusion:** A wide range of neurological manifestations, such as central nervous system and peripheral nervous system manifestations, can happen in COVID-19 studied cases, regardless of disease severity, with higher incidence in severe category of studied cases. In evaluation of studied cases with COVID-19 and neurological symptoms, detailed history and neurological examination, as well as proper assessment by expert neurologists, are required.

**Keywords:** Complication, Coronavirus disease 2019, Manifestations, Multicenter, Neurological

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an unpredicted coronavirus infection, is wreaking havoc on global population’s health and, as a result, global economy, even though fever, cough, and fatigue are the most common symptoms of coronavirus disease 2019 (COVID-19). Aside from these, other symptoms of that illness include headache, dyspnea, and diarrhea. In most serious forms, pneumonia, acute respiratory distress syndrome, and multiorgan failure may occur [1].

The new SARS-CoV-2 virus reaches cells through the viral structure spike (S) protein that binds to angiotensin-converting enzyme-2 (ACE-2) receptor and subsequently downregulates ACE-2. This causes increase in production of vasoconstrictor AngII and decrease in production of vasodilator angiotensin. AngII also functions like proinflammatory cytokine via angiotensin receptor 1 (AT1R).

Coronaviruses are known to be neurotropic. Participation of the nervous system can be attributed to either direct action of these viruses on nervous tissue or indirect action via activation of immune-mediated mechanisms. While the first action is visible during acute phase of illness, the second may not be visible for days, weeks, and even months after acute phase [2].

The presence of ischemic strokes in COVID-19 appears to be caused by three major mechanisms.
These include hypercoagulability, vasculitis, and cardiomyopathy with global blood supply reduction. Furthermore, it is possible that cytokine storm associated with this disorder is the reason of hemorrhagic strokes, Corad (2020). Furthermore, many neurological diseases (such as multiple sclerosis, Guillain–Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy, and myasthenia) have immunological basis and may be exacerbated and triggered by COVID [3].

Based on neurological symptoms, brain computed tomography (CT)/MRI and electroencephalography (EEG) investigations were performed. High-resolution chest CT scans and laboratory results (total leukocyte count with lymphocyte count, D-dimer, and C-reactive protein and serum ferritin) of all patients were evaluated.

The aim of the study was to define any neurological manifestations and problems of definite COVID-19 infection patients, & and relation with onset and evolution of the infection.

2. Patients and methods

This study was cross-sectional research carried out at Menoufia Governorate that included 200 studied cases with COVID-19. All participants over 18 years admitted for COVID-19-positive COVID-19 infection (positive PCR test) are included and patients below 18 years and not fulfilling criteria of diagnosis of COVID-19 infection are excluded.

The cases according to neurological event will be subjected to full history taking, complete clinical examination, CT or MRI brain, nerve conduction study, EEG, and EMG).

Demographic data including age, sex, and BMI. Comorbidities include – hypertension (on antihypertensive medications or established history of blood pressure>160/90 mmHg on at least two occasions) – diabetes mellitus (DM) (past history of DM at two independent readings before the COVID-19 symptoms or elevated HBA1c on admission or on antidiabetic medications). Dyslipidemia (previous history of hyperlipidemia, on cholesterol 76-lowering drugs, or persistent elevation of plasma level of cholesterol, triglycerides, low-density lipoprotein, and high-density lipoprotein). Smoking classified into two categories: nonsmokers/former smoker (never smoked regularly or quit regular smoking >5 years), smokers (regular daily cigarette smoking >5 years).

All cases underwent full neurological history and neurological examination. The neurologic examination is divided into several steps. These steps include the following:

(1) Higher functions.
(2) Cranial nerves.
(3) Sensory system.
(4) Motor system.
(5) Reflexes.
(6) Cerebellum.
(7) Meninges.
(8) Folstein Mini-Mental State examination.

2.1. Neurological imaging

CT brain, MRI brain. nerve conduction study (NCS) and EMG: if the patient presented with weakness suspected of acute polyneuropathy. EEG if seizure is predicted. Cerebrospinal fluid (CSF) study if needed.

Data were obtained from the archived files of the selected COVID-19 patients, in addition to the patient who was admitted at isolated ICU and inpatient rooms.

The Ethical Consideration General rules of ethics and confidentiality of patients’ data fulfilled.

2.2. Statistical analysis

Data collected were analyzed with Statistical Package for Social Sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Mean and SD of quantitative data were used. Frequency and percentage of qualitative data were used.

3. Results

More than half of this study group were females (65.5%), their mean age 42.96, nearly half of the study group age (30 to <50 years) (44%) (Table 1).

There were 27% of the study group who had obesity, 22% had DM, 19.5% had hypertension, and 11.5% had smoking habit (Table 2).

| Table 1. Demographic data distribution among study group (N = 200). |
|---------------------|-----------------|---------------------|
| Demographic data    | n (%)           |                      |
| Sex                 |                 |                      |
| Female              | 131 (65.5)      |                      |
| Male                | 69 (34.5)       |                      |
| Age group           |                 |                      |
| <30 years           | 43 (21.5)       |                      |
| 30 to <50 years     | 88 (44.0)       |                      |
| 50 to <70 years     | 58 (29.0)       |                      |
| ≥70 years           | 11 (5.5)        |                      |
| Range               | 18–86           |                      |
| Mean ± SD           | 42.96 ± 15.63   |                      |
dizziness, only 6% of them had vision impairment, 19% of them had migraine headache and 13% had tension headache, more than half of them had myalgia, and 77% of them had manifestations (Table 3).

Most of the study group had no nerve affection 94.5%, 90% had not stroke, only 6.5% had fits, 14.5% had disturbed level of consciousness, 1% had GBS, 2% had encephalitis, and 26% had total complications (Table 4).

There were 77% of the study group who had total manifestations and complications. The most manifestations the study group had been: 65.5% of the study group had smell abnormality (41% had presenting features of smell abnormality and 24.5% had early smell abnormality), 61.5% had loss of taste (39.5% had presenting features of loss of taste, 22% had early 1–7 days). About 56% had myalgia (28.5% had presenting features, 19.5% had early 1–7 days, and 8% had late 8–15 days). At least 40.5% had headache (21.5% had presenting features, 14% had early 1–7 days, and 5% had late 8–15 days) (Table 5).

4. Discussion

Various approaches can cause neurological manifestations in COVID-19 studied cases, such as viral neurotropism, cerebral hypoxia caused by respiratory failure, and immune-mediated mechanisms mediated by cytokine storm acting on ACE-2 receptors with subsequent endothelial dysfunction [4].

The primary aim of the research was to show any neurological manifestations and complications seen by definite COVID-19 infection patients, as well as their relationship to the beginning and progression of the illness.

Data were obtained from the archived files of the selected COVID-19 patients, in addition to patients who were admitted at isolated ICU and inpatient...
rooms at Menoufia University Hospitals, Shebin El-Kom Teaching Hospital, El-Bajur General Hospital, Menoufia General Hospital, and Sirs-Ellian General Hospital. The duration of the recruiting period was from February 2021 to August 2021.

Neurological symptoms in hospitalized COVID-19 studied cases were assessed in research, 154 (77%) of 200 studied cases were evaluated with neurological involvement.

In the study of Liotta et al. [5], in COVID-19 studied cases, neurologic manifestations were present at COVID-19 onset (42.2%), at hospitalization in (62.7%), and at any time while disease course in (82.3%) [5].

There were many neurological symptoms such as central nervous system (CNS) and peripheral nervous system (PNS).

The most common typical PNS was smell abnormalities (65%). Our outcomes found that the presence of neurological manifestations and complications was significantly associated with female sex (65.5%), obesity (27%), DM (22%), hypertension (19.5%), and presence of comorbidities (15%).

Patients with neurological manifestations were older than those without neurological affection. The present research showed that headache is the most common CNS symptom that presents in 41%, taste impairment in 61.5%, smell impairment in 65%, seizures occurred in 6.5%, and cerebrovascular disease (CVD) in 10%. GBS present in 1%, CNS infection present in 2%.

In our study, headache was present in 81 (41%) patients, 43 patients with presenting manifestation, and 28 patients early and 10 patients late. The intensity of headache was described as moderate to serious. Headaches were described as having tension-like quality and mostly located in the forehead region. They were present on average 2 days from onset of COVID-19 symptoms.

In research of Essmat [6], the most common central CNS manifestation was headache, whereas the most common PNS manifestations were smell and taste impairment (PNS).

Although in research of Makda et al. [7], dizziness was the most common CNS manifestation. In one meta-analysis, the most common CNS symptom was headache, whereas the most common PNS symptom was smell disturbance, which is consistent with our findings [8].

In our study, CVD was found in 20 (10%) studied cases. Seven (3.5%) of these studied cases were evaluated as hemorrhagic CVD, 12 (6.0%) patients were detected as ischemic stroke, and one (0.5%) as venous infarctions with 11 patients with presenting manifestation and seven patients early and two patients late. CVD symptoms began ~10 days after onset of COVID-19 symptoms.

SARS-CoV-2 has been linked to CNS symptoms such as cerebrovascular strokes (ischemic, hemorrhagic, and cavernous sinus thrombosis (CVST)). COVID-19 has been linked to a wide range of CVDs [9].

According to current research, venous and arterial thromboembolic problems occur in 5–15% of studied cases with severe COVID-19 during current pandemic [10].

| Table 5. Manifestations and complications in temporal relation to coronavirus disease 2019 infection. |
|---|---|---|---|---|
| Manifestations (N = 154 ‘77%) | Early (1–7 days) | Late (8–15 days) | Total |
| Smell abnormality | 82 (41.0) | 49 (24.5) | 0 | 131 (65.5) |
| Loss of taste | 79 (39.5) | 44 (22.0) | 0 | 123 (61.5) |
| Dizziness | 17 (8.5) | 21 (10.5) | 6 (3.0) | 44 (22.0) |
| Vision impairment | 3 (1.5) | 5 (2.5) | 4 (2.0) | 12 (6.0) |
| Headache | 43 (21.5) | 28 (14.0) | 10 (5.0) | 81 (40.5) |
| Myalgia | 57 (28.5) | 39 (19.5) | 16 (8.0) | 112 (56.0) |
| Complications (N = 52 ‘26%) | | | | |
| Nerve affection | 4 (2.0) | 2 (1.0) | 5 (2.5) | 11 (5.5) |
| Stroke (N = 20) | | | | |
| Ischemic | 7 (3.5) | 4 (2.0) | 1 (0.5) | 12 (6.0) |
| ICH | 4 (2.0) | 3 (1.5) | 0 | 7 (3.5) |
| CST | 0 | 0 | 1 (0.5) | 1 (0.5) |
| Fits | 7 (3.5) | 3 (1.5) | 3 (1.5) | 13 (6.5) |
| DCL | 5 (2.5) | 18 (9.0) | 6 (3.0) | 29 (14.5) |
| GBS | 1 (0.5) | 0 | 1 (0.5) | 2 (1.0) |
| Encephalitis | 2 (1.0) | 1 (0.5) | 1 (0.5) | 4 (2.0) |
| All (N = 154 ‘77%) | | | | |
|
CST, cavernous sinus thrombosis; DCL, disturbed level of consciousness; GBS, Guillain–Barré syndrome; ICH, intracerebral hemorrhage.
All three stroke subtypes were identified in our research, with higher preponderance of ischemic types, which is consistent with previous research outcomes [4].

Acute hemorrhagic necrotizing encephalopathy with scattered hemorrhages, on the other hand, has previously been reported [11].

In our study, 29 patients developed disturbed level of consciousness with five patients presenting manifestation and 18 patients early and six patients late, for which many underlying mechanisms were postulated, autopsies of encephalopathic victims were found on hypoxia and cerebral edema. Furthermore, toxic and metabolic causes may be involved [12].

In the study of Leonhard et al. [13], the most prevalent neurological signs and syndromes were acute encephalopathy [1845 (49%) of 3740 studied cases].

Observational series of 58 consecutive studied cases admitted for COVID-19-associated acute respiratory distress (ARDS) revealed neurological features. Delirium was present in the majority of studied cases (69%). In 39 studied cases, upper motor neuron indications were seen (67%). Brain's MRI revealed leptomeningeal enhancement and cortical signal changes. CSF was analyzed in seven studied cases, and one studied case had elevated protein levels [14].

Scullen et al. [15] evaluated retrospective data of 27 COVID-19 critically ill studied cases. Neuroimaging was performed on all 27 studied cases who had neurological complications. Except for one, all of the studied cases had altered states of consciousness. COVID-19-associated encephalopathy was diagnosed in 20 (74%) of studied cases based on neuroimaging. Five (19%) studied cases were diagnosed with COVID-19-associated vasculopathy, while the remaining two (7%) studied cases were diagnosed with COVID-19-associated acute necrotizing encephalopathy. T2/FLAIR hyperintensity in basal ganglia, corpus callosum, and diffuse deep white matter were the most common MRI results.

In our study, anosmia was present in 131 (65%) patients with 82 patients presenting, 49 patients early and no late presentation, and ageusia was 123 (61.5%) patients with presenting 79 patients, 44 patients early and not late.

The prevalence of anosmia and ageusia varies greatly between experiments, ranging from 5% in Chinese research, Mao et al. [3], to about 88% in an Italian study by Lechien et al. [16].

In our study, myalgia was present in 112 (56%) patients with 57 patients presenting, 39 patients early and 16 patients late.

Infection-associated myalgia is caused by interleukin-1, which detaches amino acids from muscle, resulting in muscle aches by Cooney et al. [17].

Myalgia and fatigue are one of the most common symptoms in COVID-19, reported in 10–74% cases [14]. Skeletal muscle injury with serum creatinine kinase levels above 200 U/l was observed in 11% of COVID-19 hospitalized cases, particularly in studied cases with concurrent liver and renal dysfunction.

As regards nerve affection with total affection of 11 patients with eight patients with facial, two patients trigeminal, and one with sciatica, four patients with presenting, two patients with early, and five late.

In our study, encephalitis was present in four (2%) patients with two patients presenting, one patient early, and one patient late. Viral encephalitis diagnosed with MRI brain (bilateral temporal hyper intense lesions) and CSF sample and clinical picture.

The symptoms of viral encephalitis start to appear on average 7 days from onset of COVID-19 symptoms.

Mortality rate of studied cases with encephalitis-like COVID-19 complication is 13.4%, nearly quadruple 3.4% in general population of COVID-19 studied cases [18]. It may thus be beneficial to be wary of encephalitis-like COVID-19 side effect because, while uncommon, it can have serious consequences [19].

Numerous risk factors for encephalitis-like COVID-19 side effect were identified. Demographic risk factors like advanced age and underlying comorbidities may increase risk of COVID-19 infection problems, such as development of encephalitis [20].

Furthermore, studied cases who are severely ill with COVID-19 are at much greater risk of developing encephalitis [14].

Moriguchi et al. [21] proposed hypothesis that suggested direct brain infiltration. Seizures occurred in 13 (6.5%) patients, seven patients presenting, three patients early and three patients late, seven (2.6%) of these patients were generalized tonic–clonic seizures, three (1%) patients with focal seizures, and three (1%) patients with focal-to-generalized seizures. However, in the study of Essmat [6], the frequency of seizures was 18% of patients with neurological affection. Seizures usually start on average 7 days from onset of COVID-19 symptoms.

In our study, GBS was present in two (1%) patients. One patient was diagnosed as GBS on average 2 weeks after diagnosis with COVID-19 and rehospitalized, one patient presented with sensory motor manifestations and axonal nerve injury in NCS, and one patient presented with motor and cranial nerves affection and demyelination in NCS.
The study discovered that GBS is the most common cause of acute flaccid paralysis. The most common type is immune-mediated acute-onset demyelinating polyradiculoneuropathy (acute inflammatory demyelinating polyneuropathy), which typically manifests as ascending weakness, loss of deep tendon reflexes, and sensory deficits. GBS is diagnosed based on outcome of clinical, electrophysiological, and CSF tests (classically alburninocytological dissociation) [13].

4.1. Conclusion

A wide range of neurological manifestations, such as CNS and PNS manifestations, can happen in COVID-19 studied cases, regardless of disease severity, with greater incidence in severe category of studied cases. In evaluation of studied cases with neurological symptoms, detailed history and neurological examination, as well as proper assessment by expert neurologists, are required.

Consent statement

Approval was obtained from the ethical committee of the Faculty of Medicine, menoufia University. At the time of enrolment, a written informed consent was obtained from the enrolled patients.

Conflict of interest

There are no conflicts of interest.

References