ORIGINAL ARTICLE

Cross-sectional Cranial CT Imaging Findings and Patterns in Clinically Diagnosed COVID-19 Cases in a Tertiary Referral Center

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ABSTRACT

Background. Coronavirus Disease 2019 (COVID-19), caused by the SARS-CoV-2 virus, presents not only as a respiratory ailment but also poses risks of neurological complications whose underlying mechanisms remain unclear. These complications range from mild to severe and may involve direct invasion of the central nervous system (CNS), disruption of the blood-brain barrier, or systemic cytokine effects. Diagnostic challenges persist due to the suboptimal sensitivity of RT-PCR assays.

Objective. The present study aimed to review the contrast and non-contrast enhanced cranial CT images of all diagnosed COVID-19 patients in a tertiary referral center with the clinical impression of non-traumatic and non-operative CNS pathologies.

Methods. We conducted a cross-sectional study analyzing CT images of COVID-19 patients with neurological symptoms. Among 51 included patients, plain CT scans were predominantly used, revealing no acute infarcts or hemorrhages in the majority, while frontal lobe involvement was notable in cases with pathology. Chronic infarcts or ischemic changes were observed in over half of the cases, primarily affecting the anterior circulation. Only one case of meningitis was documented.

Results. In the final analysis, 51 patients met the inclusion criteria out of the initial 64 enrolled. The study population, predominantly male with a mean age of 58.02 ± 20.87 years, mainly comprised patients solely diagnosed with COVID-19. Plain CT scans were favored over contrast-enhanced scans (76.50%, n = 39). While most patients had no acute infarcts or hemorrhages, the frontal lobe was commonly affected among stroke patients (9.8%, n = 5). Additionally, a significant portion of patients without acute stroke findings exhibited chronic infarcts or ischemic changes (57.69%, n = 15).

Conclusions. This study sheds light on the radiological patterns of CNS involvement in COVID-19 patients, highlighting frequent frontal lobe involvement possibly attributed to hypercoagulability and endotheliitis. Further research with larger sample sizes and MRI utilization is recommended to enhance our understanding of CNS manifestations in COVID-19. This study contributes to understanding COVID-19 neurological sequelae, particularly in terms of radiological patterns, among patients presenting with neurological symptoms. The findings highlight the need for comprehensive evaluation and management of neurological complications in COVID-19 patients.

Keywords: COVID-19, stroke, diagnostic radiology

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INTRODUCTION

Since its initial emergence in Wuhan, China, Coronavirus Disease 2019 (COVID-19) has posed a significant global threat. Despite being a relatively recent discovery, our understanding of its pathophysiology remains limited.

The disease is attributed to the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), primarily transmitted between humans through respiratory droplets and contaminated surfaces. Upon entry into cells, SARS-CoV-2 targets the transmembrane angiotensin-converting enzyme-2 (ACE2) protein found in various organs, including the lungs, heart, blood vessels, gastrointestinal tract, and kidneys. This interaction renders these tissues susceptible to infection, allowing the virus to hijack cellular machinery for replication and spread.[1,2] Lesser known, but increasingly recognized, is the ability of COVID-19 to induce neurological damage post-infection. These complications range from mild symptoms like headaches and myalgias to more serious conditions such as stroke, psychosis, and anosmia.[4] Inflammatory cytokines triggered by COVID-19 infection can induce endothelial dysfunction and coagulopathy, increasing the risk of stroke. Hemorrhagic stroke is also associated with COVID-19, possibly due to increased blood pressure and ACE-2 level reduction.[1,3-5] Other neurological disorders include encephalopathy, encephalitis, brain fog, depression, and anxiety. The exact mechanisms underlying these conditions remain unclear, but hypotheses suggest pulmonary dysfunction, direct CNS invasion by the virus, or breach of the blood-brain barrier by systemic cytokines. Additionally, social isolation during the pandemic may contribute to some CNS disorders.[3] Comparisons with the SARS virus of 2003 indicate similarities in neuroinvasion potential, with evidence of SARS-CoV-2 presence in the cerebrospinal fluid (CSF) of patients exhibiting meningitis and encephalitis.

Presently, the definitive diagnosis of COVID-19 is made by using reverse transcriptase-polymerase chain reaction (RT-PCR) assay, which performs accurately in a laboratory setting.[1] However, the actual sensitivity relies on factors like symptom duration, viral load, and test sample quality; a pooled sensitivity from a meta-analysis of 25 nasopharyngeal RT-PCR assays showed 89% sensitivity with substantial heterogeneity, while another meta-analyses showed that nasopharyngeal and sputum RT-PCRs have a pooled sensitivity of 73-97%.[4,5] The similar meta-analyses also comment that other biological samples other than nasopharyngeal swabs do have limited use due to lower sensitivities.[4,5]

In light of this, neurological sequelae from COVID-19 infections relies on an adjunct modality to provide an initial look on this complication. Recently, the role of computed tomography (CT) in COVID-19 is constantly evolving, with modest scientific evidence suggesting that it may play an integral role in the early detection and treatment of CNS pathologies such as meningitis, encephalitis, and stroke associated with COVID-19 infection. Thus, the present study aimed to review the contrast and non-contrast enhanced cranial CT images of all diagnosed COVID-19 patients in a tertiary referral center with the clinical impression of non-traumatic and non-operative CNS pathologies.

METHODS

Study Design

This is a cross-sectional study analyzing radiology report database and CT images of COVID-19 patients with clinical and radiological CNS pathologies in a tertiary referral center in the Philippines. All CT scan results covering April – September 2020 from the database of the Department of Radiology, along with their charts, were reviewed. Records were included in the study if 1) patient was an RT-PCR confirmed and admitted COVID-19 cases in a tertiary referral center, and 2) CT scan records were available, as requested for clinical impression and/or radiologic findings of non-traumatic and non-operative CNS pathologies, which includes meningitis, encephalitis, and stroke. Records were excluded from the study if 1) the patients presented with traumatic brain injury, post-operation, or with intracranial masses, or 2) COVID-19 negative patients, including suspected and probable ones. The total number of cases within the time period were taken into consideration.

Afterwards, the scans were anonymized, and loaded to the Digital Imaging and Communications in Medicine (DICOM) system. Baseline demographics (age, sex) were taken for each included record. The patterns of involvement of the typical and atypical regions of the brain - parietooccipital, frontal, temporal, cerebellum, thalamus, brainstem, and basal ganglia were recorded. Abnormal hypodensities and enhancements, as well as the presence or absence of atypical features such as hemorrhage, were determined through the anonymized scans. The findings were independently reviewed by two of the authors, and any discrepancies were assessed by the third independent radiologist.

Statistical Analysis

All confirmed cases of encephalitis, meningitis, and stroke were tabulated by the patterns of involvement of the typical and atypical regions of the brain - parietooccipital, frontal, temporal, cerebellum, thalamus, brainstem, and basal ganglia, and were recorded and statistically analyzed for its incidence in distribution. Chi-square test was utilized to determine any association between sex and area of involvement, while multinomial logistic regression was utilized to determine any correlation between age and area of involvement.

Ethical Considerations

This research proposal was submitted and approved (Study code: UPMREB 2020-387-01) by the UP-Manila Research Ethics Board prior to the project implementation. The research team complied with the ethical guidelines in the conduct of health research as stated in the National Ethical Guidelines for Health Research handbook.

RESULTS

Overall, there was a total of 64 patients enrolled in the study; however, only 51 patients met the inclusion criteria and thus were included in the eventual analysis. The mean age of the study population was 58.02 ± 20.87 years, predominantly consisting of males (62.7%, n = 32). Plain CT was used for more than three-fourths of the study population (76.50%, n = 39) as compared to plain CT with contrast enhancement (23.50%, n = 12).

Patients were classified based on the antecedent history of the radiological study. Most of the patients only have COVID-19 without any disease history (68.60%, n = 35); the remainder comprised patients with previous cardiac (9.80%, n = 5), neurological (11.80%, n = 6), infectious (3.9%, n = 2), and neoplastic diseases (5.90%, n = 3). No definite evidence of acute infarcts or hemorrhages was seen in most cases (56.9%, n = 29), while for those with definite pathology, the frontal lobe (9.8%, n = 5) was the most commonly involved area of stroke or hemorrhage. Among those with no definite evidence of acute stroke pathology, 57.69% of them (n = 15) have evidence of chronic infarcts or ischemic changes. The summary of the CT scan findings are shown in Table 1. Other areas of involvement are shown in Table 2, with representative CT cuts shown in Figure 1.

Chi-square test did not show any significant associations between sex and area of involvement (p = 0.127), CT scan findings (p = 0.842), and pathology (p = 0.65). Multinomial logistic regression showed that there was no significant associations between age and area of involvement (Nagelkerke R^2 = 0.341, p = 0.544), and CT scan findings (Nagelkerke R^2 = 0.858, p = 0.051).

Table 1. Summary of CT Scan Findings among the 51 Cases Reviewed for the Study

CT scans		Count	Percentage (%)
No findings	No evidence of pathology	29	56.9
With findings	Infarct	13	25.4
	Hemorrhage	8	15.7
	Meningitis	1	2.0

Table 2. Areas of Involvement among Patients with COVID-19 Presenting with Neurological Symptoms of Infarct, Hemorrhage, or Meningitis

CT scans with findings (n = 22, 43.1%) Area of involvement	Count	Percentage of total cases (%)
Brainstem	1	2.0
Capsule	2	3.9
Cerebellum	2	3.9
Cerebrum	4	7.8
Frontal	5	9.8
Ganglia	1	2.0
Meninges	1	2.0
Multiple	3	5.9
Occipital	2	3.9
Parietal	1	2.0

DISCUSSION

The cause of these CNS symptoms have not yet been thoroughly studied, but some of the theories point toward the infection causing depression of the brainstem reflex that senses oxygen depletion.[6] The incidence of COVID-19-related neurological symptoms ranged from 7.7% to almost 100% across nine studies from different countries[7], although these studies suffered from high heterogeneity. However, there has been no study to prove that the virus penetrates the brain and interacts with these receptors. SARS-CoV-2 exhibits a similar neurotropic potential with its close cousin, the coronavirus behind the 2003 severe acute respiratory syndrome (SARS) epidemic; SARS could infiltrate neurons and is implicated in inducing SARS-related encephalitis.[8,9] Traces of SARS-CoV-2 were discovered in the cerebrospinal fluid (CSF) of COVID-19 patients who developed meningitis and encephalitis, which suggests penetrance to the CNS.[10]

In this study, we aimed to document and describe radiological CNS pathologies (stroke, encephalitis, and meningitis) using a conventional cranial CT scan in confirmed COVID-19 patients. We observed that age and sex also were not significantly associated with acute CNS pathology development. This is unlike the established notion that baseline demographics (older age, male sex) did not affect stroke development in usual.[11,12] Interestingly, a cohort of 10,881 COVID-19 patients admitted in several referral hospitals across the Philippines also did not observe any association between age/sex and stroke incidence among infected patients.[13] Additionally, the majority of our patients who had an antecedent history of COVID-19 infection with no other comorbidities showed no definite evidence of stroke or hemorrhage at the time of study. A multicenter review of COVID-19 patients in Italy likewise observed that around 66% of those patients with neurological symptoms showed no acute findings on brain CT scan.[14] In this study, more than half of those with absent evidence of stroke displayed chronic infarcts or ischemic changes, which are risk factors for acute stroke development.[15,16] Similar to our study, almost two-thirds of those with previous cardiac or neurological abnormalities developed stroke. COVID-19 may potentiate underlying vascular risk factors in this subset of patients while predisposing newly infected patients to develop stroke; this is also similar to the conclusion for the multi-center cohort in the Philippines, wherein they observed that there are similar cardiovascular and metabolic risk factors associated with stroke.[13] This reinforces that COVID-19 may only have a small contribution to stroke incidence among patients with comorbidities, and that these outweigh any predisposition

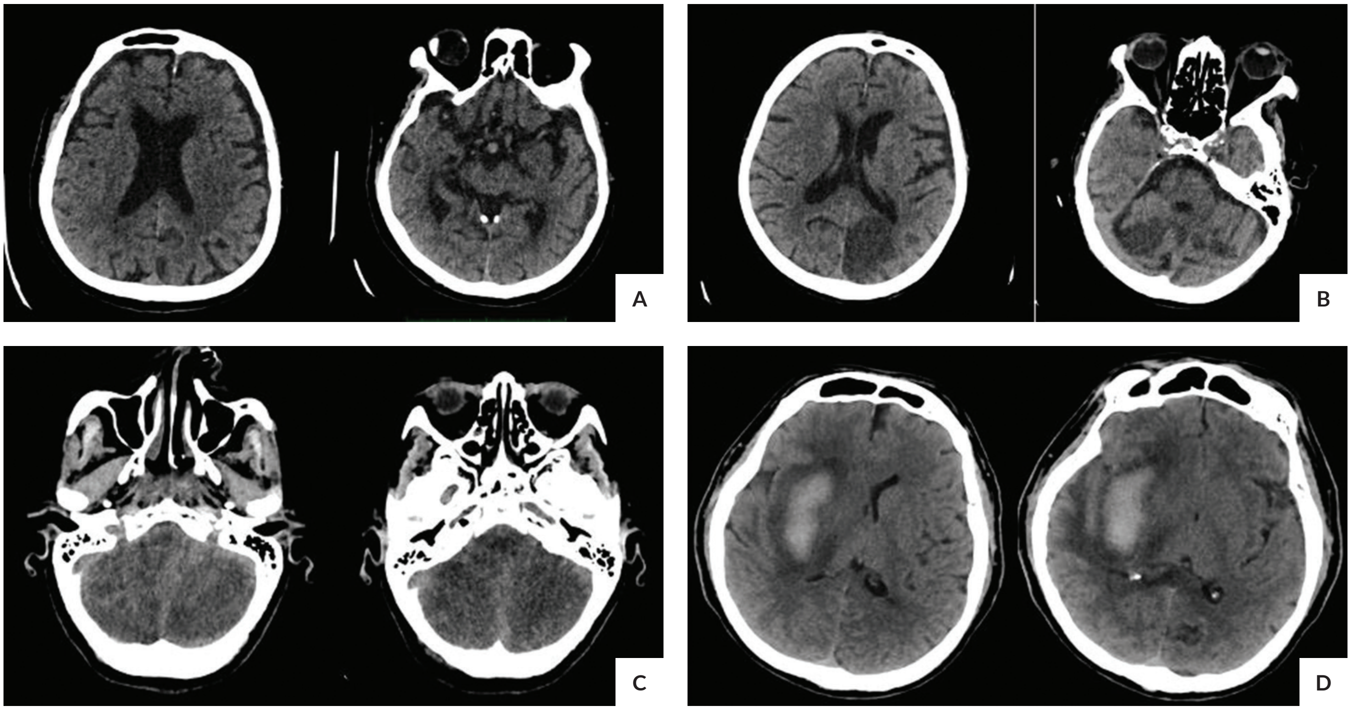

Figure 1. ***Representative cranial tomography (CT) cuts for the most common areas affected in COVID-19 patients presenting with neurological changes.*** **(A)** 83/M, COVID +, No evidence of acute intracranial hemorrhage or major vascular territory infarct. Microvascular white matter ischemic changes. **(B)** 84/M, COVID +, non-arousable. CT findings show multiple hypodense foci, bilateral cerebellar hemispheres and brainstem. **(C)** 67/F, COVID +, Subacute infarcts in the bilateral cerebellar hemispheres. **(D)** 37/M, COVID +, Subacute parenchymal hemorrhage, right external capsule. All cuts were taken with the patients in supine position using a GE Revolution 64 slice CT scanner, 5.0 mm slices.

to stroke that increased age and male sex imparts. Infection alone, however, may serve as an important prognostic factor in predisposed patients.[17]

The anterior circulation was the predominantly affected circuit in the study population, with less common involvement of the posterior circulation (occipital lobe, cerebellum, brainstem), as similarly observed in the literature.[17] The predominant lobe affected was the frontal lobe, which was also reported in a handful of studies that describe similar evolutions of stroke in the frontal lobe as well.[18-20] Interestingly, involvement of multiple areas, even those involving near-total or total areas of the cerebrum, in a quarter of patients was seen; this trend was also similar to the previously cited meta-analysis.[8] The combination of a hypercoagulable state and endotheliitis may lead to microvascular thrombosis, allowing for multi-territorial involvement as evident in more than a quarter of patients.[21,22] However, additional laboratory parameters to establish a hypercoagulable state, as well as advanced imaging techniques such as phase contrast magnetic resonance imaging (PC-MRI) and color-coded duplex ultrasonography (CDUS), may be of importance in future endeavors to explore this hypothesis.

Only one case of meningitis was documented among our study population. In the absence of CSF testing for COVID-19, and as the differential diagnosis in the antecedent history of this patient is tuberculous in origin, the involvement of another viral infection in the meningitic process of our single case remains unknown. There have been only a limited number of reports of primary meningitis secondary to COVID-19 infection.[10,23-25] Interestingly, two of these studies showed no evidence of neurological abnormality on CT scan.[23,24] One article described hypoattenuation within the thalamus on CT scan, with further MRI study confirming rim-enhancing lesions within the thalamus and medial temporal lobes consistent with hemorrhage.[25] Another described ventriculitis and encephalitis within the hippocampus and right mesial lobe.[10] Future studies may be more informative in the setting of a larger sample size and the addition of non-COVID-19 stroke patients to serve as controls to the study population. This will allow comparison as to the differences in terms of patterns of radiological signs that may be pathognomonic to COVID-19 alone. Also, barring the limitations of resources in future research, contrast-enhanced CT scans or MRI may be utilized to better characterize and identify areas of involvement in the brain of COVID-19 patients afflicted with stroke, meningitis, or encephalitis, as well as confirm equivocal CT scan findings in the setting of strong clinical suspicion of neurological abnormality.

CONCLUSION

Overall, it was evident that COVID-19 patients presenting with neurological signs have variable brain imaging patterns but are nonetheless dominated by hemorrhages and infarcts similar to previous findings.[4] To our knowledge, this was the first local study to describe areas of involvement in Filipino COVID-19 patients presenting with neurological symptoms. We hope that this research may bolster information on COVID-19 neurological sequelae, especially in terms of pathophysiological and radiological knowledge among this specific study population.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

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