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Brain Incidental MRI-Findings among COVID-19 Patients: A Systematic Review

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Abstract

Introduction: Currently, case reports and case series are the main source of evidence regarding brain MRI findings in patients with COVID-19. Due to limited information of neurological findings of COVID-19 during MRI scanning, we conducted a systematic search with the aim to review and assess brain MRI findings linked to COVID-19.

Methods: Electronic search was conducted in to a comprehensive approach in major medical databases such as PubMed, Embase, and the Cochrane Library. Initially, for inclusion in this review, studies had to satisfy the following criteria: (1) Recruitment of patients diagnosed with COVID-19; (2) Examination of brain MRI findings; (3) Provision of adequate information to enable assessment of brain MRI outcomes; (4) Utilization of either observational or interventional study designs; (5) Publication of the study in the English language; and (6) Availability of the publication as an original research article within a peer-reviewed journal. Case reports and case series were excluded and only cohort and case-control studies were included in the review. A careful conduction of a systematic data extraction was performed, using excel sheets to perform data extraction by two independent reviewers. Finally, a narrative synthesis of the results were reported in the following section of the review.

Results: The electronic search yielded a comprehensive collection of 105 brain neuroimaging studies concerning individuals affected by COVID-19. Among these, 53 studies centered on assessing neurological symptoms devoid of detailed brain topography, thus excluding them from further consideration. Subsequently, a total of 23 studies, which focused on the examination of brain changes associated with SARS-CoV-2 infection, were finally selected for the conclusive review. This selection comprised 9 cohort studies and 14 case-control studies, each contributing unique insights. Furthermore, the assessment of the quality of included articles was conducted with precision, employing the Joanna Briggs Institute (JBI) Critical Appraisal Checklists designed for observational studies. This evaluation yielded results of commendable compliance, ranging from 67% to 100% across the evaluated studies.

Conclusions: The observed brain changes linked to SARS-CoV-2 infection in individuals affected by both acute and mild cases of COVID-19 predominantly centered around the olfactory brain network, encompassing limbic and prefrontal regions. The exact mechanisms behind these disruptions within these brain areas, whether they stem from direct viral involvement or indirect influences, still remain to be definitively established.

Keywords: ***MRI, COVID-19, Investigations, Brain, Neurology***.

Introduction

The pandemic of Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2), demonstrated an effect beyond the respiratory system and affect other systems such as the central nervous system (CNS) [1]. These CNS complications could be considered as a spectrum of conditions, such as intracranial hemorrhage, acute brain infarction, cerebral vein thrombosis, and other inflammatory conditions that affect the CNS. Moreover, other conditions such as posterior reversible encephalopathy syndrome (PRES), shows an association with COVID-19 infections [2, 3]. As the pandemic evolved, more complications have been linked to COVID-19. The clinical manifestation of PRES differ and ranging from mild symptoms like headache, altered mental status, seizures, to a serious conditions such as visual impairment [4].

In a series of clinical cases in Wuhan, China, among 214 hospitalized patients due to COVID-19, 36.4% of these patients had neurological symptoms [5]. These symptoms ranged from mild symptoms such as dizziness, headaches, problems in consciousness, to severe events of acute cerebrovascular incidents. Moreover, several case reports illustrates situations where neurological manifestations were the initial signs of corona virus infection [6, 7].

Initial identified neurological conditions that were associated with COVID-19 including acute hemorrhagic necrotizing encephalopathy associated with COVID-19 [8], later on researchers presented more neuroimaging observations. These findings are different and ranged from encephalitis and meningitis, hemorrhagic posterior reversible encephalopathy syndrome (PRES), acute disseminated encephalomyelitis (ADEM), cerebral venous thrombosis, and acute ischemic stroke [9-11]. Recently, many publications explaining neuroimaging findings related to COVID-19 since the emergence of SARS-CoV-2. However, it's important to note that most of these publications are comprised of case reports or series, which have limited empirical strength for establishing the epidemiology of specific neuroimaging findings related to COVID-19. The brain is considered as one of the targeted sites of corona virus (SARS-CoV-2) infection, which resulted in the emergence of neurological symptoms including loss of smell and taste [12]. Many systematic reviews have been conducted to investigate abnormalities detected in brain imaging for neurological conditions as a prominent feature of COVID-19 [13, 14]. These reviews illustrated that neurological consequences associated with COVID-19, such as abnormalities in brain parenchyma, subcortical micro- and macro-bleeds, and cortico-subcortical swelling [15]. While these reviews provide essential picture to the detection of neurological features of COVID-19, they shed light on radiological findings associated with COVID-19. Hence, demonstration of the neurological manifestation is important because it illustrates direct viral penetration into the brain via the olfactory pathways or viral invasion through the cardiorespiratory center of medulla oblongata. To show the functional effects of these radiological manifestations, neuroimaging can be used to map out the precise brain regions associated with defective brain functions.

During MRI scans, brain of COVID-19 patients showed a characteristic feature of encephalopathy syndrome is the presence of white matter edema, which usually occurs in the posterior parietal and occipital regions of the cerebrum. Currently, case reports and case series are the main source of evidence regarding brain MRI findings associated with PRES in patients with COVID-19. Due to limited information of neurological findings of COVID-19 during MRI scanning, we conducted a systematic search with the aim to review and assess brain MRI findings linked to COVID-19.

Methods

Electronic search was conducted in to a comprehensive approach in major medical databases such as PubMed, Embase, and the Cochrane Library, covering studies and reports that have been published from 2019 to databases until Juni 2023. The main focus of the review was to identify studies that aligned with certain inclusion criteria. Initially, for inclusion in this review, studies had to satisfy the following criteria: (1) Recruitment of patients diagnosed with COVID-19; (2) Examination of brain MRI findings; (3) Provision of adequate information to enable assessment of brain MRI outcomes; (4) Utilization of either observational or interventional study designs; (5) Publication of the study in the English language; and (6) Availability of the publication as an original research article within a peer-reviewed journal. Case reports and case series were excluded and only cohort and case-control studies were included in the review. Based on the title an abstracts, a primary screening was conducted and eligible studies were identified.

Secondly, A careful conduction of a systematic data extraction was performed, using excel sheets to perform data extraction by two independent reviewers. The primary areas of focus revolved around a diverse spectrum of brain MRI findings linked with COVID-19. Extraction of data was done for certain characteristics such as general characteristics of the study, details concerning the study population, duration of the follow-up period, , the course of the intervention, radiological outcomes related to brain findings including encephalopathy, cerebral vein thrombosis, and other features. In addition to aspects related to the clinical features such as symptom severity, quality of life, and other relevant factors. Finally, a narrative synthesis of the results were reported in the following section of the review.

Results and discussion

The electronic search yielded a comprehensive collection of 105 brain neuroimaging studies concerning individuals affected by COVID-19. Among these, 53 studies centered on assessing neurological symptoms devoid of detailed brain topography, thus excluding them from further consideration. Subsequently, a total of 23 studies, which focused on the examination of brain changes associated with SARS-CoV-2 infection, were finally selected for the conclusive review. This selection comprised 9 cohort studies and 14 case-control studies, each contributing unique insights. Furthermore, the assessment of the quality of included articles was conducted with precision, employing the Joanna Briggs Institute (JBI) Critical Appraisal Checklists designed for observational studies. This evaluation yielded results of commendable compliance, ranging from 67% to 100% across the evaluated studies. Two major MRI findings in brains of COVID-19 patients were found in the include studies. One relate to acute effect of corona virus infection and those related to localized brain repercussions. Acute stroke was a most common neurological complication associated with COVID-19, and documented in 12 of the 23 studies included in the review [16-26]. The prevalence of acute stroke represents a wide range from 1.9 to 52 %, with an average mean of 22.7% in the included studies. The selection criteria for participants included in the analysis were 11 studies targeted individuals displaying neurological symptoms, 6 studies focused on admitted patients, and 6 studies targeted on non-hospitalized patients. The changes affecting the olfactory and corpus callosum structures were reported in 48% of the included studies, manifesting across a spectrum that ranged from 2 to 100% across the various studies.

Brain alterations:

The patients with COVID-19 showed a range of brain alterations, which become particularly common during the later stages of the corona virus infection. These changes differed in the site they affect and in the intensity of the alterations. These alterations include incidence of subcortical micro- and macro-bleedings, instances of cerebral swelling and haemorrhages that were usually happened within the gray and white matter of the brain. Many studies [16, 27, 28] focused on the investigations of brain changes during the severe phase of the COVID-19 infection. However, these investigations seems to be dependent on the experience of neuro-radiologists who inspected brain MRI scans. For instance, researchers found micro-bleedings in certain brain areas such as the corpus callosum, internal capsule, middle cerebellar peduncles, and subcortical white matter. These micro-bleedings are commonly found in patients with acute respiratory distress syndrome (ARDS), who had prolonged stays in the intensive care units (ICUs) in accompany with delayed recovery of consciousness [11]. Moreover, patients with COVID-19 who had multiple medical and neurological comorbidities that

Table (1): Summary of findings demonstrates number of studies and the affected areas in the brain

Finding	Number of Studies	Prevalence/Affected Areas
Total Studies Included	23	MRI Findings in Olfactory Regions increased Signal Intensity, Olfactory Bulb Abnormalities. Subcortical micro- and macro-bleedings, cerebral swelling, haemorrhages, white matter abnormalities. Prevalence: 1.9% to 52%, Average: 22.7%
Study Types	Cohort: 9, Case-Control: 14	Variability in Findings Among Acute COVID-19 Patients: Micro- and Macro-bleeds, Swelling, Haemorrhage, Different Brain Tissues Affected Influence of Comorbidities and Treatment Possible Factors for Variability. Impact on Olfactory System: Consistent in Mild Cases and Post-Recovery. MRI Findings in Cohort Studies: Signal and diffusion abnormalities in Corpus Callosum, Basal Ganglia, Medial Temporal Lobe, Frontal, Parietal, Occipital, Temporal Areas
Compliance with JBI Critical Appraisal	Ranged from 67% to 100%	Common Brain Alterations in Corpus Callosum, Gray and White Matter. Brain Alterations in Severe COVID-Common in ICU Patients, Micro-bleedings in Corpus Callosum, Brainstem Abnormalities.
Other brain Alterations	12	Acute Stroke in COVID-19. Parenchymal Brain Abnormalities in Autopsy Microbleeds, Microbleeds, Cortico-subcortical swelling, White Matter Changes, Asymmetrical Olfactory Bulbs.

showed certain white matter abnormalities, particularly on the splenium of the corpus callosum and the brainstem [16]. Furthermore, an autopsy study conducted on patients who died from COVID-19 found an assortment of parenchymal brain abnormalities, spanning subcortical microbleeds, macrobleeds, cortico-subcortical swelling, non-specific changes in white matter, and asymmetrical olfactory bulbs [28]. Several cohort studies, that were included in the review, investigate the acute effects of COVID-19 and its association with brain alterations [19-21, 24]. These cohort studies used radiological assessments of MRI images, with adequate sample sizes, and statistical power. Consistent with the findings from the case-control studies, cohort studies showed a spectrum of abnormalities which affected different brain regions. In their study, Chougar et al. detected signal and diffusion abnormalities within the corpus callosum and basal ganglia (including the substantia nigra, globus pallidus, and striatonigral complex) among COVID-19 patients with neurological symptoms [19]. Kremer et al. reported that signal abnormalities mainly affected the medial temporal lobe, and these MRI findings were most common in patients with severe COVID-19. Additionally, Kandemirli et al. found signal intensity irregularities within the frontal (cingulate gyrus), parietal, occipital, and temporal (insula) areas among a group of hospitalized COVID-19 patients in ICU care unit with underlying comorbidities [29].

In contrast to the limited findings mentioned earlier, a group of four cohort MRI studies involving hospitalized COVID-19 patients has revealed consistent trends in abnormal signal intensity, particularly involving specific brain regions. Clearly, the olfactory bulb and tract were investigated in these studies [21, 30], as well as the corpus callosum [24, 30]. Within a relatively small cohort of COVID-19 patients experiencing coma or neurological deficits, Conklin et al. detected alterations in signal intensity within the corpus callosum. Similarly, another study by Dixon et al. reported instances of micro-bleedings in the corpus callosum and brainstem among COVID-19 patients [24].

Similarly, Klironomos et al. identified disruptions within the corpus callosum, along with increased signal intensity in the olfactory bulb and tract as frequent abnormalities in COVID-19 patients [30]. Furthermore, Lin et al. reported abnormal increases in signal intensity specifically within the olfactory bulb without concurrent volume changes in COVID-19 patients [21]. Taking a more targeted approach to assess brain olfactory integrity, Strauss et al.

conducted a case-control MRI study, employing a region-of-interest methodology to calculate normalized values within the olfactory bulb. A significant statistical differences in olfactory hyperintensity were observed in COVID-19 patients compared to controls with anosmia [17].
While certain consistent brain abnormalities have been detected, such as those affecting olfactory regions and the corpus callosum, the overall findings among acute COVID-19 patients had substantial heterogeneity. These variations encompass a range of abnormalities, including micro- and macro-bleeds, swelling, and hemorrhage, which affect different types of brain tissue including parenchymal, cortical, subcortical, and white matter. The diversity in findings might be attributed to a combined impact stemming from distinctive medical and neurological comorbidities, as well as the intensive treatment received by these patients. Exploring SARS-CoV-2-infected individuals exhibiting less severe symptoms presents a promising avenue to probe the intrinsic effects of COVID-19 on the brain in a manner that is distinct from severe comorbidities.

Localized brain repercussions of COVID-19:
While the potential impact of SARS-CoV-2 infection on different brain regions is being explored, there is a noticeable consistency in its influence on the olfactory system, particularly in cases of mild infection and post-recovery. In the context of mild COVID-19 cases, two smaller MRI case series, one of which also focused on persistent loss of smell [31], employed radiological examination of brain MRI scans to reveal areas of hypersignal intensity lesions in the olfactory bulbs [22, 31] and the olfactory cortex [31]. In a subset of COVID-19 patients exhibiting leukoencephalopathy, characterized by damage to white matter tissue, Freeman et al. [25] identified patterns of abnormal MRI signal distribution encompassing the corpus callosum, brainstem, and cerebellum. The impact of COVID-19 on brain morphometry and function may extend systematically. These changes can be subtle, especially in the early stages of the disease, potentially eluding visual inspection. The characterization of such brain alterations may benefit from group-level statistical comparisons, as demonstrated in the subsequent five case control studies.
The included studies focused on evaluating cerebral glucose metabolism in preselected individuals with COVID-19 and neurological symptoms yielded significant insights. Through a principal component analysis, notable reductions in metabolism were discerned within the parietal and frontal association cortices of patients in comparison to control subjects. Interestingly, patients demonstrated an absence of heightened metabolism in the brainstem, cerebellum, and mesial temporal lobe structures. An investigation by Crunfli et al. [32] focused on cortical anomalies among non-hospitalized individuals diagnosed with COVID-19, contrasting them with healthy volunteers. Employing a surface-based morphometry approach on brain MRI scans, the study aimed to detect variations in gray matter thickness across the brain's surface. Those with COVID-19 exhibited diminished thickness in regions such as the olfactory sulcus, lingual gyrus, and calcarine sulcus, while thickness increased in areas including the central sulcus and superior occipital gyrus when juxtaposed with the control group. The observed changes in the orbitofrontal region were plausibly linked to the virus's influence on this cortical region, consistent with the proposed neuroinvasive mechanism of SARS-CoV-2 that capitalizes on the olfactory nerves as an entry point [28].

Two PET investigations into long-COVID, conducted by Sollini et al. [17] and Guedj et al. [33], further illuminated persistent brain alterations. An overarching hypometabolic pattern was identified in the parahippocampal gyrus and thalamus of long-COVID patients relative to melanoma patients [17]. Intriguingly, COVID-19 patients who endured lingering anosmia or ageusia displayed hypometabolism in both the parahippocampal gyrus and orbitofrontal cortex. Guedj et al. [33] unveiled hypometabolism in the rectal/orbital gyri, encompassing the olfactory gyrus, and the temporal lobe, which encompassed the amygdala and hippocampus. These findings were particularly pronounced in individuals who experienced symptoms at least three weeks post-COVID-19 infection. The study revealed that the frontal cluster's hypometabolism, including the olfactory gyrus, was exacerbated in patients using angiotensin-converting enzyme (ACE) drugs for hypertension, while those employing nasal decongestant spray exhibited an improvement. This trend lends credence to the concept of ACE receptors serving as an olfactory conduit for neurotropism in COVID-19 cases. While the exploration of this domain remains limited, initial observations do lend credence to the existence of localized brain alterations in cases of mild infection and post-recovery. Among the case control studies examined, a noteworthy convergence of findings was observed in some of them, particularly concerning modifications within the central olfactory system. These changes manifested as variations in glucose metabolism, brain volume, signal intensity, and cortical thickness [17, 21, 33]. Additionally, consistent perturbations were noted in the functionality and structure of the insula and para-hippocampus. However, it is imperative to acknowledge the presence of discrepancies between studies, as findings remain dispersed across different regions, encompassing occipital, parietal, and temporal areas.

Conclusions

In conclusion, the observed brain changes linked to SARS-CoV-2 infection in individuals affected by both acute and mild cases of COVID-19 predominantly centered around the olfactory brain network, encompassing limbic and prefrontal regions. The exact mechanisms behind these disruptions within these brain areas, whether they stem from direct viral involvement or indirect influences, still remain to be definitively established. To gain a deeper understanding of the origins of these neural impairments, further longitudinal investigations, particularly under controlled study settings, are imperative. Such studies have the potential to not only uncover the underlying causes of these cognitive alterations but also shed light on their potential long-term repercussions.

Conflict of interests

The authors declared no conflict of interests.

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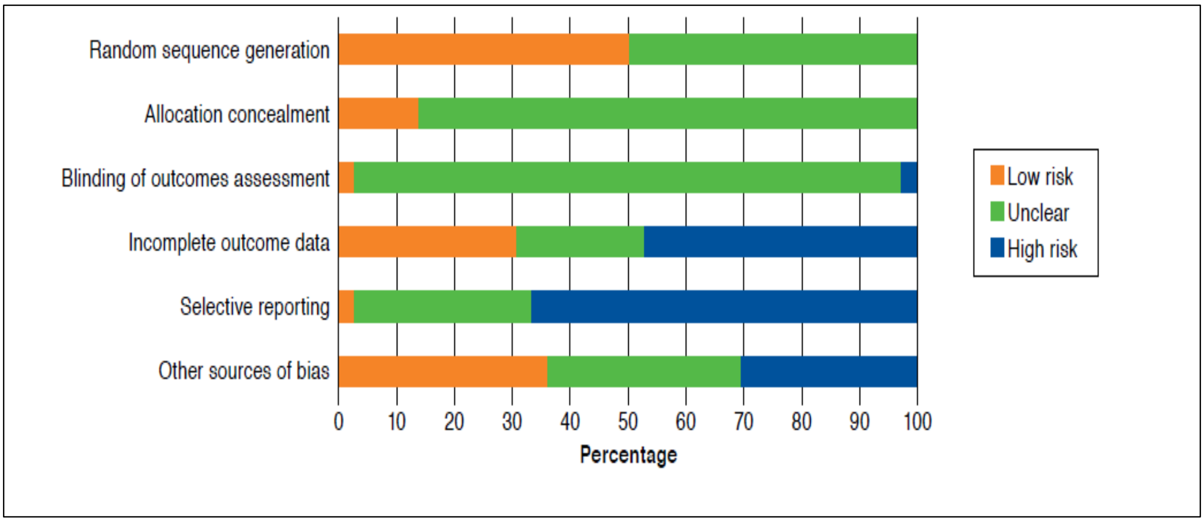

(Figure 1): Risk of Bias in Included Studies Presented as Percentage Across All Studies


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