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Review Article

COVID-19 and Brain complications in adult and pediatric patients: A review on neuroimaging findings

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ABSTRACT

In this review, we will discuss the neuroimaging findings of patients with COVID-19 from the outbreak (late December 2019) to the end of October 2021. PubMed, Scopus, Google Scholar, Science Direct, ProQuest, Web of Science and the World Health Organization database (January 01, 2020, to October 30, 2021) were searched for related published articles. In each of the databases, the appendix search strategies were performed and the below keywords were used: COVID-19"OR"coronavirus disease 2019" AND "brain MRI" OR "brain magnetic resonance imaging" OR "brain CT" OR "neuroimaging". In total, neuroimaging findings of 1550 patients, with ages from 1-96 years, were analyzed. Most brain neuroimaging findings include hyperintensity, Cerebral venous thrombosis, intraventricular and subarachnoid hemorrhage, infarction, leukoencephalopathy, acute ischemic strokes and posterior reversible encephalopathy syndrome (PRES) in adult patients and severe encephalopathy, stroke, infarction, CNS infection/demyelination, neuritis or polyradiculitis, venous thrombosis, Guillain-Barré syndrome, and longitudinally extensive myelitis, and myositis in pediatric patients. Our findings showed that the most important complication of the coronavirus is not just respiratory complications, because although transiently, COVID-19-related brain complications are seen in pediatrics as well as adults, and families should pay more attention to health care.

1. Introduction

Coronaviruses belong to the family of coronaviridae and the order Nidovirales [1, 2]. These viruses have a single-strand, positive-sense RNA genome (encapsulated within a membrane) that is between 16 and 32 kilobases in length and have a variety of hosts including camels, dogs, cats, bats and mice [3]. Previous research has shown that most human coronavirus infections are moderate because, in the last two decades, the rate of infection with both SARS and MERS has been around 10,000 cases, with mortality rates of 10% and 37%, respectively [4]. Novel coronavirus-2019 is now a pandemic worldwide and poses a serious threat to global public health [5]. Coronavirus disease (COVID-19) has attracted the attention of the whole world because of its widespread, especially as human-to-human transmission has been confirmed [6]. However, with the higher outbreak of the disease, the mortality

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rate is increasing; more clinical findings could be effective in preventing and managing the disease [7]. Although at first the articles focused more on respiratory complications, in later articles various brain complications were discussed[8]. In several studies, various neurological symptoms have been reported for patients with COVID-19 including dizziness, headache, ataxia, and confusion [9]. Brain imaging of patients with COVID-19 makes the neurologic complications of the disease more apparent[10]. Therefore, this study aimed to review the imaging findings of pediatric and adult patients with COVID-19 and their brain complications.

2. Materials and Methods

2.1. Search strategy

The systematic search for related articles was performed on different databases including PubMed, Scopus, Google Scholar, Science Direct, ProQuest, Web of Science and the World Health Organization database. The published articles were restricted from January 01, 2020, to October 30, 2021. This study was done using a combination of several keywords including: 'COVID-19', 'coronavirus disease 2019', 'brain MRI', 'brain magnetic resonance imaging', 'brain CT', and 'neuroimaging'.

2.2. Data collection

All clinical studies in which patients with COVID-19 underwent brain CT/MRI were included. Furthermore, to ensure the comprehensiveness of the results, we also searched the reference lists of the selected articles. We included articles in the English language. The exclusion criteria in this study were as: Review articles. The outcome of interest was a different type of brain lesions and complications caused by coronavirus disease 2019 in patients who underwent brain imaging. A total of 175 studies were retrieved through the search, of which 142 were excluded after the full-text screening, leaving 33 studies that were included.

3. Results

Based on the results, approximately 30% of the studied patients were female and the others were male. The age range of patients was between 22-96 years and 9 days to 16 years for adults and pediatrics, respectively. According to the results, it can be founded that brain complications are more common in patients over 50 years of age and their frequency is lower in younger patients. In addition, it is more common in male patients than in women. The neuroimaging findings of 1550 patients with positive RT-PCR tests are summarized in (Table 1).

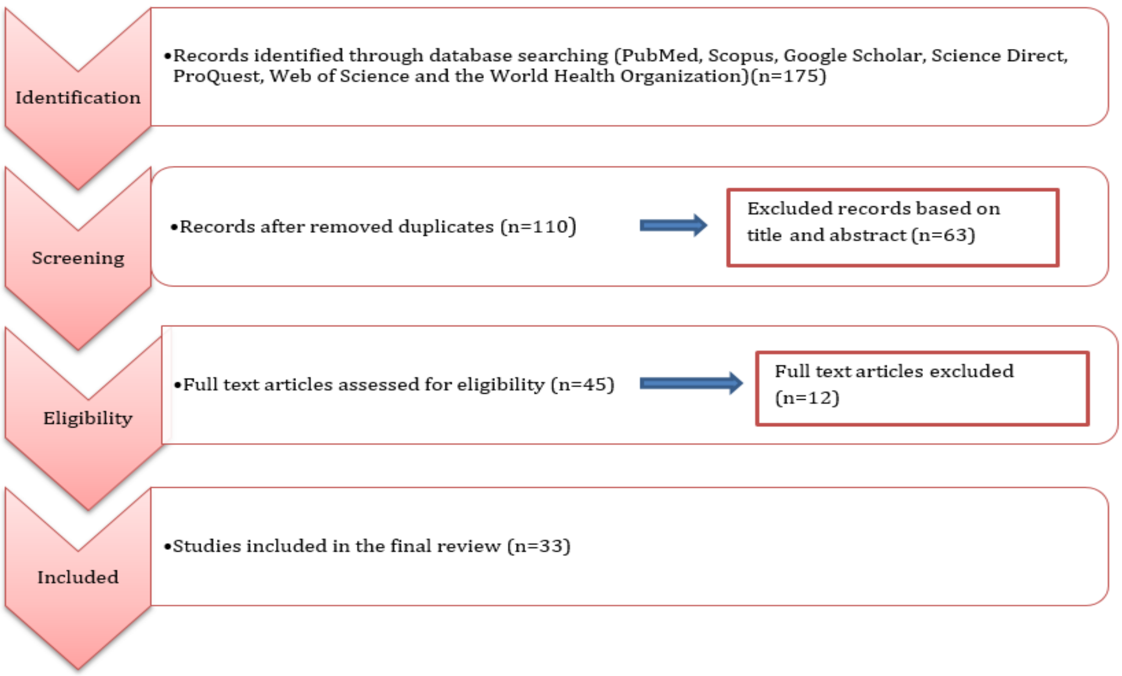

Fig. 1. Flowchart describing the study design process

Table 1. MRI findings and clinical signs of patients with COVID-19

Gender	Country/ Imaging Modality	Age	Common indications for imaging	Neuroimaging finding	Ref.
Female	Belgium/MRI	33	-	Left parietal cortical CVT	[11]
Male	Japan/MRI	24	He had transient generalized seizures that lasted about a minute. He had obvious neck stiffness.	Hyperintensity in the right mesial lobe and hippocampus - meningitis/encephalitis.	[12]
Male	USA/CT-MRI	59	The patient was found to be encephalopathic so brain imaging was requested	Hyperintensity in the subcortical	[13]
4 Males and 2 Females	USA/CT-MRI	60-76	Altered mental status and neurologic symptoms between admission days 15 and 30	Hyperintense signal in the deep white matter of both cerebral hemispheres -Leukoencephalopathy	[14]
Male	Canada/ CT-MRI	57	Abnormal mental status, deranged coagulation parameters, and markedly elevated D-dimer levels- right-arm weakness	Extensive petechial hemorrhages	[15]
Male	Canada/ CT-MRI	62	Abnormal mental status, deranged coagulation parameters, and markedly elevated D-dimer levels	Intraventricular hemorrhage (IVH) and Subarachnoid hemorrhage (SAH)	[15]
Female	USA/CT-MRI	59	A CT of the head was unremarkable	IVH + subcortical and corpus callosum microhemorrhages	[16]
Male	USA/CT-MRI	60	A CT of the head was unremarkable	Hyperintensity and diffusion restriction throughout The cerebral	[16]
Female	USA/CT-MRI	35	A CT of the head was unremarkable	Numerous small foci of susceptibility Within the subcortical and throughout the corpus callosum- microhemorrhages.	[16]
Male	USA/CT-MRI	48	A CT of the head was unremarkable	Hyperintense foci within the WM, and in the spinal cord at C1- infarct.	[16]
Male	USA/CT-MRI	41	CT of the head performed 4 weeks after intubation was unremarkable	Hyperintensity of the globi pallidi	[16]
2 Male	France/MRI	52 and 44	delayed recovery of consciousness	Ring-shaped lesions involving the periventricular and deep white matter, hyperintense on corpus callosum-hemorrhage	[17]
2 Males, 2 Females	Italy/MRI	46-63	agitation and spatial disorientation	Multifocal involvement of the cortex - hyperintense in the parietal, occipital and frontal regions. Minimum involvement of the adjacent subcortical white matter was evident in only a few lessons	[18]
Female	Italy/MRI	25	nasal fibroscopic evaluation results were unremarkable, and noncontrast chest and maxillofacial computed tomography results were negative	Cortical hyperintensity - hyperintensity in olfactory bulbs	[19]
2 Females 7 Males	Switzerland/MRI	55-79	Confusion, agitation, Delayed recovery of consciousness	Microbleeds in the corpus callosum and internal capsule as well as middle cerebellar peduncles	[20]
Female	USA/CT-MRI	58	-	Acute necrotizing hemorrhagic encephalopathy	[21]
150 Males /92 Females	USA/CT-MRI	mean age, 68.7 years	altered mental status, syncope/fall, focal neurologic deficit	Nonspecific white matter microangiopathy, chronic infarct, acute or subacute ischemic infarct, acute hemorrhage	[22]
98 Males and 52 Females	USA/CT-MRI	22–96 years	Altered mental status-concern for infarct-concern for intracranial hemorrhage- hypoxia-seizure- headache	Hemorrhage, infarction, and leukoencephalopathy	[23]

Gender	Country/ Imaging Modality	Age	Common indications for imaging	Neuroimaging finding	Ref.
158 Males and 120 Females	USA/CT-MRI	median age 64 years	-	Ischemic strokes and intracranial hemorrhages, microhemorrhages with a predilection for the corpus callosum, abnormal olfactory nerves	[24]
21 Males and 29 Females	Turkey/MRI	median age 63 years	-	Accompanying subcortical and deep white matter signal abnormality	[25]
69 Males and 39 Females	Italy/CT-MRI	median age 69 years	-	Acute ischemic infarcts and intracranial hemorrhage	[26]
30 Males and 7 Females	France/MRI	mean age of 61	-	Signal abnormalities, non-confluent multifocal white matter hyperintense lesions - microhemorrhages	[27]
138 Males and 47 Females	Sweden/CT-MRI	mean age of 62	-	Intra-axial susceptibility abnormalities - Ischemic and macrohemorrhagic- leukoencephalopathy	[28]
9 Males and 2 Females	USA/MRI	mean age of 53 years	-	Hyperintensity in bilateral supratentorial deep and subcortical white matter - microhemorrhages	[29]
48 Males and 28 Females	France/MRI	mean age of 58.5 years		Acute ischemic infarct-deep venous thrombosis-multiple microhemorrhages- seizure-related perfusion abnormalities- multifocal enhancing white matter lesions- restricted diffusion foci within the corpus callosum-hypoxic-ischemic lesions- posterior reversible encephalopathy syndrome (PRES)-metabolic abnormalities - neuritis	[30]
43 Males and 21 Females	France/MRI	20–92 years		Ischemic strokes-leptomeningeal Enhancement- encephalitis	[27]
38 patients	UK/CT-MRI		The most common indications were delirium, focal neurology, and altered consciousness	Subacute infarct, acute infarct, basal ganglia haemorrhage, and subarachnoid haemorrhage- acute haemorrhagic necrotising encephalopathy	[31]
59 patients	USA/MRI	mean age of 64.5 years		Acute infarcts- subacute infarcts- chronic infarcts, abnormal basal ganglia signal from hypoxemia-microhemorrhage	[32]
50 Males and 40 Females	Italy/CT-MRI	mean age 69 years		CVD- acute ischemic strokes (AIS)- intracerebral hemorrhages- subarachnoid hemorrhages (SAH) - posterior reversible encephalopathy syndrome (PRES)-encephalitis- demyelinating diseases- acute disseminated encephalomyelitis (ADEM)- acuity of chronic subdural hematoma (csdh)- Guillain Barré syndrome.	[33]
39 patients	Brazil/CT-MRI			CNS demyelination- acute stroke.	[34]
Male	Japan/CT-MRI	44		Severe brain swelling	[35]
Girl	India/CT	9-year-old		Infarction- acute ischaemic stroke	[36]
Female	USA/CT	37		Subacute infarcts	[37]
Female	USA/CT	47		Intraparenchymal hemorrhage with surrounding cerebral edema	[37]
38 Paediatric patients	USA/CT-MRI	1-16 years		Multifocal lesions in brain white matter, vasculitic patterns with ischaemic lesions, enhancing neuritis or polyradiculitis, venous Thrombosis, splenial lesions of the corpus callosum, longitudinally extensive myelitis, and myositis.	[38]
2 Boys and 2 Girls	UK/CT-MRI	8-15		Hypodensity of the splenium of the corpus collosum (SCC)- hyperintensities in the SCC	[39]
43 Boys and Girls	USA/CT-MRI	2.5-15.6 years		Severe encephalopathy- stroke- CNS infection/demyelination- Guillain-Barré syndrome/variants- acute fulminant cerebral edema	[40]
Boy	USA/MRI	9-day-old		Multiple foci in the periventricular and deep white matter and corpus Callosum- viral encephalitis.	[41]

4. Discussion

Covid 19 disease caused by the new coronavirus was initially diagnosed with clinical symptoms similar to influenza and respiratory distress [42]. However, subsequent research showed that various neurological symptoms such as headache, inability to walk, cerebral hemorrhage, cerebral infections, etc. can be seen in patients with COVID-19 [43, 44]. It should be noted that most recent research has shown that SARS covid 19 infection is not limited to the respiratory system [45]. Therefore, due to the importance of neurological damage, any neurological signs and symptoms related to COVID-19 patients should be monitored and evaluated by MRI and CT scan [46]. Based on the results of this study, it was found that in patients with symptoms of confusion, agitation, delayed recovery of consciousness, abnormal or altered mental status, deranged coagulation parameters and markedly elevated D-dimer levels, the neuroimaging indication was necessary. In addition, it was found that a negative PCR test and also no chest complications did not indicate patients have COVID-19, because some studies have shown that the patient's brain CT/MRI shows signs of coronavirus infection. Neuroimaging findings in patients with COVID-19 indeed have similarities in most cases, but it is not possible to say with certainty which complication is more common in these patients, because in every patient CT and MRI, have a range of findings. Cortical CVT is one of the rare causes of stroke with an annual incidence of 15.7 per million. Factors contributing to this complication include acquired or genetic thrombophilia, infections of the face, neck and head, and some systemic diseases [47]. In the absence of the above factors, based on MRI findings in a patient with COVID-19, CVT complications were observed, so Baudar *et al*. suggested that coronavirus infection as a trigger co-factor for CVT [11]. Hyperintensity seems to be one of the most common brain complications of COVID-19, which indicates lesions that are widely produced by demyelination and loss of axons, impairing the transmission of neural messages. Meningitis is another complication of coronavirus which was observed with increasing hyperintensity. Meningitis is an inflammation of the meninges. The most common causes of meningitis are viral and bacterial infections [48, 49]. Moriguchi *et al*, reported that hyperintensity along the wall of the right lateral ventricle and hyperintense signal changes in the right mesial temporal lobe and hippocampus, suggesting meningitis/encephalitis [12]. Intraventricular and subarachnoid hemorrhage is another brain complication of COVID-19 which is common in older patients and so far it has not been reported in pediatric patients. Posterior reversible encephalopathy syndrome (PRES) is another complication of COVID-19. PRES is more commonly used as a complication in systemic hypertension, toxemia pregnancy, uremia, and chemotherapy. It has also been reported with infection and sepsis[50]. Numerous researchers stated that although there was no evidence of hypertension and other factors contributing to the development of PRES in patients with COVID-19, typical PRES symptoms in CT/MRI findings included confluent predominantly posterior subcortical and external capsule edema signal, with increased diffusivity and no associated contrast enhancement was found [30, 33]. Another complication of COVID-19 is acute ischemic strokes which are related to possible underlying causes including coagulopathy, endothelial dysfunction, cardioembolism, and direct viral-mediated neuronal injury [51]. Infarction is also a brain complication that has been reported in both adult and pediatric patients [36, 37]. As a result of this complication, the blood supply to the target tissues is disrupted and there is a decrease in oxygen supply, edema, and finally necrosis or death in the tissues. Another complication of COVID-19 is leukoencephalopathy. Hyperintensity in the white matter is associated with leukoencephalopathy [52]. Lang *et al*. reported that COVID-19-associated leukoencephalopathy may be due to hypoxia. They announced there was evidence of damage to the white matter of the brain in the studied patients, which may be due to the hypoxia of COVID-19 disease. It should be noted that severe or prolonged hypoxia causes problems in the process of secretion and production of myelin, which in turn causes brain damage [14]. Encephalopathy is another complication of COVID-19 [53]. One of the most important clinical signs of COVID-

19 encephalopathy is altered consciousness. Also, changes in cortical and subcortical T2/FLAIR signals are common neuroimaging abnormalities [54]. Other CT/MRI findings especially in pediatric patients with COVID-19 include an unusual DWI pattern with ring and nodular spots in the periventricular and white matter of the brain. such imaging findings could have potentially suggested inflammatory lesions such as acute disseminated encephalomyelitis, which is thought to occur from cross-reactivity in immunity to viral antigens, triggering an autoimmune attack on the CNS [38, 41].

5. Conclusion

Contrary to popular belief, the most important complication of the coronavirus is not just respiratory complications. Since the outbreak of the COVID-19 pandemic, several articles have addressed a possible relationship between SARS-CoV-2 virus infection and neurologic symptoms. It seems that coronavirus can have short-term, long-term and even lifelong brain complications in patients, especially in adults. Since complications related to COVID-19 have been reported in children and even infants, families should pay more attention to health issues. Also, physicians and radiologists if they encounter unexplained neurological findings during the COVID period, should consider infection with this virus. However, many studies still need to be done to determine the long-term brain complications of this disease.

Conflict of Interest

The authors hereby declare that they have no conflict of interest.

Author's contributions

All authors equally participated in designing experiment analysis and interpretation of data. All authors read and approved the final manuscript.

Consent for publications

All authors have read and approved the final manuscript for publication.

Availability of data and material

The authors have embedded all data in the manuscript.

Informed Consent

The authors declare not used any patients in this research.

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