The main changes in neuroradiology of patients with Covid-19: an integrative review

As principais mudanças na neuroradiologia de pacientes com Covid-19: uma revisão integrativa

Tarciana Maria Pereira de Lima
PhD Student in Biochemistry and Physiology
Institution: Universidade Federal de Pernambuco (UFPE)
Address: Avenida Professor Moraes Rego, 1235, Cidade Universitária, Recife – PE, CEP: 50670-901
E-mail: tarcimpdelima@gmail.com

João Gabriel de Lima Raulinho
Graduating in Medicine
Institution: Universidade Federal de Pernambuco (UFPE)
Address: Avenida Professor Moraes Rego, 1235, Cidade Universitária, Recife – PE, CEP: 50670-901
E-mail: jgabriellr13@gmail.com

Matheus Barros de Albuquerque
Graduating in Medicine
Institution: Universidade Federal de Pernambuco (UFPE)
Address: Avenida Professor Moraes Rego, 1235, Cidade Universitária, Recife – PE, CEP: 50670-901
E-mail: matheus.balbuquerque@ufpe.br

Maria de Fátima Viana Vasco Aragão
PhD in Neuropsychiatry and Behavioral Sciences
Institution: Universidade Federal de Pernambuco (UFPE)
Address: Avenida Professor Moraes Rego, 1235, Cidade Universitária, Recife – PE, CEP: 50670-901
E-mail: fatima.vascoaragao@gmail.com

Belmira Lara da Silveira Andrade da Costa
Post-Doctorate in Biological Sciences with an Emphasis in Neurophysiology
Institution: Universidade Federal de Pernambuco (UFPE)
Address: Avenida Professor Moraes Rego, 1235, Cidade Universitária, Recife – PE, CEP: 50670-901
E-mail: belmira.costa@ufpe.br

ABSTRACT
Covid-19 is a viral disease, caused by SARS-CoV-2, with a cyclical epidemiological behavior, causing systemic complications, mainly in the neurological field. In these cases, the patient needs to be evaluated clinically and by complementary exams, such as brain computed tomography (CT) and
magnetic resonance imaging (MRI). In the last years, efforts have been made in order to clarify molecular mechanisms involved in this disease. Several studies have demonstrated the importance and variety of neuroimaging findings, most of which point to alterations related to hemorrhagic, inflammatory and prothrombotic events, bringing an increased risk of death. The aim of this review was to gather the recent evidence by imaging approach on the neurological early and long term risks especially those involved with unfavorable clinical damage, presence of comorbidities and invasive procedures. The present data indicates that Infection with SARS-CoV-2 brought a diversity of neurological changes in adults and the elderly, with long-term effects on the cognition. However, special interest and investigation needs to be given to the neonatal and pediatric cases, due to the inherent risks of the disease, development of systemic inflammatory syndromes and reported deaths.

Keywords: Covid-19, epidemiology, neuroimaging.

RESUMO
A Covid-19 é uma doença viral, causada pelo Sars-CoV-2, com um comportamento epidemiológico cíclico, causando complicações sistêmicas, principalmente no campo neurológico. Nesses casos, o paciente precisa ser avaliado clinicamente e por exames complementares, como tomografia computadorizada cerebral (TC) e ressonância magnética (RM). Nos últimos anos, têm sido feitos esforços para esclarecer os mecanismos moleculares envolvidos nessa doença. Vários estudos têm demonstrado a importância e variedade de achados de neuroimagem, a maioria dos quais apontam para alterações relacionadas a eventos hemorrágicos, inflamatórios e protrombóticos, trazendo um aumento do risco de morte. O objetivo desta revisão foi reunir as evidências recentes por meio da abordagem imagiológica sobre os riscos neurológicos precoces e de longo prazo, especialmente aqueles envolvidos com danos clínicos desfavoráveis, presença de comorbidades e procedimentos invasivos. Os dados atuais indicam que a infecção por Sars-CoV-2 trouxe uma diversidade de alterações neurológicas em adultos e idosos, com efeitos a longo prazo na cognição. No entanto, é necessário dar especial interesse e investigação aos casos neonatais e pediátricos, devido aos riscos inerentes à doença, ao desenvolvimento de síndromes inflamatórias sistêmicas e às mortes relatadas.


1 INTRODUCTION
Covid-19, (co)rona (vi)r us (d)isease, which means “coronavirus disease”, reported in 2019, is a viral disease, caused by SARS-CoV-2, with an incubation
time of around 3 to 14 days, with the main signs and symptoms being fever, dry cough, changes in taste and smell, headache, muscle and joint pain, sore throat, gastrointestinal symptoms, among others, and there may be differences in according to existing viral variants and immunological protection arising from immunization (FIOCRUZ, 2020; OPAS, 2022).

Its first report was made in December 2019, in the city of Wuhan, China, as pneumonia of unknown origin, but its etiology was discovered a week later. On March 11, 2020, it was declared by the World Health Organization (WHO) as a pandemic, due to its characteristics of territorial transmission and the need for international interventions for adequate control and treatment (PAHO, 2022).

In the world, until March 2023, the number of reported cases of Covid-19 was approximately 760 million, with more than 6.5 million deaths. Brazil was the sixth country in accumulated cases, with about 37 million people infected, and the second in number of accumulated deaths (699,276). Our country had the first case reported on February 26, 2020. Despite this amount, 79.23 people are fully vaccinated, per 100 inhabitants (MINISTRY OF HEALTH, 2022; WHO, 2022).

The pandemic behaves in a cyclical manner, with peaks of cases in various regions and countries, according to the levels of transmission, sanitary measures used to control the disease, number of inhabitants, socioeconomic conditions, population displacement control, comorbidities of the affected, number of immunized and circulating viral variants, among other characteristics (Silva & Oliveira, 2020). According to the World Health Organization (WHO), since mid-July 2022, there has been a stabilization of new cases of Covid-19, after some peaks faced worldwide at the beginning of the year (WORLD HEALTH ORGANIZATION, 2022).

Due to the epidemiological behavior, number of cases and varying deaths, several organizations came together to define patient care, prevention and follow-up protocols, trying to minimize complications and sequelae, rationalizing scarce resources in the face of the pandemic context (Edlow et al., 2020; Rodríguez-Pardo et al., 2020; Sebastian et al., 2020; Sharma et al., 2020).

SARS-CoV-2, in order to gain access to target cells and cause human
infection, needs to bind to angiotensin-converting enzyme 2 (ACE-2) type membrane receptors, present in various tissues, such as those of the respiratory, cardiovascular and renal systems. This receptor is also highly expressed in the central nervous system (CNS), which contributes to the disruption of the blood-brain barrier and the appearance of lesions. The appearance of acute necrotizing encephalopathy, encephalitis/meningitis, Giullian-barré syndrome and other pathologies have been reported, as well as a decrease in serum anti-inflammatory cytokines and an increase in pro-inflammatory factors associated with Covid-19 (Accorsi et al., 2020).

In view of this, some studies point to the pathophysiological mechanisms of systemic complications by the new coronavirus, especially in the neurological field. The main theories state that the virus can cause damage by direct dissemination via hematogenous and olfactory pathways, or indirectly by activating a pro-inflammatory or autoimmune pathway (Pons-Escoda et al., 2020).

2 METHODOLOGY

The present study is an integrative literature review. This research method allows for a broad and systematic synthesis of results acquired in experimental or non-experimental research, already carried out on a topic or issue, allowing reviewers to compile study findings without affecting their original idea (Soares et al., 2014).

The study was carried out based on searches in the LILACS and PubMed databases, through the Virtual Health Library. The descriptors available in DeCs were used: “Neuroradiology” and “Covid-19”. The guiding question of the research to be answered was: “What are the main findings in neuroradiology associated with Covid-19?”.

For its construction, six stages were used: I. Elaboration of the guiding question; II. Literature search; III. Data collect; IV. Evaluation of the studies found; V. Interpretation of results; SAW. Presentation of the review (Souza; Silva; Carvalho, 2010). Inclusion criteria were: articles found in the cited databases and
with abstracts/texts available in full. Published articles that were not available in full and that the subjects did not correspond to the subject of this work were excluded from the study.

The search was carried out by three researchers, analyzing the literature independently, after applying the inclusion and exclusion criteria. Subsequently, the chosen articles were observed and those that presented divergence were included in the development of this integrative review.

Figure 1 – Methodology for selection of articles.

Source: Authors (2023).

3 EVALUATION OF NEUROIMAGING IN COVID-19 CASES

At the beginning of the pandemic, very little was known about the multisystem involvement of the new coronavirus, mainly at the level of nervous tissue, however, many scientists worldwide reported the appearance of various brain lesions in patients with Covid-19, with no change at first. Typical for this disease, but complications, especially for the group of people with other associated chronic diseases (Noh, 2020; Martinez-Barbero et al., 2020; Morbelli et al., 2020; Fischer et al., 2020; Goldberg, 2020; Goh et al., 2020; Toledano-Massiah et al., 2020).

In cases where it is impossible to collect tissue for histopathological study, as well as in cases of in vivo patients, it is extremely important to use virtual tools, such as magnetic resonance imaging, to predict histological changes,
corroborated with research on bodies postmortem, at the level of the olfactory bulb, where there was the presence of vascular lesions and changes in the integrity of the blood-brain barrier (Aragão et al., 2021).

A study carried out in two diagnostic imaging units, using computed tomography (CT) and magnetic resonance imaging (MRI), evaluated the association between clinical, radiological and neurological aspects of the symptoms of patients with Covid-19. Most patients had only undergone CT of the chest, with fewer of them investigating neurological symptoms through CT or MRI of the skull. Among these symptoms, the most prevalent ones were headaches, convulsions, disorientation, which corroborated the imaging lesions suggestive of bleeding and microbleeding in the region close to the olfactory bulb (Aragão et al., 2021).

Aragão et al. (2020) has evaluated the radiological findings, through magnetic resonance imaging of the olfactory bulb, of five patients diagnosed with Covid-19 and clinical complaint of anosmia (total or partial), in addition to fever, headache and cough. They observed that microvascular mechanisms, involving microbleeding or damage to the blood-brain barrier, may be involved in the pathophysiology of this disease.

Through the evaluation of magnetic resonance, few and not severe alterations of the olfactory bulb were found, suggesting that SARS-CoV-2 invades the brain through the olfactory pathway and causes a dysfunction of sensorineural origin. However, such studies indicate that some neuroimaging changes may be limited to the initial phase of the infection. Thus, anosmia, a manifestation related to neurological changes in Covid-19, should be considered for the identification and isolation of patients, preventing the spread of the disease (Polini et al., 2020).

Hernández-Fernández et al. (2020) evaluated patients diagnosed with Covid-19 admitted to a hospital over 50 days. There were 1683 admissions, of which 23 (1.4%) developed cerebrovascular disease, with a poor and lethal prognosis for the group. The patients underwent imaging, histopathological (brain biopsies) and laboratory tests, where a characteristic radiological pattern of
subarachnoid hemorrhage, parieto-occipital leukoencephalopathy, microbleeds and single or multiple focal hematomas were identified. Brain biopsies performed showed signs of thrombotic microangiopathy and endothelial damage, with no evidence of vasculitis or necrotizing encephalitis. Ferritin was increased during stroke episodes.

The utilization of images for diagnosis and treatment of several diseases has been applied in order to allow a more accurate diagnosis, rather than more invasive procedures. In this sense, both CT (computed tomography) and MRI (magnetic resonance imaging) are being used, especially in the post-COVID era, in order to screen and identify diseases, following well-defined protocols, assessing risk and benefit, as in the cases of evaluations of fetal malformations and use of MRI (Rajagopalan et al., 2021).

The use of PET scan was evaluated in a research with radiolabels of the main neurotransmitters, such as GABA and Glutamate, since hACE 2 type receptors are abundant in glutamatergic cells, and can be used to locate damage in specific areas, changes in neurotransmission and of metabolic parameters. The fluorine glycoside analogue (FDG) is the most used radiolabel, its hypometabolism may be an indication of metabolic dysfunction in the brain of a patient with Covid-19, in areas such as the prefrontal cortex. Furthermore, oxygen markers can also be used to detect hypoxia. Despite the high cost of the test, its use in more severe cases of the disease, along with markers of neurological and metabolic function, can help to identify pathological characteristics of neurodegenerative disorders with greater precision (Fontana et al., 2020).

A study corroborated the appearance of clinical neurological manifestations in patients hospitalized with Covid-19 and with comorbidities. Ischemic and hemorrhagic vascular events such as ischemic strokes, intraparenchymal hemorrhages, microhemorrhages, subarachnoid hemorrhage, dural sinus thrombosis and posterior reversible encephalopathy syndrome have been observed on CT, MRI, MRA and angiographic computed tomography (CTA) of the brain, with the presence of comorbidities arterial hypertension and diabetes mellitus (Scullen et al., 2020; Klironomos et al., 2020; Reinaux et al., 2022).
In addition to the vascular effects, the presence of encephalitis has also been reported in several studies. The MRIs of the brain showed, in greater quantity, hypersignal in the white matter regions, followed by the temporal lobe and thalamus. On CT, the presence of white matter hypodensity and hemorrhagic foci were common. These tests were performed on patients who had a history of altered level of consciousness, seizures, psychiatric symptoms, headache, myalgia, asthenia and myoclonus (Mawhinney et al., 2020; Scullen et al., 2020; Koupaei et al., 2022).

4 ACUTE EFFECTS OF COVID-19 ON NEUROIMAGING

Jegatheeswaran et al. (2022) analyzed brain images, mostly acquired by MRI, of patients admitted with Covid-19 in a tertiary hospital. The main alterations found were microhemorrhages (58.8%), acute ischemia (52.9%), SWI abnormalities (23.5%) and asymmetric sulcal effacement suggesting possible focal encephalitis (5.8%).

Sadok and Oliveira (2022) described a calcifying lesion in CT of the brain, from a patient with Covid-19, unvaccinated, investigating seizures. This alteration, known as the rare Fahr syndrome, may have been a diagnostic finding during the patient's neurological evaluation.

A retrospective study evaluated CT and MRI brain images of 242 patients diagnosed with infection by the new coronavirus and neurological symptoms, pointing to the presence of nonspecific microangiopathy of the white matter and chronic infarction, with a lower relation to the presence of acute or subacute ischemic infarction and acute hemorrhage; such findings demonstrate that neuroimaging alterations may not be present early on at acute Covid-19 infections (Radmanesh et al., 2020).

Despite the performance of neurological imaging tests being linked to the need to investigate complications in patients already diagnosed with Covid-19, some patients were diagnosed with the viral infection, after pulmonary findings typical for this virus and specific tests, in a screening by trauma, in New York (Jain et al., 2020; Smith et al., 2020), demonstrating that there was no presence
of specific signs and symptoms, such as cough, fever and asthenia, with the presence of syncope and falls from standing height, trauma investigation and the accidental discovery of SARS-CoV-2 infection.

In New York, at the height of the first peak of the pandemic, 3556 hospitalized patients diagnosed with Covid-19 infection underwent imaging tests for neurological investigation. Out of these, 32 patients (0.9%) had a proven ischemic stroke, possibly due to dysfunction of blood coagulability, associated with higher mortality (Yaghi et al., 2020).

Rare neuroimaging findings have been described in the literature, among them the presence of alterations suggestive of acute necrotizing encephalopathy, through thalamic changes and cerebral neutrophilia, confirmed by biopsy and the presence of small vessel vasculitis, hemorrhages and necrosis (Rettenmaier et al., 2021).

Review studies have demonstrated the effects of the new coronavirus on the central and peripheral nervous system, in addition to the neuro-ophthalmic system, evaluated through neuroradiological findings, such as: eye fundus nodules, papilledema, cerebral pseudotumor syndrome, optic neuritis, acute disseminated encephalomyelitis, vascular injury with thromboembolism and infarction, leukoencephalopathy, hypoxic gray matter injury, hemorrhage, infectious meningitis/encephalitis, acute necrotizing hemorrhagic encephalopathy, cranial neuropathy, Guillain-Barré and Miller Fisher syndromes, nystagmus and other eye movement abnormalities (Langley et al., 2020; Marsiglia; Chwalizs; Maher, 2021).

Brain damage can be well evaluated using radiological images acquired through CT and MRI, corroborating the clinical signs and symptoms. At an acute form, vascular alterations, bleeding and axonal/glial necrosis are found, perceived by signs of hyperdensity. These are also present in chronic cases, mainly changes suggestive of leukoencephalitis and leukoencephalomalacia, once again bringing the suggestion of vascular impairment (vasculitis), autoimmune/inflammatory action and others, arising from Covid-19 (Lang et al., 2021; Lersy et al., 2021).
Certain inflammatory endothelial factors predispose patients with SARS-CoV-2 infection to cerebrovascular disorders, corroborated by exams such as brain MRI and CT, which show hemorrhagic lesions, arterial constriction, areas of ischemia and hyperdensity. Despite the above, further investigation is still needed so that the details of the correlations of these diseases can be listed (Arandela et al., 2021).

In view of the publications related to the neurological involvement of patients affected by Covid-19, there are signs and symptoms such as: anosmia, encephalopathy, ischemia, seizures, hemorrhages, myositis and involvement of several cranial nerves, associated with an increased risk of death for these patients. patients, among other manifestations of an inflammatory nature (Agarwal et al., 2020; Choi et al., 2020; Jain et al., 2020; Katz et al., 2020; Valdes et al., 2020; Deeb et al., 2021).

Neuroimaging findings are varied, affecting frontal, parietal, temporal and occipital lobes, demonstrated by signs of hyperdensity, associated with edema and restriction of blood flow or hemorrhages. Description of alterations in microstructures, mainly at the metabolic level, have also been described in the hippocampus and in the olfactory bulb (Sharifian-Dorche et al., 2020; Samkaria & Mandal, 2021).

As the neuroimaging findings are correlated, it is noted the presence of alterations in the level of consciousness, neurological deficit, syncope and laboratory blood tests, such as C-reactive protein, D-dimer level and lymphocyte count, showing an increase in prothrombotic events is observed. in patients with Covid-19 compared to the control group (Avci et al., 2020; Dhillon et al., 2020; Nicholson et al., 2020; Kavak et al., 2021). In addition to these severity factors, the length of stay and the need for invasive procedures to maintain life demonstrate a positive correlation with the presence of changes in neuroimaging in patients with SARS-Cov-2 infection (Abenza-Abildúa et al., 2020; Yonn et al., 2020).
5 LONG-TERM EFFECTS OF COVID-19 ON NEUROIMAGING

Lersy et al. (2022) evaluated the brain images, through MRI and FDG-PET/CT, of 31 patients who had COVID-19 and neurological symptoms. Examinations of the acute phase, 3 and 6 months after the viral condition were analyzed. Signs of leptomeningeal enhancement, microhemorrhages, ischemic strokes, thickening of the arterial walls (cerebral vasculitis) and demyelinating lesions were found in the exams of the acute period, which progressed with stabilization in most cases. In the angiographic evaluation, by magnetic resonance imaging (MRA), there was an improvement in cerebral perfusion; neurocognitive assessment was also performed, demonstrating that there were no serious sequelae in this area, but only poor performance.

The changes in radiological images can persist at the central nervous system level for a long period, as was brought about by Grach et al. (2022), in the case report of a patient with Post-Covid-19 Syndrome. In this case, 9 months after the initial infection, areas with hypometabolism in the frontal, occipital and parietal regions were observed on PET scan.

Several studies have been carried out in the field of neurology, neuroimaging and Covid-19, relating acute and chronic events. In this context, a certain heterogeneity was observed both in the neurological signs and symptoms and in the images obtained from the patients. MRI and CT analyzes demonstrated the presence, in the early days of SARS-Cov-2 infection, of microbleeding, ischemia and other vascular events. In the long term, patients report symptoms in the cognitive area, headache and others, but brain images are within normal limits, serving as a basis for ruling out other diseases (Kuumar et al., 2020; Kremer et al., 2022).

A neuroimaging analysis sought to understand the changes that occurred in the cortex after recovery from Covid-19. The study demonstrated that the most severe version of the disease showed changes in both white matter composition and cerebral blood flow, with changes in the left hemisphere: in the insula, hippocampus and superior temporal gyrus, indicating the vulnerability of the limbic system to SARS-CoV -two. The milder infection, despite the risks of
developing sequelae, had similar results to the control, which draws attention to the consequences in vulnerable groups of the severe form of the disease, since it has an inflammatory storm in the brain as an indirect factor, which makes follow-up by neuroradiological exams is essential in the recovery of patients (Edlow et al., 2020; Qin et al., 2021)

Studies with patients with different types of cancer and positive for infection by the new coronavirus found a correlation with the presence of cytokines in the cerebrospinal fluid. RT-PCR (reverse transcriptase reaction followed by polymerase chain reaction test) for SARS-CoV-2 in the fluid was negative, however with the accumulation of inflammatory mediators, which can persist for months after the convalescence of the respiratory symptoms factors, suggesting a risk for the onset of neurological complications even in the absence of more obvious neuroradiological signs (Remsik et al., 2021).

In view of this, additional neurological evaluation has become extremely important, corroborating the use of tomographic or magnetic resonance images and the presence of signs and symptoms. Neuroimaging findings are varied and often indicate underlying vascular and inflammatory changes, some situations bring rarer complications that deserve detailed attention (Serrano-Serrano et al., 2020).
Figure 2 – Relationship between neuroradiology and Covid-19.

**Neuroradiology and COVID-19**

**Physiopathology**
- Direct
  - Hematogenic
  - Olfactory
- Indirect
  - Proinflammatory
  - Autoimmune

**Neuroradiological Alterations**
- Ischemic strokes
- Microbleeds
- Encephalitis
- Haematomas
- Blood-brain barrier disruption

**Symptoms**
- Disorientation
- Seizures
- Anosmia
- Encephalopathy
- Headache

**Signs and Symptoms of Severity**

**Comorbidities**

**Neurological Complications**

CT, MRI of the Brain: Basic exams, "Gold" standard

Source: Authors (2023).
6 ASSOCIATION OF EFFECTS OF VACCINATION AND NEUROLOGICAL EVENTS IN COVID-19

With the prospect of worldwide vaccination against SARS-COV-2 as well as the increased scientific knowledge about the prevention and treatment of this disease, McKeigue et al. (2021) sought to verify the relationship between medical reports of cerebral venous thrombosis and vaccination against Covid-19. They noted that of the 50 Scottish patients evaluated by neuroimaging, 17 had thrombotic events in the post-vaccination period. However, this study alone, with a small number of participants, cannot be used to define the adverse effects, harms and/or benefits of these immunobiologicals.

Some cases of cerebral thrombotic events, paralysis of the facial nerve and myelitis in vaccinated patients, with the first dose of vaccine, in the last 8 days, were reported in 3 patients, in the study by Corrêa et al. (2021), evaluated with neuroimaging. It included brain and spinal MRI, combined with other complementary exams and clinical evolution. Despite these notes, longitudinal studies with the possible adverse effects of vaccines against Covid-19 are needed for a better definition of cost-effectiveness.

6.1 NEONATAL AND PEDIATRIC NEUROIMAGING IN COVID-19: INFLUENCE OF THE PRESENCE OF COMORBIDITIES

Many studies have been developed in order to evaluate the neurological system of adults and the elderly, considering that they are the part of the population most affected by Covid-19 and have the greatest suffering in instances of long-lasting Covid symptoms. However, the neonatal and pediatric public is also at risk from infection with the new coronavirus, especially the group with comorbidities, such as asthma, Down syndrome, diabetes, myopathies or other neurological diseases, which can develop serious forms, such as Multisystem Inflammatory Syndrome Pediatric (SIM-P) (WHO, 2022).

Martin et al. (2021) published a case study of a 9-day-old newborn with Covid-19. There were marks compatible with viral encephalitis in the developing brain, restrictive foci in the corpus callosum and in the periventricular area. The patient showed improvement of the disease, with normal development after 2
months of diagnosis and subsequent treatment. Notwithstanding this, it is important to note the risks related to neonatal infection with the new coronavirus and the use of neuroradiological images as a way to assist in the treatment.

A study carried out in Wuhan, with newborns infected in their first days of life, in the height of the pandemic in 2020, as the mothers tested positive for Covid-19 as of the time of delivery, had those infants evaluated during the 9 months after birth. The study was comparative, following the guidelines of the Declaration of Helsinki and used another uninfected group for evaluation. In the cognitive points system, the group infected with the new coronavirus had a lower average grade compared to control, but still within the range considered normal. In the T2 CT scan, the most affected areas were the precuneus, the parahippocampal gyrus and the caudal nucleus, with a decrease in gray matter. Thus, it is important to be alert to the possible decrease in volume in these regions in newborns and their possible cognitive impacts (Yan et al., 2021).

Neurological findings on brain MRI of children with multisystem inflammatory syndrome and SARS-COV-2 were rare compared with changes in other organ systems (Ucan et al., 2022).

An evaluation of 38 children living in 10 different countries, including Brazil, sought to establish a relationship between severe neurological findings and childhood infection with SARS-CoV-2. The most common imaging pattern was severe post-infection disseminated encephalomyelitis in 16 patients, in addition to myelitis (8 patients) and neuritis (12 patients). Although neurological complications in children were less common compared to adults, they can be fatal, as in 4 cases that had no previous comorbidities. The infection causes a breakdown of the blood-brain barrier, in the choroid plexus, this mechanism facilitates the entry of other microorganisms, vasculitis and micro-bleeding. Multisystem inflammatory syndrome (MIS-C) was present in just under a third of patients (Lindan et al., 2021).

7 CONCLUSION

Several studies have demonstrated the importance and variety of neuroimaging findings in patients with Covid-19, most of which point to alterations
related to hemorrhagic, inflammatory and prothrombotic events, with some rare exceptions, bringing an increased risk of death for those with greater damage. Neurological, laboratory, unfavorable clinic, length of stay, presence of comorbidities and invasive procedures.

Infection with SARS-CoV-2 brought a typical pattern of changes in adults and the elderly, but special interest and investigation needs to be given to the neonatal and pediatric range, due to the inherent risks of the disease, development of systemic inflammatory syndromes and reported deaths.

The acquired knowledge of patterns in imaging of the central nervous system of patients with Covid-19 supports both early and long-term diagnosis, clinical/surgical treatment, as well as recovery and rehabilitation.
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