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REVIEW

A case-based systematic review on the SARS-COVID-2-associated cerebrovascular diseases and the possible virus routes of entry

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) sparked a global pandemic that continues to affect various facets of human existence. Many sources reported virus-induced acute cerebrovascular disorders. Systematically, this paper reviews the case studies of COVID-19-related acute cerebrovascular diseases such as ischaemic stroke, intracerebral hemorrhage, and cerebral sinus thrombosis. We also spoke about how SARS-CoV-2 can infect the brain and trigger the aforementioned disorders. We stated that SARS-CoV-2 neuroinvasion and BBB dysfunction could cause the observed disorders; however, further research is required to specify the mechanisms and pathogenesis of the virus.

Keywords COVID-19 · Intracranial hemorrhage · Cerebrovascular · Ischemic stroke · Cerebral venous sinus thrombosis

Introduction

Coronaviruses (CoVs) are enveloped, single-stranded RNA viruses that belong to the Coronavirinae subfamily of the Coronavirdiae family of the Nidovirales order (Halaji et al. 2020). The nucleocapsid of the virion is made up of genomic RNA and phosphorylated nucleocapsid (N) protein. It is buried between phospholipid bilayers and protected by spike proteins; the membrane (M) protein (a type III transmembrane glycoprotein) and the envelope (E) protein of the virus envelope are found among the spike (S) proteins. This virus is named corona because of its crown-like look (Li et al. 2020a, b; Mohammadpour et al. 2021). The COVID-19, with more than 127 million cases and 2.7 million deaths, caused a worldwide pandemic. It had many devastating effects on different aspects of human life worldwide (Heiat et al. 2021; Mirzaie et al. 2020).

Although SARS-CoV-2 mainly causes acute respiratory distress syndrome (ARDS), it has also been reported to be a neuroinvasive agent (Achar and Ghosh 2020; Allahyari et al. 2021; Mirzaei et al. 2020). In a retrospective sample of COVID-19 patients from Wuhan, China, neurological signs were seen in 36.4% of overall patients and 45.5% of patients with severe infections (Mao et al. 2020). Cerebrovascular disease is defined as a condition in which a part of the brain is damaged briefly or fatally due to ischemia or bleeding. Acute cerebrovascular disorders are among the most frequent comorbidities in COVID-19 patients (Aghamollaei et al. 2021; Mirzaei et al. 2020; Wang et al. 2020).

In this systematic review, we focused on the reported cases of acute cerebrovascular disorders diagnosed with COVID-19. We also discussed the possible mechanisms of entry of the virus regarding cerebrovascular disorders.

Methods

A systematic literature search including articles published from January 1, 2020, to April 15, 2021, was performed on PubMed using different combinations of the following search terms: "COVID-19," "Coronavirus," "Sars-Cov-2," and "ischemic stroke," "cerebrovascular," "intracranial hemorrhage," "intracranial bleeding," "subarachnoid hemorrhage," "intracerebral hemorrhage," and "cerebral venous sinus thrombosis." The PubMed was searched as follow:

"(((((((COVID-19 Coronavirus Sars-Cov-2) AND (ischemic stroke)) OR ((COVID-19 Coronavirus Sars-Cov-2) AND (cerebrovascular))) OR ((COVID-19

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Coronavirus Sars-Cov-2) AND (intracranial hemorrhage))) OR ((COVID-19 Coronavirus Sars-Cov-2) AND (intracranial bleeding))) OR ((COVID-19 Coronavirus Sars-Cov-2) AND (subarachnoid hemorrhage))) OR ((COVID-19 Coronavirus Sars-Cov-2) AND (intracerebral hemorrhage))) OR ((COVID-19 Coronavirus Sars-Cov-2) AND (cerebral venous sinus thrombosis))."

Only articles published in English were reviewed. The articles reporting case data on stroke mechanism and etiology, sex, age, past cardiovascular risk factors, COVID symptoms, admission National Institutes of Health Stroke (NIHSS) score, D-dimer levels, and acute stroke treatment were selected for the review and those without the clinical description of the cases were excluded. Afterwards, the collected articles were reviewed, and relevant articles were used for data extraction. Two authors independently searched and reviewed the titles, abstracts, and keywords of collected papers and resolved the issue in case of uncertainty and disagreement before continuing to the next step. All the procedures of literature search, article selection, and data synthesis were performed according to the PRISMA checklist 2009, which is a known and standard protocol for reporting systematic reviews (Liberati et al. 2009). IBM SPSS Statistics for Windows version 10.0 (IBM, Armonk, NY, USA) were used for statistical analysis of the data. The results are reported as the mean ± SD.

Results

The study selection pathway is shown in Fig. 1. Five hundred eighty-four articles were excluded from a total of 733 articles published from January 1, 2020, to April 15, 2020, because they either were not in English or did not report a clinical case. Due to the lack of relevant titles or abstracts, 52 articles were excluded from the remaining 149. From the remaining articles, 25 were excluded because although they were related to COVID-19 and cerebrovascular diseases, case descriptions of ischemic stroke (IS), intracranial bleeding, or CVST, and individual clinical data were not reported. The remaining 71 articles (127 patients) that satisfied the criteria mentioned above were included in this review. In this review, 80 cases of patients developed IS during COVID-19 infection (Aasfara et al. 2021; Abdulkadir et al. 2020; Agarwal et al. 2020; Al-Mufti et al. 2021; Al Saiegh et al. 2020; Appavu et al. 2021; Ashraf and Sajed 2020; Avula et al. 2020; Bessa et al. 2020; Bigliardi et al. 2020; Burkert and Patil 2020; Co et al. 2020; Dakay et al. 2020a, b; de Almeida Lima et al. 2020; de Lorenzo Alvarez et al. 2021; Deliwala et al. 2020; Dumitrascu et al. 2020; Efendizade et al. 2020; El Nahas et al. 2020; Elshereye and Erdinc 2020; Eskandarani

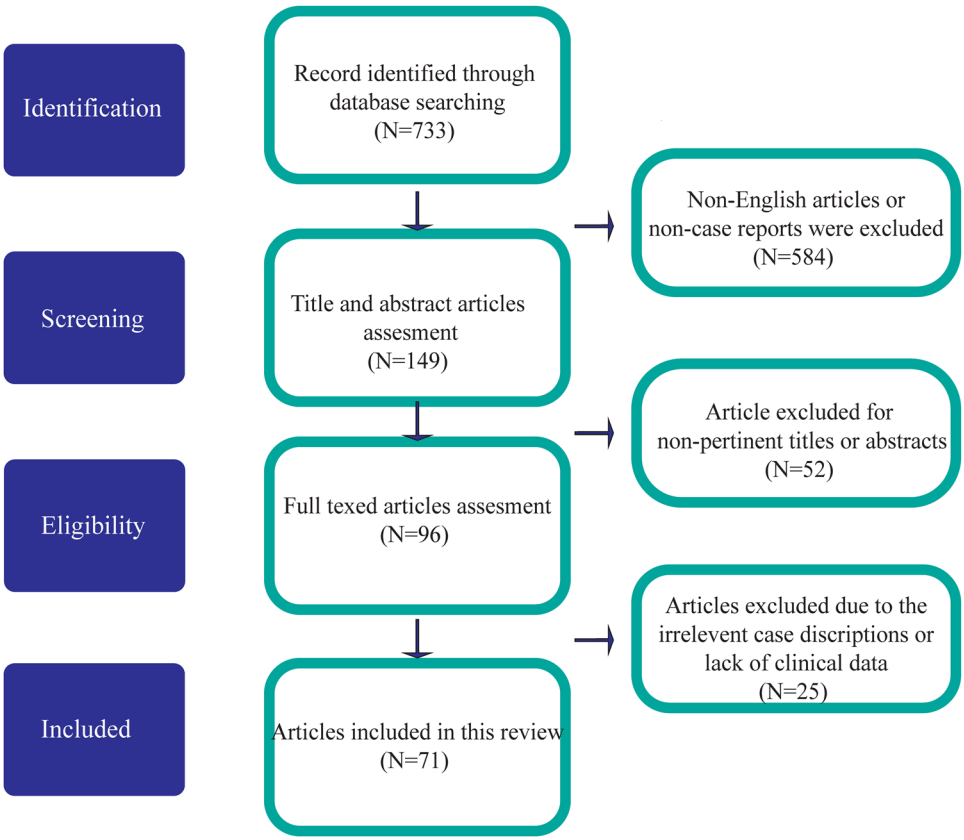

Fig. 1 Study selection pathway

et al. 2021; Fu et al. 2021; Garg et al., 2020; Gemcioglu et al. 2020; Goette et al. 2020; Goldberg et al. 2020; Guillan et al. 2020; Iqbal et al. 2021; Kwon et al. 2020; Mahboob et al. 2020; Mansour et al. 2020; Mirzaee et al. 2020; Morassi et al. 2020; Mowla et al. 2020; Patel et al. 2020a, b; Patel et al. 2020a, b; Prasad et al. 2021; Priftis et al. 2020; Rajdev et al. 2020; Rascón-Ramírez et al. 2020; Roy et al. 2021; Valderrama et al. 2020; Viguier et al. 2020; Zhai et al. 2020), 32 cases developed intracranial hemorrhage (Ahmad et al. 2021; Al-Mufti et al. 2021; Al Saiegh et al. 2020; Carroll and Lewis 2021; Cezar-Junior et al. 2020; Dakay et al. 2020a, b; Dakay et al. 2020a, b; Fayed et al. 2020; Flores et al. 2020; Ghani et al. 2020; Haider et al. 2020; Heman-Ackah et al. 2020; Krzystanek et al. 2021; Morassi et al. 2020; Motoie et al. 2020; Mousa-Ibrahim et al. 2021; Rajdev et al. 2020; Savić et al. 2020; Thibodeau et al. 2021; Thu et al. 2020; Zahid et al. 2020), and 15 cases CVST (Bolaji et al. 2020; Cardoso et al. 2021; Dakay et al. 2021; Guendouz et al. 2021; Haroon et al. 2020; Kaur et al. 2021; Khazaei et al. 2021; Nwajei et al. 2020).

Types of studies

Only case reports and case series were included.

Ischemic stroke

Eighty patients with IS were reported (Table 1), among which 65% were male. The average age was 59 years old. Eighty percent of patients (64 patients) reported having a history of vascular risk factors. The most significant past medical histories were hypertension (43 patients, 53.09%) and diabetes mellitus (22 patients, 27.5%). Ten patients (12.5%) had a previous stroke or transient ischemic attack (TIA). The symptoms of COVID-19 were reported in 54 patients (67.5%); 41 (51.25%) had cough, 39(48.75%) had fever, and 24 (30%) had dyspnea. The NIHSS score was reported in 44 cases (55%), with an average of 11.53 and a range of 2 ± 36. In 37 patients (46.25%), D-dimer has been reported with a mean value of 13,277 [± 57,927] ng/mL (range 300–350,000). Ferritin level was reported in 26 patients (32.5%) with a mean value of 1235 ± 2251 ng/mL. In 35 patients (43.75%), the WBC count was reported (mean: 9320 ± 3750/mm^3; range: 200–18,900). Platelet count reported in 38 cases (47.5%; mean: 244,29 ± 115,62/mm3; range: 9000– 569,000). The level of C-reactive protein (CRP) has been reported in 58 (72.5%) patients (mean: 246.9 ± 459.00 mg/L; range: 0.1–2200). The short-term outcomes have been reported in 64 patients (80%); the results showed that 28 patients (35%) survived ad discharged from the hospital, ten patients (12.5%) were critically ill and stayed in the intensive unit care ICU, and 25 patients (3125%) were expired.

Table 1 Characteristics of ischemic stroke–associated COVID-19 patients

Patient characteristics	Values No.–%; mean [± SD]; (range)
Age (years)	59.21 ± [16.80]; (8–88)
Sex	35% female
Cardiovascular risk factors	80%
Arterial hypertension	53.75%
Diabetes mellitus	27.50%
Hyperlipidemia	12.50%
Atrial fibrillation	5%
Coronary artery disease	17.50%
Smoking	10%
Obesity	6.25%
Previous stroke or TIA	12.50%
NIHSS	11.52 ± [6.29]; (2–36)
COVID-19 symptoms	67.50%
Fever	48.75%
Cough	51.25%
Dyspnea	30%
Vomiting and diarrhea	13.75%
Body aches or myalgias	12.50%
D-Dimer (ng/mL)	13,276.69 ± [57,926.9]; (300–350,000)
Ferritin (ng/mL)	1234.64 ± [2251.2]; (0.113–10,576)
WBC counts (10^3/μL)	9.32 ± [3.8]; (0.2–18.89)
Platelet count (10^3/μL)	244.29 ± [115.6]; (9–569)
CRP (mg/L)	246.90 ± [459]; (0.1–2200)
Short-term outcome	80%
Survival	35%
critically ill	12.50%
Death	31.25%

Intracerebral hemorrhage

Thirty-five cases of acute Intracerebral hemorrhage associated with COVID-19 have been reported (Table 2). Among these cases, 20 patients (62.5%) had an intracerebral hemorrhage (ICH), ten patients (11.43%) had subarachnoid hemorrhage (SAH), and two patients (6.27%) had both SAH and ICH. Eighteen patients (56.52%) were male, and 14 patients (43.75%) were female. The average age of the patients was 55.56 ± 16.32 years. Twenty-six patients (81.25%) had a history of cardiovascular risk factors. The most common risk factors were arterial hypertension (16 patients, 50%), diabetes mellitus (6 patients, 18.75%), and obesity (6 patients, 18.75%).

Table 2 Characteristics of intracranial hemorrhage–associated COVID-19 patients

Patient characteristics	Values No.–%; mean [± SD]; (range)
Age (years)	55.56 ± [16.3]; (13–82)
Sex	56.25% female
Cardiovascular risk factors	81.25%
Arterial hypertension	50%
Diabetes mellitus	18.75%
Hyperlipidemia	9.38%
Atrial fibrillation	3.13%
Coronary artery disease	6.25%
Smoking	3.13%
Obesity	18.75%
Type of intracranial bleeding	100%
ICH	62.50%
SAH	31.25%
SAH + ICH	6.25%
COVID-19 symptoms	81.25%
Fever	50%
Cough	46.88%
Dyspnea	50%
Vomiting and diarrhea	6.25%
Body aches or myalgias	18.75%
D-Dimer (ng/mL)	4263.31 ± [5598.3]; (1040–19,720)
Ferritin (ng/mL)	3504 ± [3088.2]; (800–8530)
WBC counts (10^3/μL)	14.91 ± [10.6]; (5.7–43.1)
Platelet count (10^3/μL)	242.67 ± [133.8]; (131–539)
CRP (mg/L)	204.83 ± [262.1]; (4–1070.8)
Short-term outcome	87.50%
Survival	28.13%
Critically ill	6.25%
Death	53.13%

ICH neurology is characterized by changes consistent with consciousness with focal symptoms such as motor or sensory deficits, aphasia, and dysarthria in most patients.

The COVID-19 symptoms have been reported in 26 patients (81.25%); fever 16 (50%), dyspnea 16 (50%), and cough 15(46.88%) were the most common symptoms.

The D-dimer level was reported in 17 patients (53.13%) with an average of 4263.31 ± 5598.25 and a range of 1040–19,720, whereas the level the ferritin level was reported only in 5 patients (15.63%) with an average of 3504 ± 3088 ng/mL. WBC count was reported in 11 patients (34.4%) with an average of 14,910 ± 10,610/mm^3; a range of 5700–43,100. In addition, CRP levels were reported in 15 patients (46.88%) with an average of 204.83 ± 133.82 mg/L and a range of 4–1070.8. The platelet count was reported in 9 patients (28.13%) with an average of 242,670 ± 133,820/mm^3, and a platelet range of 131,000–539,000.

Table 3 Characteristics of cerebral venous sinus thrombosis–associated COVID-19 patients

Patient characteristics	Values No.–%; mean [± SD]; (range)
Age (years)	45.33 ± [19.4]; (17–79)
Sex	40% female
Cardiovascular risk factors	53.33%
None	20%
Arterial hypertension	13.33%
Diabetes mellitus	13.33%
Smoking	0%
Obesity	20%
COVID-19 symptoms	60%
Fever	46.67%
Cough	33.33%
Dyspnea	20%
Vomiting and diarrhea	20%
Body aches or myalgias	0%
Asymptomatic	6.67%
Sinus and vein involvement	86.67%
Transverse sinus	66.67%
Straight sinus	20%
Sigmoid sinus	33.33%
Vein of Galen	13.33%
Superior sagittal sinus	60%
Inferior sagittal sinus	6.67%
Internal cerebral veins	6.67%
Hemorrhagic transformation	33.33%
D-Dimer (ng/mL)	1091.77 ± [1558.4]; (2.41–4770)
Ferritin (ng/mL)	420.25 ± [356.3]; (24–812)
WBC counts (10^3/μL)	8.36 ± [4]; (4–15.7)
Platelet count (10^3/μL)	233.43 ± [106.1]; (113–425)
CRP (mg/L)	111.86 ± [177.3]; (.29–600)
Short-term outcome	100%
Survival	93.33%
Critically ill	6.67%
Death	6.67%

The result of the short-term outcome of the 28 patients (87.5%) is as follows; 9 patients survived (28.13%), two remain critically ill (6.25%), and 19 patients were expired (53.13%).

Cerebral venous sinus thrombosis

Sixteen cases of CVST associated with COVID-19 were reported, 9 of them (60%) were males, 40% were female, the average age was 45.33 ± 19.40, and case age range was 17–79 years (Table 3) (28, 39, 122–130).

The cardiovascular risk factors have been reported for 8 cases (53.33%). Obesity in three patients (20%) was the

most common risk factor. The COVID-19 symptoms were reported for 9 patients (60%). The main symptoms were fever 7 (46.67%), cough 5 (33.33%), and dyspnea 3 (20%). In addition, one patient reported being asymptomatic. Headache and change in mental states with focal signs such as motor and sensory deficits, aphasia, impaired perception, and epilepsy were neurological manifestations of CVST in patients with COVID-19. Sinus and vein involvement was reported in 13 patients (86.67%). Transverse sinus with 10 (66.67%) reported cases and superior sagittal sinus with 9 reported cases (60%) were the most common sinus involvements. Besides, venous infarction with hemorrhagic transformation was reported in 5 patients (33.33%). The D-dimer level was reported in 9 cases (60%) with an average of 1091.8 ± 1558 ng/mL and a range of 2.41–4770 ng/mL. The Ferritin level was detailed in 4 patients (26.67%) with the mean value of 420.25 ± 356 ng/mL. The WBC count level was reported in 8 patients (53.33%) with an average of 8360 ± 4020/mm^3; also, the platelet count level was reported in 8 patients (53.33%) with an average of 233,430 ± 106,130/mm^3. The CPR level was reported in11 patients (73.33%) with an average of 111.86 ± 177 mg/L. The short-term outcome was available for all patients; 13 patients (93.33%) survived, one patient (6.67%) was critically ill, and one patient (6.67%) died.

The possible routes of entry

The entry route of a virus into the brain directly affects pathogenic pathways that trigger neurological symptoms. The entry route of SARS-CoV-2 into the brain is still unknown. However, based on the neurological symptoms of COVID-19, two potential routes may be proposed: transneuronal spread via the olfactory nerves and hematogenous spread after crossing the blood–brain barrier (BBB) (Achar and Ghosh 2020; Allahyari et al. 2021; Kumar et al. 2020).

The former can result in loss of smell and taste. In this case, SARS-CoV-2, which is found in the nasal endothelium, can attach to motor proteins and move with it along sensory and olfactory nerves to the brain (Briguglio et al. 2020; Eliezer et al. 2020). A retrospective analysis of 114 COVID-19 patients from the Nord Franche-Comté hospital declared that 47% of them had anosmia (Klopfenstein et al. 2020). The frequency of olfactory disorder ranges across nations, which differs from 33.9 to 68% (Meng et al. 2020). Brann et al. (2020) have discovered ACE2 expression in human olfactory epithelium sustentacular cells, horizontal basal cells, and Bowman's gland, which explains the anosmia associated with COVID-19 and can also be proof for the transneuronal spread via the olfactory nerves mechanism. On the other hand, cerebrovascular symptoms, such as stroke, appear when SARS-CoV-2 have been transmitted through the vascular system after respiratory tract inflammation (Baig 2020). In that case, SARS-CoV-2 can then circulate across the cerebral vascular system. However, to migrate to the brain, it needs to permeate into the blood–brain barrier (BBB) (Achar and Ghosh 2020; Hosseini et al. 2021). The BBB is a semi-permeable membrane that separates blood vessels from brain parenchyma and vascularizes the CNS. It specifically regulates which molecules are allowed to move through (Abbott 2002). Transcellular migration, paracellular migration, and the "Trojan horse" technique are the three major pathways through which a virus can cross the BBB (Fig. 2) (Dahm et al. 2016). Viruses infect host endothelial cells to cross the BBB through transcellular migration. Viruses penetrate close junctions created by BBB endothelial cells during paracellular migration (Robinson and Busl 2020). A virus is engulfed by phagocytic host cells such as neutrophils and macrophages during the Trojan horse technique. SARS-CoV-2 can use a single or a mixture of these mechanisms (Dahm et al. 2016). SARS-CoV-2 can use either ACE2 and associated viral entry receptors in vascular endothelium, blood cells such as dendritic cells and macrophages, or cytokine storm on the blood–brain barrier to cross the BBB (Kumar et al. 2020).

ACE2 receptor–based invasion

SARS-CoV-2 binds to a human cell surface receptor named angiotensin-converting enzyme 2 (ACE2) through the receptor-binding domain (RBD) of its spike (S) protein. Moreover, it appears that cleavage of the viral S protein by proteases such as transmembrane protease serine 2 (TMPRSS2) or cathepsin L (CTSL) is necessary to penetrate host cell membrane fusion and activate virus infectivity. ACE2 has been shown to co-express with TMPRSS2/CTSL in specific cell subsets through human tissue groups, including the brain (Lan et al. 2020; Zhu et al. 2013). If SARS-CoV-2 enters the cell, it starts replication in the cytoplasm. The genome is first transcribed by an RNA-dependent RNA polymerase unique to SARS-CoV-2. The resulting antigenome template is then transcribed to generate positive-strand RNA and mRNAs, which are then capped and polyadenylated to create peptides. Viral RNA is dispersed to adjacent cells via viral exocytosis. Hence, the expression of ACE2 and associated proteases such as TMPRSS2, CTSL, and FURIN on the host cell is necessary for the entry of SARS-CoV-2 (Shang et al. 2020). The broad distribution of ACE2 protein in neurons and cells near the lumen in human brain organoids has been observed previously. SARS-CoV-2 can invade brain organoids and can be prevented by utilizing ACE2 specific antibodies or by applying cerebrospinal fluid to a patient with COVID-19. Therefore, ACE2 is needed for brain organoid infection (Pavillet and Selvakumar 2020; Song et al. 2020). The presence of ACE2 and related proteases in the vascular

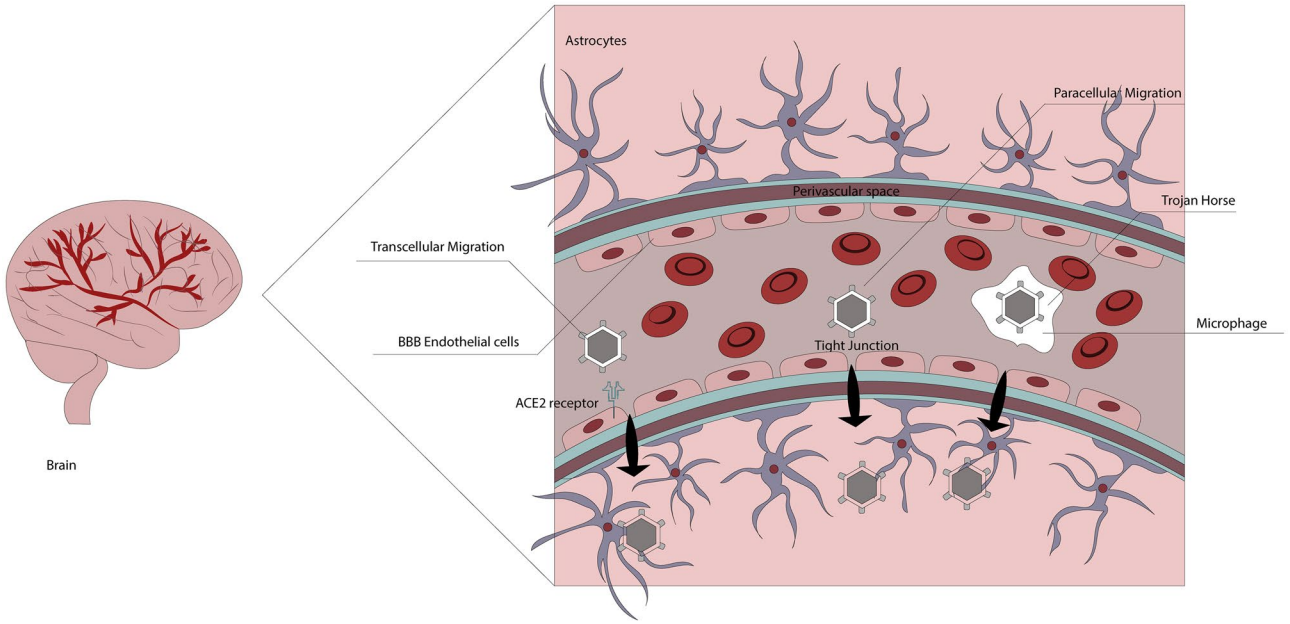

Fig. 2 (SARS-CoV-2) hematogenic pathway to the central nervous system (CNS). On this route, SARS-CoV-2, by three strategies, including transcellular

endothelium as well as concrete signs of SARS-CoV-2 invasion suggests that the hematogenous passage to the brain seems plausible (Sungnak et al. 2020; Ziegler et al. 2020).

Cytokine storm

Cytokines are glycosylated polypeptides that play an immunomodulatory role in immune responses. In the late stages of the infection, neurological effects can also occur due to the cytokine storm's indirect chemical impact (Allan and Rothwell 2001; Mehta et al. 2020). Pro-inflammatory cytokines promote activation of the immune cells at the site of infection, which brings leukocytes to the infection, helping the immune system respond by producing higher levels of inflammation (Zhang and An 2007). Nevertheless, infection by SARS-2 frequently causes overexpression of cytokines called a "cytokine storm," which results in the overactivation of the inflammatory response (Wong et al. 2004). TNF-α, IFN-γ, IL-2, IL-4, IL-6, IL-8, and IL-10 levels, for example, were shown to be higher in COVID-19 patients. In addition, patients with severe COVID-19 have been shown to have elevated levels of pro-inflammatory cytokines compared to the patients with non-severe COVID-19 (Han et al. 2020; Qin et al. 2020). This "cytokine storm" may also cause the BBB to become permeable, making viral entry via the hematogenous route easier. For instance, IL-6 has been shown to play a major role in the immune dysregulation of COVID-19 patients (Mandel et al. 2020). Besides, in vitro study of IL-6 also showed the reduction of interendothelial adherens and tight junction proteins, resulting in increased paracellular permeability in human brain microvascular endothelial cells (Rochfort et al. 2014). On the other hand, anti-IL-6 neutralizing antibodies have been found to decrease BBB permeability caused by ischemia, indicating that IL-6 may play a role in BBB malfunction in disorders including ischaemic injury in the ovine fetus (Zhang et al. 2015). In addition to IL-6, patients with COVID-19-associated neurological signs were shown to have higher amounts of IL-8 in their cerebrospinal fluid (Benameur et al. 2020). Endothelial cells and microglia in the CNS produce IL-8, which plays an integral role in leukocyte extravasation into the BBB (Ehrlich et al. 1998). Thus, the sudden production of pro-inflammatory cytokines during the cytokine storm raises the level of immune responses. However, a cytokine storm can stimulate the inflammatory response and disrupt the BBB (Daneman and Prat 2015). As a result, the function of endothelial cells, pericytes, and astrocytes to inhibit immune cells from infiltrating the brain is compromised. According to reports, the resultant neuroinflammatory reaction may cause severe brain harm. It may also trigger clotting of the cerebral vasculature, which may cause stroke-like symptoms (Mizuguchi et al. 2007; Varatharaj and Galea 2017).

Discussion

Stroke can result from acute and chronic infection (Grau et al. 2010). Acute ischemic stroke is a sudden lack of blood supply to a region of the brain, culminating in a loss of neurologic functionality. It is triggered by thrombosis

or embolism, which obstructs a cerebral artery that supplies a particular region of the brain (González et al. 2011). In accordance with our study, one of the most frequent acute cerebrovascular diseases seen in COVID-19 populations is stroke. Ischemic stroke occurs at a rate of 5.7% (Li et al. 2020a, b). Li et al. (2020b) reported 4.6% of 219 COVID-19 patients with acute ischemic stroke were more than one-third of hospitalized patients. Hassett and Frontera (2021) also reported a stroke rate of 1–2% in hospitalized COVID19 patients of 17 healthcare networks from four countries. Based on the initial reports from Wuhan, patients with COVID-19-associated stroke tend to be older, have a severe infection, and have cardiovascular risk factors, like diabetes, hypertension, and stroke history (Li et al. 2020a, b). Other available data, on the other hand, also confirmed the prevalence of stroke in younger patients (> 50 y/o) with no vascular risk factors (Fifi and Mocco 2020).

The intracerebral hemorrhage caused by COVID-19 infection is less frequent than ischemic stroke, with confirmed incidence rates ranging between 0.2 and 0.4% (Hassett and Frontera 2021). However, the fatal rate for hospitalized patients with COVID-19-associated intracerebral hemorrhage was over 50% [6]. The ICHs associated with COVID-19 seem to be more intraparenchymal with lobar location and multicompartmental; they also have multiple foci; there are few reported cases of nonaneurysmal subarachnoid hemorrhage (Kirschenbaum et al. 2020).

The development of a blood clot in the dural venous sinuses, which withdraws blood from the brain, is known as cerebral venous sinus thrombosis (CSVT) (Agrawal et al. 2016). CSVT-associated COVID-19 is also less frequent than acute ischemic and hemorrhagic stroke. Also, the patients with CSVT seem to have fewer medical past history; in one study by Tu et al. (2020), almost 60% of patients had no significant prior medical problems.

Conclusions

The recent reports of a severe epidemic COVID-19 have demonstrated that COVID-19-associated acute cerebrovascular disorders pose a risk to patients' lives. The most common causes of COVID-19-associated cerebrovascular disorders are acute ischemic stroke, followed by intracerebral hemorrhage, and cerebral sinus thrombosis. Based on the current evidence, a hematogenous route of viral brain entry, which can cross the BBB, and justify cerebrovascular symptoms, is entirely plausible for COVID-19. Also, there are other causes, such as cytokine storm, that can induce neuroinflammation, and result in the COVID-19 neurological symptoms. Thus, identifying COVID-19-associated acute cerebrovascular diseases as a possibly lethal organ failure, as well as its mode of action and entry route, is crucial for early empirical treatment to rescue critically sick COVID-19 patients. However, there is little conclusive evidence of SARS-CoV-2 unique neuropathogenic. Further research is required to obtain a better insight into its pathogenesis, laboratory diagnosis, and treatment.

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Data availability Data will be made available upon request.

Declarations

Conflict of interest The authors declare no competing interests.

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