Subarachnoid Hemorrhage in Patients with SARS-CoV-2 Infection

Subjects: Neurosciences

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Subarachnoid hemorrhage (SAH) is a life-threatening condition associated with high mortality and substantial long-term morbidity. The SARS-CoV-2 virus is a new pathogen that causes a disease with variable clinical manifestations. Although the Coronavirus disease 2019 (COVID-19) is associated with hypercoagulopathy, patients may also present with cerebral hemorrhage, including SAH.

Keywords: subarachnoid hemorrhage ; SARS-CoV-2 ; COVID-19

1. Introduction

Subarachnoid hemorrhage (SAH) is a life-threatening condition resulting from the accumulation of blood between the arachnoid and the pia mater membranes. Acute bleeding into the subarachnoid space can be because of several causes. The most frequent bleeding cause is the nontraumatic spontaneous SAH. The majority of primary SAH is due to the rupture of an intracerebral aneurysm in adults or cerebral arteriovenous malformation in children. However, in adults, the patients with primary SAH may present with no evidence of cerebral aneurism or other vascular malformations (non-aneurysmal SAH) in about 10% of cases (perimesencephalic and other angiogram-negative SAH) [1][2][3][4].

The secondary SAH etiologies include trauma, the reversible cerebral vasoconstriction syndrome, posterior reversible encephalopathy syndrome (PRES), cerebral amyloid angiopathy, cerebral vasculitis, cerebral venous sinus thrombosis, coagulopathies, tumors, drugs, septic emboli from endocarditis, or iatrogenic causes [1][2].

Although SAH is a rare cause of stroke, accounting for 1–6% of all strokes [5], the patients present high mortality and substantial long-term morbidity [5][6]. Although in the past decades, the mortality rates of SAH have decreased, it remains a severe neurological problem. For example, it is estimated that 10–15% of patients die before reaching the hospital [7], and about 25% of patients die within 24 h [7][8]. In the first month, hospitalized patients have an average mortality rate of 40% [8][9][10], and approximately half of affected individuals die in the first six months. The morbidity and mortality increase with age and are dependent on the overall health status of the patient [5][6]. Among survivors, more than one-third will present major neurologic deficits. In addition, cognitive deficits were reported even in patients considered to have a good outcome [11].

The timely recognition and adequate treatment of SAH are essential, and key management recommendations include several aspects related to SAH complications [6][12]. Among complications, the most important include: hydrocephalus, rebleeding, delayed ischemia, intracerebral hemorrhage, intraventricular hemorrhage, increased intracranial pressure, seizures, left ventricular systolic dysfunction, and myocardial infarction [1][4][13].

2. Subarachnoid Hemorrhage in Patients with SARS-CoV-2 Infection

The SARS-CoV-2 virus is a new pathogen that causes a disease with variable clinical manifestations. Although the Coronavirus disease 2019 (COVID-19) is associated with hypercoagulopathy, patients may also present with cerebral hemorrhage, including SAH, spontaneous intracerebral parenchymal hemorrhage, and diffuse petechial cerebral hemorrhage. The incidence of intracranial hemorrhage, including SAH, was reported to be 0.3–1.2% [14].

However, studies on the neurological complications of SARS-CoV-2 infection report different epidemiological data according to the COVID-19 waves. This could be due to the impact of different healthcare strategies or the virulence of the different SARS-CoV-2 strains. For example, one study reports that SAH was present in 2% of the neurological cases in the first and 4% in the second wave [15]. Interestingly, a study comparing 2086 patients with COVID-19 and ischemic stroke with a cohort of 166,586 ischemic stroke controls found that the COVID-19 patients were less likely to present

hypertension, dyslipidemia, and smoking history. However, they were more likely to be male, younger, and present with diabetes, obesity, acute coronary syndrome, venous thromboembolism, acute renal failure, and comorbid intracerebral hemorrhage or SAH [16]. Compared to the years before the pandemic, the research found that there was a higher proportion of ischemic stroke and intracerebral hemorrhage but a lower percentage of SAH and transient ischemic attack among patients with SARS-CoV-2 infection [17]. In patients hospitalized with pneumonia due to COVID-19, among 1040 individuals, 79.42% presented neurological symptoms. However, cerebral hemorrhage occurred in 1.08% of patients and SAH in 0.24% [18]. In mechanically ventilated patients with COVID-19 who died, although the leading cause of death was hypoxemic respiratory failure (77.8%), cerebrovascular accident accounted for 3.2% of deaths, and SAH for 1.6% [19].

Several studies indicated a decrease in the incidences of patients with acute cerebrovascular conditions [20][21][22][23][24][25] and aneurysmal SAH [20][26][27] during the early stages of the COVID-19 pandemic. A more extensive cross-sectional study, including 49 countries and 187 centers, investigated the differences in the incidence, severity of aSAH, and the treatment modality of ruptured aneurysms during the first year of the COVID-19 pandemic comparing it with the preceding year [28]. The authors found that there were 16,247 aSAH admissions and 344,491 COVID-19 admissions, with 8300 ruptured aneurysms coiling and 4240 ruptured aneurysms clipping procedures. They report a decline in the number of aSAH admissions (−6.4%; 95%CI −7.0% to −5.8%; p = 0.0001) during 2020 compared with 2019, most pronounced in hospitals with high-volume SAH and high-volume COVID-19 cases. In addition, the authors noted a trend towards a decline in mild and moderate SAH presentations (mild: −5%; 95% CI −5.9% to –4.3%, p = 0.06; moderate: −8.3%; 95% CI −10.2% to –6.7%; p = 0.06). Nonetheless, there was no difference in higher SAH severity [28]. The study also noted a similar overall 4.1% decrease in non-traumatic SAH admission. Consequently, the authors endorse the possibility that the aSAH rates may not have been modified, but the patients were shifted to being treated at hospitals with lower-volume COVID-19 cases if high-volume hospitals were overwhelmed with patients with SARS-CoV-2 infections [28].

Hemorrhages may affect multiple organs, including the central nervous system (CNS) [29]. The pathophysiology is not yet fully elucidated, and multiple factors were implicated: microthrombosis with secondary hemorrhage, dysregulated coagulation, vascular hyperpermeability in the context of SARS-CoV-2 infection cytokine storm, endotheliitis, and vasculitis [29]. For example, the affinity of SARS-CoV-2 for angiotensin-converting enzyme 2 (ACE-2) receptors, which are expressed in endothelial and arterial smooth muscle cells in the brain, may trigger local inflammation that causes a vasculitic process. Therefore, the viral infection will damage the intracranial arteries, predisposing the vessel wall to rupture, a mechanism that could potentially explain the pathogenesis of hemorrhagic stroke [30].

In patients with COVID-19 and aneurysmal SAH, the rupture of the aneurysm was assumed to be produced due to endothelial dysfunction. In addition, as the SARS-CoV-2 downregulates the expression of the ACE-2 receptors, the disruption of the renin-angiotensin-aldosterone system may cause an uncontrolled elevation in blood pressure, which is exacerbated by preexisting hypertension; thereby, the risk of bleeding is substantially increased [31]. Some authors proposed that the hyperinflammatory state also seen in COVID-19, with hypercytokinemia and inflammation, could contribute to vascular degeneration that will lead to aneurysm formation and size or morphology change, consequently resulting in rupture and bleeding [32].

It is noteworthy that the hypothesis of an infectious cause for aneurysm rupture was rejected several decades ago. Earlier studies on the association between viral infections and SAH failed to support the hypotheses that intracranial aneurysms may develop because the initiating event of a viral infection produces any direct arterial damage, and aneurysm rupture may be temporally related to the infection [33].

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