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ORIGINAL ARTICLE

Intracerebral Hemorrhage Post-COVID 19 Infection

KHALID W. AL-QULITI[1], RAKAN M. ALHUJEILY[2], OBAID M. ALJARBOU[3]
[1]Neurology Division, Department of Medicine, College of Medicine, Taibah University, Al-madinah Almunwwarah 42353, Saudi Arabia. kquliti@taibahu.edu.sa
[2]College of Medicine, Taibah University, Al-madinah Almunwwarah 42353, Saudi Arabia. Rakanma97@gmail.com
[3]College of Medicine, Taibah University, Al-madinah Almunwwarah 42353, Saudi Arabia. Mj.obaid1997@gmail.com
Corresponding author: Khalid W. Al-Quliti, Neurology Division, Department of Medicine, College of Medicine, Taibah University, Al-madinah Almunwwarah 42353, Saudi Arabia. Email: kquliti@taibahu.edu.sa, Contact: (+966) 0148460008

ABSTRACT

Background: COVID 19, which can lead to neurological complications including intracerebral hemorrhage (ICH), has caused a challenging worldwide pandemic. We aim to highlight the clinical, radiologic and laboratory characteristics, as well as functional outcomes of patients with COVID-19, who either presented with ICH or subsequently developed ICH.

Methods: Related PubMed articles and studies on ICH and COVID-19 (published from January 2020 to October 2021, were searched. Our inclusion criteria included all articles written in English, involving COVID-19 patients confirmed via PCR test and admitted to hospital or ICU, and large ICH on neuroimaging.

Results: We collected 23 published studies with an association between COVID-19 and ICH, focusing on the clinical profile, neuroimaging findings and management. The risks for ICH includes comorbidities like hypertension, diabetes, chronic kidney disease and malignancy, and anticoagulation therapy. In one study parenchymal haemorrhages with mass effect and herniation showed a very high mortality rate and most of those patients received either a therapeutic or prophylactic dose of anticoagulates prior to ICH discovery.

Conclusion: ICH and COVID-19 are rare but with high morbidity and mortality. Thus, it is important to recognize early those patients at high risk of having ICH, mainly those patients with comorbidities and on anticoagulation therapy, to improve health care outcomes.

Keywords: COVID-19, Intracerebral hemorrhage , Anticoagulants

INTRODUCTION

COVID-19 is a global healthcare challenge which manifested into a worldwide pandemic. Its clinical picture ranges in severity from minor symptoms, such as flu-signs, fever, sore throat, dry cough, fatigue, headache, and mild shortness of breath, to severe conditions such as acute respiratory distress syndrome (ARDS) and multiorgan failure. The most common neurological symptom is anosmia, although encephalopathy is common among critically ill patients. Contracting COVID-19 also increases the risk of having ischemic and hemorrhagic strokes[1]. Hypertension is the most important risk factor for spontaneous ICH. It causes chronic changes in small cerebral arteries resulting in atherosclerotic changes. Affected arteries display prominent degeneration of the media and smooth muscle. Additionally, fibrinoid necrosis of the sub-endothelium with microaneurysms and focal dilatation may be seen in some patients. Lipohyalinosis, associated with long-duration high blood pressure is a typical mechanism in non-lobar ICH. Also, cytokines activate the inflammatory cascade which can cause secondary injury in hypertensive ICH that includes interleukin (IL), vascular endothelial growth factor (VEGF) and tumor necrosis factor-a. The most common locations of hypertensive ICH are putamen/globus pallidus (56%), thalamus (31%), and brainstem or cerebellum (7%)[2]. Another cue for ICH is cerebral amyloid angiopathy (CAA), a condition with accumulating amyloid B (AB) protein along the leptomeningeal, cortical and cerebellum vessels, which lead to vessel degeneration resulting in cortical superficial siderosis and cerebral microbleeds. The incidence of CAA is 5% in those older than 65 years[2]. Other causes of ICH when chronic kidney disease (CKD) is present is cerebrovascular small vessel disease which plays a major role in the hypertensive ICH mechanism. Patients with CKD who have platelet dysfunction are at increased risk for ICH. Infections such as herpes simplex virus, syphilis, varicella, SARS-CoV-2 are associated with ICH through vasculitic infiltration of the blood vessels. Malignancy, either solid or hematologic, may cause ICH in the case of primary brain tumor, metastatic disease or vascular involvement[2]. ICH can cause a catastrophic neurological disorder. A recent study of ICH in a sample of 33 patients, classified ICH as mild 9%, mild to moderate 17%, moderate 33%, severe 25%, and very severe 16%. ICH has a poor prognosis and mortality after one month is estimated at 40%[3]. SARS- CoV-2 pathogen invades the central nerves system (CNS) and causes infection to neurons and glial cells. It affects CNS through olfactory bulb and/or hematogenous spread. Pathogens can cross the blood–brain barrier transcellularly, paracellularly and/or through infected phagocytes (the so-called Trojan-horse mechanism). The pathological mechanism may involve angiotensin-converting enzyme-2 (ACE-2), a carboxypeptidase that converts angiotensin II to angiotensin, an essential component of the renin-angiotensin system (RAS) which is neuroprotective. The ACE-2 receptor may play a role in ICH by binding SARS-CoV-2 to the ACE-2 receptor, leading to downregulation of RAS and increasing the risk for hemorrhagic stroke. Also, it induces the inflammatory cascade — causing a massive release of inflammatory markers and cytokines including IL-2 and TNF-a4 that affects the integrity of the blood brain barrier[4-7]. We aim to highlight the clinical, radiologic and laboratory characteristics as well as functional outcomes of patients with COVID-19, who either presented with ICH or subsequently developed ICH after contracting COVID-19.

METHODOLOGY

PubMed was searched to explore related articles and studies on ICH and COVID-19 published from January 2020 to October 2021. Our inclusion criteria: all articles written in English, involving COVID-19-positive patients confirmed through a PCR test, admitted to hospital or ICU, and large ICH on neuroimaging. . Twenty-three articles met our inclusion criteria.

RESULTS

We found 23 published studies with an association between COVID-19 and ICH focusing on the clinical profile, neuroimaging findings, and management. Pavlov et al., reported that 65.8% of COVID-19 patients with intracerebral hemorrhage were male, between the ages of 31 to 78 years old[8]. A number of cases were reported with different clinical profiles and neuroimaging findings. One recent retrospective study of 22 patients with ICH and COVID-19 showed 12 patients (54.4%) had confirmed COVID-19 with no significant past medical history, and 10 patients (45.5%) had a cerebrovascular event as the first manifestation of COVID-19, The duration of symptoms in patients with COVID-19 from the onset of symptoms and neurological manifestation was 4 days, Seventeen patients had acute ischemic stroke, three patients had aneurysm rupture, and two had sinus thrombosis, their laboratory studies showed elevated D-dimer (3497.4 ± 6754.3 ng/dl), CRP (20.8 ± 37.9 mg/dl), and IL-6 (41.6 ± 62.0 pg/dl)[9].

Another study of 239 COVID-19 cases that assessed the neurological manifestations in those patients, found the three most common symptoms were fever (33.1%), headache (26.7%), and trigeminal neuralgia (3.3%). Only 0.8% of these cases had ICH[10]. Benger et al., reported a case series of five patients diagnosed with COVID-19, complicated by ICH and admitted to hospital with a variety of clinical features. One patient, a 41-year old male with well-controlled hypertension, deteriorated and was admitted to the intensive care unit. Another patient with a history of recurrent deep venous thrombosis (DVT) and pulmonary embolism (PE), and hypertension presented with dysarthria and left-sided hemiparesis. They also reported a 64-year-old patient with no past medical history who presented with deteriorated level of consciousness; her brain CT showed subacute right-sided ganglio-capsular ICH[11].

Other studies reported COVID-19 patients with ICH showing different findings in neuroimaging. Nawabi et al., reported 18 patients with confirmed COVID-19 associated with ICH whose neuroimaging findings included subarachnoid haemorrhage (72.2%), parenchymal haemorrhage (33.3%), intraventricular haemorrhage (16.7%) and subdural haemorrhage (5.6%)[12]. A recent case of a 79-year-old man with loss of consciousness and a Glasgow Coma Scale of 7,showed a massive ICH in the right hemisphere with both intraventricular and subarachnoid haemorrhage on his brain CT[13]. Dogra et al., identified 33 COVID-19 patients with ICH in their cohort study of patients aged 37-83 years; parenchymal haemorrhages and mass effect with herniation occurred in five patients (15.2%) and the mortality rate was 100%. The remaining 28 patients (25%) had punctate haemorrhages, 17 (60.7%) had small-moderate sized haemorrhages, and four (14.3%) had large single-site haemorrhages. Almost all patients received either a therapeutic or prophylactic dose of anticoagulation[14].

DISCUSSION

The association between ICH and COVID-19 has been considered clinically in previous research. Many cases were reported and discussed the relationship of ICH in COVID-19 patients[15]. Khattar el al., reported the case of a 42-year-old patient with COVID-19-related ARDS and bilateral large ICH after heparin drip initiation, who was admitted with high levels of ferritin[16]. Ferritin is correlated with high mortality in COVID-19 patients and indicates the importance of biomarker levels to guide management[17, 18]. A recent retrospective study found that most often ICH occurred in COVID-19 patients with therapeutic anticoagulation settings resulting in a high death rate (86.4%) [19]. Multiple mechanisms contributing to ICH in COVID-19 include decreased platelet levels and prolonged prothrombin time, along with over activation of fibrinolytic cascade[20]. Also, patients with SARS-CoV-1 were reported to have increased tissue plasminogen activator and thrombomodulin plasma levels, which are associated with high incidence of hemorrhagic events[21]. The American Society of Haematology and American Society of Chest Physicians recommend avoiding full-dose anticoagulation for prevention of thromboembolism in COVID-19 patients given the unclear benefits and the potential high risk of bleeding in this vulnerable population[22,23].

CONCLUSION

The association between ICH and COVID-19 is uncommon. However, it is important for health care providers caring for COVID-19 patients to identify early-on those at high risk for ICH — mainly patients with comorbidities like hypertension, diabetes, chronic kidney disease and malignancy, and those receiving anticoagulation therapy — to improve morbidity and mortality rates and healthcare outcomes.

REFERENCES

1- Margos NP, Meintanopoulos AS, Filioglou D, Ellul J. Intracerebral hemorrhage in COVID-19: A narrative review. J Clin Neurosci. 2021 July; 89:271-78. doi: 10.1016/j.jocn.2021.05.019.

2- Nobleza COS. Intracerebral Hemorrhage. Continuum (Minneap Minn). 2021 Oct 1; 27(5):1246-77. doi: 10.1212/CON.0000000000001018.

3- Tilling EJ, El Tawil S, Muir KW. Do Clinicians Overestimate the Severity of Intracerebral Hemorrhage? Stroke. 2019 Feb; 50(2):344-48. doi: 10.1161/STROKEAHA.118.022606.

4- Sweid A, Hammoud B, Bekelis K, Missios S, Tjoumakaris SI, Gooch MR, et al. Cerebral ischemic and hemorrhagic complications of coronavirus disease 2019. Int J Stroke. 2020 Oct; 15(7):733-42. doi: 10.1177/1747493020937189.

5- Nannoni S, de Groot R, Bell S, Markus HS. Stroke in COVID-19: A systematic review and meta-analysis. Int J Stroke. 2021 Feb; 16(2):137-49. doi: 10.1177/1747493020972922.

6- Bermejo-Martin JF, Almansa R, Torres A, González-Rivera M, Kelvin DJ. COVID-19 as a cardiovascular disease: the potential role of chronic endothelial dysfunction. Cardiovasc Res. 2020; 116(10):e132-e33. doi:10.1093/cvr/cvaa140

7- Sardu C, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G. Hypertension, Thrombosis, Kidney Failure, and Diabetes: Is COVID-19 an Endothelial Disease? A Comprehensive Evaluation of Clinical and Basic Evidence. J Clin Med. 2020; 9(5):1417. doi:10.3390/jcm9051417

8- Cheruiyot I, Sehmi P, Ominde B, Bundi P, Mislani M, Ngure B, et al. Intracranial hemorrhage in coronavirus disease 2019 (COVID-19) patients. Neurol Sci. 2021; 42(1):25-33. doi:10.1007/s10072-020-04870-z 9. Sweid A, Hammoud B, Bekelis K, Missios S, Tjoumakaris SI, Gooch MR, et al. Cerebral ischemic and hemorrhagic complications of coronavirus disease 2019. Int J Stroke. 2020; 15(7):733-42. doi:10.1177/1747493020937189

10. Karadaş Ö, Öztürk B, Sonkaya AR. A prospective clinical study of detailed neurological manifestations in patients with COVID-19. Neurol Sci. 2020; 41(8):1991-95. doi:10.1007/s10072-020-04547-7

11. Benger M, Williams O, Siddiqui J, Sztriha L. Intracerebral haemorrhage and COVID-19: Clinical characteristics from a case series. Brain Behav Immun. 2020; 88:940-44. doi:10.1016/j.bbi.2020.06.005

12. Nawabi J, Morotti A, Wildgruber M, Boulouis G, Kraehling H ,Schlunk F, et al. Clinical and Imaging Characteristics in Patients with SARS-CoV-2 Infection and Acute Intracranial Hemorrhage. J Clin Med. 2020; 9(8):2543. doi:10.3390/jcm9082543

13. Sharifi-Razavi A, Karimi N, Rouhani N. COVID-19 and intracerebral haemorrhage: causative or coincidental? New Microbes New Infect. 2020; 35:100669. doi:10.1016/j.nmni.2020.100669

14. Dogra S, Jain R, Cao M, Bilaloglu S, Zagzag D, Hochman S, et al. Hemorrhagic stroke and anticoagulation in COVID-19. J Stroke Cerebrovasc Dis. 2020; 29(8):104984. doi:10.1016/j.jstrokecerebrovasdis.2020.104984

15. Abbas R, El Naamani K, Sweid A, Schaefer JW, Bekelis K, Sourour N, et al. Intracranial Hemorrhage in Patients with Coronavirus Disease 2019 (COVID-19): A Case Series. World Neurosurg. 2021; 154:e473-e80. doi:10.1016/j.wneu.2021.07.067

16. Khattar NK, Sharma M, McCallum AP, Oxford BG, Zeb H, Suliman SA, et al. Intracranial hemorrhage in a young COVID-19 patient. Interdiscip Neurosurg. 2020; 22:100878. doi:10.1016/j.inat.2020.100878

17. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Paul Singh IP, et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. N Engl J Med. 2020; 382(20):e60. doi:10.1056/NEJMc2009787

18. Shoenfeld Y. Corona (COVID-19) time musings: Our involvement in COVID-19 pathogenesis, diagnosis, treatment and vaccine planning. Autoimmun Rev. 2020; 19(6):102538. doi:10.1016/j.autrev.2020.102538

19. Kvernland A, Kumar A, Yaghi S, Raz E, Frontera J, Lewis A, et al. Anticoagulation use and Hemorrhagic Stroke in SARS-CoV-2 Patients Treated at a New York Healthcare System. Neurocrit Care. 2021; 34(3):748-59. doi:10.1007/s12028-020-01077-0

20. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood. 2020; 135(23):2033-40. doi:10.1182/blood.2020006000

21. Goeijenbier M, van Wissen M, van de Weg C, Jong E, Gerdes VEA, Meijers JCM, et al. Review: Viral infections and mechanisms of thrombosis and bleeding. J Med Virol. 2012; 84(10):1680-96. doi:10.1002/jmv.23354

22. Moores LK, Tritschler T, Brosnahan S, Carrier M, Collen JF, Doerschug K, et al. Prevention, diagnosis, and treatment of VTE in patients with covid-19: Chest guideline and expert panel report. Chest. 2020; 158(3):1143-63. doi: 10.1016/j.chest.2020.05.559

23. American Society of Hematology. COVID-19 and VTE/anticoagulation: Frequently Asked Questions. 2020. https//www/hematology.org/covid-19/covid-19-and-vte-anticoagulation.