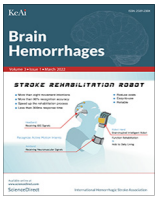
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Brain Hemorrhages xxx (xxxx) xxx

Contents lists available at ScienceDirect

Brain Hemorrhages

journal homepage: www.keaipublishing.com/en/journals/brain-hemorrhages/



Case Report

Intracerebral hemorrhage associated COVID-19 patient with normal coagulation profile after ECMO treatment: A case report

Wael Osman Amer [a,b], Hussein Awad El gharieb [a,c], Hossam Ibrahim [d], Ahmed Alanazi [e], Mostafa Meshref [a,*]

[a] Neurology Department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt
[b] Professor of Neurology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt
[c] Assistant Professor of Neurology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt
[d] Consultant Intensive Care, King Salman Armed Forces Hospital, Tabuk, Saudi Arabia
[e] Training Internal Medicine Resident, King Salman Armed Forces Hospital, Tabuk, Saudi Arabia

ARTICLE INFO

Article history:
Received 16 July 2022
Received in revised form 4 August 2022
Accepted 9 August 2022
Available online xxxx

Keywords:
Coronavirus
Extracorporeal membrane oxygenation (ECMO)
ICH
Coagulation profile

ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is a novel coronavirus-caused infectious acute respiratory disease that can progress to severe acute respiratory distress syndrome (ARDS). For severe cases, extracorporeal membrane oxygenation (ECMO) is an excellent treatment option. ECMO had a number of side effects, including bleeding. Intracerebral hemorrhage can occur in COVID patients due to a variety of mechanisms, including covid's effect on ACE-2 receptors and subsequent hypertension, coagulopathy, DIC, or medication, such as anticoagulant use.

Case: We present a case of a 53-year-old male COVID-19 patient who developed multiple, massive, severe intracerebral hemorrhages (ICH) despite a normal coagulation profile after ECMO treatment.

Conclusion: COVID-19 can progress to severe acute respiratory distress syndrome (ARDS), necessitating the use of extracorporeal membrane oxygenation (ECMO). Although ICH is not a common complication in patients with COVID-19 disease, it is unknown why this patient had a lower threshold of ICH despite having a normal coagulation profile.

Introduction

Coronavirus disease 2019 (COVID-19) is a novel coronavirus-caused infectious acute respiratory disease.[1] The disease may progress to severe and refractory acute respiratory distress syndrome (ARDS), necessitating the use of extracorporeal membrane oxygenation (ECMO).[2] ECMO appears to be an effective method of treating ARDS in a variety of conditions, including COVID-19.[2,3] ICH occurs less common with COVID-19 infected patient about (0.7 %),but has a high mortality rate.[4,5] However, some studies showed increased the risk ICH occurrence in COVID-19 cases on ECMO treatment and the percentage became (20 %).[6] This variability in increasing the haemorrhage risk with ECMO use because of multiple factors including ECMO duration, antithrombotic therapy, altered intrinsic coagulation, renal function status, blood components' need, rapid hypercapnia at ECMO initiation, and even pre-ECMO morbidity.[7]

Case presentation

A 53-year-old male patient who had previously been healthy was admitted to another hospital as a case of ARDS with a high probability of COVID-19 infection. The patient was mechanically ventilated when he arrived. The plan was to start ECMO treatment. The right femoral vein was cannulated with a 23-gauge French cannula for venous access and a 21-gauge French cannula for arterial return during the procedure, with no immediate complications. After being connected to VV ECMO with 4.1 l cardiac output ECMO flow, the patient's saturation improved from 69 to 97 percent. The patient was then transferred to our hospital. On arrival, he was vitally stable, and the pump speed was 2800 RPM, ECMO flow 4.1 l FIO2 100 percent sweep gas flow 2.5LPM, peripheral saturation 89 percent, MAP 65 mmHg, no heparin infusion or bolus given except 10,000 units during cannulation, activated clotting time was 163 until 200 sec, PTT was until 121 sec, and INR was 1.51. Three hours later, the patient's pupils were discovered to be 4 mm dilated, and an urgent brain CT was ordered, which revealed multiple cavitary lesions with air-fluid level and hemorrhagic transformation as illustrated in Fig. 1 which showed the ICH

* Corresponding author.
E-mail address: mostafameshref1988@gmail.com (M. Meshref).

https://doi.org/10.1016/j.hest.2022.08.002
2589-238X/

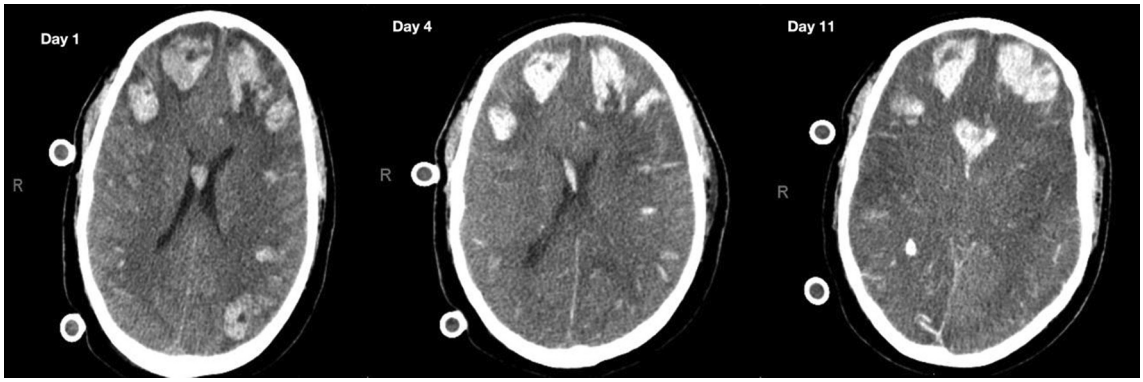


Fig. 1. CT brain which showed ICH progression over admission days.

progression over the admission days. The swab was tested for COVID-19 infection using RT-PCR. Furthermore, even with an optimal coagulation profile, the hemorrhage worsened over time, and no specific pattern was observed, as shown in Fig. 2 which showed images of the last CT brain which illustrated massive multiple ICH with increased ventricular compression, increased IVH, increased SAH and increased the inferior displacement of the cerebellar tonsils (herniation). During ECMO, the patient was ventilated as follows: pressure control (PC) with pressure support (PS), tidal volume (TV) was target 3–4 ml/kg, PEEP decreased 14 to 5 cmH2o, respiratory rate (RR) was 12/min, arterial blood gas (ABG) was partial pressure of oxygen (PO2) was 71.2, co2 was 44.3, and mixed venous saturation was 66 percent. Our national guidelines protocol for Covid 19 management includes antibiotics, antiviral Covid-19 treatment, vitamin replacement, steroids, and cytokine IL6 antagonist Tocilizumab IV two doses as protocol. With fixed acceptable coagulation profiles during case follow up as shown in Table 1, there was an improvement in chest X-ray and ABG. Bacterial growth was not detected in blood cultures. The echocardiogram was normal. The patient was continued on ECMO treatment and ICU supportive measures for eleven days, but unfortunately, he died because of severe COVID-19 infection and massive ICH.

Discussion

Coronavirus disease 2019 (COVID-19) is a new coronavirus-caused acute infectious respiratory disease.[1] COVID-19 disease can progress to severe acute respiratory distress syndrome (ARDS) lead to consider extracorporeal membrane oxygenation (ECMO).[2] ECMO appears effective to treat ARDS in many conditions include COVID-19.[2,3] Bleeding is one of the most serious ECMO complications, but achieving a normal coagulation profile can help prevent it.[2] Our patient's coagulation profile was kept normal and optimal (no heparin infusions or boluses were given except for 10,000 units during cannulation). COVID-19 disease, on the other hand, appears to be a risk factor for coagulopathy,[8] and to reduce the influence of precipitating events, Anticoagulation is typically achieved by a continuous intravenous infusion of unfractionated heparin (UFH) targeting an APTT of 60–80 s, as well as activated clotting time (ACT) with a treatment target of 180–220 s.[9] Fluid-blood levels in acute intracerebral hemorrhage may indicate the presence of coagulopathy with moderate sensitivity and high specificity, according to CT findings.[10] ICH is uncommon in COVID-19 patients and is associated with a high mortality rate.[11] The pathophysiology of ICH in a COVID-19 patient is unknown; however, there was massive ICH in our case despite the use of therapeutic anticoagulation. This hemorrhage could be explained by hypoxia in Covid-19 patients, which causes disruption of the blood brain barrier and increased susceptibility to intracerebral hemorrhage, according to Rich et al.[12] While Ding et al. demonstrated the neuroinvasive potential of corona virus in his study on corona-related types,[13,14]. Varga et al. and Ackermann et al. also found autopsy evidence of vasculitis in SARS-Cov-1. Endothelial damage occurs in SARS-Cov-2, and microscopic descriptions of endothelial cerebral veins may result in microscopic bleeds and eventual intracerebral hemorrhage.[15–17] Multiple studies have drawn attention to the facilitated entry of COVID-19 in its host, which has been shown to be via the Angiotension Converting Enzyme 2 (ACE2) receptors of the Human cell surface mediated by its S-Protein, patients with hypertension have reduced ACE2 expression in patients with Covid-19 virus occupied this receptors with furthermore reduction

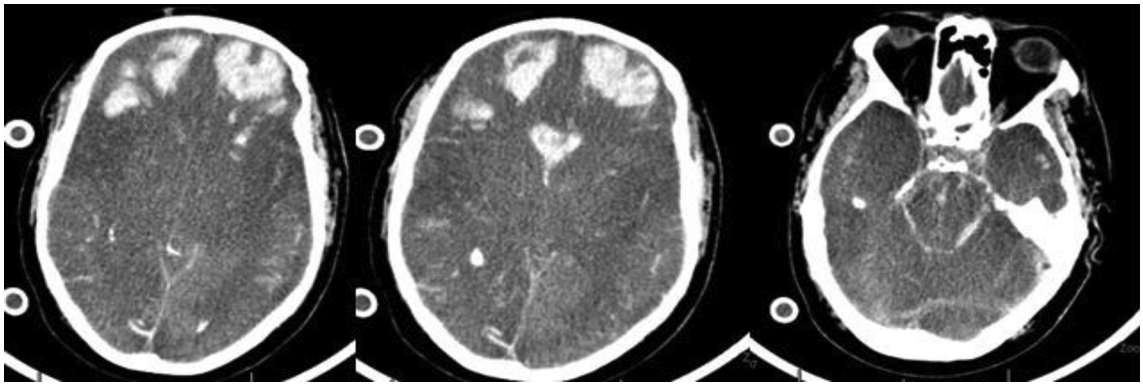


Fig. 2. Last follow up CT brain which showed massive multiple ICH with increased ventricular compression, increased IVH, increased SAH and increased the inferior displacement of the cerebellar tonsils (herniation).

Table 1
Showed the case follow up coagulation profile.

Day/ Serial Coagulation screen	(PT) Reference value (11–13.5 *sec.*)	(APTT) Reference value (60–80 *sec.*)	(INR) Reference value (0.8–1.2)	(ACT) Reference value (70–120 *sec.*) our treating target was (180–220) Reference value for therapeutic anticoagulant (up to 600 *sec.*)
Day 1	21.30	81.10	1.60	215
Day 2	20.10	33.10	1.51	173
Day 3	20.80	28.50	1.56	225
Day 4	25.80	42.10	1.92	228
Day 5	21.60	36.40	1.62	164
Day 6	19.90	33.30	1.50	232
Day 7	19.50	32.10	1.47	179
Day 8	18.80	32.10	1.42	135
Day 9	17.60	29.30	1.33	172
Day 10	17.50	34.80	1.33	126
Day 11	17.10	36.80	1.30	137

of ACE2 with subsequent increase the risk of ICH with elevated blood pressure.[18] Another hypothesis proposed Covid-19 patients frequently have prolonged prothrombin time and coagulopathy, which increases the risk of secondary intracerebral haemorrhage.[19] Furthermore, Covid-19 infection causes distinct coagulopathy in the form of increased D-dimer concertation, prolonged prothrombin time, platelet dysfunction, and DIC, as described by Ding et al. in their study of Corona virus-related types.[13] Other studies support that COVID-19 patients with severe illness are also at risk for ICH.[20,21] According to some studies, the use of anticoagulants is associated with an increased risk of ICH in the future.[21] Hence, We described a COVID-19 patient who developed multiple massive ICH hemorrhages despite receiving a low prophylactic dose of low molecular weight heparin and having a normal optimal coagulation profile. The hemorrhage worsened over time even with an optimal coagulation profile, as shown in Fig. 1. We supposed that the cause of this ICH is due to both the COVID-19 infection severity and also the ECMO treatment usage with co-existence risk variables. Those variables includes the ECMO duration, usage of antithrombotic therapy, altered intrinsic coagulation, renal function status, blood components' need, rapid hypercapnia at ECMO initiation, and even pre-ECMO morbidity.[7] Our findings highlight the importance of further research into coagulation abnormalities in Covid-19 patients in order to assess the risk of hemorrhagic complications as a result of COVID-19 disease.

Conclusion

COVID-19 can progress to severe acute respiratory distress syndrome (ARDS), necessitating the use of extracorporeal membrane oxygenation (ECMO). Although ICH is not a common complication in patients with COVID-19 disease, it is unknown why this patient had a lower threshold of ICH despite having a normal coagulation profile.

Compliance with ethical standards.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of King Salman Armed Forces Hospital (KSAFH) on December 5th 2020 (KSAFH-REC-2020-376). Written informed consent was obtained from the patient.

Data access statement

All manuscript data are available and included in the study and already there is an ethical approval. If furthers documents or images needed we will provide it.

Funding statement

The study is Self-Funded.

References

1. Sadeghi Dousari A, Taati Moghadam M, Satarzadeh N. COVID-19 (Coronavirus Disease 2019): A new coronavirus disease. *Infect Drug Resist*. 2020;13:2819–2828. https://doi.org/10.2147/IDR.S259279.
2. Usman AA, Han J, Acker A, et al. A case series of devastating intracranial hemorrhage during venovenous extracorporeal membrane oxygenation for COVID-19. *J Cardiothorac Vasc Anesth*. 2020;34(11):3006–3012. https://doi.org/10.1053/j.jvca.2020.07.063.
3. Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome. *JAMA*. 2009;302(17):1888. doi:10.1001/jama.2009.1535
4. Dogra S, Jain R, Cao M, et al. Hemorrhagic stroke and anticoagulation in COVID-19. *J Stroke Cerebrovasc Dis*. 2020;29(8). https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104984 104984.
5. Kvernland A, Kumar A, Yaghi S, et al. Anticoagulation use and hemorrhagic stroke in SARS-CoV-2 patients treated at a new york healthcare system. *Neurocrit Care*. 2021;34(3):748–759. https://doi.org/10.1007/s12028-020-01077-0.
6. Seeliger B, Doebler M, Hofmaenner DA, et al. Intracranial hemorrhages on extracorporeal membrane oxygenation: differences between COVID-19 and other viral acute respiratory distress syndrome. *Crit Care Med*. 2022;50(6):e526–e538. https://doi.org/10.1097/CCM.0000000000005441.
7. Fletcher-Sandersjöö A, Thelin EP, Bartek J, et al. Incidence, outcome, and predictors of intracranial hemorrhage in adult patients on extracorporeal membrane oxygenation: A Systematic and Narrative Review. *Front Neurol*. 2018;9. https://doi.org/10.3389/fneur.2018.00548.
8. Lee SG, Fralick M, Sholzberg M. Coagulopathy associated with COVID-19. *Can Med Assoc J*. 2020;192(21):E583–E. https://doi.org/10.1503/cmaj.200685.
9. Fletcher Sandersjöö A, Bartek J, Thelin EP, et al. Predictors of intracranial hemorrhage in adult patients on extracorporeal membrane oxygenation: an observational cohort study. *J Intensive Care*. 2017;5(1):27. https://doi.org/10.1186/s40560-017-0223-2.
10. Deng F, Lorensini B. Intracranial haemorrhage with fluid-fluid level. In: *Radiopaedia.Org*. Radiopaedia.org; 2016. doi:10.53347/rID-47615.
11. Cheruiyot I, Sehmi P, Ominde B, et al. Intracranial hemorrhage in coronavirus disease 2019 (COVID-19) patients. *Neurol Sci*. 2021;42(1):25–33. https://doi.org/10.1007/s10072-020-04870-z.
12. Riech S, Kallenberg K, Moerer O, et al. The pattern of brain microhemorrhages after severe lung failure resembles the one seen in high-altitude cerebral edema. *Crit Care Med*. 2015;43(9):e386–e389. https://doi.org/10.1097/CCM.0000000000001150.
13. Ding Y, Wang H, Shen H, et al. The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. *J Pathol*. 2003;200(3):282–289. https://doi.org/10.1002/path.1440.
14. Arabi YM, Harthi A, Hussein J, et al. Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV). *Infection*. 2015;43(4):495–501. https://doi.org/10.1007/s15010-015-0720-y.
15. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet (London, England)*. 2020;395(10234):1417–1418. https://doi.org/10.1016/S0140-6736(20)30937-5.
16. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med*. 2020;383(2):120–128. https://doi.org/10.1056/NEJMoa2015432.
17. Benger M, Williams O, Siddiqui J, Sztriha L. Intracerebral haemorrhage and COVID-19: Clinical characteristics from a case series. *Brain Behav Immun*. 2020;88:940–944. https://doi.org/10.1016/j.bbi.2020.06.005.

18. Beyerstedt S, Casaro EB, Rangel ÉB. COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. *Eur J Clin Microbiol Infect Dis*. 2021;40(5):905–919. https://doi.org/10.1007/s10096-020-04138-6.
19. Md Noh MSF. COVID-19 and cerebral hemorrhage: proposed mechanisms. *J Neuroradiol*. 2021;48(2):125–126. https://doi.org/10.1016/j.neurad.2020.05.007.
20. Pavlov V, Beylerli O, Gareev I, Torres Solis LF, Solís Herrera A, Aliev G. COVID-19-related intracerebral hemorrhage. *Front Aging Neurosci*. 2020;12. https://doi.org/10.3389/fnagi.2020.600172.
21. Sharifi-Razavi A, Sedaghat Z, Baziboroun M, Karimi N. COVID-19 accompanied with intracerebral hemorrhage: a case series. *Arch Clin Infect Dis*. 2020;15(4). https://doi.org/10.5812/archcid.104877.