

Case Report

Acute Ischemic Stroke as the Presenting Feature of COVID-19 in the Young and Pregnant

Nermila A. Ballmick, MD,¹ Jiri F. Kubac, MD,¹ Hossein Akhondi, MD¹

Abstract

Introduction

Coronavirus disease (COVID-19) is an emerging and rapidly evolving public health issue that has become globally widespread and an overwhelming pandemic. Clinical manifestations of the disease include asymptomatic carrier states, acute respiratory distress syndrome, and even multiorgan dysfunction. Here, we present a unique and rare case of an acute ischemic stroke (AIS) in an asymptomatic pregnant woman with no predisposing medical illnesses.

Discussion

An 18-year-old G2P1 African American woman at 7 weeks gestational age with no significant medical or family history presenting to the Emergency Department during the initial phases of the pandemic with complaints of new onset left arm and left leg weakness with National Institute of Health Stroke Scale (NIHSS) of 10. Computed tomography of the brain showed an acutely evolving ischemic infarction in the right middle cerebral artery territory. Other etiologies for causes of her ischemic stroke were ruled out through supporting laboratory testing. Since she did not present early enough due to concerns about the Coronavirus pandemic, tissue plasminogen activator was not administered. COVID-19 was suspected, confirmed and deemed the likely explanation of the cause of her acute ischemic large-vessel stroke. The patient was treated with aspirin and clopidogrel daily and showed significant improvement of her left-sided weakness. She eventually regained her ability to walk and was still pregnant at the time of follow-up.

Conclusions

COVID-19 can be difficult to diagnose since the presentation can vary widely and initial presentation may range from asymptomatic carrier states such as in our patient. In this case, we explain how we reached a diagnosis of AIS likely secondary to COVID-19 and provide further discussion regarding the neurological manifestations and treatment in pregnancy.

Keywords

stroke; acute ischemic stroke; SARS-CoV-2; COVID-19; coronavirus infections/complications; thrombophilia; hypercoagulable state; pregnancy; pandemics

Introduction

The Coronavirus disease 2019 (COVID-19) is a global pandemic that has affected more than 48 million people, caused over 1.2 million deaths worldwide and is increasing daily.¹ Over the past few months, researchers, scientists and clinicians have witnessed a myriad of different clinical presentations of COVID-19, ranging from asymptomatic carrier states to severe acute respiratory distress syndrome. Although COVID-19 has a predilection for the respiratory

system, several case reports have been published which show that the virus can also involve hematologic and neurological systems.²⁻⁴ In particular, we investigate the incidence of large-vessel ischemic stroke in the young and pregnant as a complication of the COVID-19 infection. We present a unique case of an acute ischemic stroke (AIS) in an asymptomatic pregnant woman with no predisposing medical illnesses.

Author affiliations are listed at the end of this article.

Correspondence to:
Nermila Asha Ballmick, MD
MountainView Hospital
Internal Medicine Residency
Sunrise Health Consortium
2800 N. Tenaya Way
Las Vegas, NV 89128
(Nermila.Ballmick@HCAhealthcare.com)

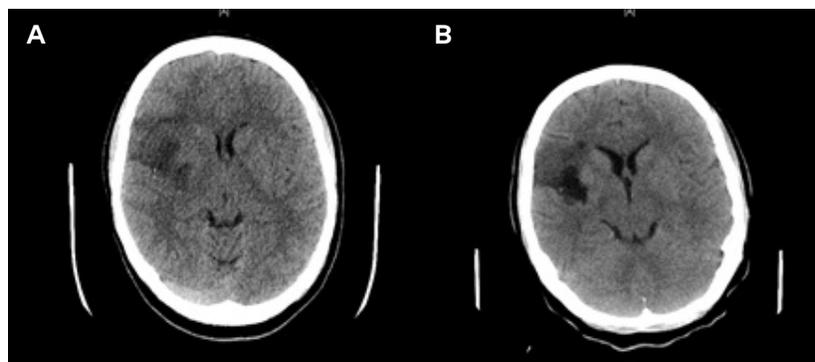


Figure 1. A) Computed tomography (CT) of the brain without contrast showing ill-defined low-attenuation in the right frontal temporal lobe and associated basal ganglion with hyperdense right middle cerebral artery. B) A repeat CT of the brain without contrast 2 months later showing a chronic right frontal MCA distribution cortical infarct.

Clinical Findings

An 18-year-old pregnant African American woman (G2P1001) with no significant medical history besides migraine headaches presented to the Emergency Department (ED) during the initial phases of the pandemic with complaints of new-onset left arm and left leg weakness. The patient stated that she initially woke up around noon three days prior to initial presentation with complaints of left face, arm and leg numbness. At that time, she also had a right-sided headache that lasted all day and was still persistent at the time of admission. She stated that she normally has migraine attacks without associated weakness or numbness but reported inability to ambulate with this new episode. Shortly prior to this, the United States declared a national state of emergency in response to the COVID-19 pandemic. Several states enacted stay-at-home orders to mitigate the spread of SARS-CoV-2, the virus that causes COVID-19, to reduce the burden on the U.S. healthcare system. For this reason, the patient did not want to visit an obstetrician for prenatal care, which also delayed her from seeking earlier medical attention.¹ However, the weakness was persistent and she eventually arrived at the ED for further evaluation three days after her symptoms began.

Initial physical examination revealed left-sided facial paralysis, asymmetrical smile and left upper extremity weakness (3/5 strength). She exhibited decreased bilateral yet symmetrical reflexes. Her speech was intact without evidence of dysarthria or aphasia. On presenta-

tion, National Institutes of Health Stroke Scale (NIHSS) was noted to be 10 (scores range from 0 to 42, with higher numbers indicating greater stroke severity). The patient was outside of the tPA window; therefore, she was admitted to the hospital without need for thrombolysis.

Upon further work-up, urine drug screen was positive for ethanol of 0.021% and cannabinoids. Pelvic ultrasound showed single live early intrauterine pregnancy at seven weeks of gestation. A computed tomography (CT) of the brain with appropriate shielding of the uterus was obtained (**Figure 1A**) which was notable for an acutely evolving ischemic infarction in the right middle cerebral artery (MCA) territory with hyperdense middle cerebral artery. Magnetic resonance imaging (MRI) of the brain with contrast (**Figure 2**) confirmed the CT findings. Magnetic resonance angiography (MRA) of the head showed near complete occlusion of the right MCA and its branches starting 7.5 mm from its origin. MRA of the neck, magnetic resonance venogram (MRV) of the head, MRI of the cervical spine and bilateral lower extremity duplex were all negative. A 2-Dimensional Echocardiogram showed no patent foramen ovale. Complete blood count and coagulation panel were both within normal range. Fibrinogen level was 409 mg/dL (Normal: 291-538 mg/dL) and D-dimer was 1.11 $\mu\text{g/L}$ (Normal: 0.32 – 1.29 $\mu\text{g/L}$), both within normal limits for 2nd trimester pregnancies. Hypercoagulable studies were ordered (**Table 1**) and negative. Our patient was diagnosed with an acute ischemic stroke (AIS) of the right middle cerebral artery region. She was discharged from the hospital

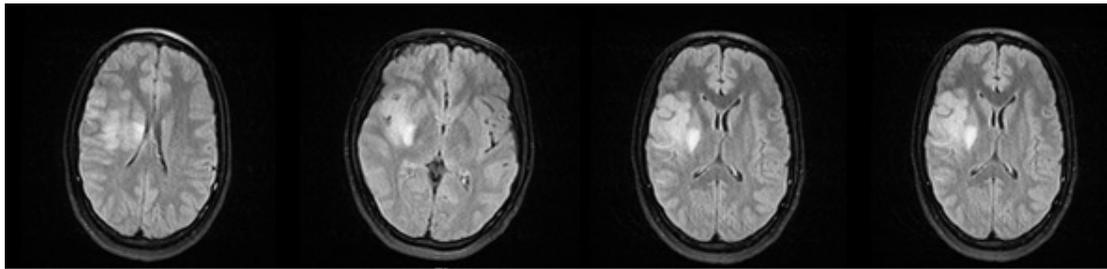


Figure 2. T2-FLAIR weight cerebral Magnetic Resonance image (MRI) of the brain without contrast, axial sections showing an incomplete right MCA flow void. There is a large middle right MCA distribution region of hyperintense diffusion signal.

to an acute rehabilitation facility on aspirin 81 mg daily and clopidogrel 75 mg daily. She was instructed to continue both medications for the entire duration of her pregnancy and to discontinue aspirin after delivery. A decision to avoid statin was made per maternal-fetal medicine given that the patient was in her first trimester and its use is contraindicated in pregnancy.

The patient followed up with the Graduate Medical Education Continuity Clinic after discharge. A repeat CT of the brain without contrast (**Figure 1B**) showed a chronic right frontal MCA distribution cortical infarct. Since there was no apparent recognizable etiology for her stroke, a SARS-CoV-2 Antibody IgG test was ordered at that time, which was noted to be positive (Reference range: negative). A nasopharyngeal swab to detect current infection was not ordered at that time since the patient did not exhibit the classical symptoms of COVID-19, and it was also not ordered during her hospitalization since testing was not readily available for asymptomatic patients. The patient showed significant improvement with outpatient physical therapy, regained some motor function in her left upper extremity and was still pregnant at the time of follow-up.

Discussion

The annual incidence of AIS in young African American women less than 35 years of age is approximately 20.7 out of every 100,000 cases. However, the incidence of pregnancy-related strokes in the same demographic is 52.5 out of every 100,000 deliveries. Approximately 10% of

all strokes are associated with pregnancy, with 40% occurring during the antepartum period and 50% of those occurring postpartum.⁵⁻⁷ Evidence states that healthy pregnant women have both an increased generation of thrombin and fibrinogen and a decreased production of protein S, leading to prothrombotic state. Therefore, they are at an increased risk of intravascular inflammation and thrombosis during pregnancy. This hypercoagulable physiologic condition can be exaggerated in the setting of infection, genetic mutations or autoimmune conditions.⁸⁻¹⁰ In fact, recent studies from The International Society of Thrombosis and Haemostasis has generated a simple algorithm for the management of COVID-19 coagulopathy with recommendations to administer low-molecular-weight heparin in pregnant women with COVID-19 to prevent thrombotic complications with COVID in pregnant patients. In addition, since our patient had a history of migraines with aura, this also increases risk of stroke 15- to 17-fold, even without the synergistic effect of COVID-19.¹¹

Given that our patient developed a large-vessel AIS during the antepartum period at seven weeks gestation, it suggests that there may have been a synergistic factor, not explained by pregnancy alone, that contributed to her unusual presentation.

Since our patient had no significant risk factors for ischemic stroke besides pregnancy, she was worked up for secondary causes. Autoimmune diseases, genetic mutations and blood disorders were all considered but resulted negative

Table 1. Negative Hypercoagulable Labs

Factor V Leiden Mutation
Antithrombin III Antigen
Free Protein S Antigen
Protein S Antigen
Protein C Antigen
Protein C Activity
APC Resistance
Lupus Anticoagulant aPTT
Dilute Russell Viper Venom
Factor II Mutation
JAK2 Mutation (PCR)
JAK2 Exon 12 Background
HIV 1 & 2 Ag/Ab 4th Gen
Anti-phospholipid antibody
Antinuclear Antibody
c-ANCA
Proteinase 3 (PR3)
p-ANCA
Atypical p-ANCA
Myeloperoxidase Antibody
Beta-2-GPI IgG Antibody
Beta-2-GPI IgA Antibody
Beta-2-GPI IgM Antibody
Anti-Prothrombin IgG
Phosphatidylserine IgG
Phosphatidylserine IgM
Anti-Cardiolipin IgG Ab
Anti-Cardiolipin IgA Ab
Anti-Cardiolipin IgM Ab

upon further workup as seen in **Table 1**. With the rising evidence of large-vessel thrombosis in young adults with COVID-19,¹² our patient was screened with serologic IgG antibody testing. Despite being asymptomatic, our patient tested positive for SARS-CoV-2 IgG antibodies and this was our likely explanation as to the identifiable cause of her AIS diagnosis. Although the exact mechanism is still unknown, several studies have noted the virus induces cytokine production, which causes a hypercoagulable state through changes in lipid metabolism and platelet aggregation. Consequently, these overall prothrombotic

changes induce platelet instability and rupture leading to AIS as a life-threatening complication of COVID-19.¹³⁻¹⁶ SARS-CoV-2 in pregnancy can not only affect the host but also the fetus leading to fetal demise and even preterm labor. Luckily, our patient's pregnancy was unaffected despite her neurological sequelae.

This case also serves to highlight some of the public health issues of the COVID-19 pandemic. Since social distancing, facial mask wearing and hand hygiene became the new preventative guidelines, patients who developed symptomatic conditions delayed seeking hospital-level care leading to poorer clinical outcomes.¹ If our patient arrived promptly to the hospital when her symptoms initially began, then she may have been within the thrombolytic window for administration of intravenous tPA. Since pregnancy is not a contraindication for tPA, our patient may have been a candidate for thrombolysis if she had presented to the hospital sooner.¹⁷ Subsequently, treatment of her AIS included combination antiplatelet therapy with clopidogrel and aspirin, both of which have been shown to reduce the risk of recurrent stroke during the first three months. Although statins are also used for the prevention of recurrent strokes, they were not prescribed to our patient given its contraindication in pregnancy. Consequently, our patient was safely treated for an acute large-vessel stroke without fetal complications and also showed meaningful clinical recovery with improvement of her initial presenting symptoms.

Conclusion

COVID-19 can be difficult to diagnose since the presentation can vary widely. COVID-19 has been shown to induce a prothrombotic state in young adults leading to an increased risk of acute ischemic stroke (AIS), which is a life-threatening medical condition. After an extensive work-up, we can conclude that the cause of this patient's large-vessel ischemic stroke was most likely due to the COVID-19 infection. This case serves to highlight the importance of attending prenatal care, seeking medical attention in a timely fashion and detecting the SARS-CoV-2 virus in asymptomatic patients. These patients with neurological symptoms may be presenting with signs of COVID-19, which could lead to earlier medi-

cal attention and better clinical outcomes for patients.

Conflicts of Interest

The authors declare they have no conflicts of interest.

The authors are employees of MountainView Hospital-Nevada, a hospital affiliated with the journal's publisher.

This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

Author Affiliations

1. MountainView Hospital-Nevada, Las Vegas, NV

References

1. Lange SJ, Ritchey MD, Goodman AB, et al. Potential Indirect Effects of the COVID-19 Pandemic on Use of Emergency Departments for Acute Life-Threatening Conditions - United States, January-May 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(25):795-800. Published 2020 Jun 26. <https://doi.org/10.15585/mmwr.mm6925e2>
2. Faried A, Dian S, Halim D, et al. The neurological significance of COVID-19: Lesson learn from the pandemic. *Interdiscip Neurosurg.* 2020 December;22:100809. <https://doi.org/10.1016/j.inat.2020.100809>
3. Abou-Ismael MY, Diamond A, Kapoor S, Arafah Y, Nayak L. The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management [published online ahead of print, 2020 Jun 20]. *Thromb Res.* 2020;194:101-115. <https://doi.org/10.1016/j.thromres.2020.06.029>
4. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020;191:145-147. <https://doi.org/10.1016/j.thromres.2020.04.013>
5. Bushnell CD. Stroke in women: risk and prevention throughout the lifespan. *Neurol Clin.* 2008;26(4):1161-xi. <https://doi.org/10.1016/j.ncl.2008.05.009>
6. James AH, Bushnell CD, Jamison MG, Myers ER. Incidence and risk factors for stroke in pregnancy and the puerperium. *Obstet Gynecol.* 2005;106(3):509-516. <https://doi.org/10.1097/01.aog.0000172428.78411.b0>
7. Tate J, Bushnell C. Pregnancy and stroke risk in women. *Womens Health (Lond).* 2011;7(3):363-374. <https://doi.org/10.2217/whe.11.19>
8. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* 2020;395(10229):1033-1034. [https://doi.org/10.1016/s0140-6736\(20\)30628-0](https://doi.org/10.1016/s0140-6736(20)30628-0)
9. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19. *N Engl J Med.* 2020;382(17):e38. <https://doi.org/10.1056/nejmc2007575>
10. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med.* 2020;46(6):1089-1098. <https://doi.org/10.1007/s00134-020-06062-x>
11. Di Renzo GC, Giardina I. Coronavirus disease 2019 in pregnancy: consider thromboembolic disorders and thromboprophylaxis. *Am J Obstet Gynecol.* 2020;223(1):135. <https://doi.org/10.1016/j.ajog.2020.04.017>
12. Oxley TJ, Mocco J, Majidi S, et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. *N Engl J Med.* 2020;382(20):e60. <https://doi.org/10.1056/nejmc2009787>
13. Di Renzo GC, Giardina I. Coronavirus disease 2019 in pregnancy: consider thromboembolic disorders and thromboprophylaxis. *Am J Obstet Gynecol.* 2020;223(1):135. <https://doi.org/10.1016/j.ajog.2020.04.017>
14. Belani P, Schefflein J, Kihira S, et al. COVID-19 Is an Independent Risk Factor for Acute Ischemic Stroke. *AJNR Am J Neuroradiol.* 2020;41(8):1361-1364. <https://doi.org/10.3174/ajnr.a6650>
15. Bova IY, Bornstein NM, Korczyn AD. Acute infection as a risk factor for ischemic stroke. *Stroke.* 1996;27(12):2204-2206. <https://doi.org/10.1161/01.str.27.12.2204>
16. Avula A, Nalleballe K, Narula N, et al. COVID-19 presenting as stroke. *Brain Behav Immun.* 2020;87:115-119. <https://doi.org/10.1016/j.bbi.2020.04.077>
17. Gartman EJ. The use of thrombolytic therapy in pregnancy. *Obstet Med.* 2013;6(3):105-111. <https://doi.org/10.1177/1753495x13488771>