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.

Hereditary angioedema and COVID-19 during pregnancy: Two case reports

Amanda Salih, MD, MPH[a,b], Aaron Chin, MD[c], Manisha Gandhi, MD[d], Amir Shamshirsaz, MD[d,e], Hennie Lombaard, MD[d], and Joud Hajjar, MD, MS[a,b,f]

Clinical Implications

Data regarding outcomes for pregnant women with hereditary angioedema and coronavirus disease 2019 (COVID-19) are unknown. However, pregnancy is potentially a risk factor in triggering severe disease in COVID-19 and hereditary angioedema. Implications for C1 esterase inhibition in patients with COVID-19 are discussed.

Hereditary angioedema (HAE) is a rare disorder typified by deficient or dysfunctional C1 esterase inhibitor (C1-INH). Patients with HAE experience bradykinin-mediated recurrent angioedema and are at risk for fatal asphyxiation. HAE and coronavirus disease 2019 (COVID-19) pathophysiologically overlap via activation of complement, contact, and coagulation systems, and in the production of proinflammatory cytokines.[1] Both HAE and COVID-19 can independently lead to an exaggerated inflammatory response. Common pathway blockade through C1-INH may dampen inflammation and improve outcomes.

An increase in the incidence of flares among patients with HAE with COVID-19 has been reported without worsening COVID-19 outcomes.[2-5] However, data regarding COVID-19 among pregnant patients with HAE are lacking. We describe the clinical course of 2 unvaccinated patients with HAE type 1 who became infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) while pregnant.

The first patient, a 20-year-old Hispanic female with known HAE type 1 (*SERPING1* c.707 T>C), presented at 22-week' gestation with abdominal pain and extremity swelling. Before presentation, she was maintained on subcutaneous C1-INH at 60 IU/kg with good disease control. Routine surveillance screening in the emergency department for SARS-CoV-2 infection was positive by PCR during the peak of the alpha variant, before the Emergency Use Authorization of the COVID-19 vaccine. She would later report sudden anosmia and ageusia. She received 2500 IU of intravenous human C1-INH with resolution of swelling and abdominal pain. No antenatal effects on fetal well-being occurred during pregnancy despite flare.

The second patient, a 24-year-old obese (body mass index = 40) Hispanic female with a history of seizure disorder and HAE type 1 (SERPING1 c.666_667deltTC, p.Q223DfsX33), presented with headache, cough, congestion, and nausea with vomiting at 27-week' gestation following exposure to a household contact with COVID-19. Before presentation, she was maintained on subcutaneous C1-INH at 60 IU/kg with good disease control. She refused COVID-19 vaccination before becoming infected. Positive home antigen testing was confirmed by PCR testing during the delta variant time frame. She was hypoxic on presentation to the emergency department and required supplemental oxygen. A chest X-ray revealed hypoinflated lungs and multifocal basilar consolidative opacities. She was treated with ceftriaxone and azithromycin. Because of her risk profile, therapy was escalated to remdesivir, dexamethasone, and baricitinib. Notably, she required no additional C1-INH and her pregnancy progressed expectantly.

Pregnancy is a unique, dynamic immune state. Pregnant women have demonstrated increased susceptibility to respiratory infections.[6] They are also at increased risk for more severe disease from COVID-19, as evidenced by increased rates of intensive care unit admission and increased requirements for mechanical ventilation when compared with nonpregnant women with SARS-CoV-2.[7] Hormonal fluctuations, and the physiologic stress of pregnancy, delivery, and lactation, can also potentiate HAE flares.[8] Angioedema flares can symptomatically mirror both pregnancy and COVID-19. Parallels, including gastrointestinal symptoms, shortness of breath, and edema, can pose diagnostic challenges.

We report on 2 patients with HAE type 1 and COVID-19 during pregnancy. Pregnancy is a potential independent risk factor for severe disease in COVID-19 and HAE. Despite multiple independent risk factors for poor outcomes, our patients fared well. This might be attributed to C1-INH therapy blunting the dysregulated inflammatory response associated with HAE and COVID-19. Consensus guidelines endorse plasma-derived C1-INH as first-line treatment for HAE during pregnancy due to its demonstrated favorable safety profile.[9,10] C1-INH diminishes activation of complement and subsequent lung injury, reduces vascular permeability, and decreases lung edema and thrombo-inflammation tendency. Therapeutics targeting components of the innate immune system, such as C1-INH, have demonstrated some reported clinical improvement in severe COVID-19.[11] Additional investigations regarding COVID-19 and C1-INH, including patients without complement disorders, are needed to elucidate conclusions further. Patients with HAE remain at risk for life-threatening flares and may benefit from HAE prophylaxis during the pandemic.

[a]Department of Pediatrics, Baylor College of Medicine, Houston, Tex
[b]Pediatric-Immunology, Allergy, and Retrovirology, Texas Children's Hospital, Houston, Tex
[c]Department of Medicine, Baylor College of Medicine, Houston, Tex
[d]Department of Obstetrics and Gynecology - Maternal-Fetal Medicine, Texas Children's Hospital/Pavilion for Women, Houston, Tex
[e]Department of Critical Care Medicine-St Luke's and Baylor College of Medicine, Houston, Tex
[f]Adult-Immunology, Allergy, and Retrovirology, Texas Children's Hospital, Houston, Tex

This research received no specific grant from any funding agency from the public, commercial, or not-for-profit sectors.

Conflicts of interest: J. Hajjar has relevant financial relationships with proprietary interests with The Texas Medical Center Digestive Diseases Center (research grant includes principal investigator, collaborator or consultant, and pending grants as well as grants already received), Jeffrey Modell Foundation (research grant includes principal investigator, collaborator or consultant, and pending grants as well as grants already received), Immune Deficiency Foundation (research grant includes principal investigator, collaborator or consultant, and pending grants as well as grants already received), Baxalta (research grant includes principal investigator, collaborator or consultant, and pending grants as well as grants already received), Chao Physician-Scientist Foundation (research grant includes principal investigator, collaborator or consultant, and pending grants as well as

grants already received), Takeda (Consultant/Advisory Board Member), Pharming (Consultant/Advisory Board Member), Horizon (Consultant/Advisory Board Member), and Alfaisal University (ad hoc consultancy/speaker). A. Swennes acts as a consultant for AbbVie, Merck, and OraSure Technologies. The rest of the authors had no financial relationships to disclose.

Received for publication July 15, 2022; revised November 7, 2022; accepted for publication November 25, 2022.

Available online December 24, 2022.

Corresponding author: Amanda Salih, MD, MPH, or Joud Hajjar, MD, MS, Immunology, Allergy, and Retrovirology, Texas Children's Hospital, Baylor College of Medicine, 300 Bates Ave, Ste 330, Houston, TX 77030. E-mail: Amanda.Salih@bcm.edu. Or: Joud.Hajjar@bcm.edu.

2213-2198

https://doi.org/10.1016/j.jaip.2022.11.045

REFERENCES

1. de Nooijer AH, Grondman I, Janssen NA, Netea MG, Willems L, van de Veerdonk FL, et al. Complement activation in the disease course of coronavirus disease 2019 and its effects on clinical outcomes. J Infect Dis 2020;223:214-24.
2. Kanani A. A case report of COVID-19 virus infection in a patient with hereditary angioedema. ResearchSquare. Preprint posted online July 14, 2020. doi: 10.21203/rs.3.rs-41261/v1.
3. Grumach AS, Goudouris E, Dortas Junior S, Marcelino FC, Alonso ML, Martins RD, et al. Covid-19 affecting hereditary angioedema patients with and without C1 inhibitor deficiency. J Allergy Clin Immunol Pract 2021;9:508-10.
4. Olivares MM, Zwiener RD, Panqueva LM, Contreras Verduzco FA, Mansour E, Rodriguez JA, et al. Covid-19 triggers attacks in HAE patients without worsening disease outcome. J Allergy Clin Immunol Pract 2022;10:855-8.
5. Milota T, Sobotkova M, Smetanova J, Bloomfield M, Vydlakova J, Chovancova Z, et al. Risk factors for severe COVID-19 and hospital admission in patients with inborn errors of immunity—results from a multicenter nationwide study. Front Immunol 2022;13:835770.
6. Rasmussen SA, Kissin DM, Yeung LF, MacFarlane K, Chu SY, Turcios-Ruiz RM, et al. Preparing for influenza after 2009 H1N1: special considerations for pregnant women and newborns. Am J Obstetr Gynecol 2011;204:S13-20.
7. Ellington S, Strid P, Tong VT, Woodworth K, Galang RR, Zambrano LD, et al. Characteristics of women of reproductive age with laboratory-confirmed SARS-COV-2 infection by pregnancy status—United States, January 22–June 7, 2020. MMWR Morb Mortal Wkly Rep 2020;69:769-75.
8. Martinez-Saguer I, Rusicke E, Aygören-Pürsün E, Heller C, Klingebiel T, Kreuz W. Characterization of acute hereditary angioedema attacks during pregnancy and breast-feeding and their treatment with C1 inhibitor concentrate. Am J Obstetr Gynecol 2010;203:131.e1-7.
9. Busse PJ, Christiansen SC, Riedl MA, Banerji A, Bernstein JA, Castaldo AJ, et al. US HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. J Allergy Clin Immunol Pract 2021;9:132-150.e3.
10. Brooks JP, Radojicic C, Riedl MA, Newcomer SD, Banerji A, Hsu FI. Experience with intravenous plasma-derived C1-inhibitor in pregnant women with hereditary angioedema: a systematic literature review. J Allergy Clin Immunol Pract 2020;8:1875-1880.e3.
11. Nilsson B, Persson B, Eriksson O, Fromell K, Hultström M, Frithiof R, et al. How the innate immune system of the blood contributes to systemic pathology in Covid-19-induced ARDS and provides potential targets for treatment. Front Immunol 2022;13:840137.