2020

Presentation of Severe Acute Respiratory Syndrome-Coronavirus 2 Infection as Cholestatic Jaundice in Two Healthy Adolescents

A. Perez
D. Kogan-Liberman
S. Sheflin-Findling
*Zucker School of Medicine at Hofstra/Northwell*, ssheflin@northwell.edu
A. Raizner
K. L. Ahuja
*Northwell Health*, kahuja3@northwell.edu

*See next page for additional authors*

Follow this and additional works at: [https://academicworks.medicine.hofstra.edu/articles](https://academicworks.medicine.hofstra.edu/articles)

*Part of the Pediatrics Commons*

**Recommended Citation**
Perez A, Kogan-Liberman D, Sheflin-Findling S, Raizner A, Ahuja KL, Ovchinsky N. Presentation of Severe Acute Respiratory Syndrome-Coronavirus 2 Infection as Cholestatic Jaundice in Two Healthy Adolescents. . 2020 Jan 01; 226():Article 6687 [ p.]. Available from: [https://academicworks.medicine.hofstra.edu/articles/6687](https://academicworks.medicine.hofstra.edu/articles/6687). Free full text article.

This Article is brought to you for free and open access by Donald and Barbara Zucker School of Medicine Academic Works. It has been accepted for inclusion in Journal Articles by an authorized administrator of Donald and Barbara Zucker School of Medicine Academic Works. For more information, please contact academicworks@hofstra.edu.
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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Presentation of Severe Acute Respiratory Syndrome-Coronavirus 2 Infection as Cholestatic Jaundice in Two Healthy Adolescents

Adriana Perez, MD1, Debora Kogan-Liberman, MD1, Shari Sheflin-Findling, DO2, Aileen Raizner, MD1, Kanya L. Ahuja, MBBS2, and Nadia Ovchinsky, MD, MBA1

Liver abnormalities in severe acute respiratory syndrome-coronavirus 2 infection, including hepatitis and cholestasis, have been observed in adults and are associated with worse outcomes. We describe 2 adolescents with cholestasis and hepatitis with mild presentation of severe acute respiratory syndrome-coronavirus 2 lacking typical symptoms. Our intention is to raise index of suspicion for testing and protective equipment use. (J Pediatr 2020;226:278-80).

As of June 25, 2020, the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) resulted in >9.4 million confirmed cases worldwide and >482 000 deaths worldwide, including >2.3 million cases and >121 000 deaths reported in the US, among which were 84 pediatric deaths in persons <24 years of age by June 13 2020.1-3

In the US, 22% of the population is comprised of infants, children, and adolescents <18 years of age.4 SARS-CoV-2 affects adults and children in dramatically different ways. Early pediatric epidemiologic data of 3 studies with 1391 and 2135 children from Wuhan, China, and 2572 US children demonstrated that the majority had mild symptoms compared with adults, but may serve as vectors of transmission in society.4-6 North American pediatric intensive care units collaborative report from March and April 2020 confirmed these findings, but also noted that severe illness in children is significant, albeit far less frequent, compared with adults.7 Infants and children with comorbidities were particularly vulnerable to COVID-19.6–8

No previous study to date has reported an association between COVID-19 and acute cholestasis in the pediatric population. The incidence of liver injury in adult patients with COVID-19 ranges from 14.8% to 53%, being more significant in severe cases and ranging up to 78% among fatal cases.9 Liver abnormalities described included elevation of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), mildly elevated bilirubin levels, high gamma-glutamyl transferase, and low albumin levels (2.6-3.3 g/L).9,10

We present 2 cases of acute hepatitis with clinically apparent jaundice and cholestasis without biliary obstruction associated with SARS-CoV-2 infection. Both adolescents lacked other typical features of COVID-19 respiratory tract infection and had a mild disease course. Given significant variability of COVID-19 symptoms in children, providers had a high index of suspicion and tested these patients with an unusual presentation.

### Methods

Institutional review board approval was obtained at Albert Einstein College of Medicine. These case reports were exempt from institutional review board oversight at Feinstein Institutes for Medical Research of Northwell Health. Patients described here are unique to this report and are excluded from our registry of COVID-19 patients. Demographic information and clinical, laboratory, and imaging results were examined.

**Case 1**

A 16-year-old boy presented to the emergency department (ED) of the Children’s Hospital at Montefiore in the Bronx, New York, with 1 day of scleral icterus, epigastric abdominal pain, nausea, 2 episodes of nonbloody, nonbilious emesis, decreased oral intake, and dark urine. No respiratory symptoms or diarrhea were present. The patient and family reported staying at home in the preceding 3 weeks without any exposure to sick contacts, a known COVID-19 case, essential workers, or travel. Patient denied any drug or alcohol use.

His medical history was significant for elevated serum hepatic enzymes with acute cholestasis 3 years previously, secondary to cholelithiasis for which he underwent cholecystectomy. His hepatic enzymes and bilirubin level had normalized. He was found to carry reduced activity in uridine diphasphate-glucuronosyltransferase A1 gene associated with Gilbert syndrome.11

---

ALT Alanine aminotransferase
AST Aspartate aminotransferase
COVID-19 Coronavirus disease 2019
ED Emergency department
SARS-CoV-2 Severe acute respiratory syndrome-coronavirus 2
Upon arrival to the ED, he was noted to have tachycardia to 128 bpm and was afibrile. Physical examination was notable for scleral icterus, dry mucous membranes, and epigastric tenderness. He was found to have significantly elevated serum AST and ALT at 655 U/L and 767 U/L, respectively. Conjugated hyperbilirubinemia was also detected with total bilirubin/direct bilirubin at 3.6/2.2 mg/dL. Gamma-glutamyl transferase was 147 U/L. Liver synthetic function, international normalized ratio, albumin, and platelets were normal (Table). Ultrasound examination of the liver and biliary tree was normal.

Given his prior history of cholelithiasis with cholecystectomy and concern for an obstructive process, magnetic resonance cholangiopancreatography was obtained to further assess for any anatomic abnormalities and revealed no evidence of intrahepatic or extrahepatic ductal dilatation or biliary stricture. Although he had no fever or respiratory symptoms, COVID-19 hepatitis was considered in the differential diagnosis, and his SARS-CoV-2 polymerase chain reaction test was positive. The patient was admitted for monitoring. No treatment targeting COVID-19 was initiated owing to a lack of supporting evidence and otherwise well-being. Airborne/special contact precautions were maintained during his hospitalization. The patient never developed respiratory or other systemic inflammatory symptoms. After 24 hours, his direct bilirubin level decreased to 0.4 mg/dL. Three weeks after discharge, AST/ALT decreased to 47/76 U/L and total bilirubin remained elevated at 1.7 mg/dL with normal direct fraction of <0.5 mg/dL (consistent with prior diagnosis of Gilbert).

Case 2
A 17-year-old previously healthy young woman presented to the ED at Cohen Children’s Medical Center in New York’s Nassau County with 4 days of fever, acute onset of jaundice, and dark urine. She had developed urinary urgency without fever or dysuria 6 days before presentation. She was seen at a clinic, where a urine culture was obtained that was negative. Four days before presentation, her urine turned dark orange/brown and she developed fever with maximum temperature of 103°F. She also complained of chills and night sweats, and had an episode of nonbloody diarrhea. On the day of presentation, she noted that the whites of her eyes seemed to be yellow. No respiratory symptoms (cough, congestion, and/or difficulty breathing) were present. She had no abdominal pain, nausea, or vomiting. She no longer experienced urinary urgency or dysuria. There was no prior history of cholelithiasis, jaundice, or liver disease. She denied any drug or alcohol use. She confirmed no exposure to a case of COVID-19 or recent travel.

In the ED, she had tachycardia to 111 bpm and was afibrile. Physical examination revealed a nonobese female with scleral icterus without abdominal tenderness. Laboratory test results revealed elevation of serum AST and ALT to 154 and 294 U/L, respectively. One month prior, AST and ALT levels obtained during annual physical examination were normal (11 and 15 U/L, respectively). Total and direct bilirubin levels were 3.4/1 mg/dL and gamma-glutamyl transferase was 147 U/L. Liver synthetic function, international normalized ratio, albumin, and platelets were normal (Table).

An abdominal ultrasound examination revealed hepatomegaly (16.1 cm span) with normal echogenicity and without any gallstones, sludging, or bile duct dilation. SARS-CoV-2 polymerase chain reaction test on nasal specimen was positive. She was discharged home from the ED with close follow-up. Two weeks later, serum AST and ALT levels were 56 and 147 U/L respectively, with total and direct bilirubin levels of 0.6/0.2 mg/dL.

Discussion
Mild cholestasis in COVID-19 was described in a pediatric patient from Wuhan, China. A 55-day-old infant with pneumonia and acute cardiac injury developed mild hepatitis (AST/ALT of 100/84 IU/L) and conjugated hyperbilirubinemia (total bilirubin/direct bilirubin 2/1.4 mg/dL), which resolved with clinical improvement.

The incidence of liver injury in adult patients with COVID-19 can range from 14.8% to 78.0%. One study of adults with severe COVID-19 admitted to the intensive care unit did not report a significant difference in percentage of patients with liver dysfunction between survivors and nonsurvivors, although biochemical test results of the nonsurvivors showed more abnormalities.

The cause of liver injury can be multifactorial, from drug-induced liver injury (owing to use of antiviral or antibiotic agents, corticosteroids, and natural remedies), hepatic...
congestion associated with high positive end-expiratory pressure, and/or direct liver damage by virus-induced T lymphocytes.\textsuperscript{9,14} High levels of proinflammatory cytokine molecules were found in patients with COVID-19 activating T-helper 1 cell response and inducing dysregulation of the innate immune response.\textsuperscript{9,14} A postmortem liver biopsy obtained in a patient with COVID-19 from Wuhan, China, demonstrated moderate microvesicular steatosis and mild lobular and portal activity, indicating either virus- or drug-induced liver injury.\textsuperscript{9,15}

Recent evidence indicates that angiotensin converting enzyme II is likely the cell receptor of SARS-CoV-2.\textsuperscript{16,17} Chai et al were able to identify expression of angiotensin converting enzyme II within bile duct epithelial cells (cholangiocytes), but not hepatocytes in healthy liver tissues.\textsuperscript{18} Cholangiocytes are known to play an important role in liver regeneration and immune response, which could be a mechanism underpinning acute cholestasis we observed.\textsuperscript{19}

In our 2 cases of acute cholestasis with hepatitis, the patients lacked typical features of COVID-19 such as fever, cough, shortness of breath, myalgia, sore throat, or significant gastrointestinal symptoms, as well as any signs of inflammatory dysregulation seen in multisystem inflammatory syndrome in children.\textsuperscript{4,19} Both patients were nonobese adolescents without underlying liver disease or other comorbidities.

Our patients had a mild clinical course. Extensive evaluation for cholestasis may not be necessary in otherwise healthy pediatric patients with SARS-CoV-2 infection. Imaging can be limited to those with symptoms concerning for biliary obstruction. Further studies are needed to ascertain whether a higher rate of cholestasis is associated with SARS-CoV-2 infection in children and adolescents. Recognition and identification of children and adolescents with acute cholestasis secondary to SARS-CoV-2 is important for management, appropriate infection control and proper use of personal protective equipment.

Submitted for publication Jun 29, 2020; last revision received Jul 11, 2020; accepted Jul 17, 2020.

Reprint requests: Nadia Ovchinsky, MD, MBA, Director, Division of Pediatric Gastroenterology, Hepatology, and Nutrition Pediatric Hepatology, Medical Director, Pediatric Liver Transplant, Associate Professor of Pediatrics, Albert Einstein College of Medicine, Children’s Hospital at Montefiore, 3411 Wayne Ave, 7th Floor, Bronx, NY 10467. E-mail: novchinsky@yahoo.com

References

1. World Health Organization. Coronavirus disease (COVID-19) outbreak situation. 2019. www.who.int/emergencies/diseases/novel-coronavirus-. Accessed June 26, 2020.

2. CDC. Coronavirus Disease 2019 (COVID-19), Cases, Data and Surveillance. Cases in the U.S. www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html. Accessed June 26, 2020.

3. CDC. National Center for Health Statistics. Provisional Death Counts for Coronavirus Disease (COVID-19). Weekly updates by select demographic and geographic characteristics. www.cdc.gov/nchs/nvss/covid_19weekly/#AgeAndSex. Accessed June 19, 2020.

4. Coronavirus Disease 2019 in Children- United States, February 12-April 2, 2020. MMWR Morb Mortal Wkly Rep 2020;69:422-6.

5. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 infection in children. N Engl J Med 2020;382:1663-5.

6. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 among children in China. Pediatrics 2020;145.

7. Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. JAMA Pediatr 2020 [Epub ahead of print].

8. Sun D, Li H, Lu XX, Xiao H, Ren J, Zhang FR, et al. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center’s observational study. World J Pediatr 2020;16:251-9.

9. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int 2020;40:998-1004.

10. Palogiannis P, Zinelu A. Bilirubin levels in patients with mild and severe Covid-19: a pooled analysis. Liver Int 2020;40:1787-8.

11. Erlinger S, Arias IM, Dhumeaux D. Inherited disorders of bilirubin transport and conjugation: new insights into molecular mechanisms and consequences. Gastroenterology 2014;146:1625-38.

12. Cui Y, Tian M, Huang D, Wang X, Huang Y, Fan L, et al. A 55-day-old female infant infected with 2019 novel coronavirus disease: presenting with pneumonia, liver injury, and heart damage. J Infect Dis 2020;221:1775-81.

13. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475-81.

14. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.

15. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020;8:420-2.

16. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003;426:450-4.

17. de Wilde AH, Snijder EJ, Kikker M, van Hemert MJ. Host factors in coronavirus replication. Curr Top Microbiol Immunol 2018;419:1-42.

18. Chai X, Hu L, Zhang Y, Han W, Lu Z, Ke A, et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. bioRxiv 2020;2020.

19. Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. J Pediatr 2020;16:251-9.

20. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theorchis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395:1607-8.