

Severe Hepatitis in Pediatric COVID-19

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Abbreviations:

coronavirus disease 2019 (COVID-19); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); Alanine transaminase (ALT); Aspartate aminotransferase (AST); Multisystem Inflammatory Syndrome in Children (MIS-C); Total bilirubin (Tbili); International normalized ratio (INR); Lactate dehydrogenase (LDH); Pediatric Acute Liver Failure Study Group (PALFSG); Computed tomography (CT); Pediatric intensive care unit (PICU); electroencephalogram (EEG); Gamma-glutamyl transferase (GGT)

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SA and TD equally contributed to design of the manuscript, collection of clinical data and drafting the manuscript and are co-first authors. LKK, AAS and CC provided oversight in drafting and critical review of the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and approved the final manuscript.

Abstract

Hepatic involvement in COVID-19 is typically characterized as mild hepatitis with preserved synthetic function in children. Severe hepatitis is a rare complication of COVID-19 infection that has not been extensively described in the pediatric population. We report a case series of 4 previously healthy children who presented with significant hepatitis as the primary manifestation of COVID-19 infection. Two of these patients met criteria for acute liver failure. None of the patients had respiratory symptoms. One patient was found to have complement dysfunction resulting in microangiopathic features and was treated successfully with eculizumab. This case is in line with adult post-mortem data showing that more severe cases of hepatic dysfunction secondary to COVID-19 infection may be associated with complement activation and microangiopathic features. Liver function should be evaluated in cases of severe COVID-19, and SARS-CoV-2 infection should be considered as a cause of acute severe hepatitis even in patients without significant respiratory or other systemic symptoms.

What is known:

1. COVID-19 can cause elevated liver enzymes in children.
2. Severe hepatitis in COVID-19 is typically associated with significant respiratory or systemic symptoms.

What is new:

1. COVID-19 in the absence of significant respiratory or other symptoms may be associated with pediatric acute severe hepatitis and even acute liver failure.
2. Complement hyperactivation can be associated with hepatic dysfunction in COVID-19 and may improve with targeted therapy.

Introduction

Since the first clinical description of coronavirus disease 2019 (COVID-19) and its etiologic agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in Wuhan, China in late 2019, the medical and scientific communities have been tirelessly attempting to eradicate and treat manifestations of this novel pathogen (1). Hepatic involvement in COVID-19 in children is typically characterized by alanine transaminase (ALT) and aspartate aminotransferase (AST) elevation with preserved liver synthetic function (2). Severe hepatic dysfunction can be seen in Multisystem Inflammatory Syndrome in Children (MIS-C), which typically occurs several weeks after the initial SARS-CoV-2 infection rather than during acute infection (3,4). However, there is a paucity of literature describing pediatric cases of severe hepatic impairment as a primary manifestation of acute SARS-CoV-2 infection. Here we review the current literature and describe a case series of children with acute SARS-CoV-2 infection who had severe acute hepatitis as the primary manifestation of COVID-19.

Case presentation

Case 1

A previously healthy 6-month-old female presented to the emergency department (ED) due to new onset irritability, poor feeding, recurrent emesis and progressive lethargy over a span of 24 hours. Upon arrival to ED she was noted to be unresponsive with Glasgow coma scale of 8 and shallow breathing. Exam was notable for hypothermia (95.5C), epistaxis and decreased pupillary light response. Her laboratory assessment in the ED was suggestive of hepatic dysfunction with significantly elevated AST, ALT, total bilirubin (Tbili), international normalized ratio (INR), lactate, ammonia, and lactate dehydrogenase (LDH) with hypoalbuminemia, hyponatremia and hypoglycemia (table 1). Coagulopathy did not resolve with vitamin K administration, meeting Pediatric Acute Liver Failure Study Group (PALFSG) criteria for acute liver failure (ALF) (5). Her toxicology and acetaminophen screens were negative, and infectious evaluation was notable for positive SARS-CoV-2 PCR via nasopharyngeal swab on the same day symptoms arose. Evaluation for age-specific causes of ALF including other infections (urine and blood culture as well as Parvovirus B19, Hepatitis A/B/C, Epstein-Barr Virus, Herpes Simplex Virus and Cytomegalovirus) was unremarkable. Screening evaluation for inborn errors of metabolism including plasma amino acids, urine organic acids, acylcarnitine profile and pyruvate/lactate ratio were non-diagnostic. A head computed tomography (CT) showed no intracranial hemorrhage. Treatment was initiated with vancomycin and ceftriaxone for presumed sepsis. She became more responsive upon admission to the pediatric intensive care unit (PICU) after fluid and dextrose resuscitation. Her immunological work up was notable for elevated ferritin, procalcitonin, and IL-8 suggestive of sepsis (table 2). Her SARS-CoV-2 PCR became negative within 24 hours of presentation and SARS-CoV-2 anti-nucleocapsid IgG was positive, suggestive of onset of infection at least 10 days prior. Over the subsequent days, she recovered with supportive care. AST, ALT, INR, and bilirubin all significantly improved prior to discharge. At the time of follow-up one month later, hepatic function results were normal.

Case 2

A previously healthy 4-month-old male presented to the ED due to feeding difficulties, vomiting, hypotonia, diaphoresis, and progressive lethargy over 12 hours. In the ED, he was febrile (38.7C), tachycardic, tachypneic, hypotensive, and unresponsive. His labs were notable for hypoglycemia, *leukopenia*, thrombocytopenia, and elevated AST, ALT, total bilirubin, lactate, ammonia, and INR (table 1 and 2). Coagulopathy did not resolve with vitamin K, and he met ALF criteria. SARS-CoV-2 PCR via nasopharyngeal swab was sent one day after symptoms began and resulted as positive. Work-up for other causes of ALF was negative including infectious (Hepatitis A/B/C, Cytomegalovirus, Epstein-Barr Virus, Human Herpes Virus 6, Parvovirus B19, Parechovirus, Adenovirus and blood/urine cultures) and inborn errors of metabolism. His toxicology and acetaminophen screens were negative. Echocardiogram showed normal biventricular function. He was intubated, fluid resuscitated with isotonic saline and dextrose, and started on epinephrine infusion. Empiric vancomycin, ceftriaxone, and acyclovir were initiated. His infectious evaluation was notable for persistent positive SARS-CoV-2 PCR via nasopharyngeal swab and tracheal aspirate both 2 and 9 days after symptoms began. SARS-CoV-2 anti-nucleocapsid IgG was tested 4 days after symptoms began and was negative. Inflammatory workup was notable for elevated ferritin and normal soluble IL-2 receptor, ESR, and CRP. His cytokine panel had mild elevations in interferon gamma, IL-10, and TNF-alpha and moderate elevations in IL-6 and IL-8 (table 2). He had evidence of acute kidney injury (creatinine-0.7 mg/dL, normal range for age: 0.1-0.4) and seizure activity on video electroencephalogram (EEG). Due to elevated soluble C5b9 (complement membrane attack complex) and low C3 and C4 in the setting of anemia and thrombocytopenia associated with hepatic, renal, and neurologic disease, he was treated with eculizumab for presumed thrombotic microangiopathy. Liver function improved prior to discharge and had normalized by the time of last follow-up 8 months later. His SARS-CoV-2 anti-nucleocapsid IgG was tested 6 months after presentation and was positive.

Case 3

A previously healthy 16-year-old female presented with cough, congestion, and fever. SARS-CoV-2 PCR via nasopharyngeal swab 3 days after the onset of symptoms was positive. Her parents' SARS-CoV-2 PCR via nasopharyngeal swabs were also positive. She was seen at a local ED for emesis and abdominal pain. CT scan at that time was unremarkable, and liver enzymes were elevated (AST 334 U/L, ALT 358 U/L). She was subsequently discharged home but returned to care due to persistent severe abdominal pain, at which point her liver enzymes, LDH, and ferritin were markedly elevated with leukopenia and a prolonged INR that was responsive to Vitamin K and thus did not meet PALFSG criteria for ALF (table 1). Antibiotics were initiated for presumed acute abdomen, and the patient was admitted to the PICU where she received 80mg IV methylprednisolone for empiric treatment of COVID-19. Other significant findings included low CD3+CD8+ and CD3+CD4+ cell subsets on flow cytometry, low C3 and C4, elevated soluble IL-2 receptor, and elevated neopterin (table 2). Work-up for other causes of severe hepatitis was negative including infectious (Hepatitis A/B/C, Cytomegalovirus, Epstein-Barr Virus, Human Herpes Virus 6, Parvovirus B19, Herpes Simplex Virus, Enterovirus, Adenovirus, and blood/urine

cultures), autoimmune (anti-nuclear antibody, anti-smooth muscle antibody, anti-liver kidney microsomal antibody), and Wilson's disease (ceruloplasmin). Her toxicology and acetaminophen screens were negative. SARS-CoV-2 anti-nucleocapsid total antibody testing was negative, consistent with acute infection. She had evidence of stage 1 hepatic encephalopathy which resolved by the time of discharge. Liver enzymes and INR improved prior to discharge and had normalized at the time of follow-up 1 month later.

Case 4

A previously healthy 11-year-old male presented with non-bloody, non-bilious emesis and abdominal pain. He was afebrile without other symptoms. He was admitted to the hospital for intravenous fluids due to dehydration. Labs were significant for markedly elevated ALT and AST and elevated gamma-glutamyl transferase (GGT) with normal bilirubin and INR (table 1). SARS-CoV-2 PCR testing via nasopharyngeal swab 2 days after the onset of symptoms was positive. Work-up for other causes of hepatitis was negative including infectious (Hepatitis A/B/C, Cytomegalovirus, Epstein-Barr Virus), autoimmune (anti-nuclear antibody, anti-smooth muscle antibody, anti-liver kidney microsomal antibody), and alpha-1 antitrypsin deficiency (phenotype MM). Immunophenotyping as was done in the other patients included in table 2 was not done in this patient given swift recovery. Symptoms improved quickly, and he was discharged home. All liver enzymes at the time of follow-up 2 months post-discharge were normal.

Discussion

Hepatic involvement has been widely reported in acute SARS-CoV-2 infection in adults in the presence or absence of respiratory symptoms (6-8). Mild elevation of liver enzymes without associated liver dysfunction is commonly seen, with resolution of hepatitis as the clinical course of COVID-19 improves (9). More significant hepatic dysfunction can be seen in severe COVID-19 with respiratory failure and has been associated with increased morbidity and mortality (10, 11). Severe hepatic disease as a primary manifestation of acute SARS-CoV-2 infection, however, is unusual, although rare cases of isolated acute hepatitis secondary to COVID-19 have been reported (12). Possible mechanisms of liver injury include a direct viral cytotoxic effect, mitochondrial protein interaction, endothelial dysfunction, and systemic inflammatory response to the virus (13).

There are fewer studies describing hepatic involvement in acute SARS-CoV-2 infection in the pediatric population, and most cases reported describe mild elevation of liver enzymes (14). Severe SARS-CoV-2 infection resulting in multi-organ failure and MIS-C have been associated with significant hepatitis in children (2, 4). However, severe acute hepatitis or ALF as the primary manifestation of acute SARS-CoV-2 infection without significant respiratory or systemic involvement has been rarely described (15).

In this case series, we present 4 patients with severe hepatitis and liver dysfunction due to acute SARS-CoV-2 infection without significant respiratory involvement. Each patient had evidence of SARS-CoV-2 infection based on positive PCR, though the timing of infection may have varied. These patients did not meet criteria for MIS-C (fever for over 24 hours, laboratory evidence of inflammation, multisystem organ involvement, no alternative

diagnoses, and recent SARS-CoV-2 infection, all of which must be met) nor hemophagocytic lymphohistiocytosis (HLH) 2004 criteria (16, 17). In case 1, the rapid clearance of detectable virus by PCR from the upper respiratory tract and positive anti-nucleocapsid IgG antibodies against SARS-CoV-2 suggests a more subacute presentation with onset of infection at least 10-14 days prior. Cases 2 and 3 had negative antibody testing along with positive SARS-CoV-2 PCR, indicating acute COVID-19, and case 4 had positive PCR shortly after the onset of symptoms. While degree of systemic involvement varied, none of the cases had severe respiratory symptoms or met criteria for anti-viral directed treatment of SARS-CoV-2 infection. In all cases, there were no preexisting liver conditions reported, and a broad work-up for other primary causes of liver disease was negative. We describe two infants with PALF, and this is a novel observation as previous reports of COVID-19 hepatitis in infants only described mild elevation in liver enzymes without hepatic dysfunction (18). There were also no reported co-morbidities such as obesity or diabetes in our series, which have been associated with more severe COVID-19 presentation (2).

A novel observation in this case series is the association of dysregulated complement response and hepatic dysfunction as part of the clinical presentation (cases 2 and 3). Both patients had evidence of complement hyperactivation (low C3 and C4), and case 2 was treated with complement-directed therapy, resulting in rapid improvement in liver function. It has been established that microangiopathy and complement activation are integral in the pathogenesis of COVID-19 as a cytokine storm syndrome, and targeting the complement cascade shows promise as a therapeutic approach in this subset of patients (19). In line with these findings, the main effect of SARS-CoV-2 infection on the liver appears to be predominated by cytokine-mediated injury (20). A common histological feature of hepatic dysfunction in the livers of adults with severe SARS-CoV-2 infection is endotheliitis with sinusoid microangiopathy (21). The swift clinical improvement seen in case 2 after treatment with eculizumab demonstrates the importance of evaluating for microangiopathy as part of COVID-19 associated hepatic dysfunction and considering targeted therapy.

Limitations of our study include that this was an observational case series and that clinical evaluation and treatment was not standardized and was at the discretion of the treating providers. Additionally, laboratory evaluation for immunological work-up was variable and histologic data was not available.

Conclusion

We describe 4 pediatric patients with severe acute hepatitis as the predominant feature of SARS-CoV-2 infection, with 3 cases presenting with acute COVID-19 and one with a more subacute presentation. Liver function should be evaluated in cases of severe COVID-19, and SARS-CoV-2 infection should be considered as the cause of acute severe hepatitis even in patients without significant respiratory or systemic symptoms. More severe cases of hepatic dysfunction may be associated with complement activation and microangiopathic features. Further data are needed to better characterize the immune phenotype and pathophysiology of severe hepatic dysfunction as part of SARS-CoV-2 infection.

Footnote

All participants were consented for publication of de-identified patient data as part of SARS-CoV-2 registry and IRB# 20-018076 at Children's Hospital of Philadelphia and exempt from IRB approval at Lurie Children's Hospital. Of note, cases 1 and 2 were previously included in the cohort study described by Kehar et al (22).

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Table 1- Characteristics of study population during hospital course.

Patient No.	Age/Sex	Ethnicity/race	Length of stay (days): a. Hospital ward b. ICU	SARS-Cov2 PCR	Respiratory support	Inotropes	GCS nadir	AKI/ Dialysis	AST (U/L) Peak/ Nadir	ALT (U/L) Peak/ Nadir	Tbili/Dbili (mg/dL) a. Peak b. Nadir	INR Peak/ Nad-r	Alb (g/dL) Nadir/Peak	Glu (mg/dL) Nadir	Ammonia (umol/L) Peak	LDH (U/L) Peak	Treatment
1*	6mo/F	African American	a. 13 b. 5	Positive	Room Air	No	8	No/No	4307/56	6392/25	a.12.2/8.3 b. 0.6/0	7.4/ 0.96	2.1/5	<30	140	2692	Supportive
2†	4mo/ M	African American	a. 15 b. 10	Positive	Intubated	Epi	N/A	Yes/No	10,110/48	9,080/25	a. 6.3/3.7 b. 0.5/0	5/ 0.87	2.3/5.6	7	54	2,461	Ecilizumab
3**	16yo/ F	Caucasian	a. 2 b. 3	Positive	Room air	No	15	No/No	6,255/17	11,150/36	a. 0.6/0.2 b. 0.3/0.2	2.5/1.0	3.1/4.6	70	114	>2500	1 dose of MP
4***	11yo/ M	Caucasian	a. 0 b. 1	Positive	Room air	No	15	No/No	650/21	1932/18	a. 1.2/0.2 b. 0.5/0.2	1.2/1.0	3.9/5.0	82	N/A	341	Supportive

AKI-acute kidney injury; Alb- Albumin; ALT- alanine aminotransferase; AST-aspartate aminotransferase; Epi- epinephrine; GCS-Glasgow coma scale; Glu- glucose; ICU-intensive care unit; INR- international normalized ratio; LDH- lactate dehydrogenase; MO-months old; MP-methylprednisolone; PCR- polymerase chain reaction; YO- years old

* Patient 1- peak AST/ALT/Tbili/Dbili/INR/Ammonia/LDH and nadir Alb were during first 72 hours of admission. Nadir AST/ALT/Tbili/Dbili/INR/Ammonia/LDH and peak Alb were during follow up visits 1-2 months after discharge.

! Patient 2- peak AST/ALT/Tbili/Dbili/INR/Ammonia/LDH and nadir Alb were during first 72 hours of admission prior to administration of Eculizumab. Nadir AST/ALT/Tbili/Dbili/Ammonia/LDH were during follow up visits 2 and 7 months after discharge. Nadir INR and peak Alb were close to discharge after administration of Eculizumab.

** Patient 3 – peak AST/ALT/Tbili/INR/Ammonia/LDH and nadir Alb were during first 72 hours of admission. Nadir AST/ALT/Tbili/Dbili/INR/Ammonia/LDH and peak Alb were during follow up visits 4-5 months after discharge.

*** Patient 4 - peak AST/ALT/Tbili/INR/Ammonia/LDH and nadir Alb were during first 72 hours of admission. Nadir AST/ALT/Tbili/Dbili/INR/Ammonia/LDH and peak Alb were during follow up visits 1-2 months after discharge.

Table 2- Immune characteristics of patients during hospital course.

Patient No	Age/sex	WBC (K/uL) Nadir/peak	ANC (per/uL) Nadir/peak	ALC (per/uL) Nadir/peak	Hb (g/dL) Nadir	Platelets (K/uL) Nadir/peak	ESR (mm/hr)	CRP (mg/dL) (normal range)	IL-6 (pg/dL) (normal range)	Ferritin (ng/mL)	D-dimer (ug/mL FEU) peak	SIL2R pg/mL (normal range)	Procal (ng/mL) peak	C3/C4 (mg/dL) (normal range)	other
1*	6mo/F	4.9/ 19.8	1600/ 9400	1840/ 8220	6.6	91/ 339	N/A	0.5 (0-0.9)	4.3 (< 3.5)	1,748	17,414	N/A	2.2	N/A	IL-6- 134 pg/mL (0-10) Factor 5- 11% Factor 7- 1%
2!	4mo/ M	3.1/ 15.3	820/ 8890	930/ 6850	6.7	34/ 554- after eculizumab	<1	1 (0-0.9)	75.4 (< 3.5)	39,270.5	64,702	1113 (398-1940)	4.7	C3: 65 (73-165) C4: 4.8 (16-45)	Sc5B-9 924 (<244 ng/mL) peak. Repeat 189 after eculizumab. IL-8- 271 pg/mL (0-10) Factor 5- 3% Factor 7- 9% Had decrease response to TLR2- TLR6, TLR5, TLR7- TLR8 and TLR4. Normal response to TLR2- TLR1
3**	16yo/ F	1.4/ 12.5	1100/ 10640	240/ 2950	10.8	164/ 225	4	1.5 (0.2-1)	3.3 (< 1.8)	> 40,000	4.82	1118 (175.3- 858.2)	N/A	C3: 17.9 (86-184) C4: < 1.7 (20-59)	Neopterin- 20 (<10) Factor 5 and 7 low Flow cytometry (per/mm ³): Low CD3+CD8+ 120 (332 - 1,307) Low CD3+CD4+ 173 (548 - 1,720)

ANC- absolute neutrophil count; ALC – absolute lymphocyte count; ; C3- complement C3; C4- complement C4; CRP- C reactive protein; ESR- erythrocyte sedimentation rate; Hb-hemoglobin; MO-months old; procal- procalcitonin; SIL2R – soluble IL-2 receptor; TLR- Toll-like receptor; WBC- white blood count; YO- years old

* Patient 1- WBC/ANC/ALC/Hb nadir listed were during first 3 days of admission, platelet nadir was on day 7 of admission. WBC/ANC/ALC peak listed on day 3 of admission and Platelets peak at follow up visit 3 weeks after discharge. IL-6, Ferritin, D-dimer, Procal, IL-8 and factor factor 5/7 values listed were during first 72 hours of admission.

! Patient 2- WBC/ANC/ALC/Hb/Platelets nadir listed were during first 5 days of admission prior to administration of Eculizumab. WBC/ANC/ALC/Platelets peak listed were at day of discharge after administration of Eculizumab. IL-6, Ferritin, D-dimer, SIL2R, Procal, C3/C4 IL-8, Sc5B-9, Factor 5/7 and TLR response panel listed were during first 72 hours of admission prior to administration of Eculizumab.

** Patient 3 - WBC/ANC/ALC/Hb/Platelets nadir listed were at time of admission. WBC/ANC/ALC/Platelets peak listed were within 1-2 weeks after admission. IL-6, Ferritin, D-dimer, SIL2R, C3/C4, neopterin, factor 5 and 7, and flow cytometry results listed were during the first 72 hours of admission.