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## Case Report

# New viral hepatitis caused by covid-19 virus- A case report

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### ABSTRACT

During the current COVID-19 pandemic, the assessment, and management of patients are challenging. The clinical features of COVID-19 are heterogeneous and subtle in many cases. Although diffuse alveolar damage and acute respiratory failure are the main features of COVID-19, the impairment of other organs are also seen. Gastrointestinal symptoms are common in pediatric patients with COVID-19 as SARS-CoV-2 is able to enter gastrointestinal epithelial cells. However, these complaints can also be caused by a COVID-19-independent concomitant abdominal pathology. Therefore, patients with fever with acute abdominal pain, anorexia, nausea, vomiting and diarrhea need to be assessed very thoroughly. Previous studies reported that COVID-19 was likely to result in liver injury. Based on clinical cases, we present our approach of management of children with symptoms and signs of viral hepatitis and concomitant suspicion of COVID-19.

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## 1. Introduction

Several cases of pneumonia caused by an unknown etiological agent was reported in the Chinese city of Wuhan in December 2019. The full genome sequence analysis revealed the etiological agent to be a corona virus that is divergent from the corona virus that caused Severe Acute Respiratory Distress Syndrome (SARS) and middle east respiratory syndrome (MERS).<sup>1</sup> This new Corona virus was named “Severe Acute Respiratory Syndrome Corona virus 2” (SARS-CoV-2) by the World Health Organization (WHO). The disease caused by SARS-Cov-2 was “Coronavirus disease 2019”-COVID-19.<sup>1</sup> COVID-19 pandemic is a major public health crisis threatening humanity at this point of time.

Modes of transmission of disease are direct inhalation of infected droplets (produced during coughing or sneezing by infected person) and direct contact with surfaces and fomites soiled by infected respiratory secretions.<sup>2</sup> Exact duration of viability of virus on surfaces may be few

hours to few days. The survival duration is likely to be considerably low at higher temperature and low humidity conditions.<sup>2</sup> Children usually become symptomatic after an incubation period of 2-14 days. Median incubation period has been assessed to be 5 days. Most patients with COVID-19 have respiratory tract infection associated with SARS COVID infection. The clinical symptoms include fever, cough, sore throat, breathlessness or shortage of breath, fatigue, myalgia, dizziness, headache, seizure, rash, conjunctival congestion, mucositis, abnormal coagulation, loss of smell, loss of taste and shock. Few children present with gastrointestinal symptoms like diarrhea, vomiting and abdominal pain or other atypical symptoms. Symptoms and signs of COVID-19 are nonspecific and mimic any viral illness. Some of them may progress to severe and systematic disease characterized by ARDS, sepsis and septic shock. Multiorgan failure include acute kidney injury, acute liver injury and acute cardiac injury which can cause potentially long-term damage to heart, liver and kidneys.<sup>3</sup> Even presentation as meningoencephalitis is seen. We here serialize two cases, who presented with fever and jaundice of 1–2-week durations.

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## 2. Case Presentation

### 2.1. Case 1

A 5-year-old previously healthy girl was admitted in our hospital with abdominal pain for 4 days and fever and vomiting for 2 days as the chief complaints. Child had severe abdominal pain: non colicky, dull aching, non-radiating, diffuse pain. Child had vomiting for 2 days, 2-3 episodes per day, which was non projectile, non-bilious and not blood stained. Child also had yellowish discoloration of urine for 2 days. There was no history of contact to a COVID-19 patient or symptomatic acquaintances. No history of any ingestion of herbal medicines. The child had a normal birth and growth history and received vaccinations according to plan.

On clinical examination, child was febrile, temperature 104°F, RR-24/min, PR- 96/min, BP-90/60 mm Hg, Spo2-99%. Child was conscious and alert. The sclera was icteric. There was no throat congestion, no lymphadenopathy, no edema, no enlargement of tonsils. No rash or bleeding points were seen. There were no signs of respiratory distress. Breath sounds were normal, bilaterally heard in all lobes, without rhonchi or crackles. The heart rate and rhythm were normal. The abdomen was soft, not distended, tenderness was present over periumbilical region and right hypochondrium. Liver was palpable 3 cm below right costal margin with a liver span of 10 cm. Liver was soft, smooth with rounded margins and tender.

#### 2.1.1. Evaluation during hospitalization

Since admission child had high grade fever which persisted at a lower level until 3rd day. Laboratory investigations showed a total White blood cell count of 6900 leukocytes/mm<sup>3</sup> with 69% neutrophils and 26% lymphocytes/mm<sup>3</sup>. C Reactive protein was negative. Child had a high D-Dimer of 8134 with elevated liver enzymes SGOT-1490 and SGPT-1125.

Alkaline phosphatase was increased to 413. Total bilirubin was also increased to 2.4 mg/dl with Direct bilirubin 1.3 and Indirect bilirubin 1.1 (Direct bilirubin >0.5 mg/dl abnormal). Serum lipase also showed an elevated value of 117. Total serum protein and serum electrolytes were within normal limits. Dengue NS 1, IgG, IgM was negative and SARS COV-2 Antibody IgM came positive with a titer of 1.33, a value greater than 1 indicating that the specimen is reactive for anti-SARS CoV-2 IgM. Chest x-ray was normal.

In view of severe abdominal pain Ultrasound abdomen was done on day of admission which showed? multiple calculi in pancreas parenchyma with decreased parenchymal thickness suggestive of acute on chronic pancreatitis. Moderate ascites and Right sided pleural effusion were present. Gall bladder wall appeared thickened and edematous suggestive of acalculous cholecystitis.

**Table 1:** Patients clinical manifestation and laboratory results

Characteristics	Reported values
Age	5 years
Sex	Female
Temperature	102 °F
Pulse	92/minute
BP	90/60 mm Hg
Respiratory rate	22/minute
Spo2	99%
White blood cell count	6900
Neutrophil count	69
Lymphocyte count	26
Hemoglobin	9
PCV	25
Platelet count	2.8
C- Reactive Protein	5
ESR	16
SGOT	1490
SGPT	1125
D- Dimer	8134
Serum Ferritin	73
S-Lipase	117
S-Amylase	30
LDH	275
Total Bilirubin	2.4
Direct Bilirubin	1.3
Indirect Bilirubin	1.1
Total Protein	6.8
Serum Albumin	3.8
Serum Globulin	3
Serum Sodium	141
Serum Potassium	4.1
Serum Calcium	8.3
ALP	413
DENGUE NS, IgM, IgG	Negative
HBs Ag	Negative
Hepatitis A virus spot test	Negative
SARS CoV-2 Antibody IgM	Positive
SARS CoV-2 Antibody IgG	Negative

#### 2.1.2. Treatment

Considering the clinical findings, blood investigation reports and ultrasonography findings, child was treated with intravenous fluids maintenance and intravenous cefotaxime. On DOA 2, Inj. Enoxaparin 0.5 mg/kg/dose subcutaneous was started in view of increased D-Dimer, given for 7 days. Oral Azithromycin was also given for 5 days. Vitamin C and zinc supplements were also started. On DOA-3, Tab. prednisolone was started at a dose of 1mg/kg/dose OD and was given for 5 days. ON DOA-5, hepatic enzymes, total bilirubin and D-Dimer levels were repeated which showed good improvement. SGOT-258(On admission-1490), SGPT-278(On admission-1125), Total bilirubin levels came normal-0.9(previous value-2.6) with direct bilirubin 0.4(previous-1.3).

D-Dimer value also showed an improvement from 8134 to 4402. On DOA-11, hepatic enzyme levels and D-Dimer were repeated second time, both were within normal limits, child was asymptomatic and was discharged home.

## 2.2. Case 2

A 13-year-old boy presented with fever for 7 days, abdominal pain and vomiting for 3 days and yellowish discoloration of eyes for 2 days. Child had abdominal pain for 3 days, which was diffuse, dull aching mild pain with no radiation. Child also had non-projectile, non-bilious vomiting for 3 days, 2-3 episodes per day. Parents observed yellowish discoloration in child's eyes for 2 days. No history of treatment with herbal medicines. No history of contact with COVID-19 patients.

On clinical examination, child was febrile, 100°F, with RR-18/min, PR-82/min, BP-100/70mm Hg, Spo2-99%. Child was conscious and alert. Sclera appeared icteric. There was no throat congestion, no lymphadenopathy, and no enlargement of tonsils. The heart rate and rhythm were normal. The abdomen was soft, non-distended with tender hepatomegaly. Liver was palpable 4cm below Right costal margin, with a liver span of 11cm. Liver was soft, smooth and with rounded margins.

Laboratory investigations showed a total white blood cell count of 6980 leukocytes/mm<sup>3</sup> with 56% neutrophils and 38% lymphocytes/mm<sup>3</sup>. CRP was negative. Liver enzymes were elevated-SGOT-492, SGPT-750 and ALP-723. Total bilirubin was also increased to 15.6 mg/dl with direct bilirubin 2 and indirect 13.6 mg/dl. Total protein was within normal limits. Dengue NS, IgM, IgG was negative. Weil-Felix test also reported negative and SARS COV-2 Antibody IgM came positive with a titer of 1.94, a value greater than 1 indicating the specimen is reactive for SARS-CoV-2 IgM.

### 2.2.1. Treatment

Considering the clinical findings and investigation reports, child was treated with intravenous fluids maintenance and intravenous antibiotic ampicillin and cloxacillin for a period of 5 days. Vitamin C and Zinc supplements were given. Tab Ivermectin was given for a period of 5 days. In view of increased D-Dimer, Inj. Enoxaparin 0.5mg/kg/dose subcutaneous was given for a period of 7 days. After 5 days, child was asymptomatic, hepatic enzyme levels were improved with SGOT-105(On admission-492) and SGPT-287(On admission-750). Total bilirubin also decreased to 5.2 mg/dl from 15.6 mg/dl at admission and child was discharged on request on DOA-7.

## 3. Discussion

The novel coronavirus severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is currently estimated

**Table 2:** Patients clinical manifestation and laboratory results

Characteristics	Reported values
Age	13 years
Sex	Male
Temperature	100°F
Pulse	82/minute
BP	100/70 mm Hg
Respiratory rate	20/minute
Spo2	99%
White blood cell count	6980
Neutrophil count	57
Lymphocyte count	39
Hemoglobin	12.4
PCV	36.8
Platelet count	3.1 lakh
C- Reactive Protein	9
SGOT	492
SGPT	750
D- Dimer	1300
Total Bilirubin	15.6
Direct Bilirubin	2
Indirect Bilirubin	13.6
Total Protein	8.3
Serum Albumin	3.6
Serum Globulin	4.7
ALP	723
DENGUE NS, IgM, IgG	Negative
Weil-Felix test	Negative
Hepatitis A virus spot test	Negative
SARS CoV-2 Antibody IgM	Positive
SARS CoV-2 Antibody IgG	Negative

to have infected more than 3 million individuals worldwide. Currently, fever and cough remain the most prevalent symptoms in SARS-CoV-2. Cardiovascular and hematological complications are frequent and have been associated with poor prognosis. Gastrointestinal symptoms are also common. Furthermore, over one-third of infected patients develop a broad spectrum of neurological symptoms. The skin, kidneys, endocrine organs, eyes and liver are also affected by systemic COVID-19 disease.<sup>2</sup>

The SARS-CoV-2 virus is an enveloped, single-stranded virus, and the angiotensin-converting enzyme 2 (ACE2) receptor is considered as the major receptor for the viral spike protein and critical for infectivity. The ACE2 protein is found at high levels in the colon, biliary system, and liver, and viral RNA shedding occurs in the GI tract.<sup>4</sup> These data indicates that the SARS-CoV-2 may have tropism for the GI tract and liver, and they can be the sites of active viral replication causing either direct or indirect tissue injury.

This case report helps to understand the characteristics of COVID-19-related liver injury and its correlation with clinical outcomes. In COVID-19 patients the most common hepatic manifestation is represented by elevated hepatic transaminases, both aspartate aminotransferase (AST) and

alanine aminotransferase (ALT); mild elevations in gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP) and total bilirubin are also reported.<sup>5</sup> Serum albumin is decreased in severe cases. Published reports suggest that AST is more frequently elevated than ALT.<sup>4</sup> Elevation of AST more than ALT is observed here in the first case. Elevated alkaline phosphatase is rare, and an increase in bilirubin has less commonly been observed. However, interestingly, in our both cases, AST, ALT, ALP and Total bilirubin was elevated with normal serum albumin. Elevated transaminases suggests that the liver damage might be directly caused by viral infection of liver cells.

Liver histology in deceased patients with COVID-19 demonstrated that histopathological findings are highly suggestive for marked derangement of intrahepatic blood vessel network secondary to systemic changes induced by virus. From this it is clear that COVID-19 virus target not only lung parenchyma but also cardiovascular system, coagulation cascade and endothelial layer of blood vessels.<sup>6</sup> Liver damage could be directly caused by viral infection of liver cells because SARS-CoV-2 utilizes the angiotensin converting enzyme 2 (ACE2) as docking and entry receptor on host cells. Based on single-cell sequencing and animal model analysis of liver tissue, the specific expression of ACE2 in bile duct epithelial cells was 20 times higher than that in hepatocytes suggesting that SARS-CoV-2 might directly bind to ACE2- positive cholangiocytes to dysregulate liver function.<sup>7</sup>

In SARS infection, viral RNA was detected in liver tissue.<sup>4</sup> Further, recently published data suggest that mitochondrial proteins may directly interact with the virus, providing a potential explanation for the AST-dominant injury profile.<sup>4</sup> The levels of IL-2-receptor (IL-2R) and IL-6 are significantly increased in the serum of COVID-19 patients and correlate with disease severity.<sup>5,6</sup> Lu et al. proposed that lymphocytopenia and C-reactive protein levels were independently correlated with liver injury in COVID 19 patients suggesting that the main mechanism of liver damage might be an inflammatory cytokine storm.<sup>7</sup> Cytokine storm is one of the most potent physiological stresses that result in a hyper-inflammatory condition and leads to organ damage.<sup>8</sup> High levels of IL-2, IL-6, IL-7, IL-10, TNF- $\alpha$ , GM-CSF, IP-10, MCP-1, and MIP-1 $\alpha$  were observed in patients with severe COVID-19.<sup>9</sup> Additionally, acute liver injury was also more prominent in these patient.<sup>7,9</sup> Acute liver injury and cytokine storm, both are observed in the severe form of COVID-19.

Sepsis is a common clinical condition in COVID-19 patients and is also a major physiological stress.<sup>5,6</sup> Many mechanisms can cause end-organ damage during sepsis. Reactive oxygen species, ischemia-reperfusion injury, sepsis-induced cholestasis, and drug toxicity injury are some of the mechanisms that could cause sepsis-induced liver injury. Moreover, hypo-perfusion and a hyper-inflammatory state result in an unfavorable

microenvironment that leads to liver injury.<sup>8</sup>

COVID-19 patients take certain drugs, such as paracetamol, oseltamivir, and lopinavir/ritonavir, which are known to be hepatotoxic. Therefore, a combination of virus-mediated hyper-inflammatory state and drug hepatotoxic result in the acute liver injury observed in COVID-19 patients. The main COVID-19 liver damages are moderate micro vesicular steatosis and mild inflammation at the lobules and portal region, which reflects drug toxicity.<sup>4</sup>

Hepatic congestion contributes to hepatic injury in severe COVID-19 infection. Congestive hepatopathy can also occur as a consequence of acute cardiomyopathy and it is commonly associated with elevations in aminotransferases and GGT. Severe ischemic hepatitis is characterized by severe AST-predominant hepatitis and may be observed in critically ill patients with COVID-19.<sup>4</sup> As COVID-19 is not always associated with abnormal liver biochemistries, all children with elevated hepatic transaminases should be evaluated for underlying liver disease and/or coexisting infection.

#### 4. Conclusion

COVID-19 added another dimension to liver diseases. There is a high prevalence of abnormal liver biochemistries in patients with COVID-19. Considering the risk for additional injury due to the complications and management of moderate-to-severe disease, it is important to monitor hepatic enzymes during the course of disease.

The primary clinical manifestation of COVID-19 infection in children is not necessarily a pulmonary disease in all cases. The involvement of multiple organ systems, including the gastrointestinal (GI) tract and liver, with more than 60% of patients presenting with GI symptoms (anorexia, diarrhea, nausea, and vomiting) and a significant proportion presenting with elevated liver biochemistries is observed in COVID-19 in children.

#### 5. Conflict of interest

The authors declare that they have no competing interests.

#### 6. Source of Funding

None.

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