CASE REPORT

Coronavirus disease -19 Presenting As Acute Liver Failure In A Child

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Coronavirus disease 2019(COVID-19) caused by Severe Acute Respiratory Syndrome Corona Virus 2(SARS CoV2) is the biggest global health crisis today. It mainly affects respiratory system though can also cause gastrointestinal and liver dysfunction and rarely affects other systems[1,2]. While multiple studies on liver dysfunction associated with COVID-19 are available in adults there is limited data on its effects in children[3]. Furthermore, liver dysfunction associated with SARS CoV2 infection presents a management dilemma. As per our literature search there is no case reported of COVID-19 infection presenting with acute liver failure (ALF) in the pediatric population. We present the case of a 21months old toddler with COVID-19 infection presenting with ALF who was successfully managed with COVID convalescent plasma along with other supportive therapies.

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CASE REPORT

A 21 months old female presented to the emergency room with history of moderate grade, continuous fever for seven days, vomiting and loose stools, 5-6 per day for four days along with excessive drowsiness. There was no significant past and family history. On examination, the child was hemodynamically stable, febrile, drowsy, icteric and was having intermittent extensor posturing. Her random blood sugar was 28mg/dl, so immediate 10% Dextrose was given @5ml/Kg following which the blood glucose normalised. Her weight and height were on 50th centile (z score 0 to -1) as per World Health Organization (WHO) growth charts. On systemic examination, there was hepatomegaly with mild abdominal distension and no clinical ascites. Her neurological examination revealed brisk deep tendon reflexes and bilaterally equal and sluggishly reactive pupils. Initial reports showed low hemoglobin, leucocytosis with low normal platelet count, international normalized ratio (INR) of 12.28, aspartate aminotransferase (AST) 1308 International Unit/Litre(IU/L), alanine aminotransferase (ALT) 686 IU/L, alkaline phosphatase (ALP) 101 IU/L and gamma glutamyl transferase (GGT) 77 IU/L, total serum bilirubin(TSB) 6.2 milligram/decilitre(mg/dl), albumin 2.3gram/dl. Her ammonia was 66 micromole/L, inflammatory markers were high with normal C Reactive Protein (CRP), triglyceride and renal functions. Complete workup for etiological diagnosis of acute hepatic failure was sent (***serial reports in Table 1***). Real time Reverse Transcriptase (RT) PCR for SARS CoV 2 (ICMR approved) was sent in view of persistent fever which came positive. Her Hepatitis A, E, Ebstein Barr virus IgM and Antinuclear antibody came negative. Blood and urine cultures were negative.

The child was intubated for poor Glasgow Coma Score and an urgent computerized tomography (CT) Scan head was done which revealed no gross abnormality, while CT chest showed Covid-19 Reporting and Data System (CO-RADS) 5 changes in both lungs which favoured diagnosis of acute COVID-19 infection. **(Figure 1)**. Her echocardiography was normal.

She was started on Meropenem along with dexamethasone @0.6mg/kg/day as per unit COVID protocol. Due to significant coagulopathy, patient was given intravenous (IV) vitamin K(10mg) and started on N - acetyl cysteine infusion @ 100mg/Kg/day, 3% sodium chloride infusion as per ALF and suspected raised Intra cranial tension(ICT) management protocol. In view of severe COVID-19 infection with ALF in our patient and very limited safe treatment options available for this age group, IV immunoglobulin @2gm/Kg was given empirically along with COVID-19 convalescent plasma twice after due consent from parents. There was a serial improvement in INR, transaminases and bilirubin. **(Figure 2a&2b).**

The child was extubated on day 3 of admission. The respiratory status of the child remained stable throughout the admission. Despite improvement in sensorium, the child had persistent fever and multiple repeat COVID-19 PCR were positive over the next 21 days. However, no seizure or hypoglycemia was observed after hospitalization. The child was discharged after 24 days in a hemodynamically stable state with a negative COVID PCR report.

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Table 1: Laboratory values of the patient during hospital stay

Lab test / Day	1	2	4	8	14	21
Hemoglobin (Gm/ dl)	8.6	6.3	9.7	10.7	10.8	
Platelet (x10^9)	133	75	157	100	695	
Total Leucocyte (x10^9)	13.3	9.4	19.9	23	17	
Neutrophil/Lymphocyte(%)	72/18(3.8)					
CRP (mg/dl)	1.1		0.7	1.2	1.3	
Ferritin (ng/ml)	6999.7		257			
Lactate dehydrogenase(U/L)	1567		403		224	
PT (Seconds)	138.6	41.4	25.2			
INR	12.28	3.71	2.27	1.8	1.4	1.1
AST(IU/L)	1308	3637.4	948.4	77	42	32
ALT(IU/L)	686.9	3765.8	2766	631.4	167	44
GGT(IU/L)	77.3	67.8	81	100.6	90.8	75
ALP(IU/L)	101					
TSB (mg/dl) (Direct)	6.2 (3.1)	4.1 (1.6)	4 (1.5)	1.1(0.3)	0.7 (0.2)	0.5
T Protein (Gm/ dl)	3.9	7.6	6.9	7.3	7.9	
Albumin (Gm/ dl)	2.3	2.6	2.6	3.5	3.9	4.1
S Ammonia (Umol/L)	66					
D Dimer (ng/ml)	10340					

INR International normalized ratio, PT Prothrombin time, AST Aspartate amino transferase, ALT Alanine amino transferase, ALP Alkaline phosphatase, GGT Gamma glutamyl transferase TSB Total serum bilirubin

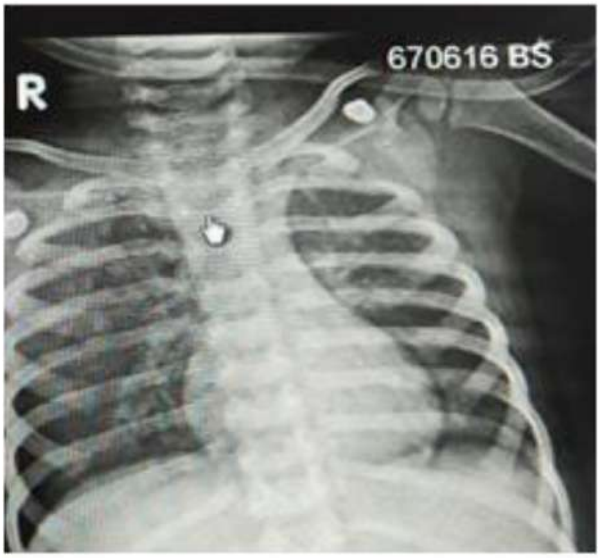

Figure 1a: X ray Chest (PA view)

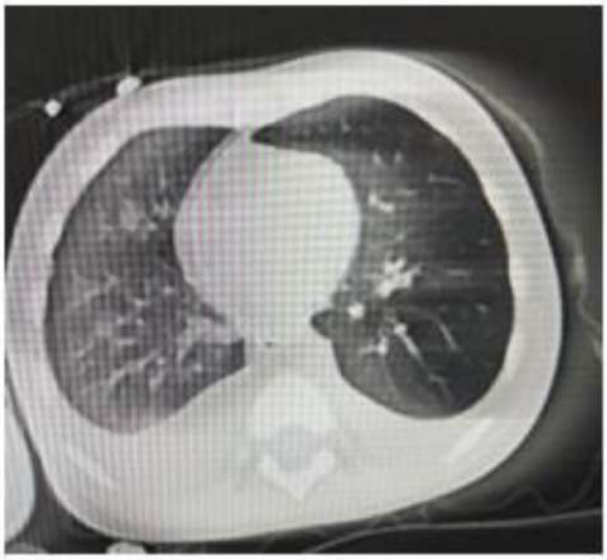

Figure 1b: CT Chest

DISCUSSION

SARS CoV2 infected children have a milder disease course and a better prognosis than adults due to their special immune response system. Liver injury may result from direct pathogenic effect by the virus; systemic inflammation or; by drug toxicity. The angiotensin converting enzyme 2(ACE2) receptor, a postulated mode of entry of the virus, is expressed by 2.6% of hepatocytes and 59.7% of cholangiocytes.[4,5] The association of severity of COVID-19 with underlying chronic liver disease or other liver diseases has been studied in adults with limited data.[6]

Several studies on adult COVID-19 patients show incidence range of elevated ALT, AST 2.5%-50.0% to 2.5%- 61.1% respectively, increased TSB in 0%-35.3% with no significant elevations of ALP and GGT levels in most except in NAFLD patients who showed elevated GGT predicting a more severe course.[6,7]Our patient had raised AST, ALT, TSB with normal GGT and ALP. Different studies show conflicting results to suggest significance of these abnormal liver enzymes. In a

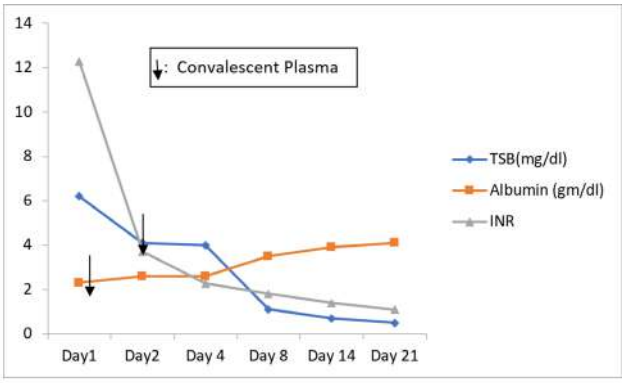

Figure 2a: Total serum bilirubin (TSB), Albumin and INR during course of illness

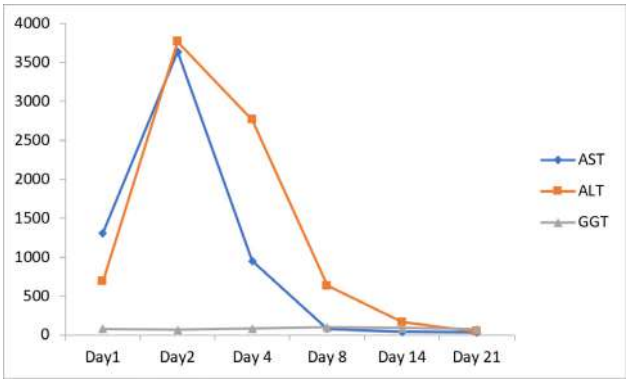

Figure 2b: Liver enzymes during the course of illness

Table 2: Various studies showing deranged liver enzymes

Study	N(COVID 19 positive) NS: Non severe S: Severe	Median age (yr)	Abnormal AST	Abnormal ALT	Comments
Guan et al[1]	1099 **NS**: 615 **S**: 142	47	18.2% 39.4%	19.8% 28.1%	
Huang et al[1]	41 **NS:** 25 **S:** 13	49(41-58)	25% 62%	- -	
Yang et al[8]	710 **S:** 52	59.7(SD 13)	29%		No difference between survivors and non survivors
Phipps et al[2]	2273	65		Mild : 45% Moderate :22% Severe : 6.4%	Mild (<2X ULN) Mod :2-5X ULN Severe: >5X ULN
Wang et al[6]	**31**	**7.1(0.5-17 yr)**		**Mild: 22%**	
Qiu et al[5]	**36**	**8.3(0-16yr)**		**Mild : 5.5%**	
Zhu et al[7]	**10**	**Neonates**		**Mild:20%**	**Mothers COVID 19 positive**
Our Patient	**1**	**1.9yr**		**Severe**	**ALF**

large cohort of 1099 patients, Guan et al[8] observed elevated AST, ALT in 18.2% and 19.8% with non severe disease while 39.4% and 28.1% with severe disease. Similarly, Huang et al[9] reported higher proportion of liver injury in intensive care unit (ICU)patients (61% vs 25.0%). On the contrary, Wu et al and Wang et al[10] showed no significant differences. Severe acute liver injury due to COVID-19 has been described in adults rarely[11,12] but no case has been reported in children. Similar prevalence of raised liver enzymes has been reported from the US[2]; INR was normal to slightly deranged in most; low serum albumin was observed in severe disease. Our patient had high neutrophil to lymphocyte ratio of 3.8 and low serum albumin which are considered as predictors of severe disease in adults, though same have not been studied in children. Three studies on 36, 31 and 10 children and neonates with laboratory confirmed COVID-19 from different provinces in China showed minimal increase in liver enzymes in two, seven and two cases with normal final outcome [13,14,15] Results from different studies have been tabulated in **Table 2.**

Since COVID-19 in children is associated with minimal or no increase in ALT and AST levels, American Association for the Study of Liver Diseases (AASLD) suggests evaluating all children with abnormal liver enzymes for underlying liver diseases as they might be at a greater risk for severe disease[17].

Our patient presented with diarrhea and ALF with no underlying liver disease. The hepatic involvement appears more of parenchymal type in our patient in view of very high AST, ALT, normal GGT, ALP, raised LDH, severely deranged INR and cholestasis. Though raised D dimer and ferritin can be secondary to ALF, cytokine storm or HLH secondary to COVID -19 infection contributing to the severity of illness cannot be totally refuted however in view of short history, persistent positive COVID PCR at 21 days, and no significant involvement of any other system, we attribute this as a manifestation of acute COVID infection. The abnormal movements at admission could be attributed to hypoglycemia secondary to severe liver disease as CT brain and ammonia was normal and sensorium showed good response within 48 hours. Whether the prolonged COVID PCR positivity and

ALF have any association, or whether severe parenchymal injury is secondary to more expression of ACE2 receptors in hepatocytes of these patients needs to be proved with larger cohort from other centers. Our case is important as this is the first reported pediatric case in world with acute COVID-19 infection presenting either primarily as ALF or secondary to HLH and responding to conservative management and convalescent plasma therapy with no adverse effects. Further studies are needed to understand the exact pathophysiology of ALF in acute COVID-19 infection.

CONCLUSION

Deranged liver enzymes can be seen in children with COVID-19 infection but are usually mild and do correlate with other markers of inflammation. ALF can be a rare manifestation in children and responds well to conservative management and convalescent COVID plasma therapy.

Further Reading:

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