Original Research Paper

Volume - 11 | Issue - 06 | June - 2021 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Pediatrics

COVID-19 INDUCED HEPATITIS IN PAEDIATRICS: A CASE SERIES

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ABSTRACT **Purpose:** Global pandemic caused by Novel Corona virus has severely affected healthcare system. With limited data on the disease, coupled with large number of cases has made patient management more difficult for clinicians. It becomes more challenging for Pediatricians in view of scarce data on various manifestations of COVID-19. Because of large number of cases, it is mandatory for every clinician to understand extra-pulmonary manifestations of COVID-19. Here we attempt to throw some light on hepatic manifestations of COVID-19. We believe, it will help clinicians for early identification of the possible hepatic impairment in patients, identification of patients at higher risk of that hepatic impairment, prompt management and avoidance of possible complications arising from it. **Methods:** Our hospital is converted into dedicated COVID- Care centre since the commencement of pandemic. We observed strong association between COVID-19 pneumonia and hepatic impairment. We observed trends of hepatic enzymes and USG abdomen picture of liver in six patients of COVID-19 pneumonia. **Results:** Hepatic impairment in the form of hepatitis followed by hepatic abscess and rupture was found as common pattern of liver injury in our case series. This pattern of correlates with hepatic injury secondary to ischemic liver damage. Absence of intra-hepatic viral inclusion bodies and virus particles further supports this mechanism. **Conclusion:** Hepatic involvement in COVID-19 is an important extra-pulmonary manifestation. Early detection of impaired liver enzymes is important to prevent complications like rupture of hepatic abscess.

KEYWORDS : Extra-pulmonary manifestations of COVID-19, COVID-19-Induced Hepatitis, Hepatic Injury associated with COVID-19

Introduction

Since the emergence of a novel corona virus (Severe Acute Respiratory Syndrome corona virus 2 [SARS-CoV-2]) disease in China in 2019, world is living under constant threat of this global pandemic[1]. With 72 million cases worldwide and over 1.6 million deaths [2] attributable to this pandemic, emphasis has been given on the study of various aspects of the disease and its treatment. Novel corona virus disease emerged as predominantly a respiratory system disease with a spectrum ranging from mild flu-like symptoms to a fulminate form of acute respiratory distress syndrome leading to death[3]. Despite predominant respiratory involvement, the disease is found to have multisystem involvement [4,5]. Involvement of hepatobiliary system is one of the prominent symptoms of the disease[6]. Apart from cytopathogenic changes caused by virus, hepatic involvement in novel corona virus disease is often linked to alcohol consumption, pre-existing liver disease, history of use of hepato-toxic medications, genetic and environmental factors[7]. Study of the disease course in pediatric population removes major factors like alcohol and history of hepato-toxic medications, allowing us to focus mainly on the cytopathogenic effects of virus. Physiologic response to viral insult differs in adults and children. Immature hepatic parenchyma may not respond in same way to virus and the anti-covid medications like oseltamivir and azithromycin. Majority of the COVID-19 related published data is from China and other countries and also mainly from adult population. Here we present our experience of 6 cases of covid induced hepatitis in Indian Pediatric population as ours being Tertiary Care COVID-19 dedicated hospital located in Mumbai.

Case: 1

A 3-year-old male child with fever for 15 days and difficulty in breathing associated with poor oral intake and dry cough for 5 days, with the diagnosis of right pleural effusion with consolidation. On examination, child was febrile 38.8 ^{0}C with Heart Rate of 122/min and Respiratory Rate of 32/min and mild sterno-costal and intercostal retractions, breath sounds decreased on right side with soft and Hepatomegaly of 3 cm with liver span of 9 cms, and provisional diagnosis of right sided pleural effusion and consolidation with hepatomegaly under evaluation.

On Admission Liver Function Tests values were deranged, USG abdomen suggested right heterogeneous mass (liver Abscess), with No growth on pus culture and blood culture, moderate ascites and cystitis. CT abdomen revealed ruptured liver abscess with sub pulmonic collection along with bilateral patchy consolidation and minimal pleural effusion. In view of large collection, insertion of pig tail catheter was done by Pediatric Surgeon. The child was started on Inj piperacillin + tazobactum (100 mg/kg/dose) & Amikacin (15 mg/kg/day), Inj Metronidazole (10 mg/kg/dose), along with Oseltamivir (12 mg/kg/dose). Post procedure, child developed episodes of desaturation and required mechanical ventilation. Child succumbed despite best resuscitative measures with 5 days of hospital stay.

Table 1 Day wise Investigation Chart of Patient 1

Investigation/date/day of illness	26/04/20 / Day 15	Reference Range
WBC	12,000/uL	5500-15500/uL
RBC	4.2×10^{6}/uL	$3.9–5.3\times10^{6}$ /µL
HB	7.8 gm%	11.5–14.5 gm%
Platelets	4,90,000/uL	150,000–450,000/µL
AST	101U/L	15–50U/L
ALT	35U/L	10–25 U/L
Alkaline Phosphatase	876 U/L	80 – 310 U/L
Ca/Phos	8 mg%/2.1 mg%	8.8-10.6mg% -- 3.8–6.5 mg%
T.Prot/Albumin	5.5 gm%/2.4 mg%	6.0–8.0gm% -- 3.7–5.5mg%
BUN/S.Creat	07 mg%/0.7 mg%	5–25mg%-- 0.12–1.06mg/dL
T.bilirubin	0.3 mg%	< 1.0 mg%
SE/Na/K	140 mg%/3 mg%	136–145mg% -- 3.5–5.5mg%
INR	15.3/1.44	12.2- 15.5 secs /0.8-1.2

Case: 2

A 4-year-old male child with pain in abdomen for 3 days and fever for 4 days with history of decreased urine output. General examination was unremarkable. On respiratory auscultation Breath sounds reduced on right side with no adventitious sounds. Per Abdomen examination

revealed right epigastric tenderness with hepatomegaly of 3 cm with Liver span of 9cm with provisional diagnosis of acute febrile illness with liver abscess.

USG abdomen showed liver abscess with no organism seen on pus culture in right lobe of liver in segment 7 with peripheral liquefaction amounting 100 cc Aspirated pus showed degenerated WBC on microscopy with proteinaceous material with no growth in pus culture. Child was started on Inj piperacillin + tazobactum (100 mg/kg/dose) Inj.Amikacin (15mg/kg once daily), Inj metronidazole (10mg/kg once daily) for 14 days and Syrup Oseltamivir (12 mg/kg/dose) for 5 days. After receiving this treatment, patient was discharged after 14 days of Hospital stay.

Table 2 Day wise Investigation Chart of Patient 2

Investigation / day of illness	30/04/ Day 2	02/05/ Day 5	14/05 Day 17	Reference Range
WBC	56.9×10^3/uL	43.5×103/uL	9.4×10^3/uL	5500-15500/uL
RBC	4.22×10^6/uL	4.76×106/uL	4.30×10^6/uL	3.9–5.3×10^6 /µL
HB	7.2 gm%	gm%	9.1 gm%	11.5–14.5 gm%
Platelets	590×10^3/uL	796×103/uL	900×10^3/uL	150000-450,000/µL
AST	61	26	--	15–50U/L
ALT	12 U/L	11 U/L	--	10–25 U/L
Ca/Phos	--	9.2 mg%/3.0 mg%	--	8.8-10.6mg% --3.8–6.5 mg%
T.Prot/Albumin	--	5.6 gm%/3.0 mg%	--	6.0–8.0gm% -- 3.7–5.5gm%
BUN/S.Creat	09 mg%/0.2 mg%	07 mg%/0.5 mg%	--	5–25mg%--0.12–1.06 mg%
T.bilirubin	0.7 mg%	0.3 mg%	--	< 1.0 mg%
Sr/Na/K	134/4.5	133/4.0	--	136–145mg% -- 3.5–5.5mg%
Alkaline phosphatase	--	542 U/L	--	150-380 U/L
PT/INR	--	14.9/1.07	--	12.2- 15.5 secs /0.8-1.2

Case: 3

3-month-old male child with yellowish discolouration of eyes for 3 days with fever for last 2 days. General examination revealed presence of icterus. On abdominal examination child had umbilical hernia measuring 2×2 cm with hepatomegaly 4 cm below right sub costal margin with liver span of 9 cm with suspected cholestasis / cholecystitis. Viral Markers for HIV, HBsAg, and HCV were negative with normal PT- INR values. USG abdomen revealed acalculous cholecystitis with Umbilical hernia. Child started on Inj Cefotaxime (100 mg/kg/day twice a day) stopped after 2 days, Syp Azithromycin (10 mg/kg daily dose) & Syrup Oseltamivir (12 mg/kg/dose) along with Udiliv, cholestyramine sachet 1 sachet daily (1 sachet/ 4 g) and syrup Vit. D (1 ml = 400 IU) with 400 IU daily. A gradual reduction of liver enzymes was observed, in view of clinical improvement child was discharged after 8 days of hospital stay.

Table 3 Day wise Investigation Chart of Patient 3

Investigation/ day of illness	10/05/ Day 3	12/05/ Day 5	Reference Range
WBC	14.1×10^3/uL	--	5000-19500/uL
RBC	3.6×10^6/uL	--	2.70-4.50×10^6
HB	9.6 g/dl	--	9.0-14.1 g/dl
Platelets	298×10^3/uL	--	150–450×10^3/µL
AST	223	150	9–80 units/L
ALT	167	122	12–45 units/L
Ca	7.9	--	8.8–10.8 mg/dL
T.Prot/Albumin	6.0/4.0	6.2/3.9	4.7-6.7gm%--3.8-5.4gm%
BUN/S.Creat	--	07/0.5	8–28 mg%--0.3–0.7 mg/dL
T. Bilirubin	2.0	0.3	< 2 mg/dL
SE/Na	134	133	130–147 mEq/L
SE-K	4.5	4.0	3.4–5.6 mEq/L
ALP	1673	--	150-420 units/L
LDH	1552	--	170–580 units/L
PT/INR	15.4/1.11	--	12.2–15.5sec--0.8–1.2
HIV/HbsAg/HCV	--	Negative	--

Case: 4

A 6-year-old male child with fever for 6 days, abdominal pain and vomiting for 2 days. General examination revealed icterus. On abdominal examination hepatomegaly with 4 cm below right subcostal margins with liver span of 10 cms and just palpable spleen, generalized tenderness all over abdomen, suspected acute febrile illness with tender hepatomegaly. Viral markers were Negative. Provisional diagnosis of Viral Hepatitis was made.USG abdomen suggestive of mild hepatomegaly & raised echogenicity of liver with mild to moderate ascites. CT abdomen suggestive of Hepatomegaly with resolving hepatitis. Child was started on Inj cefotaxime(100 mg/kg/day) and Inj metronidazole (10 mg/kg/dose) along with multi vitamins. Child Discharged after Hospital stay of 9 days.

Table 4Day wise Investigation Chart of Patient 4

Investigation / day of illness	07/06/ Day 2	08/06/ Day 3	09/06/ Day 4	10/06 / Day 5	11/06/ Day 6	Reference Range
Hemoglobin	11.6	12.3	11.2	10.1	9.7	11.5–14.5 gm%
WBC	4300	7400	6400	11300	13400	5000-19500/uL
Platelets	115	102	107	221	204	150–450×10^3/µL
AST	--	9116	5046	--	268	15–50U/L
ALT		3797	3573		500	10–25 U/L
T.Bilirubin	--	4.10	3.9	--	2.5	< 1.0 mg%
D.Bilirubin	--	3.20	2.9	--	--	< 0.2 mg/dL
ALP	--	519	--	--	268	150–380 U/L
T.Protein/Alb	--	6.0/3.2	5.9/2.0	--	--	6.0–8.0gm% -- 3.7–5.5gm%
BUN/S.creat	--	–	--	11/0.5	11/0.68	5–25mg%--0.12-1.06mg%
ESR	26	--	--	--	--	
S/E : Na/K	--	126/4.4	--	132/3.2	--	136–145mg% -- 3.5–5.5mg%
PT/INR	--	--	--	--	15.6/1.12	12.2–15.5sec-- 0.8–1.2

Case 5

8-year-old male presented with fever for 5 days, vomiting and lethargy for 3 days & decreased urine output in shock. Child immunized for age and developmentally normal. General examination revealed maculopapular rash on face, vitals normal, with unremarkable systemic examination with provisional diagnosis of acute febrile illness and hypovolemic shock .Child started on Inj piperacillin + tazobactum (100 mg/kg/dose) , Syrup Azitrhomycin(10 mg/kg/dose) & Maintaince IV fluids. Child had required inotropes in view of shock with dengue IgG positive status. Child was tapered Off Inotropes after adequate urine output with BP maintaining between 50th& 95th centile. Child's 2nd swab came negative and became hemodynamically stable was afebrile for more than 3 days was discharged after a hospital stay of 6 days.

Table 5 Day wise Investigation Chart of Patient 5

Investigation/Date/ day of illness	06/06/ Day 6	07/06/ Day 7	08/06/ Day 8	Reference Range
Hb	8.1 g/dL	7.7	6.8	11.5—15.5 g/dL
TLC	9300/uL	15300	12200	3.9–5.3×10^6 /µL

Platelets	73000/uL	127000	146000	150000-450,000/µL
ALT	--	25	19	15–50U/L
AST		13	16	10–25 U/L
T.Bilirubin	--	0.3	0.3	< 1.0 mg%
D.Bilirubin	--	--	--	--
ALP	--	--	--	175–420 U/L
T.Protein/Albumin	6.1mg%/3.2mg%	--	--	8.8-10.6mg% --3.8–6.5 mg%
BUN/S.creat	09/0.38	10/0.71	05/0.4	5–25mg%--0.12–1.06 mg%
S/E : Na/K	137/3.5	138/2.8	136/3.7	136–145mg% -- 3.5–5.5mg%

Case 6

8-month-old male child presented with fever high grade intermittent in nature associated with rash for 4 days, loose stools for 3 days and cold for 1 day. Child Immunized for age and developmentally normal with unremarkable birth, family and past history. On examination child was afebrile with tachycardia (pulse rate of 122/min) regular with normal volume, respiratory rate of 30/min, peripheral pulses well felt. Per Abdomen, liver palpable 4 cm below the costal margin with Liver span of 6.5 cm with provisional diagnosis of acute gastroenteritis and viral hepatitis. Child was started on IVF & Inj cefotaxime (100 mg/kg/day) for 6 days which later on was upgraded to Inj Piperacillin + Tazobactum (100 mg/kg/dose) in view of persistently raised counts and clinical worsening of child along with Inj metronidazole (10 mg/kg/dose), USG abdomen was unremarkable. Repeat Liver enzymes showed falling AST/ALT titres. Child discharged after 12 days of hospital stay.

Table 6 Day wise Investigation Chart of Patient 6

Investigation/ Date/ day of illness	12/08/20/Day 4	15/08/20/ Day 7	17/08/20/ Day 9	18/8/20 / Day 10	19/08/20 Day 11	20/08/20 Day 12	24/08/20
WBC	–	--	33×10^3/uL	--	--	17.08×10^3/uL	12.39×10^3/uL
Hb	--	--	8.3 g/dL	--	--	8.4 g/dL	9.2 g/dL
RBC	--	--	3.73×10^6/uL	--	--	3.58×10^6/uL	3.93×10^6/uL
Platelets	--	--	813×10^3/uL	--	--	1097×10^3/uL	916×10^3/uL
SGOT/PT	2373/3148	88/1233	59/419 U/Lt	67/331 U/Lt	--	--	53/75 U/Lt
Ca/Phos	--	--	8.6/5.1 mg%	9.4/4.6 mg%	--	--	9.5/-- mg%
T.prot/Albumin	--	--	5.8/3.2 G%	5.9/3.3 G%	--	--	6.3/3.7 G%
Na/K	--	--	135/6.7 meq/L	136/6.4 meq/L	--	--	137/.3meq/L
BUN/S.creat	--	--	07/0.5 mg%	07/0.4 mg%	--	--	05/0.3 mg%
Clot Culture	--	--	--	No Growth	No Growth	--	No Growth
HIV/HbsAg/ HCV	--	--	Negative	--	--	--	--
URINE R/M	--	--	--	--	--	--	--
Urine Culture	--	--	--	--	--	No Growth	--
Blood Culture	--	--	--	--	--	No Growth	--

Discussion:

Various studies have suggested multisystem involvement of novel corona virus disease although the virus primarily affects lung parenchyma. Various organ systems affected are CNS, Renal System, Hepatobiliary System etc. SARS-C0V-2 has been found to exhibit a spectrum of disease ranging from mild to fatal. However, it has found to follow a mild course in children. It may be asymptomatic or may present with mild flu like symptoms ie cough, weakness and fever[8][9]. Upper respiratory symptoms are usually accompanied by diarrhoea, nausea, vomiting and hepatitis like picture [9]. Entry into the lung parenchyma is facilitated by attachment of viral receptors to ACE-2 receptors. ACE-2 receptors are also found on hepatic parenchyma that suggests the possible route of hepatic involvement [10][11]. Histopathological analysis conducted in patients with SARS have confirmed presence of virus in hepatic parenchyma[12]. Drug induced hepato-toxicity has also been postulated as a cause of covid induced hepatitis[15], however in our case series all the patients presented with hepatic involvement at the time of admission ie before administration of Azithromycin and Oseltamivir. 5 out of 6 cases presented with hepatomegaly and associated gastrointestinal symptoms. 2 patients had developed hepatic abscess, out of which one hepatic abscess was ruptured. Viral markers ruled out other aetiology of viral hepatitis. Microscopic examination of pus aspirate was found to contain numerous pus cells, but no organisms were visualised. This suggests hepatic abscess could be reactionary in nature secondary to necrosis caused by pneumonia associated hepatic hypoxia[15].

Our findings correlated with previous studies suggesting mild, reversible and transient nature of hepatic damage [15][16]. Only one patient out of 6 patients succumbed to illness, patient had presented with ruptured hepatic abscess and could not be revived even after resuscitative measures. In rest of the 5 patients, hepatic enzymes were transiently raised to more than double the upper normal range and promptly returned to normal on treatment within days of initiation. Use of hepatoprotective drugs wasn't required in any of our patients for hastening recovery. Response to regular line of treatment was satisfactory.

Conclusion:

Although the disease runs mild course in children, clinicians should be vigilant for multiorgan involvement. As asymptomatic upper respiratory disease is often encountered with SARS-Cov-2 in Pediatric population, any child with gastro-intestinal symptoms along with icterus and/or raised transaminases should be investigated by RT-PCR. Symptomatic children with raised transaminases should be subjected to further radiological evaluation by keeping in mind the possibility of hepatic abscess. Any child with positive covid status and hepatic involvement should be evaluated for underlying liver disease.

Acknowledgements:

We wish to acknowledge and thank the Dean of our institute, Dr Ramesh Bharmal for giving permission to publish this article.

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