



Original Research Article

Hepatitis –A late manifestation of COVID-19 in pediatric population?

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ABSTRACT

Objective: Complete spectrum of covid 19 infection in children as well as its sequelae is still unknown to the world even after two years of ongoing pandemic. Many manifestations of covid 19 have been missed and are yet to be identified. In this study, we aim to hypothesize hepatitis as a probable late manifestation of COVID-19 infection in children.

Materials and Methods: It was a descriptive retrospective study, in which we have included twenty patients who presented with hepatitis in the pediatric department of a secondary level care centre in Sagar from May to July 2021. And we investigated them further to find out the cause of Hepatitis.

Results: Among the 20 patients with HEPATITIS, 15 were tested for covid antibody levels, out of them 14 had raised level of SARS-CoV-2 antibody titre.

Conclusion: Pediatricians should recognize that the clinical spectrum of COVID-19 in children can be wider than previously described, often with hepatitis as late manifestation of COVID-19 in children, apart from MIS-C.

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1. Introduction

World was hit firstly by the SARS-CoV-2 infection in late December 2019 starting from Wuhan, the capital of Hubei province in the People's Republic of China.¹ Its first wave hit India in mid 2020 with involvement of primarily older population and presented with chiefly respiratory system involvement. While in the second wave more younger and pediatric population also got involved with secondary involvement of gastro-intestinal system.² Second wave of covid-19 pandemic in India peaked during the month of May and June 2021 during which a large number of

population got infected.³ Second wave in India was more fatal than first wave and infact proved to be a Psunami causing more than 2.5 lakhs Deaths.⁴ While paediatric population did get infected, majority of them were either asymptomatic or developed minor illnesses. In India <12% of all confirmed cases were in individuals <20 year of age.⁵ Only few of them developed severe manifestations, and of all the deaths due to covid 19, only <2% were contributed by <20 years age group.⁶ However in the months just after the peak of covid in adults, significant number of children also developed delayed manifestations of covid in the form of MIS-C that is multisystem inflammatory syndrome in children, in which children mostly presented with high grade unremitting fever, rashes(57%) along with

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involvement of gasro-intestinal (70%) and cardiovascular system (52%). Those with severe form of disease presented with neurological symptoms, hepatitis and acute kidney injury.⁷ WHO defined criteria for the diagnosis of MIS-C which include a wide range of clinical symptoms as well as laboratory investigations for the confirmation.⁸ During the same period when incidence of MIS-C was rising, we reported number of patients presenting with hepatitis. These patients did not fulfil all the criteria for the diagnosis of MIS-C. Through this study, we want to emphasise that is quite possible that many children might had also developed delayed manifestations of COVID-19 in the form of hepatitis which did not fulfil the diagnostic criteria of MIS-C. Hence, the complete spectrum of covid and post covid symptoms in children are still to be identified and documented by further studies. The aim of this study was to describe a broader clinical spectrum of COVID-19 in children. In this study, we are reporting cluster of paediatric patients who developed hepatitis, just after the peak of covid infection in adults, when incidence of MIS-C in children was also increasing simultaneously.

2. Materials and Methods

We conducted a retrospective study in the department of pediatrics in a secondary level multispeciality hospital located in Sagar city, the divisional headquarter of bundelkhand region of Madhya Pradesh. We included patients <18 years of age, of any sex, with clinical features of Hepatitis who were admitted in this hospital from may 2021 to July 2021. All these patients who met the inclusion criteria, were screened for covid 19 infection with rapid card test. All of these patients were negative for covid 19 antigen test. A detailed work up was further planned for each patient including complete hemogram, liver function test, IgM for hepatitis A, IgM for Hepatitis E, antigen test for Hepatitis B, PT/INR, widal test, CRP, LDH and Covid Antibody Titre. We defined hepatitis as presence of both of the following: a) the presence of clinical jaundice, b) elevated levels of serum bilirubin, SGOT and SGPT in blood samples. SGOT and SGPT levels greater than twice the upper limit of normal were taken as significant. We had not included patients who had jaundice secondary to haemolytic diseases, liver disorders, obstructive causes, and we also excluded newborns from the study.

We analyzed the data obtained from these patients; the information was analyzed using case counting and descriptive statistics, and calculating median(range), quartiles and percentages.

3. Results

During a period of 60 days starting from 28th May 2021 to 26th July 2021, total 20 cases of hepatitis were admitted. Out of them 11 were male and 9 were female (Figure 1).

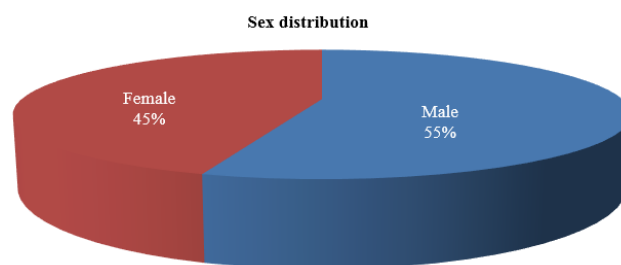


Figure 1: Showing distribution according to sex.

Age of the children ranged from 2 years to 15 years with mean age of children 6.7 years (Figure 2). All the twenty children (100%) were negative for active SARS-CoV-2 infection by Rapid Antigen test. None of the patients (0%) with hepatitis had a previous chronic medical condition.

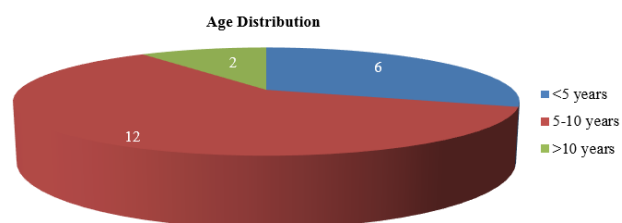


Figure 2: Showing distribution according to age.

Their duration of stay ranged between 2 to 7 days with mean average duration of stay 4.6 day (Figure 3).

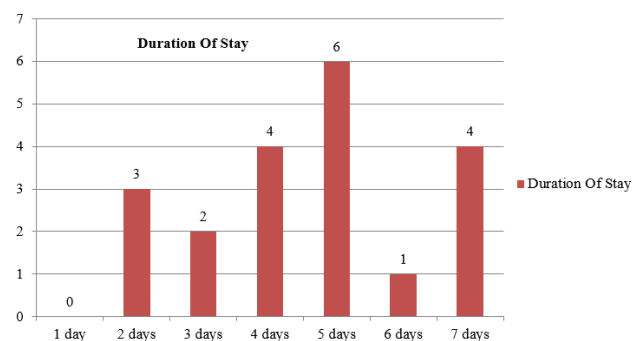


Figure 3: Showing distribution according to duration of stay.

Average haemoglobin level was 10.8 gm/dl with range from 8.6 gm/dl to 14 gm/dl. Average TLC count was 7684/cumm with range of 2200/cumm -13500/cumm. Average neutrophil percentage was 56.5 percent with range from 29% to 80%. Average lymphocyte percentage was 37.63 percent with range from 14% to 64%. Average platelets count was 2.54 lakh/cumm with range from 1 lakh/cumm to 4.61 lakh/cumm.

CRP was done in 14 patients, its value was more than 1 mg/dl in 3 patients; with average value of 0.586 mg/dl

and range of 0.21 to 2.12mg/dl. Total serum bilirubin, direct bilirubin, SGOT and SGPT were done in all 20 patients. Average value of serum total bilirubin was 6.568 mg/dl with range of 2.15 to 18.06 mg/dl. Average value of direct bilirubin was 4.15 mg/dl with range of 1.07 to 10.83 mg/dl. Mean value of SGOT was 1849.8 U/L with range of 104.1 to 5844.0 U/L. Mean value of SGPT was 1952 U/L with range of 110 to 5685 U/L. PT test was done in 5 patients with mean value of 19 sec and range of 16 to 22 sec. Mean value of INR in these 5 patients was 1.52 with the range of 1.26 to 1.78. Serum protein and serum albumin was done in 8 patients. Average value of serum protein was 5.97 gm/dl with range of 4.83 to 6.73 gm/dl and average value of serum albumin was 3.14 gm/dl with range of 2.52 to 3.75 gm/dl.

Serum LDH was done in 8 patients with average value of 1934 U/L and range from 812 to 5976 U/L. Serum ferritin and D-dimer test could be done in only 1 patient; value of serum ferritin was 385 ng/ml and value of D-dimer was 1380 ng/ml in this patient. HbsAg test was done in all 20 patients, and the result was negative in all of them. Elisa test for IgM antibody against hepatitis A and hepatitis E could be done in only one patient and the result was negative. Widal test was done in four patients and all the patients were positive for Widal test in titre above 1:160 due to amnesic reaction. Dengue test was done in two patients and both the patients were negative for dengue test (Table 1).

Anti covid-19 antibody titre was done in 15 patients. Out of 15 patients, 14 patients had elevated level of antibody titre, while only one patient had low level of antibody titre. Average value of anti covid antibody titre was 43.13 U/ml and the range was from 0.22 to 99.10 U/ml (Figure 4).

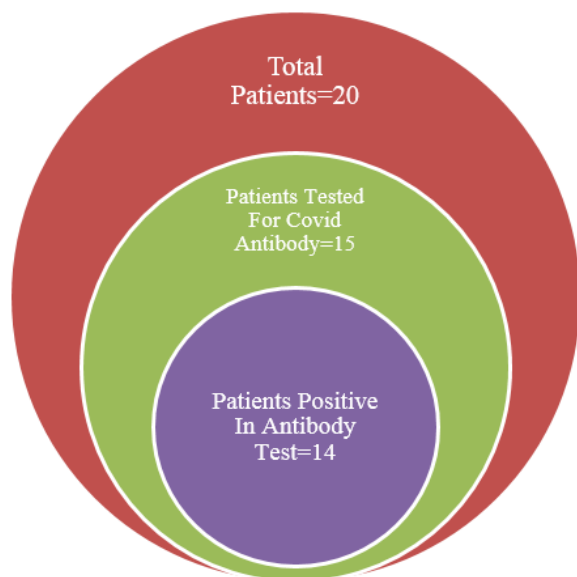


Figure 4: Showing positive patients for covid antibody test.

Further detailed work up to rule out other etiologies of hepatitis could not be done due to financial constraints and early recovery of the children. Only symptomatic and supportive treatment was given to all the admitted patients. Intravenous steroids and IVIG were not given to any patient. No patient developed acute liver failure or coagulopathy or encephalopathy during hospitalization. And all the patients recovered fully and were successfully discharged from the hospital with mean duration of stay of 4.6 days.

4. Discussion

The clinical suspicion of SARS-CoV-2 infection in children has been a challenge for physicians worldwide. Mild form of hepatitis is a well known symptom of active covid 19 infection in children and only in very few instances, it has been seen that children with covid 19 had presented with significant hepatitis.⁹ Many case series have been published, but none of them have reported hepatitis alone as a delayed manifestation of SARS-CoV-2 infection in children. In adult patients, Covid 19 induced hepatitis defined as a Benign New Transient Hepatitis is known which is characterised by gradual onset, elevated AST and ALT, dilated sinusoids with lymphocytic infiltration of liver parenchyma, non obstructive jaundice, stable underlying liver disease with no radiological new hepatobiliary changes.¹⁰ While hepatitis as a delayed complication of SARS-CoV-2 infection is not known in adults. Moreover, significant hepatitis was usually seen in adult patients who were severely ill, those who received hepatotoxic drugs or those who were already chronic hepatitis patients.¹¹

In adult patients suffering from covid 19, approximately 15% have liver test abnormalities and those patients with severe form of illness seem to have higher rates of liver dysfunction.¹² While in pediatric population, Hepatitis mainly has been reported as a part of covid 19 associated multisystem inflammatory syndrome in which child may present with prominent gastro-intestinal and hepatic involvement.¹³ However few studies have reported hepatitis to be a manifestation of acute covid 19 infections in children. According to Brisca et al, SARS COV-2 infection may present as acute hepatitis in children.¹⁴

In study done by Antala et al, they have reported significant hepatitis in four children who had primary manifestations of acute covid 19 infection. Two of these patients met diagnostic criteria for acute liver failure; however none of these patients had respiratory symptoms.¹⁵

Similarly in a case report by Varun et al, they reported a child who presented with fever and acute abdomen in acute liver failure and was tested positive for covid 19.¹⁶

However in study by Giorgio et al, they found that even children with chronic liver disease did not have an increased risk for severe disease course.¹⁷

In study by Zhu et al, they analysed outcome of 10 neonates born to mother with covid 19 pneumonia and

Table 1: Laboratory characteristics of pediatric patients with hepatitis (N=20)

Investigation	Number	Mean	Range
Hemoglobin	19	10.8gm/dl	3.6-14 gm/dl
TLC	19	7684/cumm	2200-13500/cumm
Lymphocyte	19	37.63%	14-64%
Platelets	17	2.546 lakh/cumm	1- 4.61lakh/cumm
SGOT	20	1849.795 U/L	104.1- 5844U/L
SGPT	20	1952 U/L	70- 5685 U/L
Total serum bilirubin	20	6.568mg/dl	2.15- 18.06mg/dl
Direct bilirubin	20	4.1485mg/dl	1.07- 10.83mg/dl
Serum protein	8	5.97gm/dl	4.83- 6.73gm/dl
Serum albumin	8	3.14gm/dl	2.52- 3.75gm/dl
PT	5	19 sec	16- 22sec
INR	5	1.518	1.26- 1.78
Covid antibody titre	15	43.128U/ml	0.22- 99.1U/ml
CRP	14	0.586 mg/dl	0.21- 2.12mg/dl
LDH	8	1934.25 U/L	812- 5976U/L
Serum ferritin	1	385 ng/ml	385 ng/ml
D dimer	1	1380 ng/ml	1380 ng/ml
HBsAg	20	All negative	
Elisa for hepatitis A	1	Negative	
Elisa for hepatitis E	1	Negative	
Dengue test	2	Both negative	
Widal test	4	All positive in >1:160 titre	

reported only 2 neonates with abnormal liver function tests.¹⁸

However in one case report by Pessoa et al, they have reported a case of hepatitis in a 5 year old male child in whom primary work up for all the other causes of hepatitis was negative. They attributed the cause of hepatitis to be related to covid 19 infections as proved by the presence of covid antibody along with negative RTPCR report.¹⁹

In our study, out of 15 patients tested for covid 19 antibody, 14 were tested positive with positive rate of 93%, while the Sero survey showed that the presence of covid19 antibody in children aged 10-17 years was 25.3%,²⁰ so it is clear that positivity for covid 19 antibody in these patients with hepatitis is not due to chance but clearly has some association with asymptomatic or mild covid 19 infection in past which might have got remain unrecognised. Whether the hepatitis was late manifestation of asymptomatic SARS-CoV-2 infection in children just like MIS-C need to be confirmed by further studies.

The testing capacity for SARS-CoV-2 antibody titre in this region of Madhya Pradesh was limited and available to only those patients who were financially strong. Many children with symptoms consistent with hepatitis in the community were not tested and consequently not diagnosed. This was the main drawback of our study along with inability to do extensive investigations in all the patients. However, our study may serve to consider hepatitis as a sole manifestation of covid 19 infection in children which need to be further confirmed by more studies and to reconsider diagnostic criteria for SARS-CoV-2 infection in children.

Clinicians should recognize that the clinical spectrum of COVID-19 in children can be wider than previously described and different from the adult presentation. The complete spectrum of symptoms (clinical pattern) requires more investigations and further studies.

5. Conclusion

A broader description of the SARS-CoV-2 infection in children is of paramount importance for its clinical suspicion in children. Although our study was retrospective and included a limited number of patients, it explored a different clinical spectrum of SARS-CoV-2 infection in pediatric patients. Since these cases occurred in the period immediately after the peak of SARS-CoV-2 infection in adults, and during this period it was quite unusual to have so many cases of hepatitis in children all of a sudden, with majority of them having raised antibody titre for SARS-CoV-2 infection. All these things clearly demonstrate that there can be temporal association of hepatitis with SARS-CoV-2 infection. So our result suggests that SARS-CoV-2 infection can often presents with hepatitis alone as delayed complication of SARS-CoV-2 infection in children. Hence, signs and symptoms of hepatitis, even in the absence of other clinical criteria of active COVID-19 infection or MIS-C should raise suspicion.

6. Ethics Clearance

Institutional Ethics Committee of Bundelkhand Medical College Sagar.

7. Source of Funding

None.

8. Conflict of Interest

None.

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