RESEARCH

CLINICAL PROFILE OF HEPATITIS A AND ITS COMPLICATIONS IN CHILDREN AGED BETWEEN 1-12 YEARS IN TERTIARY CARE CENTRE

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Abstract

Background: Acute viral hepatitis is a common cause of acute jaundice in India. Every year, we are getting outbreaks of viral hepatitis, most commonly in rainy season, leading to significant morbidity and mortality, so that appropriate measures can be taken to rectify deficits in the management of such patients for better outcome. Aims: To study the clinical profile of hepatitis A infection and its complications in paediatric age group. **Materials and Methods:** Prospective observational study conducted on 140 children admitted in department of paediatrics, with clinical features of hepatitis with anti HAV IgM ELISA positive for a period of 20 months Children of age 1-12 years in all children with jaundice and hepatitis A serum IgM positive included in study. **Result:** 15% of hepatitis A positive children had diffuse maculopapular rash all over the body at the time of presentation. Evidence of hepatomegaly and splenomegaly is 80% and 25% respectively. 30% Paediatric hepatitis. Benign course of hepatitis A infection in 1-12 of age group is 70% complete resolution in 4 weeks. Infection in late childhood is associated with severity of the disease and atypical presentations which is 30% with prolonged cholestasis, ALF, pancytopenia as order of prevalence. Prolonged cholestasis is the most common (12%) atypical presentation but a favourable outcome. 50% of prolonged cholestasis cases had radiological evidence of dilated CBD with Gall bladder sludge. Less than 1% of prolonged cholestasis had cholelithiasis. Thrombocytopenia is mild to moderate in all cases without any bleeding manifestations. Pancytopenia was found in 8 (6%) cases. among them in 7 cases had hypoplastic or aplastic bone marrow findings and cases recovered completely without any mortality. In the total study population only one case of Hepatitis a virus induced secondary HLH was diagnosed which is succumbed to death. 11% of children with hepatitis A virus infection had ALF which is most dreaded complication and associated with high mortality. **Conclusion:** Prevalence of the disease from early childhood to late childhood and adolescence which is associated with severity of the disease and atypical presentations. So, public awareness programmes to maintain hygiene, clean drinking water, use of sanitary toilets and vaccination against hepatitis B and A should be promoted by the health care professionals.

INTRODUCTION

Hepatitis A is an acute infectious disease caused by HAV. Disease heralded by nonspecific symptoms such as fever, chills, headache, fatigue, generalised weakness followed by anorexia, nausea, vomiting, jaundice. The disease spectrum is characterised by occurrence of numerous, subclinical or asymptomatic cases. The disease is benign in most of the cases with complete recovery in weeks. Case fatality of icteric cases is less than 0.1% from ALF. Geographical areas can be characterised as having high, intermediate or low levels of hepatitis A infection.

In developing countries with very poor sanitation conditions, 90% children have been infected with hepatitis A virus in early childhood. Those infected in early childhood do not experience any noticeable symptoms. Epidemics are uncommon because older

children and adults are generally immune. Symptomatic disease rates in these areas are low and outbreaks are rare. The developing countries with transitional economies, and regions where sanitary conditions are variable, children often escape infection in early childhood. Ironically, these improved economic and sanitary conditions may leads to higher susceptibility in older age groups and higher disease rates, as infection occurs in adolescents and adults, and large out-breaks can occur. Paradoxically, with transition from high to intermediate endemicity, the incidence of clinically significant hepatitis A increases. In developed countries with good hygienic conditions, infection rates are usually low. Disease may occur among adolescents and adults in high risk groups, such as injecting drug users, homosexual men, and people travelling to areas of high endemicity.[1]

HAV infection is highly contagious. Transmission occurs mostly by person-person contact through faecal-oral route. Parenteral transmission occurs rarely. Mean incubation period for HAV infection is 3 weeks. Faecal excretion starts in late incubation period, reaches its peak before onset of symptoms and relives by 2weeks after the onset of jaundice in older persons. Duration of viral excretion is prolonged in infants. Therefore patient is contagious before clinical symptoms are apparent and remain so until viral shedding stops.

HAV responsible for acute hepatitis often results in icteric illness with clinical symptoms like other form of viral gastroenteritis particularly in young children. The illness is more likely to be symptomatic in older adolescents and adults and in immune-compromised. It is often characterised by an acute febrile illness with an abrupt onset of anorexia, nausea, malaise, vomiting and jaundice with a duration typical of 7-14 days in most of the cases. Other organ systems can be affected during acute hepatitis infection like regional lymph nodes and spleen may be enlarged, moderately hypoplastic to aplastic bone marrow has been reported. Small intestine tissue may show changes in villous structure and ulceration. Acute pancreatitis, myocarditis have been reported. Though rarely nephritis, arthritis, vasculitis and cryo-globulinemia can result from circulating immune complexes and serositis. In most of the cases it recovers completely, but in some cases it can produce acute liver failure and prolonged cholestasis syndrome and other systems involvement.

As India is witnessing transitional economy with variable sanitary conditions, as compared to past decades, Indian hepatitis A epidemiology shifting from high to intermediate endemicity. Urban population who are susceptible for infection in adolescent and adult age group are increasing gradually because most of children are not exposed to infection in early childhood. Outbreaks of disease in this population leads to severity of the disease and atypical manifestations which increases with increasing age.[2] Studies on clinical spectrum and complications of hepatitis A are documented in adult age group but very low number of studies are documented in paediatric population. This study focuses on hepatitis A clinical features, atypical presentations and also on complications in paediatric age group.

MATERIALS AND METHODS

Prospective observational study done at Institute of child health, Niloufer hospital, Hyderabad. The study was conducted on 140 children admitted in department of paediatrics, Niloufer hospital with clinical features of hepatitis with anti HAV IgM ELISA positive for a period of 20 months from January 2019 to September 2020.

Inclusion criteria:

Children of age 1-12 years in all children with jaundice and hepatitis A serum IgM positive.

Exclusion criteria:

Children with jaundice and positive for other hepatotrophic virus, other known infections and with other underlying systemic disorders.

Methodology:

This study was conducted in Niloufer hospital, Hyderabad which is a tertiary care centre with 35000 In-patient admissions to Pediatric department. Department consists of six units and one emergency department with one triage room and PICU. Basic lab investigations are available round the clock. Haemodynamically stable cases are directly admitted in units. Haemodynamically unstable cases are admitted and treated in emergency unit. All children between the ages 1-12 years with signs and symptoms of viral hepatitis are tested for hepatitis A virus infection. Informed written consent was taken from guardian regarding enrolment in the study and follow-up Specific diagnosis is made by detection of HAV-specific immunoglobulin M in the blood. Which is gold standard for diagnosis of hepatitis A. IgM anti-HAV is tested using enzyme linked immunosorbent assay (ELISA). Which as sensitivity of 99 % and specificity of 95% 3. Children who are referred to Niloufer hospital with IgM anti-HAV ELISA positive report were enrolled directly in study as hepatitis A positive cases.

For all anti HAV IgM positive cases detailed history was taken regarding the disease such as icterus, fever, vomiting, loose motions, abdominal distention and rash. Special mention was given to atypical presentations such as prolonged cholestasis, haematological manifestations, and acute liver failure. Duration of the symptoms were also recorded. Detailed clinical examination including vitals parameters, head to toe examination and systemic examination were done and recorded in case record form.

Follow up of these patients was done regarding the progression of the illness for every 3 days including laboratory parameters. Children with total serum

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bilirubin of more than 5 mg/dl at 4th week of illness were followed up every fortnightly up to 3 months duration including laboratory parameters.
All basic laboratory investigations were done and also sent to anti HAV IgM teset for all cases. Children with no complications or with clinical improvement were discharged and recorded as discharge in the study. Children who are succumbed during the hospital stay was recorded as death. Prolonged cholestasis, acute liver failure, pancytopenia was taken as atypical manifestations in this study.

Statistical methods:
Data entry was done and analysed using Microsoft excel 2013 version. Data presented as percentages, pie charts, bar charts, column charts.

RESULTS

Mean age of 140 cases is 6.7 years. According age criteria more cases are observed in >5 years of age group (n) 82 and compared to <5 years which is (n) 58. Under 2 years of age very less number of children are effected (n) 11.

Table 1: Incidence according to the age and gender

Age in years	Cases	Cases
<2 years	11	8%
3 to 5 years	47	34%
6 to 9 years	44	31%
10 to 13 years	38	27%
Gender		
Males	68	48.6%
Females	72	51.4%

Table 2: clinical manifestations and number of children affected

Presenting complaints	Number of children affected	Percentages
Icterus	140	100
Fever	105	75
Vomiting	82	58.6
Cholestasis	26	18.6
Rash	22	15.7
Bleeding manifestations	19	13.6
ALF	16	11.4

All most all cases have yellowish discoloration of skin and urine (n)135, fever (n)105, vomiting (n) 82, loose motions (n) 15, Rash (n) 22 in cases at the time of presentation.
Common physical findings observed are Icterus in all cases, Pallor in (n) 60 cases Hepatomegaly in (n) 111 (79%) cases, Splenomegaly is observed in (n) 29 that is 20% cases. Except for the cases which presented with ALF (n) 16. Rest of the cases presented without life threatening clinical features.

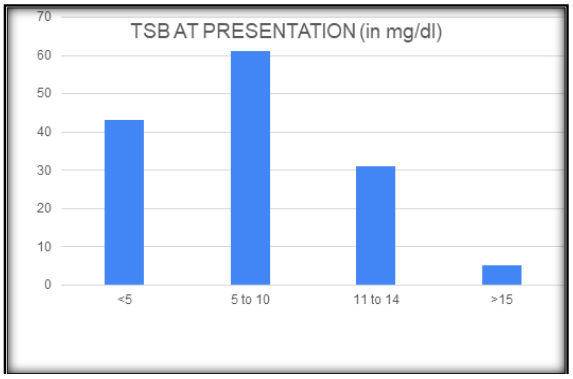

Figure 1: Range of TSB at the time of presentation

More number of cases are presented in a range of 5 to 10. 36 cases are presented with TSB more than 10 which are ALF and cholestasis.

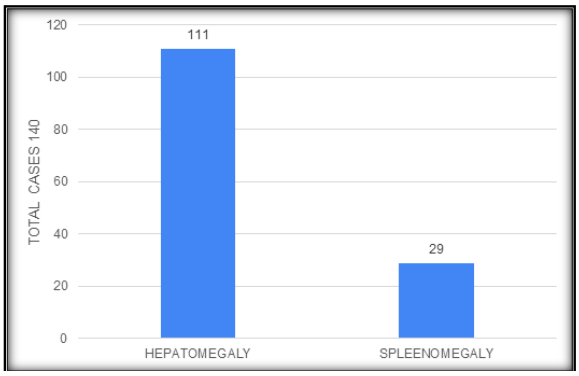

Figure 2: Organomegaly and their incidence

Hepatomegaly in (n) 111 (79%) cases, Splenomegaly is observed in (n) 29 that is 20% cases.

Table 3: Duration and clinical presentations

Duration	Number of cases	Percentages
2 months	104	74%
3 months	122	87%
Presentations		
Total atypical presentations	43	30%
Prolonged cholestasis	17	12%
ALF	16	11%
Pancytopenia	8	9%
thromboctopenia	8	9%
Heamolysis	2	1.4
HLH	1	0.7

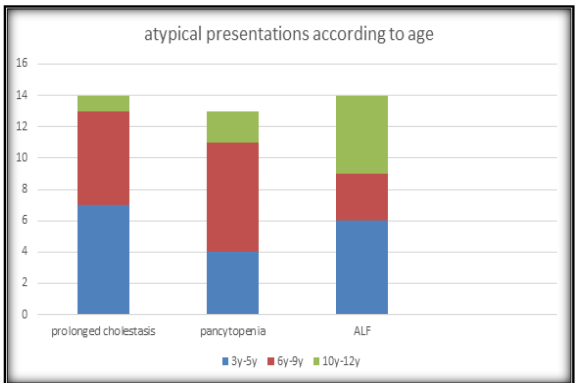

Figure 3: Atypical presentations according to age

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Out of 140 cases 17 (12%) cases complicated with prolonged cholestasis mean age for atypical presentation is 7.5 years.

Table 4: haematological manifestations and their incidence.

Haematological findings	Number of cases	Percentages
Anaemia (HB<10)	60	42.8
Thrombocytopenia	8	5.7
Leukopenia	12	8.6
Pancytopenia	8	5.7
Haemolysis	2	1.4
Hypoplastic or aplastic anaemia	7	5
HLH	1	0.7
Radiological findings		
Pleural effusion	28	20
Serositis	37	26.4
Dilated CBD	6	4.3
Gall bladder sludge	2	1.4

In 18 (12%) cases haematological manifestations are observed. Mean age of presentation is 8.5 years for haematological manifestations. Anaemia is observed which is clinically evident through pallor and haemoglobin <10 in 60 cases which is mostly attributed to underlying iron deficiency anaemia. Haemolysis is observed in 2 cases coombs test positive in those cases. Thrombocytopenia is observed in 8 cases. Pancytopenia is observed in 8 cases with a mean age of 9.4 years which indicates more atypical presentations in older children and adolescents as observed in other studies also among them males are 5, females 3. CXR findings suggestive pleural effusion in 28 cases which is in 20 % cases. it is right sided and mild to moderate in all cases. Serositis is observed in 37 cases that is 33 % cases which is evident through gall bladder wall edema and mild ascites.

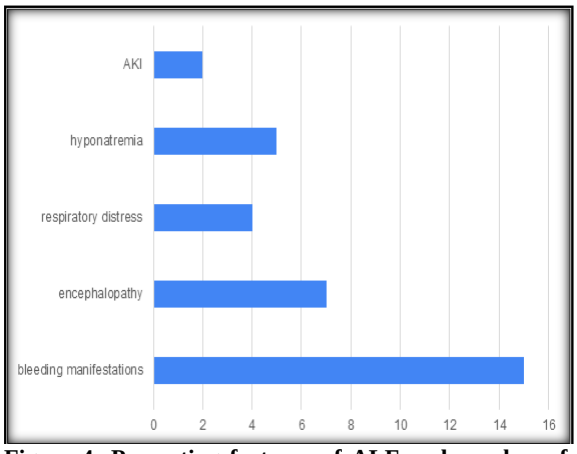

Figure 4: Presenting features of ALF and number of cases.

Bleeding manifestations are observed in (n) 15 cases. Encephalopathy observed in (n) 7 cases. Respiratory distress in (n) 3 cases, in these cases distress is due to abdominal distension which is so severe and causing respiratory distress and pleural effusion which is adding to it.

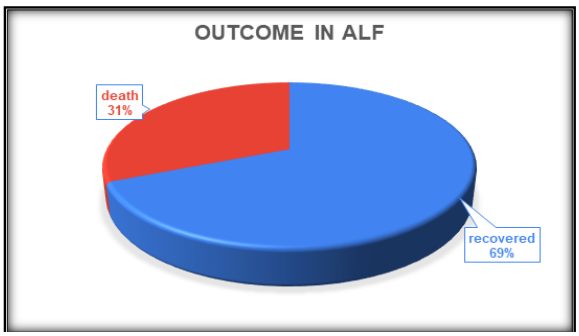

Figure 5: Outcome in ALF

Outcome in ALF cases - Among 16 cases 11 cases improved with conservative management gradually, required prolonged hospital stay.

Table 5: outcome in atypical presentations.

	Recovered cases	Death
Prolonged cholestasis	17	0
Pancytopenia	7	1
ALF	11	5

Case fatality is 3% that is 6 cases which are presented to hospital very late stages of ALF presented with encephalopathy grade 3-4 and HLH.

Table 6: Biochemical recovery time

Complete recovery time	Number of cases	Percentages
<2 months	106	75%
<3 months	18	12%
>3 months	13	9%

Recovery in most of the cases is < 2months ie 75% cases.

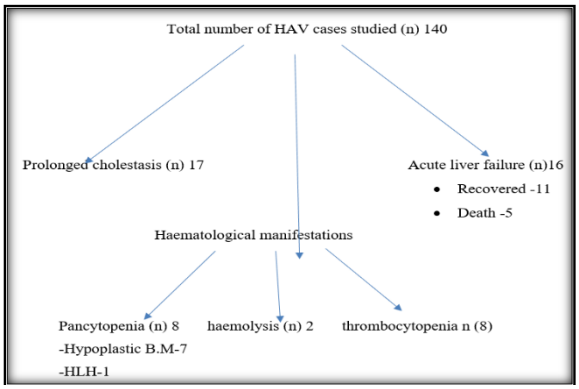

Figure 6: representing various atypical presentations and their incidence.

DISCUSSION

Total 140 cases are cases are collected in study period which are directly admitted and referred from various hospitals to Niloufer Hospital among them male and female cases are approximately equal that is male (n) 68 and female (n) 72.[3] Mean age of 140 cases is 6.7 years. According age criteria more cases are observed in >5 years of age group (n) 82 and compared to <5 years which is (n) 58. Under 2 years of age very less number of children are effected (n) 11. Which is

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similar to other studies done in recent times in India and other developing countries. Chitamber at al,[4] demonstrated a significant ($p<0.05$) shift in epidemiology of HAV infection among children aged 5-10 years from 96.7% in 1983 to 85.1% in 1995. Murhekar at al,[5] study also showed similar data and support this epidemiological shift.[6] Acharya at al,[7] opined that due to increasing hygienic and sanitary conditions which led to a shift in epidemiology of HAV infection. More people living in urban areas and with higher socioeconomic status were at risk of infection later in life compared with rural areas and low socioeconomic groups. As a result more children are reaching late childhood and adolescence without being previously exposed to hepatitis A infection and therefore long term protection. Because the risk of severe infection, complications and atypical presentations are more in late childhood, adolescents and adults hence there is a need for long-term protection.

Except for the cases which presented with ALF (n) 16. Rest of the cases presented without life threatening clinical features. All most all cases have yellowish discoloration of skin and urine (n)135, fever (n)105, vomiting (n) 82, loose motions (n) 15, Rash (n) 22 in cases at the time of presentation. Common physical findings observed are Icterus in all cases, Pallor in (n) 60 cases Hepatomegaly in (n) 111 (79%) cases, Splenomegaly is observed in (n) 29 that is 20% cases. Tong MJ et al[6] study in 59 cases similar findings observed such as most common presentation is yellowish discolouration and fever and fallowed by gastrointestinal manifestations. Most frequent physical findings observed were hepatomegaly and jaundice. Jenisha jain and Mayank jain study of combined HAV,[7] HEV observed splenomegaly in 21% cases. Yellapu radhakrishna study from Lucknow similar rate of splenomegaly in 20 % cases.[8]

Mean presenting laboratory tests included TSB 7.3 mg/dl; SGPT -1017 u/l; SGOT – 725 u/l; ALP – 387 u/l. in present study which is higher than some studies. It may be due to more number of atypical presentations included as prolonged cholestasis and ALF which are presented with higher TSB. More number of cases are presented in a range of 5 to 10. 36 cases are presented with TSB more than 10 which are ALF and cholestasis.

In 18 cases TSB is more than 2 mg/dl after 2 months of disease onset. In 13 cases more than 2mg/dl even after 3 months of disease onset. S.G Munoz-Martinez et al[20] study showed spontaneous remission in 90% cases

Compared to Tong MJ Study in our study average tsb is more that is 7.3 and AGPT is 1017 compared to 1442, SGOT is low 725 compared to 1952, ALP is more compared to that study.[6] Among 140 cases atypical presentations or complications are observed in (n) 43 cases which is (30%) with a mean age for atypical presentation is 7.5 years in present study. When compared to other studies. Vikrantsood et al,[9] study done at Institute of liver and biliary sciences, New Delhi among 431 cases with median age of 11 years atypical presentations were observed in 201 cases (44%). Higher incidence of atypical presentation in New Delhi can be explained by high mean age in cases that is 11 years late childhood and adolescence are associated with more atypical presentations and complications. In Mustafa et al study it is as 32 cases (13%). Trayambak Samantha et al,[10] study among 229 cases 32 (14%) presented with atypical presentations with a mean age of 7.7 years which is similar in present study.

Table 7: showing comparison of atypical presentations in various studies

	Vikrantsood study,[9]	**Trayambak Samantha study,[10]**	**Present study**
Sample size	431	229	140
Prolonged cholestasis	66(15%)	14 (4%)	17 (12%)
ALF	92 (21%)	9 (4%)	16 (11%)
Haematological manifestations	25 (25%)	8 (4%)	10 (7.4%)

Among atypical presentations most of them are late childhood or adulthood median age of 7.5 years. In present study among the cases (n) 16 (11%) cases presented with ALF. mean age of presentation is 6.4 years.

Cases are diagnosed as acute liver failure with the criteria.[2] So as per criteria Bleeding manifestations are observed in (n) 15 cases, Encephalopathy observed in (n) 7 cases, Respiratory distress in (n) 3 cases, in these cases distress is due to abdominal distension which is so severe and causing respiratory distress and pleural effusion which is adding to it. Acute kidney injury is observed in (n) 2 cases which is evident through elevated blood urea and decreased urine output. Hypernatremia observed in (n) 5 cases. Among 16 cases (n) 5 cases died, all 5 cases have INR more than 5 and have bleeding manifestations at the time of presentation, 4 cases have severe abdominal distension, hypernatremia is observed in 3 cases. Outcome in ALF cases - Among 16 cases 11 cases improved with conservative management gradually, required prolonged hospital stay. Death happened in 5 cases i.e is 30% of ALF cases. Death rate is noted in vikrantsood9 study is among 92 cases 28 cases (30%) died and 9 (10%) cases underwent liver transplantation which is not done in our cases. rest of the children are survived with native liver. Collectively regarding ALF compared to other studies in vikrantsood 9 study more number of cases are observed fallowed by present study fallowed by Mustafa et al study.

Various haematological complications observed are anemia, pancytopenia, thrombocytopenia and haemolytic anaemia. In 18 (12%) cases haematological manifestations are observed. Mean age of presentation is 8.5 years for haematological manifestations. Anaemia is observed which is clinically evident through pallor and haemoglobin

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<10 in 60 cases which is mostly attributed to underlying iron deficiency anaemia. Haemolysis is observed in 2 cases coombs test positive in those cases. Thrombocytopenia is observed in 8 cases. Pancytopenia is observed in 8 cases with a mean age of 9.4 years which indicates more atypical presentations in older children and adolescents as observed in other studies also among them males are 5, females 3.

Among these 8 cases workup for other causes of pancytopenia is done no other cause is found except for 1 case is turned out as HLH which is fitting into diagnostic criteria and treated correspondingly. When compared to other studies vikrantsood study 25 cases 6 % cases are associated with haematological manifestations.[9] Haemolysis in 14 cases and HLH is present in 9 cases. In Mustafa et al,[11] study total 8 cases i.e only 3 % case s are associated with haematological manifestations. In present study also 11 cases 8 % associated with atypical haematological manifestations as pancytopenia, HLH and haemolysis.

Table 8: Clinical manifestations in comparision with various studies

Manifestations	Present study	Vikrantsood et al,[9]	Jenisha jain et al,[7]
Haematological	18 (12%)	24 (5%)	8 (9%)
Haemolysis	2 (2.7%)	14 (3.2%)	5 (6%)
Thrombocytopenia	8 (5.7%)	0	3 (3.7%)
HLH	1 (1.4%)	9 (2.1%)	0
Pancytopenia	7 (5%)	0	0

Haemolysis is present in less number of cases compared to both studies. Thrombocytopenia is higher when compared to jain,[7] study which is 3.7% and not mentioned in vikrantsood study.[9] HLH is diagnosed in one case which is presented as pancytopenia and diagnosed based on criteria. Pancytopenia in these cases id explained by bone marrow aspiration studies which are suggestive of hypoplastic or aplastic bone marrow picture suggestive of viral induced suppression of bone marrow.

Out of 140 cases 17 (12%) cases complicated with prolonged cholestasis. When compared to other studies prolonged cholestasis is observed less than jain and vikrantsood,[9,11] study and relatively equal as Mustafa study. In present study mean TSB for prolonged cholestasis is 12 mg/dl. Ultrasonography findings of biliary tract in those 17 cases we observed Dilated CBD as per age criteria in 6 cases and gall bladder sludge is observed in 3 cases, cholelithiasis in 1 case. These ultrasonography findings in prolonged cholestasis can explain the pathophysiology of prolonged cholestasis.

CXR findings suggestive pleural effusion in 28 cases which is in 20 % cases. it is right sided and mild to moderate in all cases. Serositis is observed in 37 cases that is 33 % cases which is evident through gall bladder wall edema and mild ascites. Gross ascites found in 8 cases causing respiratory distress. In Mustafa et al,[11] study it is 3 % children are presented with gross ascites. Which similar in present study. In Jain study it is very high that is 24%. Ultrasonography of biliary system showed dilated CBD in 6 cases as per age.

Present at the time of presentation in 2 cases which is 1.4%. AKI is present in children who are presented with ALF. Blood urea is more elevated in those children. In Vikrantsood study AKI is present in 6 cases which is 1.5 % similar in our study.[9] Hyponatremia is observed in 3 cases in these cases sodium is <130 and have ALF.

Case fatality is 3% that is 6 cases which are presented to hospital very late stages of ALF presented with encephalopathy grade 3-4 and HLH. Case fatality observed in vikrantsood,[9] study is 28 cases that is 6 %. Which is some higher than present study. Among 6 cases which are succumbed, 5 cases presented with ALF and INR > 3 in 4 cases >2.5 in 1 case. 2 cases were found to have AKI at presentation. Abdominal distension and severe ascites is observed in 4 cases. Average TSB is 15.8 mg/dl. Average SGPT is 4500 u/l and average SGOT is 2200 u/l.

CONCLUSION

Hepatitis A infection in children typically presents with fever, icterus, vomiting and loose stools. Almost all cases had vomiting at the time of presentation preceded by icterus and fever. 15% of hepatitis A positive children had diffuse maculopapular rash all over the body at the time of presentation. In the total study population only one case of Hepatitis a virus induced secondary HLH was diagnosed which is succumbed to death. 11% of children with hepatitis A virus infection had ALF which is most dreaded complication and associated with high mortality.

Almost all cases of ALF had coagulopathy at the time of presentation, followed by encephalopathy, electrolyte abnormalities, and renal failure. ALF is associated with high mortality when it is associated with late stages of encephalopathy, electrolyte abnormalities like Hyponatremia (<130), AKI. Improved hygiene, transitional economy, and increasing urban population led to the shift of hepatitis A virus infection from high endemicity to intermediate endemicity. This epidemiological shift in the prevalence of the disease from early childhood to late childhood and adolescence which is associated with severity of the disease and atypical presentations.

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