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Pediatrics

A STUDY OF HEPATIC INVOLVEMENT IN CHILDREN WITH DENGUE FEVER

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ABSTRACT

Objective: To study the spectrum of hepatic involvement in various presentation of dengue fever and predilection of severe forms of dengue fever by early detection of elevated liver enzymes

Methods: This prospective observational study conducted at government hospital,with Ns1ag antigen, and IgM, IgG capture ELISA. Children with pre-existing liver disease and children with other infections causing hepatitis like malaria, hepatitis B, enteric fever, leptospirosis are excluded.

Results: Total 396 cases were included in current study. Males: females were 1.21:1. Fever was present in 100% cases, vomiting in 34.34%, pain abdomen in 51%, arthralgia / myalgia in 44.9%, malena in 12.10% rash in 33.10%. Hepatomegaly (65.40%) was the most common presentation followed by gallbladder wall edema (54.29%), ascites (44.44%), pleural effusion (34.09%). Mean values of Hb, Hct and platelets were 9.52gm/dl, 36.02%, 38382/cmm respectively. The mean total bilirubin, albumin, AST, ALT, Alk phosphatase level were 1.085mg/dl, 4.95g/dl, 280.69U/L, 178.17 U/L and 146.93 U/L respectively. The mean PT, aPTT, INR, BT and CT were 15.91sec, 37.36sec, 1.04, 6.101 mins and 5.65 mins respectively. Liver function tests AST, ALT and Alkaline phosphatase, bilirubin were deranged in children with severe dengue and dengue with warning signs compared to dengue without warning signs

Conclusion: Our study suggests that significant rise of liver enzymes helps in recognition of severe forms of dengue infection.

KEYWORDS :

INTRODUCTION

Dengue is a mosquito borne infection found in tropical and sub-tropical regions around the world. In recent years, transmission has increased predominantly in urban areas and has become a major international public health concern[1].

The incidence of Dengue has grown dramatically around the world in recent decades. Over 25 billion people (40% of the world's population) are now at risk from Dengue. WHO currently estimates, there may be 50-100 million dengue infections worldwide every year[1].

Severe Dengue was first recognized in the 1950s during dengue epidemics in the Philippines & Thailand. Today severe dengue affects most Asian and Latin American countries and has become a leading cause of hospitalization and death among children in these regions[1].

Unusual clinical manifestations of dengue fever have become more common in the last few years. Although the liver is not a major target organ, hepatic dysfunction is a well-recognized feature, often characterized by acute hepatitis, with pain in the right hypochondrium of abdomen, hepatomegaly, jaundice and raised aminotransferase levels[2-19]. Liver dysfunction as a result of dengue infection can be a direct viral effect on liver cells or an adverse consequence of dysregulated host immune response against the virus[6-12]

Although the number of patients affected by the disease is increasing each year, little work has been done in this area. Since our hospital is a tertiary care hospital, we do see a lot of children with dengue infection including those with atypical manifestations, so an attempt has been made to know the extent of hepatic dysfunction and to relate it with severity of disease

MATERIALS AND METHODS

STUDY DESIGN: This is a Hospital based prospective observational study conducted at government general hospital, Kurnool. 728 cases were admitted in the hospital for suspected dengue fever. Out of which, 396 cases were confirmed by dengue NS1Antigen and IgM, IgG antibody by ELISA technique. **AIM:** To study the spectrum of hepatic involvement in various presentation of dengue fever and to assess predilection of severe forms of dengue fever by early detection of elevated liver enzymes. **EXCLUSION CRITERIA**: Children with pre-existing liver disease and children with other infections causing hepatitis like malaria, hepatitis B, enteric fever, leptospirosis. **INCLUSION CRITERIA**: Children with dengue fever confirmed by dengue NS1 antigen, and IgM, IgG capture ELISA cases in the age group of 6 months to 12 years irrespective of sex admitted in the Department of Pediatrics, government general hospital, Kurnool. **INVESTIGATIONS**: Complete blood count, NS1antigen, serum dengue IgM or IgG antibodies. Liver function tests. Other tests like activated partial thromboplastin time, prothrombin time, international normalized ratio bleeding time, clotting time and ultrasonogram abdomen done

OBSERVATION AND RESULTS

Out of 728 cases,396 cases were confirmed by dengue serology, which were taken into the study. Age wise distribution is mentioned in the table below. In the present study 54.79% were males and 45.20 % were females. The male: female sex ratio was **1.21:1.** Fever was present in all the cases. Pain abdomen, malena were more common in severe dengue and vomiting and rash more in DWS group. Complains of myalgias more in DWWS and DWS group

Signs like facial puffiness, ascites, hepatomegaly, petechiae gall bladder wall, pleura effusion were more common in severe dengue and dengue with warning signs. Icterus is seen only in 15 children presented with severe dengue. Hepatomegaly is more common in severe dengue and dengue with warning signs.

Age group	Severe dengue	With warning signs	Without warning signs	Total
<1year	7	7	14	28
1-5years	33	55	58	146
6-12years	48	77	97	222
Total	88	139	169	396

Comparison of presentations of dengue in different age group

Comparison of Symptoms and signs in Dengue fever

Symptoms	Dengue without warning signs(n=169)	Dengue with warning signs(n=139)	Severe Dengue(n=88)
Fever	169(100.0%)	139(100.0%)	88(100.0%)
Vomiting	19(11.2%)	81(58.2%)	36(40.90%)
Pain abdomen	45(26.62%)	95(68.34%)	62 (70.45%)
Myalgia	72(42.60%)	71(51.07%)	39(44.31%)
Malena	0(0.0%)	4(2.87%)	40(45.45%)
Rash	38(22.48%)	56(40.28%)	35(39.77%)
Facial puffiness	5 (2.95%)	56 (40.28%)	64 (72.72%)
Petechiae	1 (0.59%)	54 (38.84%)	81(92.04%)
Icterus	0(0.0%)	0 (0.0%)	15(17.04%)
Hepatomegaly	72(42.60%)	99 (71.22%)	88 (100%)
Ascites	13(7.69%)	105(75.53%)	58(65.90%)
G.B. wall edema	37(21.89%)	108(77.69%)	69(78.40%)
Pleural effusion	0(0.0%)	96(69.06%)	39(44.31%)

Laboratory Parameters

Measurement	Mean	Range	
		Min	Max
Hb	9.52	7.2	13
Hct	36.02	20	42
Platelet	38382	9,200	1,25,000
Total bilirubin	1.085	0.4	2.8
Sr. Proteins	6.609	5.4	7.5
Albumin	4.952	4.0	6.9
AST	280.69	110	971
ALT	178.17	40	451
Alk.phosp	146.93	75	348
PT	15.91	12	28
APTT	37.36	24	100
INR	1.04	0.9	2
BT	6.101	3.3	10.1
CT	5.626	3.2	8.2

The degree of AST levels elevation was evaluated and classified into four groups according to AST levels during the period of infection. Higher levels of AST were found in dengue without warning signs. The degree of ALT levels elevation was evaluated and classified into four groups according to ALT levels during the period of infection. Higher levels of ALT were seen in patients with severe dengue. Higher levels of alkaline phosphatase were seen in patients with severe dengue compared to dengue with warning signs and dengue without warning signs.

AST Levels in Dengue Fever

AST	GRADES	Dengue without warning signs	Dengue with warning signs	Severe Dengue
<40 (n)	Grade A	0	0	0
40-120 (1-3)n	Grade B	6	0	0
121-400 (4-10)n	Grade C	163	139	41
>400 (>10n)	Grade D	0	0	47

ALT Levels in Dengue Fever

ALT	DWWS	DWS	Severe Dengue
<40 (n)	2	2	0
40-120 (1-3)n	74	10	3
121-400 (4-10)n	93	127	77
>400 (>10n)	0	0	8

Alkaline Phosphatase levels in Dengue fever

Alkaline Phosphatase	DWWS	DWS	Severe Dengue
<125	88	36	8
125-250	81	103	75
>250	0	0	5

DISCUSSION

There are 4 distinct, but closely related, serotypes of the virus that cause dengue (DEN-1, DEN-2, DEN-3 and DEN-4). Recovery from infection by one provides lifelong immunity against that particular serotype. However, cross-immunity to the other serotypes after recovery is only partial and temporary. Subsequent infections by other serotypes increase the risk of developing severe dengue. Dengue fever is classified into dengue without warning signs, dengue with warning signs and severe dengue depending on the clinical manifestations. Hepatic dysfunction is common in dengue infection and the degree of liver dysfunction in children varies from mild injury with elevation of transaminase levels to severe injury with jaundice and coagulopathy.

In this study out of 396, 169 cases included in the dengue without warning sign group (DWWS) ,139 in dengue with warning signs group (DWS) and 88 in the severe dengue group.

AGE: In the present study, 28 children were under the age of 1year. Out of 28, 7 children presented with severe dengue, 7 presented with warning signs and remaining 14 children presented without warning signs. In the age group of one to five years,58 children presented without warning signs, 55 children are with warning signs and 33 had severe dengue. In children between 6 to 12 years, 97 children had dengue without warning signs, 77 children presented with warning signs and 48 children with severe dengue.

SEX: In this study, male children were 217 and female children were 179.Male: female ratio was 1.21:1. There was no preponderance of dengue infection for particular gender noted in our study.

CLINICAL FEATURES: Children with Dengue fever in our study most commonly presented with fever (100%). Results were comparable with earlier studies L Kabila et al, Kazunori et al, Anju agarwal et al. This might be attributed to fever being the main symptom for which most of the parents seek health care.

Pain abdomen was seen in 51% of our cases which was compared to earlier studies which had an incidence of 40 to 50%. In the present study pain abdomen was seen in 45 children (26.62%) in DWWS group, 95 (68.34%) in DWS group and in severe dengue group pain abdomen was present in 62 children (70.45%). Higher incidence of pain abdomen was observed in severe dengue.

In dengue without warning signs group 19 out of 169 children presented with vomiting. In dengue with warning signs group 81 out of 139 children presented with vomiting. In severe dengue group 36 out of 88 children presented with vomiting. Overall incidence of vomiting is 34.34% which was more compared to earlier studies. In this study, myalgias was seen in 44.9% of cases, which was more in severe dengue and dengue with warning sign groups. In this study Malena was observed in 48 cases, more common in severe dengue 40 in number,8 cases in dengue with warning sign group, absent in dengue without warning signs.

Out of 396 cases, skin rash was seen in 130(33.1%) children, more common in dengue with warning sign, severe dengue group compared to dengue without warning sign group. Facial puffiness was noticed in 125(31.81%) cases, 5 cases in DWWS group,56 cases in DWS group,64 cases in severe dengue group. Petechiae was noticed in 136(34.59%) cases, which was more in severe dengue and DWS groups. We observed 1 case in DWWS group,54 cases in DWS group, 81 cases in severe dengue group.

Icterus was noticed in 15(4.29%) cases only. All cases were in severe dengue group with a percentage of 17.04. Hepatomegaly was seen in 65.40% of cases which is more comparable to study done by Shudhankar et al which had an incidence of 43.8%. In the group of dengue without warning signs 72 out of 169 children had hepatomegaly. In dengue with warning signs 99 out of 139, in severe dengue group out of 88 children hepatomegaly is seen in 88 children, presence of an enlarged liver is observed more frequently in severe dengue and dengue with warning signs compared to dengue without warning signs.

Ascites was seen in 41.41% of the cases which is comparable to earlier studies which reported an incidence of 28 to 46%. Ascites was noticed in 13 out of 169 in DWWS group with a percentage of 7.69, and 105 cases out of 139 with a percentage of 75.5 in DWS group and 58cases out of 88 seen in severe dengue group with a percentage of 65.90. here we observed that ascites more in DWS group and in severe dengue group.

Gall bladder wall edema was seen in 54.29% of children. In DWWS group had 37 cases out of 169(21.89%), 108 out of 139(77.69%) in DWS group,69 out of 88(78.40%) in severe dengue group were noticed gall bladder edema by abdominal ultrasound. Gall bladder wall edema was noticed more in DWS and severe dengue group. Pleural effusion was noticed in 34.99% of the study sample. This was seen in DWS and severe dengue groups with a percentage of 56.80%,44.31% respectively which was comparable in other studies. This was not observed in DWWS group.

LABORATORY INVESTIGATIONS

In the present study, the mean hemoglobin at presentation was 9.52 g/dl. Minimum hemoglobin in our study is 7.2 g/dl and maximum value of haemoglobin is 13 g/dl. In other studies, it ranged from 10.8 g/dl to 13.7 g/dl. In our study the mean hematocrit is 36.02. Minimum haematocrit value is 20 and maximum value of hematocrit is 42. The mean value of platelet in present study is 38382 cells/cmm and minimum value of platelet count is 9,200 cells/cmm and maximum value of platelet count is 1,26100 cells/cmm.

In this study, in children with dengue fever without warning signs, 163 children had AST elevation of 4 -10 times the normal value. In children with dengue with warning signs 139 cases had AST elevation of 4-10

times the normal value. In children with severe dengue 41 children had AST elevation 4-10 times the normal value. In severe dengue group 47 children had AST value above 10 times the normal value. AST elevation increased with severity of disease

In children with dengue fever without warning signs 74 children had ALT elevation 1-3 times the normal value and 93 children had ALT elevation 4--10 times the normal value. In children with dengue fever with warning signs 10 children had ALT elevation 1-3 times the normal value and 127 children had ALT elevation 4-10 times the normal value. In severe dengue group out of 88 three children had ALT elevation of 1-3 times the normal value and 77 children had elevation between 4-10 times, remaining 8 children had more than 10 times elevation. Elevation in ALT is directly proportional to severity of disease.

In children with dengue without warning signs ALP is <125 in 88 children and between125-250 in 81 children. In children with dengue fever with warning signs 36 children had ALP value less than 125 and 103 children had values between 125-250. In children with severe dengue 8 children had ALP values less than 125 and 175 children had ALP values between 125- 250 and 5 children had ALP values above 250.Alkaline phosphatase values were increased with severity of disease

The mean total bilirubin level in the present study was 1.085 mg/dl. Other studies reported mean total bilirubin levels of 0.8 mg/dl to 0.93 mg/dl. In children with dengue without warning signs mean total bilirubin is 1.014mg/dl. In children with dengue with warning signs mean total bilirubin is 1.05. In children with severe dengue mean total bilirubin is 1.27. Bilirubin elevation is more in children with severe dengue compared to dengue with warning signs and dengue without warning signs

In the present study the mean value of serum proteins was 6.609g/dl. In children with severe dengue the mean value of serum proteins is 6.59g/dl. In children with dengue with warning signs mean value of serum proteins is 6.42g/dl. In children with dengue without warning signs mean value of serum proteins is 6.61g/dl. There is no variation in the value of serum proteins with severity of dengue

In the present study the mean value of serum albumin was 4.952g/dl. In children with severe dengue the mean value of serum albumin was 4.96g/dl. In children with dengue with warning signs mean value of serum albumin was 4.95g/dl. In children with dengue without warning signs mean value of serum albumin was 4.94g/dl. There is no variation in the value of serum proteins with severity of dengue. The mean serum bilirubin level in the present study was slightly more with earlier study done by Chinna et al[4,] prakash o et al and Jagadish et al[22.] In the study, jaundice was seen in 15 cases out of 396 case which was not seen in the other studies.

All the liver function tests (Total bilirubin, AST, ALT and Alk phosphatase) were higher in children with severe dengue compared to dengue fever with warning signs and dengue fever without warning signs which is comparable to earlier studies.

The mean AST and ALT levels were 280.69 and 178.17 U/L respectively. The mean value of AST was significantly higher than the mean values of ALT which is comparable to other studies. This differs from the pattern in viral hepatitis, the exact cause of which is uncertain. It has been suggested that it may be due to excess release of AST from damaged monocytes during dengue infection.

The mean PT and aPTT levels were 19.68. and 46.29 in severe dengue group. The mean Prothrombin time (PT), mean activated partial thromboplastin time (APTT) were significantly higher in the severe dengue compared to dengue with warning signs and dengue without warning signs.

Derangements in this study are either due to more virulent strain of dengue infection or virus is more hepatotoxic. Therefore further studies are required to highlight the possible hepatotropic nature of this virus as well as virulence and type of virus.

Mean ALP value in our study is 146.93u/l and minimum ALP value in our study is 86u/l and maximum ALP value in our study is 348u/l. Liver involvement occurred through an inflammatory process in the parenchyma provoked directly or indirectly by the virus, reducing the diameter of the lumen of the biliary canaliculus, causing obstruction and leading to bilirubinemia, jaundice and elevated alkaline phosphatase levels as reported in earlier studies which is in accordance with our study.

Outcome

In our study, the mortality rate was 1.01% and all the 4 patients had low platelet count, high hematocrit, elevated alkaline phosphatase and deranged liver enzymes, elevated prothrombin time, INR, and they were finally in a stage of multi organ dysfunction**.** This mortality rate was comparable with Jagadish k et al[22] studies which showed 0.9% mortality.

CONCLUSION

Dengue is the most rapidly spreading mosquito borne viral disease in the world. Its incidence has increased in the present decade by 30-fold. Presence of fever, jaundice and hepatomegaly in endemic areas should arouse the suspicion of dengue hepatitis. Liver involvement is known to be common among children with dengue infection. Upon injury to the liver the enzymes AST & ALT are released into the blood stream. In dengue infection the levels of AST are greater than ALT which is in contrast to the finding observed in viral hepatitis. Significant rise of liver enzymes helps in recognition of severe forms of dengue infection. Mortality was decreased with early diagnosis and institution of appropriate line of management.

LIMITATIONS OF PRESENT STUDY

Repetition of liver function tests not done in this study and follow up of the cases after discharge from our hospital also not done. liver biopsy was also not done in this study groups.

RECOMMENDATIONS FOR FURTHER STUDY

According to present study there is statistically significant association between abnormality of liver function tests and severity of dengue fever., it is not enough to confirm the association. It requires large number of samples for confirmation. Further the limitations of present study like repetition of liver function tests and follow up of cases should be done.

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