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STUDY OF HEPATIC INVOLVEMENT IN ADULT PATIENTS SUFFERING FROM DENGUE INFECTION IN A TERTIARY CARE HOSPITAL IN KOLKATA.

Medicine

Sukanta Debnath MBBS, DPH, MD (Tropical Medicine),Senior Resident

Bikram Das* MBBS, DTCD, MD (Tropical Medicine), Senior Resident *Corresponding Author

Mehebubar Rahman MBBS, DCH, MD (Tropical Medicine) Associate Professor, Department of Tropical Medicine, School of Tropical Medicine, Kolkata

Rama Prosad Goswami Professor, MBBS, MD(Tropical Medicine), Department of Tropical Medicine, , School of Tropical Medicine, Kolkata

ABSTRACT

Dengue virus has been found to have profound effect on multiple organs including liver. This Single centre, prospective, observational study evaluated the clinical profile, liver function in dengue infected 125 adult patients admitted at inpatients department and assessed its correlation with clinical severity over 5 days after admission. Clinically 72 % patients were classified as Dengue without warning signs (DWNS), 19 % as Dengue with warning signs (DWWS) and 9% as patients of severe Dengue (SD). SD patients presented significantly earlier by 1day (mean 3.82 days) than others. Hepatomegaly was found in 39% patients, acalculous cholecystitis in 9% & both were significantly more common in SD patients. Mean SGOT & SGPT values were 117.3 IU/L, 114.9 IU/L & 78.9 IU/L, 78.2IU/L at day 1 and day 5 respectively. SGOT above 80 IU/L was observed in 72.7%, 54.2% and 50% of patients with SD, DWWS and DWNS respectively. Only 27.3% patients with SD had raised serum SGPT level >80 IU/L & 9.1% had bilirubin ≥1 mg/dL at day1. Mean INR was significantly higher in day5 (1.05±0.16) compared to day 1(1.00±0.14).

KEYWORDS

Dengue, liver, hepatitis, hypertransaminasemia, acalculous cholecystitis

INTRODUCTION:

Dengue fever is an acute systemic viral infection transmitted between humans by Aedes mosquitoes. It is a major public health problem throughout the Tropical & sub-tropical regions of the world. Today an estimated 2.5 billion people, about 40% of the world's population, live in areas in Asia, the Pacific, the Americas, Africa, and the Caribbean in over 100 countries where Dengue is endemic [1],[2],[3],[4].Infection with Dengue Virus (DENV) can be asymptomatic or can result in a wide spectrum of disease, varying from a mild, non-specific viral illness to Dengue fever (DF) to the more severe forms of the disease – Dengue haemorrhagic fever (DHF) and Dengue shock syndrome (DSS)[3] . Dengue has been found to have profound effect on multiple organ systems including the liver. Starting from asymptomatic elevated transaminase levels to acute liver failure (ALF), Dengue may present all the features of acute liver disease and should be considered in differential diagnosis of acute hepatitis[5],[6].

Liver damage is a common complication of Dengue infection and transaminase levels are a valuable marker for monitoring these cases. Hepatic injury and elevation of liver enzymes in Dengue may mimic conventional viral hepatitis. In endemic areas Dengue fever should be considered in the differential diagnosis of hepatitis [7].Hepatic manifestations are either a result of direct viral toxicity or dysregulated immunologic injury in response to the virus [8].Clinical features suggestive of hepatic involvement in Dengue are abdominal pain, nausea, vomiting and anorexia. Varying degrees of hepatomegaly, abdominal pain and anorexia are found more frequently in Dengue fever (DF) than in Dengue haemorrhagic fever (DHF) [7]. Among the liver enzymes the greatest alterations are observed in elevation of aspartate transaminase (AST) more than alanine transaminase (ALT). DHF and Dengue shock syndrome (DSS) cause greater elevation of AST, ALT and alkaline phosphatase (ALP) compared to DF suggesting a transient derangement of liver function of greater severity in those patients [6],[7]. ALF is a severe complication of Dengue, leading to hemorrhage, disseminated intravascular coagulation (DIC) and encephalopathy [8]. ALF in Dengue has been ascribed mostly in children though it may occur in adults also [7], [8]. Although viral hepatitis and drugs are the predominant cause of ALF, infectious diseases such as Dengue are being more and more recognized as an etiological agent especially where Dengue is endemic[5].

The objective of this observational study was to study the clinical profile of Dengue virus infected patients and to determine the relationship between liver function tests and clinical spectrum of Dengue infection.

MATERIALS AND METHODS:

This single centre, prospective, observational study was done at in-patient department of Carmichael Hospital for Tropical Diseases, Calcutta, School of Tropical Medicine, Kolkata for a period of one year (July 2016 to June 2017).A case of Dengue fever was defined as per NVBDCP criteria [9]. Patient known by history/examination to have any pre-existing liver disease and patient known to take drugs affecting liver function (e.g. anti-tubercular drugs, fluconazole, valproate, OCP etc.) were excluded from the study. All consecutive patients >18 years of age presenting at inpatient department meeting the inclusion and exclusion criteria during the study period were included in the study, after obtaining informed consent.. A total of 125 patients were included in the study. All the selected patients were subjected to detailed assessment including focused interview and history elicitation with particular emphasis relating to liver involvement. After getting approval from the ethics committee, venous blood samples were taken after clinical diagnosis. Samples were taken on day1 or at the day of admission whatever was feasible, and on day 5 of admission. All two venous blood sample were tested for bilirubin, SGOT, SGPT, alkaline phosphatase, albumin, globulin, complete hemogram, fasting blood sugar, urea, creatinine and relevant radiological investigations were done. Appropriate day sample was sent for Dengue NS1 ELISA and Dengue IgG, IgM and Chikungunya IgM. The clinical severity classification of dengue was done as per Modified Dengue severity classification, PAHO/WHO [10].

Table 1: Modified Dengue Severity Classification, PAHO/WHO

Dengue without warning signs - DNWS	Dengue with warning signs DWWS	Severe Dengue – SD
Person who lives or has travelled to areas with Dengue transmission in the last 14 days and presents with fever, usually of 2 to 7 days duration, and at least 2 of the following criteria: 1. Nausea/ vomiting 2. Exanthema 3. Headache/ retro-orbital pain 4. Myalgia and arthralgia	Every Dengue case that, near and preferably at defervescence, presents one or more than 1 of the following signs: 1. Intense abdominal pain or tenderness 2.Persistent vomiting 3.Fluid accumulation (ascites, pleural effusion, pericardial effusion)	Every Dengue case that has one or more of the following manifestations: 1. Shock or respiratory distress due to severe plasma leakage. Shock evidenced by: weak or undetectable pulse, tachycardia, cold extremities, and capillary perfusion>2 seconds, pulse pressure ≤ 20 mmHg: hypotension in late phase.

Dengue without warning signs - DNWS	Dengue with warning signs DWWS	Severe Dengue – SD
5. Petechiae or positive tourniquet test 6. Leukopenia Cases also include any child coming from or living in an area with Dengue transmission, with acute febrile illness, usually of 2 to 7 days and no apparent focus.	4.Mucosal bleed 5. Lethargy/restlessness 6.Postural hypotension 7.Liver enlargement >2 cm 8. Progressive increase in hematocrit	2.Severe bleeding: based on evaluation by the attending physician (e.g. hematemesis, melena, ample metrorrhagia, central nervous system [CNS] bleeding) 3. Severe organ involvement, such as liver impairment (AST or ALT ≥1000 IU), CNS (impaired mental state), heart (myocarditis), or other organs

RESULTS:

Among the study population 58% (73) were male and 42% (52) were female. Eight (6.4%) HIV infected patients were also included among the 125 study population. Three patients had Plasmodium vivax, 2 had Chikungunya and 1 had coinfection with Scrub typhus. Youngest patient recruited in the study were 18 years and eldest 66 years. Mean age was 32.3± 11.7 years while median was 35 years. Mean age of males was 31 ±10.5 years while that for females was 34 ±13.3 years.

Fig 1: Histogram showing age distribution of the patients.(n=125)

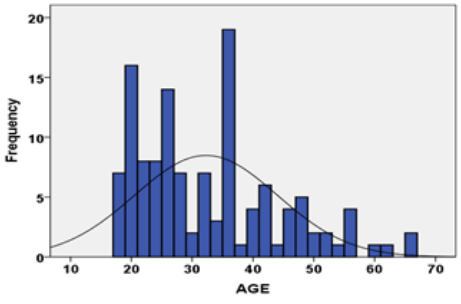
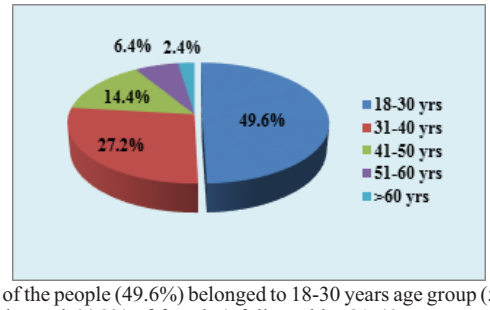


Fig 2: Study population according to age group (n=125)



Most of the people (49.6%) belonged to 18-30 years age group (53.5% of males and 44.2% of females) followed by 31-40 years age group 27.2% (31.5% of males and 21.2% of females), 41-50 years age group 14.4% (9.6% of males and 21.2% females), 6.4%(2.7% of males and 11.5% of females) belonged to age group 51-60 years and 2.4 % to 60 years and above (2.7% of males and 1.9% of females).

Fig 3: Classification of patients according to Dengue severity (n=125)

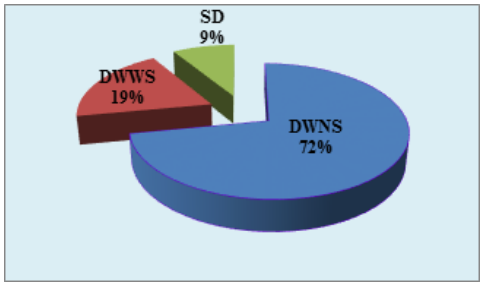


Table 2: Distribution according to age group and Dengue severity (n=125)

Age Group(%)	Dengue Severity		
	DWNS	DWWS	SD
18-30 yrs	49(79)	11(17.7)	2(3.2)
31-40 yrs	21(61.8)	12(35.3)	1(2.9)
41-50 yrs	11(61.1)	0	7(38.9)
51-60 yrs	7(87.5)	0	1(12.5)
>60 yrs	2(66.7)	1(33.3)	0
Total	90(72)	24(19.2)	11(8.8)

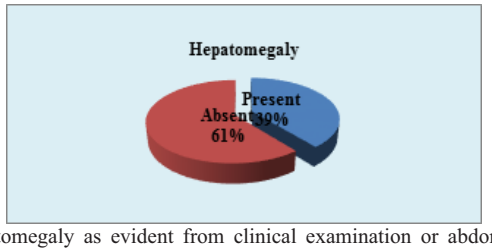
Table shows 38.9% patients of 41-50 years age group developed features of severe Dengue, while 12.5% of 51-60 years age group and only 2.9% and 3.2% patients of 31-40 years and 18-30 years age group respectively suffered from severe Dengue. Among all the patients who were classified as suffering from Dengue without warning signs(DWNS) majority 54.4% were from age group 18-30 years, 23.3% from 31-40 years, 12.2%,7.8% and 2.2% were from age group 41-50years,51-60 years and >60 years age group respectively. Among patients with warning signs (DWWS) 50% were from 31-40 years and 45.8% were from 18-30 years age group. Patients classified as suffering from severe Dengue (SD) 63.6% were from 41-50 years age group followed by 18.2% from 18-30 years age group. These differences are found to be statistically significant (p<.001).

Table 3: Symptoms at presentation (multiple response)

Presenting Symptoms (%)	Age group (years)					% among total
	18-30	31-40	41-50	51-60	>60	
Fever	100	100	100	100	100	100
Headache	72.6	73.5	61.1	25	33.3	67.2
Retroorbital pain	38.7	61.8	38.9	37.5	33.3	44.8
Bodyache/Arthralgia	69.4	70.6	83.3	50	33.3	69.6
Abdominal pain	50	47.1	44.4	75	66.7	50.4
Diarrhoea	33.9	29.4	27.8	25	0	30.4
Nausea/Vomiting	37.1	26.5	50	25	0	34.4
Cough and cold	9.7	35.3	0	25	33.3	16.8
Drowsiness	1.6	0	0	12.5	0	1.6
Rash	54.8	35.3	38.9	25	33.3	44.8
Bleeding from any site	3.2	2.9	16.7	25	0	8

Fever was present in all the patients. Bodyache and arthralgia reported by 69.6% , headache by 67.2% and retro-orbital pain by 44.8% patients. Abdominal pain was complained by 50.4% patients. Rash in any form and retro-orbital pain was a common feature reported by 44.8% patients. Diarrhoea, nausea/vomiting were reported by 30.4% and 34.4% patients respectively. 16.8% patients complained of cough and cold. Bleeding from any site reported by only 8 % of the study population, while only 2 patients (1.6%) presented with drowsiness. Mean fever duration at presentation was 4.7 days (S.D 1.7 days, minimum 1 day, maximum 8 days). Mean of total fever duration was 6.4 days (S.D 1.4 days, minimum 2 day, maximum 10 days).The mean of "fever duration at presentation" for the patients with severe Dengue is 3.82 days which is less than other two groups-Dengue with warning signs and Dengue without warning signs 4.29 days and 4.99 days respectively. This difference is statistically significant (p=0.03).

Fig 4: Distribution of hepatomegaly (clinical and or USG)



Hepatomegaly as evident from clinical examination or abdominal ultrasonography was found in 39% of the patients.

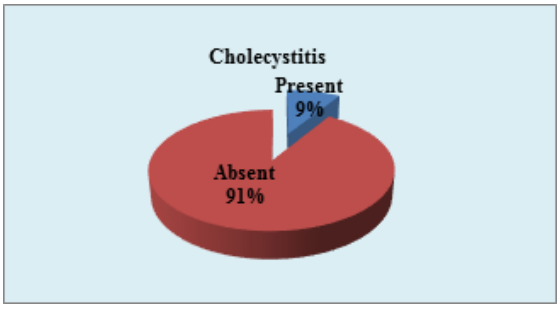
Table 4: Association between hepatomegaly and Dengue severity. (χ2=12.07,df=2,p=0.002)

Hepatomegaly		Dengue Severity			Total
		DWNS	DWWS	SD	
Present	Number	27	14	8	49
	% within Dengue Severity	30.0%	58.3%	72.7%	39.2%

Absent	Number	63	10	3	76
	% within Dengue Severity	70.0%	41.7%	27.3%	60.8%
Total	Number	90	24	11	125

Table 4 shows 72.7 % patients of severe Dengue had hepatomegaly. This is significantly higher (p=0.002) than presence of hepatomegaly in patients of DWWS (58.3%) and patients of DWNS (30%).

Fig 5 : Distribution of cholecystitis (USG)



Cholecystitis as evident from abdominal ultrasonography finding of GB wall thickening or pericholecystic edema was found in about 9% of the patients.

Table5: Association between cholecystitis and Dengue severity. (χ2=11.6,df=2,p=0.003)

Cholecystitis		Dengue Severity			Total
		DWNS	DWWS	SD	
Present	Number	5	2	4	11
	% within Dengue Severity	5.6%	8.3%	36.4%	8.8%
Absent	Number	85	22	7	114
	% within Dengue Severity	94.4%	91.7%	63.6%	91.2%
Total	Number	90	24	11	125

36.4% patients of severe Dengue had cholecystitis. This is significantly higher (p=0.003) than presence of cholecystitis in patients of DWWS (8.3%) and patients of DWNS (5.6%).

Table 6: Mean biochemical parameters at day1 and day 5.

Parameter	Mean and Standard deviation(S.D)				P value
	Mean value at day 1	S.D	Mean value at day 5	S.D	
Bilirubin (mg/dL)	0.7	0.47	0.8	0.54	0.006
SGOT (IU/L)	117.3	111.4	114.9	93.5	0.70
SGPT (IU/L)	78.9	63.7	78.2	55.6	0.86
ALP (IU/L)	88.5	53	90.9	45	0.31
Albumin (g/dL)	3.8	0.4	3.7	0.6	0.29
Urea (mg/dL)	22	11.2	19.7	7.1	**<0.01**
Creatinine (mg/dL)	1.09	0.32	1.03	0.28	**0.06**
Triglyceride (mg/dL)	155.86	79.28	161.66	70.11	0.09
INR	1.00	0.14	1.05	0.16	**0.005**

Mean SGOT at day 1 was 117.3±111.4 IU/L(min 10 IU/L ,max 760) and at day 5 was 114.9±93.5 IU/L(min 30 IU/L, max 671 IU/L). This decline is not statistically significant (p=0.7).Mean SGPT at day 1 was 78.9±63.7 IU/L(min 10 IU/L ,max 377 IU/L) and at day 5 was 78.2±55.6 IU/L(min 19 IU/L, max 350 IU/L). This decline is not statistically significant (p=0.86).Mean ALP at day 1 was 88.5±53 IU/L (min 21 IU/L , max 389) and at day 5 was 90.9±45 IU/L (min 21 IU/L, max 237 IU/L). This rise is not statistically significant (p=0.31).Albumin showed an insignificant decline. Serum urea showed a decreasing trend of 22 mg/dL to 19.7 mg/dL at day1 to day5 respectively. This decline is statistically significant. Mean serum creatinine at day1 was 1.09 mg/dL and at day 5 was 1.03 mg/dL, this was also not significant (p=0.06). Patients of 31-40 years age group had mean SGOT of 150.5 ±129.2 IU/L and 151.4 ±97.1 IU/L on day1 and day 5 respectively. This age group had the highest mean SGOT among all the age groups.75.9% of patients aged above 40 years had SGOT >80 IU/L on day1, and 45.8% of ≤40 years aged patients had SGOT >80 IU/L on day1. This difference is statistically significant (p=0.005).

Table 7: Association between serum SGOT at day 1 and Dengue severity.(χ2=2.05,df=2,p=0.358)

SGOT at Day1 (IU/L)		Dengue Severity			Total
		DWNS	DWWS	SD	
≤80	Number	45	11	3	59
	% within Dengue Severity	50.0%	45.8%	27.3%	47.2%
>80	Number	45	13	8	66
	% within Dengue Severity	50.0%	54.2%	72.7%	52.8%
Total	Number	90	24	11	125

Patients of 31-40 years age group had mean SGPT of 102.2 ±93 IU/L and 101.6 ±69 IU/L on day1 and day 5 respectively. This age group had the highest mean SGOT among all the age groups. 24.1% of patients aged above 40 years had SGPT >80 IU/L on day1, and 34.4% of ≤40 years aged patients had SGPT >80 IU/L on day1. This difference is statistically not significant (p=0.3).

Table 8: Association between serum SGPT at day 1 and Dengue severity.(χ2=1.309,df=2,p=0.52)

SGPT at Day1 (IU/L)		Dengue Severity			Total
		DWNS	DWWS	SD	
≤80	Number	63	14	8	85
	% within Dengue Severity	70.0%	58.3%	72.7%	47.2%
>80	Number	27	10	3	40
	% within Dengue Severity	30.0%	41.7%	27.3%	32.0%
Total	Number	90	24	11	125

Only 27.3% patients with severe Dengue had raised serum SGPT level >80 IU/L at day1. 41.7% and 30% patients of DWWS and DWNS have SGPT >80 IU/L. But these differences are not statistically significant (p=0.52).

Only 9.1% of patients with severe Dengue had bilirubin ≥1 mg/dL at day 1, whereas these values were 37.5% and 21.1% for patients with warning signs and without warning signs respectively. These differences are not significant (p=0.122). Raised serum alkaline phosphatase above 80 IU/L were observed in 36.4%, 41.7% and 42.2% of patients with SD, DWWS and DWNS respectively. However these differences are not significant (p=0.93).

Table 9 : Mean of biochemical parameters at day1 and day 5 of patients classified as Dengue without warning signs(DWNS) n=90.

Parameter	Mean and Standard deviation(S.D)				P value
	Mean value at day 1	S.D	Mean value at day 5	S.D	
Bilirubin (mg/dL)	0.68	0.31	0.84	0.5	0.002
SGOT (IU/L)	109.4	96.9	104.9	71	0.451
SGPT (IU/L)	75.6	62	73.6	50	0.517
ALP (IU/L)	89.3	54	89.94	44.2	0.821
Albumin (g/dL)	3.8	0.5	3.7	0.6	0.347
Urea (mg/dL)	22.09	11.4	20.2	6.8	0.067
Creatinine (mg/dL)	1.1	0.3	1.03	0.27	0.023
Triglyceride (mg/dL)	150.9	74.8	158.1	63.2	0.124

Among the biochemical parameters for patients of DWNS group bilirubin, alkaline phosphatase and triglyceride showed an increasing trend, all others showed a decreasing trend. Except for bilirubin and creatinine differences for all other parameters are statistically not significant at 95% confidence interval.

Table 10: Mean of biochemical parameters at day1 and day 5 of patients classified as Dengue with warning signs(DWWS) n=24.

Parameter	Mean and Standard deviation(S.D)				P value
	Mean value at day 1	S.D	Mean value at day 5	S.D	
Bilirubin (mg/dL)	0.96	0.77	1.0	0.75	0.740
SGOT (IU/L)	152.5	161.9	167.7	148.9	0.461
SGPT (IU/L)	91.5	67	105.9	71.8	0.267
ALP (IU/L)	91.5	55.4	98.6	51.5	0.216
Albumin (g/dL)	3.9	0.3	3.6	0.7	0.138
Urea (mg/dL)	22.3	9.4	18.5	7.4	0.47
Creatinine (mg/dL)	1.08	0.24	1.06	0.28	1.0
Triglyceride (mg/dL)	175.8	100	179.3	96.8	0.274

Among the biochemical parameters for patients of DWWS group bilirubin, SGOT, SGPT, alkaline phosphatase (ALP) and triglyceride showed an increasing trend, Albumin, urea and creatinine showed a decreasing trend. None of the differences are statistically significant at 95% confidence interval.

Table 11: Mean of biochemical parameters at day1 and day 5 of patients classified as severe Dengue (SD), n=11.

Parameter	Mean and Standard deviation(S.D)				P value
	Mean value at day 1	S.D	Mean value at day 5	S.D	
Bilirubin (mg/dL)	0.68	0.62	0.72	0.28	0.806
SGOT (IU/L)	108.1	78.9	96.8	47.9	0.731
SGPT (IU/L)	71.4	72.2	64	40.9	0.765
ALP (IU/L)	75.2	26.3	81.9	38	0.381
Albumin (g/dL)	3.6	0.5	4	0.3	0.36
Urea (mg/dL)	21	14.8	18.4	9	0.479
Creatinine (mg/dL)	0.9	0.4	1	0.4	0.818
Triglyceride (mg/dL)	152.3	63	152.1	54	0.978

Among the biochemical parameters for patients of DWWS group bilirubin, alkaline phosphatase, albumin and creatinine showed an increasing trend, whereas SGOT, SGPT, urea and triglyceride showed a decreasing trend. None of the differences are statistically significant at 95% confidence interval.

Table 12: Mean values of INR for different classes of Dengue on day 1 and day 5

Dengue severity classification	Mean and Standard deviation(S.D) of INR			
	Mean value at day 1	S.D	Mean value at day 5	S.D
DWNS (n=90)	0.97	0.11	1.02	0.15
DWWS (n=24)	1.02	0.11	1.06	0.11
SD (n=11)	1.27	0.16	1.29	0.19

Mean (n=125) INR on day1 and day 5 were 1.00±0.14 & 1.05±0.16. Mean INR for DWNS, DWWS and SD on day1 and day5 were 0.97,1.02;1.02,1.06&1.27,1.29 respectively.

In this study 8(6.4) patients were found to be co-infected with HIV and Dengue virus. Among the biochemical parameters for patients of HIV, Dengue co-infected group only bilirubin showed an increasing trend though statistically insignificant, whereas other parameters showed increasing trend. Only differences of SGOT mean values is significant statistically (p=0.044). Among the study population 3(2.4%) patients had co-infection with Plasmodium vivax. All were classified DWNS . All 3 patients had palpable liver <2cm, 1 had just palpable splenomegaly. They had hematological and biochemical parameters comparable to the population. Two (1.6%) patients had co-infection with Chikungunya virus. All were DWNS.

One patient presented with Scrub typhus co-infection. He had day1 leucocytosis of 13.5 x 103 /cmm with 60% neutrophil and thrombocytopenia (40x 103 /cmm). His SGPT was more than SGOT183 IU/L and 203 IU/L respectively and ALP 389 IU/L. He recovered with fluid resuscitation and doxycycline .

CONCLUSION:

Clinical and laboratory features of 125 adult Dengue patients were analysed with special reference to hepatic function. Common symptoms were headache, body ache (~70%), abdominal pain, retro-orbital pain and rash (~50%). Liver was enlarged in 39% patients, 9% had acalculous cholecystitis. Among all patients 19% had warning signs and 9% had severe Dengue, none of them died. Hypertransaminesemia was found in about half. Mean SGOT and SGPT of 117.3±111.4 and 78.9 ±63.7 in day1 declined to 114.9±93.5 and 78.2±55.6 in day5. Only 27.3% patients with severe Dengue had raised serum SGPT level >80 IU/L at day1 and serum SGOT above 80 IU/L was observed in 72.7% patients with severe dengue. Mean INR for DWNS, DWWS and SD on day1 and day5 were 0.97, 1.02; 1.02, 1.06 and 1.27, 1.29 respectively. Mean INR is significantly higher in day5 compared to day 1. In this study 8 (6.4%) patients were found to be co-infected with HIV and Dengue virus. All of them were classified as Dengue without warning signs and had uneventful recovery. Dengue infection being a systemic disease SGOT rise was more profound than SGPT. Larger studies are needed to search for a possible cut off value of SGOT at day 1 to predict severe dengue.

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