ORIGINAL RESEARCH PAPER
Volume - 13 | Issue - 09 | September - 2024 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

CLINICAL PROFILE, LIVER DYSFUNCTION AND OUTCOME AMONG DENGUE INFECTED CHILDREN

Paediatrics

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ABSTRACT

Introduction: Since 1967, reports of dengue infection-related hepatic damage have been made. Transaminase increase and mild damage are two types of liver dysfunction. Typically, transaminase abnormalities are self-limiting and could be used to forecast evaluating the severity of the illness. There is ample literature on liver involvement in dengue illness in adults. However, the pattern of liver dysfunction and changes in LFTs in children with dengue has not been extensively studied. Thus, we aimed to study demographic data & to determine hepatic dysfunction prevalence in dengue patients while carrying out research in paediatric population. **Methodology:** From July 2023 to July 2024, Paediatric department, VMGMC, Solapur, India, conducted a prospective observational cross sectional study. **Result:** About 120 children (70, boys), median age 72 (48–96) months, were analyzed (NSD, n = 49; SD, n = 71). Elevated transaminases (91.66%) was the most common abnormality. Maximum abnormalities in LFTs peaked at day 5 (AST, ALT) and day 7 (Alkaline Phosphatase [ALP]) of illness. Elevated transaminases was found to be higher in SD than NSD (100% vs. 79.59%, P = 0.006). Severe hepatitis developed such as ALF (P < 0.001) more commonly than those with mild to moderate hepatitis. Sixteen patients died, 14(19.71%) whom had severe hepatitis (P < 0.05). **Conclusion:** Many children with dengue have liver involvement. Severe hepatitis in dengue is associated with significant organ dysfunction and poor outcome.

KEYWORDS

Dengue, Liver dysfunction, Paediatric patients

INTRODUCTION

Aedes mosquitoes carry the dengue virus (DENV), the most significant arthropod-borne illness, which infects humans [1]. Each of the four serotypes of the dengue virus (DENV-1, DENV-2, and DENV-3 and DENV-4) can result in the illness that can Dengue fever manifests as a mild, self-limiting sickness. (DF), or as the illness's more severe variations, Dengue shock or dengue hemorrhagic fever (DHF) syndrome (DSS) [2]. The updated classification of In 2009, the WHO classified dengue as having either symptoms of severe dengue [3]. Despite the following classification, the vast majority of the research generally employ the more well-liked DHF, DSS, and DF categorization in order to define a case.

Infection with the dengue virus poses a threat to public health in tropical and subtropical areas of the globe. Dengue fever is endemic in nearly every state in India. the primary reason for hospital admission [4]. The illness had a distribution that was primarily urban a few decades ago, but there are also current reports from peri both rural and urban locations [5,6]. In 2019 the National Program to Control Vector-Borne Diseases around 1.5 lakh laboratory confirmations were reported. dengue cases [7]. Thus, it's feasible that The burden of dengue fever is wildly underestimated in India.

Since 1967, reports of dengue infection-related hepatic damage have been made [8]. Transaminase increase and mild damage are two types of liver dysfunction. Significant damage to the hepatocytes, which causes jaundice. Hepatic dysfunction is caused by both the virus's disturbed host immunological response and direct hepatotoxicity. Even so, there have only been a few instances of fulminant hepatic failure. Typically, transaminase abnormalities are self-limiting and could be used to forecast evaluating the severity of the illness [9, 10]. There is ample literature on liver involvement in dengue illness in adults. However, the pattern of liver dysfunction and changes in LFTs in children with dengue has not been extensively studied.[11]Thus, we aimed to study demographic data & to determine hepatic dysfunction prevalence in dengue patients while carrying out research in paediatric population.

Methodology:

From July 2023 to July 2024, Paediatric department, VMGMC, Solapur, India, conducted a prospective observational cross sectional study. Written informed consent taken from parents. The permission of ethics was acquired from the ethical committee. It is a tertiary care hospital. Every patient admitted, aged 1 to 12 years having a fever lasting 2 to 12 days, as well as any one of the following symptoms: rash, bleeding or swelling without a cough & cold underwent dengue screening. The study only included instances of dengue that were serologically confirmed. To confirm dengue, a number of laboratory techniques were used, including identification of dengue-specific IgM antibodies (anti-DEN IgM cap) use commercial enzyme-linked immunosorbent assays. A second test for dengue IgM was carried out one week following the negative results of the first test. Dengue confirmed case was defined by the presence of positive DENV IgM or Dengue NS1or detection of DENV RNA by polymerase chain reaction in plasma, provided that the clinical picture was consistent with dengue, and no alternative diagnosis was established. Patients diagnosed with fever from other causes, those with preexisting chronic liver disease, those who had been given NSAIDs for the treatment of dengue prior to admission and those in whom a written consent was not obtained were excluded from the study.

None of the patients were given any hepatotoxic drug except paracetamol during admission. Complete blood counts, serum electrolytes, urea, creatinine and tests for were performed. Hepatic involvement due to hepatotropic viruses was excluded. Serial daily venous blood samples were obtained for monitoring of LFTs until discharge. LFTs included serum bilirubin, transaminases (ALT, AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), serum albumin, total proteins and International Normalized Ratio (INR).

The children enrolled underwent a complete medical workup at presentation that incorporated a detailed history and examination including a general and systemic examination. In emergency room, resident doctors were instructed to obtain blood samples (routine and LFTs), chest radiograph and ultrasonography at admission. Next day (within 24 hours) onwards, a study physician was allocated for daily case assessment, blood samplings and follow-up until discharge. They were trained in case classification as per World Health Organization (WHO) 2009 and management of patients according to updated guidelines on treatment of dengue in children.[12] There is ample literature on liver involvement in dengue illness in adults. Patients, in whom complications developed, were transferred from the general wards to the pediatric intensive care unit and continued with daily clinical assessment by the same study physician. The patients were categorized based on the modified WHO classification of 2009 into non-severe dengue (Constituted dengue with or without the warning signs) and severe dengue. [12]

The sample size was calculated to be 120, assuming the anticipated prevalence of hepatic dysfunction in dengue to be around 50% [13] assuming α error 5% (Zα = 1.96) and β error 20% (Zβ = 0.842) and a power of 80%, with a precision of 5%, according to the following formula:

Case defination[12]
DF: Fever and at least two features: ocular pain, headache, muscle or joint pains, cutaneous rash, bleeding manifestations and reduced leukocyte count.

DHF: Fever, thrombocytopenia (≤ 100 × 109/L), bleeding manifestations and evidence of plasma leakage. DSS: DHF with tachycardia or low pulse pressure (< 20 mmHg) or hypotension (systolic blood pressure < 90 mmHg).

The modified categorization of WHO in 2009 includes dengue with or without warning signs or severe dengue.

Dengue: Fever and two of these: nausea, vomiting, skin rash, bodyache, leukopenia, or any warning sign.

Warning signs include pain in the abdominal or presence of tenderness, persistent vomiting, clinical evidence of fluid accumulation like effusions and ascites, bleeding, lassitude or restiveness, liver enlargement, or rise in hematocrit (≥ 20%) with rapid reduction in thrombocyte count (< 50000/ mm3).

Severe dengue: Evidence of severe plasma leakage, bleeding and organ impairment. Organ impairment includes hepatic involvement in form of transaminases elevated beyond 1000 IU/L and central nervous system manifestations like alteration in sensorium or cardiac or other organ involvement.

We categorized our study cohort into 3 groups on the basis of ALT levels: Mild (up to 5 times normal), Moderate (5–10 times) and Severe hepatitis (>10 times).

ALF in these children was defined by pediatric acute liver failure criteria [14]:
(1) absence of a known, chronic liver disease; (2) liver-based coagulopathy that is not responsive to parenteral vitamin K and (3) INR between 1.5 and 1.9 with clinical evidence of encephalopathy or 2.0 and higher regardless of the presence of clinical encephalopathy. Encephalopathy or alteration in sensorium due to liver failure or dengue encephalitis is difficult to differentiate; so, for the ease of patient selection, we used INR >2 for defining ALF.

Statistical Analysis
All values are expressed as mean and number (percentage). Chi square test was used to compare categorical variables and Fischer exact test was used when numbers were too small to perform the $\chi 2$ testing. Continuous data were compared by non-parametric tests (Mann-Whitney U and Kruskall-Wallis test). The Wilcoxon signed-rank test was used when comparing 2 related samples. All calculations were performed using the SPSS statistical package (SPSS Inc., Chicago, IL) version 23. A P-value of <0.05 was taken as significant.

RESULTS:
A total of 120 admitted children (boys, n = 70) with serologically confirmed dengue infection at a median age of 72 (48–96) months were analyzed. Majority of our patients were >2 years of age with only 13 (10.83%) patients being ≤2 years of age. Most patients had SD (n = 71) with 49 having NSD (Dengue, n = 11; Dengue with warning signs, n = 38). The median duration of illness was 5 (5–9) days and fever was a universal symptom in all (100%) followed in frequency by body ache in 95 (79.16%). Abdominal pain, nausea/vomiting and anorexia were seen in 62.50%, 43.33% and 32.5%, respectively. Evidence of plasma leakage was seen in 58 (48%) cases (ascites, n = 20; pleural effusion, n = 16; body swelling, n = 22), evident on median day 5 (4–7) of illness. Some bleeding manifestations were found in 25 patients (skin rash, n = 8, epistaxis, n = 5; gastrointestinal bleeding, n = 12); however, severe bleeding occurred in 6 (gastrointestinal bleeding requiring blood and blood products transfusion, n = 5; intracranial bleeding, n = 1). Hepatomegaly and clinical jaundice was detected in 39.16% and 12.5% of cases, respectively. About 48.3% patients had mild hepatitis, 19.16% had moderate hepatitis & 10% had severe hepatitis. (Table 1)

Table 2 shows that the elevated transaminases and their median values were significantly higher in SD group in comparison to NSD (100% vs. 79.59, P < 0.001). It was noteworthy that patients having mild hepatitis were almost equally distributed between SD and NSD group, while patients having moderate to severe hepatitis were significantly higher in SD group. Distribution of elevated ALP levels was similar in both groups. Evidence of plasma leak age in terms of hypoproteinaemia (P = 0.01) and hypoalbuminemia (P = 0.04) was significantly higher in SD. Mortality was significantly higher in SD.

DISCUSSION:
In this study, we found that liver dysfunction is widespread in acute dengue sickness and that its intensity is linked to both poor outcome and disease severity. Numerous elements have been linked to dengue fever that is more severe, especially young people. Probably due to increased microvascular fragility, aging is prevalent. [8,15,16]. However, the same observation was not revealed in our study. In this study, no difference in severity of hypoproteinaemia, elevated transaminases and outcomes was observed between the 2 groups.

Hepatomegaly and clinical jaundice in dengue have been reported in 43%–100% and 1.7%–17%, respectively, in various studies.[11,17-19] Similar observations were seen in our cohort too. The presence of jaundice with hepatomegaly in dengue is of paramount importance as this may simulate the common infections like acute viral hepatitis, malaria and enteric hepatitis which are not uncommon in countries like India. Elevated hepatic enzymes in dengue have been reported by researchers, ranging from 36.4% to 96% in pediatric and adult literature.[11,20.21] In majority, AST was higher than ALT [19,22] similar to our observations. The most probable reason for this finding is that other sources apart from the liver could also be contributing to the rise in serum AST like erythrocytes, cardiac and skeletal muscles, kidney and brain tissue in addition.[23] Hence, rise in AST might not be a true reflection of hepatic involvement. For the same reason, we chose only ALT levels for subgroup analysis of degree of hepatitis.

There is a possible association between severity of hepatic injury and dengue severity hence high level of aminotransferase could serve as an indicator of disease severity.[14] The median AST/ ALT values have been found to be higher for SD than for uncomplicated dengue.[14,24] It was noteworthy that those with severe hepatitis had significantly higher incidence of severe bleeding and organ dysfunction such as encephalopathy, AKI and shock.

We observed that the transaminase elevation starts in the first 3 days and peaks around day 5 of illness. A similar result has been shown by Fernando et al [25] in 55 adult patients of dengue, where highest AST levels were seen on day 6 of illness and it was higher in patients with SD.33 In second week of dengue illness (critical phase) due to leakage of plasma, many patients have hypoproteinaemia and hypoalbuminemia, which is a very well-known phenomenon [13]. In contrast, we observed maximum decline in serum protein and albumin around the day 5 of illness.

Coagulation abnormality and ALF are other important issues in dengue, which is frequently reported. Saha et al34 reported coagulopathy (INR>1.5) in 11% of their 1226 serologically proven dengue patients. Studies from India and Thailand have shown that dengue is an important cause of ALF in children contributing to 18.5% and 34.3%, respectively.[26,27] We found coagulopathy and ALF in 14.16% of cases.

Table 1 : Distribution of dengue patients according to clinic-demographic variables

Parameters		Frequency	Percentage
Gender	Boys	70	58.33%
	Girls	50	41.66
Age	≤ 2 years	13	10.83%
	>2 years	107	89.00%
Type of dengue	SD	71	59.16%
	NSD	49	40.84%
Symptoms	Fever	120	100.00%
	Body ache	95	79.16%
	Abdominal pain	75	62.50%
	Nausea/Vomiting	52	43.33%
	Anorexia	39	32.50%

Plasma Leakage	Ascites	20	16.66%
	Pleural effusion	16	13.33%
	Body swelling	22	18.33%
Bleeding Manifestation	Skin rash	8	6.66%
	Epistaxis	5	4.16%
	Gastro-intestinal bleeding	12	10.00%
Clinical findings	Hepatomegaly	47	39.16%
	Clinical jaundice	15	12.50%
Severity od Hepatitis	Mild	58	48.33%
	Moderate	23	19.16%
	Sever	12	10.00%

Table 2: Clinical and Biochemical Profile of Dengue patients

Parameter	NSD (n = 49)	SD (n = 71)	p Value
Age, months	72 (48–102)	84 (60–96)	0.87
Age ≤2 years	3 (6.12%)	10 (14.08%)	0.3
Duration of symptoms, days	6 (5–10)	5 (5–7)	0.34
Hepatomegaly (>2 cm below costal margin)	23 (46.9%)	24 (33.80%)	0.06
Hepatomegaly on ultrasound	34 (69.38%)	54 (76.05%)	0.58
Evidence of plasma leakage	11 (22.44%)	34 (47.88%)	0.02
Elevated transaminases (AST or ALT >40 IU/L)	39 (79.59%)	71 (100%)	0.0001
Elevated AST (>40 IU/L)	36 (73.46%)	68 (95.77%)	0.006
Elevated ALT (>40 IU/L)	27 (55.10%)	67 (94.36%)	0.0001
Severity of hepatitis (based on ALT)			
Mild	23 (46.93%)	35 (49.29%)	0.41
Moderate	3 (6.12%)	20 (30.98%)	0.02
Sever	1 (2.04%)	11 (15.49%)	0.01
Thrombocytopenia (<100,000/mm3)	25 (71.42%)	52 (73.23%)	0.6
Hypoproteinaemia (≤5.8 g/dL)	12 (24.48%)	38 (53.52%)	0.01
Hypoalbuminemia (≤3.1 g/dL	8 (16.3%)	26 (36.61%)	0.04
Elevated ALP	14(28.57%)	12(16.90%)	0.12
ALF (INR>2)	5 (10.20%)	12 (16.90%)	0.39
Mortality	2(4.08%)	14(19.71%)	0.041

CONCLUSION:

Many children with dengue have liver involvement. Severe hepatitis in dengue is associated with significant organ dysfunction and poor outcome. liver aminotransferase elevation is quite common in dengue infection. SD patients have higher transaminase levels and have more frequent 10-fold rise in liver enzymes. Dengue patients who have severe hepatitis have higher incidence of severe bleeding, organ

dysfunction and mortality. Monitoring of LFTs is crucial in dengue infection to identify severe hepatitis and ALF in early course of illness and improve outcomes.

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