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Hepatocellular Damage in the Patients Presenting with Dengue Fever

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ABSTRACT

Background: Dengue fever is becoming endemic in Pakistan as shown by its increasing prevalence in the summer seasons for almost the last decade. Elevation of liver enzymes indicating underlying liver damage, is a common phenomenon and may be associated with other complications.

Objective: To find out the frequency of hepatocellular damage in the patients presenting with dengue fever as evident by elevated liver enzymes.

Material and Methods: This was a descriptive study performed in the medical unit of Hayatabad Medical Complex Peshawar Pakistan. Patients were consecutively collected from the wards, outpatients, and emergency department. The patient's collection was from the year 2022 epidemic from 10th Jul to 23rd Oct. Patients with consistent clinical features, were diagnosed on the bases of dengue NS1 test and antibodies titers. Liver enzymes, complete blood counts and ultrasound were performed to find out any evidence of liver damage and plasma leaks as evident by pleural effusion or ascites. Alanine aminotransferase (ALT) of more than 50 U/L was considered as elevated in our study. Patients with elevated liver enzymes due to expected reasons other than dengue fever as per clinical records, were excluded from the study. The patient's data was noted on a preformed Performa for further analysis.

Results: We consecutively collected 500 patients for the study. The number of male patients was 59% (n=295) while female patients were 41% (n=205). The age range was 15 to 75 years (mean 45, SD 21.32). The overall frequency of elevated (ALT) was 68.2% (n=341). Stratification of patients according to the ALT level shows that only 13.68% were having an ALT level of more than 300 U/L. The frequency was 45.45% in patients without complications, 91.60% in patients with warning signs, 85.71% in severe dengue and 100% with acute liver failure. Patients with an alanine aminotransferase (ALT) of =>300U/L were having a hospital stay of 5 to 12 days (mean 8.81, SD 2.6) days verses 4 to 9 days (mean 5.8, SD 1.9) in the patients having <300U/L

Conclusion: Most of the patients with dengue fever have elevated alanine aminotransferase level indicative of underlying hepatocellular damage. Such patients usually recover without any serious consequences except those having elevation of 300U/l or more whose hospital stay was prolonged, and a smaller percentage was associated with acute liver failure.

Keywords: dengue fever, dengue NS1, hepatocellular damage, liver enzymes, hospital stay.

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INTRODUCTION

The cases of dengue fever are increasing in number year by year in Pakistan and becoming endemic. Though cases are being reported throughout the year, but the surges occur in the humid months of summer season. According to the National Institute of Health (NIH) Islamabad, 22,938 dengue fever cases were reported in Pakistan in 2017, more than 3,200 in 2018, 24,547 cases in 2019, and 3,442 cases in 2020. From 1 January to 25 November 2021, a total of 48,906 cases including 183 deaths (mortality of 0.37 per cent) were reported in the country[1]. According to WHO report, about 10000 cases were reported from the Khyber Pakhtunkhwa in 2021 with a mortality of 0.1%.[2] When we look at the past figures the death toll due to dengue fever decreased with the passing years in Pakistan likely because of the development of immunity. The 2005 to 2016 figures show 71650 reported cases in Pakistan with 757 deaths (1.05%mortality). The worst situation was in 2011 when 21685 cases were reported with 350 deaths (1.6% mortality).[3]

Worldwide urbanization and travels have led to the surges in dengue fever.[4] In tropical countries like Pakistan, overcrowded populations, hot and humid weathers, and poor hygiene providing favorable environmental conditions for the vectors, may be the added reasons for dengue fever spread.

Dengue fever is now endemic in almost 125 countries of the WHO regions.[5] Since most of the cases may be mild and not reported at all, therefore under reporting might have led to underestimate of the true prevalence, social, economic, and disease burden of dengue fever.[5]

The dengue fever virus belongs to the family of RNA viruses that is flavi virus genus/Flaviviridae family. There are four serotypes of dengue virus named as (DENV-1, DENV-2, DENV-3, and DENV-4).[6] The transmission is by the bite of female vector Aedes aegypti mosquito which breads in the summer and humid environment. That is why dengue fever surges occur mostly in the summer. The mosquito lays eggs mostly in the

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clean stagnant water commonly in the houses like washroom utensils, and ground ditches.

The common clinical features of dengue virus infection like fever with chills, body pain, headache, and flu like symptoms may be very similar to other common viral infections. Some features like retro orbital pain, bleeding from gums or nose may be typical of dengue fever.[7] Dengue fever has many serious complications including plasma leak, severe hemorrhage, shock, hepatitis and vomiting leading to dehydration. Hepatocellular damage as evident by the elevated liver enzymes is one of the most common complications of dengue fever in the endemic regions.[8] There are many mechanisms involved in the hepatocellular damage by the dengue virus infection like direct viral effects on hepatocytes and Kupffer cells, immunological hyperactivity via a T cell-mediated cytokine storm, and circulatory failure that leads to decrease liver perfusin.[9]

There are many studies which shows the relationship of elevated liver enzymes i.e., hepatocellular damage and the severity of the dengue fever. The elevated liver enzyme like alanine aminotransferase (ALT) and the platelets count are mostly inversely co related with each other.[10] In this cross-sectional observational study, we will find out the frequency of elevated ALT which is associated with most of the dengue complications. Being one of the severity indicators in the WHO dengue case classification,[11] we can use the elevation of ALT along with or without some other severity parameters, for decision making to either admit or manage the case as outpatient.

MATERIAL AND METHODS

This was a descriptive cross-sectional study performed in the medical unit of Hayatabad Medical Complex Peshawar Pakistan which is a tertiary care hospital catering for population of Peshawar and surrounding rural areas. Total number of patients were 500 who were consecutively collected from the wards, outpatients, and emergency department. The patient's collection was from the year 2022 epidemic from Jul to Oct months. The sample size calculation was made using these parameters: Confidence interval 95%, margin of error 5%, population proportion 50%, and population size unlimited. Institutional ethical approval certificate was obtained 587/HEC/B&PSC/2022 dated 19/11/2022. The preformed proforma for the patient's collection was distributed amongst the doctors on duty in their respective stations. Patients with presenting with fever, chills and frontal headache for 1 to 10 days were diagnosed on the bases of dengue NS1, IgG, and IgM antibodies on immunochromatographic strip method. All tests were performed from the main laboratory of Hayatabad Medical Complex as routine requirement for dengue patients. Patients having positive NS1, or IgM antibodies tests were considered as having dengue fever.

Complete blood counts to look for associated thrombocytopenia, liver enzymes like ALT to look for the possible liver damage, and ultrasound abdomen & chest were performed to find out any plasma leaks as evident by pleural effusion or ascites. Hepatocellular damage was assessed from the elevated alanine aminotransferase (ALT) level in the serum. A level of more than 50 U/L was considered as elevated as per the reference range of the main laboratory of our institution. WE used the 2009 World Health Organization case definition for defining the severity of the patients.[11] Patients with elevated liver enzymes (ALT>100U/L), and an INR of >2 with or without hepatic encephalopathy were labelled as having hepatic/liver failure.

Patients with elevated liver enzymes (ALT>50 U/L) due to expected reasons other than dengue fever like hepatitis B & C, high triglyceride level causing steatohepatitis, known hepatotoxic drugs, etc. as per clinical examination, investigations, and past clinical records, were excluded from the study. The patient's biodata, clinical features and investigations were noted on a preformed Performa for further statistical analysis. The frequencies were calculated by the Microsoft excel program.

RESULTS

This cross-sectional observational study included 500 patients. The number of male patients was 59% (n=295) while female patients were 41% (n=205). The age range was 15 to 75 years (mean 45, SD 21.32). About 34% (n=170) of the patients' data was from the year 2020 & 21, rest of the other patients were collected in the summer of 2022. The collected patients include both who were admitted to the hospital (25.2% n=126) and those who were treated as outpatients (75% n=375). The main reasons for admission were, severe vomiting and inability to take orally, blood pressure

less than 100mmHg or shock, hemorrhage with platelets count less than $50x10^9$/L (NR=150 to 400 x 10).

Table 1 shows the stratification of all patients according to the ALT levels while table 2 stratified the patients according to the severity as per the WHO case classification 2009[10] along with frequency of elevated liver enzymes in each group. About 51% (n=255) of patients were without complications, 46%(n=230) with warning signs, 7.2%(n=36) with severe dengue and 1.8%(n=9) with acute liver failure (ALF).

The overall frequency of elevated alanine aminotransferase was 68.2% (n=341) while it was higher in the patients with dengue complications as compared to those without complications (Table 02). Patients with an alanine aminotransferase of =>300U/L were having a hospital stay of 5 to 12 days (mean 8.81, SD 2.6) days verses 4 to 9 days (mean 5.8, SD 1.9) in the patients with <300U/L.

Table 01. Stratification of Patients According to the ALT Level

ALT <50 U/L	ALT 50-289 U/L	ALT =>300 U/L	Total
31.2% n=156	55% n=275	13.8% n=69	100% n=500

ALT: Alanine Transaminase

Table 02. Frequency of Elevated ALT in Patients with different Severity Level.

Group of Patients	DF	Dengue Warning	Severe Dengue	ALF
Total Number	50% n=250	43.6% n=218	7.36% n=37	1.8% n=9
ALT <50 U/L (Normal)	54.4% n=136	8.25% n=18	16.2% n=6	0
ALT >50 U/L (Elevated)	45.6% n=114	91.7% n=200	83.78% n=31	100% n=9

ALT: Alanine Transaminase

Abbreviations: DF; Dengue fever (without complications). ALF; Acute liver failure. WHO dengue severity classification[10] is applied in this table. Patients with some complications who couldn't be classified properly were counted in both warning and severe dengue.

DISCUSSION

Dengue fever may present with varying degree of severity ranging from mild dengue fever (DF) and just flu like symptoms to the dengue hemorrhagic (DHF) and dengue shock syndrome (DHS). Plasma leakage and elevated alanine aminotransferase (ALT) are one of the most important investigations showing the underlying severity of dengue fever. According to the WHO case classification 2009,[11] a high ALT of 1000 U/L or more and patient with plasma leak as evident by pleural effusion, ascites, and hemoconcentration (elevated hematocrit level) are indicators of severe dengue fever. In our study we used the WHO case classification 2009 for stratification of the patients which divides the patients into dengue fever (DF), patient with warning signs and severe dengue. (Table 02).

Multiple organ involvement like liver, kidneys, and brain in the patients of dengue virus infection, have been described in the literature. Hepatocellular involvement in the patients of dengue fever has been mentioned as the most common complication in many research studies[12] and may be present up to varying level in mild DF, DHF and DHS. There are multiple mechanisms of hepatocellular injury due to dengue virus infection like direct viral toxicity but the most considered one is the immunological damage to the liver.[9]

The exact frequency may be somewhat difficult because of many patients do not present to the hospital facility due to mild symptoms in our setups. However, the frequency of elevated liver enzymes in the patients of dengue fever is reported to be quite high but mostly asymptomatic

and rarely with serious consequences.[13] The incidence and severity of dengue complications is more in the children as compared to adults.[14] According to our study, the elevation of ALT in all patients of dengue fever was 68.2% while it was 45.6% in patients without complications (DF), 91.6% with warning signs, 85.7% with severe dengue and 100% with acute liver failure (Table 02). Some other literature from the tropical areas showing 66.7% in patients without warning signs, 78.6% in patients with warning signs while 91.7% in complicated dengue.[15] A Brazilian study shows the elevation of ALT in dengue fever patients as 65.1% indicating that elevated liver enzymes may be an important indication of liver injury but may not directly correlate with the severity of the illness.[16]

Our study reports the frequency of acute liver failure in dengue patients as just 1.8% (n=9) which is reported as 5.2% in some other studies.[17] The mortality of acute liver failure in dengue fever patients is about 60% in adult population as mentioned in some Thai literature[18] while it was 20% (n=1) in our study. This significant mortality difference may be because of small number of patients with acute liver failure which was 6 out of 1926 patients in this study and 9 out of 500 patients in our study. While looking at the past dengue record in Pakistan[1,3] the mortality seems to be decreased in the country. Reason may be some awareness in the masses and the development of immunity against dengue virus.

CONCLUSION

Elevated ALT and aspartate aminotransferase (AST) levels are very commonly seen in patients of dengue fever indicative of underlying hepatocellular damage. Most of such patients are asymptomatic of liver disease. Such patients usually recover without any serious consequences except those having elevation of 300U/l or more whose hospital stay was prolonged, and a smaller percentage was associated with either shock or acute liver failure.

Study Limitations:

In some cases, dengue fever may present with mild symptoms like flu and fever without vomiting, hemorrhage, or shock therefore all patients may not present to the hospital so exact frequencies may not be calculated. The expected frequency of different disease complications may be higher in patients admitted or presented to the emergency room in the tertiary hospitals.

Prospects:

If further large scale studies are performed on the subject and significance of alanine aminotransferase elevation and its association with complications of dengue fever, then we may be able to predict the severity of dengue fever from a simple test of ALT and even it may be helpful for decision of patient admission to the hospital.

REFERENCES

1. Khan U, Azeem S. The rising toll of dengue cases in Pakistan every year: An incipient crisis. Annals of Medicine and Surgery. 2022 Apr;76:1035-49. doi:10.1016/j.amsu.2022.1035-49
2. Ahmad S, Aziz MA, Aftab A, Ullah Z, Ahmad MI, Mustan A. Epidemiology of dengue in Pakistan, present prevalence, and guidelines for future control. Int J Mosq Res. 2017;4(6):25-32.
3. Wilder-Smith A, Gubler DJ. Geographic expansion of dengue: the impact of international travel. Medical Clinics of North America. 2008 Nov 1;92(6): 1377-90.
4. Murray NE, Quam MB, Wilder-Smith A. Epidemiology of dengue: past, present and future prospects. Clinical epidemiology. 2013; 5:299-309
5. Jiang L, Liu Y, Su W, Cao Y, Jing Q, Wu X, et al. Circulation of genotypes of dengue virus serotype 2 in Guangzhou over a period of 20 years. Virology Journal. 2022 Mar 18;19(1):47.ttps://doi.org/10.1186/s12985-022-01773-7
6. Leowattana W, Leowattana T. Dengue hemorrhagic fever and the liver. World Journal of Hepatology. 2021 Dec 12;13(12):1968-76
7. Guzman MG, Halstead SB, Artsob H, Buchy P, Farrar J, Gubler DJ, et al. Dengue: a continuing global threat. Nature reviews microbiology. 2010 Dec;8(12):S7-16.
8. Lewis J, Mitra A, Chang M. Acute liver failure in a patient with dengue shock syndrome. ACG Case Reports Journal. 2020 Apr;7(4):e00371. doi: 10.14309/crj.0000000000000371
9. Swamy AM, Mahesh PY, Rajashekar ST. Liver function in dengue and its correlation with disease severity: a retrospective cross-sectional observational study in a tertiary care center in Coastal India. Pan Afri Med J. 2021;40:(261). doi.org/10.11604/pamj.2021.40.261.297-95
10. World Health Organization, Special Program for Research, Training in Tropical Diseases, World Health Organization. Department of Control of Neglected Tropical Diseases, World Health Organization. Epidemic, Pandemic Alert. Dengue: guidelines for diagnosis, treatment, prevention and control. World Health Organization; 2009.
11. Martina BE, Koraka P, Osterhaus AD. Dengue virus pathogenesis: an integrated view. Clinical microbiology reviews. 2009 Oct;22(4):564-81.
12. Fernando S, Wijewickrama A, Gomes L, Chameera T, Punchihewa, Madusanka SDP, *et al.* Patterns and causes of liver involvement in acute dengue infection. BMC Infect Dis.2016;16:319. https://doi.org/10.1186/s12879-016-1656-2

13. Tantawichien T. Dengue fever and dengue haemorrhagic fever in adolescents and adults. Paediatrics and international child health. 2012 May 1;32(sup1):22-7.
14. Lee LK, Gan VC, Lee VJ, Tan AS, Leo YS, Lye DC. Clinical relevance and discriminatory value of elevated liver aminotransferase levels for dengue severity. Plos Neglected tropical diseases. 2012 Jun 5;6(6):e1676.
15. Tan SS, Bujang MA. The clinical features and outcomes of acute liver failure associated with dengue infection in adults: a case series. Brazilian Journal of Infectious Diseases. 2013; 17:164-9.
16. Mon KK, Nontprasert A, Kittitrakul C, Tangkijvanich P, Leowattana W, Poovorawan K. Incidence and clinical outcome of acute liver failure caused by dengue in a hospital for tropical diseases, Thailand. The American Journal of Tropical Medicine and Hygiene. 2016 Dec 7;95(6):1338-44.

DATA SHARING STATEMENT: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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AUTHOR'S CONTRIBUTION
The following authors full fill authorship criteria as per ICMJE guidelines;

Shah N, Shah MM:	Idea conception, data acquisition, final approval, agreed to be accountable for all the work.
Kumar D:	Design of the work, drafting the work, critical rivision, final approval, agreed to be accountable for all the work.
Khattak IQ:	Data analysis, drafting of the work, final approval, agreed to be accountable for all the work.
Khan I:	Data interpretation, critical revision, final approval, agreed to be accountable for all the work.