ELEVATED ALANINE AMINOTRANSFERASE AS A SEVERITY INDICATOR IN DENGUE FEVER

Nazir shah[1], Mian Mufarih Shah[1], Gul Rukh[1], Imran Khan[1], Nasir Mehmood[2]

Abstract

Background: Dengue fever is becoming endemic in Pakistan as shown by its increasing prevalence in the late summer season for almost the last decade. The characteristic clinical features of dengue fever are high grade fever, retro orbital headache, and nausea vomiting. Apart from thrombocytopenia which may lead to hemorrhage, elevated liver enzymes are also an important biochemical abnormality which may be associated with some warning signs for the complicated dengue fever. The aim of this cross sectional and comparative study is to find out the frequency of elevated alanine aminotransferase in dengue fever and its association with the severity of illness.

Methodology: This study was performed in the medical unit of Hayatabad Medical Complex Peshawar from Sep to Nov 2021. Total 243 patients, 147 males and 96 females, were included in this study. Patients were consecutively collected from the wards and medical outpatient's department, both who needed admission to the hospital and those who could be managed as outpatient. The age range of the patients was 15 to 74 years. The patients with compatible history and clinical examination were diagnosed on dengue antigen test the dengue NS1. After diagnosis, the patients were subjected to different other investigations like liver enzymes and functions, renal function, and peripheral blood smear. Those patients who were with other co morbidities like congestive heart failure, chronic kidney and liver diseases or acute viral hepatitis, were excluded from the study. Persistent vomiting, plasma leak as evident by pleural effusion or ascites and any type of hemorrhage were taken as warning signs for severe dengue.

Results: This study included 243 patients with dengue NS1 positive dengue fever. Male patients were 147 (60.5%) while females were 96 (39.5%). The age range was 15 to 74 years (mean 38.6 & SD +_18.45). The frequency of elevated alanine aminotransferase of 80U/L or more was found to be 51.44% (n=125).

Elevated alanine aminotransferase was found in 38% of the patients without severity signs, 75.9% of the patients with persistent vomiting, 65.17% of the patients with Plasma leak as evident by pleural effusion or ascites and 62.12% of the patients with hemorrhage.

Conclusion: Elevated alanine aminotransferase level is an important indicator for severity of dengue fever. Elevated alanine aminotransferase level of more than 80 U/L has strong association with persistent vomiting, plasma leak and hemorrhage.

Key words: Dengue fever, alanine aminotransferase, hemorrhage, plasma leak, vomiting

Address for Correspondence:
Dr. Mian Mufarih Shah
Department of Medicine, Hayatabad, Medical Complex, Peshawar.
mianmufarih458@gmai.com

……..

1. Hayatabad Medical Complex, Peshawar
2. DHQ Hospital Haripur, KPK

INTRODUCTION

Dengue virus disease was previously considered as sporadic infection and causing dengue fever after long intervals[1]. Now Dengue virus infection has alarmingly increased in its frequency throughout the world especially the tropical countries like Pakistan in the last decade. It is becoming endemic in Pakistan since its recent reemergence in 2016 in Punjab province of Pakistan [2]. During the outbreak in 2011, about 21685 dengue cases were reported with 350 deaths, while the 2016

figures show 71649 dengue reported cases with 757 deaths[3].

The dengue fever, also called as break bone fever is caused by the dengue virus infection. Dengue virus is an RNA virus of Flaviviridae family and is spread by Aedesegypti female mosquito bite. There are four different serotypes of dengue virus (DEN-1, DEN-2, DEN-3, and DEN-4)[4]. There is no cross immunity between these four types, therefore a person infected by one serotype can be infected by the other serotype as well with rather more severe complications like dengue hemorrhagic and dengue shock syndromes[5].

Dengue fever affects almost all the age group people but tends to be more prevalent in the younger (15-45) age groups [6]. Incubation period of dengue fever may range from 3 to 10 days. Patients with dengue fever are mostly symptomatic but some patients may remain asymptomatic or with minimal symptoms. The most important initial symptoms of dengue fever are nausea, vomiting, fever with chills, headache, flu like symptoms and retro orbital pain. In some patients the dengue fever may become severe and leads to hemorrhage due to thrombocytopenia, plasma leakage due to increased capillary permeability, shock or multiple organ failure. Joints pain and lymphadenopathy may be rare signs[7].

The most frequent complicated forms of dengue are dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) which are the common causes of death in dengue fever patients. Dengue fever can also have significant effects on the liver and liver functions. Dengue fever may lead to hepatitis and fulminant hepatic failure in some patients with elevated liver enzymes. Elevated ALT along with other liver enzymes may indicate the severity of the illness[8]. Liver injury in dengue fever may be due to multiple reasons like hypoxia due to decreased liver perfusion, direct hepatotoxicity of the virus and immunological injury. Elevated liver enzymes ALT and AST are the most important indicators for liver injury[8]. Apart from indicating the liver injury, elevated ALT and AST are the indicators for severity of dengue fever and its poor outcomes as well[9].

The aims and objectives of this study is to find out the frequency of elevated alanine aminotransferase (ALT) level and its association with the severity of illness in the patients of dengue fever. Apart from the thrombocytopenia which is an indicator for the hemorrhagic complications of dengue fever, elevated ALT may be a guide for the supportive management and decision regarding hospitalization.

MATERIAL AND METHODS

This cross sectional and comparative study was performed in the medical unit of Hayatabad Medical Complex Peshawar from Sep to Nov 2021. Total 243 patients were randomly collected for the study from the wards and medical OPD. Some patients needed to be admitted while others were managed as outpatients. All patients with compatible history and clinical examination were diagnosed on the basis of dengue antigen test (dengue NS1). After clinical examination, all patients were subjected to tests of liver enzymes, renal function tests, peripheral blood smear and electrolytes. The liver enzyme ALT was repeated in most of the patients after 3 days and average of the two values was taken as the final value for that specific patient. The ALT level of 40 U/L was taken as the upper limit of normal as per the reference range of the concerned main laboratory of Hayatabad Medical Complex. Ultrasound abdomen and chest was performed for all the patients to find out any pleural effusion or ascites which are the indicators for capillary leak.

This study aimed at two findings, one to find out the frequency of elevated ALT in dengue fever and secondly to find out the association of elevated ALT with the disease severity.

Persistent vomiting i.e., vomiting causing dehydration or multiple times every day during the course of the illness, any hemorrhage like bleeding gums, nose, hematuria, hemoptysis etc. and plasma leaks as evident by pleural effusion or ascites were taken as warning or severity signs. These three severity parameters are classified amongst the warning

signs in WHO classification for severity of the dengue fever[10].

We divided the patients in to two groups e.g., groups according to the ALT values (Table-2) and made a comparison between these groups regarding the mentioned severity parameters to find out their association with elevated ALT levels. The SPSS 21 software was used to analyze the data statistics.

Patients who may have ascites or pleural effusion due to other reasons like congestive cardiac failure, chronic liver or renal disease as evident by the clinical history, examination and previous medical record were excluded from the study. Similarly patients having elevated liver enzymes due other viral hepatopathies or drug induced liver injury as evident by their clinical history and examination, were also excluded from the study. In this study we didn't include the patients with dengue shock and multi organ failure.

RESULTS

This cross sectional and comparative study included 243 patients who were clinically having dengue fever and dengue NS1 antigen positive. The number of male patients was 147 (60.5%) while the females were 96 (39.5%). The age range was 15 to 74 years (mean 38.6 ± 18.45). The frequency of elevated ALT of more than twice of the upper limit of normal (80U/L) was found to be 51.44% (n=125) while the frequencies of elevated ALT in different age and gender groups were not significantly different from each other's values. The frequencies of different variables related to the study population are shown in table 1.

In this study 54% (n=131) patients were without severity signs, 32.5% (n=79) with persistent vomiting, 46% (n=112) with plasma leak as evident by ascites or pleural effusion and 27.16% (n=66) were with dengue hemorrhage (Table 1). Elevated ALT (ALT>80U/L) was present in 38% of the patients without severity signs, 75.9% of the patients with persistent vomiting, 65.17% of the patients with Plasma leak as evident by pleural effusion or ascites and 62.12% of the patients with hemorrhage (Table 2).

Table 2 shows the association of the elevated ALT with the three mentioned warning/severity parameters. Group A patients with ALT less than 80 U/L were 48.55% (n=118), group B with ALT level more than 80 U/L were 51.44% (n=125) (Table 1).

To know the significance of elevated ALT in association with the three mentioned warning/severity signs, we compared the complication profile of group A (ALT <80 U/L) with the groups B (ALT >80U/L) (Table 2) which shows significant association of elevated ALT with the mentioned severity signs of dengue fever.

Table:1 Characteristics of study population (n=243)

Gender,	**No. (%)**
Male	60.49%) (n=147)
Female	39.5% (n=96)
Age groups, No. (%)	
15 – 40 years	40.74%(n= 99)
41 – 60 years	36.21%(n=88)
More than 60 years	23.045%(n=56)
ALT level	**No. (%)**
≤ 80 IU/L	48.56%(n=118)
> 80 IU/l	51.44%(n=125)
Severity of Dengue, *	**No. (%)**
Dengue without severity	53.9% (n=131)
Persistent Vomiting	32.5%(n=79)
Plasma leak	46.1%(n=112)
Dengue hemorrhage	27.16 (n=66)

*Severity classification WHO case definition 2009[10]

*Patients having more than one severity signs were counted in each respective group

Table 2: Frequencies of ALT > 80 U/L in different disease severities

Severity level*	Group A ALT IU/L	Group B	P value*
	≤ 80 IU/L	> 80 IU/l	
Dengue without severity signs	61.77% (n=81)	38.23% (n=50)	
DF with persistent vomiting	24.05% (n=19)	75.94% (n=60)	0.0001
DF with plasma leak	34.82% (n=39)	65.17% (n=73)	0.0001
DF with hemorrhage	37.88% (n=25)	62.12% (n=41)	0.0009

*P Values were calculated from comparison of ALT level in severe with non-severe cases

*Patients having more than one severity signs were counted in each respective group

DISCUSSION

Dengue fever has become the second most common mosquito born infection after malaria. This is a viral infection spread by the bite of an infected female aedesaegypti mosquito. Dengue fever has become endemic in Pakistan and some other tropical and subtropical countries and about one third of the world population is at risk[11]. Most of the patients with dengue fever may have mild symptoms or rarely may be asymptomatic at all. Some of the patients may develop severe complications. About 5-10% of people may progress to severe dengue fever complications like dengue hemorrhagic (DHF) and dengue shock syndrome[12].

Most of the studies conducted on this topic performed both the AST and ALT because the reversal of the AST/ALT ratio is considered as the important predictor for dengue severity. This study included only ALT (the main indicator of liver toxicity by dengue fever) for two important reasons, one the ALT test is easily available and cheap, and secondly the aspartate amino transferase (AST) has various sources including the heart, striated muscles, erythrocytes, apart from the liver, whilst alanine aminotransferase (ALT) is primarily a liver enzyme[13].

Laboratory analysis of the patients initially shows elevation in leukocyte count and ALT levels which may be considered as the initial warning signs for subsequent complications[14]. This study showed elevated ALT of more than twice the upper limit of normal in 51.44% (n=125) patients and also revealed the significance of elevated ALT as warning sign for complicated dengue fever. A study conducted in Thailand, showed elevated ALT of more than twice the upper limit of normal in 69% of hospitalized dengue patients[15]which is higher from our study of 51.44%. The reason may be that we made selection from all patients presenting to the OPD and ER instead of those who needed hospitalization.

This study showed increased frequency of dengue fever complications in patients having elevated ALT as compared to those having normal or a value of less than 80 U/L (Table-2). This is in accordance to some other literature showing that elevated levels of serum ALT and ALP were observed more frequently in dengue hemorrhagic fever (DHF) (20 and 12 patients respectively) compared to uncomplicated dengue fever (DF) (16 and 8 patients respectively). Thirty six percent (36%) DHF and (24%) DF patients had concomitant elevation of ALT and ALP levels. Sixteen percent (16%) DHF and 3 (12%) DF patients had serum ALT levels of more than 200 U/L[16].

A study conducted in Sudan showed liver injury in the patients of dengue fever as evident by elevated ALT in about 84% of the patients. The same study showed comparatively higher elevation in complicated patients[17]. In our study the overall frequency of elevated ALT of more than twice the upper limit of normal (ULN) was 51.44% while it was 74.73% in patients with vomiting and dehydration, 63.55% in patients with plasma leaks as evident by pleural effusion or ascites on ultrasound and 63.16% in patients with hemorrhage. The frequency of elevated ALT of more than twice ULN in patients without any of

these severity parameters was 28% (n=38) (Table 2).

CONCLUSION

Apart from the thrombocytopenia, elevated alanine aminotransferase level was found to be an independent severity parameter in the patients of dengue fever. The most prominent clinical warning signs associated with elevated ALT, were severe nausea and vomiting leading to dehydration or blood pressure less than 100 systolic, increased frequency of plasma leak and increased frequency of hemorrhage. High ALT values of more than 300 U/L may be a good predictor of associated complications or impending complications of dengue fever.

DECLARATION

Author contribution

1. Dr Nazir Shah created the idea, made the patient Performa, write down and composed the article
2. Dr Mian Mufarih shah helped in collection of patients
3. Dr Gul Rukh helped in collection of the patients
4. Dr Imran khan helped in collecting the references
5. Dr Nasir Mehmood helped in collection of the patients

Conflicts of interests: Nil

Funding: this study was not funded by any organization

Acknowledgement

We acknowledge the work of OPD and emergency room staff for their work in timely investigations of the patients. We also acknowledge the hard work by postgraduate trainees of the unit who helped in collection of the patients.

We acknowledge the guidance and timely supervision by Dr Sheraz Jamal Khan the head of Medical C unit Hayatabad Medical Complex.

REFERENCES

1. Malavige GN, Fernando S, Fernando DJ, Seneviratne SL. Dengue viral infections. Postgraduate medical journal. 2004 Oct 1;80(948):588-601.

2. Naqvi SA, Jan B, Shaikh S, Kazmi SJ, Waseem LA, Nasar-u-minAllah M, Abbas N. Changing Climatic Factors Favor Dengue Transmission in Lahore, Pakistan. Environments. 2019 Jun;6(6):71.

3. 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.

4. Kurane I. Dengue hemorrhagic fever with special emphasis on immunopathogenesis. Comparative immunology, microbiology and infectious diseases. 2007 Sep 1;30(5-6):329-40.

5. Warkentien T, Pavlicek R. Dengue fever: historical perspective and the global response. J. Infect. Dis. Epidemiol. 2016;2(15).

6. Khan J, Khan I, Ghaffar A, Khalid B. Epidemiological trends and risk factors associated with dengue disease in Pakistan (1980–2014): a systematic literature search and analysis. BMC public health. 2018 Dec;18(1):1-3.

7. Kalayanarooj S. Clinical manifestations and management of dengue/DHF/DSS. Tropical medicine and health. 2011:1112080193-.

8. Fernando S, Wijewickrama A, Gomes L, Punchihewa CT, Madusanka SD, Dissanayake H, Jeewandara C, Peiris H, Ogg GS, Malavige GN. Patterns and causes of liver involvement in acute dengue infection. BMC infectious diseases. 2016 Dec;16(1):1-9

9. Ahmed A, Alvi AH, Butt A, Nawaz AA, Hanif A. Assessment of dengue fever severity through liver function tests. J Coll Physicians Surg Pak. 2014 Sep 1;24(9):640-4.

10. Hadinegoro SR. The revised WHO dengue case classification: does the system need to be modified?.Paediatrics and

international child health. 2012 May 1;32(sup1):33-8.

11. Khetarpal N, Khanna I. Dengue fever: causes, complications, and vaccine strategies. Journal of immunology research. 2016 Oct;2016.

12. World Health Organization, Special Programme 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.

13. Zubair A, Qureshi AA, Jafri SA. Assessment of Dengue Fever Severity Through Liver Function Test. InDengue-Immunopathology and Control Strategies 2017 Jul 26. IntechOpen.

14. Soni A, Patel PM, Malhi NS, Avasthi GL. Spectrum of liver dysfunction in patients with dengue infection and the markers of severe disease: study from a tertiary care centre in Punjab. J Liver Res DisordTher. 2017;3(4):00063.

15. Treeprasertsuk S, Kittitrakul C. Liver complications in adult dengue and current management. Southeast Asian J Trop Med Public Health. Vol 46 (Supplement 1) 2015

16. Walid SF, Sanusi S, Zawawi MM, Ali RA. A comparison of the pattern of liver involvement in dengue hemorrhagic fever with classic dengue fever. Southeast Asian Journal of Tropical Medicine and Public Health. 2000 Jun 1;31(2):259-63.

17. Ageep AK. Degree of liver injury in Dengue virus infection. Journal of General and Molecular Virology. 2012 Oct 31; 4(1):1-5.