



A ASSOCIATION OF ABNORMAL COAGULATION PROFILE AND LIVER ENZYMES WITH DENGUE INFECTION AND THEIR SIGNIFICANCE AS PREDICTORS OF ASSESSING SEVERITY OF DISEASE

Subramani Murugesan

Assistant Professor, Department of Internal Medicine, Vellore Medical College.

Vinoj murugesan*

Assistant surgeon , GH Rasipuram *Corresponding Author

ABSTRACT

CONTEXT: Dengue fever is one of the most severe arthropod borne viral diseases in terms of human mortality and morbidity. The major cause of mortality is DHF/ DSS. There are multiple reasons for abnormal haemostasis such as vascular endothelial damage. Thrombopahty and coagulation abnormalities. Various studies have revealed significant abnormalities in the coagulation and inflammation systems in dengue fever. The imbalance between coagulation and fibrinolysis may be used a prognostic marker

AIM OF THE STUDY

- To assess the liver enzyme and coagulation profile alterations among dengue patients .
- To follow up dengue patients over a period of 10 days and asses the progression of disease.
- To asses correlation between the abnormal lab parameters and their significance as early predictors of fluid leakage and bleeding

SETTINGS AND DESIGN

Analytical Case Control Study.

MATERIALS AND METHODS: This The study will be conducted on 100 dengue patients admitted to GRH , Madurai during the study period of 12 months

INCLUSION CRITERIA:

- Patients presenting with fever from a dengue endemic
- H/o headache , joint pain , nausea , vomiting
- lab confirmed dengue
- positive tourniquet test

EXCLUSION CRITERIA:

- Patients with bleeding diathesis .
- Patients on Anticoagulant therapy .
- Alcoholics .
- CLD patients

A previously designed proforma was used to collect the demographic and clinical details of the patients. All the patients underwent detailed clinical evaluation, appropriate investigations,

STATISTICAL ANALYSIS

One way ANOVA, Pearson correlation and Chi square test.

RESULTS

- 1) SGOT and SGPT elevation proved to be an early predictor in the progression of Dengue fever to Dengue Haemorrhagic fever
- 2) aPTT prolongation proved to be an even early predictor in the progression of Dengue to Dengue haemorrhagic fever and hence rapid intervention prevented the dreaded complications of dengue .

KEYWORDS : Dengue , hepatic enzymes , PT , aPTT , INR .

INTRODUCTION:

One of the most rapidly spreading mosquito-borne viral disease in the world is Dengue. In the last 50 years, incidence has increased 30-fold with increasing geographic expansion to new countries and, in the present decade, from urban to rural settings (Figure 1.1). An estimated 50 million dengue infections occur annually (Figure 1.2) and approximately 2.5 billion people live in dengue endemic countries (1). The 2002 World Health Assembly resolution WHA55.17 (2) urged greater commitment to dengue by WHO and its Member States. Of particular significance is the 2005 World Health Assembly resolution WHA58.3 on the revision of the International Health Regulations (IHR) (3), which includes dengue as an example of a disease that may constitute a public health emergency of international concern with implications for health security due to disruption and rapid epidemic spread beyond national borders. The fever of dengue is similar to any other viral illness and is highly difficult to differentiate from others . There may or may not be a rash during fever or defervescence . The symptoms of DF may not be very distinguished and signs of bleeding or capillary leakage may be absent.

Majority of the dengue virus infected persons are asymptomatic but symptomatic patients may present with undifferentiated fever, non-severe and severe manifestation. Some patients with dengue virus infection present with severe manifestations like shock, plasma leakage, bleeding and organ involvement. Based on thrombocyte count, haematocrit, evidence of capillary leakage, bleeding and hypotension. DHF has been divided into four grades.¹⁵(Refer 3.8) Non severe cases may be DF and DHF grade I and II without significant bleeding. Severe dengue may be DHF III and IV with or without significant bleeding . DHF grade I and II may be severe when they

present with significant bleeding or with metabolic and electrolyte abnormalities. Sometimes DF may present with life threatening significant bleeding without evidence of capillary leakage or haemoconcentration. Some dengue Fever patients may also present with multiple organ involvement without bleeding and shock. In some patient there may be unusual atypical presentation also.

MATERIALS AND METHODS:

STUDY POPULATION:

The study will be conducted on 100 dengue patients admitted to GRH , Madurai during the study period of 12 months

INCLUSION CRITERIA:

- Patients presenting with fever from a dengue endemic
- H/o headache , joint pain , nausea , vomiting
- lab confirmed dengue
- positive tourniquet test

EXCLUSION CRITERIA:

- Patients with bleeding diathesis .
- Patients on Anticoagulant therapy .
- Alcoholics .
- CLD patients

DATA COLLECTION:

A previously designed proforma was used to collect the demographic and clinical details of the patients. All the patients underwent detailed clinical evaluation, appropriate investigations,

STUDY PROTOCOL:

DESIGN OF STUDY:

- Prospective study

PERIOD OF STUDY:

May 2018 To December 2018 (8 months)

METHODOLOGY:

History was taken on details and duration of fever from a dengue endemic H/o headache , joint pain , nausea was noted . Platelet count, prothrombin time and INR,liver function tests including serum bilirubin, serum transaminases, serum albumin was estimated.

LABORATORY INVESTIGATIONS:

Platelet count,liver function tests including serum bilirubin, albumin, globulin,transaminases, prothrombin time activated partial thromboplastin time and INR.

STATISTICAL ANALYSIS:

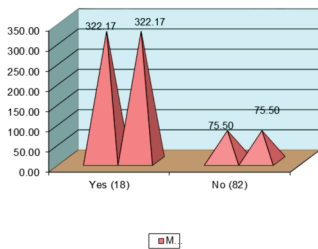
The information collected regarding all the selected cases were recorded in a master chart. Data analysis was done with the help of computer by using SPSS software and Sigma Stat 3.5 version (2012). Using this software, percentage, mean, standard deviation and 'p' value were calculated through one way ANOVA, Pearson correlation and Chi square test and P value of <0.05 was taken as significant.

1) RESULTS:

SGPT in DHF vs Dengue fever

DHF vs SGPT	Mean	S.D	p' value	
Yes (18)	322.17	180.71		
No (82)	75.50	86.90	<0.001	Significant

DHF VS Mean SGPT COMPARISON

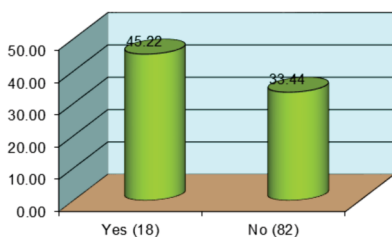


Comments : There is statistically significant elevation of SGPT in DHF

9) aPTT in DHF vs Dengue fever:

DHF vs Aptt	Mean	S.D	p' value	
Yes (18)	45.22	7.08		
No (82)	33.44	3.30	<0.001	Significant

DHF VS Mean Aptt COMPARISON

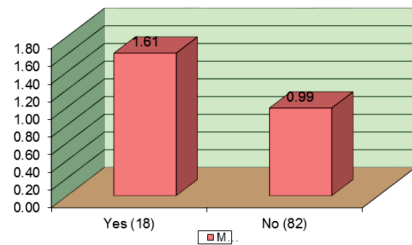


Comments : Statistically significant elevation of aPTT among DHF patients when compared to dengue fever patients

9) INR in DHF vs Dengue :

DHF vs INR	Mean	S.D	p' value	
Yes (18)	1.61	0.39		
No (82)	0.99	0.22	<0.001	Significant

DHF VS INR COMPARISON



Comments: INR elevation also corresponds to the severity of dengue but doesn't correlate with the aPTT values hence can not be statistically significant

DISCUSSION:

- Our study was done to assess the usefulness of aPTT in predicting the severity of dengue in a tertiary hospital in Madurai
- Among the dengue patients there were 81 patients in 20 to 40 age group 11 patients were more than 40 , 8 patients were less than 20 years of age
- Among the gender predilection , females were affected more than males
- Secondary dengue was found to involve about 36 patients 36 percent had IgG positivity
- Among the dengue fever patients 18 patients had dengue haemorrhagic fever and developed complications and were needing treatment
- The mean platelet count among dengue fever patients were 76,300 And the mean platelet count among the patients with dengue haemorrhagic fever was 27,000
- The average platelet count fall occurred during the 4th day and was more severe among the dengue haemorrhagic fever patients
- The average SGOT in dengue haemorrhagic fever patients was 587 and among dengue fever patients was 113 . there was statistically significant elevation . dengue haemorrhagic fever patients had a higher SGOT when compared to the Dengue fever patients
- The average SGPT in dengue haemorrhagic fever patients was 322 and among dengue fever patients was 75 . there was statistically significant elevation . dengue haemorrhagic fever patients had a higher SGPT when compared to the Dengue fever patients but not as statistically significant as SGOT
- The average PT in dengue haemorrhagic fever patients was 17.8 and among dengue fever patients was 12.4 . there was statistically significant elevation . dengue haemorrhagic fever patients had a higher prothrombin time when compared to the Dengue fever patients
- The average INR in dengue haemorrhagic fever patients was 1.61 and among dengue fever patients was 0.99. there was statistically significant elevation . dengue haemorrhagic fever patients had a higher INR when compared to the Dengue fever patients
- The average aPTT in dengue haemorrhagic fever patients was 45.22 and among dengue fever patients was 33.2 . there was statistically significant elevation . dengue haemorrhagic fever patients had a higher aPTT when compared to the Dengue fever patients with MPV and severity of ischemic stroke. As the MPV increases the severity (MRS)^{2,3} of stroke increases.

CONCLUSION:

- 1) SGOT and SGPT elevation proved to be an early predictor in the progression of Dengue fever to Dengue Haemorrhagic fever
- 2) aPTT prolongation proved to be an even early predictor in the progression of Dengue to Dengue haemorrhagic fever and hence rapid intervention prevented the dreaded complications of dengue .

ACKNOWLEDGEMENTS:

We express our sincere thanks and gratitude to the Dean, Government Rajaji Hospital and Madurai Medical College for permitting us to conduct this study. We express our deep sense of gratitude to HOD medicine for his support in the study.

We are extremely grateful to all our Assistant Professors and PG Residents of Department of Medicine for their constant source of cheer and encouragement throughout the study. We thank all our patients who have formed the backbone of my study, without them this work would not have been possible. We are also thankful to paramedical staff of all departments for their concern.

There is no financial interest in this study.

REFERENCES

1. World Health Organization. Global Strategy for Dengue Prevention and Control: WHO 2012-2020
2. Limkittikul K, Brett J, L'Azou M. Epidemiological trends of dengue disease in Thailand (2000-2011): a systematic literature review. *PLoS Negl Trop Dis*. 2014;8(11):e3241.
3. Isarangkura PB, Pongpanich B, Pintadit P, Phanichyakarn P, Valyasevi A. Hemostatic derangement in dengue haemorrhagic fever. *Southeast Asian J Trop Med Public Health*. 1987;18(3):331-
4. Van Gorp EC, Setiati TE, Mairuhu AT, Suharti C, Cate Ht, Dolmans WM et al. Impaired fibrinolysis in the pathogenesis of dengue hemorrhagic fever. *J Med Virol*. 2002 Aug; 67(4):549-54.
5. Roy A, Sarkar D, Chakraborty S, Chaudhuri J, Ghosh P. Profile of hepatic involvement by dengue virus in dengue infected children. *N Am J Med Sci*. 2013 Aug;5(8):480-5.
6. Lin SW, Chuang YC, Lin YS, Lei HY, Liu HS, Yeh TM. Dengue virus nonstructural protein NS1 binds to prothrombin/thrombin and inhibits prothrombin activation. *J Infect*. 2012;64:325-34.
7. Cabello-Gutiérrez C, Manjarrez-Zavala ME, Huerta-Zepeda A, Cime-Castillo J, Monroy-Martínez V, Correa BB et al. Modification of the cytoprotective protein C pathway during Dengue virus infection of human endothelial vascular cells. *Thromb Haemost*. 2009 May;101(5):916-28.
8. Sosothikul D, Seksarn P, Pongsewalak S, Thisyakorn U, Lusher J. Activation of endothelial cells, coagulation and fibrinolysis in children with Dengue virus infection. *Thromb Haemost*. 2007 Apr;97(4):627-34.
9. Orsi FA, Angerami RN, Mazetto BM, Quaino SK, Santiago-Bassora F, Castro V, et al. Reduced thrombin formation and excessive fibrinolysis are associated with bleeding complications in patients with dengue fever: a case-control study comparing dengue fever patients with and without bleeding manifestations. *BMC Infect Dis*. 2013 Jul 28;13:350.
10. Huerta-Zepeda A, Cabello-Gutiérrez C, Cime-Castillo J, Monroy-Martínez V, Manjarrez-Zavala ME, Gutiérrez-Rodríguez M et al. Crosstalk between coagulation and inflammation during Dengue virus infection. *Thromb Haemost*. 2008 May;99(5):936-43.
11. Chen LC, Shyu HW, Lin HM, Lei HY, Lin YS, Liu HS et al. Dengue virus induces thrombomodulin expression in human endothelial cells and monocytes in vitro. *J Infect*. 2009 May;58(5):368-74.
12. Budastra N, Arhana BNP, Mudita IB. Plasma prothrombin time and activated partial thromboplastin time as predictors of bleeding manifestations during dengue haemorrhagic fever. *Paediatrica Indonesiana* 2009; 49(2): 69-74.
13. Huang Y, Liu C, Wang S, Lei H, Liu H, Lin Y, et al. Activation of Coagulation and Fibrinolysis during Dengue Virus Infection. *Journal of Medical Virology* 2001; 63(3):247-51. [http://dx.doi.org/10.1002/10969071\(200103\)63:3<247::AID-JMV1008>3.0.CO;2-F](http://dx.doi.org/10.1002/10969071(200103)63:3<247::AID-JMV1008>3.0.CO;2-F)
14. Chuansumrit A, Tangnaratchakitt K. Pathophysiology and management of dengue hemorrhagic fever. *Transfusion Alternatives in Transfusion Medicine*. 2006; 8(suppl s1):3-11. <http://dx.doi.org/10.1111/j.1778428X.2006.00025.x>
15. Liu J, Khor B, Lee C, Lee I, Chen R, Yang KD. Dengue haemorrhagic fever in Taiwan. *Dengue Bulletin*. 2003; 27:19-24.17. Al-Busafi SA, Ghali P, Wong P, Callaway E. Dengue fever climbs the social ladder. *Nature* 2007; 448: 734-735.
16. Munasinghe DR, Amarasekera PJ and Fernando CF. An epidemic of dengue-like fever in Ceylon (chikungunya—a clinical and haematological study. *Ceylon Medical Journal* 1966; 11: 129-42.
17. Mendis NM. Epidemiology of dengue-like fever in Ceylon. *Ceylon Medical Journal* 1967; 12: 67-74.
18. Gagnon SJ, Mori M, Kurane I, et al. Cytokine gene expression and protein production in peripheral blood mononuclear cells of children with acute dengue virus infections. *Journal of Medical Virology* 2002; 67: 41-6.
19. Atukorale V, Meedin, F., Malavige, G.N., Wijesinghe, T, Jayaratne, S.D., Fernando, N., Ogg, G.S.,. Molecular characteristics of dengue viral serotypes responsible for dengue epidemic in year 2010. In: Sri Lanka Medical Association Annual Congress. Colombo, 2011
20. Kanakarathne N, Wahala WM, Messer WB, et al. Severe dengue epidemics in Sri Lanka, 2003-2006. *Emerging Infectious Diseases* 2009; 15: 192-9.
21. Weaver SC, Vasilakis N. Molecular evolution of dengue viruses: contributions of phylogenetics to understanding the history and epidemiology of the preeminent arboviral disease. *Infection Genetics and Evolution* 2009; 9: 523-40.
22. Mathew A, Rothman AL. Understanding the contribution of cellular immunity to dengue disease pathogenesis. *Immunological Reviews* 2008; 225: 300-13.
23. Guzman MG, Kouri G, Valdes L, Bravo J, Vazquez S and Halstead SB. Enhanced severity of secondary dengue-2 infections: death rates in 1981 and 1997 Cuban outbreaks. *Revista Panamericana de Salud Pública* 2002; 11: 223-7.
24. Messer WB, Gubler DJ, Harris E, Sivananthan K and de Silva A M. Emergence and global spread of a dengue serotype 3, subtype III virus. *Emerging Infectious Diseases* 2003; 9: 800-9.
25. Kyle JL, Harris E. Global spread and persistence of dengue. *Annual Review of Microbiology* 2008; 62: 71-92.
26. Duyen HT, Ngoc TV, Ha DT, et al. Kinetics of Plasma Viremia and Soluble Nonstructural Protein 1 Concentrations in Dengue: Differential Effects According to Serotype and Immune Status. *Journal of Infectious Diseases* 2011; 203:1292- 300.