EVALUATION OF SERUM INTERLEUKIN-6 AND TUMOR NECROSIS FACTOR-ALPHA LEVELS IN PATIENTS WITH DENGUE FEVER – A TERTIARY CARE HOSPITAL BASED STUDY

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INTRODUCTION

Dengue is an leading flavivirus infection transmitted by Aedes mosquitoes of intertropical area which may be due to increased urbanization and air travel [1]. It is characterized by severe plasma leakage, accumulation of fluid, organ impairment and hemorrhages [2] patients presenting with dengue infection can be classified into two groups: One with warning signs of bleeding and hepatosplenomegaly and the other without symptomatic signs [3,4]. It has been observed that benign cases turns to severe dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) which could be attributed to the host pathogen interaction in which redox state of the body is altered along resulting in DHF/DSS [7].

Cytokines and other inflammatory mediators play a key role in modulating immune response to dengue infection, but in some cases, it may lead to improper responses in patients. It has been noticed that TNF-α can influence endothelial cells and can lead to activation resulting in DHF/DSS [7].

METHODS

The prospective cohort study was taken up involving 50 adults diagnosed with dengue fever and admitted to Mysore Medical College and Research Institute from December 2015 to November 2016. Institutional Ethics Committee permission and informed consent have been obtained during the study. From all patients regarding any comorbid conditions, medications have been collected. Detailed history has been taken and clinical examination was carried out. Venous blood samples were collected and serum separated out for estimation of IL-6 and TNF-α levels using ELISA.

Inclusion criteria

Subjects aged more than 18 years, diagnosed as having dengue on the basis of Ig M and NS 1 ELISA test for dengue fever were included in the study.

Exclusion criteria

Subjects not willing to give consent, subjects suffering from malaria and typhoid, subjects having diabetes mellitus, and subjects suffering from chronic illness such as chronic kidney disease, chronic liver disease, pregnant women, immunocompromised state, and subjects with alcoholic liver disease were excluded from the study.

RESULTS

IL-6 levels on days 3rd and 5th of dengue infection

On day 3rd of dengue infection, the IL-6 levels are raised significantly suggesting the role of inflammation associated with infection. On 5th day, the level of IL-6 decreased significantly which is observed in Fig. 1.

TNF-α levels on days 3rd and 5th of dengue infection

On day 3rd of dengue infection, the TNF-α levels are raised significantly which could be attributed to inflammation. Interestingly on the 5th day, the level of TNF-α remained same which is observed in Fig. 2.

DISCUSSION

Cytokines and other inflammatory mediators play a key role in modulating immune response to dengue infection, but in some cases, it may lead to improper responses in patients. It has been noticed that TNF-α can influence endothelial cells and can lead to activation resulting in DHF/DSS [7].

IL-6 is one of the endogenous acting pro-inflammatory cytokine having greater endothelial permeability. Multiple studies have suggested the role of IL-6 in developing severity of dengue infection which can be noticed during the course of infection and illness severity [8-12].
Thus, the current study helped in understanding the role of pro-inflammatory cytokine and inflammatory mediators involvement during course of dengue infection. TNF-α could be a potential biomarker in understanding severity of dengue infection.

**CONCLUSION**

The study concludes that the IL-6 and TNF-α plays a key role in understanding pathogenesis of severity of dengue infection, TNF-α being more sensitive in reaction to pathogen. However, further molecular studies are required in understanding the pathways involved and developing a suitable biomarker in establishing severity of dengue.

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**AUTHORS’ CONTRIBUTIONS**

RD initiated and conducted study and SBS helped in the preparation of manuscript.

**CONFLICTS OF INTEREST**

The author(s) declare(s) that they have no conflicts of interests to disclose.

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**REFERENCES**

1. Rodenhuis-Zybert IA, Wilschut J, Smit JM. Dengue virus life cycle: Viral and host factors modulating infectivity. Cell Mol Life Sci 2010;67:2773-86.
2. Stanaway JD, Shepard DS, Undurraga EA, Halasa YA, Coffeng LE, Brady OJ, et al. The global burden of dengue: An analysis from the global burden of disease study 2013. Lancet Infect Dis 2016;16:712-23.
3. Haider Z, Ahmad FZ, Mahmood A, Waseem T, Shaflq I, Raza T, et al. Dengue fever in Pakistan: A paradigm shift: changing epidemiology and clinical patterns. Perspect Public Health 2015;135:294-8.
4. Tahir U, Khan UH, Zubair MS, Bahar EM. Wolbachia piopietens: A potential candidate for combating and eradicating dengue epidemics in Pakistan. Asian Pac J Trop Med 2015;8:989-98.
5. World Health Organization. Dengue Guidelines for Diagnosis, Treatment, Prevention and Control. Geneva: World Health Organization; 2009.
6. Castillo-Macias A, Salinas-Carmona MC, Torres-López E. Immunology of viral infections with a high impact in Mexico: Dengue, chikungunya, and zika. Med Univ 2017;19:198-207.
7. Scheller J, Chalaris A, Schmid-Arras D, Rose-John S. The pro-and anti-inflammatory properties of the cytokine interleukin-6. Biochim Biophys Acta 2011;1813:878-88.
8. Sriram BS, Ravichandar V. An experimental study evaluating the influence of quercetin on monosodium glutamate induced depression in Swiss albino male mice. Asian J Pharm Clin Res 2019;12:292-4.
9. Ober D, Nguyen TL, Shen L, Ha DQ, Huong VT, Benyoucef S, et al. Tumor necrosis factor alpha levels in plasma and whole-blood culture in dengue-infected patients: Relationship between virus detection and pre-existing specific antibodies. J Med Virol 1998;54:216-8.
10. Hober D, Poli L, Roblin B, Gestas P, Chungue E, Granic G, et al. Serum levels of tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), and interleukin-1beta (IL-1beta) in dengue-infected patients. Am J Trop Med Hyg 1993;48:324-31.
11. Juffrie M, Meer GM, Hack CE, Hasnoot K, Sutaryo, Veerman AJ. Inflammatory mediators in dengue virus infection in children interleukin-6 and its relation to C-reactive protein and secret phospholipase A2. Am J Trop Med Hyg 2001;65:70-5.
12. Kautner I, Robinson MJ, Kuhnle U. Dengue virus infection: Epidemiology, pathogenesis, clinical presentation, diagnosis and prevention. J Pediatr 1997;131:516-24.
13. Kittigul L, Tenprom W, Sujirarat D, Kittigul C. Determination of tumour necrosis factor-alpha levels in dengue virus infected by sensitive biotin-streptavidin enzyme-linked immunosorbent assay. J Virol Methods 2000;90:51-7.
14. Kun G, Bailey RE. Cytokine responses to dengue infection among...
Puerto Rican patients. Mem Inst Oswaldo Cruz 1994;89:179-82.

15. Kurane I, Ennis FA. Immunopathogenesis of dengue virus infections. In: Gubler DJ, Kuno G, editors. Dengue and Dengue Hemorrhagic Fever. London: CAB International; 1997. p. 273-90.

16. Kurane I, Innis BL, Nimmannitya S, Nisalak A, Meager A, Janus J, et al. Activation of T lymphocytes in dengue virus infections. High levels of soluble interleukin 2 receptor, soluble CD4, soluble CD8, interleukin 2 and interferon-gamma in sera in children with dengue. J Clin Invest 1991;88:1473-80.

17. Kurane I, Meager A, Ennis FA. Induction of interferon alpha and gamma from human lymphocytes by dengue virus-infected cells. J Gen Virol 1986;67:1653-61.

18. Lanciotti RS, Calisher CH, Gubler DJ, Chang GF, Vorndam V. Rapid detection and typing of dengue from clinical samples by using reverse transcriptase-polymerase chain reaction. J Clin Microbiol 1992;30:545-51.

19. Laur F, Murgue B, Deparis X, Roche C, Cassar O, Chunge E. Plasma levels of tumour necrosis factor alpha and transforming growth factor beta-1 in children with dengue 2 virus infection in French Polynesia. Trans R Soc Trop Med Hyg 1998;92:654-6.

20. Malavigne GN, Fernando S, Fernando DJ. Seneviratne SL. Dengue viral infections. Postgrad Med J 2004;80:588-601.