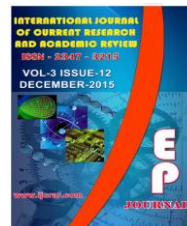




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A Comparative Study on Inflammatory Biomarkers in Dengue cases Vs. Other Febrile Illness

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A B S T R A C T

World Health Organization (WHO) data suggest that at least 100 countries are endemic of Dengue virus transmission. The average case fatality rate is around 5%, and mainly among children and young adults (Beatty *et al.*, 2007). In DHF, fluid accumulation in cavities takes place, which may activate the inflammatory biomarkers in the body. In present study, the dengue infected patients and patients with other febrile illness were screened for the biomarkers such as CRP, ASLO and RA factor. The erythrocyte sedimentation rate was performed and the higher values of ESR was found in both Dengue and also in OFI patients. The results show that these biomarkers are present in both dengue and OFI patients.

Introduction

Dengue virus (DENV) infection is one of the mosquito-borne viral diseases with a major impact on public health, globally (Guzman *et al.*, 2010). World Health Organization (WHO) data suggest that at least 100 countries are endemic of Dengue virus transmission. About 3.5 billion people, 55% of the world's population living in tropical and subtropical regions are at risk, with about 50 million DENV infections occurring annually and approximately 500,000 requiring hospitalization annually (WHO, 2009). The average case fatality rate

is around 5%, and mainly among children and young adults (Beatty *et al.*, 2007).

In DHF, fluid accumulation in body cavities, thrombocytopenia, and coagulopathy frequently occur. However, the mechanisms by which these pathophysiological changes occur is incompletely understood. The production of Interleukin 6 (IL-6), a cytokine of central importance can be induced by IL-1 and TNF, and other cytokines. IL-6 stimulates the synthesis of

acute-phase proteins such as C-reactive protein (CRP), Anti streptolysin O and in some cases, the rheumatoid factor by the liver. The CRP is a protein produced in the liver when there is inflammation anywhere in the body. Special techniques have to be used to measure the CRP. The more inflammation in the joints the higher the CRP. The CRP is a more sensitive measure of inflammation than the ESR. This is because in the normal situation there is very little if any CRP in the blood. The RF is an auto-antibody (a type of protein made by the immune system that acts against the person's own body tissue) found in the blood of patients with rheumatoid arthritis. It can also be found in the blood of patients with other inflammatory diseases and also in some other individuals, particularly the elderly. Thus, the presence of RF does not necessarily indicate the presence of rheumatoid arthritis. There is no way of predicting whether an individual who has RF in their blood will or will not go on to develop rheumatoid arthritis. Furthermore there is no way of preventing this from happening. ASO antibodies are produced about a week to a month after an initial strep infection. The amount of ASO antibody (titer) peaks at about 3 to 5 weeks after the illness and then tapers off but may remain detectable for several months after the strep infection has resolved. A negative ASO or ASO that is present at very low titers means the person tested most likely has not had a recent strep infection. This is especially true if a sample taken 10 to 14 days later is also negative (low titer of antibody). An elevated titer of antibody (positive ASO) or an ASO titer that is rising means that it is likely that the person tested has had a recent strep infection. ASO titers that are initially high and then decline suggest that an infection has occurred and may be resolving. Increased plasma levels of IL-6 are present in most patients with various bacterial

infections and are related to clinical outcome. Erythrocyte sedimentation rate (ESR) during the first hour is a simple and low cost exam. It measures the rate of sedimentation of erythrocyte of a blood sample in a graduated test tube maintained in a vertical position during one hour. Consequently, given the effect of dengue on morbidity and mortality and the impossibility of a more complete investigation when there are many suspected cases, ESR would be useful to help diagnose with diagnosis whenever this disease is suspected.

In the present study we examined the inflammatory biomarker circulating levels of CRP, ASLO and RF also ESR values in children with dengue virus infection. The main goal of the study was to analyze whether levels of these circulating inflammatory mediators on admission are related to the severity of illness and the occurrence of complications.

Materials and Methods

The study was conducted in Rajiv Gandhi Government Women and Children Hospital, Puducherry, from September 2014 to November 2014 for period of three months which the peak seasons of Dengue virus infections. The pediatric patients were taken for the study purpose. 30 known dengue positive cases were chosen randomly and 20 cases which are non dengue febrile illness caused other viral or bacterial infections. For these fifty cases CRP, ASLO, RA factor (J.mithra & co.,) was performed as per the manufacturer instructions. ESR was performed by When anticoagulated whole blood is allowed to stand in a narrow vertical tube for a period of time, the RBCs – under the influence of gravity - settle out from the plasma. The rate at which they settle is measured as the number of

millimeters of clear plasma present at the top of the column after one hour (mm/hr).

Results and Discussion

The level of 6µg / ml, 400 IU /ml, 8 IU /ml of blood was found to be positive for CRP, ASLO, and RA factor respectively. Of 30 dengue cases 23.3% (7 cases) were found to be positive for CRP, 16.6% (5 cases) were found to be positive for ASLO and 40 % (12 cases) was found to be positive for RA factor. No case was found positive for all the three inflammatory mediators. Out of 20 OFI cases, 75% (15 cases) were found to be positive for CRP, 50% (10 cases) were found to be positive for ASLO and 25% (5 cases) was found to be positive for RA factor. The presence inflammatory biomarkers such as CRP, ASLO, RA factor in dengue and other febrile illness was compared with age group and gender was tabulated in the table.2. Only one case was found to be positive for all the three inflammatory mediators. The result was represented in the Figure 1. The ESR value of both dengue and other febrile illness patients were noted that the dengue patients show nearly 60% of raised ESR values. On the other hand the other febrile illness patients show 45% of raised ESR level. The raised ESR values among the age group and gender was compared in the table 1.

In dengue virus infection the patient will have the symptoms include severe joint and muscle pain, swollen lymph nodes, headache, fever, exhaustion, and rash. The presence of fever, rash, and headache (the "dengue triad") is characteristic of dengue fever. These symptoms may in turns activate the IL 6 and it enhances the secretary inflammatory mediators and metabolites like CRP, ASLO, RA factor (Kurane et al., 1992). The classic markers of infection are fever and leukocytosis. Although cheap and

easy to measure, body temperature is a specific, but not sensitive, marker of infection (Van der pol et al., 1994). Infection is frequently not the cause of fever in febrile critically ill patients. On the other hand, there is no relation between fever and disease severity (Mold et.al., 1982). High fever can be associated with minor infections such as streptococcal tonsillitis, while a normal temperature or even hypothermia is possible in very severe situations such as peritonitis. In addition, fever is influenced by many non-infectious factors, such as antipyretics and ambient temperature. Despite all these limitations, body temperature continues to be used as a criterion of sepsis diagnosis. This indicates that in other infections OFI (other febrile illness), the level of these inflammatory biomarkers will rise in huge quantity which may be due to the primary or secondary bacterial infections. But in the case of RA factor, the rise is seen in the case of dengue and chikungunya which may be due to acute joint pain. This rise is also may be acute and the level falls when the myalgia and arthralgia sets off. In dengue illness there is no case positive for all the three mediators but on the other hand, there was one found positive for all the three biomarkers. This result was similar to the results of kurane and Ennis, 1992.

The erythrocyte sedimentation rate (ESR) is a complementary exam that initially was developed to help diagnose pregnancy; currently it is more commonly used in Rheumatology, and it has become important for the diagnosis and accompaniment of diseases such as rheumatic arthritis, systemic lupus erythematosus and rheumatic disease (Collare et al., 2004). The ESR exam is a low-cost and sensitive, though unspecific test for documenting inflammatory, infectious and neoplastic processes (Santos et al., 2000).

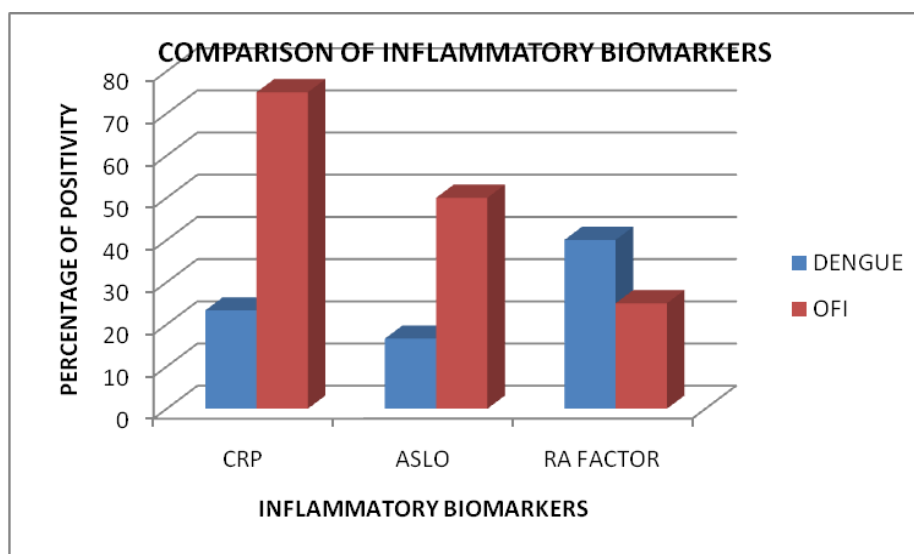
Table.1 ESR Profile in Dengue and Other Febrile Illness Patients Compared by Age Group and Gender

Age group	Dengue patients						OFI					
	No. of Male child			No. of Female child			No. of Male child			No. of Female child		
	ESR value			ESR value			ESR value			ESR value		
	Normal	High		Normal	High		Normal	High		Normal	High	
≤1	1	1	-	2	1	1	2	1	1	2	2	-
≥1 to 5	6	2	4	5	3	2	3	2	1	6	2	4
≥5 to 12	7	3	4	9	3	6	4	2	2	3	2	1

Table.2 Presence of Inflammatory Biomarkers in Dengue and Other Febrile Illness Patients Compared by Age Group and Gender

Age group	Dengue patients							
	No. of Male child				No. of Female child			
	No. of cases positive for				No. of cases positive for			
	CRP	ASO	RA		CRP	ASO	RA	
≤1	1	1	-	-	2	1	-	
≥1 to 5	6	2	1	3	5	1	2	3
≥5 to 12	7	1	1	3	9	1	1	3

Figure.1 Comparison of Inflammatory Biomarkers in Dengue and OFI Cases



During our study, we found that 60% of patients had ESR values above the reference values; generally this was because these patients had diseases associated with dengue, most commonly, other febrile

illness. It is a valid conclusion that the ESR value is proportional to the intensity of the inflammatory response. The percentage of male patients with normal ESR values was greater than for female patients. We believe

this to be a consequence of more common bacterial urinary infections and anemia in female patients; these are pathologies that increase ESR. Also, women normally have greater rates of hemosedimentation (Santos et al., 2000). The patients who are below the age of 1 year have no inflammatory biomarkers and also show normal ESR values. The higher age group showed the presence of these inflammatory biomarkers and also raised ESR values. Children usually more prone to infections often and also showed increased ESR rate.

Conclusion

The present study shows that the presence of inflammatory biomarkers in dengue infected persons in remarkable level. The intra comparison between the three markers shows the level of CRP and RA factor were found to be high. But on the other hand, OFI all the three biomarkers are seen in more cases when compared to dengue cases. This may due to primary or secondary bacterial infections seen in the case of Other than dengue febrile illness. we conclude that ESR is within normal limits in most cases of dengue, independent of its clinical manifestation; this is mainly due to the hemoconcentration found in dengue patients, along with hypoalbuminemia and hypofibrinogenemia. This contrasts with the ESR profile in patients with bacterial diseases and should be incorporated into diagnostic exclusion criteria for dengue.

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