SERUM TUMOR NECROSIS FACTOR ALPHA LEVELS IN PLASMODIUM VIVAX MALARIA

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SUMMARY: The increase in Tumor Necrosis Factor alpha (TNF-alpha) in Plasmodium falciparum malaria (PFM) has been shown at many previous studies. We aimed to investigate the TNF-alpha levels of Plasmodium vivax malaria (PVM).

The study consisted of 19 Plasmodium vivax (PV) patients and a control group of 18 healthy persons. The serum TNF alpha levels were measured by radio-immunoassay method.

The TNF alpha levels of the patients (mean=19.67, ± sd ±5.502 pg/ml) were statistically higher in relation to those of the control group (4.63±0.52 pg/ml; p<0.02).

Significant increase in TNF alpha in PFM has been shown. It is established that the increase in TNF in PVM is at a lower extent. It is necessary to investigate with further studies the relationship between the clinical signs at paroxysmal periods of PVM patients and serum TNF levels.

Key Words : Tumor necrosis factor alpha, plasmodium vivax malaria.

INTRODUCTION

The Çukurova Region underwent malarial epidemics from time to time because of its climate, physical conditions and biological ambient factors. Eradication efforts lowered the incidence of the malaria in the region to 10.66 per hundred-thousands in 1989. The agent responsible for the malarial cases is Plasmodium Vivax (PV). The clinical course of these cases is much milder than Plasmodium falciparum (PF) infections (1).

TNF alpha is a mediator with broad-spectrum of inflammatory reactions. It is secreted principally by macrophages, and partially by lymphocytes and natural killer (NK) cells. It is known that TNF alpha causes hemorrhagic necrosis in tumors and cachexia in mice; induces secretion of several immunomoduators from macrophages, neutrophils, esinophils and endothelial cells; and presents inflammatory activities (2).

The clinical studies demonstrated TNF to cause toxic side effects such as headache, nausea, vomiting, fever, chills and myalgia. These effects remind symptoms of malaria in men. TNF elevations were observed in sera of patients with severe malarial infection (3).

The mortality reaches to 20% at cerebral malaria; an important complication of severe falciparum malaria (4). The mechanism in cerebral malaria is explained as the adherence of red blood cells to cerebral capillary endothelial cells with the help of ICAM-1 (Intercellular Adhesion Molecule-1). TNF shows its effect by increasing the expression of ICAM-1 in endothelial cells (4,5). In anemia as an another important complication of severe malaria, TNF may be effective by indirectly increasing the erytrophagocytosis (6). The presence of a great number of

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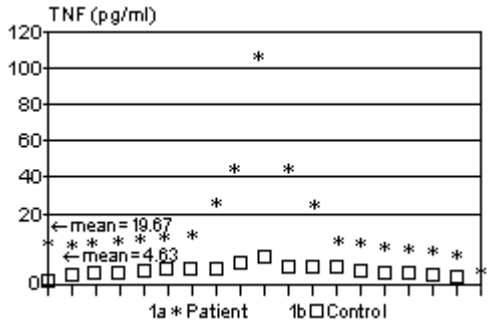
Figure 1: The distribution of serum TNF alpha values of PVM patients (1a) and the control group (1b).



parasites in the host in severe malaria may cause complications by causing endogenous TNF secretion. But a mild clinical picture may be seen in cases with severe disease, also. The role of TNF inhibitors are suggested in these cases. Soluble TNF receptors stabilize TNF by binding it before its transformation into its active form (4).

In previous studies the relationship between high TNF levels at acute episodes of PFM and severe clinical presentation were shown (3). We could not however, find sufficient studies in literature concerning serum TNF levels of PVM presenting with a mider clinical picture. A study in literature reported in paroxysmal period a higher increase in plasma TNF alpha levels in non-immune PVM cases than semi-immune PVM cases (7). We aimed to investigate serum TNF alpha levels of active PVM cases in non-endemic Çukurova Region.

MATERIALS AND METHODS

Of the 19 patients (6 women, 13 men; mean age 24) presented with complaint of fever at the Primary Health Centers of Adana City Dogankent Health Education and Research Region and were diagnosed as PVM depending on findings of thick blood film Venous blood samples were taken and their sera were conserved at a temperature of -30°C. As a control group 18 healthy persons (7 women, 11 men with a mean age of 30, none of whom gave the history of previous malarial infection, were included in the study.TNF alpha levels of sera from patients and of control cases were studied with radio-immunoassay kits (Medgenix, Fleurus-Belgium). All samples underwent investigation at the same time.

Sera from patients and from the control group and the standard samples placed in tubes covered previously with anti-TNF alpha were incubated with anti-TNF alpha marked with I125 for 20 hours at room temperature. They were washed twice and fluid in the tubes was aspirated. The Remaining precipitate underwent evaluation in automatic gamma counter (ICN Biomedicals). The TNF levels of the samples were compared to the standard values and calculated automatically in pg units/ml.

RESULTS

The mean TNF alpha levels of the PVM patients in acute febrile period (mean=19.67 s.e.±5.502 pg/ml) were statistically higher in relation to those of the control group (4.63±2.23 s.e.±0.52 pg/ml $p<0.02$).

The distribution graphics of TNF alpha values of the patient and of the control group are shown in Figure 1.

DISCUSSION

Previous studies reported close relationship of significantly elevated TNF alpha levels with high mortality rate in severe PFM. On the contrary the mortality rate was found far less elevated in PMF cases with mildly elevated TNF alpha levels (less than 100 pg/ml) (3).

We found a statistically significant elevation of TNF levels in the sera of PVM cases which have a milder clinical presentation ($p<0.02$). The mean TNF level of our cases, all of whom presented with mild symptoms, was below 100 pg/ml, (19.67±23.99 pg/ml). This observation supports previous studies reporting a parallel increase in the TNF alpha level to the severity of the disease in human falciparum malarial infection (3) and in experimental animal models (8). According to the literature TNF in severe cases of PFM help to clear the parasites away from the circulation. So a higher risk of becoming asymptomatic carrier has been suggested in cases with low TNF alpha levels.

All our cases selected for this study were primary cases. As it is well known, that exacerbations may be seen in PVM. A previous study reported lower TNF levels in semi-immune PVM cases in endemic regions, compared to those of non-immune cases (7). In our non endemic region it is necessary to investigate TNF levels during recurrences in PVM patients. We also suggest the need for investigation of the relationship between clinical signs and TNF levels in non-fertile periods in Plasmodium vivax cases.

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