УДК 576.895.2 / 576.32/.36

LEVEL OF IFN-Г, TNF-A AND IL-10 AMONG SUDANESE INFECTED BY MALARIA PARASITE

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Received 22.08.2020
Received in revised form 12.10.2020
Accepted 19.10.2020

Malaria still remains one of the oldest documented diseases of humans in the world. This study was aimed to measure the concentration of cytokine levels (IFN-γ, TNF-α, IL-10) in Sudanese malarial patients in serum specimens. 148 malaria positive patients were included in this study. The specimens were collected from three different areas: Kosti, Al-Greif Sharq, and El-Jayli Area. All specimens were examined using both blood films and ICT Pf/Pan. The overall mean of parasite counts were 22.36 x 109 parasite/L. After 14 days 54 of the participants returned back for follow up after completion of the anti-malarial treatment and the same previous tests were repeated again. 70 participants were selected to measure the concentration of cytokines according to the inclusion and exclusion criteria of the study. They were classified into two groups endemic and non-endemic and compared to their corresponding control groups and to the treated participants. The mean levels of IFN-γ, TNF-α, and IL-10 in serum of malarial patients from non-endemic area, was 59.94 pg/mL, 42.78 pg/mL, and 109.87 pg/mL respectively. The mean level of IFN-γ, TNF-α, and IL-10 in the serum of the malarial patients from the endemic area, was 14.26 pg/mL, 52.26 pg/mL, and 131.99 pg/mL respectively. IFN-γ and IL-10 showed a higher concentration when compared to a healthy control group (IFN-γ: E: $p = 0.040$/NE: $p < 0.000$; IL-10: $p < 0.000$ for both areas). Also showed higher concentrations when compared to the treated groups in both areas (IFN-γ: $p = 0.010$; IL-10: $p < 0.000$; TNF-α: E: $p = 0.760$/NE: $p = 0.650$). In the opposite TNF-α showed a significant difference with lower concentration when compared to the healthy group in both areas ($p < 0.000$). In this study both pro-inflammatory (IFN-γ, TNF-α) and anti-inflammatory (IL-10) cytokines for both endemic and non-endemic areas were elevated during infection and both decreased after treatment.

Keywords: Malaria, IFN-γ, TNF-α, IL-10, cytokines, Sudan, ICT Pf/Pan

DOI: 10.31857/S1234567806060048

Malaria is one of the most common diseases in the world. More than half the world population lives in malaria infected areas specially in Sudan where the latest WHO data published in 2017, reported that the number of malaria cases was 1305000 and the number of deaths reached 3,471 (Malaria in Sudan, 2017). Although it is a treatable disease, it has severe and may be deadly complications like cerebral malaria if doesn't treated (Centers for Disease Control…, 2015). There are many reviews about the relation between the clinical symptoms that caused by malaria parasite and the imbalance between cytokines that can lead to serious complications with regard to the main function of them by activating the effective molecules that kill malaria parasite (Perlmann, Troye-Blomberg, 2002; Nmorsi et al., 2010; Perera et al., 2013). However sometimes the over production of certain cytokines may lead to a serious deadly complications (Mandala et al., 2017). This concept can be used to minimize the complication of malaria by using them in vaccine, immunotherapy, or as diagnostic markers (Angulo, Fresno, 2002). In order to determine how cytokines vary with disease severity and syndrome, a study enrolled in the year 2017 in Malawian children presenting with cerebral malaria (CM), severe malarial anaemia (SMA) and uncomplicated malaria (UCM), with healthy controls. They analyzed serum cytokines concentrations in acute infection, and in convalescence. With the exception of IL-5, cytokine concentrations were highest in acute CM, followed by SMA, and were only mildly elevated in UCM. Cytokine concentrations had fallen to control levels when re-measured at one month of convalescence in all three clinical malaria (Mandala et al., 2017). In endemic area of Brazil there was study that aimed to characterize alterations in haematological patters and circulating plasma cytokines and chemokine levels in patients infected with *Plasmodium vivax* or *Plasmodium falciparum* during the acute and convalescent phases of infection whom compared with a healthy control. Thrombocytopenia, eosinopaenia, lymphopaenia and an increased number of band cells were observed in the majority of the patients during acute phase which returned to normal values at convalescent phase. This study was found a significantly higher for both *P. vivax* and *P. falciparum* patients of interleukin (IL)-6, IL-8, IL-17, interferon gamma (IFN-γ), tumour necrosis factor alpha (TNF-α), macrophage inflammatory protein-1β and granulocyte-colony stimulating factor levels than controls during acute phase which maintained high levels during the convalescent phase. IL-10 was detected at high concentrations during the acute phase, but returned to normal levels during the convalescent phase (Rodrigues-da-Silva et al., 2014). In Nigeria Nmorsi et al. (2010) examined the array of some pro- and anti-inflammatory cytokines, namely, interleukin-4 (IL-4), interleukin-10 (IL-10), interferon-γ (IFN- γ), interleukin-5 (IL-5), interleukin-6 (IL-6), interleukin-12 (IL-12) and tumor necrosis factor-α (TNF- α) concentrations in some Nigerians with *falciparum* malaria. They concluded that IL-4, IL-5, IL-6, IL-10, IL-12, TNF-α, and IFN-γ are involved in the immune-pathology and immune-regulation of uncomplicated and complicated malaria infections. IL-6, IL-12,

IFN-γ and IL-10 depressed in complicated/severe malaria may not provide any protective immunity and may be indicators of poor prognosis in *Plasmodium falciparum* infected Nigerian children. In this study is meant to look for the levels of some cytokines in the serum of Sudanese.

MATERIALS AND METHODS

This is a case control study conducted in three famous areas known to have a high prevalence of malaria. The study was approved by the Ministry of Health and The National Ribat University ethical. One hundred forty eight malaria positive patients recruited from the medical center in Aljraif East (n = 40), the medical center in El-Jayli (n = 23) area (Non-endemic areas/NE), and malaria center in Kosti (n = 85) (Endemic area/E) during period 2015 to 2018. Ninety four of the participants were males and fifty four were females. All samples were collected under special criteria: patients diagnosed as having malaria, permanent resident in the study area, not taking anti-malarial drug at least 2 weeks, free from other common infectious diseases, and willing to be involved in the study by signing a consent form. All specimens were diagnosed by both Giemsa stained thick-thin blood film (10 % v/v) and ICT Pf/Pan (Healgen Malaria Pf/Pan One Step Rapid Test). The parasite density was determined per μL of blood by counting the asexual form of them against TWBCs.

Serum was obtained the collected blood in plain vacutainer tube to measure the cytokines. The levels of cytokines (TNF-α, IFN-γ, and IL-10) were measured by sandwich ELISA kit (biolegend/ ELISA MAX™ Deluxe Sets). Each cytokine included with standard curve as directed by the manufacture that started from top standard concentration (IFN-γ: 500 pg/mL, TNF-α: 500 pg/mL, and IL-10 250 pg/mL) then six two fold serial dilutions of these top standard which run by ELISA parallel with the specimens. The absorbance of the ELISA was read by spectrophotometer at 450 nm within 15 minutes. Using Graph Pad Prism 7 program the standard curve was plotted with analyte concentration on the x-axis and absorbance on the y-axis. After 14 days all the steps of diagnosis were repeated for the cured patients. All data were analyzed online on web site http://www.socscistatistics.com considering 0.050 as significant values using Microsoft Office Exel 2007.

RESULTS

The overall mean of parasite counts were 22.36 x 10^9 parasite/L. The mean of parasites count in endemic area was 30.46 x 10^9 parasites/L and in the non-endemic area 13.28 × 10^9 parasites/L. The most prevalent *Plasmodium* species was *P. falciparum* 93.24 % (n = 138), then mixed infection of *P. falciparum* + *P. malariae* as 3.38 % (n = 5), and both *P. vivax* alone and mixed infection of *P. falciparum* + *P. vivax* with the same percentage 1.35 % (n = 2), and finally *P. malariae* alone was 0.68 % (n = 1) (fig. 1).

After fourteen days 54 of the participants returned back for follow up after completion of the anti-malarial treatment and the same previous tests were repeated again. 85.19 % (n = 46) of participants were free of malaria parasite and the parasiteamia of 14.81 % (n = 8) was decreased significantly to 0.03 × 10^9 parasite/L ($p < 0.000$).

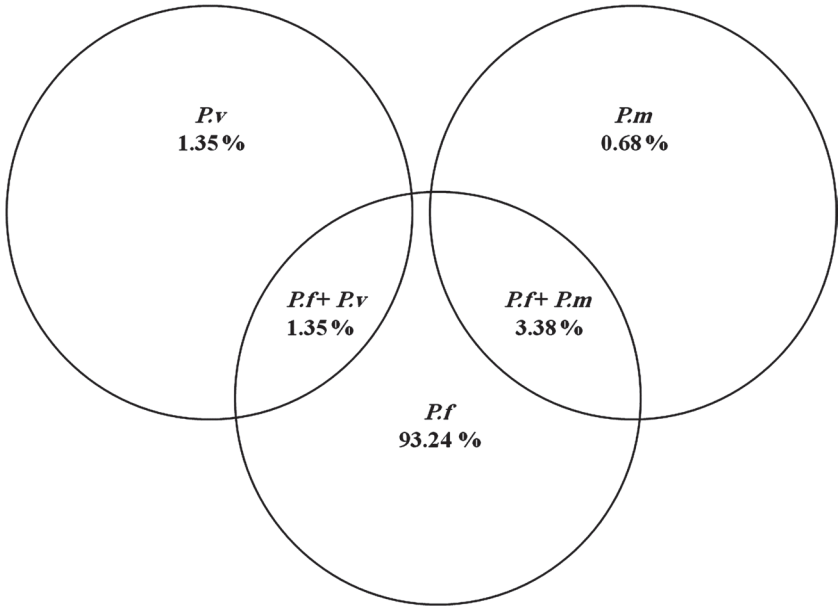

Figure 1. The percentages of the detected *Plasmodium* species: *P.f – Plasmodium falciparum, P.m – P. malariae, P.v – P. vivax.*

Seventy participants were selected to measure the concentration of cytokines (IFN-γ, TNF-α, IL-10) in serum according to the inclusion and exclusion criteria of the study. They were classified into two groups according to the endemicity of malaria parasite at these areas (endemic and non-endemic) and compared to their corresponding control groups and to the treated participants.

The group from non-endemic area was thirty three that compared to twenty participants of control group and twelve of the treated participants. The mean levels of IFN-γ, TNF-α, and IL-10 in serum of patients from non-endemic area before anti-malaria treatment was 59.94 pg/mL, 42.78, and 109.87 pg/mL respectively. All values of the cytokines in the serum of the malaria infected group showed significant difference when compared to the control group. The levels of the cytokines in the control group as follows: IFN-γ 6.57 pg/mL ($p < 0.000$), TNF-α 70.22 pg/mL ($p < 0.000$), and IL-10 1.16 pg/mL ($p < 0.000$). After anti-malarial treatment the level of the cytokines showed variations as follow: IFN-γ decreased significantly to 9.99 pg/mL ($p = 0.010$), TNF-α decreased insignificantly to 41.88 pg/mL ($p = 0.650$), and IL-10 decreased significantly to 5.02 pg/mL ($p < 0.000$) (table 1).

The group from endemic area was thirty seven that compared to twenty four participants of the control group and eighteen as a group of after treatment. The mean level of the IFN-γ, TNF-α, and IL-10 of the patients from the endemic area before anti-malarial treatment was 14.26 pg/mL, 52.26 pg/mL, and 131.99 pg/mL respectively. The mean level of the

cytokines of the control group (IFN-γ, TNF-α, IL-10) was 9.62 pg/mL, 117.06 pg/mL, 1.51 pg/mL respectively. There was a significant difference between the patients and the control group as follows: IFN-γ (significant, $p = 0.040$), TNF-α (significant, $p < 0.000$), and IL-10 (significant, $p < 0.000$) (table 2).

After the anti-malarial treatment the cytokines showed variations as follow: IFN-γ was decreased significantly (7.90 pg/mL, $p = 0.010$), TNF-α was decreased insignificantly (51.84 pg/mL, $p = 0.760$), and IL-10 was decreased significantly (3.91 pg/mL, $p < 0.000$) (table 3).

There is a significant difference between cytokines of endemic and non-endemic sera of healthy control as follows: IFN-γ: $p = 0.010$, TNF-α: $p < 0.000$, and IL-10: $p = 0.010$ (table 4).

Table 1. Mean of cytokines levels in the non-endemic area

	Patients			Control ($n = 20$)	
Cytokines	Before treatment ($n = 33$)	After treatment ($n = 12$)	*P*-vales	Cytokines level	*P*-vales
IFN-γ	59.94	9.99	0.010	6.57	< 0.000
TNF-α	42.78	41.88	0.650	70.22	< 0.000
IL-10	109.87	5.02	< 0.000	1.16	< 0.000

Table 2. Comparison of the mean cytokines levels (pg/ml) in the serum between the patients and controls in the endemic area

Cytokines	Patients (n=37)	Control (n=24)	*P*-vales
IFN-γ	14.26	9.62	0.040
TNF-α	52.26	117.06	< 0.000
IL-10	131.99	1.51	< 0.000

Table 3. The difference in the mean cytokines levels in serum (pg/ml) after treatment in the endemic area

Cytokines	Before treatment (n=37)	After treatment (n=18)	*P*-vales
IFN-γ	14.26	7.90	0.010
TNF-α	52.26	51.84	0.760
IL-10	131.99	3.91	< 0.000

Table 4. Comparison of the mean cytokines levels in serum of healthy control among non-endemic and endemic areas

Cytokines	Non-Endemic Areas	Endemic Areas	*P*-value
IFN-γ	6.57	9.62	0.010
TNF-α	70.22	117.06	<0.000
IL-10	1.16	1.51	0.010

DISCUSSION

Malaria is one of the most common diseases in Sudan. The World Health Organization – WHO published data in 2017 reporting the rate of total death due to malaria was 1.30 % (Malaria in Sudan, 2017). Now a days there are many trials to eradicate this disease and their complications permanently (Pan American Health Organization / World Health Organization — PAHO/WHO, 2018; WHO, 2018). These complications are shared between parasites and/or immune responses where the cytokines are one of them (Medina et al., 2011). This study aimed to measure the concentration of cytokines levels (IFN-γ, TNF-α, IL-10) in Sudanese malarial patients in serum samples.

During infection there are several pro-inflammatory cytokines like IFN-γ and TNF-α induced by many inflammatory cells like Th1 cells, CD8+ cells, NK cells, and macrophage. These cytokines are stimulated by malarial antigens leading to elimination of parasite or immuno-pathological effects in case of persistent response (Goldsby et al., 2002; Khan, 2008; Medina et al., 2011). In contrast the anti-inflammatory cytokines like IL-10 which induced by Th2 cells mainly and other inflammatory cells inhibit the pro-inflammatory cytokines (Couper et al., 2008; Akdis et al., 2016). As seen in this study both pro-inflammatory (IFN-γ, TNF-α) and anti-inflammatory (IL-10) cytokines in serum for both endemic and non-endemic areas were elevated during infection and both were decreased after cure maintaining the balance between them (pro/anti-inflammatory) as reported by Rodrigues-da-Silva et al. (2014) to avoid any immuno-pathological effects that mentioned by Medina et al. (2011). These cytokines showed significant difference to IFN-γ and IL-10 (endemic IFN-γ: $p = 0.040$; non-endemic IFN-γ: $p < 0.000$; IL-10: $p < 0.000$ for both areas) with higher concentrations when compared to healthy control group which agreed with Mandala et al. (2017), Medina et al. (2011), and Tatfeng, Agbonlahor (2010). Also the concentrations were higher when compared to the treated group in both areas (IFN-γ: $p = 0.010$; IL-10: $p < 0.000$) which agreed again with Mandala et al. (2017). TNF-α showed insignificant difference with higher concentration when compared to treated group (endemic area: $p = 0.760$; non endemic-area: $p = 0.650$) which agreed with a previous studies in elevation but not in significance. But this result agreed with Gandapur, Malik (1996) where the difference between the levels of TNF-α cytokine showed insignificant higher concentration in severe malaria than mild one and suggested that the population has some degree of immunity. Also they reported that the young trophozoite may be microscopically undetectable which support the positive correlation between parasite count and concentration of TNF-α in their study. TNF-α showed significant difference with lesser concentration in healthy group in both areas ($p < 0.000$) which disagreed with previous studies, where the TNF-α as pro-inflammatory cytokines should be increased during infection for protection to be higher than healthy one. But the inhibition of production of TNF-α is reported by many authors to be due to many possible

factors that act as anti-TNF-α during infection. Some microbes can act as immunosuppressive by enhancing production of IL-10 leading to decreasing in neutrophil counts and tumor necrosis factor α level (Hellgren et al., 2009). Another reason for this concept, the co-infection with some helminthes can modulate the immune response to malarial parasites by making more anti-inflammatory cytokines (IL-10) (Hartgers et al., 2009). Also the co-infection with Gram negative enteric bacilli can inhibit the production of TNF-α. This organism may be related to counter regulatory activities of IFN-induced increased nitric oxide (NO) that down regulate nitric oxide synthase (NOS) inducing cytokines, such as TNF-α, through a feedback mechanism (Davenport et al., 2016). The co-infection with HIV leading to depletion in CD4, CD8 and lowered serum levels of immunological mediators (Tatfeng, Agbonlahor, 2008). There are some foods which naturally inhibit the production of TNF-α like fatty fish, red fruits, tomatoes, red meat, nutritional yeast, honey, caffeine, dates, lactoferrin, ginger, Hibiscus sabdariffa (Karkadı) (Fakaye, 2008; Isa et al., 2008; Cohen, 2018). Beside that there are certain drugs can suppress TNF-α like aspirin, artemisinin, erythromycin, and paracetamol (Brandts et al., 1997; Schultz et al., 1998; Wang et al., 2011; Lutgen, Munyangi, 2018). During the disease the rate of consumption of patients may be reduced leading to reduction in expression of mRNA of TNF R2 in muscle (Hofmann et al., 1994). Finally the presence of certain genes can inhibit the expression of TNF-α (Mendonça et al., 2014). Beside that, there are other factors which increase production of TNF-α as seen in healthy control people like a long exposure to sun-light which contain UV-A irradiation that induces synthesis of IL-6 and TNF-α (Avalos-Diaz et al., 1999). Also the consumption of large amount of caffeine (coffee) can increase the level of TNF-α; and insufficient ingestion of fruit or vegetables may increase the TNF-α (Cohen, 2018). The continuous exposure of the immune system to malaria parasite leads to a high concentration of cytokines. That was obvious in the detected levels of the cytokines from the healthy candidates in the endemic area when compared to those from the non-endemic one. The difference was significantly higher in those from the endemic area (IFN-γ: $p = 0.010$, TNF-α: $p < 0.000$, IL-10: $p = 0.010$). Also this was true about parasite counts (endemic area: 30.46×10^9 parasites/L; non-endemic area: 13.28×10^9 parasites/L) which agreed with Wroczyńska et al. (2005).

CONCLUSION

In this study both pro-inflammatory (IFN-γ, TNF-α) and anti-inflammatory (IL-10) cytokines in serum for both endemic and non-endemic areas were elevated during infection and both decreased after cure maintaining the balance between them (pro/anti-inflammatory) to avoid any immuno-pathological effects.

ACKNOWLEDGEMENT

We are grateful to The National Ribat University and Prof. Moawia M. Mukhtar from The Institute of Endemic Diseases-Khartoum University for providing some facilities for this work. We would also like to acknowledge the personnel in the health centers for their great help in the collection of the specimens.

REFERENCES

Akdis M., Aab A., Altunbulakli C., Azkur K., Costa R.A., Crameri R., Duan S., Eiwegger T., Eljaszewicz A., Ferstl R., Frei R., Garbani M., Globinska A., Hess L., Huitema C., Kubo T., Komlosi Z., Konieczna P., Kovacs N., Kucuksezer U.C., Meyer N., Morita H., Olzhausen J., O'Mahony L., Pezer M., Prati M., Rebane A., Rhyner C., Rinaldi A., Sokolowska M., Stanic B., Sugita K., Treis A., van de Veen W., PhD, Wanke K., Wawrzyniak M., Wawrzyniak P., Wirz O.F., Zakzuk J.S., Akdis C.A. 2016. Interleukins (from IL-1 to IL-38), interferons, transforming growth factor β, and TNF-α: Receptors, functions, and roles in diseases. Journal of Allergy and Clinical Immunology138(4): 984–1010. https://doi.org/10.1016/j.jaci.2016.06.033

Angulo I., Fresno M. 2002. Cytokines in the pathogenesis of and protection against malaria. Clinical and Diagnostic Laboratory Immunology 9 (6): 1145–1152. DOI: 10.1128/CDLI.9.6.1145–1152.2002

Avalos-Diaz E., Alvarado-Flores E., Herrera-Esparza R. 1999. UV-A irradiation induces transcription of IL-6 and TNF alpha genes in human keratinocytes and dermal fibroblasts. Revue du rhumatisme (English ed.) 66 (1): 13–19.

Brandts C.H., Ndjavé M., Graninger W., Kremsner P.G. 1997. Effect of paracetamol on parasite clearance time in *Plasmodium falciparum* malaria. The Lancet 350 (9079): 704–709. https://doi.org/10.1016/S0140-6736(97)02255-1

Centers for Disease Control and Prevention -CDC - Malaria - About Malaria - Disease 2015. Available from: https://www.cdc.gov/malaria/about/disease.html (20 August 2020)

Cohen J. 2018. How to Inhibit TNF-alpha Naturally. SelfHack. Available from: https://www.selfhacked.com/blog/supplements-lifestyle-factors-influence-tnf-interleukin-6-il-6/ (20 August 2020)

Couper K.N, Blount D.G., Riley E.M. 2008. IL-10: the master regulator of immunity to infection. The Journal of Immunology 180(9): 5771–5777. doi: 10.4049/jimmunol.180.9.5771

Davenport G.C., Hittner J.B., Otieno V., Karim Z., Mukundan H., Fenimore P.W., Hengartner N.W., McMahon B.H., Kempaiah P., Ong'echa J.M., Perkins D.J. 2016. Reduced parasite burden in children with *falciparum* malaria and bacteremia coinfections: role of mediators of inflammation. Mediators of Inflammation. 2016: 4286576. http://dx.doi.org/10.1155/2016/4286576

Fakaye T. 2008. Toxicity and immunomodulatory activity of fractions of *Hibiscus sabdariffa* Linn (family Malvaceae) in animal models. African Journal of Traditional, Complementary and Alternative Medicines 5(4): 394–398.

Gandapur A.S., Malik S.A. 1996. Tumor necrosis factor in *falciparum* malaria. Annals of Saudi medicine16 (6): 609–614. https://doi.org/10.5144/0256-4947.1996.609

Goldsby R.A., Kindt T.J., Osborne B.A., Kuby J. 2002. Immunology, 5th ed., New York:W. H. Freeman, 553 p.

Hartgers F.C., Obeng B.B., Kruize Y.C.M., Dijkhuis A., McCall M., Sauerwein R.W., Luty A.J.F., Boakye D.A., Yazdanbakhsh M. 2009. Responses to malarial antigens are altered in helminth-infected children. The Journal of Infectious Diseases199 (10): 1528–1535. https://doi.org/10.1086/598687

Hellgren U.M., Leino M., Aarnisalo A.A., Mussalo-Rauhamaa H., Alenius H., Reijula K. 2009. Low tumor necrosis factor α levels and neutrophil counts in nasal lavage after mold exposure. Annals of Allergy, Asthma & Immunology 102 (3): 210–215. https://doi.org/10.1016/S1081-1206(10)60083-X

Hofmann C., Lorenz K., Braithwaite S.S., Colca J.R., Palazuk B.J., Hotamisligil G.S., Spiegelman B.M. 1994. Altered gene expression for tumor necrosis factor-alpha and its receptors during drug and dietary modulation of insulin resistance. Endocrinology 134(1): 264–270. https://doi.org/10.1210/endo.134.1.8275942

Isa Y., Miyakawa Y., Yanagisawa M., Goto T., Kang M. S., Kawada T, Morimitsu Y., Kubota K., Tsuda T. 2008. 6-Shogaol and 6-gingerol, the pungent of ginger, inhibit TNF-α mediated downregulation of adiponectin

expression via different mechanisms in 3T3-L1 adipocytes. Biochemical and Biophysical Research Communications 373 (3): 429–434. https://doi.org/10.1016/j.bbrc.2008.06.046

Khan M.M. 2008. Immunopharmacology: role of cytokines, Creighton University Medical Center, Omaha, United States, Springer Science + Business Media, 266 p.

Lutgen P., Munyangi J. 2018. Platelets, eryptosis, amiodarone, aspirin, Artemisia. Pharmacy and Pharmacology International Journal 6(5): 377–381. DOI: 10.15406/ppij.2018.06.00205

Malaria in Sudan2017.World Life Expectancy. Available from: https://www.worldlifeexpectancy.com/sudan-malaria (20 August 2020)

Mandala W.L., Msefula C.L., Gondwe E.N., Drayson M.T., Molyneux M.E., MacLennan C.A. 2017. Cytokine profiles in Malawian children presenting with uncomplicated malaria, severe malarial anemia, and cerebral malaria. Clinical and Vaccine Immunology24 (4): e00533-16. https://doi.org/10.1128/CVI.00533-16

Medina T.S., Costa S.P., Oliveira M.D., Ventura A.M., Souza J.M., Gomes T.F., Vallinoto A.C.R., Póvoa M.M, Silva J.S., Cunha M.G. 2011. Increased interleukin-10 and interferon-γ levels in *Plasmodium vivax* malaria suggest a reciprocal regulation which is not altered by IL-10 gene promoter polymorphism. Malaria Journal 10(1): 264. https://doi.org/10.1186/1475-2875-10-264

Mendonça V.R., Souza L.C., Garcia G.C., Magalhães B.M., Lacerda M.V., Andrade B.B., Gonçalves M.S., Barral-Netto M. 2014. DDX39B (BAT1), TNF and IL6 gene polymorphisms and association with clinical outcomes of patients with *Plasmodium vivax* malaria. Malaria Journal 13 (1): 278. https://doi.org/10.1186/1475-2875-13-278

Nmorsi O.P.G., Isaac C., Ukwandu N.C.D., Ohaneme B.A. 2010. Pro–and anti–inflammatory cytokines profiles among Nigerian children infected with *Plasmodium falciparum* malaria. Asian Pacific Journal of Tropical Medicine 3 (1): 41–44. https://doi.org/10.1016/S1995-7645(10)60029-6

Pan American Health Organization / World Health Organization -PAHO/WHO. The Road to Malaria Eradication - Update 2018. 2018. Available from: https://www.paho.org/hq/index.php?option=com_content&view=article&id=14191:the-road-to-malaria-eradication-update-2018&Itemid=40275&lang=en (20 August 2020)

Perera M.K., Herath N.P., Pathirana S.L., Phone-Kyaw M., Alles H.K., Mendis K.N., Premawansa S., Handunnetti S.M. 2013. Association of high plasma TNF-alpha levels and TNF-alpha/IL-10 ratios with TNF2 allele in severe *P. falciparum* malaria patients in Sri Lanka. Pathogens and Global Health 107 (1): 21–29. https://doi.org/10.1179/2047773212Y.0000000069

Perlmann P., Troye-Blomberg M. 2002. Malaria and the immune system in humans. Chemical Immunology 80: 229–242.

Rodrigues-da-Silva R.N., Lima-Junior J.C., Fonseca B.P.F., Antas P.R.Z., Baldez A., Storer F.L., Santos F., Banic D.M., de Oliveira-Ferreira J. 2014. Alterations in cytokines and haematological parameters during the acute and convalescent phases of *Plasmodium falciparum* and *Plasmodium vivax* infections. Memórias do Instituto Oswaldo Cruz 109 (2): 154–162. http://dx.doi.org/10.1590/0074-0276140275

Schultz M.J., Speelman P., Zaat S., van Deventer S.J., van der Poll T. 1998. Erythromycin inhibits tumor necrosis factor alpha and interleukin 6 production induced by heat-killed *Streptococcus pneumoniae* in whole blood. Antimicrobial agents and chemotherapy 42 (7): 1605–1609. DOI: 10.1128/AAC.42.7.1605

Tatfeng M.Y., Agbonlahor D.E., 2008. Proinflammatory cytokines and haematological indices in HIV seropositive adults with uncomplicated *Plasmodium falciparum* malaria. Tropical Medicine and Health 36 (2): 75–79. https://doi.org/10.2149/tmh.2008-04

Tatfeng Y.M., and Agbonlahor D.E., 2010. Age-related cytokine profile in uncomplicated *Plasmodium* malaria infection. Colombia Médica 41 (4): 323–327.

Wang Y., Huang Z., Wang L., Meng S., Fan Y., Chen T., Cao J., Jiang R., Wang C. 2011. The anti-malarial artemisinin inhibits pro-inflammatory cytokines via the NF-κB canonical signaling pathway in PMA-induced THP-1 monocytes. International Journal of Molecular Medicine 27 (2): 233–241. https://doi.org/10.3892/ijmm.2010.580

World Health Organization – WHO 2018. Malaria control: the power of integrated action. Available from: https://www.who.int/heli/risks/vectors/malariacontrol/en/ (20 August 2020)

Wroczyńska A., Nahorski W., Bąkowska A., Pietkiewicz H. 2005. Cytokines and clinical manifestations of malaria in adults with severe and uncomplicated disease. International Maritime Health 56 (1–4): 103–114.

УРОВЕНЬ ЦИТОКИНОВ IFN-γ, TNF-α И IL-10 В КРОВИ СУДАНЦЕВ, ИНФИЦИРОВАННЫХ МАЛЯРИЙНЫМ ПАРАЗИТОМ

Аль Сайед С. Е. А., Малик А. Х., Муса Х. А.

Ключевые слова: малярия, IFN-γ, TNF-α, IL-10, цитокины, Судан, ICT *Pf/Pan* тест

РЕЗЮМЕ

Малярия по-прежнему остается одной из старейших зарегистрированных в мире болезней человека. Целью предлагаемого исследования является измерение уровней концентрации цитокинов (IFN-γ, TNF-α, IL-10) в образцах сыворотки крови у больных малярией пациентов в Судане. Всего было изучено 148 больных малярией пациентов. Образцы сыворотки были собраны в трех различных регионах Судана: г. Кости, Аль-Грейф Шарк и территория возле г. Эль-Джайли. Все образцы были изучены с использованием как мазков крови, так и метода иммунной хроматографии (тест Pf/Pan). Среднее число паразитов в образцах составило 22.36×10^9 паразитов на 1 л. Через 14 дней 54 пациента, лечившихся от малярии, были вновь исследованы с применением вышеописанных методов. 70 пациентов были отобраны для измерения концентрации цитокинов согласно критериям включения и исключения, использованных в работе. Эти пациенты были разделены на две группы (из эндемичных и не эндемичных по малярии районов), данные по которым сравнивали с соответствующими контрольными группами и с данными по пациентам, подвергавшимся лечебным процедурам. Средний уровень концентрации цитокинов IFN-γ, TNF-α и IL-10 в сыворотке крови больных малярией из не эндемичных районов составили соответственно 59.94 пг/мл, 42.78 и 109.87 пг/мл. Средний уровень концентрации цитокинов IFN-γ, TNF-α и IL-10 в сыворотке крови больных малярией из эндемичных районов составили соответственно 14.26 пг/мл, 52.26 и 131.99 пг/мл. IFN-γ и IL-10 характеризовались более высоким уровнем концентрации в сравнении с контрольной группой здоровых пациентов (IFN-γ: E: $p = 0.040$/NE: $p < 0.000$; IL-10: $p < 0.000$, для обоих регионов). Более высокую концентрацию наблюдали и при сравнении с группами лечившихся от малярии пациентов из обоих регионов (IFN-γ: $p = 0.010$; IL-10: $p < 0.000$; TNF-α: E: $p = 0.760$/NE: $p = 0.650$). Кроме того, цитокин TNF-α достоверно отличался более низкой концентрацией при сравнении с группой здоровых пациентов в обоих регионах ($p < 0.000$). Согласно нашим данным, концентрация как про-воспалительных (IFN-γ, TNF-α), так и противовоспалительных (IL-10) цитокинов у пациентов из эндемичных и неэндемичных регионов повышалась при заражении малярией и понижалась после проведения лечебных процедур.