[Egyptian Journal of Basic and Applied Sciences 4 (2017) 185–189](http://dx.doi.org/10.1016/j.ejbas.2017.05.002)



Contents lists available at [ScienceDirect](http://www.sciencedirect.com/science/journal/2314808X)

Egyptian Journal of Basic and Applied Sciences

journal homepage: [www.elsevier.com/locate/ejbas](http://www.elsevier.com/locate/ejbas)

Full Length Article

Alterations in T-helper cell type 1 and blood cell parameters in malaria-infected patients



Olarewaju Abdulkareem Babamale [a](#_bookmark0),[⇑](#_bookmark2), Adam Olaitan Abdulkareem [b](#_bookmark1), Olufunke A. Opeyemi [a](#_bookmark0),

Uade Samuel Ugbomoiko [a](#_bookmark0)

a *Parasitology Unit, Department of Zoology, University of Ilorin, Ilorin, Nigeria*

b *Physiology Unit, Department of Zoology, University of Ilorin, Ilorin, Nigeria*

# a r t i c l e i n f o

*Article history:*

Received 13 October 2016

Received in revised form 11 May 2017 Accepted 11 May 2017

Available online 23 May 2017

*Keywords:* Cytokine Thrombocytopenia Parameters Alterations Prevalences

# a b s t r a c t

Malaria is a global public health disease. Haematological and cytokine alterations are the major sources of its pathological conditions. Therefore, blood and serum of patients attending health centres were screened to investigate the effects of *Plasmodium falciparum* on the T-helper cell type 1 and blood cell parameters using Enzyme linked immunosorbent assay and automatic hematology analyzer respectively.

Approximately 55% of malaria-infected patients with average parasitaemia of 2523.64 parasite/ll of

blood concurrently suffered anaemia, thrombocytopenia, leucopenia, microcytosis and hypochromasia. However, thrombocytopenia and leucopenia were age-specific and their prevalences in children within

≤10 years were higher. These disease conditions significantly vary with severity of malaria infection (p < 0.05). Blood parameters with the exception of RBC and MCHC were significantly lower in the infected

patients (p < 0.05) with 12.9% and 41.2% reduction in haemoglobin and platelet counts respectively. A high plasma concentration of IL-10, IL-12, INF-c and TNF-a, ratio of IL-10/TNF-a (1.86) and IL-10/INF-c (1.55) were recorded among the malaria-infected groups. This study revealed that unregulated interac- tion of the parasite with host immune response has important consequences in disease progression

and thus relevant for therapeutic and vaccine development.

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1. Introduction

Malaria is still a life-threatening parasitic disease in many coun- tries worldwide, causing between 80 and90% morbidity and mor- tality in sub-Saharan Africa [[1,2]](#_bookmark18). In this region, *Plasmodium falciparum* and *P. vivax* are common human malaria parasites and the prognosis is severe [[3]](#_bookmark7). The activities of their erythrocytic asex- ual stages in asymptomatic and symptomatic patients are impor- tant foci in the pathogenesis [[4,5]](#_bookmark7). Infections in less immuned individuals, especially young children and pregnant women are always severe, resulting in anaemia, thrombocytopenia, leucopenia and other haematological disorders [[4]](#_bookmark7). Most infected individuals are incapacitated for days due to recurrent clinical episodes attrib- uted to the release of malaria pigment (hemozoin) and other toxic factors such as glycosylphosphatidylinositol (GPI) when the infected erythrocytes rupture [[5]](#_bookmark7).

Previous studies [[6,7]](#_bookmark7) showed that *P. falciparum*, upon invasion of red blood cell, interferes with rigidity and deformability

\* Corresponding author.

*E-mail address:* [olas4nice2004@yahoo.co.uk](mailto:olas4nice2004@yahoo.co.uk) (O.A. Babamale).

properties of the cell to permit the direct exchange of metabolites. Consequently, inflammatory cytokines (TNF-a, IL-1, IL-10 and IFN- c), cascade coagulation and sequestration of parasitized RBCs increase, and thus the manifestations of malaria infection ensued [[8–10]](#_bookmark7).

However, a steady balance between pro- and anti-inflammatory responses is obligatory to elicit anti-parasitic activities and enhance parasite clearance; otherwise an uncontrolled production

of pro-inflammatory cytokines, such as IL-6, TNF and IFN-c may

lead to severe malaria syndromes thereby suppressing T-cell response [[11,12]](#_bookmark7). The resulting protective Th1-dependent immune responses to blood-stage malaria infection are mediated by IFN-c

and TNF-a to optimize nitric oxide production [[13,14]](#_bookmark8).

Report [[15]](#_bookmark9) has shown that infections due to *P. falciparum* result in progressive structural, biochemical, and mechanical modifica- tions of the host cells that lead to life-threatening complications. Information on the mechanism of alteration in infected host cell required in predicting the severity of malaria is limited. This study therefore investigated the effect of *P. falciparum* on the type 1 T- helper cell and blood cell parameter amongst the malaria infected patients in Ilorin, Kwara state, Nigeria for better understanding of

<http://dx.doi.org/10.1016/j.ejbas.2017.05.002>

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host-parasite interaction which can be exploited in the effective management of malaria infection.

1. Materials and methods
   1. *Study design, sample and data collection*

The blood and serum of patients attending health centres in Ilorin, Kwara State (located at Lat. 8° 300 N and Long. 8° 500 N and Long. 4° 200 E and 4° 350 E), Nigeria were used for this study. Thick and thin blood films were prepared and stained with Giemsa and

*P. falciparum* was identified under oil immersion microscope. The estimation of parasitaemia was done by counting the number of parasites per 200 white blood cells (WBC) on blood films. Complete blood cell counts was conducted using an automatic hematology analyzer (Pentra ABX) and peripheral blood smears were per- formed for routine differential blood cellular quantification.

In accordance with manufacturer’s recommendations, the levels of TNF-a, IL-I0 and IL-12 in the serum were determined using Enzyme linked immunosorbent assay, (ELISA) Kit procured from Abcam, Cambridge, United Kingdom. The test kits were sensitive detecting cytokines levels at less than 0.8 pg/ml and cross reactiv-

ity was not observed for any other proteins tested.

* 1. *Ethical clearance and procedure for data collection*

The study protocol was approved by University of Ilorin ethical review committee and the Medical and Information Management units of selected health centres in Ilorin, Kwara state. The approval detail of the study was contained in the letter with reference num- ber KW/REF/GT0126.

* 1. *Statistical analysis*

Statistical analysis was performed with SPSS version 20; (SPS Inc., Chicago IL). Descriptive statistics were expressed as means and standard deviations while the student’s t-test and Chi square analysis were applied to determine the differences in haematolog- ical parameters and cytokines levels. Comparison of associations between the haematological parameters and parasite density were assessed using the Pearson’s linear regression. The level of statisti- cal difference was set at p < 0.05.

1. Results

Of the total 223 out-patients (100 males and 123 females) with average age of 21.41 years enrolled in the study, 55.2% was

infected with *Plasmodium falciparum* with average parasitaemia of 2523.64 parasite/ll of blood ([Table 1](#_bookmark3)). Approximately, 25%, 26% and 5% of malaria-infected individuals had low, moderate and severe infection respectively. Similarly, 55.2% and 41.7% of

infected patient were anaemic and thrombocytopenic respectively. [Table 2](#_bookmark4) shows that the prevalences of haematological disorder among the malaria-infected patients was not sex related (P > 0.05) but thrombocytopenia and leucopenia were age –specific with high prevalences in children within age-group of ≤10 years. However, these disease conditions significantly vary with degree of malaria infection (p < 0.05). For instance, 12.9% and 41.2% reduc- tion were observed in haemoglobin and platelet counts among infected participants.

[Table 3](#_bookmark5) revealed that lower values of red blood cell, packed cell volume, haemoglobin and differential counts of neutrophil, plate- lets and white blood cells were recorded among malaria patients. High plasma concentrations of IL-10, IL-12, INF-c and TNF-a, also

ratio of IL-10/TNF-a (1.86) and IL-10/INF-c (1.55) were obtained

Table 1

Demographical and clinical characteristics of study population.

N (%)

|  |  |
| --- | --- |
| Sex (Male/Female) | 100/123 |
| Mean Age + Std.dev. | 21.41 ± 10.27 |
| Number infected with malaria | 123(55.2) |
| Mean intensity + Std.dev | 2523.64 ± 4.47 |
| *Degree of malaria infection* |  |
| No Infection | 100(44.8) |
| Low | 55(24.7) |
| Moderate | 57(25.6) |
| Severe | 11(4.9) |
| *Anaemia* |  |
| Malaria patient | 123(55.2) |
| Uninfected patient | 7(3.1) |
| *Thrombocytopenia* |  |
| Malaria patient | 93(41.7) |
| Uninfected patient | 21(9.4) |

among the infected patients ([Table 3](#_bookmark5)). Further analysis indicated that haematological indices significantly decreased (p < 0.05) whereas immunological indices increased with increasing para- sitaemia ([Table 4](#_bookmark6)).

1. Discussion

Pronounced haematological and cytokine alterations are trade- marks in malaria infection and other infectious diseases [[4,13,14]](#_bookmark7). The current study confirms that anaemia, thrombocytopenia, hypochromasia and leucopenia were common disorders in malaria infected patients. This is similar to reports in many malaria- endemic settings worldwide [[16–19]](#_bookmark10). However, the relative sever- ity of the haematological disorders varied, similar in infected male and female but higher in young children. This observed age and sex relative pattern of morbidity is a common characteristic in ende- mic areas in Africa [[20,21]](#_bookmark11). The severity of these disorders is observed to be increasing with parasite density in infected individ- uals except in the case of hypochromasia which is more prevalent among individual with low parasite density. This observation is concordant with reports of Erhart et al. [[22]](#_bookmark12) and Saravu et al. [[23]](#_bookmark13). Anaemia is a common clinical indicator of severe malaria in children [[24,25]](#_bookmark14), a phenomenon that follows inhibition of erythro- poiesis and massive destruction of both parasitized and non- parasitized red blood cells. The low mean haemoglobin concentra- tion (Hb) and packed cell volume (PCV) observed in our infected patient indicate anaemic condition. This is similar to many reports [[26–28]](#_bookmark15). The reduction in Hb and PCV increases with the intensity of infection in malaria [[29]](#_bookmark16). Thus, individual with severe malaria

are more susceptible to severe anaemia.

Thrombocytopenia and platelet dysfunction are another impor- tant pathological conditions observed in 76.4% malaria infected group in this study. This agrees with previous findings [[30–33]](#_bookmark17). Other studies [[34,35]](#_bookmark19) reported that 95% of falciparum malaria patient had thrombocytopenia. The mechanism of this disease con- dition has been well described [[36–38]](#_bookmark19). The authors postulated that immune mediated lysis, sequestration in the spleen and a dys- poietic process in the bone marrow diminish platelet production which may probably lead to reduced platelets subpopulation in the circulation. However, the pathogenic mechanisms by which platelets mediate disease severity in patients with falciparum malaria remain to be delineated. Previous study [[39]](#_bookmark19) revealed that platelets in patients with *P. falciparum* expressed Toll-like recep- tors (TLRs), which release prepackaged inflammatory mediators such as Nitric oxide (NO), a key mediator of platelet homeostasis. A decreased bioavailability of NO in patients with severe malaria may contribute to increased platelet activation and consumption

Table 2

Prevalence of haematological disorders with respect to age, sex and infection status of the malaria infected participants.

Haematological conditions

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Variables | No. examined | Anaemia (%) | Thrombocytopenia (%) | Leucopenia (%) | Microcytosis (%) | Hypochromasia (%) |  |
| Overall | 123 | 100(81.3) | 94(76.4) | 93(75.6) | 26 (21.1) | 56 (45.5) |  |
| *Sex* |  |  |  |  |  |  |  |
| Male | 55 | 44 (80.0) | 42 (76.4) | 44(80.0) | 12 (21.8) | 22(40.0) |  |
| Female | 68 | 56 (82.4) | 52 (76.4) | 49(72.1) | 14 (20.6) | 34(50.0) |  |
| P. value |  | 0.739 | 0.350 | 0.308 | 0.818 | 0.517 |  |
| *Age group (years)* |  |  |  |  |  |  |  |
| ≤10 | 23 | 21 (91.3) | 20 (86.9) | 20(86.9) | 4 (17.4) | 11(47.8) |  |
| 11–20 | 25 | 19 (76.0) | 16 (64.0) | 19 (76.0) | 7 (28.0) | 10 (40.0) |  |
| 21–30 | 59 | 49 (83.1) | 46 (77.9) | 14(23.7) | 11 (18.6) | 27 (45.8) |  |
| ≥31 | 16 | 11 (68.8) | 12 (75.0) | 7(43.8) | 4 (25.0) | 8 (50.0) |  |
| P. value |  | 0.289 | 0.005 | 0.028 | 0.791 | 0.531 |  |
| *Malaria infection* |  |  |  |  |  |  |  |
| Low | 55 | 38 (69.1) | 42 (76.4) | 37(67.3) | 9 (16.4) | 29 (52.7) |  |
| Moderate | 57 | 54 (94.7) | 44 (77.2) | 46(80.7) | 16 (28.1) | 23(40.4) |  |
| Severe | 11 | 8 (72.7) | 8 (72.7) | 10(90.9) | 1 (9.1) | 4 (36.4) |  |
| P. value |  | 0.002 | 0.002 | 0.018 | 0.174 | 0.047 |  |

Table 3

Comparison of haematological and immunological indices among infected and uninfected individuals in the study populations.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Uninfected patients |  |  | Infected patients |  | P. value |
| Mean ± Std.dev. | 95% CI |  | Mean ± Std.dev. | 95% CI |  |
| *Hematological indices*  RBC (103/ll) | 3.68 ± 0.88 | 3.17–3.79 |  | 3.46 ± 0.63 | 3.55–3.77 | 0.724 |
| Haemoglobin (g/dl) | 14.44 ± 0.63 | 10.22–15.66 |  | 9.09 ± 1.54 | 6.82–9.37 | <0.001 |
| PCV (%) | 33.96 ± 4.92 | 32.22–35.71 |  | 26.45 ± 4.07 | 25.73–27.18 | <0.001 |
| MCHC (g/dl) | 32.53 ± 2.55 | 31.63–33.44 |  | 32.17 ± 5.37 | 31.22–33.13 | 0.712 |
| MCV (pg) | 89.83 ± 15.20 | 84.44–95.22 |  | 71.90 ± 8.03 | 70.46–73.33 | <0.001 |
| MCH (pg) | 31.01 ± 4.66 | 29.36–32.66 |  | 26.81 ± 2.85 | 26.29–27.31 | <0.001 |
| WBC (103/ll) | 3.82 ± 0.69 | 36.09–41.75 |  | 3.21 ± 0.85 | 31.18–34.13 | 0.007 |
| Neutrophil (103/ll) | 2.03 ± 0.42 | 19.11–22.77 |  | 1.21 ± 0.57 | 11.41–13.48 | <0.001 |
| Basophil (103/ll) | 0.02 ± 0.003 | 22.25–23.18 |  | 0.04 ± 0.02 | 38.63–44.88 | <0.001 |
| Eosinophil (103/ll) | 1.43 ± 0.18 | 14.66–15.56 |  | 3.26 ± 0.51 | 30.33–35.15 | <0.001 |
| Platelet count (103/ll) | 80.27 ± 10.07 | 76.70–83.84 |  | 47.16 ± 26.31 | 42.46–51.85 | <0.001 |
| *Immunological indices* |  |  |  |  |  |  |
| INF-c (pg/ml) | 41.43 ± 9.81 | 39.27–4.32 |  | 51.04 ± 8.57 | 43.63–54.74 | <0.001 |
| TNF-a (pg/ml) | 27.65 ± 8.28 | 26.10–2.91 |  | 42.37 ± 5.52 | 40.18–44.35 | <0.001 |
| IL-10 (pg/ml) | 25.18 ± 13.18 | 27.32–3.10 |  | 79.01 ± 10.07 | 20.19–30.17 | 0.278 |
| IL-12 (pg/ml) | 10.82 ± 10.13 | 6.07–11.21 |  | 23.11 ± 0.20 | 20.02–20.70 | 0.282 |
| IL-10/TNF-a ratio | 0.91 ± 1.52 | 0.32–0.96 |  | 1.86 ± 1.31 | 0.31–2.12 | 0.001 |
| IL-10/INF-c ratio | 0.61 ± 0.84 | 0.47–0.80 |  | 1.55 ± 0.26 | 0.61–1.98 | 0.001 |

Table 4

Variation of haematological and immunological indices with intensity of infection.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Intensity of infection |  |  | P. value |
| Low | Moderate | Severe |  |
| *Haematological indices*  RBC (103/ll) | 3.77 ± 0.64 | 3.63 ± 0.63 | 3.31 ± 0.45 | 0.208 |
| Haemoglobin (g/dl) | 9.46 ± 1.49 | 8.98 ± 1.44 | 7.7 ± 1.49 | <0.001 |
| PCV (%) | 27.78 ± 4.47 | 25.74 ± 5.19 | 25.30 ± 2.99 | <0.001 |
| MCHC (g/dl) | 31.59 ± 6.27 | 32.32 ± 4.70 | 34.37 ± 2.93 | 0.416 |
| MCV | 72.01 ± 5.62 | 71.05 ± 9.16 | 75.70 ± 11.28 | <0.001 |
| MCH (pg) | 27.30 ± 3.20 | 26.66 ± 2.31 | 24.96 ± 2.80 | <0.001 |
| WBC (103/ll) | 3.45 ± 0.85 | 2.99 ± 0.86 | 3.21 ± 0.48 | <0.001 |
| Neutrophil (103/ll) | 1.12 ± 0.53 | 1.22 ± 0.58 | 1.67 ± 0.46 | <0.001 |
| Basophil (103/ll) | 0.05 ± 0.001 | 0.04 ± 0.001 | 0.01 ± 0.002 | <0.001 |
| Eosinophil (103/ll) | 3.50 ± 1.33 | 3.41 ± 1.62 | 1.52 ± 0.62 | <0.001 |
| Platelet count (103/ll) | 51.00 ± 19.70 | 47.18 ± 26.42 | 46.36 ± 27.65 | <0.001 |
| *Immunological indices* |  |  |  |  |
| INF-a (pg/mL) | 43.5 ± 15.07 | 49.04 ± 19.31 | 52.92 ± 12.22 | <0.001 |
| TNF-c (pg/mL) | 40.3 ± 11.28 | 42.35 ± 17.63 | 42.71 ± 18.84 | <0.001 |
| IL-10 (pg/mL) | 48.93 ± 17.39 | 69.37 ± 13.90 | 80.60 ± 23.18 | 0.008 |
| IL-12 (pg/mL) | 20.5 ± 21.08 | 30.81 ± 14.93 | 27.61 ± 13.09 | <0.001 |
| IL-10/TNF-a | 1.21 ± 0.05 | 1.64 ± 0.56 | 1.89 ± 0.92 | 0.061 |
| IL-10/INF-c | 1.12 ± 0.23 | 1.41 ± 0.24 | 1.52 ± 0.73 | 0.024 |

[[39–41]](#_bookmark19). The trend of decreasing platelets with increasing levels of parasitaemia observed in this study has been previously noted for malaria infection due to *P*. *falciparum* [[22,23]](#_bookmark12).

We further observed low value of differential WBC counts among infected malaria patient as compared to uninfected ones. This finding is in direct contrast with report of Ladhani et al. [[42]](#_bookmark19) but consistent with many studies [[30,22,43]](#_bookmark17). The association of *P. falciparum* malaria to low WBC count has been suggested to be attributable to sequestration and accelerated destruction of leuko- cytes [[44]](#_bookmark20). Further studies have shown that the production of proinflammatory cytokines by parasite immunogenic antigen (Gly cosylphosphatidylinositol) increase phagocytosis of RBC and WBC,

thus causing TNF-a, causing altered hemopoiesis [[45,46]](#_bookmark21).

Cytokines are considered to act as double-edged swords in the pathogenesis of malaria, especially in *P. falciparum* infections [[47,48]](#_bookmark26). The high levels of innate immune response in malaria infec- tion is driven by malarial pigment (hemozoin, Hz), and glycosylphos- phatidylinositols (GPIs) in the circulating monocytes and neutrophils, and resident macrophages [[49,50,44]](#_bookmark22). In this study, plasma concen-

trations of TNF-a, IFN-c, IL-10 and IL-12 increased with increasing

parasite density and it is in accordance with the report of Mugweru and his colleagues [[51]](#_bookmark22). However, T-helper cell type 1 cytokines is essential to achieve elimination of infection with less damage to the host. Walther et al. [[52]](#_bookmark22) noted that expression of these pro- inflammatory cytokines may have far reaching consequences on dis- ease outcome such as fever, paroxysms, anaemia, cerebral malaria and many other systemic infection symptoms [[51,53–55]](#_bookmark22). It has been

postulated that induction of TNF-a delocalizes ferroportin in the

reticuloendothelial system that mediates stimulation of macrophage and intestinal iron absorption. This, however, decreases iron absorp- tion and enhances the release of hepcidin to the circulation, which its increased serum level is often associated with severe malaria anaemia [[56,57]](#_bookmark22). Development of Th1 response can be antagonized indirectly by IL-10, which inhibits the production of proinflammatory cyto- kines. IL-10 induces B-cell proliferation. The inhibition of interferon

and TNF-a secretion by IL-10 synthesis has been reported to be

important in counteracting the pathological role of macrophages in cerebral malaria [[58]](#_bookmark23). This accounted for high level of this cytokine and its relative smaller ratio with TNF-a in the infected group and it

is consistent with many other studies [[59,12]](#_bookmark24). Much consistent evi- dence based on experimental models and human *P. falciparum* infec- tion suggests increased IL-10 levels may favor parasite multiplication by inhibiting parasite-killing effector mechanisms in humans and mice [[60,61]](#_bookmark25).

In conclusion, outcome of this study underscores haematologi- cal alterations as the hallmark pathological conditions of malaria infection and their significance in the prediction of severe infec- tion. It also revealed that unregulated interaction of the parasite with host immune response can have important consequences for disease progression. Therefore, it becomes pertinent to incorpo- rate findings of this study in the on-going malaria vaccine and effective therapeutic development.

Acknowledgments

The authors are grateful to the medical directors of children specialist hospital and University of Ilorin Health Centre for their supports. We equally appreciate our participants and our numer- ous project students (Akande, OA; Afolayan, MA; Aderibigbe, EK; Shuaib, AB) for their supports during sample collection and data analysis. We are indeed very grateful to you all.

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