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Titer: TNFα, a Peripheral Marker of a Placental Plasmodium Infection

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ABSTRACT

Introduction: Pregnancy-associated malaria (PAM) remains a public health problem. These consequences result from the placental inflammation responsible for the disruption of maternal-fetal exchanges causing fetal distress, weight loss and spontaneous miscarriages hence the importance of the laboratory diagnosis of placental malaria during the prenatal consultation. It is in this context that this study was carried out and aimed to establish the profile of the concentrations of TNFα in correlation with the PAM.
Material and methods: This was a cross-sectional and analytical study carried out in the maternity ward of the Talangai referral hospital (R. of Congo). Thick gout, placental appositions and TNFα assay were performed with peripheral blood, placenta and cord blood.
Results: The incidence of plasmodium in peripheral blood, placenta and umbilical cord was 36.54%, 23% and 7.84%, respectively. There was no statistically significant difference in the distribution of peripheral blood, placenta and cord parasitaemia. TNFα of the placenta was significantly higher than peripheral TNFα. Peripheral blood TNFα correlated with peripheral parasitaemia and placental TNFα concentration.
Conclusion: The peripheral, placental and cord malaria index of pregnancy-associated malaria in our study remains of concern, especially since the study population was from an urban setting. TNFα concentrations have shown interesting patterns and correlations that may be predictive of placental infection.

Key words: malaria, placenta, cytokines, incidence, diagnosis.

INTRODUCTION

Malaria harms the health of the mother, puts her at increased risk of death and impacts the health of the fetus, resulting in prematurity and low birth weight. It is in this context that The WHO World Malaria Report 2019 includes a special section on the burden of malaria and its consequences in women and children.

In the context of the biological management of PAM, the direct or indirect demonstration of the presence of plasmodium is a problem that has been resolved at the present time. However, despite numerous funding from the United Nations and private partners, the biological boundary between symptomatic and asymptomatic malaria remains a puzzle. Several studies according to location and population have been carried out to evaluate the production of Ig and cytokines which are indicative of active malaria infection at the peripheral or placental level [1, 2, 3]. It follows that peripheral biomarkers of

placental inflammation may be of particular interest in the biological monitoring of pregnant women.

Pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, can be protective against malaria by their ability to induce the destruction of parasites by monocytes / macrophages and neutrophils [2, 4]. IL-10 is an essential cytokine for both protection and immunopathology in malaria. The elevated IL-10 levels observed during episodes of malaria may be beneficial by reducing the inflammatory response, but may be detrimental by decreasing the cellular immune responses to parasite control. At most, studies have shown that peripheral blood levels of IL 10 increase when parasites bind to CSA (Chondroitin Sulfate A) [5, 6, 7].

In view of the above, the identification of key immune mediators, peripheral witnesses of placental malaria in childbirth still requires specific research to refine the number of determinant biomarkers. To do this, the main objective of this work was to study the profile of TNFα concentrations in correlation with PAM.

METHODOLOGY

The study was carried out at the Talangai Base Reference Hospital in the Department of Brazzaville in the Republic of Congo. The biological analyzes took place in the Laboratory of Training, Research and Biomedical Analysis of the Faculty of Health Sciences of the University Marien Ngouabi in the Republic of Congo.

It was an analytical cross-sectional study that took place over a period of 6 months. Simple random draw was the sample collection method used. The study population consisted of all HIV-negative women coming to the center for childbirth, 56 pregnant women, divided according to:

- the presence or absence of plasmodium in peripheral blood, placenta and cord;
- taking prophylactic treatments: G1, no prophylaxis (intermittent preventive treatment with sulfadoxine-pyrimethamine or other treatments), G2, irregular prophylaxis, G3, regular prophylaxis.

Heavy gout was performed routinely in all women giving birth. The thick drop of peripheral blood and cord was stained with 10% diluted Giemsa supplemented with a rapid diagnostic test (RDT). Parasite density was assessed by counting the number of parasitized in proportion to the number of leukocytes on a field microscope and a double-blind reading was taken by two experienced microscopists.

A volume of 2 to 5 ml of blood was drawn in an EDTA tube and in a dry tube during childbirth. Two appositions on the maternal side of the placenta were made, fixed in air and stained with MGG (May Grumwald Giemsa). The elements sought were parasitized red blood cells and intra-macrocytic pigments. Placental malaria infection is diagnosed by the presence of trophozoites or schizonts. The Blood Formula Count was performed using an impedance variation technology hematology meter (Yimuzen H550).

Plasma concentrations of TNF-α were determined by the Elisa method. The DIAsource TNF-α-ELISA kit is a solid phase "Enzyme Amplified Sensitivity Immunoassay" performed on microplates. The assay uses monoclonal antibodies directed against distinct epitopes of TNF-α. Calibrators and samples react with monoclonal capture antibody covering the wells and with monoclonal antibody labeled with peroxidase. Enzymatically labeled bound antibody is measured with a chromogenic reaction. Optical densities were determined by the PHOMO ELISA reader using a 450nm filter.

The realization of this project to respect the ethical rules of research involving human beings (Declaration of Helsinki and CIOMS). The protection of personal data and the confidentiality of the results was ensured by coding the names and the results are issued only to the participant alone.

Statistical analysis was done on Excel and on Graph pad software.

RESULTS

- ***Sociodemographic characteristics of the study population***

The sample size was 56 pregnant women. It was divided into three groups: no prophylaxis, G1 (IPT and others), irregular prophylaxis (G2), regular prophylaxis (G3). The G2 group of pregnant women with irregular prophylaxis methods was the most representative with 50.41%.

The distribution of pregnant women by age group showed that the age extremes ranged from 15 to 40 years with an average age of 25.29 ± 6.45. The majority age group of pregnant women was that of 20 and 35 years, followed by the age group ≤ 19 years with a statistically significant difference between age group (Ordinary one-way ANOVA, P value: 0.0003).

The comparison between different methods of antimalarial chemotherapy (G1, G2, G3) and the socio-demographic characteristics was presented in Table I.

Table I: Comparison between different methods of antimalarial chemotherapy (G1, G2, G3) and socio-demographic characteristics.

Parameter	P value	Significance
Niveau d'instruction vs G1, G2, G3	0,5859	NS
Age maternel vs G1, G2, G3	*0,5046*	NS
Gravidity vs G1, G2, G3	*0,3609*	NS
Parity vs G1, G2, G3	: 0,8857	NS

NS : Not Significant, vs ; face

- ***Characteristics of biological parameters***

Incidence of malaria in peripheral blood and placenta

The incidence of malaria in peripheral blood in our study was 36.54% and placental blood was 23.53%. The incidence of malaria in the cord blood was 7.84%.

Table II: Distribution of parasitaemia and TNFα level in peripheral blood and placenta.

	Peripheral blood parasitaemia		Placental blood parasitaemia	
	Mean (n)	**Pvalue**	**Mean (n)**	**Pvalue**
Gestity				
Primigeste	244 (15)	0,2394	1467 (15)	0,2841
Multigeste	1233 (37)		513,9 (36)	
Parity				
Primipare	487,8 (16)	0,3536	1375 (16)	0,356
Multipare	1275 (34)		531,3 (32)	
	TNFα peripheral blood		TNFα placental blood	
	Mean (n)	Pvalue	Mean (n)	Pvalue
Apposition/ GE négatif	0,105 (28)	0,2145	0,2288 (31)	0,2596
Apposition/ GE positif	0,1291 (14)		0,1690 (11)	

n : effective *GE : thick drop*

Comparison of the concentration of parasitaemias between the peripheral, placental and cord level

The distribution of peripheral blood, placenta and cord parasitaemia was shown in Figure 1.

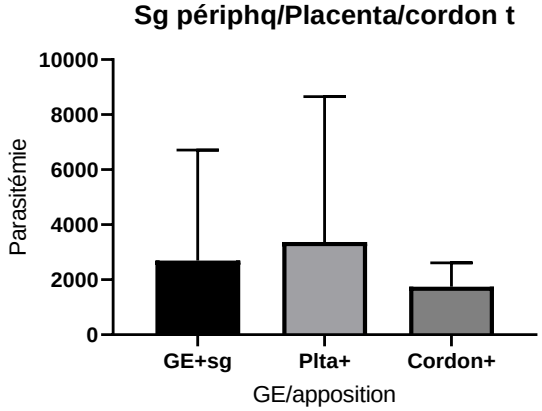

Figure 1: Distribution of peripheral blood, placenta and cord parasitaemia

There was no statistically significant difference in the distribution of peripheral blood, placental and cord parasitaemia (ANOVA, P = 0.7966).

Comparison of TNFα concentration between peripheral and placental level

The distribution of TNFα concentrations at the peripheral and placental level was shown in Figure 2.

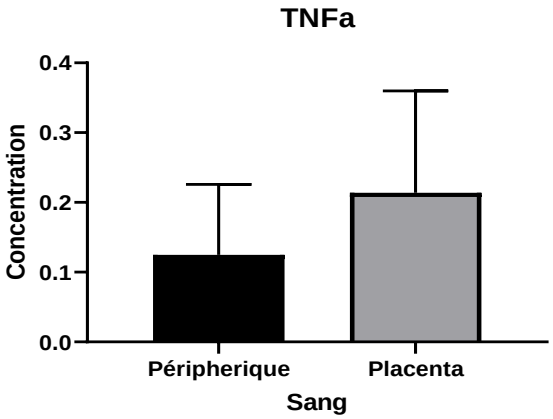

Figure 2: Distribution of the TNFα concentration at the peripheral and placental level.

The distribution of TNFα concentrations at the peripheral and placental level showed a statistically significant difference (Paired t test, P value: 0.0017). The mean of the TNFα concentration in peripheral blood in our study was 1.06 pg / ml with extremes between 0.94 and 1.99 pg / ml, the mean of the TNFα concentration in the placenta was 1, 21pg / ml with extremes between 0.97 and 2.60pg / ml.

Correlations between TNFα levels and peripheral and placental parasitaemias

The correlations between TNFα levels and parasitaemias at the peripheral and placental level were shown in Table III.

Table III: Correlations between the levels of TNFα and the parasitaemias of the peripheral and placental level.

		Peripheral parasitaemia	Peripheral TNFα	Placental TNFα
Placental parasitaemia	R		-0,1209	-0,1541
	Effective		40	42
	P (two-tailed)		0,4575	0,33
	Significance		No	No
Placental TNFα	R	0,08149	0,01796	
	Effective	42	42	
	P (two-tailed)	0,6079	0,9079	
	Significance	No	No	
Peripheral TNFα	R	0,392		
	Effective	42		
	P (two-tailed)	0,0102		
	Significance	Yes		

DISCUSSION

- ***Sociodemographic characteristics of the study population***

The study of socio-demographic characteristics was based on the factors influencing the fight against malaria in pregnant women. Thus women giving birth were divided into three groups.

In the present study, the age factor had no impact on the use of antimalarial drugs for prevention. Famanta et al. in 2010 corroborated the same assertion in their work in Mali [8].

Parity and gestity reflected the experience of parturients in managing a pregnancy. They did not have a significant impact on the use of antimalarial drugs for

prevention (Table I). These results are in agreement with those of Bakoua and al. in 2010 and Guindo et al. in 2007 [9, 10].

Biological parameters

- ***The peripheral blood plasma index***

The incidence of plasmodia in peripheral blood in our study was 36.54%. This result was similar to those of Samia Omer in 2017 in Sudan, Bouyou in 2010 in Gabon and Achidi in 2007 in Cameroon who reported 37.8%, 27.6% and 25.4% respectively [11, 12, 13]. Diagne et al. in 2000 had obtained from thick drops of peripheral blood a plasmodic index of 56% [14]. However, these results were higher than those of Bakoua in 2010 in Congo, of Guindo in 2007 in Mali and of Elghazali in 2003 in Sudan which had respectively 6.1%, 9.1% and 5.6% [9, 10, 15]. These differences could be explained by the following factors: stable or weak transmission zones, annual rainfall period, urban or peri-urban environment and the choice of the study population (on intermittent preventive treatment or not).

There was a statistically significant difference in the distribution of parasitaemia between groups of women. However, the mean G1 parasitaemia of parturients without prophylaxis was higher than those of the G2 and G3 groups. These results demonstrate the impact of chemotherapy on the parasite load corroborated by numerous previous studies [16, 17, 18]. The mean of the parasitaemia of the G3 group, with regular treatment, was higher than that of the G2 group, with irregular treatment, which was in contradiction with the literature [19, 20, 21, 18]. Responses from parturients during the survey may explain this observation.

Although some authors have reported an association between the Plasmodium Index and pregnancy, in our study the relationship between the two parameters was not established (P value: 0.6261). There was also no statistically significant difference between parasitaemia and parity (P value: 0.8692). Guindo and al. in 2007, Elghazali and al. in 2003 corroborated this assertion [10, 15]. The random selection of largely asymptomatic parturients and the stable transmission area of our study could explain these results.

43% of parturients in our study had moderate anemia and 4% severe anemia. The anemia rate in our study was characteristic of developing countries, ranging from 9% to 60% (WHO, 2005) and is close to those observed by Nosten and al. 1991 with 35.4%, Luxemburger and al. 1997 in Thailand with 40%, Diarra and al. 2003 in Mali with 54.5% and Sidibé et al. 1992 with 58.4% [22, 23, 24, 25].

- ***Placental Blood Plasmodium Index***

We chose placental apposition as one of the indicators of malaria in childbirth because of its easy realization and greater sensitivity compared to thick peripheral blood drop [26]. Compared to low birth weight or anemia, it is not multifactorial and depends only on the presence of the parasites.

The prevalence of placental malaria was 23% in our study. This result was significantly lower than that of Samia Omer in Sudan (58.9%) and higher than those obtained by Ndao in Senegal (8.1%), Guindo in Mali (10.3%) and Jyoti Singh in India (12%) [11, 27, 10, 28]. Taking preventive antimalarial treatments during pregnancy and the area of seasonal transmission could explain this difference. In fact, 72% of parturients in the Ndao study compared to 8.13% in our study declared that they had followed their prevention on a regular basis [27].

The distribution of placental parasitaemia according to pregnancy was not statistically significant (Table II). However, the mean placental parasitaemia in the primigravidae in our study was higher than the average in the multigest. Likewise, the mean parasitaemia of primiparas was higher than that of multiparas. These results were consistent with the hypothesis that the acquisition of humoral antimalarial immunity increased in proportion to the numbers of exposure. This assertion was not

verified at the peripheral blood level in our study (Table II). This lack of correspondence could be explained by the complexity of the immune response associated with the ranking aspect (primi, pauci, multi ...) of gestity and parity.

- ***Profile and correlations of TNFα concentrations in peripheral and placental blood***

The TNFα concentrations of parturients with positive and negative heavy gout did not show significant differences. However, the mean TNFα concentrations of parturients with heavy gout positive were higher than those with heavy gout negative. These results showed that the presence of Plasmodium through the molecular patterns associated with pathogens activates the effectors of immunity, hence the increase in the concentration of TNFα.

Peripheral blood parasitaemia showed a significant correlation with peripheral TNFα concentrations. These results agree with the observations of Kern and al. in 1992, Gonçalves and al. in 2012 that TNFα has a biological activity on plasmodium infection by activating parasite clearance [29, 30]. Likewise, Grau and al. in 1989, Michal Fried and al. in 2017 corroborated this assertion by associating the increase in TNFα with severe malaria syndromes [31, 32]. In view of the above, the TNFα level could be considered as a determining biomarker, indicating an active infection of the plasmodium in the peripheral blood. Thus, determining the concentration of peripheral TNFα could be an essential complementary laboratory diagnosis for thick gout since it expresses an active immune response.

The mean of the TNFα concentration at the peripheral level was correlated with the mean of the TNFα concentration at the placenta (Table III). The mean TNFα concentration in the placenta was significantly higher than that in peripheral blood (Figure 2). These results show that the concentration of TNFα at the peripheral level could predict placental malaria infection by indicating a pro-inflammatory reaction.

TNFα being a mediator of the pro-inflammatory reaction; these results could also reflect the susceptibility of the placental environment to molecular patterns associated with pathogens of Plasmodium. In addition, the placenta represents the sequestration medium for parasitized erythrocytes or the site of induction and action of TNFα. Pamela and al. in 2011 demonstrated in mice the consequences of TNFα following the induction of TLR4 by LPS (lipopolysaccharides) on the end of gestation [7]. Grau and al. in 1989 observed in their study the elevated placental concentrations of TNFα in relation to miscarriages although it was possible to establish with certainty the relationship between elevated concentrations at the placental level of TNFα and other malaria infection syndromes such as episodes of fevers [31].

Peripheral TNFα concentrations did not correlate with placental parasitaemia. This result is in the same direction as that of Figure 1 which showed a non-significant difference between peripheral, placental and umbilical parasitaemia.

The lack of correlation could be explained by the complexity of the immune response, in particular at the level of immunological mediators which are characterized by pleiotropism and redundancy. The largely asymptomatic nature of our parturients could explain the lack of significance in the statistical analysis of certain biological variables. It is in this dispute that certain authors such as Michal Fried and al, in 2017, Diouf and al. in 2015, Whitney and al. in 2011 were unable to establish these correlations with certainty [17, 32, 33].

CONCLUSION

The peripheral, placental and cord plasmodium index of malaria associated with pregnancy in our study remains of concern, especially since the study population was urban, i.e. accessible to

health services. Thus, the reassessment of socio-demographic and therapeutic factors in the fight against malaria in pregnant women in this study area is highly desirable.

TNFα concentrations presented interesting profiles in peripheral and placental blood in our study. Our results had shown that the concentration of TNFα in the peripheral blood of parturients was associated with peripheral parasitaemia and the concentration of placental TNFα. Peripheral TNFα concentrations could thus predict placental infection.

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