Full Length Research Paper

Altered total cholesterol and triglyceride levels during the course of *Plasmodium falciparum* infection in children

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Changes of lipid parameter concentrations are observed in patients suffering from malaria. However, there are few data on their evolution during the course of the infection and their relationship with the infection parameters. The levels of triglycerides (TG) and total cholesterol (TC) were measured during and after uncomplicated *Plasmodium falciparum* malaria in 122 children. The relationship with the antimalarial drug treatment, the parasite density and haemoglobin levels was also assessed. Mean TG levels were high before the treatment (1.9 ± 1.2 mmol/L) and at day 3 post-treatment (2.3 ± 1.3 mmol/L), then subsequently decreased to reach normal level from day 7. A negative correlation was found between haemoglobin (Hb) levels and TG (rho = -0.47; *p* < 0.01); previous high parasitaemia at inclusion was associated with a subsequent increase of TG levels after treatment administration. The majority of patients with hypertriglyceridemia were anaemic at day 3 (n = 20/20) and at day 7 (n = 18/19). Only 5 (4.1%) patients had hypertriglyceridemia at day 28. A trend toward a negative correlation between TC levels and parasite density was observed (rho = -0.18; *p* = 0.05). Mean TC concentration was significantly lower at day 0 when all the patients were parasitaemic (3.0 ± 1.0 mmol/L) compared to day 3 (3.7 ± 1.2 mmol/L) (*p* = 0.01). Mean CT was low during the first week and at day 28, 71 (58.2%) children still had a subnormal CT levels. No relationship was found with the type of antimalarial drug. Transient hypertriglyceridemia and hypocholesterolemia are observed during the course of *P. falciparum* infection. High TG levels seem to be related to the malaria related haemolysis.

Key words: Malaria, cholesterol, triglycerides, antimalarial, Gabon.

INTRODUCTION

Lipid parameter changes have been reported during the course of malaria infection. Although the mechanisms involved are not fully understood, some hypotheses have been raised from *in vivo* and *in vitro* studies (Cuisinier et al., 1990; Visser et al., 2013). Some fatty acids are produced and required for the parasites biosynthetic

pathways. Extracellular lipids are also implicated in *Plasmodium (P.) in vitro* growth (Vial et al*.,* 2003; Elford et al*.,* 1995). Cholesterol and triglycerides are the most common studied lipid parameters during malaria infection. Concerning cholesterol, it is now admitted that cell membrane cholesterol is implicated in the immune evasion and the pathogenesis of malaria due to *P. falciparum* (Sein and Aikawa, 1998; Bansal et al., 2005). Both parameters have been associated with the intra-erythrocytic parasite development and the maintenance of trophozoïtes stage (Sherman, 2003; Vial et al., 1999). It is also suggested that cholesterol metabolism involved in the parasite growth could be used as target for new treatments and cholesterol and triglyceride serum level modifications during malaria used as diagnostic tools (Kitt et al., 1992; Badiaga et al., 2002; Mitamura et al., 2003).

Controversial data are reported concerning total cholesterol and triglyceride levels during plasmodial infection; hypocholesterolemia and hypercholesterolemia are reported during the acute phase of the infection; hypertriglyceridemia is often described during the first two weeks of the infection (Parola et al., 2004; Ayoola et al., 2012). However, very few studies have examined the *in vivo* relationships between the levels of these lipids and the factors implicated in the pathophysiology of clinical malaria. Liver function disorders and anaemia caused by red blood cell destruction are the main markers of uncomplicated malaria beside fever. They are charac-terized by a decrease in hemoglobin levels and an increase in liver enzymes. Exogenous lipids used by the parasite could be derived from either the red cell membrane that contains phospholipids or liver where some are synthesized (Haldar et al., 2002). Furthermore, antimalarial treatment has been shown to be responsible for changes in triglycerides and cholesterol levels in patients with malaria (Davis et al., 1995; Bouyou-Akotet et al., 2010). Thus, the present study was designed to analyze the relationship between parasitaemia, total serum cholesterol, triglyceride and hemoglobin levels, in *P. falciparum*-infected patients treated with different antimalarial drugs.

MATERIALS AND METHODS

Study site

This was an analytical study performed at the Department of Parasitology of the Faculty of Medicine of Libreville, the capital city of Gabon. This country is considered hyper- to meso-endemic with a malaria prevalence ranging from 11 to 39.5% (Mawili-Mboumba et al., 2013).

Study population

Data were collected from children aged six months to 10 years suffering from uncomplicated malaria who took part in two clinical trials performed between 2005 and 2006 as described elsewhere (Bouyou-Akotet et al., 2010; Nsimba et al., 2008). These patients were treated either with amodiaquine (AQ), sulfadoxine-pyrimethamine (SP) or artesunate-mefloquine (AM) according to their age and/or weight following World Health Organization (WHO) guidelines. They were included with the following criteria: presence of *P. falciparum* mono-infection, fever or history of fever during the last 24 h, absence of signs of severe malaria, malnutrition or other severe underlying infectious or chronic disease.

Procedures

Eligible children were hospitalized during three days and followed up until day 28 (D28). At inclusion, clinical and socio-demographical data (age, sex and body mass index, BMI) were recorded. Biological data which included malaria diagnosis results, hemoglobin (Hb), triglycerides (TG) and total cholesterol (TC) measurements performed at day 0 (D0) prior to the administration of the antimalarial, day 3 (D3), day 7 (D7) and day 28 (D28) were used for the analysis. According to the design of the clinical trials, Hb was not measured at D3 for AQ and SP treated patients, at D7 for AM patients as well as TC at D7 for AM patients

P. falciparum infection was detected by microscopy using the Lambaréné method (Planche et al., 2001). Briefly, thick smears were prepared as follows: 10 µl of blood were layed on a 10 by 18 mm area of a microscope slide, then dried and stained with 10% giemsa. The parasitaemia was expressed as number of parasites per microliter of blood (p/µl). Smears were read by two experienced technicians using a light microscope (× 100 oil immersion lenses). They were considered negative if no parasite was seen after the examination of at least 100 oil immersion fields in a thick blood smear.

Hb measurements were performed using a Coulter counter (SKTS, Coulter Corporation). Total cholesterol and triglyceride concentrations were determined by using standard enzymatic procedures on an automatic clinical chemistry analyser (Visual, Biomerieux®).

Definitions

Anaemia was defined as an Hb concentration below 11 g/dl, hypocholesterolemia or low total cholesterol when serum cholesterol level was below 4.0 mmol/L and hypertriglyceridemia when serum triglyceride level was higher than 1.88 mmol/L.

Ethical considerations

The study was approved by the public health ministry of Gabon. The clinical trials performed for AQ, SP and AM evaluation were all approved by the National Ethics Committee. None of the children required additional blood collection for this study and data were analyzed for the patients with available blood smears, Hb and biochemistry results. The children's parents or guardians were informed about the study, and their oral consent was required prior to data use.

Data analysis

Demographic and laboratory data of patients were entered into Epi-info version 6.0 (February 9, 2005 CDC Atlanta) database and

Table 1. Distribution of biological parameters according to the day of follow up and the treatment.

Parameter	D0	D3	D7	D28	p
Parasitaemic	122 (100.0)	38 (31.1)	0 (0.0)	0 (0.0)	<0.01
Anaemic [n (%)]	109 (89.3)	34* (100.0)	107(87.1)	69 (56.6)	<0.01
Triglycerides					
Hypertriglycéridemia [n (%)]	48 (39.3)	70 (57.4)	19 (21.6)	5 (4.1)	<0.01
Mean TG concentration, mmol/L (±SD)					
Study population	1.9 (±1.2)	2.3 (±1.3)	1.4 (±0.5)	1.0 (±1)	<0.01
-AQ	1.8 (±0.7)	1.9 (±0.8)	1.3(±0.6)	0.9 (±0.4)	0.03
-AM	1.8 (±0.9)	2.7 (±1.8)	1.3 (±0.5)	0.8 (±0.7)	<0.01
-SP	2.0 (±1.6)	2.4 (±1.1)	1.5 (±0.6)	1.3 (±0.6)	<0.01
Total cholesterol					
Hypocholesterolemia [n (%)]	109 (86.9)	83 (68.0)	(51.0)	71 (58.2)	<0.01
Mean TC concentration, mmol/L (±SD)					
Study population	3.0 (±1.0)	3.7 (±1.2)	4.0 (±1.1)	3.9 (±1.9)	0.03
-AQ	3.7 (±0.6)	3.8 (±1.3)	3.9(±1.1)	3.5 (±0.7)	NS
-AM	2.6 (±0.6)	3.5 (±0.9)	**	4.3 (±1.0)	<0.01
-SP	3.4 (±1.1)	3.9 (±1.2)	4.1 (±1.1)	4.0 (±0.9)	<0.01

*Hb levels available only for AM patients, **Biological tests not performed.

exported into Stata 9.2 (Stata Corporation, College Station, TX USA) for analysis. Median parasitaemia was estimated only in the group of patients with positive blood smears. Variables were summarized as frequencies, means ± standard deviation and median (25th to 75th percentiles) for the parasite density. Differences between groups were assessed using chi-squared or Fisher's exact tests for proportions, Student's t-test and analysis of variance (ANOVA) or Kruskal-Wallis test or Wilcoxon as appropriate for continuous variables. The Spearman rank test was used to identify the correlations. A *p*-value less than 0.05 was considered significant.

RESULTS

Total cholesterol and triglyceride levels were measured in sera from 122 children followed up during 28 days post-treatment. Their mean age and body mass index (BMI) were 35 ± 15 months, 15 ± 2 kg/cm^2 and 52 (43%) were girls. According to the treatment, 40 (33%) received AQ, 48 (39%) SP and 34 (28%) AM.

Evolution of parasite density and Hb levels

At D0, the parasite density of AQ and SP patients was 12500 (3810 to 25040) parasites/µl (p/µl); it was 50225 (17150 to 171500) p/µl in the AM group. At D3, 1 (0.3%) AM, 14 (35%) AQ and 23 (5%) SP treated children were still parasitaemic (*p* < 0.01). From D7, there was no

detected microscopic infection in the whole study population. The mean Hb level remained below 12 g/dl during the follow-up. It significantly increased in the whole study population, varying from 8.6 ± 1 g/dl at D0 to 10.8 ± 0.9 g/d at D28 (*p* < 0.01). At D3, the mean Hb was 8.6 ± 1.0 g/dl in the group of patients treated with AM; at D7, it was 9.3 ± 1.4 g/dl and 9.1 ± 0.9 g/dl in the AQ and SP groups, respectively.

Relationship between of lipid levels and the type of antimalarial drug

Both lipid parameters, TC and TG, were modified at inclusion and their profile was subnormal or normal from D7 within each group of treatment (Table 1). Mean TG significantly decreased between D0 and D3 and reached a normal level from D7. TG concentration was the highest at D3 in AM patients (Table 1). Mean CT was the lowest at D0 when all the patients were parasitaemic, it significantly increased until D28 (Table 1). Overall, no change in TC and TG was related to any specific antimalarial.

P. falciparum infection and lipid parameters

Patients with malaria had a higher mean level of TC at D3 compared to D0 (*p* < 0.01) (Table 2). Indeed, a non-

Table 2. Lipid levels (mmol/L) according to the presence of malaria and anaemia.

| Parameter	*P. falciparum* infection			Anaemia		
	Yes	No	P	Yes	No	P
DAY 0, n	**122**	**0**		**109**	**13**	
Total cholesterol, mean (±SD)	3.0 (1.0)	NA	-	2.3 (1.0)	3.3 (0.1)	0.15
Hypocholesterolemia,n(%)	106 (86.9)	NA	-	96 (88.1)	10 (76.9)	0.23
Triglycerides, mean (±SD)	1.9 (1.2)	NA	-	2.0 (1.2)	1.3 (0.6)	0.01
Hypertriglyceridemia, n(%)	48 (39.3)	NA	-	45 (41.3)	3 (23.1)	0.23
DAY 3, n	**38**	**84**		**34***	**0**	
Total cholesterol, mean (±SD)	3.8 (1.1)	3.7 (1.3)	0.4	3.5 (0.9)	NA	-
Hypocholesterolemia,n(%)	22 (72.6)	61 (57.9)	0.3	26 (76.5)	NA	-
Triglycerides, mean (±SD)	2.0 (1.2)	1.8 (1.3)	0.3	2.7 (1.8)	NA	-
Hypertriglyceridemia, n(%)	20 (52.4)	50 (59.5)	0.4	20 (58.8)	NA	-
DAY 7, n	**0**	**88****		**69**	**19**	
Total cholesterol, mean (±SD)	NA	4.0 (1.1)	-	4.0 (1.1)	4.3 (1.4)	0.6
Hypocholesterolemia,n(%)	NA	45 (51.1)	-	41 (59.4)	4 (21.0)	0.01
Triglycerides, mean (±SD)	NA	1.4 (0.6)	-	1.5 (1.2)	1.3 (0.8)	0.3
Hypertriglyceridemia, n(%)	NA	19 (21.6)	-	18 (26.1)	1 (0.05)	0.03
DAY 28,n	**0**	**122**		**69**	**53**	
Total cholesterol, mean (±SD)	NA	3.9 (1.9)	-	3.8 (1.0)	4.0 (0.9)	0.3
Hypocholesterolemia,n(%)	NA	71 (58.2)	-	43 (62.3)	28 (32.8)	0.01
Triglycerides, mean (±SD)	NA	1.0 (1.0)	-	1.2 (1.3)	0.9 (0.4)	0.04
Hypertriglyceridemia, n(%)	NA	5 (4.1)	-	45 (41.3)	3 (23.1)	0.04

significant negative correlation was found between the parasite density and TC level at D0 (Rho = -0.18; p = 0.05), whereas it was Rho = -0.02 (p = 0.8) at D3 when the parasitaemia was the lowest, 140 (80 to 400) p/µl versus 16250 (4500 to 37500) p/µl at D0. Moreover, hypocholesterolemia decreased from 86.9% at day 0 to 68.0% at day 3 (p < 0.01) (Table 1). Patients treated with AM who had the highest median parasite density (50225 versus 12500 p/µl) also had the lowest mean CT before treatment administration (Table 1). No relationship was found between mean TG levels and *P. falciparum* parasite density at inclusion: there was no correlation (Rho = 0.1; p = 0.3) and no difference in parasite density between the group of patients with hypertriglyceridemia (19250 [4100 to 67725] p/µl) and those with normal TG (13750 [4000 to 34200] (p = 0.5). However, a trend toward a positive correlation between parasite density and TG concentration existed at D3 (Rho = +0.27; p = 0.07). D0 parasitaemia and TG at D3 in the same patients were strongly correlated (Rho = +0.34; p < 0.01). Likewise, at D3, the mean TG concentration was the highest among the AM patients who had the highest mean parasitaemia at D0 before the treatment administration (Table 1).

Anaemia and lipid parameters

There was a significant negative correlation between HB level and TG (Rho = -0.41; p < 0.01) at D0, it varied from Rho = -0.22 (p = 0.1) at D3, Rho = -0.30 at D7 to Rho = -0.14 (p = 0.1) at D28 when none of the children were parasitaemic. Furthermore, from D0 to D7, a drop of 0.7 to 1.1 g/dl of the mean Hb levels was observed in patients with hypertriglyceridemia (8.2 to 8.6 g/dl), while it was less than 0.6 g/dl in those with a normal TG level (8.9 to 9.5 g/dl) (p < 0.04) (Figure 1). Among the 34 and the 88 patients seen at D3 and D7, respectively, the near total of those with hypertriglyceridemia (n = 20/20 at D3 and n = 18/19 at D7) were anaemic (Table 2). CT levels were not significantly correlated to Hb concentration with a Rho varying from -0.02 to -0.13 (p > 0.1). Likewise, mean Hb remained comparable throughout the follow-up in case of hypocholesterolemia (8.9 to 10.8 g/dl) or normal cholesterol (9.0 to 10.9 g/dl) (Figure 1b), although the frequency of hypocholesterolemia remained important

A
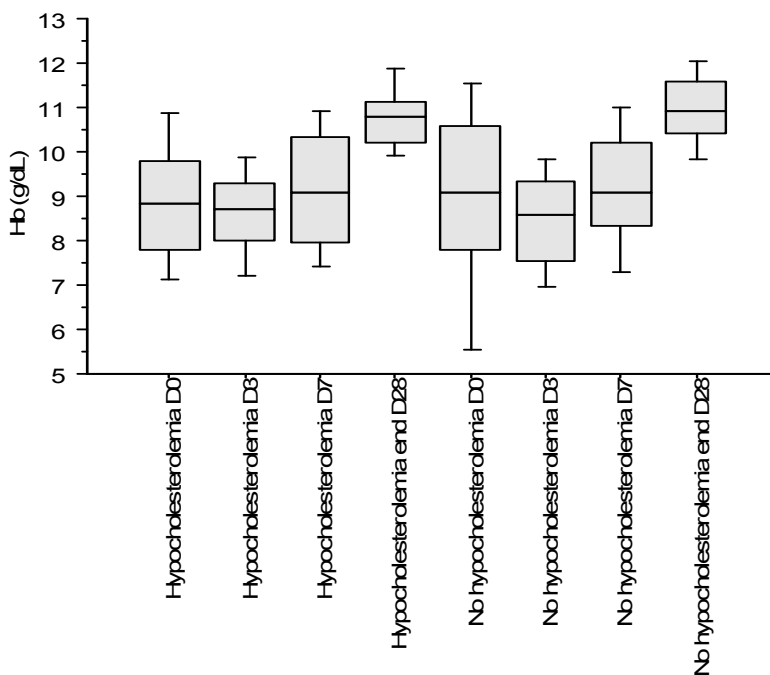
B
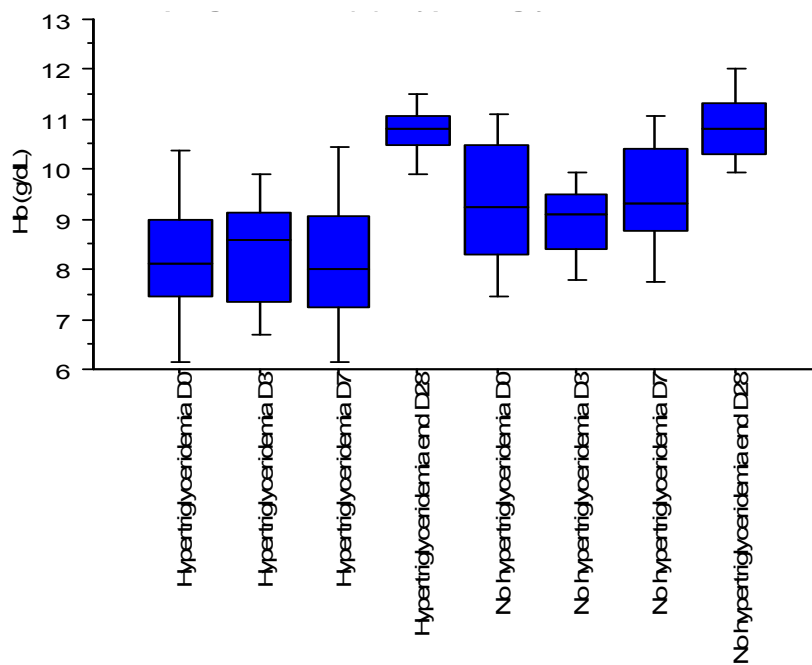
Figure 1. Box plots of hemoglobin levels during the follow-up according to the presence or the absence of hycholesterol emia (A) and hypertriglyceridemia (B).

after the disappearance of parasites (Table 2).

DISCUSSION

The present study confirmed that *P. falciparum* infection is characterized by hypertriglyceridemia and hypo-cholesterolemia. The decline of TC and the raise of TG observed have been shown to be more pronounced during malaria episode (Visser et al., 2013). In agreement with previous reports, these modifications that are accentuated during the parasitaemic phase of the disease are transient and present in both complicated and uncomplicated malaria compared to other febrile diseases (Batista et al., 1996; Badiaga et al., 2002). Few studies have analyzed the impact of the treatment on both lipid parameter profiles. Their evolution is not specific to any antimalarial drug, although the normalization of mean total cholesterol and TG levels were concomitant to the decrease of the parasite density and prevalence observed from day 7 post-treatment. TC levels seem to slowly normalize as highlighted by the borderline mean level (3.9 mmol/L) determined at day 28. Other authors reported a period of two weeks to six months after antimalarial treatment for TC normalization, whereas TG usually normalize within two weeks (Kim et al., 2008).

The study population was composed of patients who participated to three clinical trials, thus without any significant co-infection. One can assume that the lipids changes observed are specific to malaria, although they exist in other diseases. Nevertheless, other risk factors for hypocholesterolemia and hypertriglyceridemia such as ethnicity, socioeconomic status, type of alimentation, other hematological disorders or infectious diseases should be also recorded and considered to have a complete interpretation of these observations (Hoffmeister et al., 2001; Bansal et al., 2005; Feingold et al., 1993).

TG levels are found significantly higher in malaria patients, their level seem to increase with the severity (Maguire et al., 1991; Mfonkeu et al., 2010). It is not known if the malaria parasite produces essential lipids for its development or if it induces host lipid hyperoxidation. However, the present data highlight a clear relationship between high TG level and anaemia, an association which was stronger after antimalarial drug administration in patients with high parasite density. One hypothesis is that these TG are derived from the phospholipids released by the red blood cell membrane following hemolysis. Although this way has never been investi-gated, hypertriglyceridemia is described in diseases with haemophagocytosis (Visser et al., 2013). During malaria, oxidative derivate production is one of the host mechanisms of defense against the parasite. This oxidative stress induces peroxidation that is deleterious

for the erythrocyte membrane; it is also responsible for an increase of TG which is correlated to lipidic peroxides (Vial et al., 1999).

The occurrence of hypocholesterolemia during plasmodial infection is supposed to be partly host specific due to an acute phase reaction and parasite related factors (Kasturi et al., 2002). HDL cholesterol fraction is the major lipid source for the parasite growth (Faucher et al., 2002). The decrease of cholesterol level seems to be related to the parasite multiplication during its life cycle. Indeed, a mature schizonte is composed of eight to 32 merozoïtes which require cholesterol for their membrane formation, their replication and for the maintenance of their infectivity (Sinnis et al., 1996). Thus the parasite that is able to adapt to low lipid environment uses other lipids sources such as hepatocytes where some lipids are synthesized (Imrie et al., 2004). The fact that the frequency of hypocholesterolemia decreased when the proportion of *P. falciparum* infected decreased is in favor with the use of this lipid by the parasite.

In conclusion, transient cholesterol and triglycerides variations are common during the course of malaria. These modifications last at least two weeks. Hypocholesterolemia is associated with the presence of malaria parasite, whereas hypertriglyceridemia seems to be related to the hemolysis of infected red blood cells. These lipid parameters changes are not related to a specific antimalarial drug.

ACKNOWLEDGEMENT

Conflict of interest

None to declare.

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