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Association of Haptoglobin Gene Polymorphism with Uncomplicated Malaria Cases in Elfasher, Northern Darfur State, Sudan

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Malaria is an acute febrile illness caused by *Plasmodium* parasites. Malaria was one of the major problems in Sudan, recently the emergence of malaria in Northern Darfur lead to the outbreak in the 2018 and 2019 high morbidity and mortality, the host parasites interaction may be one the reason.

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Haptoglobin is an acute phase protein that binds haemoglobin, preventing iron loss and renal damage. It also serves as an antioxidant, has antibacterial activity, and modulates many aspects of the acute phase response.

Methodology: To determine polymorphism in Haptoglobin genes in malaria patients, using polymerase chain reaction (PCR) in Elfasher city Northern Darfur State, durning the transmission season of August 2020 to December 2021.

A total of 142 individuals were included, 26.8% males and 73.2%females. (Data variables were demographic, clinical, parasitological and some hematological parameters), were reported using chi square test. Comparisons of continuous variables using the one-way analysis of variance ANOVA for parametric data and Kruskal Wallis test for non-parametric data. An alpha value of < 0.05 denoted a statistically significant difference in all statistical comparisms.

Results: Association of Hp genotypes and the risk of uncomplicated malaria were analyzed by age and gender. Hp1-1 genotype was most frequency (44.4%) compared to other genotypes. The Hp1-1, Hp2-1 and Hp2-2 genotypes were found in 88.9%%, 100% and 71.1% of female patients, respectively. None of age and gender factors revealed statistically significant association (*P* = 0.05). The Hp2-2 genotype was higher with 89.2% on malaria patients with fever compared to other genotypes. It is possible that the Hp2-2 genotype protects against a range of malaria symptoms, but we did not find a significant association between Hp genotypes and malaria clinical symptoms (*P* = 0.05).

Conclusion: This research revealed that Hp 1–1 and Hp 2–1 genotypes each occur in nearly 4 in 10 children and the Hp 2–2 genotype occurs in 2 of 10 children. There was no correlation with the prevalence of uncomplicated malaria. To fully comprehend the significance of these genotypes in malaria protection, more research on the effects of haptoglobin genotypes on the severity of P. falciparum malaria is required.

Keywords: Haptoglobin; polymorphism; uncompleted malaria; Elfasher.

1. INTRODUCTION

“Malaria is an acute febrile illness caused by *Plasmodium* parasites, which are spread to people through the bites of infected female *Anopheles* mosquitoes. There are 5 parasite species that cause malaria in humans, and 2 of these species – *P. falciparum* and *P. vivax* – pose the greatest threat. *P. falciparum* is the deadliest malaria parasite and the most prevalent on the African continent. *P. vivax* is the dominant malaria parasite in most countries outside of sub-Saharan Africa. It can be asymptomatic or develop into mild symptoms including fever, and a minority of infections progress to severe complications that might result in death” [1].

“In 2020, nearly half of the world's population was at risk of malaria. High risk groups of contracting malaria and developing severe disease are infants, children under 5 years of age, pregnant women and patients with HIV/AIDS, as well as people with low immunity moving to areas with intense malaria transmission such as migrant workers, mobile populations and travelers” [2].

“Haptoglobin is an acute phase protein capable of binding hemoglobin, thus preventing iron loss and renal damage. Haptoglobin also acts as an antioxidant, has antibacterial activity and plays a role in modulating many aspects of the acute phase response. There are 3 major Haptoglobin phenotypes--Hp (1-1), Hp (2-1) and Hp (2-2). Possession of a particular phenotype has been associated with a variety of common disorders (e.g. cardiovascular disease, autoimmune disorders, malignancy), a fact which can only be explained by the idea that possession of a particular phenotype offers some protection against the development of these disorders. Knowledge of phenotype could therefore aid in the prognosis of disease and allow treatment to be better tailored to suit an individual's needs” [3].

“Haptoglobin irreversibly binds oxygenated cell-free hemoglobin, thus preventing the accumulation of free radicals and resultant oxidative tissue damage” [4]. “These complexes are rapidly removed from the circulation by phagocytosis by monocytes and tissue macrophages after binding to their CD163” [5].

2. MATERIALS AND METHODS

This was across sectional study conducted in the different hospitals and Health centers in Elfasher

city of Northern Darfur State during the transmission July to November 2021.

2.1 Sample Size

Sample size was calculated using single population proportion formula and considering the following assumption [6]. The prevalence level of malaria was based on Federal Ministry of Health which is estimated that the prevalence in Sudan was 10.3% with95% confidence interval, 5% marginal error. Finally, a total of 142 patients will be included in the study from health centres and hospitals in Elfasher city

The formula n = 3.84 p (1-p)/ (precision) 2
Proportion=0.103, precision=0.05
$n=3.84*0.103(1-0.103)/ (0.05)^2 = 142$

2.2 Blood Samples

Blood sample was obtained from 142 patient positive for falciparum malaria. In K_2-EDTA and deliver to the haematology laboratory to perform the full blood count using an automated particle cell counter -Sysmex.

2.3 Direct Microscopic Examination

"Thin films were fixed with methanol, and both thin and thick films were stained with 10% Giemsa stain for 15 minutes. All dried slides placed in slides boxes and were examined by laboratory technologist at the health center laboratory in. The presence of malaria parasites on thick blood smear and the identification of *Plasmodium* species from smear was done, through oil immersed objective (100×), at 1000× magnification" [3]. "The thick smear was used to determine whether the malaria parasites were present or absent and thin smear was used to identify the type of *Plasmodium* species. During the microscopic examination, a slide was regarded as negative after 200 fields had been examined without finding of *Plasmodium* parasite by two laboratory technologists. To assure quality of the microscopic examinations, all positive and 10% of the negative slides were reexamined by a third reader to remove discrepant result" [7].

2.4 Rapid Diagnostic Tests for Malaria (RDT)

"Malaria rapid diagnostic tests emerged in the early 1990s into largely unregulated markets, and uncertain field performance was a major concern for the acceptance of tests for malaria case management. RDT was performed in lab from 15 micrometer EDTA blood sample with 2 drops from buffer and the result was recorded within 10 mins" [8-9].

Fig. 1. Sudan map showing location of Northern Darfur State: Source
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2.5 Haptoglobin Genotyping

The Haptoglobin genotype was determined by PCR as described previously [10] with few modifications. Briefly in total volume of 25 µL reactions contained 5µl genomic DNA, 5 µl of ready master mix (Solis BioDyne, Estonia (Qiagen, Hilden, Germany), and 0.25 µmol/L of each primer (A/B). Oligonucleotide primers A and B were used for amplification of a 1757-bp Hp 1 allele-specific sequence and a 3481-bp Hp 2 allele-specific sequence. Primers were purchased from Macrogen, Koria. The amplification reactions were conducted on a DNA Engine Cycler (BioRad) under the following conditions: initial Denaturation for 3 minutes 94°C; 94°C 30 seconds, 57°C primers A/B for 30 seconds, 72°C for 2 minutes, 35 cycles; and final extension for 10 minutes at 72°C. After amplification 10 µL PCR product of A/B primers were separated on a 1% agarose in 1X TBE buffer.

3. RESULTS

Of the142 study subjects, their average age was 26.9 ranging from 10 months to 81 years old. The majority of the patient groups were more than 25 years old (58.5%) compared to less than 25 years old (41.5%). The gender distribution was (26.8%) males and (73.2%) females. The level of hemoglobin were in normal range in malaria patients (mean=10.05) and mean platelet was (220,119). According to parasitemia most of the patients (40.8%) was categorized as intermediate. The characteristics of the study group are summarized in Table 1.

The observed Haptoglobin genotype showed Hp 2-2 (90.1%) more frequent than others Hp genotype. The overall allele frequency for the Hp2 allele was (91.9%), while Hp1 allele occurred at an allele frequency of (8.1%) which was in accordance with the Hardy-Weinberg equilibrium. The distribution of the Hp genotypes in the study is presented in Table 2.

The most frequency of parasite count according to age group was as follows: less than 5 years of ages, 62.5% categorized as intermediate; 5-14 years of ages, 48.0% as intermediate; 15-24 years of ages, 42.3% as slightly high; 25-34 years of ages, 43.8% as slightly high; 35-44 years of ages, 38.9% as slightly high; more than 44 years of ages, 52.9% expressed as intermediate [6]. There was no significant association between age group and parasite count (*P*=0.05*)*.

The association of Hp genotypes and the risk of uncomplicated malaria were then analyzed by age and gender. Among age 25-34 years, Hp1-1 genotype was most frequency (44.4%) compared to other genotypes. The Hp1-1, Hp2-1 and Hp2-2 genotypes were found in 88.9%%, 100% and 71.1% of female patients, respectively. None of age and gender factors revealed statistically significant association *P*=0.05*)* Table 3.

3.1 Distribution of Hp Genotypes by Age Group among Malaria Patients

Of these children group, 33.3% carried the Hp1-1 genotype, 20.0% and 22.7% carried Hp2-1 and Hp2-2 genotypes, respectively. In this figure, the majority of malaria patients were higher in adults with Hp2-1 (80.0%), compared with adults with other genotypes Fig. 2.

Table 1. Table showed the baseline characteristics among patients with malaria infection

Characteristics		Patient N=142
Age group N (%)	<5	8(5.6)
	5-14	25(17.6)
	15-24	26(18.3)
	25-34	48(33.8)
	35-44	18(12.7)
	≥45	17(12.0)
Gender N (%)	Male	38(26.8)
	Female	104(73.2)
Haemoglobin (g/dL) mean(range)		10.05(4-14)
Platelet(µL) mean(range)		2201,197 (50,000-920,000)
Parasite counts N (%), [6].	Low(+)	21(14.8)
	Intermediate(++)	58(40.8)
	Slightly high(+++)	52(36.6)
	High (++++) [6].	11(7.7)

N: number of study subjects

Table 2. Distribution of Haptoglobin genotypes in the study group

Hp Genotype	Patients N (%)
Hp1-1	9(6.4)
Hp2-1	5(3.5)
Hp2-2	128(90.1)
Allele Hp1	23(8.1)
Allele Hp2	261(91.9)

Table 3. Characteristics of study population, by Haptoglobin genotype

Characteristics	Hp1-1 n=9	Hp2-1 n=5	Hp2-2 n=128	chix^2, p-value
Age group N(%)				
<5	1(11.1)	1(20.0)	6(4.7)	10.55, 0.393
5-14	2(22.2)	0	23(18.0)	
15-24	1(11.1)	0	25(19.5)	
25-34	4(44.4)	2(40.0)	42(32.8)	
35-44	0	0	18(14.1)	
≥45	1(11.1)	2(40.0)	14(10.9)	
Gender N(%)				
Male	1(11.1)	0	37(28.9)	3.25, 0.197
Female	8(88.9)	5(100)	91(71.1)	

P=0.05 (not statistical significantly)

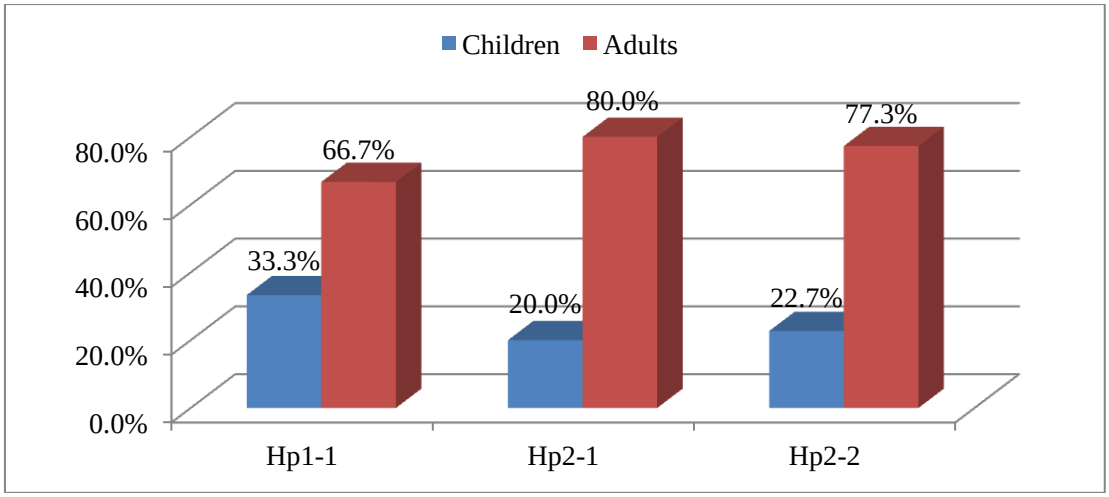

Fig. 2. Distribution of Hp genotypes by age group among malaria patients

Table 4. Comparison of parasites density in relation to Haptoglobin genotype

Parasitemia	Hp1-1 N(%)	Hp2-1 N(%)	Hp2-2 N(%)	chix^2, p-value
Low(+)	3(33.3)	1(20.0)	17(13.3)	4.69, 0.585
Intermediate(++)	3(33.3)	2(40.0)	53(41.4)	
Slightly high(+++)	2(22.2)	1(20.0)	49(38.3)	
High(++++)	1(11.1)	1(20.0)	9(7.0)	

(P=0.05).not statistical significantly

Malaria was studied in relation to Haptoglobin genotypes by level of parasitemia. The results showed that (41.4%) from Hp2-2 were expressed as intermediate while 40.0% and 33.3% were intermediate malaria parasitemia from Hp2-1 and Hp1-1, respectively, but this association was not statistically significant (*P*=0.05*)* Table 4.

In this study, the three main Hp genotypes among patients were evaluated against Hb and platelet. The mean Hb level (9.6) was the same in Hp 1-1 andHp2-1, and (10.1) in patients carrying Hp2-2 genotype. For mean platelet level, the Hp1-1 was observed as highest mean (240000) compared to others Hp genotype. All these different were not statistically significant (P-value > 0.05) Table 5.

The finding of the study showed the relation between Hp genotypes and parasites count according to age. Children with Hp1-1 genotype low parasitemia (66.7%) and Hp2-2 more parasitemia (51.7%). At slightly high parasitemia, the adults with Hp2-2 genotype were than adults with Hp1-1 or Hp2-1 genotype. No association was found between Hp genotypes and parasite count (P-value>0.05) Table 6.

Table 5. Comparison of hemoglobin and platelet in relation to Haptoglobin genotype

Parameter	Hp1-1	Hp2-1	Hp2-2	F-test, p-value
Haemoglobin (g/dL mean(range)	9.56(6-11)	9.60(7-11)	10.1(4-14)	0.82, 0.443
Platelet(μL) mean(range)	240000.0(53000-580000)	190800.0(167000-231000)	219867.19(50000-920000)	0.24, 0.885

(P=0.05).not statistical significantly

Table 6. Distribution of parasite count by Hp genotypes among children and adults

Parasitemia	Children N(%)			Adults N(%)		
	Hp1-1	Hp2-1	Hp2-2	Hp1-1	Hp2-1	Hp2-2
Low(+)	2(66.7)	0	4(13.8)	1(16.7)	1(25.0)	13(13.1)
Intermediate(++)	1(33.3)	1(100)	15(51.7)	2(33.3)	1(25.0)	38(38.4)
Slightly high(+++)	0	0	8(27.6)	2(33.3)	1(25.0)	41(41.4)
High(++++)	0	0	2(6.9)	1(16.7)	1(25.0)	7(7.1)
$chix^2$, p-value	6.39, 0.380			3.02, 0.806		

P-value>0.05 not statistical significantly

Table 7. Distribution of parasite density byHp genotypes with gender

Parasitemia	Male N(%)			Female N(%)		
	Hp1-1	Hp2-1	Hp2-2	Hp1-1	Hp2-1	Hp2-2
Low(+)	1(100)	-	6(16.2)	2(25.0)	1(20.0)	11(12.0)
Intermedite(++)	0	-	18(48.7)	3(37.5)	2(40.0)	35(38.5)
Slightly high(+++)	0	-	12(32.4)	2(25.0)	1(20.0)	37(40.7)
High(++++)	0	-	1(2.7)	1(12.5)	1(20.0)	8(8.8)
$chix^2$, p-value	4.55, 0.208			2.71, 0.844		

P-value>0.05 not statistical significantly

Table 8. The relation of the most common clinical malaria with Hp genotypes

Symptom	Hp1-1 N(%)	Hp2-1 N(%)	Hp2-2 N(%)	$chix^2$, p-value
Fever	8(7.2)	4(3.6)	99(89.2)	0.67, 0.716
Headache	8(7.0)	3(2.6)	104(90.4)	1.80, 0.406
Vomiting	5(6.3)	2(2.5)	72(91.1)	0.51, 0.773
Diarrhea	2(10.0)	1(5.0)	17(85.0)	0.71, 0.703
Nausea	2(5.7)	0	33(94.3)	1.75, 0.416
Abdominal pain	1(4.5)	0	21(95.5)	1.13, 0.568

P-value>0.05 not statistical significantly

This study also examined the effect of Hp genotypes on malaria parasitemia according to gender. Only one male with Hp1-1 genotype had low parasite count; whereas (48.7%) with Hp2-2 genotype had intermediate parasitemia. Thirty seven (40.7%) female patients with Hp2-2 had slightly high parasitemia. Parasite count among gender did not differ between the Hp genotypes (P-value>0.05) Table 7.

We found that the Hp2-2 genotype was higher with (89.2% malaria patients with fever symptom compared to other genotypes. The same can be symptoms. It is possible that theHp2-2 genotype protects against a range of malaria symptoms, but we did not find a significant association between Hp genotypes and any particular primary malaria clinical symptoms (P-value>0.05) Table 8.

3.2 The Distribution Hp Genotypes and Hemoglobin Level among Children and Adults

The study group showed that median of hemoglobin level is not clearly overlap with Hp genotypes among age group. That mean Hb level among age group did not differ between the Hp genotypes (P-value>0.05) Fig. 4.

3.3 The Distribution Hp Genotypes and Platelet Level among Children and Adults

In this figure, the study observed that median of platelets level clearly overlap with Hp genotypes among age group. That mean platelet level among age group did not differ between the Hp genotypes (P-value>0.05) Fig. 4.

4. DISCUSSION

"Although Hp has been studied extensively in the past, the finest molecular details of the observed differences in interaction between Hp and others hematological factors are not yet fully understand" [11].

In this study it was shown that Haptoglobin genotypes prevalence, Hp1-1, Hp2-1 and Hp2-2 were found in 6.4%, 3.5% and 90.1% respectively of the patient's in Elfasher- Northern Darfur State. The overall allele frequency was 8.1% for the Hp1 allele and 91.9% for the Hp2 allele. We show that Hp genotype frequencies of Hp 2-2 were associated with uncomplaticated malaria compare with Hp1-1.

"Pervious study done in Nigerian , show low Hp 2-2 genotype relative to other genotypes in breast cancer patients co- infected with malaria ; they concluded that low Hp 2-2 genotype is associated with lower malaria risk in breast cancer Nigerian women" [12].

In Sudan a previous study was done by Osman et al., 2016, showed that "no significant association was found between Haptoglobin phenotypes and type 2 diabetic patients" [13].

Our findings on the relationship between Haptoglobin genotype Hp2-2, frequency and susceptibility of malaria infection, Could be assuming that because the Hp2-2 hemoglobin complex is taken up more efficiently by macrophages as compared with Hp1-2 or Hp1-1.

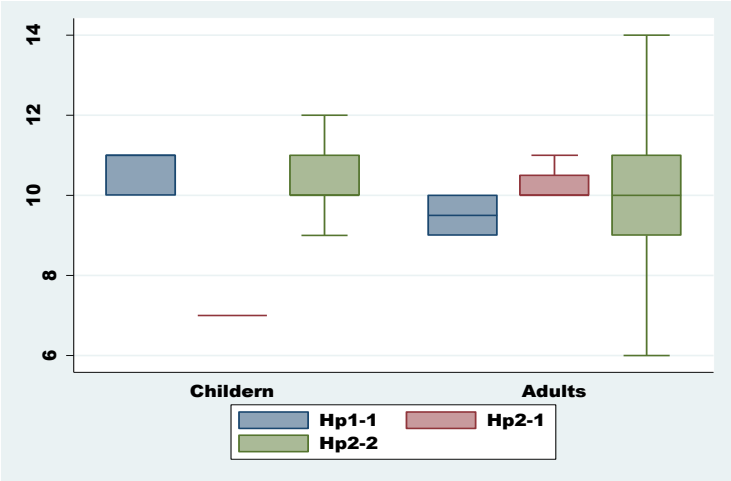

Fig. 3. Box plot showing the distribution Hp genotypes and hemoglobin level among children and adults

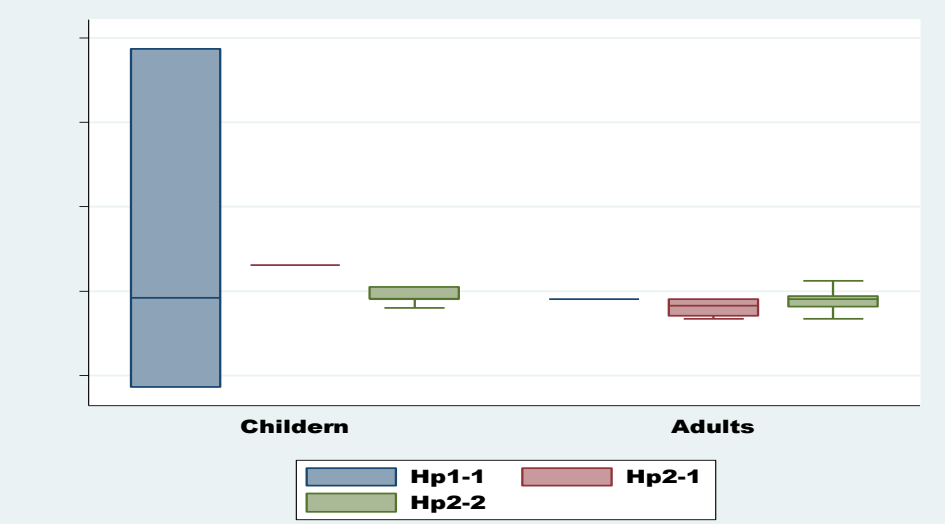

Fig. 4. Box plot showing the distribution Hp genotypes and platelet level among children and adults

In the present study the median of hemoglobin level clearly overlap with Hp genotypes among age group. That mean Hb level among age group did not differ between the Hp genotypes (*P*=0.05).

An association of Hp genotypes with incidence of uncomplicated malaria was not observed, In study done by Lwanira in Uganda in 2022, alough we found an association of uncomplicated malaria with Hp2-2 genotype [14], it was found that "Hp2-2 phenotype was significantly malaria patients as well as in complications of malaria disease".

"A growing number of genetic association studies reported that inflammation –related genes had a role in determining the course of the disease and clinical outcomes of infection. Has not yet an action of individual genetic variants has been difficult to resolve and in some cases genetic variants appear to have pleitropic effect" [15], however, the study done by Lwanira et al in 2020 , they found Hp1 allele was present at an allele frequency of 59%, while we found 6.4% [16].

In view of our study and those from Uganda [17], it appears that "the different Haptoglobin genotypes may or may not influence reduced risk of malaria infection and development of the disease. The outcome of the relationship between Haptoglobin genotypes and disease may be influenced by disease determinants including age, ethic group and environmental factors" [18].

5. CONCLUSIONS

Based on this study, the Hp 1-1 and Hp 2-1 genotypes are present in about 4 out of every 10 children, whereas the Hp 2-2 genotype is present in 2 out of every 10 children. There was no correlation with the prevalence of uncomplicated malaria. To fully comprehend the significance of these genotypes in malaria protection, additional research on the influence of haptoglobin genotypes on the severity of P. falciparum malaria is required.

CONSENT

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

The ethical consideration was obtained from state Ministry of Health ethical committee, Northern Darfur.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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