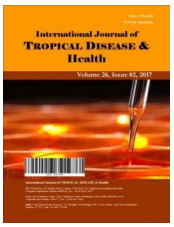

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Sickle Cell Disease and Severity of Malaria

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Authors' contributions

This work was carried out in collaboration between all authors. Authors IA, M Daou and M Doutchi participated in writing the manuscript and analyzing the results. Authors MMA, SB and KM conducted the study. Author MML participated in writing the project and the manuscript. Authors RHL and DYH participated in the statistical analysis of the data. Author IML drafted the project, analyzed the results and wrote the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: The relationship between sickle cell disease and malaria remains controversial and the hypothesis that sickle cell disease protects against malaria is widespread.
Methodology: A descriptive and retrospective study over a two-year period (2014-2016) was conducted in pediatric departments of the National Hospital of Niamey (NHN). The objective is to assess the relative risk between sickle cell disease and the severity of malaria.

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Results: Nine hundred and seventy four (974) patients infected with *Plasmodium falciparum* were included in this study. Thirteen point twenty four percent (129/974) of patients had sickle cell disease, of which 93.8% (121/129) had SS form and 6.2% (8/129) SC form. Seventy-nine point eight percent (103/129) of sickle cell patients had severe malaria (RR = 0.9, p = 0.17). Ninety six point one percent (99/103) of patients with severe malaria were homozygous SS versus 3.8% (4/103) who were heterozygous SC (RR = 0.6, p = 0.05). Eleven point forty three percent (4/35) of sickle cell patients died of malaria (RR = 0.1, p = 0.4). Seventy-five percent (3/4) of the deceased sickle cell were homozygous SS versus 25% (1/4) who were heterozygous SC (RR = 5, p = 0.2).

Conclusion: Heterozygous sickle cell patients have less severe malaria than homozygotes. Malaria is more severe and more lethal in homozygous sickle cell patients. A strategy for the prevention of sickle cell malaria should be developed during periods of high transmission.

Keywords: Relationship; sickle cell disease; malaria; Severe and Niger.

1. INTRODUCTION

Sickle cell disease is a hereditary disease with autosomal recessive Mendelian transmission. It is characterized by a structural abnormality of hemoglobin. A glutamic acid of the β-chain in position six is replaced by valine. The abnormal sickling hemoglobin Hb S results from the mutation of the 6th codon of the ß gene. The normal codon of the β gene (GAG) is mutated to an abnormal codon (GTG) [1].

In hypoxic environment this abnormal hemoglobin polymerizes, making the red cells rigid, disrupting the red blood cell membrane, altering the membrane function by increasing its ion permeability, causing dehydration. Finally, it crystallizes and irreversibly deforms the red blood cell sickle. The irreversibly sickled red blood cells, which are characteristic of sickle cell disease, are rigid, undeformable, have a short life span and are responsible for vaso-occlusive crises [2].

According to the World Health Organization (WHO), more than 330.000 infants are born each year with hemoglobinopathy, 83% with sickle cell disease and 17% with thalassemia. These disorders are responsible for about 3.4% of deaths in children under 5 years of age [3]. In Niger, the prevalence of sickle cell disease is 16,28% in 2015 [4]. Their hemoglobin profile shows that there are 87% healthy carriers (AS), 3% of SS, 3% of SC, 3% of AC and 4% of unknown hemoglobin [4].

Sickle cell disease is a hereditary disease that is particularly prevalent in African populations. It has long been known that heterozygote carriers are protected against malaria. This explains the match of the distribution area of sickle cell disease with malaria endemic areas [5].

Several hypotheses have been put forward to explain the relationship between sickle cell disease and malaria: The first hypothesis of Haldane (1949), then taken up by Allison (1954), argues in favor of a selective advantage of AS heterozygous subjects against malaria. This is an example of a negative epistasis effect [6]. The second hypothesis is that sickle cell disease modifies the cytoplasmic membrane of the red blood cell thus reducing its infection and consequently the parasite burden. This hypothesis puts a direct mechanism of interaction in sickled cells and *Plasmodium* reducing the ability of parasites to infect red blood cells [2]. The third hypothesis is that the parasite development was not adapted in the sickled cells. In fact, hemoglobin S would create an environment in the red blood cell, which is not favorable for the growth of *Plasmodium*, and the spleen would filter the sickled cells. Sickle cell tolerance to malaria is thought to be due to inhibition of oxygen-dependent parasite growth. Indeed, the parasitic growth in red blood cells of heterozygous patients in a hypoxic medium is inhibited. The polymerization of hemoglobin is responsible for this inhibition [5,7]. Finally, the fourth hypothesis evokes a tolerance of *Plasmodium* via the Nrf2 / HO-1 system. Indeed, heme oxygenase 1 (HO-1) is an enzyme strongly expressed during hemoglobinopathy via a mechanism involving the Nrf2 transcription factor. However, the carbon monoxide produced by HO-1 stabilizes hemoglobin and prevents the release of free heme into the circulating blood, the cytotoxic effects of which contribute to the pathogenicity of malaria [8].

Despite all assumptions, a paradoxical question remains in many minds. How does sickle cell disease, which protects against malaria infection, seem to be a factor of malaria severity? In order to evaluate the relationship between sickle cell disease and the severity of malaria, we conducted a retrospective and descriptive study, in the pediatric departments of the NHN.

2. METHODOLOGY

2.1 Type and Site of Study

This is a descriptive, analytical and retrospective two-year study (2014-2016) that aims to describe the relationship between sickle cell disease and the severity of malaria. The study was conducted at the pediatric services of NHN.

2.2 The Population of Study

The study population consists of 974 children aged 0 to 15 years, hospitalized in the pediatric departments of NHN for malaria. All children included are confirmed by microscopy. The criteria of inclusion were children with uncomplicated or severe malaria. Severe malaria has been defined by the presence of at least one of the WHO severity criteria [9]. The criteria of exclusion were malaria associated with another disease. The diagnosis of sickle cell disease was made by Emmel sickling test and the types of hemoglobin were determined by electrophoresis at the biology laboratory of the NHN.

2.3 Data Collection Tools

The data was collected using patient medical records. The variables (Sex, age, site, uncomplicated malaria, severe malaria, type of severe malaria, sickle cell disease, type of hemoglobin, glycaemia and hemoglobin level…) collected were used to describe the epidemiological, clinical and biological characteristics of patients with both severe malaria and sickle cell disease.

2.4 Statistical Analysis

The data was captured and analyzed using EPI INFO software version 7.0. The multivariate analyzes was used to study the associations between malaria and sickle cell disease. The relative risk (RR) between sickle cell disease and severe malaria factors on the one hand and sickle cell disease and risk of death on the other hand were calculated. A *p values* less or equal to 0,05 are considered significant.

3. RESULTS

3.1 Characteristics of Population

Nine hundred and seventy four (974) patients infected with *Plasmodium falciparum* were included in the study. Eighty-three zero point six percent (809/974) of these cases of malaria are complicated against 16.94% (165/974) which are not complicated. Thirteen point twenty four percent (129/974) of the patients had sickle cell disease. The mean age of the patients was 53.69 months (SD = 41.23; IC95%: [3; 168]). Male-female sex ratio was 1.28.

3.2 Clinical Features

Seventy-nine point eight percent (103/129) of sickle cell patients had severe malaria (RR = 0.9, p = 0.17). Ninety-six point one percent (99/103) of homozygous SS had severe malaria compared to only 3.8% (4/103) heterozygous SC (RR = 0.6, p = 0.05). The main clinical manifestation of malaria in sickle cell patients was severe anemia. In fact, 73.64% (95/129) of sickle cell patients had severe anemia, 3.88% (5/129) convulsions and 22,48% (29/129) others associated signs.

Eleven point forty three percent (4/35) of sickle cell patients died of malaria (RR = 0.1, p = 0.4). Seventy five percent (3/4) of sickle cell deaths were homozygous SS versus 25% (1/4) who were homozygous SC (RR = 5, p = 0.2). All sickle cell deaths have been caused by severe anemia, which may be associated with hypoglycemia or respiratory distress (Table 1).

3.3 Biological Characteristics

The biological characteristics of patients are summarized in Table 2.

4. DISCUSSION

This retrospective study describes the relationship between the severity of malaria and the genotype profile of patients' hemoglobin in the pediatric services of NHN.

This study shows that heterozygotes are protected against severe forms of malaria. Only 3.8% of heterozygous SC had severe malaria

Table 1. Relationship between severe malaria and sickle cell disease

Hemoglobinopathy	Severe malaria		
	(%)	RR	*p* value
Sickle cell disease	13.24% (129/974)	0.9	0.17
Homozygous SS	96,1% (99/103)	0.6	0.05
Heterozygous SC	3,8% (4/103)		
Hemoglobinopathy	**Death**		
	(%)	**RR**	***p* value**
Sickle cell disease	11.43% (4/35)	0.1	0.4
Homozygous SS	75% (3/4)	5	0,2
Heterozygous SC	25% (1/4)		

Table 2. Biological characteristics

Biological characteristics	Percentage or main	Standard deviation and IC95%
Homozygous SS	93.8%	-
Heterozygous SC	6.2%	-
Main of parasite density	4947 P/µL	SD=4115; [25; 999.800]
Main of hemoglobin	7.7 g/dL	SD=2.8; [1,6:14,9])
Severe aneamia	21.3%	-
Main of platelets	222505 platelets /µL	SD=197742; [1000; 963000]
Blood glucose	3.7 mmol/L	SD=1.9; [0,28; 6,9]
Hypoglyceamia	28.9%	-

compared to 96.1% of homozygous SS (RR = 0.6, p = 0.05). A three-arm control case study in Uganda shows that heterozygosis is a significant protection against severe malaria [10]. The protective mechanism does associated to the parasite-red blood cell interaction. A cross-sectional study in Cameroon found that patients with normal hemoglobin (Hb A) and patients with abnormal hemoglobin (Hb S) are infected on average with the same number of parasitic clones [11].

Homozygous patients are more killed by malaria than heterozygotes. In fact, 75% of homozygotes died compared to only 25% (RR = 5, p = 0.2). This gives an advantage to the heterozygotes that will be selected [12].

The mechanism by which homozygotes are eliminated is severe anemia. In fact, all sickle cell patients have died of severe anemia, which may be associated with respiratory distress or hypoglyceamia.

Hemoglobin is the main component of red blood cells and supplies oxygen to tissues and organs [13]. It is a tetramer molecule of 67000 daltons consisting of 4 subunits called globins. Each subunit is composed of an iron atom coordinated by a porphyrin, a protein chain and possibly a small molecule such as CO (Mono-Carbon Oxide), NO (Mono-Nitrogen Oxide) or O2 (Molecular Oxygen) [14]. Iron has the ability to associate and easily dissociate from oxygen, giving to hemoglobin molecule the ability to carry oxygen [13]. On the other hand, malaria is a febrile and hemolytic erythrocytopathy caused by a parasite of the genus *Plasmodium*, transmitted by mosquito bites of the *Anopheles* genus. Thus, it is easy to see that a tint of the structure of hemoglobin associated with parasitic hemolysis results in severe anemia, hypoxia, respiratory distress and subsequent death. More than 50% of children with sickle cell disease die before the age of five, according to the World Health Organization [15].

The main genotypes of the patients consulted are respectively 0.08% SC, 12.42% SS and 85.75 AA. Comparable genotypes are found in all countries of West Africa. In Abidjan, Côte d'Ivoire, Stéphane K et al. found the genotypes 1.55% SC, 0.39 SS and 83.7% AA [16].

Sickle cell disease is a major problem that complicates the management of malaria in pediatric departments. This is one of the main antecedents of malarious consultation because 13.24% of malarious patients had sickle cell disease. For all these reasons, sickle cell

disease must be prevented from malaria by a specific strategy such as chemoprevention of seasonal sickle cell malaria.

5. CONCLUSION

Sickle cell disease is a major public health problem in Niger. It is also a factor of severity of malaria. Heterozygous make less severe malaria than homozygous. Malaria is more severe and more lethal in homozygous. A sickle cell-specific malaria prevention strategy needs to be developed during periods of high transmission.

CONSENT AND ETHICAL APPROVAL

As per university standard guideline participant consent and ethical approval has been collected and preserved by the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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