

Short Research Article

Sickle cell disease and severity of malaria

Summary: 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 A and B of the National Hospital of Niamey (HNN). The objective is to assess the relative risk between sickle cell disease and the severity of malaria.

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 have SS hemoglobin versus 3.8% (4/103) who have hemoglobin 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 have hemoglobin SS versus 25% (1/4) who have hemoglobin 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.

Key words: Relationship, Sickle cell disease, Malaria, Severe, Niger

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

29 hemoglobin Hbs results from the mutation of the 6th codon of the β gene. The normal
30 codon of the β gene (GAG) is mutated to an abnormal codon (GTG)(1).

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

37 According to the World Health Organization (WHO), more than 330.000 infants are
38 born each year with hemoglobinopathy, 83% with sickle cell disease and 17% with
39 thalassemia. These disorders are responsible for about 3.4% of deaths in children under
40 5 years of age (3). In Niger, the prevalence of sickle cell disease is 16,28% in 2015 (4).
41 Their hemoglobin profile shows that there are 87% healthy carriers (AS), 3% of SS, 3%
42 of SC, 3% of AC and 4% of unknown hemoglobin (4).

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

47 Several hypotheses have been put forward to explain the relationship between sickle
48 cell disease and malaria: The first hypothesis of Haldane (1949), then taken up by
49 Allison (1954), argues in favor of a selective advantage of AS heterozygous subjects
50 against malaria. This is an example of a negative epistasis effect(6). The second
51 hypothesis is that sickle cell disease modifies the cytoplasmic membrane of the red
52 blood cell thus reducing its infection and consequently the parasite burden. This
53 hypothesis puts a direct mechanism of interaction in sickled cells and *Plasmodium*
54 reducing the ability of parasites to infect red blood cells (2). The third hypothesis is that
55 the parasite development was not adapted in the sickled cells. In fact, hemoglobin S
56 would create an environment in the red blood cell, which is not favorable for the growth
57 of *Plasmodium*, and the spleen would filter the sickled cells. Sickle cell tolerance to
58 malaria is thought to be due to inhibition of oxygen-dependent parasite growth. Indeed,
59 the parasitic growth in red blood cells of heterozygous patients in a hypoxic medium is

60 inhibited. The polymerization of hemoglobin is responsible for this inhibition (5), (7).
61 Finally, the fourth hypothesis evokes a tolerance of *Plasmodium* via the Nrf2 / HO-1
62 system. Indeed, heme oxygenase 1 (HO-1) is an enzyme strongly expressed during
63 hemoglobinopathy via a mechanism involving the Nrf2 transcription factor. However,
64 the carbon monoxide produced by HO-1 stabilizes hemoglobin and prevents the release
65 of free heme into the circulating blood, the cytotoxic effects of which contribute to the
66 pathogenicity of malaria(8).

67 Despite all assumptions, a paradoxical question remains in many minds. How does
68 sickle cell disease, which protects against malaria infection, seem to be a factor of
69 malaria severity? In order to evaluate the relationship between sickle cell disease and
70 the severity of malaria, we conducted a retrospective and descriptive study, in the
71 pediatric A and B departments of the National Hospital of Niamey (HNN) to determine
72 the relationship between severity of malaria and sickle cell disease.

73 **METHODOLOGY**

74 **1) Type and site of study**

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

78 **2) The population of study**

79 The study population consists of 974 children aged 0 to 15 years, hospitalized in the
80 pediatric departments of HNN for malaria. All children included are confirmed by
81 microscopy. The criteria of inclusion were children with uncomplicated or severe
82 malaria. Severe malaria has been defined by the presence of at least one of the WHO
83 severity criteria (9). The criteria of exclusion were malaria associated with another
84 disease. The diagnosis of sickle cell disease was made by Emmel sickling test and the
85 types of hemoglobin were determined by electrophoresis at the biology laboratory of
86 the National Hospital of Niamey.

87 **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 and type of hemoglobin, glycaemia, hemoglobin level...) collected were used to describe the epidemiological, clinical and laboratory characteristics of patients with both severe malaria and sickle cell disease.

3) 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 value less or equal to 0,05 is considered significant.

RESULTS

1. Characteristics of population

Nine hundred and seventy four patients (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 (13.24% or 129/974) of the patients were sickle cell patients. The mean age of the patients was 53.69 months (SD = 41.23; IC95%: [3; 168]). Male-female sex ratio was 1.28.

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 patients with SS hemoglobin had severe malaria compared to only 3.8% (4/103) with SC hemoglobin (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 have hemoglobin SS versus 25%

(1/4) who have hemoglobin 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.

3. Biological characteristics

Eighty three point eight percent (121/129) sickle cell had SS hemoglobin and 6.2% (8/129) had hemoglobin SC. The average parasite density of patients is 4947 P/μL (SD =4115; IC95%: [25; 999.800]). The average hemoglobin is 7.7 g/dL(SD =2,8; IC95%: [1,6;14,9]). 21.3% of patients have a hemoglobin level of less than 5 g/dL otherwise have severe anemia. The average platelet count is 222.505 platelets/μL(SD =197742; IC95%: [1000; 963.000]). Thirty six point seven percent (36.7%) of patients have a platelet count of less than 100.000 platelets/μL. Blood glucose: The average blood glucose is 3.7 mmol/L (SD =1,9; IC95%: [0,28; 6,9]). Twenty-eight point nine (28.9%) had blood glucose lower than 2.2 mmol/L. **Table I** summarizes the association between severe malaria and sickle cell disease.

Table I: Relationship between severe malaria and sickle cell disease

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

132

133 **DISCUSSION**

134 This retrospective study describes the relationship between the severity of
135 malaria and the genotype profile of patients' hemoglobin in the pediatric services of
136 Niamey National Hospital.

137 This study shows that heterozygotes are protected against severe forms of malaria. Only
138 3.8% of patients with hemoglobin SC had severe malaria compared to 96.1% of patients
139 with SS hemoglobin (RR = 0.6, p = 0.05). A three-arm control case study in Uganda
140 shows that heterozygosis is a significant protection against severe malaria (10). The
141 protective mechanism does associated to the parasite-red blood cell interaction. A
142 cross-sectional study in Cameroon found that patients with normal hemoglobin (Hb A)
143 and patients with abnormal hemoglobin (Hb S) are infected on average with the same
144 number of parasitic clones (11).

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

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

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

The main genotypes of the patients consulted are respectively 008% 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 are sickle cell patients. For all these reasons, sickle cell disease must be prevented from malaria by a specific strategy such as chemoprevention of seasonal sickle cell malaria.

CONCLUSION

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

Disclaimer regarding Consent/Ethical Approval:

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

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analysis of the data; IML: Drafted the project, analyzed the results and wrote the manuscript.

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