

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. Epidemiological, clinical and biological characteristics have been described.

Results: 974 malarious patients records were examined. They are all infected with *P. falciparum*. 13.24% (129/974) of patients had sickle cell disease, of which 93.8% (121/129) had SS form and 6.2% (8/129) SC form. 79.8% (103/129) of sickle cell patients had severe malaria (RR = 0.9, p = 0.17). 96.1% (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). 11.43% (4/35) of sickle cell patients died of malaria (RR = 0.1, p = 0.4). 75% (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: Relation, Sickle cell disease, Malaria, Severe, Niger

INTRODUCTION

Sickle cell disease is a hereditary disease with autosomal regressive Mendelian transmission. It is characterized by a structural abnormality of hemoglobin, in which glutamic acid of the β -chain in position six is replaced by valine. The abnormal

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 deoxygenated environment this abnormal hemoglobin polymerizes and sticks to the
32 red blood cell membrane, altering the membrane function by increasing its ion
33 permeability and dehydration. Finally, it crystallizes and irreversibly deforms the red
34 blood cell sickle. These red blood cells, which are characteristic of sickle cell disease, are
35 rigid, undeformable, have a short lifespan and are responsible for vaso-occlusive
36 complications (2).

37 According to the World Health Organization (WHO), more than 330,000 infants are
38 born each year with hemoglobinopathies, 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 16.43% in 2015. The
41 hemoglobin profile shows that there are 87% healthy carriers (AS), 3% of SS, 3% of SC,
42 3% of AC (4).

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

47 Several hypotheses have been put forward to explain the relationship between sickle
48 cell disease and malaria: The first theory is emitted in 1949 by Haldane, then taken up
49 in 1954 by Allison, who argues in favor of a selective advantage of AS heterozygous
50 subjects against malaria. This is an example of a negative epistatic 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 falciformed red blood cells and
54 *Plasmodium* reducing the ability of parasites to infect red blood cells (2). The third
55 hypothesis is the adaptation of parasite development in the falciformed red blood cell.
56 In fact, hemoglobin S would create an environment in the red blood cell which is
57 unfavorable for the growth of *Plasmodium*, and the falciformed red blood cells would be
58 filtered by the spleen. Sickle cell tolerance to malaria is thought to be due to inhibition
59 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 severe malaria? 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 A and B departments of the National Hospital of Niamey (HNN) by calculating the risk relationship between severity malaria and sickle cell disease.

METHODOLOGY

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. She was taken to pediatric services A and B of Niamey National Hospital.

2) The population of study

The study population consists of 974 children aged 0 to 15 years, hospitalized in the pediatric departments of HNN for malaria. All children included are confirmed malarious by a thick drop. Severe malaria has been defined by the presence of at least one of the WHO severity criteria (9). The type of hemoglobin was confirmed by electrophoresis in the biology laboratory of the National Hospital of Niamey.

2) Data collection tools

The data was collected using survey cards. The variables collected were used to describe the epidemiological, clinical and laboratory characteristics of patients with both severe malaria and sickle cell disease.

3) Statistical analysis

89 The data was captured and analyzed using EPI INFO software version 7.0. The
90 multivariate analyzes made it possible to study the associations between malaria and
91 sickle cell disease. The relative risk (RR) between sickle cell disease and severe malaria
92 factors on the one hand and sickle cell disease and risk of death on the other hand were
93 calculated.

94 **RESULTS**

95 **1. Epidemiological characteristics**

96 Nine hundred and seventy four patients (974) infected with *Plasmodium falciparum*
97 were included in the study. 83.06% (809) of these cases of malaria are complicated
98 against 16.94% (165). 13.24% (129/974) of the patients were sickle cell patients. The
99 mean age of the patients was 53.69 months (6 = 41.23 [3; 168]). Sex ratio of 1.28.

100 **2. Clinical features**

101 Seventy-nine point eight percent (79.8% or 103/129) of sickle cell patients had severe
102 malaria (RR = 0.9, p = 0.17). 96.1% (99/103) of patients with SS hemoglobin had severe
103 malaria compared to only 3.8% (4/103) with SC hemoglobin (RR = 0.6, p = 0.05). The
104 main clinical manifestation of malaria in sickle cell patients is severe anemia. In fact,
105 71.32% (92/335) of sickle cell patients had severe malaria due to anemia. Only 2.33%
106 (3/146) had convulsions.

107 11.43% (4/35) of sickle cell patients died of malaria (RR = 0.1, p = 0.4). 75% (3/4) of
108 sickle-cell deaths have hemoglobin SS versus 25% (1/4) who have hemoglobin SC (RR =
109 5, p = 0.2). All sickle cell deaths have been caused by severe anemia, which may be
110 associated with hypoglycaemia or respiratory distress.

111 **3. Biological characteristics**

112 93.8% (121/129) sickle cell had SS hemoglobin and 6.2% (8/129) had hemoglobin SC.
113 The average parasite density of patients is 4947 P / μ L. The average hemoglobin is 7.7 g
114 / dL. 21.3% of patients have a hemoglobin level of less than 5 g / dL otherwise have
115 severe anemia. The average platelet count is 222505 platelets / μ L. 36.7% of patients
116 have a platelet count of less than 100,000 platelets / μ L. Blood glucose: The average

117 blood glucose is 3.7 mmol / L. 28.9% had a blood glucose lower than 2.2 mmol / L.
118 Table I summarizes the association between severe malaria and sickle cell disease.

119 **Table I: Relationship between severe malaria and sickle cell disease**

Hemoglobinopathies	Severe malaria		
	(%)	RR	p*
sickle cell disease	13,24% (129/974)	0,9	0,17
SS form	93,8% (121/129)	0,6	0,05
SC form	6,2% (8/129)		
Hemoglobinopathies	Death		
	(%)	RR	p*
sickle cell disease	11.43% (4/35)	0,1	0,4
SS form	75% (3/4)	5	0,2
SC form	25% (1/4)		

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122 DISCUSSION

123 This retrospective study describes the relationship between the severity of malaria and the
124 genotype profile of patients' hemoglobin in the pediatric ward of Niamey National Hospital.

125 This study shows that heterozygotes are protected against severe forms of malaria. Only 6.2%
126 of patients with hemoglobin SC had severe malaria compared to 93.8% of patients with SS
127 hemoglobin (RR = 0.5, p = 0.05). A three-arm control case study in Uganda shows that indeed
128 heterozygosity is a significant protection against severe malaria (10). The protective
129 mechanism does not lie in the red-parasite blood cell interaction as a cross-sectional study in
130 Cameroon found that patients with normal hemoglobin (Hb A) and patients with abnormal
131 hemoglobin (Hb S) are infected on average with the same number of parasitic clones (11).

Homozygous patients are more eliminated 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 eventually 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 hypoglycaemia.

Hemoglobin is on one hand the main component of red blood cells and allows the supply of tissues and organs in oxygen (13). It is a tetramer molecule of 67,000 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 readily dissociate from oxygen, giving the hemoglobin molecule the ability to carry oxygen (13). On the other hand, malaria is a febrile and haemolytic 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 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. Sickle cell disease is a target 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.

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