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Malaria and sickle cell anemia: report of complications and clinical management of three patients in a highly endemic area FOR Plasmodium vivax malaria in the Brazilian Amazon

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Summary

Background: In tropical regions, malarial infection is an important cause of sickling syndromes in patients with sickle cell anemia.

Case Report: The authors report the benign evolution of three children with the diagnosis of sickle cell anemia (SCA) who became infected with malaria in the Brazilian Amazon. Sometimes sickling syndromes can be misdiagnosed as severe falciparum malaria or secondary bacterial infection. The clinical management of patients with this association of diseases is difficult and should be centered on early diagnosis, early efficacious antimalarial treatment, blood transfusions, careful parenteral hydration and therapy with antibiotics.

Conclusions: Further studies are needed to describe the clinical pattern of patients with SCA in areas highly endemic for *P. vivax*.

Key words: **Malaria • sickle cell anemia • *plasmodium vivax***

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Background

Malaria is the most important parasitic disease affecting humankind, infecting 500 million people and causing between 1 and 3 million deaths each year[1]. Sickle cell anemia (SCA) (HbSS) is a chronic genetic disease characterized by periods of exacerbation of symptoms, traditionally called sickling syndromes. Despite the malaria resistance by the sickle cell trait (SCT) (HbAS), in tropical regions, malarial infection is an important cause of sickling syndromes in patients with SCA. Nevertheless, limited data exist about the clinical management of these patients, especially in areas highly endemic for *Plasmodium vivax* malaria.

Case Report

CASE 1

A 4-year-old girl with SCA (diagnosed by hemoglobin electrophoresis, as the other following cases) was admitted to the hospital because of a 3-day high fever, chills, vomiting, intense pain in the lower limbs, chest pain and dyspnea. Physical examination showed a somnolent child with moderate dehydration, tachypnea, tachycardia, paleness, mild jaundice and splenomegaly. A complete blood count showed white-blood cells (WBC) of $35x10^3/mm^3$ with normal differential count, hemoglobin 4.3 g/dL and mild thrombocytopenia. Total bilirubin level was 4.3 mg/dL, (indirect fraction 2.43 mg/dL). A thick blood smear disclosed *Plasmodium vivax*. There were lung infiltrates in the chest roentgenogram. Red blood cells were transfused and chloroquine was initiated in concert with parenteral hydration, intravenous analgesia, oxygen therapy and ceftriaxone. On the third day, parasitemia was negative. The child was discharged on the seventh hospitalization day. Primaquine was initiated afterwards.

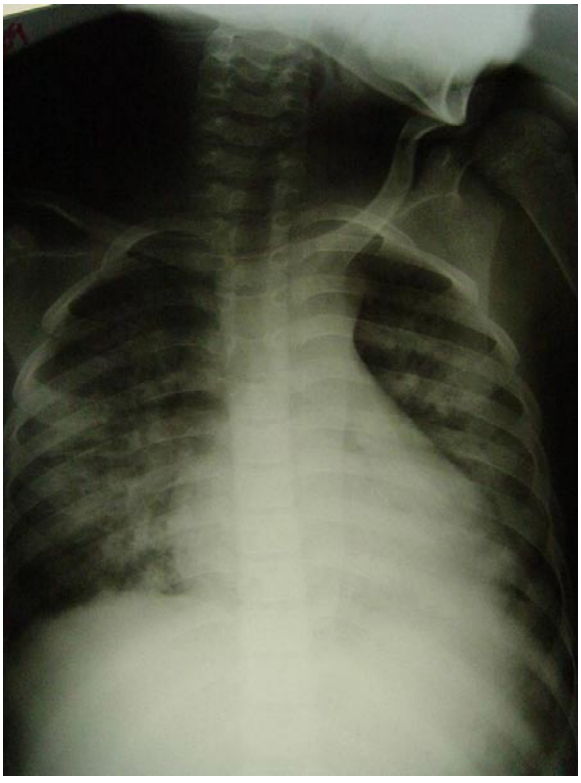

Figure 1. Chest roentgenogram of case 2 with bilateral diffuse infiltrates.

CASE 2

A 10-year-old boy with diagnosis of SCA for five years searched the hospital because of a 3-day history of high fever, fatigue, generalized pain and jaundice. On physical examination, the child was lethargic, icteric, tachypneic, tachycardic, pale and dehydrated. Painful spleen and liver were palpable. *P. vivax* was observed at the thick blood smear. Admission exams revealed high levels of bilirubin (total fraction 40.9 mg/dL, direct fraction 30.3 mg/dL) and anemia (hemoglobin 6.6 g/dL). WBC: $13x10^3/mm^3$. Chloroquine and analgesics were prescribed. On the second hospitalization day, the child became worse, evolving with alternate periods of irritability and lethargy, fever, acute respiratory failure, cyanosis, hypotension and tachycardia. Total bilirubin arose to 57.8 mg/dL (direct fraction 38.2 mg/dL). Hemoglobin level reduced to 5.2 g/dL and WBC increased to $15x10^3/mm^3$. Oxygen saturation on nasal catheter was 88%. One pack of red blood cells was transfused and oxygen support was instituted. On the third hospitalization day, the child was in respiratory distress, febrile, icteric, pale and somnolent, complaining of intense generalized pain and chest discomfort, and he was transferred to the intensive care unit (ICU). Chest roentgenogram showed bilateral diffuse infiltrates (Figure 1). WBC increased to $18x10^3/mm^3$ (71% neutrophils and 6% band forms). A control thick blood smear disclosed *Plasmodium falciparum* and thus intravenous artesunate plus mefloquine were promptly administered. Therapeutics with cefotaxime, parenteral hydration in minimal volumes and transfusion of another pack of red blood cells was started. On the fifth day, parasitemia had already decreased and the child improved. The PCR confirmed the mixed infection. Primaquine was prescribed 15 days later.

CASE 3

A 9-year-old boy presented at the hospital with a 4-day history of high fever, and moderate myoarthralgia. Past medical history was remarkable for SCA

diagnosed eight months earlier. Physical examination on admission showed a responsive child with high fever, dehydration, paleness, tachypnea, tachycardia and jaundice. On chest ascultation, there were bilateral rales and a pulmonary systolic murmur. Liver and spleen were enlarged. Laboratory tests revealed accentuated WBC ($55x10^3/mm^3$) (52% neutrophils and 10% band forms), hemoglobin 5.5 g/dL and total bilirubin 4.8 mg/dL (direct fraction 1.6 g/dL). Chest roentgenogram showed bilateral infiltrates in the lung fields. Soon after admission, ceftriaxone was prescribed and one pack of red blood cells was transfused. *P. vivax* and *P. falciparum* trophozoites were noticed in a routine hematological test. Artesunate and mefloquine were initiated. Negativation of peripheral parasitemia was observed two days later. On the sixth day the child improved. Blood culture disclosed *Enterobacter sp.* The patient was lost to follow-up and no primaquine was used.

Discussion

In 1949, Haldane hypothesized that the high prevalence of hemoglobinopathies in malaria-endemic areas resulted from protection conferred against malaria [2]. Inherent complications of SCA result in increased mortality and morbidity when malarial infection occurs. Most of the reported cases of malaria in children with the SCT are related to asymptomatic children with diagnosis of SCA who acquired malaria, developed clinical flare-up of their underlying disease and required admission to hospital, as seen in the reported children [3,4]. The clinical management of patients with SCA and malaria brings many clinical challenges, some of them frequently neglected in the literature.

The acute chest syndrome can be caused by pneumonia, sickling of erythrocytes in the pulmonary circulation or acute pulmonary edema due to malaria [5,6]. Chest roentgenograms are usually non-specific and the final diagnosis often remains obscure. There is also a dilemma on how to hydrate theses patients, once generous hydration is advised in patients with exacerbation of SCA, but should be avoided in malaria at expenses of causing pulmonary edema. Current guidelines for the fluid management of children recommend only the provision of maintenance fluids, and volume expansion is restricted to those with decompensated shock or signs of severe dehydration [7]. Current guidelines also recommend early empirical broad-spectrum antibiotic therapy [8-10].

In endemic areas for malaria, in children presenting with severe anemia, malaria is diagnosed in 18-66% of these children [3,11]. Unfortunately no steady state hematological values from these reported children were available. Blood transfusion is a key element of management of these patients, frequently resulting in dramatic clinical improvement. Although simple transfusion was chosen, exchange transfusion could have a dual indication in these patients because this method permits simultaneous parasitic clearance and removal of sickled cells.

P. falciparum treatment shall include a more potent schizonticidal drug (e.g. artemisinin derivatives) in order to promote faster clearance of the parasites and control the infectious process that is triggering the acute clinical worsening. Primaquine is used to avoid relapses in *P. vivax* malaria, but to complicate matters, this drug is myelotoxic and induces hemolysis in patients with G6PD deficiency and therefore is not advisable in SCA patients with severe anemia. Therefore, in countries endemic for *P. vivax*, the radical cure of these patients poses an extra difficulty. A few inconclusive studies on the malaria chemoprophylaxis to this group of patients have been conducted so far [12].

There is good evidence to recommend that children with SCA who start a febrile illness after being in an endemic area for malaria seek medical consultation quickly for early diagnosis. The cases reported reinforce malaria (*P. falciparum* and/or *P. vivax*) as a cause of clinical worsening of children with SCA in tropical areas, precipitating painful crisis, acute chest syndrome and severe anemia. Further studies in a populational basis are still needed in order to define the pattern of clinical problems of patients with SCA and SCT infected with *P. vivax* (80% of the malaria cases in Brazil). Most of the studies on malaria and SCA are focused on Africa, but *P. vivax* is the major species in Asia and the Americas [13].

Conclusions

In conclusion, clinical management of patients with this association of diseases is difficult and should be centered on fast parasitic clearance, blood transfusions, careful parenteral hydration, broad-spectrum antibiotics and general support measures, for which the availability of ICU's in the tropics is essential.

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