

Ischaemia of the Extremities of the Four Limbs in a 4-Month-Old Infant at University Teaching Hospital of Bouaké (Côte D'ivoire): An Unusual Presentation of Severe Malaria

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Abstract

Malaria is a public health problem worldwide and particularly in sub-Saharan Africa. The criteria for severe malaria are known and include clinical and biological criteria. The occurrence of symmetrical distal ischemia in all four limbs is an unusual complication of severe malaria in infants under 6 months of age. Most of the cases reported concern children over two years of age, adults and the elderly. We report the case of a 4-month-old infant at Bouaké University Hospital with several manifestations of malaria severity and on the 5th day of disease progression a rapidly fatal distal ischemia of the four limbs. The objective of the study was to describe the main epidemiological, diagnostic, therapeutic and evolutionary aspects of this unusual complication for improving prognosis.

Keywords: Infant, Severe malaria, Distal limb ischemia, Côte d'Ivoire.

INTRODUCTION

Malaria is the world's leading parasitic endemic disease. It is a febrile erythrocytopathy caused by protozoa of the genus Plasmodium and transmitted by the bite of a vector insect, Anopheles[1]. Globally, the number of malaria cases is estimated at 219 million in 2017 with 435,000 deaths. Children under 5 years of age are the most vulnerable to malaria and account for 61% (266,000) of malaria deaths worldwide[2]. Five species of plasmodium are pathogenic to humans but P. falciparum is the most prevalent malaria parasite causing 99.7% of malaria cases in 2017 in Africa[2]. It is also responsible for almost all serious forms of malaria, so WHO defines severe malaria as the presence in a patient of asexual forms of Plasmodium falciparum in the blood associated with 15 serious clinical and biological manifestations[3]. The main manifestations are anemia, cerebral malaria, prostration, respiratory distress, cardiovascular collapse or shock, abnormal bleeding, jaundice, hemoglobinuria, hypoglycemia,

metabolic acidosis, renal failure, hyperlactatemia and hyperparasitemia[3]. Among the signs of malaria severity, symmetrical distal ischemia of the limbs is not included. However, authors have reported cases of malaria complicated by distal ischemia of the limbs. These reported cases most often concern children over 2 years of age [4, 5], adults [6, 7] and the elderly [8, 9]. Management of this ischemia is difficult, often resulting in amputation of the affected limb or death of the patient. We report a case of severe malaria with distal ischemia of all four limbs in a 4-month-old infant at Bouaké University Hospital. The objective of the study was to describe the main epidemiological, diagnostic, therapeutic and evolutionary aspects of this unusual complication for improving prognosis.

CASE REPORT

Male infant, 4 months old, admitted to the paediatric emergency room of the Bouaké University Hospital for respiratory difficulties. Signs began 3 days before admission with diarrhea of 4 pasty stools, vomiting

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without fever, cough and cold. Treatment including antidiarrhoea medication, ibuprofen, paracetamol, artemether-lumefantrine and metronidazole has been initiated and progress under this treatment has been towards respiratory distress. The infant was born at term by the vaginal route without incident. He was exclusively breastfed and stature-weight growth was normal. The vaccines in the expanded programme of immunization were not up to date for age and the infant did not sleep under a long-lasting insecticide-treated net. The socio-economic conditions of the parents were modest. The physical examination noted a normal consciousness with adynamia, a fever at 38.5°C, a heart rate at 144 beats per minute, a respiratory rate at 55 cycles per minute, a weight at 6 kg, a palmoplantar pallor. The pulmonary examination objectified non-riple respiratory distress to pulmonary auscultation. Heart sounds were regular without heart murmurs and peripheral pulses were well perceived. The ENT and abdominal examination were normal. The diagnostic hypotheses evoked in front of this table of decompensated anemia were martial deficiency anemia decompensated by intercurrent infection, severe malaria in its anemic form and sepsis. The results of the additional examinations carried out are presented in Table 1. The initial diagnosis of severe anemic malaria was retained. The treatment initiated included oxygen therapy (3 litres of oxygen/min), transfusion of 100 millilitres of compatible erythrocyte concentrate in the ABO and Rhesus systems, artesunate injection (20 mg direct intravenous injection at H0, H12 and H24 on the first day and 20 mg intravenously from the

second day onwards), injectable paracetamol (90 mg slow intravenous injection every 6 hours of time) and a hydroelectrolytic and energetic intake with glucose at 5% enriched in electrolytes (250 millilitres of glucose at 5% with 7.5 millilitres of sodium chloride, 5 millilitres of potassium chloride and 2.5 millilitres of calcium gluconate). The evolution was marked on day 1 of hospitalization by the occurrence of a generalized tonic-clonic seizure treated with diazepam (3 milligrams slow intravenous injection until the seizure stopped), a coma with a Blantyre score of 2/5, and the persistence of respiratory distress with bronchial obstruction requiring several oropharyngeal aspirations. On day 2 of hospitalization, the infant experienced respiratory arrest and was ventilated with a mask for 30 minutes. This resulted in coldness of the extremities with symmetrical ischemia of the hands and feet (Figure 1). The lumbar puncture performed reduced a clear cerebrospinal fluid with a rockwater appearance to macroscopy and absence of germs in the culture. The Doppler ultrasound of the heart and vessels performed was normal. The prothrombin level was 50%. The determination of fibrinogen level and D-dimers could not be performed. In view of the worsening clinical situation, probabilistic antibiotic therapy with ceftriaxone has been combined with antimalarial treatment. Prescribed heparin therapy was not honoured by the parents. The progression under this treatment was stationary and the ischemia progressed in 6 days to dry gangrene of the hands and feet. The infant's death occurred after 10 days of hospitalization.



Fig1. Symmetric ischemia of the extremities of the four limbs in a 4-month-old infant at Bouaké University Hospital

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Table 1. Paraclinical examinations performed and their results

Paraclinical examinations		Results	Reference values
Hemogram	White cells ($10^3/\text{mm}^3$)	12	5 - 15
	Redcells ($10^6/\text{mm}^3$)	2.1	3.5 - 4.5
	Hemoglobin (g/100 mL)	6	10 - 13
	Hematocrit (%)	18	35
	Averageblood volume (μ^3)	80	75 - 85
	Mean corpuscular hemoglobin content (pg)	30	27 - 32
	Mean corpuscular hemoglobin concentration (%)	33	32 - 36
	Platelets ($10^3/\text{mm}^3$)	60	200 - 350
Thick drip		15000 / μL	
Blood smear		<i>Plasmodium falciparum</i>	
Serumiron ($\mu\text{mol/L}$)		25	9 - 32
Ferritin ($\mu\text{g/L}$)		200	50 - 250
Transferrine (g/L)		3	2 - 3.6
Protein reactive C (mg/L)		4	< 6
Blood Urea (mmol/L)		1.8	1.6 - 6.5
Blood Creatinine ($\mu\text{mol/L}$)		40	30 - 70
Blood sugar level (mmol/L)		5.4	2.2 - 5.5
Prothrombin level (%)		50	70 - 100
Blood cultures		Negative	
Chest X-ray		Normal	
Blood types		A positive	
HIV serology		Negative	
Bacteriology of cerebrospinal fluid		Sterile cerebrospinal fluid	
Cardiac and vessel echo doppler		Normal	

DISCUSSION

The clinical case reported is a picture of severe malaria in a 4-month-old infant with multiple manifestations of severity and symmetrical distal ischemia of the four limbs of rapidly fatal progression. Symmetric limb ischemia or gangrene is defined as symmetric ischemic disease of two or more limbs in the absence of obstruction of large blood vessels[10]. It is an extremely rare and catastrophic condition in children[11]. There are many factors that favour limb ischemia, but classically, there are two main groups: infectious and non-infectious factors. [12]. Concerning infectious factors, the germs often implicated are pneumococcus, staphylococcus, meningococcus, pseudomonas[13, 14] and dengue, rubella and varicella-zoster viruses[15, 16]. Rare cases of limb ischemia due to *Plasmodium falciparum*, the main parasite of severe forms of malaria, have been described in the literature[4, 5, 8, 17]. Distal ischemia in this 4-month-old infant could lead to discussion of other etiologies in addition to malaria, including severe bacterial infection or arteriopathy. But the hypothesis of arteriopathy and severe infection were

disproved respectively by normal Doppler ultrasound of the heart and vessels and the normality of blood culture, cerebrospinal fluid and C-reactive protein. Despite the absence of D-dimer and fibrin dosage in the infant's medical record due to the inadequacy of the hospital's technical facilities, coagulopathy complicating malaria appeared more likely and would explain the symmetrical distal ischemia of the four limbs.

Distal limb ischemia associated with severe malaria results from obstruction of blood vessels by parasitized red blood cells and disseminated intravascular coagulation (DIC). The patho physiological mechanism of coagulopathy during malaria involves a cascade of phenomena including thrombocytopenia, platelet dysfunction, coagulation activation, lack of coagulation inhibitors, deficient fibrinolysis, cytokine production, endothelial cell activation, cytoadherence and tissue factor expression[18]. The coexistence in this immunocompetent 4-month-old infant of several manifestations of severity (respiratory distress with respiratory arrest, severe anemia, convulsions, coma) of malaria could explain the occurrence of

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symmetrical distal ischemia in all four limbs. The cases of symmetric limb ischemia reported so far in the literature concern children over 2 years of age[4, 5, 19, 20, 21, 22], adults[6, 23] and the elderly[8, 24]. To our knowledge, no cases have yet been reported in infants under 6 months of age in Côte d'Ivoire. Limb ischemia occurred in infants on day 5 of disease progression. This time lag is within the 2 to 9 day range described in the literature[7, 8, 21]. Ischemia affects the infant's hands and feet symmetrically. Thamhankar et al[4] reported ischemia of the toes, fingers, ear lobes with spots on the arms and legs in a 2.5 year old child in India. This topography of ischemia during malaria has also been reported in adults by authors [7, 25, 26, 27]. The infant's management consisted of intravenous administration of Artesunate and support for vital functions. Heparin therapy and limb amputation could not be performed in infants. As ischemia is extremely rare in the infant population, there are no consensual management guidelines[11]. Heparin therapy and amputation have been used in children [5, 19, 21]. The course of treatment was unfavourable with the infant's death after 10 days in hospital. Edwards et al [19] in Zimbabwe and Chittichai et al [20] in Thailand reported a favourable progression without amputation in children treated with antimalarial drugs and heparin.

CONCLUSION

Symmetric distal ischemia of the four limbs is a rare complication of severe malaria in infants under 6 months of age in malaria-endemic areas. It results from a disseminated intravascular coagulation mechanism. The prognosis in the absence of multidisciplinary management including cardiologist, pediatrician, intensive care unit and pediatric surgeon is bleak. Primary prevention is based on sensitizing parents to make infants sleep under the long-acting insecticide-treated net.

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