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Research Article

Severe malaria with invasive bacterial infections in children in a paediatric service in sub-Saharan Africa

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ABSTRACT

Background: Isolated or associated with other conditions, malaria is responsible for the death of a child every minute, mostly in sub-Saharan Africa. The main objective was to determine the epidemiological, clinical, and biological aspects and outcomes of severe malaria associated with invasive bacterial infections in children.
Methods: A prospective analytical study was conducted at Charles de Gaulle Paediatric University Teaching Hospital between 1 July and 31 August 2014 in Ouagadougou, Burkina Faso. Children with severe malaria and invasive bacterial infections were included.
Results: There were 140 children with severe malaria of whom 13.6% exhibited signs of invasive bacterial infection. Co-infection was significantly higher in children under 24 months (p = 0.02) who came from rural areas (p <10^{-6}). Respiratory distress (p = 0.03), shock (p = 0.0006), severe anaemia (p = 0.03), hypoglycaemia (p <10^{-6}), and high parasitaemia (p = 0.001) were significantly more frequent in cases of co-infection. Invasive bacterial infections included acute meningitis (11.4%) and pulmonary and digestive bacteraemia (3.2%). Identified pathogens were *Streptococcus pneumoniae* (10 cases), *Haemophilus influenzae* (six cases), and *Salmonella typhi* (three cases). The overall mortality rate was 6.4%; the mortality rate in co-infection cases was 16% vs. 1% in cases of isolated severe malaria (p = 0.0004).
Conclusions: Invasive bacterial infections were frequently associated with severe malaria in children in our paediatric service. The prognoses were poor, and affected children must be systematically sought and appropriately treated to contribute to the reduction of mortality in children under five years of age.

Keywords: Children, Co-infections, Invasive bacterial infections, Severe malaria

INTRODUCTION

Severe acute febrile illnesses are the main cause of hospitalisation and deaths in children in Africa.[1] The majority of these diseases are due to malaria and invasive bacterial infections (IBI), which are endemic in the tropics. Clinical symptoms are polymorphic and non-specific, so distinguishing among the pathologies is often difficult. The challenge for paediatricians facing acute febrile infections in this environment is to differentiate severe malaria from IBI or the coexistence of both in the same child. The risk of inappropriate treatment following a wrong diagnosis is thus higher in such situations. The World Health Organization (WHO) has stated that malaria is responsible for the death of a child every minute, mostly in Africa.[2] The lethality of malaria in Africa is higher in children when associated with bacterial infection.[3-5]

The transmission of malaria is high in Burkina Faso, where malaria is responsible for 66 265 hospitalisations/y (case fatality rate [CFR] 5.8%) among children 0-14 years of age and for the deaths of 57.2% of children under 5 years of age. The main bacterial infections are in the respiratory tract (10 539 cases; CFR 2.9%), typhoid/paratyphoid fever (1283 cases; CFR 1.1%), and bacterial meningitis (714 cases; CFR 18.4%).[6] Anti-malarial drugs and antibiotics are systematically co-administered in health centres for the treatment of children with severe fever, because severe malaria and IBI are difficult to discriminate. This practice is also advocated by the WHO Integrated Management of Childhood Illness strategy at the level of peripheral health facilities due to the lack of competent caregivers and technical equipment.[7] Referral hospitals, however, should be able to provide an accurate diagnosis to streamline prescriptions and increase their efficiency. A good strategy for the management of malaria and IBI co-infection cannot be developed without a thorough understanding of their occurrence. This study thus aimed to describe the characteristics of severe malaria and IBI co-infection at Charles de Gaulle Paediatric University Teaching Hospital (CHUP CDG) in Ouagadougou, Burkina Faso.

METHODS

Study site

CHUP CDG is a tertiary health centre that receives not only all the children from Ouagadougou but also those referred from other health facilities in the country. Hospital statistical data show that 85 of 1156 cases of malaria hospitalised in 2013 resulted in death, demonstrating a CFR of 7.4%.[6]

Study design

This prospective cross-sectional analytic study covered a period of two months from 1 July to 31 August 2014 and included all children of both sexes aged 0–15 years referred for severe malaria. Clinical examination and complementary exploration helped the diagnosis of IBI. We systematically performed thin and thick blood smears for each child admitted with signs of severe malaria to characterise the asexual malarial parasites, blood counts, and C - reactive protein (CRP) levels, lumbar punctures with cerebrospinal fluid (CSF), and blood cultures. Other tests (e.g. urine, stool culture, and X rays) were performed based on the clinical information.

Definitions

We defined a case of severe malaria as any patient with at least one of the WHO clinical or laboratory criteria associated with a positive peripheral *Plasmodium falciparum* parasitaemia.[8] IBI was defined as bacteraemia and/or meningitis. Bacteraemia was diagnosed by the isolation of pathogenic organisms from blood cultures. Meningitis was defined as a positive CSF, a white cell count >10/µL in the CSF, or a positive bacterial antigen test or gram stain. Otherwise, sepsis was considered in a child with leucocytosis, with CRP >20 mg/L and procalcitonin (PCT) >7 µg/L.

Data collection and analysis

Sociodemographic and clinical variables and those for complementary investigations and outcomes were collected in a pro forma designed for this study before analysis using Epi-Info™ 3.3.2 (Centres for Disease Control, Atlanta, USA). The Chi-square test was used for comparisons between qualitative variables. Statistical significance was set at $p < 0.05$.

RESULTS

Epidemiological data

Of the 850 children hospitalised during the study period, 443 were referred for severe malaria. Of these 443 children, 140 met the criteria of severe malaria, of which 91 were boys and 49 were girls, demonstrating a male: female sex ratio of 1.85:1. Children aged 6-24 months accounted for 44.3% of the sample, and the average age of the patients was 30 months (Range: 2 months to 11 years). In 94.3% of the cases, the patients resided in urban areas.

Clinical presentation, laboratory findings, and risk factors for severe malaria-IBI co-infection

Of the 140 children with severe malaria, 19 (13.6%) exhibited signs of IBI. The identified IBI included bacterial meningitis (16 cases; 11.4%) and bacteraemia of pulmonary and digestive origins (three cases; 2.2%). *Streptococcus pneumoniae* (10 cases), *Haemophilus influenzae* (6 cases), and *Salmonella typhi* (three cases) were the identified bacterial pathogens.

The main sociodemographic factors associated with co-infection were young age ($p = 0.02$) and residence in a rural area ($p < 10^{-6}$). Clinically and biologically, respiratory distress ($p = 0.03$), shock ($p = 0.0006$), hypoglycaemia ($p = 0.03$), severe anaemia ($p = 0.03$), high parasitaemia ($p = 0.001$), and leucocytosis ($p < 10^{-6}$) were significantly associated with co-infection (Table 1).

Outcome

The hospital duration was significantly longer for co-infections ($p < 10^{-6}$). The global mortality rate was 6.4%. The CFR was 16% for co-infection and 1% for isolated

severe malaria; this difference was statistically significant (p = 0.0004).

Table 1: Demographic, clinical, biological, and outcome risk factors associated with severe malarial and invasive bacterial co-infection.

Risk factor	Bacterial and severe malarial co-infection		*P value*
	Yes (n = 19)	No (n = 121)	
Age (months)			
<24	13	65	0.02
≥24	6	56	
Sex			
Male	14	77	0.4
Female	5	44	
Residence			
Rural	06	02	$<10^{-6}$
Urban	13	119	
Respiratory distress			
Yes	17	79	0.03
No	2	42	
Shock			
Yes	8	14	0.0006
No	11	107	
Haemoglobin (g/L)			
<50	11	40	0.03
≥50	8	81	
Glycaemia (mmol/L)			
<2.2	10	8	$<10^{-6}$
≥2.2	9	113	
Parasitaemia (/µL)			
>100000	11	28	0.001
≤100000	8	93	
Leucocytosis (≥20000WBC/mm^3)			
Yes	16	9	$<10^{-6}$
No	3	112	
Duration of hospitalization (days)			
>3	18	55	$<10^{-6}$
≤3	1	66	
Death			
Yes	8	1	$<10^{-6}$
No	11	120	

DISCUSSION

Frequency of severe malaria-IBI co-infection

IBI was associated with severe malaria in 13.6% of the patients. This frequency is similar to those reported for Ghana (12%)[5] and Nigeria (17.7%),[9] but is higher than those reported for Kenya (7.8%),[4] Gambia (5%),[10] and Malawi (4.6%).[11] A previous study had reported 2.7% for rural Burkina Faso.[12] Our result, however, is three-fold lower than that reported for Nigeria by Ayoola *et al*, (38.2%).[13] The differences in frequencies between studies may depend not only on the methodology used, but also on the epidemiology of bacterial infections in the various countries. Antibiotics, which are indiscriminately prescribed in Africa, may also be misused in outpatients, a situation that prevents the collection of microbiological evidence of bacterial infections when patients are hospitalised. Emergency services in developed countries, pending the results of biological cultures, should prescribe antibiotics only for elevated levels of CRP and/or PCT.[14,15] In our context of a developing country, we recommend adding leucocytosis (>20 000 neutrophils leucocytes/mm^3) to these two biological parameters.

The causative bacteria

The main bacterial pathogens in our study were, in order of frequency, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Salmonella typhi*. These bacteria have also been commonly reported in other studies, albeit at different frequencies, in addition to *Staphylococcus aureus* and *Escherichia coli*.[3,9,10,12,13] Several factors may have influenced our results, including the diagnostic methods used and the antibiotic treatments often received by children prior to admittance to the hospital.

Characteristics of severe malaria-IBI co-infection

A sociodemographic analysis indicated that young age and rural residence were significantly associated with co-infection. Young age has also been reported as a risk factor for co-infection by Berkley *et al*, Evans *et al*, Ladhani *et al*, and Modiano *et al*.[4,5,16,17] The immature immune systems of infants and the loss of maternally transmitted immunity six months after birth may contribute to co-infections. This physiological immunodeficiency is aggravated by promiscuity, unsanitary conditions, malnutrition, and delays in diagnosis and treatment commonly seen in low-resource settings. The clinical shock and the respiratory distress observed in this study have also been reported in other African studies.[3,5,16] Our findings were biologically consistent with those of some African studies[3-5,16,18] where parasitaemia, severe anaemia, hypoglycaemia, and leucocytosis were commonly present in co-infections. These findings suggest that bacterial infection is a co-factor for anaemia and hypoglycaemia in severe malaria. Concomitant infections likely increase the risk of anaemia and hypoglycaemia in malarial patients by activating the reticuloendothelial system, as in bacterial sepsis infections demonstrated by Miller *et al*.[19]

Bacterial infection can significantly increase mortality in severe malaria.[3,4,17] In our study, the CFR rose from 1% in isolated severe malaria to 16% when associated with IBI. Mortality can be 3-5-fold higher in co-infections

than in isolated severe malaria.[4,5,10,17] Other factors such as younger age, severe anaemia, and hypoglycaemia could intervene as risk cofactors for death

CONCLUSION

Co-infection of severe malaria with invasive bacteria was frequent in hospitalised children in our paediatric service. This morbid association should be suspected in young children with shock, respiratory distress, and a severe pallor with high neutrophil leucocytosis, CRP, and/or PCT. In emergencies, the decision to prescribe an antibiotic in association with an anti-malarial drug is easily made. The results of subsequent microbiological cultures may or may not justify this therapeutic choice.

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REFERENCES

1. WHO Young Infants Study Group. Bacterial etiology of serious infections in young infants in developing countries: results of a multicenter study. Pediatr Infect Dis J. 1999;18:S17-22.
2. WHO. World malaria report 2013. Accessed online from 2014.
3. Akpede GO, Sykes RM. Malaria with bacteraemia in acutely febrile preschool children without localizing signs: coincidence or association/complication? Am J Trop Med Hyg. 1993;96:146-50.
4. Berkley J, Mwarumba S, Bramham K, Lowe B, Marsh K. Bacteraemia complicating severe malaria in children. Ann Royal Soc Trop Med Hyg. 1999;93:283-6.
5. Evans JA, Adusei A, Timmann C, May J, Mack D, Agbenyega T, et al. High mortality of infant bacteraemia clinically indistinguishable from severe malaria. Q J Med. 2004;97:591-7.
6. Burkina Faso Ministry of Economy and Finance (eds). Statistics Directory 2013. Ouagadougou: INSD. Dec. 2014 ;376p.
7. WHO. Prise en charge intégrée des maladies l'enfant (PCIME).
8. WHO. Severe falciparum malaria. Royal Soc Trop Med Hyg. 2000;94:56-9.
9. Ganiyu AO, Abayoni OB, Oludele AE, Gladys FA. Leucocytes migration and nitro blue tetrazolum assay in Nigerians children with bacteraemia and malaria parasitemia. Asian Pac J Allergy Immunol. 2004;22:213-8.
10. Enwere G, Van Hensbroek MB, Adegbola R, Palmer A, Onyiora E, Weber M, et al. Bacteraemia in cerebral malaria. Ann Trop Pediatr. 1998;18:275-8.
11. Bronzan RN, Taylor TL, Mwenechanyas T, Tembo M, Kayira K, Bwanaisa L, et al. Bacteremia in Malawian children with severe malaria: prevalence etiology, HIV co infection and outcome. J Infect Dis. 2007;95:895-904.
12. Maltha J, Guiraud I, Kaboré B, Lompo P, Ley B, , Bottieau E, et al. Frequency of severe malaria and invasive bacterial infections among children admitted to a rural hospital in Burkina Faso. PLoS One. 2014;9(2):e89103.
13. Ayoola OO, Adeyyeino AA, Osinusi K. Concurrent bacteraemia and malaria in febrile Nigerian infants. Trop Doct. 2005;35:34-6.
14. Gendrel D. Use of procalcitonin at the pediatric emergency room. Arch Pediatr. 2004;11:582-4.
15. Lorrot M, Moulin F, Coste J, Ravilly S, Guérin S, Lebon P, et al. Procalcitonin in pediatric emergencies: comparison with C-reactive protein, interleukin-6 and interferon alpha in the differentiation between bacterial and viral infections. Presse Med. 2000;29:128-34.
16. Ladhani S, Lowe B, Cole AO, Kowuondo K, Newton CR. Changes in white blood cells and platelets in children with Falciparum malaria: relationship to disease outcome. Br J Haematol. 2002;119(3):839-47.
17. Modiano D, Sirima BS, Konaté A, Sanou I, Sawadogo A. Leucocytosis in severe malaria. Trans R Soc Trop Med Hyg. 2001;95:175-6.
18. Biemba G, Dolmans D, Thuma PE, Weiss G, Gordeuk VR. Severe anaemia in Zambian children with Plasmodium falciparum malaria. Trop Med Int Health. 2000;5(1):9-16.
19. Miller SI, Wallace RJ Jr, Musher DM, Septimus EJ, Kohl S, Baughn RE. Hypoglycaemia as a manifestation of sepsis. Am J Med. 1980;68:649-54.

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