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Severe and complicated malaria in KwaZulu-Natal

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Objective. To describe severe and complicated malaria, including the common complications, causes of death and predictors of poor outcome.

Design. Retrospective case series.

Setting. King Edward VIII Hospital, Durban, Natal, a referral centre.

Patients. One hundred and forty-three consecutive patients (88 males, 55 females; median age 25 years, range 2 - 86 years) admitted with a microscopic diagnosis of *Plasmodium falciparum* malaria from 1984 to 1991.

Main outcome measures. A univariate analysis comparing survival and death for categorical and continuous data for various complications was performed using the *t*-test or χ^2-test (or Fisher's exact test in the case of small cell sizes). Variables that showed significance on univariate analysis ($P < 0.1$) were used in a multivariate analysis to determine which contributed independently to survival or death.

Results. The case fatality rate was 11.1% (15/135) and the commonest complications were hyperparasitaemia (30%), renal failure (17%), acidaemia (14%), jaundice (10.4%) and cerebral malaria (6%). The commonest complications in patients who died were renal failure (10 patients), cerebral malaria (7), hyperparasitaemia (6) and severe anaemia (5). Multivariate analysis using a logistic regression model showed a high parasite load and cerebral malaria (relative risks of 11.9 and 51.8 respectively) and high urea levels to be the significant predictors of poor outcome (95% confidence intervals 1.53 - 91.9, 2.74 - 100.0 and 1.01 - 1.09, respectively).

Conclusions. Patients with high parasite densities, cerebral involvement and renal dysfunction need urgent attention with parenteral chemotherapy, intravenous fluid replacement and early referral to a tertiary hospital with facilities for intensive monitoring and supportive treatment.

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Severe falciparum malaria is defined by the demonstration of asexual forms of *Plasmodium falciparum* in patients with a potentially fatal manifestation or complication of malaria in whom other diagnoses have been excluded.[1] Such patients require special management including parenteral chemotherapy. The purpose of attempting to describe severe falciparum malaria is twofold: (*i*) to alert clinicians and other health care workers to the symptoms and signs associated with progression to life-threatening disease, for which urgent and special treatment is required, including parenteral chemotherapy, or referral to a level of health services where this can be given; and (*ii*) to allow for the comparison of study populations in different geographical areas and the interpretation of data such as efficacy of various treatments, morbidity, mortality, and long-term sequelae.

No single definition of severe and complicated malaria is satisfactory or relevant in all clinical situations. Age and supposed immune status affect the prognostic significance of the height of fever and parasitaemia. In parts of the world where falciparum malaria is holo- or hyper-endemic, most cases of severe malaria occur among young children over the age of 6 months, with the greatest mortality in those between 1 and 3 years of age.[2] In areas of lower endemicity severe malaria occurs in both adults and children.

An informal technical meeting on severe and complicated malaria sponsored by the World Health Organisation was held in June 1985.[1] The purpose was to review in detail what is known about severe and complicated malaria, so that guidelines for management of clinical cases to reduce mortality at all levels of health services could be prepared. A second informal technical meeting on this subject was held in March 1988 to review the latest knowledge and experience, and update the findings of the first meeting.[2]

Northern Natal has the highest prevalence of falciparum malaria in South Africa,[3] and this area represents the most southern distribution of the infection in Africa. Sharp[4] showed in 1991 that although very little transmission of the disease occurs outside this area, the disease pattern within it has changed significantly and the transmission of malaria is now epidemic or seasonal.[4] The present study was conducted to describe severe and complicated malaria, including its common complications and outcome, at King Edward VIII Hospital, Durban.

Patients and methods

The hospital records of all patients with a final diagnosis of falciparum malaria admitted to King Edward VIII Hospital, Durban, from January 1984 to December 1991 were studied. This hospital has 1 934 beds and is a teaching and tertiary referral hospital for KwaZulu-Natal, which has a total population of 7.9 million inhabitants. Although Durban itself is not a malaria-endemic area, the hospital accepts referrals from district and regional hospitals situated in endemic areas. In addition many patients are self-referred, without previous attendance at a primary or secondary health centre. The patients reported on are therefore not representative of the general population.

The data collection followed the guidelines suggested in the report of the first informal technical meeting of the WHO on severe and complicated malaria.[1] This included demographic, clinical, haematological, biochemical and therapeutic information, as well as outcome. The definition of severe manifestations and complications closely followed those recommended by the report of the second informal

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technical meeting.[2] For the purposes of this retrospective study, the strict definitions of cerebral malaria as proposed by Warrell *et al.*[5] and Molyneux *et al.*[6] in adults and children respectively were not adhered to. Where the clinical records described the patient as having cerebral malaria, this was accepted as a severe manifestation.

Statistical analysis

Survival and death were compared with regard to age, parasite count, haemoglobin concentration, white cell count, and urea, creatinine and bilirubin values. The following complications were considered in the analysis: presence of cerebral malaria, severe anaemia (haemoglobin < 5.0 g/dl), hyperparasitaemia (parasite load > 5%), renal failure (serum creatinine > 265 µmol/l), chloroquine-resistant malaria (*in vivo* or *in vitro*), acidaemia (HCO_3 < 15 mmol/l) and jaundice (bilirubin > 50 µmol/l).

For univariate analysis, the *t*-test or the χ^2-test (or Fisher's exact test in the case of small cell sizes) was used where appropriate. Relative risks and 95% confidence intervals (CIs) were calculated for the associations between the outcome variable and complications. Variables that showed significance on univariate analysis ($P < 0.1$) were used in a multivariate analysis to determine which ones contributed independently to survival or death. For multivariate analysis, logistic regression was used.

Results

One hundred and forty-three patients with a microscopic diagnosis of *P. falciparum* malaria were admitted in the 8 years between 1984 and 1991 inclusive. There were 88 males and 55 females, with a median age of 28 years (range 2 - 86 years). In 52 cases the patient was referred from a primary or secondary care facility. For 8 patients the outcome was unknown. A total of 15 patients died, giving a case fatality rate of 11.1% (15/135). The peak age of admission was in adolescents and young adults (10 - 30 years). Patients most often contracted malaria from the local endemic area of northern KwaZulu-Natal (58 cases), followed by visitors returning from Mozambique (27) and Malawi (17). In 32 cases no history of travel to an endemic area was recorded (Table I).

Table I. Regions where malaria was contracted

Region	No. of patients
Northern KwaZulu-Natal	58
No travel or residence in endemic area	32
Mozambique	27
Malawi	17
Zambia	2
Swaziland	2
Zimbabwe	1
Botswana	1
Eastern Transvaal	1
Tanzania	1
Namibia	1

The clinical features on admission included vomiting (34 patients), jaundice (28), splenomegaly (62), hepatomegaly (48), convulsions (10) and loss of consciousness (3). Table II lists the complications diagnosed, either on presentation or while in hospital. In only 77 patients was the parasite load quantified; in 23 of these cases more than 5% of the erythrocytes were infected with *P. falciparum* (hyperparasitaemia), and 6 of these patients died (Table II). The mean parasite density was 22.3% in 9 patients in whom the parasite load was quantified and who died compared with 4.2% in 68 patients who survived. Acidaemia, convulsions and spontaneous bleeding occurred more frequently than hypoglycaemia, severe anaemia and circulatory collapse (Table II). Eleven patients had superadded infections, 3 of the urinary tract and 8 of the chest.

Table II. Complications and mortality data from falciparum malaria in 135 patients*

Complications	No. of patients/ No. tested†	Deaths
Cerebral malaria	9	7
Severe anaemia (Hb < 5.0 g/dl)	6/137	5
Renal failure (serum creat. > 265 µmol/l)	24	10
Pulmonary oedema	4	2
Hypoglycaemia (glucose < 2.2 mmol/l)	2/68	1
Circulatory collapse	0	0
Spontaneous bleeding	9	3
Generalised convulsions	10	3
Acidaemia (HCO_3 < 15 mmol/l)	15/111	3
Blackwater fever	1	0
Hyperparasitaemia (> 5%)	23/77	6
Jaundice (bilirubin > 50 µmol/l)	8/77	1
Hyperpyrexia (> 40°C)	5/128	0

* Not mutually exclusive.
† No. of patients for whom the data were available.
Hb = haemoglobin.

Renal failure (serum creatinine > 265 µmol/l), the commonest complication, occurred in 24 patients, 10 of whom died (Table II). Of the 24 patients with renal failure, 10 underwent dialysis (8 peritoneal dialysis, 2 haemodialysis). The remainder responded to rehydration with intravenous fluids. Only 3 of the 10 patients who died underwent dialysis. The mean serum creatinine level was 476 µmol/l (range 103 - 1 020 µmol/l) in those who died compared with 246 µmol/l (range 30 - 1 830 µmol/l) in the survivors. Two patients had hepatorenal failure; their parasite densities were 15% and 10%, and 1 of them died. Nine patients, of whom 7 died, were assessed as having cerebral malaria. The mean age for the 10 patients who had convulsions was 25 years (range 6 - 60 years).

Thirty-four patients required blood transfusion, 8 peritoneal dialysis, 2 haemodialysis and 1 an exchange transfusion. Chloroquine was the most frequently used drug (105 patients), followed by quinine (47 patients). The frequency of use of the different antimalarial agents is shown in Table III. Eighty-two patients were treated with chloroquine alone, 28 with quinine alone, and 18 with both drugs. Of those who received chloroquine 10.4% died, and of those who received quinine 12.2% died (not significant). Seven patients showed *in vivo* or *in vitro* evidence of chloroquine resistance. The mean duration of symptoms before presentation was 8 days in both the survivors and the patients who died.

Table III. Antimalarial agents used for therapy*

Drugs	No. of patients
Chloroquine	105
Quinine	47
Fansidar (sulfamethoxazole/pyrimethamine)	3
Primaquine	8
Daraclor (chloroquine/pyrimethamine)	8

* Not mutually exclusive.

The univariate analysis for categorical data and for continuous data for survival versus death is shown in Tables IV and V respectively. Multivariate analysis using a logistic regression model showed high parasite loads and cerebral malaria (relative risks of 11.9 and 51.8 respectively) and high urea levels to be the significant predictors of poor outcome (Table VI).

Table IV. Univariate analysis comparing survival and death with regard to categorical data for various complications

Variable	No.	Deaths (%)	*P*-value	RR	95% CI
Haemoglobin					
< 5 g/dl	6	16.67	NS	1.862	0.286 - 12.195
⩾ 5 g/dl	123	8.94			
Parasite load					
> 5%	22	31.82	0.004	5.952	1.686 - 20.83
⩽ 5%	56	5.36			
Creatinine					
⩾ 265 µmol/l	22	36.36	0.0025	5.263	1.764 - 15.87
< 265 µmol/l	56	6.90			
HCO_3					
< 15 mmol/l	15	26.67	0.049	3.42	1.14 - 10.31
⩾ 15 mmol/l	90	7.78			
Bilirubin					
> 50 µmol/l	7	14.29	NS	3.05	0.364 - 25.64
⩽ 50 µmol/l	64	4.69			
Cerebral malaria					
Yes	9	77.78	< 0.0001	12.195	5.714 - 25.64
No	125	6.40			
Chloroquine-resistant malaria					
Yes	7	14.29	NS	1.295	0.197 - 8.475
No	127	11.02			

RR = relative risk.

Table V. Univariate analysis comparing survival and death with regard to continuous data (mean ± standard deviations)

	Survivors		Deaths		
Variable	No.	Mean ± SD	No.	Mean ± SD	*P*-value
Age	119	26.42 ± 17.25	15	42.67 ± 22.88	0.0172
WCC	117	8.46 ± 9.17	11	10.89 ± 4.51	NS
Platelets	109	192.33 ± 134.24	10	107.0 ± 86.62	0.014
Urea	98	13.128 ± 17.62	14	30.20 ± 19.06	0.0059
Hb	117	9.958 ± 3.01	12	9.317 ± 3.073	NS
Creatinine	68	242.18 ± 374.7	12	476.0 ± 299.89	0.0281
Sodium	99	133.28 ± 5.613	14	133.07 ± 11.91	NS
HCO_3	94	21.315 ± 4.796	11	14.764 ± 7.91	0.0212
Bilirubin	67	27.37 ± 30.76	4	88.25 ± 113.33	NS
AST	63	46.84 ± 39.03	4	177.50 ± 58.30	0.019

WCC = white cell count; Hb = haemoglobin; AST = aspartate aminotransferase.

Table VI. Multivariate analysis (logistic regression model) showing the significant predictors of death

Variable	Estimate	*P*-value	RR	95% CI
Hyperparasitaemia	2.475	0.018	11.91	1.53 - 91.9
Urea	0.048	0.015	1.05	1.01 - 1.09
Cerebral malaria	3.947	0.008	51.8	2.74 - 100.0

RR = relative risk.

Discussion

Since 1984 malaria notifications in South Africa have increased substantially.[4] This increase can be attributed to the heavy seasonal rainfall and resistance of the mosquito to insecticides and of the parasite to chemotherapeutic agents. Chloroquine resistance was first described in Natal in 1985,[7] and subsequent studies have shown high levels of resistance.[8] A recent clinical study in northern KwaZulu-Natal has shown that the disease pattern has changed over the decades, and strongly suggests that the previously semi-immune state of the population now no longer exists.[9,10] This change in the clinical profile of the infection would be compatible with the change in the transmission pattern from an endemic to an epidemic form, resulting in reduced acquired immunity to the parasite.

The present study confirms that all ages are predisposed to infection, including severe manifestations. This is unlike the age distribution in semi-immune populations, where children bear the brunt of the disease. None of the 32 children (age 2 - 12 years) in our study cohort died. The high mortality rate (10.5%) reflects the more serious cases seen at a referral hospital. The majority of patients in this study contracted the infection from local endemic areas; this is in contrast to a similar study at a major teaching hospital in Johannesburg, where almost all the patients contracted the infection in other countries.[11] The Johannesburg General Hospital does not serve a malarious area, and the city is a major entry and exit point for travel to countries in sub-Saharan Africa. The commonest causes of mortality in that study were also renal failure and cerebral malaria.

Renal failure, one of the commonest complications, occurred in 17% (24/143) of the patients, with a mortality rate of 42% (10/24). These figures are remarkably similar to those of Stone *et al.*[12] in a non-immune population, where the overall mortality rate in patients with renal impairment was 45%, compared with 10% in those without. The natural history is of reversible dysfunction which, in a minority of cases, progresses to established acute renal failure.[2] The early detection and correction of hypovolaemia and dehydration are essential to prevent this. Although a high urea level was a statistically significant predictor of death in our study, the relative risk was only 1.05 (95% CI 1.01 - 1.09). This probably reflects the reversible nature of the uraemia.

Cerebral malaria, although not frequently diagnosed (6%), was almost uniformly fatal (7/9 patients). This may be an underestimate, however, since some patients may not have been referred because their clinical condition prevented transfer over long distances. The mortality rate for cerebral malaria ranges from 10% to 50% in treated patients,[5] yet most survivors have no easily detectable neurological deficit. Obstructed microcirculatory flow due to 'sludging' of red cells in capillaries and venules is thought to be at least

partly responsible.[2] A recent study has suggested that anticardiolipin antibodies may also play a role in the cerebral manifestations of falciparum malaria.[13] The age distribution of the patients with convulsions suggests that these were not febrile convulsions, but rather due to cerebral complications such as cerebral oedema.

High parasite densities and acidaemia were also commonly seen in this series. Field[14] showed in 1949 that poor outcome in falciparum infection was directly related to high parasite density, although the reverse was not true. This finding implies that the level of parasitaemia is not the only factor determining malaria mortality; the immune status of the population is also a major determinant. Hypoglycaemia and circulatory collapse were distinctly uncommon; these complications may have been overstressed in previous studies. Chloroquine was the commonest antimalarial drug used for treatment during the study period, followed by quinine. Resistance to chloroquine was demonstrated in 7% of the patients, although this is probably an underestimate, since in most severe cases quinine therapy was commenced on admission to hospital. Drugs such as mefloquine and halofantrine were not available for use in South Africa during the period of this study.

Delay in presentation to hospital did not appear to be a factor contributing to mortality, since both survivors and those who died had the same mean duration of symptoms (8 days) before admission. In conclusion, high parasite densities, cerebral involvement and renal dysfunction were the predictors of poor outcome. Patients with these complications need urgent attention with parenteral chemotherapy, intravenous fluid replacement and early referral to a tertiary hospital with facilities for intensive monitoring and supportive treatment. Intravenous quinine should be commenced immediately if any features indicating severe malaria become evident.

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