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Admission diagnosis of cerebral malaria in adults in an endemic area of Tanzania: implications and clinical description

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Summary

Background: Cerebral malaria is commonly diagnosed in adults in endemic areas in Africa, both in hospitals and in the community. This presents a paradox inconsistent with the epidemiological understanding that the development of immunity during childhood confers protection against severe disease in adult life.
Aim: To establish the contribution of *Plasmodium falciparum* infection in adults admitted with neurological dysfunction in an endemic area, to assess the implications of an admission clinical diagnosis of 'cerebral malaria' on the treatment and clinical outcome, and to describe the clinical features of patients with malaria parasitaemia.
Design: Prospective observational study.
Methods: We studied adult patients admitted with neurological dysfunction to Muhimbili National Hospital, Dar-es-Salaam, Tanzania from October 2000 to July 2001. A full blood count was done and serum creatinine, blood glucose and *P. falciparum* parasite load were measured.
Results: Of 199 patients (median age 34.5 years), 38% were diagnosed as 'cerebral malaria' on admission, but only 7.5% had detectable parasitaemia, giving a positive predictive value of 13.3%. Only 1% fulfilled the WHO criteria for cerebral malaria. The prevalence of parasitaemia (7.5%) was less than that observed in a group of asymptomatic controls (9.3%), but distribution of parasite densities was higher in the patients. Mortality was higher in patients with no parasitaemia (22.3%) than in those with parasitaemia (13%).
Discussion: Cerebral malaria was grossly overdiagnosed, resulting in unnecessary treatment and insufficient investigation of other possible diagnoses, which could lead to higher mortality. Extension of this misperception to the assessment of cause of death in community surveys may lead to an overestimation of the impact of malaria in adults.

Introduction

Cerebral malaria, one of a number of severe manifestations of infection with *Plasmodium falciparum*, is an important cause of malaria mortality worldwide. Over the last 20 years, the clinical features of cerebral malaria have been extensively characterized in adults in Southeast Asia[1,2] and Papua New Guinea,[3] and in children in Africa.[4–7] The paucity of reported cases in adult Africans, with the exception of a few from areas of varying endemicity,[8–12] is consistent with the epidemiological understanding that severe morbidity is limited by the development of immunity under the stable

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endemic conditions prevailing in much of Africa.[13] However, this epidemiological concept contrasts with clinical experience in some areas of Africa, where 'cerebral malaria' is commonly diagnosed both in hospitals and in the community. In Tanzania, malaria has been reported to be responsible for between 10% and 50% of adult admissions, out-patient clinic attendance and deaths.[14–17]

To examine the incidence and clinical features of cerebral malaria among adult Tanzanians in an area of stable malaria transmission, we prospectively studied patients admitted with neurological dysfunction to a large urban hospital in Tanzania. Our aim was to determine the contribution of *Plasmodium falciparum* infection to neurological dysfunction in adults. In addition, we attempted to assess the implications of an admission diagnosis of 'cerebral malaria' on the treatment and clinical outcome. Finally, the clinical and laboratory features of the patients with peripheral malaria parasitaemia were described, in an attempt to define the possible spectrum of neurological presentations of malaria in adult Tanzanians.

Methods

Study site

The study was done at Muhimbili National Hospital (MNH), in Dar-es-Salaam on the coast of Tanzania. Dar-es-Salaam is the largest of the country's 20 regions, and serves as the commercial and administrative centre. Malaria is endemic in Dar-es-Salaam. Transmission occurs throughout the year, with a seasonal increase in intensity that coincides with the two rainy seasons, March to May and October to December. MNH, located in Ilala, one of the three districts of Dar-es-Salaam, is a teaching hospital affiliated to Muhimbili University College of Health Sciences (MUCHS). Although it is the national referral centre, it also functions as a district/regional hospital to approximately 2.4 million Dar-es-Salaam residents. MNH has 1400 beds, 350 being distributed across five adult medical wards. There is a mean of 25 admissions to the medical wards each day.

Recruitment

We studied three of the five adult medical wards from October 2000 to July 2001. Patients were recruited on the three days each week when one of the medical firms was admitting. The admitting doctor was responsible for the initial screening and resuscitation of all patients. Any patient aged 15 years or more, with neurological dysfunction on admission or from the history during the current illness, was recruited. Neurological dysfunction included prostration (inability to sit unaided), altered level of consciousness (obtunded to coma) and acute psychiatric features associated with features suggestive of organic disease such as fever or systemic upset. All patients who fulfilled these inclusion criteria were recruited into the study after they or their relatives had given informed consent. With unconscious patients, permission was sought when they regained consciousness. Patients were assessed within 12 h of admission by the investigators, and data were recorded on standardized proformas. To estimate the prevalence of asymptomatic malaria parasitaemia in the community, patients were recruited from the orthopaedic wards from May to July 2001. The demographic information collected included age, sex, occupation, place of birth and current residence.

Procedures

Forearm venous blood (10 ml) was taken into EDTA for full blood count and into empty sterile vacutainers for the measurement of serum creatinine. A thick blood smear was made either from capillary blood sample in the wards or from the venous sample in the laboratory. Slides were stained with 10% Giemsa solution and *P. falciparum* asexual parasites were counted against 200 white blood cells (WBC). The parasite density was calculated using the mean white cell count (7.1 mm^{-3}) of the normal population. A slide was considered negative if no trophozoites were seen after 200 high power fields were examined. The slides were reread at the KEMRI Centre for Geographic Medicine Research Coast (CGMRC) in Kilifi, Kenya. Any discrepancies were resolved by further examination. Haemoglobin level and white cell counts (total and differential) were done by Coulter counter (model CD 1200). From October to December 2000, patients who were admitted with impaired consciousness or suspected diabetes mellitus had their venous blood glucose measured in the hospital biochemistry department. Thereafter, all patients recruited into the study had blood glucose concentrations measured using Glucometer Elite (Bayer) in the wards.

All patients who presented with clinical features of meningitis had a lumbar puncture and were started on intravenous benzyl penicillin 5.0 MU and chloramphenicol 1 g given every 6 h. Patients who did not have obvious signs of meningism, with or without peripheral malaria parasitaemia, were started immediately on intravenous quinine at a dose of 600 mg dihydrochloride salt in 500 ml

dextrose saline, given every 8 h. If there was no clinical improvement in these patients after 24 h, a lumbar puncture was done. However, if there were any focal neurological signs or evidence of raised intracranial pressure, lumbar puncture was not performed. Investigations for cerebrospinal fluid included, Gram stain, white cell count (total and differential), protein and glucose concentrations, India ink staining for *Cryptococcus neoformans*, Ziehl-Nielsen staining for acid-fast bacilli and bacterial culture for 48 h. For the control population from the orthopaedic wards, a thick blood smear was made from capillary blood and the parasite density was calculated as in the patients.

Ethical approval

The study was approved by the Muhimbili University College of Health Sciences research committee, which is responsible for ethical clearance of studies carried out in the hospital, in accordance with the national policy for ethical approval.

Data entry and analysis

All clinical and laboratory data were entered using Epi Info software (version 6.04d, 1997) incorporating range checks. The data were subsequently converted into FoxPro files (version 6.0, 1999). Analysis was done using Stata (version 7.0; 2000). Continuous variables with a normal distribution were compared between groups by t tests. For variables without a normal distribution, the Mann-Whitney U test was used. Categorical variables were compared using the χ^2 test and Fisher's exact test. A p value of <0.05 was considered significant. The sensitivity of the admission diagnosis of 'cerebral malaria' as a screening test to predict parasitaemia was calculated as the proportion of patients with clinical 'cerebral malaria' and parasitaemia (true positives) to all patients with an admission diagnosis of clinical 'cerebral malaria'. The specificity was calculated as the ratio of patients with no 'cerebral malaria' and who had no parasitaemia (true negatives) to all patients with negative parasitaemia. The positive predictive value of the admission diagnosis was determined by the proportion of patients with parasitaemia amongst all patients with clinical diagnosis of cerebral malaria on admission. Next, the working diagnoses on admission were assessed, and the implications on final diagnosis, treatment and outcome. Finally, the clinical and laboratory features of patients with positive and negative parasitaemia were compared.

Results

Between October 2000 and July 2001, 1259 (24%) patients out of 5359 admitted to the general medical wards had a clinical diagnosis of malaria, of whom 183 (3.4%) were defined by admitting doctors as 'cerebral malaria'.[18] Two hundred and seventeen patients from one medical firm fulfilled the inclusion criteria of neurological dysfunction and were recruited into the present study. Complete data including the results of malaria parasitology were available for 199 patients. Mean age at admission was 34.5 years (range 15–81 years) with 20% aged 41–55 years. There were 139 (68.8%) men. Fifteen patients (7.5%) had positive parasitaemia, with a geometric mean of 56.84 per μl (95%CI 16.24–198.91). This compares with 15/157 (9.3%) asymptomatic controls admitted to the orthopaedic wards, with a geometric mean of 11.9 per μl (95%CI 4.68–30.25) (Fisher's exact 0.46). The baseline features of the orthopaedic controls were similar to those of the study group.

Table 1 Working diagnoses of patients admitted with neurological dysfunction recruited into the study

Diagnosis	Frequency of diagnosis (*n*)
Malaria	75
Cerebrovascular accident	43
Meningitis	27
Clinical diagnosis of HIV-related opportunistic infection or AIDS	23
Diabetes mellitus	21
Epilepsy and seizures	18
Cryptococcal meningitis	13
Peripheral neuropathy	13
Cardiovascular causes*	11
Psychosis	10
Pulmonary tuberculosis	10
Paraplegia: tabes dorsalis	11
Poisoning: drugs, alcohol	5
Hepatic encephalopathy	5
Pneumonia	3
Toxoplasmosis	2
Tuberculosis of the spine	2
Anaemia	2
Guillain-Barré syndrome	2
Encephalitis	2
Others**	5

*Arrhythmia, hypertension, congestive cardiac failure, infective endocarditis. ** Space-occupying lesion, septicaemia, asthma, Kaposi's sarcoma, carcinoma of prostate (one each).

Analysis by admitting diagnosis

The major diagnostic groups on admission are shown in Table 1. Malaria was the commonest diagnosis, made in 75/199 (38%) patients presenting with a neurological dysfunction. Figure 1 illustrates the division of the study population into four main groups on the basis of admission clinical diagnosis, and subsequently by the presence of peripheral parasitaemia. Of the 75 patients who had an admission clinical diagnosis of cerebral malaria and received parenteral quinine, 65 (86%) turned out to have no detectable malaria parasites in their peripheral blood. Therefore the specificity of the admission clinical diagnosis as a screening test was 64.7%. Five (33%) patients with detectable malaria parasitaemia were not diagnosed clinically as cerebral malaria on admission. Therefore, the sensitivity of the admitting diagnosis of cerebral malaria as a screening test was 66.7%, with a positive predictive value of only 13.3%.

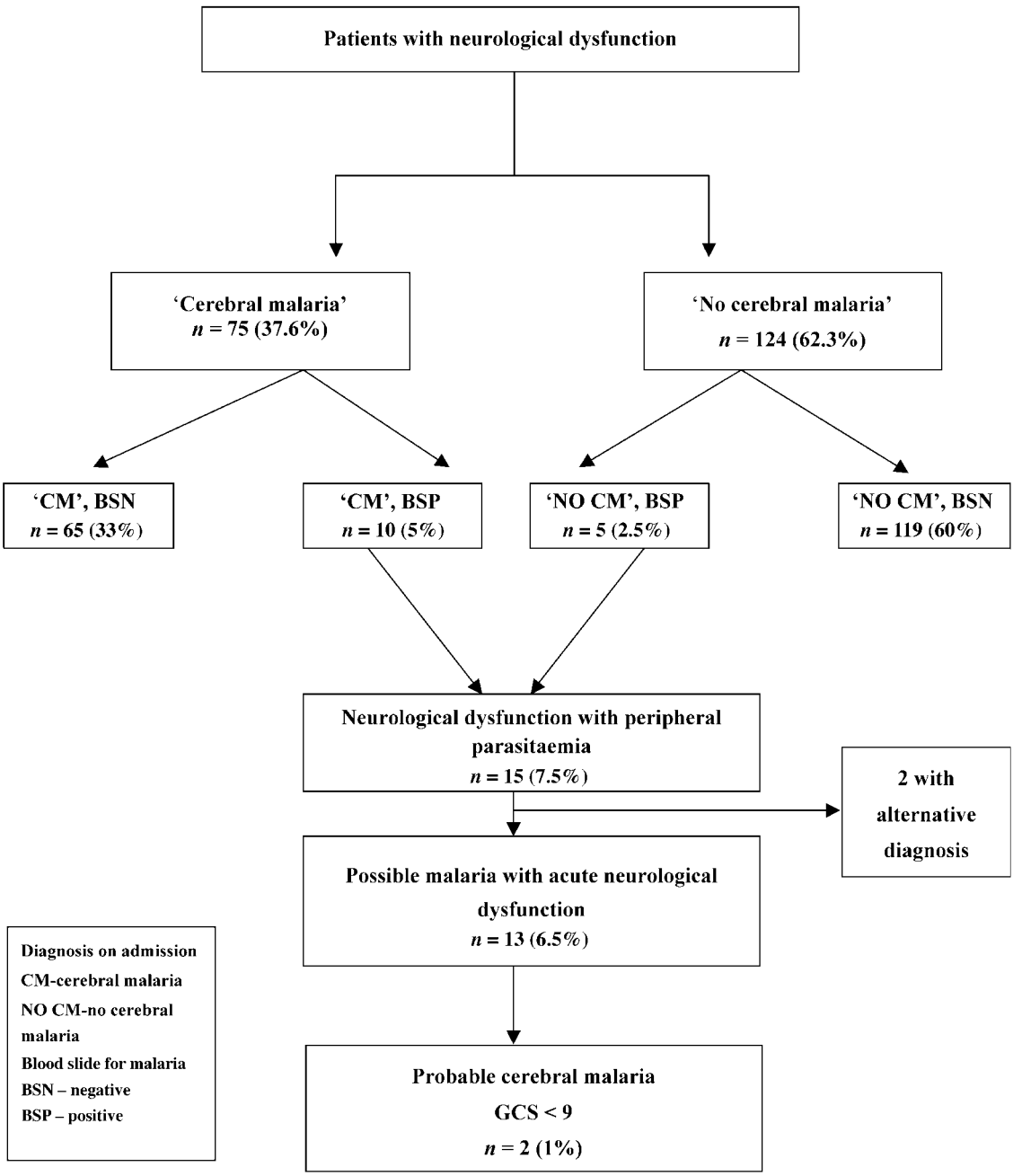

Figure 1. Flow chart of patients.

Analysis by malaria parasitaemia

Table 2 summarizes the clinical and laboratory features of patients with malaria parasitaemia (possible malaria patients) compared with patients without parasitaemia in the study population (no malaria). The commonest neurological features in both groups were acute psychiatric events (43%) and altered level of consciousness (72%), although there was no significant difference between patients with parasitaemia and those without ($p = 0.71$ and $p = 0.99$, respectively). Using the Glasgow coma scale (GCS) to assess the level of consciousness objectively, of the 15 patients with malaria parasitaemia, only two (13.3%) had a GCS $\leqslant 9$. This compares to 14/184 (7.6%) in the group with no malaria parasitaemia with GCS < 9 ($p = 0.48$). Fever and convulsions occurred more often in patients with malaria parasitaemia, but the difference from patients without parasitaemia was not statistically significant. In general, laboratory characteristics were similar in the two groups. The overall mortality in the study population was 43/199 patients (22%); two of the patients who died had malaria parasitaemia. The case fatality rate of patients with malaria parasitaemia was 2/15 patients (13.3%) compared to 41/184 (22.3%) deaths in patients with no parasitaemia ($p = 0.5$).

Discussion

In the past, the term cerebral malaria has been applied to a wide range of neurological manifestations of malaria with potentially disparate pathophysiological mechanisms and outcomes. More recently, most research studies have adopted a standard definition of cerebral malaria as the presence of unrousable coma (in adults a GCS of 9 or less) in the presence of asexual stages of *P. falciparum* in the blood stream, and after the exclusion of other causes of encephalopathy.[2,19] While important in allowing comparisons between research studies, this definition of cerebral malaria has been criticized as being too narrow[20] and it is certainly the case, that in clinical practice, any degree of impairment of consciousness or any other

Table 2 Baseline characteristics of patients

Characteristic	*n*	Malaria parasitaemia	No malaria parasitaemia	Overall	p, χ^2
Total sample	199	15 (7.5)	184 (92.5)		
Age (years) GM (95%CI)	199	30 (23.6–36.4)	34.9 (32.1–37.6)	34.5 (31.9–37.1)	0.330
Male (*n* %)	199	12 (80)	127 (69)	139 (69.8)	0.715
Altered consciousness[1]	199	10 (67)	123 (67)	133 (66.8)	0.995
Prostration[2]	185	10 (67)	98 (53.3)	108 (58.4)	0.598
Acute psychosis[3]	185	7 (47)	72 (39.1)	79 (43)	0.712
Neurological deficit[4]	185	5 (33)	68 (37)	73 (39.5)	0.847
Hypertension[5]	185	0	37	37 (20)	0.084
Fever[6]	183	12 (80)	94 (51)	106 (58)	0.268
Convulsions[7]	183	2 (13.3)	8 (4.3)	10 (5.5)	0.159
GCS <9	198	2 (13.3)	14 (7.6)	16 (8.08)	0.479
Death	199	2 (13.3)	41 (22.3)	43 (23.5)	0.502
Haemoglobin (g/dl) GM (95%CI)	198	10.6 (8.9–12.3)	10.65(10.22–11.07)	10.64(10.23–11.05)	0.953
<5		1 (6.67)	11 (5.98)	12 (6.0)	0.919
White cell count ($\times 10^9$/l) GM (95%CI)	199	6.8 (5.4–8.5)	6.9 (6.4–7.5)	6.9 (6.4–7.5)	0.586
>11		2 (13.33)	32 (17.39)	34 (17.1)	0.732
Erythrocyte sedimentation rate		65.3 (36.7–115.9)	54.2(46.9–62.7)	55 (47.9–63.2)	0.353
Serum creatinine (μmol/l)[8]GM (95%CI)	199	90.6 (66.8–122.9)	100.9(91.9–100)	100 (91.6–109.3)	0.528
>120		3 (20)	52 (28.3)	55 (27.6)	0.594
Blood glucose (mmol/l) GM (95%CI)	158	5.2 (3.4–7.9)	5.1 (4.6–5.5)	5.1 (4.6–5.5)	0.851
<2.2		0 (–)	6 (3.3)	6 (3.8)	0.485
Cryptococcal meningitis	35	0 (–)	13 (–)	13 (37.1)	0.304

[1]Altered level of consciousness from history or on presentation, ranging from obtunded to coma. [2]Unable to sit unaided. [3]Physical/verbal aggression, bizarre behaviour, inappropriate moods or mood swings, hallucinations and lack of interest [4]Focal or diffuse deficit in cranial, peripheral nervous system. [5]BP $\geqslant$140/90 mmHg; [6]Reported on admission from the history or on presentation. [7]Generalized or focal seizures. [8]Malarial acute renal insufficiency/dysfunction $>$120(μmol/l). GCS, Glasgow coma scale. GM, geometric mean.

neurological involvement should be taken as a potentially serious manifestation of malaria.[21] In the current study we have therefore adopted both approaches: the standard definition allowing comparison with other studies in different groups, and the broader approach capturing other potentially important neurological manifestations of severe malaria.

Cerebral malaria was the commonest working diagnosis in patients admitted to a general medical ward with acute neurological symptoms, being made in 75 of 199 (38%) patients. However, only 15 of 199 patients (7.5%) had acute neurological symptoms associated with proven malaria infection. Therefore, the positive predictive value of the admission clinical diagnosis as a screening test is 13.3%. In the 15 patients with malaria parasitaemia, two cases had very low parasite densities and an obvious alternative diagnosis. A man of 34 with 173 parasites per μl had evidence of acute alcohol intoxication, and the other case was a man of 40 with 207 parasites per μl and paraplegia, who had clinical features of TB of the spine. Thus malaria could be considered the possible prime aetiological agent in only 13 of 199 patients with acute neurological presentations (6.5%) and only two cases (1%) could have fulfilled the WHO criteria of cerebral malaria.

The fact that 87% of patients received antimalarial treatment but were found not to have malaria parasitaemia demonstrates serious overdiagnosis of cerebral malaria on admission in patients with neurological dysfunction, resulting in many patients' receiving unnecessary antimalarial therapy. In Malawi, changing from a policy of presumptive diagnosis to one of microscopy-based diagnosis in the management of uncomplicated malaria in an urban hospital adult out-patient clinic resulted in an estimated annual saving of US$ 14 000.[22] However, this analysis may be oversimplified, as it could be argued that the benefits of over-treating outweigh the risks of not treating a true case, especially where diagnostic facilities are limited or of uncertain quality.[23] One cannot absolutely exclude the possibility that a few of the slide-negative cases had cerebral malaria, either because parasites were sequestered in the brain at the time of presentation[24,25] or because prior treatment had reduced parasite density without modifying the course of the disease. However, truly 'slide–negative' cerebral malaria is probably very rare, although it can only be confirmed in those rare fatal cases in which a post-mortem needle necropsy or autopsy confirms the diagnosis. Of equal concern is the risk that the wrong diagnosis may divert attention from excluding or treating other potentially important conditions.[26] The diagnostic label of 'cerebral malaria' on admission is convenient, especially when the laboratory facilities are inadequate and expensive, but it may lead to diagnostic and therapeutic complacency. This may have an important impact on outcome, as suggested in this study. Although the difference was not statistically significant ($p = 0.5$), mortality was higher in the patients with no parasitaemia (22.3%) than in those with parasitaemia (13%).

Was malaria even the primary diagnosis in all 13 patients with acute neurological dysfunction and malaria parasitaemia? In malaria endemic areas, the presence of a *P. falciparum* parasitaemia *per se* is not necessarily evidence of a causative role in the clinical presentation.[27–29] Thus the prevalence of parasitaemia in patients with acute neurological symptoms (7.5%) was no greater than that observed in a control group of patients admitted to the orthopaedic ward (9.3%), as in previous reports from Tanzania.[29,30] An extreme interpretation of the data would be that the presence of malaria parasites was coincidental, and that the patients had other diagnoses, for instance viral encephalopathies, which could not be diagnosed with available resources. Although the chances of *P. falciparum* being the cause of an acute illness increases with parasitaemia,[29,31] there is difficulty in determining a diagnostic cut-off level, particularly in immune adults who may become symptomatic at very low parasite densities. In this study, the parasite densities were higher in patients than in asymptomatic controls. The considerations discussed above illustrate the difficulties both of making and excluding a definitive diagnosis of cerebral malaria in adults in areas of stable endemicity. It is important to stress that, in clinical practice, the diagnosis of cerebral malaria must be considered in any patient with neurological symptoms. Any evidence of infection with malaria parasites should prompt immediate treatment with parenteral antimalarials, but should not inhibit further investigation of other possible causes.

Although there were no significant differences between the 13 patients with peripheral parasitaemia and the slide-negative patients, the clinical features of this group are consistent with those reported in other series of adult cerebral malaria patients. In the group of patients with neurological dysfunction and malaria parasitaemia, there were two main presenting syndromes: acute psychosis and altered level of consciousness. The psychiatric symptoms included verbal or physical aggression and bizarre behaviour without a previous history of mental illness, followed by resolution of symptoms after antimalarial therapy. There was no history of

the use of antimalarial drugs such as mefloquine or chloroquine, which are known to cause psychosis. These findings suggest a neuropsychiatric complication of malaria, malaria psychosis, which has previously been reported[32–35] but has rarely been documented in endemic areas.[36] Convulsions were rare in this series, with only three patients (6.7%) presenting with a history of convulsions. No patient had convulsions observed in hospital. This is not surprising, as adults are less prone to convulsions than children,[19] in whom up to 80% with cerebral malaria may have convulsions.[4] This low incidence is also consistent with reports of a decreasing incidence from 50% to 20% in Southeast Asian adults.[37] Acute renal failure is a common complication of severe malaria in adults[38] and less common in children.[7] Three of our 15 patients with malaria parasitaemia (20%) were admitted with renal dysfunction, similar to the 17% previously reported from South Africa[12,39] and 30% from SE Asia.[38] Jaundice, abnormal bleeding and haemoglobinuria (characterized as dark or black urine) less common in our patients than has been reported in non-immune adults. Hypoglycaemia and severe anaemia were also rare.

The most important finding of our study is that cerebral malaria is overdiagnosed on admission in routine practice. The experience reported here may be typical of that in many large hospitals in malaria endemic areas of Africa, and suggests the need for an improvement in diagnostic accuracy. Although further research is essential to determine the clinical features that could be used to increase the positive predictive value of a diagnosis of cerebral malaria in adults on admission, use of such clinical clues will prove effective only if the clinicians' approach to management is changed fundamentally. Overdiagnosis of cerebral malaria probably discourages further investigation, so that other conditions are neither identified nor treated. Extension of this misperception to the assessment of community-reported deaths may result in an overestimation of the contribution of malaria to adult mortality in some areas.

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