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Burden, features and outcome of neurological involvement in acute falciparum malaria in Kenyan children

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Abstract

Context—*Plasmodium falciparum* appears to have a particular propensity to involve the brain, but the burden, risk factors and full extent of neurological involvement have not been systematically described.

Objective—To determine the incidence and describe the clinical phenotypes and outcome of neurological involvement in African children with acute falciparum malaria.

Design, setting and patients—A review of records of all children younger than14 years admitted to a Kenyan District Hospital with malaria, from January 1992 through December 2004. Neurological involvement was defined as convulsive seizures, agitation, prostration, impaired consciousness or coma.

Outcome measures—The incidence, pattern and outcome of neurological involvement.

Results—Of 58,239 children admitted, 19,560(33.6%) had malaria as the primary clinical diagnosis. Neurological involvement was observed in 9,313(47.6%) children and manifested as

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seizures (6,563/17,517, 37.5%), agitation (316/11,193, 2.8%), prostration (3,223/15,643, 20.6%), impaired consciousness or coma (2,129/16,080, 13.2%). In children <5 years, the mean annual incidence of admissions with malaria was 2,694/100,000 and the incidence of malaria with neurological involvement was 1,156/100,000. However, re-admissions may have led to a 10% overestimate in the incidence. Children with neurological involvement were older (median [inter quartile range] age 26[15-41] vs 21[10-40] months, $p<0.001$), had a shorter duration of illness (2[1-3] vs 3[2-3] days, $p<0.001$) and a higher geometric mean parasite density (42.0 [95%CI 40.0-44.1] vs 30.4 [95%CI 29.0-31.8]$\times 10^3/\mu l$, $p<0.001$). Factors independently associated with neurological involvement included past history of seizures (adjusted OR 3.50 95%CI 2.78-4.42), fever ≤2 days (adjusted OR 2.02 95%CI 1.64-2.49), delayed capillary refill time (adjusted OR 3.66 95% CI 2.40-5.56), acidosis (adjusted OR 1.55 95% CI 1.29-1.87) and hypoglycemia (adjusted OR 2.11 95% CI 1.32-3.37). Mortality was higher in patients with neurological involvement (4.4% [95% CI, 4.2%-5.1%] vs 1.3% [95% CI, 1.1%-1.5%], $p<0.001$), and at discharge, 159 out of 7281 (2.2%) had neurological deficits.

Conclusions—Neurological involvement is common in children with acute falciparum malaria. It is associated with metabolic derangements, impaired perfusion, parasitemia and has increased mortality and neurological sequelae. The study suggests that malaria exposes many African children to brain insults.

Keywords

Neurological involvement; burden; acute falciparum malaria; children

Introduction

Malaria is a leading cause of ill health in tropical countries. In 2002, over 2 billion people were exposed to malaria and there were an estimated 515 million clinical episodes of acute *Plasmodium falciparum* infection. Over 70% of these episodes occurred in sub-Saharan Africa and mainly affected children <5 years1.

Plasmodium falciparum is the most common cause of severe malaria and in children this typically manifests as severe anemia, prostration, repeated seizures, impaired consciousness, hypoglycemia and metabolic acidosis2. Uniquely, *Plasmodium falciparum* infected erythrocytes sequester within deep vascular beds, particularly in the brain3. Neurological involvement (NI) may manifest as seizures, impaired consciousness or coma4. Recent studies demonstrate that nearly a quarter of the children who survive cerebral malaria or malaria with complicated seizures are at risk of persistent neurological and cognitive impairments and/or epilepsy5-7. Apart from cerebral malaria8, the burden, manifestations, risk factors and consequences of NI in malaria have not been fully described. This study determined the incidence, clinical phenotypes, associated factors and outcome of NI in acute falciparum malaria in Kenyan children.

Methods

Study design

Records of all children admitted to Kilifi District Hospital (KDH) with a parasitological diagnosis of malaria over a 13-year period from January 1992 through December 2004 were reviewed. We compared clinical and laboratory features of patients with and without NI on admission.

Study area

KDH is located on coastal Kenya and admits approximately 5,000 children annually. It serves a predominantly rural population and is the only hospital that admits very sick children from the surrounding communities. The annual entomological inoculation rate (the number of times an individual is bitten by mosquitoes infected with *Plasmodium falciparum* in one year) in the catchment area ranges from <1 to 120 infectious bites per year9. The area has been described in detail elsewhere10.

Study population

Eligible children had asexual forms of *P. falciparum* parasites detected on blood films with malaria as the only or main diagnosis. Neurological involvement4 was defined as:

- **i.** history of convulsive seizures during the presenting illness reported by the parent or observed on admission to hospital.
- **ii.** the presence of agitation (abnormally high level of activity or irritability),
- **iii.** prostration (inability to sit upright or breast feed)2 ,
- **iv.** impaired consciousness (Blantyre coma score less than 5)11, 12
- **v.** coma (unable to localise a painful stimulus i.e cerebral malaria)11, 13 .

We included prostration as a neurological feature since it is difficult to differentiate neurological and severe systemic causes of prostration in children.

Admission procedures and inpatient care

Admission data was collected on standardized proformas that had a conserved basic format and otherwise varied according to ongoing clinical studies. The proformas detailed the medical history and the physical examination14. As part of the research activities of the center, parents of children admitted to the hospital were invited to consent for their clinical data to be used for disease surveillance.

Emergency resuscitation and inpatient care was provided according to standard protocols13, 15. Severe malaria was treated with parenteral quinine or arthemeter until patients could tolerate oral medication, when antimalarial therapy was completed with a full course of first line drugs according to the national guidelines in Kenya. Those with life threatening features were closely monitored on the high dependency unit. Nursing staff performed clinical assessments of vital signs, seizures and level of consciousness every 4-6 hours. Physicians' reassessments were at 4 and 24 hours after admission and then, daily. Mechanical ventilation was not available. Patients without life threatening features (impaired consciousness, repeated seizures or respiratory distress)2 had daily assessments on the general ward.

Laboratory procedures

At admission, blood was drawn for a full blood count, blood glucose, thick and thin films (stained for malaria parasites with 10% Giemsa) and from 1998, for blood culture16. Among those with life threatening features, a venous sample was drawn for acid base status and plasma electrolytes. Metabolic acidosis was defined as a base deficit >8. Hypokalemia was defined as plasma K^+<3.0mmol/L, hyperkalemia as K^+>5.0mmol/L and hyponatremia as Na^+<135mmol/L. Lumbar punctures were performed according to a standard protocol to exclude pyogenic meningitis17. A cerebrospinal fluid (CSF) leukocyte count of up to 10/μl was considered normal18. All tests including the parasitological diagnosis of malaria are performed in a certified research laboratory with a system for regular internal and external audits.

Data management and statistical analysis

For this analysis, we classified admissions as with or without NI. We determined the mean incidence of admissions with malaria and of malaria with NI in a defined study area using population denominators projected from the 1989 (for the years 1992–1998) and the 1999 (for years 2000-2004) Government of Kenya census. The yearly population estimate was calculated from the intercensal population growth rate of 2.9% between the censuses19, 20. Admission clinical characteristics of the two groups of patients were compared to describe features associated with NI and a p-value<0.05 was considered statistically significant. Comparisons were performed only for patients for whom data was available. Categorical variables were compared using Pearson's Chi square test. For approximately normally distributed data, means were compared with the student's t-test and the Wilcoxon Rank-sum test used for skewed data. We performed multivariable logistic regression analysis with NI as the dependent variable to identify features independently associated with NI. In building the multiple regression model, we included clinical and laboratory features with p values<0.1 on univariate analysis and identified the independent variables by backward elimination. Similarly, we compared the characteristics of patients with prostration to describe the associated features. Using the conservative Bonferroni approach to multiple comparisons, we adjusted the level of significance α for the additional comparisons (prostration $\alpha<0.025$) and death or neurological sequelae ($\alpha<0.017$). Data analysis was performed using Stata Version 9 (Stata Corporation Inc. Texas).

Results

Burden of malaria with neurological involvement

A total 58,239 children were admitted to KDH during the study period. Of these, 22,441 had malaria parasites detected on blood smears and 19,560 (33.6%) had malaria as the primary clinical diagnosis (figure 1). Of the 19,560 admissions with malaria, neurological features were present in 9,313 (47.6%) at admission, compared to 7,794 of the 35,798 (21.8%) admissions without malaria ($p<0.001$).

The mean annual incidence of admissions with malaria among children<5 years over the study period was 2,694 (range 1,506 – 3,744) per 100,000 and of malaria with NI was 1,156 (range 474 – 2075) per 100,000 (figure 2). The peak incidences (3,794 and 1,181 per 100,000 respectively) were in the first year of life. A marked decline in incidence was observed in children older than 5 years: the incidence of admissions with malaria or malaria with NI were 344 per 100,000 and 120 per 100,000 in children 5–9 years and, 39 and 9 per 100,000 in children 10-14 years respectively.

We were unable to exclude re-admissions due to malaria over the whole study period, a fact that could have led to an over-estimate of the incidence. In order to examine this, we estimated the proportion of children who could have had re-admissions for malaria using data of children admitted from mid April 2002 to December 2004, when each child obtained a unique identification number that was used during all subsequent admissions. Using this identifier, 348/3421 (10.2%) children were found to have had more than one admission. Therefore, about 10% of the incidence data provided here may be an over estimate contributed by re-admissions with malaria.

Features of neurological involvement on admission

Seizures—Seizures were the commonest neurological feature of acute falciparum malaria and were reported or observed (at admission) in 37.5% (table I). Seizures were uncommon before the age of 6 months. After 12 months, the age specific prevalence increased rapidly reaching a peak prevalence of 48.6% among patients 27–33 months. Patients with seizures

had a shorter duration of illness and higher parasitemia (table II). Multiple seizures were common with 56% of those with a history of seizures reporting two or more episodes during the illness. In 22% of children, seizures lasted longer than 30 minutes, fulfilling the definition of status epilepticus.

During the course of the inpatient stay, seizures were observed in 13.3% of children with NI. These were not associated with hypoglycemia or hyponatremia. Temperature appeared to influence seizure manifestation; 63% of generalized seizures were reported in febrile children compared to 54% secondarily generalized seizures and 44% focal seizures (χ^2 for linear trend=7.235, p=0.007). The recurrence of seizures in the ward was associated with increased mortality (12.8 vs 1.2 %, p<0.001).

Among 6,212 children asked about seizures during previous illnesses, a history of seizures was more common (41.5%) among those admitted with seizures compared to those without (15.1%), p<0.001. The majority of these past seizures were associated with febrile illnesses including respiratory tract infections and malaria.

Prostration—Sixty percent of patients with prostration reported a seizure. We examined the clinical risk factors for prostration among 2,967 consecutive children assessed for both seizures and prostration. Children without seizures were more likely to have severe anemia, acidosis or hypoglycemia. Prostration with seizures was associated with higher parasitemia. Seizures (adjusted OR 2.44 95%CI 2.04-2.93, p<0.001), delayed capillary refill time (adjusted OR 5.24 95%CI 3.72-7.38, p<0.001), hypoglycemia (adjusted OR 3.85 95%CI 2.73-5.43, p<0.001), metabolic acidosis (adjusted OR 1.92 95%CI 1.61-2.29, p<0.001) and high parasite density (adjusted OR 1.01 95%CI 1.00-1.10, p=0.001) were independently associated with prostration.

Impaired consciousness—Impaired consciousness was associated with seizures, older age, higher parasite density, hypoglycemia and acidosis but not hyponatremia (table II). Patients with seizures and normal consciousness on admission had less metabolic derangements compared to those with impaired consciousness. Comatose patients were ill for longer prior to admission compared to either those with agitation or prostration.

Overlap between the features of NI was common, particularly seizures and prostration or seizures and impaired consciousness. All patients with agitation had at least one other feature of neurological involvement i.e. seizures, prostration or impaired consciousness.

Deterioration in level of consciousness after admission—Deterioration in consciousness during admission was observed in 219/1,533(14.3%) children with NI admitted to the high dependency unit. It was associated with recurrence of seizures and abnormal motor posturing but not duration of illness, admission temperature, parasite density, hypoglycemia, metabolic acidosis, hyponatremia or severe anemia. However, secondary deterioration in consciousness was associated with higher mortality than established impaired consciousness (38.6 vs 12.8%, p<0.001). Some children developed agitation during the course of the admission. This was associated with worsening level of consciousness and increased mortality.

Factors associated with NI in falciparum malaria

Clinical features—Children with NI were older and had a shorter history of illness (table III). The median duration of illness was 2 days in patients with NI compared to 3 days in those without NI and the majority of children admitted with <2 days of fever had NI (65.4 vs 34.6%, p<0.001). Apart from seizures, the previous medical history in the two groups was

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similar. Features of shock or impaired perfusion and metabolic acidosis were associated with NI. Vomiting, diarrhea and cough were less common in patients with NI. Additional diagnoses, particularly respiratory tract infections, were less common among children with NI.

Laboratory findings—Overall, 15.3% of patients had severe anemia (Hb<50 g/L). There was no clear association between the hemoglobin concentration and level of consciousness (table II). Although NI was observed at low levels of parasitemia, the proportion with NI increased with rising parasitemia: NI was present in 40% of patients with parasite densities <100,000/μl, 50% of patients with 100,000-500,000/μl and in over 60% of those with densities >1,000,000/μl (χ^2 for trend =120, p<0.001).

Among patients with life threatening features, the commonest biochemical derangements were hyponatremia, acidosis, hyperkalemia, hypoglycemia and elevated plasma creatinine (table III). Only metabolic acidosis, hypoglycemia and hyperkalemia were significantly associated with NI.

Factors independently associated with neurological involvement—Clinical and laboratory features associated with NI on univariate analysis with a p value <0.1 (table III) were entered in a logistic regression model to identify those features independently associated with NI. These included past history of seizures, hypoglycemia, acidosis, delayed capillary refill and duration of fever shorter than 2 days. An additional diagnosis (co-morbidity) and severe anemia were independently associated with absence of NI (table IV).

Outcome

The median duration of hospital stay including deaths was 3 (IQR 2 – 4) days and was similar in patients with and without NI overall. However, compared to those without any alteration of consciousness, patients with impaired consciousness stayed longer in the wards, (3 [IQR 2-4] vs 2 [1-4] days, p<0.001).

Mortality—Overall, 542 children died. Neurological involvement was associated with increased mortality: 4.4% (95% CI 4.2-5.1) died compared to 1.3% (95% CI 1.1-1.5) of those without NI. Mortality increased with lower levels of consciousness at admission (table I). Children with cerebral malaria had the highest mortality, especially those admitted without a history of seizures (22.2 vs 13.6%, p=0.006). Respiratory arrest (often associated with brainstem signs) occurred more commonly in children with NI (37.2 vs 18.2% of all deaths, p=0.031) while cardio-respiratory arrests (associated with severe metabolic acidosis or anemia) were more common in children without NI. At univariate analysis, several clinical and laboratory features (coma, respiratory distress, a temperature gradient between the periphery and the trunk, delayed capillary refill time, splenomegaly, hepatomegaly, severe anemia, high parasitemia, hypoglycemia, bacteremia, hyperkalemia, thrombocytopenia, and leucocytosis) were associated with increased mortality. Factors independently associated with death were impaired consciousness/coma, hypoglycemia, severe anemia, bacteremia, hyperkalemia and respiratory distress (table V). The same risk factors were associated with death in the subset of patients with NI.

Neurological deficits on discharge—One hundred fifty nine children out of 7,281 (2.2%) with NI had neurological deficits at discharge. Neurological deficits were observed in 2.1% of survivors with seizures, 4.4% with agitation, 3.6% with agitation and 6.4% of those with impaired consciousness or coma. Deficits included motor disorders (spasticity and central hypotonia), ataxia, movement disorders (choreo-athetoid, tremors and dystonic posturing), visual, hearing and speech impairments, and continuing epileptic seizures.

Behavioral problems were reported in 11% of those with neurological deficits and included hyperactivity, violent and impulsive behavior, hallucinations, excessive eating and fear/anxiety. Presentation with impaired consciousness (adjusted OR 6.9 95%CI 4.6-10.2, $p<0.001$) and recurrence of seizures in hospital (adjusted OR 2.7 95%CI 1.9-4.1, $p<0.001$) were independently predictive of neurological deficits at discharge.

Discussion

Neurological involvement occurred in almost half of all children admitted with acute falciparum malaria and commonly manifested as seizures, prostration, impaired consciousness or coma. It was associated with increased mortality and neurological sequelae. Although prostration may be a general feature of severe systemic illness, the occurrence of seizures in 60% suggests frequent involvement of the CNS.

Burden of NI in children with acute falciparum malaria

In children aged <5years, the mean incidence of admission with malaria in this area with <1-120 infectious mosquito bites a year was 2,694/100,000 and at least 1,156/100,000 were exposed to malaria related brain insults annually between 1992-2004. The risk was lower in children older than 5 years.

In 1998, the mid-term year for this study, there were an estimated 94.3 million children <5 years and 77.8 million children 5-9 years living in areas with stable malaria transmission in sub-Saharan Africa21. Applying our estimates to this population denominators, at a minimum 2,540,442 children <5 years were admitted to hospitals with malaria of who 1,090,108 had exposure to potential brain injury every year from 1992 to 2004. Similar annual figures for children 5-9 years are 267,632 and 93,360 respectively. These numbers are an absolute minimum as they do not account for children from the study area who did not attend our hospital. Previous estimates from the study area indicate that two thirds of deaths in children <5 years occur outside the hospital22. In addition, the annual EIR in the study area (<1–121)9 is lower than the overall figures for the continent (0–884)23. This estimates also do not include areas with unstable (epidemic prone) transmission in Africa. However, 10% of the incidence may be an over estimate due to the inclusion of re-admissions in the numerator. Traditionally, NI in childhood falciparum malaria has been defined as cerebral malaria, the extreme form of NI, and has been characterised by seizures and coma15. The study shows that emphasis on cerebral malaria alone may be missing other syndromes with the potential to damage the brain. We found that <20% of those with neurological illness attributable to malaria fulfilled the definition of cerebral malaria and propose the term “malaria with neurological involvement” to include all. The public health importance of such NI is enormous: recent studies described a combination of long-term neurological and cognitive impairments in 24% of children exposed to cerebral malaria or malaria with multiple seizures5 and an increased risk for epilepsy6, 24. In addition, the longer duration of inpatient stay and more severe illness may translate into higher healthcare costs. It is estimated that the cost of treating malaria with cerebral features in a child in district hospitals in sub-Saharan Africa is US$ 44-105 compared to US$ 33-57 for that without cerebral features25.

Risk factors for neurological involvement

Seizures were reported in almost 40% of children admitted with malaria compared to 12% of children with other acute medical illnesses. The proportion of patients with NI and in particular seizures, increased until 1997. Possible reasons for this include an increasing awareness of the problem, patient selection or a growing confidence of the community in the ability of the hospital to manage seizures26. Seizures were associated with high parasitemia,

but not fever or hyponatremia, supporting the hypothesis that falciparum malaria might be epileptogenic *per se*27-30. The presence of additional neurological features supports the hypothesis of direct cerebral involvement. However, it is also likely that some seizures in malaria are simple febrile seizures similar to those seen in non-malaria endemic areas. It is also notable that not all children with cerebral malaria reported seizures and those without seizures had a worse outcome suggesting there are other mechanisms by which coma might develop.

Several factors may contribute to the pathogenesis of NI in childhood malaria; biochemical perturbations (hypoglycemia, acidosis), impaired perfusion, high parasitemia and, some children may have a predisposition to seizures (higher frequency of past history of seizures). Although peripheral parasitemia correlates poorly with vascular sequestration3, 31, high parasite density does predict poor outcome in cerebral malaria11. This may be due to systemic derangements in immunological, metabolic and cardio-respiratory functions. These changes may be associated with altered consciousness32 and may precipitate or lower the threshold for seizures. We propose that NI in falciparum malaria may arise from:

- **i.** A *direct effect* of sequestered parasites possibly through parasite induced toxins or immune responses to sequestered parasites on neuronal/blood-brain barrier function or mechanical vascular blockage.
- **ii.** An *indirect effect* from parasite induced local and systemic metabolic derangements or impaired perfusion (impaired delivery of substrates).

Genetic susceptibility to seizures33 including febrile seizures may be important. Acute and long-term imaging studies, especially magnetic resonance imaging, will greatly assist in determining pathogenesis.

Outcome of malaria with neurological involvement

Overall, involvement of the CNS was associated with increased mortality and neurological sequelae in survivors. The risk of death and neurological damage increased with lower levels of consciousness at admission (table II). The proportion of children admitted with metabolic acidosis or hypoglycemia also increased with worsening level of consciousness and rising mortality. Children with single seizures without additional neurological features had low mortality (minimal risk) but the presence of prostration, impaired consciousness or secondary deterioration in consciousness was associated with increased mortality (high risk). Identification and supportive treatment may improve outcome in these patients34.

Two percent of the patients with NI and in particular those with impaired consciousness or repeated seizures, had gross neurological deficits at discharge similar to that previously described32. At least one tenth of those with deficits had behavioral problems. Future studies should characterise these behavior disorders and suggest intervention measures.

Apart from the difficulties in ascertaining re-admissions, the study suffers from the limitations of relying on retrospective data from one hospital, based only on inpatients, possible incomplete parental reporting and the possibility that some children in the study area could have received care from other health units. These have the consequence of under reporting the extent of the burden of malaria and its sequelae. Our data also does not allow analysis of any contribution of HIV infection to NI. This is clearly an important area that needs further study.

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Conclusion

NI is common in children admitted with acute falciparum malaria and goes beyond what has been traditionally regarded as “cerebral malaria”. It is associated with a history of seizures in previous illnesses, impaired perfusion, perturbations in biochemical functions, high parasitemia, mortality and neurological deficits. The high frequency of NI suggests that annually, many children in sub-Saharan Africa are exposed to malaria related brain insults. Control of malaria may allow many more children achieve their full potential.

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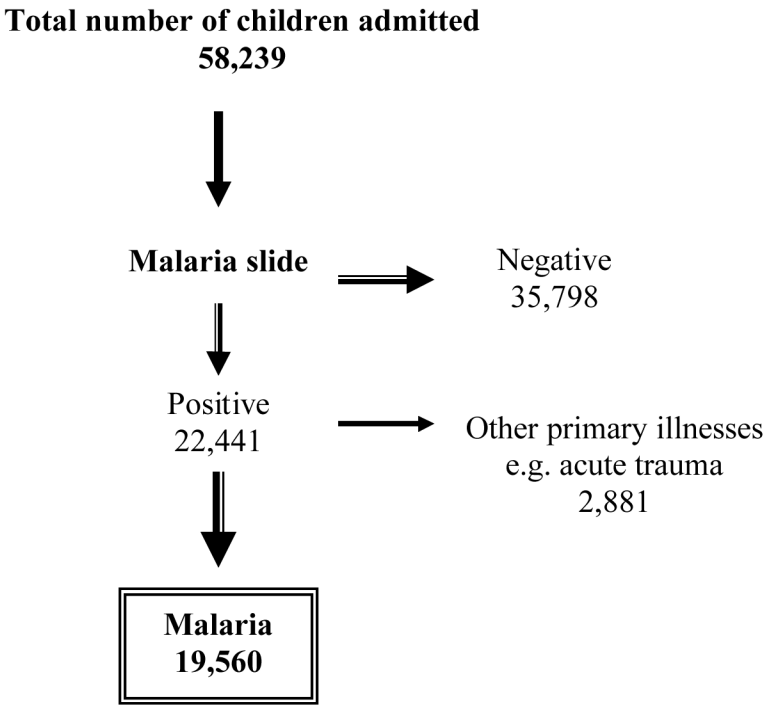

Figure 1.
Children admitted with malaria to KDH from 1992 – 2004

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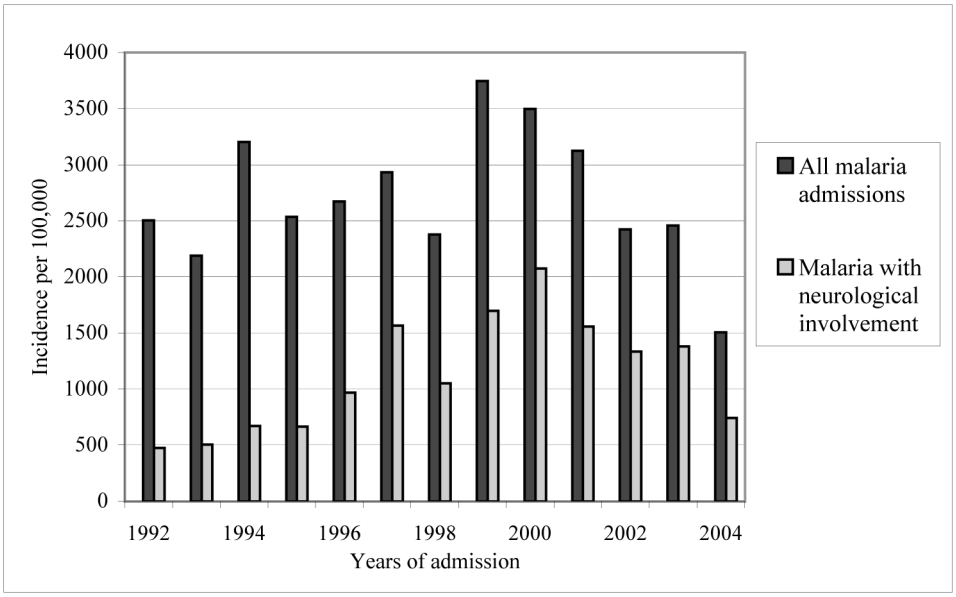

Figure 2.
The incidence of admissions with malaria and of malaria with neurological involvement in children in Kilifi District Hospital from 1992 – 2004

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Table I

Features of neurological involvement in children with falciparum malaria on admission to hospital and outcome of treatment, 1992-2004

Features of neurological involvement on admission	Number of patients with systematically collected data available observed, (%)	Patients in who feature was	Case fatality*, (%)
No neurological involvement	19,560	10,247 (52.4)	130/10,247 (1.3)
Seizures	17,517	6,563 (37.5)	251/6,563 (3.8)
Agitation	11,193	316 (2.8)	15/316 (4.7)
Prostration	15,643	3,223 (20.6)	215/3,223 (6.7)
Impaired consciousness or coma	16,080	2,129 (13.2)	190/2,129 (8.9)

* Five hundred and forty two children died. The excess number of deaths when added is due to overlap of seizures or agitation with prostration or impaired consciousness/coma.

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Table II

Clinical, Hematological and Biochemical Factors Associated With Changes in Consciousness

	No. of Patients Assessed (n=19,560)	Normal Consciousness		Agitation (n=316)	Prostration (n=3,233)	Impaired Consciousness or Coma (n=2,129)
		No Seizures (n=10247)	Seizures (n=3951)			
Age, median (IQR), mo	19,459	22 (10-41)	25 (14-38) ***	24 (12-42) *	27 (15-43)	28 (16-44) ***
Seizures	17,517	0 (0)	3,951/3951 (100) ***	146/291 (50.2) ***	1742/2967 (58.7) ***	1512/2129 (71.0) ***
Duration of illness, median (IQR), d	17,226	3 (1-3)	2 (1-3) ***	1(0-3) ***	2 (1-3) ***	3 (0-3) **
Admission temperature, mean (SD), ° C	15,109	38.6 (1.2)	38.7 (1.2) ***	38.2 (1.3) *	38.0 (1.4) ***	38.1 (1.3) ***
Delayed capillary refill time	11,072	212/4680 (4.5)	98/2724 (3.6) *	56/291 (19.2) ***	336/2151 (15.6) ***	264/1574 (16.8) ***
Parasite density, geometric mean (95% CI), $\times 10^3/\mu l$,	19,560	36.5 (33.4-39.8)	42.2 (39.2-45.4) ***	38.8 (29.8-42.8)	42.6 (38.6-46.9) ***	45.0 (36.8-55.0) ***
Hypoglycemia	4,898	70/1457 (4.8)	56/1442 (3.9)	16/150 (10.7) ***	208/1466 (14.2) ***	126/785 (16.0) ***
Hemoglobin mean (SD), g/L	19,051	77 (28)	95 (31) ***	86 (36) ***	100 (33) ***	85 (44) ***
Metabolic acidosis	5,911	735/2007 (36.6)	466/1366 (34.1)	101/182 (55.5) ***	955/1665 (57.4) ***	595/1017 (58.5) ***
Hyperkalemia	6,005	50/1917 (2.6)	82/1236 (6.6) *	22/147 (14.0) ***	303/1720 (17.7) ***	239/1229 (19.5) ***
Hyponatremia	6,016	1026/1922 (53.4)	696/1236 (56.3)	81/157 (51.6)	941/1724 (54.6)	641/1232 (52.0)

Abbreviations: CI, confidence interval; IQR, interquartile range.

† Values are expressed as number (percentage) unless otherwise indicated

* P<0.05 (All values compared to normal consciousness with no seizures).

** P<0.01

*** P<0.001

Table III

Admission characteristics

	Neurological Involvement, No. (%) of Patients*		*P* Value
	Present	**Absent**	
Male, sex	4884/9310 (52.5)	5361/10246 (52.3)	0.85
Age, median (IQR) in mo	26 (15 – 41)	21 (10 – 40)	<0.001
Head circumference <-2 SD for age†	371/3305 (11.2)	226/1935 (11.7)	0.62
Weight for height Z score <-2†, (wasting)	1241/5732 (21.7)	810/4408 (18.4)	<0.001
Past seizures	1338/3841 (34.8)	349/2371 (14.7)	<0.001
Fever	6019/6231 (96.6)	4718/4894 (96.4)	0.57
Vomiting	1336/5339 (25.0)	1638/4361 (37.6)	<0.001
Cough	1996/6230 (32.0)	2144/4893 (43.8)	<0.001
Diarrhoea	530/5585 (9.5)	646/4883 (13.2)	<0.001
Duration of illness, median (IQR), d	2 (1 – 3)	3 (2 – 3)	<0.001
Axillary temperature, mean (SD), °C	38.4 ± 1.4	38.6 ±1.5	>0.99
Jaundice	102/6042 (1.7)	83/4529 (1.8)	0.58
Delayed capillary refill	646/6392 (10.1)	212/4680 (4.5)	<0.001
Temperature gradient†	809/3840 (21.1)	351/2371 (14.8)	<0.001
Splenomegaly	4271/9313 (45.9)	6404/10247 (62.5)	<0.001
Hepatomegaly	662/6391 (10.4)	286/4679 (6.1)	<0.001
Respiratory distress‡	1209/6521 (18.5)	906/5331 (17.0)	0.03
Sustained nasal flaring	528/4884 (10.8)	249/3022 (8.2)	<0.001
Deep breathing	760/6520 (11.7)	221/5329 (4.1)	<0.001
Subcostal retractions	658/6227 (10.6)	579/4890 (11.8)	0.03
Severe anemia	870/9307 (9.3)	2039/9744 (20.9)	<0.001
Metabolic acidosis	1910/3904 (48.9)	735/2007 (36.6)	<0.001
White blood count, mean (SD), × $10^3/\mu l$	13.7 (8.9)	14.7 (10.3)	<0.001
Parasite density, geometric mean (95% CI), $\times 10^3/\mu l$	42.0 (40.0-44.1)	30.4 (29.0-31.8)	<0.001
Hypoglycemia	322/3441 (9.4)	70/1457 (4.8)	<0.001
Thrombocytopenia	1295/3652 (35.5)	929/2859 (32.5)	0.01
Hyponatremia	2249/4094 (54.9)	1026/1922 (53.4)	0.26
Potassium level			
Hyperkalemia	70/4088 (1.7)	50/1917 (2.6)	0.02
Hyperkalemia	595/4088 (14.6)	188/1917 (9.8)	<0.001
Impaired renal function (creatinine >0.90mg/dL [80 μmol/L])	665/3659 (18.2)	311/1619 (19.2)	0.37
Bacteremia	126/5627 (2.2)	122/4151 (2.9)	0.03
Comorbidity§	924/9313 (9.9)	1901/10247 (18.6)	<0.001

Abbreviations: CI, confidence interval; IQR, interquartile range

[*] Unless otherwise indicated

[+] Using the 1978 WHO standards

[†] Subjective temperature difference between the trunk and the peripheries

[‡] Presence of sustained nasal flaring, deep acidotic breathing or subcostal retractions

[§] Presence of an additional diagnosis when the primary diagnosis is malaria

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Table IV

Features independently associated with neurological involvement in children admitted with acute falciparum malaria

Features	Unadjusted OR (95%CI)	Adjusted OR (95% CI)	P value
Past seizures	3.10 (2.71 – 3.54)	3.50 (2.78 – 4.42)	<0.001
Fever ≤ 2 days	1.58 (1.45 – 1.72)	2.02 (1.64 – 2.49)	<0.001
Delayed capillary refill	2.37 (2.01 – 2.79)	3.66 (2.40 – 5.56)	<0.001
Hypoglycemia	2.05 (1.56 – 2.71)	2.11 (1.31 – 3.32)	0.002
Severe anemia	0.39 (0.36 – 0.42)	0.78 (0.62 – 0.98)	0.043
Metabolic acidosis	1.66 (1.48 – 1.185)	1.55 (1.29 – 1.89)	<0.001
Co-morbidity (presence of an additional diagnosis)	0.48 (0.44 – 0.52)	0.38 (0.30 – 0.47)	<0.001

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Table V

Features independently associated with mortality

Features associated with death in all patients with malaria	Unadjusted OR (95%CI)	Adjusted OR (95% CI)	P value
Impaired consciousness or coma	15.86 (12.11-20.80)	4.06 (2.03 – 7.07)	<0.001
Respiratory distress	8.25 (6.40 – 10.64)	4.47 (2.66 – 7.54)	<0.001
Severe anemia	1.84 (1.49 – 2.25)	3.08 (1.75 – 5.42)	<0.001
Hypoglycemia	10.95 (8.04–14.88)	2.46 (1.40 – 4.35)	0.002
Hyperkalemia	10.86 (8.49–13.90)	3.83 (2.27 – 6.45)	<0.001
Bacteremia	4.86 (3.04 - 7.50)	5.01 (1.93 – 13.04)	0.001
Seizures on the ward	10.25 (7.20–14.38)	3.56 (2.03 – 6.20)	<0.001