Convulsions with Malaria: Febrile or Indicative of Cerebral Involvement?

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Summary

Evaluation of 446 infants and young children (6 months to 5 years olds) with malaria parasitaemia showed a significant relationship ($P < 0.05 - < 0.001$) (a) between coma and age, pattern of convulsions, haematocrit, and blood glucose, and (b) between the severity of parasitaemia and risk of convulsions, prevalence of hepatosplenomegaly, and severe anaemia. No significant relationship was observed between convulsions and temperature or haematocrit. Comatose children were older and had a higher prevalence of repeated convulsions, severe anaemia, and hypoglycaemia than non-comatose children. Convulsions, hepatosplenomegaly, and severe anaemia were more prevalent in children with moderate–severe parasitaemia. It is concluded that convulsions with malaria are more often a manifestation of cerebral dysfunction rather than being simply febrile in nature. All forms of cerebral dysfunction in malaria, including repeated convulsions, should be managed as being clinical manifestations of cerebral malaria.

Introduction

Parents in the tropics fear the occurence of a convulsion which is often the first sign of a febrile illness.[1,2] Convulsions may be febrile[3–5] or non-febrile[5–7] in malaria. Although cerebral malaria is common,[5,8] there is a wide variation in the reported frequency of its occurence relative to the prevalence of malaria.[5]

One possible contribution to the poorer prognosis of febrile convulsions in the tropics,[3] compared to temperate countries,[9] is the undefined role of cerebral involvement in malaria. Clinical differentiation between convulsions with malaria due to fever and cerebral involvement is difficult[3,4,10] and the latter can only be confirmed during life by brain biopsy[7] which is impractical.

WHO[11] and others[12–14] argue that fever alone can cause drowsiness, confusion, delirium, and convulsions which do not necessarily imply cerebral involvement and suggest using the presence of unrousable coma only in diagnosis. Others[15,16] suggest that all manifestations of cerebral disturbance, including repeated convulsions, indicate cerebral malaria. WHO[11] recognizes a practical need for the latter view which is supported by observations of an association between the severity of parasitaemia, frequency of convulsions, and development of coma.[4,17]

Early recognition and treatment is important to improved outcome in cerebral malaria.[18–20] Although manifestations of cerebral dysfunction other than unrousable coma can, indeed, be simply fever-induced, they could additionally be early warning signs of cerebral involvement. Thus, convulsions lead to deterioration of level of consciousness in cerebral malaria.[14]

Many ill children in malaria-endemic areas are managed in general hospitals and general practice clinics staffed by physicians with limited experience, training, and supervision. In such settings, controversies on what is cerebral malaria, though possibly of immense academic interest in tertiary—care centres, are likely to be misleading and can cause avoidable lapses in management. Also, earlier case identification and treatment can reduce the burden on intensive care facilities which are beneficial in the management of severe malaria,[19] but are in high demand and short supply.

This report further examines the clinical case definition of cerebral malaria based on the findings in children with malaria, with and without convulsions, who were seen in an emergency room.

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Patients and Methods

Four-hundred-and-forty-six infants and children (6 months to 5 years old) with fever (rectal temperature of at least 38.0°C)[21] were recruited during a 1-year period (24/10/88–23/10/89) at the Children's Emergency Room, University of Benin Teaching Hospital, Benin City, Nigeria. Benin City is located in Southern Nigeria, which is holoendemic for malaria.[4] The inclusion criteria were absence of localizing signs of infection, other than clear rhinorrhoea, and presence of asexual forms of malaria parasitaemia.

The children were evaluated by history and physical examination using a standard protocol. Coma was graded from I to V as previously described.[22] Grade III–V correspond to unrousable coma as described by the WHO.[11] To aid in analysis, level of consciousness was classified into three—fully conscious, light coma (coma grades I and II) and deep coma (grades III–V). Hepatomegaly (more than 2 cm of palpable liver enlargement)[23] and complex febrile convulsions (prolonged, multiple or focal convulsions)[24] were defined as previously described.[23,24]

Children with coma or convulsions had a lumbar puncture done to exclude meningitis. Malaria parasitaemia was diagnosed from examination of Giemsa-stained thick and thin blood films prepared from peripheral venous blood samples. Parasitaemia was quantified on a scale of severity from +1 to +4 as described by Bruce-Chwatt.[25] Additional investigations of haematocrit and random blood glucose determinations were also undertaken using peripheral venous blood samples. Severe anaemia was defined as a haematocrit of 20.0 per cent or less[11] and hypoglycaemia as blood glucose of 2.2 mmol/l or less.[11]

Statistical analysis was by means of unpaired Student's t-test, χ^2 test for differences in frequencies and χ^2 test for trend. The children were classified into two groups with a total of five subgroups—seizures absent (fully conscious, light coma) and seizures present (fully conscious, light, and deep coma).

Results

Three-hundred-and-seven presented with convulsions while 139 were without convulsions. All had *P. falciparum* parasitaemia. There were 247 (55 per cent) males and 199 (45 per cent) females. There were no significant differences in male:female ratio between children with and without convulsions or with and without coma.

The presenting temperature was in the range of 38.0–38.9°C in 137 (31 per cent), 38.9–40.9°C in 298 (67 per cent) and ≥41.0°C in 11 (3 per cent). Mean (SD) of temperature among children without convulsions was 39.2 (0.84)°C in fully conscious children and 39.2 (0.92)°C in those in light coma while among those with convulsions it was 39.3 (0.87)°C in fully conscious, 39.3 (0.85)°C in lightly comatose, and 39.1 (0.75)°C in deeply comatose children. No significant relationship was observed between temperature and convulsions or coma.

Among children with convulsions, past history of convulsions with fever was positive in 41 (13 per cent), family history in 77 (25 per cent), and both in 29 (9 per cent), while 160 (52 per cent) had no such history. There was no significant relationship between the presence or absence of a positive past or family history and the prevalence or depth of coma.

Relationship between age, haematocrit, and severity of parasitaemia and coma

Mean age was lower and mean haematocrit higher in fully conscious compared to comatose children (P values ranged <0.02–<0.001) (Table 1). This was irrespective of the presence or absence of convulsions. The trend of level of consciousness with age and haematocrit is further shown in Table 2. Younger children were less likely to be comatose than older ones ($P<0.001$), while severely anaemic children were more likely to be comatose than those with higher haematocrits ($P<0.001$). There was no significant relationship between coma and the severity of parasitaemia (Table 1).

Relationship between pattern of convulsions and coma

Overall, the frequency of simple versus complex convulsions was 75/83 (simple/complex), 47/71, and 8/23 among children in full consciousness, light coma, and deep coma, respectively ($\chi^2=5.48$, df$=2$, $0.05<P<0.1$). Complex convulsions were commoner among those in deep coma than in those in full consciousness (74 *v.* 53 per cent, $P<0.05$).

Convulsions were generalised in 276 (90 per cent) and focal in 31 (10 per cent), but this was unrelated to the level of consciousness. 181 (59 per cent) had brief episodes of convulsions while 126 (41 per cent) had prolonged episodes. Prolonged convulsions were more frequent in deeply comatose children (20/31 or 65 per cent) compared to those in light coma (42/118 or 36 per cent) ($P<0.01$). There was a significant positive correlation between the number of convulsions and level of consciousness ($P<0.001$) (Table 3). Single episodes of convulsions were rarer in deeply comatose (10/31 or 32 per cent) compared to fully conscious (103/158 or 65 per cent) ($P<0.001$) or lightly comatose (61/118 or 52 per cent) ($P=0.05$) children.

Relationship between blood glucose and coma in children with convulsions due to malaria

Fifteen (5 per cent) were hypoglycaemic, 58 (19 per cent) were hyperglycaemic while 234 (76 per cent) were

TABLE 1

(A) Mean (SD) of age, haematrocrit, and parasitaemia in children with malaria

	Convulsions present			Convulsions absent	
	Fully conscious ($n=158$)	Light coma ($n=118$)	Deep coma ($n=31$	Fully conscious ($n=122$)	Light coma ($n=17$)
Age (months)	27.4 (13.2)	35.5 (15.5)	38.7 (17.2)	24.1 (14.8)	36.7 (12.2)
Haematocrit (%)	25.0 (8.0)	32.5 (8.1)	21.1 (8.1)	27.1 (6.5)	20.9 (9.0)
Parasitaemia	2.19 (1.07)	2.35 (1.12)	2.29 (1.11)	2.08 (0.96)	2.1 (0.92)

Figures are shown as mean (SD).

(B) Significant P values/comparisons

	Convulsions present			Convulsions absent	
	Fully conscious	Light coma	Deep coma	Fully conscious	Light coma
Convulsions present:					
Fully conscious					
—age	—	<0.001	<0.001	—	—
—haematocrit	—	<0.02	<0.02	<0.02	—
Convulsions absent:					
—age, haematocrit	—	<0.001	<0.001	—	<0.001
—parasitaemia	—	<0.05	—	—	—
Light coma					
—age, haematocrit	<0.01	—	—	—	—

TABLE 2

Age, haematocrit, and coma in children with malaria

	Convulsions present			Convulsions absent		
	Fully conscious *n* (%)	Light coma *n* (%)	Deep coma *n* (%)	Fully conscious *n* (%)	Deep coma *n* (%)	Total *n* (%)
Age (months)*						
6–24	75	40	9	73	3	200
	(47.5)	(33.9)	(29.0)	(59.8)	(17.6)	(44.8)
>24–60	83	78	22	49	14	246
	(52.5)	(66.1)	(71.0)	(40.2)	(82.4)	(55.2)
Haematocrit (%)**						
⩽20	50	56	16	25	8	155
	(31.6)	(47.5)	(51.6)	(20.5)	(47.1)	(34.8)
21–30	66	39	11	54	9	179
	(41.8)	(33.0)	(35.5)	(44.3)	(52.9)	(40.1)
⩾31	42	23	4	43	—	112
	(26.6)	(19.5)	(12.9)	(35.2)	—	(25.1)

*$\chi^2=25.46$, df=4, $P<0.001$.
**$\chi^2=32.02$, df=8, $P<0.001$.

normoglycaemic. Of the latter, 12 (4 per cent) had blood glucose between 2.2 and 2.8 mmol/l. Hypoglycaemia was significantly more common among deeply comatose children ($P<0.01$) (Table 4).

Relationship between temperature, parasitaemia, and haematocrit and convulsions

No relationship could be demonstrated between the pattern of convulsions (simple *v.* complex, brief *v.*

TABLE 3
Frequency of convulsions and level of consciousness in children with malaria

No. of convulsions	Level of consciousness: Fully conscious *n* (%)	Light coma *n* (%)	Deep coma *n* (%)	Total *n* (%)
Single	103 (65.2)	61 (51.7)	10 (32.3)	174 (56.7)
2–4	42 (26.4)	41 (34.7)	11 (35.5)	94 (30.6)
>4	13 (8.4)	16 (13.6)	10 (32.2)	39 (12.7)
Total	158 (100.0)	118 (100.0)	31 (100.0)	307 (100.0)

$\chi^2 = 19.43$, df = 4, $P < 0.001$.

TABLE 4
Blood glucose and level of consciousness in children with malaria and convulsions

Blood glucose (mmol/l)	Level of consciousness: Fully conscious *n* (%)	Light coma *n* (%)	Deep coma *n* (%)	Total *n* (%)
≤2.2	3 (1.9)	5 (4.2)	7 (22.6)	15 (4.9)
>2.2–2.8	5 (3.2)	5 (4.3)	2 (6.5)	12 (3.9)
>2.8–6.7	120 (75.9)	85 (72.0)	17 (54.8)	222 (72.3)
>6.7	30 (19.0)	23 (19.5)	5 (16.1)	58 (18.9)
Total	158 (100.0)	118 (100.0)	31 (100.0)	307 (100.0)

$\chi^2 = 25.31$, df = 6, $P < 0.001$.

prolonged, generalized *v.* focal, or single *v.* multiple) and rising temperature, parasitaemia or haematocrit.

Relationship between parasitaemia and convulsions, temperature, hepatosplenomegaly, and haematocrit
The association between increasing severity of parasitaemia and the prevalence of convulsions approached significance ($0.05 < P < 0.1$) (Table 5). No relationship could be demonstrated between parasitaemia and temperature (Table 5). The prevalence of hepatosplenomegaly ($P < 0.001$) and severe anaemia ($P < 0.05$) both increased significantly with parasitaemia (Table 5).

Discussion

Findings in this study suggest that convulsions with malaria are more often indicative of cerebral disturbance rather than being simply febrile in nature. No correlation was observed between temperature and level of consciousness. In contrast, the level of consciousness correlated with the prevalence of severe anaemia and hypoglycaemia, both of which are a measure of the severity of malaria infection.[6,11] The correlation between the severity of parasitaemia and prevalence of convulsions approached significance. Also, comatose children had a mean age which was higher than the peak age for febrile convulsions.[3,9] Furthermore, the prevalence of other characteristics expected in children with febrile convulsions (positive family or past history of convulsions and a rise in prevalence of convulsions with temperature)[3,9,26] were not significantly different between comatose and non-comatose children. Our findings are, therefore, in support of treating all manifestations of cerebral dysfunction,[15] including repeated convulsions,[4,16] as being indicative of cerebral involvement in malaria.

Deeply comatose children had a greater tendency to

TABLE 5
Parasitaemia and temperature, convulsions, hepatosplenomegaly, and haematocrit in children with malaria

	Parasitaemia				
	+1 *n* (%)	+2 *n* (%)	+3 *n* (%)	+4 *n* (%)	Total *n* (%)
Temperature (°C)* (children with convulsions only)					
38.0–38.9	72 (72.0)	65 (74.7)	41 (62.1)	41 (75.9)	219 (71.3)
⩾40.0	28 (28.0)	22 (25.3)	25 (37.9)	13 (24.1)	88 (28.7)
Convulsions**					
present	100 (69.4)	87 (64.4)	66 (65.4)	54 (81.1)	307 (68.8)
absent	44 (30.6)	48 (35.6)	35 (34.6)	12 (18.2)	139 (31.2)
Hepatosplenomegaly***					
Hepatomegaly or splenomegaly only	47 (32.6)	46 (34.1)	28 (27.7)	20 (30.3)	141 (31.6)
Hepatosplenomegaly	37 (25.7)	36 (26.7)	44 (43.6)	32 (48.5)	149 (33.4)
None	60 (41.7)	53 (39.2)	29 (28.7)	14 (21.2)	156 (35.0)
Haematocrit†					
⩽20	45 (31.2)	37 (27.4)	41 (40.6)	32 (48.5)	155 (34.8)
21–30	55 (38.2)	57 (42.2)	39 (38.6)	28 (42.4)	179 (40.1)
⩾31	44 (30.6)	41 (30.4)	21 (20.8)	6 (9.1)	112 (25.1)

*$\chi^2 = 3.8$, df = 3, $P > 0.05$.
**$\chi^2 = 7.0$, df = 3, $0.5 < P < 0.01$.
***$\chi^2 = 20.1$, df = 6, $P < 0.01$.
†$\chi^2 = 18.3$, df = 6, $P < 0.01$.

present with repeated convulsions and lower temperatures. Fever, below hyperpyrexial levels, is a beneficial response to infections.[21,27] A trend towards lower temperatures in deeply comatose children could, therefore, be indicative of impaired defences or a more severe infection.

Many children were fully conscious and even without convulsions in the presence of high fever and heavy parasitaemia while others with lower temperatures and mild-moderate parasitaemia had convulsions and other manifestations of cerebral dysfunction. These observations, which cannot be explained by the currently accepted hypothesis of the pathogenesis of severe malaria,[11] require further investigations. Age might be an important factor as infants are relatively protected against severe malaria[28] and comatose children in the present study had a higher mean age than non-comatose ones. Also, parasite count in falciparum malaria is dynamic with sequestration of parasitized red cells in deep tissue capillary beds occuring during the maturation of schizonts.[11,28] Mild–moderate peripheral blood parasitaemia is, therefore, compatible with severe manifestations of malaria. Sequestration can also explain the absence of a predictable rise in the prevalence of deep coma with rising parasite counts.

This study could not demonstrate any significant relationship between haematocrit and risk of convulsions, although both the haematocrit and number of convulsions correlated with the level of consciousness. Hendrickse *et al.*[4] observed a rise in the prevalence of convulsions with increasing haematocrit and suggested that non-anaemic children manifested greater cerebral dysfunction because of the higher load of red cells available for parasitisation. Ikpatt *et al.*[17] observed the reverse. Our results and others[4] demonstrate a positive correlation between the severity of parasitaemia and the prevalence of severe anaemia. Also, in the present study, the prevalence of hepatosplenomegaly, (though a rather crude measure of antigen load), correlated positively with the severity of parasitaemia. These observations indicate that the frequency of convulsions, severity of anaemia, depth of coma, etc., are probably a better reflection of the severity of infection than parasite counts. Previous reports[29] also indicate that the occurence of cerebral malaria, the most severe manifestation of malaria,[11] has no relationship to parasite counts.

Anaemia and severe anaemia, both of which were commonly observed in this study, are frequent in children with malaria.[4,11,28] Also, both hypoglycaemia[3] and hyperglycaemia[30] have been observed in children with febrile convulsions. Hypoglycaemia has been particularly associated with severe malaria.[6,11,13] The lower prevalence of hypoglycaemia in our patients contrasts with that observed in children with febrile convulsions in Ibadan.[3] This is probably because the administration of cow's urine mixture, a more or less regular cause of hypoglycaemia,[31] to convulsing children, which is commonly practiced in Ibadan,[3] is rare in Benin City (personal observations).

We conclude that convulsions with malaria more often reflect cerebral involvement rather than the effect of fever. All manifestations of cerebral dysfunction in malaria, including rousable coma and repeated convulsions, are indicative of cerebral involvement in varying degrees.

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