

Indicators of Fatal Outcome in Paediatric Cerebral Malaria: A Study of 134 Comatose Papua New Guinean Children

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Genton B (Papua New Guinea Institute of Medical Research, PO Box 378, Madang, Papua New Guinea), Al-Yaman F, Alpers M P and Mokela D. Indicators of fatal outcome in paediatric cerebral malaria: A study of 134 comatose Papua New Guinean children. *International Journal of Epidemiology* 1997; **26**: 670–676.

Background. No comprehensive data on the clinical features and the prognosis of cerebral malaria in the South Pacific are available at present. We conducted a prospective study in children with cerebral malaria to assess the case fatality rate (CFR) in the region and to identify potential risk factors for death.

Methods. We recruited 134 children admitted to the Madang General Hospital between April 1991 and October 1993 with a strictly defined diagnosis of cerebral malaria. Besides clinical examination, we collected a blood sample for parasitological, haematological and biochemical assessment.

Results. The CFR was 11.9% and the prevalence of residual neurological sequelae at discharge was 1.5%. The proportion of children presenting with deep coma (12%) or hypoglycaemia (17%) was lower in our study than in African ones, where severe complications are more frequent. Also mortality associated with hypoglycaemia on admission was lower. Clinical or laboratory conditions significantly associated with death were deep coma, malarial anaemia and hyperleucocytosis.

Conclusions. All conditions associated with deep coma, such as shock, hypoglycaemia and acidosis, should be corrected. Also prompt administration of blood transfusions to patients with anaemia is likely to reduce the occurrence of death in Papua New Guinean children with cerebral malaria.

Keywords: cerebral malaria, Papua New Guinea, predictor, mortality, sequelae

Usual estimates of case fatality rate (CFR) in paediatric cerebral malaria range between 6 and 50%.¹ Since the studies did not use the same case definition, useful comparisons cannot be made. A fatality rate of 50% may occur among children living in rural areas with limited access to specialist treatment,² but is certainly an over-estimation for children attending hospitals with reasonable resources. In such settings, all the studies report a CFR of less than 30%. In a drug trial in Ghana including 113 cases of cerebral malaria, the CFR was as low as 5%, and the occurrence of neurological sequelae was 8%.³ In the four largest studies in Africa, mainly observational, including more than 100 children with cerebral malaria, the CFR were 15% in Malawi⁴ and Congo,⁵ 16% in The Gambia⁶ and 17% among the cerebral malaria group in Kenya.⁷ The respective prevalence of residual neurological sequelae were 9% in Malawi and Congo and 8% in The Gambia. Thus, when investigators use

the same case definition and involve a sample size large enough to achieve sufficient confidence, they obtain very similar results, at least in the African region, even if the studies are carried out at different time periods and with different drug types and regimens.

Most of the published studies of cerebral malaria outside Africa have taken place in Thailand and Vietnam and included mainly adults. The few papers on cerebral malaria in the Pacific region report low CFR, i.e. 2% in Indonesia⁸ and 6% in the Madang Province of Papua New Guinea (PNG),⁹ but the cases were not strictly defined. Because of the lack of comprehensive data on cerebral malaria in this part of the world, we studied prospectively 134 children admitted to the Madang General Hospital with strictly defined cerebral malaria. The objectives of the study were i) to assess the CFR and the rate of residual neurological sequelae, and ii) to identify risk factors for poor outcome which can be assessed at the bedside, and to see if these prognostic indicators differ from those in other regions, where CFR are potentially higher. Another component of the study, which has been the subject of one report already,¹⁰ was

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to investigate some mechanisms which are supposedly involved in the pathogenesis of cerebral malaria in Africa, such as rosetting formation or cytoadherence, and to see if these phenomena also occur in children with cerebral malaria in areas with a potentially lower fatality rate.

METHOD

Study Site

The study was conducted in the Madang Province, on the north coast of Papua New Guinea. This area has a tropical climate with high annual rainfall (2.5–5 m). A wet season is normally recognized between October and May, but there is intense all-year-round transmission of malaria. Parasitization is common in children and the incidence of clinical fever has been estimated to range from three to six episodes per year in 2–14 year old children.¹¹ There is a typical pattern of declining prevalence of malaria-associated febrile illness and parasite density with age.¹² Malaria has been reported to be the cause of 4–17% of deaths in children under 10 years old.¹³ Health services in the area consist of aid posts at the village level and health subcentres or health centres which serve about 10 villages where patients can be given intramuscular (i.m.) or intravenous (i.v.) treatments and be admitted for a few days. There is one referral provincial hospital in Madang which serves the town and its surroundings, including the densely populated unplanned settlements. Antimalarial drugs can only be obtained from the above-mentioned health facilities.

Patients

All children with cerebral malaria who have been admitted to the Madang General Hospital between April 1991 and October 1993 were included in the study. A case of cerebral malaria was defined according to published criteria,¹⁴ i.e. a person with coma persisting for more than 30 min after a generalized convulsion and with confirmed *Plasmodium falciparum* asexual blood stage parasitaemia. In order to quantify the depth of consciousness, we developed a modification of the Blantyre coma score described by Molyneux *et al.*⁴ Only verbal and motor responses were taken into account as the assessment of the eye response was considered to be too subjective. From these two responses, a score could be calculated (minimum = 0, maximum = 4). Only children with an abnormal score (≤ 3) were included in the study. All cerebral malaria patients had a white cell count in the cerebrospinal fluid of $<10/\mu\text{l}$. In all, 73 sera were screened for the presence of IgG antibodies for flavivirus, known to be the main cause of viral encephalitis

in PNG. The 46 sera which were positive for IgG were re-examined for specific IgM antibodies and all were found to be negative.

Data Collection

The clinical history was obtained from a parent or guardian. Prior treatment was recorded from the health book. All children were examined by the paediatrician in charge (DM) on admission, after initial treatment had been administered in the emergency department. Blood was collected by venepuncture into EDTA tubes. Thick and thin films were stained with Giemsa and the number of malaria parasites per 200 white blood cells (WBC) was counted. The number of asexual forms per microlitre was then calculated from the measured WBC count. Haemoglobin and glucose levels were determined using Hemocue photometers. Glycaemia was measured only in children who presented during daytime. The haematocrit was measured by capillary tube centrifugation. Neurological sequelae were assessed at discharge and at day 21.

Management

Children were managed in the paediatric ward, according to standardized treatment regimens for severe malaria.¹⁵ Intramuscular (i.m.) quinine 7.5–10 mg/kg was administered twice daily, irrespective of the prior treatment. When the child could swallow, oral quinine 7.5–20 mg/kg was given, up to the time they had fully recovered. A single dose of Fansidar^R (20–50 mg/kg sulfadoxine/1–2.5 mg/kg pyrimethamine) and primaquine 0.38–0.75 mg/kg were given on the first day of oral treatment. Convulsions were treated with i.m. paraldehyde and children with repeated convulsions were given oral phenobarbitone. Most children with anaemia of less than 5 g/dl and signs of cardiovascular or respiratory distress were transfused with packed cells.

Statistical Analysis

Groups for continuous variables were chosen on the basis of accepted clinical cutoff points (i.e. hypoglycaemia: blood glucose <40 mg/dl [2.2 mmol/l]; hyperleucocytosis: WBC count $>10\,000/\mu\text{l}$; malarial anaemia: haemoglobin <5 g/dl or a haematocrit $<15\%$ associated with a *Pf* parasitaemia $>10\,000/\mu\text{l}$; hyperparasitaemia: a parasite count $>500\,000/\mu\text{l}$; hyperpyrexia: axillary temperature $>40.0^\circ\text{C}$; malnutrition: a weight-for-age Z score >2 SD below the corresponding NCHS reference median [WAZ <2]; tachypnea: a respiratory rate $>40/\text{min}$.; deep coma: a coma score = 0).

Logistic regression models were fitted for all variables, with death as the outcome variable. All variables with a *P*-value of ≤ 0.1 , as well as age, were included in

a multivariate model. There was no evidence of significant confounding; therefore the results of crude analysis are presented below. The likelihood ratio test from EGRET (Statistics and Epidemiology Research Corporation, Seattle, US) was used to estimate the odds ratios of dying and the 95% confidence intervals (CI).

RESULTS

We recruited 134 children with cerebral malaria. Six other cases were not included because hospital records were unavailable, but none of those died or had neurological sequelae. Table 1 summarizes the main demographic, clinical and laboratory conditions of the whole sample. Ages ranged from 11 months to 11 years (mean 4.2 years), 74 (55%) were living in villages. They had all been ill for a period varying from half a day to 7 days (mean 3 days). Some 81/132 (61%) had a recent history of anti-malarial treatment. The mean duration of quinine treatment among survivors was 3.25 days.

Sixteen children died. The CFR was thus 11.9% (95% CI: 6–18%) and 69% of the deaths occurred within 24 h of admission. Gastric haemorrhage was present in one child who died. Two children (1.5%, 95% CI: 0.2–5.3%) survived with residual neurological sequelae present at discharge and on day 21. Both were 2 years of age. One had a right hemiplegia and the other one had involuntary movements. These last two cases have been excluded from the analysis presented below. Though they do not belong to the group of the children who died, in terms of management they should be considered as such.

Relationships between Demographics, Clinical Features, Laboratory Findings and Outcome

The prevalence of conditions or clinical features which are not WHO defining criteria for severe disease is shown in Table 2. The associated mortality for each condition is presented. Children who had a pretreatment, whatever it was, those who were malnourished and those who had hyperleucocytosis tended to be more at risk of dying than the ones without additional complication ($P = 0.057$, $P = 0.072$ and $P = 0.049$ respectively). The prevalence of conditions included in the WHO criteria for severe malaria and their associated mortality is presented in Table 3. Children with malarial anaemia were 6.1 times more likely to die ($P = 0.028$). Only six children met the latter definition. None of them were hypoglycaemic. The coma score was 0, 1 and 2 in the three who died with this condition. Two of the latter received transfusions. Children who had a deep coma were 5.1 times more likely to die ($P = 0.003$) than the ones without the condition.

TABLE 1 *Demographic, clinical and laboratory conditions of all cerebral malaria cases on admission*

Condition	Patients with available admission data No.	Prevalence No. (%)	Mean (SD)
Age (months)	134		50 (28)
Female sex	134	57 (43)	
Residence	134		
Village		74 (55)	
Settlements		48 (36)	
Town		12 (9)	
Prior treatment	133	81 (61)	
Amodiaquine		34 (26)	
Chloroquine		8 (6)	
Quinine		39 (29)	
History <3 days	63	31 (49)	
Duration of symptoms (days)	63		3 (2)
Coma score	134		
0		17 (13)	
1		35 (26)	
2		53 (40)	
3		26 (19)	
4 ^a		3 (2)	
Malnutrition ^b	121	57 (47)	
WAZ score	121		-1.93 (1.29)
Enlarged spleen	123	94 (76)	
Hyperpyrexia ^c	132	3 (2)	
Temperature	132		38.2 (1.1)
Tachypnea ^d	120	19 (16)	
Respiratory rate (/min.)	120		34 (9)
Pulse rate (/min.)	123		121 (23)
Shock	132	2 (2)	
Jaundice	132	8 (6)	
Hyperparasitaemia ^e	134	7 (5)	
Pf density ($\times 10^3/\mu\text{l}$)	134		124 (237)
Hypoglycaemia ^f	86	14 (16)	
Glycaemia (mg/dl)	86		92 (66)
Malarial anaemia ^g	134	6 (5)	
Haemoglobin (g/dl)	133		8.2 (2.3)
Haematocrit (%)	119		26 (8)
Hyperleucocytosis ^h	134	66 (50)	
White cell count ($\times 10^3/\mu\text{l}$)	134		11.3 (6.2)

^a Coma score of 2 on day 1.

^b Weight-for-age Z-score > 2SD below the corresponding NCHS reference median.

^c Axillary temperature >40.0°C.

^d Respiratory rate >40/min.

^e Parasite count >500 000/ μl .

^f Blood glucose <40 mg/dl (2.2 mmol/l).

^g Haemoglobin <5 g/dl or a haematocrit <15% associated with a Pf parasitaemia >10 000/ μl .

^h White blood cell count >10 000/ μl .

TABLE 2 Prevalence of demographic, clinical and laboratory conditions not included in the WHO criteria for severe malaria, and associated mortality

Condition	Patients with admission data available No.	Prevalence No. (%)	Mortality	Odds ratio ^a (95% confidence interval)	P-value
Female sex	132	56 (42)	7 (13)	1.06 (0.38–2.94)	0.91
Residence	132				
Village		73 (55)	8 (11)	1	
Settlements		47 (36)	6 (13)	1.33 (0.25–7.06)	0.86
Town		12 (9)	2 (17)	1.57 (0.31–7.87)	
Prior treatment	130	80 (62)	13 (16)	4.33 (0.96–19.6)	0.057
History <3 days	62	30 (48)	6 (20)	2.26 (0.54–9.47)	0.27
Malnutrition ^b	121	57 (47)	10 (18)	2.98 (0.90–9.78)	0.072
Tachypnea ^c	118	19 (16)	3 (16)	1.61 (0.42–6.15)	0.485
Enlarged spleen	121	93 (77)	10 (11)	0.74 (0.22–2.45)	0.62
Hyperleucocytosis ^d	132	66 (50)	12 (18)	3.2 (1.00–10.2)	0.049

^a Using a logistic regression model.

^b Weight-for-age Z-score > SD below the corresponding NCHS reference median.

^c Respiratory rate >40/min.

^d White blood cell count >10 000/ μ l.

TABLE 3 Prevalence of clinical and laboratory conditions included in the WHO criteria for severe malaria, and associated mortality

Condition	Patients with admission data available No.	Prevalence No. (%)	Mortality	Odds ratio ^a (95% confidence interval)	P-value
Severe manifestations					
Deep coma ^b	132	16 (12)	6 (38)	5.12 (1.72–15.3)	0.003
Malarial anaemia ^c	132	6 (5)	3 (50)	6.12 (1.48–25.4)	0.028
Shock	130	2 (2)	0 (0)	0 (0.00–41.8)	1.00
Hypoglycaemia ^d	85	14 (16)	3 (21)	1.77 (0.45–7.01)	0.41
Other manifestations					
Jaundice	130	8 (6)	1 (13)	1.1 (0.13–8.90)	0.93
Hyperpyrexia ^e	130	3 (2)	0 (0)	0 (0.00–17.9)	1.00
Hyperparasitaemia ^f	132	7 (5)	0 (0)	0 (0.00–5.22)	0.60
One or more of the above manifestations ^g	132	69 (52)	13 (19)	4.26 (1.19–15.3)	0.026

^a Using a logistic regression model.

^b Coma score = 0.

^c Haemoglobin <5 g/dl or a haematocrit <15% associated with a *Pf* parasitaemia >10 000/ μ l.

^d Blood glucose <40 mg/dl (2.2 mmol/l).

^e Axillary temperature >40.0°C.

^f Parasite count >500 000/ μ l.

^g Including all children.

Mortality was 38% for the children presenting with a coma score of 0, 15% with a score of 1, 7% with a score of 2 and 4% with a score of 3. The relative risks and significance levels were very close to those above when variables with a *P*-value \leq 0.1 and age were included in a multivariate model (data not shown). The children who had one or more of the manifestations listed in Table 3

were 4.3 times more likely to die than the children who had none of these conditions (*P* = 0.026). Among these manifestations, only malarial anaemia and jaundice were significantly associated (odds ratio 9.8, 95% CI: 1–89, *P* = 0.044).

Because the grouping for continuous variables is always somewhat arbitrary, we fitted univariate logistic

TABLE 4 Logistic regression model for potential predictors of mortality in cerebral malaria

Variable	Patients with admission data available No.	Mean (SD)	Coefficient (95% confidence intervals)	Odds ratio	P-value
Age (months)	132	50(28)	-0.006	0.99 (0.99-1.01)	0.565
Duration of symptoms (days)	62	3(2)	0.161	1.17 (0.86-1.60)	0.307
Temperature (°C)	130	38.2(1.1)	0.077	1.08 (0.66-1.76)	0.756
Pulse rate (/min.)	121	121(23)	0.003	1.00 (0.98-1.03)	0.797
Respiratory rate (/min.)	118	34(9)	0.037	1.04 (0.98-1.09)	0.176
WAZ score	121	-1.93 (1.29)	0.016	0.98 (0.65-1.49)	0.941
Pf density ($\times 10^3/\mu\text{l}$)	132	125 (238)	0.0002	1.00 (1.00-1.00)	0.835
Glycaemia (mg/dl)	85	93(66)	0.006	0.99 (0.98-1.01)	0.339
Haemoglobin (g/dl)	131	8.2(2.4)	-0.271	0.76 (0.61-0.96)	0.021
Haematocrit (%)	118	26(8)	-0.10	0.90 (0.84-0.97)	0.006
White cell count ($\times 10^3/\mu\text{l}$)	132	11.3 (6.2)	0.076	1.08 (1.01-1.15)	0.016

regression models for all continuous variables. Results obtained with categorical variables were confirmed, as shown in Table 4. Haematocrit, haemoglobin and white blood cell count were all significant predictors of mortality in univariate analysis. Again, results of the multiple regression analysis (fitting either haemoglobin or haematocrit with the other variables with a P -value ≤ 0.1) were very close to those obtained with the univariate model (data not shown).

DISCUSSION

The fatality rate of paediatric cerebral malaria in PNG was 11.9% in the present study. This rate is higher than the 6% found by Stace *et al.* in the same hospital 15 years ago.⁹ This difference may be partly due to the fact that they used a definition of cerebral malaria which was less restrictive, and may have included milder cases who were less likely to die than ours. Emergence of *P. falciparum* parasites resistant to quinine and Fansidar^R may have contributed to worsen the prognosis of severe malaria in the area.^{16,17} Indeed, half of the patients who were pre-treated had received quinine, some for a period of 3 days before admission.

Our CFR of 11.9% is lower than the one which has been reported in large series from Africa for the last 10 years.⁴⁻⁷ The difference is not so dramatic and the confidence limits include most of the rates recently published. However, it is unlikely that larger series of strictly defined cerebral malaria will be collected in the future, since it is now recognized that any impairment of consciousness is associated with an increased mortality.⁷ All such cases will be included in further clinical trials, so comparisons will be less meaningful. Although access to health facilities or care-seeking

behaviour may be different between PNG and Africa, our lower fatality rate does not seem to be due to selection bias. Indeed all children included in our study satisfied the WHO criteria for cerebral malaria.

So why is it that CFR is lower in PNG than in Africa, although the estimated ratios of cerebral to mild malaria and severe to mild malaria are very similar? One of the findings which differs between our study and the African ones is the depth of coma on admission. The prevalence of children with a coma score of 0 was lower in our study than in the studies in Africa (12% versus 24%).⁴ Since we have shown, as has been found everywhere else, that depth of coma is an important, if not the most important, predictor of poor outcome, we can relate the lower CFR of cerebral malaria in PNG to a less severe impairment of neurological functions. The reduced gravity in PNG could be related to a lower parasite load. Indeed we measured much lower parasite densities in our cases than in the African ones. However, parasite count in the peripheral blood correlates poorly with disease severity, possibly because it does not account for the parasites sequestered in the cerebral microvessels, which are the major determinant of the pathogenesis. Parasite density was indeed not a predictor of poor outcome in our study. Difference in virulence between PNG and African strains of *P. falciparum* may be more important than differences in parasite load to explain the lower severity of cerebral malaria in PNG. We know that parasite isolates vary substantially within an area but also between regions in their ability to bind to endothelial cells and to non-infected red blood cells;¹⁸⁻²⁰ two mechanisms supposed to contribute to the pathogenesis of cerebral malaria. The ability of parasite isolates to form rosettes and the efficiency of the rosetting phenomenon in compromising cerebral

circulation, and hence neurological function, also appears to vary from place to place. Indeed, as in Thailand,²¹ we were not able to detect any difference in the ability to form rosettes between the parasite isolates obtained from children with cerebral malaria and those from children with uncomplicated malaria.¹⁰ This is in contrast with all studies from Africa²²⁻²⁴ and may account for the differences in mortality between PNG and Africa.

Besides cytoadherence characteristics, parasites may also differ geographically in their ability to induce metabolic changes, namely hypoglycaemia. In our series of cerebral malaria, prevalence of hypoglycaemia was lower than in African studies (16% versus about 25%).^{4,25} This may be related to qualitative differences of parasite-derived molecules to induce hypoglycaemia,²⁶ but also to quantitative differences, i.e. to the reduced parasite load in PNG. The demonstration of an inverse correlation between parasite density and glycaemia in our study and in others²⁷ supports the latter hypothesis. Low prevalence of hypoglycaemia in our cerebral malaria cases may explain the low mortality and the low occurrence of sequelae since hypoglycaemia has been shown in other studies to be a predictor of poor outcome.^{4,7,25,27,28} One can argue that the low prevalence of hypoglycaemia may be related to sampling bias as only 85 out of 132 children had an admitting blood glucose measurement. If this may be true, it still remains that mortality in those who presented with hypoglycaemia was lower in Madang than in Africa (21% versus about 46%)⁴. Thus PNG patients may be less susceptible to the deleterious effects of hypoglycaemia than African children.

Still considering host characteristics, we observed a higher rate of enlarged spleen in our study than in Malawi (77% versus 42%).⁴ This may reflect stronger immune responses, which would help to clear parasitaemia more quickly and more efficiently in PNG children than in African ones, leading to less severe complications in the former.

The lower prevalence of deaths or sequelae in PNG may be due to better case management in this country than in Africa. Evidence for this is difficult to assess. Case management can certainly differ from one country to another but it may also vary from one hospital to the next in a given country.

Besides providing some explanation for the potentially better prognosis of cerebral malaria in PNG than in Africa, our study was aimed at identifying risk factors for death, in order to improve case management and hence outcome in PNG. It is often argued that such findings are of marginal interest since any child with neurological impairment should receive the best

possible treatment urgently. We know, however, that such a statement is somewhat idealistic in countries where malaria is endemic; and resources, in terms of qualified staff, medication, test kits and monitoring equipment, are often not sufficient to meet all the needs. Identification of bedside risk factors can help to set up priorities. We identified deep coma, malarial anaemia and hyperleucocytosis as significant predictors of death. To reduce the number of deaths, all efforts should be done to improve the level of consciousness, such as correction of shock, hypoglycaemia and acidosis as well as good control of fits and appropriate treatment of the malaria. Close monitoring and quick action must be taken in patients with severe anaemia, especially if associated with high density parasitaemia. Strict criteria have to be used for the administration of blood transfusions, so that children who will certainly benefit from this intervention will be identified. If the haemoglobin or haematocrit values are useful criteria, the clinical condition of the patient must also be considered, in particular the presence of respiratory distress, which has been shown in African studies to be associated with poor prognosis.^{7,29} For Thai adults, close monitoring of glycaemia during the course of the treatment is advocated.³⁰ However, this may not be very effective in reducing the occurrence of severe complications in the PNG children, especially for those who are normoglycaemic on admission, as long as a regular maintenance therapy is provided.²⁷ Finally, the finding that children with hyperleucocytosis are more at risk of dying than those with normal white cell count, which is in agreement with earlier work,^{4,31} underlines the necessity of excluding a concomitant complicating infection, e.g. aspiration bronchopneumonia, in all children with cerebral malaria. In case of doubt, a broad-spectrum antibiotic should be given in combination with the anti-malarial treatment. Alternatively, the association between leucocytosis and poor outcome may be explained through the relationship of tumour necrosis factor (TNF) to both severe complications and white cell count. Indeed, TNF is known to be in high concentration in patients with the most severe disease,³² and to increase the peripheral white cell count when infused into human subjects.³³

ACKNOWLEDGEMENTS

We thank the staff of Madang General Hospital, Ward 4, for their help and co-operation in collecting the samples of the cerebral malaria cases. A Raiko, M Baisor and K Baea for the follow-up of the children, R Sanders for performing the antibody screening test for flavivirus, and S Allen and N Alexander for useful discussions and comments on the manuscript.

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(Revised version received August 1996)