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DOI

[10.1016/S0022-3476\(97\)70135-5](https://doi.org/10.1016/S0022-3476(97)70135-5)

Publication date

1997

Published in

The Journal of Pediatrics

[Link to publication](#)

Citation for published version (APA):

Boele van Hensbroek, M., Palmer, A., Jaffar, S., Schneider, G., & Kwiatkowski, D. (1997). Residual neurologic sequelae after childhood cerebral malaria. *The Journal of Pediatrics*, 131, 125-129. [https://doi.org/10.1016/S0022-3476\(97\)70135-5](https://doi.org/10.1016/S0022-3476(97)70135-5)

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Residual neurologic sequelae after childhood cerebral malaria

Michaël Boele van Hensbroek, MD, Ayo Palmer, MD, Shabbar Jaffar, MSc, Gisela Schneider, MD, and Dominic Kwiatkowski, FRCP

Background: Cerebral malaria is an important cause of pediatric hospital admissions in the tropics. It commonly leads to neurologic sequelae, but the risk factors for this remain unclear and the long-term outcome unknown.

Objective: The purpose of this study was to identify the common forms of neurologic sequelae that occur after cerebral malaria, their evolution over time, and the major clinical risk factors for residual disability.

Study design: Prospective study in 624 children admitted with cerebral malaria to two hospitals in The Gambia, West Africa.

Results: We found that 23.3% of survivors had neurologic sequelae on discharge from the hospital. By 1 month the proportion had decreased to 8.6%, and at 6 months only 4.4% of survivors were found to have residual neurologic sequelae. The most common forms of neurologic sequelae were paresis and ataxia, often found in combination with other neurologic abnormalities. In a multiple logistic regression analysis, depth of coma on admission, multiple convulsions, and duration of unconsciousness were the only three independent risk factors. Hypoglycemia and lactate acidosis were not predictive of sequelae, although they are important risk factors for fatality.

Conclusion: This finding raises the possibility that fatal outcome and neurologic sequelae arise from separate pathologic processes. (J Pediatr 1997;131:125-9)

Cerebral malaria is an important cause of pediatric hospital admissions in the tropics.^{1, 2} On discharge from the hospital, a significant number of patients still have gross neurologic abnormalities.³

To date, there have been few attempts

to quantify the burden of such sequelae in the community, but in regions where cerebral malaria is common the socioeconomic impact is potentially huge. An important unresolved question is the prognosis of children who have neurologic abnor-

malities on discharge, although it is clear that a certain proportion recover with time.^{3, 4} Another critical issue is why neurologic sequelae occur in some cases of cerebral malaria but not in others, and whether this is caused by specific clinical factors that could be prevented. We sought to address these questions by a prospective study of Gambian children with cerebral malaria, identifying the common forms of neurologic sequelae, their evolution over time, and the major clinical risk factors for residual disability.

TNF Tumor necrosis factor

METHODS

Study Population

The study was carried out in The Gambia, West Africa. Patients were recruited at the Royal Victoria Hospital, which is the major referral center for the western part of the country, and at Sibanor Health Centre, a mission hospital that serves as a primary/secondary health facility for a mainly rural population. Unconscious children aged 1 to 9 years were enrolled in the study if they met all of the following criteria: (1) a Blantyre coma score of 2 or less, (2) asexual forms of *Plasmodium falciparum* identified on a thick blood film smear, (3) no other identifiable cause of coma, and (4) informed consent from parent or guardian. The Blantyre coma score is a modification of the Glasgow Coma Scale designed for use in young children and is the summation of verbal response (rated between 0 and 2),

From Medical Research Council Laboratories, and the Department of Paediatrics Royal Victoria Hospital, Banjul, and the Sibanor Health Centre, Sibanor, The Gambia; Department of Tropical Medicine, University of Amsterdam, Academic Medical Centre, Amsterdam, The Netherlands; and University Department of Paediatrics, John Radcliffe Hospital, Oxford, United Kingdom.

Supported by the special program of the United Nations Development Program, the World Bank, and the World Health Organization for research and training in tropical diseases. Dr. Boele van Hensbroek was supported by grants from the Netherlands Foundation for the Advancement of Tropical Research and by Ter Meulen foundation. Dr. Kwiatkowski is supported by the Medical Research Council.

Submitted for publication Apr. 12, 1996; accepted Nov. 15, 1996.

Reprint requests: D. Kwiatkowski, FRCP, Department of Paediatrics, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom.

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0022-3476/97/\$5.00 + 0 9/21/79362

Table I. Clinical and laboratory variables in children with cerebral malaria by neurologic status at 6-month follow-up

Variables	Survivors with sequelae (n = 20)	Survivors without sequelae (n = 432)	p
History and examination on admission			
Age (mo)	49 (23.5)	48 (21.5)	0.87
Coma before admission (hr)	12 (9-24)	6 (3-12)	<0.0001
Convulsions before admission (%)	90.0	90.0	1.0
Rectal temperature (°C)	39.3 (1.1)	38.8 (1.1)	0.03
Pulse rate (per min)	153 (25.7)	146 (21.4)	0.10
Respiratory rate (per min)	54 (13.7)	50 (14.9)	0.18
Coma score (%) ^a			
0	30.0	17.4	—
1	55.0	28.9	—
2	15.0	53.7	0.003
Laboratory findings on admission			
Geometric mean parasite count (/μl)	48,084	46,238	0.94
Hemoglobin (gm/dl)	8.9 (2.1)	8.2 (2.5)	0.22
Leukocytes (×10 ⁹ /L)	18.2 (11-30)	11.3 (8-17)	0.01
Hypoglycemia (%) [†]	40.0	15.0	0.008
Lactate (mmol/L)	3.1 (2-4.9)	3.3 (2-6.5)	0.71
During hospital stay			
Duration of coma (hr)	116 (48-250)	24 (12-42)	<0.0001
Multiple convulsions (%)	65.0	20.1	<0.0001
Repeated hypoglycemia (%)	20.0	3.5	0.007

Values are shown as mean (SD), median (interquartile range) or percentage. Other variables examined, and found to be unassociated with neurologic sequelae, were admission weight, recent chloroquine treatment, presence of severe anemia (hemoglobin <5 gm/dl) and time since last food or drink.

^aBlantyre modification of the Glasgow Coma Scale.⁵

[†]Hypoglycemia was defined as a blood glucose level <2.2 mmol/L.

motor response (0-2) and gaze (0-1). The maximum total score is therefore 5; a score of 2 indicates failure to localize a painful stimulus; and a score of 0 indicates total unresponsiveness to painful stimulation.⁵

Design

The neurologic sequelae after cerebral malaria were studied prospectively during a 3-year period. The study formed part of a large trial in which the antimalarial agent artemether was compared with standard quinine therapy, and a monoclonal antibody against tumor necrosis factor (anti-TNF therapy) was compared with placebo, using a standard 2 × 2 factorial design.^{6,7} Further details of these intervention studies are published elsewhere.^{7,8}

Clinical Assessment and Management During Hospitalization

On admission, history and clinical findings were recorded on standardized forms (data available on request). A venous blood sample was obtained for diagnosis of malaria, blood glucose estimation, and for blood culture, hematologic, and biochemical studies. Hypoglycemia, defined as a blood glucose level of <2.2 mmol/L, was treated immediately with 1 ml/kg of 50% glucose administered intravenously. Convulsions were treated initially with diazepam (0.5 mg/kg rectally or 0.3 mg/kg intravenously), if necessary followed by administration of paraldehyde (0.1 ml/kg). Children with repeated or refractory convulsions received phenobarbi-

tone, 15 mg/kg intramuscularly. Lumbar puncture was performed, unless clinically contraindicated, to exclude meningitis. While children were comatose, fluids were given by intravenous infusion (4% glucose/0.18% saline solution). Blood transfusion (15 ml/kg) was given if the packed cell volume was below 15%. Patients allocated to receive artemether had intramuscular injections of Paluther (Rhône-Poulenc, France) into the anterior aspect of the thigh for 4 days, at an initial dose of 3.2 mg/kg followed by daily doses of 1.6 mg/kg. Those allocated to the quinine group received intramuscular injections of quinine dihydrochloride (Rotexmedica GMBH, Trittau, Germany) into the anterior aspect of the thigh for 5 days, at an initial dose of 20 mg/kg followed by 10 mg/kg 12 hourly. In addition to the artemether/quinine randomization, each child was assigned to receive either anti-TNF therapy (5 mg/kg) or placebo, given as a single intravenous dose. Vital signs for each child were recorded every 4 hours for the first 24 hours and then every 6 hours until discharge. Blood glucose measurements were repeated after 4 and 12 hours and as clinically indicated. Detailed recordings were made of the type and duration of convulsions that occurred during hospitalization.

Neurologic Assessment on Discharge and Follow-up

At the time of discharge, a detailed neurologic examination was performed. A child was defined as having neurologic sequelae if he or she had at least one of the following neurologic abnormalities: paresis, ataxia, hearing defects, visual field defects, aphasia, repeated afebrile convulsions, behavioral abnormalities, or developmental regression. The severity of paresis was defined as mild (if there was difficulty with fine motor activity in the affected extremity), moderate (absence of normal function in the involved extremity), or severe (no or little function in the involved extremity). The severity of ataxia was defined as mild (if the patient was able to sit but not walk unassisted), moderate (if the patient required assistance in

sitting and walking), or severe (if the patient was unable to sit or walk without falling).⁹ At 1 month after admission, all survivors were asked to return for a further detailed neurologic assessment by a clinical investigator (A.P., M.BvH., or G.S.) who was unaware of the results of the discharge examination and the treatment the child received while hospitalized. The investigation included a questionnaire on the child's behavior and performance and a detailed examination recorded on standardized forms (available on request). Those who had neurologic sequelae at 1 month were reviewed by the same clinical investigator 6 months after admission. Those without evident sequelae at 1 month were visited at home, for their 6-month follow-up, by a field worker who would complete a questionnaire answered by the parent about the child's health and performance. If there was any doubt concerning the child's performance, he or she was referred to the clinical investigator for further evaluation. Only the children with residual sequelae at their 6-month follow-up visit were seen annually thereafter by the clinical investigator until the end of the study (June 1995).

Statistical Methods

Because the study formed part of a large intervention trial, we first examined the effect of each intervention on the incidence of neurologic sequelae. The sequelae rate did not differ between the artemether and quinine groups (odds ratio 0.62, 95% confidence interval 0.21 to 1.78; $p = 0.5$), but anti-TNF therapy was associated with an increased risk of residual sequelae when compared with placebo (odds ratio 3.2, 95% confidence interval 1.1 to 11.5; $p = 0.04$). Therefore the incidence of neurologic sequelae is presented both for the entire population, and separately for each of the anti-TNF therapy and placebo groups. In multiple regression models, we adjusted for both antimalarial treatment and anti-TNF therapy.

To find the set of variables that provided prognostic indicators of neurologic sequelae, associations between each variable and neurologic sequelae outcome

Table II. Predictors for residual neurologic sequelae by regression analysis

Variables	Model by variable group*		Final model*	
	OR	95% CI	OR	95% CI
History and examination on admission				
Coma duration before admission ≥ 12 hr	5.2	1.9-14.3		
Coma score 0 or 1	6.9	1.9-25.3	7.4	1.8-29.7
Laboratory data on admission				
Hypoglycemia	3.1	1.1-8.6		
Leukocytes $\geq 15 \times 10^9/L$	3.5	1.3-9.4		
During hospital stay				
Duration of coma ≥ 48 hr	11.2	3.0-42.4	13.4	3.4-52.4
Multiple convulsions	6.0	2.0-18.3	7.1	2.2-22.7

To find the variables that independently predicted neurologic sequela, a multivariate regression analysis was performed on all variables with $p < 0.1$ in the univariate analysis shown in Table I. The variables were divided into three groups (clinical admission data, laboratory data, and clinical features after admission). First we identified significant predictors within each group (column 2), which were then entered into a combined model (column 4).

OR, Odds ratio; 95% CI, 95% confidence interval.

*Adjusted for antimalarial and "anti-TNF therapy" effect.

were first investigated in a univariate analysis. All variables with a p value ≤ 0.1 were then considered in a multivariate analysis for which unconditional logistic regression was used. A set of prognostic indicators associated with neurologic sequelae was found from each of the following groups of variables: (1) the history and examination, (2) basic laboratory investigations, and (3) observations made of the child during their hospital stay. The prognostic variables from these three groups were then investigated together to produce a final model. At each stage, variables were added sequentially in order of their importance as ascertained in the univariate analysis. Once a final model was reached at each stage (i.e., no remaining terms were significant), each variable was then dropped (one at a time) to determine whether it was still significant in the presence of the other variables. Significance was assessed by changes in deviance with associated p values.

The study was approved by the Gambian Government/Medical Research Council Laboratories Ethical Committee. The conduct of the study was monitored by the Tropical Disease Research Program of the World Health Organization.

RESULTS

Patient Characteristics

Between 1992 and 1994 a total of 624 children with cerebral malaria were studied, 388 at the Royal Victoria Hospital and 236 at Sibanor Health Centre. Ages ranged from 12 to 113 months (mean 47 months) and 52% were boys. The duration of illness before admission ranged from less than 1 day to 14 days (median 2 days), and of coma between less than 1 hour to 3 days (median 6 hours). One hundred and thirty-four (21.5%) children died in the hospital, and one child died at home 4 days after discharge. Among the children who died in the hospital, death occurred within 12 hours after admission in 63 (47%) and within 24 hours in 96 (72%) children. The description below elaborates on the various aspects of the children who survived but had residual neurologic sequelae.

Predictors of Neurologic Sequelae

Table I shows the relevant clinical details categorized according to patients with residual neurologic sequelae at 6-month follow-up and those who made a full recovery. To assess the prognostic importance of variables collected on admis-

Table III. Prevalence of various forms of neurologic sequelae after cerebral malaria at 1-, 6-, and 18-month follow-up*

Sequelae	1 month (n = 466)	6 months (n = 452)	18 months
	Total no. patients (single/multiple)	Total no. patients (single/multiple)	No. with NS/No. followed up*
Paresis	11 (4/7)	7 (1/6)	4/5
Ataxia	13 (5/8)	5 (0/5)	3/5
Hearing defects	5 (0/5)	3 (2/1)	1/3
Visual field defects	3 (1/2)	2 (0/2)	1/2
Aphasia/dysarthria	7 (2/5)	4 (0/4)	4/4
Behavior problems	8 (7/1)	4 (2/2)	1/2
Development regression	4 (0/4)	4 (0/4)	2/3
Convulsions	5 (4/1)	1 (0/1)	1/1

Single denotes the number of children in whom it is the only neurologic abnormality; *multiple*, number of children in whom sequelae form part of multiple neurologic abnormalities.
 NS, Neurologic sequelae.
 *Number of children with residual sequelae at 18 months against total number followed up from the 6-month residual sequelae group (e.g., 5 of 7 paretic children at 6 months were seen at 18 months, 4 of whom were still paretic).

sion or during hospitalization, we first performed a univariate analysis. This analysis showed that children in whom residual neurologic sequelae developed had significantly longer duration of coma before admission, had a higher temperature, and a deeper coma on presentation and were more often hypoglycemic. In addition, these children took significantly longer to recover from coma and were more likely to have had recurrent convulsions and recurrent hypoglycemic episodes. The variables of Table I were then entered in a multiple logistic regression model as described in the Methods section. Three variables were identified as key prognostic indicators: coma score on admission, multiple convulsions, and coma duration during hospital stay (Table II). The latter factor was the strongest predictor of neurologic sequelae. Fourteen percent of the children who were in a coma for 2 days had neurologic sequelae ($p < 0.0001$). The risk increased to 39% if coma persisted for more than 5 days ($p < 0.0001$).

Prevalence and Recovery

ONE-MONTH FOLLOW-UP

Neurologic assessment was performed at 1 month in 466 (95.1%) of the 490 survivors. Four (3.5%) of the 114 children

with sequelae at the time of hospital discharge were lost to follow-up. The prevalence of sequelae decreased from 23.3% on discharge to 8.6% by 1-month follow-up (the prevalence was 6.4% in the placebo group and 10.8% in the anti-TNF therapy group, $p = 0.14$). At 1-month follow up, 25% of the children discharged with neurologic sequelae had not recovered, and an additional 12 new instances of sequelae were detected among the children who were not noted to have neurologic sequelae at discharge. All of the 12 new cases involved mild sequelae; 11 had recovered by 6 months and the remaining patient recovered before the 18-month follow-up.

SIX-MONTH FOLLOW-UP

The neurologic assessment at 6 months was performed in 452 (92.4%) of the 489 survivors. Overall the prevalence of residual sequelae had declined to 4.4% of survivors (prevalence 2.2% in the placebo group and 6.7% in the anti-TNF therapy group, $p = 0.04$). This difference is discussed more fully in reference 8. Four new cases of sequelae were detected at 6-month follow-up.

EIGHTEEN-MONTH FOLLOW-UP

Neurologic assessment at 18 months was restricted to the children with resid-

ual sequelae at 6 months. Fourteen of the 20 children with residual neurologic sequelae at 6 months were in the study for 18 months. Thirteen of these were traced; only 3 had made a full recovery. Five of the children with residual sequelae at 18 months were examined again at 30 months and none showed any significant improvement during that period.

Type of Sequelae

Details of the various types of neurologic sequelae and the recovery over time are listed in Table III. In general, children with only one neurologic abnormality were more likely to make a full recovery when compared with children with multiple neurologic abnormalities (92% with one neurologic abnormality made a full recovery between 1 and 6 months, compared with 18% with multiple abnormalities, $p < 0.0001$). Children with mild paresis or ataxia, the two most common neurologic abnormalities, were completely recovered by 6 months. Most of the children with severe paresis and ataxia showed some improvement over time, but only a minority made a full recovery. Hearing and visual field defects varied in severity from complete blindness or deafness to mild visual impairment or some hearing difficulty. Aphasia tended to persist, although some children improved to a level of dysarthria or made a full recovery. Behavioral problems became apparent during the follow-up visits, and were often reported by the parents in the first place and subsequently confirmed by the investigator. They presented as restlessness, concentration problems, hallucinations, or aggressive behavior and tended to be transient. Developmental regression was seen in children with multiple severe neurologic abnormalities. Some children had no sequelae other than recurrent convulsions (that were not related to a febrile illness) but this outcome was relatively uncommon.

DISCUSSION

Among 490 children who survived cerebral malaria, we found that more than 20% had neurologic abnormalities at hos-

pital discharge but only 4% had detectable sequelae when examined 6 months later. Although it is possible that some children had subtle impairment that was not apparent on clinical examination, it is clear that the majority of those with neurologic sequelae show a substantial degree of recovery. However, the problem of sequelae is not insignificant, because it is likely that this residual group represents many thousands of children who are permanently handicapped each year in regions where malaria is endemic.

The pattern of neurologic abnormalities was highly variable. The most frequent sequelae were paresis and ataxia, which were often associated with multiple abnormalities. They were more likely to lead to residual sequelae than auditory or behavioral impairment, which tended to result in a good recovery. Behavioral problems were found in 2% of survivors assessed at 1 month. Problems ranged from mild attention disorders to grossly abnormal patterns of behavior with hallucinations and aggressive attacks. To prevent overreporting in this heterogeneous group, we included only those cases of abnormal behavior that were reported by the parents and independently confirmed by the investigator; however, in the absence of a case-control study, other reasons for the behavioral abnormalities such as hospitalization cannot be formally excluded. Although such behavior abnormalities were very disturbing for family and teachers, they usually lasted only a few months. At the other extreme of the spectrum was gross developmental regression, seen in 1% of survivors. These severely handicapped children were often blind, deaf, aphasic, and parietic.

The identification of risk factors is important because they may provide an insight into the pathogenesis of neurologic sequelae and possible means of prevention. In various smaller studies, hypoglycemia, anemia, repeated convulsions,

and duration of unconsciousness have been identified as risk factors.^{3, 4, 10} However, their independence was not investigated because they were identified in a univariate analysis only. In defining risk factors, other studies have combined neurologic sequelae and fatal outcome, which is justifiable if sequelae and death share a common pathologic pathway.⁵ In our multivariate analysis, depth of coma, multiple convulsions, and coma duration were the only three independent risk factors for sequelae (with 48 hours as the best clinical cutoff for coma duration; data not shown). All of the children who had neurologic sequelae could be identified from these three factors. An important observation is that hypoglycemia and lactate acidosis, which are strong predictors of fatality,^{5, 11, 12} were not independently predictive of neurologic sequelae. This finding raises the possibility that fatal outcome and neurologic sequelae arise from separate pathologic processes. The link between repeated convulsions and the development of neurologic sequelae highlights the importance of controlling convulsions. Convulsions in cerebral malaria are very common,^{13, 14} often recurrent, and difficult to control with the conventional treatment available in the tropics. Aggressive treatment is further limited by the absence of intensive care units with respiratory support.

We thank the nursing and medical staff of the Royal Victoria Hospital and Sibanor Health Centre, Dr. S. Forck, Dr. H. Memming, Dr. E. Onyiorah, Dr. G. Enwere, Dr. J. Frenkel, Dr. A. Nussmeijer, Dr. G. Dolan, Sr. R. Wilson, L. Bayo, and L. Manneh for recruitment and follow-up of the study patients; and Dr. B. Greenwood for support and advice during the study.

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