Severe anaemia in childhood cerebral malaria is associated with profound coma.

Richard Idro

Department of Paediatrics and Child Health, Mulago Hospital, P.O Box 7051, Kampala – Uganda.

ABSTRACT

Background: Severe anaemia in children with cerebral malaria has been associated with respiratory distress secondary to lactic acidosis and/or hypoxia. The ensuing metabolic derangement may further depress the level of consciousness culminating in presentation with profound coma. This association has poorly been studied.

Objective: To determine the relationship between profound coma at presentation and the presence of severe anaemia in children with cerebral malaria.

Methods: This cross-sectional study involved 100 children with cerebral malaria who were consecutively recruited at admission in the Paediatric emergency unit of Mulago hospital in Uganda from July to December 2000. Clinical and laboratory evaluation was done using the hospital's guidelines for the management of severe malaria. The exposure factor of interest was severe anaemia (Hb < 5.0 g/dl) and occurrence of profound coma (Blantyre coma Scale 0) was the outcome measure.

Results: Severe anaemia and profound coma were seen in 20% and 9% of the children respectively. Severe anaemia was independently associated with profound coma, adjusted OR 1.34 (CI 1.17 – 1.95), p = 0. 002 and age < 3 years, adjusted OR 1.42 (CI 1.13 – 1.54), p = 0.001). Thirty percent of those with severe anaemia had deep sighing (acidotic) breathing compared to only 15% of those with haemoglobin (Hb) > 5 g/dl, OR 1.21 (CI 0.90 – 1.64), p = 0.118. There was no association between the malaria parasite density and severe anaemia. A similar proportion of those with severe anaemia regained consciousness within 24 hours compared to those with Hb > 5 g/dl (30 vs 42.5 %), OR 1.56 (0.65 – 3.71), p = 0.307.

Conclusions: The findings suggest that profound coma in cerebral malaria may not only result from primary malaria encephalitis but possibly also from a metabolic dysfunction due to severe anaemia.

African Health Sciences 2003; 3(1): 15 - 18

INTRODUCTION

Severe malaria continues to be a leading cause of childhood mortality especially in sub-Saharan Africa.[1, 2] Presentation with altered consciousness, respiratory distress and/or severe anaemia has been associated with most of the deaths and a combination of the 3 syndromes is particularly devastating.[3] In endemic areas, severe malaria tends to affect younger children and present as malaria with severe anaemia. Cases of cerebral malaria are then seen with increasing numbers in relatively older children and in areas of lower endemicity.[4]

The occurrence of severe anaemia in children with cerebral malaria has been described previously. In their series of cerebral malaria in Malawi, Molynuex et al demonstrated that a third of the children needed blood transfusion as a result of severe anaemia.[5] Severe anaemia has also been associated with respiratory distress secondary to lactic acidosis and/or hypoxia.[2, 6] This metabolic derangement may further depress the level of consciousness leading to profound coma at presentation. Little information is available about this. The objective of this study was to describe the association between profound coma and severe anaemia in children with cerebral malaria.

Dr Richard Idro
Department of Paediatrics and Child Health
Mulago Hospital
P.O Box 7051,
Kampala – Uganda.
Fax: +256 – 41 – 530022
Email: idro1@hotmail.com

METHODS

Study design

A cross sectional study was conducted to describe the prevalence of severe anaemia (Hb < 5 g/dl) in children with cerebral malaria and its association with the profound coma at presentation. Children with strictly defined cerebral malaria[2] and admitted to the Paediatric emergency unit of Mulago (the national referral hospital and a 1500 bed facility) in Uganda between July and December 2000 were consecutively recruited and followed up until discharge or death. The history, physical examination, haemoglobin, blood sugar, parasite density, and the outcome was recorded. The depth of coma was assessed using the Blantyre coma scale and the blood sugar measured using a sure step (life scan 1998 USA) glucometer. A child

was said to have profound coma if the total Blantyre score was 0 (Best motor response is non specific or absent, no verbal response and eye movement is undirected). The malaria parasite density was determined by counting the parasites against 200 white blood cells and the figure converted to parasitaemia per microlitres after determining the total white cell count.

A standard treatment regime of quinine and supportive therapy of anti-convulsants (diazepam), antipyretic (paracetamol), blood transfusion, 2 hourly turning, and fluids were administered as appropriate.[2] Hypoglycaemia was corrected with 25% dextrose (2 ml/kg) and the patients were then fed through nasogastric tubes with milk and soups until they were able to take oral feeds. Oxygen was administered to children in respiratory distress. The patients were monitored closely until they stabilized and were then reviewed every 24 hours except when more frequent reviews were needed. A minimum sample size of 97 children with cerebral malaria was obtained using an annual admission minimum of about 400 children with cerebral malaria, with a prevalence of severe anaemia at 25% in these cases and the smallest acceptable prevalence of 17.5%.

Ethical considerations

Institutional consent was given by Makerere University Faculty Research Committee and informed consent obtained from the caretakers of the children. Confidentiality was ensured and results of importance to the attending physicians communicated.

Statistical analysis

Chi-squared and t-tests were used to test for significance of association between the clinical features and severe anaemia. The odds ratio and p value were used as measures of significance with a p value <0.05 considered significant. For cells with small numbers, Fisher's exact test was used. Variables with p values < 0.10 were then entered in a regression model to assess the interaction or joint effects of variables with the occurrence of severe anaemia.

RESULTS

During the study period, July – December 2000, one hundred children with cerebral malaria were seen. Of these, 55% were males and 45% females and the age range was 3 – 132 months with a mean of 40.2 months. Fifty percent of the children were under 3 years of age.

The prevalence of severe anaemia among these children was 20%. The presenting history and physical examination are as presented in table 1.

Table 1 Clinical features in children with severe malaria anaemia and cerebral malaria.

Clinical features	Hb < 5.0 g/dl N=20	Hb ³ 5.0 g/dl	OR (95% CI) N=80	P value
Previous admission for malaria (%)	3 (15)	18 (22.5)	0.61 (0.16-2.31)	0.461
Previous transfusion (%)	3 (15.0)	6 (7.5)	2.18 (0.49-9.59)	0.378*
Anti-malarial before admission (%)	14 (70)	56 (70)	1.00 (0.43-2.35)	1.000
Mean duration of illness in hrs(SD)	53.3(26.6)	56.5 (29.4)	-	0.659
Convulsions (%)	16 (80)	72 (90)	0.82 (0.54-1.23)	0.218
Focal convulsions (%)	4 (20)	6 (7.5)	3.08 (0.78–2.20)	0.110*
Difficult breathing (%)	5 (25)	10 (12.5)	2.33 (0.70-7.82)	0.173*
Vomiting (%)	9 (45)	49 (61.3)	0.52(0.19-1.39)	0.188
Mean age in months (SD)	22.0(11.6)	44.7 (30.8)	-	0.002
Jaundice (%)	3 (15)	29 (36.3)	0.38 (0.12-1.19)	0.068
Mean temperature ^{o}C (SD)	38.4 (1.2)	38.1 (1.2)	-	0.483
Profound coma (BCS 0, %)	5 (25)	4 (5)	6.33 (1.52-26.37)	0.015*
Acidotic(deep sighing)breathing (%)	6 (30)	12 (15)	1.21 (0.90– 1.64)	0.118
Hypotension	1 (5)	4 (5)	1.00 (0.11-9.47)	1.000
Hepatomegaly (>2 cm BCM, %)	16 (80)	51 (63.8)	1.97 (0.72-5.43)	0.167
Splenomegaly (%)	15 (75)	38 (47.5)	2.10 (0.96–4.61)	0.028
Mean parasite density ($x10^3/\mu l$,SD)	161 (310)	155 (276)	-	0.928
Hypoglycaemia (%)	1 (5)	8 (10)	2.11 (0.25-17.93)	0.485

*Fishers exact test.

Profound coma, a lower mean age and splenomegaly were significantly associated with the presence of severe anaemia but not respiratory distress as shown in table 1. More than two thirds of the children had received anti malaria drugs prior to presentation. Chloroquine had been given to over 50%, others being sulphadoxine-pyrimethamine, quinine and amodiaquine. Prior anti malaria drugs had no impact on the occurrence of severe anaemia. The presence of severe anaemia also had no influence on the outcome in terms of the occurrence of death, neurological sequelae, duration of hospital stay or that of coma as shown in table 2. The mean parasite densities in the two groups were also not any different. All children with neurological sequelae had haemoglobin above 5 g/dl.

Table 2 Outcome in children with severe malaria anaemia and cerebral malaria

Clinical feature	Hb< 5g/dl	Hb> 5g/dl	Odds ratio	P value
Conscious within 24 hours (%)	6 (30.0)	34 (42.5)	1.56 (0.65-3.71)	0.307
Convulsions after 24 hours (%)	1 (5.0)	2 (2.5)	2.05(0.18-23.84)	0.492
Neurological sequelae	-	5 (6.3)	0.94(0.89-0.99)	0.580*
Death (%)	1 (5.0)	6 (7.5)	0.65 (0.07-5.72)	1.000*
Mean No. of days in hospital (SD)	3.3 (1.7)	3.4 (2.1)	-	0.789

*Fishers exact test.

All the 20 severely anaemic children were transfused in addition to 10 others who had rapidly progressive anaemia. The mean haemoglobin concentration among children 3 years and above compared to those less than 3 years was 8.81(SD 2.38) and 6.26 (SD 2.60) g/dl respectively ($p < 0.001$). The mean age of children who needed blood transfusion was also significantly lower (20 vs 48 months).

Table 3 Regression model for clinical and demographic factors associated with severe anaemia in childhood cerebral malaria.

Clinical feature	Adjusted Odds ratio (95% CI)	P value
Constant	1.46 (0.98 - 5.97)	0.064
Age < 3 years	1.42 (1.13 - 1.54)	0.000
Jaundice	1.08 (0.94 - 1.28)	0.251
Profound coma	1.34 (1.17 - 1.95)	0.002
Splenomegaly	1.07 (0.91 – 1.23)	0.486

On regression analysis, only age < 3 years and profound coma were shown to be independently associated with severe anaemia as shown in table 3.

DISCUSSION

The relationship between the presence of severe anaemia and the occurrence of profound coma in children with cerebral malaria was investigated. The prevalence of severe anaemia in the current study (20%) and the number of children who were transfused (30%) is comparable to figures previously described.[5,7] This study has, in addition, demonstrated that apart from young age[4], strong association exists between severe anaemia and profound coma in children with cerebral malaria.

Severe anaemia is known to be associated with a reduction in the oxygen carrying capacity of circulating blood resulting into tissue hypoxia. It is possible that the resulting metabolic derangement may further depress the level of consciousness in a child with cerebral malaria leading to profound coma. Hypoxia from anaemia and the sequestration of red blood cells in the microcirculation may also result in increased anaerobic respiration leading to the production of large quantities of lactic acid. This is may manifest as respiratory distress with acidotic breathing.[2, 5] Indeed, despite our failure to determine the serum lactate levels, 30% of the children with severe anaemia had acidotic (deep sighing) breathing, compared to only 15% of those with haemoglobin > 5g/dl. This difference was however not statistically significant.

Studies on cerebral malaria in Kenya by Marsh and colleagues postulated that the World Health Organization criteria for cerebral malaria is fulfilled by four possibly distinct groups of children.[8] Each of the four groups have different pathogenic pathways to coma with one group suffering from severe metabolic derangement. The children with severe metabolic disturbance can regain consciousness quickly upon adequate resuscitation.[8, 9]The lack of acid base status in this study notwithstanding, the results from our study appear to support this view. This therefore calls for aggressive resuscitation measures for children with profound coma especially if they have severe anaemic.

ACKNOWLEDGEMENTS

Sincere thanks go to Prof J Tumwine, Dr CAS Karamagi, Mr JB Lwanga, and Fr E Ovure for the invaluable help rendered. Kulika Charitable Trust, the Nuffield foundation, and Child Health Development Centre, Makerere funded the study.

REFERENCES

1. Stephen J C, Thomson C M. Mapping malaria in Africa. *Post grad Doctor- Africa*. 1999; **3:**46-52.
2. WHO. Severe falciparum malaria. *Trans R Soc Trop Med Hyg*. 2000 **94** (suppl).1:1-45.
3. Marsh K, Forster D, Waruiru C, Mwangi I, et al. Indicators of life threatening malaria in African children. *New Eng J Med* 1995; **332** (21): 1399 - 404.
4. Modiano D, Sirima B.S, Sawadogo A, et al. Severe malaria in Burkina Faso: urban and rural environment. *Parasitologica* 1999 **41**:251-54.
5. Molyneux M E, Taylor T E, Wirima J J, Borgstein A. Clinical features and prognostic indicators in Paediatric cerebral malaria; a study of 131, comatose Malawian children. *Quart J Med* 1989; **265**: 441 - 459.
6. Warrell D.A. Management of severe malaria. *Parasitologica* 1999; **41**: 287–94.
7. Schellenberg D, Menendez C, Kahigwa E et al. African children with malaria in an area of intense *Plasmodium falciparum* transmission: features on admission for death and risk factors for death. *Am J Trop Med Hyg* 1999; **61**(3): 431 – 8.
8. Marsh K, English M, Crawley J, Peshu N. The pathogenesis of severe malaria in African children. *Ann of Trop Med Parasitol* 1996; **90**(4): 395- 402.
9. Jaffer S, Van Hensbroek NB, Palmer A, Schneider G, Green wood B. Predictors of fatal outcome following childhood cerebral malaria. *Am J Trop Med Hyg* 1997; **57**(1): 20 - 4.