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Pattern and predictors of neurological morbidities among childhood cerebral malaria survivors in central Sudan

Adil Mergani[1], Ammar H. Khamis[2], E.L. Fatih Hashim[3], Mohamed Gumma[4], Bella Awadelseed[4], Nasr Eldin M.A. Elwali[5] & Ali Babikir Haboor[6]

[1]*College of Applied Medical Sciences, Taif University, Turabah, Saudi Arabia;* [2]*Department of Family and Community Medicine, College of Medicine, University of Dammam, Dammam, Saudi Arabia;* [3]*Faculty of Medicine, University of Sinnar, Sinnar, Sudan;* [4]*Singa Hospital, Ministry of Health, Sudan;* [5]*Department of Biochemistry, College of Medicine, Al Imam Muhammad Ibn Saud Islamic University, Riyadh, Saudi Arabia;* [6]*Faculty of Medicine, University of Gezira, Wad Medani, Sudan*

ABSTRACT

Background & objectives: Cerebral malaria is considered a leading cause of neuro-disability in sub-Saharan Africa among children and about 25% of survivors have long-term neurological and cognitive deficits or epilepsy. Their development was reported to be associated with protracted seizures, deep and prolonged coma. The study was aimed to determine the discharge pattern and to identify potential and informative predictors of neurological sequelae at discharge, complicating childhood cerebral malaria in central Sudan.

Methods: A cross-sectional prospective study was carried out during malaria transmission seasons from 2000 to 2004 in Wad Medani, Sinnar and Singa hospitals, central Sudan. Children suspected of having cerebral malaria were examined and diagnosed by a Pediatrician for clinical, laboratory findings and any neurological complications. Univariate and multiple regression model analysis were performed to evaluate the association of clinical and laboratory findings with occurrence of neurological complications using the SPSS.

Results: Out of 940 examined children, only 409 were diagnosed with cerebral malaria with a mean age of 6.1 ± 3.3 yr. The mortality rate associated with the study was 14.2% (58) and 18.2% (64) of survivors (351) had neurological sequelae. Abnormal posture, either decerebration or decortication, focal convulsion and coma duration of >48 h were significant predictors for surviving from cerebral malaria with a neurological sequelae in children from central Sudan by Univariate analysis. Multiple logistic regression model fitting these variables, revealed 39.6% sensitivity for prediction of childhood cerebral malaria survivors with neurological sequelae ($R^2 = 0.396$; $p=0.001$).

Interpretation & conclusion: Neurological sequelae are common due to childhood cerebral malaria in central Sudan. Their prediction at admission, clinical presentation and laboratory findings may guide clinical intervention and proper management that may decrease morbidity and improve CM consequences.

Key words Childhood cerebral malaria; neurological sequelae; predictors

INTRODUCTION

Cerebral malaria (CM) is the most severe neurological complication of falciparum malaria and is considered a leading cause of neuro-disability in sub-Saharan Africa[1]. Full recovery from neurological complications associated with CM had been reported earlier[2], although, many children sustain severe brain injury after cerebral malaria and about 25% show long-term neurological and cognitive deficits or epilepsy[3-4]. Neurological damage has only been recently recognized as a common sequelae of CM in African children[5]. In non-immune adults, neurological sequelae are uncommon, although a variety of post-malarial syndromes have been described[6]. In children, the rate of permanent neurological complications following recovery from cerebral malaria was initially thought to be very low. Follow-up studies had reported that it was higher than originally thought, with up to 10% of patients suffering some sort of neurological impairment. Recent studies in African children with CM have reported that the incidence of neurological sequelae was reported in 10.9% of survivors[7-8]. About 50–84% of children recovered completely, usually within the first six months after discharge while up to 55% recovered after 18 months of discharge. This may be an overestimation due to incomplete follow-up. The development of neurological sequelae in African children is associated with protracted seizures, deep and prolonged coma[8–10]. Anemia was implicated as a predisposing factor for sequelae due to CM in one study but not in others[5, 8]. Some studies have shown an association between the development of sequelae and pathophysiological processes such as raised intracranial

pressure (ICP)[11]. The pattern of neurological sequelae in children differs from adults[6]. In children, these ranges from weakness and hearing impairment to severe sequelae such as hemiplegia, quadriplegia, epilepsy and cortical blindness[12]. In addition, unmeasured long-term consequences such as subclinical learning difficulties in children who recovered from cerebral malaria may occur[13]. Aims of this study were to characterize the discharge pattern of neurological sequelae and to identify the potential and informative predictors for neurological morbidity, complicating childhood cerebral malaria in central Sudan.

MATERIAL & METHODS

A cross-sectional prospective study was carried out during malaria transmission seasons from 2000 to 2004 in Wad Medani, Sinnar and Singa hospitals, central Sudan. These cities lie along the Blue Nile. This area is endemic for *P. falciparum* with high seasonal incidence during the rainy season from August to November. A second peak of transmission follows from January to March during irrigating cotton in Gezira scheme. Hence, the data were collected during the rainy seasons and the second peaks of transmission. Most of severe malarial cases in this area are admitted into one of these three hospitals. The study was approved by Ethical Committee at NCI, Gezira University and consents from all patients families to participate in the study were collected.

A total of 940 children suspected of having CM were examined and investigated by a Pediatrician. Cerebral malaria (CM) was defined as an unarousable coma that persisted for >30 min after cessation of any convulsion, in the presence of asexual stages of *Plasmodium falciparum* parasite on thick blood film, for which no etiological explanation other than malaria can be attributed[15]. Coma was assessed every 12 h. Furthermore, if the child had transient convulsions at admission, coma score was assessed 30 min after convulsions had ceased. Glasgow coma scale (GCS) for children over 10 yr-old[14] and the modified Glasgow scale, the Blantyre coma score (BCS), to be applicable for children under 10 yr were used[15]. Unarousable coma was considered in child if a GCS summated score of four or less for elder children (≥ 10 yr), and a BCS summated score of two or less in younger children (< 10 yr) was obtained[15-16].

Only 409, out of the 940 examined children, were diagnosed as having cerebral malaria (CM); 160 (39%) from Wad Medani, 220 (54%) from Sinnar, and 29 (7%) from Singa. All children with CM were treated with Quinine dihydrochloride at a dose of 10 mg/kg of the salt (maximum, 600 mg) as a continuous infusion in 5% dextrose to prevent quinine-associated hypoglycemia over 4 h every 8 h. Patients with recurrent or multiple seizures were treated with intramuscular Phenobarbital at a dose of 10 mg/kg. Dehydration or hypovolemia were corrected with 0.9% saline or 5% dextrose saline by intravenous (iv) infusion[17-18]

Statistical analysis was performed with the SPSS (version 16.0) package for Windows (SPSS Inc., Chicago, USA). Survivals were grouped based on the presence or absence of neurological sequelae. Data were presented as frequency tables and mean ± standard deviations (X ± SD). Clinical and laboratory factors such as level of consciousness, duration of coma, posture, multiple seizures, anemia, blood urea and hypoglycemia were compared in those with and without sequelae using univariate analysis for significance by use of chi-square or Fisher's exact test, where counts were < 5. *P*-values <0.05 were regarded as significant. Significant variables those retrieved by univariate analysis were further fitted by multiple regression model analysis.

RESULTS

Demographics and clinical presentation of study subjects

A total of 409 children, were diagnosed as having CM, after excluding the patients with negative blood films for asexual stages or having other diseases that may contribute to the coma. The mean age of the study subjects was (6.1 ± 3.3) years; the minimum age case was one yr-old and the maximum aged case was 15 yr-old. In all, 223 (54.5%) patients were males and 186 (45.5%) were females, and there was no significant difference in age between them (p=0.77). The highest incidence of the disease was found among the age group (4–6 yr), although both sexes showed different peaks of incidence, for males at the fifth year and for females at the third year of age with no significant differences (p=0.054) (Fig. 1). The

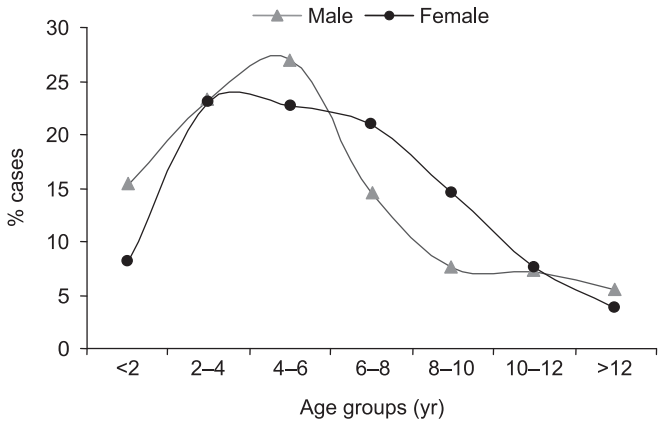

Fig. 1: Distribution of study subject according to age and gender.

clinical presentation and biochemical findings of the study subjects (409) at admission are shown in Table 1.

Cerebral malaria outcome among the study subjects

The mortality rate associated with the study subjects was 14.2% (58) and 18.2% (64) of survivors (351) had neurological sequelae. The frequencies and types of encountered neurological sequelae are shown in Table 2. The most common type of complication was hemiparesis that was encountered in 37.5% (24) of the survivors with neurological sequelae, four children of them were associated with blindness.

Table 1. Clinical presentation and biochemical findings of the study subjects

Clinical and biochemical finding	Frequency (%)/ Mean±SD
Lag period from disease onset to hospitalization (h)	4.27 ± 2.931
Convulsion (focal)	59 (14.5)
Abnormal posture (Decorticated or Decerebrated)	65 (15.9)
Eye pupil reactivity to light	230 (56.2)
Meningeal irritation signs	41 (10)
Acute respiratory distress	28 (6.8)
Coma GS at admission	1.87 ± 1.691
Coma duration (hours)	34.81 ± 28.327
TWBCs (cell/dL)	6370 ± 2787
Hb (g/dL)	8.1 ± 2.1
RBS (g/dL)	91.85 ± 33.7
Blood urea (g/dL)	29.95 ± 17.75

Table 2. Residual neurological sequelae and their frequencies among CM survivals at discharge

Residual neurological sequelae	Frequency (%)
Hemiparesis	20 (31.25)
Hemiparesis and blindness	4 (6.25)
Hemiplegia	8 (12.5)
Aphasia	8 (12.5)
Quadriplegia and blindness	4 (6.25)
Quadriplegia and aphasia	4 (6.25)
Quadriparesis	8 (12.5)
Quadriparesis and blindness	4 (6.25)
Quadriplegia	4 (6.25)
Total	64 (100)

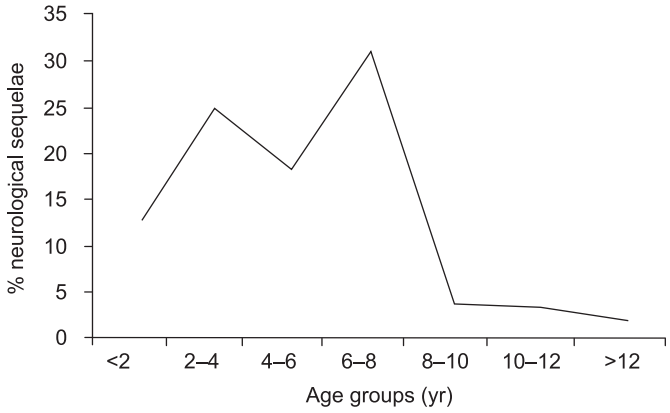

Fig. 2: Distribution of neurological sequelae in study subjects according to their age.

Informative predictors for neurological sequelae due to CM among survivals

The neurological morbidity rate among survivals at discharge was 18.2% (64). The frequency of neurological sequelae in study subjects according to their age is shown in Fig. 2. Comparisons of demographics and clinical findings between healthy survivals and those with neurological morbidities are shown in Table 3. Abnormal posture either decerebration or decortication, focal convulsion and coma duration of >48 h were significant predictors of surviving with neurological sequelae due to CM as per univariate analysis. Result from multiple regression analysis fitting the same variables was very close to those obtained with the univariate model. This indicates that children who have been admitted with CM, and having one or more of the manifestations listed in Table 4, are at higher risk for surviving with neurological sequelae than others who had neither of them ($R^2 = 0.396$; $p = 0.001$).

Table 3. Comparison of demographics and clinical findings between survivals

Demographics and clinical findings	Survival		Odds ratio	*P*-value
	Healthy	Neurological sequelae		
Gender (Male)	54.7%	62.5%	1.208	0.159
Age in years (Mean)	6.20 ± 3.21	5.66 ± 2.89	0.434	0.511
Lag period from disease onset to hospitalization (h)	4.13 ± 3.047	4.89 ± 2.265	1.993	0.160
GS at admission (Mean)	2.08 ± 1.973	1.50 ± 1.79	1.321	0.251
Coma duration in hours (Mean)	31.89 ± 23.516	47.27 ± 41.222	4.141	0.0
Hb g/dl (Mean)	8.1 ± 2.142	8.7 ± 2.388	2.829	0.094
Blood urea (Mean)	27.37 ± 15.702	25.79 ± 8.606	3.649	0.057
RBS at admission (Mean)	89.85 ± 34.812	79 ± 38.171	0.530	0.467
Abnormal posture (Decorticated or Decerebrated)	14.2%	50%	6.053	0.0
Focal convulsion	8.6%	50%	10.583	0.0

Table 4. Informative predictors of neurological sequelae among cerebral malaria survivals

Informative predictor	Univariate analysis			Multiple logistic regession analysis		
	P-value	Odds ratio	CI 95%	*P*-value	Odds ratio	CI 95%
Decerebration and decortication	0.0	6.053	3.328–11.009	0.0	5.313	2.652–10.644
Coma duration >48 h	0.0	4.141	2.138–8.023	0.0	3.824	1.852–7.904
Focal convulsion	0.0	0.583	3.646–30.720	0.0	11.322	5.525–23.204

Fitness of the model: $R^2 = 0.396$; $p<0.001$.

DISCUSSION

Earlier studies in consequences of childhood CM had suggested full neurological recovery of children. Although in this study, neurological morbidities were encountered in 18.2% of survivors (351) at the time of discharge. The complications included hemiparesis, blindness, quadriplegia, quadriparesis, hemiplegia and aphasia. Our result is comparable to Bondi's[8] study done in the children's emergency room, University College Hospital, Ibadan, Nigeria, which reported that 17.7% of CM survivors had developed neurological sequelae as opposed to 12% seen in the Gambian children admitted with CM[19]. However, the frequencies of neurological sequelae observed in Papua New Guinea[20] (1.5%) and Mulago Hospital, Kampala[21] (5%) are lower than what we have reported in this study. This may be due to better medical care and management facilities in these countries as level of medical services may differ from one country to another and even within the same country between different hospitals.

No comprehensive data on the clinical features of cerebral malaria and their prognostic value are available at present in the Sudan. However, the largest experience on the importance of these prognostic variables is from Africa, although there is considerable geographic variation in their relative importance. The assessment of the presenting clinical manifestations to identify informative predictors of the neurological sequelae associated with 18.2% of survivors in this study has revealed that abnormal posture (decerebration or decortications), focal seizure and prolonged coma (coma duration of >48 h) are significant informative predictors of neurological sequelae, according to the univariate analysis. Prolonged coma of >48 h in the study subjects is found to associate with 5-time significantly higher risk for patients discharged with a neurological defect [confidence interval (CI): 2.538–8.867; $p = 0.0$].

This is similar to what was reported in many studies done in Africa, demonstrating that prolonged coma is a major risk factor for persisting neurological and cognitive impairments following CM[19, 22-23]. Coma arises because of sequestration of packed red blood cells (pRBCs) in cerebral capillaries and post-capillary venules resulting in reduction in the supply of oxygen and other nutrients to the brain; however, patients who may have similar numbers of sequestered parasites in other tissues, but not the brain, would not be expected to develop a full-blown cerebral syndrome[24]. Rupture of sequestered pRBCs in the brain was thought to be associated with increased local secretion of tumour necrosis factor-α which triggers the secretion of nitrous oxide (NO) [25-26]. The NO causes disturbance in permeability through the blood-brain barrier and may interfere with the neurotransmission[27], leading to alteration in the consciousness and may cause coma[28]. Further, it may cause neurological damage and sequelae[29]. Other researchers suggested that circulating malaria toxins, kinins, increase the permeability of the brain blood barrier (BBB), causing an efflux of plasma out of the vessels, thereby, concentrating the red blood cells within the cerebral vasculature and ultimately producing stasis of the blood, cerebral oedema and coma[30-31].

Seizures are a common presenting feature in children with CM, and neurologic deficits have been described in survivors of CM[18, 32], although neurologic impairment after an episode of CM may not be limited to the neurologic deficits seen at discharge. Their frequency in this study was 97.6% (399), of them 58 (14.5%) had focal convulsion. Analysis of their association with prognosis of childhood CM in this study revealed that children admitted with CM and presented with focal convulsion were at 11-times higher risk for survival with a neurological deficit (CI: 3.646–30.720; p=0.0). Our result is consistent with the observations reported by other studies in Nigerian and Ugandan children of Africa[18, 21, 23], indicating that focal convulsions are associated with neurological sequelae due to CM .

Abnormal motor posturing is a common feature of cerebral malaria in children and it is an indication of severe brain injury. Abnormal motor posturing is associated with features of raised intracranial pressure and recurrence of seizures, although intracranial hypertension may be the primary cause[33]. In this study, abnormal posturing is strongly associated with development of neuro-

logical sequelae among survivors showing around six times increased relative risk (CI: 3.328–11.009; p=0.0). Similar results were demonstrated in other studies reporting strong association with abnormal posturing and survival of patients from CM with neurological deficits[23, 34].

Further, our result was supported by multiple logistic regression analysis showing 39.6% sensitivity for prediction of childhood CM survivors with neurological defects. This is consistent with several previous studies that have demonstrated an association between these clinical manifestations and neurological sequelae. Similar observation was reported by Meremikwu *et al*[23] who declared that prolonged coma, focal seizures and abnormal posturing (decorticate/decerebrate) were associated with increased risk of neurological sequelae among childhood cerebral malaria survivors in Calabar, Nigeria.

CONCLUSION

Neurological sequelae are common due to childhood cerebral malaria in central Sudan. Their prediction from clinical presentation and laboratory findings at admission are good prognostic indicators in cerebral malaria diagnosis in African children and may guide clinical intervention and proper management to decrease morbidity and improve CM consequences. Abnormal posture either decerebration or decortication, focal convulsion and coma duration of > 48 h are significant predictors of surviving with neurological sequelae due to childhood CM as presented in this study. Further, studies are recommended to confirm the value of these clinical parameters in prediction of prognosis of childhood CM in other populations, and to identify other clinical findings that may have a prognostic value in improving clinical practices and decreasing CM morbidities.

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Correspondence to: Dr Adil Mergani, College of Applied Medical Sciences-Turabah, Taif University, Saudi Arabia.
E-mail: a.alahmar@tu.edu.sa; ad_merg@hotmail.com

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