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Does a relationship exist between plasma and cerebrospinal fluid Beta-endorphin levels and prognostic factors in Nigerian children with cerebral malaria?

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Abstract

Background: Cerebral malaria is the most lethal form of malaria for which various prognostic factors have been described in earlier studies. This study aimed to determine the relationship between beta (β)-endorphin levels in the cerebrospinal fluid (CSF) and plasma of children with cerebral malaria at Ile-Ife, Nigeria and some identified poor prognostic factors of the disease.

Methods: This descriptive cross-sectional study was conducted at the Children Emergency Ward of a Nigerian tertiary hospital (Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria) Forty children with cerebral malaria were studied. We measured the CSF and plasma levels of β-endorphins and determined their relationship with some identified poor prognostic factors of cerebral malaria.

Results: The mean plasma β-endorphin level was significantly higher in subjects with low serum bicarbonate compared with those with normal levels (p=0.029). Higher mean plasma and CSF β-endorphin levels were found in patients with profound coma, respiratory distress, abnormal pupillary reaction, abnormal posturing and the presence of retinal changes than those without these characteristics.

Conclusion: The higher mean β-endorphin levels in children with some poor prognostic factors of CM suggest a role of β-endorphin in the prognosis of CM. Further studies with a larger population are suggested to establish this role.

Keywords: Prognostic factors, Severe malaria, Endorphin, Outcome.

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Introduction

Cerebral malaria (CM) is regarded as the most lethal complication of malaria which is described as a rapidly progressive, diffuse encephalopathy characterised by altered consciousness, parasitaemia with Plasmodium falciparum and the absence of other causes of coma [1]. It contributes about 20-30 percent [2] of paediatric severe malaria cases with case fatality rates ranging between five and fifty percent [1,3]. Among children with cerebral malaria, clinical or laboratory factors that have been found to significantly contribute to poor prognosis include deep coma, multiple convulsions, malarial anaemia, hyperleucocytosis, low plasma bicarbonate, prolonged coma recovery time (CRT), abnormal breathing pattern, absent corneal reflex, absent pupillary reflex, retinal haemorrhage, mean haemoglobin level on admission, high blood urea levels and hypoglycaemia among others [4-7]. Monebenimp et al [8] in Cameroon, found that factors associated with death in CM were prolonged fever clearance time (FCT), coma recovery time (CRT), mean haemoglobin level on admission, high blood urea levels and hypoglycaemia. On the other hand, Oluwayemi et al. [9] in Ado-Ekiti, Southwestern Nigeria, identified clinical and laboratory predictors of mortality in CM as age less than 3 years, abnormal breathing pattern, absent corneal reflex, absent pupillary reflex, retinal haemorrhage, hypoglycaemia and leucocytosis [9].

Inflammatory response is very important in the pathogenesis of many infectious diseases including malaria and markers of this response are important mediators of the inflammatory process [10]. These markers of infection include acute phase proteins, components of the complement system, cytokines and adhesion molecules such as interleukins [1-9], TNF-α, IFN-α, soluble intracellular adhesion moleucule-1 (sICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and cell surface markers of neutrophils [10-12]. Other markers such as lactate, erythrocyte sedimentation rate, caspase, lipoproteins, thioredoxin and opioids have also been studied [10] In severe malaria, inflammatory markers that have been implicated in the severity and outcome of disease include TNF-α, IFN-α, interleukin 1, 6 and 8, nitric oxide, CD54+, CD11c+ and CD56+ [11,12]. Thuma et al. [13] in a study on Zambian children to determine the distinct clinical and immunologic profiles in severe malarial anaemia and CM found that elevated tissue PAI-1 levels and thrombocytopaenia showed the strongest associations with CM

[14]. In another study by Armah et al., [15] on Ghanaian children who died of CM postmortem CSF biomarkers such as IL-1, IL-8, IP-10 and TNF-α were significantly elevated in CM mortality group when compared to severe malarial anaemia and non-malaria deaths group. Thus, some markers of inflammation, cytokines and proteins have been studied in CM and their levels appear related to severity and outcome of disease [15].

Beta-endorphin, an endogenous opioid peptide neurotransmitter is known to play a role in neuroendocrine regulation and modulation of cerebral blood flow [16]. It is also known that endorphin levels rise during stress, convulsions, hypoxia and inflammation [17,18] Cytokines such as TNF-α have been postulated to contribute to the production of β-endorphin in inflamed tissues [19]. Since these trigger factors for increased β-endorphin levels are also implicated in the pathophysiology of CM, we hypothesized that β-endorphin levels in plasma and CSF may be markers of poor prognosis in CM. In an earlier publication, we reported that higher β-endorphin levels were found in children with CM at discharge compared with admission and higher levels in children who died compared with survivors [20]. However, there have been no reports testing the possible association of differential levels of plasma and/or CSF β-endorphin with already established poor prognostic factors of CM. This possibility remains largely unexplained but for this report which is part of a larger study on the CSF and plasma β-endorphins levels in CM.

Research Methodology

Forty children with CM, comprising twenty-five males and fifteen females aged between six months to fourteen years were recruited. CM was defined by the WHO criteria as follows [20]: (1) Unarousable coma (Blantyre Coma Score ≤ 2) for more than 30 minutes (2) Asexual forms of Plasmodium falciparum parasitemia (3) Exclusion of other common causes of loss of consciousness (such as meningitis, head trauma).

Also excluded were children with history suggestive of underlying chronic medical conditions such as chronic kidney disease, sickle cell anemia, cerebral palsy, seizure disorder and children whose parents or guardians did not give consent to participate in the study [21].

Ethical approval for the study was obtained from the Ethics and Research Committee of the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC).

Clinical and laboratory assessment

The level of consciousness was determined using the Blantyre Coma Scale (BCS) [22] Detailed neurologic examination was done including checking for signs of meningeal irritation, corneal reflex, pupillary size and reflex, cranial nerve function, muscle power, muscle tone, deep tendon reflexes and posture. Fundoscopy was done by one of the investigators (OEO) who had a prior training on fundoscopy at the Ophthalmology Unit of the hospital. The retinal features found were categorised as normal or varying degrees of malaria retinopathy - retinal whitening, vessel whitening, retinal haemorrhage and papilloedema [21]. Following the diagnosis of CM, prognostic factors of the disease were sought for and documented. This includes presence of deep coma, multiple convulsions, absent corneal reflex, retinal haemorrhages, respiratory distress/ acidotic breathing, and coma recovery time. The laboratory parameters used to assess prognosis include: random blood glucose, serum bicarbonate, serum urea, presence of malaria anaemia, and the presence of leucocytosis.

Lumbar puncture was done on these subjects as a routine procedure to exclude meningitis [23-27]. One milliliter of the CSF was taken in a plain bottle for the determination of β-endorphin level while one mL of blood was also taken from each subject at admission for the measurement of their β-endorphin level. CSF and plasma were then transported in ice packs to the laboratory for analysis.

CSF and plasma β-endorphin levels were determined using ELISA kit E90806Hu obtained from USCN Life Sciences, China at a research laboratory located at the Department of Biochemistry, Obafemi Awolowo University (OAU) Ile-Ife. OAU is the sister institution of the OAUTHC and is 15 minutes' drive away [28,29]. The kit utilizes a competitive enzyme inhibition immunoassay technique for the in-vitro quantitative measurement of β-endorphin in human serum, plasma, cerebrospinal fluid and other biological fluids with the inter- and intra-assay coefficients of variation (CV) of <12 percent and <10 percent respectively. The other CSF and blood samples were analysed at the microbiology, haematology and chemical pathology laboratories of the OAUTHC as appropriate.

Patients were treated according to standard WHO antimalarial treatment guideline 30 as adopted by the Pediatric unit of the OAUTHC. Other treatment profiles such as blood transfusion, correction of hypoglycemia, administration of intravenous fluids, anticonvulsants, sodium bicarbonate and nursing care were given as necessary.

The subjects were monitored till eventual outcome. The various parameters monitored during admission included the vital signs, level of consciousness and other neurologic signs, number and type of convulsions. Following regain of consciousness, a detailed neurologic assessment was repeated to identify any neurologic sequel. Outcome of illness were classified into three groups: full recovery, recovery with neurologic sequel and death.

Data analysis

Data was analyzed using the IBM SPSS software for Windows version 20.0. Two tailed independent t-test, one-way analysis of variance (ANOVA) and bivariate linear regression were used to determine the association of plasma or CSF β-endorphin levels with the prognostic factors of CM. The level of statistical significance for the various tests of associations was set at probability value (p value) of less than 0.05.

Results

Clinical signs at admission

The frequency of clinical signs in the children with CM is shown in Table 1. The common general physical signs were

fever (77.5 %), respiratory distress (45.0 %) and pallor (45.0 %). Respiratory distress was observed in 18 (45.0 %) of the subjects while acidotic breathing was noticed in 14 (35.0 %). The four subjects who had features of respiratory distress but without deep acidotic breathing had anemic heart failure. Thirty five (87.5%) of the subjects had hepatomegaly of varying sizes while 12 (30.0%) had splenomegaly. Some of the subjects had multiple physical signs. The mean total number of convulsion was 4.0 ± 3.6 episodes (range of 0 to 20 episodes). The mean coma recovery time (CRT) was 54.9 ± 55.2 hours with a range of 9.0 to 288 hours while the mean fever clearance time (FCT) was 40.7 ± 29.5 hours with a range of 12 and 144 hours.

Table 1. *Pattern of clinical findings at presentation in children with cerebral malaria.*

Clinical findings	Number	Percentage
Blantyre coma score		
0	3	7.5
1	11	27.5
2	26	65
Cornea reflex		
Present	18	45
Absent	22	55
Pupillary size		
<3 mm	25	62.5
3-5 mm	15	37.5
Pupillary reaction		
Brisk	29	72.5
Sluggish	10	25
Not reactive	1	2.5
Fundoscopic findings		
Normal	26	65
Retinal haemorrhage	5	12.5
Vessel whitening	5	12.5
Retinal whitening	3	7.5
Papilloedema	1	2.5
Posture		
Normal	34	85
Decorticate	4	10
Decerebrate	2	5
Tone		
Normal	13	32.5
Hypertonia	18	45
Hypotonia	9	22.5
Reflex		
Normal	14	35
Hyperreflexia	17	42.5
Hyporeflexia	9	22.5
Ankle clonus		
Present	1	2.5
Absent	39	97.5

Laboratory parameters

The mean (± SD) CSF β-endorphin level for all children with CM at admission was 1.8 ± 0.9 pmol/ L (range: 0.8-3.4 pmol/ L) while the mean (± SD) plasma β-endorphin levels also at admission was 3.1 ± 2.0 pmol/ L with a range of 1.0 to 10.4 pmol/ L. Table 2 shows the mean values of other laboratory parameters in the children with CM.

Table 2. *Mean values of other laboratory findings.*

Serum parameters	Mean ± SD	Minimum	Maximum
Random blood sugar (mmol/ L)	5.9 ± 2.1	1.8	10.4
Serum sodium (mmol/ L)	128.5 ± 8.4	103.0	144.0
Potassium(mmol/ L)	3.8 ± 0.7	2.8	5.2
Bicarbonate (mmol/ L)	21.3 ± 2.1	17.0	26.0
Urea (mmol/ L)	6.9 ± 4.2	2.4	23.8
Creatinine (µmol/ L)	92.1 ± 48.2	27.0	249.0
Packed cell volume (%)	25.3 ± 7.6	7.0	39.0
White blood cell count (cells/ µL)	11,413.8 ± 7689.5	4,500.0	42,100.0
Neutropils (%)	63.1 ± 13.7	28.0	86.0
Lymphocyte (%)	36.7 ± 13.7	14.0	72.0

Relationship between β-endorphin levels and the prognostic factors of CM

The factors that were used in rating prognosis of CM and for which association with β-endorphin levels was explored included level of consciousness at diagnosis, total number of convulsions, respiratory distress and coma recovery time (CRT).

Table 3 shows the relationship between the plasma and CSF β-endorphin levels and selected poor prognostic factors. As shown on Table 3, the mean plasma and CSF β-endorphin levels were higher in patients with deep coma (BCS=0), presence of retinal changes, abnormal pupillary reaction and abnormal posturing though not statistically significant. The mean plasma and CSF β-endorphin levels were found to be lower in patients with respiratory distress and multiple convulsions than those without. The mean plasma β-endorphin levels were higher in subjects with low serum bicarbonate compared with those with normal serum bicarbonate reaching statistical significance (p=0.029) while there was no significant

difference between the mean CSF β-endorphin levels among subjects with low serum bicarbonate compared with those with normal serum bicarbonate.

Relationship between CSF and plasma β-endorphin levels and other features of severe malaria in the children with cerebral malaria

CSF and plasma β-endorphin levels and other features of severe malaria present in the children with CM. Twenty four (60%) of the children with cerebral malaria had multiple convulsions while eighteen (45.0%) had severe anaemia. Acidotic breathing and haemoglobinuria occurred in 14 (35.0%) and 8 (20.0%) of the children respectively. CSF β-endorphin levels were only significantly lower in subjects with multiple convulsions compared with those without multiple convulsions (p=0.02).

Relationship between β-endorphin levels at admission and coma recovery time.

Figure 1 shows the relationship between β-endorphin levels at admission and coma recovery time. There was no significant association between plasma β-endorphin levels at admission and CRT while CSF β-endorphin levels showed mild reduction with increasing CRT. The was also not statistically significant (p=0.802 and 0.664 for plasma and CSF β-endorphin levels respectively).

Table 3. *Association between plasma and CSF β-endorphin levels and the prognostic factors of CM.*

Prognostic factors	Frequency (n=40)	Mean Plasma β-endorphin	p value	Mean CSF β-endorphin	p value
Clinical parameters					
Blantyre Coma Score*					
0	3	4.6 ± 2.5	0.241	2.3 ± 1.4	0.450
1	11	2.4 ± 1.8		1.6 ± 0.9	
2	26	3.2 ± 2.0		1.8 ± 0.9	
Retinal changes**					
Present	14	3.3 ± 2.5	0.536	1.8 ± 0.9	0.417
Absent	26	2.9 ± 1.8		1.7± 0.9	
Pupillary reaction**					
Brisk	29	2.4 ± 0.8	0.09	1.8 ± 0.9	0.42
Sluggish	11	3.4 ± 2.3		1.4 ± 0.9	
Abnormal posturing**					
Present	6	3.5 ± 1.0	0.525	2.0 ± 1.2	0.09
Absent	34	3.0 ± 2.1		1.7 ± 0.9	
Cornea reflex**					
Present	18	3.0 ± 2.5	0.771	1.8 ± 0.9	0.936
Absent	22	3.2 ± 1.6		1.8 ± 1.0	
Laboratory parameters					
Random blood sugar*					
Hypoglycaemia	2	2.5 ± 1.1	0.552	1.8 ± 0.9	0.735
Normal	34	3.2 ± 2.1		1.8 ± 0.9	
Hyperglycaemia	4	2.1 ± 1.1		2.1 ± 1.3	
Serum bicarbonate**					
15-20 mmol/L	17	3.9 ± 2.4	0.029	2.9 ± 0.1	0.201
21-30 mmol/L	23	2.5 ± 1.5		1.6 ± 0.9	
Packed cell volume (%)*					
< 15	3	2.4 ± 0.6	0.912	1.7 ± 0.8	0.669
15-20	10	3.2 ± 2.1		1.9 ± 0.9	
21-30	16	3.3 ± 2.4		1.6 ± 0.8	
>30	11	2.9 ± 1.8		2.1 ± 1.1	
Serum urea**					
< 5.8 mmol/L	20	2.9 ± 1.8	0.578	1.8 ± 0.9	0.996
>5.8 mmol/L	20	3.3 ± 2.3		1.8 ± 0.9	
White blood cell count**					
< 11000 cells/m^3	13	3.2 ± 1.0	0.791	1.8 ± 0.9	0.868
> 11000 cells/m^3	27	3.0 ± 1.3		1.8 ± 1.0	

Outcome of illness in cerebral malaria patients

The outcome of cerebral malaria among the affected children in this study is as shown in Figure 2.

Relationship between β-endorphin and neurological sequelae in patients with cerebral malaria

There was no statistically significant risk of elevated CSF and plasma β-endorphin in children who developed neurological sequelae from CM (p values >0.05).

Discussion

This study presents new information on the relationship between the poor prognostic factors for CM and the plasma and CSF β-endorphin levels in children at admission. Among the poor prognostic factors of CM studied, plasma and CSF β-endorphin levels were found to be higher in subjects with profound coma while long coma recovery time (CRT) was associated with lower plasma β-endorphin and CSF β-endorphin levels. Thus, a rise in β-endorphin levels appears to be related with depth of coma rather than duration of coma.

The positive association found between β-endorphin levels and depth of coma in this study is similar to findings by Hamel in an experimental study on intraventricular injection of opioid peptides which suggest an influence of opioid peptides on states of consciousness. Elevated β-endorphin levels have been reported in the CSF of patients with cerebral infarction and acute stroke and the opioid antagonist, naloxone has been found to bring about some improvement in the level of consciousness in these patients. Contrary to the findings from the present study, Hamel et al. [24] found that CSF β-endorphin levels tend to decrease parallel to a drop in depth of coma as well as with long-standing comatose states. He however found no correlation between plasma β-endorphin and state of consciousness.

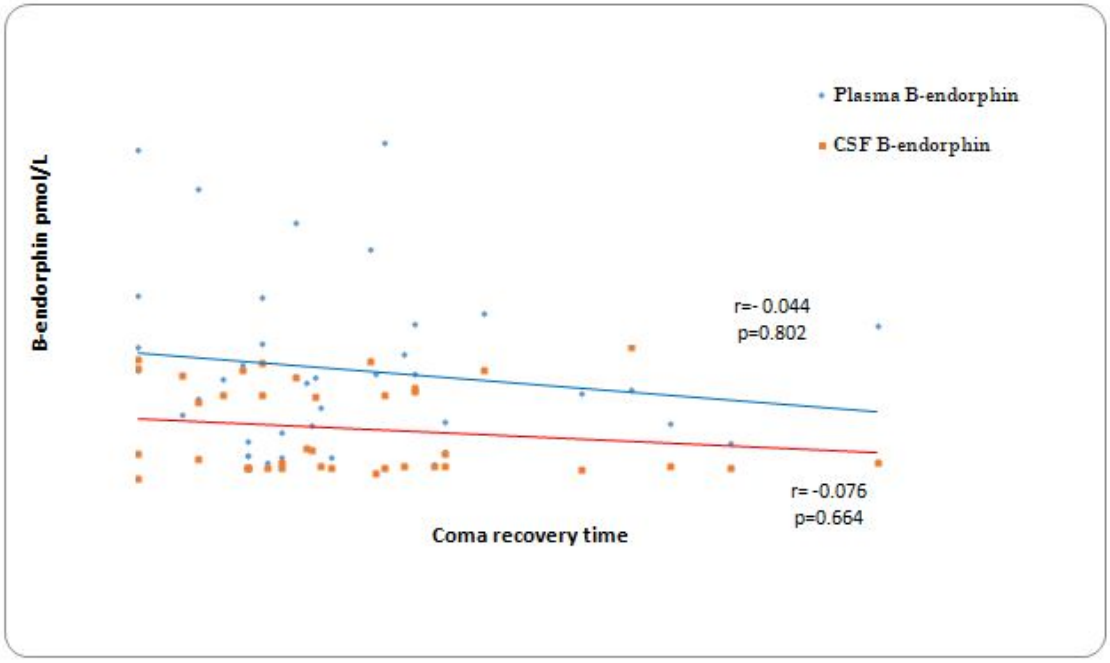

Figure 1. *Relationship between plasma and CSF β-endorphin levels and coma recovery time (r=correlation coefficient).*

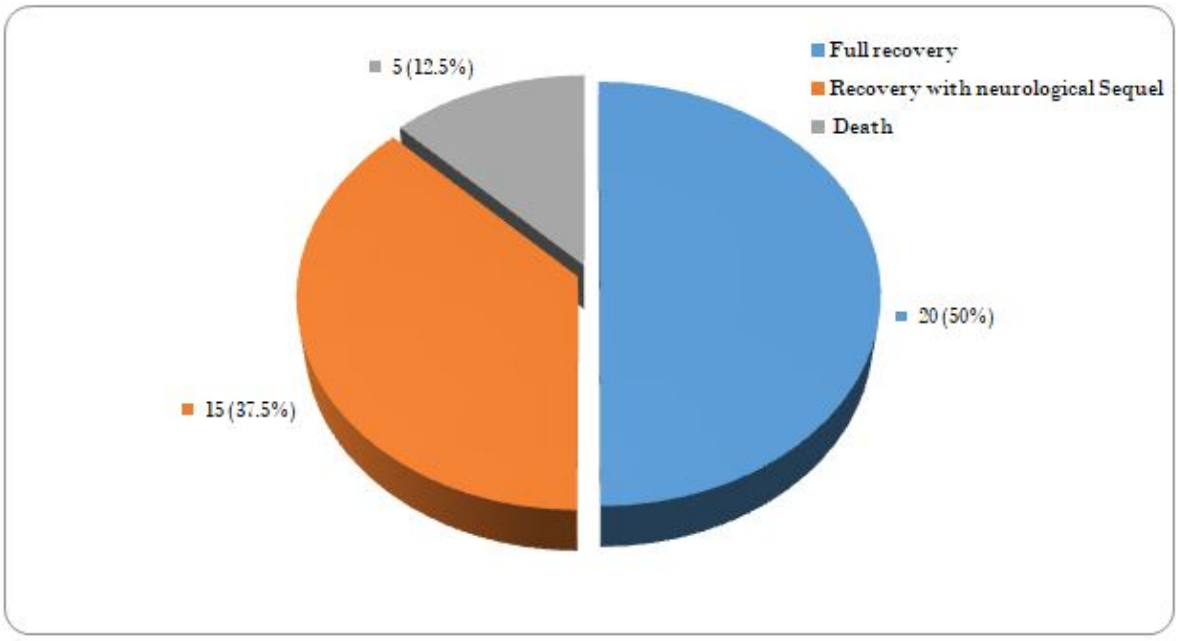

Figure 2. *Outcome of illness with cerebral malaria.*

In another study on neurosurgical patients with head injury, all the patients had significantly higher CSF β-endorphin levels than the controls. CSF β-endorphin levels in patients with mild head injury (GCS: 13-15) with skull fracture were reported to be significantly higher than those who had severe head injury (GCS<8). There was no correlation between the CSF β-endorphin levels and the GCS scores of the patients. It was deduced that elevated β-endorphin levels are associated with acute CNS lesions. It appears that relationship between β-endorphin levels and depth of coma remains unclear as shown in the conflicting findings of the studies above although this uncertainty may be due to the different natures of the CNS insults.

We observed low serum bicarbonate in 42.5 percent of the subjects with CM. The mean β-endorphin level of 3.9 ± 2.4 obtained from the plasma of those with low serum bicarbonate was significantly higher than those with normal bicarbonate level (p=0.029) as we earlier reported [21]. The microcirculatory obstruction that occurs in CM probably causes lactic acidosis as a consequence of anaerobic glycolysis.

Bender et al and Shepard from independent studies identified acidosis and increased serum lactate as likely triggers of increased β-endorphin production following exercise. The same mechanism can be responsible for the elevated β-endorphin level seen in these our patients with CM.

The mean plasma and CSF β-endorphin levels has been found to be higher among the patients who died from cerebral malaria than those who recovered either fully or with neurologic sequelae [28,29]. There is paucity of data on the association of β-endorphin with outcome of infections of the CNS. However, elevated β-endorphin levels have been reported in victims of sudden infant death syndrome. This elevation in β-endorphin levels has been attributed to premorbid hypoxia in these patients. The finding that majority of those with profound coma died and had elevated β-endorphin levels may suggest an association with poor outcome in these patients. A larger longitudinal study will be required to further substantiate these observations. Deep coma associated with elevated β-endorphin levels may become predictive of poor outcome in CM. If so proven, assay of β-endorphin levels where feasible may help select the patients that will require more innovative measures to aid survival. Though we did not find β-endorphin levels to be significantly associated with the risk of developing neurologic sequelae, further studies with a larger sample size may be worthwhile.

Conclusion

The findings from the present study show higher mean plasma β-endorphin levels in children with some poor prognostic factors of CM such as deep coma, respiratory distress and low serum bicarbonate though only a weak association was found between CSF and plasma β-endorphin levels and some of these factors. Further studies with larger sample size may be needed to determine the usefulness of β-endorphins as a predictor of prognosis and outcome in CM.

References

1. World Health Organisation. Severe and complicated malaria. (2nd edn) Trans R Soc Trop Med Hyg 1990; 84: 1-65.
2. Orimadegun AE, Fawole O, Okereke JO, et al. Increasing burden of childhood severe malaria in a Nigerian tertiary hospital: Implication for control. J Trop Paediatr 2007; 53: 185-189.
3. Phillips RE, Solomon T. Cerebral malaria in children. Lancet 1990; 336: 1355-1360.
4. Hanson J, Lee SJ, Mohanty S, et al. A simple score to predict the outcome of severe malaria in adults. Clin Infec Dis 50; 5: 679-685.
5. Greenwood BM, Bradley AK, Greenwood AM. Morbidity and mortality from malaria among children in rural Gambia, West Africa. Trans R Soc Med Hyg. 1987; 81: 478-486.
6. Genton B, Al-Yaman F, Alpers MP, et al. Indicators of fatal outcome in paediatric cerebral malaria: A study of 134 comatose Papua New Guinean children. Int J Epid 1997; 26: 670-676.
7. Oguche S, Omokhodion SI, Adeyemo A, et al. Low plasma bicarbonate predicts poor outcome of cerebral malaria in Nigerian children. WAJM 2002; 21: 276-279.
8. Von Seidlein L, Olaosebikan R, Hendriksen ICE, et al. Predicting the clinical outcome of severe falciparum malaria in African children: findings from a large randomized trial. Clin Inf Dis 2012:1-11
9. Monebenimp F, Bisong CE, Chiabi A, et al. Clinical and biological factors associated with treatment outcome of cerebral malaria in children under five in Yaounde. J Neuropara 2010; 1: 1-5.
10. Oluwayemi IO, Brown BJ, Oyedeji OA, et al. Clinical and laboratory predictors of cerebral malaria in suburban Nigeria. J Infect Dev Ctries. 2013; 7: 600-607.
11. Bantel H, Lugering A, Poremba C, et al. Caspase activation correlates with the degree of inflammatory liver injury in chronic hepatitis c virus infection. Hepatology 2001; 34: 758-67.
12. Gimenez FC, Pino P, Mazier DF, et al. Tumor necrosis factor alpha in the pathogenesis of cerebral malaria. Cell Mol Life Sci. 2003; 60: 1623-35.
13. Noone C, Parkinson M, Dowling DJ, et al. Plasma cytokines, chemokines and cellular immune responses in pre-school Nigerian children infected with Plasmodium falciparum. Malaria J 2013; 12:5.
14. Thuma PE, Van Dijk J, Bucala R, et al. Distinct clinical and immunologic profiles in severe malarial anemia and cerebral malaria in Zambia. J Infec Dis 2011; 203: 211-219.
15. Armah HB, Wilson NO, Sarfo BY, et al. Cerebrospinal fluid and serum biomarkers of cerebral malaria mortality in Ghanaian children. Malaria J 2007; 6: 147.
16. Frederickson RCA, Geary LE. Endogenous opioid peptides: A review of physiological, pharmacological and clinical aspects. Prog Neurobiol 1982; 19: 19-69.
17. Koneru A, Satyanarayana S, Rizwan S. Endogenous opioids: Their physiological role and receptors. Global Journal of Pharmacology. 2009; 3: 149-53.
18. O'connor TM, O'halloran DJ, Shanahan F. The stress response and the hypothalamic-pituitary-adrenal axis: From molecule to melancholia. QJM 2000; 93(6): 323-33.
19. Sacerdote P, Brini AT, Locatelli L, et al. Tumor necrosis factor alpha differentially regulates beta-endorphin concentrations and proopiomelanocortin RNA in the anterior and neurointermediate pituitary *in vivo*. Neuroimmunomodulation 1994; 1: 357-60.
20. Olorunmoteni OE, Adeodu OO, Oseni SBA, et al. Cerebrospinal fluid and plasma β-endorphin levels in children with cerebral malaria. Brain Behav 2017: e00673.
21. World Health Organization: Severe and complicated malaria. (2nd edn) Trans R Soc Trop Med Hyg 1990; 84: 1-65.
22. Molyneux ME, Taylor TE, Wirima JJ, et al. Clinical features and prognostic indicators in paediatric cerebral

malaria: A study of 131 comatose Malawian children, QJM.1989; 71: 441-59.

23. World Health Organization. Guidelines for the treatment of malaria. WHO; 2010.
24. Hamel E. CSF endorphines in acute and chronic CNS conditions. Neurosurg Rev 1988; 11: 193-9.
25. Paşaoglu H, Inci Karaküçük E. Endogenous neuropeptides in patients with acute traumatic head injury, I: cerebrospinal fluid beta-endorphin levels are increased within 24 hours following the trauma. Neuropeptides. 1996; 30: 47-51.
26. Bender T, Nagy G, Barna I, et al. The effect of physical therapy on beta-endorphin levels. Eur J Appl Physiol 2007; 100: 371-82.
27. Shephard RJ. Sepsis and mechanisms of inflammatory response: Is exercise a good model? Br J Sports Med 2001; 35: 223–230.
28. Storm H, Rognum TO, Saugstad OD, et al. Elevated beta-endorphin immunoreactivity in the cerebrospinal fluid in victims of sudden infant death correlates with hypoxanthine in vitreous humour. Euro J Pedi 1993; 152: 935-8.
29. Coquerel A, Buser M, Tayot J, et al. Beta-endorphin and neurotensin in brainstem and cerebrospinal fluid in the sudden infant death syndrome. Neurochem Int 1992; 20: 97-102.

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