Original article:

A Correlation of Cerebral Malaria with Changes in Neurological and Gastrointestinal System: A Prospective Study

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Abstract

Background: Cerebral malaria is the most severe neurological complication of infection with Plasmodium falciparummalaria. It is a clinical syndrome characterized by coma and asexual forms of the parasite on peripheral blood smears. Mortality is high and some surviving patients sustain brain injury which manifest as long-term neuro-cognitive impairments. Hence; we planned the present study to evaluate correlation of neurological and gastrointestinal changes occurring in cerebral malaria patients.

Materials & methods: The present study included assessment of correlation of neurological and gastrointestinal changes occurring in cerebral malaria patients. A total of 30 cerebral malaria patients were included in the present study. Radio-diagnostic modalities were carried out including MRI, CT scan, and complete hematologic investigations for assessing the neurological and gastrointestinal manifestations. All the results were recorded and analyzed by SPSS software.

Results: A total of 30 patients with confirmed diagnosis of cerebral malaria were included in the present study. The overall prevalence of neurological manifestation was 26.6%. Means serum creatinine levels in CM patients was found to be 118.5 (µmol/L). Mean serum aspartate aminotransferase levels and means serum total bilirubin levels were found to be 121.7 and 69.5 (µmol/L) respectively.

Conclusion: Significant amount of neurological and gastrointestinal manifestations are seen in patients with cerebral malaria.

Key words: Cerebral Malaria, Gastrointestinal, Neurological

Introduction

Cerebral malaria (CM) is the most severe neurological complication of infection with Plasmodium falciparummalaria. It is a clinical syndrome characterized by coma and asexual forms of the parasite on peripheral blood smears. Mortality is high and some surviving patients sustain brain injury which manifest as long-term neuro-cognitive impairments.[1- 3] Every year, there are over 500 million clinical cases. One percent of symptomatic infections may become complicated and develop into severe malaria. Severe malaria may manifest as anemia, hypoglycemia, metabolic acidosis, repeated seizures, coma or multiple organ failure and is estimated to cause over one million deaths annually. Cerebral malaria is the most severe neurological manifestation of severe malaria. The clinical hallmark of cerebral malaria is impaired consciousness, with coma the most severe manifestation.[4, 5] This is thought to be causes by parasitized red blood cells (pRBCs) sequestered in cerebral micro-circulation, but other authors attribute the impaired consciousness to metabolic factors and inflammatory mediators.[6, 7] Under the light of above mentioned data, we planned the present study to evaluate correlation of neurological and gastrointestinal changes occurring in cerebral malaria patients.

Materials & methods

The present study was conducted in the department of General Medicine of Haridev Joshi Hospital, Dungarpur, Rajasthan, and included assessment of correlation of neurological and gastrointestinal changes occurring in cerebral malaria patients. Ethical approval was taken from institutional ethical committee and written consent was obtained after explaining in detail the entire research protocol. A total of 30 cerebral malaria patients were included in the present study. Exclusion criteria for the present study included:

- Patients who had taken antimalarial drugs before admission
- Patients whose urine samples were found to be negative for 4-aminoquinolones and sulphonamides,
- Patients with history of any type of systemic illness
- Patients with history of any known drug allergy
- Patients with renal impairment
- Pregnant subjects

Patients were categorized as affected with sever falciparum malaria blood parasite level was more than 5 percent. Radio-diagnostic modalities were carried out including MRI, CT scan, and complete hematologic investigations for assessing the neurological and gastrointestinal manifestations. All the results were recorded and analyzed by SPSS software. Univariate regression curve was used for assessment of level of significance. P- value of less than 0.05 was taken as significant.

Results

A total of 30 patients with confirmed diagnosis of cerebral malaria were included in the present study. Mean age of the patients was 41.5 years. Among thirty patients, 18 were males while the remaining 12 were females. Hemiplegia and dystonia were the most common manifestation encountered in the present study. The overall prevalence of neurological manifestation was 26.6%. Means serum creatinine levels in CM patients was found to be 118.5 (µmol/L). Mean serum aspartate aminotransferase levels and means serum total bilirubin levels were found to be 121.7 and 69.5 (µmol/L) respectively.

Discussion

In the present study, we analyzed a total of 30 CM patients and observed that 26.6 percent of the patients had neurological manifestations. Viriyavejakul P et al investigated the liver pathology of severe P. falciparum malaria as well as the regulation and occurrence of apoptosis in cellular components of formalin-fixed, paraffin-embedded liver tissues. The liver tissues used in the study came from patients who died from P. falciparum malaria with hyperbilirubinaemia (total bilirubin (TB) $\geq$ 51.3 µmol/L or 3 mg/dl) (12 cases), P. falciparum malaria without hyperbilirubinaemia (TB $<$ 51.3 µmol/L) (10 cases); and patients who died due to accidents, whose liver histology was normal (the control group) (10 cases). The histopathology of the liver tissue was studied by routine histology method. Caspase-3 and nuclear factor kappa B (NF-κB) p65 expressions were determined using immunohistochemistry. The severity of liver histopathology, occurrence of apoptosis and NF-κB p65 activation in P. falciparum malaria were associated with higher TB level. Significant correlations were found between NF-κB p65 expression and apoptosis in Kupffer cells and lymphocytes in the portal tracts. Hyperplastic Kupffer cells and portal tract inflammation are two main features found in the liver tissues of severe P. falciparum malaria cases.[11] Among gross motor deficits, hemiplegia, diplegia, quadriparesis or quadriplegia may be observed after CM. Disorders in movement and gait can be noted, including

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ataxia, choreoathetosis, dystonia and poor neck control, as well as feeding difficulties. Dai et al demonstrated that motor coordination impairment was associated with dysregulation of Akt and GSK3β signaling in a murine model of CM. The inhibition of the Akt pathway results in modifications in neuronal integrity, since it is a protein kinase playing a key role in the insulin signaling pathway and an important regulator of apoptosis, being consequently important for cell viability, although via an GSK3β-dependent pathway. In addition, the intracranial hypertension may contribute to the motor sequelae, given that it reduces the cerebral perfusion pressure, nutrient and oxygen delivery and, where death does not occur, subsequent global ischemic injury and brainstem compression can lead to cerebral atrophy, which may result in motor and cognitive impairment.[11, 12]

Convulsions in CM are common and inflammatory products such as quinolinic acid contribute to the neuropathology, considering that this metabolite from the kynurenine pathway is a N-methyl-D-aspartate agonist that causes neuroinflammation, convulsions, and cell death. Dobbie et al demonstrated that quinolinic acid provokes seizures in animals, possibly, altering the neurotransmission excitatory and triggering long-term deleterious effects on cognitive function and/or behavior. Sokol et al demonstrated irreversible neuron damage after long-term seizure activity, followed by gliosis and focal atrophy, resulting in more seizures and brain damage. The epilepsy (recurrence of seizures without apparent cause) occurs in approximately 10% of pediatric cases and may be occasioned by focal or global hypoxia or ischemia. The epileptogenesis mechanisms are unclear. Structural brain damage and the presence of Durck's malarial granuloma may contribute to the epileptogenesis mechanisms; however, other factors should also be considered, like genetic propensity.[12- 14]

Gastrointestinal symptoms are common during the acute phase of malarial infection. These symptoms include nausea, vomiting, abdominal pain, and diarrhea. Impaired intestinal function, resulting in a transient reduction in the absorption of D-xylose, has been described in patients with Plasmodium falciparum malaria, thus suggesting the presence of intestinal damage.[15]

The pathogenesis of the neurological and gastrointestinal complications of falciparum malaria requires further elucidation. Studies using MRI, particularly with novel contrast media, might be helpful in this regard. EEG will determine the role of seizures as a cause of poor outcome, and can be used to monitor the effect of antiepileptic drugs. In the future, efforts to establish a highly specific definition of cerebral malaria will also be impotant, and noninvasive monitoring of intracranial pressure and cerebral blood flow might be informative in this regard. The further investigation of potential adjunctive therapies, such as antiapoptotic agents, is warranted, and neurocognitive impairment or markers of brain damage should be used as outcomes in these studies.[16]

Conclusion

From the above results, the authors conclude that significant amount of neurological and gastrointestinal manifestations are seen in CM patients. However; future study is recommended.

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Table 1: Demographic details of the patients

Parameter	**Number**
Mean age (years)	41.5
Males	18
Females	12
Mean weight (Kg)	62.1

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Table 2: Neurological manifestations of the patients

Manifestations		No. of patients	Percentage
Neurological	Hemiplegia	2	6.7
	Diplegia	1	3.3
	Quadriplegia	1	3.3
	Quadriparaesis	1	3.3
	Ataxia	1	3.3
	Dystonia	2	6.7
Total prevalent		8	26.6

Table 3: Gastrointestinal manifestations of the patients

Parameter		Value
Serum levels	Mean serum creatinine level (µmol/L)	118.5
	Mean serum total bilirubin levels (µmol/L)	69.5
	Mean serum aspartate aminotransferase levels (µmol/L)	121.7
Gastric symptoms (No. of patients)	Nausea	12
	Vomiting	10
	Abdominal pain	10
	Diarrhea	11

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