Neurological involvement in patients with falciparum malaria; frequency and prognostic value

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Objective: The objective of this study was to evaluate the prognostic significance of neurological manifestations in falciparum malaria.

Methods: We analyzed adult patients with malaria admitted from 2001 to 2003, diagnosed by asexual forms of Plasmodium falciparum in peripheral blood films and identified cases of malaria with neurological involvement. A patient was classified as having neurological involvement if they reported or had one or more of the following symptoms; headache, altered mental status, seizures, neck rigidity, brisk reflexes, cranial neuropathy and hyper or hypotonia.

Results: A total of 454 patients were included in the study. Out of these, 123 (27%) were diagnosed as complicated (severe) malaria and 331 (73%) as uncomplicated malaria at admission. Overall 70 (15.4%) patients had evidence of neurological involvement at initial evaluation. Twenty-seven patients out of 123 (22%) with complicated malaria and 43 patients out of 331 (13%) with uncomplicated malaria had neurological involvement. Over all, 16 (4%) patients died, 13 (11%) had complicated malaria (n = 123) and 3 (1%) had uncomplicated malaria (n = 381). Mortality in patients having neurological involvement (n = 70) was 9 (13%) as compared to 7 (2%) in patients with malaria having no neurological involvement (n = 384). This difference was statistically significant (p = 0.012). Seizure was identified as predictor of mortality on Univariate analysis [OR 5.091 (1.835–14.121)].

Conclusion: Fifteen percent of patients with falciparum malaria admitted to our hospital had neurological symptoms and neurological involvement was associated with increased mortality.

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1. Introduction

Malaria is a common parasitic infection worldwide affecting 5% of the world’s population at any time [1]. More than two billion people are exposed to Plasmodium falciparum in malaria endemic areas translating into 515 million malaria episodes and more than one million malaria-related deaths each year [2].

Neurological involvement in falciparum malaria is well known and usually manifests as altered mental status, psychosis, seizures, focal deficits and coma [3,4]. The term cerebral malaria has long been used in literature to describe any CNS disturbance in malarial infection. However a stricter case definition for cerebral malaria was suggested in the 1980s, defining cerebral malaria as a deep level of unconsciousness in the presence of Plasmodium falciparum parasites, after exclusion of hypoglycemia, renal failure, sepsis, meningitis and other metabolic disturbances [5,6]. Coma in patients with falciparum malaria is typically divided into two types; cerebral malaria and secondary encephalopathy due to sepsis, renal failure and metabolic disturbances. One study looked at more than 19,000 children with falciparum malaria, neurological involvement was seen in 47.6% of children and manifested as seizures (37.5%), agitation (2.8%), prostration (20.6%), and impaired consciousness or coma (13.2%) [7]. Others found 2.4% prevalence of cerebral malaria among travelers with falciparum malaria [8].

In our clinical practice we observed that a number of patients labeled as uncomplicated malaria had neurological symptoms and brain involvement on neuroimaging. These patients could possibly represent mild or early forms of cerebral malaria. Prognostic value of neurological manifestations in uncomplicated malaria patients is not well known. Thus the objective of our study was to determine neurological manifestations of falciparum malaria in adults.
and evaluate the prognostic value of early neurological manifestations particularly in patients who presented as uncomplicated malaria.

2. Methods

A retrospective chart review of 454 adult patients with confirmed diagnosis of falciparum malaria admitted from 2001 to 2003 at Aga Khan University Hospital, Karachi was undertaken. The Charts were identified by ICD-9 coding system. The diagnosis was confirmed by presence of asexual forms of Plasmodium falciparum in peripheral blood films. Patients with organ dysfunction (renal failure, jaundice, pulmonary edema, coma, convulsions, and severe anemia) were labeled as complicated malaria (WHO guidelines 2006).

Data was extracted from patients’ charts. Our Hospital uses a standardized Performa (admission form) which includes complete history, review of systems, physical examination findings, initial laboratory and radiological evaluation, provisional and differential diagnosis, diagnostic and therapeutic plan and attending notes. We reviewed all patients with falciparum malaria. Patients were divided in two groups: complicated and uncomplicated malaria based on established criteria. Patients with falciparum malaria are routinely admitted including uncomplicated cases for observation as they can progress into complicated malaria. Additionally, all patients were divided in two groups based on presence or absence of neurological symptoms (headache, altered mental status, seizures, neck rigidity, brisk reflexes, cranial neuropathy and hyper or hypotonia).

### Table 1
Neurological symptoms in patients with falciparum malaria (n = 70).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Complicated malaria (n = 123)</th>
<th>Uncomplicated malaria (n = 331)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with neurological symptoms</td>
<td></td>
<td></td>
<td>0.9</td>
</tr>
<tr>
<td>Coma</td>
<td>14 (11%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Stupor</td>
<td>4</td>
<td>9</td>
<td>0.18</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>9</td>
<td>31 (10%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Confusion</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>13 (10%)</td>
<td>23 (8%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Seizures</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Neck rigidity</td>
<td>18 (15%)</td>
<td>9</td>
<td>0.16</td>
</tr>
<tr>
<td>Brisk reflexes</td>
<td>12 (10%)</td>
<td>53 (16%)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

### Table 2
Comparison of patients with and without neurological symptoms.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients with neurological involvement (n = 70)</th>
<th>Patients without neurological involvement (n = 384)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean) years</td>
<td>44 ± 29</td>
<td>46 ± 30</td>
<td>0.10</td>
</tr>
<tr>
<td>Male sex</td>
<td>45 (65%)</td>
<td>242 (36%)</td>
<td>0.679</td>
</tr>
<tr>
<td>Complicated malaria</td>
<td>27 (39%)</td>
<td>96 (25%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Uncomplicated malaria</td>
<td>43 (61%)</td>
<td>288 (75%)</td>
<td>0.087</td>
</tr>
<tr>
<td>Outcome, death</td>
<td>9 (13%)</td>
<td>7 (2%)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

### Table 3
Univariate analysis of prognostic factors for mortality in falciparum malaria patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors n = 438 (%)</th>
<th>Died n = 16 (%)</th>
<th>Odds ratio [95% CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck rigidity</td>
<td>21 (5)</td>
<td>6 (37)</td>
<td>1.997 (0.556–7.169)</td>
<td>0.044</td>
</tr>
<tr>
<td>Seizures</td>
<td>1</td>
<td>3 (22)</td>
<td>5.091 (1.83–14.12)</td>
<td>0.013</td>
</tr>
<tr>
<td>Headache</td>
<td>31 (7)</td>
<td>5 (30)</td>
<td>1.588 (0.629–4.009)</td>
<td>0.05</td>
</tr>
<tr>
<td>Brisk reflexes</td>
<td>63 (12)</td>
<td>2 (10)</td>
<td>0.29 (0.09–0.96)</td>
<td>0.11</td>
</tr>
<tr>
<td>Comatose</td>
<td>11 (3)</td>
<td>3 (21)</td>
<td>2.19 (0.63–8.86)</td>
<td>0.18</td>
</tr>
<tr>
<td>Male sex</td>
<td>286 (65)</td>
<td>12 (75)</td>
<td>1.476 (0.682–3.193)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

### 3. Results

A total of 454 patients were included in the study. Out of these, 123 (27%) were diagnosed as complicated (severe) malaria and 331 (73%) as uncomplicated malaria on admission. Overall 70 (15.4%) patients had evidence of neurological involvement at initial evaluation. Twenty-seven patients out of 123 (22%) with complicated malaria and 43 patients out of 331 (13%) with uncomplicated malaria had neurological involvement.

Demographic features, presentation and laboratory and imaging findings of these 70 patients with neurological symptoms were as follows. Age range was 15–80 years (mean 44 ± 29 years). Forty-five (65%) were males. Mental status changes were present in all patients and included coma in 14 (20%) patients, stupor in 13 (19%) patients, drowsiness in 40 (59%) patients and confusion in 3 (3%) patients. Other presenting neurological symptoms included headache in 13 (19%) patients and seizures in 4 (6%) patients. None of the patients presented with hemiparesis. Other findings included neck rigidity in 18 (27%) patients, brisk reflexes in 12 (16%) patients, hypertonia in 8 (11%) patients, bilateral up going plantar responses in 6 (9%) patients and cranial nerve palsies in 3 (5%) patients (Table 1). Sixteen patients (23% of those with neurological involvement) had CSF studies done. CSF was abnormal in 10 patients with average protein 41.9 mg/dL, average glucose 81.9 mg/dL and average WBC’s 5.6 cells per cubic millimeter. None of these CSF samples showed organisms on staining or routine bacterial cultures. CSF PCR done for HSV was sent for a few patients only and all results were negative. Twenty-one patients (30%) had CT scans and 9 patients (13%) had MRI Brain scans. CT scan findings included normal (67%), diffuse cerebral edema (19%), infarcts (9%) and inter hemispheric hemorrhage (5%). MRI scan findings included normal in 6 (55%) patients, diffuse cerebral edema in 1 (11%) patient, hyper intense signals in corona radiata and centrum semiovale on T2 and FLAIR images in 1 (11%) patient and hemorrhages in 1 (11%) patient. EEG was performed in 13 (19%) patients showing diffused slowing in 77% of patients while 23% had normal EEGs.

Non-neurological features in patients with falciparum malaria included fever (97%), generalized weakness (67%), dehydration (61%), vomiting (45%), myalgia (42%), respiratory distress (38%) and abdominal pain (19%). Twenty-seven (39%) patients had complicated malaria and 43 patients (61%) were labeled as uncomplicated malaria on admission (Table 1). Overall, 16 (4%) patients died of which 13 (11%) were in the complicated malaria (n = 123) group and 3 (1%) were in the uncomplicated malaria (n = 381) group. Mortality in patient having neurological involvement (n = 70) was 9 (13%) as
Prognosis for adult cerebral malaria is known with mortality rates ranging from 20 to 25%. However, prognosis for patients with malaria and toxic, metabolic encephalopathy ranges from 30 to 50% [9]. Multiple prognostic factors have been identified including respiratory distress, circulatory failure, hyporeflexia, high parasite load, coma, severe anemia and renal failure [10,11]. Neurological and renal dysfunction were most important predictors of poor prognosis in one study [12].

Prognostic factors for severe (complicated) malaria and cerebral malaria are well reported. Multiple scoring systems demonstrating extent and severity of organ dysfunction in complicated malaria have been validated. Acidosis and cerebral malaria are identified as main independent predictors of outcome [13]. Age was identified as an independent risk factor for fatal outcome in falciparum malaria though incidence of anemia and seizures decrease with age among these patients [14]. Multiple convulsions at admission are associated with neurological sequelae among children [10].

Little information is available on prognostic factors in patients with uncomplicated malaria. A study from Thailand reported that 4% patients with uncomplicated malaria progressed to complicated malaria. This study found that parasitemia and dehydration to be important predictors of progression [15]. We believe that it is important to identify these patients who present as uncomplicated malaria and then progress to complicated malaria. Findings of our study indicate that neurological involvement in patients with falciparum malaria predicted increased likelihood of mortality especially in complicated malaria group. Morbidity was so low in the uncomplicated malaria group that we were unable to identify predictors of mortality in this group. Presence of headache, neck rigidity and seizure in an otherwise uncomplicated malaria patient may represent early forms of cerebral malaria and potential for progression into severe or complicated malaria. Predictive value of these factors is however limited by wide confidence intervals with little allowance for confounders. This is largely attributable to low mortality in the presence of number of confounding variables and is a limitation in our study. These findings have to be confirmed in prospective studies with a larger number of patients. Current definition of cerebral malaria is only useful for prognosis and excludes number of potentially treatable cases with early or milder forms of cerebral malaria. We strongly recommend that definition of cerebral malaria should include milder cases or early forms of cerebral malaria.

Most patients with neurological dysfunction did not undergo neuroimaging or CSF analysis. CSF analyses were performed to identify patients with co-existing meningitis but staining and cultures were negative for bacterial infection in all patients. The role and yield of CSF analysis in these patients should be evaluated in prospective studies. CT/MRI (done in 43% patients) findings and CSF abnormalities (done in 23% patients) were not significant predictors of mortality on univariate analysis. Prognostic value of combined headache, neck rigidity, seizure abnormal CSF and abnormal MRI may be valuable in future studies with more extensive work up among these patients.

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**Contributors:** Mohammad Wasay, MBBS, MD, FRCP, contributed to study design, data analysis and manuscript writing, Asif Taqi, MBBS, MD, and Huma Aziz, MBBS, MD, data acquisition, data analysis and manuscript writing and Iqbal Azam, MSC, and M. Asim Beg, MBBS, PhD, data analysis and manuscript writing.

### References