Short communication

Bacteraemia in adult patients presenting with malaria in India

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ABSTRACT

Severe falciparum malaria is a major health problem in Odisha, India, contributing to high mortality. Multi organ dysfunction is a predominant manifestation of severe disease in Odisha, unlike in Africa, where cerebral malaria and anaemia are common. There are several studies implicating bacteraemia with severe malaria in African children while there are no reports in adults in India. This study has addressed this issue by enrolling 67 P. falciparum infected adult patients categorized into severe and uncomplicated malaria. Blood culture failed to confirm bacteraemia in any sample with the exception of one case of uncomplicated malaria. Study is inconclusive with regard to use of antibiotics in adult patients.

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1. Introduction

Malaria is a major cause of morbidity and mortality in India. The National Vector Borne Disease Control Programme (NVBDCP), India, has reported that 1.8 million cases of malaria and 1000 malaria related deaths occur annually (NVBDCP, 2004). However, the World Health Organization (WHO) estimates that figure to be 20 million cases and 15,000 deaths (WHO, 2009). The state of Odisha, India, is endemic to P. falciparum infection and contributes 29.8% of deaths related to the infection (NVBDCP, 2004; Sharma et al., 2004). The clinical profile of the disease in the state has changed over the years with multi-organ dysfunction (MOD) being a dominant presentation contributing to high mortality.

The pathogenesis of severe disease is related to host and parasite interaction and it is also believed that malaria strongly predisposes individuals to bacteraemia (Scott et al., 2011). There is accumulating evidence showing coexistence of malaria and invasive bacterial infections as a frequent and life-threatening condition in many endemic African settings (Bassat et al., 2009). Streptococcus pneumoniae, Gram-negative bacteria, Staphylococcus aureus and non-typhoid Salmonella (NTS) were the most frequently isolated microorganisms among severe malaria cases, with NTS being the commonest (Bassat et al., 2009; Were et al., 2011). Children with P. falciparum infection who acquire invasive bacteria have an increased risk of severe malaria anaemia (SMA), cerebral malaria (CM), respiratory distress, and mortality although having a low incidence of high density parasitemia (Berkley et al., 1999; Were et al., 2011). Some investigators have described an association of bacteraemia with a higher mortality in children with severe malaria, and so recommend antibiotics in addition to anti-malarial drugs (Berkley et al., 1999). However, it is not established that bacteraemia is the cause of increased mortality and there is no convincing evidence to date that routine antibiotics would reduce mortality in this context. There are no reports on bacteraemia in adults with severe malaria in India. This study aims to investigate the association of bacteraemia with different categories of severe malaria in adults in a tertiary care center in an endemic region.

2. Materials and methods

2.1. Study site and participants

The study was conducted at S.C.B. Medical College, Cuttack, Odisha, India between 2008 and 2009. Most of the patients belonged to districts having an average annual parasitic index (API) 6.67 (NVBDCP, 2010). Adult patients admitted to the Department of Medicine with a short history of fever were clinically examined in detail and screened for P. falciparum infection by Giemsa-stained thick and thin blood smears. Smear negative patients were subjected to immune chromatography test (SD Bio Standard Diagnostics India), and nested polymerase chain reaction (PCR). Individuals infected only with P. falciparum were included. Those with history of prior antibiotic administration were excluded from the study. Detailed physical examination was done along with routine haematological and biochemical
tests to assess severity. Clinical categorization was done based on WHO guidelines (WHO, 2000). Uncomplicated malaria (UM) was defined as patients with fever and evidence of falciparum infection in the blood. Severe malaria (SM) was categorized into three groups based on distinct clinical features: (1) cerebral malaria (CM), (2) non-cerebral severe malaria (NCSM) and (3) multi-organ-dysfunction (MOD) (Panda et al., 2011). CM was further defined as patients with altered sensorium, GCS (Glasgow coma scale) of ≤10. NCSM patients had one of the several manifestations of severe malaria without cerebral involvement, namely severe anaemia (haemoglobin < 5 g/dl), acute renal failure (serum creatinine > 3 mg/dl), jaundice (serum bilirubin > 3 mg/dl), acute respiratory distress syndrome (PaO2/FIO2 < 200), haemoglobinuria (dark red or black coloured urine positive for haemoglobin) and shock (systolic BP of < 80 mmHg). MOD was diagnosed based on presence of two or more organ involvement like CNS (GCS ≤ 10), respiratory (PaO2/FIO2 < 200), renal failure (serum creatinine > 3 mg/dl) and hepatic dysfunction (conjugated bilirubin > 50% of total, ALT/AST > 3 times of normal, prolonged prothrombin time). The study was approved by the Institutional Ethics Committee of the Medical College and blood samples were collected after written consent of the patients or accompanying person.

2.2. Polymerase chain reaction

GenElute™ Blood Genomic DNA Kit (SIGMA) was used to isolate genomic DNA from whole blood according to the manufacturer’s instructions. As described earlier by our group, genus and species specific nested PCR technique was used to detect P. falciparum and/or P. vivax infections (Panda et al., 2011). Briefly, primary PCR was performed to detect Plasmodium genus and in secondary PCR, the amplicon of primary PCR was treated as a template to detect Plasmodium at species level. As P. falciparum is the major cause of malaria (>80%) followed by P. vivax (10–15%), in the population under investigation (Ranjit, 2006), only species specific primers for P. falciparum and P. vivax were used in secondary PCR to diagnose plasmodium infections.

2.3. Blood culture

The site selected for venipuncture was disinfected using 70% isopropyl alcohol followed by iodine to prevent contamination by bacterial flora of skin. The top of the collection bottle was cleaned using 70% isopropyl alcohol immediately before collection. Two samples were collected over a 30–60 min interval. 10 ml of blood was drawn into a syringe and was aseptically introduced into commercially available glucose broth w/0.05% SPS (HiSafe blood culture system, Himedia Laboratories, Mumbai, India). Then the culture bottles were incubated at 35–37°C for 6–18 h, followed by manual detection by macroscopic visualization and serial blind sub culture onto blood and MacConkey agar up to 5 days for each sample (Forbes et al., 2007; Trevino and Ross, 2007). Then the results were interpreted.

2.4. Statistical analysis

Statistical analyses were performed by using GraphPad Prism (version 5.01). Data were expressed as mean ± SEM. Differences between means were analysed by unpaired Student’s t test. A P value of <0.05 was considered to reveal a significant difference.

3. Results

3.1. Clinical categories

A total of 67 adult patients were enrolled in the study including 8 UM and 59 patients of SM. NCSM (n = 23) was the commonest manifestation in this cohort with 10 patients having renal failure, 9 patients with hepatopathy and 4 patients with severe anaemia, respectively. Out of 22 patients with MODS, 15 patients had 2 organ involvement and 7 patients had more than 2 organ involvement. There was no significant difference in duration of illness between patients of UM when compared to patients with other subtypes of SM. Patients with MODS was associated with highest mortality rate (Table 1).

3.2. Baseline characteristics of biochemical and haematological profile

There were no significant differences in the levels of Hb, DC, TLC, FBS, TPC between patients with uncomplicated and severe malaria. The difference in levels of serum bilirubin, SGOT, SGPT, serum urea, serum creatinine was significant in patients with severe disease (Table 2).

3.3. Blood culture results

Blood samples from all patients were cultured according to previous protocols (Forbes et al., 2007; Trevino and Ross, 2007). There was no growth of bacteria in any of the blood culture samples with the exception of one uncomplicated case where the organism Streptococcus pyogenes was isolated (Table 2).

4. Discussions

This study of 67 adult patients with falciparum malaria has been extensively categorized into various degrees of severity in order to analyse bacteraemia in individual groups. The presence of MODS, which is unique in this study population, provides a group of patients with very severe disease and high mortality to evaluate if bacteraemia is a contributory factor in disease severity. Unlike African children where severe malaria is commonly restricted to CM, severe anaemia and respiratory distress (Berkley et al., 2007; Nkurunziza et al., 2007) were significantly associated with Gram-negative bacteraemia. To the best of our knowledge, this is the first study to report bacteraemia in Indian patients with severe malaria.
et al., 1999; Were et al., 2011), the disease repertoire in adults is more varied (Panda et al., 2011). In this context, the comparison of bacteraemia in two study populations has significant importance.

In the present study, in one out of 8 cases of uncomplicated malaria *Streptococcus pyogenes* was isolated. This translates into a prevalence of 12.5% among adult patients admitted with uncomplicated malaria. This is significant but the sample size is small. The role of bacteraemia in this case was difficult to ascertain since the patient recovered with anti-malarial therapy. Interestingly, bacteraemia was not detected in any of the samples of severe malaria irrespective of disease severity. This is in contrast to data on African children in whom bacteraemia is between 5% and 7% (Bassat et al., 2009; Scott et al., 2011). It has been observed to be associated with severe malaria (Bassat et al., 2009). The adult population may be more resistant to bacterial invasion unlike African children whose immune status is not comparable. None of our patients were undernourished and haemoglobin levels were mostly moderate. The reason for development of MOD is not known and the role of bacteraemia as a contributory factor is inconclusive. The prevalence of bacteraemia in African children with severe malaria is in order of 5–7% (Bassat et al., 2009; Scott et al., 2011) taking that figure into consideration the current study has a power of only 59% to detect bacteraemic prevalence of 5%. The power of the study is low, therefore a larger study including more number of adult cases of severe malaria from different geographical areas will provide information if the problem is area specific.

In summary, bacteraemia is uncommon in adult patients with severe malaria and antibiotic therapy should be individualized based on the clinical picture.

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### Conflict of interest statement
No conflict of interest.

### Acknowledgements
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### Appendix A. Supplementary data
Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.actatropica.2012.04.001.

### References


### Table 2
Biochemical, haematological parameters and blood culture results of study population.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>UM (n=8)</th>
<th>SM (n=59)</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (gm/dL)</td>
<td>9.71 ± 0.43</td>
<td>9.68 ± 0.28</td>
<td>0.9674</td>
</tr>
<tr>
<td>TLC (cm³)</td>
<td>7950 ± 546.4</td>
<td>8441 ± 316.3</td>
<td>0.4549</td>
</tr>
<tr>
<td>Neutrophil (%)</td>
<td>62.55 ± 2.85</td>
<td>63.59 ± 2.12</td>
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</tr>
<tr>
<td>Lymphocyte (%)</td>
<td>32.65 ± 2.76</td>
<td>35.10 ± 2.09</td>
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</tr>
<tr>
<td>TPC (cm³)</td>
<td>169600 ± 30890</td>
<td>171905 ± 16360</td>
<td>0.9514</td>
</tr>
<tr>
<td>FBS (mg/dL)</td>
<td>119.5 ± 17.18</td>
<td>145.3 ± 13.52</td>
<td>0.3227</td>
</tr>
<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>0.87 ± 0.09</td>
<td>6.89 ± 1.14</td>
<td>0.0053</td>
</tr>
<tr>
<td>SGOT (IU/L)</td>
<td>49.44 ± 5.32</td>
<td>99.49 ± 8.23</td>
<td>0.002</td>
</tr>
<tr>
<td>SGPT (IU/L)</td>
<td>43.50 ± 4.47</td>
<td>63.37 ± 4.55</td>
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<tr>
<td>ALP (IU/L)</td>
<td>125.6 ± 18.94</td>
<td>158.9 ± 11.34</td>
<td>0.1697</td>
</tr>
<tr>
<td>Serum urea (mg/dL)</td>
<td>38.05 ± 4.51</td>
<td>117.6 ± 9.31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.23 ± 0.06</td>
<td>4.07 ± 0.70</td>
<td>0.0321</td>
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</table>

Blood culture results

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<th>NA</th>
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</table>

Note: UM, uncomplicated malaria; SM, severe malaria; HB, haemoglobin; TLC, total leucocyte count; TPC, total platelet count; FBS, fasting blood sugar; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; ALP, alkaline phosphatase, NA, not applicable.

* Determined by unpaired Student’s “t” test.