Falciparum malaria in malaria-naive travellers and African visitors

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Summary

Background: Patients from malaria-endemic areas who present in non-endemic countries with Plasmodium falciparum malaria are often assumed to have some degree of immunity. If this were reliably true, it would simplify their management.

Aim: To determine whether being born and resident in a malaria-endemic country is a predictor of clinical course in UK admissions for malaria.

Design: Prospective observational study.

Methods: We compared clinical and laboratory parameters between two groups of adult patients with acute P. falciparum malaria, admitted to the Hospital for Tropical Diseases in London: one born and resident in non-endemic countries (n = 167); the other born and resident in malaria-endemic countries of Africa (n = 93). Patients were excluded if they had taken prophylaxis or prior treatment.

Results: There were no differences between these two groups in terms of peak parasitaemia or time to parasite clearance. There was a significantly higher risk of malaria-naive patients having peak parasitaemia >5% (OR 4.5, 95%CI 1.5–13.2). Of those usually resident in Africa, 31% required parenteral treatment compared to 41% of the malaria-naive group. Of the visitors from Africa, 4.3% needed admission to the Intensive Therapy Unit (ITU), although there was a tendency for more malaria-naive patients to require ITU care (OR 2.69, 95%CI 0.9–8.1).

Discussion: While there are differences in presentation between those who are malaria-naive and those who live in malaria-endemic African countries, making assumptions about the immunity or clinical course of an individual patient with malaria presenting in the UK on the basis of presumed history of exposure is unwise.

Introduction

Some degree of immunity to malaria is acquired by people living in areas where the disease is endemic, as a result of repeated exposure to Plasmodium falciparum. The precise mechanisms that underlie the acquisition of malarial immunity are the subject of intensive research, but are not well understood.1 This immunity is acquired at variable speeds, and is often rapidly lost when individuals move away from endemic areas.2 In highly endemic areas of Africa, clinical practice demonstrates that adults who are repeatedly infected with malaria seldom become critically ill, and often tolerate parasites without developing symptoms.3 This observation is sometimes used to advocate different treatment
practices for patients with malaria who present in non-endemic areas. Some centres suggest that individuals with *P. falciparum* malaria who are assumed to be 'semi-immune' on the basis of their exposure history, do not require admission to hospital and can be treated on an out-patient basis. If true, this would be useful for these patients as it would save them an unnecessary admission.

The Hospital for Tropical Diseases (HTD) in London sees 150–250 patients with *P. falciparum* each year. Approximately two-thirds are born and raised in a malaria-endemic area, usually West Africa; the remaining third are individuals resident in the UK since birth, who acquire their disease while travelling. We compared clinical and laboratory parameters between patients who were either clearly resident since birth in non-endemic countries or born and currently resident in endemic countries in Africa, in an attempt to determine whether the clinical presentation or course of their illness differed.

**Methods**

We collected detailed clinical and laboratory data on all cases of malaria admitted to the hospital since 1996. This study used these prospectively collected data to identify all patients who acquired their infection in Africa between 1996 and 2003. This study was designed to compare those who are definitely malaria-naive with those who have spent their whole lives living in malaria-endemic countries where differences in exposure are clear. Two clearly defined sub-groups of patients were identified for this retrospective study: those who were born in non-endemic areas where malaria is not endemic (and therefore malaria-naive); and those who were both born and still resident in endemic areas of sub-Saharan Africa (and who therefore might be assumed on exposure criteria to have some degree of immunity). Exclusion criteria were therefore designed to exclude those where residence status was less clear-cut. Immigrants from malaria-endemic countries living in Europe and those who came from non-endemic countries, but who had lived in Africa, were excluded. We also excluded all those who had taken chemoprophylaxis or had previously received treatment for the current episode of malaria, as this would affect the presentation and course of the disease.

The data from the database were supplemented with a retrospective review of case notes. Clinical data included travel history, country of birth, country of current residence, duration of illness, temperature on admission, the need for parenteral treatment, the need for intensive care and duration of admission. Laboratory data included parasite count at presentation, peak parasite count, duration of parasitaemia, the presence of schizonts and/or gametocytes and haematological parameters.

All patients were admitted and treated with quinine according to standard HTD protocol. Parenteral treatment was given according to a pre-defined and agreed protocol, in which it is given to all patients where any WHO criteria of severe disease are met,5 patients with a parasitaemia >2% or schizonts seen in the peripheral blood at presentation, or where oral treatment cannot be tolerated. Quinine was continued with daily blood films and once asexual parasitaemia had cleared, patients were given a second agent, usually sulfadoxine-pyrimethamine (Fansidar).

Automated full blood counts were performed in the Dept of Haematology. All parasitological investigations were performed in the same specialist laboratory. Data were entered into Microsoft Excel and analysed using STATA 8 (Statacorp). Non-parametric continuous data were compared between the groups using the Wilcoxon Rank Sum test. Categorical data were compared between the groups using the χ² test, except in one case (indicated in the text) where Fisher’s exact test was used. Odds ratios for various categorical factors are presented, and a multivariate model was constructed to adjust for pre-determined confounding factors using logistic regression.

**Results**

Between 1 January 1996 and 31 December 2003, a total of 902 patients aged >15 years were admitted as a result of *P. falciparum* malaria. Predefined exclusion criteria for this study meant that of these the following were excluded: 320 who had taken anti-malarial prophylaxis or had treated themselves for malaria; 260 who were born in Africa but were presently residing in a non-endemic area; 23 who were born in non-endemic parts of the world but were presently living in endemic areas of Africa; 23 who acquired falciparum malaria outside Africa (mostly South Asia); and 16 who were treated before being transferred to HTD and had a negative blood film for asexual parasites by the time of arrival.

Two hundred and sixty patients therefore met the admission criteria. Of these, 167 (median age 35 years, 40% female) were both born and normally resident in non-endemic parts of the world and could be assumed to be malaria-naive. The remaining 93 (median age 31 years, 46% female) were
both born and normally resident in malaria-endemic parts of Africa (visitors from Africa). The two groups were almost indistinguishable in terms of their time to presentation (measured as number of days from first symptoms), presenting temperature, median parasitaemia at presentation and peak parasitaemia, white cell count and platelet count (Tables 1 and 2). There was a significantly lower haemoglobin in the ‘resident’ group at presentation. The time between reported onset of symptoms and presentation was similar, with malaria-naive patients taking a median of 4 days to present (IQR 2–6) and the visitors from Africa a median of 3 (IQR 2–6.6). The frequency with which both schizonts and gametocytes were seen in the peripheral blood did not differ between the two groups (Table 1).

While median parasite counts were similar in the two groups, at the higher end of the parasitaemia range there were differences. The proportion of patients with parasitaemia >2% (a widely used cut-off for instituting parenteral treatment in non-endemic countries) was similar between the two groups. Malaria-naive individuals had a significantly higher risk of parasitaemia >5%, the WHO cut-off for parenteral treatment (OR 4.5, 95%CI 1.5–13.2) (Table 1). Thirteen patients had a parasitaemia of >10%, a threshold where some consider exchange transfusion; all were malaria-naive (p = 0.005, Fisher’s exact test). Median time to clearance was 3 days in both groups, but six (6%) of the visitors from Africa and 26 (16%) of the malaria-naive patients took 5 days or more to clear parasitaemia (p = 0.04).

One patient in this study died, a woman in the malaria-naive group who developed cerebral malaria complicated by acute renal failure. In addition, parenteral treatment was considered necessary according to modified WHO criteria for 66 (40%) of the naive group and 29 (31%) of the African visitors (OR 0.7, 95%CI 0.4–1.2). Eighteen malaria-naive patients (10.7%) and four patients in the visitors group (4.3%) required treatment on the ITU (OR 2.69, 95%CI 0.88–8.1). When adjusted for the potential confounding factors age, gender and the time between onset of symptoms and initiation of therapy this OR was 2.1 (95%CI 0.7–6.7).

### Discussion

Malaria is a serious disease which kills millions worldwide and claims lives in the UK every year. This study set out to examine whether there are clinically important differences between those who are normally resident in highly malaria-endemic countries and those who have no previous exposure who present with malaria in a European setting. It aimed to address a practical question—can history of exposure be used to guide clinical decisions?

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<thead>
<tr>
<th>Table 1</th>
<th>Parasitology data</th>
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<tbody>
<tr>
<td></td>
<td>Malaria-naive (n = 167)</td>
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<tr>
<td>Mean parasitaemia at admission (range)</td>
<td>0.32% (0.001–45%)</td>
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<tr>
<td>Parasitaemia &lt;2%</td>
<td>119 (71%)</td>
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<tr>
<td>Parasitaemia 2–4.9%</td>
<td>20 (12%)</td>
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<td>Parasitaemia 5–10%</td>
<td>15 (9%)</td>
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<tr>
<td>Parasitaemia &gt;10%</td>
<td>13 (7.8%)</td>
</tr>
<tr>
<td>Median peak parasitaemia (%) (range)</td>
<td>0.4% (0.0001–45)</td>
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<tr>
<td>Patients with gametocytes at admission</td>
<td>25 (15%)</td>
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<td>Patients with schizonts at admission</td>
<td>24 (14%)</td>
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<th>Table 2</th>
<th>Temperature and haematological values at admission</th>
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<tr>
<td></td>
<td>Malaria-naive (n = 167)</td>
</tr>
<tr>
<td>Median temperature (°C) (range)</td>
<td>37.9 (35.5–40.4)</td>
</tr>
<tr>
<td>Median haemoglobin (g/dl) (range)</td>
<td>13.6 (7.8–16.8)</td>
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<tr>
<td>Median platelets (x10^9/l) (range)</td>
<td>98 (6–524)</td>
</tr>
<tr>
<td>White cells (x10^9/l) (range)</td>
<td>5.2 (3–44)</td>
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*Wilcoxon Rank Sum test.
Taking the presentation, parasitological and other laboratory indices, and course of malaria in the groups as a whole, the presentation was similar. Some differences are, however, clear. There was a significantly increased risk of hyperparasitaemia (>5% or >10%) in the malaria-naive group, and a non-significant trend towards having more admissions to ITU. The lower haemoglobin levels of African visitors on admission may indicate that they had had malaria asymptomatically for longer before they developed symptoms and presented. On the other hand, 4% of the patients born and resident in endemic countries in Africa required admission to ITU, and approximately a third had disease of sufficient severity on objective criteria to warrant parenteral treatment.

There have recently been calls to consider treating ‘semi-immune’ individuals who present with malaria in the UK differently from those who have no immunity. There is an assumption that those who are semi-immune can be treated as out-patients, whilst those who are non-immune should be admitted (J. Klein, British Infection Society, 2004). This is based on the observation that adults resident in highly malaria-endemic parts of sub-Saharan Africa seldom develop severe disease and are considered semi-immune. The logic of this position is reasonable, but depends entirely on being able to determine immunity from residence criteria alone. There are no laboratory tests which can guide decisions about immunity. The evidence from this study is that determining immunity from exposure history is difficult. All the patients in this study from Africa were both born, and had as their main country of residence, a highly malaria-endemic country in sub-Saharan Africa. This is a much stricter definition than that of being born and resident for the first 5 years of life, which is currently used by many to define immunity. There were clearly some differences between the two groups, especially in peak parasitaemia, but despite that, a substantial proportion had disease which can be classified as either complicated or severe by WHO criteria.

It is important to acknowledge the limitations of this study. It is not addressing, nor able to address, more basic questions about mechanisms of immunity; only a prospective study with detailed geographical exposure history would be able to do this. The definition of being resident in an endemic area is necessarily crude, as within every country there are wide ranges of transmission; a resident of central Lagos or of highland Tanzania has minimal malaria exposure, despite living in a highly endemic country. Any more sophisticated definition would, however, probably be unworkable in a clinical context. The data are also limited to those parameters which are recorded prospectively in our database (e.g. residence), or are measured in laboratories (so may be considered objective). Retrospective data can be reliably determined from case-notes and charts, as they are recorded in a standard way on all (e.g. temperature, use of parenteral treatment, admission to ITU). Some potentially relevant data, such as time since arrival in the UK, are usually recorded in case-notes but not in a standardized way, which can make the information unreliable, and we have not included such data.

The most important objective clinical indicators of severity of disease, taken contemporaneously, are decision to administer parenteral treatment and admission to ITU. The decision to give parenteral treatment was made according to a well-established protocol modified from WHO criteria which use objective criteria, and is unlikely to be subject to significant bias. The decision to admit to ITU may be subjective, and this observational study cannot exclude the possibility that the attending clinician’s decision may have been swayed in borderline cases by assuming some degree of immunity among residents of an endemic area. If so, however, it seems likely that clinicians would be less, rather than more, likely to admit patients to ITU if they thought that they were semi-immune. In our hospital, ITU resources are under considerable pressure, and it is very unlikely patients would be admitted there unless critically ill.

The data reported in this study are slightly at variance with previously published retrospective studies of imported malaria. In a study of 194 cases of P. falciparum malaria seen at a single hospital in northern Italy, all 17 of the severe cases (defined using WHO criteria) were malaria-naive travellers, while none of 46 immigrants to Italy—assumed to be semi-immune—developed severe disease. Similar observations have been reported from Brescia in Italy and from Norway. However, none of these studies were designed primarily to examine this question; data were reported in passing, and no clear definition of what constitutes an ‘immigrant’ was given.

The similarities in the presentation of malaria-naive travellers and semi-immune individuals born and resident in endemic African countries with falciparum malaria, and the numbers with severe or potentially complicated disease are likely to reflect the highly selected nature of African patients presenting in the UK, rather than undermining the widely accepted observation that severe adult malaria is rare in most of sub-Saharan Africa. Those who have flown to Europe are by definition wealthier than average. In many parts
of Africa, the more affluent are more likely to live in urban areas with relatively low malaria transmission, often in screened houses, meaning they have less opportunity to develop immunity. The entomological inoculation rate (EIR), the number of infecting bites experienced per person per year, varies greatly between different areas of Africa, and this will have a considerable effect on the rate of acquisition of immunity to the disease. These results therefore give no insight into the mechanisms of malarial immunity, but rather address a clinical question: is it possible on residence history to identify reliably those patients with falciparum malaria who are semi-immune? When dealing with individual patients born and living in Africa who present in the UK, the answer to this question on the current evidence is ‘no’. Since immunity to malaria is known to wane rapidly without re-exposure, it is even less likely to be the case in those who, while born in Africa, have emigrated and lived in the UK for many years.

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References


