Concurrent malaria and enteric fever in Pakistan

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ABSTRACT

Introduction: The precise incidence of concurrent malaria and enteric fever in most geographical areas is largely unknown, and no data on such an association exists in Asia. Because both malaria and enteric fever are hyperendemic in Pakistan, we sought to determine the frequency, epidemiology, and clinical and laboratory features of dual malaria and enteric fever in a tertiary care setting.

Methods: We conducted a retrospective case-control study of 1,891 patients hospitalised with malaria over a ten-year period and identified 21 patients with concurrent culture-proven enteric fever.

Results: Cases with dual infection had significantly more gastrointestinal symptoms at the time of admission, including nausea, vomiting, abdominal pain, and/or diarrhoea compared to matched control subjects with uncomplicated malaria (p-value is less than 0.006). Cases were more likely to have a continuous rather than intermittent fever (p-value is less than 0.0001), delayed defervescence in response to antimalarial treatment (p-value is less than 0.006), normal or low white blood cell counts (p-value is less than 0.04), relatively higher platelet counts among cases versus control (p-value is less than 0.05) and serum haemoglobin (p-value is less than 0.06), elevated alanine aminotransferase levels (p-value is less than 0.02), and a prolonged hospital stay (p-value is less than 0.03). The negative predictive values for gastrointestinal symptoms, continuous fever pattern and delayed defervescence were 80 percent, 72 percent and 74 percent, respectively.

Conclusion: Patients with malaria who have marked gastrointestinal symptoms, continuous pattern of fever and persistence of fever for more than 24 hours after appropriate antimalarial therapy, should be investigated or empirically treated for concurrent enteric fever. The absence of the above clinical features in patients with uncomplicated malaria should reassure physicians that there is no concurrent typhoid fever.

Keywords: enteric fever, malaria, tropical infection, typhoid,

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INTRODUCTION

Malaria and enteric fever are among the most prevalent tropical diseases worldwide. The annual global incidence of malaria is estimated at 300 to 500 million cases, with more than 100 million cases occurring in sub-Saharan Africa alone and with an estimated one million deaths, mostly in infants and children. There are approximately 12.5 million estimated cases of enteric fever each year, with more than 62% of these occurring in Asia and 35% in Africa[1,2]. An association between malaria and enteric fever was first described in the medical literature in the middle of the 19th century, and was given the label typhomalarial fever by the United States Army[3]. In the last 20 years, this relationship between malaria and salmonellae has been confirmed by additional studies from Africa that largely describe a higher incidence of non-typhoidal salmonella bacteraemia among patients with malarial parasitaemia[4,5]. The precise incidence of concurrent malaria and enteric fever (i.e. caused by *Salmonella typhi* or *S. paratyphi*) in most geographical areas, including Pakistan, is largely unknown, and no data on such an association exists from Asia. Because both malaria and enteric fever are hyperendemic in Pakistan, we sought to determine the frequency, epidemiology, and clinical and laboratory features of dual malaria and enteric fever in a tertiary care setting.

METHODS

This case-control study was conducted at the Aga Khan University Hospital (AKUH) in Karachi, Pakistan, a 537-bed primary and tertiary care teaching institution serving a population of eight to 12 million. Computerised medical records, and parasitology and blood culture log books of the clinical microbiology

laboratory were retrospectively reviewed in order to identify patients admitted over a ten-year period (1992-2002) from whom plasmodium and typhoidal or paratyphoidal *Salmonella* species were simultaneously detected.

Patients admitted to AKUH with undifferentiated fever, typically have malaria smears and one set of blood cultures drawn, before any form of treatment is given. A diagnosis of malaria was made on the basis of the presence of fever and microscopical examination of thin and thick peripheral blood smears demonstrating malarial parasites. A total number of 1,891 cases of malaria that required hospitalisation were identified during the study period. Of these, 21 (1.11%) subjects were concurrently found to have blood cultures positive for either *S. typhi* or *S. paratyphi*. Clinical and laboratory features, length of hospital stay, and outcomes of patients with dual infection were compared with randomly-selected, age- and sex-matched control subjects hospitalised and treated for uncomplicated malaria infection during the same study period.

Fever patterns were determined from patients' histories and from hospital temperature charts. The degree of parasitaemia in each case was semi-quantitatively reported as scanty (1-10 parasites per 100 high-power fields), moderate (10-100 parasites per 100 high-power fields), or heavy (>100 parasites per 100 high-power fields). Appropriate therapy for malaria was taken as any recommended drug or drug combination of suggested duration. At AKUH, hospitalised patients treated for malaria typically have follow-up blood smears performed 24 and 48 hours after initiation of treatment to document adequate clearing of parasitaemia. Antimalarial treatment failure was not a cause of persistent fever in any study subject.

Statistical interpretation of data was performed using the computerised software programme, Statistical Package for Social Sciences (SPSS) version 11.0 (Chicago, IL, USA). Chi-square test was used to compare categorical variables and the matched student's t test was used to compare continuous variables. A p-value of <0.05 was considered statistically significant.

RESULTS

For cases, the median and mean patient ages at the time of initial presentation were five years and 9.7 years, respectively (range: one to 38 years), with a male:female ratio of 15:7. An equal number of control subjects were identically matched for age and sex. The median duration of symptoms prior to admission was 9.1 days (range: one to 30 days) for cases versus 8.1 days (range: one to 28 days) for control subjects. Signs and symptoms at the time of admission for both cases and controls are shown in Table I. Patients with concurrent malaria and enteric fever had significantly higher frequencies of gastrointestinal symptoms (p=0.006) compared to the control subjects with malaria alone. The negative predictive value of gastrointestinal symptoms was 80%.

The physical findings on clinical examination, including hepatosplenomegaly, were not significantly different in both groups. However, the pattern of fever before and after the initiation of antimalarial treatment was of a continuous type in 13 of 21 (62%) patients with dual infection, while all 21 patients with uncomplicated malaria had an intermittent fever pattern (p<0.001 and negative predictive value of 72%). Resolution of fever on antimalarial treatment took >24 hours in patients with dual

Table I. Clinical features of patients with concurrent malaria and typhoid fever (cases) and patients with uncomplicated malaria (controls).

Clinical features	Cases (n = 21)	Controls (n = 21)	p-value
Duration of symptoms (in days)*	9.14 ± 7.29	8.05 ± 7.09	NS
Fever			
Continuous	13	0	**0.0001**
Intermittent	8	21	**–**
Resolution of fever+			
Gradual (>24 hrs)	16	7	**0.006**
Abrupt (<24 hrs)	5	14	
Gastrointestinal symptoms	18	9	**0.006**
Nausea	16	6	**0.003**
Vomiting	16	7	**0.006**
Abdominal pain	6	1	**0.04**
Diarrhoea	6	1	**0.04**
Hospital stay (in days)*	5.33 ± 3.04	3.38 ± 1.80	0.02

*: mean ± standard deviation; +: after antimalarial treatment; NS: not significant.

Table II. Laboratory values in patients with concurrent malaria and typhoid fever (cases) and patients with uncomplicated malaria (controls).

Laboratory features	Cases (n = 21)	Controls (n = 21)	p-value
Haemoglobin (g/dL)*	10.5 ± 2.3	9.3 ± 2.9	0.06
White blood cell count (10^9/L)*	7.1 ± 3.6	13.6 ± 9.3	**0.04**
% neutrophils*	63.1 ± 13.9	55.2 ± 20.2	NS
% lymphocytes*	31.0 ± 18.9	30.4 ± 11.2	NS
Platelet count (10^9/L)*	134 ± 73.9	83.4 ± 61.7	**0.05**
Elevated ALT	16	8	**0.02**

*: mean ± standard deviation; NS: not significant; ALT: Alanine aminotransferase levels showed marked variability among cases with a mean value of 93.1 ± 103.5 IU/L, but were not significantly different from controls (p = 0.24).

infection (p=0.006 and negative predictive value of 74%). Cases and control subjects were infected with either *Plasmodium vivax* (13/21 cases and 12/21 controls) or *P. falciparum*. The degree of parasitaemia between the two groups was not significantly different. Comparisons of various admission laboratory results are shown in Table II. None of the cases or control subjects died of infection, and all patients had negative blood smears for malarial parasites and/or blood cultures at subsequent follow-up visits.

DISCUSSION

To our knowledge, this is the first study from the Indian subcontinent to describe dual infection with malaria and enteric fever. Most previous studies from Africa have largely reported an association between malaria and non-typhoidal salmonellosis. In a study cohort of 200 patients presenting with fever, Ammah et al reported a 32.5% incidence of microbiologically-proven concurrent infection with malaria and *S. typhimurium* (diagnosed via blood and/or stool positive for salmonellae) compared with *S. typhi* (17%) and *S. paratyphi* (2.0%) (p<0.05)[4]. In another study of Gambian children, malarial infection was present in 11% of patients with *S. typhi* septicaemia and 42% of patients with non-typhoidal salmonellae[6]. In contrast, in our study of dual malaria-salmonella infection, 21 of 22 positive blood cultures for salmonellae grew *S. typhi* (16/21) or *S. paratyphi A or B* (5/21) (one patient with *S. enteritidis* was excluded from analysis), reflecting the predominance of these species as causes of salmonella bacteraemia in Pakistan.

The prevalence of plasmodium slide positivity among the children treated for malaria in Pakistan was found to be 5.9%[7]. In another study, 40% of the bone marrow examined showed the presence of malaria parasites[8]. The community prevalence of asymptomatic malaria parasitaemia in Pakistan is not known but in a study from India, it was reported as 2.9%[9]. In contrast, the prevalence of asymptomatic parasitaemia was 17% at enrollment but 5-17% for the remainder of the study among a cohort of Ugandan children[10]. Similarly, the annual typhoid fever incidence rates in Pakistan are not known but an annual incidence rate of 198 and 980 per 100,000 were reported from Vietnam and India, respectively. Between 60% and 90% of people with typhoid in these countries do not receive medical attention or are treated as outpatients[11,12]. We found that the occurrence of dual malaria and enteric fever at our teaching hospital in Pakistan was low at 1.11%, a finding very different from the higher incidence of 11-17% reported from Africa[4,6]. We are unsure just how many of our patients with positive malaria smear had blood cultures simultaneously drawn, and so the precise incidence of dual infection in our population is uncertain.

The major disease symptoms in our study cohort were similar to those frequently seen in malaria alone, including gastrointestinal features. However, subjects with dual infection had significantly higher rates of nausea, vomiting, abdominal pain, and diarrhoea, all common presenting features of enteric fever (p=0.006). Unlike the intermittent fever pattern generally seen with malaria, patients with dual infection tended to exhibit a continuous fever more typical of enteric fever (p<0.0001). For clinicians, this latter pattern, as well as the delayed resolution of fever (>24 hours) after starting antimalarial treatment (p=0.006), should raise the clinical suspicion of dual infection in areas endemic for these two infectious diseases.

Thrombocytopaenia occurs frequently in malarial infection. In a recent study, a decreased platelet count was present in 43% to 58% of children with *P falciparum* malaria[13]. Haemophagocytosis is an important mechanism in producing neutropaenia, anaemia and thrombocytopaenia in several infectious diseases, including enteric fever[14]. We found thrombocytopaenia in both of our study groups, although it was a more frequent laboratory finding among control subjects with uncomplicated malaria; this may be partly attributed to relatively (although not significantly) higher parasite loads in controls, which may have contributed to a lower platelet count in this group compared to cases with dual infection (the median platelet count among cases and controls were 108 and 64 10^9/L, respectively). Leukopaenia with neutropaenia and a relative lymphocytosis are common haematological findings in enteric fever[15]. Mild elevations in liver enzymes are often seen in both enteric fever and malaria; in our study, more cases with dual infection had elevated serum alanine aminotransferase (ALT) levels (p<0.01).

There are several limitations to this study. First, it is not certain how many patients hospitalised with malaria had blood cultures drawn, thus making the incidence of dual infection imprecise. Patients admitted to AKUH with undifferentiated fever typically have malaria smears and one set of blood cultures drawn, before any form of treatment is given, but this diagnostic approach was not part of a standard protocol during the study period and so cases of concomitant enteric fever could have been missed. Second, no attempt was made to determine how many patients with malaria had taken antibacterial

medication prior to hospitalisation, thus potentially preventing the isolation of *Salmonella* if present.

In conclusion, dual infection with malaria and enteric fever is a very uncommon occurrence in our region of the world, even though both diseases are prevalent. Patients with malaria and marked gastrointestinal symptoms, a continuous pattern of fever, and persistence of fever for more than 24 hours after appropriate antimalarial therapy, should be investigated or empirically treated for concurrent enteric fever. The negative predictive values and the absence of the above clinical features in patients with uncomplicated malaria, should reassure physicians that there is no concurrent enteric fever. In geographical settings like Pakistan, where malaria is more frequently occurring than enteric fever and where resources are very limited, blood cultures may not be necessary for patients at the time of hospitalisation for undifferentiated fever, pending results of peripheral blood smears.

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