THE CLINICAL AND EPIDEMIOLOGICAL FEATURES OF CHILDHOOD MALARIA IN A MODERATELY ENDEMIC AREA OF SRI LANKA

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Abstract. This study describes some clinical and epidemiological features of childhood malaria in a moderately endemic area of southern Sri Lanka. Six hundred and sixty-two children, who experienced 1,138 attacks of malaria, and 172 children, who experienced 202 attacks of acute non-malarial fever, were followed over a period of two years. Of the 1,138 malaria infections followed, 776 were due to *P. vivax*, 359 were due to *P. falciparum*, and 3 were mixed infections. The majority of children presented within the first three days of the onset of symptoms. Headache (96%), feeling cold (81%) and arthralgia (77%) were the commonest presenting symptoms. Two hundred and sixty-four children experienced more than one attack of malaria. The clinical and epidemiological features of childhood malaria that have important implications for the planning and targeting of preventive measures are discussed.

INTRODUCTION

Malaria in childhood is often preceded by a brief illness with rather non-specific features and its diagnosis in the absence of clinical or parasitological investigations can be difficult (Snow and Marsh, 1998). Death due to malaria in childhood is a relatively rare event when the disease burden facing an entire population is considered. Babies born to mothers who had malaria during pregnancy are at risk of being low birth weight as a result of intrauterine growth retardation (Steketee and Wirima, 1996). In hyper- and holoendemic areas, parasitemia appears in an increasing proportion of children over the first few months of life, the rate of increase being a measure of the transmission intensity. The great majority of these infections are probably asymptomatic, although it is difficult to establish this as a fact in a community in which there are frequent childhood ailments from a variety of possible causes. However, from the age of a few months onwards, infected infants may develop severe disease (Greenwood *et al*, 1991). The figures and case fatality rates of severe disease probably differ between populations according to transmission characteristics, health service provisions, parasite drug sensitivities and a variety of parasite and host factors.

In order to reduce the morbidity and mortality due to malaria, the goal of the recently launched Roll Back Malaria Initiative of the World Health Organization, knowledge of the epidemiology of the disease in high risk groups such as children is needed. The impact of malaria on the morbidity and mortality of children living in high transmission areas such as Africa has been reported extensively. However, in South-East Asia, where malaria inoculations are low and seasonal, infection and deaths from malaria are highest among young adults as they are more exposed through occupation or journeys in malaria transmission areas (Anthony and Pongvongsa, 1998). Age-specific data on malaria are needed for the formulation of rational drug policies for the

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treatment of malaria (Anthony and Pongvongsa, 1998). The objective of this study was to describe the important clinical and epidemiological features of malarial infections of children, in a typical, moderately endemic area of Sri Lanka.

MATERIALS AND METHODS

The study was carried out in the Kataragama and Buttala areas, which are situated in the Moneragala District of the dry zone of southern Sri Lanka, from January 1998 to December 1999. Eight hundred and thirty-four children below 12 years of age who presented at malaria diagnosis and treatment centers in the area were included in the study. Of the 834 children, 662 presented with malaria while 172 presented with an acute non-malarial febrile illness that in almost all children, was found to be an acute upper respiratory tract infection. Malaria infections were monitored by activated passive case detection and parasite densities (both parasitemia and gametocytemia) were recorded. Malaria was diagnosed on detection of malaria parasites in a Giemsa-stained thick blood smear while species identification and parasite densities were obtained from thin blood smears. The parasitemia and gametocytemia were estimated by the formula used by Fleck and Moody (1993). The number of parasitized red blood cells were counted in 10 fields and an average was taken; this figure was divided by the average number of red blood cells per field and multiplied by 100, and the final figure was expressed as the percentage of parasitized erythrocytes (Fleck and Moody, 1993).

Children who were positive for *P. vivax* were treated with oral chloroquine phosphate (25mg/kg body weight) for three days and primaquine (0.25mg/kg) orally for five days; children who were positive for *P. falciparum* were treated with oral chloroquine phosphate (25mg/kg body weight) for three days and primaquine (0.75mg/kg) orally as a single dose.

The clinical severity of disease was determined in the children aged five years or above by a questionnaire that was developed and validated by Karunaweera *et al* (1992). The questionnaire contained a series of frequently associated symptoms of malaria which were scored, based on the patients perception of the symptom, as 0 if the symptom was absent, 1 if the severity of the symptom was mild, 2 if it was of a moderately severe nature and 3 if it was severe. The scores of individual symptoms were added in order to obtain a total clinical score for each child. The average score for all symptoms was calculated.

RESULTS

Characteristics of malaria infections

Six hundred and sixty-two children who had 1,138 episodes of malaria were followed up during the study. Of the 1,138 malaria infections followed, 776 were due to *P. vivax*, 359 were due to *P. falciparum*, and three were mixed infections. The distribution of the two plasmodial species among males and females was similar with 574 episodes of malaria occurring in males and 561 in females. *P. falciparum* infections were commoner in the older children. Of the 662 children, 398 experienced a single attack of malaria during the study period, while 143, 61, and 60 experienced two, three and four or more infections respectively. One third of all the malaria infections occurred in children of less than six years of age.

Characteristics of non-malarial fevers

One hundred and seventy-two children who had 202 episodes of acute non-malarial fever were followed up during the study. Of the 172 children, 145 experienced a single episode of non-malarial fever, 25 experienced two episodes while one student each experienced three and four episodes respectively. Less than 15% of the episodes were in children of less than six years of age.

Parasitemia and gametocytemia

Of the malaria infections in which para-

site counts were performed at the time of presentation, the average density of blood-stage malaria parasites (mean parasitemia) of the 763 episodes of *P. vivax* infection was significantly higher ($p<0.001$) than the mean parasitemia of the 353 episodes of *P. falciparum* infection (Table 1). Of the episodes of *P. vivax* infections 79.8% had gametocytes in the peripheral blood; in contrast, only 6.5% of *P. falciparum* infections had circulating gametocytes. The mean gametocytemia of the *P. vivax* infections was significantly greater ($p<0.001$) than that of the *P. falciparum* infections.

Clinical symptoms and signs

The prevalence of the symptoms associated with malaria and non-malarial fevers is given in Fig 1. The three most frequent symptoms identified in the children with malaria were headache (96%), feeling cold (81%) and arthralgia (77%) while the three most frequent symptoms of children with non-malarial fever were headache (94%), feeling cold (60%) and anorexia (49%) (Fig 1). Arthralgia was also a prominent symptom among children with non-malarial fevers with 48% of children experiencing it. The average clinical score for each of the symptoms for the children with malaria and non-malarial fevers is given in Fig 2. The overall severity of clinical disease was greater during a malarial infection than during a non-malarial infection.

Duration of symptoms

The majority of the children (approximately 75% for both *P. falciparum* and *P. vivax*) with malaria presented within the first three days of the onset of symptoms; in the

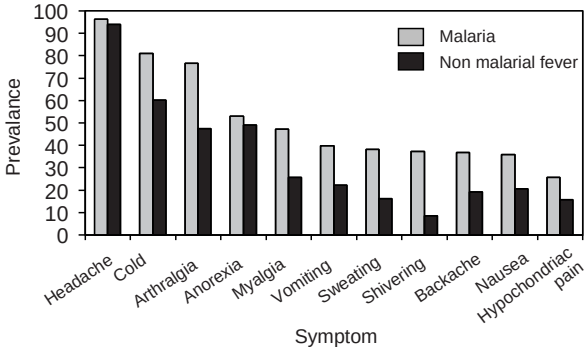

Fig 1–Prevalence of associated symptoms at the times of presentation.

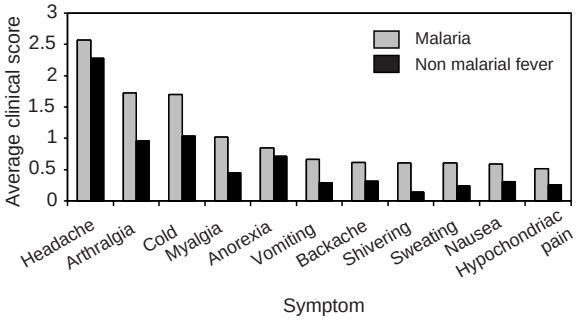

Fig 2–Average scores of individual symptoms at the time of presentation.

Table 1
Parasitemia and gametocytemia in malaria infections in childhood.

Species	Parasitemia			Gametocytemia	
	Geometric mean	SD	No. with gametocytes (%)	Geometric mean	SD
P. falciparum (n=353)	0.0066	4.593	23 (6.5)	0.0020	0.0129
P. vivax (n=763)	0.0061	2.615	609 (79.8)	0.0462	0.0560
F statistic[a]	574.81			214.99	
p-value	<0.001			<0.001	

[a]F-statistic comparing the geometric means between the two species.

Table 2
Selected characteristics of infection by past history of malaria.

Present infection	Previous infection	Clinical score (only children above 5 years)			Parasitemia (all children included in the analysis)			Gametocytemia		
		n	Mean	SD	n	Geometric Mean	SD	n	Geometric Mean	SD
P. falciparum	**Within 6 months**									
	P. falciparum	74	12.567	6.24	87	0.009	6.70	87	0.0046	0.015
	P. vivax	39	12.256	5.68	53	0.006	6.10	53	0.0004	0.002
	F statistic[a]	0.067			1.720			3.819		
	p-value	0.796			0.192			0.053		
	After 6 months									
	P. falciparum	8	11.125	7.92	9	0.003	4.21	9	0.0000	0.00
	P. vivax	16	15.125	5.67	20	0.003	10.25	20	0.0000	0.00
	F-statistic[a]	2.039			0.117			-		
	p-value	0.167			0.735			-		
P. vivax	**Within 6 months**									
	P. falciparum	27	11.703	6.01	41	0.060	4.46	41	0.553	0.068
	P. vivax	126	12.420	5.79	213	0.073	3.07	213	0.052	0.054
	F-statistic[a]	0.337			0.878			0.093		
	p-value	0.563			0.350			0.761		
	After 6 months									
	P. falciparum	11	13.091	6.72	16	0.023	8.49	16	0.0396	0.066
	P. vivax	22	11.636	5.29	28	0.074	5.15	28	0.0745	0.093
	F-statistic[a]	0.463			4.301			1.669		
	p-value	0.501			0.044			0.203		

[a]F-statistic compares the two species.

case of non-malarial fevers, almost 50% of the children presented within 24 hours of the onset of symptoms.

Severity of clinical disease

The mean total clinical scores for both *P. falciparum* and *P. vivax* infections were similar, the values being 11.55 and 11.37 respectively (p=0.673). Among malaria patients, there was no significant difference in the mean total clinical scores between male (mean total clinical score=11.24) and female (mean total clinical score=11.61) children. The mean total clinical score in the children with non-malarial fever was 6.97, the mean clinical scores of males and females being 6.50 and 7.58 respectively (data not shown).

Clinical immunity

Clinical immunity was assessed using the total clinical scores for a given parasite density. The clinical scores with successive infections increased slightly but the increase was not statistically significant.

Table 2 gives the total clinical score, parasitemia and gametocytemia of an episode of malaria by species in relation to previous infection with the homologous or heterologous species for two time intervals. A re-infection within six months with the heterologous species gives rise to a milder disease compared with infection by the homologous species. However, if the re-infection occurs after a period of six months, the disease is milder if the

infection is due to the homologous species.

Resistant *P. falciparum* infections

Forty-three *P. falciparum* infections occurred within 28 days of a previous infection. For the purposes of this study, these infections were considered to be resistant to the first-line treatment, chloroquine. On questioning the parents/guardians or the children, it was established that the correct dosage of the drug had been administered and that no other drug with anti-malarial activity was taken during the interval between the first and second visits. Of these 43 children, one child presented on the seventh day of the primary infection and was classified as having RII resistance as the parasitemia was less than 25% that of the primary infection; 12 (28%) children presented between eight and fourteen days of the primary infection, indicating RI early resistance; 30 (69.7%) children presented between fifteen and twenty-eight days of the primary infection, indicating RI late resistance.

DISCUSSION

This study describes some of the important clinical and epidemiological features of malaria in childhood in Sri Lanka. Of the 1,138 malaria infections followed up at the malaria diagnosis and treatment centers, 776 were due to *P. vivax*, 359 due to *P. falciparum* and 3 were mixed infections.

At the time of presentation, the parasitemia in *P. vivax* patients was significantly higher than in *P. falciparum* patients: this may have been due to the sequestration of cells parasitized by *P. falciparum*. Furthermore, gametocytes were present in the peripheral blood in fewer than 10% of the *P. falciparum* patients compared with 80% of the *P. vivax* patients: this was probably due to the longer time taken for the development of *P. falciparum* gametocytes. The proportion of children with *P. vivax* infections having gametocytes in their peripheral blood was higher than the 27% reported by Gunawardena (1998) from the same area. However, Gunawardena's population comprised all age groups and this may explain differences in the development of anti-parasite immunity, which in turn leads to fewer gametocytes.

The significantly lower proportion of *P. falciparum* patients having gametocytes has important implications for malaria control. If effective treatment is provided to these patients, transmission of the disease would be prevented in approximately 94% of the patients as they would be treated before the development of gametocytes. The impact of early diagnosis and prompt treatment on the transmission of *P. falciparum* is reflected in the Pv:Pf ratio in the Kataragama area, which is approximately 2:1. In the case of *P. vivax*, the impact of early diagnosis and prompt treatment on transmission may not be as marked, due to approximately 80% of patients having gametocytes at the time of presentation.

Approximately 75% of the children with malaria presented within 72 hours of the onset of the symptoms. The majority of children presented on the third day, probably following the second spike of fever. Among children who experienced acute non-malarial fevers, most children presented on the first day of symptoms, probably due to the continuous nature of the fever. The few non-malarial fevers that presented at the malaria diagnosis and treatment centers may not be a true reflection of the incidence of acute non-malarial febrile illness in the area. It is possible that children with symptoms suggestive of acute non-malarial illness would have presented at other clinics in the area which provide treatment for such illnesses in addition to malaria, unlike the malaria diagnosis and treatment centers which only provided treatment for malaria.

It has been reported that one in ten children who die of malaria in endemic areas do so at home without having had any medical attention (Greenwood *et al*, 1987). The absence of severe malaria in the population in Kataragama may be due to the provision of early diagnosis and prompt free treatment.

In populations living in areas where malaria transmission is less intense, such as Sri Lanka,

the development of clinical immunity in children, as seen in tropical Africa, is not found. During the follow up of these children over a two year period, the total clinical score, which is an indication of the degree of clinical immunity, increased with repeated infections, although not significantly. Similar results were reported among children who acquired malaria in the Lao People's Democratic Republic, where malaria transmission is similar to that in Sri Lanka, in that children did not exhibit the expected degree of immunity (Anthony and Pongvongsa, 1998). However, in the adult population in the same area of Sri Lanka, Gunawardena (1998) and Karunaweera *et al* (1998) have shown that there is acquisition of clinical tolerance following multiple malarial infections.

Two hundred and sixty-four of the 662 children experienced more than one attack of malaria. A re-infection within six months with the heterologous species gave rise to a milder disease compared with infection with the homologous species. The findings of this study are not consistent with those of Jeffrey (1966) and Gunawardena (1998) who reported that acquired immunity was very effective against the same species and strain. This is probably due to the fact that the latter study, which was conducted in the same area, included adults who had been resident in the area for a considerable period of time and would probably have developed a reasonable degree of clinical tolerance, unlike the children in this study who culturally are more protected against malaria and indulge in behaviors that expose them to less risk of infection.

During the two-year follow up period, there were 43 chloroquine resistant *P. falciparum* infections detected. Of these 43 infections, only one infection was of RII resistance, the rest being of RI resistance. The proportion of resistant *P. falciparum* infections in this population is lower than that previously reported from both the same area, and Sri Lanka in general, an estimated 30-40% (Handunnetti *et al*, 1996); this discrepancy is hard to explain.

The clinical and epidemiological features of malaria in childhood in this study have important implications for the planning and targeting of effective preventive measures: vital in developing countries such as Sri Lanka. The lack of development of an appreciable level of immunity in the age group studied, in an area of moderate intensity of malaria transmission, makes it important to provide adequate diagnostic and treatment services to reduce morbidity and mortality. The symptom profile of children with malaria and non-malarial fevers being similar, it is essential that a reliable method of diagnosis other than clinical diagnosis should be available. Van der Hoek *et al* (1998) reported that clinical diagnosis is not a reliable method of diagnosing malaria. Given the large amounts of resources that are being invested in human development programs such as school education, it is necessary to provide the basic healthcare services that are needed to address diseases of public health importance in this particular age group so that the maximum benefits of the investments will be reaped.

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