Patterns of Acquired Anti-Malarial Immunity in Sri Lanka

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Malaria has been endemic in large parts of Sri Lanka for most of this century and probably throughout historical times. The endemic part of the island comprises the dry zone of Sri Lanka occupying the southern and eastern two thirds of the country. We have established a study area in a rural population surrounding the small town of Kataragama in the far south of Sri Lanka. In this region *Plasmodium vivax* malaria has been endemic for at least two decades since the break down of the malaria eradication programme in the late 1960's. Since about 1987 there has been in addition a resurgence of *P. falciparum* malaria which had been largely absent from this population since before the start of the malaria eradication campaign in the mid 1950's. At the time of the study reported here the case incidence rate of both species together in the region around Kataragama was roughly 1 per person per year, although the distribution of infections throughout the population was quite uneven. In the present investigation we have attempted to record the patterns and nature of immunity to malarial infection aquired in this endemic region of Sri Lanka.

MATERIALS AND METHODS

A study population of 1,942 individuals in the malaria endemic region around Kataragama was selected and monitored over an 18 month period between January 1992 and July 1993 by passive case detection. A field clinic was established in the viscinity within 2 kilometers of all members of the study population. A data base was formed which included full census details of the study population and records of every attendance at the field clinic together with parasitological and clinical records of all cases diagnosed positive for malarial infection. During the period of the study 1,748 cases of malarial infection were recorded. These included 1,000 cases of *P.vivax* and 744 cases of *P. falciparum*; 4 cases of mixed infection were found. The cases were not evenly distributed within the study population; 1,168 individuals did not report to the clinic with malarial infection during the study; 357 individuals reported with a single malarial infection during the course of the study; 417 individuals reported twice or more with malaria.

The data collected was analysed to determine the effects of successive infections of homologous or heterologous infections of *P.vivax* or *P. falciparum* on clinical disease and parasitaemia. Clinical disease was recorded according to a score sheet of symptoms each of which was accorded a severity score by verbal interview with the patient (Karunaweera et al. unpublished). The sum of the individual scores for different symptoms was used as the total clincal score for an individual patient. In our system the maximum achievable clinical score is 33.

In addition to the absolute clinical score, as described above, we have also calculated a clinical score per parasite for each patient in order to reflect clinical severity of infection in relation to the density of circulating parasites at the time of presentation. This value was calculated by dividing the clinical score by the % parasitaemia at the time that the patient presented at the clinic. The % parasitaemias, absolute clinical scores and clinical scores per parasite were analysed for: (i) "1st" infections of *P. vivax* or *P. falciparum* (only those infections from at least 6 months after the start of the study are included in the "1st" infection category to ensure that at least this period of time had elapsed since a previous infection); (ii) infections preceeded by one recorded clinical episode of one or other species and (iii) infections preceeded by more than one such episode.

In making the present analysis the median value (ie. the value at the centre of the distribution of

values in the study group) of each parameter was used to make comparisons between data sets.

RESULTS

Taking account of the total number of cases recorded during the study period, the absolute clinical scores for both *P. vivax* and *P. falciparum* infections were similar, the median scores being 13.0 and 13.3 respectively.

In successive infections with the homologous species of malaria parasite (ie *P.vivax* following *P.vivax* or *P.falciparum* following *P.falciparum*) the absolute median clinical scores fell for both species of parasite. The drop in score from first recorded infection to that after at least two previous homologous infections was greater for *P.vivax* (from 13.0 to 9.2) than for *P.falciparum* infections (from 13.3 to 11.0).

Calculation of clinical score per parasite at the time of presentation, however, showed up major differences between infections due to the two species. Almost 4 times as many peripheral blood parasites were associated with the absolute median clinical score of "1st" *P.vivax* infections as were associated with "1st" infections of *P. falciparum*. Thus the "clinical burden" per peripheral circulating parasite appeared to be almost 4 times as great for *P. falciparum* as for *P.vivax*.

In successive infections with *P.vivax* the clinical score per parasite fell relatively much further than did the clinical score itself. Thus the clinical score per parasite after "multiple" homolgous infections of *P.vivax* was on average only 27% of that in the "1st" infections. By contrast the average clinical score per parasite after "multiple" homologous infections of *P.falciparum* was 87% compared to that in "1st" infections of this species.

Thus in the context of the present study population successive infections of *P. vivax* appeared to induce a much greater degree of clinical tolerance or immunity to circulating parasites than did successive infections of *P. falciparum*, which actually induced very little such tolerance.

We also examined the effect of successive infections of the heterolgous species on the acquisition of clinical tolerance to each species of parasite. Successive infections of *P. falciparum* appeared to have little effect on clinical tolerance to a subsequent *P. vivax* infection. By contrast, successive infections of *P. vivax* conferred a degree of clinical tolerance to a subsequent *P. falciparum* infection which was similar to that to a homologous *P. vivax* infection, as described above.

Thus our results indicate that successive *P.vivax* infections within a period of a few months to a year led to a marked degree of clinical tolerance of circulating parasites of either *P. vivax* or *P. falciparum*. Successive infections of *P. falciparum*, on the other hand, had little or no effect on the clinical response to circulating parasites of either species in this study.

In spite of the evidence given here for the induction of clinical tolerance to blood parasites of *P. vivax* and *P. falciparum* following successive infections of the former, there was no evidence that there was a general increase in tolerance with age in the endemic population as measured by passive case detection. Indeed tolerance to both species of malaria was lower in the older sections of the population than in the younger.

Mass blood surveys of the total population showed that parasite densities were slightly lower in the older age groups (>20 years) compared to younger age groups (<20 years) and that this reduction in parasite densities was to a similar degree for both *P.vivax* and *P.falciparum*. This suggests that a small degree of anti-parasitic immunity may have been acquired with age in this population.

DISCUSSION

The conditions of malaria transmission at Kataragama have offered an ideal opportunity to study the acquisition of immunity to both *P. vivax* and *P. falciparum* under conditions of moderate endemicity and to examine the interactions between these species of parasite on immunity to each. Our results indicate that there is relatively little age-acquired increase of anti-parasitic immunity to either parasite in this community. Nor did clinical tolerance to infection to either parasite species increase with age or duration of residence in the Kataragama area. There was indeed a steady decline in clinical tolerance to circulating parasites as the age of members of the population increased.

In spite of these observations, however, there was strong evidence that successive infections of *P.vivax* within a few months of each other led to marked increase in clinical tolerance of infection. The clinical tolerance induced by *P. vivax* was, moreover, almost as effective in protecting against

subsequent *P. falciparum* infections as it was against *P. vivax*. By contrast there was little evidence that *P. falciparum* infections induced clinical tolerance either to subsequent homologous infection or to heterologous infection with *P. vivax*.

These results indicate that clinical tolerance to malarial infection is elevated as a result of successive malarial infections within a few months but that these infections did not lead to a progressive age acquired increase in clinical tolerance of malarial infections under the transmission conditions at Kataragama. This would be consistant with the absence of any long term memory for such tolerance. It is noteworthy, however, that the overall level of clinical tolerance to malarial infection in this population from an area of moderate endemicity is, nevertheless, considerably greater than that of patients from non-endemic areas such as we have observed attending the General Hospital in Colombo, the capital of Sri Lanka (Karunaweera et al. unpublished data). We suggest that the rate of inoculations experienced in the Kataragama population is such as to maintain an equilibrium level of clinical tolerance significantly greater than that experienced by non-endemic patients but well short of complete clinical tolerance to infection.

We also note with interest the progressive decline with age in the degree of clinical tolerance in the Kataragama population. This, we suggest, could reflect innate changes in the immuno/pathophysiological status of human beings as they age.

The clinical tolerance to malarial infection found in these studies was induced by *P. vivax* only and not to a great degree by *P. falciparum*. The tolerance induced by *P. vivax* was, however, almost as effective against *P. falciparum* as it was against the homologous species. This observation seems to imply, on the one hand, a lack of species specificity as regards the effector limb of the induced clinical tolerance while, on the other hand, indicating a species-specific difference, at least in efficiency, between the two species of parasite in their ability to induce the tolerance.

REFERENCE

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