TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE (2003) 97, 198–199

Increased frequency of malaria attacks in subjects co-infected by intestinal worms and *Plasmodium falciparum* malaria

André Spiegel[1], Adama Tall[1], Georges Raphenon[2], J.-F. Trape[3] and Pierre Druilhe[4] *[1]Unité d'Epidemiologie, and [2]Laboratoire d'Analyse Médicale, Institut Pasteur de Dakar, B. P. 220, Dakar, Sénégal; [3]Laboratoire de Paludologie, Institut pour la Recherche et le Développement, B. P. 1386, Dakar, Sénégal; [4]Unité de Parasitologie Biomédicale, Institut Pasteur, 28 rue du Dr Roux, 75015 Paris, France*

Abstract

The influence of intestinal worm infections on malaria was studied in individuals from Dielmo, Senegal in 1998. Results suggest that, compared with those infected, individuals free of helminths had the same degree of protection against malaria as that provided by sickle-cell trait, the most potent factor of resistance to malaria identified to date.

Keywords: malaria, *Plasmodium falciparum*, helminths, sickle-cell trait, Senegal

Introduction

We have previously observed that the immune response to malarial antigens was biased towards non-cytophilic antibody classes in children and adolescents, compared with adults where the cytophilic classes immunoglobulin (Ig) G1 and IgG3 predominated (Bouharoun & Druilhe, 1992).

In view of the demonstrated effect of cytophilic antibodies in cooperation with blood monocytes (Bouharoun & Druilhe, 1992), this observation provided one of the first clues to explain the long delay in the establishment of protective immunity to malaria under conditions of natural exposure. It also suggested that artificial immunization by vaccines with appropriate ajduvants may directly induce cytophilic classes of antibodies. It was, however, unclear why a non-cytophilic humoral response imbalance prevailed in children in endemic areas and why this persisted for so many years. We formulated the hypothesis that very high helminth loads prevailing in children, compared with adults, could account for this phenomenon. Indeed the induction of T helper type 2 lymphocyte-related cytokines by worms, particularly interleukin 4, could influence the isotype switch in malaria-specific lymphocytes and therefore bias the antibody response.

Preliminary support for this hypothesis was obtained from observations in 2 cohorts of age-matched (2–15 years) children in Madagascar, one treated with levamisole, the other receiving vitamin C as a placebo. Although there was an unchanged prevalence of malaria attacks during the first year of follow-up, a marked and significant decrease of parasite prevalence, spleen rate and malaria attack rate was observed during the second year of study in the group treated with anthelmintics compared with the controls (Jambou *et al.*, 1998).

Since levamisole has immunomodulatory properties, we looked for a situation where no therapeutic intervention would be needed, i.e. where individuals with similar characteristics of age and exposure, but some already carrying intestinal worms and others not, could be followed-up.

Materials and Methods

We used the existing set-up of Dielmo in Senegal, where numerous malaria studies, and particularly extremely close monitoring of clinical attacks, have been in place for more than 10 years (Trape *et al.*, 1994). The inhabitants receive free medical care and, after initial haematological, biochemical, clinical, and parasitological check-ups, all intestinal parasite infections detected were treated in 1989.

Our study took place in May 1998, involving a detailed stool examination of 80 children aged 1–14 years (1 year, 6 individuals; 1–4 years, 23; 5–9 years, 36; 10–14 years, 15). This revealed that 13 of the 80 children had been reinfected, 5 by *Ascaris lumbricoides*, 6 by *Ancylostoma duodenale* and 3 by *Trichuris trichiura*. The clinical–epidemiological set-up in the village of Dielmo provides very close monitoring of malaria as it includes a daily follow-up (24 h per day, 7 d per week) of the 247 inhabitants on a year-round basis (Trape *et al.*, 1994). Moreover, we had developed a stringent diagnostic criterion, the pyrogenic threshold of parasite density, characteristic of each age group, to distinguish malaria from other fevers (Rogier *et al.*, 1996). For the study of the influence of intestinal worms, we relied on those clinical attacks of malaria detected during the 6 months preceding the stool examination (November 1997–April 1998) and during the 6 months following the stool examination (May–October 1998). As a positive control for factors which influence the number of malaria attacks, we relied on 9 worm-free children who carried the sickle-cell trait, which influences occurrence of malaria attacks and has been widely documented in other studies and confirmed in Dielmo (Dieye *et al.*, 1997). During this 1-year follow-up of the cohort of 80 children, a total of 27 243 person-day clinical observations were analysed and a total of 313 malaria attacks were identified (66 in those carrying worms and 247 in those who were not). For statistical analysis, we employed the Poisson regression and calculated the adjusted incidence density rate (IDR) where the effect of age and the use of bednets in the population under study are taken into account. The results were expressed as the relative risk (RR) of presenting with a malaria attack in each age group, in the helminth-carrying individuals and in the individuals with haemoglobin S, for the 1-year study period.

Results

The risk of presenting with a clinical malaria attack increased in subjects with intestinal worms (RR = 1.54, $P = 0.003$) compared with helminth-free children. As in other studies, the influence of age was marked; conversely, the influence of glucose-6-phosphate dehydrogenase deficiency or the use of bednets were not significant.

When the same analysis was applied to those subjects with normal haemoglobin (AA) or sickle-cell trait (AS or SS), the strong protective effect of sickle-cell anaemia was confirmed (12 malaria attacks vs. 301 in AA individuals). Interestingly, the RR of presenting a malaria attack in people with normal haemoglobin was increased compared to those with haemoglobin S, in the same proportion (RR = 1.65, $P = 0.006$) as in the helminth carriers compared to helminth-free indivi-

Address for correspondence: Pierre Druilhe, Unité de Parasitologie Bio-Médicale, Institut Pasteur, 25 Rue du Dr Roux, 75015 Paris, France; phone +33 1 45 68 85 78, fax +33 1 45 68 86 40, e-mail druilhe@pasteur.fr

duals. In other words, for the 1-year follow-up, the protection afforded by the sickle-cell trait was of the same magnitude as that of being free of helminth infection.

Conclusions

Our study confirmed the initial indications obtained in the smaller group followed-up in Madagascar and excludes the possibility of an immunomodulatory role of levamisole in those results. Our results indicate that the lack of helminth infection conferred the same degree of protection against malaria as that provided by sickle-cell trait carriage, the most potent factor of resistance to malaria identified to date.

The fact that the results are significant despite the relatively small size of the cohort studied suggests that the influence of worm infection is strong. These observations need to be repeated in other settings and with larger cohorts since, if confirmed, they may provide a simple and very low-cost means of reducing the clinical malaria burden. We therefore hope that our initial results will stimulate further investigations in the same direction.

Acknowledgements

We are grateful to the villagers of Dielmo for their active participation and continuing collaboration in the project, and to all members of the research team from Institut Pasteur, IRD and the University who contributed to this study.

Ethical statement

The project was explained in detail to the village population, and implemented only after receiving consent from them or their parents; it was approved by the national Ethical Committee of the Republic of Senegal.

References

Bouharoun, H. & Druilhe, P. (1992). *Plasmodium falciparum* malaria: evidence for an isotype imbalance which may be responsible for delayed acquisition of protective immunity. *Infection and Immunity*, **60**, 1473–1481.

Dieye, A., Rogier, C., Trape, J.-F., Sarthou, J.-L. & Druilhe, P. (1997). A parasitological re-assessment of the HLA-Class-I associated resistance to severe malaria. *Parasitology Today*, **13**, 48–49.

Jambou, R., Rasamoel, P., Ralamboranto, L., Milijoana, R., Raharimalala, L., Pecarere, J. L. & Druilhe, P. (1998). *Change in response to malaria induced by repeated treatment of children with levamisole.* Paper presented at Malaria, Gordon Research Conference, Somerville College, Oxford, UK, 26–31 July 1998.

Rogier, C., Commenges, D. & Trape, J.-F. (1996). Evidence for an age-dependent pyrogenic threshold of *Plasmodium falciparum* parasitemia in highly endemic populations. *American Journal of Tropical Medicine and Hygiene*, **54**, 613–619.

Trape, J.-F., Rogier, C., Konate, L., Diagne, N., Bouganali, H., Canque, B., Legros, F., Badji, A., Ndiaye, G., Ndiaye, P., Brahimi, K., Faye, O., Druilhe, P. & Pereira da Silva, L. (1994). The Dielmo project. A longitudinal study of natural malaria infection in a community living in a holoendemic area of Senegal. *American Journal of Tropical Medicine and Hygiene*, **51**, 123–137.

Received 23 August 2002; revised 4 October 2002; accepted for publication 11 October 2002

Book Review

Essential Malariology, 4th edition. David A. Warrell & Herbert M. Gilles (editors). London: Arnold, 2002. xii + 348 pp. Price £65.00. ISBN 0-340-74064-7.

In the intervening decade since the 3rd edition of *Bruce-Chwatt's Essential Malariology*, the complete genome sequence of *Plasmodium falciparum* has been determined and new, major disease control initiatives are again under way; the forthcoming demise of this parasite has never looked more likely. Unfortunately, in terms of global reduction of disease burdens and associated transmission, malaria has a long, chequered history of dashed hopes and abandoned dreams. For reasons succinctly stated by the editors in their opening preface, effective control of malaria, this quintessential tropical malady, has often proven to be a challenge in excess of what medical science can offer.

Malariology should not be judged upon these grounds alone. Few would disagree that great advances have been made and many lives have been saved. Recent progress in laboratory studies, clinical case management, and mosquito biology all receive attention and this 4th edition of *Essential Malariology* takes a comprehensive, up-to-date tour covering all aspects, current and old, pertinent to a practical understanding of this disease. In short, this compact single volume is highly erudite and beautifully illustrated, inclusive of 39 colour plates. Clearly the authors, editors and publisher have taken great care to arrange this book into a clear, concise synthesis.

The book's format is well structured throughout; each chapter also contains a useful reference list. *Essential Malariology*'s content is, in part, a little too demanding even for the keen postgraduate or newly qualified clinician, and this hardback is also slightly overpriced for this audience. It would, however, be a very sound investment for those who are committed to pursuing a career involving this important and uniquely fascinating disease. From this perspective the book's clear format and structure set a standard to which other tropical disease texts should aspire. It is a truly exemplary treatise.

Starting with a historical outline and finishing with progress in malaria vaccination and clinical trials, the 13 chapters are carefully set out, originating singularly or jointly from a highly distinguished international panel of 19 contributing authors. The interface between clinical and scientific disciplines is well bridged. Traditional aspects, e.g. parasitology, diagnostic methodology and vector control, are also given good airings. I particularly liked the book's appendix where a checklist of the major anopheline vectors was provided. There are also 3 informative chapters on clinical features of the disease as well as another 3 on immunology, pathology and treatment/prevention.

Without wishing to be unduly negative, on putting the book down I felt oddly disquieted. The tone of this synthesis is too retrospective and it is strangely weak on future areas of development within malariology in terms of further basic research and its translation into operational control methods. Quality books such as this should not only set out to educate their readers, which this does admirably, but also provide them with guidance on where key priorities lie. The contemporary debate of 'bednets or genomics' received scant analysis and, as a hypothetical example, which of the following would be most worthwhile pursuing: development of real-time polymerase chain reaction methods for better parasite detection, creation of transgenic mosquitoes refractory to infection, or detailed population genetic studies of *Plasmodium* spp. for drug resistance monitoring? Perhaps we just have to work these out for ourselves.

J. Russell Stothard

Biomedical Parasitology Division
Department of Zoology
Natural History Museum
Cromwell Road
London SW7 5BD, UK