Hyperreactive malaria in expatriates returning from sub-Saharan Africa

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Summary

The extreme presentation of hyperreactive malaria is hyperreactive malarial splenomegaly syndrome (HMS). Some patients present with a less pronounced syndrome. To investigate whether the degree of splenomegaly correlates with the degree of immune stimulation, whether prophylaxis or recent treatment play a role, and whether short therapy alone is effective, we examined retrospectively the medical records of expatriates with exposure to \textit{P. falciparum} who attended our outpatient department from 1986 to 1997, particularly subacute symptoms or signs, strongly elevated malarial antibodies and elevated total serum IgM. We analysed duration of stay, prophylaxis intake, spleen size, serum IgM levels and response to antimalarial treatment. Serum IgM levels were significantly higher in patients with larger splenomegaly. The use of chloroquine alone as treatment for presumptive or proved malaria attacks was correlated with larger spleen size. Short adequate antimalarial therapy resulted in marked improvement or complete recovery. In nine patients the hyperreactive response reappeared after re-exposure, in four of them twice. We conclude that patients with subacute symptoms but without gross splenomegaly may have very high levels of IgM and malarial antibodies, and relapse on re-exposure, suggesting the existence of a variant of the hyperreactive malarial splenomegaly syndrome without gross splenomegaly.

keywords malaria, hyperreactive malarial splenomegaly, splenomegaly

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Introduction

In 1981 Fakunle set major and minor diagnostic criteria for the tropical splenomegaly syndrome (Table 1). Splenomegaly, elevated antimalarial antibodies, serum IgM > 2 SD above the mean of a given population, and favourable response to long-term treatment or prophylaxis are mandatory criteria. In 1983 an international group proposed to replace the former denomination ‘tropical splenomegaly syndrome’ (TSS) with ‘hyperreactive malarial splenomegaly’ (HMS), in order to differentiate splenomegaly of obscure origin from splenomegaly related to malaria (Bryceson et al. 1983).

Repeated malaria infections provide strong stimulatory signals to human B lymphocytes. This B-cell activation is partly T-cell dependent and antigen-specific, resulting in the generation of large amounts of malarial antibodies. Plasmodial proteins, however, also stimulate B cells directly in an antigen-nonspecific way, causing the production of polyspecific IgM including auto-antibodies (e.g. rheumatoid factor) and nonsense IgM, which is typically polyclonal (Jimmy et al. 1996). A functional CD8 T-cell defect has been proposed as the mechanism of both specific and nonspecific IgM overproduction in HMS (Hoffman et al. 1984). One group has claimed that CD8-specific auto-antibodies induced by malaria cause the suppressor defect, but their observation has yet to be confirmed (Piessens et al. 1985).

At the end of the 1980s subacute malaria became more frequent in travellers and residents returning from malarious countries, probably due to the emergence of chloroquine-resistant \textit{P. falciparum} strains and partial suppression of the infection by ineffective prophylaxis or treatment (Sansonetti et al. 1986; Charmot & Coulaud 1988; Van Gompel et al. 1991). Some patients with subacute malaria develop high
J. Van den Ende et al. Hyperreactive malaria in expatriates

Major diagnostic criteria: always present

- gross splenomegaly in older children and adults
- high antibody levels for *P. falciparum*
- elevated serum IgM (at least 2 standard deviations above the mean of the population)
- clinical and immunological response to long-term appropriate therapy

Minor diagnostic criteria

- hepatic sinusoidal lymphocytosis (> 80% of cases)
- normal cellular and humoral immune responses to antigenic challenge, included PHA
- hypersplenism
- lymphocyte proliferation (in some populations)
- occurrence within families, tribes

**Table 1** Diagnostic criteria for hyperreactive malarial splenomegaly (Fakunle 1981)

<table>
<thead>
<tr>
<th>Major diagnostic criteria: always present</th>
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<td>- gross splenomegaly in older children and adults</td>
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<td>- clinical and immunological response to long-term appropriate therapy</td>
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Patients and methods

From January 1986 to December 1997 we examined 49 expatriates with subacute malaria and a hyperreactive response in the outpatient department of the Institute of Tropical Medicine, Antwerp, Belgium. The patients fulfilled the following criteria: recent residence in a country endemic for *P. falciparum*; subacute symptoms (fever, weight loss, night sweats or fatigue) or signs (splenomegaly or haemolysis) without symptoms of acute malaria; strongly elevated malarial antibodies; and elevated total serum IgM (IgM > 350 mg/dl).

Spleen size was classified in three groups: a negative spleen palpation or a sonographic maximum diameter 14 cm or less was regarded as no splenomegaly; palpable spleen less than four fingers below the costal margin or maximal sonographic diameter between 14 and 18 cm was regarded as mild splenomegaly; a diameter of 18 cm or more, or a spleen that descended at least four fingers below the costal margin was reported as gross splenomegaly. In the case of a 6-year-old patient, a splenic diameter of 13 cm was considered as gross splenomegaly (this case has been described in detail elsewhere (Van den Ende et al. 1994).

Relevant laboratory results included a thick film and a peripheral blood smear, full blood cell count, reticulocyte count, serum haptoglobin, lactate dehydrogenase, total gammaglobulin content, IgG and IgM immunoglobulin content. Until 1993 the parasite load was determined as the number of trophozoites in 100 high power fields (10×) in a thick film. From 1994, the parasite load was given in parasites/μl. With a sample of thick films read both per field and per μl, we calculated that one parasite per one field equalled on average 839 per μl.

Malarial antibodies were measured by indirect immunofluorescence (IFAT) (Voller & Draper 1982). In the first years of the study dilution was limited to 1/640, but in recent years extensive titration was ordered, hence the cut-off for strongly elevated malarial antibodies was 1/640 before 1994, but 1/5120 after 1994.

The following work-up was added to exclude other concomitant diseases associated with splenic enlargement: determination of urea, creatinine, uric acid, bilirubin, liver enzymes; serologic testing for HIV, syphilis, hepatitis B, schistosomiasis, filariasis, amoebiasis; serum protein electrophoresis; urinalysis; parasitology of faeces with concentration technique (Loughlin & Spitz 1947); chest X-ray; ultrasound of liver, spleen and kidneys. Blood cultures, serologic testing for trypanosomiasis, leishmaniasis and brucellosis, a Coombs test, search for auto-antibodies and determination of osmotic resistance of erythrocytes were added if indicated.

Statistical analysis

The EPI-INFO program (CDC, WHO) was used. For comparison of dichotomous variables we used the chi-square test, and for comparison of continuous variables between groups the Kruskall–Wallis test.
Results

Detailed description of two typical cases

A 51-year-old Belgian mechanic had been working in Eastern Zaire for 6 years. He had a negative medical history and denied malaria prophylaxis intake during the last years. In April 1989 he developed a malaria attack and was treated with quinine. His fever disappeared, but he continued to complain of fatigue, weight loss, night sweats and diarrhoea until August 1989, when he attended the outpatient department of the Institute for Tropical Medicine, Antwerp, five days after returning to Belgium. Clinical examination revealed gross splenomegaly, confirmed sonographically (maximal diameter of 19 cm). Laboratory investigations gave the following results: negative thick smear, haemoglobin 11.6 g/dl, reticulocyte count 3.7%, sedimentation rate 74 mm/h, haptoglobin level 10 mg/dl (normal > 50), lactate dehydrogenase 259 IU/dl (normal < 240), malarial antibodies 1/10240, serum IgG 3110 mg/dl and serum IgM 2160 mg/dl. The patient received one-day treatment with mefloquine 1500 mg/24 h. After 2 weeks he was free of symptoms, except for some fatigue. Clinical examination showed an unchanged spleen. Most laboratory values were identical, with the exception of the sedimentation rate which had decreased to 54 mm/h, and serum IgM which had dropped to 1350 mg/dl. Mefloquine treatment was repeated once. The patient returned to Zaire with a prophylaxis of proguanil 200 mg/day and chloroquine 300 mg/week and was seen again 7 months later. He had complied with chemoprophylaxis and was free of malaria attacks. He had no complaints. The maximum diameter of the spleen was 15 cm. The sedimentation rate was 15 mm/h, haemoglobin 15 g/dl, haptoglobin 73 mg/dl, antiplasmodial antibodies 1/2560, IgM 229 mg/dl.

A 62-year-old Belgian missionary, living in Zaire since 1957, had a medical check-up in 1984, without complaints. Physical examination was normal. An anti-*P. falciparum* IFAT titre of > 1/640 was detected. Malaria prophylaxis was proposed, but neglected. In 1986 he consulted with diarrhoea, vomiting and weight loss of 8 kg. A thorough work-up could not elicit an aetiology for the diarrhoea. No spleen was felt on abdominal palpation. Sedimentation rate was 81 mm/h, the thick film contained rare trophozoites of *P. falciparum*, malarial antibodies exceeded 1/640 and serum IgM content was 1295 mg/dl. Chloroquine was prescribed. The patient spent 6 months in Belgium, and the sedimentation rate dropped to 21 mm/h. In Zaire he again neglected malaria prophylaxis, and returned to Belgium in 1989 with diarrhoea, fatigue and weight loss. Physical examination was negative. The thick film did not show parasites, the sedimentation rate was 63 mm/h, the malarial antibodies 1/5120, and the serum IgM 1720 mg/dl. Antinuclear antibodies were 1/80. Circulating immune complexes were detected. The maximum sonographically measured diameter of the spleen was 15 cm. Again, no cause for the diarrhoea was detected. After initial treatment with quinine and doxycycline, mefloquine (1500 mg in one day) was added because laboratory parameters did not improve. After two months, all symptoms had disappeared, including the diarrhoea. The sedimentation rate had dropped to 35 mm/h and IgM to 910 mg/dl. Prophylaxis with chloroquine 300 mg once a week, and proguanil 200 mg/day, was prescribed. This time, prophylaxis was regularly taken, but in 1992 diarrhoea and weight loss recurred. Physical examination was negative. Haemoglobin was 11.8 g/dl and the sedimentation rate 102 mm/h. A thick film showed four trophozoites of *P. falciparum* per 100 microscopic fields (10 × 100). Malarial antibodies ranked as high as 1/10240 and IgM was 2680 mg/dl. Anticytoplasmatic antibodies were 1/5000 with a speckled pattern. The spleen was not enlarged sonographically. One-day treatment with halofantrine (1500 mg) was prescribed. The patient remained in Belgium. After 6 months he was symptom-free, the sedimentation rate was 38 mm/h, the malarial antibodies 1/10240, the IgM 925 mg/dl and the anticytoplasmatic antibodies 1/640.

Analysis of the study population

Of the 49 patients, 43 (86%) were Belgian, two Greek, one Arabic, one Italian and two Spanish. The median age was 58 (range 10–76), the sex ratio 3.9 (39M : 10F). All were residents in Sub-Saharan Africa, and the median duration of residence was 32 years (range 5–48 years). One patient became symptomatic 18 months after leaving Africa. Thirty-six patients had returned to Belgium less than 1 month earlier, 13 consulted one month or later after return (median 11 days).

For 40 patients, reliable data on prophylaxis intake were available: 16/40 (40%) took regular, 3/40 (7%) took irregular and 21/40 (52%) took no prophylaxis. Only three patients took regimens that at that time could be considered adequate in a region with increasing chloroquine resistance: two took chloroquine 300 mg/week plus proguanil 200 mg/day, one took Maloprim® (pyrimethamine-dapsone) one tablet/week. Five of 10 patients (50%) without splenomegaly took regular prophylaxis, as did 5/13 (38%) with mild, and 6/17 (35%) with gross splenomegaly (*P* = 0.74). Twenty-four patients reported one or more presumptive or proved malaria attacks in the previous 6 months. Eleven of these patients used only chloroquine as curative treatment. There was no significant correlation between the presence of previous attacks and spleen size (*P* = 0.36), but among those with previous attacks, the use of chloroquine alone was correlated with larger spleen size (*P* = 0.03).

Forty-two (85%) patients had symptoms, 38 (77%)
had constitutional symptoms, mainly irregular fever or sub-acute low grade fever (19/38), fatigue (28/38) or weight loss (22/38). Symptoms lasted for a median of 3 months (range 0–12 months). Seventeen patients had gross splenomegaly, 19 mild and 13 no splenomegaly. There was no significant difference between the three splenomegaly classes in occurrence and duration of symptoms in general, or in presence of constitutional symptoms.

The thick film was positive in 27 patients. Twenty-four had low parasitaemia (< 1 parasite per field or < 839 parasites per μl), the highest parasite load was 8/field. A positive thick film was not correlated with splenomegaly class (P = 0.55). The mean serum IgM level and the sedimentation rate were correlated with splenomegaly class (P = 0.003, res. P = 0.001) (Table 2). Haemoglobin and thrombocytes were not. Forty-two of the patients had laboratory evidence of ongoing haemolysis. Lowering of all three cell-lines (erythrocytes, leucocytes and thrombocytes), suggesting hyper-splenism was present in 4/16 (25%) of the gross splenomegaly group, in 3/17 (17%) of the mild splenomegaly group, and in 2/13 (15%) of the nonsplenomegaly group (P = 0.78).

Thirty-nine patients were followed for at least 2 weeks in Belgium (median 6 weeks). In all patients, classical short antimalarial therapy resulted in clear improvement of all parameters or led to complete recovery. In nine patients the syndrome reappeared at least once after re-exposure, in four it reappeared twice. Two patients (e.g. case report 2) relapsed despite reported regular prophylaxis with chloroquine/ proguanil.

**Table 2** Comparison between splenomegaly classes

<table>
<thead>
<tr>
<th>Splenomegaly</th>
<th>none n = 13</th>
<th>mild n = 19</th>
<th>gross n = 17</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgM* mean</td>
<td>763</td>
<td>817</td>
<td>1640</td>
<td>0.003</td>
</tr>
<tr>
<td>IgM* range</td>
<td>399–1440</td>
<td>420–1620</td>
<td>471–4310</td>
<td>0.55</td>
</tr>
<tr>
<td>ESR † mean</td>
<td>54</td>
<td>50</td>
<td>87</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* IgM: immunoglobulin M, mg/dl
† ESR: sedimentation rate, mm/1 h

Discussion

Classically, there is a latent period of 5–10 years of exposure to malaria preceding the development of clinically recognizable HMS (Fakunle 1981). We found that prolonged residence in endemic areas is apparently also a prerequisite for hyper-reactive immune stimulation in subacute malaria.

In the presence of very high malarial antibodies and a high level of IgM, and in the absence of other causes of splenomegaly after a thorough work-up, no attempt was made to confirm the diagnosis of HMS with liver biopsy, which is considered a minor criterion and not useful for patient management purposes (De Cock et al. 1987). Although enlargement and lymphocytic infiltration of hepatic sinusoids was formerly referred to as a pathognomonic sign, it is also seen in Felty’s syndrome, non-tropical idiopathic splenomegaly or Dacie’s syndrome, hairy-cell leukaemia, malignant histiocytosis, mononucleosis, and in cases of chronic lymphocytic leukaemia with high IgM production (Crane 1986).

Thirteen patients consulted one month or later after return, one patient after 18 months. Apparently, mere withdrawal of exposure was not sufficient for disappearance of symptoms. All patients who could be followed had gradual improvement of all parameters after treatment with one of the classical antimalarial regimens. We conclude that there is no need for long-term treatment or prophylaxis outside endemic regions.

We observed the effect of short treatment in the absence of re-exposure, instead of the effect of prophylaxis, originally required in the major criteria for HMS set by Fakunle. If we omit this criterion, we can state that 17 patients had HMS. The other patients met all other major criteria except for gross splenomegaly. We question whether HMS is a distinct syndrome rather than the endpoint of a spectrum of hyperreactive malaria, as suggested by the correlation of spleen size with IgM content, which reflects immune stimulation. Some authors also found that IgM content follows spleen size, and that this is rather a continuum. (Stuiver 1974; De Cock et al. 1986; Brabin 1988).

The tendency towards relapse on re-exposure in three patients with mild or absent splenomegaly, even with (reportedly) correct prophylaxis in one patient, supports the impression that they were affected by a syndrome similar to HMS. One could argue that these patients returned to a highly endemic region, and protected themselves poorly against mosquito bites. The subacute and constitutional nature of symptoms, and the recurrence despite correct prophylaxis in two cases, point towards a pathogenesis other than classical malaria.

The rarity of imported hyperreactive malaria is a major obstacle to further research. We need to define the exact role of prophylaxis and irregular treatment, and to determine if anti-CD8 antibodies could help in distinguishing between presentations. Research should also address the impact of the hypothetical endemic counterpart of this hyperreactive syndrome without gross splenomegaly on morbidity in tropical countries.

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Hyperreactive malaria in expatriates

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