Short Report: Treatment of Suspected Hyper-Reactive Malarial Splenomegaly (HMS) in Pregnancy with Mefloquine

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Abstract. Malaria infections in pregnancy are associated with adverse outcomes for both mother and child. There are few data on hyper-reactive malarial splenomegaly, an aberrant immunological response to chronic or recurrent malaria in pregnancy. This retrospective assessment reviewed the impact of mefloquine treatment on pregnant women with suspected hyper-reactive malarial splenomegaly in an area of low malaria transmission in the 1990s, showing significant reductions in spleen size and anemia and anti-malarial antibody titers without any notable negative effect on treated women or their newborns.

Malaria infections in pregnancy are associated with distinct epidemiological, pathophysiological, and clinical features, including a greater risk of complications during the acute course of the illness and adverse outcomes for both the mother and her child.[1,2] Hyper-reactive malarial splenomegaly (HMS; historically known as Tropical Splenomegaly Syndrome" [TSS] or "Big Spleen Disease") is one of the most common causes of a markedly enlarged spleen in malaria-endemic regions, whereas uncomplicated malaria and schistosomiasis are common causes of splenomegaly.[3,4] HMS is thought to represent an abnormal polyclonal B-cell-mediated response to recurrent or chronic malaria infection,[5–7] which results in marked splenomegaly and functional hypersplenism.[5] Although there is no single diagnostic test, cases can be identified using a defined set of clinical, laboratory, and histological criteria including gross splenomegaly (spleen size $\geq$ 10 cm below the costal margin), elevated immunoglobulin M (IgM) titers (often defined as $\geq$ 2 SD above the local mean), the presence of high titers of anti-malarial antibodies, evidence of a lymphocytic hepatic sinusoidal infiltrate on liver biopsy, absence of evidence of a neoplastic lymphoproliferative disorder, and a reduction in spleen size ($\geq$ 40% over 6 months) in response to effective anti-malarial treatment.[8] HMS is more common in certain ethnic groups (e.g., 80% prevalence in some tribes in New Guinea), and the association of severe HMS with HLA-DR2 is further evidence in support of an underlying host predisposition.[9] Treatment consists of prolonged courses of effective anti-malarial therapy. Reduction in splenic mass is associated with a reduction in serological parameters.[10,11]

There are few data in the literature addressing HMS in pregnancy,[12,13] which is of particular relevance given the susceptibility of pregnant women to malaria, the risk of splenomegaly in pregnancy in terms of anemia, thrombocytopenia, and increased susceptibility to infection, and the anxiety related to the safe administration of anti-malarial medication to pregnant women. This retrospective analysis aimed to characterize the effects of mefloquine treatment on spleen size and maternal IgM, IgG, and anti-malarial antibodies in pregnant women with splenomegaly in an area of low seasonal transmission on the Thai-Myanmar border.

This survey was undertaken at the Shoklo Malaria Research Unit (SMRU), Mae Sot, Thailand, between May 1994 and February 1997. Pregnant women were screened weekly for malaria by blood smear and every second week for anemia by hematocrit. Spleen size measurement was part of the routine obstetric examination. Any woman with significant splenomegaly (defined locally as $\geq$ 5 cm enlargement) and with a negative malaria film was given 5 mg/kg mefloquine weekly (Lariam, Roche Pharmaceuticals, Basel, Switzerland) as part of standard clinical practice to reduce anemia. A venous blood sample (3 mL) was sent to the Mae Sot Hospital for hemoglobin electrophoresis for detection of β-thalassemia (no test was available for α-thalassemia at that time). If during subsequent follow-up the spleen became impalpable, treatment was given for a further 2 weeks and then stopped; if the splenomegaly was unresponsive, treatment was stopped at 12 weeks. Women were followed up to delivery and neonatal outcomes were recorded.

Thirty-six women with suspected HMS were identified and treated as described; residual plasma samples from routine blood counts were stored for 31 of these women at the time of diagnosis and each time the woman was followed up. These samples were taken as part of routine clinical care. One hundred and twenty-nine samples (median samples per individual interquartile range [IQR]: 5 [3–6]) were processed for total IgM and IgG (Minineph, The Binding Site, Birmingham, UK); anti-malarial antibody titers (ELISA, DiaMed, Switzerland) were measured in a smaller subset of 87 samples taken from 23 cases (median samples per individual [IQR]: 4 [3–5]; mean value for duplicate tests obtained on 57 samples). Single samples taken from 29 malaria-smear negative pregnant women without splenomegaly from the same geographical area, population, and collected within the same time frame, were used as unmatched controls; total IgM and IgG were measured on all of these samples, and anti-malarial antibodies in a subset of five (mean value for duplicate tests obtained on all samples).

Concomitant rates of splenomegaly in the 3,503 women enrolled to antenatal care during the same period were 3.8% (134) for splenomegaly of any size and 1.0% (36) for splenomegaly $\geq$ 5 cm. By contrast, from May 2007 to September 2010 these proportions had dropped markedly to 0.5%

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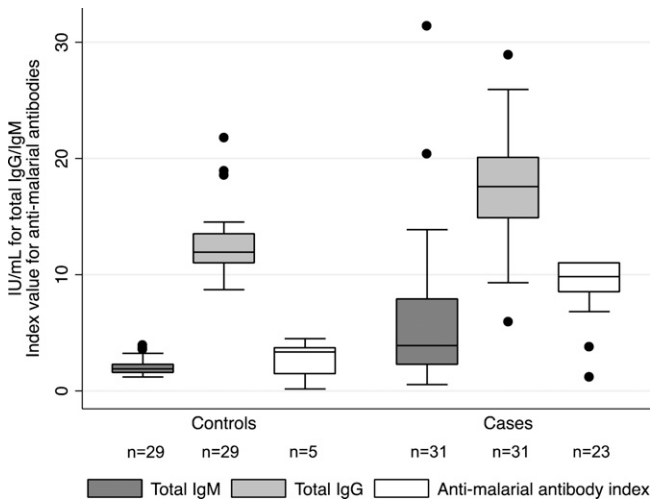
FIGURE 1. Values of control and pre-mefloquine treatment (for cases) total immunoglobulin M (IgM), IgG, and anti-malarial antibody index results.

(69 of 12,067) and 0.3% (40), respectively; which corresponded with a reduction in the incidence of *Plasmodium falciparum* malaria in the population.[14]

Of the 31 of 36 women with suspected HMS for whom blood samples were available, 7 (23%) had splenomegaly of ≥ 10 cm at enrollment, 17 (55%) a serum IgM concentration ≥ 2 SD above the local controls, and 18 (58%) responded to treatment with a reduction in spleen size of ≥ 40%. Three (10%) women met all of these criteria and 13 (42%) only two.[2] Minor criteria defined as hepatic sinusoidal lymphocytosis, normal lymphocyte response to phytohemagglutinin stimulation, lymphocyte proliferation, were not assessed.[1]

A median of 9 (2–25) weekly mefloquine treatments were provided per woman. Pre-mefloquine treatment plasma titers for cases were significantly higher than controls for all measurements (Figure 1): total IgM was 6.1 (95% confidence interval [CI] 3.8–8.5) versus 2.1 (95% CI 1.8–2.4) IU/mL, $P = 0.001$; total IgG was 17.6 (95% CI 15.9–19.3) versus 12.5 (95% CI 11.5–13.6) IU/mL, $P < 0.0001$; and anti-malarial antibody index values were 9.1 (95% CI 8.1–10.2) versus 2.6 (95% CI 0.43–4.85), $P < 0.0001$. Significant reductions in spleen size (linear regression: co-efficient −0.14; SE 0.03; [95% CI −0.20–0.07]; $P < 0.0001$) and in anti-malarial antibody index values (linear regression: co-efficient −0.69; SE 0.03; [95% CI −0.13–0.01]; $P = 0.02$) were observed with mefloquine treatment. Decreases in IgM and IgG titers were also observed, although these did not reach statistical significance. Five women had complete resolution of splenomegaly. Splenic reduction (median [range]) was observed in women with and without abnormal hemoglobin-typing (available for 30 women): 4 (0–8) cm with normal hemoglobin typing ($N = 16$), 2.5 (1–6) cm with homozygote β-thalassemia ($N = 4$); 3 (1–7) cm with β-thalassemia trait, $N = 9$; and no change in one with hemoglobin-E disease ($P = 0.381$). The proportion of women with splenic reduction ≥ 40% was 75% (12 of 16) of women with normal hemoglobin typing and 57.1% (8 of 14) of women with abnormal hemoglobin typing, $P = 0.442$.

Women with suspected HMS were significantly older and of higher gravidity, with a mean age of 30 versus 24 years ($P = 0.0009$) and 5 versus 3 pregnancies ($P = 0.019$), and on aver-

age, had a 17% proportional reduction in hematocrit at the start of antenatal screening than contemporary controls: 28.8% (95% CI 26.6–31.0%) versus 34.8% (95% CI 33.3–36.4%; $P < 0.0001$). The mean hematocrit before delivery in women treated with mefloquine (5 mg/kg/week) increased to 31.5% (95% CI 26.6–31.0%; $P = 0.05$) from baseline, whereas the hematocrit values in control women fell significantly to 32.6% (95% CI 31.2–34.0%; $P = 0.009$). There was no difference in mean birth weights between the two groups: 2,910 g (95% CI 2,704–3,118 g) in cases versus 2,989 g (95% CI 2,856–3,123 g; $P = 0.50$) in controls. One baby in the group with splenomegaly was born prematurely (< 37 weeks). All babies in both groups had normal post-natal assessments ($N = 50$).

There are limitations to this retrospective analysis: the sample size was small reflecting the relative rarity of HMS in this population (prevalence 1%); the control group was contemporary but unmatched; and there were no malaria polymerase chain reaction data that have been used in other settings to confirm low-density parasitemias in putative HMS patients,[15] thereby confirming active malaria infection as the direct cause of splenomegaly. Other causes of splenomegaly were also not explicitly ruled out, although there is no schistosomiasis in the area, the rate of human immunodeficiency virus and syphilis remains very low (< 0.4%), and none of these women died of malignancy-related maternal deaths. The raised anti-malarial antibody titer results presented here are similar to a series of 50 Hmong refugees from Thailand examined in Minnesota, North America, with a spleen > 2 cm.[16] Despite these limitations, we show that in a group of women with a spleen size ≥ 5 cm and negative malaria films, treatment with mefloquine led to reduction in spleen size and decrease in anemia, without any adverse outcomes. Splenic reduction of ≥ 40%[8] was also seen in women who did not meet all the conventional criteria for HMS: in this analysis it was a feature of 5 of 7 (71%) and 10 of 13 (77%) of women with one and two major criteria of HMS, respectively; and in women with abnormal hemoglobin typing. This suggests that in a malarious area mefloquine is useful even when splenomegaly is thought to be caused by hemoglobinopathy.

Total IgM and IgG titers were elevated in women with splenomegaly, and anti-malarial antibodies were inevitably present. Statistically significant decreases were not observed in all of the serological parameters on treatment, perhaps because of the relatively short period of follow-up (range for last follow-up sample: 5–29 weeks). Weekly mefloquine can be used for the treatment of HMS in pregnancy in areas where *P. falciparum* parasites remain sensitive to the drug.

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