Novel biomarkers in the pathogenesis of placental malaria in sub-Saharan Africa

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Citation for published version (APA):
Owens, S. (2012). Novel biomarkers in the pathogenesis of placental malaria in sub-Saharan Africa Amsterdam: Rozenberg

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SUMMARY

This thesis presents original data on various biomarkers of placental malaria which previously have been sparsely featured in the medical literature but which may provide fresh insights into the pathogenesis of this condition. These include some common red cell antigenic variants linked with disease susceptibility, previously unreported observations of parasite-placental interactions, new components of the parity-specific malaria immune response to infection, and functional consequences of placental malaria for the neonatal immune system.

Chapter 1

This chapter is a review of the recent literature on pregnancy malaria in general and placental malaria in particular. Key aspects of epidemiology, pathology, immunology and functional consequences of the infection are outlined. The chapter highlights areas that have been recommended for further research, including how the interaction of maternal endocrine and immune systems may predispose to malaria in pregnancy, consequences of malaria-induced placental inflammation for placental function and immunological studies of the pathological processes of placental malaria.

Chapter 2

Although ABO histo-blood group antigens have not been shown to have any specific physiological function, individual phenotypes have been reported to be associated with a variety of conditions, including infection and cancer. The geographical distribution of ABO blood groups varies markedly, suggesting that powerful selection factors may have influenced gene spread. Chapter 2 is a systematic review of the epidemiological, clinical and immunological evidence linking ABO blood group phenotypes and malaria risk. On meta-analysis there were clear associations between group A and clinical severity, and group O and milder disease in children. Among pregnant subjects, two studies reported an association of similar magnitude between blood group O and induction of parity-specific immunity to placental malaria in multigravidae living under conditions of high malaria transmission. Several mechanisms relating to these associations are explored in the context of the glycobiology of malaria infection.

Chapter 3

An analysis of the associations between placental malaria, parity and ABO histo-blood group antigens among 97 women delivering in Kumasi, Ghana is reported. In contrast to the previous pregnancy studies outlined in Chapter 2 and other subsequent work, blood group A rather than blood group O was identified as a risk factor for placental malaria in primiparae. There was no association between blood group and malaria among multiparae. These observations are consistent with those made in non-pregnant individuals.
Chapter 4

As described in Chapter 1, *P. falciparum* parasites that bind to chondroitin sulphate A express unique variant surface antigens termed VAR2CSA which are intimately involved in placent al sequestration of infected erythrocytes. As further outlined in Chapters 2 and 3, the association of placental malaria with the mother’s ABO blood group phenotype suggests that additional mechanisms are involved in this process. Sialic acid-dependent characteristics of the placental syncytiotrophoblast could be important as glycolipid and glycoprotein-bound sialic acids vary between ABO blood group phenotypes. In this analysis we describe the lectin histochemistry of placental *P. falciparum* placental infection in order to characterise sialic acid-dependent placental features and to determine if significant differences in intensity of staining occur in relation to lectin-binding characteristics and categories of placental infection (past, chronic and no infection). Microvillous expression of Neu5Ac(α2,6)Gal/GalNAc sequences which were bound by the lectin from Sambucus nigra (SNA-1) was greatly increased in placental biopsies from Zambian women with chronic *P. falciparum* infection showing, by electronic image analysis, a significant trend compared to samples with past or no infection (p=0.002). This suggests a specific syncytiotrophoblast response to *P. falciparum* malaria. Expression of α2,6-linked sialic acid, demonstrated by the binding of SNA-1, has been associated with intercellular repulsion in tissues from patients with cancer, and such repulsion resulting from increased α2,6 sialylation of chorionic villi could influence the density of intervillous parasitaemia. Sialic acid expression should be examined in placental malaria to identify if this is a malaria-specific phenomenon, and to determine its relation to placental inflammation and pregnancy outcomes.

Chapter 5

This chapter reports the occurrence and co-factor dependence of anti-phospholipid antibodies (aPL) in placental malaria from an original cross-sectional study conducted in Kumasi, Ghana. It was postulated that circulating aPL, which are co-factored with the plasma apolipoprotein β2 glycoprotein I (β2GPI), might contribute to the inflammatory vasculopathy observed in the placenta with chronic malaria infection and in certain pregnancy complications, while co-factor independent aPL might feature in the immune response to placental parasitaemia, as has been observed in peripheral parasitaemia in non-pregnant individuals and in other infections. Anti-cardiolipin, anti-phosphatidylerine and anti-β2GPI enzyme-linked immunosorbent assays (ELISAs) were performed on sera from 103 HIV non-infected gravid women. Placental malaria, both active and past infection, was diagnosed in 33/103 (32%), based on placental histology. In multiparae, β2GPI-independent IgM antibodies to cardiolipin (p =0.018) and phosphatidylerine (p=0.009) were observed, which were most pronounced in past placental malaria infection. In primiparae, no association emerged between aPL and placental malaria. Trends for improved clinical parameters were identified in infected women with levels of anticardiolipin beyond the 99th multiple of the median for a healthy, non-malarious population. This study in placental malaria reports parity associations of β2GPI-independent aPL profiles, and does not support a role for β2GPIdependent aPL. It is of significance in the context of the known parity differences in pregnancy malaria immunity.
Chapter 6

It has recently been suggested that the acquisition of adult malarial immunity in highly endemic areas is dependent on host pubertal maturation and androgen production. The serum concentration of dihydroepiandrosterone sulphate (DHEAS), the most abundantly secreted human androgen, predicted resistance to P. falciparum infection in non-pregnant young adults in western Kenya. There are no published data on the role of DHEAS in pregnancy malaria. A secondary analysis of stored sera from the previous cross-sectional study of placental malaria in Kumasi, Ghana was undertaken and is presented in this chapter. The aim was to assess the association between DHEAS concentrations, sampled at parturition and measured using ELISA, histological changes of placental malaria and markers of malarial morbidity, in a cohort of 104 HIV-uninfected women. DHEAS concentration was associated with maternal age and parity. In univariate analysis there was a weak inverse association between DHEAS concentration and malaria infection in primiparae (p=0.062), although adjusted analyses showed no association between DHEAS and maternal haemoglobin concentration or birth weight, key markers of pregnancy malaria morbidity. DHEAS production may be a factor in the acquisition of pre-pregnancy malarial immunity and warrants further study especially in younger primiparae. Explanatory mechanisms involving aPL are postulated, based on recent rodent models of malaria modulation by 16α-bromoepiandrosterone (EPI), an analogue of DHEAS.

Chapter 7

This chapter presents the primary analysis of the cross-sectional study of placental malaria conducted in Kumasi, Ghana. The efficiency of transplacental transfer of measles-specific antibody, measured in cord and maternal sera using ELISA and expressed as a ratio, was assessed in relation to placental malaria. Infection at delivery was associated with a 30% decrease in expected cord measles antibody titres. Uninfected women who received anti-malarial drugs during pregnancy transmitted 30% more antibody than those who received none. Infants born to mothers with placental malaria may be at increased risk of measles in the early months of life and may benefit from earlier vaccination. The benefits of malaria control during pregnancy may include reduced risk of infectious diseases during infancy.

Chapter 8

The thesis concludes with a general discussion of its data in the context of the current paradigms of placental malaria. The importance of pre-pregnancy malaria immunity for primiparae is highlighted and postulated to account for the observations made of blood group phenotypes and DHEAS production in determining host susceptibility to malaria infection. The functional consequence of placental malaria for infant immune development is suggested as a priority research theme and discussed in the context of the race to find an effective vaccine for pregnancy-associated malaria.