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The role of interleukin-6 in vitamin A deficiency during *Plasmodium falciparum* malaria and possible consequences for vitamin A supplementation

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SUMMARY

Kinetics of serum levels of interleukin-6 (IL-6) were studied in patients with acute *Plasmodium falciparum* malaria in relation to vitamin A and its binding proteins, retinol binding protein (RBP) and pre-albumin. It was found that IL-6 levels followed the rise and decrease of parasitaemia by 12 hr and correlated inversely with levels of vitamin A and its binding proteins. These data suggest that vitamin A supplementation alone might still be insufficient to restore a malaria-induced vitamin A deficiency.

Vitamin A (retinol) deficiency and malaria are major public health problems in developing countries. Vitamin A deficiency is recognized as a leading cause of blindness and increases mortality and morbidity in respiratory infections and diarrhoea.[1] A longitudinal study conducted in Tanzania[2] has shown that blood retinol levels are inversely correlated with *Plasmodium falciparum* parasitaemia. More recently, in Congo,[3] a transverse study confirmed that there is a significant relationship between vitamin A deficiency and malaria. The reasons for this remain unclear. This correlation might result from a complex interplay between cytokines, acute phase proteins and malaria parasites. Acute phase protein secretion by the liver is controlled by different cytokines including IL-6.[4] IL-6 release is itself induced by a malaria infection.[5,6] Vitamin A is stored in the liver and its transport involves formation of a three-component complex consisting of retinol binding protein (RBP), pre-albumin and retinol itself. We therefore investigated the possibility that RBP and pre-albumin are modulated during acute *P. falciparum* malaria.

Seven non-immune French adults, six males and one female, aged between 27 and 50, mean 36·7 years, with good nutritional status and no evidence of hepatic or renal dysfunction, were admitted to our hospital for acute *P. falciparum* malaria and followed up and treated with halofantrine (3 × 500 mg at 6 hr intervals). Their blood RBP, pre-albumin, retinol and IL-6 levels were determined at selected intervals and analysed in conjunction with the kinetics of parasitaemia. Statistical analyses were performed using non-parametric Pearson and Kruskal–Wallis tests on the entire series of determinations. Sex- and age-matched healthy French individuals ($n=80$) were used as controls.

As can be seen in Fig. 1, a rise in IL-6 levels (measured using a double sandwich enzyme-linked immunosorbent assay from Medgenix, Fleurus, Belgium) was found to follow the course of parasitaemia and to correlate significantly with a delay of 12 hr. Admission levels of RBP, pre-albumin (measured by automatic

Table 1. IL-6 versus vitamin A and its binding proteins in the serum of malaria-infected patients

	IL-6	RBP
RBP	$r=-0{\cdot}450$ $P=0{\cdot}004$	
Pre-albumin	$r=-0{\cdot}536$ $P=<0{\cdot}0001$	0·939 <0·0001
Vitamin A	$r=-0{\cdot}480$ $P=0{\cdot}002$	0·883 <0·0001

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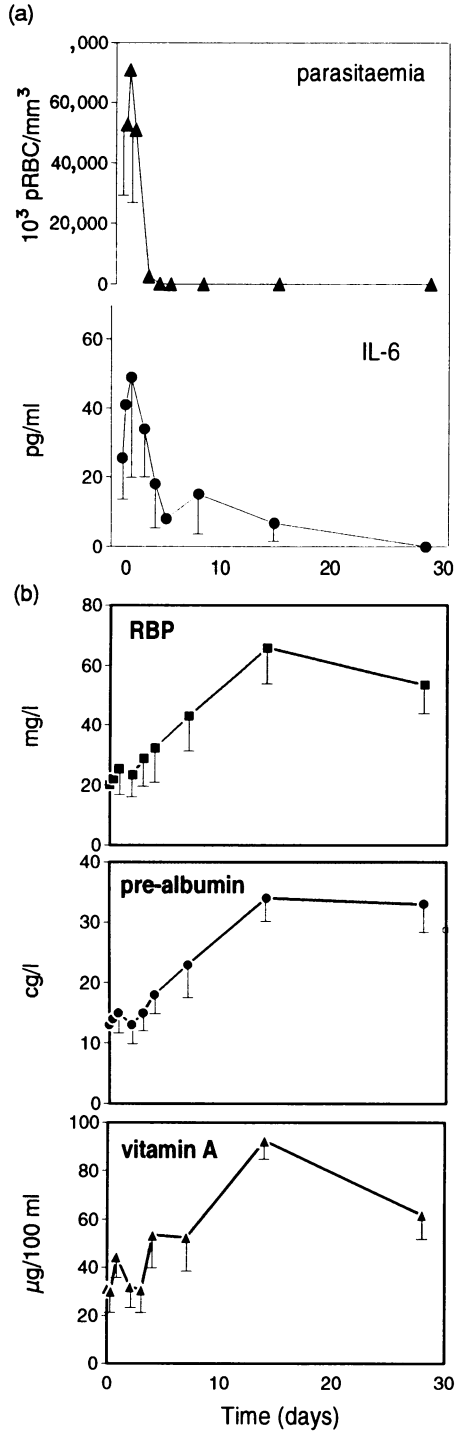

Figure 1. Kinetics of parasitaemia, IL-6, vitamin A and its binding proteins in malaria-infected patients. (a) Parasitaemia and IL-6 levels correlated significantly with a delay of 12 hr ($r=0{\cdot}34$, $n=39$, $P=0{\cdot}037$). (b) Admission levels of RBP, pre-albumin and vitamin A were lower than controls (Mann–Whitney $P=0{\cdot}006$, 0·0001, 0·0011, respectively, with mean values of $48{\cdot}9\pm12$ mg/l, 43 ± 11 cg/l, $52{\cdot}7\pm8{\cdot}6$ µg/100 ml in controls $n=80$) and rose progressively in the ensuing days (Kruskal–Wallis $P=0{\cdot}0009$, 0·0005 and 0·013, respectively). Time represents the number of days after admission.

Behring laser nephelometry) and vitamin A (determined by reverse phase high performance liquid chromatography with spectrophotometric detection at 325 nm) were lower than controls but rose progressively in the ensuing days and were significantly higher than the admission levels by Day 7. The serum retinol levels correlated inversely with the degree of parasitaemia ($r=-0{\cdot}338$, $P=0{\cdot}035$, $n=39$), as previously reported,[2] while RBP, pre-albumin and retinol levels did so inversely with IL-6 (Table 1).

Although cytokines such as IL-6 do decrease synthesis of RBP and pre-albumin by hepatocytes, it is unknown what proportion of the decrease in plasma levels of these proteins results from decreased synthesis and what proportion of increased removal from the vascular space. Rather than infection reducing retinol transport and delivery to target tissues, serum levels of retinol and its binding proteins may be decreased during infection because of enhanced delivery to the tissues.

In view of these data, it is conceivable that during an acute malaria attack, the reduction in serum retinol levels is the result of a cascade of events: malaria parasite proliferation induces the release of IL-6 which causes a decrease in the serum level of RBP and pre-albumin, thus impeding the transport of vitamin A from the liver to its target tissues. Consequently, vitamin A supplementation alone might still be insufficient to restore a malaria-induced vitamin A deficiency. These results were obtained from a small cohort of non-immune patients and further investigations should be carried out on patients living in endemic regions.

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