Immunopathology of nephropathies associated with malaria*

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Immune complexes play an important role in the pathogenesis of malaria-associated nephropathies. Two main types of lesion are demonstrable: (a) *acute (transient–reversible) lesions typical of falciparum infections in man, with mild clinical symptoms developing a week or two after infection. Renal biopsies at that time show deposits of immunoglobulins, complement, and sometimes antigen. The lesions respond to antimalarials.* (b) *Chronic (progressive) lesions characteristic of quartan infections in man, developing slowly into a chronic stage with persistent proteinuria and gradually deteriorating renal function and hypertension. Renal biopsies at the onset of the disease show deposits of immunoglobulins, complement, and* P. malariae *antigens in glomerular capillary walls. Antimalarial therapy has no effect. Recent immunochemical findings confirm that these lesions are of the immune-complex type and are associated with malaria infection. However, several questions remain to be solved.*

Nephropathies associated with tropical parasitic infections and compatible with the depositing of immune complexes in glomerular capillary walls have been described in experimental animals and man in three main tropical infections: malaria, schistosomiasis, and trypanosomiasis. The most convincing evidence for an immune-complex type of renal lesion has been established in malaria.

Evidence in support of a causal relationship between malaria and nephropathies (apart from case history observations) was based on time-trend studies in communities (13, 14, 15, 16, 32) and on the prevalence of the nephrotic syndrome, which is much higher in malarious areas of Africa than in non-malarious areas (19, 26). However, there was a general feeling that the epidemiological evidence of this relationship should be strengthened (48) and more detailed immunopathological studies have therefore been carried out. Although kidney damage may be produced by either acute or chronic malaria infection (12), the lesions differ in certain respects.

ACUTE (TRANSIENT–REVERSIBLE) LESIONS

In experimental models of acute infections, deposits of immunoglobulins, complement, and antigen were detected in glomeruli of rhesus monkeys as early as 9 days after infection with *P. cynomolgi* (45). Similarly, in rodent malaria infections, Ehrich & Voller (11) found immunoglobulin deposits in the kidneys of mice 8 days after infection with *P. berghei-yoelii* and Boonpucknavig et al. (5, 6) described the granular deposits of *P. berghei* antigens in glomeruli of mice 7 days after infection. On light microscopy, the characteristic changes were hyperplasia and hypertrophy of mesangial cells and endothelial cells with PAS-positive material, and irregular thickening of the basement membranes. In the later stages, polymorphonuclear leukocytes or malarial pigment-laden macrophages were observed (5). Similarly, endothelial proliferation and the presence of electron-dense materials in mesangial areas and later on in the basement membrane were seen with the electron microscope (7). No lacunae were reported.

In man, glomerulonephritis and nephrotic syndrome occurring during the course of falciparum infections have been described as more-or-less acute diseases responding in most cases to antimalarial therapy (3, 18, 34, 36). Bhamarapravati et al., (4) examined kidney tissues obtained from 10 patients with albuminuria during acute falciparum malaria (9 biopsies and 1 autopsy) and found deposits of immunoglobulins (mainly IgM) and complement localized in the glomerular basement membrane and in the mesangial areas of all but one case; malarial antigen was observed in 2 cases (immunofluorescence

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technique). The interval between the first day of fever and the day of biopsy in these 9 patients with positive deposits varied from 6 to 23 days. The only case with negative immunofluorescence findings (but still with mild albuminuria) was biopsied on the 38th day. Histologically, expansion of mesangial areas with or without proliteration of the mesangial cells, and hyperplasia and hypertrophy of the endothelial cells, were found. Glomerular basement membranes were irregularly thickened and electron-dense deposits but no lacunae were recorded on electron-microscopy. The authors concluded that the immune complexes in *P. falciparum* clear relatively fast and that the glomerular injury is reversible, since urinary abnormalities disappeared completely after antimalarial therapy.

CHRONIC (PROGRESSIVE) LESIONS

On the other hand, human nephropathies associated with quartan malaria infections have been reported as having a chronic progressive character (2, 17, 27) with no response to antimalarial treatment and poor response to corticosteroids (1, 20, 28, 48). The studies from Nigeria demonstrated granular deposits in glomerular capillary walls by immunofluorescence in the vast majority of patients with typical nephrotic syndrome. In renal biopsies from 93 patients (50 children and 43 adults) immunoglobulins G and M were present in 96%, the third component of complement in 66%, and *P. malariae* antigen in 25% of cases, as shown in Table 1 (21, 22, 24). Examination of eluates from nephrotic kidney specimens confirmed the presence of specific anti-*P. malariae* antibodies in most of them. Similar findings of glomerular deposits in 13 Ugandan patients were reported by Ward & Kibukamusoke (46).

The size and distribution of immunoglobulin deposits (as estimated by immunofluorescence) varied from a coarse to a fine granular pattern. This difference may be essential, as we have found a certain correlation between the patterns of immunofluorescence and the response to treatment in nephrotic Nigerian children. Good responses to prednisolone, azathioprine, and cyclophosphamide were recorded in patients with coarse and/or mixed granular patterns of immunofluorescence but not in cases with a fine granular pattern, as shown in Table 2 (20, 24). Furthermore, it was found that the distribution of IgG subclasses in glomerular deposits was related to the pattern. Typical coarse granular deposits always had positive G_3 subclass, either alone or in combination with others, but never G_2. A mixed pattern also always had G_3, but in some cases G_2 participated. In cases with a fine granular pattern all subclasses were found, with a predominance of G_2 (8 out of 12), as shown in Table 3 (24). Positive staining for the third component of complement was more closely related with the presence of IgM than with individual subclasses of IgG; however, the 5 cases showing a fine granular pattern with G_2 only were complement-negative. These cases had poorly selective proteinuria and a bad outcome.

Correlation of immunofluorescence findings with clinical data and the response to treatment indicates that (*a*) the fine granular pattern of immunoglobulin deposits in glomerular capillary walls (characterized by positive staining for IgG with a predominance of G_2 and negative complement) may be even more progressive than the coarse granular pattern, positive for IgG (G_3), IgM, and complement; (*b*) the classical conception of complement-induced damage is valid in most cases but non-complement-induced injury should also be considered; and (*c*) the

Table 1. Incidence of positive immunofluorescence staining for immunoglobulins, complement, and antigens in renal biopsies of patients with nephrotic syndrome

	No. examined	Immunoglobulins				Complement C_3	Antigens	
		total GG	G	G + M	M		*P. malariae*	*P. falciparum*
children	50	48	17	27	4	33	9[a]	0[a]
adults	43	42	23	16	3	25	11	1
total	93	90	40	43	7	58	20[b]	1[b]

[a] 36 examined.
[b] 79 examined.

Table 2. Correlation of immunofluorescence patterns with response to treatment in nephrotic children

	Immunofluorescence staining					Response to treatment		
pattern	total	IgG	IgM	IgG & IgM	complement	good	fair	none
coarse granular	19	5	2	12	16	7	3	9
mixed granular	15	3	0	12	12	3	1	11
fine granular	7	6	0	1	1	0	0	7
total	41	14	2	25	29	10	4	27

examination of renal biopsies may not only provide information on actual damage but also have prognostic value.

Morphological changes seen in renal biopsies of patients with nephropathies associated with *P. malariae* varied. In children, the most common lesion was a localized or diffuse thickening in the capillary wall of the tuft with PAS-positive segmental sclerosis of peripheral capillary loops and with mesangial cell increase (48). This lesion progressed to total glomerular sclerosis and secondary tubular atrophy. Attempts were made to grade these changes into 3 groups according to the extent and severity of lesions (20). In adults, the most common lesion was a proliferative glomerulonephritis characterized by swelling of the glomerular tuft, proliferation of the endothelial cells, and occasional lobulation.

Table 3. Distribution of IgG subclasses in glomerular deposits with regard to patterns of immunofluorescence and positivity of complement (renal biopsies from nephrotic patients)

Immunoglobulin pattern	Immunofluorescence staining (subclasses of IgG)				
	complement positive			complement negative	
	Positive for IgG and IgM (17 cases)				
coarse granular	G_3	G_3			none
	G_{13}	G_{34}			
mixed granular	G_3	G_{23}	G_{134}		
	G_3	G_{23}	G_{134}		
	G_3	G_{23}	G_{234}		none
	G_{13}		G_{1234}		
ine granular	G_1				G_{124}
	Positive for IgG only (17 cases)				
coarse granular	G_{134}				G_3
					G_{134}
mixed granular	G_3				G_3
	G_{134}				
	G_{134}				
ine granular	G_{13}			G_2	G_2
	G_{23}			G_2	G_3
	G_{14}			G_2	G_{23}
				G_2	

Electron microscope studies on biopsies obtained from patients with *P. malariae*-associated nephropathies showed considerable variation (2, 21), but a certain correlation between patterns of immunofluorescence and the ultrastructure was found (24, 48): the coarse granular pattern was closely related to the deposits of electron-dense materials localized within the glomerular basement membrane, usually on the epithelial side. Progressive cases showed masses of dense material distributed throughout the basement membrane, especially in cases with positive complement. The fine granular pattern did not show the typical circumscribed deposits of electron-dense material but in some cases there were irregular deposits within the basement membrane on the endothelial side. Another difference between immunofluorescence patterns was in the proliferation of cells: increase cellularity was rather rare with a coarse granular pattern but it was typical in cases with a fine granular pattern (primarily endothelial cells). Foot processes of the epithelium were quite distinct in a few cases and had fused or totally coalesced in others, but this was without any relation to the pattern of immunofluorescence. The presence of small lacunae distributed irregularly throughout the basement membrane, described by

White (47), was not confirmed in our study, in which the biopsy samples were examined independently by two laboratories (those of Dr A. C. Allison, London, and of Dr J. R. Goodman and Dr C. F. Piel, San Francisco). Similarly, no lacunae were found in biopsies of patients with nephropathies from other countries of Africa (Dr L. Morel-Maroger, personal communication, 1974).

SOLUBLE IMMUNE COMPLEXES

The existence of soluble immune-complexes circulating in subjects with malaria has been considered for some time, but they have been detected only recently.

Soluble antigens were demonstrated in the serum of patients (mainly children) after acute falciparum infections with high parasitaemia by McGregor et al. (35) and Wilson et al. (50) in Gambia and by Williams & Houba (49) in Nigeria. Wilson et al. showed the heterogeneity of these antigens with respect to their physical and/or physicochemical properties. These antigens circulate either free or bound in immune-complexes that are in excess of antigen (23). McAlister (33) described serologically active antigens of *P. falciparum* isolated from erythrocytes of infected *Aotus trivirgatus* monkeys. The fact that precipitins (either present in serum or prepared from erythrocytes) are identical in human beings and in *A. trivirgatus* monkeys with falciparum infections was demonstrated by Wilson & Voller (51, 52) and by Williams & Houba (49).

P. malariae soluble antigens circulating free or bound in soluble immune-complexes, suspected by Allison et al. (2), can be demonstrated only with difficulty (D. Bidwell & A. Voller, unpublished observations, 1973). We thought that this might be due to the low concentration of the antigens released or to the relatively unsensitive techniques used for their detection. Therefore, we applied a polyethylene-glycol technique combined with radioisotope tracers to detect them in the serum of infected *A. trivirgatus* monkeys and in infected human serum (24, 25).

In the monkeys, *in vivo*, " complexing " of specific IgG injected by the intravenous route was demonstrated by increased insolubility in 7.5% polyethyleneglycol in plasma samples (Table 4). The levels of precipitates containing I^{125}-labelled (specific) IgG were significantly higher in the plasma of monkeys infected with the relevant strain, i.e., either *P. brasilianum* or *P. falciparum*, than in the plasma of the non-infected control monkey (No. 151); they were also higher than those containing I^{131}-labelled normal IgG without malarial antibodies. Only one monkey (No. 131) showed a higher level of polyethyleneglycol precipitate of normal IgG; however, in this monkey, the test for the presence of rheumatoid-

Table 4. *In vivo* " complexing " of I^{125}-labelled antimalarial IgG and of I^{131}-labelled normal IgG in *A. trivirgatus* monkeys [a]

Monkey No.	Infected with	Duration of infection	% Polyethylene-glycol precipitate [b]		
			I^{125}-labelled IgG (anti-*P. malariae*)	I^{125}-labelled IgG (anti-*P. falciparum*)	I^{131}-labelled IgG (normal)
151	(control)		1.7		< 1.0
122	*P. brasilianum*	9 months	14.7		< 1.0
131	*P. brasilianum*	7 months	17.9		23.3 [c]
143	*P. falciparum*	43 days		13.8	< 1.0
148	*P. falciparum*	26 days		7.8	< 1.0
149	*P. falciparum*	26 days		8.8	< 1.0
150	*P. falciparum*	26 days		5.4	< 1.0

[a] Monkeys Nos. 122, 131, and 151 were injected with I^{125}-labelled anti-*P. malariae* IgG (0.07 mg per kg of body weight; Nos. 143, 148, 149, and 150 received I^{125}-labelled anti-*P. falciparum* IgG (0.1 mg/kg). All monkeys received also I^{131}-labelled normal IgG (0.1 mg/kg).

[b] Percentage of radioactive precipitate at 7.5% (final concentration) polyethylene-glycol in plasma collected 18 h after the injection.

[c] Sample positive for rheumatoid factor.

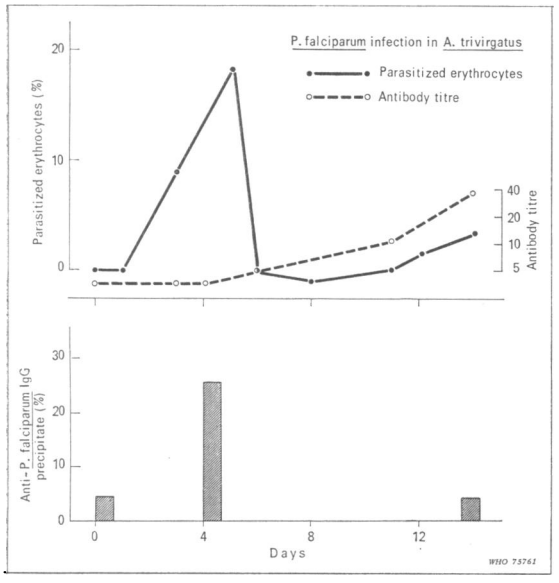

Fig. 1. Binding of specific antibody to soluble antigens at the beginning of infection.

factor-like antiglobulins was positive. The amount of specific IgG insoluble in 7.5% of polyethylene-glycol was lower in monkeys with infections of shorter duration.

The serum of infected monkeys, obtained when parasitaemia was high but without detectable antibody, bound I^{125}-labelled specific IgG added *in vitro* into complexes that precipitated at 7.5% of polyethylene-glycol. A typical example in falciparum infection is illustrated in Fig. 1. Similar results were obtained with the serum of monkeys infected with *P. brasilianum*.

Serum from Nigerian nephrotics, which had been incubated *in vitro* with I^{125}-labelled specific IgG (anti-*P. malariae* or anti-*P. falciparum*) or with normal control IgG and precipitated with a 7.5% final concentration of polyethylene-glycol showed a certain insolubility in all cases examined. However, significantly higher levels of precipitates were found in 4 out of 6 cases when IgG isolated from serum containing *P. malariae* was applied (Table 5).

These findings might be explained by the binding of specific IgG either to macromolecular antigens alone or to soluble antigen–antibody complexes in circulation.

The serum levels of complement components (C3, C3PA, and C4) in the monkeys rose after infection, the highest levels coinciding with peaks of parasitaemia. A decrease to low levels was detected when antibody was produced (31), which is consistent with an activation of the classical complement pathway.

Table 5. *In vitro* complexing of I^{125}-labelled anti-malarial IgG in patients with nephrotic syndrome

Patient No.	% Polyethylene-glycol precipitate [a]		
	anti-*P. malariae* IgG	anti-*P. falciparum* IgG	Control IgG
1	26.0	9.8	12.6
2	13.5	13.7	8.7
3	10.7	10.2	7.7
4	19.8	6.5	8.8
5	22.0	5.7	12.6
6	20.0	9.9	4.8
control	9.0	4.3	7.4

[a] % of radioactivity in precipitate of sera incubated with I^{125}-abelled IgG of differing antibody specificity.

LOCALIZATION OF SPECIFIC ANTIBODY IN THE KIDNEYS

Houba & Lambert (24) and Houba et al. (25) demonstrated faster disappearance of specific antibody from circulation after its injection by the intravenous route and its increased deposition in renal tissue. Table 6 shows that the amounts of specific IgG eluted from isolated glomeruli in *A. trivirgatus* experimental infections were significantly higher than those of normal IgG and/or those found in control (noninfected) monkeys. The localization of specific antibody (IgG) injected by the intravenous route was studied also in renal biopsies obtained from nephrotic patients in Nigeria (24, 31): Table 7 shows the amounts of IgG eluted from kidney samples obtained 24 hours after intravenous injection of IgG with different antibody specificities.

These observations indicate the binding (" complexing ") of specific antibody to soluble antigens and/or soluble immune complexes and their increased deposition in kidney (glomerular) lesions. They also strengthen the hypothesis that *P. malariae* antigens play an important role in the pathogenesis of chronic progressive nephropathies occurring in malarious areas.

Table 6. Amounts of IgG eluted from glomeruli after intravenous injection in *A. trivirgatus* monkeys infected with malaria

Monkey No.	Infected with	Duration	I^{125}-labelled IgG injected [a]	Amount (in ng) of IgG eluted from glomeruli (per kidney)	
				I^{125}-labelled specific IgG	I^{131}-labelled normal IgG
151	(control)		anti-*P. malariae*	0.16	0.04
122	*P. brasilianum*	9 months	anti-*P. malariae*	1.05	0.04
131	*P. brasilianum*	7 months	anti-*P. malariae*	1.82	0.09
143	*P. falciparum*	43 days	anti-*P. falciparum*	0.48	none
148	*P. falciparum*	26 days	anti-*P. falciparum*	0.86	0.04
149	*P. falciparum*	26 days	anti-*P. falciparum*	0.41	none
150	*P. falciparum*	26 days	anti-*P. falciparum*	0.30	none

[a] The amounts of I^{125}-labelled specific IgG and I^{131}-labelled normal IgG injected by the intravenous route were the same as in Table 1.

Table 7. Amounts of I^{125}-labelled antimalarial IgG deposited in the kidneys of nephrotic patients after intravenous injection

No. of patients	IgG injected	Amount (in ng) of labelled IgG per g of tissue	
		homogenate (after last washing)	eluate (supernatant)
1	anti-*P. malariae*	9.86	9.85
4	*anti-P. malariae*	13.29	12.56
2	anti-*P. falciparum*	6.34	5.13
5	anti-*P. falciparum*	6.08	3.98
3	(control) [a]	3.07	1.82
6	(control) [a]	4.60	2.08

[a] No malarial antibodies.

DISCUSSION

Several important questions arise: (*a*) How does the lesion start? (*b*) Why does quartan malaria seem to be implicated in the etiology of these chronic progressive lesions? (*c*) What factors are responsible for the chronicity (perpetuation) of these lesions?

Malarial parasites are rarely present in the lesions (44) and have been demonstrated only in fatal malaria cases (38). Boonpucknavig et al. (6, 7) described parasitized erythrocytes in glomerular capillaries at the beginning of *P. berghei* infection in mice. The corpuscular form of antigen changed into the granular form, present in endothelial and mesangial cells, when antibody was produced (second week of infection). Therefore, the possibility that soluble malarial antigens and/or soluble immune complexes (trapped in the basement membrane) initiate the damage, seems more plausible. However, the original concept (40) of glomerular basement membrane damage by enzymes, such as lysozyme (3.2.1.17), may be still valid, since Suzuki (39) described granulocytes showing cytoplasmic extensions towards the glomerular endothelial cell layer in mice infected with *P. berghei*.

Infections with *P. malariae* are more often chronic and there may be prolonged liberation of antigens. There is strong evidence that *P. malariae* merozoites recycle in hepatic cells and thereby maintain the infection for very long periods (9). Immune response seems to be less effective to *P. malariae* than to *P. falciparum*; hence, moderate levels of soluble antigen–antibody complexes may circulate for a long time and form the " balanced " complexes required for localization in kidney tissue (10). Another possible explanation for the persistence of immune-complexes may be the low affinity of antibodies (8, 37, 43). Moreover, the possibility of local formation of immune-complexes in the vascular walls exists (29). In this case, localized immune-complexes may play the role of an immunoabsorbant binding either antigenic determinants or antibody-combining sites during filtration through renal glomeruli (30). If we

accept the importance of affinity, the replacement phenomenon of low affinity by high affinity antibodies cannot be excluded. This hypothesis seems quite relevant to our observations that immunoglobulins are eluted from renal tissue at two different pH levels (one of them between 5.5 and 6.0; the other, below 3.0).

The fact that only a small proportion of subjects with malariae infections develop renal lesions is still rather obscure and obviously depends on many other factors. The experimental data on *A. trivirgatus* monkeys showed similar results: Voller et al. (41) described a nephrotic syndrome (oedema and proteinuria) with deposits of IgM in one monkey (splenectomized) about 20 weeks after an infection that was resistent to antimalarials and progressed to a fatal outcome. Several other monkeys, some splenectomized, were infected with quartan malaria (42); in acute infections, proteinuria and IgM deposits in glomeruli were observed in all monkeys; in chronic infections, IgM and C3 deposits were present in some of them. Although all these animals developed some pathological changes, only one of them developed a typical nephrotic syndrome comparable to that occurring in man.

A very important question to consider is that of the factors that may be responsible for the chronicity of these lesions, e.g., for the perpetual immunoglobulin deposits in the capillary walls, which we demonstrated on repeated biopsies in patients with nephrotic syndrome who did not respond to therapy (22). It seems unlikely that these deposits are due to the constant supply of malarial antigens, since their detection decreases with the duration of the disease, and the progress of the disease is not affected by intensive antimalarial therapy (22, 48). Therefore, the possibility exists that malarial immune complexes trigger off a pathogenic sequence in which other mechanisms are later involved.

Autoimmune mechanisms have been considered from different aspects: (*a*) the release of autologous antigens as a result of plasmodium-inflicted damage or the liberation of altered tissue components, caused by deposited complexes, as well as the formation of antibodies. The participation of glomerular basement membrane constituents seemed to be unlikely, since the linear pattern of immunofluorescence was extremely rare in these nephropathies and all the eluates from the nephrotic kidneys examined failed to react with glomerular basement membrane on sections from normal kidney. Tubular antigens should be considered, since an intensification of tubular lesions (deposits of immunoglobulins and complement in proximal tubular cells) was observed in repeated biopsies (22). (*b*) There may be a self-perpetuating process (" vicious circle ") resulting from the formation of antiglobulins, immunoconglutinins, etc. (*c*) Cross-reactivity of plasmodial antigens with some autologous substances, such as DNA or RNA, may be involved—in which case plasmodial antibodies may initiate a chronic process similar to the nephritis occurring in systemic lupus erythematosus. These possibilities should be further investigated.

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RÉSUMÉ

IMMUNOPATHOLOGIE DES NÉPHROPATHIES ASSOCIÉES AU PALUDISME

Il est maintenant largement démontré que les immuncomplexes jouent un rôle important dans la pathogénèse des néphropathies associées au paludisme. Les résultats des études immunopathologiques font apparaître deux principaux types de lésions observables chez l'homme et l'animal d'expérience:

a) Lésions aiguës (passagères-réversibles), typiques des infections à *falciparum* chez l'homme, dans lesquelles des symptômes cliniques assez légers apparaissent une à deux semaines après l'infection; des biopsies rénales pratiquées à ce moment montrent des dépôts d'immunoglobulines, de complément et quelquefois d'antigène. Ces lésions réagissent favorablement aux antipaludiques et les anomalies urinaires ainsi que les dépôts d'immuncomplexes dans les glomérules disparaissent habituellement au bout de 4 à 6 semaines.

Dans des modèles expérimentaux d'infections aiguës, on a trouvé des dépôts d'immunoglobulines, de complément et d'antigène dès le neuvième jour suivant l'infection dans les glomérules de singes rhésus infectés par *P. cynomolgi* et 7 à 8 jours après l'infection chez des souris infectées par *P. berghei*.

b) Lésions chroniques (progressives), caractéristiques des infections paludéennes de type fièvre quarte (*P. malariae* chez l'homme et/ou le singe *Aotus trivirgatus*). Ces lésions apparaissent plus lentement et évoluent vers la chronicité avec une protéinurie persistante, de l'hypertension et une lente détérioration de la fonction rénale. On trouve dans les biopsies rénales des dépôts d'immunoglobulines, de complément et d'antigène anti-*P. malariae* dans les parois des capillaires des glomérules dès le début de la maladie. Le traitement antipaludique est absolument inefficace. Chez les sujets qui ne réagissent pas aux corticostéroïdes ou à d'autres traitements (c'est-à-dire la majorité des cas), les dépôts d'immunoglobulines et de complément sont persistants comme le montrent des biopsies répétées à un à deux ans d'intervalle.

En corrélant les résultats de l'immunofluorescence aux données cliniques et à la réaction aux traitements, on remarque que: *a*) l'aspect finement granulaire des dépôts d'immunoglobulines dans les parois des capillaires des glomérules (caractérisés par une coloration positive pour l'IgG, avec prédominance de G_2 et de complément négatif) pourrait avoir un caractère plus progressif que l'aspect granulaire grossier, positif pour l'IgG (G_3), l'IgM et le complément; *b*) si le concept classique de lésions induites par le complément est valable dans la plupart des cas, il convient d'examiner également la possibilité de lésions non induites par le complément; et *c*) l'examen des biopsies rénales peut non seulement fournir des renseignements sur les lésions existantes, mais peut aussi avoir une valeur pronostique.

L'examen au microscope électronique a confirmé le dépôt d'immuncomplexes dans la membrane basale des glomérules, en général près de la face épithéliale mais, dans les cas chroniques, sur toute l'épaisseur de la membrane.

Des observations immunochimiques récentes ont confirmé: 1) la présence d'antigènes solubles circulant dans le sang à l'état libre ou lié à l'anticorps (formant des immuncomplexes solubles dans un excès d'antigène) dans le paludisme à falciparum et à fièvre quarte, et 2) la localisation de l'anticorps spécifique dans les glomérules rénaux.

Toutes ces observations confirment l'appartenance de ces lésions au type à immuncomplexes et font ressortir leur association à l'infection paludéenne. Un certain nombre de questions restent toutefois en suspens, notamment la raison pour laquelle le paludisme à fièvre quarte semble impliqué dans l'étiologie des lésions chroniques, et la nature des facteurs responsables de l'auto-entretien de ces lésions.

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