

CLINICAL AND BIOLOGICAL STUDY OF *LOA LOA*

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Abstract. Clinical and biological evaluations were carried out on 84 Congolese patients with parasitologically confirmed *Loa loa* filariasis (without concurrent infection with other filariae) and on 98 controls without filariasis. Of the patients, 72 presented with microfilaremia; another 12 with negative blood tests were seen towards the end of an episode of subconjunctival migration of the adult worm. The incidence and severity of the clinical signs depended upon the method of recruitment. The 3 most common signs were pruritus and edema (both occurring in successive acute episodes affecting mainly the hands and forearms) and subconjunctival migration of adult filariae. Papulovesicular eruptions were located mainly on the arms. Headaches and arthralgia were noted more frequently than in the controls. No relation was found between the ABO blood groups and loiasis. Eosinophilia (higher in patients with symptoms) and raised serum IgE levels were found in nearly all patients and were strongly marked in ~66%. A positive correlation was observed between these 2 parameters. Fluorescent antibody levels (adult filaria *Dipetalonema viteae* antigen) were comparatively low in patients with microfilaremia.

Loa loa filariasis occurs exclusively in Africa and is endemic in the rain forest of Central Africa. In the Congo, loiasis is found chiefly in the southern and central areas of the country in cleared or primary forest areas.¹ In some villages, the prevalence of microfilarial carriers was about 40%,² a very high rate which has seldom been exceeded.³

Although the clinical signs of loiasis are well-known, subconjunctival migration of the adult worm having been reported for the first time by Mongin in 1770,⁴ most publications present isolated cases usually observed in European or American expatriates. Moreover, many publications on the symptomatology of this filariasis deal with proven or suspected visceral, mostly cerebral but also cardiac or renal, complications. This aspect was emphasized recently by Nuttman and others⁵ in their report of 20 cases occurring in temporary residents. Indeed, none of the 73 references mentioned the usual manifestations of loiasis observed in large numbers of indigenous patients. The same applies to our complementary survey of the literature. Thus we thought it would be interesting to report a clinical and biological study of 84 Congolese patients with loiasis without concurrent infection with other filariae.

MATERIALS AND METHODS

Between 1984 and 1986, 142 patients with parasitologically confirmed microfilaremia filariasis and 98 control subjects without filariasis, all Congolese, were enrolled in a systematic study conducted at the Institut Supérieur des Sciences de la Santé in Brazzaville. Two-thirds of the patients had been referred by the Blood Bank of the Brazzaville General Hospital after microfilariae had been detected in their blood. The others had been referred by various health centers of the city for examination by a specialist. The control subjects also came from the Blood Bank, but did not present with microfilaremia, dermal microfilariae, or previous histories of adult worm migration. The control subjects and filariasis patients sent by the Blood Bank were either voluntary blood donors or, more often, relatives or friends of hospitalized patients receiving blood transfusions.

In order to detect filarial infection, each patient was interviewed about their medical history, current signs, and specific medication. A routine clinical examination was carried out to detect pruritus, skin eruptions, edema, arthralgia, headaches, subcutaneous cysts, and subcutaneous and subconjunctival migration of adult worms.

TABLE 1

Predominant clinical signs observed in 84 loiasis patients (without concurrent infection with other filariae) and in 98 control subjects

	Group I patients* n = 54		Group II patients† n = 30		Control subjects n = 98	
	Frequent	Infrequent, former, nonexistent, or uninterpretable	Frequent	Infrequent, former, nonexistent, or uninterpretable	Frequent	Infrequent, former, nonexistent, or uninterpretable
Pruritus‡	27 (50%)	27 (50%)	25 (83.8%)	5 (16.7%)	8 (8.2%)	90 (91.8%)
Skin eruptions	15 (27.8%)	39 (72.2%)	10 (33.3%)	20 (66.7%)	5 (5.1%)	93 (94.9%)
Edemas	11 (20.4%)	43 (79.6%)	25 (83.3%)	5 (16.7%)	2 (2%)	96 (98%)
Arthralgia	8 (14.8%)	46 (85.2%)	8 (26.7%)	22 (73.3%)	7 (7.1%)	91 (92.9%)
Headache	16 (29.6%)	38 (70.4%)	10 (33.3%)	20 (66.7%)	12 (12.2%)	86 (87.8%)
	Group I			Group II		
AF§ Migration	Recent	Former	Nonexistent or uninterpretable	Recent	Former	Nonexistent or uninterpretable
Subconjunctival	5 (9.3)	16 (29.6)	33 (61.1)	19 (63.3)	4 (13.3)	7 (23.3)
Cutaneous	0	1 (1.9)	53 (98.1)	2 (6.7)	1 (3.3)	7 (90)

* Patients referred by the Blood Bank of Brazzaville General Hospital.

† Patients referred to the parasitology outpatient department by health centers.

‡ Excluding pruritus after chloroquine.

§ AF = Adult Filariæ.

Laboratory tests included the detection and enumeration of microfilariae in the blood and skin. Two thick smears of capillary blood, calibrated at 20 mm³, were taken from patients' fingertips between 0900 and 1100 hours. The mean microfilarial density was evaluated each time (result given for 20 mm³). Two calibrated (2.3 mm Holth pliers) snips taken from the iliac crests were placed in 50 µl saline and read after 2–4 hr.

Overall, 142 patients presented with microfilaræmia filariasis. Of these, 84 showed loiasis without concurrent infection with other filariae by parasitological blood and skin tests. Among these, 72 showed microfilaræmia after examination of 40 mm³ blood; 12 patients with negative blood tests were seen towards the end of episodes of subconjunctival migration of adult worms, confirmed by physicians. The Blood Bank referred 54 cases (Group I) and health centers referred 30 cases (Group II). The 98 control subjects were all referred by the Blood Bank. As a result of the recruitment method, a large proportion of both loiasis patients and control subjects were men aged 20–40 years. The patients were comprised of 61 men (72.6%) and 23 women (age 10–70 years; mean 34 years). The controls were comprised of 74 men (75.5%) and 24 women (age 18–52 years; mean 31 years).

The majority of loiasis patients and a fair proportion of the controls underwent the following additional laboratory tests: ABO blood grouping (53 patients and 80 controls); evaluation of eo-

sinophilia (57 patients and 37 controls); determination of total IgE levels using an immunoenzyme technique (Phadezym IgE Prist Kits, Pharmacia, France) for 51 patients and 40 controls; and screening for antibodies to filariasis by indirect immunofluorescence (IIF) using 5 µm thick frozen sections of adult filaria *Dipetalonema viteae* embedded in a hamster heart as antigen (58 patients and 78 controls).

RESULTS

Clinical manifestations

The incidence and characteristics of the main clinical manifestations of loiasis observed are summarized in Tables 1 and 2. Pruritus, skin eruptions, edema, arthralgia, and headaches were classified into 2 categories: as manifestations occurring frequently or as former manifestations, unstated, or uninterpretable responses. Headaches were considered frequent if they occurred at least twice a month other than during fever. Observations regarding adult worm migration were classified into 3 categories: recent episodes (occurring within the previous 3 months), former episodes, and unstated or uninterpretable responses. In control subjects, this symptom was of course nonexistent, since only individuals who denied its occurrence were selected as controls.

Patients in Group II showed more symptoms (both edema and pruritus occurred in 83.8% of

the cases) than patients in Group I (20.4% presented edema, 50% pruritus). This difference can be accounted for by the method of recruitment. In the control subjects, edema and pruritus were observed in only 2% and 8.2% of the cases, respectively. Since adult worm migration (subconjunctival rather than cutaneous) is a frequent reason for seeking medical advice, it is not surprising that this symptom occurred more frequently in Group II (78.6%). However, adult worm migration was reported in nearly 33% of patients in Group I. Furthermore, 12 of the 19 patients (63%) in Group II with recent subconjunctival migration had no detectable microfilaremia. For headache and arthralgia, which are not typically filarial manifestations, significant differences were observed between Group II patients (33% and 27%, respectively) and control subjects (12% and 7%, respectively; $P < 0.01$). The incidence of headache was also higher in Group I patients than in the controls (30% vs. 12%; $P < 0.05$).

The common characteristics of the predominant signs, pruritus and edema, were determined by considering only the patients (in both groups) who had given sufficiently precise replies at the interview (Table 2). Pruritus was taken into account only if it was unrelated to 4-aminoquinoline therapy and if real discomfort was experienced. Edema was considered frequent if it occurred at least every 2 months, and transient if it lasted < 3 days. Pruritus was found to be localized in most cases, mainly on the hands, wrists, and forearms. It was characterized by successive acute episodes and various degrees of severity. Similarly, edema affected preferentially the hands, wrists, and forearms. Edema on the face, the classic localization, was rare. Although painless and transient in most patients, it sometimes caused marked functional impairment and the migratory aspect was not always obvious. The arms were also the preferential site for skin eruptions. Headaches were characterized mostly as hammering in the forehead. Arthralgia often affected several joints, primarily the knees and wrists; the elbows and ankles were also frequently mentioned, but not the shoulders, hips, or hands.

Biological data

Microfilarial density. In the 72 patients with microfilaremia, the mean microfilarial density was 58.7/20 mm³ (range 0.5-340). There were

TABLE 2
Clinical characteristics of pruritus and edemas observed in loiasis patients without concurrent infection with other filariae

	Description*				Localization*					
	Diffuse	Localized	Severe	Mild	Episodic†	Continuous	Face	Arms	Trunk	Legs
Pruritus‡	16 (42.1%)	22 (57.9%)	20 (51.3%)	19 (48.7%)	32 (86.5%)	5 (13.5%)	3 (8.8%)	21 (61.8%)	6 (17.6%)	4 (11.8%)
Edemast	4 (7.7%)	48 (92.3%)	52	52	52 (100%)	0 (0%)	6 (12.5%)	36 (75%)	3 (6.2%)	3 (6.2%)
				39	37				34	

* Only those cases in which the description was sufficiently precise were taken into account.

† Including only frequent pruritus.

‡ Including frequent and infrequent edemas.

TABLE 3
Distribution of filariasis patients and control subjects by blood type

	Blood types			
	A	B	AB	O
Loiasis patients n = 53	17%	15.1%	7.5%	60.4%
Control subjects I* n = 80	22.5%	20%	5%	52.5%
Control subjects II† n = 13,045	21.7%	21.1%	3.7%	53.4%

* Subjects with negative tests for filariasis.

† Total of blood donors in 1985.

no differences between Group I and Group II patients.

ABO blood group. The ABO blood distribution was similar among loiasis patients and control subjects. Type O was found in slightly more than 50% of the subjects, types A and B in about 20% each, and type AB was infrequent (Table 3).

Eosinophilia. Eosinophilia was found in nearly all cases ($>500/\text{mm}^3$ in 94.7% of the patients). The level was high ($>1,000/\text{mm}^3$) in 68.4%, with a mean of $1,457/\text{mm}^3$ and a range of 248–3,341). Of the control subjects, 27% presented eosinophilia levels of $>500/\text{mm}^3$ and 5.4% levels $>1,000/\text{mm}^3$; the mean level for controls was $279/\text{mm}^3$ and the range was 210–1,324. The level was higher in Group II patients than in Group I patients ($1,807/\text{mm}^3$ vs. $1,322/\text{mm}^3$; $t = 2.29$, $df = 55$, $P < 0.05$). In the 4 patients without detectable microfilaremia but with measured eosinophilia, the level was $2,295/\text{mm}^3$ (Table 4).

Serum IgE. IgE levels were high. Over 600 IU/ml were found in 80.4% of the cases, and $>2,000$ IU/ml in 66%. The mean level of 4,280 IU/ml is lower than the true mean, as values $>15,000$ IU/ml, observed in 4 cases, were not exact determinations. The mean IgE levels were similar in Groups I and II. In the control subjects, IgE values were also high, though much lower than in the patients. The mean level for controls was 1,680 IU/ml with a range of 50–7,200. Levels >600 IU/ml and $>2,000$ IU/ml were present in 72.5% and 25.5% of the subjects, respectively (Table 4).

Specific fluorescent antibodies. A titer of at least 1/200, considered as indicative of immunological filariasis with the method used in this study, was found in only 51.7% of the cases. The geometrical mean reciprocal titer (GMRT) was 69.3 (range 0–3,200). It should be noted that of the 5

patients without microfilaremia who had experienced a recent episode of filarial migration, 4 presented positive serologic results. Among the controls, 12.8% were positive and the GMRT was 9.8 with the highest level being 800 (Table 4).

Correlations. A positive correlation was noted for IgE and eosinophilia levels in loiasis patients (47 validated, $r = 0.341$, $P = 0.019$). This correlation can be taken into account since the distribution for eosinophilia was normal, but deviated slightly for IgE levels. Two other positive correlations related to loiasis patients were observed: IgE level–IIF titer and microfilaremia–IIF titer. These correlations are questionable, since the distribution of IIF titer deviated too far from the normal distribution.

DISCUSSION

In endemic areas, *Loa loa* filariasis often occurs with *Mansonella perstans* filariasis and sometimes with onchocerciasis or even with streptocerciasis. These 4 diseases are endemic in the Congo,^{1,6} unlike lymphatic filariasis, which we have never diagnosed in indigenous subjects. Among 142 patients with microfilaremia filariasis in our study, 20 presented with *L. loa* and *M. perstans*, 9 with *L. loa* and *Onchocerca volvulus*, 1 with *L. loa*, *M. perstans*, and *O. volvulus*, and 28 with *M. perstans* alone.

In the absence of published investigations on loiasis involving sufficiently large numbers of patients with parasitological evidence in which other filarial infections are excluded, it is difficult to make any comparative analysis of the usual clinical and biological signs of the disease. Although fewer symptoms are observed in the indigenous population than in temporary residents, in spite

TABLE 4
Blood eosinophilia, total serum IgE, and fluorescent filaria antibody levels

		n	Mean*		Range	Percent positive (threshold 1/200)
			Ar	Geo		
Blood Eosinophilia/mm ³	Patients					
	Group I	41	1,322	—	248–3,105	—
	Group II	16	1,807	—	536–3,341	—
	Total	57	1,457	—	248–3,341	—
	Control	37	279	—	210–1,324	—
Serum IgE IU/ml†	Patients					
	Group I	39	4,324	—	100->15,000	—
	Group II	12	4,131	—	120->15,000	—
	Total	51	4,280	—	100->15,000	—
	Control	40	1,680	—	50–7,200	—
Filarial IIF Reciprocal titer‡	Patients					
	Group I	42	—	66.4	0–3,200	50%
	Group II	16	—	77.4	0–1,600	56.2%
	Total	58	—	69.3	0–3,200	51.7%
	Control	78	—	9.3	0–800	12.8%

* Ar = Arithmetic; Geo = Geometrical.

† Levels above 15,000 IU/ml (4 patients) were not exactly determined, thus the true means are greater than those shown.

‡ Rather than a geometrical mean reciprocal titer, this is a William's mean taking into account the values equal to zero. The value of zero was attributed to the cases for whom the reaction was negative at a dilution of 1/100.

of the fact that microfilaremia develops less frequently in temporary residents⁵ (this also applies to lymphatic filariasis),^{7,8} we have demonstrated in this study that such symptoms do occur. The incidence and severity of clinical signs depend on the method of recruitment, being higher in the patients referred by the health centers. However, symptom-free forms are not infrequent. A good host-parasite adaptation is the argument commonly put forward to explain this fact.⁹ This may involve a genetic predisposition,¹⁰ immunological receptiveness following prenatal sensitization,¹¹ or both. Tissue and blood groups do not seem to be involved.

In contrast with other forms of microfilaremia filariasis, the number of carriers of *Loa loa* microfilariae does not usually exceed 33% of the population,³ even in hyperendemic areas.¹² It is interesting to note the large numbers of cases of conjunctival adult filaria migration in subjects without detectable microfilaremia, in spite of the high fertility of the female worm.¹³ This was observed as early as 1913¹⁴ and again in this study (12 cases).

Pathological manifestations are mainly related to allergic reactions produced by the elimination of antigenic substances by migrating adult filariae or by microfilariae recently released in the dermis.^{15,16} The same antigens produce eosinophilia

and high IgE levels, which in turn produce a defense mechanism with antibody-dependent cell cytotoxicity,¹⁷ which is partly responsible for the destruction of microfilariae.

The arms are the preferential site of pruritus, edema, and skin eruption. Localization on the hands and the lower half of the forearms, especially for edema, seems highly suggestive of loiasis. It is rarely found in onchocerciasis. The characteristics of edema (occurring in successive acute episodes, moving from 1 place to another) are also quite different from edema occurring in other filariasis. Although painless, they often cause functional impairment and numbness. This preferential localization seems to be related to the site of adult filariae. In 1905, Penel¹⁸ reported the dissection of a patient which revealed 34 adult worms in the superficial connective tissue and under the superficial aponeurosis of limb muscles and tendons, primarily in the arms.

Filariae creeping beneath the skin is seldom demonstrated in Africans, but the worm can be found in edema, leading to abscess formation following specific therapy. This was seen on 2 recent occasions in the Congo (data not shown). Migration under the conjunctiva is frequent and, as a rule, quite benign. Following treatment with local remedies and for unsuccessful attempts at extraction, the filariae may die in situ and remain

there for several months without any marked functional impairment.¹⁹ Intra-ocular involvement is extremely rare, and is probably due to the early penetration of a larva via the blood and not to the penetration of an adult worm through the sclera.²⁰

The incidences of headache and arthralgia, which are not the usual signs of loiasis, are worth noting. These symptoms occurred or became more severe in the first few days of treatment with Diethylcarbamazine (DEC), this being related to microfilaria lysis.²¹ Microfilariae have been demonstrated in synovial fluid.²² No clinically-obvious glandular lesions were observed.²³

The classical visceral complications (encephalitic, cardiac, and renal) were not systematically or satisfactorily investigated. Few patients in our study had a high density of microfilariae. The mean microfilarial density was comparatively low, the maximum density being 340/mm³. Given the periodicity of microfilaraemia, blood samples were always taken after 0900 hours, when microfilaraemia was at least 50% of its maximum value (maximum reached at 1300 hours).²⁴ Most of the patients had resided several years in Brazzaville where loiasis is not transmitted. Transmission occurs in surrounding rural areas. The southwest of the Congo is a highly endemic region. Recently, 6 cases of loiasis encephalitis following DEC therapy were observed.²⁵

A relationship between the ABO blood groups and *Wuchereria bancrofti* filariasis, showing a larger number of type A subjects and a lesser number of type B subjects, has been reported in Japan.²⁶ No such relationship could be found for loiasis in Nigeria.²⁷

Similarly, few publications refer to the rise in blood eosinophilia or IgE level. Each case was reported individually and always occurred in temporary residents.⁵ Until this study, our experience in the Congo was similar. The findings presented here show that eosinophilia and raised IgE levels also occur in the indigenous population, but the values are lower. Persistent high eosinophilia may be the cause of chronic African endomyocardial fibrosis.²⁸ It is interesting to note the positive correlation between eosinophilia and IgE levels and also the higher levels of eosinophilia in Group II patients who exhibited more symptoms.

The low sensitivity of IIF serological tests can partly be accounted for by the high percentage

of patients with microfilaraemia (54 of 58 tested). Indeed, microfilaraemic patients with filariasis in general²⁹ and loiasis in particular³⁰ have lower antibody levels than patients without microfilaraemia. The results obtained in the controls (positive in 13% of the cases) suggest that some of the subjects may have had filariasis without specific clinical or parasitological manifestations. However, false positive responses related to another helminthiasis, in spite of the high threshold selected, cannot be ruled out. The comparatively high eosinophilia and serum IgE levels are also indicative of concurrent parasitic infection³¹ (for example, intestinal nematode infections, which are quite frequent in Brazzaville itself³² and in unselected filariasis patients).

Acknowledgments: The authors are grateful to Gérard Niel and Jean Sainte-Laudy, Laboratoire de Parasitologie, Centre Hospitalier Pitié-Salpêtrière, Paris, France, for laboratory facilities.

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