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Clinical Features of Imported Loiasis: A Case Series from the Hospital for Tropical Diseases, London

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Abstract. We retrospectively analyzed the background, clinical features, and treatment response of 50 cases of imported loiasis who presented between 2000 and 2014 to the Hospital for Tropical Diseases (HTD), London, United Kingdom. Of them, 29 were migrants from, and 21 were visitors to, countries where the disease is endemic. Clinical features differed between these groups. Migrants experienced fewer Calabar swellings (odds ratio [OR] = 0.12), more eye worm (OR = 3.4), more microfilaremia (OR = 3.5), lower filarial antibody levels, and lower eosinophil counts ($P < 0.05$ for all tests). Among 46 patients who were started on treatment at HTD, 33 (72%) received diethylcarbamazine (DEC) monotherapy as first-line treatment, and among 26 patients who were followed up after treatment, seven (27%) needed a second course of treatment. There were 46 courses of treatment with DEC, and 20 (43%) of them had reactions. All patients with microfilaremia $> 3,000$ microfilariae/mL and all those with an elevated C-reactive protein (CRP) (≥ 5 mg/L) before treatment had reactions ($P = 0.10$ and $P = 0.01$, respectively). These data suggest that monotherapy with DEC may not be the optimal treatment for patients with loiasis, particularly for those with a high microfilarial load.

INTRODUCTION

Loiasis is a systemic filarial infection caused by *Loa loa*. It is also called “African eye worm” as adult worms can be seen intermittently under the conjunctiva of infected people. Another characteristic symptom is transient and migratory edema, usually on the peripheries, known as Calabar swellings. Loiasis is transmitted by adult female *Chrysops* flies and its epidemiology is largely dependent on the distribution of the fly: loiasis is confined to forest areas of central and west Africa.¹ More than 10 million people are estimated to be infected,² and in some areas loiasis is the most common reason for visiting hospital.³

Loiasis is also seen as an imported infection among visitors (travelers and expatriates) and migrants. One survey among travel clinics showed loiasis constituted 25% of filarial infection seen in non-endemic countries.⁴ Previous reports have described differences in the clinical features between visitors to and migrants from endemic areas. Patients from non-endemic countries are more likely to present with Calabar swellings, eosinophilia, and positive filarial serology, but are less likely to have microfilaremia and eye worm.^{5–8} These differences are thought to result from differences in immunological responses to the worm,^{7,9,10} but it is unclear whether this is because of host genetic differences or other factors such as the duration of infection or the age at which infection occurred.

Traditionally, the mainstay treatment is chemotherapy with diethylcarbamazine citrate (DEC) but significant reactions during treatment commonly occur. Fatal encephalopathy is known to be associated with the density of microfilariae.^{11,12} Corticosteroids and antihistamines are often used concomitantly to reduce the severity of these reactions, although this is based on expert opinion rather than shown by clinical studies.^{13,14}

Loiasis, even as an imported disease, is relatively uncommon outside west and central Africa, and most patients with imported disease are treated at specialist centers. This study retrospec-

tively analyzed the demographics, clinical features, and treatment response of 50 patients with loiasis seen at the Hospital for Tropical Diseases (HTD), London, United Kingdom, between 2000 and 2014.

PATIENTS AND METHODS

Patients who had a working or final diagnosis of loiasis were identified from two databases, which recorded all inpatients and outpatients presenting to HTD between 2000 and 2014. Cases were defined according to the following criteria. Proven cases were those with confirmed microfilaremia of *L. loa* in peripheral blood or those who had adult worms extracted, usually from the eye. Probable cases were defined as those with a clinical diagnosis of Calabar swellings and/or eye worm, supported by treatment response and/or with positive filarial serology, and who had been to west or central Africa but had negative blood tests for microfilaremia. There were 30 proven and 22 probable cases, but for two of the confirmed cases, the case notes could not be traced. The following were extracted from case notes and electronic records: demographic data, travel history, presenting symptoms and signs, laboratory data, details of treatment, and follow-up. Some records were missing and the number of cases included was noted in the analysis. To investigate different exposure effects on loiasis, we classified patients into two groups: Africans from endemic countries (migrants) and all others (visitors).

Duration of stay in an endemic area was calculated as the sum of the duration of any stay(s) in endemic countries. Maximum incubation period was calculated as the time between first entry to an endemic country and the onset of symptoms or day of diagnosis if asymptomatic.

The load of microfilaremia was assessed by filtration technique, usually using 20 mL peripheral blood collected in citrate tubes around midday (“day bloods”) reflecting the periodicity of the infection.

Filarial serology was assessed by an enzyme-linked immunosorbent assay (ELISA) using a soluble extract of *Brugia pahangi* adult worms. The results were expressed in banded levels of optical density from 0 to 9, with a level of 1 or above regarded as positive.

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Eosinophilia was defined as a peripheral blood eosinophil count of more than $0.45 \times 10^9/L$. C-reactive protein (CRP) was defined as positive when it was ≥ 5 mg/L.

Reactions to treatment were defined as new symptoms or worsening of pruritus during and within 7 days after the start of chemotherapy.

STATA/IC 13.1 (StataCorp LP, College Station, TX) was used to analyze the data with Mann–Whitney's *U* tests and two-sided *t* tests for analyzing quantitative data as appropriate. The first quartile (Q_1) and third quartile (Q_3) are shown in square brackets [Q_1 – Q_3] and 95% confidence intervals (CIs) are shown in parentheses. For categorical data, χ^2 tests or Fisher's exact tests with two-sided uncorrected *P* value were used as appropriate.

RESULTS

Background of patients. Migrants and visitors had different characteristics (Table 1). The median age at first symptoms among migrants was 11 years younger ($P = 0.003$). Median duration of stay in endemic areas among migrants (270 months) was longer than that among visitors (6 months). Similarly, the maximum incubation period was longer among migrants (294 months in median) than that among visitors (10.5 months, $P < 0.001$).

The most common countries of acquisition among migrants were Nigeria (16/29, 55%) and Cameroon (9/29, 31%), whereas those among visitors were Cameroon (6/20, 30%), Central African Republic (4/20, 20%), and Gabon (3/20, 15%). Information from one visitor was not available.

Symptoms and signs. Migrants experienced fewer Calabar swellings (odds ratio [OR] = 0.12, 95% CI = 0.03–0.47, $P = 0.002$) and more eye worm (OR = 3.4, 95% CI = 1.0–11.4, $P = 0.049$). Other eye symptoms, such as redness, swelling of the conjunctiva, and a sensation of worms crawling under the eyelids, were relatively common (42% of all patients). The frequency of other symptoms was not different between the groups and physical examination was usually unremarkable (Table 2).

Calabar swellings were commonly reported on the extremities: hand or wrist (19/30, 63%), forearm (21/30, 70%), upper arm (3/30, 10%), leg (10/30, 33%), and feet (7/30, 23%). Other sites included eyelids (5/30, 17%), lips, postauricular area, neck, and chest. Of the patients, 37% reported pain and 47% had itchiness at the sites of swellings, but only 10% described both. Duration of any one swelling ranged from several hours to about 2 weeks.

Eight patients had both Calabar swellings and eye worm. Five of these (63%) had swellings 6–128 months earlier. Three

(38%) had both at almost the same time, and there were no cases where eye worm preceded Calabar swellings.

Laboratory findings before treatment. Total eosinophil counts were lower among migrants ($P = 0.004$), although the proportion of patients with eosinophilia was high in both groups (72% of migrants and 86% of visitors) (Table 3). Microfilariae were seen more frequently among migrants (OR = 3.5, 95% CI = 1.0–11.7, $P = 0.04$). The number of microfilariae in microfilaremic patients was not different ($P = 0.63$), although the maximum microfilarial load in migrants was higher than that in visitors (301,000 and 5,600 microfilariae/mL [mf/mL], respectively). Filarial serology was positive less frequently (OR = 0.27, 95% CI = 0.07–0.98, $P = 0.05$) and with lower optical density among migrants ($P = 0.004$).

"Night bloods" for microfilaremia, taken around midnight, were examined in seven of 28 cases who had microfilaremia to rule out the possibility of coinfection with *Wuchereria bancrofti*. None of them were found to be coinfecting.

Treatment options. Information about treatment was available for 48 cases. Of them, 46 started treatment of loiasis at HTD. The treatment of choice was DEC (33/46, 72%) but, because of problems with consistent supply of this drug and dependent on the microfilarial load, other anthelmintics were used: ivermectin alone (4/46, 9%), albendazole alone (4/46, 9%), ivermectin followed by DEC (3/46, 7%), albendazole plus ivermectin (1/46, 2%), and albendazole followed by DEC (1/46, 2%). Decisions in all of the albendazole plus ivermectin group, 75% of the albendazole group and half of the ivermectin group could be attributed to the limited supply of DEC at that time. A combination of ivermectin or albendazole followed by DEC was chosen on clinical grounds for some patients with higher microfilarial loads.

The dose of DEC was 600 mg/day for 21 days for all patients except one who was given 450 mg/day adjusted to his body weight. DEC was started from a low dose (50 mg/day) and was gradually increased to the full dose over 2–4 days. The ivermectin dose was based on body weight: approximately 0.2 mg/kg/day ranging from 12 to 20 mg/day as a single dose. The albendazole dose was 400 mg/day for 21 days for all patients except one who was given 800 mg/day. In all patients with microfilaremia except one, DEC was started as an inpatient, while other drugs were sometimes prescribed on an outpatient basis.

Reaction. In total and allowing for retreatments, there were 71 courses of treatment. Reactions were reported during 21 (30%). The only marked reaction was severe pruritus, which necessitated an interruption of treatment with DEC

TABLE 1
Characteristics of patients stratified by migrants and visitors

	Migrants	Visitors	<i>P</i> value*
Number of patients	29	21	–
Age at first symptom (in years)	Median: 25.0 [21.0–31.0] ($N = 29$)	Median: 36.0 [27.0–51.0] ($N = 21$)	0.003
Sex	Male: 14 (48%) Female: 15 (52%)	Male: 16 (76%) Female: 5 (24%)	–
Duration of stay in endemic countries (months)	Median: 270 [201–310] Minimum: 36 Maximum: 636 ($N = 28$)	Median: 6 [3–30] Minimum: 1.25 Maximum: 120 ($N = 13$)	< 0.001
Maximum incubation period (months)	Median: 294 [240–340] Minimum: 48 Maximum: 642 ($N = 20$)	Median: 10.5 [8–48] Minimum: 4 Maximum: 144 ($N = 10$)	< 0.001

– = not applicable.

*Mann–Whitney's *U* tests are used.

TABLE 2
Symptoms and signs among migrants and visitors and OR for migrants on appearance of symptoms and signs

	Migrants (<i>N</i> = 29)	Visitors (<i>N</i> = 21)	OR (95% CI)	<i>P</i> value*
Symptoms				
Calabar swellings	12 (41%)	18 (86%)	0.12 (0.03, 0.47)	0.002
Eye worm	15 (52%)	5 (24%)	3.4 (1.0, 11.4)	0.049
Other eye symptoms	14 (48%)	7 (33%)	1.9 (0.59, 5.8)	0.30
Fever	5 (17%)	3 (14%)	1.3 (0.29, 5.4)	0.78
Arthralgia	3 (10%)	5 (24%)	0.37 (0.09, 1.6)	0.20
Myalgia	1 (3%)	3 (14%)	0.21 (0, 1.7)	0.17
Pruritus	9 (31%)	2 (10%)	4.3 (0.90, -)	0.07
Urticaria/rash	3 (10%)	4 (19%)	0.49 (0.11, 2.2)	0.39
Asymptomatic	1 (3%)	0 (0%)	-	0.39
Physical signs				
Calabar swellings	8 (28%)	9 (43%)	0.51 (0.16, 1.6)	0.27
Eye worm	9 (31%)	4 (19%)	1.9 (0.52, 6.9)	0.35
Fever	3 (10%)	1 (5%)	2.3 (0.30, -)	0.48
Lymphadenopathy	1 (4%)	0 (0%)	-	0.39

CI = confidence interval; OR = odds ratio; - = not applicable.

* χ^2 tests are used.

in one patient. The other 20 reports were mild and tolerable. There were 20 reactions (43%) among patients treated with DEC and one (7%) among patients treated with ivermectin. There were no reports of reactions among patients treated with albendazole (*N* = 8) or albendazole plus ivermectin (*N* = 4). There could have been reporting bias depending on whether patients were hospitalized or not, although most treatment was started during hospitalization: DEC (33/46), ivermectin (4/14), albendazole (5/8), and albendazole plus ivermectin (1/4).

Next, we assessed factors that were associated with reaction in patients treated with DEC as first treatment. All patients with microfilaremia > 3,000 mf/mL had reactions (100% versus 46%, *P* = 0.10). All patients with raised CRP (≥ 5.0 mg/L) before treatment had reactions (100% versus 35%, *P* = 0.01). Planned preventive use of corticosteroid was not associated with reaction; 60% of users and 44% of nonusers experienced reaction (*P* = 0.48).

Treatment outcome. A total of 36 patients (75%) received one treatment course, 10 patients (21%) received two, one patient (2%) received four, and one patient (2%) received five courses. Sixty courses of treatment from 41 patients were followed up after completion of treatment for a median period of 95 [24–291] days. The percentage of patients who underwent retreatment after the first course was 27% (7/26) for DEC, 60% (3/5) for ivermectin, 67% (2/3) for albendazole, 50% (1/2) for ivermectin plus albendazole, and 0% (0/2) for ivermectin followed by DEC. Seven patients received two courses of a

DEC-containing regimen. None received DEC more than twice. The reasons for the second treatment of the DEC-containing regimen were recurrent Calabar swellings (*N* = 4), recurrent eye worm (*N* = 1), persistent microfilaremia (*N* = 1), and persistent eosinophilia (*N* = 1). Eight patients did not receive DEC treatment. Of these, only three had confirmed clinical improvement after therapy, and the other five were lost to follow-up.

DISCUSSION

Characteristics of symptoms. Classically, Calabar swellings are said to be non-tender.³ However, more than one-third of the patients with Calabar swellings complained of pain or itch. This is consistent with a previous report from endemic areas.¹⁵ Although Calabar swellings typically appear on extremities,^{3,13} some patients experienced swellings on other parts of the body: swellings on the eyelid were seen more frequently than that on the upper arms in this series.

“Other eye symptoms” were more frequently seen than eye worm. This could be due to unnoticed eye worm because conjunctivitis has been reported after the observation of eye worm.¹⁶

Differences between migrants and visitors. This study confirms previous findings on differences between migrants and visitors; Calabar swellings and positive filarial serology were reported less frequently whereas eye worm and microfilaremia were reported more frequently among migrants; eosinophilia was commonly found among both groups (Table 4).

TABLE 3
Characteristic laboratory findings among migrants and visitors and OR for migrants on positive findings

	Migrants	Visitors	OR (95% CI)	<i>P</i> value
Eosinophilia	21/29 (72%)	18/21 (86%)	0.4 (0.1, 1.8)	0.26*
Geometric mean of eosinophil counts (95% CI) ($\times 10^9$ /L)	0.71 (0.50–1.00) (<i>N</i> = 27)	2.04 (0.97–4.28) (<i>N</i> = 18)	-	0.004†
Microfilaremia	20/29 (69%)	7/18 (39%)	3.5 (1.0, 11.7)	0.04*
Microfilarial load in microfilaremic patients (mf/mL)	Median 759 IQR [167–6,265] Maximum 301,000 (<i>N</i> = 20)	Median 1,172 IQR [50–2,000] Maximum 5,600 (<i>N</i> = 6)	-	0.63‡
Positive filarial serology	14/27 (52%)	16/20 (80%)	0.3 (0.1, 1.0)	0.05*
Median serology levels in seropositive patients [IQR]	2.0 [2.0–4.0] (<i>N</i> = 14)	5.0 [4.0–7.0] (<i>N</i> = 14)	-	0.004‡

CI = confidence interval; IQR = interquartile range; mf = microfilariae; OR = odds ratio; - = not applicable.

* χ^2 tests were used.

†*t* test was used.

‡Mann-Whitney's *U* tests were used.

TABLE 4
Summary of present and past studies on imported loiasis comparing migrants with visitors

	Present study		Gobbi and others ⁸		Gantois and others ⁶		Churchill and others ⁵		Klton and others ^{7,17,18}		Antinori and others ⁹ (review of case reports)	
	Migrants	Visitors	Endemic cases	Non-endemic cases	Born in endemic area	Born in non-endemic area	Africans	Expatriates	Expatriates	Expatriates	Immigrants	Expatriates/travelers
Number	29	21	30	70	24	23	51	49	42	54	47	
Age at diagnosis (years)	27†	38†	33.4*	51.3*	31*	37*	25.6†	33.4†	26†	30†	30†	
Sex (Male:Female)	14:15	16:5	—	—	9:15	9:14	19:32	28:21	24:18	33:21	16:31	
Calabar swelling	12/29 (41%)	18/21 (86%)	14/30 (47%)	63/70 (90%)	12/24 (50%)	18/23 (78%)	18/51 (35%)	40/49 (82%)	40/42 (95%)	12/54 (22%)	30/46 (65%)	
Eye worm	15/29 (52%)	5/21 (24%)	13/30 (43%)	12/70 (17%)	8/24 (33%)	6/23 (26%)	23/51 (45%)	8/49 (16%)	4/42 (10%)	29/54 (54%)	25/47 (53%)	
Eosinophilia	21/29 (72%)	18/21 (86%)	22/30 (73%)	58/70 (83%)	19/23 (83%)	20/21 (95%)	33/49 (67%)	45/48 (94%)	42/42 (100%)	28/41 (68%)	41/43 (95%)	
Microfilaraemia	20/29 (69%)	7/18 (39%)	19/30 (63%)	16/70 (24%)	13/24 (56%)	10/23 (43%)	38/51 (75%)	14/49 (29%)	4/42 (10%)	32/41 (78%)	19/42 (45%)	
Positive filarial serology	14/27 (52%)	16/20 (80%)	— (60%)	— (81%)	14/14 (100%)	12/12 (100%)	5/18 (28%)	28/30 (93%)	42/42 (100%)	—	—	
(ELISA)												
Reaction to DEC	20/46 (43%)	—	3/36 (8.6%)	—	0/11 (0%)	—	22/108 (20%)	—	> 16/20 (> 80%) ¹⁷	—	—	
Treatment failure of DEC	7/26 (27%)	—	14/25 (56%) [‡]	—	3/10 (30%)	—	9/75 (12%)	—	20/32 (63%) ¹⁸	—	—	
Follow-up period	95 days†	—	—	—	422 days*	—	3 months†	—	4.5 years† ¹⁸	—	—	

DEC = diethylcarbamazine; ELISA = enzyme-linked immunosorbent assay; — = data not available.

*Mean.

†Median.

‡Patients treated with ivermectin plus DEC. Eosinophilia is defined as an eosinophil count $> 0.50 \times 10^9/L$ (except this study and the study by Gobbi: $> 0.45 \times 10^9/L$). Follow-up periods include data from all patients regardless of the treatment regimens. Treatment outcomes in the cohort of Klton and others⁷ were supplemented by results from other studies,^{17,18} which included the same cohort.

Treatment outcome. Although the definition of cure and duration of follow-up varied between previous reports, treatment failure was reported among 10–65% of patients treated with DEC. This variation in failure rate may be explained by differences in the microfilarial burden between patients in each study. An alternative explanation may be different length of follow-up and/or criteria for re-treatment between studies. Although these factors make it difficult to assess the efficacy of DEC, it would appear that the rate of treatment failure may be around one in three if DEC is used alone. However, neither ivermectin nor albendazole can provide a cure for the disease without DEC as DEC is the only drug that kills the adult worm.³ A combination of DEC given after ivermectin or albendazole may be the most appropriate strategy, depending to some extent on the microfilarial load with albendazole used as first-line treatment in those with very high burdens. Reported rates of reaction are variable, ranging from 0%⁶ to > 50%.^{14,17} This might be due to the variable criteria for defining a reaction. The evidence in favor of corticosteroid use against reaction is unclear. In this series, preventive use of corticosteroids did not have an impact on the rate of reaction, though this might be because high-risk patients with high microfilaraemia were more likely to receive corticosteroids. A previous series reported a very low incidence of reactions even though none of those patients received corticosteroids.⁶ Preventive use of antihistamine drugs has been suggested to reduce the severity but not the frequency of adverse reaction.³

Risk factor for reactions. A high microfilarial load is a known risk factor for encephalopathy after treatment, although there is a report of a patient with a level as low as 700 mf/mL who became encephalopathic.²⁰ Rapid clearance of microfilaraemia is supposedly responsible for the development of encephalopathy, but only a few studies have examined pretreatment microfilarial density in patients with encephalopathy.^{21,22} It has been suggested that a reduction of more than 30,000 mf/mL in 3 days may increase the risk of encephalopathy occurring.²³

This study suggests that raised CRP before treatment may also be a predictive risk factor for mild reactions. An increase in CRP after treatment has been reported among those who have severe adverse events after ivermectin,²⁴ and is assumed to be related to the absolute number of microfilariae killed by treatment.²³ This could not be confirmed in this study because few of the patients were examined in the first few days of treatment without corticosteroid.

In summary, the success rate of DEC as first-line treatment of loiasis is unsatisfactory. Other treatment regimens including combinations of drugs should be investigated, particularly among patients with a high microfilarial load.

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