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Review

Imported *Loa loa* filariasis: three cases and a review of cases reported in non-endemic countries in the past 25 years

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SUMMARY

Objectives: The aim of this study was to highlight the increasing chance of Western physicians encountering patients (both immigrants and expatriates/travelers) seeking help for loiasis.
Methods: We describe three cases of imported loiasis observed at two hospitals in Italy and France, and present a review of all previously published cases in the medical literature in the last 25 years (1986–2011). The search was performed using PubMed and Scopus databases using the terms "*Loa loa*" AND "loiasis".
Results: We reviewed 101 cases of imported loiasis of which 61 (60.4%) were reported from Europe and 31 (30.7%) from the USA. Seventy-five percent of infestations were acquired in three countries: Cameroon, Nigeria, and Gabon. Overall, peripheral blood microfilariae were detected in 61.4% of patients, eosinophilia in 82.1%, eye worm migration in 53.5%, and Calabar swellings in 41.6%. However, Calabar swellings and eosinophilia were more common among expatriates/travelers, whereas African immigrants were more likely to have microfilaremia. Eye worm migration was observed in a similar proportion in the two groups. Only 35 patients (including the three described here) underwent clinical follow-up for a median period of 10.5 months (range 1–84 months); clinical relapse occurred in three of these patients and persistence or reappearance of blood microfilaria in another two.
Conclusions: Due to increasing travel and the migration of people from the endemic countries of West Africa to Europe and the USA, we speculate on the possible emergence of loiasis. Western physicians should be aware of the typical (eye worm migration and Calabar swellings) as well as unusual clinical presentations.

1. Introduction

Loiasis is a neglected nematode infestation that is endemic in the rainforests of western and central Africa, from a latitude of 8–10° N to 5° S. The disease is transmitted to man by tabanid flies of the genus *Chrysops*.[1] It is especially common in Cameroon, the Republic of Congo, the Democratic Republic of Congo, the Central African Republic, Gabon, Equatorial Guinea, and Nigeria.[1,2] In a recent survey using the rapid assessment procedure for loiasis (identified with the acronym RAPLOA), which combines a history of eye worms with the level of endemicity of the infection, it was estimated that nearly 30 million people live in high to intermediate risk areas with a prevalence of eye worm history exceeding 20%.[2,3] In the medical literature loiasis is also referred to as 'African eye worm' because one of its possible manifestations is the pathognomonic migration of the adult worm under the conjunctiva.[4] Several local names, such as yolo li (yolo = worm; li = eye) and guildé guité (guildé = worm; guité = eye) are used by the different ethnic groups in eastern Cameroon to indicate the disease.[5] The other most common clinical presentation of loiasis is the intermittent appearance of subcutaneous, non-pitting and non-tender edema, which is frequently localized to the extremities; these are also known as 'Calabar swellings'.[1]

We describe herein three patients with imported ocular loiasis (two African immigrants presenting over the course of 12 months and one French traveler) managed at two medical centers, one in

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Milan (Italy) and one in Marseille (France). Furthermore, we provide a discussion on the clinical management of the disease and a review of all imported (in non-endemic countries) cases of loiasis published from 1986 up to December 2011.[6–92] Because of increased immigration to Europe and the USA from areas endemic for loiasis and also an increase in travel to these endemic areas, physicians need to be familiar with the clinical manifestations and the correct management of this neglected filariasis.

2. Methods

We retrieved all articles published in the English, French, German, Italian, and Spanish language literature over the last 25 years (1986–2011) using PubMed and Scopus. The search was conducted using the terms "*Loa loa*" AND "loiasis". Additional cases were identified by reviewing the reference lists of the original articles. Single case reports identified and published from countries endemic for loiasis were excluded.

For the purpose of the present study patients were defined as follows: (1) as immigrants when coming from endemic countries and subsequently residing in non-endemic countries; (2) as expatriates when born and raised in non-endemic countries and subsequently temporarily resident in endemic countries for occupation or humanitarian purposes, and returning to their original country when their assignment was completed; (3) as travelers when traveling for less than 2 months in endemic countries. Eosinophilia was defined as an eosinophil count in the blood exceeding 0.5×10^9 cells/l, or a percentage $\geq$8% when an absolute number was not available.

In the three newly reported cases, the diagnosis of ocular loiasis was based on the observation of the passage of the adult worm in the eyelid or under the conjunctiva. The presence of microfilariae was determined by examining thin and thick blood smears obtained at noon and stained with Giemsa.

A nested PCR amplification was performed in two cases using the primers originally described by Touré et al., which amplify the repeat 3 sequence (15r3) of the gene encoding the *Loa loa* 15-kD polyprotein, with minor modifications.[93] The presence and integrity of human genomic DNA in each sample was assessed by performing a simple PCR using human β-globin-specific primers that amplify a 252-bp fragment. Estimation of the circulating parasitemia burden was obtained by performing eight serial 5-fold dilutions starting from 1 μg of whole blood DNA for each time-point and performing a simple PCR using primers $15r3_1$–$15r3_2$ for *Loa loa* and β-globin for human genomic DNA amplification, as previously described. Briefly, PCR conditions were identical to those described in the nested PCR protocol, except that the total number of amplification cycles was of 60 instead of 40. The *Loa loa* parasite burden was arbitrarily expressed as the number of parasites/150 000 human cells using 5 copies of the parasite sequences and 5 copies of human β-globin as the sensitivity of the simple PCR reaction. Since it is known that the repeat 3 region of the 15-kD polyprotein is repeated three times in the genome, the number of parasites present was calculated as a third of the number of the estimated DNA copies present in each sample.

Data were analyzed using the Chi-square test for dichotomous variables and the two-tailed *t*-test or Mann–Whitney *U*-test for continuous variables.

3. Case reports

3.1. Patient 1

A 27-year-old woman originating from Cameroon presented to the emergency department (ED) of a hospital in Legnano (Italy) in July 2009, complaining of a 'foreign body sensation' in her left eye, which had started several hours before. On examination there was a left conjunctival injection, and a subconjunctival yellowish worm-like organism was seen moving in the inferior fornix (Figure 1A). Following a telephone consultation, a provisional diagnosis of ocular loiasis was made and the patient was discharged from the ED and referred to our outpatient clinic. On evaluation 2 days later no worm was visible on gross examination or by slit lamp evaluation. On physical examination she appeared to be a healthy pregnant woman at week 16 of gestation. She had been living in Italy since 2002 and initially did not recall any previous symptoms that could be relevant to the present diagnosis. However, she subsequently referred to a similar episode of ocular worm migration that had occurred when she was 17 years old and living in Cameroon.

Additional investigations showed a white blood cell count of 6.9×10^9/l with 13% eosinophils; liver enzymes and renal function were normal. A peripheral blood smear drawn at 2 p.m. was positive for the presence of sheathed microfilariae of *Loa loa* (Figure 1B). Subsequent examination of a wet peripheral blood sample under light microscopy confirmed these organisms to be viable and motile. In consideration of the early pregnancy we decided not to treat the patient immediately. Instead we checked the patient at regular intervals (19, 24, 27, 31, and 34 weeks of gestation) and on each occasion confirmed the persistence of blood microfilaremia and eosinophilia. During this time the patient complained of another episode of ocular worm migration and two episodes of swelling of the right ankle. In January 2010 she had a normal labor and delivered a healthy female baby weighing 3900 g. Examinations of the cord and peripheral blood of the newborn were negative for the presence of microfilariae. In contrast, rare microfilariae could be observed in the intervillar vascular lacunae of the mother's placenta (Figure 1C).

After delivery, the patient was treated twice (1 month apart) with a single dose (200 μg/kg) of ivermectin (Stromectol®, Merck Sharp & Dohme, Whitehouse Station, NJ, USA) associated with prednisone, but this therapy was unsuccessful in clearing the peripheral blood microfilariae. Four months after delivery, when the patient had stopped breast-feeding, treatment with albendazole (Zentel®) 400 mg twice daily for 4 weeks was attempted, but after the end of treatment peripheral blood microfilariae were still present, albeit at a lower concentration, as evidenced by a semi-quantitative nested PCR (Figure 1D). We thus obtained diethylcarbamazine (DEC) and treated the patient accordingly (6 mg/kg/day for 21 days). No microfilariae could be detected 3 months later in a sample of peripheral blood collected at noon, either by direct microscopic examination or by nested PCR (Figure 2). Similarly, the patient's 9-month-old daughter tested negative for blood microfilariae and for the presence of *Loa loa*-specific DNA. At the last follow-up visit, 17 months after the end of DEC treatment, no recurrences were registered and blood microfilariae were still undetectable.

3.2. Patient 2

A 25-year-old African woman from Douala, Cameroon presented to the ophthalmic ED of Fatebenefratelli e Oftalmico Hospital in Milan in May 2010 complaining of pruritus of 24-h duration and a burning and foreign body sensation in her left eye. On ophthalmological examination, a translucent, coiled and motile worm was visualized subconjunctivally in the lower temporal quadrant of the eye (Figure 3, A and B). The eye was slightly injected but otherwise normal. A diagnosis of ocular loiasis was made based on the epidemiology, clinical history, and ocular images, and the patient was referred to our outpatient clinic the following day. Her past medical history was unremarkable and she

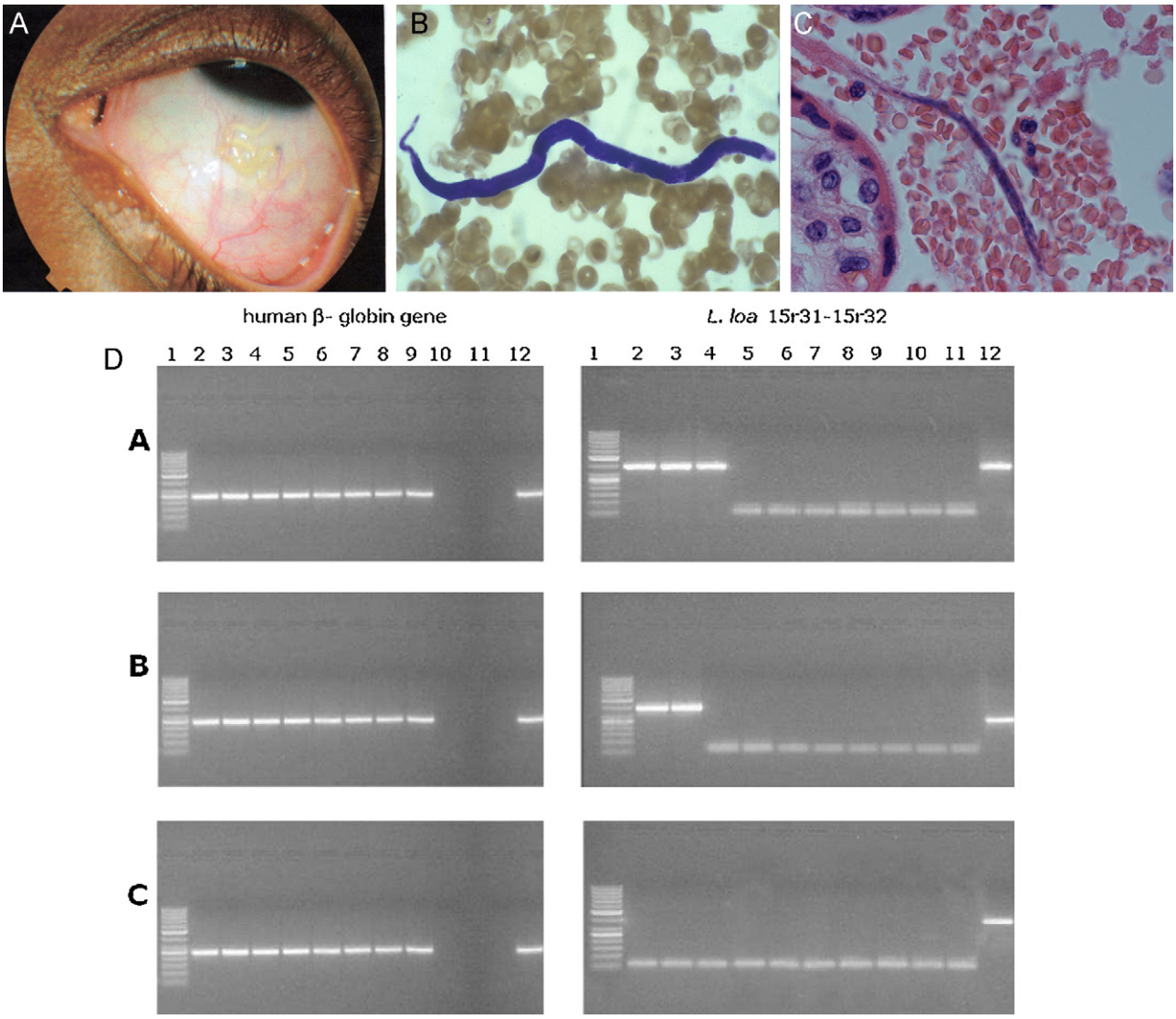

Figure 1. (A) Patient 1: appearance of the yellowish worm migrating under the patient's left conjunctiva. (B) Microfilaria of *Loa loa* in peripheral blood film; Giemsa ×300. (C) Microfilaria of *Loa loa* observed in the intervillous space of the placenta of patient 1. (D) PCR on peripheral blood of patient 1: lane A, 5 parasites/150 000 cells T0, T1, T2, T3 (from July 16 to July 19, 2010); lane B, 1 parasite/150 000 cells T4, T5, T6 (from July 20 to July 22, 2010); lane C, undetectable parasite (i.e., <1 parasite/150 000 cells) at T7 (October 28, 2010).

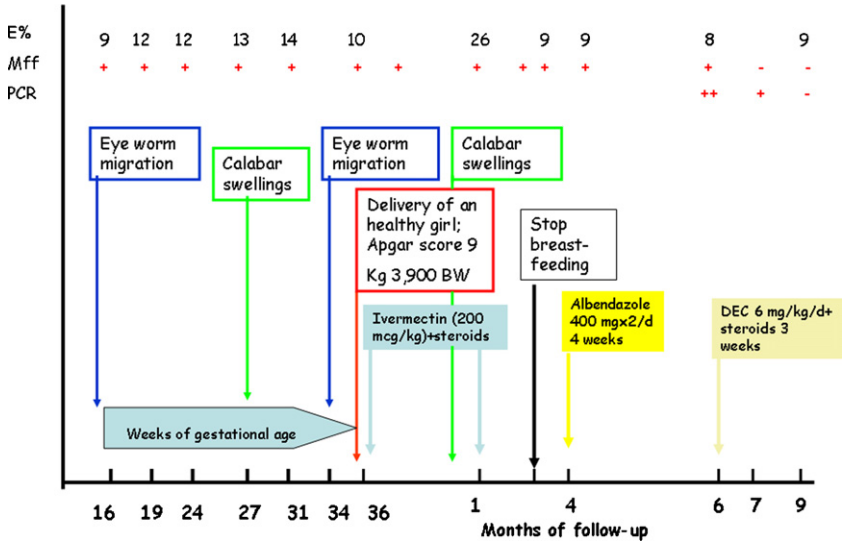

Figure 2. Schematic representation of the clinical outcome of patient 1 (E, eosinophils; mff, microfilariae).

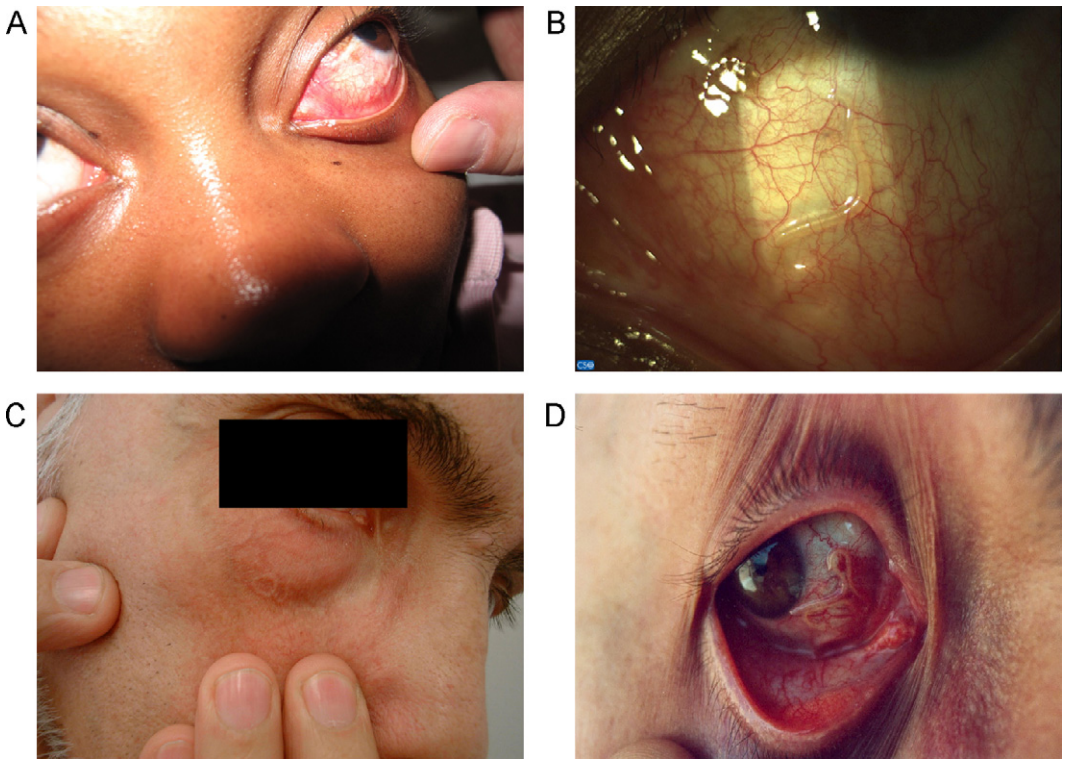

Figure 3. (A) Cordon-like appearance of the worm in the inferior bulbar conjunctiva of patient 2. (B) Translucent white thread-like structure of the adult worm visualized under a slit lamp in patient 2. (C) Subcutaneous thread-like swelling under the inferior right eyelid of patient 3. (D) Cordon-like appearance of the worm in the inferior bulbar conjunctiva of patient 3.

reported having been resident in Italy since 2003 with her last journey to Cameroon having occurred 1 year before. On evaluation she had conjunctival injection of the left eye and the worm was still visible on gross examination. Blood analysis showed normal leukocytes (5.310×10^9/l) without eosinophilia (1.5%). Peripheral blood smears obtained for 3 consecutive days at noon were always negative for microfilariae. On the second day of observation the worm disappeared from her eye. She received a single day treatment of ivermectin 200 μg/kg (total dose 12 mg), followed by a 21-day course of DEC 4 weeks later. No recurrence of the ocular worm passage was observed during the ensuing 6-month follow-up. Interestingly, *Loa loa*-specific peripheral blood nested PCR was repeatedly negative, both before the inception of anthelmintic therapy and during the relatively short follow-up, in accordance with the results of direct microscopic examination.

3.3. Patient 3

In 1998, a 58-year-old French man was admitted to the infectious disease and tropical medicine department in Marseille, France for a mobile subcutaneous lesion of the trunk that had appeared a few days after surgery of an aortic aneurysm, performed after an autologous blood transfusion. Within a few days, he complained of pruritus associated with a mobile foreign body in the eyelid and conjunctiva in the right eye (Figure 3, C and D). His past medical history was unremarkable; however in 1990 he had stayed for several months in Mouila, Gabon. On initial clinical examination, only a diffuse pruritus was noted, without fever. Laboratory tests revealed 6.5×10^9 leukocytes/l with 16% eosinophils and normal liver enzymes and renal function. Total IgE was elevated (3700 kIU/l). A chest radiograph was normal. A peripheral blood smear was positive for the presence of sheathed microfilariae of *Loa loa* with the detection of 20–30 parasites/ml. The patient then received a course of DEC 400 mg/day for 15 days, followed a few months later by 3 successive courses of 6 weeks of doxycycline. Doxycycline was used with the intention of reducing the microfilaremia by eradicating *Wolbachia*, a symbiont of filarial worms. At the time of treatment it had not yet been demonstrated that *Loa loa* does not contain *Wolbachia*.[94] However, subcutaneous passage and ocular worm migration recurred, together with the persistence of peripheral blood eosinophilia. He finally received a single day treatment with ivermectin 200 μg/kg (total dose 12 mg) in 2005 and showed no recurrence at the 5-year follow-up.

4. Literature review

From an analysis of the literature for the period 1986–2011, we identified 46 patients with imported loiasis presenting with eye worm migration: 27 immigrants from Africa and 19 expatriates or travelers, of whom 12 were from Europe, two each from the USA and Africa, and the remaining three patients from Australia, Sri Lanka, and Israel. These 46 cases, plus the two migrant patients in the case reports above, are summarized in Table 1. We identified a further 52 patients presenting initially with other clinical manifestations: 23 immigrants from Africa and one from Philippines and 28 expatriates and travelers, of whom 12 were from Europe, 14 from the USA, and one each from New Zealand and Japan. These 52 cases, plus the expatriate patient described in the case reports above, are summarized in Table 2. Sixty-one cases (60.4%) were reported from Europe[8,12,16,17,19–21,24,26–29,31–37,42,43,45–48,51–54,56,59,61,63,64,67,69,70,72–74,77,79–83,86–88,90–92] (including cases in the present report (PR)) and 31 (30.7%) from the USA.[6,13,15,22,23,25,30,40,41,44,49,50,55,57,58,60,62,65,66,68,71,75,76,78,85,89]

Overall, both sexes were equally represented, but with a predominance of females among expatriates/travelers and of males among immigrants (Table 3). The median age was 30 years (range 4–73 years), with no difference between expatriates/travelers and

Table 1
Forty-eight cases of imported loiasis presenting with ocular involvement ('eye worm migration') published between January 1986 and December 2011

Reference, year of publication	Sex, age (years)	Status	Country of origin	Country of residency/travel	Microfilaremia/ concentration	WBC/eosinophils, $\times 10^9$/l (% eosinophils)	Other manifestations	Treatment/follow-up
6, 1987	M, 25	Immigrant	Cameroon	USA/Cameroon 15 years earlier	No	3.1/0.434 (14%)	No	Surgical extraction; DEC 3 weeks/NR
7, 1988	M, 20	Immigrant	Nigeria	India, 9 months residency/Nigeria	Yes/NR	NR/ (28%)	Calabar swellings; subcutaneous worm migration; fever; urticarial rash	Surgical extraction; DEC 3 weeks/9 months asymptomatic
8, 1988	F, 29	Traveler	Germany	Germany/West Africa[a]	Yes/9900 mff/ml	20.0/11.200 (56%)	Eyelid worm migration	Apheresis (2 cycles) + ST/NR
9, 1989	F, 32	Traveler	Zambia	Zimbabwe/Zambia	No	NR/ (28%)	No	Surgical extraction; DEC 3 weeks/NR
10, 1989	F, 14	Expatriate	Sri Lanka	Sri Lanka/Nigeria for 6 years	No	12.8/2.688 (21%)	Calabar swellings	Surgical extraction/DEC 5 weeks/NR
11, 1990	M, 35	Expatriate	Germany	Australia 30 months/Africa[a]	Yes/NR	NR/ (38%)	No	DEC 3 weeks/NR
12, 1991	M, NR	Expatriate	Italy	Italy/Nigeria for 3 years	Yes/NR	11.5/3.105 (27%)	No	Surgical extraction; steroids + DEC 3 weeks/12 months asymptomatic
13, 1992	M, 36	Immigrant	Ghana	USA 6 years residency/Nigeria several times before leaving Ghana	Yes/2000 mff/ml	7.1/0.994 (14%)	No	Surgical extraction; apheresis + steroids + DEC 3 weeks/NR
14, 1992	F, 28	Expatriate	Australia	Australia/West Central Africa[a]	No	NR/yes	No	Surgical extraction; DEC 3 weeks/12 months asymptomatic
15, 1992	M, 19	Immigrant	Nigeria	USA/Nigeria	No	NR	No	Surgical extraction/NR
16, 1993[b]	M, 57	Expatriate	Italy	Italy/Africa[a] for 20 years	Yes/NR	NR/yes	No	Surgical extraction, DEC 3 weeks/4 months (1 relapse of microfilaremia at 3 months)
17, 1993	F, NR	Immigrant	Nigeria	UK/Nigeria	NR	NR/ (16%)	No	Surgical extraction; DEC 3 weeks/18 months asymptomatic
18, 1993	F, 52	Expatriate	Israel	Israel/Nigeria for 10 years (returned 7 years before presentation)	Yes/NR	8.0/2.080 (26%)	Calabar swellings	Steroids + DEC 3 weeks/NR
19, 1995	F, 23	Traveler	Germany	Germany/Cameroon 2 years before	Yes/2000 mff/ml	NR/ (13%)	No	Surgical extraction; steroids + DEC 3 weeks/NR
20, 1995	F, 31	Expatriate	Italy	Italy/Cameroon	Yes/NR	NR/ (40%)	Calabar swellings	DEC 3 weeks/NR
21, 1995	M, 31	Immigrant	Ghana	Germany/Ghana	Yes/3600 mff/ml	NR	No	Surgical extraction; DEC 3 weeks + mebendazole/NR
22, 1996	M, 32	Immigrant	Ghana	USA 3 years residency/Ghana	Yes/NR	11.0/4.290 (39%)	Lethargy after starting DEC; *Loa loa* identified in CSF	Steroids + DEC 3 weeks/NR
23, 1998	M, 40	Immigrant	Ghana	USA 12 years residency/Nigeria, Ethiopia	Yes/3300 mff/ml	NR/0.617	No	Apheresis + steroids + DEC 3 weeks/ 12 months asymptomatic
24, 1998	M, 26	Immigrant	Cameroon	Germany 6 weeks/Cameroon	NR	NR/ (34%)	No	Steroids + DEC 3 weeks/NR
25, 1999	F, 25	Traveler	USA	USA/Gabon	NR	NR/ (44%)	Calabar swellings; three nodules (finger, arm, breast); nodule biopsy positive for *Loa loa*	DEC 6 courses; mebendazole 7 doses; suramin; albendazole 3 weeks/ recurrence at 19 months
26, 2002	M, 38	Immigrant	Ghana	Belgium/Nigeria (1985) and Ivory Coast (1986)	Yes/15.2 mff/ml	NR/no	No	Surgical extraction; DEC 2 weeks/NR
27, 2002	M, 30	Immigrant	Cameroon	Germany, 5 years/Cameroon	NR	NR/ (7.8%)	No	DEC 3 weeks/NR
28, 2002	M, 28	Immigrant	Cameroon	Germany, 5 weeks/Cameroon	NR	NR/NR	No	Surgical extraction/NR
29, 2004	F, 35	Expatriate	Germany	Germany/Central Africa 6 month stay 5 years before	No	NR/ (25%)	Calabar swellings	Surgical extraction; DEC 3 weeks + mebendazole/NR
30, 2005	M, 43	Immigrant	Nigeria	USA 9 years/Nigeria	No	NR/No	No	Surgical extraction/lost to follow-up
31, 2005	F, 34	Immigrant	Cameroon	Switzerland 2 years/Cameroon	Yes/418 mff/ml	NR/ (19.6%)	Calabar swellings	Albendazole 2 weeks; steroids + DEC 3 weeks/NR
31, 2005	F, 17	Immigrant	Cameroon	Switzerland 12 years/Cameroon	No	NR/NR	Calabar swellings	Surgical extraction/NR
31, 2005	F, 31	Traveler	Switzerland	Switzerland/Cameroon 8 years before	No	NR/yes	No	Albendazole 3 weeks; steroids + DEC 4 weeks/NR
31, 2005	F, 45	Immigrant	Cameroon	Switzerland/Cameroon	NR	NR/yes	No	Albendazole 2 weeks; steroids + DEC 4 weeks/NR

Table 1 (*Continued*)

Reference, year of publication	Sex, age (years)	Status	Country of origin	Country of residency/travel	Microfilaremia/ concentration	WBC/eosinophils, $\times 10^9$/l (% eosinophils)	Other manifestations	Treatment/follow-up
32, 2006	M, 23	Immigrant	Africa[a]	Germany 5 years/Africa	No	NR/NR	Calabar swellings	Surgical extraction, DEC 3 weeks/NR
33, 2006	F, 8	Immigrant	Equatorial Guinea	Spain, 6 years/travel to Equatorial Guinea 2 years before	No	NR/0.700	Calabar swellings; urticaria	DEC 3 weeks/NR
34, 2006	M, 34	Traveler	UK	UK/Cameroon 12 years before	Yes/2000 mff/ml	NR/1.520	No	Surgical extraction; albendazole 3 weeks/NR
35, 2006	F, 20	Immigrant	Cameroon	Switzerland/Cameroon (last visit 5 years earlier)	Yes/820 mff/ml	NR/ (18.5%)	Hepatitis following ivermectin treatment	Albendazole 3 weeks; ivermectin single dose; DEC 4 weeks/NR
36, 2007	M, 24	Immigrant	Cameroon	Spain, 6 years/visiting country of origin once a year	NR	NR/NR	No	Surgical extraction/NR
37, 2007	M, 27	Immigrant	Democratic Republic of Congo	Spain for 8 months/ Democratic Republic of Congo	Yes/NR	4.1/0.287 (7%)	No	Surgical extraction; albendazole 3 weeks/NR
38, 2008	F, 29	Expatriate	Mauritius	Korea, 5 years/Cameroon (from 1996 to 2000)	Yes/NR	NR/ (37%)	Calabar swellings	Surgical extraction; ivermectin single dose/lost to follow-up
39, 2008	M, 42	Immigrant	Nigeria	Australia 2 years/Nigeria	Yes/NR	NR/1.180	No	Surgical extraction; albendazole 3 weeks/NR
40, 2008	M, 30	Immigrant	Cameroon	USA 2 years/Cameroon	Yes/4910 mff/ml	6.4/0.512 (8%)	No	Apheresis + steroids + DEC 3 weeks/NR
41, 2008	M, 29	Immigrant	Gabon	USA/Gabon	No	4.3/0.391 (9.1%)	No	Surgical extraction/NR
42, 2009	F, 38	Expatriate	Norway	Norway/Congo 2 years	No	NR/NR	Subcutaneous worm migration	Surgical extraction; DEC/NR
43, 2010	F, 33	Traveler	Switzerland (Italy)	Switzerland/Angola 7 years before	No	NR/ (8%)	No	Surgical extraction/NR
44, 2010	M, 25	Traveler	USA	USA/Equatorial Guinea 2 years before (12 days)	No	NR/yes	Calabar swellings	DEC/6 months asymptomatic
45,[c] 2010	F, 21	Traveler	UK	UK/Nigeria 6 years before	Yes/125 mff/5 ml	NR/yes	Calabar swellings	Surgical extraction; steroids + DEC/NR
46, 2011	M, 35	Immigrant	Ghana	UK/Ghana 8 years before	NR	NR/NR	No	Surgical extraction/NR
46, 2011	F, 20	Immigrant	Cameroon	UK/Cameroon 6 years before	NR	NR/NR	No	Surgical extraction/NR
47, 2011	F, 37	Immigrant	France	UK/Congo	Yes/55 mff/20 ml	NR/NR	No	Surgical extraction; ivermectin single dose; steroids + DEC 3 weeks/12 months asymptomatic
PR, 2011	F, 27	Immigrant	Cameroon	Italy/Cameroon 7 years before	Yes/400 mff/ml	6.9/0.897 (13%)	Calabar swellings	Ivermectin + steroids; albendazole 2 weeks; steroids + DEC 3 weeks/17 months asymptomatic
PR, 2011	F, 25	Immigrant	Cameroon	Italy/Cameroon 1 year before	No	5.31/0.080 (1.5%)	No	Ivermectin; DEC + steroids 3 weeks/6 months asymptomatic

CSF, cerebrospinal fluid; DEC, diethylcarbamazine; F, female; M, male; mff, microfilariae; NR, not reported; PR, present report; ST, standard treatment (drug not specified); WBC, white blood cells.

[a] Country not reported.

[b] Case reported twice (Campo S, Carta S, Gasparri V, Nowakowski M. Peripheral eosinophilia due to "Loa loa" infection. Eur J Intern Med 1995;6:127–8).

[c] This case was also reported in reference 46.

Table 2
Fifty-three cases of imported loiasis presenting with manifestations other than ocular, published between January 1986 and December 2011

Reference, year of publication	Sex, age (years)	Status	Country of origin	Country of residency/travel	Microfilaremia/ concentration	WBC/eosinophils, $\times 10^9$/l (% eosinophils)	Clinical manifestations	Radiographic findings	Treatment/follow-up
48, 1986	M, 28	Immigrant	Cameroon	France/Cameroon	Yes/35 000 mff/ml	NR/1.600	Itching, proteinuria, hematuria; kidney biopsy: evidence of *Loa loa* microfilariae in glomeruli and vessels	ND	Apheresis + steroids + DEC 3 weeks/9 months asymptomatic
49, 1986	F, 4	Expatriate	USA	USA/Central African Republic 1 year	No	25.3/15.433 (61%)	Recurrent Calabar swellings	ND	DEC 2 cycles of 2 weeks /36 months asymptomatic
50, 1987	F, 5	Expatriate	USA	USA/Cameroon	No	NR/ (30%)	Recurrent Calabar swellings	ND	DEC 3 weeks/NR
8, 1988	M, 32	Expatriate	Germany	Germany/Nigeria	Yes/4340 mff/ml	13.4/7.900 (59%)	Routine check-up: eosinophilia	ND	Apheresis (4 cycles) + ST
51, 1989	F, 37	Expatriate	France	France/Gabon 4 years	Yes/ND	7.6/2.736 (36%)	Ascites due to liver cirrhosis; *Loa loa* identified in ascitic fluid	ND	DEC 4 weeks/NR
52, 1989	M, 27	Immigrant	Cameroon	France 4 years/Cameroon every year	Yes/NR	5.4/0.324 (6%)	Mild fever (37.5 °C) and acute knee arthritis; *Loa loa* microfilariae identified in knee effusion	ND	Steroids + DEC 3 weeks/NR
53, 1989	F, 40	Expatriate	Sweden	Sweden/Congo	No	NR/NR	Breast lesion; history 13 years before of Calabar swellings and eye worm migration	Mammography: multiple spiral- and rod-shaped calcifications	NR
54, 1990	M, NR	Immigrant	Cameroon	Switzerland/Cameroon	NR	8.9/0.890 (10%)	Calabar swellings; acute arthritis	Knee radiograph: negative	DEC 3 weeks/NR
55, 1990	F, 56	Immigrant	Cameroon	USA/Cameroon	No	4.5/0.130 (3%)	Routine check-up; breast biopsy: calcified dead worm	Mammography: linear and rounded calcifications	NR/NR
56, 1991	M, 32	Expatriate	New Zealand	UK/Gabon, Nigeria	No	NR/3.500	Recurrent Calabar swellings; carpal tunnel syndrome; lymphadenopathy and splenomegaly[a]	ND	DEC 3 weeks/NR
57, 1992	F, 29	Expatriate	USA	USA/Gabon	NR	NR/NR	Recurrent Calabar swellings; breast biopsy: positive for *Loa loa*	Mammography: serpiginous calcification within a lesion	NR/NR
58, 1992	M, 40	Immigrant	Ghana	USA 6 months/Ghana	Yes/590 mff/ml	18.4/0.184 (1%)	Chest pain, productive cough, dyspnea, intermittent fever; thoracentesis: *Loa loa* in pleural fluid	Chest X-ray: pleural effusion	Apheresis + steroids + DEC 3 weeks/4 months asymptomatic
59, 1992	M, 46	Traveler	France	France/Cameroon, Congo 4 months earlier	No	NR/4.000	Acute arthritis (positive serology for *Loa loa*)	ND	Steroids + DEC 2 cycles of 3 weeks/NR
60, 1993	M, 38	Expatriate	USA	USA/Gabon	No	8.6/1.720 (20%)	Recurrent Calabar swellings	Arm X-ray: subcutaneous edema	DEC 3 weeks/3 months asymptomatic
60, 1993	F, 39	Expatriate	USA	USA/Nigeria	No	7.5/0.375 (5%)	Recurrent Calabar swellings	ND	DEC 3 weeks/NR
60, 1993	F, 53	Traveler	USA	USA/Nigeria	No	4.9 (normal)	Recurrent Calabar swellings	ND	DEC 3 weeks/NR
61, 1993	F, 35	Immigrant	Africa[b]	Belgium/Africa	Yes/>1000 mff/ml	NR/0.390	Infertility; *Loa loa* from oocyte retrieval[c]	ND	NR/NR
62, 1993	M, 23	Expatriate	USA	USA/Democratic Republic of Congo	No	13.1/3.013 (26%)	Recurrent Calabar swellings	ND	DEC 3 weeks/NR
63, 1994	M, 52	Immigrant	Cameroon	France/Cameroon	Yes/150 mff/ml	16.2/4.860 (30%)	Calabar swellings; weight loss, arthro-myalgias, dry cough	Chest X-ray and CT scan: apical lobe infiltrate	Steroids; ivermectin single dose + DEC 3 weeks/4 months asymptomatic
64, 1994	F, 26	Expatriate	Spain	Spain/Equatorial Guinea for 2 years	Yes/NR	NR/3.720	Calabar swellings	ND	DEC 3 weeks/NR
65, 1995	F, 13	Expatriate	USA	USA/Cameroon 7 years earlier (for 18 months)	No	19.9/3.675 (29%)	Recurrent Calabar swellings; eye worm migration	Plain X-ray foot and ankle: no bony abnormalities or evidence of effusion	Surgical extraction; DEC 3 weeks/3 months asymptomatic
66, 1996	M, 24	Traveler	USA	USA/Cameroon, Niger, Nigeria 3 years earlier	ND	NR/NR	None reported (examination for a trauma)	US abdomen: multiple hypodense lesions in the spleen	Splenectomy;[d] DEC/12 months asymptomatic

Table 2 (*Continued*)

Reference, year of publication	Sex, age (years)	Status	Country of origin	Country of residency/travel	Microfilaremia/ concentration	WBC/eosinophils, $\times 10^9$/l (% eosinophils)	Clinical manifestations	Radiographic findings	Treatment/follow-up
66, 1996	F, 27	Traveler	USA	USA/Nigeria 5 years earlier	No	NR/3.500	None reported (employment examination); 2 months after splenectomy, eye worm migration and Calabar swellings	US and CT abdomen: multiple hypoechoic lesions in the spleen	Splenectomy;[d] DEC/24 months asymptomatic
67, 1997	M, 27	Immigrant	Cameroon	France/Cameroon	Yes/400 mff/ml	NR/1.060	Chronic proteinuria, microscopic hematuria;[e] kidney biopsy: evidence of *Loa loa* microfilariae within glomeruli	ND	Ivermectin 2 doses/NR
68, 1997	M, 43	Expatriate	USA	USA/Gabon 6 years earlier	Yes/NR	NR/ (18%)	Exertional dyspnea with restrictive pattern on pulmonary function tests; *Loa loa* microfilariae identified in BAL; Calabar swellings and one episode of eye worm migration	Chest X-ray: bilateral interstitial infiltrates	Apheresis; DEC 3 weeks; 8 weeks asymptomatic
69, 1998	M, 49	Expatriate	Denmark	Denmark/Cameroon	ND	NR/3.370	Pain and swelling forearm (thrombosis ulnar veins)	US: normal venous flow from the cubital vein; contrast venography: occlusion of the ulnar veins	DEC 3 weeks/6 months asymptomatic
70, 1998	F, 17	Immigrant	Cameroon	Switzerland 2 years/ Cameroon	Yes/NR	NR/No	Recurrent subcutaneous worm migration	ND	Surgical extraction + DEC 4 weeks/NR
71, 1998	M, 38	Immigrant	Philippines	USA/Democratic Republic of Congo 3 years	NR	NR/ (47%)	Calabar swellings, pruritus	NR	NR/NR
72, 1998	F, 71	Immigrant	Cameroon	France/Cameroon 10 years earlier	NR	NR/NR	Routine check-up;	Mammography: linear calcifications	NR/NR
72, 1998	F, 36	Immigrant	Cameroon	France/Cameroon 18 years earlier	NR	NR/NR	Mastodynia	Mammography: linear calcifications	NR/NR
25, 1999	F, 27	Expatriate	USA	USA/Gabon 3 years	NR	NR/1.869	Recurrent Calabar swellings	ND	DEC 4 courses of 3 weeks; albendazole 3 weeks/84 months asymptomatic
25, 1999	M, 29	Expatriate	USA	USA/Gabon	No	NR/1.160	Recurrent Calabar swellings	ND	DEC 3 courses of 3 weeks; albendazole 3 weeks/84 months asymptomatic
73, 2001	M, 21	Traveler	UK	UK/West-Central Africa	Yes/NR	22.1/14.900 (67%)	Calabar swellings; proteinuria, microhematuria, leg edema (nephrotic syndrome); kidney biopsy: MCGN	ND	DEC 2 courses of 3 weeks/ 22 months, 1 relapse
74, 2001	F, 55	Immigrant	Cameroon	Switzerland/Cameroon	Yes/152 mff/ml	6.51/0.846 (13%)	Unspecified; delirium following 3 days of albendazole	MRI: focal lesions in the white matter compatible with small infarcts	Albendazole 3 days/1 month asymptomatic
75, 2002	F, 33	Immigrant	Nigeria	USA/Nigeria 3 years before	Yes/3800 mff/ml	NR/2.600 (32%)	Recurrent Calabar swellings	ND	Apheresis + steroids; DEC 3 weeks/3 months asymptomatic (negative blood film and PCR)
76, 2002	F, 24	Expatriate	USA	USA/Gabon 31 months earlier	No	15.6/4.992 (32%)	Recurrent Calabar swellings; muscle cramps; hepatomegaly	ND	DEC 3 weeks/NR
77, 2002	M, NR	Immigrant	Cameroon	Italy/Cameroon	Yes/NR	NR/ (15%)	Itching, paresthesia, headache, arthralgias	ND	Albendazole 3 weeks/NR
78, 2003	F/19	Immigrant	Cameroon	USA 4 years/Cameroon	NR	NR	Routine gynecological examination; *Loa loa* identified in Pap test	ND	NR/NR
79, 2004	F, 73	Traveler	Switzerland	Switzerland/Cameroon	Yes/2500 mff/ml	NR/0.910 (13%)	Calabar swellings; dyspnea, weight loss; thoracentesis: *Loa loa* identified in pleural fluid	Chest X-ray and CT: pleural effusion and mediastinal mass[f]	Steroids; DEC 3 weeks; albendazole 3 weeks/14 months asymptomatic

Table 2 (*Continued*)

Reference, year of publication	Sex, age (years)	Status	Country of origin	Country of residency/travel	Microfilaremia/ concentration	WBC/eosinophils, $\times 10^9$/l (% eosinophils)	Clinical manifestations	Radiographic findings	Treatment/follow-up
80, 2004	F, 28	Immigrant	Nigeria	Spain/Nigeria	Yes/1000 mff/ml	7.5/1.500 (20%)	Recurrent Calabar swellings	ND	DEC 3 weeks/NR
81, 2005	F, 39	Traveler	Spain	Spain/Cameroon	No	NR/ (40%)	Recurrent Calabar swellings	ND	Albendazole 4 weeks/9 months asymptomatic
82, 2005	M, 44	Immigrant	Equatorial Guinea	Spain/Equatorial Guinea 1 year earlier	Yes/300 mff/ml	6.38/0.976 (15.3%)	Recurrent Calabar swellings	ND	DEC 3 weeks/3 months asymptomatic
83, 2006	F, 14	Expatriate	Germany	Germany/Cameroon	Yes/5000 mff/ml	NR/1.200 (17%)	None reported (routine blood examination)	ND	Albendazole 3 weeks; DEC 3 weeks/NR
84, 2008	F, 21	Traveler	Japan	Japan/Cameroon	No	7.3/2.190 (30%)	Recurrent Calabar swellings; eye worm migration	ND	Ivermectin 2 courses of 1 day/7 months asymptomatic
85, 2008	F, 41	Immigrant	Cameroon	USA/Cameroon	Yes/3270 mff/ml	NR/0.350 (5%)	None reported; examination for infertility with *Loa loa* isolated from ovarian follicular fluid	ND	Apheresis; single dose ivermectin; DEC 3 weeks/NR
86, 2009	M, 36	Immigrant	Senegal	France/Gabon	Yes/8000 mff/ml	NR/0.810	Intermittent gross hematuria; kidney biopsy showed intralumen *Loa loa* microfilariae	ND	Steroids + ivermectin 1 dose + DEC[g]/NR
87, 2010	M, 69	Immigrant	Equatorial Guinea	Spain/Equatorial Guinea	Yes/NR[h]	NR/2.600	Itching, myalgias, productive cough	ND	DEC + mebendazole 4 weeks/NR
88, 2010	M/42	Immigrant	Equatorial Guinea	Spain/Equatorial Guinea	Yes/220 mff/ml[h]	NR/1.700	Proteinuria, hypertension, anasarca (nephrotic syndrome); kidney biopsy: collapsing glomerulopathy	ND	DEC 3 weeks/24 months asymptomatic
89, 2010	M, 26	Immigrant	USA	USA/West-Central Africa	Yes/>3000 mff/ml	NR/2.800 (18%)	Blood eosinophilia (2 years)	ND	Apheresis + steroids; DEC/NR
90, 2011	F, 28	Expatriate	Italy	Italy/Gabon 3 years earlier	Yes/172 mmf/13 ml	NR/3.300	Recurrent Calabar swellings; peripheral neuropathy	US abdomen: multiple hypoechoic lesions in the spleen	Steroids; ivermectin single dose + albendazole 4 weeks/12 months asymptomatic
91, 2011	M, 28	Immigrant	Nigeria	Italy/Nigeria 6 months earlier	Yes/7000 mff/ml	5.44/2.284 (42%)	Blood eosinophilia	Chest X-ray: negative; US abdomen: negative	Steroids; ivermectin 2 doses + albendazole 3 weeks/2 months persistence of microfilariae
92, 2011	F, 17	Immigrant	Equatorial Guinea	Spain/Equatorial Guinea 3 months earlier	Yes/NR	NR	Check for anemia during pregnancy	ND	Mebendazole/1 month after meningoencephalitis
PR, 2011	M/58	Expatriate	France	France/Gabon 8 years before	Yes/20–30 mff/ml	6.5/1.040 (16%)	Calabar swellings, pruritus; eye and subcutaneous worm migration	ND	DEC 2 weeks; doxycycline 3 courses of 6 weeks; ivermectin single dose/ relapse before ivermectin administration; asymptomatic at 60 months

BAL, bronchoalveolar lavage; CT, computed tomography; DEC, diethylcarbamazine; M, male; F, female; MCGN, type 1 mesangiocapillary glomerulonephritis; mff, microfilariae; MRI, magnetic resonance imaging; ND, not determined; NR, not reported; ST, standard treatment (drug not specified); US, ultrasound; WBC, white blood cells.

[a] A diagnosis of *Trypanosoma brucei gambiense* was established and treated with suramin.

[b] Country not reported.

[c] According to the authors, microfilariae probably originated from inadvertent puncture of small vessels on the ovarian surface.

[d] Both patients underwent splenectomy for a suspected lymphoma with subsequent diagnosis of loiasis.

[e] Discovered during hospitalization for malaria.

[f] Thymoma diagnosis after excision.

[g] The patient developed encephalopathy and worsening proteinuria after DEC administration; microfilariae were recovered from cerebrospinal fluid and urine.

[h] Double infection with *Loa loa* and *Mansonella perstans*.

Table 3
Clinical and laboratory findings among immigrants in comparison with travelers/expatriates in the present series and in two other published series

	Present series		*p*-Value	Churchill et al.[95]		*p*-Value	Klion et al.[96]		*p*-Value
	Expatriates/travelers	Immigrants		Expatriates	Immigrants		Non-endemic	Endemic	
Number of patients	47	54	-	49	51	-	42	51	-
Sex (M/F)	16/31	33/21	$p=0.01$	28/21	19/32	$p=0.07$	24/18	51/0	NR
Age (median, range), years	30 (4–73)	30 (8–71)	$p=0.9$	33.4 (13–67)	25.6 (8–40)	$p=0.0001$	26 (6–49)	37 (19–55)	$p=0.2$
Interval of time from first/last potential exposure and diagnosis (range)	108 (2–576) weeks[a]	200 (2–864) weeks	$p=0.2$	15 (5–156) months[b]	276 (18–468) months	$p<0.0001$	24 (6–48) months	252 (12–600) months	NR
Microfilaremia	19/42 (45.2%)	32/41 (78%)	$p=0.1$	14 (29%)	38 (75%)	$p<0.0001$	4 (9.5%)	46 (90.2%)	$p<0.001$
Geometric mean + SD	2913 + 3421 ($n=8$)	3449 + 7242 ($n=23$)	$p=0.98$	35 ($n=6$)	1024 ($n=19$)	$p=0.012$			
Eosinophilia	41/43 (95.3%)	28/41 (68.3%)	$p=0.3$	45/48 (94%)	33/49 (67%)	$p=0.0025$	42 (100%)	27 (52.9%)	$p<0.001$
Geometric mean	4042 + 3971 ($n=26$)	1251 + 1199 ($n=29$)	$p<0.0001$	3382	747	$p<0.0001$	3026	370	$p<0.001$
Eye worm migration	25/47 (53.2%)	29/54 (53.7%)	$p=0.88$	8 (16%)[c] 2 (4%)[d]	23 (45%) 9 (18%)	$p=0.0038$ $p=0.07$	4 (10%)	8 (16%)	$p=0.6$
Calabar swelling	30/46 (65.2%)	12/54 (22.2%)	$p=0.01$	40 (82%)[c] 24 (49%)[d]	18 (35%) 10 (20%)	$p<0.0001$ $p=0.0039$	40 (95%)	8 (16%)	$p<0.001$
Other manifestations	17/47 (36.2%)	20/54 (37%)	$p=0.89$	2 (4%)	5 (10%)	NS	12 (28.6%)	11 (21.6%)	NS

F, female; M, male; NR, not reported; NS, not significant; SD, standard deviation.
[a] Median time since last exposure.
[b] Median time since first exposure.
[c] History.
[d] Actual finding.

immigrants (Table 3). The African country of acquisition of loiasis was not specified in nine cases;[8,11,14,16,29,49,61,73,89] 75% of the infestations were acquired in the countries of Cameroon (38/92, 41.3%), Nigeria (19/92, 20.7%), and Gabon (12/92, 13.0%)[6–8,10,12,13,15,17–20,23–28,30,31,34–36,38,40,41,45,46,48,50–52,54,55,57,59,60,63,65,67–70, 72,74–81,83–86,90,91] (including PR cases). For three patients, more than one country had been visited (Gabon and Nigeria,[56] Cameroon and Congo,[59] and Cameroon, Nigeria, and Niger[66]). Microfilaremia was more common in immigrants (78.0%)[7,13,21–23,26,31,35,37,39,40,47,48,52,58,61,63,67,70,74,75,80,82,85–88,91,92] (including PR cases) than in expatriates and travelers (Table 3). In contrast, peripheral blood eosinophilia (95.3%)[8–12,14,16,18–20,25,29,31,34,38,43–45,49–51,56,59,60,62,64–66,68,69,73,76,79–81,83,84,90] (and PR) and Calabar swellings (65.2%) [10,18,20,25,29,38,44,45,49,50,53,56,57,60,62,64,65,68,73,76,79,81,84,90] (and PR) were more often observed in expatriates/travelers than in immigrants. Ocular eye worm migration was observed to the same extent in immigrants (53.7%)[6,7,13,15,17,21–24,26–28,30–33,35–37,39–41,46,47] (and PR) and in expatriates/travelers (53.2%)[8–12,16,18–20,29,38,42,45,53,65,66,68,84] (and PR).

Four patients also experienced subcutaneous worm migration[7,42,70] (and PR). Other unusual manifestations included pulmonary involvement,[58,63,68,79] acute arthritis,[52,54,59] carpal tunnel syndrome,[56] calcified breast nodules containing the nematode,[25,53,55,57,72] skin nodules,[25] splenic lesions,[66,90] vein thrombosis,[69] nephrotic syndrome,[48,67,73,86,88] infertility,[61,85] and peripheral neuropathy.[90] Apart from detection in peripheral blood, microfilariae were detected in ascitic fluid,[51] pleural effusion,[58,79] and bronchoalveolar lavage,[68] ovarian follicular fluid, oocytes, and cervicovaginal cytology specimens,[61,78,85] breast and kidney biopsies,[48,55,57,67,86] knee effusion,[52] cerebrospinal fluid and urine,[86] and from spleen tissue after splenectomy.[66]

Of those patients presenting with ocular loiasis, 21 were treated with medical therapy (15 with DEC, two with DEC plus mebendazole, two with albendazole, one with ivermectin, and one with ivermectin plus DEC) associated with surgical extraction of the adult worm from the eye.[6,7,9,10,12–14,16,17,19,21,26,29,32,34,37–39,42,45,47] Nine patients underwent surgical extraction only.[15,28,30,31,36,41,43,46] Eighteen patients were treated with different schemes of therapy: sequential administration of albendazole and DEC,[31] DEC alone,[23,40,44] ivermectin followed or preceded by albendazole and DEC[35] (and PR), and multiple courses of DEC followed by mebendazole and albendazole.[25] Patients presenting with clinical manifestations different from eye worm migration (Table 2) were treated with DEC in 24 cases,[48–52,54,56,58–60,62,64,65,68–70,73,75,76,80,82,88,89] and by splenectomy done for suspected splenic lymphoma followed by DEC in two patients.[66] Ivermectin was employed alone in two patients,[67,84] and followed by DEC or albendazole in five patients.[63,85,86,90,91] Two patients treated with multiple unsuccessful courses of DEC were subsequently treated with albendazole,[25] whereas another two patients were treated with albendazole plus DEC.[79,83] Albendazole alone was employed in two patients.[77,81] Finally, in another four cases the drug used was not specified.[8,53,55] Overall, 11 subjects underwent apheresis to reduce the high microfilarial loads,[8,13,23,40,48,58,68,80,85,89] and 26 patients received corticosteroid therapy prior to antifilarial drug treatment in order to avoid high antigen release[12,13,18,19,22–24,31,40,47,48,52,58,59,63,75,79,86,89–91] (and PR).

An acute hepatitis[35] and a nephropathy with proteinuria and hematuria[67] were probably precipitated following ivermectin single dose consumption. Two patients developed encephalitis following DEC administration: a severe picture (with a Glasgow coma scale score of 9) together with worsening proteinuria in one case[86] and with lethargy and frontal release signs in the other patient.[22] The latter patient also had microfilariae disclosed in the cerebrospinal fluid. Both recovered uneventfully after stopping DEC and subsequently resumed the drug without further problems. Moreover, one case of encephalopathy with delirium and a case of meningoencephalitis were described following treatment with albendazole and mebendazole.[74,92]

A follow-up period was reported for only 35 (34.7%) patients overall (including our three patients) for a length of time ranging from 1 to 84 months (median 10.5 months)[7,12,14,16,17,23,25,44,47–49,58,63,65,66,68,69,73–75,79,81,82,84,88,90,91] (and PR). With the exception of four patients, one of whom had a relapse of microfilaremia 3 months after the end of treatment,[16] one with persistence of microfilaremia 2 months later,[91] and two patients with the recurrence of symptoms,[25,73] the remaining 31 patients remained

asymptomatic during the follow-up.[7,12,14,17,25,47–49,58,63,65,66,68,69,73–75,79,81,82,84,88,90,91] (and PR).

5. Discussion

In this review we analyzed 101 cases of loiasis (including the three reported here by us) observed outside endemic areas and published in the literature in the last 25 years. Although possibly biased by the fact that the analysis was based generally on single case reports observed in different countries over a long period of time, it allowed us to compare the clinical presentation among different populations (i.e., expatriates/travelers versus immigrants) with a sample size of the same order as the two largest studies previously published on this topic.[95,96] Over 91% of all cases were observed in Europe (60.4%)[8,12,16,17,19–21,24,26–29,31–37,42,43,45–48,51–54,56,59,61,63,64,67,69,70,72–74,77,79–83,86–88,90–92] (and PR) and the USA (30.7%).[6,13,15,22,23,25,30,40,44,49,50,55,57,58,60,62,65,66,68,71,75,76,78,85,89]

In our case series, the length of time from the last potential exposure to the time of appearance of clinical symptoms was an overall median of 120 weeks (range 2–864 weeks), with 108 weeks for expatriates/travelers (range 2–576 weeks) and 200 weeks for immigrants (2–864 weeks). In the retrospective study of Churchill et al., the median time since first exposure to appearance of symptoms was 15 months (range 5–156 months) for expatriates and 276 months (range 18–468 months) for immigrants.[95] Although adopting the first or last potential exposure to areas of endemicity to measure the 'clinical prepatency' made a comparison of the results of the present study with those of Churchill et al. unfeasible, and recognizing that both are imprecise and biased variables, it is nevertheless evident that a difference exists in the time of presentation, which is much longer for immigrants in comparison with expatriates/travelers. This is confirmed by recent data from the GeoSentinel Network showing that the majority of patients with *Loa loa* infection had traveled for between 1 and 6 months and that 77% of patients with loiasis (excluding visiting friends and relatives and immigrants) presented within 1–6 months after their return.[97] Although it is commonly believed that prolonged exposure in an endemic area is necessary for the acquisition of *Loa loa* infection, more recent data seem to suggest that infection can also occur after short periods of exposure, such as those commonly observed in travelers, and in this regard both Moffet et al. and Landry et al. have reported the development of loiasis after an exposure as short as 12 days.[44,79] Thus, it is important to consider this diagnosis not only in immigrant and expatriates, but also in travelers who visit endemic areas for even short periods of time.

Overall, eosinophilia was observed in 82.1% of patients and microfilaremia was detected in 61.4% of all cases described here; the possible absence of microfilariae in the peripheral blood of people who have suffered from subconjunctival migration of at least one adult worm is a well known phenomenon called occult loiasis.[98] A genetic predisposition has been implicated as a mechanism responsible for the patient becoming microfilaremic once infected by *Loa loa*.[99] A more recent study conducted in Cameroon showed that the acquisition of microfilaremia is gender-dependent (males being more frequently affected than females) and associated with a higher level of exposure to infective larvae.[100] Nevertheless, in agreement with the two previous studies comparing the clinical presentation of loiasis among visitors to endemic areas and natives of these areas who have either migrated or not to non-endemic countries, our review of the literature confirms that peripheral blood eosinophilia and Calabar swellings are observed much more frequently among expatriates and travelers and conversely that the presence of blood microfilaremia is more common among immigrants.[95,96] However, in contrast to the results reported in the study of Churchill et al.,[95] we were unable to demonstrate a much higher frequency of eye worm migration among immigrants in comparison with expatriates/travelers. Interestingly, Klion et al.,[96] comparing unselected patients from Benin with a selected group of expatriates referred to their center, found a very low prevalence of eye worm migration in both groups with no statistically significant difference.

As well as the two characteristic and well known clinical features that are commonly associated with *Loa loa* infestation, i.e., Calabar swellings and subconjunctival migration of the adult parasites, in the present review we noted other manifestations that are quite unusual, some which are not mentioned in tropical medicine textbooks. These include five patients with a nephropathy characterized by a nephrotic syndrome in four cases,[48,67,73,86,88] splenic lesions in three patients, two of whom underwent splenectomy for a suspected lymphoma,[66,90] and four patients with pulmonary involvement[58,63,68,79] presenting with pleural effusion in two cases[58,68] and lobar or interstitial infiltrates in the other two cases.[63,79] Also five women had breast nodules (containing *Loa loa* in three cases), which were disclosed either on routine check-up mammography or during the work-up investigation of a palpable breast lesion.[53,55,57,72] Five cases of calcification of the breast attributed to *Loa loa* have previously been reported in Congolese women, but have also been observed in association with *Wuchereria bancrofti*.[101,102] Finally, three patients with acute arthritis,[52,54,59] one patient with leukocytoclastic vasculitis,[60] and two patients with infertility in whom *Loa loa* were identified in follicular liquid and oocytes were described.[61,85]

Among the above cited unusual features, renal involvement characterized by proteinuria and hematuria is probably the most frequent, being observed by Klion et al. in a similar percentage of patients from endemic and non-endemic areas (22% and 21%, respectively).[95] Although the mechanism responsible for renal involvement is unknown, immune complexes[67,73,86,88] were observed in four patients and microfilariae[67,86] in two. However, the four patients with a nephrotic syndrome had complete remission after treatment with DEC or ivermectin.[48,67,73,88] It is worth noting that a nephrotic syndrome with focal segmental glomerulosclerosis and microfilariae within afferent glomerular arterioles has been described in a Congolese woman who died of renal failure, and another unproven case of glomerulopathy has been reported in another Congolese man also presenting with encephalopathy despite antifilarial treatment.[103,104]

Pulmonary involvement was described in the study of Klion et al. in only two expatriates (5%), one with pleural effusion and the other with a pulmonary infiltrate.[95] Interestingly two of the four patients with pulmonary involvement reviewed here had pleural effusion and in both cases microfilariae were identified in the pleural fluid.[58,79] We are aware of another case of pleural effusion with microfilariae of *Loa loa* identified in the pleural fluid in a Cameroonian HIV-positive patient who was successfully treated with ivermectin.[105]

Regarding our case series, both women originating from Cameroon had been living in Italy for 7 years when they presented with ocular loiasis. However, the second patient had visited her country of origin 1 year before. Interestingly, the first woman recalled a previous episode of eye worm at the age of 17 years when she was living in Cameroon. Therefore, we can assume that the infestation in the latter case dates back at least 10 years; it has been shown that microfilariae usually mature into adult worms in approximately 1 year, but this process can take up to 4 years and the adult worms can live for up to 17 years in the human host.[1]

The second point of interest with regard to the first case presented here is the diagnosis of ocular filariasis during pregnancy, which gives rise to two major questions: the first about drug management of this condition during pregnancy and

the second about the possible vertical transmission of *Loa loa*, an issue that remains controversial. An old report of two cases of asymptomatic loiasis discovered during pregnancy indicated that treatment with DEC was employed after delivery and that there was no evidence of microfilariae crossing the placenta.[106] In contrast, two case reports from Nigeria suggested transplacental transmission of microfilariae of *Onchocerca volvulus*, the agent of onchocerciasis.[107,108] Moreover, transplacental migration and transmission of the nematode *W. bancrofti* was demonstrated to have occurred in a single case report from the USA involving a Dominican woman[109] and in at least 10% of microfilaremic women from Haiti.[110] In our case, despite the fact that microfilariae were readily detected by microscopy in the placenta, the analysis of cord and peripheral blood of the newborn were negative by both microscopy and nested PCR. Moreover, when retested with both methods at the age of 9 months, the patient's daughter remained negative, thus confirming the absence of transplacental transmission of *Loa loa*. Finally, as far as treatment of a pregnant woman is concerned, in accordance with the manufacturer's indications we first attempted the treatment of our patient with ivermectin only after delivery; she was then further treated with albendazole when lactation had ended (i.e., when the baby was 4 months old). However, as shown in Figure 2, we were only able to clear the microfilariae from the peripheral blood of the mother by treatment with DEC.

Our second case was remarkable for the fact that despite the evident ocular passage of the adult worm, we were repeatedly unable to demonstrate the presence of microfilaremia, not only by microscopy but also using a nested PCR of peripheral blood drawn at the same time. Previously, using the same protocol employed by us, Touré et al. were able to demonstrate that this PCR assay is 100% specific and 95% sensitive in detecting occult infection (i.e., patient with adult worm passage but without demonstrable circulating microfilariae).[93]

The utility of PCR in the diagnosis and management of loiasis is actually unclear; its use in the field has been suggested, with the aim of identifying occult cases by screening large human populations. Treatment of such properly identified cases will result in a significant reduction in the 'community filarial load'. Very recently researchers from Cameroon and the USA developed a real-time quantitative PCR that is able to detect a single microfilaria in a 20 μl dried blood spot (equivalent to a burden of 50 microfilariae (mff)/ml).[111] Although the authors acknowledged that this method should be used in clinical laboratories where real-time PCR equipment is available, they nevertheless suggested the possibility of incorporating the target into loop-mediated isothermal amplification (LAMP), ultimately making its use feasible at the point-of-care in endemic areas. However, in a study conducted among returned expatriates, travelers, and immigrants, the same authors showed that a real-time PCR directed against *Loa loa* and *W. bancrofti* was equally sensitive compared to blood filtration for detecting microfilaremia of both worms.[112] Researchers from Spain used a nested PCR for *Loa loa* on more than 500 blood samples and demonstrated a higher sensitivity of molecular diagnosis in comparison with Knott's concentration technique.[113]

The third patient, a French man who had worked in Gabon for several months, developed ocular loiasis 8 years after his stay in Africa. Interestingly, clinical manifestations coincided with surgery due to an aortic aneurysm. After an initial treatment with DEC he underwent treatment with doxycycline, which failed to control relapses of the disease. Doxycycline is generally used to eliminate *Wolbachia* endobacteria that are harbored by many filarial nematodes.[94] However, by using electron microscopy, histology, immunohistology, and PCR it has been shown that *Loa loa* filariae do not harbor Wolbachia endobacteria in the numbers required either for vertical transmission of the bacteria or for embryogenesis of the filariae.[114] Thus, these results are against the use of tetracycline for patients with microfilaremia due to *Loa loa*.

DEC, ivermectin, and albendazole are the drugs currently employed for the treatment of loiasis, but each of them is characterized by several limitations.[1] DEC has long been the drug of choice for the treatment of loiasis since it displays both micro- and macro-filaricidal activity on the parasite. However, patients with a high initial microfilarial load (>8000 mff/ml) are at risk of developing serious reactions – ones that may be lethal – such as encephalopathy.[115] Another limitation of treatment with DEC is the requirement of multiple courses of therapy in order to achieve clinical and parasitological cure, as demonstrated by a study conducted on expatriates who were followed-up for long periods of time.[116] A third possible limitation in the use of DEC, as highlighted by the two cases observed in Italy, is the difficulty in obtaining the drug; in fact DEC is no longer marketed in Europe and is available in the USA only through the Centers for Disease Control and Prevention (CDC).

Ivermectin has been claimed to have a marked microfilaricidal effect against *Loa loa* lasting for at least 1 year after a single dose of 150/μg.[117] However, it has no macrofilaricidal effect and a severe encephalopathy has also been recognized following administration of this drug in patients with a high microfilarial load.[118] In the present review a case of hepatitis and one of nephropathy were registered after ivermectin treatment.[35,67] The drug is generally not recommended in pregnant and lactating women, but several studies have suggested that the risk of congenital malformation or abortion is not higher when the drug is inadvertently used in pregnant women.[119] Based on the fact that ivermectin levels in human breast milk are low[120] and on the recent recommendations of the Mectizan Expert Committee, we used ivermectin (albeit unsuccessfully) for the treatment of our first patient when she was lactating.[121,122] Finally albendazole (at a dosage of 200 mg twice daily for 3 weeks) has been shown to decrease microfilarial loads progressively and slowly as a consequence of a primary embryotoxic activity.[123] In this regard it has been proposed that albendazole be used in a sequential two-step treatment (before DEC or ivermectin) for patients with a high level of microfilaremia in order to avoid severe adverse effects.

The great heterogeneity of treatments registered among patients reported in the present review is a matter of concern and reflects problems with the availability of such drugs and the absence of evidence-based guidelines. Moreover, only one patient in three had a documented follow-up, showing a relapse in about 14% of cases, a figure that is similar to the experience reported by Churchill et al. in London.[95] However, it should be highlighted that in the study by Klion et al.[116] conducted on expatriates and characterized by a stringent definition of successful treatment and with a long follow-up, only 38% of patients were considered cured after a single course of DEC.

Two more issues – apheresis to reduce high level microfilaremia and eye surgery to remove the adult worm – are controversial and deserve some comment.

In the mid-1980s, several case reports advocated the use of apheresis to reduce microfilaremia before starting DEC therapy.[8,48,124] However, in a recent review based on the guidelines of the American Society for Apheresis, loiasis is not mentioned among the infectious diseases that can be treated with this procedure.[125]

As far as the need to surgically extract the adult worm from the eye during its ocular passage, it appears from our review that this therapy is frequently employed (i.e., 31/52, 59.6%),[6,7,9,10,12–17,19,21,26,28–32,34,36–39,41–43,45–47,65] and in about 17% of cases this was the only treatment performed in patients with the disease.[15,28,30,31,36,41,43,46] It might be anticipated that when patients are first seen by ophthalmologists this is the rule.

However, we believe that surgical extraction is generally unnecessary (as seen in our patients), and as suggested more authoritatively by the late Sir Patrick Manson a century ago because: "it is safe to conclude that the particular loa that may show itself about the eye or elsewhere is only one of many".[126] Since we agree with this statement, whether or not the worm is extracted it is essential to treat the patient with a systemically active drug.

In conclusion, based on our experience together with the results of the literature on imported loiasis, we expect that what we are seeing in Europe and the USA might be the tip of the iceberg of a neglected disease that could be emerging as the consequence of increased travel and migration. Physicians should be aware of both the typical manifestations and of possible unusual presentations: in both cases the travel history is essential to guide the diagnosis in the right direction.

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