Differences in the Clinical and Laboratory Features of Imported Onchocerciasis in Endemic Individuals and Temporary Residents

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Abstract. Many parasitic infections have different presenting features in endemic individuals (ENDs) and immunologically naive temporary residents (TRs). Temporary residents with loiasis often display acute symptoms and hyper-eosinophilia, in contrast to a parasite-induced subclinical state in chronically infected ENDs. Few studies have examined differences in ENDs and TRs infected with the related filarial parasite *Onchocerca volvulus*. We identified 40 TRs and 36 ENDs with imported onchocerciasis at the National Institutes of Health between 1976 and 2016. All study subjects received an extensive pretreatment medical history, physical examination, and laboratory investigations. We performed additional parasite-specific serologic testing on stored patient sera. Asymptomatic infection occurred in 12.5% of TRs and no ENDs ($P = 0.06$). Papular dermatitis was more common in TRs (47.5% versus 2.7%, $P < 0.001$), whereas more pigmentation changes occurred in ENDs (41.7% versus 15%, $P = 0.01$). Only endemic patients reported visual disturbance (13% versus 0%, $P = 0.03$). One TR (3.3%) had onchocercal eye disease, compared with 22.6% of ENDs ($P = 0.053$). Absolute eosinophil counts (AECs) were similar in ENDs and TRs ($P = 0.5$), and one-third of subjects had a normal AEC. Endemic individuals had higher filarial-specific IgG4 and were more likely to be positive for IgG4 antibodies to Ov-16. Temporary residents and ENDs with imported *O. volvulus* infection presented with different dermatologic manifestations; ocular involvement occurred almost exclusively in ENDs. Unlike *Loa loa*, clinical differences appear not to be eosinophil-mediated and may reflect chronicity, intensity of infection, or the presence of *Wolbachia* in *O. volvulus*.

INTRODUCTION

Onchocerciasis is a neglected tropical disease caused by the filarial parasite *Onchocerca volvulus*, which can lead to chronic debilitating skin and eye pathology. At least 18 million are infected, and 180 million live in at-risk areas worldwide, primarily in Africa.^{1,2} With increasing global population migration and travel to remote destinations, clinicians in nonendemic areas continue to encounter imported filarial infections in migrants and travelers.^{3–5} However, many parasitic infections manifest differently in life-long residents of endemic areas and in expatriates infected during temporary residence abroad.^{3,6,7} Travelers infected with the related filarial parasite *Loa loa* display parasite-driven immune hyperreactivity with Calabar swellings, urticarial rash, marked eosinophilia, and a shift toward a T helper 2 (Th2) cytokine response.^{6,8} Endemic subjects with *L. loa* and *Wuchereria bancrofti* have comparatively few symptoms, demonstrating parasite-specific immune hyporesponsiveness despite a much higher parasite burden.^{6,9}

Few studies have directly compared endemic individuals (ENDs) and temporary residents (TRs) with onchocerciasis. The only contemporary systematic evaluation of ENDs and TRs with onchocerciasis observed eye disease and onchocercal nodules exclusively in endemic patients, who also had a higher burden of infection.¹⁰ Endemic individuals with *Onchocerca* had a robust eosinophilia and Th2 response, which was the opposite of immunologic findings previously observed in *L. loa*. However, differences in the region of *O. volvulus* exposure and study setting were potential confounders, as most TRs had imported infection from Africa, whereas ENDs were evaluated in a remote setting in an endemic area of South America (without access to hospital-based laboratory and clinical facilities). A recent analysis of all case

reports of imported *O. volvulus* infection corroborates that eye involvement, onchocercal nodules, lymphadenopathy, and skin lichenification and atrophy occur almost entirely in immigrants/refugees, whereas travelers have more acute unilateral limb swelling and papular rash.^{11,12} By contrast, historical expatriate cohorts noted ocular disease in 20–34% of TRs,^{13,14} although these expatriates had longer exposure periods without access to treatment, suggesting that disease burden and chronicity may influence clinical phenotype.

Disease expression in endemic populations with ongoing exposure to *O. volvulus* may also be different from those in migrants who have left the endemic area. One cohort of Ethiopian migrants to Israel noted substantial hyperreactive onchodermatitis at a much higher prevalence than that observed in the endemic area itself, a finding suggestive of immunologic shifts linked to immigration that contributed to acute dermatologic symptoms.¹⁵ Heterogeneity in disease manifestations in both ENDs and TRs suggests a complex interaction of host and parasite factors, including intensity of infection, chronicity, strain, geographic area of acquisition, host genetics, and individual immune response.^{16–20}

We aimed to systematically compare symptom timing, clinical presentation, physical examination findings, and laboratory findings associated with *O. volvulus* infection in ENDs and TRs evaluated in a nonendemic tertiary care setting. We further sought to determine whether the paradigm of parasite-induced immune hyperresponsiveness in TRs observed in the non-*Wolbachia*-containing *L. loa* also holds true in onchocerciasis.

MATERIALS AND METHODS

Study subjects. We included all patients with active *O. volvulus* infection evaluated by the Clinical Parasitology Section of the Laboratory of Parasitic Diseases (LPD), National Institute of Allergy and Infectious Diseases (NIAID) between 1976 and 2016. Patients with active onchocerciasis all had exposure in an *O. volvulus*-endemic region and met at least

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one of the following criteria: microfilariae (mf) visualized on “skin-snip” or slit-lamp examination; *O. volvulus* DNA detected by polymerase chain reaction (PCR) testing of “skin snips”; positive antifilarial antibody testing, in addition to either a positive Mazzotti provocation test with diethylcarbamazine or a characteristic posttreatment reaction; or positive antifilarial antibody testing with characteristic clinical symptoms of *O. volvulus* infection.^{4,21} Only a subset of patients received Mazzotti provocation testing, which was historically used to aid in diagnosing patients with suspected infection, a normal slit-lamp examination, and without evidence of dermal mf. Mazzotti provocation testing was used only in study subjects evaluated before the year 2000.

The study was conducted under protocols approved by the NIAID Institutional Review Board, including the registered protocols NCT00001230 and NCT00001645. All patients gave informed consent to participate. Characteristics of a subset of TRs were previously described.^{10,21}

Patient evaluation. All patients received a detailed baseline medical history review and a complete physical examination. Clinical assessments were performed by NIAID LPD physicians with experience in the diagnosis of parasitic infections. Baseline evaluation included a dilated slit-lamp examination performed by an ophthalmologist to exclude onchocercal eye disease.

Laboratory investigations and parasitologic testing. All patients received baseline laboratory investigations, including a complete blood count with differential, metabolic panel, and quantification of immunoglobulins.⁶ Eosinophilia was defined as an absolute eosinophil count (AEC) ≥ 500 cells/mL. Skin snips were collected from all patients to visualize dermal *O. volvulus* mf by microscopy and/or to detect *O. volvulus* DNA through PCR. Skin-snip examination was performed using standard technique, using a Holth-type corneal scleral punch (Storz Instruments, St. Louis, MO).¹⁰ For patients with potential exposure to *L. loa*, Nuclepore™ filtration (Whatman, Pleasanton, CA) was performed with 1 mL of whole blood collected between 10 AM and 2 PM and/or *L. loa* PCR testing of whole blood.⁶ For patients with suspected *W. bancrofti* infection, Nuclepore™ filtration of whole blood collected between 10 PM and midnight and/or circulating antigen testing using the TropBio assay (JCU Tropical Biotechnology Private Limited, Queensland, Australia) was performed.^{6,22}

Parasite-specific immunoassays and recombinant antigen testing. Testing for antibody response to a crude extract of filarial antigens and recombinant filarial-specific proteins was performed on stored patient sera from the earliest study time-point available. IgG and IgG4 responses to *Brugia malayi* adult antigen (BMA) were measured by ELISA as described previously. Normal values were defined based on the upper 99% confidence limits for 62 unexposed North Americans.^{21,23}

Antibody responses to the recombinant filarial antigens *Wb*-123,²⁴ *LI*-SXP-1,²⁵ and *Ov*-16²⁶ are highly species specific. We measured IgG and IgG4 antibodies to *Wb*-123, *LI*-SXP-1, and *Ov*-16 using a Luminex™ platform (Bio-Plex MAGPIX multiplex reader; Bio-Rad, Hercules, CA).^{10,24,25} Cutoff signal/noise values of ≥ 20 for IgG and ≥ 5 for IgG4 were based on receiver operating characteristic analyses using a large panel (> 100) of sera of individuals with no known travel outside North America and with panels of serum of patients with bona fide, mf-positive single filarial infections (e.g., *L. loa*, *W. bancrofti*, or *O. volvulus*).

Eosinophil granule proteins. Major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), and eosinophil peroxidase (EPO) were measured using a Luminex xMAP multiplexed immunoassay (Luminex Corporation, Austin, TX). The limit of the assay was 0.55 μ g/mL for MBP, 1 μ g/mL for ECP, 0.24 μ g/mL for EDN, and 0.43 μ g/mL for EPO.²⁷

Statistical analysis. Categorical variables were compared using Fisher’s exact test. Continuous variables were analyzed using nonparametric testing with the Mann–Whitney *U* test. We used geometric means (GMs) with 95% CIs as measures of central tendency.

Univariate and multivariate linear regression analyses were performed to evaluate the association between two outcomes (AEC and BMA-IgG4 level) and covariates, including gender, duration of exposure to the endemic area, and parasitic coinfection. Covariates were chosen based on the a priori hypothesis of potential confounding of the relationship between endemicity and the outcome of interest. Univariate logistic regression was performed to examine risk factors for onchocercal eye disease. Data were analyzed using Stata statistical software version 13 (StataCorp LP, College Station, TX).

RESULTS

Patient characteristics. We identified 40 TRs and 36 ENds with active *O. volvulus* infection. Fifteen of 36 (41.6%) ENds and 21/40 (52.5%) TRs met the inclusion criteria based on the presence of mf or *O. volvulus* DNA in skin snips, whereas the remainder were diagnosed based either on a positive Mazzotti test/posttreatment reaction with positive antifilarial serology or on exposure, classic symptoms, and positive antifilarial serology.

Onchocerca volvulus infection was acquired mainly in West or Central Africa (70/76 [92%]) (Table 1). Most ENds acquired onchocerciasis in Cameroon (27/36 [75%]), whereas infection in TRs occurred throughout West and Central Africa, most commonly in Sierra Leone (14/40 [35%]). The TR group included 25 Peace Corps volunteers, five missionaries, four research scientists, two health-care workers, two children, and two occupational travelers. The median duration of exposure to an *O. volvulus*–endemic area was significantly shorter in TRs (28 months [range 2–207]) than in ENds (373 months [range 12–823], $P < 0.001$). The prevalence of coinfections with intestinal helminths was similar in ENd and TR groups (ENd 7/36 [19%] versus TR 3/40 [7.5%], $P < 0.18$). Four ENds (11%) and two TRs (5%) had a documented coinfection with *L. loa* ($P = 0.41$) (Table 1). No patient was coinfecting with *W. bancrofti* or *Mansonella perstans*.

Symptom timing and characteristics. Most TRs became symptomatic after repatriation (29/35 [82.9%]), whereas the majority of ENds (18/29 [62.1%]) noted symptoms before leaving the endemic area (Table 1). In those who became symptomatic in the United States, TRs manifested initial symptoms a mean of 15 months (SD: 11.2) after leaving the endemic area, whereas ENds developed symptoms a mean of 33.5 months after immigration (SD: 31.0, $P = 0.096$). Endemic individuals had a substantially longer median time from symptom onset to diagnosis (ENds 26.9 months [interquartile range {IQR} 12.0–53.8] versus TRs 6.3 months [IQR 2.8–15.2], $P < 0.001$).

Five TRs (12.5%) were asymptomatic, whereas all endemic patients manifested at least one characteristic symptom of *O. volvulus* infection ($P = 0.064$) (Table 2). Pruritus predominated in

TABLE 1
Demographic characteristics of endemic individuals and temporary residents with onchocerciasis

Characteristic	Endemic individuals, <i>n</i> = 36	Temporary residents, <i>n</i> = 40	<i>P</i> -value
Female, no. (%)	21 (58.3)	13 (32.5)	0.037
Age, years, median (IQR)	36.9 (26.7–45.2)	30.3 (27.5–38.6)	0.12
Race, no. (%)			< 0.001
Caucasian	1 (2.8)	37 (92.5)	
African or African American	35 (97.2)	3 (7.5)	
Region of acquisition, no. (%)*			0.62
West/Central Africa	35 (97.2)	35 (87.5)	
East Africa	0	1 (2.5)	
Africa, multiple regions	0	2 (5)	
Central/South America	1 (2.8)	2 (5)	
<i>Loa loa</i> coinfection, no. (%)	4 (11.1)	2 (5.0)	0.41
Intestinal helminth coinfection, no. (%)†	7 (19.4)	3 (7.5)	0.18
Helminth coinfection, no. (%)‡	12 (33.3)	6 (15)	0.1
Duration of residence in endemic area, months, median (IQR)§	373 (295–520)	28 (24–48)	< 0.001
Symptom onset in endemic area, no. (%)	18 (62.1)	6 (17.1)	< 0.001
Time to symptom onset after leaving endemic area, months, mean (SD)¶	33.5 (31.0)	15 (11.2)	0.096
Time from symptom onset to diagnosis, months, median (IQR)#	26.9 (12.0–53.8)	6.3 (2.8–15.2)	< 0.001

* West/Central Africa included Benin, Gambia, Guinea, Ghana, Ivory Coast, Liberia, Nigeria, Senegal, Sierra Leone, Togo, Angola, Cameroon, Central African Republic, Congo, Democratic Republic of Congo, Equatorial Guinea, and Gabon; East Africa included Burundi; and Central/South America included Guatemala and Venezuela.

† The most common intestinal helminths were *Strongyloides stercoralis* (six patients), hookworm (four patients), and *Trichuris trichiura* (one patient).

‡ Included infection with other filarial parasites, soil-transmitted helminths, and schistosomiasis.

§ Unable to determine for six endemic and seven temporary resident patients.

|| Excluded four asymptomatic TRs. Symptom onset location was unknown for one TR and seven ENDS.

¶ Calculated using Student's *t*-test, based on 10 endemic and 22 TR patients.

Included 23 endemic and 24 TR patients with documented symptom onset and diagnosis dates.

both groups, although more TRs described rash (26/40 [65%] versus 7/31 [22.6%], $P = 0.001$). No TR complained of visual disturbance, which occurred in 12.9% of ENDS ($P = 0.032$). Approximately 23% of patients in both groups described limb swelling ($P = 1.0$), most (81%) without *L. loa* coinfection.

Physical examination. Skin manifestations at the initial/baseline study visit differed in ENDS and TRs (Table 3). Papular onchodermatitis was present in 47.5% (19/40) of TRs but only in 2.7% (1/36) of ENDS ($P < 0.001$). Skin pigmentation changes (hyper- or hypopigmentation) occurred more frequently in ENDS (15/36 [41.7%]) than in TRs (6/40 [15%], $P = 0.01$). One endemic patient had evidence of hyperreactive onchodermatitis (sowda).

Onchocercal eye disease occurred almost exclusively in the END group. Among ENDS who underwent slit-lamp examination, seven (22.6%) had abnormalities consistent with sequelae of *O. volvulus* infection, whereas only one TR (3.3%) had onchocercal eye disease ($P = 0.053$). In univariate analysis, there was no difference in the odds of onchocercal eye disease based on gender (OR: 0.7 [95% CI: 0.15–3.1], $P = 0.6$) or region of exposure (West Africa versus Central Africa, OR: 3.9 [95% CI: 0.4–36], $P = 0.2$); however, the odds of ocular involvement increased slightly with each additional year of

residence in the endemic area (OR: 1.05 [95% CI: 1.0–1.11], $P = 0.04$). Unilateral limb edema was present in one endemic patient (2.8%) and five TRs (12.5%, $P = 0.2$), with *L. loa* coinfection in only one TR.

Laboratory investigations. Table 4 describes baseline laboratory investigations in patients who had not received antifilarial treatment within 5 years of study entry. Absolute eosinophil count was similar in TRs (GM: 797.5 cells/mL [95% CI: 502.1–1,266.7]) and ENDS (GM: 763.7 cells/mL [95% CI: 432.9–1,347.1], $P = 0.97$) (Figure 1). Multivariable regression analysis revealed no difference in AEC adjusting for gender, duration of residence in the *Onchocerca*-endemic area, and coinfection with other helminths ($P = 0.2$). Only two-thirds of patients in each group had peripheral blood eosinophilia. Polyclonal IgE was significantly higher in ENDS than in TRs (GM: 1,309 IU/mL [95% CI: 652–2,628] versus 251 IU/mL [95% CI: 139–451], $P < 0.001$), but there was no difference in the proportion with polyclonal IgE above the normal range.

Parasite-specific serologic testing. All but three patients (two TRs and one endemic patient) had elevated BMA-IgG or BMA-IgG4 (Table 5). In the subset of patients with available stored sera before antifilarial treatment, GM BMA-IgG concentrations were similar in ENDS and TRs; however, the IgG-specific percentage of total IgG (BMA-IgG/total IgG) was significantly higher in TRs than in ENDS (1.7% [95% CI: 1.0–2.8] versus 0.8% [95% CI: 0.4–1.5], respectively, $P = 0.04$) (Figure 2). Endemic individuals were more likely to have positive testing for BMA-IgG4 (89% versus 62.5%, $P = 0.015$). Among those who tested positive, ENDS had significantly higher BMA-IgG4 levels than TRs, but there was no significant difference after adjusting for gender, duration of exposure, and presence of filarial coinfection ($P = 0.7$). There was no difference between the groups in the levels of Ov-16 IgG4 ($P = 0.84$).

Eosinophil granule proteins. Because eosinophil activation is associated with tissue pathology, we assessed the

TABLE 2
Baseline symptoms before antifilarial treatment

Symptom*	Endemic individuals, no. (%)	Temporary residents, no. (%)	<i>P</i> -value
Asymptomatic	0 (0)	5 (12.5)	0.064
Pruritus	28 (90.3)	32 (80)	0.33
Rash	7 (22.6)	26 (65)	0.001
Visual disturbance	4 (12.9)	0 (0)	0.032
Limb swelling	7 (22.6)	9 (22.5)	1.0
Arthralgias	3 (9.7)	3 (7.5)	1.0

* Pretreatment symptoms were unknown for five endemic patients who had received prior therapy for *Onchocerca volvulus*.

TABLE 3
Baseline physical examination findings

Physical examination*	Endemic individuals, no. (%)	Temporary residents, no. (%)	P-value
Skin manifestations			
Papules	1 (2.7)	19 (47.5)	< 0.001
Pigmentation changes	15 (41.7)	6 (15)	0.011
Lichenification	5 (13.9)	1 (2.5)	0.096
Onchocercal eye disease†	7 (22.6)	1 (3.3)	0.053
Punctate keratitis	2 (6.5)	0 (0)	0.49
Corneal scarring	4 (12.9)	1 (3.3)	0.35
Subretinal scarring	1 (3.2)	0 (0)	1.0
Limb edema, unilateral‡	1 (2.8)	5 (12.5)	0.2
Lymphadenopathy	4 (11.1)	7 (17.5)	0.52
Subcutaneous nodules	6 (16.7)	4 (10)	0.5

* Baseline physical examination performed at the National Institute of Health first study visit, irrespective of prior treatment.

† Slit-lamp examination findings were not documented in five endemic and 10 temporary resident patients.

‡ One endemic patient had unilateral upper extremity edema. In the temporary resident group, four patients had unilateral upper extremity edema and one had unilateral lower extremity edema.

levels of eosinophil granule proteins in the serum as these are known to be a reflection of eosinophil degranulation. There was no difference between END and TR groups in the GM level of any eosinophil granule protein (Table 6). Major basic protein was significantly correlated with baseline AEC ($p = 0.63$, $P < 0.001$), as was EDN ($p = 0.63$, $P < 0.001$) and EPO ($p = 0.41$, $P = 0.009$). There was no association between ECP and AEC ($p = -0.23$, $P = 0.15$).

DISCUSSION

Our study is the only contemporary systematic comparison of TRs and ENDs with imported onchocerciasis, including 40 TRs and 36 ENDs who underwent rigorous diagnostic testing in a nonendemic tertiary care setting. Although there was substantial overlap in clinical presentation, we noted several important differences. TRs had papular dermatitis more frequently, whereas ENDs had hyper- or hypopigmentation typically associated with more chronic inflammation. Eye disease occurred in only one TR, whereas 23% of endemic patients had ocular involvement on slit-lamp examination. One-eighth of TRs were clinically asymptomatic, consistent with the 9–21% prevalence of asymptomatic infection in other expatriate cohorts^{12,14}; unexpectedly, all ENDs had at least one characteristic *O. volvulus* symptom. Most ENDs were symptomatic at the time of immigration, but in those

who developed symptoms postimmigration, median time to symptom onset was close to 3 years after leaving the endemic area. By contrast, few TRs were symptomatic at the time of repatriation, with symptom onset occurring a median of 15 months after leaving the endemic area. Temporary residents had symptoms for a median of 6 months before being diagnosed, whereas diagnosis was delayed by more than 2 years in ENDs.

Unlike with *L. loa*, differences between ENDs and TRs with imported onchocerciasis were not driven by an eosinophil-mediated immune hyperresponsive state in TRs. There was no difference whatsoever in AEC, even after controlling for gender, helminth coinfection, and duration of exposure to the endemic area. Eosinophil granule protein levels, markers of eosinophil activation, were also the same in both groups. Our results differed from those of McCarthy et al., who observed significantly higher AECs in ENDs than in TRs. Discordant results could be due to the very different composition of the END groups, as McCarthy et al.¹⁰ studied endemic patients within an endemic setting who had ongoing *O. volvulus* exposure, and presumably a higher prevalence of concomitant geohelminth infection.

Differences in ENDs and TRs could instead be linked to infection chronicity. Endemic individuals had a significantly longer duration of exposure and time to diagnosis, implying more prolonged untreated infection. Onchocercal eye disease was associated with longer exposure duration in ENDs. Endemic patients also had higher levels of BMA-IgG4 and more frequent Ov-16 IgG4 positivity, both of which likely reflect more chronic disease.

Our findings have important implications for clinicians in nonendemic countries. The substantial number of asymptomatic expatriates supports *O. volvulus* screening based on epidemiologic exposure and an active case-finding approach in travelers to the same destination.¹² Onchocerciasis should be considered in all patients with a history of travel to focal endemic areas, regardless of eosinophil count, which was normal in one-third of both ENDs and TRs.

Clinicians should also anticipate differing manifestations of imported onchocerciasis in TRs and ENDs: acute papular rash is more typical of TRs, whereas ENDs more commonly have chronic hyper- or hypopigmentation. Unilateral limb swelling was a common presenting symptom in TRs in our series and should prompt consideration of *O. volvulus*. Although normally associated with *W. bancrofti*, acute fixed unilateral limb swelling has been similarly described in case reports of expatriates with only infection with *O. volvulus*.^{28,29}

TABLE 4
Baseline laboratory investigations, in patients with no history of antifilarial treatment within 5 years

Laboratory test	Endemic individuals, GM (95% CI)	Temporary residents, GM (95% CI)	P-value
Absolute eosinophil count, cells/mL*	763.7 (432.9–1,347.1)	797.5 (502.1–1,266.7)	0.97
Eosinophils, %*	13.6 (8.6–21.7)	11.8 (8.1–17.3)	0.47
Eosinophilia, no. (%)*	13 (61.9)	17 (60.7)	1.0
White blood cell, $\times 10^3$ /mL*	5.7 (4.9–6.6)	7.3 (6.4–8.4)	0.003
Leukocytosis, no. (%)*	2 (9.5)	4 (14.3)	0.69
Polyclonal IgE, IU/mL†	1,309 (652–2,628)	251 (139–451)	< 0.001
Elevated polyclonal IgE, no. (%)†	15 (75)	11 (47.8)	0.12
Polyclonal IgG, mg/dL‡	1,968 (1,590–2,436)	1,233 (1,147–1,324)	0.001
Elevated polyclonal IgG, no. (%)‡	12 (80)	1 (4.5)	< 0.001

GM = geometric mean.

* Included 21 endemic and 28 temporary resident patients.

† Included 20 endemic and 23 temporary resident patients.

‡ Included 15 endemic and 22 temporary resident patients.

FIGURE 1. Differences between endemic individuals (ENDs) and temporary residents (TRs) in absolute eosinophil counts (AEC), white blood cell count (WBC), and Ig levels. Horizontal lines represent the geometric mean. Data points within the shaded area lie within the normal range of the assay.

A 23% prevalence of onchocercal eye disease in ENDs strongly supports routine slit-lamp examination in migrants with onchocerciasis from highly endemic areas. Ocular involvement in TRs was comparatively rare, as corroborated by multiple more contemporary case series of returned travelers.^{10,11,30} Temporary residents in our series spent a median duration of 2 years in *O. volvulus*-endemic areas and had untreated infection for 6–12 months. In historical cohorts, TR populations spent a median of 8–11 years in *O. volvulus*-endemic areas with chronic untreated infection.^{13,14}

Our data further underscore the importance of taking a thorough travel history and recognizing that symptoms of filarial infection often manifest months to years after exposure.^{19,31,32} Most TRs presented between 6 and 12 months after return, and, therefore, symptoms would be

missed at a one-time screening medical examination for tropical infections that typically occurs around the time of repatriation. Even though two-thirds of ENDs were symptomatic at the time of immigration, time to diagnosis was longer in ENDs than in TRs. Delayed diagnosis in ENDs may reflect other factors such as lack of access to health care or prioritization of other needs in the context of recent immigration. Endemic patients who were asymptomatic at the time of immigration took a median of 3 years to manifest symptoms. Although this could be due to recall bias, another study of Ethiopian migrants to Israel noted a median 1 year time lag between immigration and symptom onset and postulated that environmental changes might have resulted in immunologic shifts triggering symptomatic disease.¹⁵

TABLE 5
Baseline parasite-specific serologic testing, in patients with no history of antifilarial treatment within 5 years

Parasite-specific serology	Endemic individuals, GM (95% CI)	Temporary residents, GM (95% CI)	P-value
BMA-IgG, $\mu\text{g/mL}^*$	158.1 (100–250)	175.0 (112–275)	0.68
BMA-IgG positive, no. (%)†	34 (94.4)	37 (92.5)	0.28
BMA-IgG4, ng/mL‡	7,916 (5,167–12,128)	2,241 (1,171–4,290)	0.005
BMA-IgG4 positive, no. (%)†	31 (89)	25 (62.5)	0.015
Ratio: BMA-IgG/total IgG (BMA-IgG/total IgG)§	0.77 (0.4–1.5)	1.7 (1.0–2.8)	0.038
Ov-16 IgG4, ng/mL	676 (343–1,333)	618 (218–1,750)	0.84
Ov-16 IgG4 positive, no. (%)†	18 (50)	10 (25)	0.033

BMA = *Brugia malayi* adult antigen; GM = geometric mean; Ov = *Onchocerca volvulus*.

* Included 18 endemic and 22 temporary resident patients.

† Based on first available serum independent of prior treatment.

‡ Included 15 endemic and 13 temporary resident patients.

§ Included 12 endemic and 18 temporary resident patients.

|| Included 11 endemic and 6 temporary resident patients.

FIGURE 2. Differences between endemic individuals (ENDs) and temporary residents (TRs) in parasite-specific serologic testing. Horizontal lines represent the geometric mean. Dashed lines represent the upper limit of detection of the assay. BMA = *Brugia malayi* adult antigen; OV = *Onchocerca volvulus*.

Finally, our study has implications for laboratory testing for imported *O. volvulus*. As noted earlier, a normal eosinophil count does not exclude *O. volvulus* infection in either ENDs or TRs as one-third had a normal eosinophil count. Serum IgE levels were also poor predictors of onchocerciasis as half of TRs and one-quarter of ENDs had normal IgE levels. In North America, an antifilarial IgG4 assay is available commercially (and from the CDC) and both an anti-BMA-IgG and IgG4 are available from the LPD, NIAID. These are the only available tests to screen for suspected filarial infection in North America. In our study, relying on BMA-IgG4 to exclude *O. volvulus* infection would have missed 10% of infections in ENDs and 40% of infections in TRs. The lack of sensitivity of BMA-IgG4 in TRs likely reflects a shorter duration of infection as BMA-IgG4 may not become positive until up to 18 months after infection occurs. *Brugia malayi* adult antigen-IgG4 testing will, therefore, miss relatively newly acquired infection. Ov-16 IgG4 serologic testing is highly specific for *O. volvulus* infection but is not widely

available outside of tropical medicine reference laboratories and has lower sensitivities between 70% and 80%.

The global burden of onchocerciasis continues to decrease because of widespread ivermectin distribution.³³ Onchocerciasis, however, remains a major public health problem in areas of West Africa that are coendemic for *L. loa*, where ivermectin mass drug administration has been halted because of the risk of precipitating encephalopathy in individuals with high levels of *L. loa* microfilaremia. Despite the recent successful implementation of a test-and-not-treat strategy using point-of-care diagnostics for *L. loa*,^{34–36} both endemic populations and travelers remain at risk.^{34–36}

Our study describes differing clinical presentations of imported onchocerciasis in migrants and travelers. Unlike *L. loa*, differences in ENDs and TRs are not eosinophil-mediated and may instead be related to infection chronicity and/or the presence of *Wolbachia* in *O. volvulus*.³⁷ Further analyses and long-term follow-up of these patients are critical to understand

TABLE 6
Baseline eosinophil granule proteins, in patients with no history of antifilarial treatment within 5 years

Laboratory test*	Endemic individuals, GM (95% CI)	Temporary residents, GM (95% CI)	P-value
Major basic protein	8,758.3 (5,808.2–13,206.8)	6,416.4 (4,987.3–8,255.0)	0.13
Eosinophil cationic protein, ng/mL	26,071.6 (18,536.7–36,669.3)	23,538.3 (17,483.4–31,690.1)	0.48
Eosinophil-derived neurotoxin, ng/mL	263.3 (164.9–420.2)	321.0 (239.1–430.9)	0.13
Eosinophil peroxidase, ng/mL	24.3 (13.2–44.6)	14.8 (8.7–25.3)	0.28

GM = geometric mean.

* Included 18 endemic and 22 temporary resident patients.

the underlying pathogenetic mechanisms driving the clinical differences we observed.

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