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Amebic Liver Abscess in Israeli Travelers: A Retrospective Study

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Abstract. Amebic liver abscess (ALA) is endemic in developing countries. The epidemiology and clinical characteristics of the disease in developing countries are well described. Travelers from nonendemic countries can serve as a model for the natural history of ALA. Currently, the available literature on travelers is limited. This is a retrospective observational study on Israeli travelers diagnosed with ALA. Data regarding travel history, clinical presentation, imaging, and treatment were collected and analyzed. Among 6,867 ill returning Israeli travelers, amebiasis was diagnosed in 53 travelers (0.77%), of whom 14 were with ALA (0.2%). Twelve ALA cases (86%) had an exposure in the Indian subcontinent. The male to female ratio was 1:1, with no significant clinical differences between the sexes. The average lag period between exposure and onset of symptoms was 17.1 months. The lack of male predominance and the prolonged lag period may imply that behavioral factors are pivotal in the development of ALA. Larger case series of travelers are required.

INTRODUCTION

Amebiasis is caused by a human-specific protozoa, *Entamoeba histolytica*, which is transmitted through fecal-oral route and infection develops after ingestion of contaminated water or food.[1] In the developing world, because of poor sanitation and inadequate health education, amebiasis is still a main health concern,[2] while in developed countries the disease is rare and most cases are imported by immigrants or international travelers.[3,4]

According to the World Health Organization, amebiasis is defined as infection with *E. histolytica*, regardless of the symptoms.[5] Up to 90% of amebiasis cases are asymptomatic. Less than 10% of the symptomatic cases are complicated with an amebic liver abscess (ALA), and rarely with other extraintestinal manifestations.[1]

ALA occurs when infective trophozoites migrate hematogenously mostly to the right lobe of the liver and it is the main extraintestinal complication of the disease. Adult men aged 20–50 years are more frequently infected, although both sexes and all ages may develop ALA.[6] The clinical presentation varies but usually is accompanied by fever, rigors, and diaphoresis. Jaundice is rarely manifested. In most of the patients, cysts and trophozoites may not be seen on fecal smears concurrently with ALA diagnosis.[7]

ALA is rare among travelers. Detailed case series of imported ALA exist but they exclusively originate from France.[4,8,9] The aim of our study is to describe the presentation, clinical course, and to point out new aspects of ALA in travelers.

PATIENTS AND METHODS

Study design. This study is based on an observational retrospective cohort.

Patient population. Patients who presented with ALA to one of the two existing "post-travel" clinics in Israel—the Sheba Medical Center, Tel Hashomer, Ramat-Gan, or the Shaare Zedek Medical Center, Jerusalem, between 1999 and July 2014 were included in this study. Immigrants and foreign workers were excluded from this study.

Data regarding exposure history, travel duration, clinical presentation, treatment, and laboratory diagnosis were collected and analyzed.

Diagnosis. The diagnosis was based clinically on fever: a history of a travel to an endemic country, existence of a liver abscess (diagnosed by ultrasound, computed tomography, or magnetic resonance imaging), clinical cure with metronidazole/tinidazole as the sole treatment, with negative bacterial culture from the drained abscess, and/or a positive serological/molecular test. The tests implemented were the following: indirect hemagglutination test (Cellognost Amoebiasis®, Siemens Health Care Diagnostics, Marburg, Germany), titers of ≥ 1:128 were considered positive; enzyme-linked immunosorbent assay serology (SCIMDEX Corporation, Denville, NJ); ameba multiplex real-time polymerase chain reaction (PCR)[10] from a drained abscess; 200 μL of pus was mixed with 1 mL of NucliSENS lysis buffer. Total DNA is extracted on a NucliSENS easyMag device (bioMerieux, Marcy-l'Étoile, France). Reverse transcription PCR is run using an Applied Biosystems® 7500 machine (Applied Biosystems, New York, NY).

Statistical analysis. Descriptive statistics were used to present demographic data of the study population. *t* Test and Mann-Whitney *U* test were used to explain difference between continuous or discrete demographic data, respectively. Fisher's exact test was used to explore differences in prevalence of dichotomous data between the two sexes.

RESULTS

From 1999 to July 2014, 6,867 ill returning Israeli travelers were seen in our clinics, among them 53 were diagnosed with all forms of amebiasis (0.77%), of them 14 were with ALA (0.2% of the entire population). Thus, the rate of ALA among all cases of amebiasis is 26% (14/53). The epidemiologic characteristics of all ALA cases are presented in Table 1. The majority of the travelers (71%) were regular travelers, that is, nonorganized tours or backpackers. Twelve of the 14 cases (86%) had an exposure in the Indian subcontinent. The average age of the travelers was 36.3 ± 13.3. The travel duration

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TABLE 1
Patients and travel characteristics

Patient no.	Age (years)	Sex	Reason for travel	Travel destination	Travel duration (months)	Time from end of trip to symptoms (months)	Diagnosis
1	24	F	Regular tourists	India, Nepal, China	1 years	1 months	IHA 1:256
2	28	F	Regular tourist	Turkey	1 week	4 months	IHA 1:2048
				Brazil	1 month	1 year	
				India	1.5 months	3 year	
3	38	M	Business	Nepal	2 years	0*	ELISA+
4	23	M	Regular tourist	South America	4 months	6 months	IHA 1:1600
5	38	M	Business	India	2 weeks	1.5 months	ELISA+
6	67	F	Organized tour	India	3 weeks	4 months	Clinical diagnosis†
7	24	M	Regular tourist	India, Thailand	8 months	3 months	IHA 1:6400; ELISA+
8	22	F	Regular tourist	Nepal, Thailand	2 months	3 months	ELISA+
9	30	M	Regular tourist	Morocco	3 weeks	3 months	ELISA+
				India, Sri Lanka	5 months	6 months	
10	46	F	VFR	Gabon	1 months	6 months	IHA 1:128
11	45	F	Regular tourist	Turkey	1 week	7 years	ELISA+
				India, Nepal, Thailand	6 month	20 years	
12	29	F	Regular tourist	India, Nepal	3 months	0*	IHA 1:2048
13	40	M	Regular tourist	Thailand	2 months	10 years	IHA 1:2048, PCR from pus
				India	6 months	6 years	
14	54	M	Regular tourist	India	3 weeks	18 months	ELISA+, PCR from pus
Total	36.3 ± 13.3	F = 7 M = 7	10/14 regular tourists	12/14 Indian subcontinent	Average 4.5 ± 6.6 months (of last trip), median 1.5	Mean 17.1 ± 28.9‡ Median 4.0‡	

ELISA = enzyme-linked immunosorbent assay; F = female; IHA = indirect hemagglutination; M = male; VFR = visiting friends and relatives.
*Patients that became symptomatic during travel and therefore were excluded from the total mean and median.
†When patients had more than one trip, the last one was calculated as the potential exposure.
‡The patient had negative bacterial culture from the drained abscess and was cured by tinidazole treatment only.

varied extensively from a 1-week business trip to 1-year trip as a backpacker or 2 years of business.

The time between trip and onset of symptoms varied; two of the patients developed symptoms during their trip while the other 12 had a lag period of several months to years after return. Eight of the patients had a single trip to the tropics before the symptoms began, and the other four had several trips with different possible exposure to amebiasis. In these cases, considering the last trip as the source of infection gives an average lag period of 17.1 ± 28.9 months (median 4.0).

Most patients had a typical presentation. All patients had fever above 38.5°C and 76% of them had right upper quadrant abdominal pain. In two patients presented with dyspnea, an unexpected finding in the liver was found during investigation for a pulmonary pathology. The clinical features were accompanied by leukocytosis (average: 16,500/μL, range: 9,000–25,000/μL) and an elevated alkaline phosphatase (185.9 IU/L).

Table 2 summarizes the results of the imaging studies done. Most patients had a single liver abscess (76%). The

TABLE 2
Imaging

Patient no.	Number of abscesses	Size of abscess (cm)	Location of abscess	Imaging technique			Percutaneous aspiration	Resolution (months)*
				US	CT	MRI		
1	1	6 × 8	R	√		√	+	5
2	1	5 × 10	R	√	√	–	+	2, remnant
3	1	9 × 12	R	√	√	–	+	3, smaller
4	1	3 × 6	R	√	√	–	–	2
5	1	7 × 10	R	√	√	–	+	4
6	2	4 × 4	L	√	√	–	+	2
		1 × 1						
7	1	5 × 6	R	√	√	–	+	6, remnant
8	1	–	–	–		–	–	–
9	1	9 × 9	R	√		–	+	ND
10	2	8 × 6	R + L	√	√	–	+	4
		2 × 2						
11	1	7 × 9	L	√	√	√	+	6
12	1	5 × 7	R	√	–	–	–	10, remnant
13	1	6 × 9	R	√	√	–	+	2
14	2	5.3 × 3	R + L	√	√	–	+	–
Total	Usually 1 abscess	Average 6 × 8.75	Mostly right lobe	–	–	–	11/14	2–10

CT = computed tomography; L = left; MRI = magnetic resonance imaging; R = right; US = ultrasound.

TABLE 3
Gender aspects

	Male	Female	*P* value
Number (*N* = 14)	7 (50%)	7 (50%)	
Age (years, average)	35.3	37.3	0.79
Lag period (months, average)	14.8	14.6	0.98
WBC count (average)	18.7	14.3	0.04
ALP (IU/L, average)	165.8	206	0.64
Drainage (yes/total)	6/7	5/6*	1.0
Abscess size (cm^2, average)†	53.8	43.3	0.51
Multiple abscesses	1/7	2/7	1.0

ALP = alkaline phosphatase; ELISA = enzyme-linked immunosorbent assay; WBC = white blood cell.
*One patient—unavailable data.
†Patients with more than one abscess—the area of all abscesses was summed.

right lobe was the predominant lobe involved—in 10 cases the single liver abscess was in the right lobe, in two additional cases with two abscesses each, both the right and left lobe were involved. The average size of the abscesses was 6 × 8.75 cm. Drainage of the abscess was done in 11 of 14 patients. Remnants of disease were seen for at least 2 months after treatment and even more than 10 months.

Gender comparison. The male to female ratio was 1:1. No significant size difference between abscesses in males and females was observed ($P = 0.51$). In addition, except for a higher white cell count among males, no significant differences were observed between the sexes, including liver function tests, the number of abscesses, or the need for drainage (Table 3).

DISCUSSION

The true world epidemiology of amebiasis is changing due to molecular techniques that, in contrast to microscopic evaluation of the stool, has the ability to differ *E. histolytica* from the nonpathogenic *Entamoeba dispar* and *Entamoeba moshkovskii*.[6] Excluding the nonpathogenic cases reduces the true prevalence of amebiasis. In a molecular study from India examining 1,720 stool samples from patients with gastrointestinal symptoms, 3.5% were positive for *E. histolytica*, 9.3% were positive for *E. dispar* and 1.9% were positive for *E. moshkovskii*.[11] Implementing molecular biology techniques on 127 stool samples from asymptomatic individuals from rural areas in Brazil revealed that 0.8% were positive for *E. histolytica* and 8.7% were positive for *E. dispar*.[12] Therefore, the true incidence of ALA among patients with true *E. histolytica* intestinal amebiasis might be higher than that usually cited.[1] Regarding ALA, diagnosis with molecular techniques is relatively new and may increase the number of diagnosed cases.[13,14]

In travelers, the true prevalence of amebiasis is unknown. Most studies are relatively old and based only on microscopic evaluation of the stool.[3] Among 5,378 travelers seeking diagnosis and treatment of intestinal infections at the travel clinic of the University of Munich between 2005 and 2009, 103 (1.9%) clinically amebiasis cases were detected but only 9.7% of these cases were diagnosed as *E. histolytica* when a specific PCR was performed on stool samples.[15]

Travelers from nonendemic countries can be regarded as a model for the natural history of the disease. Currently, the available literature regarding ALA in travelers is limited to case series from France[4,9] and in one study diagnostic molecular biology techniques were applied.[8]

In the present study, 14 of 6,867 (0.2%) ill returning Israeli travelers were diagnosed with ALA. Fifty-three of these ill returning travelers presenting to the travel medicine clinic were diagnosed with amebiasis which implies that 26% of symptomatic amebiasis travelers developed invasive ALA. This relatively high proportion of ALA may reflect the decrease in the denominator, which may reflect the better differentiation of *E. histolytica* from the other nonpathogenic species and/or the assumption that mild cases of amebiasis do not reach medical attention post travel.

Israeli travelers have a travel preference to the far east.[16] Twelve of our 14 ALA cases had an exposure to the pathogen in the Indian subcontinent. This predominance is consistent with the predominance of gastrointestinal infections in travelers to the Indian subcontinent in the literature. In a multinational GeoSentinel retrospective observational analysis of 6,086 returning travelers with any gastrointestinal infection, Nepal and India had the highest reporting rate ratios of gastrointestinal infection of all countries analyzed.[17] Specifically, *E. histolytica* in travelers had the highest incidence rates recorded from the Indian subcontinent.[18] In contrast, in a recent case series of imported ALA cases to France only 19% of the cases originated from Asia (specific country of acquisition is not given) and the vast majority of the cases were imported from Africa (56%).[4] This difference is probably due to the destination preference of Africa by the French travelers.[19]

A surprising finding in our results is the lack of male predominance among patients with ALA. Male predominance is well established in the literature. In case series from endemic countries, the cited male to female ratio is between 3.2:1 and 13:1.[20–23] There are several explanations for this male predominance. Gupta presented a case series from India of 100 ALA cases, 88 males and 12 females. The highest incidence of the disease, in males, was in their third decade and in females in their fifth decade which suggest that hormonal factors contribute to the difference between sexes.[21] This assumption was supported later on in in vitro studies on mice—removal of testosterone by orchiectomy significantly reduced the size of abscesses in male mice, while substitution of testosterone increased development of ALA in female mice.[24] In contrast, in a review of literatures on invasive amebiasis and population-based parasitological studies from 1929 to 1997, a total male to female ratio of 3.2:1was observed. Yet, the higher proportion of men in nearly all categories of invasive amebiasis was seen in all age groups, that is, before, during, and after maximum hormonal activity. Therefore, they conclude that the male predominance in invasive amebiasis may not be the result of hormonal effects.[25] An immunologic assumption for the male predominance was given by Bernin and others who studied blood samples from Vietnamese ALA patients compared with asymptomatic amebiasis carriers and concluded that asymptomatic female carriers had significantly higher immunologic reaction markers and therefore developed less invasive disease than males.[20] An alternative explanation is given in an Indian case series that reported that among 220 ALA patients the majority were young or middle aged males belonging to the lower socioeconomic group and 85% gave a history of drinking toddy (fermented palm juice). Furthermore, the highest incidence of the disease occurred during the peak toddy season; therefore, they conclude that the male predominance is due to a behavioral explanation.[23]

In the three travel-related French case series of ALA immigrants, foreign workers were not excluded and the reported male to female ratio is between 2.3:1 and 3.5:1,[4,8,9] which shows male predominance but much less prominence in comparison to the ratios given in endemic countries. The male to female ratio among all French travelers to endemic countries is not given; therefore, theoretically significantly more males traveling might be the reason for the male predominance. For example, in a retrospective case series of 58 cases treated in four French military hospitals, as expected with the association to the army, the vast majority of the cases were in males (53 males versus 5 females).[26] In fact, our data from Israel show that the proportion of male to female travelers to tropical countries is almost equal (54% males and 46% females) and indeed our male to female ratio in regard to ALA is 1:1.[27] In addition, we excluded immigrants and foreign workers and therefore our figures reflect the situation in travelers more clearly. On further comparison between the epidemiological and clinical characteristics of males and females in our study (Table 3), no significant differences were observed between the sexes, including size of abscesses and severity of the disease. This lack of substantial difference supports the given ratio of 1:1. Further data regarding travelers with ALA cases imported to other developed countries are required to better shed light on the real gender aspect of ALA.

Another important observation in our results is the lag period between the end of trip and the onset of symptoms, this lag period varied but in average was prolonged: 17.1 months; however, it could even reach several years, for example, patient 11 had a minimal lag period of 7 years and a possible lag period of 20 years. Israel is a nonendemic country for amebiasis with no autochthonous cases described since 1979[28]; therefore, the possibility of exposure after the end of trip is negligible. This possible prolonged lag period has already been described—in the recent case series report from France, the median time from return from the endemic area to the onset of symptoms (N = 90 travelers) was 128 days and the maximum lag period was 14 years.[4] There are case reports of travelers with an extremely prolonged lag period such as 22, 29, 32, and even 50 years.[29–32] This kind of observation is impossible in residences of endemic countries and is of clinical interest and should be highlighted as a key point in diagnosis of ALA in returning travelers. This lag period reflects the latent period until the *E. histolytica* becomes virulent. Studies carried out to understand the mechanism involved in the changing virulence of *E. histolytica* propose different mechanisms—varying virulence of different strains of the parasite or in contrary, changes in the intestinal bacterial flora; exposure to nutrient sources and other host factors.[28] The travel experience points out that the reason for the late invasiveness could not be explained by exposure to different types of ameba as all were *E. histolytica* or different virulent strains of *E. histolytica* because the same pathogen resides in the intestine since the return from the endemic region. Thus, the most likely explanation is probably any kind of environmental and/or behavioral changes in the host or in the gut of the host (such as antibiotic treatments or changes in the bacterial flora of the gut).[33]

The main limitation of our series is the retrospective design and the small size. Our small case series is sufficient to demonstrate the long lag period between the infection time and the appearance of liver abscess; however, it might be too small to indicate that in travelers with ALA the male to female ratio of 1:1 is not only a small sample bias.

In conclusion, we present an Israeli case series of 14 travel-related ALA cases. Our series is relatively small but yet has several unique aspects. The lag period between exposure to the pathogen and onset of symptoms may take months to years, during which the patient resided in a nonendemic country. This finding highly signifies that the theory of virulent versus less virulent strains within *E. hystolytica* is not the explanation for development of ALA, but rather changes in the gut or host that are key point for the switch from a nonvirulent to virulence within the same strain. Taking together with the male predominance in tropical countries can reflect behavioral factors that are more common in the tropics. In our series, only travelers from nonendemic countries were included and indeed no male predominance was observed. We urge the need for large case series from other developed countries.

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