

Visceral Leishmaniasis in Israel, 1960–2000

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Abstract

Background: Visceral leishmaniasis was first reported in Israel (then Palestine) in 1929. In the 1960s and 1970s, it was endemic to northern Israel, but only partial data about the disease have been gathered since then.

Objective: To investigate the epidemiologic trends of visceral leishmaniasis in Israel from 1960 to 2000, and to delineate some clinical features of the infection.

Methods: Data were collected from hospital charts, scientific publications, and reports of the Ministry of Health and the Kuvin Center for the Study of Infectious and Tropical Diseases.

Results: During the last four decades, 87 cases of visceral leishmaniasis were diagnosed in Israel, 76 of them (87%) in children. In the 1960s, all 54 patients were diagnosed in the northern part of the country. The rate of infection declined significantly in the 1970s (5 cases) and then increased slightly in the 1980s (11 cases) and 1990s (17 cases). More than 50% of the cases in the 1990s were in central Israel. Children accounted for 100% of cases in the 1960s but only 58% in the 1990s. The main clinical features of the patients diagnosed in the last decade were fever, weight loss, hepatosplenomegaly and pancytopenia. Three of the adults were co-infected with human immunodeficiency virus.

Discussion: The decline in the incidence of visceral leishmaniasis in the 1970s and the slight increase in the 1980s and 1990s can be attributed to changes in the animal reservoir and vectors, and in the immunity status of part of the population exposed to *Leishmania*.

Conclusions: Visceral leishmaniasis has reemerged in Israel. This mandates better control of the animal reservoir and vectors and increased awareness to this infection.

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In the early 1900s, an English military surgeon, Sir William Boog Leishman (1865–1926) and an Irish physician, Charles Donovan, discovered oval, Giemsa-stained non-flagellated amastigotes (now known as the “Leishman-Donovan bodies”) in the splenic tissue of patients with the life-threatening disease then known as kala azar or black fever. Thereafter, researchers established that the disease is caused by the protozoa *Leishmania* and renamed it visceral leishmaniasis. The species causing VL are transmitted to humans by the female sandfly from its natural reservoir, mainly dogs, foxes, jackals, wolves, rats, and other rodents. Parental, congenital, sexual, occupational, and person-to-person transmission has also been reported.

VL is only one of several distinct syndromes caused by *Leishmania* species, which also include cutaneous leishmaniasis, diffuse cutaneous leishmaniasis and mucocutaneous leishmaniasis.

Visceral leishmaniasis presents with systemic manifestations such as weight loss, bouts of fever, hepatosplenomegaly and pancytopenia. It is the most severe form of leishmania infection and is primarily caused by *L. donovani* in the Indian subcontinent and Africa, *L. infantum* in the Mediterranean region and Middle East, and *L. chagasi* in North America. Leishmaniasis is endemic to about 90 countries on five continents [1]. In Israel, both the cutaneous and visceral forms have been reported. Cutaneous leishmaniasis is endemic to the Dead Sea Rift Valley and the Negev region in the south of Israel; the visceral form occurs mainly in the Galilee region in the north of the country [2] and also in central Israel [3].

The first case of VL in Israel (then Palestine) was described in 1929 in a 3 year old boy from Ein Harod in northern Israel [4]. Since then sporadic cases have been reported [2], but as most patients were not hospitalized it is hard to estimate the prevalence of the disease before 1960. During the following years visceral leishmaniasis became endemic to northern Israel, mostly in Arab villages. In the last decade, an emerging focus of human and canine disease appeared near the major population centers in central Israel and the Palestinian Authority [5,6].

To the best of our knowledge, few epidemiologic data of VL in Israel have been reported in the last decades. The aim of our study was to investigate the epidemiology of VL in Israel during the last four decades and to increase the awareness for this reemerging infection.

Materials and Methods

Data on the epidemiologic and clinical characteristics of VL in Israel in the last 40 years were collected from all available sources, namely, medical publications and reports of the Israel Ministry of Health and the Kuvin Center for the Study of Infectious and Tropical Disease of the Hebrew University, which is a national reference laboratory for the diagnosis of leishmaniasis. We also reviewed all available charts of patients diagnosed with visceral leishmaniasis from 1990 to 2000 at the following hospitals: Assaf Harofeh (Zerifin), Hillel Yafeh (Hadera), Kaplan (Rehovot), Sheba (Tel Hashomer), Rambam (Haifa), Western Galilee (Nahariya), Beilinson (Petah Tiqva), and Schneider (Petah Tiqva). Patients under the age of 18 were defined as children.

VL = visceral leishmaniasis

Results

The trends in the occurrence of VL in Israel from 1960 to 2000 are shown in Table 1. In the 1960s, there were 54 newly diagnosed cases of VL [5]. The incidence dropped dramatically in the next decade, to only 5 reported cases, followed by a slight increase to 11 cases in the 1980s and to 17 cases in the 1990s.

Most of the cases in the 1960s (45/54) occurred in Arab agricultural villages with low socioeconomic status located in the Western Galilee, and all infected individuals were children [7]. More recently, there was a shift of VL cases from northern Israel to the center of the country [Figure 1], and in the 1990s the Galilee region accounted for only 35% (6/17) of all new cases.

The first cases of VL in central Israel were reported in 1993 [3]. There were other epidemiologic changes over time as well. In the 1990s, only 58% of new cases occurred in children, with a drop in the relative risk to children for VL from 57 to 2.7, and in addition, more Jews than Arabs were affected [Table 2]. Throughout the period of the study, there was a male predominance, and the patients generally presented in the spring and summer (data not shown).

Table 3 shows the clinical features of patients with VL in 1990–2000. Clinical data were available for 13 of the 17 patients diagnosed during this period. All presented with prolonged fever (duration range 1–18 weeks, median 10 weeks), and a weight loss of up to 20% of body weight occurred in some patients, mostly in adults with concomitant human immunodeficiency virus infection. Hepatosplenomegaly was reported in all patients, and the spleen was more enlarged than the liver in most children. None of the children had HIV infection compared with 43% of the adults. Pancytopenia was noted in all patients. The anemia was usually normocytic. Two infants presented with Coombs-positive hemolytic anemia. Hepatocellular test abnormalities were more prominent in the adults, and 60% of the patients had laboratory evidence of unicteric hepatitis. All patients with HIV infection had a low CD4+ count ($<200/\text{mm}^3$) at the time of diagnosis of VL. In one child, bone marrow aspiration findings were consistent with a diagnosis of hemophagocytic lymphohistiocytosis associated with VL [8].

Discussion

The World Health Organization estimates that 12 million people worldwide are infected by *Leishmania*, and that 1.5 to 2 million new cases of VL are diagnosed annually [9,10]. However, only 600,000 new cases are officially reported per year [10]. Ninety percent of all cases of VL occur in South America, Africa and Asia. With the spread of HIV, an additional geographic focus of VL is emerging in the Mediterranean region of Europe and the Middle East.

The prevalence of VL depends on the distribution of vectors (sandflies), the presence of animal reservoirs, and the immune status of hosts. The trend of decline in the incidence of VL in Israel from the 1960s to the 1970s can be attributed to several factors.

● **Animal reservoirs.** The prevalence of canine leishmaniasis in the Mediterranean region varies considerably, from 1–37%. In Spain, for instance, 3–5% of all dogs are seropositive for leishmaniasis, with

Table 1. Incidence of visceral leishmaniasis in Israel, 1960–2000 and relative risk of visceral leishmaniasis for children during four decades

Period	Total no. of cases	Pediatric cases	(% of total)	Relative risk	95% CI	
					Low	High
1960–69	54	54	(100%)	57.0*	7.88	411.89
1970–79	5	4	(80%)	7.3	0.82	65.31
1980–89	11	8	(72%)	4.7	1.25	17.75
1990–2000	17	10	(58%)	2.7	1.04	7.15

* One adult case is assumed.

CI = confidence interval.

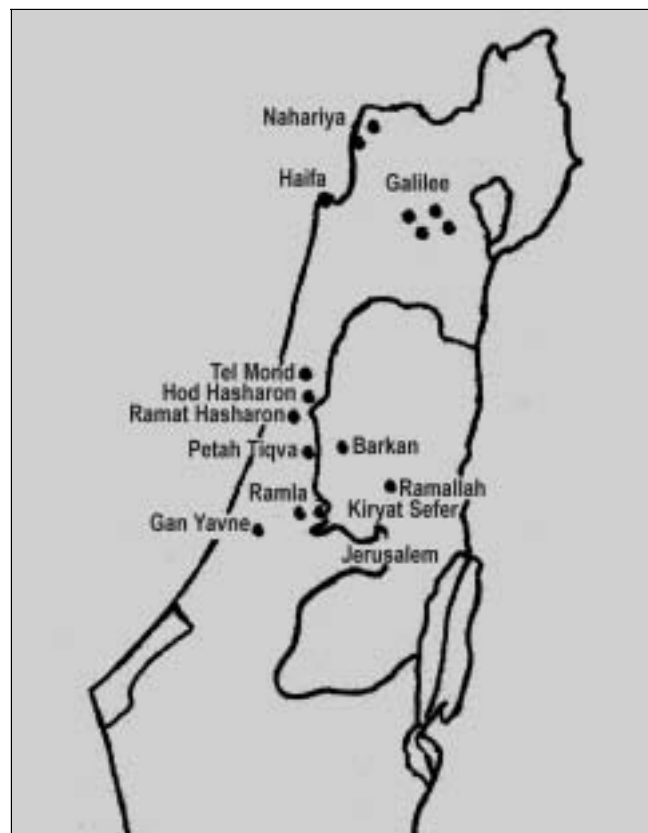


Figure 1. Geographic distribution of visceral leishmaniasis (VL) in Israel, 1990–2000. One patient was infested overseas.

Table 2. Epidemiology of visceral leishmaniasis in Israel, 1990–2000

	Children*	Adults	Total
No. of patients	10 (58%)	7 (42%)	17
Male:Female ratio	7:3	6:1	13:4
Mean age (yrs)	2.5	34.3	15.6
Region in Israel			
North	5	1	6 (35%)
Central	5	4	9 (53%)
South	0	1	1 (6%)
Elsewhere**	0	1	1 (6%)
Ethnicity			
Arab	7	0	7 (41%)
Jewish	3	7	10 (59%)

* Children ≤ 18 years.

** Patient who may have been infected abroad (Thailand)

HIV = human immunodeficiency virus

Table 3. Clinical presentation of visceral leishmaniasis in Israel, 1990–2000

	Children (n = 6)	Adults (n = 7)	Total (n = 13)
Fever >1 wk	6 (100%)	7 (100%)	13 (100%)
Weight loss*	6 (100%)	7 (100%)	13 (100%)
Hepatosplenomegaly	6 (100%)	7 (100%)	13 (100%)
Hemoglobin (g/dl, mean ± SD)	7.3 ± 1.5	8.8 ± 1.9	8 ± 1.9
White blood cells (mm ³) (mean ± SD)	4,330 ± 1,978	3,020 ± 1,498	3,734 ± 1,892
Platelets (mm ³) (mean ± SD)	126,000 ± 32,000	115,000 ± 33,000	121,000 ± 33,000
Erythrocyte sedimentation rate (mm/hr) (mean ± SD)	98 ± 17	102 ± 17	100 ± 17
Prothrombin time (INR) (mean ± SD)	1.22 ± 0.1	1.1 ± 0.1	1.18 ± 0.1
Serum albumin (g/dl) (mean ± SD)	3.5 ± 0.6	3.4 ± 0.1	3.6 ± 0.5
Serum aspartate aminotransferase (U/L) (mean ± SD)	49 ± 25	90 ± 50	66 ± 42
HIV-positive	0	3 (43%)	3 (23%)

Data available for 13 of the 17 diagnosed patients

* ≥10% of body weight

INR = International normalized ratio.

rates climbing to 20% in endemic foci [10]. In Israel, the wild canine population of stray dogs, jackals and foxes came close to extinction in the 1950s and 1960s because of a major effort to control rabies. As a result, the mean annual number of cases of human rabies in Israel dropped from 23 in 1948–1957 to 2 in 1967–1978 and to zero in 1979–1995 [11]. However, in 1996 and 1997, three new cases of human rabies were reported [12]. The last decade has witnessed a dramatic reappearance of the jackal and fox population in central and southern Israel [3], which corresponded to an increase in peridomestic vector-transmission of leishmaniasis to dogs and/or humans, and to the appearance of VL in central Israel. In the mid-1990s several dogs with leishmaniasis were diagnosed for the first time in villages located between Jerusalem and Tel Aviv, and in the Sataf Nature Reserve 2 kilometers west of Jerusalem. The appearance of this new focus of canine leishmaniasis highlighted the emergence of this disease in central Israel [3]. More recent data indicate that the disease in dogs is spreading into new areas (Baneth and Jaffe, unpublished data). The Galilee, however, remained an endemic area for VL. Five percent of dogs in the Galilee region (Wadi Hamam) tested in 1995 were found to be seropositive [14,15], and this figure is probably an underestimate as infected dogs may remain asymptomatic and seronegative for many months after exposure [16]. Polymerase chain reaction studies of biopsies obtained from infected canines and humans in Israel showed that the infection was caused by *L. infantum* [17].

● **Vector.** Most cases of VL are transmitted by the female sandfly. During the 1960s, teams from the Israel Ministry of Health performed house-to-house checks for infestation in the Western Galilee and blanketed affected areas with insecticide, mostly DDT (dichloro-diphenyl-trichloroethane) 5%. This could have contributed to the reduction in incidence of human and canine VL in the following decade [2].

● **Immune status of infected humans.** Exposure to *Leishmania* can cause an abortive or latent infection, which may explain the high prevalence of seroreactivity to *Leishmania* in endemic areas. A large serologic study in the Western Galilee, where more than 2,000 sera were examined during 1994–1996, showed that the percentage of samples positive for anti-leishmanial antibodies in people without

clinical signs of disease was approximately threefold higher than in regions where VL is not endemic [18]. The percentage of seropositive sera at certain sites in the endemic region was more than 8%. Suppression of immunity (either primary or acquired) may facilitate the clinical development of leishmaniasis. The disease develops more easily in immunocompromised patients [17,19,20] and cases of *Leishmania* and HIV co-infection are emerging. The presence of HIV infection increases the risk of VL by 100- to 1,000-fold in endemic areas [20].

Since *Leishmania* parasites and the human immunodeficiency virus are both cytopathic, their combined infection exponentially increases disease severity and fatality [18]. The decreased CD4+ cell counts in HIV-infective patients, in addition to the reduced production of interferon-gamma, can facilitate the spread of the *Leishmania* protozoa, causing poor response to therapy and relapses [21]. At the same time, VL infection, especially with *L. donovani*, has been found to up-regulate the *in vitro* transcription of HIV in T cells [20]. Serologic assays for *Leishmania* are falsely negative in approximately 43% of co-infected patients [22], especially at a late stage or during relapses, making it even harder to diagnose VL and provide proper early treatment in HIV-positive patients.

Since 1990, there has been an increase in VL-endemic regions worldwide, accompanied by a sharp increase in the incidence of the disease. This may be due, in part, to the rising incidence of AIDS in these regions. From 1990 through 1998, cases of *Leishmania* and HIV co-infection were reported from Spain, France and Italy, and about 70% of affected patients were intravenous drug users [22,23]. Three of the 17 Israeli patients with newly diagnosed VL during the last decade also had AIDS. They account for 18% of the whole VL-infected population in the country, and for 43% of all adult VL patients. During this period, 521 patients with AIDS were diagnosed in Israel [24], thus the incidence (3/521) of AIDS-VL co-infection was 0.57%. This can also explain, in part, the increase in the incidence of adult VL in Israel during the 1990s.

The demographic characteristics of the patients with VL in Israel are similar to the findings in other parts of the world.

● **Gender.** Our survey yielded a male predominance in VL. Murine models have shown that females are less likely than males to develop the clinical symptoms of VL [25]. Worldwide, males account for 83.2% of all *Leishmania*-HIV co-infected individuals [20].

● **Age.** Leishmaniasis has a peak incidence in childhood. Children younger than 5 years account for the majority of cases of vector-transmitted VL [22]. In our survey, the mean age of the children was 2.5 years, similar to other studies in the Mediterranean area [22]. Until the last decade, relatively few adults with VL had been diagnosed. In recent years, however, there was a shift in the age of

VL patients in Israel. In a retrospective analysis of 965 cases worldwide, researchers found that 85.7% were diagnosed in young adulthood (age 20–40 years) [20].

● **Ethnicity.** Before 1990, most of the affected patients in Israel were of Arab origin. Since then, the rate of the disease in the Jewish population has increased, particularly in adults.

● **Geography.** The Galilee is no longer the principle geographic focus of VL in Israel. Since 1994, VL has become more common in central Israel. This can be partially explained by the recovery of the reservoir of the wild canine population in central Israel and the occupied territories [3]. More cases of VL are reported from rural areas than cities. From 1990 through 1999, 127 cases of VL were recorded among the Palestinian population in the West Bank [6]. VL cases were found mostly in the Jenin and Hebron districts, with a mean of 12.7 cases in the West Bank/year (annual range 3–32) [6].

● **Seasonality.** Curiously, in the last decade most symptoms of VL started in the spring, particularly in May. Since 2–3 months is the accepted median incubation period in immunocompetent individuals, we assume that most events of transmission in Israel in the 1990s occurred towards the end of winter and beginning of spring, around February-March. This may be due to the unfavorable conditions for transmission of arthropod-borne diseases in the rainy season, and improved conditions in spring.

● **Clinical picture.** The clinical picture of VL in Israel is similar to that documented in other countries. As prolonged fever is the rule, VL could be a cause of fever of unknown origin in 7–17% of patients in endemic cases [20]. Hepatosplenomegaly with a predominance of splenomegaly and pancytopenia are other prominent clinical hallmarks [20]. In our survey, prominent enlargement of the spleen was found in most of the pediatric patients, but this finding was less notable in adults.

Conclusion

There has been an increase in the incidence of VL in Israel in the last two decades, which may be attributed to the re-emergence of the vector and animal reservoirs and possibly to the appearance of HIV infection.

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