Acta Tropica 176 (2017) 335–339

Contents lists available at ScienceDirect

Acta Tropica

journal homepage: www.elsevier.com/locate/actatropica

Review

Historical overview of infantile visceral leishmaniasis in El Agamy, Alexandria, Egypt

Hala A. Kassem[a,*], John C. Beier[b], Bahira M. El Sawaf[c]

[a] Institute of Environmental Studies and Research, Ain Shams University, Abbassia, Cairo, 11566, Egypt
[b] Department of Public Health Sciences, University of Miami, Miller School of Medicine, United States
[c] Faculty of Science, Ain Shams University, Abbassia, Cairo, 11566, Egypt

ARTICLE INFO

Keywords:
Visceral leishmainiasis
Egypt
El Agamy
Leishamania infantum
Phlebotomus langeroni
Urbanization

ABSTRACT

Infantile visceral leishmaniasis (IVL) is considered a rare and neglected disease in Egypt. An outbreak of the disease in El Agamy, Alexandria occurred in 1982 although the disease was previously reported 80 years before. Epidemiological and entomological studies were conducted ever since the 1982 outbreak to identify human cases, the parasite, reservoir host and the sand fly vector. *Leishmania infantum* MON-98, a new and unique zymodeme, was responsible of the disease. Stray dogs acted as the reservoir host and *Phlebotomus langeroni* was the proven vector. The parasite isolates from human cases were identical to the parasite isolates from the reservoir host and the sand fly vector. The El Agamy focus in 1982 was basically a rural Bedouin setting of recently built cement houses surrounded by lime stone fences. The numbers of human cases of IVL in this area have been declining, with the last reported case in 2005. This coincides with the completion of irregular urbanization of El Agamy which resulted in the disappearance of *P. langeroni*. In this review, we characterize the old focus of IVL in El Agamy based on published literature to identify factors underlying the appearance and disappearance of the disease.

1. Introduction

This review documents the complexity of understanding changing patterns of leishmaniasis epidemiology. In 1982, there was a focal outbreak of infantile visceral leishmaniasis (IVL) in El Agamy, situated 12 km from Alexandria, on the northern coast of Egypt. This disease had not been seen in Egypt in the previous 80 years. The outbreak raised many scientific questions and challenges to public health. Critical epidemiological and entomological studies were conducted during the 1982 outbreak to identify human cases, parasite strains, reservoir hosts and the sand fly vectors. IVL eventually disappeared from El Agamy and was explained by integrated sand fly ecology and environmental studies aimed at understanding the effects of urbanization.

The objective of this review was to characterize the old focus of IVL in El Agamy based on published literature and to identify factors underlying the appearance and disappearance of the disease. As such, this review is an account of the interdisciplinary studies conducted for over 30 years to understand the complexity of IVL. The research was critical for guiding public health and clinical management of the disease. Moreover, this review addresses how the changing environment of El Agamy initially contributed to the emergence of IVL. However, massive land use changes due to urbanization caused the disappearance of the sand fly vector species and stopped transmission. Now it is important to consider whether IVL will reappear in other locations along the northern coast of Egypt and elsewhere. The rich body of scientific studies for El Agamy focus can certainly guide future investigations.

2. Materials and methods

This review was based on a comprehensive literature review on visceral leishmaniasis in Egypt from 1900 till present with special emphasis on El Agamy IVL focus. Boolean search using the “AND” and/or “OR” was performed in PubMed, Google Scholar, Web of Science and Science Direct, with the following search terms: Egypt, El Agamy, Al Agamy, visceral leishmaniasis, kala-azar, sand flies, *Phlebotomus langeroni*, *Leishmania infantum*, *Leishmania donovani*, parasitosis, neglected tropical diseases. Research articles irrelevant to the topics dealt with in this review were excluded.

* Corresponding author.
E-mail addresses: hakassem@aucegypt.edu, hala.kassem@iesr.asu.eg (H.A. Kassem).

http://dx.doi.org/10.1016/j.actatropica.2017.08.034
Received 22 June 2017; Received in revised form 17 August 2017; Accepted 31 August 2017
Available online 08 September 2017
0001-706X/

3. Results

3.1. Epidemiology of the disease

Human visceral leishmaniasis (VL) was first reported in Egypt in 1904 by Phillips. Four cases were reported, two of which originated from the neighboring Arab countries and the other two were autochthonous. Panayotatou (1922, 1929) reported five cases of VL cured in Alexandria and attributed the rarity of the disease to the inability of physicians to perform splenic punctures. No other autochthonous IVL cases were reported from Egypt until 1982. Attention was paid to El Agamy once a physician's daughter acquired the disease while spending the summer time in El Agamy. This stimulated the public health authorities to properly diagnose cases with similar symptoms and to provide medication (Pentostam) immediately to the diseased children.

In 1982, VL was recorded in El Agamy, in Alexandria Governorate (Tewfik et al., 1983). This focus first appeared typical of the Mediterranean kala-azar, because *L. donovani* was isolated and typed from children from El Agamy (Mansour et al., 1984). Faris et al. (1986) diagnosed 20 indigenously acquired human VL cases in young children in Alexandria Governorate, 17 of which occurred in El Agamy. All patients were 3–4 years old. In 1987, Awadalla et al. (1987) further characterized *Leishmania* isolates from children from El Agamy by isoenzyme electrophoretic polymorphisms on cellulose acetate membranes and reported that the Alexandria strains were identical to *L. infantum*, which was different from *L. donovani* marker strains. Youssef et al. (1989) contributed to the resolution of this controversy. They isolated *Leishmania* parasites from two children 24 and 18 months old. The two isolates were identified by the WHO *Leishmania* Reference Center in Montpellier, France by enzyme characterization on starch-gel using 15 enzyme systems. The isolates were identified as *L. infantum* MON-98. Zymodeme MON-1 was isolated from cases of VL in man, dog, fox and rat in the Mediterranean region and certain areas of the tropics in the Old World. The authors suggested that the disease is autochthonous and the area certainly represents a classical zoonotic focus of VL in the Mediterranean region.

These findings supported the existence of an endemic focus of IVL in Alexandria in 1982 and substantiated earlier reports by Phillips (1904) and Panayotatou (1922,1929). No reports on indigenous cases between 1929 and 1982 were found probably due unfamiliarity of physicians on the presence of the disease in Egypt. This interpretation is supported by Khalil (1934) who felt that cases may go unnoticed because VL may clinically resemble splenomegaly due to other diseases common in Egyptian children.

The 1982 IVL outbreak in El Agamy definitely placed Egypt among the list of Mediterranean countries with *L. infantum*. Since the length of time leishmanial antibodies could be detected was unknown in Egypt, Londner et al. (1988) conducted a seroepidemiological study (RIA) to measure antibodies to leishmanial parasites in adults and children. They found that leishmanial antibodies were retained in two thirds of asymptomatic children and treated children for 5–7 months after detection and treatment respectively. However, one third retained antibodies for over a year. They recommended serial serosurveys for disease estimates as leishmanial antibodies persisted in humans for at least two transmission seasons.

The last human case reported from El Agamy was in 2005 (Lotfy, 2014). This coincides with the successive negative collections of vector species of sand flies from the area (Kassem et al., 2012).

3.2. The reservoir host

Visceral leishmaniasis in the Mediterranean basin has a zoontic nature with dogs serving as main domestic reservoirs while foxes, wolves and jackals represent the sylvatic reservoirs (WHO, 2010). Stray dogs were abundant in El Agamy and were captured from open areas surrounding houses where VL cases were recorded. In addition, dogs were used by local Bedouins for protecting livestock.

Several preliminary reports characterized the *Leishmania* parasites isolated from dogs in El Agamy focus of VL. Azab et al. (1984) characterized the parasite isolated from dogs by Rifaat et al. (1983) to be indistinguishable from *L. donovani* (=*L. infantum*) using the excreted factor (EF) serotype and enzyme electrophoresis. Parasite identification from two stray dogs from El Agamy were initially identified as *L. major* (Schnur et al., 1985). Immediately, Killick-Kendrick (1985) commented on this finding that "no hard evidence yet that *L. major* can cause VL in any focus and typing isolates of *Leishmania* from patients is self-evident". A reply to this correspondence was made by Schnur (1986) in which he stated that the parasite responsible for the outbreak in El Agamy was *L. donovani infantum* as characterized by EF serotyping and cellulose acetate electrophoresis.

Shetata et al. (1990) investigated the prevalence rate of the disease among stray dogs in El Agamy using the indirect immune-fluorescence assay (IFA) and enzymatically identified the parasite isolated from a stray dog as *Leishmania infantum* MON-98. This isolate had the same zymodeme as an isolate from humans (Youssef et al., 1989) which confirmed dogs as a reservoir host of human VL in El Agamy.

3.3. Sand fly species composition and bionomics in El Agamy

Documentation of sand fly species in Egypt started at the beginning of the last century (Willcocks, 1917). Sporadic surveys of sand flies were conducted subsequently (Theodor, 1948; Schmidt and Schmidt, 1962; Zein El Dine, 1972). However, no surveys for sand flies were conducted in Alexandria despite previous reports on the presence of indigenous VL cases from Alexandria (Panayotatou 1922, 1929).

Entomological surveys were conducted during the 1982 outbreak of IVL in El Agamy with a primary objective of identifying the sand fly vector. *P. langeroni* was recorded for the first time from Egypt in El Agamy and was suggested as the probable vector of the disease in the area (El Sawaf et al., 1984) because this species belongs to the subgenus *Larroussius* which includes most vectors of visceral leishmaniasis (Léger et al., 1983). Croset et al. (1978) considered this species to be rare in north Africa and only males were described. Egypt is the easternmost country in the geographical distribution of *P. langeroni* in north Africa.

Laboratory colonies established from field-collected specimens from El Agamy allowed the description of the hitherto unknown female of *P. langeroni* (El Sawaf et al., 1985) and the immature stages (Lane and El Sawaf, 1986). *P. papatasi* was the only other *Phlebotomus* species found in association with *P. langeroni* in El Agamy. Vector incrimination necessitates the finding of naturally infected sand flies. This depends upon a routine collection of sand flies and rapid and accurate identification. Morphological differentiation between *P. papatasi* and *P. langeroni* requires careful preparation of individual specimens for detailed microscopic examination, which can be hindered by dissection of sand flies for parasite detection. *P. papatasi* and *P. langeroni* were accurately separated by cellulose acetate electrophoresis using malic enzyme, phosphoglucomutase, 6-phosphogluconate dehydrogenase, and fumarate hydratase (Kassem et al., 1990; Fryauff et al., 1990). Cellulose acetate was the most reliable technique at that time. More recently, the establishment of PCR-based techniques has successfully been used to differentiate between sand fly species (e.g. Latrofa et al., 2012).

Behavioral differences between *P. papatasi* and *P. langeroni* were pointed out by El Said et al. (1986) and Beier et al. (1986a). *P. papatasi* and *P. langeroni* were found active at night outdoors from sunset to sunrise with highest activity level after midnight. *P. papatasi* was highly endophilic, readily entering houses feeding on the sleeping occupants. *P. langeroni* was basically exophilic, feeding outdoors before mid-night when people were active, and being more attracted to light traps and dog-baited traps than *P. papatasi*.

Blood-feeding patterns of *P. papatasi* and *P. langeroni* were also different. Field collected *P. papatasi* was found to be a facultative blood feeder with mixed blood meals, while *P. langeroni* was a selective