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SPOTLIGHT ON LEISHMANIASIS, PHLEBOTOMUS VECTORS AND ANIMAL RESERVOIRS IN EGYPT

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Abstract

Small-sized sand-flies about 3 mm in length are typical for many species, which helps them in the escaping notice. Females suck blood from various mammals including man, reptiles and birds, which bite is not always felt, but leaves a small round, reddish bump that starts itching hours or days later. They transmit bacterial parasitic and viral infectious diseases.

Key words: Egypt, ZCL, IVL, Sand fly vectors, Animal reservoirs, Spotlight.

Introduction

Leishmaniasis is complex zoonotic protozoan vector-borne diseases caused by more than 23 *Leishmania* species and spread by at least 93 sandflies species proven or probable vectors of the genus *Phlebotomus* in the Old World, and of genus *Lutzomyia* in the New World (WHO, 2010). But, sand flies species and subspecies validated worldwide were about a thousand (Shimabukuro *et al,* 2017). *Leishmania* species life cycle exists in two stages, the amastigote stage in cytoplasm of RNCs, monocytes and other phagocytic cells of a vertebrate host, and the promastigote one in gut of sand-fly vector (Morsy, 1996).
Sand flies ingested the amastigotes with the blood meals, multiply, and migrate forward in the gut to be regurgitated as promastigotes with saliva while biting a vertebrate host for a blood meal (Killick-Kendrick, 1979).

Leishmaniasis is classified as to the clinical pictures they cause in man into three main diseases: 1- Cutaneous leishmaniasis (CL), 2- Muco-cutaneous leishmaniasis (MCL), & 3- Visceral leishmaniasis (VL), and on the virtual morphological species identification (Morsy, 1997). Cutaneous leishmaniasis can present in different clinical forms, uncomplicated, self-healing skin lesions to debilitating, large, chronic or recurring lesions, disfiguring mucosal or muco-cutaneous lesions in mouth or nose, or diffuse cutaneous leishmaniasis (Morsy *et al,* 1997a). *Leishmania donovani* complex visceralize in man including *L. d. donovani* (Asia, mainly India and China), *L. d. infantum* (Mediterranean Countries) infects mainly children, and *L. d. chagasi* (South America) infects both adults and children (Saleh *et al,* 2015). Post-Kala-azar dermal leishmaniasis (PKDL) is a sequel of visceral leishmaniasis appears as macular, papular or nodular rash usually on face, upper arms and trunk (Zijlstra *et al,* 2003) that doesn't cause significant morbidity, but patient acts as a reservoir, active case detection is a must to control disease transmission in the area (Kumar *et al,* 2021). Most *Leishmania* species are maintained by mammalian reservoir hosts in natural foci; such as rodents, dogs, wild & domestic cats (Morsy *et al,* 1980), red fox (Morsy *et al,* 2002), jackals, sloths, hyraxes (Morsy *et al,* 1997b) and other carnivores are animal reservoirs.

In Egypt, marked increase of ZCL cases were reported in Suez Canal Zone (El Gibali and El Mansouri, 1979) and in South Sinai (Bassili *et al,* 1983). *Phlebotomus papatasi* is the main vector (El Sawaf *et al*, 1984; Lane, 1986; Soliman *et al*, 2001; Kamal *et al*, 2003; El-Naggar *et al*, 2006), and *L. major* was isolated and identified (Mansour *et al*, 1987; Wahba *et al*, 1990; Fryauff *et al*, 1993; Hanafi *et al*, 1999, El Hossary *et al*, 2000; El-Naggar *et al*, 2006; Hamadto *et al,* 2007). Hanafi *et al.* (2007) in the Northeast Sinai at an enzootic CL focus reported the seasonal rates of infected *P. papatasi* averaged 0.8%, 0.9% and 0.0 in the years 1989, 1990, & 1991 respectively, suggested an unstable transmission, and that gravid fly's rate was a good marker of physiological age and vector populations. The reservoirs were *Gerbillus pyramidum* (Morsy *et al,* 1987a), *Meriones sacramenti* (Morsy *et al*, 1993a), and *Psammomys obesus* (Morsy *et al,* 1996). Besides, Morsy *et al.* (1993b) reported natural *Leishmania* infection in two stray dogs and two *Gerbillus pyranidium* in the vicinity of Dakahlia villages.

Abdel-Motagaly and Morsy (2016) reported that 126 active ZCL patients were referred to a military fever hospital with 74, 47 & 5 lesions on the years 2013; 2014 & 2015 respectively. They had multiple lesions 90%, on lower and/or upper limbs, and ears, but rare on face. Lesions with secondary bacterial infections were treated by antibiotics, Fluconazole® 5mg/kg orally once daily for 4 weeks. Complicated lesions (73%) needed a second course and followed up to liver function tests. Cryotherapy was also used when indicated.

Besides, Morsy and Seif El-Nasr (1983) reported the first case of ZCL superimposed with skin cancer in an Egyptian infected woman back from Saudi Arabia. Morsy (2013) reported that ZCL particularly in hot area pave the way to mutation and skin cancer development. Mangoud *et al.* (2015) reported that the P53, S-phase fraction and DNA content must be considered on dealing with ZCL. They added that early diagnosis of nuclear mutation and cellular proliferation in any lesion and proper treatment would avoid the risky development of skin cancer.

Shehata *et al.* (2009) in North Sinai Governorate isolated *L. tropica* from patients in a community bordering Gaza Strip. *Phlebotomus papatasi* were found harbored *L. major*, however only non-infected individuals of *P. sergenti*, the vector for the viscero-tropic. *L. tropica*, were caught. Jacobson (2003) reported that the *L. tropica* might be confused, and grouped with *L. major* with *P. sergenti* its potential vector.

Both *Phlebotomus papatasi* and *P. sergenti* were experimentally infected by *L. major* promastigotes mixed with blood via chick-skin membrane. *P. papatasi* was more susceptible to *L. major* than *P. sergenti* confirmeing the fact that *P. papatasi* is the main *L. major* vector in Egypt (Mansour *et al*, 1987; Wahba *et al*, 1990) and abroad (Killick-Kendrick, 1990; Abou Elela *et al*, 1995). The vector-parasite correlations were reported in sand flies-*Leishmania* domain, as *Lu. whitmani-L. braziliensis* (Vexenat *et al*, 1986), *P. argentipes* & *P. papatasi-L. donovani* (Mukhopadhyay and Mishra, 1991), *P. pernicious -L. infantum* (Molina, 1991), and *Lu. intermedia-L. braziliensis* (Rangel *et al*, 1992), *Lu. trapidoi* and *Lu. gomezi-L. braziliensis* and *L. panamensis* (Jaramillo *et al*, 1994), *P. langeroni-L. infantum* and *L. major* (El Sattar *et al*, 1991; Daba *et al,* 1997), *Lu. longipalpis-L. mexicana* (Ismaeel *et al*, 1998), *P. argentipes-L. donovani* (Kumar *et al*, 2001) *P. halepensis*, *P. duboscqi*, *P. sergenti*, and *Lu. longipalpis-L. major* and *L. tropica* (Sadlova *et al,* 2003).

In Egypt, Morsy *et al*. (1990) gave illustrative keys of male and female sand-flies in the Nile Delta, with stress on *P. bergeroti, P. langeroni*, *P. papatasi,* and *P. sergenti.* The *P. papatasi*, a known vector of ZCL, *is* the predominant species all over Egypt and *P. langeroni* was reported in the West of Alexandria vicinity, but as a very rare species in some coastal cities up the Egyptian Libyan borders, where it is endemic particularly in the mountains (Morsy, 1988)

Merdan *et al*. (1992) studied the seasonal abundance and sex ratio of *P. papatasi* as well as searched for natural infected in CDC caught females for promastigotes' biochemical typing. They found that the seasonal activities started in April to the end of November, with a well-marked annual bimodal distribution. The male to female ratio was 1:2.9, and that 0.14% of 4208 females naturally harbored promastigotes, typing proved to be

Leishmania major of zymodeme LON.

Morsy *et al*. (1993c) studied the seasonal abundance, nocturnal activity, breeding sites and other relevant behavior. They found that (a) seasonal activity started in April to end of November or beginning of December, (b) females outnumbered males indoors (7.4:1) & V.V. outdoors (0.14:1), (c) blood fed females were 97.7% indoors and 29.4% outdoors, (d) nocturnal activity ranged between 6pm to 6am indoors & 8pm to 6am outdoors, & (e) immature stages were recovered from rodent burrows and poultry sheds. WHO reported two million new cases per year and 1/10 of world's population at risk (Gravino, 2004).

In Egypt, *P. langeroni* is the vector of *L. infantum* (Youssef *et al*, 1989, Shehata *et al*, 1990; Doha and Shehata, 1992). *P. papatasi* is the *L. major* vector (Wahba *et al*, 1990; Hanafi *et al*, 1998) from rodents to man (El Nahal *et al,* 1982; Morsy *et al,* 1982; 1987a; Mansour *et al*, 1987; El Hossary *et al*, 2000). Kassem *et al.* (2012) in Southern Sinai G. reported 8 *Phlebotomus* species; *P. alexandri, P. kazeruni* and *P. sergenti* were widespread, *P. papatasi* and *P. bergeroti* less frequent and *P. arabicus, P. major* and *P. orientalis* with highly restricted distributions. Samy *et al.* (2014) in North Sinai G., idetified six sand fly species; *P. papatasi*, *P. kazeruni*, *P. sergenti*, *P. alexandri*, *Sergentomyia antennata* and *S. clydei*.

Leishmania tropica was confused and grouped with *L. major*; *P. sergenti* being its potential vector (Jacobson, 2003). Vector competence of *P. papatasi* from Suez Governorate was done under laboratory conditions by feeding on a *L. major* lesion of infected hamster or membrane feeding technique (El-Naggar *et al*, 2006), results showed that a total of 204 (51%) females engorged with infected blood meal through feeding on hamster lesion. Of the sand fly's females fed on blood, 7.4% (15/204) harbored *L. major* as compared to 64.3% (132/205) of those fed on membrane, a slightly high rate.

As to IVL, there was a long history of visceral leishmaniasis from Alexandria (Panayotatou, 1922); Hassan (1968) reported a case of Kala-azar, and Rifaat *et al.* (1983) in Tanta detected anti-*Leishmania* antibodies in children. Soliman (1992) in Alexandria detected seropositivity against visceral leishmanasis. But, leishmaniasis marked impacts on humans were recognized when Tewfik *et al.* (1983) and Mansour *et al.* (1984) in Alagamy characterized *Leishmania* isolates from IVL infected children. Also, Awadalla *et al.* (1987) distinctly compared two IVL isolated from children (1.6 & 4 years old) with five marker strains, and two human isolates from Sinai and Sudan, on clinical and geographical grounds were CL and VL respectively. Seven enzymes were assessed using electrophoretic profiles on cellulose acetate membranes four of them differentiated between CL & VL strains. The two isolates were *L. infantum* MON-98, a new and unique zymodeme, which differed from *L. donovani* marker strain. Faris *et al.* (1988) in Alagamy clinically and microscopically detected 27 IVL cases from 1982-1985, side by side with 2 case/control studies. In one study, the households were more near to an open garbage container than in control one. In the second control, houses with IVL and/or seropositive children were more facing the open areas. They suggested that control programs must improve garbage disposal and focus on the peripheral located houses.

Besides, Madwar *et al.* (1985) suggested that IVL possibility in Qalyoubia Governorate, and Kabil *et al.* (1988) in Qalyoubia country side identified a case of IVM in an adult farmer (unusual host), who suffered from chronic schistosomiasis with huge hepato-splenomegaly and had never left his village. Morsy *et al.* (1992) in Abo Hamad, Sharkia G. reported lymphatic leishmaniasis as an indigenous infection in a 30-year-old male, cervical lymphadenopathy was the only clinical sign and no visceral involvement. He was successfully treated with sodium stibogluconate®. They added that lymphatic leishmaniasis must be in mind on dealing with lymphadenopathy of unknown etiology. El Mahdy *et al.* (1993) in Dakahlia G. by IHAT and dot-ELISA reported leishmanial-positive titers in 4/22 hyper-splenic patients with amastigotes detected in splenic smears on splenectomy and one culture grew promastigotes.

Khalid *et al.* (1982) in Cairo reported anti-leishmanial antibodies in stray dogs. Morsy *et al.* (1987b) in Alexandria serologically and biochemically typed *L. major* from two dogs' isolates. This was the second time (Peters *et al,* 1985) that *L. major* occurred in do gs as a misleading phenomenon in relation to the relatively outbreak of infantile kala-azar. Morsy *et al.* (1988) in an Alexandria outbreak of IVL examined rodents; *Rattus rattus, R. norvegicus* and *Mus musculus* for *Leishmania* seropositivity, they isolated flagellate parasites from two *R. norvegicus* spleens, which were identified serologically by excreted factor serotyping and enzymologically by thick starch electrophoresis of four enzymes that was quite distinct from *L. donovani, L. major* and *L. tropica*. They considered that it could be a new leishmanial entity or a flagellate parasite of another genus.

Rosypal *et al.* (2013) in Egypt examined blood samples from 50 stray dogs for antibodies to visceralized *Leishmania* spp. by commercial immunochromatographic strip assays based on recombinant antigen K39, reported positivity in five dogs.

Selim *et al.* (2021) in five governorates in Northern Egypt examined 450 asymptomatic dogs by ELISA for *Leishmania* seropositivity. They reported overall rate of 21.3%; with highest rates were in Cairo and Giza Governorates with strongly related to dogs' ages, hair length, without veterinary care or insecticides and the shelters' floor. Besides, Abuowarda *et al.* (2021) reported that the increased incidence of the asymptomatic carrier dogs acting as a significant reservoir host for *Leishmania* poses a public health.

Kassem *et al.* (2012) studied the effect of Urban development on the sand flies abundance, in an old IVL endemic focus in the North Coast of Egypt. They reported that the sand fly habitat in El Agamy entirely changed and was replaced by urban settlements.

El-Bahnasawy *et al.* (2013) reported that apart from the urbanization of the north coastal zone in the Alexandria vicinity, *P. langeroni* vector was still abundant in Al-Agamy with rare density, but this vector and *P. papatasii* were detected in El-Hamam City, Sedi Barany City, and Matrooh City. They added that employees and their families returned home from Libya suffering from with fever with or without other symptoms may be IVL patients, since its fever can be a manifestation of minor, self-limited process or can herald a progressive, life-threatening illness. Also, IVL can occur in immunosuppressed adults, such as transplant recipients and patients on immunosuppressive chemotherapy or suffered from chronic schistosomiasis (Kabil *et al,* 1988).

Meanwhile, VL and HIV reinforce each other, posing to clinical and public health problems. Both diseases overlap in endemic areas, and people living with HIV are more likely to develop VL due to reactivation of a dormant infection or clinical manifestations after primary infection. Co-infection was reported in mid-1980s in southern Europe and then in about 45 countries (WHO, 2022).

Apart from *Leishmania*, Benallal *et al.* (2022) reported that sand flies are important vectors of various human and animal pathogens; as the causative agent of Carrion's disease (Bartonellosis), caused by *Bartonella bacilliformis*. Sayed *et al.* (2022) in Assuit G. detected *B. henselae* in cats and humans, which were more in cat owners. Also, they transmit severe or even fatal illness of genus *Phlebovirus* (order Bunyavirales, family Phenuiviridae) is Toscana virus (Tesh, 1988). This virus is one of the commonest causative agents of meningitis/meningoencephalitis reported in Germany, France, Italy, and other European Countries (Wenzel *et al,* 2022).

Other viruses responsible for a *Phlebotomus*, *papataci* 3-day or sand fly fever, which was reported in Egypt (Schmidt *et al,* 1971;

Feinsod *et al,* 1987), but its presence in the Mediterranean area is unknown

Conclusion

Leishmaniasis incidence will be affected by change in urbanization, deforestation or human incursion into forested areas. Also, the climate changes affect leishmaniasis spreading by the change in temperature, humidity and rainfall that affect the size and the geographic distribution of sand fly populations.

Unfortunately, these climate changes and global warming will have catastrophic effects on man, animal, and arthropod-borne infectious diseases, as well as the whole environmental ecosystems.

Consequently, the World Society should plan to protect the human rights, and to avoid exacerbating the existing problems or creation of new problems.

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