

Review / Derleme

The infections transmitted by Sand flies in Turkey

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Summary: Vector-borne diseases are a group of infections transmitted by the bite of arthropod species such as mosquitoes, ticks and sand flies infected with a pathological agent. Certain species of Phlebotomine sand flies can transmit protozoon parasite *Leishmania*, a bacteria *Bartonella* and a group of viruses called phleboviruses worldwide. Two clinical forms of leishmaniasis in human, visceral and cutaneous, and canine leishmaniasis are seen in Turkey. Several phleboviruses and a particular Turkish strain are circulating in certain endemic areas of Turkey. Among 22 species of sand flies recorded in Turkey, 7 are proven or suspected vectors of human leishmaniasis and phlebovirus infections. Here, sand fly-borne infections are seen in Turkey, leishmaniasis and sand fly fever were briefly reviewed.

Key words: Leishmaniasis, phlebovirus infections, sand flies, vector-borne diseases.

Türkiye’de Kum sinekleri tarafından bulaştırılan infeksiyonlar

Özet: Vektör kaynaklı hastalıklar, patolojik bir ajanla infekte olmuş sivrisinekler, keneler ve kum sinekleri gibi artropod türleri ile bulaştırılan bir grup infeksiyondur. Kum sineklerinin belirli türleri bir protozoon parazit olan *Leishmania* türlerini, bir bakteri olan *Bartonella*’yı ve phlebovirüsler olarak da adlandırılan bir grup virüsü nakledebilir. Türkiye’de insanlarda leishmaniasisin iki klinik formu, visseral ve kutanöz fomları ile kanin leishmaniasis görülmektedir. Birkaç phlebovirüs ve ülkemize özgü bir Türk suşu belli bazı endemik alanlarda sirküle olmaktadır. Türkiye’de şimdiye dek kaydedilen 22 kum sineği türünden 7’si leishmaniasis ve phlebovirüs infeksiyonları açısından kanıtlanmış veya şüpheli vektörlerdir. Bu yazıda, Türkiye’de görülen kum sineği kaynaklı infeksiyonlar olan leishmaniasis ve tatarcık humması konularında bir özet verilmiştir.

Anahtar sözcükler: Leishmaniasis, kum sinekleri, phlebovirüs infeksiyonları, vektör kaynaklı hastalıklar.

Vector-borne diseases are a group of infections transmitted by the bite of infected arthropod species, such as mosquitoes, ticks and sand flies. Integrated control approaches like (i) etiological approach for true, easy and standardized country-wide diagnosis, treatment & follow up, (ii) clinical approach for clinical improvement of the patient, (iii) reservoir related approach for reducing the parasite source in the nature and (iv) vector related approach for preventing or minimizing vector-host contact, needs to be applied for controlling the vector-borne infections in the region or country. A successful epidemiological treatment can be maintained if integrated control measures can be applied for long time. The applications for controlling a particular disease in a certain region or country, the scientific knowledge about the agent, vector species, reservoir species, climate, etc have been very important. In this part, the knowledge about sand fly-borne diseases are seen in Turkey were summarized.

Sand flies can transmit the pathological agents causing different clinical pictures in tropical and subtropical areas of the world. The sand flies are

classified under the Class Insecta, Ordo Diptera, Subordo Nematocera, Family Psychodidae and Sub-family Phlebotominae. Phlebotominae sub-family consists of 6 genera: *Phlebotomus*, *Sergentomyia* and *Chinius* in the Old World and *Lutzomyia*, *Brumptomyia* and *Warileya* in the New World. Because of they are biological vectors of the various *Leishmania* species which cause pathogenicity with different clinical pictures in the human, they have medical importance. Phlebotomine sand flies are represented by more than 40 species in the Old World and 30 species in the Americas, which vector *Leishmania* spp. The vector sand fly species are generally belonging to *Phlebotomus* genus in the Old World and *Lutzomyia* genus in the New World. Sand flies are also vectors of other human pathogens, such as the bacterium *Bartonella* (bartonellosis) and viruses belonging to three different genera: Phlebovirus, Vesiculovirus, and Orbivirus. They are all named as sand fly-borne diseases (11).

The sand flies, which are smaller than other Dipters, are the flies which are in light brown, long legged, entire body is hairy including wings. Wings are in “V” shape during resting. The sand flies are Holometabol and

complete their life-cycle (egg, larva-4 phases, pupa and adult) in the humid soils with organic material. The sand flies are resting in the dark hidden locations, barns, basements, tree holes, wall cracks and nests of rodents during the day-time and become active during the night-times. Although the adults are very sensitive against the cold, 4th phase larvae are more resistant against it and pass the winter season under 5-10 cm soil as 4th phase larva. The life cycle is completed totally within 40-50 days. Some species sucks blood only from the mammals (zoophilic), some from both animal and human (zoo-antropophilic), some only from human (antropophilic). The identification of the species can be done morphologically and keys are available (10, 11).

The northern limit of sand fly distribution has changed in Europe continent from N45° to N49°. In Turkey, sand flies are present in all geographical regions with different fauna composition. The field studies related to sand flies and leishmaniasis as well as phleboviruses has being continued for long time and revealed 22 species belonging to 4 subgenera of *Phlebotomus* genus and *Sergentomyia* genus, so far. Four and three of *Phlebotomus* species have been incriminated as probable vectors for VL and CL, respectively (2, 8, 18). In Turkey, two important sand fly-borne diseases are present: leishmaniasis (human&canine; visceral&cutaneous) and phlebovirus infections.

Leishmaniasis: Zoonotic visceral leishmaniasis (ZVL) caused by *Leishmania infantum* and cutaneous leishmaniasis (CL) caused by *L. tropica* and *L. infantum* have been known in Turkey. The both diseases are notifiable diseases in Turkey since long time. The ZVL is seen in Ege, Mediterranean regions endemically and has been reported sporadically in other regions. It is reported from 38 provinces and the population under the risk is around 45 million. The official number of cases is between 50 and 60 but most cases are underreported. It is consistent with Mediterranean type and mostly seen in infants. *Leishmania* strains were isolated from VL patients in different regions and identified as *L. infantum* MON-1 by Multilocus Enzyme Electrophoresis (MLEE) also known as zymodeme analysis. Another zymodeme, *L. infantum* MON-98, was only isolated from reservoir dogs. Pentavalent antimonials (Glucantime®) and Liposomal Amphotericin B (AmBisome®) are being used for the first line drugs for treatment (12, 15).

Cutaneous leishmaniasis (CL) caused by *Leishmania* protozoan parasites is a disease which is characterized by long-term nodulo-ulcerative lesions healing spontaneously with scarring. Cutaneous leishmaniasis is seen in Southeastern Anatolia Region and eastern part of Mediterranean Region endemically/epidemicly. It has been spreading from endemic regions to other regions because of the different risk factors. CL with different clinical types was reported in 41 provinces but more than

90% of the total cases were concentrated in 5 provinces (Sanliurfa, Adana, Osmaniye, Mersin, Aydin) located in southeastern, east Mediterranean and western regions of Turkey. According to Ministry of Health official records, 46.003 new cases were reported between 1990 and 2010. Among those cases, 96% of them were reported from Sanliurfa, Adana, Osmaniye, Hatay, Diyarbakir, İçel and Kahramanmaraş provinces. Although 45% of cases were notified from Sanliurfa in past 20 years, its ratio is currently decreasing while other regions' ratios have been showing an increasing trend. Pentavalent antimonials (intralesional or systemic) are the first line drugs for treatment (9). The main causative agents are *Leishmania tropica* and *Leishmania tropica/Leishmania infantum* in Southeastern Anatolia and eastern part of Mediterranean, respectively. Isoenzyme analyses showed 9 different zymodemes among *L. tropica* strains isolated from CL patients in different endemic areas (unpublished data). Additionally, the new strains isolated from CL patients and from the vector, *P. tobbi*, in Cukurova plain were identified as *L. infantum* non-MON1 (20).

Canine leishmaniasis (CanL) caused by *L. infantum* is also important veterinary and public health problem with much higher prevalence than human infection in all regions of Turkey. Although CanL was first detected in the early 1950's, the knowledge about the epidemiology of this disease was limited in Turkey. After 1993, the epidemiological studies were carried out in 22 different provinces and the prevalence ratios were found between 1.45% and 27.5%. The overall prevalence of CanL was detected as 11.32% in Turkey (14, 16, 17). Although CanL is one of the important veterinary health problems, it is not notifiable disease in the veterinary medicine in Turkey yet.

In Turkey, leishmaniasis control program was started in 25 June 1996 and re-organized in 2003 during setting up the program for improving surveillance system of all communicable diseases. In new surveillance system, cutaneous leishmaniasis is grouped within Group A diseases (the diagnosed cases are reporting from all health facilities including private ones) list while visceral leishmaniasis is grouped in Group C diseases (the diagnosed cases are reporting from secondary and tertiary level hospitals and monitoring by sentinel surveillance). The specific strategic control program for leishmaniasis is prepared and will be started when the re-organization of Ministry of Health is completed. A National Leishmaniasis Working Group was established and epidemiological, ecological and GIS-based field works on patients, reservoirs and sand flies were carried out in 22 provinces of Turkey for better understanding the general epidemiological status in country-wide. The "Identity card" showing specific epidemiological situation has being prepared for each endemic region by the group. The working group is consisting of medical

and veterinary doctors, biologists, ecologists, molecular biologists, geographers, etc.

Leishmania infantum associated to sand fly vector species belonging to *Phlebotomus* genus *Larroussius* subgenus still represents the main risk for human infections in Europe as well as in Turkey. Due to increased migration and travelling, ongoing climate changes as well as various aspects of globalization, there is an elevated risk for the introduction and spread of sand fly-borne infections. For these reasons, the attention on leishmaniasis and other vector-borne diseases needs to be continued for preventing the public health risks.

Phlebovirus Infections: Phleboviruses (Family Bunyaviridae) are geographically distributed in Europe, Africa, Central Asia, and the Americas. Four serotypes, sand fly Sicilian virus (SFSV), sand fly Cyprus virus (SFCV), sand fly Naples virus (SFNV), and Toscana virus (TOSV), have been circulating in the Mediterranean Basin in association with the presence of sand fly vector. Sand flies are the biologic vector for phleboviruses and the virus can also be transmitted transovarially between generations and can be found in the male *Phlebotomus*. However, the virus infection rate in each subsequent generation is gradually decreased and this suggested that phleboviruses cannot be maintained in the vector population by transovarial transmission alone (2, 11). SFSV, SFNV, and other related viruses cause sand fly fever, also known as “three-day fever” or “pappataci fever”. In endemic areas, infections occur during the summer, reaching a peak in August, in parallel with the maximum activity of the sand fly vectors. Phleboviruses cause fever, myalgia, headache, ocular symptoms among people living in endemic areas. TOSV also causes neurological disorders, such as meningitis, encephalitis and meningoencephalitis (2, 3). In Turkey, first reports were published in 1975 and 1976. The seroprevalence of SFSV was reported as 5.2% in Ege region and 22% in Mediterranean region while SFNV was reported as 28.3% in Ege region and 62% in Mediterranean Region (21). Next two studies carried out in the Aegean region revealed the seroprevalence rate high for SFNV (13.9%) and low for SFSV (0.84%) (19). Later, in two specific areas, Akbuk town has been known as endemic for pappataci fever since long time and Olukbasi village an outbreak occurred in the time of the study, SFNV and TOSV activity in residents were detected, although no acute cases or virus in vectors could be identified (13). Toscana virus exposure was also detected in blood donors in Central, North and South/Southeast Anatolia of Turkey (4, 6) and its association with central nervous system infections (7). The studies on phleboviruses are increased after the outbreaks happened in three geographically different areas of Turkey (Kiraz Town in Izmir province, Kozan Town in Adana province and

Mamak Town in Ankara province) in summer of 2007 and 2008 (1). Serological, virological and molecular analysis were performed using the samples obtained from the patients and a new phlebovirus related to sand fly fever Sicilian virus was isolated and characterized from acute patient material. This new phlebovirus was named as Sand fly Fever Turkey Virus (SFTV) (1).

These studies proved that sand fly fever viruses including TOSV have a wide geographical distribution within Turkey which parallels that of proven sand fly vector species *P. papatasi* and *P. perfiliewi*, respectively (11). Recently, Phlebovirus RNA was detected in 3 *Phlebotomus major s.l.* female specimens collected from Ankara province and characterized as Sand fly Fever Turkey Viruses (5). *Phlebotomus papatasi* has very wide distribution in Turkey as well as many other places in The Old World and different *Phlebotomus* species belonging to *Larroussius* subgenus which can be potential vectors of TOSV are present in all geographical regions in Turkey. A great attention is needed, both in virological and entomological sides, to prevent or control future outbreaks of phlebovirus infections.

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