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Sandfly Fever: A Mini Review

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Introduction

Sandfly fever, also known as Pappataci fever or phlebotomus fever is an interesting disease mimicking other conditions which causes fever, myalgia and malaise along with abnormalities in liver enzymes and hematological test results [1]. Without suspicion of the disease itself or a presence of an epidemic, it is very hard to diagnose this disease in a non-endemic area, particularly if it is travel associated and if the anamnesis is not clear [1-5]. The differential diagnosis consists of a very board spectrum list of diseases such as viral, parasitic and bacterial infections. Even hematologic malignancies and bone marrow depression can be suspected in this patient group. Unless it causes neurologic involvement, the disease is usually self-limited and results with good outcome but still it causes a certain degree of morbidity and the clinic looks severe at the time of the presentation and needs a lot of initial clinical and laboratory work to clear out the diagnosis [1]. The sandfly fever has a great public health importance in endemic areas and with growing attention and awareness, the new antigenically distinct serotypes are identified from different countries in Europe, south-east Asia, central Asia and Africa [6-13]. The disease also became very important from the aspect of traveler's health and military medicine [14-17].

The Virus and the Epidemiology

The sandfly fever viruses are classified within the *Phlebovirus* genus of the *Bunyaviridae* family. Phleboviruses are enveloped RNA virus and have tripartite genom (S, M and L segments), three nucleocapsids, grow in the cytoplasm of the cell. The genus *Phlebovirus* consists of more than 60 antigenically distinct virus serotypes in two main groups: the sandfly fever group and the Uukuniemi (UUK) group [18,19]. Among the sandfly fever viruses, the Naples serocomplex and the Sicilian serocomplex are the two main serocomplexes associated with human diseases. *Karimabad* virus, *Arabia* virus, *Massilia* virus, *Punique* virus, *Tehran* virus, Toscana virus (TOSV) and "unclassified sandfly fever *Naples* virus" are among the Sandfly fever Naples virus (SFNV) serogroup according to the protein knowledgebase [19]. Although the *Arabia* virus is classified within the Naples serocomplex, the virus along with *Adria, Arumowot* and *Odrenisrou* viruses are proposed to be within the Selahabad species sero-complex of *Phleboviruses* and the taxonomy of these species are still not clear, can be accepted as unclassified phleboviruses for now [20].

Sandfly Fever Sicilian Virus (SFSV) is the other well known serotype which has a wide-geographical distribution as well. Sandfly Cyprus virus (SFCV) and recently defined Sandfly Turkey viruses (SFTV) seem to be variants of SFSV; the SFTV shows 98% and 91.8% nucleotide homology in S segment to SFCV and SFSV prototype strain Sabin respectively [1,21,22]. A Granada Virus (GRV) is reported from Spain recently and seems to be close to SFNV group [7]. Other recently found examples include *Massilia* virus from France and *Punigue* virus from Tunisia [8,9]. Figure 1 shows the distribution of the sandfly fever viruses by serotype.

The virus is transmitted to human by the bite of phlebotomine sandflies which belong to the Psychodidae family [23]. The major vector for SFSV is *Phlebotomus papatasi* while it is *P. perfiliewi* and *P. perniciosus* for TOSV and *P. major* sensu lato for SFTV as described recently [21]. Because of the life cycle of the vectors, the infection is usually seen in summer months and may cause outbreaks [1].

TOSV differs from others with its neurotropism and being an etiologic agent of central nervous system infection [24]. Although the SFSV usually causes a self limited benign disease, there are some evidences that SFTV may lead to more severe disease, prolonged fever and laboratory abnormalities even with neurological involvement [1,25].

The Mediterranean basin is the main area for sandfly fever. Reports are increasingly published every day related with the presence of the vector, the virus or the infection itself, from Spain to Croatia, from Morocco to Iran, Italy, Portugal and Turkey [7-13,26,27]. The recent studies on the sandfly fever viruses showed unexpected results like a very high percent of seropositivity among blood donors in Turkey: over 1500 sera samples were investigated and the overall seroprevalence rate was over 30% while it was as high as 65% in some cities, which means that the virus had been circulating in Anatolia far before it was recognized [27]. The same study showed also certain positivity for TOSV among patients with neurologic involvement, leading a suspicion that TOSV may have been among the frequent etiologic agents of viral meningoencephalitis in this country, which is not recognized till now [27]. Granada is another example for endemic areas of sandfly fever viruses; the area was hyperendemic for TOSV and now the prevalence of GRV is found to be as high as 15% leading a suspicion on different sandfly fever virus serotypes could had been in the same area far before they were recognized [7]. The presence of the vectors should raise the suspicion of related infectious diseases. As a matter of fact, *P. major* s.l., *P. sergenti, P. halepensis, P. papatasi, P. simici, Larrousius* spp., *P. tobbi, P. perfiliewi perfiliewi* were among the phlebotamin sandflies found in the area where SFTV outbreak had occurred [21].

Figure 2 shows a phylogenetic analysis of SFTV from sera samples of the patients and sandflies, the figure also shows the relation of other above-mentioned sandfly fever viruses.

Sandfly Fever in Non-endemic Areas, Travelers' Health and Military Medicine Issue

Sandfly fever is also very important for travelers' health; imported cases are reported in the literature from non-endemic areas due to travelling [3-5,24]. In 1997, a case of travel associated SFSV infection presenting as meningitis in female patient, after a vacation to Turkey, was reported by Becker et al. [5]. At that time, nobody knew that SFTV, which shows homology with the SFSV, exist in Turkey and the case was presented as the first meningitis case due to the SFSV, which is not usually related to neurologic involvement. After the awareness of phleboviruses, the aseptic meningitis cases are begun to be investigated

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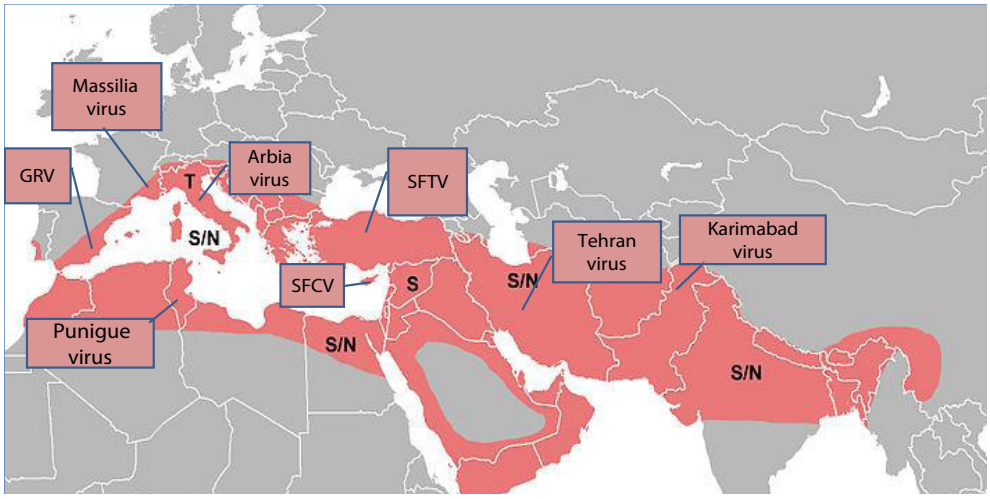

Figure 1: Distribution of sandfly fever viruses by serotype. Some of the new described ones are also indicated. S: SFSV; N: SFNV; T: TOSV; SFTV: Sandfly Fever Turkey Virus; SFCV: Sandfly Fever Cyprus Virus; GRV: Granada Virus (Adapted from Gleideberg, Sandfly fever-German Wikipedia).

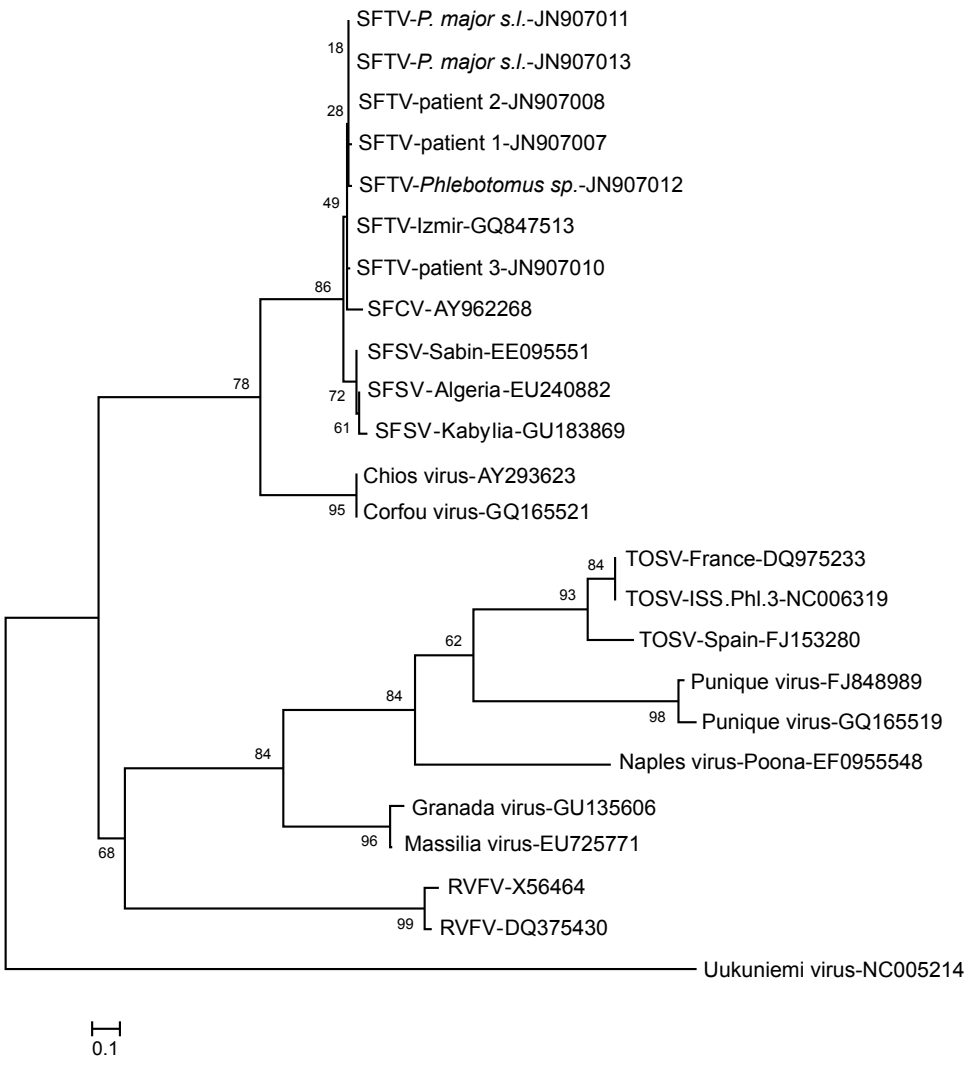

Figure 2: Phylogenetic analysis of the partial sequences of the polymerase gene segment detected in sandflies and patients from Ankara province, Turkey. GenBank accession numbers JN907007 to JN909012 represent the sequences included in the study [21], and GQ847513 is the prototype strain. Granadavirus, Punigue virus and Massilia virus are also shown [21].

for SFSV, TOSV and SFTV in Turkey and the first case of the SFTV meningitis is reported after few years it is discovered [22,25].

Other examples of travel related sandfly fever cases from the literature are as follows. There is a report from Germany about a travel related TOSV infection which ended with abducens paralysis of one of the patients who had a history of vacation to Italy [28]. Other cases with febrile disease after returning to Switzerland from Malta found to have sandfly fever. One of the patients was lucky to present with insect bites and rash giving a clue about vector-borne travel-related disease and detected for phlebotomus fever which was found to be positive [3].

Other than travelers, the disease was reported as causing outbreaks within the troops visiting Mediterranean Countries as well. As a matter of fact after its first detection in 1908 the SFSV was isolated from troops of the World War II allied army forces after the Sicily landings in 1943 [14,15,29]. After decades other outbreaks happened among the Swedish United Nations soldiers in Cyprus and the U.S. Army troops in the central Iraq in 2007 [16,17].

Clinical Features and Outcome

In general, the SFSV and the SFNV usually cause a self limited benign disease while the TOSV may lead to severe clinic with neurological involvement [1-22,24]. The sandfly fever is known as 3 days fever but the SFTV may cause prolonged fever. The SFTV differs from other reported SFSV cases with causing more severe symptoms and clinical findings. Myalgia, headache, photophobia and abdominal discomfort are prominent clinical features for SFTV. Fatigue and anorexia are not rare symptoms too. Elevated liver enzymes and creatine kinase levels along with thrombocytopenia and leucopenia are frequent findings. Some patients may have elevated alkaline phosphatase and gamma-glutamyl transpeptidase levels as well [1]. The paradox is that the abnormal hematologic findings may not start together with elevated liver enzymes and these laboratory findings may be found in the follow up of the patient in the upcoming days. Also abnormal laboratory findings may not continue together; the hematologic abnormalities turn to normal levels before the liver enzymes do [1]. These all makes the diagnosis difficult and the physician has to follow the patient very closely during the disease period. The post-asthenia syndrome may also be observed in some patients. Complete recovery may last up to 30 days [1].

The differential diagnosis includes other vector-borne diseases, viral and parasitic infections and especially hematologic diseases. The vector phlebotomus also carries leishmania and other infectious disease agents like orbiviruses from Reoviridae family and Vesiculovirus from Rhabdoviridae family and physicians have to be aware of these agents too [13,30].

The serology may be negative in the very first days of the sandfly fever virus infections and the molecular methods are more helpful in those suspected cases from endemic areas. Serology becomes positive in the following days and supports the diagnosis [1].

The neurologic involvement of the sandfly fever viruses is another issue and usually the clinical picture is attributed to TOSV. Many case reports are found in the literature about TOSV meningoencephalitis and probably many others diagnosed as unknown etiology. Some patients with positive viral load for TOSV show normal CSF findings while some show pleocytosis with increased protein levels [22].

GRV infection is usually asymptomatic but may be associated with febrile illness along with exanthema and respiratory symptoms [7].

Conclusion

Sandfly fever is seen in a wide geographic area and although it is a self limited benign disease, it may cause a severe clinical picture and need to be evaluated in the differential diagnosis of the patients presented with fever, myalgia and headache along with thrombocytopenia, leucopenia and elevated liver enzymes. Travelers should be informed before going to endemic areas during summer months. Military forces who have been in the endemic regions are also under risk and an outbreak of fever without a known source after returning home from an endemic area should raise the suspicion for sandfly fever and other possible vector-borne diseases.

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