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Dengue Fever Serology in Febrile Patients in Southeast Iran

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Abstract

Background: Dengue is a mosquito-borne viral disease that has rapidly spread in all regions in recent years. There is little information on dengue fever epidemiology in Iran. High prevalence of dengue fever in Pakistan bordering southeast Iran emphasizes the need for paying more attention to monitoring of the disease in this region. The aim of this study was to study the dengue fever seropositivity among adult febrile patients in southeast Iran.

Methods: Dengue fever virus specific IgG antibodies were measured by a commercial enzyme-linked immunosorbent assay (ELISA) in sera of 184 patients.

Results: All examined sera were negative.

Conclusions: The existence of dengue fever in eastern borders of Iran and tracking the virus vectors in the southeast Iran can be a treat for the circulation of the virus in Iran; however, we did not find any track of the seropositivity in this study and despite the high prevalence of dengue fever in Pakistan bordering southeast Iran, no dengue positive cases were found in this study. This epidemiological research is significant for local health authorities.

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Introduction

Dengue fever is one of the most rapidly spreading viral diseases in the world, despite increasing efforts to curb or reverse the upward trend. The disease is caused by dengue viruses (DENV 1–4), which are transmitted to human hosts by Aedes mosquitoes (1). DENV 1–4 are arboviruses of the Flaviviridae family and Flavivirus genus (2). Dengue virus has four serotypes that can be identified through their genomes. All

these serotypes can cause dengue fever and dengue hemorrhagic fever (3) (3). Recent estimates show that approximately 390 million people are affected with clinical form of Dengue fever (DF) infection and 96 million are infected with clear signs of clinical diseases. The potential for explosive outbreaks of dengue fever and its global increase are highly substantial. A 30-fold increase in the outbreak of dengue fever, in the last 50 years, requires assessments and integration of current strategies for reaching a 50% decline of the mortality rate and a 25% decline of dengue fever incidence by 2020. Dengue fever has been identified as a public health threat in one hundred countries with 2.5 billion population and 50–100 million people may be infected annually. Recently, there have been reports from new countries showing an expansion of the disease from urban to rural regions (4). Cases are typical in tropical, developing countries worldwide. Dengue hemorrhagic fever cases have now been confirmed in more than 60 countries and Dengue Virus is endemic in more than 100 countries, including most of Southeast Asia, South America, Central America, and the Caribbean and South Pacific regions (5). Several DF outbreaks have been reported in the Middle East countries such as Pakistan, Saudi Arabia and Yemen, during the past decade (6). Aedes mosquitoes, mainly *Ae. aegypti* and, to a lesser extent, *Ae. albopictus*, *Ae. Unilineatus* and *Ae. vittatus* can cause dengue infection in humans (7). *Ae. aegypti* species is not endemic in Iran; however, the sporadic identification of *Ae. albopictus* species in some limited regions of southeastern parts of the country has raised concerns (8). These concerns have increased in Iran, due to its common border with Pakistan, where *Ae. aegypti* and *Ae. albopictus* species exist (9). *Ae. unilineatus*, which is considered a potential vector of dengue in some areas in Pakistan, including Karachi, exists in Iranian southern coasts and it can be a risk factor for the spread of this disease in southern coasts of Iran (8). Production of antibody in the hosts varies depending on their immune status (10). The highest levels of IgM are observed about two weeks after the onset of symptoms and, usually after this period, levels are reduced in a way that they cannot be measured after 2 to 3 months. However, anti-dengue IgG levels in low titers are untraceable during the first week of the disease. After this period, serum IgG titer increases slowly and becomes measurable after a few months and probably remains measurable forever (4).

The first case of dengue fever in Iran was reported in 2008 in a patient with a history of traveling to Malaysia (11). According to the results of a study on blood donors in Sistan and Baloochestan in 2013, dengue fever seropositivity was 5.9% (12).

In fact, no comprehensive serological study has yet been conducted on dengue fever in suspected febrile Iranians. Since southeastern Iran shares its border with dengue endemic countries including Pakistan (13), the present study is the first to investigate dengue fever serology in suspected febrile patients in southeastern Iran.

Methods

Sample Collection

The study was carried out in Sistan-and-Baloochestan, Kerman and Southern Khorasan, (southwest Iran). The study was conducted on patient sera referred to central laboratory with febrile long without cause from September 2016 to December 2016. Mean age of patients was 27 years ranged from 16 to 51 years. The patients were selected through simple random sampling. The sera were transported on ice in a cool box to the virology laboratory of the Veterinary Faculty of Shahid Bahonar University of Kerman. Upon arrival, they were kept at -20°C.

Serological test

The presence of IgG antibodies against dengue fever virus was tested by Real time RT–PCR, nested RT–PCR, MAC ELISA, NS1 ELISA and PRNT in 184 febrile patients (100 males, 84 females) using a commercially available indirect enzyme-linked immunosorbent assay (ELISA) test kit (Virion\Serion, Wurzburg, Germany) and according to the manufacturer's recommendations. The plates were read at 405 nm by an ELISA reader (Anthos 2020, Austria). Optical density (OD) cut-off values and control sera were checked. Serum OD >10% above the OD cut-off value was considered positive and OD >10% below the cut-off value was considered negative.

Results

Results did not show any positive titer of dengue fever among 184 serum samples collected from susceptible patients in southeast Iran.

Discussion

Seroprevalence studies are essential for understanding the true burden of disease in the population. The insects which are vectors of pathogens are important across the world. Recently, the epidemic of mosquito-borne viral diseases including dengue fever has been reported in countries neighboring Iran such as Pakistan and Saudi Arabia (4). These countries are at serious risk of these diseases. Climatic changes in the Middle East region facilitate the spread of mosquito-borne diseases. Some mosquito species like *Aedes albopictus* and *Ae. Aegypti* can facilitate the transmission of pathogens in tropical and subtropical areas (13).

Studies show that dengue fever is the second cause of fever in patients who return from travel and the majority of cases diagnosed with dengue fever in Iran were among those returning from high-risk regions, such as Southeast Asia. Business and fun trips by Iranians to countries such as China, Thailand, India and Malaysia in warm seasons of the year increase the risk of dengue virus transmission on their way to Iran. In the only retrospective study conducted on dengue fever in Iran by Chinikar, 300 serum samples of patients who were negative in CCHF were examined of which 15 cases (5%) were diagnosed with dengue fever. Among them, eight cases had traveled to the South and Southeast Asia (14). Therefore, travelers are considered as agents of transmission of more severe subtypes of dengue virus to areas where the disease is observed in a less severe form or those which are considered free of disease. Travelers should become familiar with the ways of transmission before travel and consider strategies such as the choice of reasonable air conditioned accommodations and use of protective devices such as mosquito nets (4).

So far, some species of Aedes mosquitoes have been identified in Iran; However, *Ae. aegypti*, the most important vector of dengue virus, has not yet been reported in Iran.This could be the main reason for negative dengue fever results in the present study. In contrast, six out of the remaining seven cases in the aforementioned retrospective study were living in Sistan-and-Baloochestan and had not traveled to high-risk regions (14). The sporadic disease cases in Sistan-and-Baloochestan may be attributed to its neighboring country, i.e. Pakistan, as an endemic country. In 2008, the spread of dengue infection was reported in many Pakistan cities, especially in the north and northwest provinces neighboring Iran (15, 16) and at present, there are nine reported cases with dengue fever in Pakistan's Balushestan, which has a common border with Iran (14). More important reason is the identification of *Ae. albopictus* and *Ae. unilineatus* in both Pakistan and the southeast Iran. *Ae. albopictus* and *Ae. unilineatus* discovery in south and southeast of Iran is a great concern, as it is in other

areas of the world. Both *Ae. unilineatus* and *Ae. albopictus* might have been introduced in the southeast of Iran by ships coming from Karachi (17). In addition to dengue, the presence of these species is assumed a threat for the transmission of the zika virus. Therefore, it is highly important for the health officials in southern Iran to be prepared for rapid responses if these species are identified. Current data suggest the density of this invasive vector is at low level, but there is no obstacle for the species population to grow and spread in near future.

It is worth noting that the disease-carrying mosquitoes can easily proliferate in regions with low-hygienic conditions. Uncontrolled travels and illegal border crossing make fighting the disease more problematic and also make access to the patients more complicated. Therefore, monitoring warning signs and other environmental parameters in high-risk regions is essential to screen the disease. Prevention and reduction of the transmission of dengue virus to human depend on factors including control of mosquito vectors, recycling of containers that act as habitat for these mosquitoes, and prevention of contact between humans and vectors (4).

Conclusion

In the end, it should be noted that dengue fever can easily be misdiagnosed with similar diseases such as flu and flu like diseases, malaria and typhoid. This happens more often in nonepidemic areas (14) and requires more attention of doctors and specialists. In addition, neighboring countries, such as Pakistan where Dengue is endemic, and some other countries that are religious tourism destinations for many Iranians, such as Saudi Arabia, are always a potential risk of entry of infection to Iran (18). New techniques are required to complete integrated and stable management measures in controlling vectors through rapid decrease of the vector mosquitos spreading speed or suppression of their populations when the risk of transmitting pathogens is high. Otherwise, pathogens enter in different ways and cause an explosive outbreak of dengue fever. Future studies should focus on determining the dengue vector incidence in Iran and continued characterization of the dengue transmission cycle unique to Iran.

Despite the high prevalence of dengue fever in Pakistan bordering southeastern Iran, no dengue positive case was found in this study. This epidemiological research is significant for local health authorities.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical considerations

This study was carried out in accordance with the Code of Ethic Committee of Kerman University of Medical Sciences, Kerman, Iran (Ethic code: 941024)

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