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Locally Transmitted Dengue Fever in Iran: A Growing Concern

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Dengue virus (DENV) belongs to the *Flaviviridae* family, which includes over 70 major human pathogens, primarily affecting inter-tropical regions where 3.9 billion people reside (1). It is an arboviral disease mainly transmitted to humans by the bite of mosquitoes from the *Aedes* genus, particularly *Aedes* (Stegomyia) *aegypti* (Linnaeus, 1762), and less frequently by *Aedes* (Stegomyia) *albopictus* (Skuse) (2). Dengue virus has four serotypes: DENV-1, DENV-2, DENV-3, and DENV-4, all of which can infect humans (3). Primary DENV infection may be asymptomatic or result in mild fever, but if it progresses, it can cause coagulopathy, increased vascular fragility, and permeability, leading to dengue hemorrhagic fever (DHF). This condition can further develop into hypovolemic shock, known as dengue shock syndrome (DSS), both of which are life-threatening (4). Most dengue fever (DF) cases are self-limiting with low mortality (< 1%) when treated early with appropriate medical care. However, some patients develop severe conditions like DHF or DSS, with a mortality rate of 2% - 5% after treatment; without treatment, the mortality rate can rise to 20% (5, 6).

Epidemiological surveys indicate that DENV infects approximately two-fifths of the world's population, with nearly 390 million infections annually, leading to 500,000 hospitalizations and 20,000 deaths. DENV is prevalent in regions such as the Eastern Mediterranean, Southeast Asia, Africa, the Western Pacific, and South America (7). Approximately 2.5 billion people are at risk of contracting dengue, with 100 million reported cases of dengue fever each year, and up to 500,000 cases developing into potentially fatal DHF or DSS.

Around 80% of primary DENV infections are asymptomatic, with fewer than 20% of infected individuals showing clinical symptoms. Dengue fever is marked by severe headaches, mild fever, rashes, muscle and joint pain, nausea, and vomiting (1). DHF is characterized by high fever, hepatomegaly, hemorrhagic symptoms, shock, and cardiovascular disturbances. Initially, DHF was reported to primarily affect children under 15 years of age, but subsequent studies have indicated its occurrence in adults as well (8).

Diagnosing dengue can be challenging, depending on the stage of infection and the presence of other pathogens that mimic dengue, such as influenza, measles, Zika, chikungunya, yellow fever, and malaria (9). In individuals with low immunity, the disease can rapidly progress from mild to severe, making early laboratory diagnosis critical and potentially life-saving. The acute phase of dengue is defined as the first 1 - 7 days after symptom onset, during which DENV is typically present in the blood or blood-derived fluids, such as serum or plasma. Molecular tests like RT-PCR can detect DENV RNA during this period (10).

The convalescent phase of dengue begins more than 7 days after symptom onset. IgG antibodies should be detectable at high levels, even though IgM antibodies may still be present. IgM antibodies become detectable on days 3 - 5 of illness and persist for 2 - 3 months, while IgG antibodies develop by day 14 and last a lifetime. In cases of secondary infection, IgG levels rise within 1 - 2 days of symptom onset, along with IgM antibodies (11).

There is no specific antiviral treatment for dengue disease. The World Health Organization (WHO) has prioritized the development of a tetravalent DENV vaccine as a key strategy for dengue prevention. Typically, dengue fever resolves on its own with supportive care such as fluid replenishment, analgesics, and bed rest. There is no drug specifically used to treat

dengue, although fever can be managed with acetaminophen. Careful management is necessary for severe dengue cases. Methylprednisolone has been demonstrated in a single dose for managing bleeding, but it is not recommended by the WHO or CDC due to risks such as immunosuppression, hyperglycemia, and gastrointestinal bleeding. Additionally, no mortality benefits have been observed when treating dengue shock with this medication (10-12).

Due to the lack of effective antiviral treatments for dengue, prompt and supportive management with fluid replacement, especially in severe cases, is crucial for preventing disease progression and death. Vaccines and antiviral medications remain the two primary strategies for controlling viral diseases. Live attenuated vaccines (LAVs), which use weakened pathogens to reduce virulence, offer benefits such as delivering a range of protective antigens and inducing long-lasting immune protection. Live attenuated vaccines are considered cost-effective and promising for DENV vaccine development, showing significant replication in Vero cell culture and producing antibody levels comparable to those seen in wild-type virus infections in non-human primates. However, despite their efficacy in protecting against severe dengue in dengue-positive individuals, concerns have been raised about their use. Seronegative individuals may face an increased risk of severe dengue and a higher likelihood of hospitalization (13).

Inactivated vaccines, composed of antigenic material from a pathogen that has been rendered inactive but still provides protection, offer another approach. A DENV-2 inactivated vaccine demonstrated effectiveness in rhesus monkeys using formalin inactivation and sucrose centrifugal purification. These vaccines provide two key advantages: enhanced safety, as they cannot revert to a more harmful form, and a balanced antibody response from each serotype in a multivalent inactivated virus vaccine (14, 15).

Currently, various control strategies have been proposed to address the issue of dengue. One of the primary strategies is community-based control programs, which aim to control and eliminate active breeding sites. These programs divide the community into groups based on their education level and knowledge about the disease. Community-based initiatives have proven effective in reducing mosquito populations in some countries and play a vital role in preventing dengue virus (DENV) transmission (16). These programs focus on educating the public about the vector and disease, raising awareness, and encouraging preventive measures. However, despite the implementation of these programs in most dengue-affected countries, their effectiveness remains limited. This limitation can be attributed to various factors such as differences in country size, population, available resources, and the methods and plans employed in different regions (17, 18).

The control and prevention of DENV vectors depend on biological control methods and new strategies, as conventional control measures are ineffective against mosquitoes like *Aedes aegypti*, which bite throughout the day. Genetically modified mosquitoes have emerged as a key strategy in biological control plans. For instance, the sterile insect technique (SIT), used effectively in several countries, involves sterilizing male mosquitoes to reduce their breeding capacity (19).

In recent decades, dengue has caused several outbreaks in Asia and Latin America, with vectors like *Ae. aegypti* and *Ae. albopictus* expanding their habitat. In Iran, an outbreak in mid-2024 originated from neighboring southern countries, with most cases being imported. However, local transmission was identified in southern and northern provinces. For 120 years ago, only 75 cases of dengue fever were reported in Iran, mostly imported from Southeast Asia and Africa. However, between April and June 2024, 120 cases were observed, most of them imported from the United Arab Emirates. Notably, 11 of these cases were locally transmitted in Bandar Langeh, Hormozgan Province, with no history of travel. This local transmission signals a significant development in the spread of the virus in Iran and underscores the role of climate change as a contributing factor.

In response, several control programs have been proposed to manage DENV transmission. Prompt and accurate diagnosis is essential for early detection of DENV infection, which is beneficial for controlling transmission and disease progression. Moreover, the progression to severe disease remains unpredictable, highlighting the need to identify key biomarkers for predicting severe dengue cases.

In conclusion, dengue fever is a global public health threat that requires effective licensed vaccines, vector control measures, and early diagnostic tests to reduce the burden of this disease.

Footnotes

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