Dengue Fever

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Disease:

Dengue Fever (aka Dengue Hemorrhagic Fever)

Etiologic Agent:

Dengue fever is caused by a virus commonly known as the Dengue Virus. Specifically it has four closely related serotypes named DEN-1, DEN-2, DEN-3 and DEN-4 in the Flaviviridae family of viruses. Each serotype is approximately 65% related and can all cause the same disease and symptoms.

Transmission

The Dengue virus is transmitted via indirect transmission through the bite of a mosquito vector. The vector must feed on it's human host for 5 days to accumulate a large enough amount of virus in the blood, and it also requires 8-12 additional days of incubation before it can be transmitted to another human host.

Reservoirs

The primary reservoir of the Dengue virus is a mosquito vector called Aedes aegypti. Aedes meaning “unpleasant” and aegypti refers to origins from Africa. Aedes aegypti can be characterized by a bright silvery lyre-shaped pattern on the dorsal aspect, with white banded legs. The unique trait of this mosquito is that it is very closely associated with human habitation. It has a higher preference for human blood than any other domestic mammal. It is also able to lay eggs and hatch in many environments including indoors or outdoors and with or without presence of vegetation. Standing water is the most suitable environment to serve as a breeding ground for these mosquitoes.

A secondary mosquito vector has also been identified as Aedes albopictus. This species is found in Asia and has spread to North America and Europe, while adapting to the colder environments.
Monkeys have been suggested to be another reservoir of the virus, but it is less common and found mostly in the jungles environment. Dengue fever cannot be transmitted from direct contact between humans.

**General characteristics**

The Dengue virus is in the genus Flavivirus and as mentioned before is in the family Flaviviridae. The genome is composed of a single stranded RNA that encodes 10 genes, which produce 10 proteins, 3 structural and 7 non-structural. The structure of the virus is spherical with a nucleocapsid core surrounded by a viral envelope that protects the viral genetic material.

**Key tests for identification**

Serological testing can be conducted within the first 5 days of showing symptoms or during the early convalescent phase. Acute infection is confirmed when the virus is present within the serum, plasma, CSF or autopsy tissue via reverse transcription polymerase chain reaction (RT-PCR). The RT-PCR test is useful to detect early onset of the virus infection and has very good specificity and sensitivity, 95% and 80-90% respectively. A positive result confirms the infection, but if the patient had a negative result during the serum RT-PCR or did not submit a serum specimen and is thought to have a dengue infection, then the result will be "indeterminate". If this occurs then additional immunoglobulin testing can be conducted. IgM antibody capture enzyme-linked immunoasorbent assay, MAC-ELISA, specifically detects the IgM antibodies in people who have infected with flavivirus antigen. This test can be used later on after the acute infection because IgM levels remain high even 2 to 3 months after the initial infection. Another immunoasorbent assay, IgG ELISA, can be used to test for past dengue infection and thus differentiate between primary and secondary infections. A negative IgG in the acute phase and positive IgG in the convalescent are seen as primary infections, while secondary infections exhibit positive IgG in the acute phase and a 4 fold increase in titer in the convalescent phase. Other additional testing include the NS1 ELISA, which test for the genome that codes for the non-structural protein of the dengue virus, and the Plaque Reduction and Neutralization Test (PRNT), which is the most specific antibody test to determine infecting serotypes during the convalescent sera.

**Signs and symptoms of disease**

As the name of the disease suggests, the biggest indicator is a sudden high fever, about 104 degrees F. Other signs and symptoms include severe headaches, pain behind the eyes, nausea,
vomiting, swollen glands and a rash that appears 3 to 4 days after the fever. In serious cases, Dengue fever can be fatal due to complications of severe bleeding, respiratory distress and organ impairment, which can all lead to death. A key warning sign of the disease is a decrease in temperature (below 100 deg C) in conjunction with severe abdominal pain, persistent vomiting, rapid breathing, bloody vomit and bleeding gums.

**Historical information**

The dengue virus was first isolated in 1943 by scientists, Ren Kimura and Susuma Hotta, when they were studying blood samples of patients during an epidemic in Nagasaki Japan. World War II also aided in the spreading of the virus to different regions of the world due to large numbers of soldiers being stationed in various areas in Europe and Asia. Before modern science identified the exact virus, dengue-outbreaks were recorded in Chinese medical encyclopedias as early as 992.

In 1771, the disease was referred to as “bone-break fever” by Dr. Jose Sabater, a military physician in Puerto Rico. The name is in reference to the extreme joint and bone pain patients felt as if their bones were breaking.

The actual term “dengue” came about in 1801 when the Queen of Spain was recovering from the disease calling it “dengue”, which is Spanish for “affection, careful or fastidious”. This most likely was coined to describe the stiff movements and joint pain caused by the fever.

**Virulence factors**

The pathogenesis of how the dengue virus infects humans is not fully understood. But other animal models have shown that the virus initially infects the epithelial cell after spillover from a mosquito bite through endosome formation. As shown before, the E and M proteins located on the outer envelop of the virus aids in the binding of the skin cell surface. By forming an endosome, the virus is able to enter the cell undetected and proliferate using the cells DNA replicating machinery. Another virulence factor is that the different serotypes creates difficulty to produce a vaccine or medication that can only target one specific antigen surface marker.

**Control/Treatment**

Currently there is no known vaccine or specific medication that targets the dengue virus. Palliative treatment includes staying well hydrated while avoid using Non-Steroidal Anti-inflammatory medications such as aspirin or ibuprofen. These medications can lead to
exacerbate the hemorrhagic symptoms associated with the disease\textsuperscript{1}. Instead, to alleviate pain and control fever, people should take acetaminophen and tepid sponge baths\textsuperscript{1}.

**Prevention/Vaccine**

As stated before, there are no currently approved vaccines for public use, but certain vaccines are under development that show promise. Presently, the best method to combat the dengue virus is to prevent infection from the mosquito bite. This can be done by either protecting your body from mosquitoes via repellents, clothing and nets when sleeping, or by controlling the spread of the mosquitoes themselves. This can be done by disposing of solid wastes and man-made habitats that can hold water, which can provide a breeding ground for urban mosquitoes. Some urban areas utilize insecticides as space spraying as an emergency vector control measure.8

**Local cases or outbreaks**

The most recently known outbreak in Texas occurred in 2005 according to the CDC. The incident occurred on the border of Cameron County, Texas and Matamoros, Mexico where the suspected Dengue outbreak was identified as caused by the DEN-2 strain of the Dengue virus.\textsuperscript{2} The number of cases peaked during October and eventually resolved by December.\textsuperscript{2}

More recently, there is currently an outbreak in Hawaii with 139 confirmed cases as of December 7\textsuperscript{th}, 2015\textsuperscript{7}. The cause is still unknown and joint investigations are undergoing, but it is thought to be from other travelers bringing the disease to the island since Dengue is not endemic to the state.\textsuperscript{7} This makes sense because Hawaii is a big tourist attraction and has a suitable climate for habitation of the Dengue mosquitoes.
Global cases or outbreaks

In the mid to late 19th century, Dengue fever was considered sporadic and slow paced epidemic. This could most likely be due to the limited international traveling and thus less spreading of the disease from continent to continent. But as the technology to travel transcontinentally improved, the disease was able to rapidly diffuse to other countries and even other continents. In the last 50 years, incidence has increased 30-fold and estimated that 50 million people are infected every year.

Geographically, infection is most prevalent in developing countries in the tropics and subtropics, where water supplies are stored in home containers and volume of solid wastes are high. These factors provide favorable conditions for transmission of the main vector, Aedes aegypti.
References:


