Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/mjafi

Contemporary Issue

Discovery of fifth serotype of dengue virus (DENV-5): A new public health dilemma in dengue control

Lt Col M.S. Mustafa [a,*], Col V. Rasotgi [b], Col S. Jain [c], Lt Col V. Gupta [d]

[a] Officer Commanding, Station Health Organisation (Large), Allahabad 908406, India
[b] Director, AFMS (Pensions), O/o DGAFMS, New Delhi, India
[c] ADH & Senior Adviser (Community Medicine), HQ 11 Corps, C/O 56 APO, India
[d] Officer Commanding, 136 Station Health Organisation (Large), C/O 56 APO, India

ARTICLE INFO

Article history:
Received 24 June 2014
Accepted 21 September 2014
Available online 24 November 2014

Keywords:
Dengue fever
Serotype
Sylvatic
Dengue vaccine

ABSTRACT

Dengue fever is a re-emerging public health problem with two-fifths of the world population being at risk of infection. Till now, dengue fever was believed to be caused by four different serotypes. The fifth variant DENV-5 has been isolated in October 2013. This serotype follows the sylvatic cycle unlike the other four serotypes which follow the human cycle. The likely cause of emergence of the new serotype could be genetic recombination, natural selection and genetic bottlenecks. There is no indication of the presence of DENV-5 in India. Recent clinical trials with the promising Chimerivax tetravalent vaccine suffered a setback. Discovery of DENV-5 and more such sylvatic strains in future may further impede the Dengue Vaccine Initiative. Integrated Vector Management holds the key to sustainable dengue control. Further epidemiological and ecological studies are needed to detect additional sylvatic dengue strains.

Introduction

Dengue fever has re-emerged as a major public health challenge worldwide; with 2.5 billion people at risk of infection, more than 100 million cases and 25,000 deaths being reported annually.[1] As there is no licensed vaccine or specific treatment against dengue, preventive measures are the best strategy, which consist mainly of environmental management, spraying insecticides, and personal protective measures.

Till now, dengue infections were believed to be caused by four antigenically distinct serotypes, Dengue Virus (DENV)-1, DENV-2, DENV-3, and DENV-4; each generating a unique host immune response to the infection. These four serotypes are genetically similar and share approximately 65% of their genomes.[2] Dengue virus is transmitted to non-human primates (sylvatic form) and humans (human form) via a mosquito vector; primarily of the genus *Aedes*.

The new virus

The fifth and latest addition to the existing serotypes of dengue viruses is DENV-5 which has been announced in

* *Corresponding author*. Tel.: +91 9410430079.
E-mail address: msmustafa2001@yahoo.co.in (M.S. Mustafa).
http://dx.doi.org/10.1016/j.mjafi.2014.09.011

October 2013. DENV-5 has been detected during screening of viral samples taken from a 37 year old farmer admitted in hospital in Sarawak state of Malaysia in the year 2007. The infection in the farmer was initially thought to be an ordinary case of sylvatic dengue caused by DENV-4 which circulates among primates and *Aedes nivalis* mosquitoes in the forests of South East Asia.[3]

However, when the virus was isolated and a full genetic sequence was carried out, it was observed that the virus was phylogenetically distinct from the three previous forms of sylvatic DENV-4 and bore some similarity with DENV-2.[3] In the Sarawak outbreak, only one case was admitted and the other confirmed cases were treated on an outpatient basis, thereby indicating that the disease caused by DENV-5 is mild.

Since no new serotype of the virus had been reported for the last 50 years, it was initially believed that the new virus could be a variant of the dengue 4 serotype. However, when rhesus macaque monkeys who were pre-infected with the other four serotypes and had already recovered from the infection were infected with DENV-5, they produced a significantly different set of antibodies. This proved beyond doubt that the new virus was indeed a new serotype and not a variant of DENV-4.

Secondly, the viral titre of the secondary infections was four times higher than other serotypes, which follows the classification of a flaviviruses into serotypes based on the degree of viremia.[4]

Possible reasons for emergence of new virus

Co-circulation of multiple dengue serotypes coupled with increased human activity increases the likelihood of genetic changes, leading to diversity in virus populations. Genetic recombination, natural selection and genetic bottlenecks have been implicated as factors which may lead to the emergence of new serotypes.

Dengue viruses, being RNA viruses, have high mutation frequencies with mutation rates being more than 100 times greater than the mutation rates of DNA genomes. The accumulation of mutations is a continuing process, which, together with the possibility of intramolecular recombination due to simultaneous infections with different dengue virus serotypes, could lead to the emergence of a novel dengue virus serotype differing at one or more critical neutralising epitopes.[5]

Following extensive phylogenetic analysis, it has been hypothesised that the earlier four lineages of dengue viruses evolved in non-human primate reservoirs thousands of years ago and then jumped over from these ancestral sylvatic progenitors to humans due to clustering of sylvatic strains with human strains as a result of increased human activity. This ancestral sylvatic-DENV transmission cycle still exists and is maintained in non-human primates and Aedes mosquitoes in the forests of South East Asia and West Africa.[6]

The exact reason for emergence of DENV-5 is not clear. The new serotype has only been found in forests of Sarawak. This serotype circulates primarily amongst non-human primates and follows the sylvatic cycle unlike the other four serotypes of dengue which are transmitted between humans. Though sylvatic dengue virus strains have infected humans before, isolation of these sylvatic strains has revealed that they were closely related to one of the four current serotypes.

As was the case with the other four dengue virus serotypes, it has been suggested that DENV-5 has been circulating among non-human primates in the forests of South East Asia for centuries before jumping the human barrier. The virus has been maintained in macaques with a spillover into humans, resulting in the Sarawak outbreak. Phylogenetic evaluation revealed that DENV-5 is genetically similar to the other four serotypes, thereby hinting to a common ancestral origin.

The present threat of the surfacing of sylvatic DENV by spillover in human populations has been elicited in recent studies using laboratory models for the replication of sylvatic DENV in humans.[6] The replication profiles of low-passage DENV-2 strains representing all major genotypes were evaluated in two surrogate models – human monocyte-derived dendritic cells (moDCs) and severe combined immunodeficient (SCID) mice xenografted with human hepatoma (Huh-7) cells. It was observed that though the strains differed in their replication profiles, there was no marked difference between sylvatic and human strains. However, the replication of sylvatic DENV-2 in moDCs was remarkably similar to that of human DENV-2 from the American genotype.

Besides, the replication of human and sylvatic strains was measured in cultured cells from human (Huh-7 cells), monkey (Vero cells) and mosquito (C6/36 cells from *Aedes albopictus*) hosts; wherein human DENV strains produced considerably more progeny only in the human cells when compared to their sylvatic counterparts.

The results of the experiments involving surrogate human models and the cultured cells indicate that little or no adaptive barrier exists to prevent the emergence of sylvatic DENV in a wide range of primate hosts including humans, as has been demonstrated by the genomic analysis of the Sarawak outbreak isolate.

Jumping the human barrier by DENV-5 may be attributed to deforestation. As sylvatic dengue is native to the natural forests, deforestation activities such as uncontrolled population movement, unplanned and substandard housing, poor water storage facilities and improper waste disposal management systems provide ideal conditions for the emergence of DENV-5 by disturbing the ecological niche.[7]

Impact on dengue control

Occurrence of new cases DENV-5 may lead to new challenges in dengue control. DENV-5 has so far been linked to only one outbreak in 2007, thereby indicating that the new serotype probably has a low transmission rate. However, fresh outbreaks cannot be ruled out. Moreover, the serotype may spread to virgin areas to further complicate the situation.

As dengue has re-emerged with vengeance as a major public health problem and has spread from urban to rural areas and to countries where it was non-existent, immediate surveillance and control measures need to be put in place before DENV-5 also assumes epidemic proportions just like its predecessors. Presently, the new serotype is believed to be limited to the forest canopies of South East Asia, but in the