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A Systematic Review of Dengue Fever and Dengue-Associated Neurological Conditions Was Conducted in an Attempt to Better Understand This Disease

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Abstract

Dengue is a global arbovirus disease primarily carried by *Aedes aegypti* and *Aedes albopictus* mosquitoes. It has four serotypes (DENV1, DENV2, DENV3, and DENV4) and is classified into distinct genotypes. The epidemic is complicated by immunological interactions and viral lineage turnover. Neurological problems are commonly associated with DENV2 and DENV3, with DENV2 displaying the most severe symptoms. Direct viral invasion, host-mediated immune system reactions, or host-mediated metabolic alterations can all result in dengue-related neurological issues. The three dengue vaccinations and the significance of meta-analyses for genetic data will also be covered. Finally, establish a connection with the microRNAs associated with dengue fever, creating new opportunities for the creation of dengue treatment regimens involving microRNAs.

Introduction

The arbovirus disease dengue has spread around the world and is now an important threat to public health. From symptomatic dengue fever (DF), a small percentage of individuals may develop dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). Dengue is a single positive-stranded RNA virus from the *Flaviviridae* family (Genus *Flavivirus*) [37, 34]. *Aedes aegypti* and *Aedes albopictus* mosquitoes are the most common carriers of the dengue virus. It is the second most common mosquito-borne illness, after malaria. The clinical manifestations of hemorrhagic fever range from mild to severe.

It consists of up of a 5' untranslated region, a large open reading frame (ORF) that encodes a polypeptide chain, and a 3' UTR. The virus's translation produces ten different viral proteins, both structural and nonstructural. Dengue's four serotypes (DENV1, DENV2, DENV3 and DENV4) are further classified into distinct genotypes. DENV1 has five genotypes (I-V), DENV2 has six (Southeast Asian/ American), DENV3 has four (I-IV), and DENV4 has four (Southeast Asia, America, Thailand, and Sylvatic) [Sankoju et al., 2023]. The dengue epidemic is complicated by immunological interactions among the four circulating serotypes and the constant turnover of viral lineages.

The DENV genomic RNA encodes three structural proteins (C, PrM, and E) and

seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) [4]. Untranslated sections (5′-UTR and 3′-UTR) surround the DENV open reading frame at both its 5′ and 3′ ends. The DENV genome contains a significant amount of variation [26].

The infection confers lifelong protective immunity to the same subtype but no immunity to the other three serotypes [27]. Furthermore, previous infection with a different subtype raises the risk of developing dengue hemorrhagic fever [27]. This is due to a phenomenon known as antibody-dependent enhancement (ADE). In ADE, heterotypic non-neutralizing antibodies form complexes with dengue virus, infecting mononuclear phagocytes more efficiently. As a result, a greater number of host cells are infected, increasing viral replication and worsening clinical symptoms.

The first confirmed outbreak of dengue virus occurred simultaneously in Asia, North America, and Africa in 1779 [11]. Dengue, which is already present in over a hundred countries, is spreading from tropical and subtropical regions due to climate change [23]. In October, Bangladesh had 359 fatalities and 67,769 cases, while India had 94,198 cases and 91 deaths. African countries with documented cases include Angola, Burkina Faso, Chad, Côte d'Ivoire, Egypt, Ethiopia, Guinea, Mali, Mauritius, Sao Tome and Principe, Senegal, and Sudan. In Americas are home to the majority of dengue infections, with approximately 3.7 million confirmed cases and 1700 deaths expected by 2023.

There are four serotypes of dengue fever (DENV), ranging from DENV1 to DENV4, but neurological symptoms are frequently associated with DENV2 and DENV3 [19], with DENV 2 being the most common serotype with the highest severity at our hospital [9]. In fact, DENV2 and DENV3 were identified in cases of encephalitis, meningitis, and myelitis [5]. DENV-4 was also detected in brain cells by immunohistochemistry and in cerebrospinal fluid (CSF) of a patient with encephalitis, whereas neurological symptoms have frequently been linked to DENV2 and DENV3 [19].

It is critical to remember that dengue-related neurological problems are a complex issue caused by both the virus and the host [32]. There are three potential mechanisms: the virus's direct invasion of the central nervous system, immune responses, and metabolic changes. Direct viral neurotropism is indicated by neurological involvement, the presence of CSF viral particles, and blood-brain barrier disruption. Recent studies suggest that neuroinflammation plays a role in dengue. Non-structural 1 antigen (NS1Ag) is linked to neurological symptoms and has been shown to induce cytokine release [33]. Natural killer cells activate T-helper (Th) cells, which differentiate into Th17 and Th9 cells.

The production of pro-inflammatory cytokines by these cells damages the blood-brain barrier and allows other immune mediators to enter the brain, resulting in neuroinflammation [33]. Prior DENV infection-related neurological consequences were classified into three types: immunological responses, viral invasion, and metabolic abnormalities. DENV encephalopathy and encephalitis, especially in dengue-endemic areas, should be considered when making a differential diagnosis of various acute febrile encephalopathies, autoimmune encephalitides, and SARS-CoV2 infections.

Dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) were originally associated with it. According to recent research, dengue virus infection-related cytokine overproduction harms immune -mediated endothelial cells, increasing vascular permeability and fluid leakage, which may eventually result in global cerebral edema [17]. Without supportive therapy, death rates could be significant, and treatment results can vary.

It is interesting to note that "expanded dengue syndrome" (EDS) refers to dengue fever symptoms affecting multiple organ systems [Aris et al., 2022]. This condition is more common in high-risk groups, including the elderly, pregnant women, children, hemoglobinopathies, patients with coronary

artery disease, and those with compromised immune systems. EDS can cause complications in the hematology, renal, gastrointestinal, respiratory, and cardiovascular systems. Pregnant women, young children, the elderly, those with hemoglobinopathies, and people with weakened immune systems are all at high risk [Aris et al., 2022].

… and how does the dengue vaccination appear?

The first is the live and attenuated tetravalent vaccination Qdenga® (also known as TAK-003), developed by the Japanese laboratory Takeda [22]. After a year of use, the vaccine was found to be 80% effective when administered in two doses at three-month intervals. Indonesia approved its use in October 2022, and the European Union approved it in December 2022 [22]. The United Kingdom arrived in January 2023, followed by Brazil in the middle of the year.

Intramuscular inoculation is required for individuals who have previously experienced dengue or to prevent it in those who have not contracted the virus. Qdenga®'s primary mechanism of action is local replication and the induction of neutralizing antibodies, which provide protection against dengue fever caused by any of the four dengue virus serotypes [22].

Qdenga® activates a variety of immune system defense mechanisms, including complement-based inhibitors, complement-based fusion inhibitors, functional inhibitors against dengue 1's nonstructural protein (NS1), and cell-mediated immune responses (CD4+, CD8+, and natural killer cells). A 0.5 ml dose of the Qdenga vaccine contains live and attenuated fragments of all serotipos DENV1, DENV2, DENV3, and DENV4, with 3.3, 2.7, 4.0, and 4.5 >= log10 UFP/dosis, respectively.

On the other hand, the Advisory Committee on Immunization Practices recommends Dengvaxia®, the only dengue vaccine that is routinely used and approved by the US Food and Drug Administration [24]. Sanofi Pasteur is the manufacturer. The vaccine protects against illness caused by any of the four dengue virus serotypes. A dose contains the quimeric dengue-fiebre amarilla virus (live and attenuated), and the DICC50/dosis for all serotypes ranges from 4.5 to 6.0 log10 DICC50 [24].

Sanofi Pasteur licensed the first dengue vaccine (Dengvaxia®) in Mexico in 2015, and more than 20 countries followed, based on the safety and efficacy of two phase III trials and a single season of disease surveillance [31]. Unfortunately, the optimism that a dengue vaccine would finally be available was quickly dashed when a safety signal was detected in vaccine recipients who were dengue non-immune at the time of vaccination [30]. In the third year of the phase III clinical trial, the youngest, non-immune vaccine recipients had higher rates of hospitalization and severe dengue than their unvaccinated counterparts [10].

The Butantan-Dengue Vaccine, also called Butantan-DV, is similar to the NIH's previously tested TV003 formulation and was developed with ingredients licensed from the US NIH [Hou et al., 2022]. When they signed a co-development and licensing agreement in 2018, MSD joined the partnership. Participants in the phase III experiment, who ranged in age from 2 to 59 years old and received a single dose of vaccine, were monitored for any case of dengue, regardless of severity, caused by any strain of DENV [31]. The trial began in 2016. The trial included both immune and non-immune individuals to dengue [31].

The United States National Institutes of Health (NIH) has created two live-attenuated single-dose vaccine candidates, TV003 and TV005, using deletions and structural gene chimerization [14]. These vaccines include DENV-1, DENV-3, and DENV-4 strains that have 30 nucleotide deletions for attenuation. In phase 1 trials, there was no difference in adverse events (AEs) between vaccine and

placebo groups. Phase 2 and 3 trials are currently underway in Taiwan and Brazil [14].

The importance of meta-analysis for genetic information

Genome-wide association studies (GWAS) have identified specific genetic markers linked to increased susceptibility to dengue virus infection, which may also contribute to the development of dengue-related neurological disorders [35].

Dengue-related neurological disorders are complex problems caused by both the virus and the host. There are three potential mechanisms: the virus's direct invasion of the central nervous system, immune responses, and metabolic changes [32]. Direct viral neurotropism is indicated by neurological involvement, the presence of CSF viral particles, and blood-brain barrier disruption. Recent studies suggest that neuroinflammation plays a role in dengue. Nonstructural 1 antigen (NS1Ag) has also been linked to dengue's effect on the nervous system [25].

A notable meta-analysis published in the Journal of Neurovirology reviewed existing studies to examine the neurological consequences of dengue fever [15]. The study emphasized the need for additional research to determine the underlying genetic and immunological factors that contribute to dengue fever's neurological manifestations [8]. The study also emphasized the importance of early detection and intervention in mitigating the effects of dengue-related neurological disorders.

The genome-wide association studies (GWAS) have identified two genes that are significantly associated with dengue-specific syndrome (DSS): the major histocompatibility complex (MHC) class I chain-related B (MICB) rs3132468 and the phospholipase C epsilon 1 (PLCE1) rs3765524 and rs3740360. These genes are associated with a milder form of dengue than DSS because they activate NK cells or innate lymphocytes during viral infection. However, their relationships with clinical outcomes of infectious diseases are unclear, with one study finding no link between MICB and PLCE1 genotypes and viremia levels or clinical features [Faridah et al., 2023].

Oliveira et al. (2018) conducted a population genetics-based meta-analysis of ten markers. Seven markers (PLCE1, CD32, CD209, OAS1, and OAS3) have high-frequency MAF (20–50%), while three (MICB and TNFA genes) have intermediate-frequency MAF (5–20%). However, these markers have high discriminatory between population groups, particularly between sub-Saharan Africans and northeast/southeast Asia.

These studies suggest that specific polymorphisms can confer susceptibility or protection against specific molecular phenomena in dengue patients. TNFA protects dengue fever (DF), CD32 protects DHF, and PLCE1, MICB, and OAS3 play a role in DSS. Meta-analyses showed similar OR values, with mild individual impact. However, the meta-analysis was not informative enough to replicate the significant association between CD209 and DF/DHF.

The next strategy is to use microRNA, which can help with diagnosis and, eventually, vaccine development against dengue.

microRNAs

MicroRNAs (miRNAs) are small non-coding RNAs that play a crucial role in gene expression regulation. With over 2600 human miRNAs, they regulate the expression of about 60% of protein-coding genes in the human genome [28].

As explained by O'Brien et al. (2018), the majority of miRNAs are transcribed from DNA sequences

into primary miRNAs, which are then processed into precursor miRNAs and finally mature miRNAs. In most cases, miRNAs interact with the 3′ untranslated region (3′ UTR) of target mRNAs to cause mRNA degradation and translational repression. However, miRNAs have been shown to interact with other regions, such as the 5′ UTR, coding sequence, and gene promoters.

Su et al. (2021) indicated that microRNAs, such as miR-548 g-3p, can inhibit DENV replication by directly targeting viral genome sequences. The DENV genome's 5'-UTR contains two essential viral replication elements: a large stem-loop (SLA) structure and a short stem-loop with a cyclization sequence (5'UAR). Overexpression of miR-484 and miR-744 can inhibit virus replication by interacting with the 3'UTRs of the four DENV serotypes. Furthermore, host miR-133a can target the 3'-UTRs of all four DENV serotypes, reducing endogenous miRNA-133a expression during the infection. This antiviral effect could be mediated by the regulation of the host factor polypyrimidine tract-binding protein [7].

Su et al. (2021) also found that human primary monocytes and peripheral blood monocytes infected with DENV-2 showed a substantial upregulation of miR-146a. In addition, miR-146a targets TRAF6 and interleukin-1 receptor-associated kinase (IRAK1) to modulate the TLR signaling pathway and lower IFN-I production, allowing the host to evade an immunological response [12].

Yan et al. (2014) found that miR-252 was highly expressed in a DENV-2 infection model, down regating the expression of the E protein, which plays a crucial role in virus attachment, fusion, and assembly. This has led to the exploration of miRNA-based drug discovery. Lee et al. (2017) found that the water extract of Flos Lonicerae can upregulate Let-7a expression in human and mouse blood, which can target the NS1 region of DENV-2 to inhibit its replication. This study provides new insights for the prevention and treatment of DENV infection through the induction of innate miRNA Let-7a by honeysuckle. MiRNAs that promote viral replication by targeting viral genomes play a direct role in regulating viral infection and miRNA expression, potentially avoiding excessive production of cellular inflammatory factors and reducing the risk of dengue fever.

Castrillon-Betancur and Urcuqui-Inchima (2017) identified three miRNA candidates that might possibly inhibit DENV replication using bioinformatics predictions. They anticipated that a functional miRNA was conserved across all DENV serotypes and found miRNA candidate target locations in the 3'UTR of all four dengue serotypes. As a consequence, they postulated that miR-133a, miR-484, and miR-744 might inhibit DENV replication by targeting the DENV RNA genome's 3'UTR, especially the 3'stem loop, which includes components crucial in genome circularization and viral viability [2]. Indeed, overexpression of miR-133a, miR-484, and miR-744 in Vero cells was experimentally confirmed to demonstrate the potency of these three miRNAs in inhibiting DENV replication.

Conclusion

The complex relationship between dengue fever and its neurological aftereffects has been shown by the current investigation. New avenues for understanding and potentially mitigating the neurological impact of dengue virus (DENV) infection have been opened up by the discovery of genetic markers, including genome-wide association studies (GWAS), and the exploration of the underlying mechanisms of dengue virus neural invasion. Finally, new insights for the development of miRNA-based therapeutics will come from an understanding of the production and function of miRNAs during DENV infection and the associated signal molecules in the miRNA-mediated regulatory network.

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