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COMBATING DENGUE FEVER: CHALLENGES, PROGRESS, AND FUTURE DIRECTIONS

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Abstract: **Dengue fever poses a significant global health threat, particularly in urban areas of tropical and subtropical regions. Originating from the Flaviviridae family and Flavivirus genus, the disease is transmitted by Aedes aegypti and Aedes albopictus mosquitoes, with four serotypes causing varying clinical manifestations. Despite its historical presence since the late 18th century, dengue has surged in recent years, with the monsoon season exacerbating its spread. India, among other nations, grapples with high caseloads and fatalities. Classical dengue, dengue hemorrhagic fever, and dengue shock syndrome present distinct symptoms, impacting multiple organs including the liver and brain. Current efforts focus on vaccine development, exemplified by Dengvaxia, and monoclonal antibody therapies like mAb 2E8 and Ab513. These advancements offer hope for effective prevention and treatment strategies against dengue fever, addressing a critical public health concern worldwide.**

Keywords: **Dengue; dengue fever; public health; Vaccine**

I. INTRODUCTION:

Nowadays the greatest challenge for the world is dengue, which is the most dangerous acute viral disease. The urban areas of tropical and subtropical countries are mainly affected by this disease. “DENGUE “ the name comes from "Ka-denga pepo", which means "cramp-like seizure caused by an evil spirit". The female Aedes aegypti and Aedes albopictus are the vectors of this dengue virus. this RNA virus has four serotypes (DENV1,DENV2,DENV3,DENV4).It originated from the family Flaviviridae and the genus Flavivirus. In 1780 dengue was first introduced in Asia, Africa, and North America, in 1779 this disease got the name. In 1789, Benjamin Rush reported a case of dengue, due to breakbone fever with myalgia and arthralgia symptoms. it was the first confirmed report of dengue [3]. This article provides a detailed overview of the epidemiology of dengue fever, different clinical manifestations, affected part via dengue virus infections, and current updates of dengue vaccine and other ways to control this virus as well as this disease [1].

EPIDEMIOLOGY:

Now dengue is the most infected disease worldwide. It has drastically increased in the last few years globally. The monsoon session is the most suitable time for spreading this disease. 390 million people are affected by dengue throughout the world according to World Health Organization (WHO). In India, 151 people died till 15 October 2017, and 87,018 cases were reported for dengue. The maximum cases for dengue report comes from Kerala(18,908), Karnataka(13,235), Tamilnadu(12,945), West Bengal(5,389) and Delhi (5,220).

VARIETY OF DENGUE FEVER ALONG WITH SYMPTOMS:

Mainly three kinds of dengue have been seen now

Classical dengue:

Within 7 days these symptoms are seen ..like muscle aching, body rash, high fever,headache , vomiting, nausea, pain behind the eyes.

Dengue hemorrhagic fever[DHF]:

In Dengue hemorrhagic fever someone experiences bleeding from different external organsorgan (mouth ,gums,nose)lymph and blood vessel can damage ,internal bleeding & black vomit, feces, and stool can appear, platelet count can decrease, the stomach can be sensitized, small

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blood spot shown under the skin, pulse rate become slower.
Dengue shock syndrome [DSS]:
In the case of DSS, intense stomach pain, disorientation, hypotension or blood pressure drop, heavy bleeding, frequent vomiting, fluid leaking from blood vessels..these kinds of deadly symptoms arise.
Sometimes its becomee fatal, itits causes death [4].

Disease acceleration:
Dengue mainly effected liver as well as the brain. Hepatic dysfunction is a common symptom seen in DENV infection. Hepatocytes and Kupffer cells are prime targets of the DENV virus [12].
In the department of pediatrics, JSS Medical College Hospital, Mysore, India, a study was done to test for testing the hepatic function .They selected select 110 children (below 15 years)with serological-positive serological positive dengue fever as a sample and tested their hepatic function clinically and biochemically (from November 2008 to July 2010) [11]
After statistical analysis, it was found that Hepatic dysfunction occurs more in DHF and DSS group compared to the DF group. 79% had hepatomegaly have seen more common in the DHF (88.5%) and DSS (96%) group than in DF group[11]
Dengue virus carried by Aedes aegypti and transmitted via skin cells. DENV mainly affected the adaptive immune system, including antibody-secreting B include antibody-secreting B cells and cytotoxic T cells. Aedes mosquito transmits the DENV virus from skin cell keratinocytes to a type of dendritic cell called a Langerhans cell. This Langerhans cell activates the innate immune response which activates monocytes and macrophages(WBC), to fight against the virus. Both of these cells has phagocytic abilities,but instead of destroying the dengue virus, both of white blood cells are targeted and infected by the dengue virus. This virus also infects Lymph nodes and bone marrow, the spleen and liver, monocytes in the blood and spread all over the body[10].

Current status of dengue vaccine:
Right now,more or less half of the population in all over the world are infected with four serotypes of dengue virus . According to the report,390 million people infected by dengue infected per year [5].
The first registered dengue vaccine is Dengvaxia (CYD-TDV) which is invented by Sanofi Pasteur in Mexico in December 2015. The live recombinant tetravalent dengue vaccine is based on 17D vaccine strain of yellow fever .firstly its go through a phase III clinical trial with 3 doses series on a 0/6/12 month schedule . The vaccine can encode antigen for the four dengue serotypes ,it has 4 components. It has been registered for use in individuals 9-45 years of age [6].
In Asia & Latin America was conducted the vaccine trial over 30,000 participants aged 2 to 16 years. The vaccine's efficacy of the vaccine against laboratory -confirmed dengue, was 59.2% in the year 2014,2015 and 79.1% against severe dengue .From these data, we can conclude 93% reduction in case of severe dengue and 82% reduction in the hospitalized case for 9 years and above children. Based on the result, licensure was obtained for those aged 9–45 year ,not below 9 years for safety purpose. It was being tested by Sanofi Pasteur both seronegative and seropositive to estimate the long-term safety and efficacy of the vaccine by sero status before prior to vaccination using new diagnostics tools.
In the Philippines where Dengvaxia® was introduced (mainly through school programmes), the seroprevalence was estimated to be at least 85% . That means 85 persons are seropositive within 100 people in that sample population ,who are benefited by dengvaxia. The vaccinated people have a lower risk of severe dengue than the non-vaccinated population[13; 4].

Monoclonal antibody a new therapeutic agent of dengue:
Monoclonal antibody is just a clone of an immune cell. Due to its monovalent affinity they can bind to the same epitope recognized by the parent antibody[7]. Now researcher tries to use both serotype-specific and cross-reactive neutralizing monoclonal antibodies as a therapeutic agent. Like mAb 2E8 which can identify NS1 of all four DENV serotypes. mAb 2E8 is the responsible for the complement-mediated lysis in DENV-infected cells. From the animal(mouse) studies,it was observed that DENV induced prolonged bleeding time is reduced as well as viral antigen expression is also reduced in the skin with the application of mab 2E8. mAb 2E8 provided therapeutic effects against all four serotypes of DENV [8] mAb administration to mice as late as 1 day before severe bleeding still reduced the prolonged bleeding time and hemorrhage. So the administration of a single dose of mAb 2E8 can protect mice against DENV infection and pathological effects .from that experiment we can confer that NS1-specific mAb may be a therapeutic option against dengue disease [8].
The another most advanced candidate for monoclonal antibody is Ab513, developed by Visterra (Cambridge, Massachusetts), was engineered to binds domain III of the E protein of all 4 DENV serotypes. This antibody bind and neutralize multiple genotypes within each of the 4 serotypes, also neutralize DENV in target cells that express Fc gamma receptor (monocytes). This antibody is going for clinical trials before2017.

This monoclonal Ab513 targets a linear epitope which has a potent broadly neutralizing antibodies against the quaternary E protein dimer epitope (EDE) . These antibodies bind to E proteins and act as an inhibitor when the conformational changes occur during viral fusion via endosomal membranes. This antibody may further help to design a therapeutic agent against DENV virions [9].The goal of this vaccine is to develop a potential therapy against dengue in next decade.

II. CONCLUSION:

Dengue fever remains a pressing global health challenge, exacerbated by its resurgence in recent years, particularly during the monsoon season. The disease's diverse clinical presentations, coupled with its impact on vital organs like the liver, underscore the need for comprehensive management strategies. Promising advancements in vaccine development, exemplified by Dengvaxia, and monoclonal antibody therapies offer hope for effective prevention and treatment. However, concerted efforts in surveillance, vector control, and public awareness are crucial to curb transmission. By fostering collaboration and sustained investment in innovative interventions, we can strive towards a future where the burden of dengue fever is significantly reduced, safeguarding the health of communities worldwide.

Declaration: No conflict of interest in between all authors.

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