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Prevalence, Pathogenesis and Identification of Clinical Risk Factors Associated with Dengue Virus (DENV)

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ABSTRACT: Dengue, also called the break bone fever. Dengue disease is caused by dengue virus (DENV) having four categories that escalate by the bite of infected Aedes mosquito's family are Flaviviridae. The infected person shows the signs and symptoms from mild asymptomatic changes with fever to severe deadly dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS). Nearly 2.5- 3 billion people stay in dengue-prone areas with more than 100 million new cases ruled out every year worldwide. Number of Dengue cases has increased tremendous ratio in recent years with sudden risk of the increase in the size of human population. A condition known as viremia (medical term: virus present in blood) occurs due to spread of DENV, which represents high level of viruses in bloodstream of patient. In response the immune system gets activated and produces antibodies against the dengue viral particles, which in turn activates the complement cascade which in combination of the antibodies and WBC get rid of the virus. The cytotoxic T cells (CD8+ T) produced by the body immune system, which identifies and destroy infected cells. Dengue spreads drastically, its virus regress the immunity of body. DENV reduces the bodies' resistance and decreases the Platelets count and Hemoglobin. Fall in blood pressure and bleeding from Nose and Gums, Dehydration can occur. Small blood vessels are fragile, the fluid in the body leaks out, accumulate in the lungs. When there is bleeding, the fluid is accumulated in the stomach it can result to mortality or can be fatal. The DENV-3 infection cause Dengue Viral Hemorrhagic fever (VHFs) which is severe and fatal form of the disease. The main Dengue shock syndrome is the most severe form of Dengue Hemorrhagic fever. Dengue has presently become a complex issue according to pathophysiological, economic and ecologic. In the last 5 decades a number of treatment strategies and plans to control dengue came out in India, but the scientific studies related to various problems of dengue disease have been a limited resource in the centers where treatment was carried out. The key note point to reduce the number of disease related morbidity and mortality has to be carried out by early identification and immediate commencement of proper treatment. © 2022 iGlobal Research and Publishing Foundation. All rights reserved.

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INTRODUCTION

Dengue, a very common, acute disease, affects human population majorly in the under developed countries with poor hygiene. The globally prevalence of dengue has increased dramatically in recent decades. It's a mosquito-borne viral infection found in sub-tropical, tropical climates all over world, mostly in urban & semi-urban areas. Transmission of this virus takes place by female mosquitoes mainly by *Aedes aegypti* (larger) and *Ae albopictus* (lesser) [1, 2]. According to history norm, first epidemic shows in 1635 in West Indies [3]. In India, the first epidemic for dengue was reported in the year 1780 in Chennai and the first proved epidemic of Dengue fever (DF) took place in Kolkata, India in 1963-64. In descriptive of the word "Dengue" comes from the Swahili phrase kadinga pepo, which means "cramp -like seizure". "Break bone fever" called due to symptoms of arthralgia & myalgia [4].

Currently, Dengue, is destined as the most common disease in some category of people or confined to some particular area almost in more than 100 countries which include South-East Asia, Africa, the Eastern Mediterranean, the Americas, and the Western Pacific. Among those, South-East Asia, America & Western Pacific regions are brutally affected with Asia representing ~70% of the global burden of disease (GBD) [2]. Dengue is caused by four different strains. So, it's possible to be affected by this virus more than once in a person's life time. Dengue fever needs urgent & sudden medical care to treat the condition on time. To save entire population from this fatal disease, many researches have been continuing since 1920. But there's no proper licensed specific antiviral medication approved despite of that longer period trials. Recently, as per 2021, In India, Dengue vaccine known as CYD-TDV (Brand name: Dengvaxia) commercially available under with respective recommendation (only to previously affected patients) In March 2021, vaccine candidate TAK-003 accepted by European Medicines Agency (designated for people not previously infected) [5].

CAUSES

Here Four serotype of virus that cause Dengue that's name is DENV-1, DENV-2, DENV-3, DENV-4. Family Flaviviradae is responsible for dengue fever [6]. Dengue is caused by bite of Aedes Aegypti Mosquitoes [7]. The flow of the virus moves from the infected person blood to the mosquito which bites the person (Fig.1). Further, when this infected mosquito bites some healthy person, the virus enters that person's bloodstream and cause Dengue infection. Infected traveller carries the DENV to healthy person. When susceptible plasmid vector is found in a new area, there is risk of whole local transmission Dengue viral infection spreads if a person is infected with the dengue virus, bites the person's skin. In that case the Langerhans cells (LC) which are a type of dendritic cell in the skin who get infected with the dengue virus. Which later produce interferon's which acts as a singling protein that does not allow further spread of the infection. Other infected Langerhans cells (LC) travel to the lymph nodes along with viruses, due to which very high number of cells are infected. A condition known as viremia (medical term: virus present in blood) occurs due to spread of DENV, which represents high level of viruses in bloodstream of patient. In response the immune system get activated and produces antibodies against the dengue viral particles, which in turn activates the complement cascade which in combination of the antibodies and WBC get rid of the virus. The cytotoxic T cells ($CD8^+$ T) produced by the body immune system, which identifies and destroy infected cells [8, 9]. Dengue spreads drastically, its virus regress the immunity of body. DENV reduces the bodies' resistance and decreases the Platelets count and Hemoglobin fall in blood pressure and bleeding from Nose and Gums, Dehydration occurs [10. 11]. Small blood vessels are fragile and are leaky, the fluid in the body leaks out, it accumulate in the lungs. When there is bleeding, the fluid is accumulated in the stomach it can result to mortality or can be fatal. The DENV-3 infection cause Dengue Viral Hemorrhagic fever (VHFs) which is severe and fatal form of the disease. It causes sudden drop in platelets count level and show the bleeding in the Gums [12, 13, 14]. The main Dengue shock syndrome is the most severe form of Dengue Hemorrhagic fever [7, 15]. After the recovery from Dengue fever, the infected person gets the long term immunity to only DENV, but not to other types of virus. There are risk of developing severe Dengue fever a second, third or fourth time.[9, 16, 17]

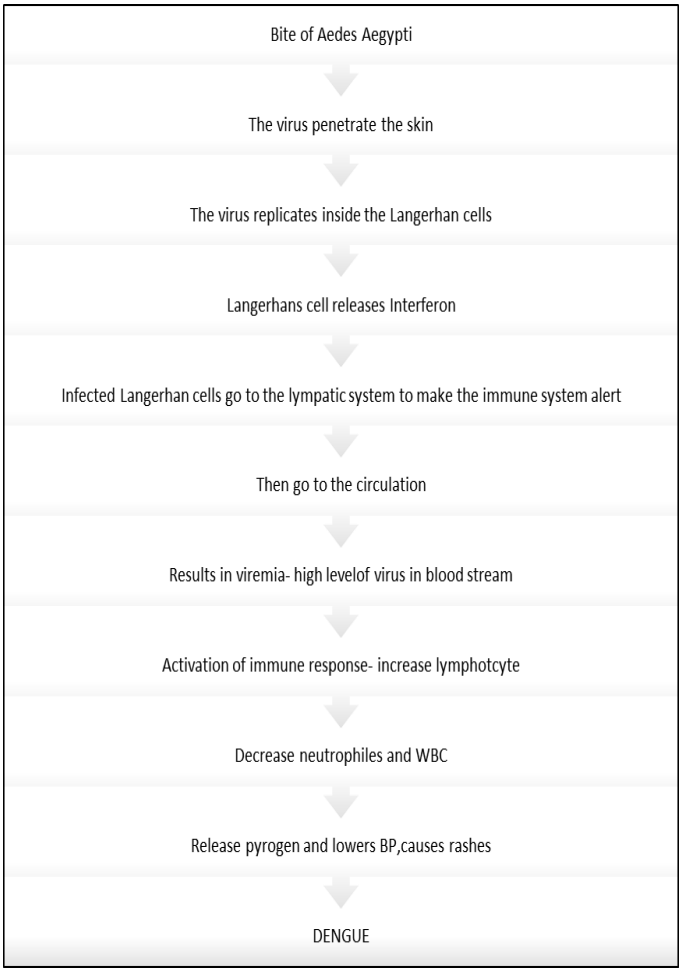

Figure 1: Mode of development of dengue

RISK FACTOR OF DENGUE OF HAEMORRHAGIC FEVER

Human risk factor Age, Sex, Clinical features, Primary infection, Secondary infection, Host response. Virus risk factor Serotype, Genotype. Abiotic risk factor Seasonal distribution, Climatic factor, Environmental factor, Epidemiological risk factor Host (Human & mosquito), Agent (Virus), Ecosystem (Abiotic & Biotic factor) [18, 19, 20].

SIGNS AND SYMPTOMS

Dengue is strong, fever that affects your children, infants & adult but minimum rate of fatality. Dengue symptoms usually start after 10-14 days of the incubation period after the bite of mosquito and symptoms last up to 2-7 days. Dengue should be diagnosed if the high fever of more than 40°C/104°F is persistent which coexist with following symptoms of chills in the febrile phase which usually begin at day 4 to 7 Last for 3 to 7 days [21, 22,]. Fever (Sudden onset & High grade greater than 38.5°C), migraine, Pain behind the Eyes, muscle pain (Myalgias), joint pain (Arthralgias), Vomiting, Nausea, Skin Rash, Febrile phase (other sign & symptoms), Lymphadenopathy, Hepatomegaly, Maculopapular rash (50% of cases, more common in the first Dengue infection, 2-5 days after fever has started), May also have respiratory symptoms, cough, nasal congestion & sore throat, may have leukopenia, thrombocytopenia, transaminitis [23, 24].

SEVERE DENGUE (CRITICAL PHASE)

Onset of the critical phase is from 3-7 days of illness. Small blood vessels are fragile and they have leaks. There is fluid accumulation in the lungs and when the is bleeding, fluid is also accumulated in the stomach which leads to respiratory distress, severe bleeding or organ impairment. Occurs in few subgroup of patient & More likely to found in the following cases: secondary infection (other serotype dengue), particularly within 18 month of firstly (Primary) infection, Patients with other medical Commodities, Occur after effervescence (3-7days), Last 24-48 hours, Thrombocytopenia (can be severe) bleeding (menorrhagia, hematochezia, melena, hematemesis, epistaxis, "Dengue hemorrhagic Fever"),Vascular Leakage, shock (included all like acute liver failure, kidney injury, CNS involvement, "Dengue Shock Syndrome", show Severe Abdominal pain, apnoea, gingivitis, Restlessness, Persistent Vomiting, hematemesis). [25] The patients in the critical phase need proper medical attention and care to avoid complications and risk of death. Some other symptoms a patient may experience including: Shaking, shivering, feeling very cold, feeling hot the time of fever breaking or after taking fever medication, symptoms of illness like cough, intense exhaustion, sometimes ear-ache may have ear infection. [26, 27]

PATHOPHYSIOLOGY OF DENGUE VIRUS

Dengue virus genetic material is RNA and it's externally covered with enveloped protein (Glycoprotein) and surrounded by a lipid bilayer envelop. Inner to the envelope there is a capsid shell containing the virus RNA genome. Dengue virus targets the immune cells i.e., cell surface receptor molecule which are of two types - Cognate receptor - Normal infection, FC-receptor -Antibody dependent enhancement. When the Aedes aegypti mosquito bites, the virus may enter into the blood stream or in epidermis or dermis layer of skin. [28, 29, 30]

STAGES OF DENGUE VIRUS REPLICATION

Fusion

Viral effect begins in the skin, when virus binds to cognate receptor or heparin sulphate and triggers endocytosis, forms a bubble-like structure called "Endosome". The virus is taken inside the cell by endosome and transports it deep inside the cell by endosome and transports it deep into the cell [30].

Disassembly

As the endosome enter deeper into the cell, the proton pumps i.e., endosome membrane gains a negative charge, the pH gets lowered and the environment become acidic interiorly the virus respond to lower pH. The virus detects these changes and conformation of the enveloped protein and form spike like structure. The tips of the spike are hydrophobic which allows it to penetrate the endosome membrane and breaks the endosome by fusing its viral membrane and releases the Dengue nucleocapsid into cytoplasm, the nucleocapsid then releases viral RNA genome [31, 32, 33].

Viral Replication and Assembly

The virus transits the host replication machinery and virus make copies of itself and translates RNA by Rough Endoplasmic Reticulum and results in polypeptide, which is cut to form ten Dengue protein.

Maturation and Release

The membrane of Endoplasmic Reticulum is used to flow the virus nucleocapsid. The immature virus goes through the Golgi and they are released from the cell, when they are matured form [34, 35].

Transmission

Dengue virus spread to community of people through the bites of infected Aedes species mosquitoes (*Ae. aegypti* or *Ae. albopictus*). These are similar to mosquito's responsible Zika and Chikungunya viruses. Mosquito to human transmission of the infection [36]. The virus is infection transfer to human, when female mosquito needs to drink blood for developing their eggs [37].

Egg

The female mosquito lays egg over the still water bodies; some species prefer natural bodies of water like ponds, stored water in container like bucket, pots or discarded tyres etc. Each female mosquito lays multiple numbers of eggs, which take two days to develop. They develop rapidly in bit high temperatures. Once mosquitos develop from its egg it enters the next development phase i.e., the larva of the life cycle.

Larva

The larva grows under water and feed over algae, other microorganism and plantings present in the water. Larva aerobic and they inhale through a tube present in their tail known as `siphon'. These larvae upturned and twig their

siphons overhead the water to get air. The larva phase is for 4 to 14 days which depends on temperature and strains. The larva enters the third stage, after development and shedding its skin several times.

Pupa

The pupa is the phase where the virus doesn't eat but stays near the water surface only for the air. Maximum energy is required for turning into adult form.

Adult

After 1 to 4 days, the mosquito shed its skin and turns into an adult form. After which, it mates both female and male feed on nectar from plants but females also need to drink blood from animal (such as human) in order to make eggs. It's at this stage that a female mosquito can transmit diseases. First the female mosquito bites and drinks blood from an individual infected with a pathogen, such as virus or parasite. The pathogen travels with the blood to an organ in the mosquito this condition called midgut Loop. After replicating in the midgut loop, the pathogen spreads to the mosquitoes' other organs, including its salivary glands. Whenever mosquito bites another individual, it can then transmit the pathogen to that individual and infect them with disease [38, 31].

HUMAN TO MOSQUITO TRANSMISSION

There are mosquitoes that don't have Dengue virus pre-existing within themselves, if such mosquitoes bite the infected people, then the DENV can be transmitted to the mosquito that can become the further carrier and can further infect the new asymptomatic persons [32].

FROM MOTHER TO CHILD

In a Pregnant condition a woman who is pregnant and infected with Dengue virus in this condition virus can pass the virus to the foetus or stay till delivery. Very few cases have been reported where dengue can spread by lactation. Also, the infection can be transmitted by means of infected blood, laboratory or health care settling exposure [39, 40].

DIAGNOSIS

Detection of dengue takes place by various methods:

Virus Isolation: It's a traditional diagnostic method to detect DENV infection. It's done by collecting blood samples from infected patients.

RT-PCR: It's a molecular method. Nucleic acid hybridization plays a great role to diagnose DENV.

Serology: Many approaches to identification of serological diagnosis used serological Assay, including hem-agglutination inhibition (HI) assays which are used to titrate the antibody response to a viral infection, western bloating, dot-blot assay, IgM-IgG antibody-capture ELISAs, NS1 that means Dengue virus.

Antigen capture: The viral proteins NS1, an identical diagnostic target as its secretion from affected parts, Combined Approaches: A single method for detection can't be possible used for diagnose DENV as there are different phases of replication and development of DENV. Detection of NS 1 antigen is difficult. Combination of NS1 method along with antibodies like IgM, IgG is the best method with good outcome for identification of positive dengue diagnosis. There are **many diagnostic kits available for taking advantage for the Sudden Treatment [41, 42].**

PREVENTION & CONTROL

Dengue patients must be safe from getting mosquito bites in the first week of illness. Virus used to circulate in the blood in this situation and transmitting of virus to new uninfected mosquitoes take place, that infects other people. Transmission of the virus by Aedes mosquito should be prevented. Breeding of vectors in human habitation is at its stake [17].

Mosquito breeding prevention

By environmental method prevention of egg-laying methods of mosquito, Disposal of solid wastes, removal of artificial man-made habitats which may hold water, Maintenance of hygiene condition in household storage of water in containers regularly, proper precautions should be taken when the water is stored in the outdoor facilities [43].

Personal protection from mosquito biting

Minimising skin exposure to mosquito by wearing proper clothes, action to reduce human-vector contact, using of protection measures like coils, vaporizer, sprays, windows screens, resistant's at home/ work place/ school, mosquito net during sleeping in daytime [43].

Community engagement

Alerting the community about its risk factors, Vector controlling programmes with the community, accurate knowledge spreading and improving participation in dengue eradication, have the proper information about the Active dengue cases mosquito should be done.

Chemical control

By using larvicides like organophosphates, biopesticides, adulticides

Biological control and Treatment

Introduction of organisms that can prey upon example-larvivorous fish, predatory copepods, viviparous species *Poecilia reticulata* [44, 45, 46, 47, 48]. Treatment As there's no particular antiviral treatment for the Dengue virus, the WHO recommended guidelines criteria strengthen upon: Fluid administration & symptomatic treatment [49]. Only symptomatic treatment is Acetaminophen (named as Paracetamol outside of US), which acts as an Antipyretic & Analgesic. Whereas Non-steroidal anti-inflammatory drugs (NSAIDS) and Aspirins are prohibited because of their antiplatelet activity, which lead to thrombocytopenia-related bleeding. As per patient's condition fluid administration is determined. In case of moderate situation oral administration is sufficient, but in critical situation patients should have been looked over frequently [50, 51]. A number of Anti-dengue therapeutic medicines (addressing viral components & host) for e.g., carbazochrome sodium sulfonate for capillary leakage prevention & brefeldin (produced by the fungus penicillium brefeldianum), ketotifen (mast cell stabilizers and a non-competitive antihistamine. At the endothelium oral drug prednisolone acts as an anti-inflammatory medication, while lovastatin which are the HMG CoA reductase inhibitors (statins) works as an antiviral & anti-inflammatory [52]. In clinical studies, Anti-DENV drugs like chloroquine

(inhibits virus-host membrane fusion), sofosbuvir (DENV 2 polymerase inhibitor), celgosivir-glucosidase l inhibitor & balapiravin nucleoside analogue also have been analysed. There are so many restrictions to overcome in improving particular anti-dengue therapy. Inflammatory (proinflammatory) cytokine responses in DENV infected mice modifies by Sunitinib/erlotinib combination. Flavonoid like Luteolin inhibits the proprotein convertase furin, which restricts the replication of DENV. Some cytokines and interleukin parameters such as TNF-alfa, IFN-gamma, TGF-beta1, IL-4, IL-6, IL-12 & IL-17 which are reduced by a recently established therapeutic miRNA approach, while several coagulants factors increased post-treatment. Methadichol helps the dengue fever patients with falling platelets recovery in a few days [53]. Antibiotic called as Minocycline blocks the demonstration of intracellular envelope proteins, the RNA production & formation of infectious virion within cells. Dengue treatment must have pan-serotype activity, cures symptoms fast, tolerated with little toxicity, comfortable in distribution & with minimal drug interactions, safe for all including pregnant women (having co-morbidities) & child [54,29]. So, the process of anti -dengue therapy is absolutely a challenging task. It's difficult to find an inhibitor which can works against all four DENV serotypes (due to difference in significant amino acid sequence diversity). Producing antibodies equally protective against all serotype is not easy, intravenous administration is favoured. There's no real animal model which resembles human DENV pathogenesis, hindering progress toward a secure & efficient treatment [55, 56].

VACCINE

A vaccine used in Dengue prevention named is DENGVAXIA (brand name) is marketed in some countries for people 9 to 45 years [57, 58]. It's a mixture of CYD-1, CYD-2, CYD-3, CYD-4, which are live attenuated tetravalent chimeric vaccine viruses, produced by using Vero cells. It's also known as CYD-TDV [59, 60, 61]. Recently in India, world's first dengue DNA vaccine was approved for use. That's developed by Ahmedabad-based Zydus Cadila, ZyCOV-D. This DNA technology-based vaccine candidate was tested on mice & succeeded with good response [62]. Simple and effective remedies: Natural home remedies usually accelerate healing process and replenish body by supplying necessary nutrients as per need. Papaya leaves play one of the best roles to fight dengue infection. Otherwise, turmeric, black pepper used as immune booster. Tulsi, pomegranate, pumpkin, beetroot, citrus fruits like lemon, kiwi are wonderful super foods to fight dengue [63].

DISCUSSION AND CONCLUSION

Projecting the future of dengue requires a systematic consideration of assumptions and uncertainties, which will facilitate the development of tailored climate change adaptation strategies to manage dengue. Dengue has become the major problem effecting the population of many under developed countries including India. According to the WHO India, the number of cases in Kerala, India has 2624 cases. While in Maharashtra, Tamil Nādu have cases between 2000—2500. Other states like Karnataka, Rajasthan got cases between 0 – 2000 but the death rate is very negligible in all the states. The number of cases has been found to be more in the teenage and the children. The maximum number of cases has reported in the rainy season and particularly in the lower-class areas like slum where the water clogging is more and the development, reproduction and transmission of the DENV is more in this area [64].

Though dengue fever is usually self-limiting disease, lack of exact monitoring and sufficient volume replacement may lead to fatal outcome. As it's none but an endemic, controlling must be a community effort. Meanwhile International collaboration is encouraged. Proper care is to be taken for vector control methods, as the spread of number cases throughout the year points to the limited time transmission of dengue virus. As, during epidemic and nonepidemic years, dengue infections are mostly prominent in the rainy and post rainy season, so proper precautions should be taken before the start of rainy both at the personal household level and by the municipal corporation of India. As a conclusion, advanced approaches are required to make proper elucidation which provides information in the article. In our future research, further factors considered are non-climatic factors, effect of different age group and population, socio-economic factors, and other risk factors in the occurrence of dengue cases, will be studied. Emphasizing its influence National anti-dengue day celebration takes place in ***India on 16th May. Theme of 2021:"Effective community engagement; key to dengue control".***

FUTURE DIRECTIONS

Accurately protruding the future of dengue by the climate change would support the health sector to take timely actions to protect the public from dengue in the future. Certain points have to be taken in consideration like incorporating the socio demographic factors into the bulging would give us more accurate judgements of dengue future. While some time the temperature in particular area might not be the most significant climatic factor causing the transmission of dengue. While some time apart from climatic changes the factors like the presence of *A. aegypti and A. albopictus*, also leads to the transmission of dengue. Other reasons like some dengue control strategies may be effective in neutralizing its spread in some areas. Routine communication between the research community and policy makers can help in control of transmission of dengue, calling for concerted efforts to be made in the future. [2]

AUTHORS CONTRIBUTION

All the authors have equally contributed in conceiving this research and designing of experiments; all authors have participated in the design and interpretation of the data; experiments and analysis; writing the paper and participated in the revisions of it. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors Mohsina F.P, Faheem IP, Mohammad Mukim, Shahana Tabassum,Shoheb tarkash , Irshad shah and Abhinandan Patil declare that there is no conflict of interest.

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