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A Review on Chikungunya and Suggesting a Hypothesis of Nano-based Drug Delivery

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Chikungunya gained insight by the 2006 epidemic seen in India and Islands of the Indian Ocean and since then it has become a major disease with no commercial vaccine available. A number of epidemiological studies have been done to trace back the evolution of the Chikungunya Virus (CHIKV) and the reasons which led to the re-emergence of the epidemic & the spread of disease across borders which pose threat in the future as seen before. In this review, based on epidemiological data available several parameters of clinical importance are being analysed and a hypothetical cure is proposed based on the mechanism of action of virus and its life cycle and the use of nano-encapsulation for efficient delivery of the drug.

Key words: Chikungunya, CHIKV, Epidemiology, Nano-encapsulation.

Chikungunya disease is caused by Chikungunya virus (CHIKV) which is an Arbovirus and is primarily transmitted via the bite of a mosquito infected with the virus. Chikungunya virus belongs to the genus *Alphavirus* and the family *Togaviridae*. It was first isolated in a febrile patient's blood in Tanzania in 1953 and Chikungunya derives its name from "*that which bends up*"[1]. After CHIKV infection, illness such as fever is caused and then comes the acute febrile phase whose duration is for 2-5 days, then it is followed by a long arthralgia disease in which the joints of the extremities are affected. No treatment is specifically available for Chikungunya only care can be taken which is based on the symptoms showcased by the disease. This disease is a re-emergence since 2004; the virus has spread into locations, such as Europe, and has led to millions of cases of disease throughout countries in and around the Indian Ocean.In last 40 years, CHIK virus has one of the largest reported outbreaks[2]. By the epidemiological studies done so far, it is reported that Chikungunya is widely distributed in Africa, Southeast Asia and India and cases are regularly reported. Millions of cases have been reported since the outbreak in January 2005 in India. There are two types of life cycle associated with chikungunya virus viz. Sylvactic cycle and urban cycle. Sylvactic cycle involve primates as host whereas urban cycle involves Man as host. Chikungunya is believed to have been originated in Africa where it has maintained in 'sylvatic cycle' involving wild

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primates and forest dwelling mosquitoes such as *Aedes furcifer*, *Ae.luteocephalus,* or *Ae.taylori*. The subsequent introduction that happened was in Asia where it got transmitted from human to human mainly by *Ae. aegypti;* lesser extent by *Ae. albopictus through* an urban transmission cycle[3].

In this review, epidemiology of chikungunya in India is focused and important conclusions are derived from them like that of re-emergence, problems in diagnosis and treatment. Based on which a hypothetical cure using nano-encapsulated drug has been proposed.

Epidemiology

Target Group

Affects all age groups in which 50% are over the age of 65 years; higher mortality rate was reported in this group. In case of children, only severe illness occurs[3]. World Health Organization (WHO) has not offered exact figures but the reports stated the disease has affected throughout the world every year[4].

Spread of disease worldwide

The virus may spread by various mechanisms but worldwide spread is accounted due to the travellers which carries the vector or virus from endemic areas[5-6]. This is evident from the number of reported cases in UK which were 79 in 2010 - an increase by 34% compared with 2009 (the majority of which was imported from India).[7] Same has also been reported in south-eastern France and Italy.[8] Another exceptionally virulent outbreak worth mentioning was in the French Island of La Reunion in the Indian Ocean, in 2005 and 2006 also affected neighbouring Islands, including Mauritius[5].

From the previously recorded data, we can arrive at an important conclusion that we cannot stick with the same set of symptoms to diagnose the disease due to the continuous mutations associated with CHIKV[9]. So, these should be studied and proper differential diagnostic procedures should be followed to bring down the number of affected cases which otherwise can again become an epidemic in future.

Recent Outbreaks of Chikungunya in India

In January 2013, Chikungunya was resurfaced in Ganjam District of Odhisa.The same district reported over 500 dengue cases in 2012, in which around 30 people were from Boxipalli district has suffered from Chikungunya[11]. There are 4 or more cases in 2013 in Ganjam District. Chikungunya cases keep appearing in diverse locations like the Ganjam district.Cases of Malaria and Chikungunya keep appearing sporadically in Pune. Many cases have appeared since January 2013, around 11 cases of Malaria infection and 8 cases of Chikungunya[12]. According to the scientists in Delhi, Chikungunya virus is mutating into a deadly strain[13]. India today reports witnessed Chikungunya outbreak just after Dengue in 2010[13]. Since its re-emergence from 2004, intensity of infection is increased from 45 per cent to 63 per cent attacks in several areas.Since no commercial vaccine is available and *Aedes aegypti* thrives in India and overlapping of symptoms with Dengue leads to wrong diagnosis and treatment because of which there can be more likely cases in the near future.

From the reports[10], Chikungunya is predominantly a non-fatal disease but can lead to mortality only in cases of elderly people. The major clinical infestations of Chikungunya are the post effects on the affected population. *Polyarthralgia* can last up to many years beyond the acute stage which forms the chronic stage of Chikungunya. The explanations for the involvement of skin connective tissues, muscles and joints is that CHIKV attack fibroblasts 95% of infected adults show symptoms after infection. Anti-CHIKV IgM is still present in 40% of patients after 18 months from infection[3].

Re-emergence of Chikungunya

Chikungunya fever was a disease of less impact, it was easily overcome by the host defence mechanism but the disease re-emergence in the Islands of the Indian Ocean was due to the mutation in the virus to overcome the host- defence barrier. The genotypic variations in different strains of CHIKV which are mainly divided into three but recently due to mutations new strains are developed. Amino acid differences between the current pandemic and pre-existing African and Asian genotype CHIKV are reported previously[14]. Amino acid differences have been identified in non structural and structural proteins.

Problems associated with Chikungunya diagnosis

Diagnosis of Chikungunya has problems associated with it due to the clinical features that match with that of Dengue Fever. Several clinical features like Fever, asthenia, myalgia,

rash and hypotension were found common in both chikungunya and dengue fever. (Thiboutot *et al*, 2010). Due to the problem in diagnosis, treatment gets delayed which results in worsening of the situation and chances of a disease to become an epidemic.

Treatment methods available

Treatment is done to cure or prevent disease. There has been no effective vaccine developed to prevent Chikungunya. In 2000, many clinical trials for the Vaccine were done, but were not successful due to discontinuation of funding for the project. To relieve the symptoms caused by the Chikungunya like fever and joint pain, commonly used drug is Paracetamol. In unresolved arthritis, when there is no relief by use of NSAIDs(Non-Steroidal Anti-Inflammatory Drugs) and Aspirins then Chloroquine Phosphate is used which is bound to give some promising results. DNA vaccine and virus like particle vector are on its clinical trial phase[4]. A promising solution found by Homology Modeling and Docking[15] to find a compound that can act on Protein nsP2 (non- structural Protein) Protease which is the main enzyme responsible for CHIKV replication. After carrying out docking studies it was found that LIGAND_4 (*N-butyl-9-[3,4-dipropoxy-5-(propoxymethyl)oxolan-2-yl] purin-6-amine*) formed the most stable interaction with nsP2 Protease which will result in stopping replication of CHIKV. So, LIGAND_4 can serve as a potential inhibitor for the drug target nsP2protease in CHIKV[15].

Hypothetical Cure Possible Using Nano-encapsulated material for Drug delivery

Based on the mechanism of replication and CHIKV's life cycle, a hypothetical cure can be proposed at different stages which can block the pathway resulting in inactivation of virus multiplication and pathological effect. CHIKV is characterised with a replication cycle which becomes complex after infecting the host, making its genome more susceptible to mutations[3]. The problem associated for coming up with a vaccine is due to the mutations which can occur in the complex process of replication as shown above. Although many attempts have been made to develop vaccine but there's no worldwide accepted vaccine currently[8].

One hypothetical cure suggested is use of nano-encapsulated materials[6] which will target the specific viral cells only preventing them to replicate rendering fewer side effects as seen in conventional methods of treatment as immune response will be suppressed. Since the major problems faced by the affected individuals is due to the self-immune system which leads to painful long term effects[1] so curbing the disease at primary stage is utmost necessary which can most effectively achieved by a vaccine but since developing vaccine for a continuously mutating virus is difficult so we can search for other technologies to bring down the after effects faced by affected individuals. Like the compound suggested by Bora *et al,* potential inhibitor of nsP2 Protease can be used as a drug which can be encapsulated by nanoparticles for specific and effective delivery of the substance. A number of nano-carriers can be used for the drug delivery viz. Micelles, Microspheres, SLN, NLC, Liposomes, Dendrimers, Emulsions, Vesicles, Polymeric Nanoparticles, Cyclodextrin Based Systems, etc[16].

CONCLUSION

Chikungunya re-emergence and recent outbreaks affected a large number of populations. 2006 Epidemic whose origin was in Indian Ocean islands further spread throughout the globe via travellers and other mechanical vectors. As a result of this epidemic NIAID (National Institute of Allergy and Infectious diseases) has put CHIKV in Category C of pathogens which comes in the same category as that of the SARS (Severe Acute Respiratory Syndrome) and influenza viruses. The clinical complications of diagnosis, treatment and the mutation in the virus were some of the main reasons of the epidemic as found by the epidemiological studies and experimental studies. Also several other important parameters which can be found out from epidemiological studies helps in learning lessons and stay prepared with preventive measures for future. Also, there exists no acceptable vaccine till date for Chikungunya due to the complexity of the viral replication method & changing antigenicity to overcome host-defence barrier. Painful after effects (like polyarthralgia, joint pains) suffered by patients lasts for months so for this a hypothetical solution is possible in drug delivery system based on recent technologies like Nano-encapsulated materials so that only specific

viral cells are targeted for stopping their replication & growth as a result of which rigorous immune response is minimized.

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