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ADVANCE REVIEW OF CHIKUNGUNYA

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ABSTRACT

Chikungunya virus (CHIKV) is a mosquito-borne alpha virus that induces in humans a disease characterized by fever, rash, and pain in muscles and joints. The virus causing Chikungunya disease was identified over 50 years ago; however, because the disease appeared only in developing countries, little research on it has been done. CHIKV infection in these animals recapitulated the viral, clinical, and pathological features observed in human disease. In the macaques, long-term CHIKV infection was observed in joints, muscles, lymphoid organs, and liver, which could explain the long-lasting CHIKV disease symptoms observed in humans. In addition, the study identified macrophages as the main cellular reservoirs during the late stages of CHIKV infection in vivo.

Keywords: *Chikungunya*, CHIKV, *Aedes* mosquitoes, Alpha virus, arbovirus.

INTRODUCTION

Chikungunya virus (CHIKV) is a mosquito-borne alphavirus (family *Togaviridae*) first described in Africa in 1953.¹ Chikungunya symptoms include severe and persistent joint pain, body rash, headache and fever. Initial symptoms are similar to dengue fever. It is usually NOT life threatening. But the joint pains can last for a long time and full recovery may take months. Usually patient gets lifelong immunity from infection and hence re-infection is very rare. Chikungunya (in the Makonde language "that which bends up") virus (CHIKV) is an insectborne

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Virus, of the genus *Alphavirus*, that is transmitted to humans by virus-carrying *Aedes* mosquitoes.² There have been recent breakouts of CHIKV associated with severe illness. CHIKV causes an illness with symptoms similar to dengue fever. CHIKV manifests itself with an acute febrile phase of the illness lasting only two to five days, followed by a prolonged arthralgic disease that affects the joints of the extremities. The pain associated with CHIKV infection of the joints persists for weeks or months, or in some cases years.^{3,4}

Signs and symptoms:-

The incubation period of Chikungunya (also called as Chicken Guinea) disease is from two to five days. Symptoms of the disease include a fever up to 40 °C (104 °F), a petechial or maculopapular rash of the trunk and occasionally the limbs, and arthralgia or arthritis affecting multiple joints.⁵ Other nonspecific symptoms can include headache, conjunctival infection, and slight photophobia. Typically, the fever lasts for two days and then ends abruptly. However, other symptoms—namely joint pain, intense headache, insomnia and an extreme degree of prostration—last for a variable period; usually for about 5 to 7 days.⁴ Patients have complained of joint pains for much longer time periods; some as long as 2 years, depending on their age.^{6,7}

Diagnosis:-



Figure 1: Common laboratory tests for chikungunya include RT-PCR, virus isolation, and serological tests

- Virus isolation provides the most definitive diagnosis but takes 1–2 weeks for completion and must be carried out in Biosafety level 3 laboratories.⁸ The technique involves exposing specific cell lines to samples from whole blood and identifying chikungunya virus-specific responses.
- RT-PCR using nested primer pairs to amplify several Chikungunya-specific genes from whole blood. Results can be determined in 1–2 days.⁸

- Preliminary diagnosis is often based on clinical features, places and dates of travel (if the person is from a non-endemic country or area), activities, and epidemiologic history of the location where infection occurred.
- Laboratory diagnosis of *arboviral* infections is generally accomplished by testing the blood or cerebrospinal fluid, or CSF (the fluid that surrounds the brain and spinal column) to detect virus-specific antibodies (Figure 1).
- During an acute infection, certain viruses can be isolated through culture or detected by nucleic acid amplification, or PCR (a technique that makes multiple copies of the viral genetic material, making it easier to detect).
- In fatal cases, nucleic acid amplification (PCR), histopathology using immunohistochemistry (a technique that uses antibodies to identify proteins in diseased cells), and virus culture of autopsy tissues can also be useful. Only a few state laboratories or other specialized laboratories, including those at the Centers for Disease Control and Prevention (CDC), are capable of doing this specialized testing.
- Serological diagnosis requires a larger amount of blood than the other methods and uses an ELISA assay to measure Chikungunya-specific IgM levels. Results require 2–3 days and false positives can occur with infection via other related viruses such as O'nyong'nyong virus and Semliki Forest Virus.⁸

Causes:-

Chikungunya fever is caused by a virus which belongs to the genus *Alphavirus*, in the family *Togaviridae*. *Chikungunya virus* is indigenous to tropical Africa and Asia, where it is transmitted to humans by the bite of infected mosquitoes, usually of the genus *Aedes*. Chikungunya virus belongs to alphavirus genus of the *Togaviridae* family. It is an "Arbovirus" (Ar-arthropod, bo-borne). CHIK fever epidemics are sustained by human-mosquito-human transmission. The word "chikungunya" is thought to derive from description in local dialect of the contorted posture of patients afflicted with the severe joint pain associated with this disease.⁹ The main virus reservoirs are monkeys, but other species can also be affected, including humans.¹⁰

Prevention:-

The best way to prevent chikungunya virus infection is to avoid mosquito bites. There is no vaccine or preventive drug currently available. Prevention tips are similar to those for other viral diseases transmitted by mosquitoes, such as dengue or West Nile. The following can help avoid mosquito bites:

- Using insect repellent containing DEET(N,N-Diethyl-meta-toluamide; also known as N,N'-Diethyl-3-methylbenzamide or NNDB), Picaridin (also known as icaridin and KBR3023), oil of lemon eucalyptus PMD(p-menthane-3,8-diol, a substance derived from the lemon eucalyptus tree), or IR3535 on exposed skin.
 - Wearing long sleeves and pants (ideally treat clothes with permethrin or another repellent)
 - Having secure screens on windows and doors to keep mosquitoes out
 - Getting rid of mosquito sources in the yard by emptying standing water from flower pots, buckets, and barrels
 - Changing the water in pet dishes and replacing the water in bird baths weekly Drilling holes in tire swings so water drains out
 - Keeping children's wading pools empty and turned on their sides when they aren't being used
- Additionally, a person with chikungunya fever can reduce the risk of spreading the fever by limiting exposure to mosquito bites. Mosquito repellents help discourage mosquito bites, as does limiting exposure to mosquitoes (by staying indoors or using screens or mosquito nets).

Transmission:-

The chikungunya virus is transmitted from human to human by the bites of infected female mosquitoes(Figure 2)Most commonly, the mosquitoes involved are *Aedes aegypti* and *Aedes albopictus*, two species which can also transmit other mosquito-borne viruses, including dengue and chikungunya. These mosquitoes can be found biting throughout daylight hours, although there may be peaks of activity in the early morning and late afternoon. Both species are found biting outdoors, but *Ae. aegypti* will also readily feed indoors.

Chikungunya viruses are transmitted to humans through the bites of infective female *Aedes* mosquitoes. The mosquitoes generally acquire the virus while feeding on the blood of an infected person. After virus incubation for eight to ten days, an infected mosquito is capable, during probing and blood feeding, of transmitting the virus for the rest of its life. There is no way to tell if a mosquito is carrying the chikungunya virus. Infected female mosquitoes may also transmit the virus to their offspring by transovarial (via the eggs) transmission, but the role of this in sustaining transmission of the virus to humans has not yet been defined.¹¹

Infected humans are the main carriers and multipliers of the virus, and serving as a source of the virus for uninfected mosquitoes. The virus circulates in the blood of infected humans for several days, at approximately the same time that they have chikungunya fever (see also clinical symptoms). *Aedes* mosquitoes may acquire the virus when they feed on an individual during this

period. In parts of Asia and Africa, the transmission cycle may also involve jungle primates that act as a reservoir for the virus.

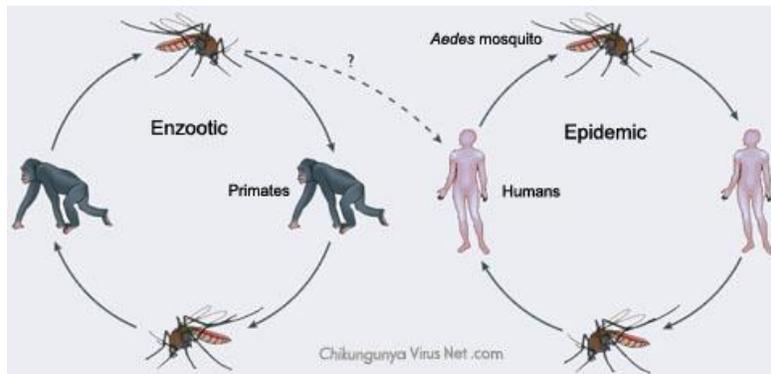


Figure2: Transmission of chikungunya viruses

Treatment:-

There are no specific treatments for Chikungunya. There is no vaccine currently available. A Phase II vaccine trial, sponsored by the US Government and published in the American Journal of Tropical Medicine and Hygiene in 2000, used a live, attenuated virus, developing viral resistance in 98% of those tested after 28 days and 85% still showed resistance after one year.¹¹ There is no antiviral drug or medicine specifically for Chikungunya. But since chikungunya is cured by immune system in almost all cases there is no need to worry. Treatment usually is for the symptoms and include taking sufficient rest, taking more fluid food and medicines to relieve pain (paracetamol for example). Aspirin should be avoided. Alternative medical systems such as ayurveda and homeopathy has specific treatments for Chikungunya. Many of these treatments are helpful in reducing the symptoms especially the joint pain. A serological test for Chikungunya is available from the University of Malaya in Kuala Lumpur, icul. Chloroquine is gaining ground as a possible treatment for the symptoms associated with Chikungunya, and as an anti-inflammatory agent to combat the arthritis associated with Chikungunya virus. Unpublished studies in cell culture and monkeys show no effect of chloroquine treatment on reduction of chikungunya disease. The fact sheet on Chikungunya advises against using aspirin, ibuprofen, naproxen and other NSAIDs that are recommended for arthritic pain and fever.¹⁰

Vaccine development:-

A virus-like particle based vaccine has protected monkeys from Chikungunya virus infection, and passive immunization from these monkeys protected immunodeficient mice against exposure to a dose of virus that would otherwise be lethal, demonstrating that the humoral response was highly protective.¹²

A DNA vaccine candidate is also being tested for Chikungunya virus. The vaccine cassette was designed based on CHIKV Capsid and Envelope specific consensus sequences with several modifications, including codon optimization, RNA optimization, the addition of a Kozak sequence, and a substituted immunoglobulin E leader sequence. These constructs induced humoral and cellular immune responses in mice.¹³

Passive immunity:-

Antibodies isolated from patients recovering from Chikungunya fever have been shown to protect mice from infection.¹⁴

Prognosis:-

Recovery from the disease varies by age. Younger patients recover within 5 to 15 days; middle-aged patients recover in 1 to 2.5 months. Recovery is longer for the elderly. The severity of the disease as well as its duration is less in younger patients and pregnant women. In pregnant women, no untoward effects are noticed after the infection. Ocular inflammation from Chikungunya may present as iridocyclitis, and have retinal lesions as well.¹⁵

Pedal oedema (swelling of legs) is observed in many patients, the cause of which remains obscure as it is not related to any cardiovascular, renal or hepatic abnormalities.

Epidemiology:-

Chikungunya virus is an alphavirus closely related to the O'nyong'nyong virus¹⁶, the Ross River virus in Australia, and the viruses that cause eastern equine encephalitis and western equine encephalitis.¹⁷ Three genotypes of this virus have been described: West African, East/Central/South African and Asian genotypes.¹⁸



Figure3: The *Aedes aegypti* mosquito biting a person

Chikungunya is generally spread through bites from *Aedes aegypti* mosquitoes, but recent research by the Pasteur Institute in Paris has suggested that Chikungunya virus strains in the 2005-2006(Figure3). Reunion Island outbreak incurred a mutation that facilitated transmission by *Aedes albopictus* (Tiger mosquito).¹⁹ Concurrent studies by arbovirologists at the University

of Texas Medical Branch in Galveston, Texas, confirmed definitively that enhanced chikungunya virus infection of *Aedes albopictus* was caused by a point mutation in one of the viral envelope genes (E1).²⁰

In Africa, chikungunya is spread via a sylvatic cycle in which the virus largely resides in other primates in between human outbreaks.¹⁷ On 28 May 2009 in Changwat Trang of Thailand where the virus is endemic, the provincial hospital decided to deliver by Caesarean section a male baby from his Chikungunya-infected mother—Khwanruethai Sutmueang, A Trang native—in order to prevent mother-fetus virus transmission. However, after delivering the baby, the physicians discovered that the baby was infected with Chikungunya virus, and put him into intensive care because the infection had left the baby unable to breathe by himself or to drink milk. The physicians presumed that Chikungunya virus might be able to be transmitted from a mother to her foetus; however, there is no laboratory confirmation for this presumption.²¹

Chikungunya virus in children:-

At the beginning of the Reunion epidemic the attack rate was proportional to age. The attack rate in children approached that observed in adults more than 18% of all children with suspected chikungunya virus infection had been hospitalised, compared with 40% of adults (data from Observatoire Regional de la Sante de La Reunion). A number of differential diagnoses must be considered in infants less than 3 months old, and lumbar puncture is often justified. Bullous rash seems frequent in children (Figure 4), and Chikungunya virus may be found by PCR in blister fluid (Figure 5).



Figure 4 :Rash and bullous cutaneous manifestations frequently



Figure 5: (Chikungunya virus can be detected by PCR in blister fluid) observed in children with Chikungunya virus

CHIKUNGUNYA IN PREGNANCY AND IN NEWBORN BABIES:-

Chikungunya virus can infect a woman during pregnancy. She would have symptoms similar to those of any woman. Most infections during pregnancy do not result in the fetus getting infected with the virus. It is only during delivery that chances of the fetus or child being infected with the virus increase. In rare cases, abortions caused by chikungunya at the time of the third trimester have been reported. Currently, there have been no reports that suggest any transmission of chikungunya virus through breast milk after being infected with chikunguniya during pregnancy.

A research was carried out in Reunion Island, France to evaluate the effect on the fetus and newborn babies of pregnant women infected with chikungunya.²² There was an outbreak of chikungunya in 2005-06 on the island. The first reported case of mother-to-child transfer of the chikungunya virus was during this outbreak. The study was carried out in 2006. There were around 1,400 pregnant women, out of which 628 were uninfected and 658 were infected with Chikungunya virus during pregnancy.²³ Out of the 1400 odd women, 27 women were infected before conceiving, and the infection date of 87 women was unknown. Out of the 658 women infected with chikungunya virus during pregnancy, 15 % of them were infected during first trimester, 59 % during second and 26 % during the third.²⁴ The outcomes of pregnancy, i.e. impact on the newborn, were compared on the basis of caesarean deliveries, preterm births, obstetric hemorrhaging, stillbirths after 22 weeks, congenital malformations, weight at the time of birth and newborn admissions. The infected ones were compared with the 655 not infected during pregnancy. No differences in the pregnancy outcomes were observed. The only noticeable difference was that the infected pregnant mothers had to be hospitalized earlier than the uninfected ones. The findings of this research clearly suggest that there is very little risk of women infected with chikunguniya during pregnancy passing it to their fetus.²⁵

Reservoirs:-

Human beings serve as the chikungunya virus reservoir during epidemic periods. Outside these periods the main reservoirs are monkeys, rodents, birds, and other unidentified vertebrates. Outbreaks might occur in monkeys when herd immunity is low; the animals develop viraemia but no pronounced physical manifestations.^{26, 27}

Chikungunya Joint Pain:-

Chikungunya fever usually starts after 2 to 4 days of virus infection. The fever causes chills and shaking of the body and is accompanied by joint pain and swelling. The joint pain is the most distinguishing feature of Chikungunya. It is usually paralyzing in effect and causes a great deal

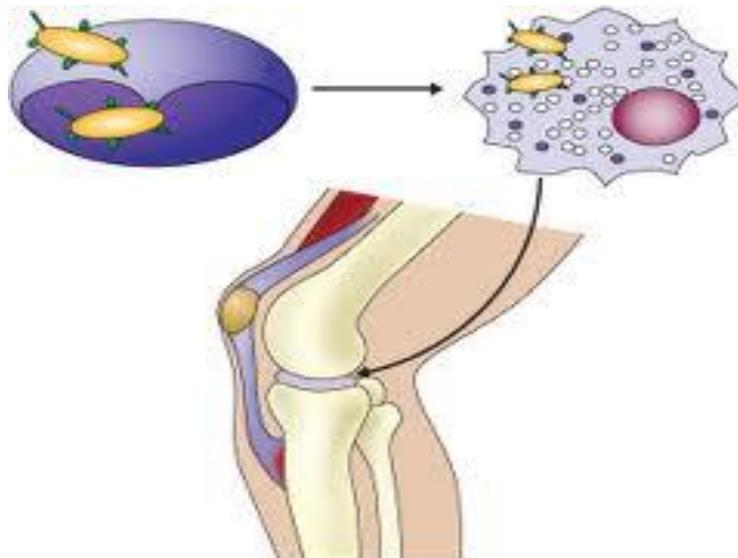


Figure 6: Chikungunya viruses (top, yellow) may hitchhike

of pain. The major areas affected are the finger joints on hand and foot and are usually swollen and painful (Figure 6). Other areas affected include wrist, elbows and hip. In fact it is common for the patient to feel pain all over the body. In many patients, movement is severely restricted due to joint pain and swelling. This means that a lot of people need to take long leaves which in many cases affect their financial well being.

In children the joint pain is usually mild in nature; however other complications such as vomiting, fits and abdominal pains are reported. In pregnant woman the biggest risk is the possibility of transfer of virus to the fetus. In addition, delivery becomes complicated if the infection starts late in the pregnancy sometimes requiring caesarean section. Chikungunya can be deadly in the case of very old and in newborns. Patients with poor immune systems may require hospitalization.

Chikungunya fever usually lasts for about 3 to 4 days and in many patients rashes are seen on the face (nose and cheeks). Sometimes rashes are accompanied by severe itching. Chikungunya joint pain usually lasts for about a week or two in majority of cases. But in some patients the joint pain can persist for months or even for years. Chronic joint pains are seen in about 1 in 10 cases of Chikungunya infection. The persistent joint pain may be mistaken for rheumatoid arthritis. Some studies suggest that Chikungunya joint pain treatment should be different from that of rheumatoid arthritis (Figure 7).

Chikungunya, a mosquito-borne viral disease that is on the rise in parts of Asia and Africa, is different from that linked to rheumatoid arthritis, Indian scientists report. Scientists at the regional centre of Indian Council of Medical Research (ICMR) at Port Blair say that the insights

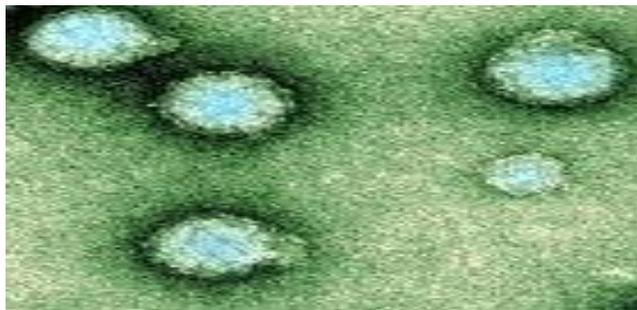


Figure 7: Chikungunya joint pain different from that in rheumatoid arthritis

have “implications in case management.” “Patients with the more common ‘rheumatoid’ arthritis, that results from an immunity problem in which the body produces antibodies against itself, are usually prescribed steroids that are not needed for chikungunya-related joint pains,” Palluru Vijayachari, ICMR regional centre director, told *SciDev.Net*. Also, unlike rheumatoid arthritis that can affect the lungs, heart and skin, chikungunya-related arthritis is restricted to bones, muscles and joints. There is yet no cure for the disease and treatment is focused on symptom relief. “The study was conducted because not much information exists about the pathological changes and evolution of symptoms in acute and chronic chikungunya disease,” Vijayachari explained. This information would help clinicians provide better care to chikungunya patients, Vijayachari said. These are preliminary findings from a three-year study initiated in 2008 on 203 patients. ICMR scientists are further studying disease progression and immune responses, which can lead to development of new and/or modified methods of treatment, Vijayachari added. According to the World Health Organization, a major outbreak of chikungunya occurred recently in the Indian Ocean islands in February 2005, followed by another in 2006, and in 2007 when several other countries in South-East Asia were also affected. A localised outbreak was reported from north-eastern Italy in 2007. Chikungunya’s symptoms are often confused with dengue, another disease spread by the same mosquito *Aedes aegyptii*. These include an abrupt onset of fever with joint pain. Other common symptoms are muscle pain, headache, nausea, fatigue and rash. The joint pain is often debilitating, but usually ends within a few days or weeks, but in some cases joint pain may persist for several months, or even years.

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