CHIKUNGUNYA-A SHORT REVIEW

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ABSTRACT

Chikungunya is a viral disease spread by the bite of infected *Aedes Aegypti* mosquitoes. It is an arbovirus that means it is an arthropod borne virus and is a member of the genus *Alphavirus,* that circulates predominantly in tropical and subtropical regions, potentially affecting over 1 billion people. Recently, an outbreak began in the western hemisphere and has resulted in over 1.8 million reported suspected cases. Infection often results in severe fever, rash and debilitating polyarthralgia lasting weeks to months. The purpose of this review is to evaluate the current state of knowledge regarding Chikungunya including clinical presentation, diagnosis, risk factors, treatment, and prevention.

Keywords: Chikungunya, Mosquitoes, Arthritis, Ribavirin, Interferon

INTRODUCTION

The Chikungunya virus (CHIKV) is an alphavirus that belongs to the Semliki Forest Virus antigenic complex [1]. Local outbreaks of CHIKV-like disease have been documented since the eighteenth century [2] and the virus was discovered in 1952 in Tanzania [3]. Over the last 50 years, CHIKV has spread beyond its African heartlands and caused explosive outbreaks comprising millions of cases in Indian Ocean islands and Asia [4]. The virus is mosquito-borne and transmission is associated with the vector species *Aedes albopictus* and *Aedes aegypti*, which are responsible for transmission cycles in urban and peri-urban environments [5]. Clinical symptoms include polyarthralgia, rash, high fever and severe headaches [6] and outbreaks are often characterized by a rapid spread and high morbidity, resulting in losses in productivity [7]. To date, four distinct CHIKV genotypes have been identified. Two genotypes - the East-Central-South African (ECSA) and the West African genotypes - occupy a basal position in the phylogeny of CHIKV [8] and are mostly enzootic in Africa. Of the remaining two genotypes, the Asian genotype is predominant in Southeast Asia, whilst the more recent Indian Ocean lineage spread from the Comoros islands in 2004 and caused a large outbreak in India and Southeast Asia in 2005-2008.

TRANSMISSION

The chikungunya virus is transmitted by the bite of an infected female Aedes mosquito. *Aedes aegypti* is most associated with the transmission of chikungunya in tropical and sub-tropical regions, but *Aedes albopictus* (Asian tiger mosquito) has been associated with chikungunya transmission in more temperate regions, such as Italy.

When the mosquito feeds on the blood of a person infected with chikungunya, the virus enters and multiplies within the mosquito. After about 8 to 10 days, the mosquito can transmit the virus to another human, and can do this for the rest of its life. Chikungunya is not spread directly from person to person. If a person acquires chikungunya abroad and becomes ill on their return to the UK, they cannot pass the infection onto anyone else. The Aedes mosquito is not present in the UK, as the temperature is not consistently high enough for it to breed. After being bitten by an infected mosquito, it may take typically between 4 and 8 days for the first symptoms (usually fever and joint pain) to develop, but it can be shorter or longer in some people.

CLINICAL MANIFESTATIONS

Chikungunya, which translates as "disease that bends up the joints," is characterized by an abrupt onset of fever with severe joint pain, and the pain may persist for weeks to years [9]. In contrast to infections with many other arboviruses, only 5 to 25% of CHIKV infections are asymptomatic. The arthralgia is typically symmetrical and primarily affects peripheral joints, including wrists, knees, ankles, and the small joints of the hand. Additional disease signs and symptoms include arthritis, with joints often exhibiting tenderness and swelling, tenosynovitis, skin rash, and myalgia, particularly in the lower back and leg muscles. In addition to these clinical features, severe neurologic and cardiac manifestations and, in some instances, deaths have been associated with CHIKV infection. These more severe outcomes often occur in neonates, in patients more than 65 years of age, and in those with underlying medical conditions. In addition, reports indicate that mother-to-infant transmission of CHIKV during delivery results in high rates of morbidity [10]. Chronic CHIKV disease can be highly debilitating, and large epidemics have severe economic impacts, highlighting the significant public health threat posed by CHIKV.

Other common symptoms of chikungunya include:

- ✓ muscle pain
- ✓ headache
- ✓ nausea
- ✓ fatigue
- ✓ rash

Occasional cases of eye, neurological and heart complications have been reported, as well as gastrointestinal complaints. Serious complications are not common, but in older people the disease can contribute to the cause of death.

RISK FACTORS

Risk factors for severe acute disease have been thoroughly investigated [11-13]. Several studies reported that, in adults, the incidence of atypical cases, severe cases, hospitalisation and the mortality rate increased with age. In pediatric populations, newborns had a high risk of severe disease. Although comorbidity and increase of age are often linked, comorbidity or underlying respiratory diseases, the use of NSAIDs prior to hospitalisation, hypertension and underlying cardiac disorders have been associated with hospitalisation or disease severity. Alcohol abuse was also associated with increased mortality.

DIAGNOSIS

Since no effective vaccines or therapeutics are available, early detection and proper diagnosis play the key role in the effective control of the infection. Infant mice inoculation and serological techniques [haemagglutination, Haemagglutination Inhibition assay, complement fixation and neutralization test (NT)] were used effectively in the identification and characterization of viruses [14,15]. The development of immunoglobulin M antibody (IgM) capture enzyme linked immunosorbent assay (MAC-ELISA) has been a major achievement in serology as it provided a rapid and reliable technique for the diagnosis of arboviruses.

Indirect Immunofluorescent antibody technique is another reliable technique for detection and identification of viral antigens from clinical samples. As is the case for most alphaviruses, detection of CHIK virus depends on isolation of the virus in blood specimens obtained from viraemic patients or in infected tissue specimens obtained from blood-feeding arthropods, which are time-consuming. Molecular diagnostic tools, such as the conventional RT-PCR, are available for the study of CHIK virus replication in virus culture supernatants or clinical samples [16,17].

TREATMENT

There is no specific vaccines or antiviral drugs to prevent or treat chikungunya. Supportive nursing care and relief of symptoms are the standard treatment. Since no specific drugs are available, supportive treatment for the symptoms i.e. analgesics, antipyretics, anti-inflammatory agents etc are generally administered. Brighton S W [18] observed chloroquine phosphate effective for chronic CHIK arthritis as they observed significant improvement in Ritchie articular index and morning stiffness in the patients. Chloroquine and its hydroxy-analogue, hydroxychloroquine are weak bases that are known to affect acid vesicles leading to dysfunction of several enzymes. Some viruses enter their target cells by endocytosis in the lysosomal compartment, where the low pH, along with the action of enzymes, disrupts the viral particle, thus liberating the infectious nucleic acid and, in several cases, enzymes necessary for viral replication. [19]

Several drugs are known to be effective against CHIKV when tested *in vitro*, but no recognised antiviral treatment is currently available.

- ✓ Antibody-based therapies: Passive immunotherapy has been used for over a century in the treatment of viral infectious disease.
- ✓ Interferon: The IFN system is capable of inhibiting virus infections in the absence of adaptive immunity.
- ✓ Small-molecule drugs: Ribavirin, the nucleoside analogue 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, exhibits antiviral activity against a variety of RNA viruses in cell culture through at least three distinct mechanisms: inhibition of the cellular protein inosine monophosphate dehydrogenase (IMPDH), immunomodulatory effects, and incorporation as a mutagenic nucleoside by the viral RNA polymerase. All three activities may play an antiviral role *in vivo* [20]
- ✓ Arbidol: The antiviral drug Arbidol (ARB) (1-methyl-2-phenyl-thiomethyl-3-carbotoxy-4-dimetylaminomethyl-5-hydroxy-6-bromoindolehydrochloride monohydrate) was developed by the Centre for Drug Chemistry, Moscow for use against respiratory viral infections.
- ✓ Furin inhibitors: Alphavirus envelope glycoproteins are initially produced first as precursors (E3E2 or p62) and during virion maturation further cleaved at short multibasic motifs.
- ✓ Structure-based-specific inhibitors: Crystal structures of the replicative proteins of CHIKV and several other alphaviruses have been reported and provide new opportunities to develop structure-based, specific inhibitors. [21,22]
- ✓ Other inhibitors of virus replication: A series of complex polycyclic molecules isolated from a rare native plant of New Caledonia (Trigonostemon cherrieri), Trigocherrins 1,2 and 6 and Trigocherriolides 7–9, have recently been tested in cellular assays against CHIKV, SINV and SFV.

PREVENTION

There is no vaccine or drug to prevent chikungunya. The only way to prevent chikungunya is to avoid mosquito bites. Aedes mosquitoes bite during the day particularly around dawn and dusk (as opposed to mosquitoes that transmit malaria, which bite at night between dusk and dawn).

A good repellent containing N, N-diethylmetatoluamide (DEET) must be used on exposed skin, together with light cover-up clothing. If sunscreen is also being used, repellent must be applied after sunscreen.

In endemic areas, control programs rely on the elimination of mosquito breeding sites in the community by regular inspections and insecticide spraying of properties (particularly during an outbreak) and the education of local residents to regularly empty standing water and keep outside areas free from waste items in which water may collect.

CONCLUSION

Currently, there is no antiviral medication available to treat the typical manifestations of chikungunya fever. Chloroquine, previously employed, should not be employed during the acute phase of the sickness. Ribavirin may be considered for severe cases, although there is a scarcity of information and the specific indications and

treatment procedure have not been determined. There is a potential for current investigations to discover new antiviral drugs. This is because more and more compounds are being linked to a well-defined mechanism of viral suppression in cell-based systems and demonstrating substantial effectiveness in animal models. Therapeutic procedures for severe instances of chikungunya fever can be developed using specific immunoglobulins or molecules that can disrupt some components of the inflammatory response linked to Chikungunya virus infection. Creating public awareness and insisting on preventive measures is necessary to avoid chikungunya fever.

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