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REVIEW ARTICLE

Chikungunya: An Emerging Threat

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ABSTRACT

Chikungunya is an important mosquito borne arboviral disease causing periodic epidemics world over. India also faces the brunt of this disease every few years which is associated with acute as well as long term consequences. The burden of this disease has been ever increasing since the 2006 outbreak, the latest outbreak occurring in 2016. Chikungunya has been typically associated with fever, joint pains and rash but during the last few epidemics, lot of atypical presentations of this common disease occurred. It was thought to be a benign self-limiting disease but in recent time, severe disease with multi-organ involvement requiring intensive care and causing mortality have been reported from India and other countries, especially in patients with co-morbid illnesses. Many patients suffer from chronic consequences of this chronic inflammatory rheumatism lasting for years, affecting the quality of life and productivity of the affected population. This review highlights the epidemiology, the changing clinical spectrum, the available diagnostic modalities and the management of acute and chronic manifestations of this challenging infection.

Disease Burden

Chikungunya virus, is an arbovirus, belonging to the family togaviridae. It is a mosquito-borne virus, transmitted mainly by *Aedes aegypti* and *Aedes albopictus*. The major manifestations of the disease are fever and debilitating joint pains. In the past few years, the virus has scaled up from obscurity to a threatening and challenging global public menace and more so in tropics and sub-tropics. The disease was spread across Asia, Africa, West Indies, Indonesia, and United States in the 18th and 19th centuries, causing several outbreaks with debilitating effects.

The nomenclature of the virus Chikungunya dates to an outbreak during 1952–53, in Tanzania. The name was derived from the local language, that meant 'that which bends' postureas noted by the local population.

Thailand experienced a massive burden of the disease during late 1950s and early 1960s. The disease spread across various parts of India in early 1960s to 1970s. The first outbreak was reported from Calcutta (present Kolkata) during 1963. In 1962–64, Madras, India experienced a major outbreak affecting 40% of the population and in 1973; Barsi, India had a major outbreak, affecting 37% of the population.

Many tropical and sub-tropical areas including Africa, Asia, Europe, and the United States of America are experiencing the current epidemic of the disease, ongoing since 2004. Amongstthe 266,000 cases of chikungunya from Reunion Island, 237 fatal cases were reported (approximate fatality rate being 1/1000). In India, Chikunguny are-emerged in 2006 after a gap of almost three decades with 1390322 clinical cases. Since then the outbreak is continuing. Delhi

reported a major outbreak of Chikungunya in 2016 with 12279 clinical cases, of which 9793 laboratory confirmed cases(http//www.nvbdcp.gov.in). A study from Ahmedabad, India revealed around 3,000 excess deaths in August to November 2006 compared to the deaths during the previous 4 years[1]. The excess deaths could be attributed to the then ongoing chikungunya epidemic though there were no clinical evidence. A 5 year morbidity study suggested that Chikungunya infected (CHIK+) patients had a higher rate of general practitioners consultation and required increased use of paracetamol, between 2008 and 2012. The joint symptoms were all statistically significant, in terms of frequency of pain attacks (40% versus 22%), intensity of pain (64% versus 38% moderate to intense pain), joint stiffness and swelling (60% versus 32%). Other constitutional symptoms including headache (42% vs 29%) and depressed mood (21vs 6%), were also statistically significant ($p<0.001$). As measured by Short form health surveys-quality of life (SF36-QoL), used for determining the social, physical and mental impact of the disease, it was evident that the above-mentioned parameters were significantly impaired in CHIK+ patients[2].

Depending on the location, the major genotypes of the virus responsible for epidemics of the disease are the Asian genotype and East Central South African (ECSA) [3].Re-emergence of both the genotypes simultaneously, after several years of relative inactivity suggests similar forces influencing this issue of emergence. Both the ECSA and Asian genotypes are responsible for the ongoing Chikungunya outbreaks across the globe. Lamu Island in Kenya was the focal point, where the current ongoing epidemic of chikungunya started in 2004, by the ECSA genotype, affecting around 13,500 people, substantially higher as compared to the other African outbreaks of the disease. About eight months later, a major outbreak affecting nearly 215,000 individuals occurred in Tanzania. ECSA genotype is isolated in the ongoing outbreak in India since 2006 till 2014 (Ref provided at the end).

America and Brazil experienced indigenous spread of an ECSA genotype virus in 2014. The Asian genotype has spread in Pacific recently. The Chikungunya outbreak in France was traced due to return of travellers from Indonesia, where the disease was indigenous from the past decade. Asian genotype was identified to be causative agent during the outbreaks of the disease in the time frame as follows: in 2012 at Papua New Guinea; in 2013 at Yap Island, and Federated States of Micronesia; in 2014 at Tokelau, Tonga, Samoa, American and French Polynesia; and in 2015 at Kiribati and the Cook Islands[4].

Vector

Aedes aegyptus is the major vector in the tropics and sub-tropics, whereas *Ae. albopictus* has been identified in the temperate and even cold temperate regions as well[5]. Water-filled natural sites like tree holes, leaf axils, plantation etc.of different kind form the niche of the species *Ae. albopictus* as compared to the *Ae. aegypti,* which is mostly in close association with human habitation. The latter uses more indoor sites including flower vases, storage vessels, and water tanks in bathrooms, unused waste etc. An important risk factor for Chikungunya as well as for other diseases transmitted by these species includes proximity of the breeding sites of these mosquitoes to the human habitation. Reductions of the natural and artificial habitats that support mosquito breeding constitute the major arms of the control and prevention strategies for the disease. Insecticides are sprayed during outbreaks to kill mosquitoes. Water bodies, storage tanks, desert coolers etc. are treated with insecticides to kill the immature larvae. Application of repellents to exposed skin and use of clothing in accordance with instructions also constitute important disease prevention measures. The preferred repellents for use include the ones with the active ingredient being DEET (N, N-diethyl-3-methylbenzamide), IR3535 (3-[N-acetyl-N-butyl]-amino-propionic acid ethyl ester), and icaridin (1-piperidinecarboxylic acid, 2-(2-hydroxyethyl)-1-methylpropylester)[6]. A sharp rise in densely populated urban cities with unplanned human civilization confers an environment conducive for the vectors, particularly for *Aedes aegypti*. This is the major contributing factor responsible for the world wide resurgence of Chikungunya in the last few decades. The last decade has experienced a tremendous rise in the number of people dwelling in cities, with around doubling from 1.7 billion to 3.5 billion. By 2030, the number is further expected to rise to 4.9 billion, with most of this being projected to occur in Asia. Increased global travel has further added impetus to the spread of the virus. Molecular epidemiological studies conducted in Cuba and Puerto Rico have thrown some light on the reason behind resultant increase in transmission of the virus. The study suggested that there occurred genetic expansion of the virus, which provided ample opportunities for successful selection of viral variants with high epidemic potential or virulence. Invasion of the vector *Aedes aegypti* into temperate regions, including Nepal, Argentina, and into rural areas of Cambodia and Indonesia provides insight into the geographical expansion of the virus. The role of *Ae. albopictu*s, as a vector in the disease transmission has been well established including India. It has been detected from

the Americas, the Europe, as well as from South-East Asia to Northern Asia (Japan and China)[7].

Clinical manifestations

Most of the people infected by the Chikungunya virus (CHIKV) become symptomatic. Onset of symptoms is usually 3–7 days after the bite of an infected mosquito. Fever and joint pain constitute the most common symptoms. Muscle pain, headache, joint swelling, and rash comprise the next common symptoms. Several muco-cutaneous manifestations have been described, the common ones being pigmentary changes, maculopapular eruption, and inter-triginous aphthous-like ulcers and vesiculo-bullous dermatosis. Death is not very often associated with Chikungunya, although the symptoms can be severe and disabling. The joint pain may persist for months in a few cases. At risk individuals for severe disease include extremes of ages, new-born, older adults (≥65 years), and people with co-morbid conditions including diabetes, high blood pressure and heart disease. Once infected with the virus, the individual is likely to be protected from future infections.

Chikungunya has always been considered a benign non-life threatening disease. But, recent studies have revealed that atypical cases comprise around 1 to 3% of all the cases, with mortality being high amongst these cases. A study on Chikungunya fever revealed that among atypical cases(n=610),the fatality was around 10%. Among the total atypical cases of 610, NSAIDs were taken by 84(14%) and alcohol abusers constituted 88 (14%)[8]. Underlying medical conditions were detected in 90% of the individuals with the disease. A noteworthy observation was made, that previously healthy individuals developed CNS manifestations like meningo-encephalitis; CVS manifestations such as pericarditis and myocarditis, myocardial infarction, and arrhythmias. Individuals with underlying medical (respiratory or cardiovascular) conditions were at increased risk of morbidity. A significant negative impact on glycaemic control resulting in greater morbidity was associated with diabetes mellitus[9]. Another important finding of the study was that, NSAIDs use before hospitalization increased the chances of disease severity manifold. This would indicate either a more severe form of the disease or hospital admission at an advanced disease condition.

Most of the patients with Chikungunya have a mild course which can be managed on outpatient basis or in wards but studies done during the recent outbreaks have shown that many patients were critically ill requiring intensive care management. Most of the patients had underlying co-morbid conditions. During the 2014-15 outbreak in French Polynesia 64 patient with Chikungunya required ICU admissions out of which 33 required invasive mechanical ventilation, 21 had severe sepsis or septic shock and 30 (46%) required renal replacement therapy. The ICU death rate for chikungunya was 28% in this study[10]. A recent study from North India done during 2016 outbreak had 60 patients requiring ICU care out of 756 total admissions. Altered sensorium was commonest indication of ICU admission and mortality was 36.67% in this study. High APACHE II Score and need for renal replacement therapy were independent predictors of mortality[11].

Diagnosis

Either Virus orantigenic components or the immune antibody response detection constitute the major targets of the available diagnostic tests. Dengue virus (DENV) and Chikungunya virus (CHIKV) are both arthropod-borne viruses, the arbo-viruses. They share a common vector belonging to the *Aedes* genus, specifically *Ae. aegypti* and *Ae. albopictus*. Both of the viruses circulate in similar geographic regions. Although DENV and CHIKV have similar presentations, as an acute febrile illness, the management strategies of the two viruses arevastly different. The outcomes of the management also pose a major challenge to the practising clinicians. Unfortunately, no single clinical or laboratory marker is available to distinguish DENV from CHIKV infection. There is also difficulty in identifying the diseases from other causes of acute febrile illness. Purpose of testing and the availability of resources comprise the other factors influencing the choice of diagnostic tests. Unique advantages and disadvantages are offered by the various diagnostic tests available. The diagnostic confidence can be significantly increased by employing a combination of the tests. The laboratory diagnosis of Chikungunya fever is done by serologic methods, virus isolation or viral RNA detection by reverse transcription–polymerase chain reaction (RT-PCR). The virus isolation is highly specific but requires high degree of expertise and specialised lab, hence is not routinely available.

The viral RNA can be detected by RT PCR or real time RT PCR or by isothermal amplification methods. It is highly sensitive and specific with rapid turnaround time and can be used for early diagnosis. Chikungunya viral RNA can be detected by real-time RT-PCR in the first week after onset of clinical illness. So, this is the test of choice when the patient

present early before the antibodies are formed usually <6 days. But PCR is not routinely available at all centres.

Detection of viral antigen by ELISA or immune-chromatographic method is another method for early diagnosis with sensitivity and specificity of 85% and 89% for serum samples. But these tests are also not widely available. The most widely available and routinely done test are for detection of host antibody response mostly. The various test for IgM antibody detection are ELISA(Enzyme linked immune sorbent assay), IFA (Immuno fluorescence assay) and PRNT(Plaque reduction neutralisation test). Immunoglobulin M (IgM) antibodies elicited are mostly detectable in serum by days 5–7 after onset of illness. ELISA is widely available, cheaper and easier to perform. The sensitivity and specificity is variable based on different kits available. Possibility of cross-reactivity with other alpha viruses remains. Elevated IgM does not distinguish recent past infection from acute infection. PRNT (Plaque reduction neutralization test is very specific for alpha viruses and gold standard for serologic test results confirmation. But requires the use of live virus and Biosafety level 3 containment)[12].

TREATMENT

Till date, no specific effective antiviral drugs are available against Chikungunya. Hence, it is essential to exclude other serious infections which may mimic Chikungunya fever, the important ones being dengue, malaria, and other bacterial infections. The tropical arthritogenic chikungunya (CHIK) virus has assumed the position of an increasingly medical and economic burden in the affected areas since 2003. The disease can often result in morbidity and long-term disabilities.

Guiding principles of clinical management

Symptomatic treatment is the mainstay goal of management. Paracetamol is the analgesic of choice, along with other drugs should only be considered if paracetamol does not give relief. Steroids are not usually indicated during the acute stage because of the risk of adverse reactions. Aspirin is avoided because of the risk of gastrointestinal and other side effects including Reye's syndrome. In recovering subjects, mild exercise and physiotherapy aid can be considered for faster recovery. Serological or viral confirmation are not essential for the beginning of treatment, it should be instituted in all suspected cases. All the suspected cases during the febrile period should be kept under mosquito nets. Mosquito control measures need to be adopted in the hospital premises as well as in the houses and the communities should be sensitized regarding the same[13].

Domiciliary management (for the signs and symptoms which do not require specialised medical help).

Adequate rest in a warm environment and avoidance of damp surroundings should be advised to all cases. During the acute stage, it is advised to avoid heat, as it may increase or worsen the joint pain. Joint damage may be reduced by cold compress. Refraining from exertion is advised. Plenty of water with electrolytes should be consumed (amounting to about two litres of home available fluids with salt in 24 hours). During periods of fever, tablets of paracetamol should be taken (even up to two 500 mg tablets four times daily). Aspirin or other self-medication analgesics must be avoided.

In hospital Management

In hospital management is warranted for the signs and symptoms requiring medical help, which includes fever persisting for more than five days, intractable and unbearable pain, postural dizziness and vertigo, cold and clammy extremities, decreased urine output, bleeding from any site under the skin or through any orifice and increase vomiting. Symptomatic treatment with paracetamol is the mainstay of the management of chikungunya fever. For patients who have been already treated with paracetamol other analgesics, starting them on one of the NSAIDS may be considered. Cold compresses are advised if initial response with the therapy is good[14]. After acute phase, warm environments, taking sun is mostly beneficial. Bleeding disorders if any, should be managed with blood components. Platelet transfusions are considered in case of bleeding with platelet counts of below 50,000 cells per cu mm. Fresh frozen plasma, or Vitamin K injections are considered if INR is greater than 2. Hemodynamic instability if observed with manifestations such as syncopal attacks, hypotension with systolic BP less than 100 mmHg or pulse pressure less than 30 mmHg; oliguria with urine output less than 500 ml per day; bleeding manifestations or with altered sensorium; the patient should be referred to a higher healthcare centre immediately. The individual should be managed in high dependency unit or in an intensive care unit[15].

Proper hemodynamic monitoring along with fluid resuscitation and timely administration of inotropes/ vasopressors is warranted. Aggressive management of the patient is essential before the subject enters into severe

cascade of irreversible tissue ischemia and various organ dysfunctions.

Principles for management of chronic phase and challenges

NSAIDS and hydroxyl-chloroquine-based regimes recommended for the management of osteo-articular manifestations. A course of steroids (response based duration on case to case basis) may be beneficial, as in chronic cases, an immunologic etiology has been suggested. Patients with contractures and deformities may have a hastened recovery with proper and timely physiotherapy. Non weight bearing exercises have a great deal to offer. To enumerate a few, slowly touching the occiput with the palm, slow ankle and leg exercises, and pulley assisted exercises. Milder forms of yoga have been advocated. Peripheral neuropathy predominantly sensory component is the one of the most common manifestations, seen in about 58% of the patients. Various neurological manifestations ranging from paraesthesia, pins and needles sensations, to the sensation of crawling of worms and disturbing neuralgias have all been well described by the patients of Chikungunya fever, either in isolation or in combination. Entrapment syndromes like carpal tunnel syndrome may get worsened or precipitated in many of these patients. Motor neuropathy is a rarer manifestation. Ascending polyneuritis has been reported in occasional cases, as a post-infective phenomenon, as observed with many other viral illnesses. Although, seizures and loss of consciousness have been observed occasionally, a causal relationship with the disease is yet to be established. Disturbing neuropathies may be managed with standard doses of anti-neuralgic drugs such as amitriptyline, carbamazepine, and gabapentin.

Post-CHIK (pCHIK) rheumatic disorders have a varied range of clinical spectrum and pose a major challenge. A study conducted by E Javelle *et al.*[16], proposed a classification for the patients of pCHIK rheumatic disorders. Patients without any previously defined arthritis were classified under pCHIK musculoskeletal disorders (pCHIK-MSD), that may be further classified as diffuse (if > 4 painful areas) or loco-regional. Further, arthritis in this group of patient can be classified into non-crystalline and crystalline disorders. Those group of patients presenting like hyperuricemia and improving with gout treatment are known as crystalline arthritis and the other group may labelled as non-crystalline arthritis or chronic inflammatory rheumatism (pCHIK-CIR). This could be further classified into two sub groups. Patients without any previous rheumatic symptoms, who developed CIR immediately after CHIK, were classified as *de novop* CHIK-CIR and those who had a pre-existing rheumatological disorder (pre-existing CIR). *De novo p*CHIK-CIR are known to develop into rheumatoid arthritis, spondylo-arthropathy or undifferentiated poly arthritis. Similarly pre-existing CIR group in those who had rheumatoid arthritis and spondylo-arthropathy were known to progress to more severe disease. Several serious issues such aschondrolysis, reduction of joint space, juxta-articular osteopenia, joint subluxation, bony erosion or destruction, and sacroiliitis noted as with other post viral syndromes. This is a major challenge in front of the world. Various groups have been successfully managed with either methotrexate, or corticosteroids or hydroxyl-chloroquine alone or in combination with each other. A few resistant cases were also given a trial with biologicals,but making any definitive conclusion at this stage would be too early. From the current scenario, nevertheless it could be inferred that CHIK virus is currently the potent cause generating an epidemic of chronic rheumatism across the globe[17]. Destructive pCHIK-CIR, although affects a minority of patients, needs to be emphasized upon. Importance of shortening the time necessary for the initiation of disease management by a medical specialist should be realized. There is an immense need of further research in this regard.

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