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Review Article

Biosensors: Clinical Lab Biomarkers and Radiologic Biosensing of the Chikungunya Virus

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Abstract

Chikungunya virus is emerging as threat in Southeast Asia along with dengue fever after mosquito bite. Its mode of transmission through mosquito is understood to initiate endemic especially in colonies with poor sanitation. Clinical manifestations are not established since its first occurrence and patients died in year 2009. Since then, clinical manifestations, diagnosis of the chikungunya virus pathophysiology and transmission of the chikungunya virus have been investigated as possible acute and chronic clinical manifestations such as rheumatologic, ophthalomogic, neurologic, hepatitis, cardiomyopathy and fever. However, various clinical lab biosensors and radiologic biosensing are needed in the state of emergency using clinical evaluation by x-ray, CT, MRI, nuclear medicine and lab investigations. A cursor review of the expected epidemiology, pathophysiology and transmission of the chikungunya virus is presented to find the possibility of clinical lab biosensors and radiologic imaging of the chikungunya virus as manifestations to help and guide healthcare professionals in making a timely diagnosis. With time, new advanced techniques of biosensing and bioimaging will certainly come out with more specific and precise detection and diagnosis of chikungunya virus to explain etiology.

Keywords: Chikungunya; Mosquito; Radio imaging sensing

Introduction

Chikungunya fever is caused by the chikungunya virus. It is caused and transmitted by the bite of infected mosquito genus *Aedes*. Virus causes arbovirus disease. Very first evidences of Chikungunya fever and deaths were in Southeast Asia in India in year 2009 [1,2]. The virus had a relatively high incidence in India, Southeast Asia, the Caribbean, Africa, France, Italy, and Australia in last five years. Later, World Cup festivities in Brazil become spotlight with possible increased incidence of the virus imported to the United States. Initially, the virus was thought as simple fever and benign clinical course. Later, its incidence increased deaths and mortality. With time, its clinical manifestations were better understood and it is now known to carry a higher morbidity by possible use of early and timely clinical lab biosensors and radiologic biosensing [1]. With advancements in biosensor techniques there is great hope of early detection and monitoring the spread of virus before it becomes a life threat. Extracellular matrix and ligament specific molecular imaging biosensors have a big role in quick detection and evaluation of virus spread.

Pathogenesis

In last five years, Chikungunya spread was established due to virus that may demonstrate a pattern of cyclic epidemics. It was characterized by outbreaks of viral disease ranging from several years to a few decades. The exact course still is not fully understood. It is observed that international travel might facilitate the introduction of the virus from endemic areas. Best evidence was chikungunya during World Cup event in Brazil. It became clear that early clinical examination by clinical lab biosensors and radiologic bioimaging certainly might decrease the risk of chingunya among athletes, business executives, diplomats, scientists and VIP dignitaries traveling abroad.

Clinical manifestations

Recently, clinical picture showed that the virus spread is abrupt and most commonly presents with high grade fever (1-2 days), rash, and arthralgias (A clinical trial of high grade fever, arthralgia and rash). The rash is mostly a maculopapular rash with irritation and seen typically over the trunk and extensor surfaces of the extremities. The arthralgias may or may not be symmetrical and usually involves severe pain in the terminal joints. Literature and case reports of the Chikungunya virus spread suggest the increased morbidity with quick neurologic impairment, ocular involvement, cardiomyopathy, fulminant hepatitis, hemorrhagic manifestations, and chronic arthritis [1,2]. The cause of quick spread mostly is natural cycle human-mosquito-human of the virus [1]. Other possibility of mosquito bite is spread of Dengue virus and developing fever.

Present trend is that biosensors and bioimaging play a significant role in diagnosis. Major success is visualizing less known neurologic, rheumatologic and cardiac pathological features sooner

Bioradiologic Imaging Manifestations:

a. Neurologic: Magnetic Resonance Imaging (MRI) suggests and indicates neurological abnormalities such as altered mental status, seizures, and focal neurologic deficits. Frequently, biosensing indications from MRI findings include nonspecific white matter changes, ventriculomegaly and enhancement of ventral nerve roots shown in Figure 1 [3,4].

b. Rheumatologic: In acute stage, MRI may sense the

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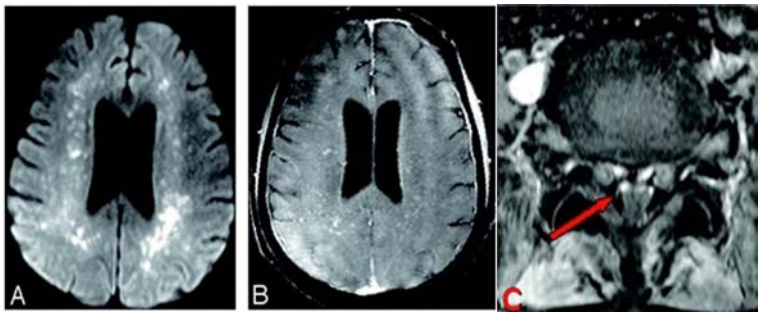

Figure 1: A. Many bilateral fronto-parietal white matter lesions are seen with restricted diffusion.
B. Post contrast enhancement is seen on T1 weighted fat-saturated images and mild ventriculomegaly.
C. Post contrast T1weighted fat-saturated axial images show enhancement of ventral nerve roots at the L4 level.

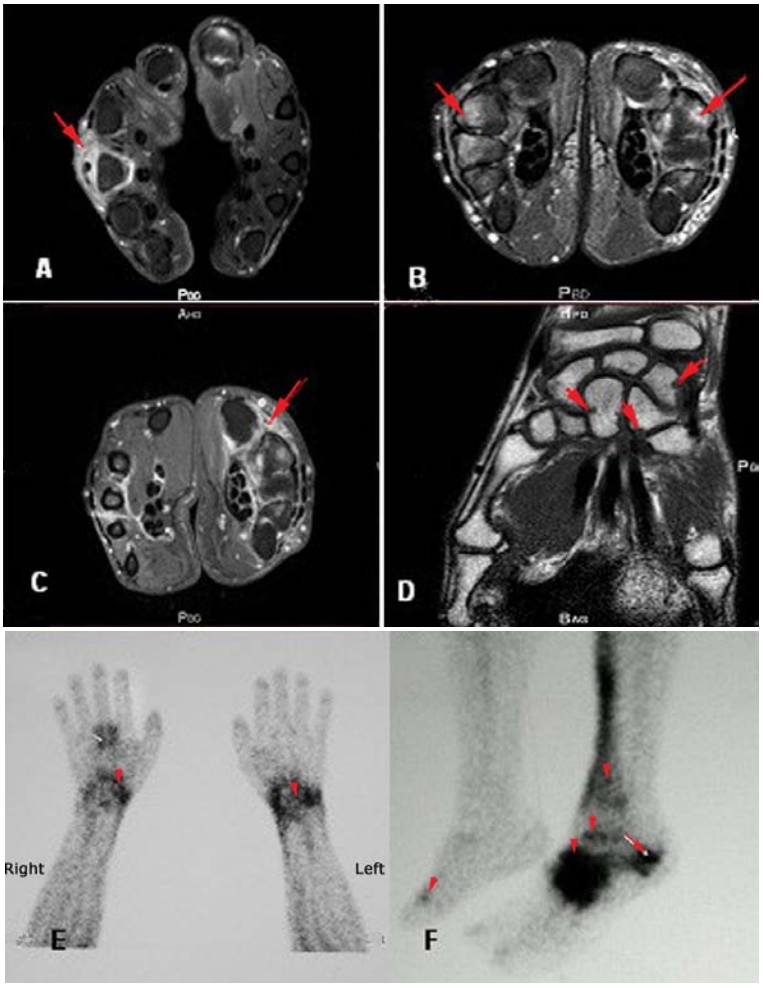

Figure 2A: Magnetic Resonance Imaging (MRI) and bone scintigraphy of the hands and wrists are shown in old aged person having chikungunya virus infection. A: Arthritis of the 3rd metacarpo-phalangeal joint of the right hand with extensor tenosynovitis associated with intra-articular swelling (shown as arrowhead on axial section, time-resolved contrast-enhanced T1-weighted sequence after Gadolinium injection with fat suppression). **B.** Bilateral periosteum inflammation and oedematouscarpitis with synovitis predominating on the left hand (arrowhead on axial section, time-resolved-enhanced T2-weighted sequence with fat suppression). **C.** Asymmetric inflammatory carpitis with multiple synovitis of flexors of the left wrist (red arrows on axial section, time-resolved contrast-enhanced T1-weighted sequence after Gadolinium injection with fat suppression). **D**. Bone destruction on the left hand (red arrows on coronal section, time-resolved contrast-enhanced T1-weighted sequence with fat suppression). **E**. Bone scintigraphy of the wrists and hands showing an intense focus of technetium 99m-labeled MDP tracer uptake, particularly in the right metacarpo-phalangeal wrist(red arrowheads). **F**. Bone scintigraphy of the left foot showing an intense focus of technetium 99m-labeled methylene disphosphonate tracer uptake(shown as red arrowheads), particularly in the left ankle.

inflammatory arthropathy associated with acute viral infection. Typical MRI visible sensors can be: periarticular soft tissue swelling, tenosynovitis, and joint effusions shown in Figure 2. Joint pain may also continue in some patients for a few months or even a few years.

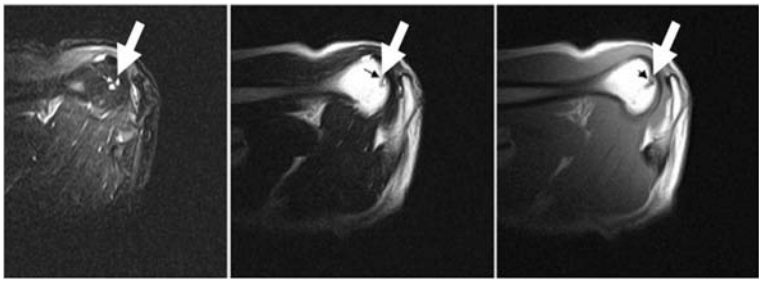

Figure 2B: Focal altered signal intensity lesions: A. hypointense on T1 weighted sequence in posterior aspect of head of humerus (coronal section); B. hyperintense on T2 weighted sequence in posterior aspect of head of humerus (coronal section); and C. hyper intense on T2 weighted fat saturated sequence in posterior aspect of head of humerus.

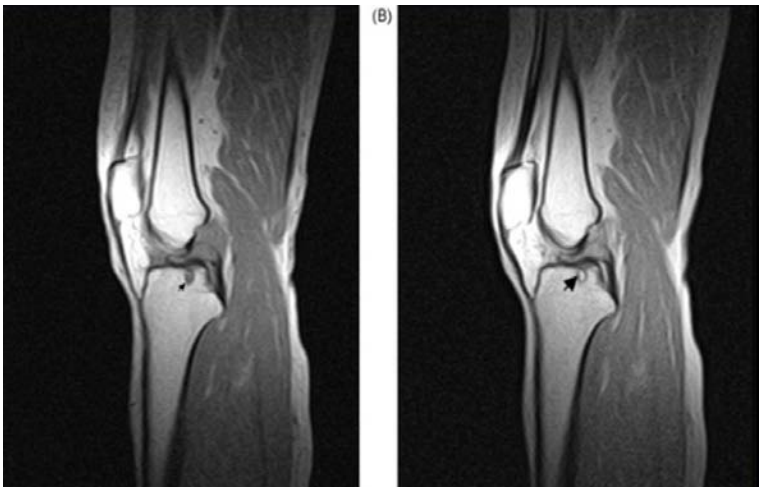

Figure 2C: Focal subchondral altered signal intensity noted just below the intercondylar region of the tibia: (A) hypointense on T1 weighted sequence (sagittal section); (B) hyper intense on T2 weighted sequence (sagittal section); and (C) hyper intense on T2 weighted fat saturated sequence.

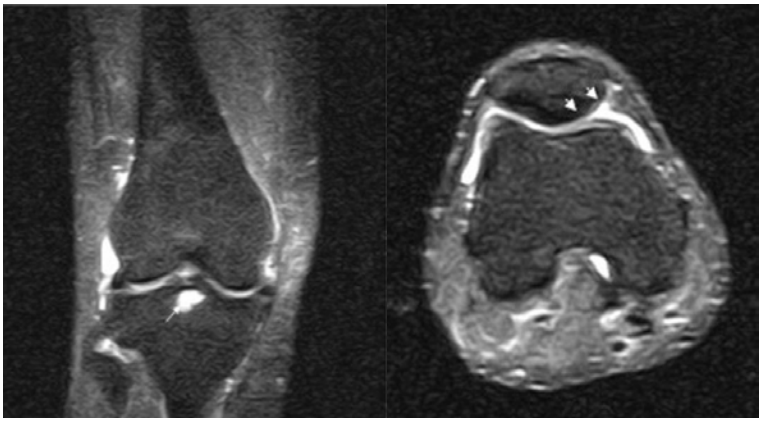

Figure 2D: Knee joint effusion with synovial thickening (shown as arrowheads) in T2 weighted fat saturated sequence.

In the chronic stage MRI visible sensors can be: radiolucent bone lesions suggestive of progressive bony erosion, mild marrow edema, synovial thickening, tendinitis, and tenosynovitis shown in Figure 3 [5].

c. Cardiologic: MR Findings associated with Chikungunya cardiomyopathy may include inflammatory changes as well as pericardial effusions shown in Figure 3 [6].

Clinical lab biomarkers:

a. Gold standard for clinical lab diagnosis is detection of the IgM and IgG antibodies as potent biomarkers using Enzyme Linked Sorbent Assay (ELISA), which may last for several weeks to three months. The IgM antibody becomes detectable 18 months after outburst of disease or onset of virus in about 40% of symptomatic rheumatic patients [5].

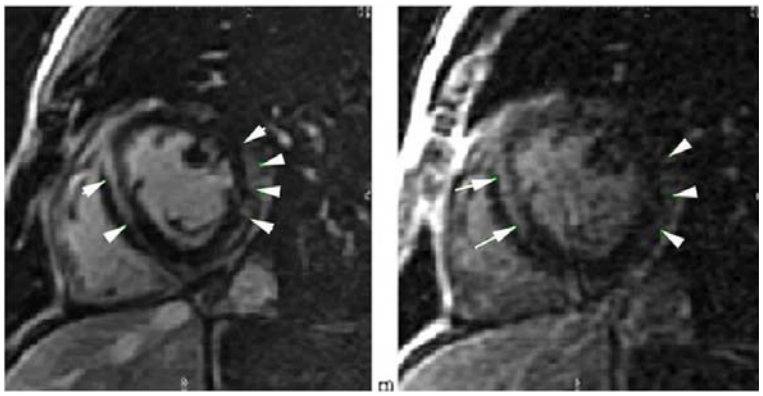

Figure 3: A. Early phase 2 min post- gadolinium injection shows mid wall septal and subepicardial inferior increase signal intensities B. Delayed phase 10 min post-gadolinium injection showing less obvious signal intensities probably reflecting myocardial necrosis associated with inflammation.

Is prevention is safe treatment? In situation of poor understanding on true cause and disease progress, only option is early detection of disease beginning by disease-sensitive biomarkers or biosensors. Author advocates mandatory practice of vigilant check of mosquito spread in clean fresh water stored in air-coolers, tanks or storage utensils to stop growing chickungunya. Such preventive measures are certainly safe tools of treatment not cure.

Management

Currently, no FDA approved or ICMR approved or European vaccine is available for complete prevention and cure of Chikungunya. More frustrating is prolonged pain and very slow healing of ligament damage sometimes more than 6 months. Still cause of slow healing is well understood and treatment of the Chikungunya virus still remains as essentially symptomatic and supportive healing [1]. Our suggestion and opinion is "precautions of Chikungunya spread is better treatment than its cure" or "Stay away from mosquito and keep clean" as indicated above.

What remains to investigate the virus spread? Still now today, no mechanisms of delayed extracellular matrix healing and recovery of ligament injury are well defined. No virus-host interactions, viral gene manipulative data, use of nanotechnology, pharmacotherapeutic research are established yet. It becomes difficult to develop molecular biosensors specific to extracellular matrix and ligament injury when no biochemical mechanism is established. Perhaps, radio imaging and inflammation biomarkers can be easily visualized to make assessment of soft tissue damage due to virus spread to rule out degree of disease progress and causes of soft tissue swelling, tenosynovitis, joint effusions, progressive bony erosion, mild marrow edema, synovial thickening and tendinitis from other sources. In future, new approaches of biosensors by recombinant DNA technology, nanotechnology, biotechnology will play a major role. Biochemical mechanisms of extracellular matrix injury and recovery, ligament and tendon soft tissue mechanics, biophysics will be investigated with better answers. So far, present strategy is left with better sense of sanitation and prevention from the root causes of virus spread through mosquito bite.

Conclusion

In conclusion, in absence of better understanding of host-virus interactions and mechanisms of its spread and limited data on virus morphology or genetic changes during viral spread soon it seems possible of greater role of early detection of biomarkers and biosensors based on new emerging tissue and disease specific clinical lab methods, radio imaging, gene manipulative techniques. New DNA recombinant techniques and nanomedicine use will prove a success in coming years.

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