Chikungunya: vision of the pain clinician

Chikungunya: a visão do clínico de dor

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ABSTRACT

BACKGROUND AND OBJECTIVES: Chikungunya is a viral disease of tropical distribution which affects individuals in different countries of the world and is associated to variable clinical presentations, characterized by the existence of two phases: acute and chronic. The acute phase is short-lasting with nonspecific symptoms. The chronic phase is marked by persistent pain, impairing patients' quality of life. This study aimed at discussing Chikungunya, from the pain clinician point of view, paying attention to its epidemiological, pathophysiological, diagnostic and therapeutic aspects, especially with regard to pain management.

CONTENTS: Chikyngunya's pathophysiology is poorly understood and involves predominantly peripheral mechanisms. It is diagnosed by observation of suggestive clinical presentation associated to specific laboratory exams. Management of patients with confirmed diagnosis involves common analgesics and anti-inflammatory drugs, in addition to steroids, antidepressants and anticonvulsants for refractory cases. Patients with chronic inflammatory rheumatic disease seem to benefit from methotrexate.

CONCLUSION: Chikungunya is a complex and still poorly understood entity. There are different therapeutic schemes to treat pain associated to it, however 40% of patients evolve with chronic pain and impairment of quality of life.

Keywords: Arthralgia, Chronic chikungunya, Fever, Pain.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A chikungunya é uma doença viral de distribuição tropical que acomete indivíduos em diferentes países do mundo e está associada a quadro clinico variável, caracterizado pela existência de duas fases: aguda e crônica. A fase aguda é de curta duração e de sintomas inespecíficos. A fase crônica é marcada pela presença de dor persistente, com comprometimento da qualidade de vida dos pacientes. O objetivo deste estudo foi discutir a chikungunya sob a ótica do clinico de dor, atentando para os seus aspectos epidemiológicos, fisiopatológicos, diagnósticos e terapêuticos, principalmente no que diz respeito ao tratamento dos sintomas álgicos.

CONTEÚDO: A fisiopatologia da chikungunya é pouco compreendida e envolve mecanismos predominantemente periféricos. O seu diagnóstico é feito por meio da observação de quadro clinico sugestivo, associado a realização de exames laboratoriais específicos. A condução dos pacientes com diagnóstico confirmado envolve a utilização de analgésico comum e anti-inflamatório, além de corticosteroides, antidepressivos e anticonvulsivantes nos casos refratários. Pacientes com doença reumática inflamatória crônica parecem se beneficiar do uso de metotrexato.

CONCLUSÃO: A chikungunya é uma entidade complexa e ainda pouco compreendida. Diferentes esquemas terapêuticos estão disponíveis para o tratamento do quadro álgico a ela associado, entretanto 40% dos pacientes evoluem com dor crônica e comprometimento da qualidade de vida.

Descritores: Artralgia, Chikungunya crônica, Dor, Febre.

INTRODUCTION

Chikungunya is a febrile acute disease associated to severe pain and frequent debilitating polyarthralgia. It is caused by the Chikungunya virus, which is an alphavirus belonging to the *Togaviridae* family, transmitted by the bite of the infected female of the *Aedes aegypti* and *Aedes albopictus* mosquito[1]. It is known that chikungunya virus is able to affect human endothelial and epithelial cells, fibroblasts, dendrites, macrophages and B cells, as well as muscle cells[2] implying the possibility of different clinical presentations.

Alphavirus arthritis, including chikungunya virus, has been related to prolonged disease. According to different authors and considering both the incidence of chikungunya in the last 10 years worldwide and the prevalence of persistent symptoms in the first year after acute infection, the cumulative number of chikungunya infected individuals suffering of disabling and long-lasting pain is estimated in 1 to 2 million[3-5]. Chikungunya is the arbovirosis associated to the highest level of rheumatologic manifestations.

Chikungunya was firstly described in 1952, in Newala, district of Tanganyika, to the East of Africa. Its name is derived from the tilted position adopted by individuals due to pain symptoms resulting from joint affection, having its origin in Tanzania and Mozambique languages[6]. Its geographic distribution includes Africa, Asia and South America, regions considered as endemic areas. However, in spite of the recognition of endemic areas, chi-

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kungunya is a threat to populations living in tropical areas with seasonal characteristics, which favor the development of *Aedes aegipti* and *Aedes albopictus.* In 2007, an infected tourist coming from India has introduced chikungunya in the North of Italy, resulting in the identification of 292 suspected cases.

This study aimed at discussing chikungunya through the vision of the pain clinician, attempting to its epidemiological, pathophysiological, diagnostic and therapeutic aspects, especially with regard to pain management.

CLINICAL PRESENTATION

Chikungunya has a broad clinical spectrum. It is known that the incubation period lasts from two to six days, with symptoms appearing four to seven days after infection. Chikungunya has two phases: acute and chronic. In the acute phase, individuals have high fever, chills, headache, vomiting, fatigue, back pain, muscle pain and symmetric arthralgia. The latter may be severe, affecting extremities, especially ankles, wrists and phalanges. Arthralgia pattern is erratic, although there is a trend for it to be more severe in the morning and worsening with more aggressive physical activity. When joint pain persists beyond the recovery period, there is the chronic phase of the disease. Here, polyarthralgia persists for weeks to years and impairs patients' quality of life (QL).

It is believed that chikungunya virus infection may contribute to the development of rheumatic inflammatory disease or even cooperate for the early diagnosis of rheumatoid arthritis and psoriatic arthritis in susceptible patients. In this context, biomarkers should be studied, such as reactive protein C, erythrocyte sedimentation velocity, rheumatoid factor, citrullinated anti-cyclic peptide antibody (anti-CCP antibody) and HLA-B27 expression[7-9]. When necessary, imaging exams should be requested. Magnetic nuclear resonance (MRI) results are represented by joint effusion, bone erosions, bone edema, synovial thickening, tendinitis and tenosynovitis. This observation contributes for the classification of chikungunya arthritis as chronic erosive inflammatory arthritis.

In a retrospective study by Javelle et al.[10], 112 patients presented criteria for chronic inflammatory rheumatologic disease. Eighteen patients had previous rheumatologic disease diagnosis and 94 had this diagnosis after chikungunya infection. Twenty-seven percent of these patients were unable to work and 77% have referred limitation in daily life activities. Half the patients with diagnosis of rheumatologic disease after chikungunya infection had radiological changes represented by musculoskeletal destruction. Mean time between acute chikungunya and radiological diagnosis of the injury was 45 months. Some patients had spondyloarthritis, sacroiliitis and bone erosions. It is believed that joint injury is a response of the immune system, with consequent autoimmune arthritis.

Different predictors have been involved in the development of this slower chikungunya presentation, characterized by persistent musculoskeletal pain. Among them there are age above 45 years, severe initial joint pain, previous arthritis[11] and strong IgG-specific response to chikungunya virus in the recovery period and chronic phase, which seem to be independent indicators of non-recovery.

It is known that chronic symptoms decrease with time after initial infection, being 88 to 100% during the first six weeks and less than 50% after three to five years, with variable results depending on the study. Total recovery time is still uncertain and some infected individuals are still symptomatic six to eight years after initial infection[12,13].

Although uncommon, severe chikungunya complications have been described, among them myocarditis, meningoencephalitis and hemorrhage. Some patients develop uveitis and retinitis. Death by chikungunya is not frequent, but may affect elderly individuals with comorbidities and children.

PATHOPHYSIOLOGY

Chikungunya pathophysiology is poorly understood and involves predominantly peripheral mechanisms. According to Chow et al.[14], acute phase is associated to viremia, that is, clinical symptoms reflecting viral load and beginning of innate immunity, being related to high level of pro-inflammatory cytokines, such as alpha-interferon and IL-6, IL1Ra, IL-12, IL-15, IP-10 and MCP-1. After this initial period, which lasts up to four days, there is a fast decrease in viremia and joint pain, with consequent improvement of QL. In the five to 14 subsequent days, period known as convalescence, patients have no longer detectable viremia, however some individuals persist with symptoms. Studies have shown that more than 40% of patients evolve to chronic disease.

Pathophysiological mechanisms of musculoskeletal pain and chronic arthritis after chikungunya virus infection are partially known. It is believed that these symptoms are caused by the early escape of the chikungunya virus from inside monocytes and consequent relocation in synovial macrophages. This hypothesis has been reinforced by the observation of persistence, for prolonged time, of chikungunya virus in muscle, joint, liver and lymphoid tissues[15].

Neurological complaints may be present in 40% of patients. From them, 10% shall evolve with persistent manifestations. Peripheral neuropathy with predominance of sensory component is the most common presentation. Motor neuropathy is rare. It is believed that pain and paresthesia may be associated to compressive neuropathy. Saxena et al.[16] have shown by means of electroneuromyographic exam and of neurological physical evaluation, that patients with chikungunya often course with peripheral neuropathic pain. It is known that neuropathic pain, in general described as sensation of electric shock or burning, is associated to more severe impairment of QL and further difficulty to manage it.

In analyzing chikungunya pathophysiology, it is observed that pain may have mixed origin, with the involvement of nociceptive and neuropathic mechanisms.

DIAGNOSIS

Diagnosis of chikungunya includes serology-based lab confirmation of the infection, real-time PCR (RT-PCR) or viral

isolation, associated to clinical presentation suggestive of the disease. Thirty percent of infected individuals are asymptomatic. IgM antibodies shown by the ELISA test may appear in two weeks, however some patients shall only produce enough antibodies to be detected by the mentioned test six to 12 weeks after initial presentation.

General lab exams should be requested. In a study in Asia[17] evaluating the evolution of chikungunya patients, leucopenia, thrombocytopenia, neutropenia and liver profile abnormalities were identified in many patients in a ratio of 94% for leucopenia and 14% for liver profile changes.

Due to similar clinical presentation, it is important to rule out the presence of rheumatoid arthritis. In chikungunya-associated arthritis, rheumatoid factor and anti-CCP antibody levels are not high, however it is critical to emphasize that studies have shown that one third of chikungunya patients meet the American College of Rheumatology criteria for the diagnosis of rheumatoid arthritis[18]. In chronic non-joint pain patients, rabdomyolisis, depression and fibromyalgia syndrome should be investigated[19].

MANAGEMENT

Notwithstanding the increasing number of chikungunya diagnoses, there is no guideline-based recommendation for its management. There is no specific antiviral therapy or preventive vaccine. Management objective, then, is to control fever, decrease immune process impact, control pain, eliminate edema, minimize the effects of rash and prevent the appearance of chronic joint injuries. Patients are oriented to adopt general care and to use drugs such as antipyretics and analgesics; however, some individuals remain symptomatic.

Among described symptoms, pain should be highlighted for its negative impact on QL of patients, being a challenge for health professionals. Simple analgesics and non-steroid anti-inflammatory drugs (NSAIDS), by blocking the formation of inflammatory mediators and prostaglandin synthesis, promote relief for most patients, however 40% of them need more potent drugs, with different action mechanisms.

Patients with chikungunya-related musculoskeletal disorders, with polyarthralgia involving hands and feet, typically with edema and other phlogiston signs, benefit from the use of short steroid cycles. It is known that steroids act decreasing the inflammatory phenomenon and blocking the immune system, especially in the acute phase of the disease[20,21]. There is no consensus with regard to the best management regimen, however some authors recommend oral prednisone in the dose of 40 to 60mg/day, for three to five days. One alternative would be 4mg oral or parenteral dexamethasone every 8h, for three days and, in refractory cases, intra-articular steroids application[10].

Patients with paresthesia should be managed with specific drugs for neuropathic pain. Among them there are tricyclic antidepressants, gabapentinoid anticonvulsants and opioids, such as tramadol[22]. Tricyclic antidepressants inhibit norepinephrine and serotonin reuptake, strengthening descending pain inhibitory pathways. Gabapentinoids, on the other hand, decrease calcium inflow and release neurotransmitters such as glutamate, substance P and the peptide genetically related to calcitonin, which are involved with persistent and difficult to control pain. Dose should be titrated as a function of patients' profile and presented clinical response. For neuropathic pain management, pregabalin should be used in the dose of 150 o 600mg/day and gabapentin in the dose of 900 to 3600mg/day[23].

Methotrexate (MTX), in the mean dose of 15mg/week, seems to be beneficial for inflammatory rheumatic polyarthritis developed after chikungunya. MTX is justified by the observation of the presence of monocytes and macrophages in sinuvial tissue of chronic patients, possibly due to virus persistence in this site[24].

Prolonged arthralgia and joint stiffness may benefit from a progressive physiotherapy program. Movement and moderate exercise also tend to improve morning stiffness and pain, however intense exercise may exacerbate pain symptoms.

CONCLUSION

Chikungunya is a complex and still poorly understood entity. It is believed that its pathophysiology involves nociceptive and neuropathic mechanisms. Different therapeutic regimens are available to control pain associated to it, however 40% of patients evolve with chronic pain and impaired QL. Further studies are needed to define the best approach to be adopted.

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