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Chikungunya Virus Infection and its Mainly Clinical Symptoms in Brazil

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Abstract

Introduction

The Chikungunya Fever is a symptomatic infection, where the infected individual can develop typical and atypical symptoms. It is transmitted through the bite of the vectors Aedes albopictus and Aedes aegypti, with an average incubation period from three to seven days.

Objectives

To demonstrate the main atypical clinical symptoms promoted by the Chikungunya virus infection, to report the main examination schemes used to diagnose the disease and to propose public measures that could help society in the fight against the pathogen.

Materials and methods

Literature review, of the integrative review type, performed using PubMed and SciELO databases.

Results

Among the relevant atypical clinical aspects of the Chikungunya infection, it is possible to highlight neurological findings. Chikungunya fever diagnosis is typically clinical, with the recommendation of the Brazilian Ministry of Health to use clinical-epidemiological criteria to define a suspected case. Laboratory confirmation of virus infection is done directly by virus isolation and by viral RNA screening, and indirectly through specific antibody screening. As a way to intervene and improve the situation of Chikungunya infection in the country, it is suggested to increase the availability of its laboratory diagnostic tests in more centers throughout the country and to promote social actions with the population, focusing not only on the virus vector, but also on other aspects involved in the disease, for example clinical signs and care services.

Conclusions

It is essential for health professionals to have extensive knowledge of clinical aspects of Chikungunya infection for the disease to be diagnosed. In addition, further studies are needed regarding the virus infection, its pathogenicity mechanisms, and possible effective and less costly treatment options. It is also important to always ratify Chikungunya infection prevention aspects in the community.

Keywords: Chikungunya; Clinical symptoms; Virus

Introduction

The Chikungunya virus (CHIKV), which belongs to the Togaviridae family, genus Alphavirus, is an RNA virus and was first isolated in humans in 1952, during the first urban cycle outbreak recognized in the modern scientific era when an epidemic struck Muawiya coast, Makondo and Rondo, now Tanzania [1]. Between the 1960s and 1990s, the virus was repeatedly isolated during numerous outbreaks in countries of Central and South Africa (Sudan, Uganda, Democratic Republic of Congo, Malawi, Zimbabwe, Kenya and South Africa), as well as in West African countries, including Senegal, Benin, the Republic of Guinea, Côte d'Ivoire and Nigeria. From the 1960s, frequent outbreaks have also been reported in Southeast Asian countries such as India, Malaysia, Indonesia, Cambodia, Vietnam, Myanmar, Pakistan and Thailand [2].

By 2013, the Americas had reported only imported cases, most of them in the United States, when, in October of that year, the first cases were reported on Saint Martin Island in the Caribbean [3]. In

December 2013, the Pan American Health Organization issued an autochthonous CHIKV transmission alert in the Americas for the first time [3]. In Brazil, the first autochthonous reports were confirmed almost simultaneously in Oiapoque (AP) and Feira de Santana (BA) in September 2014 [3]. The Brazilian Ministry of Health reported that in 2015, up to epidemiological week 15 (4/1/2015 to 4/18/2015), 3,135 suspected cases (autochthonous transmission) of Chikungunya fever were reported in the states of Amapá and Bahia, of which 1,688 were confirmed, five of them for laboratory criteria and 1,683 for clinical-epidemiological criteria [2].

Three genotypes of CHIKV were defined: West African, enzootic East-Central-South African (ECSA) and endemic/epidemic Asian, but as of 2005, a lineage of the ECSA genotype spread to India and Kenya, giving rise to the epidemic genotype of the Indian Ocean Lineage (IOL) [14]. The virus can be transmitted in a human-mosquito-human transmission and can be spread by viremic humans [4]. In Brazil, the main vectors are Aedes aegypti and Aedes albopictus, whose females have the capacity to infect humans through their bite [1].

During the inoculation of CHIKV into the human skin through the mosquito bite, its saliva is inoculated to the host along with the virus, containing a series of molecules with anti-haemostatic and immunomodulatory properties, which induces an early cellular infiltration and increased cytokines. Next, there is a phase of intense viral reproduction in cutaneous fibroblasts and macrophages, dissemination by drainage to the lymph nodes, where reproduction is intensified before the virus is released into the circulation, with subsequent dissemination and consequent damage of target organs, such as joints and muscles.

Direct inoculation of the virus into the circulation can also occur through mosquito bites. It is also worth mentioning the induction of the innate immune response, followed by the cellular immune response, with the release of several pro-inflammatory cytokines, such as interferon-alpha, interleukins, chemokines and growth factors [1].

The average incubation period of CHIKV is three to seven days. The disease can develop into three phases: acute, lasting from 7 to 14 days; subacute, lasting up to three months; and chronic, where symptoms persist for more than three months [3]. The diagnosis is made preferably through molecular assays, however, due to issues such as site infrastructure and socioeconomic conditions of the patients, the diagnosis can be made both by serological and clinical exams, where there are chances of misdiagnosis [5].

Acute infection is symptomatic in 80 to 97% of patients. The most common symptoms are sudden onset high fever (>39 °C) and arthralgia and/or arthritis (practically 100% of the cases), commonly showing a symmetric and polyarticular pattern, generally lasting 10 days, but can last for months. Joint symptoms mainly affect hands, wrists, ankles and feet, most of which are incapacitating.

Chronic joint symptoms disrupt the quality of life of the individual, with significant economic impacts due to loss of labour productivity [3]. Joint symptoms are the majority in the subacute phase, occurring in up to 50% of patients infected by CHIKV. This phase is characterized by the persistence of arthralgia/arthritis, bursitis, tenosynovitis, associated with morning stiffness and asthenia, with continuous or intermittent evolution [1].

Some lessons can be obtained from Chikungunya outbreaks. First, economic development does not protect countries from vector-borne diseases. Modern lifestyles can amplify an epidemic through travelling, population aging and solid waste production, generating breeding grounds for Aedes vectors.

Early recognition of local transmission, followed by rapid and effective vector control and other public health measures, are the only measure to prevent the occurrence of explosive outbreaks [6].

This review aims to highlight the main atypical symptoms caused by the virus, allowing for a greater exclusion of differential diagnoses in relation to Chikungunya infection, thus helping in the clinical diagnosis of the disease.

In addition, the present study will report the most commonly reported diagnostic schemes for the disease and propose possible social interventions that may assist the community in combating this pathology.

Methods

A literature review, of the integrative review type, was carried out using PubMed and SciELO databases as data sources, where articles matching "Chikungunya" and "Brazil" keywords, written in English and Portuguese, and published between 2013 to 2017, were retrieved. Original articles, qualitative research articles, review articles and case studies were included in the present study.

This review was carried out in 3 phases: screening of studies by their titles and abstracts, excluding those that did not fit the researched topic; after this, it was verified the existence of duplicated articles across both databases, excluding repeated ones; lastly the selected articles were read integrally for the construction of the present work.

The present study was conducted from December 2017 to April 2018, with a guiding question for this research: According to the surprising clinical dynamics of the infection caused by the Chikungunya virus, which are the typical and atypical signs and symptoms most frequently found?

Results and Discussion

At the time of the analysis of the present results, 164 scientific articles were found in PubMed and SciELO databases using the search criteria described herein. From those, 160 articles were found in the PubMed database, but only 13 were included in this study. In SciELO database, 20 articles were found, but only 4 were included as the other 16 were duplicated in PubMed retrieved set.

The clinical aspects described in the reviewed articles were primarily divided into typical and atypical, considering the incidence of signs and symptoms in patients, suggesting this classification by their authors.

Epidemiological Aspects in Brazil

In Brazil, according to Ordinance No. 1,271, dated June 6, 2014 (Brazilian Ministry of Health), Chikungunya fever started to be considered a disease of compulsory notification, being possible to quantify the number of cases investigated for suspicion of this arbovirus infection. Based on data collected in the Epidemiological Bulletin [7], Table 1 shows, the probable cases, confirmed cases and confirmed deaths by Chikungunya infection in Brazil from 2015 to 2017, referring to the first to last week of each year.

Year	Probable Cases	Confirmed Cases	Confirmed Deaths
2015	38.499	17.971	14
2016	277.882	151.318	216
2017	185.737	151.966	173

Table 1: Probable cases, confirmed cases and confirmed deaths of Chikungunya infection in Brazil, 2015-2017.

The media has a big impact on population awareness regarding the way the disease is transmitted, as this was an epidemic in several parts of the country. Consequently, daily news regarding Chikungunya infection made the population more aware about the likely symptoms of the disease, but mainly about eliminating the Chikungunya vector. In addition, after the epidemic, clinical studies on better conduct were also performed, which may aid the treatment, not necessarily the cure, but yet avoiding the deaths of many patients. The basic health units were essential in this effect, because primary health focuses in disease prevention, in this case, mainly vector control and since the vector is the same as for Dengue virus infection, campaigns for disease control and education of the population on the subject occur every year, thus preventing both Dengue and Chikungunya.

Until the time of the data analysis of the present study, according to the Epidemiological Bulletin of the Brazilian Ministry of Health, from December 31 of 2017 to February 17 of 2018, 7,406 probable cases of Chikungunya fever in Brazil were reported, with an incidence of 3.6 cases per 100,000 inhabitants; from which 4,106 (55.4%) were confirmed cases [8]. According to the Epidemiological Bulletin of the Ministry of Health (2017), by the same week of 2017, 10,294 probable cases of CHIKV infection were reported in the country, with an incidence rate of 5 cases per 1,000 inhabitants, from which 2,178 (21.2%) were confirmed cases, therefore, it can be noticed that there was a decrease in the incidence [9].

By analyzing the statistics in a linear fashion, one can imagine there will be a decrease in the 2018 cases in Brazil. In addition, the flow of information regarding the prevention of the disease has increased accompanying the rise in the number of affected individuals which has been appearing constantly in the media, enabling the population to act actively to fight the vector in the area.

Of all the Brazilian regions, the one with the highest number of probable cases during this period of 2018 was the Central-West region, with 3,604 cases (48.7%), and the South region with 99 cases (1.3%). As for the incidence of probable cases (number of cases/100,000 inhabitants) by geographic region, the Central-West region also has a higher incidence rate, with 22.7 cases/100,000 inhabitants. In relation to deaths within the aforementioned period, only one death by Chikungunya infection was confirmed through laboratory analysis, nevertheless there are still 7 deaths in process of confirmation or that can be discarded.

The decrease in laboratory-confirmed deaths in the Central-West region can be encouraging, as it would be a consequence of the actions and campaigns regarding Chikungunya. However, it is necessary to reflect that there is a possibility that this reduction is associated with a lack of notifications of Chikungunya virus cases, that is, the lack of confirmation of both the clinical aspects of the disease and its laboratory results. Another point to be raised is that some deaths may initially be linked to Chikungunya, however they can later be reported to have been caused by another disease, directly implicating in the number of reported deaths by Chikungunya infection. Importantly, there is also the possibility of underreporting.

Typical Clinical Aspects

According to Marques et al. there are several divergent points between the studies on CHIKV infection, due to the lack of knowledge of the mechanisms of how certain symptoms are expressed and the diversity of results found by several studies [3]. However, most studies generally agree on some common symptoms, such as abrupt onset high fever (>38.9 °C), chills, arthralgia, exanthema, myalgia, headache and photophobia, which usually last seven days [1-3]. According to the Brazilian Ministry of Health, the signs and symptoms most commonly found are fever above 38.5 °C of acute onset, joint and muscle pain, headache, nausea, fatigue and exanthema, being clinically similar to those of Dengue fever; however the main clinical manifestation differing in both diseases is severe joint pain [10]. Although Chikungunya has a low rate of lethality, it presents a high rate of mortality, as the ceaseless arthralgia leads to a reduction in the productivity and quality of life of the individual.

In addition, confirmed cases are mostly associated with severe, usually symmetric polyarthralgia and chronic arthritis affecting the hip, elbows, fingers, knees and ankles, limiting the locomotion of a patient for months [1,3]. Due to those facts, confusion in the diagnosis between this infection and infections by other endemic arbovirus diseases in the country, such as Dengue and Zika, are common. In addition to this factor, these symptoms are one of the main causes of morbidity and mortality of Chikungunya virus as they reduce quality of life and life expectancy [6].

Furthermore, it is important to note that, due to intense pains and great stiffness of the joints, the chronic arthritis caused by the infection has a great impact on the quality of life of the individuals, to the point of harming the labour relations that they develop in society. Therefore, there are patients who need to retire due to disability, because they can no longer perform their actions, thus negatively impacting the country economy, since this leads to a decrease in the number of working individuals while increasing the amount spent on pensions, as well as with the physiotherapies performed in the public health system.

Eventually, the patient may also present maculopapular exanthema on the trunk, face and extremities, pruritus, headache, fatigue, nausea, vomiting, cervical lymphadenopathy and myalgia. In addition, Chikungunya fever is characterized by leukopenia, thrombocytopenia, hypokalemia and mild to moderate elevation of liver transaminases [1,3].

Atypical Clinical Aspects

Among the symptoms found in articles selected in the literature review performed in the present study, those that were less mentioned by their authors were considered atypical manifestations, and in some studies the authors classify these signs as typical or atypical symptoms. In some of the Chikungunya fever confirmed cases, neurological symptoms have been reported similarly in adults and children, such as: meningoencephalopathy, meningo encephalomyeloradiculitis, mononeuropathies, encephalitis, Guillain-Barre syndrome, flaccid paralysis and myeloradiculitis encephalopathies, the latter presenting itself during the viraemia phase of CHIKV [4]. In addition, conditions such as obesity, rheumatoid arthritis, diabetes mellitus, lupus and multiple sclerosis turn the patient more susceptible to developing a focal neuropathy called Carpal Tunnel Syndrome, which causes inflammatory reactions, a compression of the medial nerve of the wrist and rheumatic disorders in this site, leaving the patient even more debilitated [11].

Regarding ocular symptoms, some findings have shown that CHIKV can affect: the anterior and posterior segments of the eyeball, causing retro orbital pain and conjunctivitis; only the anterior part, being able to cause uveitis, mostly associated with pigmented keratin precipitations and ocular hypertension [12]; and only the posterior portion, where manifestations such as choroiditis, neuroretinitis, optic neuritis and retinitis can be found, where the latter may occur during the fever or after weeks or months from the onset of CHIKV infection [12], where, together with iridocyclitis, consist of the atypical ocular findings noticeably more frequent [2].

Systems	Clinical Manifestations
Neurological	Meningoencephalopathy, meningoencephalitis myeloradiculitis, myeloradiculitis, facial paralysis, encephalopathies, encephalitis, Guillain-Barré syndrome, flaccid paralysis
Ocular	External ophthalmoplegia, retro orbital pain, conjunctivitis, uveitis, ocular hypertension, choroiditis, neuroretinitis, optic neuritis, retinitis, iridocyclitis
Rheumatological	Carpal Tunnel Syndrome
References:	[2,4,11,12]

Table 2: Atypical clinical manifestations of Chikungunya fever in adults.

Unlike adults, symptoms such as irritability, exanthema, hemodynamic instability, vesiculobullous rash, lower limb or generalized edema and hyperalgesia were found in neonates. In addition, there are cases in which the neonate progresses to microcephaly and neonatal encephalopathy [13], the latter being the most common complication among neonates with Chikungunya. Fifty percent of the infected infants presented pathological findings involving the nervous system, such as white matter lesions, convulsions, brain swelling and cerebral hemorrhages, sometimes progressing to permanent disability or death [4].

Systems	Clinical Manifestations
Neurological	Irritability, lesions on white matter, convulsions, swelling of the brain, cerebral hemorrhage
Cutaneous	Vesiculobullous rash, exanthema
Cardiovascular	Hemodynamic instability, edema
References:	[4,13]

Table 3: Atypical clinical manifestations of Chikungunya fever in neonates.

In general, it is known that pathologies may manifest differently (usually more severely) in paediatric and geriatric patients, which is widely found in the literature. Small differences between the symptoms and the frequency of these symptoms in relation to adults can be found, for example, display of neurological symptoms is more common among neonates than among adults [6]. In our literature review, only one case of adult neurological damage was found, in which the patient had a co-infection between Dengue and CHIKV [14].

One of the unusual clinical aspects that we should focus on and that many other researchers also focus on is the neurological symptoms. According to Torres, cerebrospinal fluid analysis of some neonates presenting symptoms of Chikungunya fever (related to cases of perinatal infection in the mother) were positive for CHIKV in RT-PCR assays [15]. Furthermore, miscarriage also occurred in some patients, where molecular investigations revealed the presence of CHIKV viral genome in the placenta, in the amniotic fluid and in the brain of the miscarried foetus.

Laboratory Diagnosis

The diagnosis of Chikungunya fever is typically clinical, since the associated symptoms of acute fever with arthralgia and/or severe acute arthritis is highly suggestive, with high sensitivity and positive predictive value in areas where the disease is endemic and where epidemics occur. Currently in Brazil, the Brazilian Ministry of Health recommends the use of clinical-epidemiological criteria to define a suspected case of Chikungunya fever [1,3].

Laboratory diagnostic of CHIKV infection can be performed directly, through viral isolation and viral RNA screening in different clinical samples, or indirectly through the search for specific antibodies

[16]. For viral RNA screening, the main molecular methods utilized are RT-PCR (Reverse-Transcription Polymerase Chain Reaction) and qRT-PCR (Real Time RT-PCR). These techniques provide a rapid and sensitive diagnosis, allowing the viral nucleic acid to be detected until approximately the eighth day after the appearance of symptoms, where the period of highest viremia comprises from the 1st to the 5th day. This is an important tool for early diagnosis of the infection, but with no utility from the 8th day of infection [16].

Regarding screening of specific antibodies, the main techniques available are: the ELISA (Enzyme-Linked Immunosorbent Assay) and the POC (Point-of-Care) immunochromatographic test. Serological tests allow for the detection of specific antibodies of the IgM type, which can be detected from the second day after the onset of symptoms (where the most recommended period for this serological investigation is from the 5th day) and of the IgG type, from the sixth day [16].

Public Health Measures

Underreporting of diseases, injuries and events are conditions that compromise the actions of public power to address public health problems. It is understood that the consequences of underreporting are many, such as the generation of rates and surveys that do not reflect the real situation of certain morbidity in the country, leading to an assumption of a false reality that there are no problems, thus preventing actions that could translate into efforts for improvement of a given scenario [17].

Through a critical perspective of the present literature review, we suggest that one of the ways to improve the problem of CHIKV infection spreading in Brazil is to invest and increase availability of laboratory diagnostic tests for CHIKV virus detection in more health centers throughout the country. With these measures, a higher number of confirmations of suspected cases and a more concrete survey of the most affected areas of Brazil can be achieved, so that more effective and specific combat measures can be established according to the conditions and characteristics of a given region. However, there is limited research addressing the reality of investments and availability of CHIKV laboratorial diagnostic tests, translated into a shortage in scientific articles, databases and government communication channels. This situation may indicate absence of public power in this aspect involving this disease.

Most recent information on governmental measures to combat Chikungunya are campaigns to combat one of the mosquito vectors, in the case Aedes aegypti, which is highlighted for also being a vector of Zika and Dengue viruses. Around September/October 2017 the government launched a campaign for awareness and mobilization of the media for society sensitization regarding actions to combat the mosquito and prevention. The National Day of Mobilization was scheduled for November 25 of 2017, with the intention of increasing visibility to the integrated effort and summoning Brazilians to participate in the process. The national mobilization was also supported by schools under the coordination of the Brazilian Ministry of Education. The educational institutions were instructed to reserve ten minutes every Friday for an awareness-raising event with the students, so that they disseminate prevention actions for their families and communities throughout the national territory.

Government measures such as mobilization of the population, transfer of information through communication devices and investment in awareness measures in schools, are essential actions in the fight not only against Chikungunya, Zika or Dengue viruses, but also against several other comorbidities affecting the population, being, therefore, valid efforts. However, it is important to highlight the need for these actions based not only on the disease vector, but also on the various aspects involving the disease such as clinical signs, care services, among others.

Conclusion

According to the present literature review, individuals with Chikungunya fever generally present standardized typical symptoms, however the infection may also lead to the appearance of symptoms not commonly displayed by most patients (atypical symptoms). It is valid to know this parameter for disease identification through these symptoms not generally found in patients, but which are of paramount importance for a more reliable clinical diagnosis and an adequate treatment.

Due to factors such as high potential of morbidity from the pathology, rendering people unproductive and with poor quality of life, along with being an imported arbovirus that has managed to establish itself well due to climatic conditions and the vector, it is of the utmost importance for more studies to be produced to further advance knowledge about the virus infection, pathogenicity mechanisms, possible treatment options (palliative or curative in the acute or chronic phase), and also seek new options for treatment that are less costly economically. Furthermore, it is important to always invest on disease prevention, since it is an important tool for reducing the number of cases and one of the simplest and most effective attitudes.

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