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Review

Long-term sequelae of chikungunya virus disease: A systematic review

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ABSTRACT

Background: The acute phase of chikungunya is well documented; less so are its long-term effects. This systematic literature review provides an overview of the currently available data.
Methods: We performed an electronic search in PubMed/Medline and checked reference lists. We included studies in English on long-term sequelae of chikungunya in adults and on long-term sequelae of congenital infection from 2000 to 2016. Case reports, reviews and studies with a follow-up shorter than 6 weeks were excluded.
Results: In total, 37 studies were included; with follow-up periods ranging from 1.5 to 72 months. Most studies were questionnaire-based studies only, in which clinical diagnoses such as arthritis, alopecia and depression were mostly recorded without professional verification.
Persisting arthralgia/arthritis (arthralgia/joint stiffness plus joint swelling) was the most frequent problem encountered. Further frequently mentioned sequelae were alopecia and depression. Quality of life was reduced in many for months to years after the acute phase of chikungunya. Female gender, older age, some co-morbidities and the severity of the acute phase were associated with persistent arthralgia. Congenital infection was associated with neurocognitive dysfunctioning in early childhood.
Conclusion: Chikungunya leads to (self-perceived) long-term sequelae in a considerable proportion of patients, impacting significantly on quality of life. Long-term chikungunya sequelae must be taken into account when dealing with this disease because of its important effect on public and individual health. Prospective large-scale, long-term studies with objective assessment of signs and symptoms attributed to the disease are needed to optimally quantify and qualify these problems.
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1. Introduction

Chikungunya virus (CHIKV) is an arthropod-borne virus, or arbovirus, transmitted by *Aedes albopictus* and *Aedes aegypti* mosquitoes [1]. Since 1999, chikungunya has (re-)emerged epidemically across tropical and subtropical areas around the globe and most recently ripped through the Americas, causing an estimated 1.675.000 cases. From early 2014 onwards, there alone, cases of acute disease had long-term health impact in a considerable proportion of those afflicted [1].

The term 'chikungunya' (meaning 'that which bends up') refers to the severe arthralgia associated with the acute phase of the infection, making an upright gait fairly impossible in many individuals afflicted [1]. The arthralgia is often bilateral, symmetric and affects multiple, mostly distal, joints [2]. Other characteristic symptoms are high fever, myalgia and headache. In addition, a skin rash, gastrointestinal symptoms, fatigue, asthenia, peripheral edema and conjunctivitis occur in relative frequency [3–8].

Long-term sequelae of arboviral infections in terms of persisting signs and symptoms have been known since long [42–46]. With regard to chikungunya, late manifestations remained poorly investigated until the epidemic spread of the disease stepped up its pace recently, beginning with the Indian Ocean islands outbreak only a decade ago [9].

The primary objective of this systematic literature review was to provide an overview of the published literature on long-term sequelae of CHIKV infections. Secondary objectives were:

- to investigate the prevalence of long-term sequelae;
- to identify study characteristics associated with a higher prevalence of long-term sequelae;

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- to investigate their impact on quality of life (QoL);
- to assess the consequences of congenital CHIKV infection for the new-born; and
- to identify factors associated with an increased risk of long-term sequelae of CHIKV infection.

2. Methods

2.1. In- and exclusion criteria

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and meta-analysis (PRISMA) guidelines [10].

In- and exclusion criteria were addressed to identify all relevant studies on long-term sequelae of CHIKV infection. We included studies from 2000 to 2016 for data collection and accepted only studies on humans, written in English. Case reports and reviews were excluded. Articles without information on manifestations and without structured results on long-term effects were excluded.

Furthermore, a follow-up of 6 weeks after the diagnosis of CHIKV infection was determined as a minimum period.

2.2. Search strategy

We searched PubMed/Medline systematically, with a last update in September 2016. Full details of our search strategy are provided in Appendix 1. We searched reference lists of the identified articles by hand for articles not identified by electronic search. At last, we checked articles for duplication and removed duplicated ones.

Titles and abstracts were screened for potentially relevant articles by one reviewer (CMN). Two independent reviewers (MvA, CMN) evaluated the selected full text articles. Discrepancies were resolved by discussion and if necessary a third reviewer (AG) was consulted.

2.3. Data extraction

We used a uniform tool to extract data from eligible papers and recorded relevant data on a summary sheet.

One reviewer (CMN) made an overview of patient characteristics, methodological characteristics, the studied population, and study period (Appendix 1). A second reviewer (MvA) checked this overview.

2.4. Definitions

2.4.1. Musculoskeletal disorders

Most studies differentiated between arthralgia and arthritis, however four studies grouped those definitions together as musculoskeletal disorders [8,11–14], Persistent arthralgia was often defined as joint pain at the time of follow-up. Four studies made a subdivision between relapsing and continuous PA, but different definitions were used [6,11,14,17].

To define arthritis, six studies [15–20] applied the American College of Rheumatology (ACR) criteria. One study [27] used a modified version of the ACR; serology and radiographic changes were not taken into account. Furthermore, in this study, the observer was not medically qualified. Moro et al. [3] defined arthritis based on a functional ability (ROAD) index. This questionnaire included 12 items and assessed the upper extremity function, the lower extremity function and the activities of daily living/work. These items represented a combination of symptoms common to early arthritis.

Yaseen et al. defined arthritis as joint pain and/or stiffness involving swelling of the joint [21].

2.4.2. Alopecia

The used definition of alopecia was the subjective experience of hair loss, without any objective measurement [3,14,22], and without specification of the hair loss pattern.

2.4.3. Depression

Depression was very often not well defined [14,23,24]. Only two studies reported on the (self-assessed) depressed mood, instead of depression [24,25].

2.5. Measurement tools

2.5.1. Tool for disability

To assess disability due to persistent arthralgia, Rahim et al. [11] applied the Health Assessment Questionnaire Disability Index (HAQ-DI). This is a questionnaire for the assessment of rheumatoid arthritis (RA). Rising, dressing, eating, walking, bathing, reaching, gripping, and performing errands were assessed on a scale from 0 to 3. The average of all scores was taken to classify disability as 0 = no difficulty, 0–1 = mild disability, 1–1.5 = moderate disability, and >1.5 = severe disability.

2.5.2. Tool for quality of life

In the section on QoL, the Short Form 36 (SF-36) questionnaire is mentioned. The QoL is scored from 0 (maximum disability) to 100 (no disability). The score consists of eight scales, globally assessing mental and physical components. The mental component score (MCS) comprises vitality, mental health, social functioning and role functioning difficulties caused by emotional problems. The physical component score (PCS) comprises general health, bodily pain and physical functioning difficulties caused by physical problems.

The Short Form 12 (SF-12) questionnaire is also mentioned in the same section [25]; this is a shorter and newer version of the SF-36.

2.5.3. Tool for developmental level of children in early childhood

In the section on congenital CHIKV, Gérardin et al. [26] mention the Revised Brunet-Lezine scale. This scale is used to assess the development of children in the early childhood (24–30 months old). The scale covers four aspects of neurodevelopment, represented in four sub-scores: movement and posture, coordination, language and sociability. Together, these sub-scores yield a mean global developmental quotient (DQ) of 100; A DQ > 85 is considered a normal development; between 70 and 80 a moderate global developmental delay, and a DQ < 70 a severe delay.

3. Results

The search flow is summarized in Fig. 1. The initial search strategy on Pubmed/Medline yielded 213 articles. Another 5 articles were identified through the search of reference lists, resulting in a total of 218 articles. After title and abstract screening, 48 articles were selected for full-text evaluations. Application of the exclusion criteria led to 37 included studies.

All studies were quantitative studies; 18 were retrospective [4,8,11,14,15,17–22,25,27–32], of which 14 (78%) were based on questionnaires [8,12,14,15,17,18,20–22,25,27–30]. Of the other 4 studies, two had included patients based on a visit to a physician, one based on both a questionnaire and a visit to a physician and in one study the method of data collection was not described. Seventeen of the 37 studies were prospective [3,5,7,12,13,16,23,24,26,33–38]. Of these, 3 were based on a questionnaire with or without a validated scoring system, 9 were based

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