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Chikungunya virus outbreak in Sint Maarten: Long-term arthralgia after a 15-month period

C.M.M. Peters[1], R. Pijnacker[2], E.B. Fanoy[2,3], L.J.T. Bouwman[4], L.E. de Langen[4], J.H.T.C. van den Kerkhof[2], J. Reimerink[2], E. Pilot[5], M. Henry[6], V. Asin Oostburg[6] & M.A.H. Braks[2]

[1]*Maastricht University, Maastricht;* [2]*Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven;* [3]*Public Health Service (GGD) Region Utrecht, Zeist;* [4]*Wageningen University Research Center, Wageningen;* [5]*School of Public Health and Primary Care (CAPHRI), Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, the Netherlands;* [6]*Collective Prevention Services, Philipsburg, Sint Maarten*

ABSTRACT

Background & objectives: The first chikungunya (CHIK) epidemic in the Americas was reported in December 2013. Chikungunya virus (CHIKV) causes an acute febrile illness and is transmitted to humans by *Aedes* mosquitoes. Although earlier studies have described long-term clinical manifestations of CHIK patients infected with the East/Central/South African (ECSA) genotype, little is known about persistent manifestations in the Caribbean region, for which the Asian genotype is responsible. The objective of this study was to describe the presence of persisting clinical manifestations, specifically arthralgia, in CHIKV-infected patients on the Caribbean Island, Sint Maarten, 15 months after onset of the disease.

Methods: This retrospective cohort study included confirmed CHIK patients that were recorded by the participating general practitioners (GPs) during the chikungunya outbreak in 2014 in Sint Maarten. Between March and July 2015, 15 months after the onset of disease, patients were interviewed *via* telephone about the presence, duration and impact of clinical CHIKV manifestations.

Results: In total, 56 patients were interviewed (median age 47 yr), of which 30 (54%) were females. Out of the total interviewed patients, 52 (93%) reported arthralgia for the first three months after the disease onset, of which 23 (44%) patients reported to have persistent arthralgia, 15 months after the disease onset. Pain intensity of persistent arthralgia was perceived as mild in the majority of patients (n = 14; 60%), moderate in 7 (30%) patients and severe in 2 (9%) patients. During the acute phase of disease, most patients had to miss school or work (n = 39; 72%) due to clinical CHIKV manifestations and reported a negative impact on daily activities (n = 36; 57%).

Interpretation & conclusion: Results suggested that persisting arthralgia is a frequent complication in CHIK patients included in the study. Future research on strain-specific clinical long-term manifestations and on their impact on daily life of patients, in the form of a comparative study between patients and controls, is recommended.

Key words Arthralgia; Caribbean; chikungunya; Sint Maarten; vector-borne diseases

INTRODUCTION

Chikungunya virus (CHIKV) is a RNA arbovirus that belongs to the genus *Alphavirus*[1]. The main vectors for CHIKV are *Ae. aegypti* and *Ae. albopictus* mosquitoes. *Ae. aegypti* is mainly found in tropical and subtropical areas, while the *Ae. albopictus* is more widespread as it can also be found in areas that have a more temperate climate[2]. Three genotypes of CHIKV have been identified: The Asian, the West African and the East/Central/South African (ECSA) genotype[3]. Chikungunya (CHIK) symptoms usually occur after an incubation period of 3–7 days, with a range of 1–12 days. About 3–25% of CHIKV-infected patients experience an asymptomatic infection[2]. Characteristic of CHIK symptoms (acute) are fever, (poly) arthralgia, myalgia, joint swelling, rash, back pain, headache, fatigue, nausea, vomiting, polyarthritis and conjunctivitis. The acute phase of CHIK lasts for 3–10 days[4–5].

Since 2005, CHIKV has spread to over 50 countries, resulting in an estimated one million cases per year[6–7]. The first local transmission of CHIKV in the Caribbean region and the Americas was reported in December 2013 on the French part of Island Saint Martin, which subsequently spread throughout the region[3]. The first case on Sint Maarten, the Dutch part of the Island, was notified on December 13, 2013. Up to October 2014, 470 laboratory-confirmed CHIK patients were reported to be diagnosed on Sint Maarten[8]. The Caribbean outbreak was caused by the Asian CHIKV-strain, which is genetically related to strains recently identified in Indonesia, China and the Philippines[9].

Research indicates that patients frequently report clinical manifestations of CHIK, to last for months or even years after the acute infection, with some patients experiencing relapses, persistent arthralgia or musculoskeletal complaints[5]. Studies conducted after the 2006 CHIKV-outbreak on the Island La Réunion reported persistent arthralgia in 53 to 60% of the study populations between 15 and 36 months after onset of the disease[10–12]. On Mauritius, 79% of patients experienced persistent musculoskeletal symptoms, 28 months after the initial CHIKV-infection[13]. Similarly, 12 months after a CHIKV outbreak in Italy, 66% of all cases reported to have experienced at least arthralgia, myalgia or asthenia while 19% reported experiencing all these symptoms[14]. In contrast, CHIKV-outbreaks in India were associated with lower rates of long-term clinical manifestations where persistent arthralgia (>12 months) was reported in 1.6–22% of the patients[15–17].

There is limited data available on long-term manifestations of CHIK in the Caribbean region. One study among travellers from the Caribbean reported that 23% (3/13) of them experienced joint pain 13 months after diagnosis[18]. A study in the US Virgin Islands found 2.5-fold increase of arthralgia among cases compared to controls at 12 months after onset of the disease[19]. Insight in the public health impact of a CHIKV-outbreak is relevant to underpin mosquito control strategies, individual preventive measures and to understand the (clinical) impact of CHIK on a patient. The objective of this study was to determine the presence of persistent arthralgia, in CHIK patients on Sint Maarten after 15 months of disease onset.

MATERIAL & METHODS

Study design and population

A retrospective cohort study was conducted among confirmed CHIK patients on Sint Maarten. Thirteen out of the 22 general practitioners (GPs) on Sint Maarten provided contact information of 320 out of 470 confirmed CHIK patients that were registered with them till August 18, 2014. Two researchers examined the medical records of potential CHIK patients together with their GP. Patients matching the case definition of a confirmed CHIK patient were included in the study cohort and their contact information was obtained. A confirmed CHIK patient was considered a person with a positive polymerase chain reaction (PCR) and/or specific positive IgM antibody test, and having both fever (>38.5 °C) and arthralgia at disease onset[3].

These patients were contacted between September and December 2014 to obtain permission for inclusion in the study and for additional contact information such as telephone numbers, after which 198 patients were found to be willing to participate in the study. Between March and July 2015, 15 months after the onset of symptoms, patients were contacted and interviewed accordingly.

Data collection

Researchers (in total 4) of the National Institute for Public Health and the Environment (RIVM) in the Netherlands used the calling feature of Skype to connect to (mobile) phones on Sint Maarten to conduct the interviews using a standardized English or Spanish questionnaire. Interviews were conducted 15 months after disease onset, between March and July 2015. The one (and only) inclusion criterion was a confirmed CHIKV infection; there was no exclusion criterion. Information was collected regarding age, gender, comorbidities, as well as the presence and anatomic location of clinical manifestations, *e.g.* arthralgia and myalgia, and medication usage. For clinical symptoms, duration was categorised in <3, 3–6, >6 and 15 months.

Moreover, for arthralgia and myalgia, an 11-point pain intensity numerical rating scale (PI-NRS) was used, ranging from 0 to 10, for scoring patients' self-perceived pain intensity at onset of the disease (M_0) and 15 months after onset of the disease (M_{15})[20]. The anatomic locations that were affected by arthralgia were assessed at the onset of the disease and 15 months after onset of the disease. The impact on the patients' daily activities was measured by asking if they missed school or work or/and if their household or daily activities were negatively impacted by CHIK complaints.

Outcomes

The primary outcomes were self-perceived persistent arthralgia and/or myalgia. Patients were considered to have persistent arthralgia and/or myalgia, if they answered to have arthralgia and/or myalgia, 15 months after disease onset. Pain intensity scores were categorised into no pain (0), mild pain (1–4), moderate pain (5–6) and severe pain (7–10). The perceived quality of life at M_{15} was recorded based on a 0 to 10 scale.

Odds ratios (OR) with corresponding 95% confidence intervals (95% CI) were calculated using logistic regression, where persistent arthralgia was associated with the presence of comorbidities. Difference between patients with or without persisting arthralgia was tested using a two-tailed Student's *t*-test. Statistical analyses were performed with STATA v14.2 software (StataCorp,

College Station, Texas), with a statistical significance set to $p < 0.05$.

Ethical considerations

Study approval is not necessary according to the Dutch medical ethical committee rules, as no medical interventions were performed and no socially sensitive questions were asked. All patients were provided with the freedom of choice whether or not they wanted to participate in the study. All patients participating in the study gave oral permission to participate in the study, to be contacted 15 months after disease onset and for their data to be used for research purpose. All data is anonymized before analysis.

RESULTS

In total, 56 of 198 (28%) patients who agreed to participate, were interviewed between March and July 2015. Of the remaining 142 patients, 110 patients were excluded because the date of disease onset was unknown, and 32 patients were excluded due to disconnected telephone numbers, not answering the telephone after calling four times at different times of the day or discontinuing the interview before completion. The included study population consisted of 30 (54%) females and 26 (46%) males (Table 1). The median age of the study population was 47 (Range: 10–73 yr). The excluded patients had a median age of 47 (Range: 4–80 yr) and 54 (38%) were male. The most commonly reported comorbidities were hypertension (n = 12; 21%) and diabetes mellitus (n = 10; 18%).

Disease characteristics and impact

The most frequently reported manifestation in the first three months after disease onset was arthralgia (n = 52; 93%). Fatigue (n = 36; 67%), morning stiffness (n = 30; 55%), and myalgia (n = 27; 50%) were reported in at least half of the patients. Other reported symptoms were joint swelling (n = 23; 43%), tasting problems (n = 21; 39%), skin rash (n = 19; 35%), and sleeping problems (n = 19; 35%) (in order of prevalence) (Table 2).

In the acute phase of the disease, arthralgia pain sites were most often, the knees (n = 38; 73%), followed by fingers (n = 30; 58%) and wrists (n = 30; 58%) (Table 3). The majority of CHIK patients reported arthralgia to be consistent (n = 31; 63%), and one-third (37%) said it was intermittent (Table 4). Arthralgia pain intensity was scored as mild in 6 (12%) patients, moderate in 5 (10%) patients, and the majority, *i.e.* 41 (79%) patients, scored it as severe. Of patients who experienced myalgia during the acute phase, 15 (56%) reported it as constant pain and 12 (44%) as intermittent pain. The pain intensity was scored as mild in 4 (15%) patients, moderate in 9 (35%) patients, and severe in 13 (50%) patients.

Table 1. Baseline characteristics of confirmed CHIK patients (n = 56) on Sint Maarten, interviewed during March–July 2015

Characteristics	n	%
Age (yr)		
<25	4	7
25–44	20	36
35–64	28	50
>65	4	7
Gender (Female)	30	54
Chronic comorbidity		
Hypertension	12	21
Diabetes mellitus	10	18
Cardiovascular disease	1	2
Rheumatoid arthritis	0	0
Other	7	13

n—No. of patients.

Table 2. Presence and duration of clinical manifestations of confirmed CHIK patients (n = 56)

Clinical manifestations	< 3 months		3–6 months		6–15 months		15 months	
	n	%	n	%	n	%	n	%
Arthralgia	52	93	28	52	23	44	23	44
Fatigue	36	67	9	17	6	11	6	11
Morning stiffness	30	58	12	23	9	17	8	15
Myalgia	27	50	7	13	6	11	6	11
Joint swelling	23	43	4	7	4	7	3	6
Tasting problems	21	39	4	7	3	6	3	6
Sleeping problems	19	35	5	9	3	6	3	6
Skin rash	19	35	1	2	1	2	1	2
Memory problems	9	17	9	17	9	17	9	17
Conc. problems	8	15	4	7	4	7	4	7

n—No. of patients.

Table 3. Frequency of reported anatomic pain locations in patients with arthralgia at disease onset (n = 52) and 15 months after disease onset (n = 23)

Anatomic pain locations	M_0		M_{15}	
	n	%	n	%
Upper body				
Finger	30	58	9	39
Wrist	30	58	6	26
Elbow	28	54	4	17
Back	23	44	3	13
Shoulder	21	40	5	22
Lower body				
Knee	38	73	11	48
Ankle	28	54	6	26
Foot	24	46	9	39
Hip	19	37	7	30

n—No. of patients; M_0—At onset of disease; M_{15}—After 15 months of disease onset.

Most patients had missed school or work (n = 39; 72%) due to clinical manifestations of the CHIKV-infection during the acute phase of disease, and reported a negative impact in household or daily activities (n = 36; 67%) (Table 5). The extent of impact on patients' daily activities and their work or school were observed to be high in approximately, half (n = 25; 47%) of the patients, moderate in one third (n = 16; 30%) of the patients, and low in 8 (15%) patients. Almost all patients (n = 53; 98%) used medication in the acute phase of the disease, mainly paracetamol (n = 46; 87%).

Persisting symptoms

Half of the patients (n = 25; 52%) reported to have arthralgia for >3 months after onset of disease. The majority of them (n = 23; 44%) still had those symptoms at M_{15}, and were considered to have persistent arthralgia. Of all the 7 (13%) patients with myalgia for >3 months after onset of disease, all except one patient still had myalgia at M_{15}. Other persistent symptoms at M_{15} mainly included memory problems (n = 9; 17%), morning stiffness (n = 8; 15%) and fatigue (n = 6; 11%).

In patients with persistent arthralgia, most frequently reported pain sites were knees (n = 11; 48%), fingers (n = 9; 39%), and feet (n = 9; 39%). The majority (n = 14; 60%) scored the persistent arthralgia's pain intensity as mild, 7 (30%) as moderate and 2 (9%) as severe. Pain intensity of persistent myalgia was scored as mild in 3 (50%) patients, moderate in 2 (33%) patients, and severe in 1 (17%) patient. Four patients (8%) reported medication use at M_{15} due to persistent clinical manifestations of their CHIKV infection. Having comorbidities was not found to be significantly associated with having persistent arthralgia after 15 months of the onset of the disease (OR: 1.43; CI: 0.45–4.51).

The mean quality of life on a 10-point scale was scored as 8 (Range: 0–10) in patients *without* long-term complications and 7 (Range: 4–10) in patients *with* long-term complications ($p = 0.119$).

Table 4. Pain intensity and type of arthralgia and myalgia reported by confirmed CHIK patients (n = 56) at disease onset and 15 months after disease onset

Characteristics	Arthralgia				Myalgia			
	M_0 (n = 52)		M_{15} (n = 23)		M_0 (n = 27)		M_{15} (n = 6)	
	n	%	n	%	n	%	n	%
Pain intensity								
Mild	6	12	14	60	4	15	3	50
Moderate	5	10	7	30	9	35	2	33
Severe	41	79	2	9	13	50	1	17
Type*								
Constant	31	63	–	–	15	56	–	–
Intermittent	18	37	–	–	12	44	–	–

*Only recorded for M_0; n—No. of patients; M_0—At onset of disease; M_{15}—After 15 months of disease onset.

Table 5. Impact of the disease in CHIK patients (n = 56) at beginning of infection

Category	No. of patients	%
Missed school or work	39	72
Household or daily activities	36	67
Impact on lifestyle		
Low	8	15
Moderate	16	30
High	25	47
Medication use at M_0	53	98
Duration of medication use		
<3 months	36	72
3–6 months	5	10
>6 months	0	0
After 15 months	4	8
Specific medicine*		
Paracetamol	46	87
Corticoid	4	8
Morphine	0	0
Other (such as traditional herbs)	14	26

*Multiple answers were possible; n—No. of patients.

DISCUSSION

This study provides indication that long-term clinical manifestations of CHIK might be frequent in patients on Sint Maarten. Almost half (44%) of CHIK patients included, reported persisting symptoms at M_{15}. The majority of cases reported their pain intensity to be mild. Furthermore, persistent fatigue, memory problems, morning stiffness and myalgia were reported in 11–17% of included patients at M_{15}.

A slightly lower rate of persistent arthralgia was reported in a study conducted in the USA among travellers returning from the Caribbean, mostly the Dominican Republic, although based on small numbers. On average 13 months after diagnosis (Range: 9–16 months), 23% (3/13) of CHIK patients without pre-existing rheumatic/musculoskeletal disease reported to have joint pain, and 32% (6/19) when including patients with pre-existing rheumatic disease[19]. However, none of the patients included in the present study had pre-existing rheumatic symptoms. In contrast, higher rates were reported in studies conducted on La Réunion[10–12, 24]. Differences could be explained by differences in CHIKV-strains or population specific factors. Apart from the study of Zeana *et al*[18] conducted in 2016, all studies mentioned above were conducted during or after outbreaks of the ECSA CHIKV-strain, while the

outbreak on Sint Maarten was caused by the Asian-strain. Studies conducted on outbreaks in India with the ECSA CHIKV-strain, report lower rates of persistent arthralgia[15–17], than the studies conducted on La Réunion[10–12]. These differences could be due to population specific factors or mutations in the ECSA CHIKV-strain.

In the current study, patients suffered for either a short period of time (< 3 months) or a long period of time (15 months) from arthralgia. Almost all patients, with arthralgia for >3 months after disease onset, had arthralgia at M_{15}. Similar studies contradict this pattern of arthralgia duration[11, 14–15, 20–21]. A study conducted in India, in which CHIK patients were followed for 18 months, reported that two-third of patients with arthralgia for >3 months, did not showed arthralgia symptom after >12 months[15]. Other studies seem to have a continuous decline in number of patients with arthralgia over the months[11, 14, 21].

Considering the severity of complaints; the majority (n = 41; 79%) of CHIK patients reported severe arthralgia at M_0, while only two (4%) patients reported severe arthralgia at M_{15}. The study conducted on La Réunion reported a similar pattern of severe pain intensity at M_0 and M_{15}, with 78 and 1% respectively[10]. A study conducted in Malaysia however reported persistent arthralgia after 20 months in 9 (23%) patients, of which six patients had mild pain, and three patients had moderate pain (none of the patients had severe pain)[22].

Knowledge about anatomic locations associated with arthralgia due to CHIK is relevant for diagnostic considerations. In this study, fingers and knees were most frequently affected by arthralgia at the onset of disease and after 15 months of the onset. Although other studies also reported these anatomic locations to be more frequent, ankles were most frequently affected by arthralgia in those studies[12, 21, 23–24]; however, this was not the case in the present study's population.

Myalgia was reported in this study to affect approximately half of the confirmed CHIK patients in the first three months after disease onset, which declined to 6 (12%) after 15 months. Higher proportions were reported in a study conducted in Italy[14], where myalgia declined from 47% at M_0 to 35% after 12–13 months. Differences could possibly be attributable to population specific factors or differences in CHIKV-strains: The CHIK-outbreak in Italy was caused by the ECSA-strain, while the Asian CHIKV-strain caused the outbreak in Sint Maarten.

In contradiction to this study, earlier studies reported an increased risk of persistent arthralgia, when having comorbidities such as diabetes and osteoarthritis[10, 12, 14]. This study had a small study population, which could explain why no association was found between having comorbidities and persistent arthralgia.

The CHIKV-infection had considerable impact on the lifestyle and daily activities of the patients. A total of 39 (72%) patients missed school or work and 36 (67%) suffered from an impact on household or daily activities during the acute phase of the disease. This is comparable to the impact reported in the study from La Réunion, in which 67% of the study population missed school or work and 75% felt restricted in household or daily activities[10]. Impact on lifestyle was only assessed for the acute phase of disease (M_0). The impact is likely to be smaller at M_{15}, given the decrease in presence and severity of clinical manifestations of CHIK compared to M_0.

Limitations

Several limitations of this study need to be considered when interpreting its results. Since this study relied on self-reported symptoms, recall bias could have occurred, as patients might have forgotten whether they had symptoms at the beginning of the infection. Recall bias is however not likely to influence the results of persistent symptoms at M_{15} as those symptoms were present at the time of the interview. Furthermore, patients with more severe clinical manifestations of CHIK might have more likely visited a GP and been diagnostically tested. These patients had higher chance of inclusion in this study, possibly introducing selection bias. Although, age and gender between respondents and non-respondents were similar, the possibility of participation bias occurrence can not be excluded, because there was no data of non-participants with regard to persistent clinical manifestations of CHIK.

Moreover, the proportion of patients with persistent arthralgia in this study might have been overestimated. Eight patients were considered to have persistent arthralgia who initially reported absence of arthralgia at M_{15}. However later during the questionnaire these patients scored their arthralgia to be mild or moderate. If these eight patients were to be excluded, the proportion of patients with persistent arthralgia would still be lower than percentages reported on the island of La Réunion, but comparable to a study conducted among travellers returning from the Caribbean[19]. Additionally, because no data was available on symptoms in the general population, it is not sure that reported symptoms such as memory problems are attributable to CHIKV infection.

CONCLUSION

This study demonstrated the presence of long-term clinical manifestations in CHIK patients on Sint Maarten,

with almost half of the patients reporting persisting arthralgia 15 months after disease onset and adds to the pool of existing evidence on long-term complications of the Asian strain. Although, the majority of patients reported persisting symptoms to be mild, this study highlights the considerable health impact on CHIK patients, especially during the acute phase of the disease. It could be recommended to doctors to take persistent arthralgia due to CHIK into consideration within a differential diagnosis of arthralgia in a CHIKV-endemic region. Furthermore, possible differences in strain-specific long-term clinical manifestations and the impact of long-term clinical manifestations on daily activities of the patient require further research. A larger study including a control group could enable identification of risk factors of long-term clinical manifestations of CHIK. Identified risk factors could be used in the development of an effective intervention in order to prevent long-term clinical manifestation of CHIK.

Conflict of interest

The authors declare that there is no conflict of interest.

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Correspondence to: Ewout Fanoy, MD, Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Antonie van Leeuwenhoeklaan 9, 3721 MA, Bilthoven, The Netherlands.
E-mail: ewout.fanoy@rivm.nl

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