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Research Article

Post-Chikungunya Joint Pain Sequelae: A Sudanese Single-Center Study

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Abstract

Background: Chikungunya has recently been reported by the WHO to account for many cases in Sudan. The infection is extremely symptomatic, with fever, skin rash, and incapacitating arthralgia, which can promote chronic arthritis and rheumatism in older patients. A few studies on chronic pain owing to the Chikungunya virus (CHIKV) infection have been issued. The aim of this study was to outline the laboratory findings and the physical symptom frequency of joint pain of the current Sudanese CHIKV outbreak, and evaluate its impact on the individual.

Methods: This cross–sectional study included 23 CHIKV-confirmed patients attending a Sudanese single private medical center between March and September 2019. The included patients were checked for rheumatoid factor (RF) value, C-reactive protein (CRP) titer, erythrocyte sedimentation rate (ESR) value, and uric acid (UA) level. Physical scrutiny was conducted and persistent symptoms were registered.

Results: The significant rheumatologic conditions were polyarthralgia 39.1%, polyarthritis 21.7%, arthralgia 17.4%, arthritis 13%, and osteoarthritis 8.8%. Swelling signs were noted in 21.9% of the patients. Joints implicated were knees 59.4%, wrists 56.3%, fingers 50%, shoulders 37.5%, feet 34.4%, ankles 31.3%, spine 18.8%, and elbow 9.4%. CRP, RF, and ESR were significantly increased in patients with persistent joints pain versus non-persistent joint pain patients (P = 0.000, 0.002, 0.008, respectively). Whereas the UA was insignificant (P = 0.920).

Conclusion: Knee joint pain remarks a significant dilemma post-CHIKV. It is noted that these remarks were linked with the risk of subsequently creating chronic sequelae. Polyarthralgia was the dominant inflammatory sequel post-Chikungunya infection.

Keywords: CHIKV, Arthritis, Arthralgia, Polyarthralgia, Polyarthritis, Sudan

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1. Introduction

Chikungunya virus (CHIKV) infection is a mosquito-borne disease that can cause prompt chronic articulations pain and arthritis [1]. CHIKV is an arbovirus transmitted by the bite of the casualty female of mosquitoes, *Aedes aegypti*, and *Aedes albopictus*. Patients with

severe contagion present with fever, headache, myalgia, rash, and joint pain. Previous outbreaks have been documented in Africa, Asia, Europe, and the Indian and Pacific Ocean islands and even Sudan [2]. CHIKV can cause extreme morbidity and, since 2005, scanty fatal cases were quantified [3]. Sudan is an African nation that fringes the Red Sea and seven nations. The atmosphere in Sudan is hot and dry. In the year 2018, 15 of Sudan's 18 States have been influenced by overwhelming downpours and floods among June and early November [2]. The circumstance made great ground for mosquitoes' reproduction. The distribution of CHIKV in the overall public is obscure in Sudan. Sporadic instances of CHIKV having co-infection with Dengue Fever have been accounted for from Sudan [2]. Nonetheless, high densities of *Aedes aegypti* have been recognized in all States of Sudan excluding Khartoum and Northern States [3]. CHIKV causes both acute and chronic disabling trouble. Beginning weeklong prostrated fevers are predominantly followed by musculoskeletal and joint pain, frank arthritis, and, more infrequently eye inflammation, vision loss, Guillain-Barre Syndrome, paralysis, vasculitis, encephalitis, hepatitis, and/or myopericarditis [4]. The term "Chikungunya" signifies "that which bends up" about the extreme arthralgia related to the intense period of infection and the subsequent posture of those afflicted. To date, the exact mechanism for CHIKV's incapacitating sequelae stay to be completely obscure. Underlying comorbidities, for example, cardiovascular disease, hypertension, concomitant osteoarthritis, obesity, and diabetes have been distinguished as conceivably expanding the seriousness of CHIKV disease. Likewise, age at the time of extreme infection has been accounted for by many examiners to be predictive of persistent arthralgia or arthritis after CHIKV infection [5]. Research conducted in the American outbreak explored that 30–70% of CHIKV infected patients experience persistent joint pain months or years after their severe sickness. There have been a few statements of the recurrence of chronic joint pain in American [6]. In this study, we examined the laboratory findings and the physical symptom frequency of joint pain of the current Sudanese CHIKV outbreak and its effect on the individual.

2. Patients and Methods

Thirty-two patients with clinically and laboratory-confirmed CHIKV infection were recorded as a portion of a prospective cross-sectional study in the period from March to September 2019. This study was started six months after the end of the current Sudanese outbreak. The diagnosis of CHIKV was immunologically verified by enzyme-linked immunosorbent assay (ELISA). A baseline survey was documented to ascertain exposure history, rheumatologic symptoms, duration of symptoms, number of joints

affected, and comorbidities. Patients defined as suffering from joint pain were taken to complete the arthritis disease activity score questionnaire [7]. Individuals who already have features or confirmed for arthritis, systemic lupus erythematosus (SLE), Sjogren's syndrome, sarcoidosis, chronic infection, and cancer were excluded from this study. All enrolled CHIKV patients were screened for rheumatoid factor (RF) titer, C-reactive protein (CRP) titer, erythrocyte sedimentation rate (ESR), and serum uric acid level.

2.1. Arthritis Severity Score

The disease activity sequelae in patients were estimated using the internationally validated disease activity score recommended by the American College of Rheumatology [7].

2.2. Quality Control

Standard operational procedures (SOPs) were carefully pursued, and quality control materials were applied for all serological tests. Moreover, the research facility quality was guaranteed by well-prepared experts and supervision during sample processing.

2.3. Sample Size calculation

The gauging of sample size was calculated using a cross-sectional statistic formula at 95% CI, 18% marginal errors with 50% of CHIKV distributed in a similar study [8]. A 10% unresponsive rate was likewise used to turn away any errors and expand the dependability of the findings. The sample size was adjusted to 32.

2.4. Laboratory analysis

For each patient, 3 ml venous blood samples were gathered under an aseptic condition in sterile plain containers for performing Uric acid level, RF and CRP titers. 2 ml venous blood samples added to 3.2% Tri-sodium citrate containers in a proportion of 1: 4 forwarded to carried out ESR (Westergren technique).

2.5. Data analysis

Data are summarized as mean ± standard deviation for continuous variables and as the number (percentage) for categorical variables. The Kolmogorov-Smirnov test was employed to assess the distributions of continuous variables and it exhibited that the variables were normally distributed for each group. Nonparametric tests, Mann-Whitney test and Wilcoxon signed rank test were used to compare CRP, RF, ESR, and UA between patients with persistent joint pain and non-persistent joint pain. The Chi-squared test or Fisher's exact test was conducted for rheumatological symptoms and diagnosis. Linear regression was applied to explore the provoke of CRP and RF with the duration of the disease. The correlation between variables was measured by Spearman's rank-order correlation analysis. $P< 0.05$ was taken statistically significant. Data were analyzed employing statistical package for social science (SPSS 24.0 version, IBN, Chicago, USA).

3. Results

A total of 32 participants were enrolled and fulfilled the criteria of the study. Of 32 patients, 16 (50%) were males and 16 (50%) were females. The baseline categories of the confirmed cases were highlighted in (Table 1). The most frequent baseline comorbidity was diabetes (13%). The most commonly influenced joints were knees joint, wrists joint, fingers joint, and shoulders joint (Table 2). The underlying joint pain during the intense infection lasted a median of 3 months, and numerous patients had sporadic and persistent joint pain after the initial infection. At the point when patients were arranged by sex, it was noted that both genders were equally prone to have CHIKV infection symptoms.

During follow-up, the median duration of joint pain was documented as 3 months. 23 out of 32 patients (71.9%) had persistent joint pain. About 48% of patients with persistent joint pain were female (Table 1). This study reported up to 6 joint involvements, including the number of joints implicated and the span of joint symptoms. The elementary infection was observed the overwhelmed majority of CHIKV infection among the studied 25 (78.1%), whereas recurrent infection was seen only in 7 (21.9%) of the patients. According to the disease activity score, most of the cases in this study are polyarthralgia (39.1%) followed by polyarthritis (21.7%), arthralgia (17.4%), and arthritis (13.0%) (Table 1).

The difference between the CHIKV infected patients with persistent joint pain and non-persistent joint pain was found to be significant in CRP, RF, and ESR ($P= 0.000$, 0.002, and 0.008, respectively). While Uric acid was insignificant between the two

groups (P=0.920) (Table 1). ESR was significantly increased in persistent joint pain (ranged 25 - 50) in 50% of patients. ESR. CRP and RF titer values were ranging between 3 and 60 (median 14.3 mg/liter) and from 4.7 - 24 (median 11.2 IU/ml), respectively. 34.4% of patients with persistent joint pain had a significant increase in RF value which indicates inflammatory arthritis. 59.4% of persistent joint pain was concerned with high CRP titer levels. 8 (25%) of patients had high RF and CRP titer values. Moreover, CRP was not affected by the duration of the disease (*P*= 0.152), unlike RF which was statistically increased with the increasing duration of the illness (*P*= 0. 013). This was highlighted by regression analysis (Figure 1, 2).

Among the participants in the present report, the most frequent joint pain symptoms recorded were knee joint pain which was experienced by 59.4% of the patients followed by wrist joint pain 56.3%, fingers joint pain 50%, shoulder joint pain 37.5%, feet joint pain 34.4%, ankle joint pain 31.3%, swelling 21.9%, spine joint pain 18.8%, and elbow joint pain 9.4%. Interestingly, the knee joint pain symptom represented the signature symptom post-CHIKV infection (*P* = 0.000) as well as wrist joint pain (*P*= 0.001), fingers joint pain (*P*= 0.002) (Table 2). However, it is great to note that these remarks were linked with the risk of subsequently creating chronic sequelae. The statistical elaboration of findings with the rheumatologic conditions is illustrated in Table 3.

In this report, age was found to be significantly correlated with the number of joint affected (r = 0.442/ $P < 0.011$), underlying disease (r = - 0.482/ $P < 0.005$), and shoulder joint pain (r = - 0.361/ P = 0.042), and negatively correlated with RF level, CRP level, and ESR level (r = 0.125/ $P < 0.494$, r = - 0.032/ P = 0.862, r = 0.176/ P = 0.336, respectively). A positive correlation was seen in the number of joint affected by ESR level, shoulder joint pain, and swelling (r = - 0.603/ $P < 0.000$, r = - 0.501/ P = 0.003, r = - 0.471/ P = 0.007, respectively). Furthermore, a significant correlation was also noted in CRP level with the number of joint affected, ESR level, knee joint pain, and shoulder joint pain (r = - 0.720/ P = 0.000, r = 0.700/ P = 0.000, r = - 0.352/ P = 0.048, r = 0.378/ P = 0.033, respectively), and negatively correlated with the number of joint affected, underlying disease, RF level, and swelling (r = - 0.004/ P = 0.985, r = 0.129/ P = 0.483, r = 0.197/ P = 0.280, r = 0.249/ P = 0.115, respectively). On the other hand, the ESR was positively correlated with CRP (r = 0.545/ P = 0.001) and negatively correlated with RF (r = 0.249/ P = 0.169).

Table 1: Baseline characteristics of the patients serologically confirmed CHIKV classified according to joint pain status

Categories	Subcategory	Persist Joint pains n= 23	No persist joint pain n= 9	P
Age	Mean±SD year	43.56±16.97	33.22±9.61	0.097
Sex	Male Female	12 (52.2%) 11 (47.8%)	4 (44.4%) 5 (55.6%)	0.705
Prior comorbidity				
	Hypertension (HTN) Diabetes (DM) HTN + DM Gout None	1 (4.35%) 3 (13.04%) 1 (4.35%) 1 (4.35%) 17 (73.91%)	0 (0%) 0 (0%) 0 (0%) 0 (0%) 9 (100%)	0.162
Relapse	Repeated infection Frist infection	7 (30.4%) 16 (69.6%)	0 (0%) 9 (100%)	0.064
Rheumatologic findings				
	CRP titer, mg/l RF titer, iu/ml Uric acid, mg/dl ESR, mm/hr	22.18±14.4 11.21±5.56 5.13±1.42 48.74±29.27	6.72±1.86 5.79±1.38 4.70±1.19 21.89±7.49	0.000 0.002 0.920 0.008
Rheumatologic diagnosis				
	Arthralgia Arthritis Polyarthralgia Polyarthritis Osteoarthritis Normal	4 (17.4%) 3 (13.0%) 9 (39.1%) 5 (21.7%) 2 (8.8%) 0 (0%)	0 (0%) 0 (0%) 0 (0%) 0 (0%) 0 (0%) 9 (100%)	0.000

4. Discussion

There are three discerned common genotypes of CHIKV: Asia, East/Central/South Africa, and West Africa. These genotypes are presented invasively throughout the Indian Ocean region [8]. Extreme CHIKV infection may cause significant physical impotency [9]. Therefore, this study was taken to elucidate the rheumatologic sequel of post-Chikungunya infection.

Arthritis/arthralgia is a flagship feature of CHIKV. Many patients were improved within a few weeks, but somewhat up to 50% reveal chronic joint pain and/or swelling. Once rheumatic symptoms persist for ≥ 3 months, this indicates a feature of chronic Chikungunya arthritis [10]. In acute CHIKV infection, many cytokines get abundant such as interleukin families (1Ra, 1β, 6, 7, 8, 12) as well as interferon-alpha (IFN-α). Therefore, T cells and the chemokine C-C Ligand 5/regulated on activation, normal T cell expressed and secreted (RANTES) decreased in severe infection. Chronic Chikungunya arthritis

Table 2: Symptoms of patients serologically confirmed CHIKV classified according to joint pain status

Categories	All confirmed cases n=32	Persist Joint pains n= 23	No persist joint pain n= 9	P
Rheumatologic symptoms				
Wrist pain	18 (56.3%)	14 (60.9%)	4 (44.4%)	0.001*
Ankle pain	10 (31.3%)	8 (34.8%)	2 (22.2%)	0.042*
Fingers pain	16 (50.0%)	13 (56.5%)	3 (33.3%)	0.002*
Elbow pain	3 (9.4%)	3 (13.0%)	0 (0.0%)	0.270
Knee pain	19 (59.4%)	16 (69.6%)	3 (33.3%)	0.000*
Spine pain	6 (18.8%)	6 (26.1%)	0 (0.0%)	0.095
Shoulder pain	12 (37.5%)	11 (47.8%)	1 (11.1%)	0.009*
Feet pain	11 (34.4%)	8 (34.8%)	3 (33.3%)	0.042*
Swelling	7 (21.9%)	7 (30.4%)	0 (0.0%)	0.064
Duration of joint pain, months				
Mean±SD	3.10±1.83	3.08±2.0	1.78 ± 0.44	0.950
Median	3.0	3.0	2.0	
Range	1 – 9	1 – 9	1 – 2	
Number of joints affected				
Mean±SD	2.63±1.89	3.65±1.07	–	0.000
Median	3.0	4.0	–	
Range	0 – 6	2 – 6	–	

**P< 0.050*

Table 3: Laboratory findings with rheumatologic conditions in the study

Parameters	Arthritis n = 3	Arthralgia n = 4	Polyarthralgia n = 9	Polyarthritis n = 5	Osteoarthritis n = 2
CRP, mg/l					
Abnormal	3 (9.4%)	1 (3.1%)	8 (25%)	5 (15.6%)	2 (6.3%)
Normal	0	3 (9.4%)	1 (3.1%)	0	0
RF, IU/ml					
Abnormal	0	4 (12.5%)	0	5 (15.6%)	2 (6.3%)
Normal	3 (9.4%)	0	9 (28.1%)	0	0
ESR, mm/hr					
Abnormal	2 (6.3%)	2 (6.3%)	5 (15.6%)	5 (15.6%)	2 (6.3%)
Normal	1 (3.1%)	2 (6.3%)	4 (12.5%)	0	0
Uric acid, mg/dl					
Abnormal	0	0	0	1 (3.1%)	0
Normal	3 (9.4%)	4 (12.5%)	9 (28.1%)	4 (12.5%)	2 (6.3%)

may elevate the levels of IL-6, IL-17, and granulocyte-macrophage-colony stimulating factor (GM-CSF) [11]. IL-17 specifically, may drive chronic joint pain, triggering the upregulation of the other pro-inflammatory cytokines (IL-1, IL-6, tumor necrosis factor (TNF-α), and matrix metalloproteinase) prompting osteoclastogenesis and bone disintegrations [12]. This study explored that both sexes are more likely to prone the risk of persistent arthralgia/arthritis. This result is not a concordance with other previous studies that have demonstrated females to be at increased risk for persistent arthralgia/arthritis

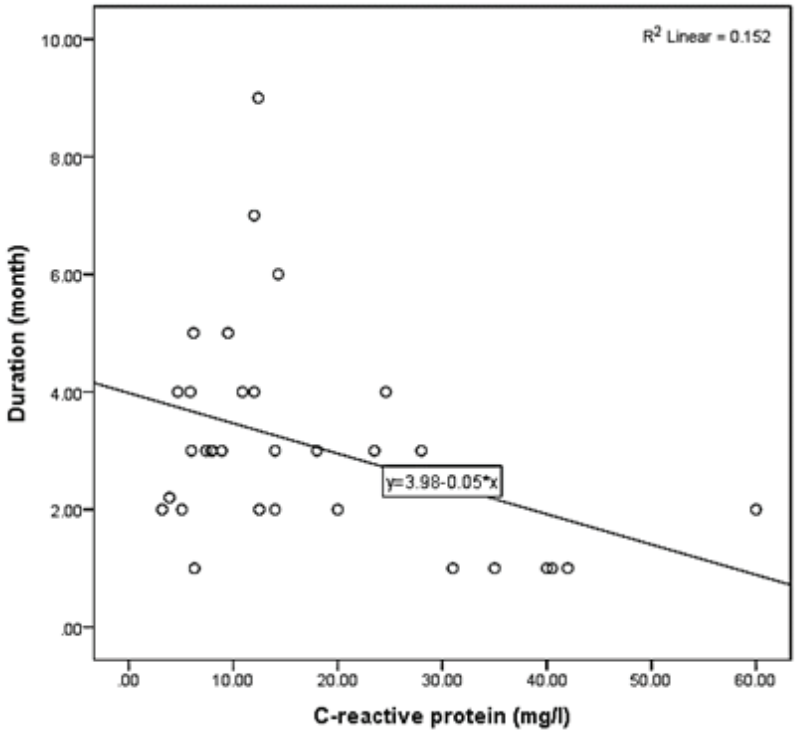

Figure 1: Relationship between C-reactive protein and the duration of CHIKV disease

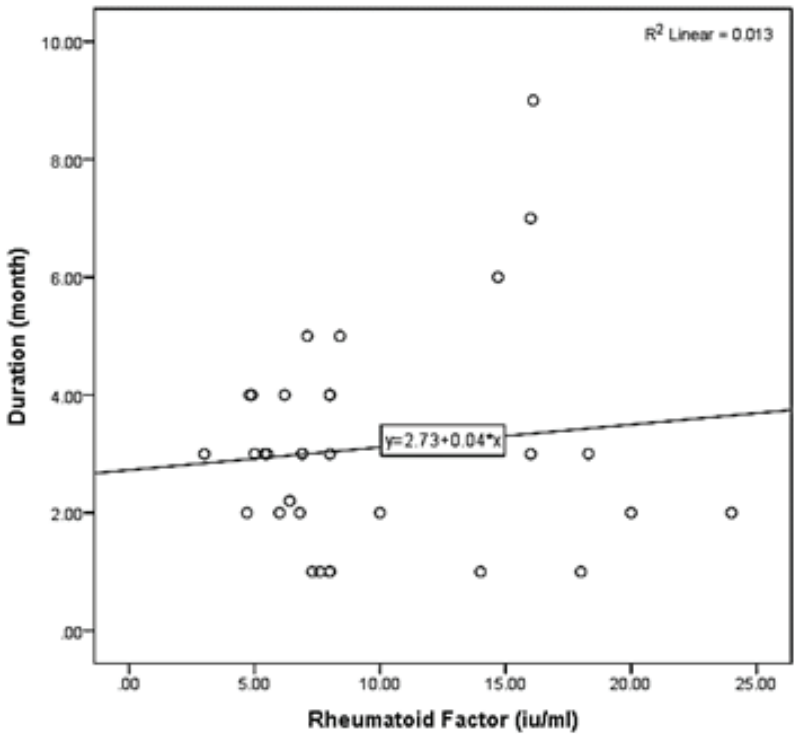

Figure 2: Relationship between rheumatoid factor and the duration of CHIKV disease

[13-15]. However, this unconformity may be excused due to a shortage of sample size. 79.1% of our studied members have been fulfilled the definition of persistent

arthralgia/arthritis, which emphatically consented with an ongoing meta-analysis on the occurrence of persistent arthralgia officiated by Rodriquez-Morale *et al* [16]. Their investigations indicated that in studies with more than 200 members, 34% of CHIKV infected patients would go on to develop persistent arthritis/arthralgia. This extent is likewise comparable to that as of the detailed by Feldstein et al [17] and is also considerable with our findings.

The intensity of CHIKV infection has recently been answered to be predictive of recovery and long-haul arthritis and arthralgia remarks [18, 19]. Similarly, in our work, a few severe symptoms, including knee pain, wrist pain, shoulder pain, finger pain, which are revealed more serious illness were examined as linked to expanded chronic disease risk. This work highlighted that knee joint pain is a countersign symptom of the disease. A finding also similar to Chang et al [20]. Thus, shoulder joint pain, wrist joint pain, finger joint pain, foot joint pain, and ankle joint pain were found significant in association with CHIKV infection. The prevalence of these symptoms was also explored in Rodriquez-Morale *et al* and van Anlst *et al* [16, 21].

The disease intensity and the following risk of arthralgia/arthritis have been interlinked with viral burden [22]. Remarkably, post-CHIKV infection sequel depends on the duration of the disease onset [23], this surveillance was accentuated to our study. Concerning rheumatologic conditions associated with the present study, polyarthralgia, polyarthritis, arthralgia, and arthritis were represented the most rheumatologic problems. These findings are similar to Heath *et al* and Ganu *et al* [23, 24]. Laboratory findings such as RF, CRP, and ESR were found to be significant in association with Chikungunya infection, this may support the evidence that the presence of increased value of these parameters is a factor implicated in the progression of Chikungunya complications [23]. Besides, this study revealed that age and the number of joint affected were also considered factors that enhance in augments of Chikungunya sequel. A significant increase in CRP results was noted in 59.4% of the study. These findings concur with Ganu et al [24]. ESR was elevated in 50% of patients as a screening marker of inflammation. RF was significantly positive in 34.4%. A determination was also likewise detected previously [20, 24]. The high titer of RF could be falsely positive or its output could have been activated by CHIKV disease [24]. This study was subject to some limitations summarized as, this is a short communication survey with very limited sample size, in addition to that, we have neglected other physical symptoms of individuals who did not seek consultation. Recall bias could not be ruled out. A prospective study with considerable expansion should be planned to monitor the structural joint damage, the therapeutic drugs used,

combined molecular and serological characterization of CHIKV, and more laboratory sophisticated analyses.

5. Conclusion

Polyarthralgia was characterized as the dominant inflammatory sequel in this study, followed by polyarthritis, and arthralgia for at least 3 months. Knee joint pain represented a significant dilemma post-CHIKV infection. Effective cure post-CHIKV symptoms sequel could improve the health of an individual.

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Competing Interest

The author declares that they have no competing interests.

Availability of Data and Material

The data which are published are always reproducible by investigators

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Ethics Approval

This study was ratified by a regional ethical review committee. Informed consent was taken from each participant of the study.

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