Pain interference, neuropathic-like symptoms, pain intensity, and symptoms of central sensitization negatively impact individual's disability after Chikungunya fever: cross-sectional study

Interferência da dor, sintomas do tipo neuropático, intensidade da dor e sintomas de sensibilização central afetam negativamente a capacidade funcional dos indivíduos após a febre Chicungunha: estudo transversal

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ABSTRACT

BACKGROUND AND OBJECTIVES: Particular pain features, such as pain interference, neuropathic-like symptoms, and central sensitization (CS) symptoms may be present in patients with Chikungunya fever and lead to functional limitations. The present study aimed to assess the association between pain characteristics and the disability in participants affected by Chikungunya fever in the chronic phase.

METHODS: A cross-sectional study was conducted with 36 participants who filled out a sociodemographic, pain characteristics (pain interference – Brief Pain Inventory, neuropathic-like symptoms – PainDETECT Questionnaire, and CS-related signs and symptoms – Central Sensitization Inventory) and disability (Health Assessment Questionnaire) questionnaires. The Spearman correlation test (rho) verified the relationship between the outcomes.

RESULTS: Most of the participants were female (77%), with a mean age of 43 years. Twenty-seven (75%) participants presented nociceptive pain and 11 (30%) had central sensitization symptoms. There was a high positive correlation between the presence of neuropathic-like symptoms and disability (rho=0.71; p<0.001) and pain intensity and disability (rho=0.76; p<0.001). A moderate positive correlation was found between the central sensitization symptoms and disability (rho=0.51; p=0.002). Moreover, there is a low positive correlation between pain interference in an individual's life and disability (rho=0.34; p=0.041).

CONCLUSION: Patients in chronic phase of Chikungunya fever revealed mild pain intensity and predominance of nociceptive pain. Pain interference, neuropathic-like symptoms, and central sensitization symptoms negatively impact individual's disability after Chikungunya fever.

Keywords: Chikungunya virus, Chronic pain, Correlation study, Disability, Pain measurement.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Características particulares da dor, como interferência da dor, sintomas do tipo neuropático e sintomas de sensibilização central (SC), podem estar presentes em pacientes com febre Chicungunha e levar a limitações funcionais. O presente estudo teve como objetivo avaliar a correlação entre as características da dor e a capacidade funcional em participantes acometidos pela febre Chicungunha na fase crônica.

MÉTODOS: Foi realizado um estudo transversal com 36 participantes que preencheram questionários sociodemográficos, de características de dor (interferência da dor – Inventário Breve de Dor, sintomas do tipo neuropático – questionário *PainDETECT*, e sinais e sintomas relacionados à SC – Inventário de Sensibilização Central) e de capacidade funcional (Health Assessment Questionnaire). O teste de correlação de Spearman (rho) verificou a relação entre os desfechos.

RESULTADOS: A maioria dos participantes era do sexo feminino (77%), com média de idade de 43 anos. Vinte e sete (75%) participantes apresentaram dor nociceptiva e 11 (30%) apresentaram sintomas de sensibilização central. Houve alta correlação positi-

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HIGHLIGHTS
- Chikungunya fever patients had mild pain intensity and disability.
- One in three patients showed signs and symptoms of central sensitization.
- The level of disability was associated with the interference of pain and neuropathic or central symptoms.

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va entre a presença de sintomas do tipo neuropático e capacidade funcional (rho=0,71; p<0,001) e intensidade da dor e capacidade funcional (rho=0,76; p<0,001). Foi encontrada uma correlação positiva moderada entre os sintomas de sensibilização central e a capacidade funcional (rho=0,51; p=0,002). Além disso, há uma correlação positiva baixa entre a interferência da dor na vida do indivíduo e a capacidade funcional (rho=0,34; p=0,041).
CONCLUSÃO: Pacientes em fase crônica da febre Chicungunha apresentaram intensidade de dor leve e predominância de dor nociceptiva. A interferência da dor, os sintomas do tipo neuropático e os sintomas de sensibilização central afetam negativamente a capacidade funcional do indivíduo após a febre Chicungunha.
Descritores: Dor crônica, Estudo de correlação, Incapacidade, Medição da dor, Vírus Chicungunha.

INTRODUCTION

Chikungunya fever (CF) is a viral disease (Chikungunya Virus – CHIKV) transmitted by a mosquito-borne alphavirus in tropical countries, affecting thousands of people when its transmitter is not under control[1,2]. Brazil had an incidence of 3.7 cases per 100,000 inhabitants in 2021, with the highest incidence in the Northeast region of the country[3]. The disease symptoms are like those provoked by other pathologies transmitted by the same vector, such as Dengue and Zika virus. However, the CF presents severe persistent arthralgia that lasts beyond the acute infectious period[4,5]. Although CF is a disease with chronic effects to the individual and a significant burden to society, there is still a lack of clinical information and scientific studies regarding this condition.
The most common pain phenotype in CF is arthralgia, despite other pain characteristics. The synovial histopathologic alterations observed after infection by CHIKV are similar to those in arthritis rheumatoid as synovial hyperplasia, vascular proliferation and perivascular macrophages infiltration[6]. Thus, the persistent painful symptomatology of CF matches the symptomatology of rheumatoid arthritis. Joint pain is common in patients with a predominance of nociceptive pain that may arise from real damage or a threat to non-neural tissue.
On the other hand, patients suffering from musculoskeletal pain also present pain characteristics associated with neuropathic pain and with signs and symptoms of central sensitization (CS)[7]. Neuropathic pain is caused by a lesion or disease of the somatosensory system, while nociplastic pain emerges from altered nociception despite any clear evidence of nociceptive or neuropathic pain[8]. Although the classification of pain predominance is broadly used in patients with musculoskeletal pain, there is no previous study with Chikungunya patients. Therefore, the impact of neuropathic-like symptoms and symptoms of CS on this population are still unknown.
The presence of chronic pain may compromise functional performance, which is related to one's capacity to perform daily activities[9]. Studies conducted in patients with CF report their pain aspects, such as its pain intensity[10], subjective characteristics[4] and impact on daily life[11]. Previous studies show a relevant functional limitation, especially in patients' daily and work activities with CF[10-12]. However, whether the pain characteristics affect the functional capacity of these patients remains unclear.
Therefore, the present study aimed to assess the association between pain characteristics and disability in participants affected by CF in the chronic phase. We hypothesized that there is a positive association between pain characteristics and disability in patients in the chronic phase of the CF.

METHODS

This research is a cross-sectional study design reported following the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE)[13] requirements that was approved by the Research Ethics Committee of Augusto Motta University Center (Centro Universitário Augusto Motta - Opinion number: 34306920.6.0000.5221) in accordance with the Helsinki Declaration for research in humans. All participants who met the eligibility criteria signed the Free and Informed Consent Term (FICT) before the study procedures.

Study participants

Participants were recruited through social networks between February and April 2021. A link to the SURVIVOR research platform was available on Facebook, Instagram, and WhatsApp posts. Those older than 18 years old with a clinical or laboratory diagnosis of persistent CF (over six months from the initial diagnosis) met the inclusion criteria. The study excluded participants who did not fulfill the entire questionnaire and those who had a rheumatic disease diagnosed before CF.

Procedures

The participants answered a self-report questionnaire that included sociodemographic and clinical characteristics (gender, age, weight, height, body mass index, physical activity practice and clinical or laboratorial diagnosis). Pain interference was measured by using the Brief Pain Inventory (BPI)[14]. Neuropathic-like symptoms were assessed by the painDETECT questionnaire[15,16]. CS-related signs and symptoms were assessed by using Central Sensitization Inventory (CSI)[17]. Disability was assessed by the Health Assessment Questionnaire (HAQ)[18]. The average time to answer the whole questionnaire was 30 minutes.
BPI[14] is one of the most widely used measurement tools for assessing clinical pain from pain conditions. It aims to evaluate the severity of pain and its interference with feeling and function in the preceding 24 hours. Regarding pain severity, each of the following items are scored from zero (no pain) to 10 (worst possible pain): worst pain, weaker pain, average pain, and pain now. The sum of these scores can range from zero to 40.
Interference with feelings is considered an affective subdimension (relations with others, enjoyment of life, and mood). On the other hand, interference with function is considered an activity subdimension (walking, general activity, and work). The sum of both subdimensions scores can range from zero to 70 points[14]. This instrument is valid and reliable for assessing pain intensity and its interference in routine activities[19]. A study showed that

BPI is a brief, useful, and valid tool for assessing pain and its impact on a Brazilian patient's life[20].

PainDETECT is a self-administered questionnaire that encompasses four domains as follows: the intensity of the pain (three questions), pain course pattern (four graphs), areas of pain and the presence of radiating pain (body chart drawing), and sensory descriptor items of pain (seven questions). For each question, six different answers are possible, with scores from zero (never) to five (very strongly). By summing up the scores given in each domain, a final score between -1 to 38 can be achieved.

PainDETECT is validated for many neuropathic pain conditions. In the last years, it was also validated for the use in mixed pain conditions such as rheumatoid arthritis, osteoarthritis, cancer pain, and lumbar spondylolisthesis. The cutoff points for the original questionnaire indicate that in the scores ≤ 12, a neuropathic component is unlikely, whereas, in the ≥ 19 scores, a neuropathic component is probable[15,21]. The Brazilian version of painDETECT was observed to be useful to identify neuropathic components in the pain of local patients[16].

CSI is an instrument developed to identify patients with symptoms associated with CS[17]. Part A assesses 25 health-related symptoms commonly observed in patients with central sensitivity syndrome. Part A is scored on a 5-point Likert scale from 0 (never) to 4 (always), with a total of 100 points, and higher scores represent an increase in the severity of symptoms. Part B is not scored and encompasses ten previous diagnoses of an individual, including seven central sensitivity syndromes and three disorders related to CS syndrome. The optimal cutoff point was established at 40/100 in patients with central sensitivity syndrome[22,23]. The severity of symptoms related to CS has been classified into sub-clinical (0–29), mild (30–39), moderate (40–49), severe (50-59) and extreme (60-100)[22-24], where higher scores indicate an increase in the severity of symptoms[25]. The Brazilian version of the CSI demonstrated strong psychometric properties[26].

The disability was assessed using the Health Assessment Questionnaire (HAQ), an assessment tool developed to verify the impact of rheumatoid arthritis on individuals' daily activities. The HAQ is a self-administered questionnaire composed of 20 questions about activities of daily living with standardized answers that identify the difficulty level for the individual to perform the activity and classify it as: "without any difficulty", "with some difficulty", "with much difficulty" and "unable to perform". It also indicates whether the individual needs orthoses or help in performing daily tasks, classifying them as (1) if they need orthosis to perform the task; (2) if they need human help to carry out the tasks; or (3) if they need orthosis and human help to perform the task. The disability classification based on the sum of the score is mild (HAQ from 0 to 1), moderate (HAQ > 1), or severe disability (HAQ > 2 to 3)[18]. This instrument was translated and adapted for Brazilian patients, and it is considered appropriate for this population[27].

Statistical analysis

Data collected on SURVIVOR® was analysed using the statistical software JASP version 0.10.2.0. (Free Bayesian statistical software, Amsterdam, The Netherlands). Demographic and clinical variables of the study participants were presented as mean and standard deviation for continuous variables. Categorical variables were presented as absolute values and frequencies. Shapiro Wilk test revealed non-parametric distribution for the primary outcomes, which were described as the median and interquartile range (IQR). The Spearman correlation coefficient (rho) was adopted to investigate the correlation between pain characteristics (pain interference, neuropathic-like symptoms, and symptoms of central sensitization) and disability due to the nonparametric distribution of the continuous variables. Correlations above 0.90 were considered very high, 0.70 to 0.89 were high, 0.50 to 0.69 were moderate, 0.39 to 0.49 were low, and under 0.29 were discrete[28]. A significance level of 0.05 was set for all statistical tests.

RESULTS

Thirty-eight participants answered the online questionnaire, and two were excluded due to the pre-existing rheumatic disease. Of the 36 participants included in the study, 28 (77.7%) were female, and the mean age was 43.7±12.5 years old. The Chikungunya fever was clinically diagnosed in most participants (69.4%) (Table 1).

Table 1. Characteristics of the study participants

	Value (n= 36)
Gender (female), n (%)	28 (77.7%)
Age (years), mean (SD)	43.5±12.5
Weight (kg), mean (SD)	71.1±21.8
Height (meters), mean (SD)	1.64±0.1
Body mass index (kg/m²), mean (SD)	26.01±7.3
Physical activity practice, yes, n (%)	19±52.7
Clinical diagnosis n (%)	25 (69.4%)
Laboratorial diagnosis n (%)	11 (30.5%)

Data are presented as mean (SD) for continuous variables and as frequency counts (%) for categorical variables.

Pain interference measured by BPI showed a median of 24.0 (IQR = 31.8) points. Participants reported presence of pain in some regions of the body, the most cited areas were the foot (16.7%), hands (11.1%) and knees (8.3%). Median pain intensity was mild, 3.0 (IQR = 4.0). Seventeen (47.2%) participants reported using of drugs to release pain.

PainDETECT questionnaire identified 27 (75%) participants with nociceptive pain, 7 (19.5%) with unclear pain, and 2 (5.5%) as neuropathic-like symptoms. CSI presented a median score of 30.5 (IQR = 25.0), and 11 (30.5%) participants scored above 40, indicating the presence of signs and symptoms related to central sensitization. The HAQ total score showed mild disability (median = 0.3). Pain characteristics and disability assessment data are presented in table 2.

There was a high positive correlation the presence of neuropathic-like symptoms and disability (rho = 0.71; p < 0.001). Similarly, a high positive correlation was found between the pain intensity and disability (rho = 0.76; p < 0.001). A moderate positive correlation was found between the presence of CS signs and symp-

Table 2. Pain and disability characteristics of participants in the chronic phase of Chikungunya fever

Characteristics	Value (n= 36)
Pain intensity, median (IQR)	3.0 (4.0)
Pain interference (0-70), median (IQR)	24.0 (31.8)
General activities	3.0 (4.0)
Mood	3.0 (4.3)
Walking ability	3.0 (5.0)
Normal work	3.5 (5.3)
Relations with other people	3.0 (4.0)
Sleep	3.0 (5.0)
Enjoyment of life	2.0 (6.0)
Pain location, n (%)	
Head	9 (25.0%)
Neck	8 (22.2%)
Upper back	6 (16.6%)
Low back	5 (13.8%)
PainDETECT, median (IQR)	7.5 (9.5)
Central Sensitization Inventory (CSI), median (IQR)	30.5 (25.0)
Health Assessment Questionnaire (HAQ), median (IQR)	0.3 (1.2)
Dressing, median (IQR)	0.0 (1.0)
Getting up, median (IQR)	0.0 (2.0)
Eating, median (IQR)	0.0 (0.0)
Walking, median (IQR)	0.0 (1.0)
Hygiene, median (IQR)	0.0 (1.0)
Reaching, median (IQR)	0.5 (2.0)
Gripping, median (IQR)	0.0 (2.0)
Other activities, median (IQR)	0.5 (1.3)

Data are presented as median and interquartile range (IQR) for continuous variables and as frequency counts (%) for categorical variables. HAQ = Health Assessment Questionnaire; BPI = Brief Pain Inventory; CSI = Central Sensitization Inventory.

toms and disability (rho = 0.51; p=0.002). Lastly, there was a low positive correlation between pain interference in an individual's life and disability (rho = 0.34; p= 0.041). Correlation results are presented in table 3.

Table 3. Correlation between pain characteristics and disability of participants in the chronic phase of Chikungunya fever

Variables	HAQ	
	rho (95% CI)	p-value
Pain intensity (BPI)	0.76 (0.57-0.87)	<0.001
Pain interference (BPI)	0.34 (0.02-0.60)	0.041
Neuropathic-like symptoms (PainDETECT)	0.71 (0.50-0.84)	<0.001
Central Sensitization Inventory (CSI)	0.51 (0.22-0.72)	0.002

Data are presented as Spearman correlation coefficient (rho) and confidence interval (CI) HAQ = Health Assessment Questionnaire; BPI = Brief Pain Inventory.

DISCUSSION

This study investigated the relationship between pain characteristics and disability manifested during the chronic phase of CF. Most participants showed nociceptive pain predominance, and about one third presented CS signs and symptoms. The findings from this study showed a significant correlation between the pain intensity, pain interference, presence of neuropathic-like symptoms and symptoms of CS and disability in patients in the chronic phase of CF.

The findings also showed a mild pain intensity in patients in the chronic phase of CF. This fact could be explained since the sample of this research presented characteristics of nociceptive pain. A study showed that patients with nociceptive pain had less pain intensity than in the case of neuropathic-like symptoms[29]. In general, the results of this study differ from those of other research, which showed that only 3% of the patients with chronic Chikungunya arthritis reported mild pain[30].

Another study reported that the mean intensity of pain was moderate[31]. The difference in mean pain intensity may be related to the duration of disease onset since the participants had a mean of 36 months of disease duration, whereas the previous study had 22 months[11]. Additionally, patients with CF often report the presence of more than one pain site. The results of this study demonstrated that the head, neck, upper back and low back were the most frequent of pain locations contrast to previous results reporting that the hand, wrist, ankle and knee were found in patients with arthralgia[4].

This study revealed that the majority of the participants (75%) had their pain classified as nociceptive, while only 5% of the sample were classified as neuropathic-like symptoms according to the painDETECT questionnaire. Previous studies showed that the prevalence of neuropathic-like symptoms in patients with Chikungunya varies between 18%[31] and 34%[32]. Although nociceptive pain predominated in the sample of this research, 30% of the patients showed symptoms of CS.

As far as is known, this is the first report that evaluated symptoms of CS and disability in CF. However, it is already known that symptoms of CS have been reported by patients with knee osteoarthritis, which is regularly considered nociceptive pain[33]. Therefore, future studies investigating CS and CF are necessary to validate the conclusions drawn from this study.

Another important finding was that patients in the chronic phase of the CF had mild disability. This finding is consistent with that of a study that revealed that a large proportion of people affected by the Chikungunya had mild disability (60%) or no disability (23.2%) in HAQ[34]. Another research showed that patients with Chikungunya arthritis had mild disability (HAQ 0.54) compared to rheumatoid arthritis[35]. In contrast, a study[32] related scores of 2.01 (HAQ) in Chikungunya virus patients, indicating moderate functional impairment. Moreover, another study reported that woman in the chronic stage of Chikungunya virus had a moderate level of disability (HAQ 1.37)[11].

The current study has many limitations. The low adherence to the online questionnaire may be related to the difficult access to

the survey link or the time spent to fill the items. Although the instruments used in the current investigation are widely used in the literature, the application of questionnaires in digital format may represent a limitation of the study since the same instruments have not yet been validated with this methodology. There is an emerging need for assessment instruments that can be used remotely or face-to-face due to technological advances and the possibility of covering a more significant number of participants for research. Besides, the coronavirus pandemic lead to a social distance, which precludes the assessment of the participants in the outpatient setting.

Patients in the chronic phase of CF had nociceptive pain predominance, but about one-third presented CS signs and symptoms, suggesting that other mechanisms were also involved. These findings provide new insight to clinicians and researchers. Clinicians should be aware that patients in the chronic phases of CF can present more than one pain mechanism.

Therefore, physiotherapists and other health professionals should consider highly accurate instruments which screen the pain mechanism predominance. This will allow the physiotherapist or other health professional to offer adequate treatment strategies to a given patient. Future studies with a large sample of CF patients in chronic phase should be carried out to assess the pain interference, pain mechanisms (i.e., nociceptive pain, neuropathic-like symptoms, and CS), and disability, for the confirmation of the findings of the present study.

CONCLUSION

Patients in chronic phase of CF revealed mild pain intensity and predominance of nociceptive pain. Pain characteristics such as pain interference, neuropathic-like symptoms, and symptoms of central sensitization negatively impact individual's disability after CF.

AUTHORS' CONTRIBUTIONS

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