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DISLENE NASCIMENTO DOS SANTOS

CARACTERÍSTICAS DA DOR E FATORES ASSOCIADOS EM INDIVÍDUOS COM E SEM INFECÇÃO PELO VÍRUS LINFOTRÓPICO DE CÉLULAS T HUMANO TIPO 1 (HTLV-1)

DISSERTAÇÃO DE MESTRADO

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Orientador: Profº. Drº Abrahão Fontes Baptista

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“ E repousará sobre ele o Espirito Santo, o espírito de sabedoria e de entendimento, o espírito de conselho e de fortaleza, o espírito de conhecimento e de temor ao Senhor. “ (Is. 11:2)

LISTA DE FIGURAS E TABELAS

LISTA DE ABREVEATURAS E SIGLAS

ATLL	Leucemia/ linfoma de células T do adulto
CAPES	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
CEP	Comitê de Ética em Pesquisa
CNPq	Conselho Nacional de Desenvolvimento Científico e Tecnológico
DN4	Questionário de Diagnóstico de dor Neuropática
EDSS	*Expanded Disability Status Scale*
ELISA	*Enzyme-Linked Immunosorbent Assay*
HTLV 1	Vírus linfotrópico de celulas T humano tipo 1
HAD	Escala Hospital de Ansiedade e Depressão
HAM/TSP	Paraparesia espástica tropical / mielopatia associada ao HTLV 1
HBV	Vírus da hepatite B
HCV	Vírus da hepatite C
HEMOBA	Fundação de Hematologia e Hemoterapia da Bahia
HIV	Vírus da imunodeficiência humana
IASP	*International Association for the Study of Pain*
INF	*Interferon*
LILACS	Literatura Latino-Americana e do Caribe em Ciências da Saúde
MEDLINE	*Medical Literature Analysis and Retrieval System Online*
NOS	*Newcastle-Ottawa Scale*
NSAIDs	*Nonsteroidal anti-inflammatory drugs*
OMDS	*Osame Motor Dysfunction Scale*
PCR	Proteína-C Reativa
PRISMA	*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*
PUBMED	Publicações Médicas

LISTA DE ABREVEATURAS E SIGLAS (Continuação)

QOL	*Quality-of-Life-Questionnaire*
TNF	Fator de necrose tumoral
VAS	*Visual Analogue Scale*
WHO	*World Health Organization*

SUMÁRIO

1. ABSTRACT

The human T lymphotropic virus type I may contribute to chronic pain ful conditions.**Objective**: To describe clinically and epidemiologically pain in patients infected with HTLV-1 and to identify the characteristics of chronic pain in these patients and compare it to individuals without the virus.**Method:** The systematic review was based on Declaration of Prisma. Four subjects searched in PUBMED, SCIELO, LILACS and BIREME data from observational studies (n≥30) related to the prevalence of pain characteristics and associated factors using the general terms: pain and HTLV. And the cross-sectional study with individuals followed by HTLV multidisciplinary clinic ambulatory, divided into three groups: HAM / TSP, asymptomatic, oligosymptomatic and comparison group (blood donors) matched for sex and age. All subjects had chronic pain (> 6 months).**Results:**2,694 articles were read and these 7 met the inclusion criteria. The back region was the most frequent with pain (53%); nociceptive and neuropathic pain were, cited as severe (40%). In the cross-sectional study sociodemographic data were homogeneous between groups, except in education and occupational level. Nociceptive pain was more frequent in the study and neuropathic pain was present only in the lower limbs of individuals with the virus. The oligosymptomatic group showed a diffuse pain and depressive symptoms; and HAM/TSP group had an impact on functional capacity, general health and social aspect of the SF36. **Conclusion**: The literature review demonstrated an often nociceptive pain, especially in the region of the back of the individuals infected with HTLV-1, often referred to as severe. The cross-sectional study noted complaints of neuropathic pain in the lower limbs infected with the virus, diffuse pain associated with depressive symptoms in oligosymptomatic group and negatively impact the quality of life of individuals with HAM /TSP.

Key words: HTLV-1. HAM/TSP. chronic pain. Myelopathy. quality of life.

RESUMO

O vírus linfotrópico de células T humano tipo 1 favorece ás condições dolorosas crônicas. **Objetivo**: Descrever clínica e epidemiologicamente a dor em pacientes infectados pelo HTLV-1 e identificar as características da dor crônica nesses pacientes e compará-lo com indivíduos sem o vírus. **Método**: revisão sistemática com base na Declaração de Prisma. Quatro sujeitos pesquisaram no PUBMED, SCIELO, LILACS e BIREME dados de estudos observacionais (n≥30) relacionados á prevalência, características e fatores associados á dor, utilizando os termos gerais: dor e HTLV. E estudo transversal com indivíduos acompanhados ambulatório multidisciplinar HTLV, divididos em três grupos: HAM/TSP, assintomáticos, oligossintomáticos e grupo de comparação de doadores de sangue, pareados por sexo e idade. Todos os indivíduos apresentaram dor crônica (>6 meses).**Resultado**: 2.694 artigos foram lidos e destes 7 preencheram os critérios de inclusão. A região das costas foi a mais frequente com a dor (53%) e foram citadas dor nociceptiva e neuropática grave para 40% dos indivíduos. No estudo transversal os dados sociodemográficos foram homogêneos entre os grupos, exceto em educação e nível ocupacional. A dor nociceptiva foi mais freqüente no estudo e a dor neuropática esteve presente em membros inferiores de indivíduos com o vírus, ausente nesta região no grupo comparação. O grupo oligossintomático apresentou uma dor difusa e sintomas depressivos; e impacto na capacidade funcional, saúde geral e aspecto social do grupo HAM/TSP. **Conclusão**: A revisão da literatura demonstrou uma dor frequentemente nociceptiva, principalmente na região das costas dos indivíduos infectados pelo HTLV-1, muitas vezes, referida como grave. O estudo transversal observou queixas de dor neuropática nos membros inferiores de infectados com o vírus, dor difusa associada a sintomas depressivos no grupo oligossintomático e impacto negativamente na qualidade de vida de indivíduos com HAM/TSP.

Palavras-chave: HTLV 1, A, HAM / TSP, Mielopatia, Dor crônica, Qualidade de vida.

2. INTRODUÇÃO

O vírus linfotrópico de clulas T humano tipo 1 (HTLV-1) infecta milhões de pessoas no mundo e tem distribuição endêmica no Caribe, África Equatorial, América do Latina e no Japão. No Brasil a prevalência varia entre os estados, sendo Salvador, capital da Bahia, o local com o maior número de casos por habitantes, com aproximadamente, 2% de infectados.

A dor é um sintoma comum na população de indivíduos infectados pelo HTLV-1. Neste contexto, as manifestações clínicas e neurológicas são múltiplas, que refletem o estado de infecção pelo vírus e podem ser desencadeadores da sintomatologia dolorosa. Dentre as doenças associadas ao HTLV-1, citam-se a leucemia/ linfoma de células T do adulto (ATL) e a paraparesia espástica tropical/mielopatia associada ao HTLV-1 (HAM/TSP) que atingem de 1% a 5% dos infectados e são as expressões mais graves da infecção. A HAM/TSP é a doença associada ao HTLV-1 mais comum em regiões tropicais como o Brasil e se apresenta com um maior comprometimento do segmento medular torácico, com fraqueza nos membros inferiores (paraparesia), hiperreflexia e sinais de liberação piramidal, tais como o sinal de Babinski. Outros sintomas como artropatia, neuropatia periférica, sensação de queimação e peso em extremidade são comumente relatados pelos indivíduos infectados pelo HTLV-1 mesmo sem mielopatia. Contudo, a maioria permanece assintomática do ponto de vista neurológico, aparentemente sem manifestações clínicas relacionadas ao vírus e são denominados de portadores assintomáticos do HTLV-1.

Foi realizada uma revisão sistemática de estudos observacionais sobre a prevalência, características da dor e fatores associados, e observou-se que os estudos referentes a este tema nesta população, até o presente momento, foram realizados na sua maioria em pacientes com HAM/TSP. Estudos que descrevem a região lombar como a mais referida com dor, seguido dos membros inferiores, sendo a natureza da dor neuropática e incapacitante. A dor interfere na autonomia e desempenho das funções básicas, associados a sintomas psicoafetivos e prejuízos a qualidade de vida.

Estudo prévio, comparando portadores do vírus assintomáticos com doadores de sangue encontrou uma maior frequência de dor articular em indivíduos com HTLV-1 sem mielopatia. Outro artigo faz referência à sintomatologia dolorosa em indivíduos assintomáticos e oligoassintomático, observando que este sintoma pode estar presente em outras fases clínica das manifestações de infecção relacionada ao vírus. E isto denota um avanço na pesquisa deste tema nesta população, sugerindo um olhar mais minucioso na busca ativa que precede a fase mais grave da doença. Os autores deste estudo relatam que a investigação dor em outras localidades precisa ser testada nestes indivíduos. Deste modo, a identificação de outros locais de dor, aparece também como uma limitação de alguns estudos publicados, assim como, o tempo de dor para adoção de medidas comparáveis entre os estudos.

O manuscrito original teve como objetivo, identificar e caracterizar a dor em indivíduos infectados com HTLV-1, buscando preencher as lacunas relatadas. O estudo traz como diferencial a comparação entre indivíduos com e sem infecção pelo vírus. Para minimizar as diferenças entre os grupos foi realizado pareamento com o sexo e a idade, contudo não foi possível controlar tempo de estudo e ocupação. Como resultados, os indivíduos oligoassintomáticos aparecem como o grupo com HTLV-1 que mais requer atenção, possivelmente a presença de bexiga hiperativa associada a sintomas depressivos pioram o quadro de dor neste indivíduo; a dor nociceptiva foi a mais frequente no estudo, entretanto, indivíduos infectados pelo HTLV-1 apresentaram dor neuropática em membros inferiores que esteve ausente nesta região em soronegativos; encontrou-se também maior comprometimento da qualidade de vida dos indivíduos com mielopatia quando comparado aos outros grupos avaliados.

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3. OBJETIVOS

3.1 GERAL

Identificar as características da dor crônica em indivíduos infectados pelo HTLV-1.

3.2 ESPERCÍFICOS

3.2.1. Objetivo da Revião Sistemática

- Realizar uma descrição clínica e epidemiologica da dor nos indivíduos infectados pelo HTLV-1.

3.2.2. Objetivos do Manuscrito Original

- Identificar e caracterizar a dor crônica em grupos de indivíduos assintomático, oligossintomático e HAM/TSP para o HTLV-1.

- Comparar as características da dor dos grupos de indivíduos infectados com HTLV-1 a um grupo de indivíduos sem o vírus.

4. ARTIGO REVISÃO

Pain prevalence, characteristics and associated factors in HTLV-1 infection: A systematic review of the literature

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Abstract

Introduction: Human T cell leukemia/lymphoma virus type 1 (HTLV-1) is a retrovirus considered the etiological agent of Tropical Spastic Paraparesis/HTLV-1 Associated Myelopathy (HAM/TSP). Chronic pain is highly frequent in this condition, but there is not still a consensus on its prevalence, associated factors and nature.

Objective: Describe clinically and epidemiologically the pain in patients infected with HTLV-1.

Methods: This systematic review was based on The Prisma Statement. Four reviewers searched PUBMED, SCIELO, LILACS and BIREME for data from observational studies (n≥30) regarding pain prevalence, characteristics and associated factors, using the broad terms HTLV and pain. No limits on publication date or language were established. Studies without pain as an outcome measure and not involving HTLV-1 were excluded.

Results: We found 2694 articles (excluding duplicates) and 7 met the predetermined criteria. The most common pain region was the low back with frequency in around 53%. Non-neuropathic (range from 52.60% to 86.8%) and neuropathic (range from 13.20% to 47.40%) natures are frequent, and was reported as severe in around 40% of the patients. Two articles used EDSS (Kurtzke Expanded Disability Status Scale) in cases and controls, but found no difference between those groups.

Conclusion: Pain is a usual complaint in HTLV-1 infected patients and back pain is the most frequent location. Nociceptive, neuropathic or both types of pain can be found, and severe pain is not rare. The degree of physical and functional disability related to pain was not relevant in infected patients.

Introduction

The Human T-cell Lymphotropic Virus type I (HTLV-1) is a retrovirus that can be transmitted by sexual contact, sharing needles and syringes, blood transfusions, through the placenta or during breastfeeding.[1,2] The prevalence of HTLV-1 is still unknown, although it is estimated that 10 million people carry the virus throughout the world. [1]

The chance of a HTLV-1 corrier develop Associated myelopathy/Tropical Spastic Paraparesis (HAM/TSP) is between 1 and 5%.[3] The prevalence is higher in the Caribbean and South American countries (about 4%) than in Japan (around 0.25%). The average prevalence is around 2% in Latin America, so it is estimated that there are 100,000 cases of HAM/TSP, making this spectrum of HTLV-1 a public health problem in this part of world. [4,5]

Nociceptive pain (resulting from inflammatory mediators) and neuropathic pain (secondary from injury and/or dysfunction in the central or peripheral nervous system) are frequent, as well as other sensory disturbances.[4,6] There are also reports of the association of HTLV-1 infection with pain conplaints as obsancal in rheumatic diseases such as Sjogren's Syndrome, Rheumatoid Arthritis, and fibromyalgia.[7]

Although a number of studies have already tried to characterize pain in HTLV-1 infection, it is not already clear weather it is a focal manifestation of the neurological complex, or a systemic disease, such as other diffuse pain syndromes. To answer these questions, it is important to reveal some relevant questions that remain unclear, such as what is its general prevalence/frequency, what are the affected sites, which is the most frequent nature of pain (neuropathic or nociceptive), and

which are the associated factors to this disabling condition. This study aimed to review the literature regarding pain characteristics and associated factors in HTLV-1 infection, trying to summarize the results of observational data.

Methods

This Systematic Review was based on the PRISMA Statement for reporting systematic reviews and metanalyses. Four independent reviewers searched PUBMED, Scientific Electronic Library Online, MEDLINE and LILACS using the broad terms: HTLV-1 and pain. The search was done in October, 2014. The search strategy is described in Appendix 1.

It were included in this review observational studies and clinical trials in which it was possible to extract data from the baseline regarding pain prevalence and associated factors in HTLV-1 infection. No language, publication date or publication status restrictions were imposed. The studies should involve more than 30 participants, aged more than 18 years old, and clarify how HTLV-1 or HAM/TSP diagnosis was done. Other study designs, studies not involving pain as an outcome measure, and the inclusion of other infections such as HIV or HTLV-2, or other neurological diseases were excluded.

Articles were firstly screened by titles, and then by abstracts. Full texts of potentially eligible studies were read and eligibility criteria applied. If there was disagreement about the inclusion or not of a certain study, a consensus meeting finally defined it. Information was extracted from each individual paper on: a) Pain prevalence in HTLV-1 infected participants, b) Clinical pain description; c) Age, gender, ethnicity,

socioeconomic status, and educational level; D) Number of participants. Risk of bias focused on specifications of how many participants were lost during the follow up, and whether the authors had some conflict of interest.

The Newcastle-Ottawa Scale (NOS)[8] was used to assess the quality of the observational and case-control studies, as there was no randomized clinical trial included in this study. This scale classifies the studies in one (low quality) to five (high quality) stars.

Results

The database search yielded 2,694 citations with no limits on publication date, including duplicates (Figure 1). Seven studies met the predetermined criteria (Table 1): six studies were identified from the database search and another study was found after a manual search. These studies were published between 2005 and 2013. The total number of patients was 575.

Approximately 70% of the included subjects were women, mean age range of 40-51 years. All patients were recruited at a HTLV-1 referral center. For diagnosis of HTLV 1 infection, three studies used the ELISA and the Western blot, two used the liquor evaluation, one used PCR. In five studies the participants were classified to the presence of HAM/TSP according to the WHO criteria. One study used De Castro-Costa classification,[9] and another one did not explain this issue.

Accordingly to NOS, three papers had good or very good quality, and four were unsatisfactory, because these studies were cross sectional that did not performed

control of confounding and were not representative of the investigated population. (Table 2)

Pain prevalence ranged between 35.3 to 88.4% in all studies. The most frequent pain site was lumbar and it results in 29.6, 36.8 (chronic pain), 63.15 (low back and lower limb), 65.3, 75.5%; [6, 10-13] one study did not describe that pain site. [14] Leg pain results in 10.4, 23.7 and 33.3%. [6,11,12] Another pain sites, such as upper limbs 25.54% eyes 23.9%, head, face and neck 7.19%, thorax and abdominal 4.13% were mentioned only once. [12,14]. In addition, the majority of participants considered low-back pain as their worst pain (67.6%). [13] The pain was classified in chronic or acute in only one paper that defined chronic pain as any pain for a minimal period of three months, with 100% of chronic pain.[11] Al-tough another paper had a minimal follow up of three months, and approximately 70.37% had chronic pain with the classification cited above. [10] In addition, low back pain had a mean duration of 11 years.[13]

When the pain was classified in HAM/TSP patients according to diagnostic questionnaire of neuropathic pain (DN4), the result was non-neuropathic (range from 52.60% to 86.8%) and neuropathic (range from 13.20% to 47.40%). [11,13] One paper was more specific, still using DN4: neuropathic (DN4-35.06%), nociceptive (DN4-27.83%) or mixed (DN4-37.11%); also assessed infected patients with HTLV-1 (HAM/TSP or not) and found 49.7% of nociceptive pain and 50.3% of neuropathic pain.[12] All this studies did not determinate the site of pain.

Regarding the primary pain, there was a significant association between the worst degree of disability with the higher likelihood of patients with neuropathic pain (P=0.016; and P=0.012, for Osame grades 5 and 6, and EDSS grade 6.0,

respectively).[11] In a similar line, there was a preponderance of intense pain in the neuropathic conditions (G= 45.908; p<0.001). [12]

The intensity of pain was assessed using the Visual Analogue Scale (VAS) in HAM/TSP patients. Considering 10 as the worst pain, the mean in one of the studies was 6 cm (95% CI 4.9 to 7.1). [10] Severe pain was found varying between 42 to 49% in HTLV-1 infected patients,[11, 12] and 73% in HAM/TSP had moderate or severe pain. [13] There was no significant preponderance of pain intensity with regard to its location in HTLV-1 infected patients (G= 3.050; p=0.803). [12]

The impact of pain on quality of life using the EDSS and OSAME, but it showed no significant difference between HAM/TSP diagnosed patients with and without pain. Using the Quality-of-Life-Questionnaire (QOL) SF-36, was detected the negative impact of the pain and it was worst when they presented with more than one painful site compared with only one painful site (RR=3.00, 95% CI: 1.37-6.59, P=0.003, Yates corrected).[11]

This site of pain seems to be related to duration of HAM/TSP: 76% with low back pain had more than 10 years of disease against 52% under 10 years. [1] Besides, the patients with chronic pain had a significantly longer duration of disease (mean 16.4 SD 6.7 y) than without this symptom, [11] and individuals who had a follow up longer than two years suffered more pain, with statistical significance.[12] Low back pain was compared with other sites of pain regarding age, gender, first clinical manifestation, Timed up and Go Test, gait, independence in activities of daily living and bodily pain domain of the SF-36. There was significant difference only in the last aspect, p<0.00 . [12] The most common descriptors of low back pain were tiring (54.3%) and sickening

(50%). On lower limbs the main descriptors were burning (77.3%), tiring (72.7%) and heavy (68.2%).[13]

When analyzing the improvement and worsening factors, demonstrate that the most frequent aggravating factors were movement (70.5%), cold weather (38.2%), remaining in a same position for a long time (36.7%) and physical effort (27.9%). The most frequent relief factors were analgesic drugs (73.5%) and rest (52.9%). The most usual analgesic drugs were common analgesics (44.1%), nonsteroidal anti-inflammatory drugs (NSAIDs) (42.6%) and tricyclic antidepressants (26.4%).[13]

Discussion

The propose of this study was to describe clinically and epidemiologically the pain in patients with HTLV-1. We aggregate 575 patients with HTLV-1, HAM/TSP or not, in seven papers selected with our search. This entire population was recruited from references centers of two countries, Brazil and United Kingdom. Approximately 70% of the samples were women, with a mean age of 40-51 years, this way affecting many patients at working age. No study gave the demographic status of the patients with pain. The authors only put this status in the whole population, which cannot be extended to the population of interest.

The range of pain prevalence varied between 35.3 to 88.4% in all studies and it could be extracted from five different studies, with an estimated mean of 67.26% at the first interview. In a study with 206 patients (case series), they found a similar result: in patients with HAM, pain was the fifth more common symptom (50.5%).[10]

The most common pain site was lumbar. Six of the seven study mentioned it and it range from 29.6 to 75.5%. The pain was often moderate to intense. Type of pain was not really conclusive because of the high variation between the studies, but showed a greater prevalence of non-neuropathic pain. Lumbar pain had an estimated median of 54.07%, which is similar with the firt full text available study who has cited it in 1994 – 50% in a Brazilian population,[15] but different in a study in Peru, patients with presumptive diagnosis of TSP, which found 79% of lumbar pain,[15] but this could be explained by the selected population. Regarding lumbar pain in HAM/TSP Peruvian children (case control study – 97 patients) 15% of infected population had lumbar pain, no significance comparing with uninfected, [17] showing that the prevalence is difference among different age groups populations.

The majority of pain was classified as chronic (≥three months), more than 70%. There are only included papers in our review about pain chronicity and HLTV-1 patients. There are no more observational studies that present that finding, but there are a necropsy study that support it. [17]

Common analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs) and tricyclic antidepressants showed some improvement in the patients at this paper. In the literature,one recent trial with eighteen months follow up (seven patients) associated Ciclosporin A with improvement in pain,[19] but another using Zidovudine plus lamivudine did not reach significance with six months of treatment with sixteen subjects.[20] In another paper, Pilates exercises significantly reduced low back pain, using proprioceptive neuromuscular facilitation, with fourteen subjects.[21] These are small trials and cannot be expanded to all HTLV-1 patients.

The EDSS and OSAME did not reach significance difference in quality of life, but the QOL SF-36 found a negative pain effect compared with no pain patients, and this is in accordance with another study in HAM/TSP subjects.[22] There were only two countries involved in our review, restricting the global generalization. The absence of demographic status makes it difficult to analyze the sample. The studies did not specified correctly the intensity and the type of pain and this classifications varied a lot between the studies as well as pain prevalence, which difficulty the analysis. Another limitation was publication of only small trials regarding pain and HLTV-1.

We can conclude here that, in HTLV-1 infected subjects, the pain prevalence is high, mostly chronic and lumbar pain was the most common region. Non-neuropathic pain were the more common type, with moderate and intense pain and a negative impact of quality of life. The pain may improve with analgesics, Ciclosporin A and Pilates.

More methodological quality and more specificity on results in observational studies and more subjects joining a trial is needed. The use of some analgesics, such as gabapentin, for neuropathic pain, should be done in patients who suffer this type of pain, but there is no trial or observational studies citation of improvement with those kind of medications.

Appendix 1 - Literature Search Strategy

Databases searched: PUBMED, SCIELO, MEDLINE, LILACS.

Limits: Human.

Filter: No filter.

1. Pain AND HTLV
2. Pain characteristics and HTLV
3. Pain prevalence and HTLV
4. Pain AND HTLV NOT adult t cell leukemia lymphoma
5. Pain AND (HTLV NOT adult t cell leukemia lymphoma) NOT HIV
6. Prevalence characteristics or pain and (HTLV NOT adult t cell leukemia lymphoma)
7. Neuropathic nociceptive or pain and HTLV and (HTLV NOT adult t cell leukemia lymphoma

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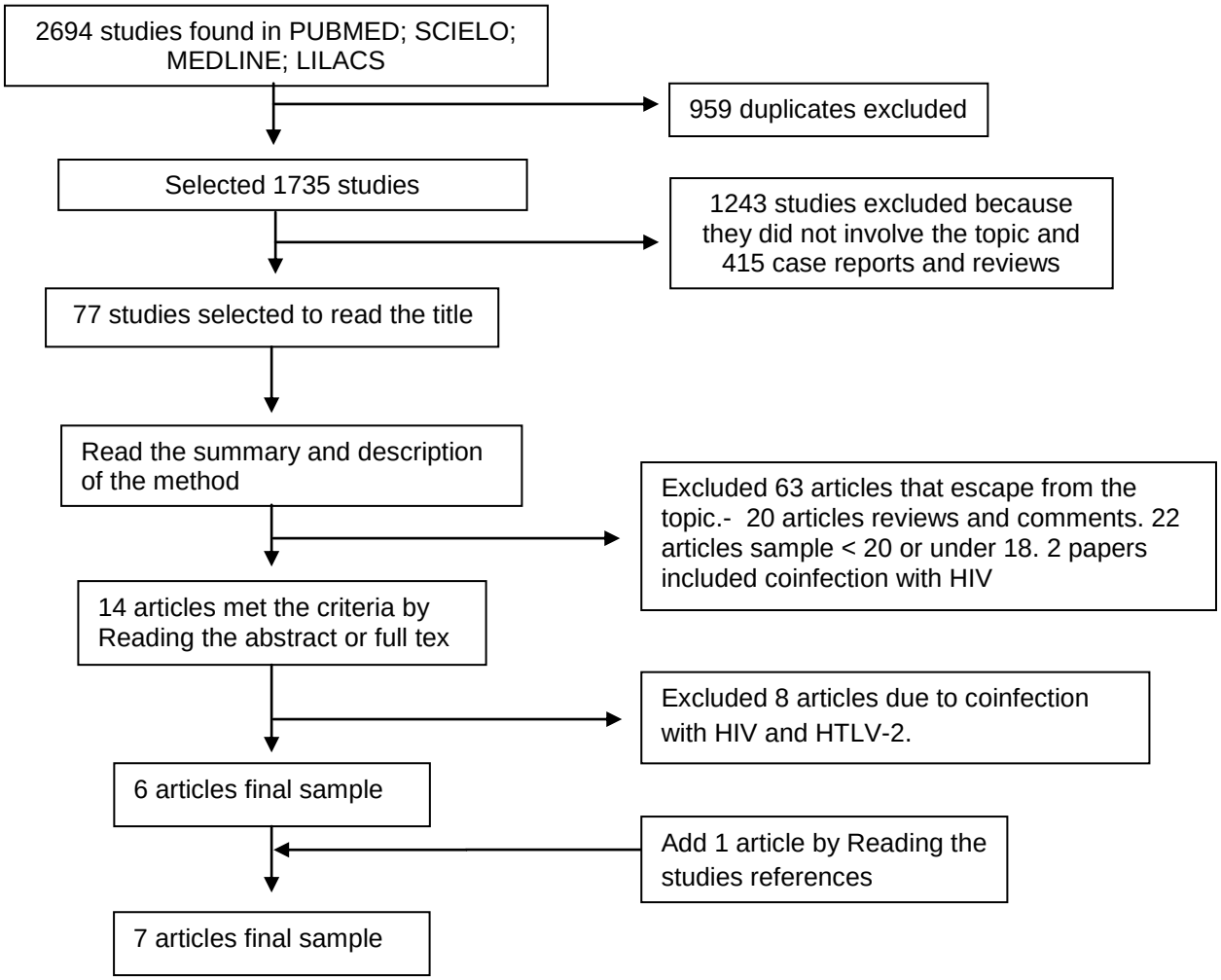

Figure 1. Flowchart of the study.

*Articles that the patients were infected with HIV, HTLV-2, HCV, HBV.

** Two articles use the same patients, but we decided to include it because they have different results

Table 1. Characteristics of studies that describe chronic pain in HTLV-1 infected individuals.

AUTHOR, YEAR	n	COUNTRY	POPULATION	STUDY DESIGN	GENDER (%FEMALES)	AGE (VARIATION)	SKIN COLOR
Martin et al, 2010	41	UK	HAM/TSP	Cohort	79.2	51(46-55)	White (12.5) Black (79.2)
Poetker et al, 2011	142	Brazil	HTLV-1*	Case-control	63.4	40.2±11.7	White (21.7) Black (49.3)
Franzoi and Araujo,2005	72	Brazil	HAM/TSP	Cross sectional	68.05	51.1 ±12.1	-
Franzoi and Araujo,2007	72	Brazil	HAM/TSP	Cross-sectional	68.05	51.1 ±12.1	-
Tavares et al, 2010	90	Brazil	HAM/TSP	Cross-sectional	70	36.7 ±15.4	-
Netto and Brites, 2011	43	Brazil	HAM/TSP	Cross-sectional	72.1	45.3 ±13.3	White (16.3) Non-white (83.7)
Mendes et al, 2013	115	Brazil	HTLV-1	Cross-sectional	69.6	48.5±13.6	White (12.2) Black (46.1)

*This work excluded HAM/TSP participants.

Table 2 - Evaluation of the studies according to NOS

AUTHOR, YEAR	STUDY DESIGN	SCORE NOS	PUNCTUATION	FAILURE IN STUDIES*
Martin et al, 2010	Cohort	Very Good	10/08	Selection of the non exposed cohort; description of the results
Poetker et al, 2011	Case Control	Very Good	09/08	Non-response rate control
Franzoi and Araujo, 2005	Cross Section	Unsatisfactory	05/02	Representative sample of the population; ascertainment of the exposure (risk factor) ; comparability between groups; description of the results; description of the statistical test
Franzoi and Araujo,2007	Cross Section	Unsatisfactory	05/02	Representative sample of the population; ascertainment of the exposure (risk factor); comparability between groups; comparability between groups; description of the results; description of the statistical test
Tavares et al, 2010	Cross Section	Unsatisfactory	05/02	Representative sample of the population; size of sample justified; comparison of survey participants; comparability between groups; description of the results
Netto and Brites, 2011	Cross Section	Unsatisfactory	05/03	Representative sample of the population; size of sample justified; comparison of survey participants; comparability between groups;
Mendes et al, 2013	Cross Section	Good	05/04	Representative sample of the population; comparison of survey participants; comparability between groups

*Annex full evaluation of NOS
Scores Star (*)

4.1 ARTIGO PRINCIPAL

De: "The Clinical Journal of Pain" <em@editorialmanager.com>

Para: Abrahão F Baptista <afbaptista@ufba.br>

Responder A: "The Clinical Journal of Pain" <julieporter529@gmail.com>

Data: 27 de janeiro de 2015 11:41:54 BRT

Assunto: CJP Submission Confirmation for Pain characteristics and associated factors in subjects with and without HTLV-1

Jan 27, 2015

Dear Prof. Baptista,

Your submission entitled "Pain characteristics and associated factors in subjects with and without HTLV-1" has been received by the journal editorial office.

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Kind Regards,

The Clinical Journal of Pain

Pain characteristics and associated factors in subjects with and without HTLV-1

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Abstract

Objective: To identify the characteristics of chronic pain in individuals with HTLV-1 compared to subjects without the virus.

Methods: Cross-sectional study in patients with HTLV-1, with positive ELISA test confirmed by Western blot, divided into three groups (HAM/TSP, Oligosymptomatic and Asymptomatic) and a comparison group of blood donors. All subjects had chronic pain. Variables analysed included demographic data, pain (visual analogue scale, McGill Inventory and DN4 questionnaire), symptoms of anxiety and depression (Hospital Anxiety and Depression Scale) and quality of life (SF-36).

Results: Sixty-six subjects with HTLV-1 were divided into the three subgroups, and 22 subjects were included in a control group, without the virus. Most sociodemographic data and lifestyle habits were homogeneous with the exception of education and occupational levels. For all the groups, nociceptive pain was the most frequent ($p<0.05$). Neuropathic pain was more frequent in the lower limbs of subjects with HTLV-1 ($p <0.05$). Oligosymptomatic participants showed diffuse pain, and depressive symptoms ($p<0.05$). Regarding the impact of chronic pain on quality of life, the domains of functional capacity, general health and social aspect were the most affected, especially in the HAM/TSP group ($p <0.05$).

Discussion: HTLV 1 neuropathic pain affects mainly the lower limbs, and precedes neurological symptoms. The diffuse pain associated with depressive symptoms is more frequent in oligosymptomatic patients. Pain impacted negatively quality of life in individuals with HTLV-1, especially in the domains of functional capacity, physical limitation, social aspect and pain in oligosymptomatic and HAM/TSP groups.

Key Words: HTLV-1; HAM/TSP; chronic pain; Myelopathy; Quality of life.

Introduction

The human T cell lymphotropic virus type 1 (HTLV-1) infects approximately 10 million persons in the world.[1,2] The infection is endemic in the Caribbean, Equatorial Africa, South and Central America and Japan.[3] In Brazil, there is not a consolidated estimation of the prevalence of the infection. However, a variation has been observed among regions, with lower frequency in the South and higher in the North and Northeast of the country. [4,5] In Salvador, a capital city in the Brazilian Northeast, 1.76% of the population is affected, and it is referenced as the place with the highest number of cases per inhabitant.[6]

There are multiple clinical and neurological manifestations of the disease resulting from HTLV-1, and pain is present in 84.5% of the subjects.[7] Leukemia/Adult T cell Lymphoma and tropical spastic paraparesis/ myelopathy associated with HTLV-1 (HAM/TSP) are the most severe expressions of the disease, and affect between 1 % and 5% of those infected.[3,8] Other symptoms, such as polymyositis, arthropathy[9,10] urological manifestations, erectile dysfunction, hyperactive bladder[11] and peripheral neuropathy[12-14] account for over 30% of the morbidities associated with HTLV-1 in the individual with HAM/TSP.[15] However, the majority of patients remain asymptomatic from a neurological point of view, apparently without manifestations related to the virus.

Reports of pain are frequent in individuals with HTLV-1, irrespective of the presence of neurological signs and symptoms.[7] The chronification of pain is an incapacitating condition[16] compromising functional capacity and independence.[17,18] It is associated with psychoaffective symptoms [19] and a negative effect on quality of life.[17-20] However, up to know, it is not known whether the characteristics of pain in these patients are related to the disease itself, as there are no studies that compare

the pain of individuals with HTLV-1 with that of persons without the virus. Therefore, the aim of this study was to characterize and identify the factors associated with chronic pain in subjects infected with HTLV-1, and compare them with a group of individuals without the virus.

Materials and Methods

A cross-sectional study was developed in the multidisciplinary outpatients clinic of HTLV of the "Hospital Universitário Professor Edgard Santos", in Salvador, Brazil, which follows-up individuals seropositive for HTLV-1. The majority of the individuals came from blood banks, families of individuals cared for in the multidisciplinary outpatient clinics and in neurology and dermatology clinics. In the outpatient clinics 440 individuals were diagnosed by the detection of antibodies of the virus by the ELISA test (*Cambridge Biotech, Worcester, MA*), confirmed by the *Western-blot* exam (HTLV Blot 2.4, *Genelabs, Science Park Drive, Singapore*). The individuals were stratified by a neurologist using the Extended Disability Status Scale (EDSS) and the Osame Motor Dysfunction Scale (OMDS). [21,22] Subjects were classified as: asymptomatic - without clinical or neurological symptomatology associated with the virus (EDSS 0 /Osame 0); oligosymptomatic - presenting minor symptoms such as hyperactive bladder, erectile dysfunction and sensory alterations (EDSS ≥2 Osame = 0); and HAM/TSP - presenting gait changes, spasticity, myelopathy, and frequently, neurogenic bladder (EDSS ≤ 2 / Osame <1).

Other possible causes of myelopathy were excluded by means of nuclear magnetic resonance of the spinal cord, serology for the hepatitis C virus (HCV), syphylis, HIV and HBV, fasting glycemia and the vitamin B12 levels (WHO Diagnostic Criterion). As the criterion for the clinical diagnosis of hyperactive bladder it was

considered the report of urinary urgency, with or without urinary incontinenceand/or nocturia.[23] The urodynamic study was used as the parameter for the diagnosis of neurogenic bladder.

Sample (Figure 1) size estimation was made considering a difference in prevalence of pain of 40% in patients with and without myelopathy, with an alpha value of 5% and study power of 80%, making it necessary to have 22 participants in each group.[20] In this grouping, the stratification made by the neurologist was considered. The individuals included, were those over the age of 20 years, who had an algic condition with a duration equal to or longer than six months, of a continuous or recurrent nature in the last three months.[16] The individuals not included were subjects with a diagnosis of rheumatological disease (systemic erythematosus lupus, rheumatoid arthritis or Sjogren's syndrome), diabetes mellitus, sickle cell anemia, myasthenia, polymiositis, Alzheimer's disease, fibromyalgia, poliomyelitis HIV, disk hernia and pain profile differing from that recommended by the International Association for the Study of Pain and/ or with difficulties in responding to the protocol used in the pain assessment. Data collection occurred in the period from July 2012 to February 2014.

The comparison group was formed by blood donors voluntarily recruited at the Hematology and Hemotherapy Foundation of Bahia (HEMOBA), in the city under study, in the period from June 2013 to February 2014. This group was defined by means of negative serology, paired by sex and age (± 5 years) and the same criteria for inclusion in and exclusion from the study were observed.

The sociodemographic and clinical data were collected by means of a standardized form. For the characterization of pain, a body diagram was used. The visual analog scale (VAS) was used for quantitative analysis and the McGill

questionnaire for qualitative analysis.[24] Pain was classified as neuropathic or nociceptive by means of the neuropathic pain diagnosis questionnaire (DN4).[25] The hospital anxiety and depression scale (HAD) was used to seek symptoms suggestive of anxiety and depression [26] and to evaluate the quality of life, the SF 36 was used.[27] The clinical conditions such as arterial hypertension, cardiopathy, Chagas disease, depression, gastritis, gastric ulcer, gastroesophageal reflux, hiatus hernia, umbilical hernia, orthopenia, and osteoporosis were classified as comorbidities.

Initially, a descriptive analysis was made by calculating the absolute and relative frequencies of the sociodemographic and behavioral variables and of the clinical conditions, as well as the measures of central tendency and dispersion, with the purpose of characterizing the profile of the studied population. The Kruskal-Wallis non-parametric test for independent samples was used to compare the medians between the groups, Chi-Square test to compare the proportions of the categorical variables and the Fisher's Exact test para variaveis com células < 5.

This study was approved by the Ethics Committee of the Professor Edgard Santos University Hospital, Federal University of Bahia, Brazil (protocol No. 21/2011). All the participants signed the Free and Informed Term of Consent (FITC).

Results

The final sample consisted of 88 subjects divided into four homogeneous groups with regard to the majority of the sociodemographic data, with the exception of educational level and occupation (Table 1). There was no difference among the groups with regard to the frequency and intensity of pain, although the reports were discretely different, when the visual analog scale was compared with the McGill inventory. As regards the topographical presentation of pain, the regions of the

neck/head/face and thorax/abdomen presented different distributions in the sample. The oligosymptomatic group was the one that most presented diffused pain and greater frequency of pain per areas evaluated. When the sample was analyzed as a whole, including individuals with and without HTLV-1, the site with the highest frequency of pain was the lower limb, with nociceptive pain predominating. In this sample, only the individuals with HTLV-1 presented neuropathic pain in the lower limbs (Table 2).

The use of drugs with analgesic action was common in individuals with HTLV-1, which hardly ever occurred among the seronegative subjects. Almost half of the asymptomatic group used some type of medication to control pain. This difference became more accentuated in the group with HAM/TSP, in which over half of the subjects used some type of medication with analgesic action. Physiotherapy was occasionally reported as an analgesic resource in subjects with HTLV-1 (Table 2).

Pain was associated with depressive symptoms in the sample, with greater frequency in the group of oligosymptomatic subjects. There was no difference among the groups with regard to the presence of symptoms of anxiety, depression associated with anxiety or with the comorbidities reported (Table 3). There was a greater extent of harm to functional capacity, general state of health and social aspect in the myelopathy and oligosymptomatic group with scores lower than 50 (Table 4).

Discussion

The aim of this study was to evaluate the characteristics of pain in individuals with HTLV-1, in comparison with subjects with chronic pain, without the virus. The endeavor was to identify whether the characteristics of pain in the group of infected

subject differed from those of non-infected persons. The results point towards a higher frequency of nociceptive pain among the individuals researched. The presence of diffused pain was associated with depressive symptoms in oligosymptomatic individuals. Only individuals with the virus presented with neuropathic pain in the lower limbs, including the subjects with an asymptomatic condition.

There is frequent complaint of chronic pain in the population as a whole, constantly associated with chronic diseases and the process of aging. [28] In the individual with HTLV-1, in addition to these factors, a series of aspects related to the virus favors the presence of pain. However, up to the present time, it was not clear whether the pain characteristics differed from those of individuals without the virus. On the other hand, as this concerns a virus that mainly acts on the nervous system, it is common to assume that pain would be predominantly neuropathic. [7,20] In the individuals with HTLV-1, the chronic pain condition may be justified by the elevation of the levels of INF-gama, TNF-alpha and chemokines, [29,30] in addition to the increase in the proviral load.[31] In these cases, the course of the chronic inflammatory process[8] mainly affects the nerve structures and complaints of numbness, weakness, tingling and sensation of weight in the extremities may coexist.[10,12] This may justify the occurrence of neuropathic pain even in the asymptomatic stage of the disease, as was found in our study.

The progression of painful symptoms in the oligosymptomatic stage may occur because of the progressive increase in tissue damage associated with progression of the infection, [31] which could lead to the appearance of diffuse symptoms. In addition, the involvement of basic functions, such as the urinary tract[32] and the increase in mood disturbances that accompany disease progression[19] may lead to an increase in

the painful symptoms. In other diseases in which there is frequently depression, [33] there is greater impact on morbidity and mortality. In subjects with HAM/TSP, this symptom has been investigated and presents a prevalence of close to 59%.[19] In this study, there was more presence of depression in the oligosymptomatic group. All of these factors together may contribute to the limitations found in the quality of life of the subjects studied, and provide feedback to the presence of mood disturbances and pain itself.

Lumbar pain is more frequent in individuals with myelopathy.[20,34,35] When comparing the pain of individuals with and without HTLV-1 we verified that the number of painful areas mentioned was similar in the asymptomatic and seronegative groups, differing from the oligosymptomatic group and from those with HAM/TSP. These latter two were similar between them, suggesting the possibility that the onset of medullary involvement may be the main source of pain in these individuals. It is possible that with medullary involvement, there is a combination of pain of mechanical origin due to muscular and movement insufficiency, associated with neuropathic pain due to nerve structures being affected. This entire condition, together with the urinary and psychiatric symptoms, would place the oligosymptomatic individual at greater risk of pain, and there would be greater functional impact. In the later stage of myelopathy there is a reduction in the complaints of pain,[35,36] however, it is not clear why this occurs.

Pain has been pointed out as being the cause of reduction in perception of the state of general health, vitality and metal health of patients with myelopathy.[18] In this study, the aspects of vitality and mental health showed no difference among the groups, while functional capacity, general state of health and social aspect, were the domains most harmed. In the presence of urinary symptoms, the harm was shown to

be greater, with impact on all the domains evaluated by the SF-36.[37] Chronic pain and urinary symptoms together, although in the absence of motor disturbances, may be the major factors for the reduction in the quality of life in individuals with HTLV-1 without evident myelopathy.

As resources used for pain control, physiotherapy was indicated for approximately 30% of the individuals with HTLV-1, and 47% of these subjects made use of some drug that interfered in the pattern of pain presented.[36,38] Self-medication was another tool used both by those infected and not infected, as the possibility of controlling the intensity of pain. Nevertheless, even with the use of these resources, pain was moderate to intense among the individuals with HTLV-1. It is possible that the low level of understanding by health professionals about the painful symptoms in these patients may lead to negligence as regards their diagnosis and adequate treatment. With the lack of attention to these aspects, patients may begin to make indiscriminate use of these resources, leading to inadequate control of the symptoms.

The results of this study should be complemented by the investigation both in systemic and local factor that may contribute to the genesis of pain in individuals with HTLV-1. We propose that future studies would investigate as systemic factors proinflammatory cytokines and proviral load, which could highlight if diffuse pain is due to a general inflammatory condition. Local factors such as peripheral nerve involvement and body mechanics imbalances would be local factors to account to increased perception of pain in the lower back and lower limbs. Finally, urological symptoms would make a negative contribution to quality of life, enhancing psychological stress, and consequently pain.

Nociceptive pain was more frequently present in the lower limbs of individuals with HTLV-1. The oligosymptomatic subjects had a higher tendency to present with a pattern of diffuse pain and depressive symptoms associated with pain. Pain had a negative impact on the quality of life of individuals with myelopathy and oligosymptomatic individuals in the domains of functional capacity, general state of health and social aspect.

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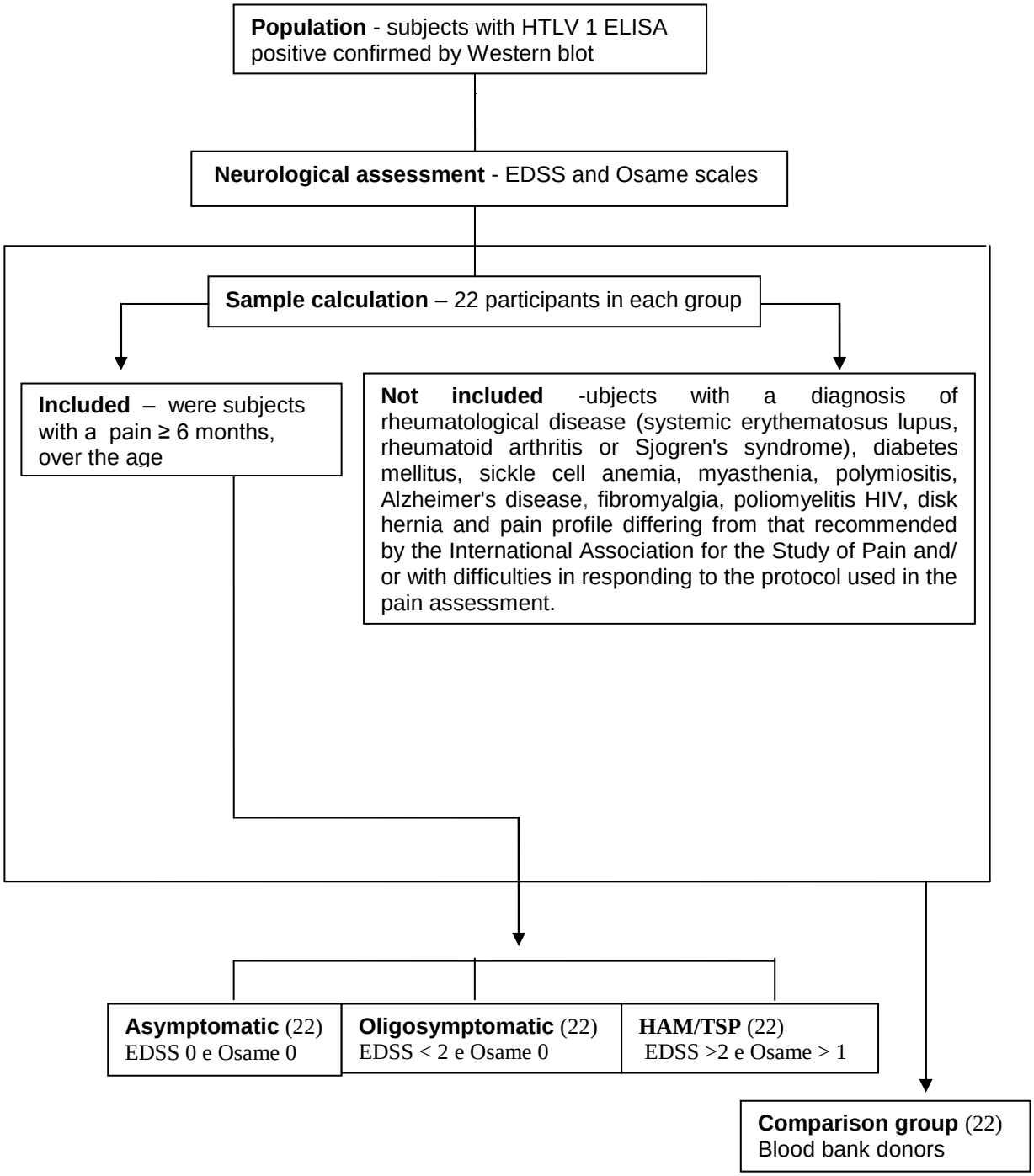

Figure 1 – Flowchart

Table 1 – Sociodemographic and lifestyle habits of subjects with and without HTLV 1 distribution, Salvador, Brazil, 2014.

Variables (n=88)	Without HTLV 1	HTLV 1			*P*
		Asymptomatic	Oligosymptomatic	HAM/TSP	
Age [a]	53 (50-57)	52 (49-54)	56 (48-65)	62 (45-65)	0.228[b]
Gender					0.231[d]
Female	17 (19)	12 (14)	18 (20)	15 (17)	
Male	05 (06)	10 (11)	04 (05)	07 (08)	
Marital status					0.489 [d]
Single	02 (02)	02 (02)	01 (01)	05 (07)	
Married	13 (15)	15 (17)	11 (12)	11 (12)	
Widower	02 (02)	01 (01)	06 (07)	03 (03)	
Divorced	05 (06)	04 (05)	04 (05)	03 (03)	
Years of study					**0.007** [d]
Did not go to school	01 (01)	-	-	-	
Up to 09 years	06 (07)	11 (13)	16(18)	16(18)	
Up to 12 years	10 (11)	10 (11)	06(07)	06(07)	
More than 12 years	05 (06)	01 (01)	-	-	
Occupation					**0.000** [d]
Retired	-	02 (02)	12 (14)	16 (18)	
Employee	15 (17)	13 (15)	04 (04)	04 (05)	
Unemployed	07 (08)	07 (08)	06 (07)	02 (02)	
Physical activity					0.680 [c]
Yes	05 (06)	08 (09)	05 (06)	07 (08)	
No	17 (19)	14 (16)	17 (19)	15 (17)	

Median – Quartile [a]; Kruskal-Wallis test [b] Chi-square test [c;] Fisher's Exact test [d]; HTLV 1- Human T-cell Lymphotropic Virus type 1; HAM/TSP- HTLV-1 Associated Myelopathy/ Tropical Spastic Paraparesis

Table 2. Characteristics of pain in subjects with and without HTLV 1 – Salvador, Brazil, 2014

Variables (n=88)	Without HTLV 1	HTLV 1			*P*
		Asymptomatic	Oligosymptomatic	HAM/TSP	
Pain intensity					
VAS [a]	08 (06-09)	07 (05-09)	09 (07-10)	08 (06-10)	0.763[b]
Mcgill [a]	25 (18 -35)	28 (19-35)	35 (24-39)	33 (27- 40)	0.076 [b]
Pain frequency					
Daily	07 (08)	07 (08)	12 (14)	13 (15)	0.129 [c]
Not daily	15 (17)	15 (17)	10 (11)	09 (10)	
Pain topography					
Head / neck	05 (06)	09 (10)	16 (18)	08 (09)	**0.007[c]**
Thorax / abdomen	08 (09)	04 (04)	13 (15)	10 (11)	**0.045[d]**
Upper limbs	10 (11)	11 (12)	15 (17)	10 (11)	0.377[c]
Lumbar	10 (11)	11 (12)	11 (12)	12 (14)	0.941[c]
Lower limbs	18 (20)	19 (21)	20 (23)	20 (23)	0.232[d]
Regions with pain					
1- Region	05 (06)	06 (07)	03 (03)	03 (03)	**0.022[d]**
2-3 Regions	13 (15)	12 (14)	05 (06)	13 (15)	
+ 4 Regions	04 (04)	04 (04)	14 (16)	06 (07)	
Nature x localization					
Head / neck					0.695[d]
Neuropathic	-	01 (01)	01 (01)	-	
Nociceptive	05 (06)	07 (08)	15 (17)	09 (10)	
Neuropathic / Nociceptive	-	-	-	-	
Thorax / abdome					0.857[d]
Neuropathic	-	-	01 (01)	01 (01)	
Nociceptive	08 (09)	04 (04)	12 (14)	08 (09)	
Neuropathic / Nociceptive	-	-	-	01 (01)	
Upper limbs					0.899[d]
Neuropathic	01 (01)	02 (02)	02 (02)	01 (01)	
Nociceptive	09 (10)	09 (10)	13 (15)	09 (10)	
Neuropathic / Nociceptive	-	-	-	-	
Lumbar					1.000[d]
Neuropathic	01 (01)	01 (01)	01 (01)	01 (01)	
Nociceptive	09 (10)	10 (11)	10 (11)	11 (12)	
Neuropathic / Nociceptive	-	-	-	-	
Lower limbs					**0.011[d]**
Neuropathic	-	05 (06)	07 (08)	07 (08)	
Nociceptive	18 (20)	12 (14)	15 (17)	13 (15)	
Neuropathic / Nociceptive	-	02 (02)	-	-	
Pain medication					
Yes	02 (02)	09 (10)	10 (11)	12 (14)	**0.008** [d]
No	20 (23)	13 (15)	12 (14)	10 (11)	
Physiotherapy for pain					
Yes	01 (01)	06 (07)	09 (10)	05 (06)	**0.032** [d]
No	21 (24)	16 (18)	13 (15)	17 (19)	

Median – Quartile [a]; Kruskal-Wallis test [b]; Chi-square test [c]; Fisher"s Exact Test [d;] VAS - Visual Analogue Scale; HTLV 1- Human T-cell Lymphotropic Virus type 1; HAM/TSP- HTLV-1 Associated Myelopathy/ Tropical Spastic Paraparesis

Table 3. Anxiety, depression and comorbidities presented in the sample – Salvador, Brazil, 2014.

Variables (n=88)	Without HTLV 1	HTLV 1			*P*
		Asymptomatic	Oligosymptomatic	HAM/TSP	
Clinical characteristics					
Anxiety					
Yes	08 (09)	07 (08)	09 (10)	09 (10)	0.912 [a]
No	14 (16)	15 (17)	13 (15)	13 (15)	
Depression					
Yes	03 (04)	05 (06)	12 (14)	06 (07)	**0.026** [b]
No	19 (21)	17 (19)	10 (11)	16 (18)	
Anxiety and depression					
Yes	03 (04)	03 (04)	09 (10)	06 (07)	0.108[b]
No	19 (21)	19 (21)	13 (15)	16 (18)	
Comorbidities					
Yes	03 (03)	03 (03)	08 (09)	08 (09)	0.246[b]
No	19 (22)	19 (22)	14 (16)	14 (16)	

Chi-square test[a]; Fisher"s Exact Test [b]; HTLV 1- Human T-cell Lymphotropic Virus type 1; HAM/TSP- HTLV-1 Associated Myelopathy/ Tropical Spastic Paraparesis

Table 4 - Scores of quality of life without subjects and HTLV 1- Salvador, Brazil, 2014.

Variables (n=88)	Without HTLV -1	HTLV 1			*p* [b]
		Asymptomatic	Oligosymptomatic	HAM/TSP	
SF 36 Domains [a]					
Physical Function	065 (045- 087)	072 (039-090)	040 (019-070)	010 (000-031)	**0.000**
Physical Role	100 (000 -100)	100 (037-100)	037 (000-100)	025 (000-100)	0.151
Bodily Pain	041 (031- 084)	051 (017-064)	051 (031-062)	040 (021-061)	0.325
General Health	079 (060-092)	072 (052-078)	062 (039-082)	047 (026-063)	**0.001**
Vitality	062 (044-071)	067 (047-086)	050 (040-066)	055 (044-075)	0.230
Social Function	075 (050-100)	100 (062-100)	075 (035-100)	050 (034-100)	**0.029**
Emotional Role	100 (025-100)	100 (091-100)	100 (049-100)	049 (000-100)	0.476
Mental Health	076 (054-085)	072 (060-096)	064 (048-077)	068 (048-092)	0.498

Median **–** Quartile [a]; Kruskal-Wallis test [b] HTLV 1- Human T-cell Lymphotropic Virus type 1; HAM/TSP- HTLV-1 Associated Myelopathy/ Tropical Spastic Paraparesis; SF 36 domains - Quality of Life Questionnaire

5. CONCLUSÕES

A revisão de literatura encontrou uma maior prevalência de dor nociceptiva em indivíduos infectados pelo HTLV-1, com frequente na região das costas e considerada severa por aproximadamente 40% dos indivíduos.

O estudo original apresentou uma maior prevalência de dor nociceptiva em indivíduos com HTLV-1 (assintomático, oligoassintomático ou com HAM/TSP) e sem o vírus (soronegativos). Contudo, a dor neuropática só foi encontrada em membros inferiores dos indivíduos com o virus.

A referência a multi locais com dor foi comum entre os grupos. Observa-se que entre os indivíduos com HTLV-1, os oligoassintomáticos sofrem mais com estás queixas, a qual esteve associada, em sua maioria, a sintomas depressivos.

Houve impacto negativo na qualidade de vida dos pacientes com HAM/TS, especialmente nos domínios capacidade funcional, aspecto geral de saúde e, aspecto social.

6. CONSIDERAÇÕES FINAIS

Com este estudo, foi possível responder alguns questionamentos referentes à dor, no indivíduo com HTLV-1, como a natureza da dor mais prevalente, principais locais de dor, presença de sintomas psicoafetivos e impacto da dor na qualidade de vida. Contudo, o tamanho da amostra não permitiu responder quais são os fatores preditores da dor nestes indivíduos.

Observou-se uma maior queixa de dor neuropática em membros inferiores em indivíduos com HTLV-1. A presença desta natureza de dor em membros inferiores de indivíduos assintomáticos pode indicar que já há ação do vírus sobre o sistema nervoso. No indivíduo oligoassintomático a presença de bexiga hiperativa já indica algum grau de comprometimento neurológico, sendo a natureza neuropática em membro inferior possível de ocorrer. Contudo, não se sabe se a dor nesta localidade precede os sintomas urinários. Um melhor acompanhamento dos indivíduos assintomáticos poderia elucidar esta questão. Analisar as citocinas pró-inflamatórias, carga proviral e controlar as condições clínicas que possam ser um confundidor precisam ser consideradas neste sentido.

Alguns pesquisadores já advertem para a necessidade de um olhar atento para os indivíduos oligossintomáticos. Nessa fase o processo inflamatório mais intenso, que pode evoluir para o estado mais grave da doença, lenta ou repentinamente. Neste grupo foi relatada de várias áreas dolorosas associadas sintomas de depressão e impacto na qualidade de vida, similar ao paciente com mielopatia. Contudo não fica claro se a presença de dor difusa é resultado de uma ação sistêmica, envolvendo as citocinas ou de uma ação mecânica sobre o nervo periférico ou o as duas condições agindo em conjunto.

7. PESPECTIVAS FUTURAS

Investigar a relação entre produção da citocinas pró-inflamatórias e aumento de carga proviral e dor em multi localidade nos indivíduos com HTLV-1 sem mielopatia.

Avaliar o comprometimento do nervo periférico e desequilíbrios da mecânica corporal em indivíduos com dor crônica e infecção pelo HTLV-1 porém sem mielopatia.

Verificar a relação entre sintomas urológicos e dor crônica e seu efeito sobre a qualidade de vida dos indivíduos com bexiga hiperativa.

Implementar projetos para o tratamento da dor nos indivíduos com infecção pelo HTLV-1.

ANEXOS

Anexo A - Parecer do Comitê de Ética

Parecer Consubstanciado de Projeto

Título do Projeto: Estudo da Dor em Pacientes Portadores de HTLV-I.

Pesquisador Responsável Dislene Nascimento dos Santos

Data da Versão 01/04/2011 | **Cadastro** 21/11 | **Data do Parecer** 01/08/2011

Grupo e Área Temática III - Projeto fora das áreas temáticas especiais

Objetivos do Projeto

- Estudar a prevalência de dor nos pacientes portadores de HTLV-I assintomáticos e portadores de bexiga neurogênica associada ao vírus, atendidos no Ambulatório Multidisciplinar de HTLV do Complexo Hospitalar Professor Edgard Santos – COMHUPES.

Objetivos específicos

i. Identificar os tipos de dor relatada pelos os pacientes infectados pelo HTLV-I;
ii. Avaliar a existência de associação entre dor e as patologias associadas ao HTLV-I;
iii. Identificar as atitudes frente à dor utilizadas por estes pacientes;
iv. Averiguar o impacto da dor no desempenho funcional e qualidade de vida destes indivíduos.

Sumário do Projeto

O Vírus Linfotrópico da célula T humana tipo I é o agente etiológico da Paraparesia Espástica Tropical / Mielopatia associado ao HTLV-I (TSP/HAM) e da Leucemia / Linfoma de célula T em adultos (ATL) 7,8 o qual tem como principal alvo de infecção, vários tipos de células T, particularmente os linfócitos T CD4+ no início e T-CD8+ na doença avançada; o que talvez influencie nas diferenças clínicas e na evolução das infecções associada ao vírus 28,29.
Desenho do Estudo: estudo de corte transversal, descritivo e base populacional.
Local: O estudo será realizado no Ambulatório Multidisciplinar de HTLV do COMHUPES/UFBA em Salvador-BA, Brasil.

População: pacientes diagnosticados com HTLV-I pelo teste ELISA e Western-blot.
Definição de População para Estudo: Os pacientes serão distribuídos em grupos de acordo com os escores de EDSS 34 (Kurtze Expanded Disability Status Scale) e OMDS 41 (Osame's Motor Disability Score) em:

- Grupo I/GI [pacientes com EDSS ≥ 2 e OSAME≥1(sintomáticos HAM/TSP)];
- Grupo II/GII [pacientes com EDSS ≥ 1 e OSAME= 0 (oligossintomáticos)] e
- Grupo III /G III [pacientes com EDSS=0 e OSAME=0(assintomáticos)].

O GI, grupo de estudo controle, será constituído de indivíduos com HAM/TSP e os GII e GIII serão os estudos de caso; sendo GII com indivíduos infectados pelo HTLV-I que apresentam manifestações urinárias e/ou disfunção eréteis, sem HAM/TSP e o GIII de portadores do HTLV-I sem manifestações de infecção pelo vírus.
Fonte de dados: dados secundários serão coletados através de formulário semi-estruturado (APENDICE -1) do banco de dados e prontuários dos pacientes atendidos no ambulatório e os dados primários serão obtidos pela a aplicação do Escala de Dor de McGill e Inventario de Atitudes frente à dor; os quais são validados e traduzidos para o português.

Análise dos dados: As variáveis categóricas serão descritas através de proporções e as variáveis contínuas por media e desvio padrão. O teste t de student será utilizado para comparação de media entre grupos e o teste do qui quadrado para a comparação entre categorias em tabelas de dupla entrada. Será considerado como significativo um p menor que 5%.

Aspectos relevantes para avaliação	*Situação*
Título	Adequado

Relação dos Pesquisadores	Adequada
Local de Origem na Instituição	Adequado
Projeto elaborado por patrocinador	Não
Local de Realização	Própria instituição
Outras instituições envolvidas	Não
Condições para realização	Adequadas
Introdução	Adequada
Objetivos	Adequados
Método	
Tipo de projeto	Pesquisa em Seres Humanos
Delineamento	Adequado
Tamanho de amostra	Total Na Instituição
Cálculo do tamanho da amostra	Adequado
Participantes pertencentes a grupos especiais	Não
Seleção eqüitativa dos indivíduos participantes	Adequada
Critérios de inclusão e exclusão	Adequados
Relação risco- benefício	Adequada
Uso de placebo	Não utiliza
Período de suspensão de uso de drogas (wash out)	Não utiliza
Monitoramento da segurança e dados	Adequado
Armazenamento de material biológico	Adequado
Instrumentos de coleta de dados	Adequados
Avaliação dos dados	Adequada - quantitativa
Privacidade e confidencialidade	Adequada
Termo de Consentimento	Adequado
Adequação às Normas e Diretrizes	Sim
Cronograma	Adequado
Data de início prevista	maio de 2011
Data de término prevista	dez 2012
Orçamento	Adequado
Solicita recursos à instituição	Não
Fonte de financiamento externa	Não
Referências Bibliográficas	Adequadas

Recomendação

Aprovar

Comentários Gerais sobre o Projeto

Todas as solicitações foram atendidas pelo pesquisador responsável, sendo assim, este projeto está adequado de acordo com as normas e resoluções do CEP- COM.HUPES.

Informações ao Pesquisador:

O sujeito da pesquisa tem a liberdade de recusar-se a participar ou de retirar seu consentimento em qualquer fase da pesquisa, sem penalização alguma e sem prejuízo ao seu cuidado (Res. CNS 196/96 - Item IV.1.f) e deve receber uma cópia do Termo de Consentimento Livre e Esclarecido, na íntegra, por ele assinado (Item IV.2.d).

• O pesquisador deve desenvolver a pesquisa conforme delineada no protocolo aprovado e descontinuar o estudo somente após análise das razões da descontinuidade pelo CEP que o aprovou (Res. CNS Item III.3.z), aguardando seu parecer, exceto quando perceber risco ou dano não previsto ao sujeito participante ou quando constatar a superioridade de regime

oferecido a um dos grupos da pesquisa (Item V.3) que requeiram ação imediata.

• O CEP deve ser informado de todos os efeitos adversos ou fatos relevantes que alterem o curso normal do estudo (Res. CNS Item V.4). É papel do pesquisador assegurar medidas imediatas adequadas frente a evento adverso grave ocorrido (mesmo que tenha sido em outro centro) e enviar notificação ao CEP e à Agência Nacional de Vigilância Sanitária – ANVISA – junto com seu posicionamento.

Relatórios parciais e final devem ser apresentados ao CEP, inicialmente em _____/_____/_____ e ao término do estudo.

Projeto aprovado.

ROBERTO BADARÓ, MD PHD
Coordenador CEP
CHUPES

Anexo B – Termo de Consentimento Livre Esclarecido

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

TÍTULO DO ESTUDO: Estudo da Dor em pacientes com HTLV-1
PESQUISADORES RESPONSÁVEIS:
INSTITUIÇÃO / DEPARTAMENTO: Complexo Universitário Professor Edgard Santos – COMHUPES / Ambulatório Multidisciplinar de HTLV
ENDEREÇO DO PESQUISADOR RESPONSÁVEL: Ambulatório Multidisciplinar de HTLV-I
No Hospital Universitário Professor Edgard Santos, situado na Rua Augusto Viana, s/n – Canela – CEP: 40.110-910 – Salvador / BA.
TELEFONE DO PESQUISADOR RESPONSÁVEL PARA CONTATO: 71-88087257
LOCAL DE COLETA DE DADO: Ambulatório Multidisciplinar de HTLV
Prezado (a) Senhor (a):

Você está sendo convidado (a) a responder as perguntas desse formulário de forma totalmente voluntária.

- Antes de concordar em participar desta pesquisa e responder este formulário, é muito importante que você compreenda as informações e instruções contidas neste documento.
- Os pesquisadores deverão responder a todas as suas dúvidas antes que você se decida a participar.
- Você tem o direito de desistir de participar da pesquisa a qualquer momento, ou deixar de responder a qualquer das questões que lhe cause constrangimento, sem nenhuma penalidade e sem perder os benefícios aos quais tinha direito.
- É necessário que o senhor (a) assine duas vias deste documento como comprovação de concordância na participação voluntária nesta pesquisa. Uma via do Termo lhe será entregue e a outra via ficara em poder do pesquisador.

OBJETIVO DO ESTUDO: Estudar a prevalência de dor nos pacientes portadores de HTLV-1 assintomáticos e sintomáticos do ponto de vista neurológico, atendidos no ambulatório multidisciplinar de HTLV do Complexo Hospitalar Professor Edgard Santos – COMHUPES.
PROCEDIMENTOS: Sua participação nesta pesquisa consiste em responder questionários sobre a dor, atitudes quando com dor, desempenho funcional e qualidade de vida. E a realização de testes de função sensitiva cutânea e de diagnostico de dor miofascial.
BENEFÍCIOS: Os participantes desta pesquisa não receberão qualquer beneficio financeiro ou privilégios quanto ao tratamento. Contudo estarão contribuindo para o conhecimento cientifico de profissionais que tem interesse em melhorar a qualidade de vida dos pacientes com HTLV.
RISCOS: A participação nesta pesquisa não representara qualquer risco de ordem física ou psicológica para você. Contudo, caso você tenho perfil para investigação de dor miofascial, a realização do procedimento pode desencadear dor ou aumentar a dor já existente.
SIGILO: As informações fornecidas por você não representam risco a sua privacidade, a mesma é garantida pelos pesquisadores responsáveis. Os sujeitos da pesquisa não serão identificados em nenhum momento, mesmo quando os resultados desta pesquisa forem divulgados.
CIÊNCIA DO (A) PESQUISADOR (A) RESPONSÁVEL PELO PROJETO:
Declaro que obtive de forma apropriada e voluntária o Consentimento Livre e Esclarecido desse sujeito de pesquisa.

Salvador, de de

_____
Assinatura do Pesquisador responsável pela pesquisa

CIÊNCIA E ACORDO DO PARTICIPANTE (sujeito da pesquisa)

Eu,_____,CPF_____aceit
o participar da pesquisa "Estudo da dor em pacientes com HTLV-I" que tem como objetivo estudar a prevalência de dor nos pacientes portadores de HTLV-1 assintomáticos e sintomáticos do ponto de vista neurológico.Fui informado que responderei questionários individualmente e realizarei teste de função sensitiva cutânea como minofilamentos de nylon após instrução de respostas; e também será investigado a presença de nódulos dolorosos através do algometria de pressão,aparelho o qual aplica uma pressão no local examinado e pode desencadear a dor ou aumentá-la. Contudo, terei a total liberdade de interromper e/ou desistir de participar da pesquisa a qualquer momento. Os questionários serão a respeito da dor, atitudes diante da dor e pensamentos catastróficos. A pesquisadora estará à disposição para esclarecer qualquer duvida relacionada às perguntas e métodos utilizados durante a pesquisa. Que esta pesquisa será publicada, respeitando o sigilo absoluto e a minha privacidade. Quaisquer danos e constrangimentos que possam vir causar a minha imagem moral, a pesquisadora será responsável. Em qualquer etapa do estudo os participantes terão acesso aos profissionais responsáveis pela pesquisa para esclarecimento de eventuais duvidas. O contato da pesquisadora Dislene dos Santos (71)88087257 ou procurá-la no Ambulatório Multidisciplinar de HTLV-I do COMHUPES. Se Houver alguma dúvida ou consideração com relação ética da pesquisa, poderei entrar em contato com o Comitê de ética e Pesquisa no Hospital Universitário Professor Edgard Santos tel.: (71) 32838140.

Declaro que fui esclarecido sobre os objetivos desta pesquisa, me propondo a responder os questionários voluntariamente sem qualquer tipo de remuneração ou custos. E que esta pesquisa não mim trará benéficos direto, entretanto estarei contribuindo para o conhecimento cientifico sobre o HTLV- 1.

Quanto aos riscos possíveis de ocorrer durante a pesquisa, entendi que esses são inexistentes, pois, não será realizada nenhuma intervenção ou procedimento invasivo.

Informo ter sido suficientemente esclarecido a respeito do estudo, ficando claro para mim a proposta da pesquisa apresentada e declaro autorizada a pesquisa. Desta forma, assino duas vias deste documento, uma mim será entregue e a outra ficará em poder do pesquisador como confirmação da autorização para realização da presente pesquisa.

Salvador, de de

_____
Assinatura do sujeito de pesquisa

_____
Assinatura Testemunha