Higher Prevalence of Fibromyalgia in Patients Infected with Human T Cell Lymphotropic Virus Type I

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ABSTRACT. ***Objective.*** Inflammatory rheumatic conditions including rheumatoid arthritis and Sjögren's syndrome have been reported in individuals infected with human T cell lymphotropic virus type I (HTLV-I). Other chronic lymphotropic virus infections such as hepatitis C and human immunodeficiency virus are associated with fibromyalgia (FM). There are no reports about the association between HTLV-I infection and FM. We evaluated the association between FM and HTLV-I infection.

Methods. We conducted a case-control study with prevalent cases. Ex-blood donation candidates with HTLV-I infection from a blood bank cohort, and healthy blood donors as a control group, were submitted to rheumatologic evaluation to compare the prevalence of FM. The following covariables were also evaluated: other rheumatic diseases, age, sex, personal income, level of education, and depression.

Results. One hundred individuals with HTLV-I infection and 62 non-infected blood donors were studied. Thirty-eight (38%) HTLV-I infected individuals and 3 (4.8%) individuals from the control group presented the diagnosis of FM (OR 12.05, 95% CI 3.53–41.17). Other rheumatic diseases were also more prevalent in the infected group (37% vs 12.9%; OR 3.80, 95% CI 1.63–8.86). In multivariate analysis adjusted by the covariables, the association between HTLV-I and FM was statistically significant (OR 9.14, 95% CI 2.42–34.52).

Conclusion. Our study shows a greater prevalence of FM in HTLV-I infected individuals, suggesting that FM may be associated with this viral infection. (J Rheumatol 2006;33:2300–3)

Key Indexing Terms:
FIBROMYALGIA EPIDEMIOLOGY
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Fibromyalgia (FM) is a chronic painful noninflammatory condition of unknown origin, characterized by diffuse pain and tender points[1,2]. Environmental exposures that have been described as triggers are physical trauma, emotional distress, endocrine disorders, immune activation related to autoimmune diseases, and chronic infections such as human immunodeficiency virus (HIV) and hepatitis C virus (HCV)[1-4]. Both viruses are lymphotropic and may cause disruption of immune regulation that leads to aberrant T cell activation and chronic inflammatory syndromes[5,6].

Human T cell lymphotropic virus type I (HTLV-I) is the causative agent of adult T cell lymphoma/leukemia and HTLV-I myelopathy/tropical spastic paraparesis (HAM/TSP) disease[7]. Several inflammatory rheumatic conditions such as rheumatoid arthritis (RA) and Sjögren's syndrome (SS) have been reported in infected patients[8]. The pathogenesis of this association is unclear, but some evidence suggests there is a disturbance in immunoregulatory mechanisms similar to those thought to cause rheumatic symptoms in HIV and HCV infected patients[8,9]. There are no reports on prevalence of FM in HTLV-I infected subjects. Our aim was to evaluate this possible association.

MATERIALS AND METHODS

A case-control study with prevalent cases[10] was carried out. Between March 2003 and December 2004, ex-blood donation candidates with HTLV-I infection followed in a blood bank cohort in Belo Horizonte, and non-infected blood donors as a control group, were submitted to rheumatic evaluation to compare the prevalence of FM and other rheumatic diseases. The infection was defined by a positive ELISA test and presence of bands for GAG (p19 and p24) and ENV (GD21) on Western blot. Infected individuals were consecutively invited to enter the study during regular cohort evaluations. Subjects from the control group were selected by random systematic sampling from the blood donors list of the Belo Horizonte Blood Bank.

The frequency of FM, as defined by the Amercian College of Rheumatology (ACR) criteria[11], was compared in both groups. Age, sex, personal income, level of education, depression, and other rheumatic diseases were studied as covariables. Depression was defined as the presence or history of a major depressive episode according to the Mini International

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Neuropsychiatric Interview[12], applied to patients at a regular psychiatric appointment of the cohort. Rheumatic diseases were analyzed as one combined group of diseases other than FM: osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, crystal-induced arthropathy, and soft tissue rheumatisms, defined by ACR accepted criteria.

In pilot studies in the Interdisciplinary HTLV-I/II Research Group cohort, the prevalence of FM in HTLV-I infected patients varied from 19% to 29% (unpublished data). To calculate sample size we used a reference value for FM prevalence in the general population of 2% and a conservative estimate in the HTLV-I infected group of 10%. With 80% power, a statistical significance level of 0.05, and a proportion of one case to one control, we estimated a sample size of n = 162 for each group. An interim analysis after 10 months of the study showed that prevalence of FM reached 30% in the infected group and 4.5% in the control group. Therefore, the sample size was recalculated using a proportion of 3 cases to 2 controls and an estimated prevalence of FM of 20% in the infected group and 4% in the control group. The recalculated sample size was n = 98 in the HLTV-I group and n = 65 in the control group.

The frequencies of the studied variables were compared in the 2 groups and statistical analysis was performed using odds ratios (OR) and 95% confidence interval (95% CI). The independent association of each studied variable and the HTLV-I infection was assessed through multiple logistic regression analysis. Variables with statistical significance in the univariate analysis were included in the initial and the final models according to the Wald statistic ($p < 0.05$) or clinical and epidemiological significance. The models were compared using the log-likelihood ratio test, and the fitness of the final model was assessed by the Hosmer-Lemeshow test. The data were analyzed using SPSS (version 11; SPSS Inc., Chicago, IL, USA).

The study was approved by the Ethics in Research Committees from the Hemominas Foundation (No. 104) and from the Federal University of Minas Gerais (No. 197/04). All studied subjects signed a written consent.

RESULTS

One hundred subjects infected with HTLV-I and 62 negative controls were included in the study. In comparison to the control group, subjects with HTLV-I were older (41.2 ± 11.2 vs 34.2 ± 11.4 yrs; $p < 0.001$) and the proportion of women was higher in this group (57.0% vs 40.3%; $p = 0.028$). Univariate analysis showed a statistically significant association between HTLV-I infection and higher age, female sex, fewer years of formal study, depression, FM, and presence of other rheumatic diseases. There was no association of HTLV-I infection and personal income (Table 1).

Regarding other rheumatic diseases, infected patients presented a higher prevalence of osteoarthritis (23% vs 8%; OR 3.40, 95% CI 1.22–9.5; $p = 0.011$), but after adjustment for age and sex this association did not reach statistical significance (OR 2.38, 95% CI 0.81–6.98; $p = 0.11$). The frequencies of soft tissue rheumatisms and inflammatory conditions such as rheumatoid arthritis and Sjögren's syndrome were also higher in the HTLV-I group, but the small number of cases did not permit statistical analysis (Table 2).

Three infected subjects (3%) presented evidence of a myelopathy compatible with HAM/TSP, but none of them had a major disability (e.g., inability to walk without help). Two of them fulfilled the diagnostic criteria for depression and FM.

In multivariate analysis, the variables of age, sex, years of formal study, depression, diagnosis of FM, and diagnosis of other rheumatic diseases were included in the initial model. Depression was excluded from the subsequent models because of lack of statistical significance in this analysis. Age and sex were retained because of their clinical and epidemiological importance. The presence of FM and other rheumatic diagnoses were correlated ($p = 0.008$); therefore we tested models with both variables and with each variable separately. In all the models there was a statistically significant association between HTLV-I infection and FM; HTLV-I was similarly associated with viral infection and years of formal study. In the model that did not include FM, there was a statistically significant association of HTLV-I infection and other rheumatic diseases. The Hosmer-Lemeshow test confirmed the fitness of models 3 and 4 (data not shown; Table 3).

DISCUSSION

More than 40 microorganisms have been associated with FM. The most frequently described are Epstein-Barr virus, parvovirus, *Borrelia burgdorferi*, hepatitis C virus, and HIV[2]. In chronic virus infections, the prevalence of FM reaches 30%, in comparison with 0 to 5% in controls[2-4]. Although the pathogenesis has not been fully clarified, infected patients have musculoskeletal complaints such as arthralgia, myalgia, and fatigue, which are understood to be a consequence of immunological disturbance[5]. In our study, HTLV-I infection and FM were strongly associated, even when adjusted for confounding factors of age, sex, social aspects, and comorbidity. To our knowledge, there are no other studies evaluating this association.

Despite the growing recognition of FM as a distinct clinical entity, little is known about its pathogenesis. Most authors propose a bidirectional interaction of peripheral nociceptive input and abnormal central pain processing, leading to chronic muscle pain, fatigue, sleep disturbance, and mood disorders[1,2]. Wallace, *et al*[13] described higher levels of interleukin 8 (IL-8) in sera, and increased concentration of IL-6 in supernatants of peripheral blood mononuclear cells from patients with FM. Because IL-8 promotes sympathetic pain and since IL-6 induces hyperalgesia, fatigue, and depression, the authors hypothesized that these may play a role in modulating symptoms in FM.

In HTLV-I infection, host factors such as humoral and cellular immune responses are determinants of persistence of infection and the development of the HTLV-I associated diseases. Several cytokines including IL-1, IL-2, IL-2Ra, and IL-6, and other B and T activated lymphocyte products such as the granulocyte-monocyte colony stimulating factor and tumor necrosis factor-α are involved in the pathogenesis of HAM/TSP, HTLV-I associated arthropathy, and Sjögren's syndrome[8,9]. Thus, it is plausible that in HTLV-I infected patients altered immune regulation, activated lymphocytes, and higher cytokine production may contribute to development of musculoskeletal complaints clinically expressed as FM.

On the other hand, Goldenberg[14] suggests that a chronic infection would be one of many events that promote a maladaptive behavior pattern, which secondarily leads to FM. In

Table 1. Simple frequencies and univariate analysis of studied characteristics in subjects with HTLV-I infection and noninfected controls.

Variables	HTLV-I Infected Subjects, No. (%), n = 100	Controls, No. (%), n = 62	OR (95% CI)
Age[a], yrs			
< 38	38 (38)	42 (67.7)	1.0
≥ 38	62 (62)	20 (32.3)	3.43 (1.76–6.68)
Sex			
Male	43 (43)	37 (59.7)	1.0
Female	57 (57)	25 (40.3)	1.96 (1.03–3.73)
Personal income[b]			
> 2 minimum salaries	43/82 (52.4)	30/56 (53.6)	1.0
≤ 2 minimum salaries	39/82 (47.6)	26/56 (46.4)	1.05 (0.56–2.07)
Formal study, yrs[c]			
≥ 8	31 (31)	42/61 (68.9)	1.0
< 8	69 (69)	19/61 (31.1)	4.92 (2.47–9.79)
Depression[d]			
No	70/94 (74.5)	53/60 (88.3)	1.0
Yes	24/94 (25.5)	7/60 (11.7)	2.60 (1.04–6.48)
Fibromyalgia			
No	62 (62)	59 (95.2)	1.0
Yes	38 (38)	3 (4.8)	12.05 (3.53–41.17)
Other rheumatic diseases[e]			
No	63 (63)	54 (87.1)	1.0
Yes	37 (37)	8 (12.9)	3.80 (1.63–8.86)

[a] Dichotomized by median age for all subjects. [b] Dichotomized by median minimum salary per month for all subjects. Eighteen subjects with infection and 6 negative controls did not answer this question. [c] Dichotomized by the median number of years of formal study of all subjects. One negative control did not answer this question. [d] Six HTLV-I infected subjects and 2 negative controls were not submitted to the psychiatric evaluation. [e] Composite of rheumatic diseases other than fibromyalgia.

Table 2. Rheumatic diseases other than FM in subjects with HTLV-I infection and noninfected controls.

Other Rheumatic Diseases	HTLV-I Infected Subjects, No. (%), n = 36/100[a]	Controls, No. (%), n = 8/62[a]
Osteoarthritis[b]	23 (23)	5 (8)
Soft tissue rheumatism	6 (6)	2 (3)
Rheumatoid arthritis	2 (2)	—
Sjögren's syndrome	2 (2)	—
Cutaneous lupus erythematosus	1 (1)	—
Other	4 (4)[c]	2 (3)[d]

[a] Some patients presented more than one rheumatic diagnosis. [b] In a simple analysis, infected patients presented a higher prevalence of osteoarthritis (23% vs 8%; OR 3.40, 95% CI 1.22–9.5; p = 0.011), but after adjustment for age and sex this association did not reach statistical significance (OR 2.38, 95% CI 0.81–6.98; p = 0.11). [c] Chronic degenerative meniscopathy (n = 2), undifferentiated arthritis (n = 1), and lumbar radiculopathy (n = 1). [d] Gout (n = 1) and chondrocalcinosis (n = 1).

HCV or HIV infected patients, anxiety and mood disturbances are reported as a consequence of preoccupation and an incurable chronic disease stigma. Decreased exercise tolerance and inactivity are common, related to symptoms of the infection itself or to the adverse effects of treatment. These factors are recognized as predictors of chronic musculoskeletal pain[2,14]. In our study, we included depression as a factor to be adjusted in the statistical analysis. Most infected subjects were asymptomatic regarding HTLV-I related diseases. Therefore, we understand that in our patients the musculoskeletal complaints could not be considered as secondary to mood disturbances or physical limitations.

The HTLV-I infected subjects also showed a higher prevalence of other rheumatic diseases when diseases were combined for analysis. Individually, the frequency of osteoarthritis was significantly higher in those infected, but this association was not statistically significant when adjusted for age and sex. This may represent a sample size limitation or a bias, since both HTLV-I infection and osteoarthritis are more frequent in women, and their prevalence increases with age. The

Table 3. Association between the HTLV-I infection and the studied variables in the different logistic regression models tested expressed as odds ratios (95% confidence intervals).

Variables	Model 1[a] OR (95% CI)	Model 2[b] OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
Age ≥ 38 yrs	1.89 (0.86–4.18)	1.71 (0.78–3.75)	1.93 (0.89–4.10)	2.16 (1.03–4.55)
Female sex	1.32 (0.58–3.00)	1.26 (0.57–2.81)	1.36 (0.62–2.99)	2.08 (0.99–4.24)
Formal study < 8 yrs	4.12 (1.88–9.02)	4.34 (2.01–9.37)	4.47 (2.08–9.60)	4.30 (2.05–8.98)
Depression	0.89 (0.28–2.83)	—	—	—
Fibromyalgia	7.90 (1.86–33.52)	8.51 (2.24–32.32)	9.14 (2.42–34.52)	—
Other rheumatic diseases	2.03 (0.76–5.45)	2.28 (0.86–6.04)	—	2.56 (1.01–6.48)

[a] Model 1 included all variables with a statistical significance ($p < 0.05$) in univariate analysis. Depression was excluded from the subsequent models due to lack of statistical significance in this analysis. Age and sex were retained because of their clinical and epidemiological importance. [b] The variables fibromyalgia and other rheumatic diagnoses were correlated ($p = 0.008$); therefore we tested models with both variables (Model 2) and with each one (Models 3 and 4).

small number of cases did not permit a statistical analysis of the association of each rheumatic disease and viral infection.

It would be important to note that in our study potential confounding factors such as coinfection and comorbidity were minimized. As blood donation candidates, both infected subjects and control subjects were submitted to the same clinical and serological triage, and *a priori* the groups differed only in HTLV-I serology status. Nevertheless, there was a statistically significant difference in age and sex between infected subjects and control subjects. This may be explained by the fact that HTLV-I prevalence is higher in women and increases with age[7], and confirmation of infection was the group selection criterion; however, we cannot rule out selection bias such as better acceptance of symptomatic subjects to join the study.

The influence of age and sex differences in the studied associations was in fact reduced by inclusion of both variables as factors to be adjusted in the multivariate analysis. The choice of a secondary population base, however, limits the study's external validity. Although the blood bank triage suggests that both groups are clinically similar, our results might have been influenced by excluding patients with more severe rheumatic diseases or other comorbidities — the so-called "healthy donor effect".

Our results suggest that fibromyalgia may be associated to the HTLV-I infection. In our study, other rheumatic diseases were also more prevalent in infected patients, but the small number of cases did not permit any conclusion about the association of each specific disease and viral infection. The study of immunological and clinical aspects of the rheumatic diseases in HTLV-I infected patients might provide valuable information about the pathogenesis of these conditions.

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