Prevalence and characteristics of fibromyalgia among HIV-positive patients in southern Israel

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ABSTRACT

Objective. *Fibromyalgia and chronic pain have previously associated with HIV infection for over two decades. We aimed to evaluate the prevalence of FMS symptoms in an ethnically heterogeneous population of HIV-infected individuals in southern Israel, applying the proposed new diagnostic criteria for diagnosis of fibromyalgia symdrome (FMS).*

Methods. *156 HIV-positive patients followed at the AIDS clinic of the Soroka University Medical Center (SUMC) who gave written informed consent were recruited in the trial. FMS was diagnosed based on the widespread pain index (WPI) and the Symptom Severity Score (SSS) comprising the modified 2011 diagnostic criteria for FMS. CD4 levels ad viral load were obtained.*

Results. *One hundred and thirty-nine patients (89.1%) were receiving HAART (Highly Active Antiretroviral Therapy). A total of 22 patients (14.1%) were found to fulfill current criteria for diagnosis of FMS. FMS-criteria positive Individuals were slightly younger than criteria-negative individuals (40.3±9.2 vs. 42.6±11.9, p=0.39), but this difference did not reach statistical significance. There was no significant difference between the groups regarding gender, family status, religion, occupation or education. No correlation was found between CD4 and viral load levels and symptoms of FMS.*

Conclusion. *Despite the dramatic improvement in management of HIV, FMS symptoms remain highly prevalent among these patients and are not directly correlated with indices of active disease. FMS is an important clinical issue to address among patients suffering from HIV infection.*

Introduction

Fibromyalgia syndrome (FMS) is a condition characterised by chronic widespread pain and fatigue, and is considered, as part of a spectrum of overlapping disorders (the so-called algo-dysfunctional syndromes), to represent the clinical manifestation of increased processing of pain within the central nervous system (1). An association between FMS and various types of chronic infection has frequently been discussed (2).

Numerous studies have reported an increased prevalence of musculoskeletal complaints, including those compatible with FMS, among HIV-positive patients (3-5). FMS-related symptoms, including myalgia, artharalgia (6) and depression (7), have been documented at increased prevalence among HIV carriers. Two studies performed over 20 years ago addressed the specific issue of FMS in HIV-positive patients. In these studies, FMS was diagnosed according to The American College of Rheumatology (ACR) 1990 criteria (8), which included the presence of widespread musculoskeletal pain of at least 3 months duration and at least 11 of 18 positive tender points by digital palpation (6, 7). In these studies, zidovudine (AZT) had been the only anti-retroviral treatment received by patients, if any.

Buskila *et al*. (6) found that 29% of HIV-infected patients examined fulfilled diagnostic criteria for FMS, a figure somewhat higher than that observed among psoriatic arthritis (PsA) patients and much lower than the figure for rheumatoid arthritis (RA) patients. Simms *et al*. (7) found FMS in 11% of 140 patients with documented HIV infection and in 41% of HIV-infected patients with musculoskeletal complaints. Notably, all the above cited research had been conducted over two decades ago. The passing of time has witnessed dramatic changes in the field of HIV treatment, *e.g*. the introduction of Highly Active Anti Retroviral Therapy (HAART) (9), which has revolu-

tionised the outcome of these patients. Simultaneously, considerable (albeit less dramatic) changes have occurred both in understanding the pathogenesis (10) as well as in the classification and diagnosis of FMS (11). Thus, in recognition of the broadening clinical spectrum of FMS, in 2010 the ACR has developed new diagnostic criteria (12), which propose to drop the use of tender-points as a diagnostic criteria. The criteria were validated and found to be 88.1% correlated with the former ACR criteria. These criteria have been further modified in 2011, classifying 93% of the study population correctly, with a sensitivity of 96.6% and a specificity of 91.8% (13). In the current study, we have endeavoured to reassess the prevalence of FMS among HIV-infected patients, applying the current up-to-date diagnostic criteria, based on the widespread pain index (WPI) and the symptom severity scale (SSS), to the HAART-era population of patients.

We have also compared 2 distinguished ethnic groups: patients of African origin and Caucasians.

Methods

HIV-positive patients under regular follow-up at the AIDS clinic of the Soroka University Medical Center (SUMC) who gave written informed consent were recruited in the trial. SUMC is a tertiary medical center in the south of Israel, serving a population of over one million people. All patients were already diagnosed as HIV-positive by Enzyme-linked immunosorbent assay (ELISA), confirmed by Western blot assay.

Patients that attended the clinic for consultation-only, those diagnosed less than 3 months before enrolment and those being examined outside the hospital (*e.g.* prisoners) were excluded. Each patient was interviewed in her/his mother tongue. Questionnaires included personal and clinical information regarding HIV status, a general musculoskeletal pain questionnaire, as well as the SSS and WPI questionnaires derived from the 2011 diagnostic criteria for FMS (13). Blood samples for CD4 and viral load were obtained from all participants.

Statistical analysis

The primary objective was to find the main characteristics of HIV-infected patients with FMS. Secondary endpoints included HIV laboratory related features such as CD4 and viral load, as well as psychological characteristics and behaviour.

All statistical analysis was performed using SPSS v. 18.0 (IBM Corp., Armonk, NY, USA). The results are presented as mean ± Standard Deviation for continuous variables, and as the total number of patients (percentage of total patients) for categorical variables. *t*-test was used for comparison of continuous variables and chi-square test for categorical variables with the use of Fisher's exact test, if needed. For ordinal or non-parametric variables the used Mann-Whitney U-test was used.

The prevalence of FMS as a binary outcome was calculated and the matched odds ratio was presented, which is the proportion of incident cases to recovered cases for each outcome. Multivariate analysis was performed with a logistic regression model using the variables: age, gender, economic status, country of origin and additional variables that showed significance in at least one of the former analyses. The results of the models are presented as the hazard ratio (HR) with 95% confidence interval (CI). A two-sided p-value <0.05 was considered statistically significant.

Results

A total of 156 HIV-positive patients that attended the clinic between 9/2011 and 3/2012 were recruited to the study. Eighty-two (52.5%) were women, 91 (58.3%) were of African origin, mostly from Ethiopia, but also from Nigeria, Sudan and Eritrea. The Caucasian group included mostly patients from the former Soviet Union, but also patients originally from India, Morocco, Algeria, Argentine, native Israelis and Arab-Bedouins.

Seven patients declined recruitment in the study and 1 patient answered only a part of the questionnaire.

Table I details the demographic and socio-economic characteristics of the study population. Among the African origin patients, 62.6% were women, while among the Caucasian patients only 38.5% were women. Most patients in the study had worked in the services sector, but in the Caucasian group there were also 15.4% of patients working in free professions. The average years of education in the Caucasian group were markedly higher compared to the African origin group (12.12 *vs.* 5.26 years, p<0.005).

There was no significant difference in the percentage of unemployment between the groups, which was above 40% in both groups.

Table II details the clinical characteristics of the study population. The average time from diagnosis of HIV was 8.18±5.62 years, and the average time under HAART was 7.11±4.96 years, with no significant difference between the groups. One hundred and thirty-nine patients (89.1%) of the patients were receiving HAART treatment. The vast majority of the African origin patients (94.5%) had been infected through heterosexual intercourse, while in the Caucasian group, 3 major groups of exposure could be identified – unprotected heterosexual intercourse (45.3%), intravenous drug abuse (29.7%) and unprotected homosexual intercourse (21.9%).

A total of 22 patients (14.1%) were found to fulfill current criteria for diagnosis of FMS.

FMS criteria positive Individuals were slightly younger than criteria-negative individuals (40.3±9.2 *vs.* 42.6±11.9, p=0.39), but this difference did not reach statistical significance. There was no significant difference between the groups regarding gender, family status, religion, occupation or education.

Native Israelis had a trend toward suffering from FMS comparing to immigrants (26.9% of the Israelis *vs.* 11.7% of the immigrants, p=0.06). Being African in origin seemed to be a protecting factor (8.5% of the African origin patients were FMS-criteria positive *vs.* 23.3% of all the others, p=0.017).

No significant differences were observed regarding the clinical characteristics of the FMS criteria positive patients compared to criteria-negative patients regarding way of HIV acquisition, years living with HIV, years on HAART or other co-morbidities (*e.g.*

Table I. Demographic and socio-economic characteristics of the study population.

Variables		Caucasian n=65	African origin n=91	*p*-value
Age		41.3±10.8	43.5±12.5	0.25
Gender – Male		40 (61.5%)	34 (37.4%)	0.003
Origin	Africa	4 (6.2%)	91 (100%)	<0.001
	North America	1 (1.5%)	0 (0%)	
	South America	3 (4.6%)	0 (0%)	
	Asia	31 (47.7%)	0 (0%)	
	Israel	26 (40%)	0 (0%)	
Family Status	Bachelor	22 (33.8%)	16 (17.6%)	0.055
	Married/ Living with a Spouse	25 (38.5%)	34 (37.4%)	
	Divorced/Separated	13 (20.0%)	33 (36.3%)	
	Widowed	5 (7.7%)	8 (8.8%)	
Religion	Jewish	49 (75.4%)	87 (95.6%)	0.001
	Muslim	4 (6.2%)	1 (1.1%)	
	Christian	12 (18.5%)	3 (3.3%)	
Occupation	Free Professions*	10 (15.4%)	0 (0%)	0.003
	Services**	35 (53.8%)	62 (68.1%)	
	Education***	10 (15.4%)	11 (12.1%)	
	Research	2 (3.1%)	1 (1.1%)	
	Arts****	3 (4.6%)	2 (2.2%)	
	Military Personnel and Security Forces	0 (0%)	3 (3.3%)	
	Homemaker	2 (3.1%)	10 (11%)	
	Commerce	2 (3.1%)	1 (1.1%)	
	Religion Affiliated	1 (1.5%)	1 (1.1%)	
Unemployed		28 (43.1%)	41 (45.1%)	0.8
Years of education Median (interquartiles)		11.5 (9.75-12.25)	0 (0-9)	0.016
Newcomers		39 (60%)	91 (100%)	<0.001
Economic Status	Below average	28 (43.1%)	50 (54.9%)	0.008
	Average	27 (41.5%)	39 (42.9%)	
	Above average	10 (15.4%)	2 (2.2%)	

*Free professions – doctors, lawyers, accountants, nurses. **Services – manual laboor, housekeeper, agriculture. ***Education – teachers, university lecturers, nannies. ****Arts – directors, actors, singers, painters, sculptors.

diabetes mellitus, cardio-vascular disease, pulmonary disease, renal disease or malignancy).

FMS-criteria positive patients reported significantly more musculoskeletal pain, including arthralgia, past arthritis, myalgia, back pain, neck pain, buttock pain, heel pain and morning stiffness (p-value ≤0.005 for all) (Fig. 1).

Out of 111 patients with musculoskeletal complaints, 19.8% (22 patients) were FMA-criteria positive.

FMS-criteria positive patients reported a significantly higher rate of general physical complaints compared with FMS criteria-negative patients, including headache (95.5% *vs*. 63.4%, p=0.003), paresthesia (63.6% *vs*. 16.8%, p<0.001), hand or face swelling (36.4% *vs*. 5.3%, p<0.001), symptoms typical of irritable bowel syndrome (54.5% *vs*. 10.7%, p<0.001), fatigue (p<0.001) and dizziness (72.7% *vs*. 32.8%, p<0.001).

While depression was significantly more common among FMS-criteria positive patients compared with criteria-negative patients, (81.8% *vs*. 39.7%, p<0.001), no significant differences between the groups were observed regarding anxiety or insomnia. The global well-being of FMS-criteria positive patients was significantly lower compared to FMS criteria-negative patients (5.95±2.20 *vs*. 3.09±2.36, p<0.001).

No significant association was observed between either CD4 levels or viral load and the prevalence of FMS.

Within FMS criteria-positive patients, no significant differences were observed between patients of African and Caucasian origin regarding age, gender, family status, religion or occupation. No significant differences were observed in clinical characteristics of FMS-criteria positive patients between individuals of African origin compared those of Caucasian origin regarding way of HIV acquisition, years living with HIV, years on HAART or other co-morbidities (*e.g*. diabetes mellitus, cardio-vascular diseases, pulmonary diseases, renal disease or malignancy).

Discussion

Musculoskeletal symptoms have long been recognised as a frequent complication of HIV infection and older data has indicated extremely high prevalence of full-blown FMS among such patients. In the current study we have found 14.1% of HIV-infected patients to fulfill current diagnostic criteria for the diagnosis of FMS, in an ethnically heterogeneous population of individuals in southern Israel. This figure appears to be significantly lower than that observed by Buskila *et al*. (6) in their 1990 report, which stood at 29%. It is however similar to the rate observed by Simms *et al*. (7) – 11%. It is considerably higher than the prevalence of FMS in the general Israeli population, which has recently been estimated to be around 2.5% (14). Notably, a wide range of prevalence rates of FMS among HIV patients have been reported in the past (15-17), most probably reflecting a range of factors, including differing geographical location, changing patterns of treatment over time and evolution of diagnostic criteria. Thus even in the HAART era, when most patients are treated and CD4 levels and viral load are generally well controlled, FMS continues to pose a major co-morbidity of HIV infection, causing a significant decrease in quality of life.

The mechanisms responsible for development of FMS among HIV-infected patients are incompletely understood. Pain in general and chronic pain in particular appears to be extremely common among such patients and may be multi-factorial. Peripheral neuropathy both due directly to viral infection and to drug side effects is frequently responsible for pain (18). Substance abuse,

Table II. Clinical characteristics of study population.

Variables		Caucasian n=65	African origin n=91	*p*-value
Mode of HIV acquisition	Homosexual intercourse	14 (21.9%)	0 (0%)	<0.001
	Heterosexual intercourse	29 (45.3%)	85 (94.4%)	
	Drug abuse	19 (29.7%)	0 (0%)	
	Blood transfusion	2 (3.1%)	3 (3.3%)	
	Vertical transmission	0 (0%)	2 (2.2%)	
Years living with HIV	Median (interquartiles)	7 (3-12)	9 (6-12)	0.53
Years on HAART	Median (interquartiles)	7 (2-8)	9.5 (6.75-12)	0.14

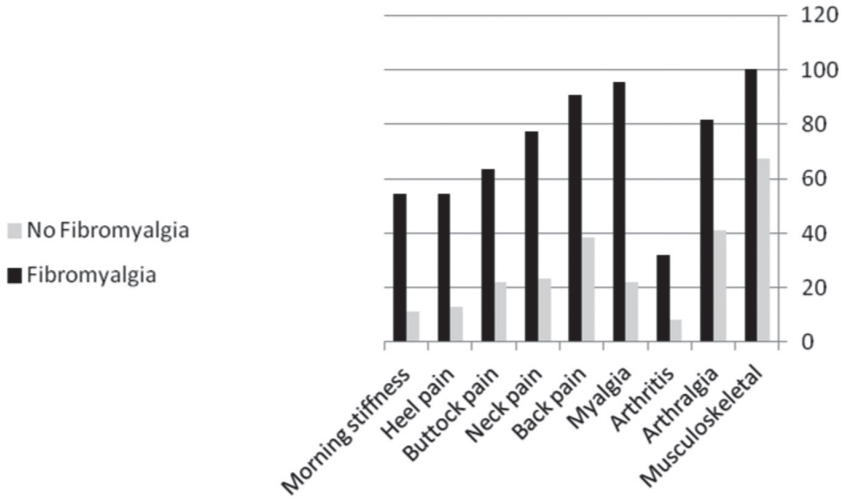

Fig. 1. Comparison between specific musculoskeletal complaints between fibromyalgia and non-fibromyalgia patients.

which is a frequent risk factor for the contraction of FMS, is also associated with chronic pain (19, 20). Recent evidence indicates, that chronic opiod exposure, both due to increased levels of endogenous opiods and to exogenous agents, can lead to the development of opiod – induced – hyperagesia and may in fact be involved in the pathogenesis of central sensitisation (21-23)]. Opiod antagonists such as low-dose naltrexone have recently been proposed as a potential treatment for FMS (24) and may exert their effect mainly by reducing glial cell activation. In addition, intriguing evidence has pointed to the possibility that HIV-related proteins such as HIV-tat-1 may interact with mu-opiod receptors both increasing pain and promoting HIV-related damage to the CNS (25). Moreover, mounting evidence has indicated that central sensitisation, currently considered to be a major underlying process in FMS and related conditions (26), is maintained and propagated by subtle forms of CNS inflammation, *e.g.* by the activation of immune-competent glia cells which in turn act on neurons to produce sensitisation (23). While the HIV virus does not directly infect neurons, microglia are infected, leading to the release of abundant neurotoxic and pro-inflammatory mediators, including chemokines, cytokines, etc. (27). Astroglia cells are also infected by HIV, leading to functional impairment of these cells (28); this in turn can lead to impaired reuptake of critical neurotransmitters such as glutamate (29), known to play an important pathogenetic role in the development of FMS (30, 31). Clearly, the precise mechanisms and locations (32) (both anatomically and on a cellular level), through which HIV infection can lead to the development of FMS, call for further elucidation.

Neuro-cognitive impairment is an additional important symptom of HIV neural damage, and has recently been correlated with specific findings on neuroimaging modalities such as fMRI (33). As this spectrum of symptoms has been incorporated into the current diagnostic criteria for FMS (in contrast to the original 1990 criteria, which did not include such symptoms), it may increase the proportion of HIV-infected individuals who fulfill FMS diagnostic criteria.

Depression is another frequent accompanying factor, both in HIV (34) and in FMS (35). Once again, as depression has been incorporated into the new diagnostic criteria for FMS (as part of the SSS), it has become relevant for this diagnosis among HIV-infected individuals.

The use of multiple medications is inherently associated with multiple drug interactions and increased frequency of side effects. Anti-retroviral medications are no exceptions and may be responsible for a spectrum of symptoms which may overlap with those of FMS (36). In addition, some patients may develop a drug-induced metabolic syndrome (37) which may have further deleterious effects regarding the establishment of chronic pain (38).

Infectious disease specialists as well as other health care providers caring for HIV-infected individuals, should remain highly vigilant to the development of pain in general and FMS in particular among such patients.

In our study, we found that newcomers immigrating to Israel are not at increased risk for FMS. Moreover, when comparing native Israelis to newcomers from Africa, the data shows that being a native Israeli is in fact a risk factor to develop FMS, compared to newcomers from Africa. Whether this difference is attributable to cultural, genetic or other factors remains an open question.

Similar to previous findings, our results indicate that lower socio-economic status appears to be a risk factor for developing FMS (39). Not surprisingly in the current study patients fulfilling FMS diagnostic criteria reported a broad spectrum of somatic symptoms besides pain, as well as describing symptoms associated with overlapping functional syndromes such as IBS. In addition, similar to previous findings (40), depression appeared to be extremely prevalent among HIV-infected patients who were FMS criteria positive – over 80%. The lack of association observed in the current study between both CD4 levels

and viral load on the one hand and the fulfillment of FMS criteria is noteworthy. Interpreting this finding one must assume that central sensitisation and resulting pain are not directly instigated by viral invasion and replication but rather by more complex process which, once initiated may run a chronic course irrespective to the ongoing activity of the initiating infection. This hypothesis may be in line with the observation, that various other infectious triggers have been associated with the development of FMS, including EBV, CMV etc, not necessarily involving a process of ongoing active viral infection (41). Additional aspects related to the initial diagnosis of HIV, such as stress, as well as subsequent alterations in the function of hypothalamic-pituitary-adrenal axis and sleep disturbances associated with HIV, could further contribute to the pathogenesis.

To our knowledge, ours is the first study examining prevalence and characteristics of FMS among HIV-infected individuals of African origin. While no significant difference was observed between the prevalence of FMS among HIV-infected individuals of African *versus* non-African origin, the absolute number of FMS criteria-positive individuals in the current study was small and thus further large-scale research is necessary in order to draw conclusions regarding the true possible differences between such ethnic groups in HIV patients.

Conclusions

FMS symptoms are common among HIV-infected individuals and can frequently overlap with important HIV-related symptoms such as pain, fatigue, cognitive difficulties and depression.

Similar to historical findings in the current stud we have found a high frequency of FMS among HIV-infected individuals, stressing the importance of this clinical aspect in the management of HIV in the current HAART era. Addressing FMS symptoms early may significantly improve the quality of life of HIV patients. Further research may shed light on the mechanisms and interactions of HIV with the central nervous system leading to central sensitisation and FMS.

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