ORIGINAL ARTICLE

Prevalence of rheumatic manifestations in HIV patients: A cross-sectional study from Manipur, India

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Abstract

Background: To estimate the prevalence of rheumatic manifestations in HIV patients and to correlate with factors such as age, sex, duration of HIV infection, highly active antiretroviral therapy (HAART) regimen, duration of HAART, Hb%, ESR, CRP and CD4 cell count.

Methods: The study involved 382 HIV patients attending a tertiary healthcare and referral centre at Imphal, Manipur for two consecutive years. A detailed history of each patient was collected and clinical examination was performed. All the subjects were tested for hepatitis B and C co-infections, and CD4 cell count. Statistical analysis was performed using SPSS software (ver. 16).

Results: Rheumatic manifestations were observed in 145 (38.06%) HIV patients, with HIV- associated arthralgia (22.57%) being the most common manifestation. HIV-associated arthralgia showed significant relation with HAART regimen (0.04), Hb% (0.02), ESR (0.04), and CRP (0.001). In addition, factors such as duration of HIV infection (0.05), Hb% (0.01), ESR (0.04), CRP (0.04) and hepatitis B co-infection (0.04) showed significantly correlation with HIV-associated fibromyalgia.

Conclusion: Increased prevalence of rheumatic manifestations was noted in HIV patients, with more incidence in HAART-sensitized population. The study highlights the need to review such manifestations at every follow-up and manage appropriately.

Keywords: HIV, AIDS, Rheumatic manifestations

Introduction

India, with approximately 2.1 million people infected HIV cases, is the third largest HIV/AIDS prevalent nation in the world.[1] According to the 2015-16 NACO reports, the highest prevalence of HIV was recorded from Nagaland (1.29%), with Manipur in the 3rd position (0.60%).[2] The co-existence of rheumatoid arthritis with AIDS has been well established.[3, 4] Rheumatic manifestations have been recognized in HIV patients since 1980s, with Reiter's syndrome being the first reported rheumatic disease.[5, 6] Since then many rheumatic manifestations has been reported with HIV infection with the prevalence ranging between 4 to 71.3%.[6] A prospective study has reported that out of 101 HIV patients evaluated for rheumatic manifestations, the involvement of musculoskeletal system was noted in 72 patients.[7]

The use of anti-retroviral drugs and highly active antiretroviral therapy (HAART), has resulted in improved survival rates among HIV and AIDS patients in the past three decades.[5] Remission has been reported in cases with HIV-associated arthritis.[4] In the post HAART era, researchers have noticed reduction in the rate of rheumatic complications, such as inflammatory arthritis and connective tissue disease in patients with AIDS.[6] Arthralgia and myalgia have been reported as the most common rheumatic manifestations in both pre- and post-combination antiretroviral therapy eras.[8] Researchers suggest that newer manifestations of rheumatic disease are likely to be described in the future. The present study evaluated the prevalence of rheumatic manifestations in HIV/AIDS patients receiving HAART treatment. The correlation of these manifestations with

variables such age, sex, duration of HIV infection, duration and HAART regimen, Hb%, ESR, CRP and CD4 cell count were also estimated.

Materials and methods

The cross-sectional, observational, descriptive study was conducted at the Department of Medicine, in a tertiary healthcare and referral centre at Imphal, Manipur for two consecutive years (2011 to 2013). The study enrolled a total of 382 HIV/AIDS subjects who were on HAART, including the treatment-naïve patients. Informed consents were obtained from all the participants. Subjects with the history of rheumatological disorders and those who refused to give consent were excluded from the study.

All the subjects were selected by random numbers created by a random number chart generator software. Demographic details such as age and sex of the subjects were recorded. Detailed history regarding HIV, including duration of the infection, mode of transmission, WHO staging, and duration and regimen of HAART was collected. All the subjects underwent routine clinical investigations including complete blood counts, random blood sugar, liver and kidney function tests, routine urine, and x-ray examination of the chest. In addition, all had undergone CD4 cell count testing with Beckinson FACS machine and screening for hepatitis B and C co-infection. Subjects with arthralgia were tested for c-reactive protein (C-RP), rheumatoid factor (RF), uric acid, and anti-nuclear antibody (ANA). Serum creatinine kinase level was tested in subjects with myopathy. Radiological investigations of lumbosacral and sacroiliac joints were done for subjects with axial involvement using X-ray scanning. Serological testing for anti-neutrophil cytoplasmic antibody (ANCA) and anti-cardiolipin (aCL) antibody was performed only in relevant cases. Statistical analysis was done using SPSS software (ver. 16).

Results

The cross-sectional study enrolled a total of 382 subjects, out of which 381 were selected. One was excluded due to history of RA. Rheumatic manifestations were reported only in 38% (145) of the subjects, with the remaining 62% (236) being naive. The M:F ratio was 1:0.56. The baseline characteristics of the study population are shown in table 1.

The corresponding most common and second common rheumatic manifestations noted were HIV-associated arthralgia (23%, n=86) and fibromyalgia (8%, n=31) with the respective M:F ratio noted for these manifestations were 1.03:1 and 0.93:1 (Table 2). All the subjects with HIV-associated arthralgia were negative for RF and ANA. The corresponding prevalences of polyarthralgia, oligoarthralgia and monoarthralgia noted were 52%, 29% and 19%. Knee was the most common joint (n=40) affected in patients with HIV-associated arthralgia, followed by elbow (n=29), ankle (n=19), and small joints of the hand (n=15) and shoulder (n=10). HIV-associated arthralgia was symmetrical in majority (72%) of the cases. The mean duration of joint pain noted was 166.36 days. Mean CD4+T cells count, serum uric acid level, and ESR noted were 457.34 cells/mm^3, 4.83 mg%, and 60.01 mm/1^{st} hr respectively.

Symptoms of HIV-associated fibromyalgia were non-specific myalgia with tenderness in more than 11 fibromyalgia points. Mean duration of symptoms in HIV-associated fibromyalgia was 170 days and the affected

Table 1: Demographic and clinical characteristics of the study population

Parameters	Total number of patients (n-381)	Without rheumatic manifestations (n-236)	With rheumatic manifestations (n-145)
Age* (years)	39.36 ± 7.616	39.16 ± 7.056	39.69 ± 8.464
Sex (M/F)	244/137	166/70	78/67
Duration of HIV infection* (days)	1,228 ± 974.46	1,120 ± 954.42	1,403 ± 984.52
HAART (sensitized / naive)	324/57	195/41	129/16
Duration of HAART* (days)	1,202 ± 882.38	1,167 ± 839.50	1,252 ±941.08
Hemoglobin* (gm %)	10.91 ± 1.72	10.91 ± 1.72	10.91 ± 1.74
ESR* (mm/1^{st} hr)	57.38 ± 34.58	53.63 ± 35.62	63.50 ± 32.01
CD4 cell count*(cells/mm^3)	379.24 ± 265.18	345.0 ± 237.75	434.90 ± 297.12

* Mean ± SD

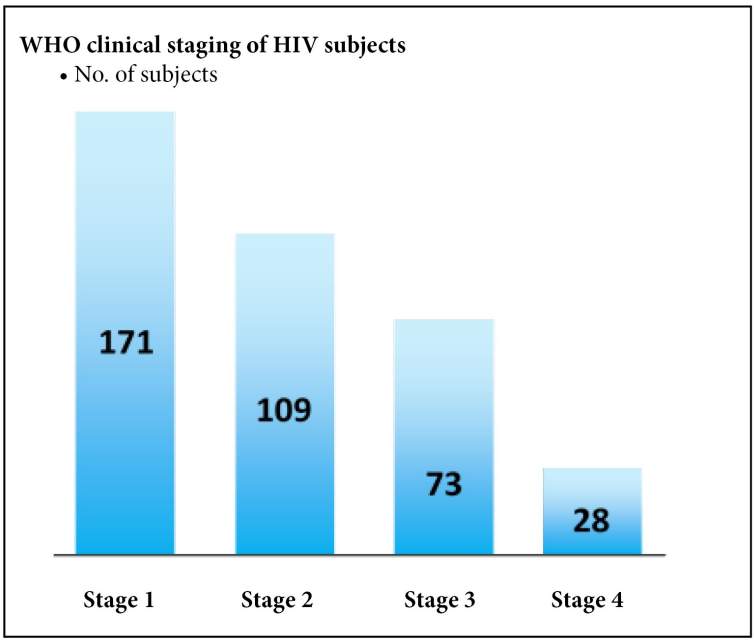
subjects (n=18) were on stavudine-based HAART regimen. Subjects with HIV-associated arthralgia and fibromyalgia mainly belonged to WHO stage 1 and 2. Enthesitis, septic arthritis, and avascular necrosis (AVN) neck femur were noted as the least prevalent rheumatic manifestations (n=1) (Table 2). Subjects with septic arthritis involving the right ankle joint belonged to WHO stage 3. In the present study population, majority of the subjects belonged to WHO stage 1 (n=171), and least number of subjects belonged to stage 4 (n=28) (Fig. 1).

Among the rheumatic group, the subjects who had diffuse infiltrative lymphocytosis syndrome (DILS) was less than 1% (n=3), with one patient being HAART naïve.

Table 2: Distribution of rheumatic manifestations with respect to HAART regimen

Rheumatic manifestations	Total no. of subjects on HAART regimen n (%)
None	236 (61.94)
HIV-associated arthralgia	86 (22.57)
HIV-associated fibromyalgia	31 (8.13)
HAART-induced myopathy	10 (2.62)
Polymyositis	9 (2.36)
Vasculitis	9 (2.36)
HIV-associated arthritis	6 (1.57)
Undifferentiated spondyloarthropathy	6 (1.57)
Cervical spondylosis	5 (1.31)
Hyperuricemia	4 (1.04)
De Quervain's tenosynovitis	4 (1.04)
Reiter's syndrome	3 (0.78)
DILS	3 (0.78)
Enthesitis	1 (0.26)
Septic arthritis	1 (0.26)
AVN neck femur	1 (0.26)

Fig. 1: Bar chart showing the distribution of the study population in various stages as per WHO clinical staging of HIV



The mean time interval of DILS development was noted as around 3 years in HIV patients. All the three patients had salivary gland enlargement with one having lacrimal gland enlargement and the others having sicca symptoms. All subjects had elevated serum creatinine kinase levels and only one patient had polymyositis in association with DILS. HIV-associated arthritis was noted in 2% (n=6) of the study population, with monoarthritis in 83% cases and polyarthritis in 17% cases. Only one subject was HAART naive. Mean ESR and CD4+ cell count noted were 65.60/1st hr and 405cells/mm^3 respectively. Only 2% (n=9) of the subjects had cutaneous vasculitis with seven patients having co-existent stroke. None of the patients with vasculitis were positive for either ANA or ANCA. HAART-related rheumatic manifestations like hyperuricemia and HAART-induced myopathy were noted in 1% (n=4) and 3% (n=10) of the subjects respectively. Gouty arthritis was not reported in any of the subjects with hyperuricemia. HAART-induced myopathy due to zidovudine, stavudine, and protease inhibitor was noted in six, three, and one patient respectively.

A statistically significant relation was observed between the duration of HAART regimen and subjects with HIV-associated arthralgia (P 0.04). In addition, the subjects with HIV-associated fibromyalgia had showed a significant relation with duration of HIV (P 0.05). Clinical factors such as Hb%, ESR, and CRP were found to be significantly related to subjects with HIV associated arthralgia and fibromyalgia (Table 3). HBV co-infection was noted to be significantly associated with HIV-associated fibromyalgia (P 0.04).

Discussion

The prevalence of rheumatic manifestations noted in the present study population with HIV was 38%. As per the previous studies, the prevalence of rheumatic manifestations in HIV patients ranges between 4-71%.[6] A cross-sectional study from Africa in 2011 has noted 29% as the prevalence, and arthralgias as the common manifestations, mainly in patients using pyrazinamide.[9] In concurrence with these findings, HIV-associated arthralgia was noted as the most common rheumatic presentation in the current study.[7, 10] The prevalence of arthralgia reported by most of the previous studies is more than 40%, whereas the current study has noted a prevalence of 23%.[10, 11] The present study has noted HIV-associated fibromyalgia as the second most common rheumatic complication in HIV patients with a prevalence of 8.13%. However, a recent study from southern Israel has reported fibromyalgia syndrome as the highly prevalent manifestation (14.1%).[12]

The literature evidence shows that the prevalence of polymyositis in association with HIV ranges between 2-7%.[13] Another prevalence study from India, conducted by Narayanan et al., involving 704 HIV subjects has reported that there were only two cases of HIV-associated arthritis and six cases of seronegative arthritis.[14] In the present study,

Table 3: Bivariate analysis of clinical and laboratory variables for HIV-associated arthralgia and HIV-associated fibromyalgia

Variables	HIV- associated arthralgia		HIV-associated fibromyalgia	
	r	*P*	*r*	*P*
Age	0.082	0.542	0.13	0.946
Sex	-0.110	0.416	0.159	0.629
WHO staging	-0.227	0.119	-0.250	0.180
HAART regimen	0.267	0.04	-0.242	0.193
Duration of HIV	0.186	0.165	0.440	0.05
HAART duration	0.141	0.17	0.299	0.192
Hemoglobin (%)	-0.290	0.029	-0.480	0.01
ESR	0.148	0.04	0.295	0.047
CRP	0.290	0.001	0.352	0.04
CD4	0.175	0.194	-0.132	0.486
Serum uric acid	-0.026	0.788	-	-
HBV co-infection	-0.044	0.388	0.362	0.04
HCV co-infection	-0.055	0.284	0.02	0.916

subjects with an inflammatory arthritis who did not fulfil the criteria for SpA and in whom serological tests like ANA, RF and anti-CCP antibodies were negative, were classified as having HIV-associated arthritis and the prevalence noted was 1.57%. The corresponding prevalances of seronegative SpA, Reiter's syndrome and undifferentiated SpA noted were 9 (2%), 3 (0.8%), and 6 (1.6%) respectively, with none of the cases reporting psoriatic SpA. Among the extra-articular manifestations, conjunctivitis, circinate balanitis, urethritis, and keratoderma blennorrhagicum were frequent. Many subjects were showing some of the features of SpA, but did not have all the features to permit a diagnosis of ankylosing spondylitis, psoriatic arthritis or reactive arthritis, and hence were classified as having an undifferentiated SpA. In Africa, the HIV epidemic was associated with an increase in the prevalence of reactive arthritis, psoriatic arthritis, and undifferentiated SpA. All these diseases were previously uncommon, possibly as a result of the low background prevalence of HLA B27.[15] In the present study, HLA B27 testing could not be performed. Three cases (0.78%) of DILS was diagnosed. The authors believe that the increased effectiveness of HAART regimen could be the probable reason for the declining incidence of DILS.[16]

In the present study, 9 (2.36%) subjects had cutaneous vasculitis with seven subjects having co-existent stroke, and CNS vasculitis was identified as the probable cause, after the excluding CNS opportunistic infections. Immunodeficiency is a risk factor for septic arthritis.[17] HIV-infected subjects have a 100-fold elevated risk of osteonecrosis compared to the general population, wherein chronic inflammation, corticosteroids in the setting of immune reconstitution, anticardiolipins, hypertriglyceridemia secondary to PI treatment have been suggested as some of the risk factors. Hip has been identified as the most frequent location of osteonecrosis, and the prevalence was estimated as around 4% by MRI.[18]

One subject with RA who had been excluded from the study experienced remission of arthritic symptoms and immunosuppression because of HIV infection. After receiving 3 years of HAART regimen, she had relapse of RA with joint pain and repeated Baker's cyst formation. Hyperuricemia was more common in patients who received stavudine-based HAART regimens. Major limitation of the study was not performing HLA B27 testing, salivary gland biopsies, and magnetic resonance imaging and magnetic resonance angiography of brain. HLA Class II associations were also not assessed.

Conclusion

The present study substantiates the previous literature evidence indicating a high prevalence of rheumatic manifestations in HIV patients, especially in HAART-sensitized population. HIV-associated arthralgia and fibromyalgia were noted as the most common manifestations. These rheumatic manifestations could hamper the quality of life of the patients due to increased pill burden and significant morbidity. Rheumatic complications should be anticipated in HAART- naive as well as HAART-sensitized patients. They should be reviewed at every visit and managed appropriately in the ART clinic program. Trends have been changing in the HIV rheumatology practice in the HAART era with decrease in some rheumatic manifestations and increase in others. Further studies need to be undertaken to keep up with changing trends in rheumatic manifestations in HIV/AIDS patients.

Competing interests

The authors declare that they have no competing interests.

Citation

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