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Research Article

Higher CD4 Count Poses HIV Positive Patients to Greater Risk of Articular Manifestations - a Vision from Eastern India

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Abtract

Background

HIV infection affects all systems and the musculoskeletal system is no exception. Till date no study has shown any association between articular manifestations and CD4 count. Our aim was to explore distributions and contributing factors of HIV related articular manifestations along with CD4+T cell count in ART naïve patients.

Materials and Methods

In this hospital-based cross-sectional observational study, 516 ART naive HIV seropositive 18 to 40 years old adults were consecutively recruited and their demographical, biochemical (including serum uric acid level) and haematological parameters were analyzed.

Observation and Results

Articular manifestations are common in HIV positive adults with a prevalence of 19.77% with predominance of female patients and unemployed patients. Presence of opportunistic infections (OI) was significantly associated with joint pain (p value <0.01). Large joints were mostly involved with knee joints involvement being most common. Higher CD4 count and better WHO staging was significantly associated with joint pain (p value <0.001). All previous studies failed to show any association of rheumatological symptoms with CD4 counts. Higher CD4 count and Uric acid levels were significantly associated with CD4 count (p value <0.001).

Conclusion

Prevalence of rheumatologic problems were high among the HIV-infected population. High CD4 count, female sex and low uric acid were noted to be significantly associated with development of rheumatologic problems. A multidisciplinary approach to early diagnosis and management is essential, often with the help of rheumatologists, for reduction of morbidity and improvement of quality of life.

Keywords: Articular manifestation; HIV infection; ART naive.

Introduction

Spectrum of rheumatologic diseases in patients with HIV infection ranges from reactive arthritis to diffuse infiltrative lymphocytosis. This is an apparent paradox in HIV infection where immunodeficiency is the rule, and reflects the complexity of regulation of immune mechanisms [1]. Since psoriatic arthritis (1985) and reactive arthritis (1987) were first described, HIV infection has been associated with various rheumatologic syndromes [2]. Before the widespread implementation of anti retroviral therapy (ART), retrospective studies calculated the risk of rheumatologic problems from 11% to 72% [3]. In ART era, these complications are declining steadily but still prevalent, especially in developing countries. All previous studies have failed to show any association of rheumatologic symptoms with CD4 counts. Our aim was to explore distributions and contributing factors of HIV related articular manifestations along with CD4+T cell count in ART naïve patients.

Materials and Methods

In this institutional review board (IRB) approved cross-sectional study 813 patients attending the HIV clinic of a tertiary care hospital of eastern India were screened over the period of 2013-15, of whom 752 were found to be eligible. Among them, ultimately 522 patients were willing to participate. 6 of them withdrew from the study. Thus 516 consecutive eligible, willing to participate, ART naive HIV positive cases (18 to 40 years) were recruited and their demographical, biochemical (including serum uric acid

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level) and haematological parameters were analyzed. Subjects who had passed up to eighth standard in school were defined as educated and educational qualification less than that was taken as uneducated. All those enrolled for the study underwent thorough clinical examination and in-depth rheumatologic examination and questionnaire survey. For qualifying joint pain Numerical Rating Scale (NRS) was used [4].

HIV infection was diagnosed based on: positive HIV antibody testing (rapid or laboratory-based enzyme immunoassay: Pareekshak Triline). This was confirmed by a second HIV antibody test (rapid or laboratory-based enzyme immunoassay: Pareekshak Trispol) relying on different antigens or of different operating characteristics. CD4 testing was done using Multiset V2.2 FACScalibur (#E97300192) software and expressed in counts/µl. HBsAg and Anti HCV antibody was assayed by Rapid ELISA kit, Anti Nuclear Antibody (ANA) by Hep-2 method, Rheumatoid Factor (RF) by ELISA. Erythrocyte Sedimentation Rate (ESR) was done by Westergren method. Serum uric acid was determined by enzymatic and colorimetric method. MRI, joint fluid analysis was done in patients having rheumatologic complaints.

Data were keyed into the Microsoft Excel and have been double checked to avoid any error in data entry. Epi info 7 software, downloaded from WHO site, have been used to manage and analyze the demographical, clinical and laboratory parameters preliminarily. The qualitative data were described in proportions and the quantitative data were described in mean and standard deviation. Odds ratio (OR), confidence interval (CI) and P value were calculated. For establishing P value chi square tests were applied for significance and P value <0.05 has taken to be significant and confidence interval is taken as 95% (95% CI). If the exact p-value is less than 0.01 it is recorded as p< 0.01, and if the exact p-value is extremely small it has been recorded as p< 0.001.

Result

Among 516 newly detected ART naive HIV positive cases of 18 to 40 years age, 102 cases (19.77%) had articular manifestations (Table 1). Among the patients having joint pain 45.10% were aged 18-30 years while 56 (54.90%) were aged >30 years (Table 2). Articular manifestations were seen in 60 female (58.82%) and 42 male (41.18%) patients (p value<0.001) (Table 2). 52.94% (54) and 37.25% (38) of people with articular manifestations were unemployed and uneducated respectively (Table 2). 90% of HIV infected cases in our study had heterosexual route of transmission.

Large joints were mostly involved (80.39%). Knee joints was involved in 42 patients (41%). 18 patients (17.65%) were having axial joint involvement, 2 patients were having small joint involvement. Monoarticular involvement was found in 26 patients (25.49%). Oligoarticular was in 64 patients (62.75%). 12 patients (11.76%) had polyarticular involvement by definition, but most of them had associated inflammatory back pain or spine invoivement. We found that most of the patients [72 (70.59%)] were on numerical rating scale (NRS) 2-5. 60 patients (58.82%) had the symptoms for <6 weeks. Morning stiffness was found in 62 patients (60.78) (Table 1). CD4 count was >350 /µl in 66.66% of patients with joint pain (p value<0.001). CD4 count was <350/µl in 92.08% of the cases having uric acid > 6mg/dl (p value<0.001). ESR was significantly associated with joint pain (p value <0.001). 92 patients (90.20%) with joint pain had total leucocyte count (TLC) <10000/µl. Opportunistic infections (OI) were significantly low in patients having joint pain (p value <0.01). Better WHO staging were significantly associated with joint pain (p value <0.01). (Table 2) 18 (17.65%) patients with joint pain had oral candidiasis, 4 (3.92%) had pulmonary tuberculosis, 2 (1.96%) had extrapulmonary tuberculosis, 8 (7.84%) had mixed infections.

Among the patients having joint pain, 6 (5.88%) were diagnosed as having HIV associated arthritis, 18 (17.64%) had axial skeletal involvement, 2 (1.96%) had small joint involvement and rest 76 (74.50%) patients were diagnosed as HIV associated arthralgia.

Regarding associated conditions, 17.65% patients with joint pain had oral candidiasis, 3.92% had pulmonary tuberculosis, 1.96% had extrapulmonary tuberculosis, 7.84% had mixed infections, and 7.84% patients had psoriasis. Myalgia was documented on 45% of the patients. 5.88% patients had urethritis and 5.88%patients had history of redness of eyes. 28 patients (27.45%) had history of dry mouth or dryness of eyes. Morning stiffness was found in 60.78%.

Serology of hepatitis B, hepatitis C and ANA was found negative in all patients. Rheumatoid Factor was found positive in 1.96% patients. We did not find any patient having septic arthritis. We did not find any history or physical finding of intravenous drug abuse in any of our patients.

MRI changes like bone marrow edema and synovial thickening was found among 5.88% patients without suggestive history or clinical finding of other etiology. We diagnosed them as having HIV associated arthritis. No patient had abnormality in X-Ray of the joints. There were 5.88% patients who had USG abnormalities of synovial thickening of affected large joints. They also had MRI abnormalities. From our study we found MRI and USG abnormalities of the joints that had no X-ray abnormalities suggesting the justification of doing higher imaging study where clinical suspicion is strong.

Discussion

In our study we found the prevalence of articular manifestation was 19.77%. It was 27% in the study by Kaddu-Mukasa et al, 63.33% in the study by Kole et al and 17.1% in the study by Ekwom et al [5-7]. Females were found to be more affected than males and it is corroborating to other similar previous studies [7]. Most of the patients had heterosexual mode of transmission corroborating to other Indian studies [6]. Most of the patients were unemployed which has not been shown in any other studies. Opportunistic infections (OI) were significantly less in patients having joint pain (p value <0.01). Arthralgia was found to be the most common manifestation similar to the study by Ekwom et al [7]. Large joints were mostly involved with knee joints involvement being most common similar to the study by Singh et al [8]. There was no

Table 1: Table showing features of joint pain among the HIV seropositive patients (n=516) and their correlation with CD4 count

	N (%)	CD4<350	CD4 350-500	CD4 >500	P VALUE
NRS*<2	14 (13.73%)	4 (11.76%)	6 (15.79%)	4 (13.33%)	0.35
NRS* 2-5	72 (70.59%)	28 (82.35%)	24 (63.16%)	20 (66.67%)	
NRS*>5	16 (15.69%)	2 (5.88%)	8 (21.05%)	6 (20.00%)	
Axial joint	18 (17.65%)	8 (23.53%)	4 (10.53%)	6 (20.00%)	0.12
Small joint	2 (1.96%)	0	0	2 (6.67%)	
Large joint	82 (80.39%)	26 (76.47%)	34 (89.47%)	22 (73.33%)	
Monoarticular	26 (25.49%)	10 (29.41%)	10 (26.32%)	6 (20.00%)	0.02
Oligoarticular	64 (62.75%)	24 (70.59%)	24 (63.16%)	16 (53.33%)	
Polyarticular	12 (11.76%)	0	4 (10.53%)	8 (26.67%)	
Duration <6 weeks	60 (58.82%)	22 (64.71%)	20 (52.63%)	18 (60.00%)	0.57
Duration >6 weeks	42 (41.18%)	12 (35.29%)	18 (47.37%)	12 (40.00%)	
Morning stiffness present	62 (60.78%)	22 (64.71%)	24 (63.16%)	16 (53.33%)	0.60
Morning stiffness absent	40 (39.22%)	12 (35.29%)	14 (36.84%)	14 (46.67%)	

*NRS- Numerical Rating Scale

Table 2: Table showing correlation between joint pain among HIV seropositive patients (n= 516) and its contributing factors

Risk factors	Joint pain present	Joint pain absent	OR*(95%CI**)	P value
Age 18-30	46 (45.10%)	170 (41.06%)	1.17 (0.75- 1.82)	0.50
Age >30	56 (54.90%)	244 (58.94%)		
Male	42 (41.18%)	251 (60.63%)	2.19 (1.41- 3.43)	<0.001
Female	60 (58.82%)	163 (39.37%)		
Unemployed	54 (52.94%)	192 (46.38%)	0.76 (0.49- 1.18)	0.26
Employed	48 (47.06%)	222 (53.62%)		
Uneducated	38 (37.25%)	160 (38.65%)	0.94 (0.59- 1.47)	0.82
Educated	64 (62.75%)	254 (61.35%)		
CD4<350	34 (33.33%)	310 (74.88%)	0.16 (0.10- 0.26)	<0.001
CD4>350	68 (66.67%)	104 (25.12%)		
Uric Acid<6mg/dl	70 (68.63%)	168 (40.58%)	3.19 (2.02- 5.12)	<0.001
Uric Acid>6mg/dl	32 (31.37%)	246 (59.42%)		
ESR***<40	58 (56.86%)	350 (84.54%)	0.24 (0.15- 0.38)	<0.001
ESR***>40	44 (43.14%)	64 (15.46%)		
TLC****<10000	92 (90.20%)	382(92.27%)	0.77 (0.37- 1.69)	0.54
TLC****>10000	10 (9.80%)	32 (7.73%)		
OI***** Present	32 (31.37%)	194 (46.86%)	1.92 (1.22- 3.08)	0.005
OI***** absent	70 (68.63%)	220 (53.14%)		
WHO stage 1,2	70 (68.63%)	218 (52.66%)	1.96 (1.24- 3.14)	0.003
WHO stage 3,4	32 (31.37%)	196 (47.34%)		

*OR- Odds ratio **CI- confidence interval ***ESR- erythrocyte sedimentation rate ****TLC- total leucocyte count *****OI- opportunistic infection

evidence of spondyloarthropathy in any of them, even in MRI or HLA-B27. Spondyloarthropathy was seen in 0.7% of case in the study conducted by Kole et al [6]. All those patients required biologics (Infliximab). In our study, only 1.96% had small joint involvement. Oligoarticular manifestation was (62.75%) mostly observed. In one study of Africa, oligoarticular presentation was found in 51.5%, 30.3% was monoarticular and 18.2% was polyarticular presentation [7]. Majority of them presented with acute to subacute articular complaints. 19.77% cases had articular manifestations in form of joint pain and 10.46% had joint swelling. Most of the patients were on NRS 2-5. 5.88% patients were found to have arthritis suggestive of HIV associated arthropathy. Myalgia was documented on 45% of the patients corroborating with the study by Kole et al, where they found it as the commonest rheumatological symptom in HIV infected adults [6]. 5.88% patients had urethritis and 5.88%patients had history of redness of eyes. 28 patients (27.45%) had history of dry mouth or dryness of eyes. Thorough investigations of those patients were beyond the scope of our study. Diffuse infiltrative lymphocytosis syndrome (DILS) is generally seen in around 3% of the HIV infected patients [3].

One of the most important observations of our study was the association of joint pain and other joint related complaints with CD4+T cell count. Overall mean CD4 count was 269.49 ± 212.57 (n=516), corroborative of similar previous studies [7]. Higher CD4 count and better WHO staging were significantly associated with joint pain (p value <0.001) signifying that joint pain is a manifestation of early disease when immunodepletion is still not severe. All previous studies have failed to show any association of rheumatologic symptoms with CD4 counts. Higher CD4+T cells are representative of better immune functioning which is responsible for immune mediated articular manifestations [6]. Uric acid levels were significantly associated with CD4 count (p value <0.001). We also found that females had low level of mean uric acid (4.76) than males (5.72) (p<0.001) and there was significant difference in mean uric acid level in patients having opportunistic infection(5.8) and patients not having such (4.86) (p<0.01). HLA-B 27 was not found positive in our study. Serology of hepatitis B, hepatitis C and ANA was found negative in all patients. Rheumatoid Factor was found positive in 1.96% patients, corroborating to an African study where all patients were ANA negative and only 2 patients were RF positive (n=300) [5]. We did not find any patient having septic arthritis. Generally septic arthritis, specially due to staphylococcus aureus is a rare condition except in patients having CD4 count below 200 cells/mm [5,6]. Whereas in an Indian study, septic arthritis was observed in 1% of patients (n=300) and most of them were intravenous drug abuser [6]. Inflammatory synovial fluid was found in 3.92% patients who had MRI changes also and diagnosed as HIV associated arthritis. Singh et al also found the joint fluids to be inflammatory with sterile culture [8].

Strengths of our study include that we have explored the relationship of rheumatological manifestations with CD4 count. Confounders like old age, patients already on ART were excluded. Cross sectional observational study design limited our ability to follow up the cases and thus causal association of CD4+T cell count or serum uric acid level with joint pain also could not be determined. The newly diagnosed HIV positive cases were studied but the duration or actual severity of HIV infection could not be assessed as HIV viral load assay could not be done.

From this hospital based cross-sectional study, we could conclude that, prevalence of rheumatologic problems were high among the HIV-infected population. Majority (74.50%) of the patients were diagnosed as HIV associated arthralgia. High CD4 count, female sex and low uric acid were noted to be significantly associated with development of rheumatologic problems. A multidisciplinary approach to early diagnosis and management is essential, often with the help of rheumatologists, for reduction of morbidity and improvement of quality of life.

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