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Low bone mineral density in institutionalized patients with HIV and psychiatric co-morbidity

Ridotta densità ossea in soggetti istituzionalizzati affetti da infezione da HIV associata a patologie psichiatriche

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INTRODUCTION

Osteoporosis occurs in HIV infected patients [1-6] as well as in common psychiatric conditions [7-9] and causes significant morbidity. Osteoporotic fractures, particularly hip fractures constitute a large and growing problem worldwide. Several studies have shown disturbances in bone metabolism and high prevalence of osteopenia and osteoporosis in HIV-infected patients [1-6]. In a recent meta-analysis prevalence of reduced bone mineral density (BMD) and osteoporosis resulted respectively 67% and 15% [1]. Furthermore another recent study showed that HIV positive women were more likely to have fragility fractures [10].
To our knowledge, there are no published studies assessing bone mineral density in HIV patients with associated psychiatric disorders, and no clinical recommendations are available to guide screening, prevention or management strategies in this population.
Depression, schizophrenia and dysthymia have been found to be linked with an increased risk of fragility fractures because of the behavioural risk factor for low BMD (smoking, alcohol abuse, sedentary life, anti-psycotic-induced hyperprolactinemia) and because of increased likeliness to fall [7-9]. Moreover psychiatric disorders are commonly underestimated in HIV care settings; however, they affect up to 50% of HIV-patients and recent research in the United States has shown, among people with serious and enduring mental disorders, an alarmingly high rate of HIV infection, ranging from 9 to 19 percent [11-14]. Therefore, the use of psychotropic medications is also common among such patients.
Most individuals on antipsychotic medications have pathologically elevated prolactin levels and show hypogonadism associated with reduction of BMD [15,16]. Furthermore recently in a large case-control study (n = 6,763 cases) current use of conventional antipsychotic drugs was associated with increased risk of hip/femur fracture compared to never users, particularly after 5-8 weeks treatment [17]. We hypothesize that HIV patients with psychiatric co-morbidity are a category of patients at higher risk of low BMD and osteoporotic fractures. We conducted a pilot cross-sectional study of institutionalized HIV population with associated psychiatric disorders compared with normal controls.

METHODS

We analyzed, in a case control study carried out between March 2006 and March 2007, 17 HIV-patients (males or pre-menopausal females) with psychiatric co-morbidity, a long-term antipsychotic and antiretroviral therapy (>24 months). These patients were recruited from

the non-profit Residential Care Facility "Don Dante Savini", (Perugia, Italy) designed for subjects in the late stages of HIV infection and psychiatric disorders (a population usually suffering from major psychiatric disorders other than personality disorder or substance abuse). In this setting - as described elsewhere - all drugs were administered and taken under the direct control of a nurse or caregiver [18].
Inclusion criteria were an age greater than 40 yr, treatment with combination antiretroviral therapy (ART) and with antipsychotic drugs (typical or atypical) for more than 24 months, plasma HIV-RNA suppressed below the limit of detection (<40 copies/mL) for at least one year. Exclusion criteria were an opportunistic infection in the past 3 months; treatment with steroids in the past 12 months; amenorrhea for more than 6 months or postmenopausal state; treatment with hormonal agents including GH, thyroid hormone, testosterone, megestrol, or oxandrolone in the past year; or an underlying medical condition, different from HIV infection and anti-psychotic drugs, predisposing to bone loss. Control healthy subjects, were Caucasian, not infected with HIV, recruited among 55 volunteers from the hospital staff, and matched with patients by age (±5 years) and gender.
All participants were required to be men or pre-menopausal women. A standardized questionnaire was used to collect data on patient demographics, and risk factors for osteoporosis. Anthropometric measures included weight, height measuring with a standard techniques, and BMI calculated as weight in kilograms divided by height squared in meters. BMD was measured on hip (femoral neck and trochanter) by DEXA with Densitometry Hologic (Discovery USA).
A standard phantom was used for the correct calibration of every site of the exams [19]. The root mean square standard deviation (RMS SD) of our densitometer was 0,063 g/cm^2 [20]. According to the World Health Organization (WHO) classification, diagnosis of osteopenia or osteoporosis was based on BMD of the femoral neck expressed as T-score; a T-score represents bone mineral density expressed as the number of standard deviations (SDs) above or below the mean BMD value for a normal young adult [21].
In conformity with WHO definitions, we used a T-score between -1 and -2.5 for osteopenia, less than -2.5 for osteoporosis.

Statistical analysis
SPSS statistical package, release 13.0 (SPSS Inc, Chicago, III) was used for all statistical analyses. Between-group differences were assessed by the use of Student's *t* tests for continuous variables. The c^2 test was used for comparing categorical variables. Values of less than 0.05 were considered significant

RESULTS

Enrolled patients were being treated with antipsychotic drugs (typical or atypical anti-psychotics) for a mean treatment period of 127±118 months. The main psychiatric diagnosis (DSM-IV criteria) [22] was included in axis I in twelve patients and in axis II in five patients, six subjects were on methadone treatment. The patients enrolled were on a stable anti-HIV-therapy (mean treatment time of 98±40 months).
The mean CD4+ T-lymphocyte count was 438 ± 222 cells/μL and 71% had a previous diagnosis

Table 1 - Osteopenia and osteoporosis in HIV patients and in control subjects.

	HIV-infected n= 17	*Controls n=34*	*p*
Age (years)	48±7	49±3	0.34
Men, %	71	71	1
Body mass index, kg/m^2	25.0±5	28±4	0.16
Current cigarette smoking, %	82	47	0.02
Pathological T-score (femoral neck), %	71	9	<0.001
Osteopenia, %	41	9	<0.001
Osteoporosis, %	30	0	<0.001
Values are mean ± SD.			

of AIDS. All patients had a plasma HIV-1 RNA level below the limit of detection of 40 copies/mL. HCV infection was present in 10/17 cases and clinical evidence of lipodystrophy in 13/17 cases. Life stile habits were sedentary in all the patients.
Selected clinical characteristics and DEXA results of HIV-infected patients and control subjects are reported in Table 1. The two groups were comparable on demographic variables including age, gender and race.
The results showed that the HIV group had significantly higher rates of low T-scores, as compared with the controls (71% *vs.* 9% $p<0.001$). The mean BMD in the 17 HIV patients was significantly lower compared with control group ($0,69\pm0,12$ g/cm^2 vs. $0,86\pm0,12$ g/cm^2, $p<0.001$). Furthermore, spontaneous fractures occurred in some HIV-infected subjects (two femoral, one vertebral, and one of ribs).

DISCUSSION

Osteopenia and osteoporosis have become an increasing concern in patients with HIV-infection. We performed a cross-sectional study in which we compared the BMD in normal controls and in institutionalized HIV-1-infected patients, who had continuously been exposed for two years or longer both antiretroviral and antipsychotic drugs.
Our data showed higher prevalence of low BMD (71%) and osteoporosis (30%) in HIV patients. Numerous medical and lifestyle factors that are prevalent among HIV-infected individuals with psychiatric disorders are associated with low BMD.
In order to minimize the potentially confounding effect of ongoing HIV-1 replication on BMD, we selected patients to have plasma HIV-1 RNA levels suppressed to below 40 copies/ml and in order to eliminate the effect of estrogens deficiency on bone loss we selected men and pre-menopausal women.
Previous studies have given conflicting results, not clarifying if the loss of bone mass is a direct consequence of viral infection or of antiretroviral drugs [1, 23-25].
The abnormalities in bone and mineral metabolism associated with HIV infection may be caused by direct invasion of osteogenic cells and bone marrow microenvironment [2]; chronic T-cell activation and persistent activation of pro-inflammatory cytokines, mainly TNF-α and interleukin-1; disturbances of calcium homeostasis with deficit of 1,25 di-hydrovitamin D, as well the involvement of mitochondrial abnormalities related with antiretroviral therapy, lactic acidemia and lipodystrophy [26-28]. In patients with intellectual disabilities anti- psychotic drugs and a reduced physical activity can significantly contribute to lower BMD.
Chronic mental illness may represent a possible important co-factor neglected in previous studies assessing BMD in HIV patients.
We suggest that mental illness and treatment with anti-psychotic drugs, particularly in a HIV setting should be considered important potential risk factors for osteoporosis and spontaneous fractures even in men and pre-menopausal women.
Psychiatric diseases and their treatment could aggravate the loss in BMD due to HIV infection and antiretroviral drugs. In cases such as those mentioned above, as well in HIV patients with other risk factors associated with osteoporosis, performance of a bone densitometry would be recommended also because in this particularly setting of HIV patients, morbidity associated with osteoporosis could be greater and management of any type of fracture could be very difficult [29].
Our study has several limitations, i.e. the influence of multiple diseases, life stile habits (including physical activity) and treatment variables could not be determined in this preliminary study (given our small sample size and cross-sectional design). However we suggest that fracture risk with the performance of a bone densitometry should be carefully evaluated for institutionalized HIV patients with psychiatric co-morbidity both in man and pre-menopausal women.

Key words: Osteoporosis, osteopenia, HIV, antiretroviral therapy, antipsychotic medication, psychiatric disorders

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SUMMARY

Osteoporosis occurs in HIV-infected patients as well as in common psychiatric conditions and causes significant morbidity. There are no published studies assessing bone mineral density (BMD) in institutionalized HIV patients with associated psychiatric disorders. We analyzed 51 subjects in a case control study: 17 HIV patients (males or pre-menopausal females) with psychiatric co-morbidity and a long-term antipsychotic and antiretroviral therapy; and 34 control healthy subjects, not infected with HIV, matched with patients by age and sex. The results show that the HIV group had significantly higher rates of pathological T-scores, as compared with the controls (71% vs. 9% $p<0.001$).
Chronic mental illness may represent a possible important co-factor influencing BMD in HIV patients. We suggest that fracture risk should be carefully evaluated for institutionalized HIV patients with psychiatric co-morbidity.

RIASSUNTO

L'osteoporosi è una patologia responsabile di una significativa morbosità, frequente in soggetti HIV infetti e presente anche in corso di patologie psichiche. Non è attualmente noto se il rischio di osteoporosi e fratture in pazienti HIV positivi possa essere influenzato dalla concomitanza di una malattia di tipo psichiatrico.
Abbiamo valutato in uno studio caso controllo 51 soggetti: 17 HIV positivi (maschi o femmine in età fertile seguiti presso una struttura residenziale per AIDS) affetti da patologie psichiche e con una lunga storia di trattamento sia con antipsicotici che con antiretrovirali e 34 soggetti di controllo, sani e confrontabili con i malati per età e sesso. I risultati mostrano che gli HIV positivi presentano un T-score *significativamente più basso rispetto ai controlli (71% vs 9%). Sulla base di tali risultati ipotizziamo che i disturbi psichici cronici possono rappresentare un co-fattore nella perdita di densità minerale ossea propria dell'infezione da HIV e riteniamo che sia consigliabile, in caso di coesistenza di HIV e malattie psichiche, eseguire una densitometria minerale ossea, ciò indipendentemente dalla presenza di altre specifiche condizioni di rischio per osteoporosi e fratture.*

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