ORIGINAL ARTICLE

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A Haemophilia, HIV and osteoporosis: an emerging problem in clinical practice

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Abstract
HIV infection is an important co-morbidity in haemophilia. Some evidences suggest that both these pathologies are related to a reduction in bone mineral density. We describe the complexity in management of a femoral fracture in a patient with severe haemophilia and a long history of treatment for HIV infection.
Key words: haemophilia, arthropathy, HIV, osteoporosi

Introduction

Haemophilia is an X-linked recessive bleeding disorder resulting from a deficiency in factor VIII (haemophilia A) or factor IX (haemophilia B) coagulation activity. The incidence is around 1/5000 and 1/25000 male births for haemophilia A and haemophilia B, respectively [1]. The severity of disease is inversely related to the amount of residual coagulation factors, and haemophilia is classified as severe (factor VIII or IX level <1%), moderate (2-5%) or mild (5-30%). The clinical hallmarks of haemophilia are joint and muscle haemorrhages, also spontaneous in severe disorder. Joint disease affects 60% of adult severe haemophiliacs and contributes to most of the morbidity of this condition [2]. Knees, ankles and elbows are the most frequently involved joints. Without adequate treatment, recurrent haemorragic episodes into the joint results early in progressive damage and long-term arthropathy, with loss of range of movement, disability and often serious pain. The treatment of haemophilia consists of replacement therapy with the deficient factor. Today, several safe plasma-derived or recombinant clotting factor concentrates are available and patients can be treated on-demand or with prophylactic regimens, that is regular infusions of factor concentrate [3]. Before 1985, on the contrary, concentrates of coagulation factors, prepared from plasma pools of up to 30000 donations, did not undergo to viral inactivation methods and any infections present in plasma donors could be transmitted to the recipient. This way, in the period from 1979 to 1985 about 70% patients with severe haemophilia were estimated to have been infected by human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) replaced haemorrhage as the leading cause of death in haemophiliacs [4]. Following the introduction of highly active antiretroviral therapy (HAART) in 1996, deaths caused by AIDS have decreased [5]. Hepatitis C infection, instead, occurred in virtually all recipients of clotting factor concentrates at their first exposure [6] and actually this infection is a major co-morbidity and a leading cause of morbidity and mortality in patients with hemophilia [7, 8].
According to data of the National Inherited Bleeding Disorders Registry 2011, in Italy patients with haemophilia are 4198, of them 253 (6%) are HIV positive, 1390 (33%) are HCV positive and 209 (5%) are HIV-HCV co-infected [9].
In this report we present the case of a haemophilic patient with chronic arthropathy, pluri-experienced for HIV treatment and osteoporosis.

Case report

The patient is a 41-years old male with severe haemophilia A (FVIII: C <1%). Since childhood, he suffered for bleedings in the knees and ankles, treated over the years with administration of cryoprecipitate, Kryobulin TIM 3 (Immuno), and Emoclot DI (Kedrion Biopharmaceuticals) on-demand. Later, post-trasfusional HCV, HBV and HIV

infections were diagnosed.
In 2000, the patient switched from on-demand treatment with plasma-derived FVIII concentrate to recombinant FVIII (Helixate, CSL Behring GmbH, Germany).
HCV has been cleared in 1990 after one course of specific treatment with interferon (Intron A 3 MU 3x weekly for 12 months).
Patient had a long history of HIV infection (first test positive in 1985), with a CD4 count permanently <200/mm^3 with percentages between 9-11%, but without any opportunistic infections. In 1991 therapy was started, the first HAART regimen was possible in 1997. Since then, with backbone always containing lamivudine and then tenofovir/emtricitabine partially active towards HIV but with complete activity against HBV, several PIs have been introduced in his regimen (saquinavir, nelfinavir, lopinavir/r) obtaining viral undetectability only for a short period of time with lopinavir/r.
Because of subsequent failure of lopinavir/r, he has been switched to NNRTI with fast development of resistance mutation because of the inefficacy of the backbone.
In 2010 the patient has been enrolled in the protocol of TMC 114, which has been added to TDF/FTC, and used with enfuvirtide to have at least two complete active drugs to gain the undetectability. Enfuvirtide was switched to raltegravir, as soon as available. In the present moment the patient has HIV RNA<20 cp/mL, CD4: 282/mm^3-16.7% on boosted darunavir 600/100 mg bid , raltegravir 400mg bid, FTC/TDF 200/245mg. HBV DNA is constantly < 20 IU/ml.
With respect to musculoskeletal function, the patient suffered for chronic haemophilic arthropathy of the knees and ankles, with loss of range of movement and consequent muscle hypotrophy leading to a mild disability in deambulation.
In March 2010, in consequence of an apparently mild trauma by accidental fall, the patient was admitted to the Department of Traumatology and Orthopaedics of University Hospital of Florence, where a compound fracture of right distal femur was diagnosed. With adequate haemostatic and antibiotic prophylaxis he underwent osteosynthesis. Surgery was difficult for observed poor quality of the bone, which was so weak and friable that orthopedists needed to stabilize femur with 4 screws. Because of a significant delay in forming the bone callus, an oral therapy with vitamin D (10000 IU weekly) and calcium (500 mg daily) in addition to one daily subcutaneous injection of Teriparatide was suggested by orthopedists.
After 3 days the patient was admitted to Emergency Department of University Hospital of Florence with diffuse abdominal pain and nausea. At the physical exam patient did not show icterus or subicterus, abdomen was plain and soft, Blumberg and Murphy signs were negative. Blood tests showed an important hyperamilasemia, hypercalcemia, mild increase of cholestasis indexes and transaminases. Ultrasound and computer tomography scan revealed an increased pancreatic volume, without signs of biliary obstruction. Treatment with vitamin D, calcium and Teriparatide was immediately stopped, a supportive care was introduced with normalization of pancreatic function indexes into 3 days. The femur fracture healing required two more months and patient was supported only with oral vitamin D, being impossible intramuscular administration because of bleeding disorder. The bone metabolism screening showed low level of 25-hydroxyvitamin D (25-OHVitD) (7ng/mL; normal range: 30-100), mild increase of parathyroid hormone (PTH) (9.5 pmol/L; normal range:1.3-7.6) with normal serum and urinary calcium and phosphorus; specific bone markers showed a faster metabolism: bone alkaline phosphatase (b-ALP) and osteocalcin were 31mcg/L (normal range: 7.0-20.1) and 49 ng/L (normal range:11-43), while telopeptide (NTX) and urinary piridinoline were 10 ng/L (2.1-5.0) and 13 nmol/mmol (2.3-5.4), respectively.
The dual energy X-ray absorptiometry (DXA) showed osteoporosis at femoral area (F-DXA) (Z-score -2.4) and osteopenia at lumbar spine (L-DXA) (Z-score -1.7).
The long period of immobilization by plaster (4 months) needed for the healing of fracture, associated to pre-existent severe arthropathy, leaded to a fixed right knee extension deformity with pain, for which the resolution was possible only by total knee arthroplasty, performed in April 2011. At the moment the patient can walks without auxilies and he is able to daily activities without significant pain.

Discussion

Our clinical case is paradigmatic with respect to the high risk of osteoporosis in adult haemophiliacs because of the possibility of its multifactorial eziopathogenesis.
Several evidences showed a strong correlation between osteoporosis and haemophilia. The pathogenesis of low bone mineral density (BMD) in haemophiliacs includes prolonged immobilization [10, 11] because of recurrent joint bleedings and consequent lack of weight-bearing exercise [12]. Haemophilic children may never obtain the peak bone mass reached by comparable healthy boys, because weight-bearing activity during youth is a more important factor for peak bone mass [11, 12]. Moreover, chronic arthropathy is a continuous trigger for an increased bone turnover mediated by pro-inflammatory cytokines and osteoclastogenesis activating factors [13, 14].
Infections play an important role too. The prevalence of osteopenia or osteoporosis in HIV-infected individuals is reported to be respectively six and three times greater than healthy population. HAART and PI-exposed individuals had higher odds (respectively 2.4 fold and 1.6 fold) of reduced BMD and osteoporosis with their respective controls [15].
HIV can impair bone homeostasis by paracrine/autocrine mechanism involving apoptosis induced by TNF-- followed gp120 cell membrane interactions [16,17] and by a suggested role in impairing the balance of the OPG/RANKL system with a decrease of this ratio [18,19].
Antiviral treatments, including PIs and ribavirin, are also associated with increased markers of bone resorption and enhanced osteoclastic activity [15, 19, 20, and 21].

In consideration of the described clinical case we carried out a study (in press) to discriminate the magnitude of the several risk factors for osteoporosis in this special population, subdividing the patients in three groups on the basis of absence (un-infected group) or presence of viral post transfusional infections (HCV mono-infected or HIV-HCV co-infected groups).
In our population we observed a high prevalence of hypovitaminosis D (87%) a part from the belonging group.
DXA showed a global reduction of BMD, but with some differences in femoral or lumbar patterns between the three groups.
BMD pattern for F DXA was similar in the three studied groups. This result could be explained by the pivotal role of the arthropathy, respect to the infection, in determining the BMD reduction at this particular site, because of loss of joint function with reduced mobility, due to recurrent haemarthrosis.
L BMD resulted to be significantly lower in co-infected group than in un-infected one, when considering both osteopenia and osteoporosis compared to normal BMD. This result is as well supported by the concept that high bone turnover states, such as HIV-induced, involve trabecular bone earlier and to a greater extent than the cortical bone. The faster bone metabolism in pts with infections is confirmed by a significant difference in co-infected and mono-infected groups in the laboratory parameters bALP and NTx.

Conclusion

The clinical case reported highlights how often because the registry age of these patients doesn't match to their biological age in consideration of the long history of each of the several diseases they are suffering from, with complex medical problems generally associated to older ages such as cardiovascular or metabolic diseases, neoplasia, renal and musculo-skeletal disorders.
On the other hand nowadays also the patients belonging to this special population get older.
In the last years, life expectancy in haemophilic patients has increased significantly, approaching values seen in the general population. In the early part of the last century, the prevalence of haemophilia was estimated to be only 4 per 100000 males while the prevalence in the 1990s was 13-18 per 100000 [22]. This represents a major success of the improved safety of therapeutic materials to treat haemophilia and of improved quality of care. Regarding HIV infection, the advent of HAART has dramatically modified the history of this disease which has been changed in a chronic situation.
For these reasons, a multidisciplinary approach may be of primary importance to individualize treatments of haemophilic patients, considering all co-morbidities and co-medications.

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