

Full Length Research Paper

Bone diseases in HIV infected children at a Nigerian Teaching Hospital

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Accepted 29 May, 2014

In a study 78 consecutive HIV infected children attending a pediatric Anti-retroviral clinic in a Nigerian Tertiary hospital over a seven year period, seven (9.0%) children had bone diseases. The 78 children were made up of 35 girls and 43 boys with their ages ranging between 9 months - 11 years. The bone diseases were single cases of, fractured humerus, fractured clavicle, septic arthritis of the left hip, osteomyelitis of the right index finger, left knee septic arthritis with dactylitis of the right fourth finger, bilateral genu valgum and unilateral genu valgum each. Complications of digital amputation and destruction of the femoral head with consequent limb shortening were recorded in the children with digital osteomyelitis and septic arthritis respectively. Healing of the femoral head and the shortened limb was noted after 2 years of HAART therapy. The differences between the 2 cases of bone diseases recorded among the 57 children on HAART, compared to 5 children that developed bone disease amongst the remainder 11 yet to be initiated on HAART is significant. ($X^2 = 5.46$, $P = 0.02$). It is concluded HAART administration is associated with lower occurrence of bone disease and good outcome amongst those with infectious bone diseases.

Key words: Bone, HIV, Children.

INTRODUCTION

The association between bone disease, HIV infection and use of highly active anti-retroviral drugs has been a topic of interest recently (Mora et al., 2010). However, there is a paucity of information on bone health in HIV infected children (Mora et al., 2010; Jacobson et al., 2005; Siberry et al., 2012). Bone disease in HIV infected children is likely to have its own peculiarity because children are actively growing and continuously building up on bone mass as opposed to adults who are expected to have an existing good critical bone mass.

Bone health in the HIV infected in developing countries is likely to be affected by the widely prevalent problem of malnutrition. The nutrient deficiencies associated with malnutrition are expected to take their toll on the bone mass. Furthermore, children in the tropics present late and at an advanced stage of HIV disease, when the effect of the virus is pronounced on the nutrition state of

the individual (Oniyangi et al., 2006; Brown et al., 2011). It is not unlikely that the critical bone mass may also be compromised at this stage. Advanced disease states are associated with more deleterious effects of the virus on the different systems and organs of the body and the bone may not be an exception.

Observations on the association between bone health and HIV infection in adults suggest increased frequencies of osteo-articular infections such as osteopenia, osteoporosis, osteonecrosis, carpal tunnel syndrome and adhesive capsulitis of the shoulder (Munhoz, 2007). Studies on the influence of anti-retrovirals on the bone show that protease inhibitors impact negatively on the bone (Munhoz, 2007). Indinivir inhibits bone formation while ritonavir inhibits osteoclasts. Tenofovir a reverse transcriptase inhibitor has recently been linked to the development of osteomalacia (Parsonage et al., 2005). The loss in bone density associated with the use of tenofovir, indinivir and retonivir makes their use contraindicated and controversial in malnourished children (Munhoz, 2007; Parsonage et al., 2005).

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Fortunately these drugs are not first line drug options for managing HIV infection according to the National Guidelines for HIV treatment in Nigeria (FMOH, 2007). The first line drug recommendations for treatment of HIV infected individuals in Nigeria are zidovudine, lamivudine, nevirapine or efavirenz. However, there is no report, to our knowledge on the association of the first line drugs recommended in Nigeria on bone health in Nigerian children or children from other countries. This observation informed our decision to study the association between bone health, HIV disease and anti-retrovirals in the HIV infected children attending the paediatric anti-retroviral clinics of the Ladoke Akintola University of Technology Teaching Hospital, Osogbo, Nigeria.

METHOD

This is a retrospective study of all the HIV infected children attending the Paediatric Antiretroviral clinic of Ladoke Akintola University of Technology Teaching Hospital, Osogbo, Osun state, Nigeria. Osun state is located in south west Nigeria and it lies between longitude 04 00E and latitude 05 588. It has an estimated population of 3.2 million people (National population commission, 2006) Osogbo is the capital city of Osun state and it is about 232km from Lagos state the commercial nerve of Nigeria.

Ladoke Akintola University of Technology Teaching Hospital, Osogbo, provides tertiary health services to the inhabitants of the state of Osun as well as the inhabitants of the neighbouring states such as Ondo, Kwara and Ekiti. The hospital provides free care for HIV infected children which is supported by the government of Nigeria and the United States President's Emergency Plan for AIDS Relief program. Ethical approval was obtained from the Ladoke Akintola University of Technology Teaching Hospital Ethics and Research Committee. All the case notes of all the children were reviewed to extract those with bone diseases between 1st of January 2007 and 31st of December 2012.

Diagnosis of HIV was based on a positive ELISA reaction and confirmed by a Western blot in children aged 18 months and older. Infections in children aged less than 18 months were established using the HIV DNA polymerase chain reaction kit. The voluntary counselling and testing method was used to diagnose all infected children with symptoms suggestive of HIV infections or those whose mothers or siblings presented with symptoms.

Information on the HIV infected children diagnosed to have bone disease between the five year period was sought. Supporting evidence such as plain radiographs of the diseased bone were also obtained and examined. Details on the age, sex, clinical presentation, clinical diagnosis, duration of admission for those admitted, outcome of the disease were extracted from the case

notes. Other details obtained from the case notes include WHO clinical staging, CD4 counts, CD4 percentage and results of investigations such as radiographs.

Other details obtained include use of anti-retrovirals, or antibiotics. All patients on HAART were treated according to the National Guideline for HIV Treatment in Nigeria which recommends that all HIV infected children be placed on first line anti-retrovirals, namely zidovudine, lamivudine, nevirapine or efavirenz (FMOH, 2007). Patients less than 2 years or weighing less than 10kg were placed on zidovudine, lamivudine, and nevirapine while those older than 2 years or weighing more than 10kg were placed on efavirenz (FMOH, 2007). The antibiotics received by the children were also recorded in cases where antibiotics were administered.

The data obtained was analyzed with PASW statistics version 18 using simple descriptive statistics such as range, mean and percentages for continuous variables. Tests for significance for associations computed for categorical variables were based on the chi-square and values less than 0.05 were regarded as statistical significant.

RESULTS

Total population studied

Seventy eight HIV infected children attended the clinic during the 5year study period. They consisted of 43 boys and 35 girls giving a male to female ratio Of 1.1:1. The ages of the 78 children studied ranged from 3 months to 13 years. Table 1 shows the age and sex distribution of the total population studied. Of the 78 HIV infected children 7 had bone diseases giving a prevalence of 9.0%.

Age and Sex Distribution of the Children with Bone Disorders

The ages of the children with bone disorders ranged from 9 months to 11years and their mean age was 5 years. Six of the seven children with bone disease were girls. The difference between the proportion of girls with bone disease (6 out of the 35) compared with the proportion of bone disease among the boys (1 out of 43) is statistically significant. ($X^2 = 5.12$, $P = 0.02$).

Types of Bone Disorders

Of the seven children with bone disorders, 3 had osteoarticular infections while 2 had fractures and the remaining two had angular deformities of the lower limb namely bilateral genu valgum and genu valrum. Of the 2 children with fractures, one had a supracondylar fracture

Table 1. Age and sex distribution of the total population studied

Age Categories	Sex		Total Population Studied	Number(%) of children with bone disease in the category
	Male	Female		
3months – <1 year	4	2	6	1(16.7)
1 year – < 5 years	16	21	37	3(8.1)
5 years - <10 years	17	8	25	1(4.0)
10years - <15 years	6	4	10	2(20.0)
Total	43	35	78	7(9.0)

of the left humerus, while the other had a non displaced left clavicle fracture. Both fractures were closed and not pathological. They occurred secondary to trauma. Concerning the three with osteoarticular infections, one had osteomyelitis of the proximal and middle phalanx of the index finger of the left hand, while another child had septic arthritis of the left hip complicated by shortening. The last child with osteoarticular infection had septic arthritis of the left knee and dactylitis of the left fourth finger, this child also had an underlying sickle cell anaemia.

Etiology of Bone Disorders

The clavicular fracture was secondary to a fall from the bed to a hard concrete floor with the area of the clavicle making contact first, while the supracondylar fracture was secondary to a fall on an outstretched hand. The digital osteomyelitis was as a result of blistering digital dactylitis, culture and sensitivity of the lesions yielded staphylococcus aureus sensitive to cloxacillin and gentamicin. On the other hand the etiological agent causing the arthritis could not be ascertained because the parents could not afford the cost for blood culture and aspirate cultures. The child with both genu valgum and valrum of the left and right leg respectively was a female child and a second of a set of twins. The twin brother he did not have angular deformities of the lower limbs.

Clinical Presentation of Patients

The patients with fractures presented with swelling, pain and inability to use the affected limbs within 24hours of injury. A supracondylar fracture and a clavicular fracture were confirmed radiologically in the two patients with fractures. The knee deformities were noted at least one year prior to presentation in both children and there was associated delay in walking. Notably, one of the children with delay in standing and walking was a female twin who lagged behind the non-HIV infected male twin with straight lower limbs and normal standing and walking developmental milestones by one and a half years.

Spontaneous swelling of the right hip associated with limping and fever of three weeks duration were the presenting features in the child with right septic arthritis. While swelling of the left knee with fever and right left fourth finger swelling were the main findings in the child of two weeks duration were the presenting features in the child with sickle cell anaemia. The remaining child with digital osteomyelitis presented with a blister and pain on the index left finger and pain in the finger with limitation of movement across the interphalangeal joints.

W.H.O Staging and CD4 Counts of the Children Studied

Of the 78 children studied two had W.H.O stage 1 disease, 5 stage 2 disease, 70 had stage disease and 1 stage four. All the seven children with bone disorders had WHO clinical stage 3 disease. The CD4 counts of the children studied, their respective CD4 percentages have been matched with their ages, diagnosis and information with use or non use of HAART in table 2.

Cases requiring admission and duration of hospitalization amongst cases with bone disorders.

Of the seven HIV infected children with bone disorders, four required admission. All the 3 children with bone infections required admission, however only the child with septic arthritis was admitted because the other two refused admission. Of the two children with fractures, only the child with supracondylar fracture required admission. Traction needed to be applied to the limb after reduction to maintain alignment. The child with septic arthritis spent 63 days on admission, while the child with supracondylar fractures stayed 14 days on admission. The child with clavicular fracture was managed on outpatient basis while the child with digital osteomyelitis refused admission.

Outcome

The child with digital osteomyelitis had developed spontaneous amputation of the terminal phalanx of the in-

Table 2. The age, Diagnosis, CD4 counts, CD4 percentage and use of HAART among the patients with the diseased bone.

Age	Diagnosis	CD4 count at presentation (cells/ μ l)	CD4 percentage	HAART administration at presentation
9 months	Digital osteomyelitis	2052	55.6%	Yet to initiate
2 years	Arthritis of the left hip	436	13.4%	Yet to initiate
2 years	Genu valgum	1502	29.9%	Yet to initiate
3 years	Arthritis of the left knee and dactylitis of the fourth right finger	45	2.2%	Yet to initiate
5 years	Bilateral Genu valgum	488	15.3%	Yet to initiate
6 years	Fractured left clavicle	646	30.0%	Initiated 2 years prior to presentation
11 years	Supracondylar fracture of left humerus	699	26.9%	Initiated 4 years prior to presentation

dex digit of the left hand at presentation. The child with septic arthritis of the left hip developed shortening associated with limping at discharge. However the limping resolved over two years. All the children with fractures had a good callus formation at the site of fracture 6-8 weeks post reduction of humeral fracture and at the site of clavicular fracture post administration of collar and cuff and analgesics. The child with the dactylitis and left knee arthritis refused admission because of financial constraints and did not improve on administration of cefuroxime alone as an outpatient. However there was a resolution of the arthritis and dactylitis after one week of addition of HAART to the antibiotic.

Antibiotic Use

The child with digital osteomyelitis was put on oral Augmentin because of financial constraints, while the child with septic arthritis was given parenteral Ceftriaxone for one week and completed the remaining 7 weeks of antibiotics on oral ampiclox because of financial constraints. Response to the oral Ampiclox was good with resolution of fever, swelling and tenderness around the hip within two weeks of drug administration. The child with the dactylitis and left knee arthritis used Cefuroxime for 6 weeks. The children with fractures were not given antibiotics.

Administration of Highly Active Anti-Retrovirals

Fifty seven of the children studied had initiated HAART at the time of the study while 21 were yet to initiate treatment. Of the seven children with bone disease only the 2 children with fractures had initiated HAART before sustaining fractures. The child with digital osteomyelitis also had amputation of the terminal phalanx at presentation and HIV diagnosis. The child failed to turn

up for follow up. The child with the hip arthritis also presented late and was started on HAART after completing six weeks of antibiotics. The child with the left knee septic arthritis and dactylitis also presented late and was started on HAART two weeks after presentation, which was when there was an assurance that the patient would ensure adherence to HAART. The differences between the 5 children with bone disease of the 21 not on HAART compared to the 2 with bone disease of the 57 who had initiated HAART before either the commencement of this study or development of bone disorder is statistically significant. ($X^2 = 5.46$, $P = 0.02$).

DISCUSSION

The present study shows that bone disorders are uncommon in HIV infected children. Osteo-articular infections, fractures and angular deformities of the lower limb were the bone disorders reported in this study. Infections were the most common diseases followed by fractures and angular deformities of the lower limbs. Previous studies also show that fractures and osteoarticular infections are uncommon in HIV infected individuals (Siberry et al., 2012; Bunderset et al., 2013; Nolan et al., 2001; Mora et al., 2001; Zuccoti et al., 2010; Robertson et al., 2012). A previous study reported an incidence rate of 0.01% for fractures among HIV infected children records and reported similar incidence risk estimates for fractures in HIV infected children and exposed children (Siberry et al., 2012). The absence of pathological fractures in the present study is consistent with previous studies (Siberry et al., 2012; Mora et al., 2001; Zuccoti et al., 2010; Robertson et al., 2012).

The preponderance of bone disease among the female sex in the present study is similar to the finding in adults which report higher rates of osteoporosis among older women (Jacobson et al., 2008; Dolan et al., 2004). An inverse correlation in the levels of testosterone and estrogen in the male and female sex respectively have been docu-

mented to be the mainly responsible for the gender predilection in bone disease (Haskelberg et al., 2011). It is however unexpected that the differences in the body hormones constitution across the sexes would be significant enough to account for a gender bias in bone disease in childhood. Low bone mineral density in HIV infected children have been attributed to delays in sexual growth, maturity, length of HIV infection, severity of HIV disease and ethnicity (Jacobson et al., 2005). Interactions between the body hormones across the different childhood ages and the human immunodeficiency virus on the bone however need to be further studied in order to confidently exclude a sex related hormonal influence on the bone in HIV infected children.

The two cases of genu valgum and genu valrum associated with paediatric HIV have not been previously reported. This association might just be casual because they occurred in the age group in which it may be physiological. The resolution in the delays in walking among the patients with genu valgum or valrum with the administration of HAART in this study may however indicate that HIV may have a role to play in the bone disease. Administration of HAART has previously been reported to have a good effect on bone and growth (Bunders et al., 2013; Nolan et al., 2001). Correction of the angular deformities in the lower limbs with the administration of HAART will however be stronger evidence in support of the positive and negative effect of HAART and the HIV on the bone respectively. Resolution of the genu valrum and genu valgum with HAART may however require a long time. On the other hand these abnormalities may correct spontaneously with time if they are just physiologic.

The influence of HAART on the bone in HIV infected children appears controversial. Previous reports suggest both beneficial and adverse effects (Nolan et al., 2001; Mora et al., 2001; Zuccoti et al., 2010). A number of factors ranging for the differences in the HAART combination, to the diversities of the HIV infected patients studied may account for the contrasting effects of HAART on the bone. This further underscores the need for more studies in this field.

Osteoarticular infections were recorded in 3.8% of the present population studied. Previous studies also report lower rates of osteoarticular infections in HIV infected individuals with estimates rates of 1.5 and 0.4 percent respectively in a study conducted at Netherlands and Italy respectively (Busch et al., 2007; Ventura et al., 1977). A recent study however reported HIV infection among 64.7% of the total 102 cases of osteoarticular infections seen at a South African hospital (Robertson et al., 2012). The high estimate rate obtained in South Africa study in comparison to the studies conducted in Italy and Netherlands may be explained by the differences in study location and methodology. South Africa has a high HIV prevalence in comparison to Italy and Netherlands which have low estimates. The South African study determined

the prevalence of HIV among subjects with bone infections while the Italian and Netherland study determined the prevalence of bone infections in HIV infected children.

The very low CD4 percentage amongst most of the HIV infected children with bone infections may suggest that immunosuppression was contributory to the disease process. Furthermore, the delays in presentation and the advanced HIV clinical stages of the children with bone infections may partly be responsible for the complications associated with the bone infections. The good outcome with antibiotics and HAART also adds further weight to the thinking/hypothesis that these complications may be avoidable with prompt administration of antibiotics and HAART. The absence of bone infections among children on HAART in the present study may indicate that it has a protective effect against bone infection. This protective effect may probably be predicated on the general improvement of the body immune function by HAART (Mora et al., 2010; Jacobson et al., 2005; Verweel et al., 2002). A spill over effect from improved immune functioning is suggested as the reason for the good healing amongst the HIV infected children on HAART in a good time period.

It is thus concluded that bone infections are unusual amongst HIV infected children on HAART. Resolution of bone disease and health was associated good outcome in bone infections and other diseases. The small sample size in the present study is however a limitation to carrying out more complex analysis and obtaining significant. Also, the association between age, gender, bone disease and the human immunodeficiency virus in the paediatric age group is unknown. Better powered studies however need to be conducted in order to obtain significant results that will provide answers to these gaps in knowledge.

ACKNOWLEDGMENTS

We are grateful to all the children studied for giving us this opportunity to learn from them. Also, we appreciate the co-operation of the medical records unit, in providing the medical records. Finally we are grateful to all the doctors and nurses who work tirelessly at the paediatric HIV unit to ensure that the children receive excellent care.

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