Osteonecrosis of the Hip (Legg-Calvé-Perthes Disease) in Human Immunodeficiency Virus-Infected Children

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ABSTRACT. Objective. Osteonecrosis of the hip has been reported in human immunodeficiency virus (HIV)-infected adults; whether this is related to HIV infection or its treatment is unknown. There has been 1 report of osteonecrosis among HIV-infected children. Specifically, avascular necrosis of the hip consistent with Legg-Calvé-Perthes disease (LCPD) was reported in 3 HIV-infected children with AIDS from Spain in 1992. We evaluated the prevalence and incidence of LCPD, the pediatric equivalent of adult osteonecrosis of the hip, in HIV-infected children participating in a prospective cohort study of long-term outcomes in HIV-infected and HIV-exposed children—Pediatric AIDS Clinical Trials Group (PACTG) protocol 219.

Methods. PACTG 219 enrolled 1464 HIV-infected and 849 HIV-exposed, uninfected children between April 1993 and September 2000. Children had periodic examinations with collection of clinical and laboratory data. The database was reviewed for reports of LCPD and other bone disorders. A prevalent case was defined as LCPD diagnosis preceding PACTG 219 enrollment and an incident case had to have occurred between enrollment and September 2000. A case-control study (matching on age, gender, and race/ethnicity, which are known to be associated with risk of LCPD and HIV infection status) was performed to investigate factors possibly associated with LCPD.

Results. Six cases of LCPD (4 prevalent cases reported at study entry; 2 diagnosed during 5837 person-years of follow-up) were observed; LCPD was seen only in children with perinatal HIV infection. LCPD prevalence was 199 per 100 000 compared with an estimated general population incidence of 6 per 100 000 person-years (95% CI: 5–7). Based on age-adjusted general population rates, the expected incidence of LCPD in PACTG 219 would have been 0.42; the age-adjusted relative risk of LCPD in HIV-infected PACTG 219 children was 4.8 (95% CI: 0.56–10.4). No cases were observed in uninfected children during 1919 person-years of follow-up on PACTG 219; the age-adjusted expected number of cases was 0.09. Median onset age was 7 years; 67% were of Hispanic or black race/ethnicity and 33% were female. Four of the 6 LCPD cases had received antiretroviral therapy before diagnosis; treatment was primarily with nucleoside reverse transcriptase inhibitors, and 2 had received protease inhibitors. Three of the LCPD cases had corticosteroid exposure before the diagnosis, but only 1 child had systemic exposure and the remaining 2 had topical exposure exclusively. In the case-control study, antiretroviral and corticosteroid therapy, CD4 cell percentage, birth weight, height for age and gender percentile, and triglyceride levels were not significantly associated with LCPD. However, the case-control study had limited power to evaluate possible associations.

Conclusion. Similar to HIV-infected adults, children with perinatal HIV infection have an increased risk for osteonecrosis of the hip, and clinicians should be alert to this diagnosis when HIV-infected children present with limp or hip pain. Whether LCPD is attributable to HIV infection itself, HIV-associated complications that could predispose to hypercoagulopathy, HIV-related therapies, or to the growth abnormalities in HIV-infected children is unknown and deserves additional evaluation.

ABBREVIATIONS. HIV, human immunodeficiency virus; LCPD, Legg-Calvé-Perthes disease; AIDS, acquired immune deficiency syndrome; PACTG, Pediatric AIDS Clinical Trials Group; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, nonnucleoside reverse transcriptase inhibitors; PI, protease inhibitors; ZDV, zidovudine; DDI, didanosine; 3TC, lamivudine; D4T, stavudine.

Osteonecrosis, or avascular necrosis of the bone, has been described in case reports in human immunodeficiency virus (HIV)-infected adults since the early 1990s. In one study, 4.4% of 339 asymptomatic HIV-infected adults were found to have evidence of osteonecrosis by magnetic resonance imaging, and in another study, the incidence of osteonecrosis in HIV-infected adults was 45...
times greater than would be expected in the general population. Recent reports have suggested that the incidence of osteonecrosis among HIV-infected adults may be increasing. In a report from the Johns Hopkins HIV Clinic Cohort, the incidence of osteonecrosis in HIV-infected adults from 1995 to 2000 increased from 0 to 4.8 per 1000 person-years.

The cause of osteonecrosis in HIV-infected persons is unknown, but it is thought to be possibly related to HIV infection itself; cytokine activation induced by HIV; or therapies for HIV- or HIV-associated conditions, including treatment with antiretroviral drugs, systemic corticosteroids, lipid-lowering agents, and/or testosterone and anabolic steroids.

There has been 1 report of osteonecrosis among HIV-infected children. Avascular necrosis of the hip consistent with Legg-Calvé-Perthes disease (LCPD) was reported in 3 HIV-infected children with acquired immune deficiency syndrome (AIDS) from Spain in 1992. LCPD is a pediatric disorder characterized by osteonecrosis of the capital femoral epiphysis. The incidence of LCPD among the general pediatric population in the United States is estimated to be 5.7 per 100 000 person-years; it is rare among black, non-Hispanic children. We report 6 cases of LCPD observed among children with perinatal HIV infection participating in a long-term outcome study, Pediatric AIDS Clinical Trials Group (PACTG) protocol 219, and the results of a case-control study to examine the association between osteonecrosis and antiretroviral therapies; corticosteroid exposure; CD4 lymphocyte exposure; CD4 lymphocyte percentage; birth weight; percentile of height for age and gender; and triglyceride level in HIV-infected children.

METHODS

The Pediatric Late Outcomes Study PACTG 219 is a prospective cohort study of HIV-infected and HIV-exposed but uninfected children designed to examine late outcomes of HIV infection and exposure to antiretroviral drugs given either as prophylaxis to prevent perinatal HIV transmission or as therapy for HIV infection. PACTG 219 opened to enrollment in April 1993 and continues to enroll patients at sites in the greater Boston area.

RESULTS

A total of 2014 HIV-infected and 849 uninfected infants, children, and adolescents were enrolled in PACTG 219 between April 2, 1993, and September 1, 2000. Population characteristics are detailed in Table 1.

Four prevalent cases of LCPD were reported at study entry. The LCPD prevalence rate was 199 per 100 000. In comparison, the estimated prevalence rate reported in the general pediatric population in the United States is 23 per 100 000. Based on the age-specific general population rates, the expected number of prevalent cases at PACTG 219 study entry
was 0.44. The age-adjusted prevalence rate ratio was 9.0 (95% confidence interval [CI]: 8.3–9.7) for HIV-infected children compared with the general pediatric population.

Two children were diagnosed with LCPD after enrollment in PACTG 219 in 5837 person-years of observation. The LCPD incidence rate was 34 per 100 000 person years (95% CI: 5.7 per 100 000 person-years). In comparison, the incidence rate reported in the general pediatric population in the United States is 5.7 per 100 000 person-years (95% CI: 5–7 per 100 000).24 Based on the age-specific general population rates, the expected number of incident cases in the PACTG 219 population was 0.42. HIV-infected children had a 4.8-fold (95% CI: 0.56–10.4) increase in age-adjusted risk of LCPD compared with the general pediatric population. In contrast, no cases of LCPD were observed in the HIV-exposed but uninfected children enrolled in PACTG 219. The expected number of cases among the uninfected children in PACTG 219, standardized by age, was 0.09.

Characteristics of the patients with LCPD are detailed in Table 2. All children fulfilled the diagnostic criteria for LCPD (see case reports).24 The median age of onset for PACTG 219 cases was 7 years (range: 4–15 years). Four of the 6 children were of minority race/ethnicity (3 Hispanic and 1 black), and a third of the cases were in female children. The median CD4 cell percentage at the time of diagnosis was 21%. Three children were below the 10th percentile for height for age and gender, 2 had triglyceride levels >150 mg/dL, and 1 was low birth weight (<2500 g).

All children with LCPD had perinatal HIV infection; none had been exposed to antiretroviral drugs in utero. At the time of LCPD diagnosis, 2 of the children had not received any antiretroviral therapy; of the 4 who had received treatment, all had received at least 1 NRTI, 1 had received an NNRTI, and 2 had received PIs (Table 3). Three of the 6 children reported exposure to corticosteroids; 2 children, however, had received only topical therapy.

Case Reports

Incident Case 1

This white male was diagnosed by radiograph with unilateral LCPD of the left hip in 1996 at the age of 6 years. Before diagnosis he had 619 days of zidovudine (ZDV) therapy; he had not received treatment with systemic or topical corticosteroids. At the time of diagnosis, he was below the third percentile for height, his CD4 cell percentage was 22%, and his triglyceride level was 48 mg/dL. This child had been previously diagnosed with parvovirus infection. He was treated symptomatically with rest and nonweight bearing for a short period of time. The LCPD resolved clinically without surgical intervention, and no subsequent bone or skeletal problems or disparity in limb length have been observed.

Incident Case 2

This Hispanic female was diagnosed by radiograph with bilateral LCPD in 1998 at the age of 15 years. Before diagnosis she had been treated with multiple NRTIs (ZDV, didanosine [DDI], lamivudine [3TC], stavudine [D4T]) for a cumulative number of 2475 days; PIs (ritonavir and saquinavir) for 355 days; and topical corticosteroid exposure for 796 days. At the time of diagnosis, she was at the 50th percentile for height, her CD4 cell percentage was 19%, and her triglyceride level was 191 mg/dL. In addition, the child had a history of chronic rhinitis, chronic mastoiditis, bilateral mild parotitis, oral can-
didiasis, and mental retardation. Treatment was nonsurgical and no additional bone abnormalities have been identified.

**Prevalent Case 1**

This Hispanic male was diagnosed with unilateral LCPD of the right hip by radiograph in 1990 at the age of 5 years. Before diagnosis, he had not received antiretroviral therapy and had 3 days of oral systemic corticosteroid exposure. At the time of diagnosis, he was below the third percentile for height, his CD4 cell percentage was 4%, and his triglyceride level was 98 mg/dL. Treatment consisted of bracing and follow-up. At the age of 11 years, there was radiologic deterioration of the right femoral head deformity. This patient died in 1999 because of HIV encephalopathy.

**Prevalent Case 2**

This Hispanic female was diagnosed with unilateral LCPD of the left hip in 1991 at the age of 4 years. She had no antiretroviral or corticosteroid therapy before her diagnosis. At the time of diagnosis, she was at the 40th percentile for height, her CD4 cell percentage was 31%, and her triglyceride level was 76 mg/dL. The child had a history of recurrent pneumonia and bronchial asthma. In April 1992, the patient was hospitalized for 2 months with acute osteomyelitis of the left femur, which later became chronic. A disparity in limb length has been observed.

**Prevalent Case 3**

This white male was diagnosed with LCPD via arthrogram and open biopsy with unilateral disease of the right hip in 1993 at the age of 7 years. Before diagnosis he had been treated with multiple NRTIs (ZDV, DDI, DDC) for 37 days. At the time of diagnosis, he was at the 60th percentile for height, and his CD4 cell percentage was 15%. Triglyceride value was not available. He had a history of spastic diplegia, developmental delay, and cerebral palsy. His birth weight was 2327 g. This child has not required surgical or medical treatment, with no additional bone abnormalities or disparity in limb length observed.

**Prevalent Case 4**

This black male was diagnosed by radiograph with unilateral LCPD of the left hip in 1999 at the age of 12 years. Before diagnosis, he had received treatment with all 3 classes of HIV drugs: multiple NRTIs (ZDV, DDI, 3TC) for 2382 days; an NNRTI (nevirapine) for 820 days; and a PI (indinavir) for 966 days. The child had not been treated with systemic or topical corticosteroids. At the time of diagnosis, he was below the third percentile for height, his CD4 cell percentage was 44%, and his triglyceride level was 229 mg/dL. This child had been previously diagnosed with ventricular hypertrophy, sinusitis, reactive airway disease, recurrent pneumonia, recurrent oral candidiasis, *Mycobacterium avium* infection, failure to thrive, developmental delay, and anemia. This patient’s LCPD resolved clinically without surgical intervention, and no additional bone abnormalities or limb length disparity has been observed.

### Results of Case-Control Study

The study included the 6 LCPD cases and 39 matched controls. The median number of controls per case was 6.5 (range: 4–9). Medication history was available for all patients, either from site records (41 children) and/or from concomitant medication forms from past PACTG clinical trials that the children had been enrolled in (4 children). Complete treatment histories from the time of birth were available for 34 of the 45 children for antiretroviral treatment and 22 for corticosteroid treatment. Height for age and gender percentile was available for 36 children, and triglyceride level was available for 26 of the 45 children. In most cases, the missing data correspond to the prevalent cases and respective controls diagnosed before 1994 whose values fell outside the 2-year window or they were not routinely collected in PACTG studies on which these children were coenrolled.

Before the LCPD diagnosis date for the LCPD cases (index cases), 67% of cases (4/6) and 79% of controls (31/39) had received treatment with at least 1 NRTI; 17% (1/6) of cases and 13% (5/39) of controls had been treated with an NNRTI; and 33% of cases (2/6) and 13% (5/39) of controls had been treated with at least 1 PI. Ten children (2 LCPD cases and 8 controls) had received no antiretroviral therapy before the index case’s LCPD diagnosis (which occurred in 1990, 1991, and 1993). Fifty percent of cases (3/6) and 41% (16/39) of controls had received treatment with corticosteroids before the index case’s LCPD diagnosis. Seventeen percent of cases (1/6) and 10% of controls (4/39) weighed <2500 g at birth;
50% of cases (3/6) and 23% of controls (9/39) were <10th height for age, gender percentile; and 40% of cases (2/5) and 29% of controls (7/24) had triglyceride levels >150 mg/dL.

Table 4 provides the unadjusted odds ratio and 95% exact CI for the association of LCPD with antiretroviral drug class, corticosteroid therapy (systemic and topical), CD4 cell percentage, birth weight, height for age and gender percentile, and triglyceride level. None of the covariates showed statistically significant associations with development of LCPD.

**DISCUSSION**

Data from our large prospective cohort of over 2800 HIV-exposed and infected children indicate a 9.0-fold increase in the age-adjusted prevalence rate and 4.8-fold increase in the age-adjusted incidence rate of osteonecrosis of the hip in children with perinatal HIV infection compared with the general pediatric population. LCPD cases occurred exclusively among children with HIV infection, with no cases in the 849 uninfected children followed in PACTG 219.

The most common form of osteonecrosis in children is LCPD. In the general pediatric population, LCPD occurs between 2 and 12 years of age, with a median age of 7 years, and is more common in males. LCPD is most prevalent in white and Chinese children, and is very uncommon among black, non-Hispanic, or Native American children. The ratio of white, non-Hispanic children to black, non-Hispanic children is approximately 10 to 1. LCPD is usually confined to one hip, although bilateral disease is observed in 10% of cases.

Reports of osteonecrosis in HIV-infected children are rare. The HIV-infected children with osteonecrosis in the PACTG 219 cohort differed in race/ethnicity and gender from the traditional child with LCPD. Four of the 6 infected children were of minority race/ethnicity, and 2 were female. Bilateral disease was observed in 1 child; an increased frequency of multisite osteonecrosis has been described in HIV-infected adults.

Half of the HIV-infected children with LCPD were below the third percentile height at the time of diagnosis. Abnormal growth, as demonstrated by low birth weight and delayed bone age, is a reported risk factor for LCPD in the general pediatric population. Deficits in growth are common in HIV-infected children, and growth failure has been associated with elevated viral load. In hemophilic boys, HIV-infected children with abnormal growth were found to have a significantly lower bone age than HIV-infected hemophiliacs without growth abnormalities and to have reduced androgen and growth hormone production compared with noninfected hemophiliacs. Deficits in bone mineral mass and calcitropic hormones were described in a study of young girls with perinatal HIV infection. Thus, HIV-infected children may have an increased risk of LCPD compared with the general population because of the growth deficits found in infected children.

A possible genetic predisposition to LCPD in the general pediatric population has been reported. Some studies have suggested that familial clustering may be attributable to inherited hyperfibrinolysis coagulation disorders (thrombophilia). In 1 study, 13% of children with LCPD were found to have the factor V Leiden mutation, an inherited defect more frequent in whites than blacks and associated with resistance to activated protein C, resulting in an increased tendency to clot. Low levels of glycoproteins protein C and protein S, also associated with increased clotting, have also been described among children with LDPD. Thrombophilic disorders can also be acquired; antiphospholipid antibodies can occur in collagen vascular diseases and are also stimulated by scarlet fever and some viral infections (eg, varicella, hepatitis, measles, and HIV). In a study of 34 symptomatic HIV-infected children, 77% were found to have decreased free protein S, and 56% had levels more than 2 standard deviations below normal. In HIV-infected adults, acquired protein S deficiency has been described, and a possible association between the presence of antiphospholipid antibodies and osteonecrosis has been described. Thus, HIV-infected children and adults could be at higher risk of osteonecrosis because of an increase in hyperfibrinolysis clotting disorders.

HIV-infected adults with osteonecrosis often have predisposing risk factors, such as cigarette smoking, excessive alcohol use, fatty liver, pancreatitis hyperlipidemia, or corticosteroid use. The increase in reports of osteonecrosis in HIV-infected adults during the late 1990s led to speculation that it may be linked to potent antiretroviral therapy, in particular with PI therapy and its known association with hyperlipidemia. However, several case-control studies have not found an association with antiret-

**TABLE 4. Estimated Odds Ratios for LCPD From the Case-Control Study**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% Exact CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroid</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.28 (0.11, 13.1)</td>
</tr>
<tr>
<td>No</td>
<td>1.0</td>
</tr>
<tr>
<td>NRTI</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.30 (0.004, 9.86)</td>
</tr>
<tr>
<td>No</td>
<td>1.0</td>
</tr>
<tr>
<td>NNRTI</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.29 (0.02, 36.3)</td>
</tr>
<tr>
<td>No</td>
<td>1.0</td>
</tr>
<tr>
<td>PIs</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.71 (0.13, +∞)</td>
</tr>
<tr>
<td>No</td>
<td>1.0</td>
</tr>
<tr>
<td>CD4 lymphocyte percentage</td>
<td></td>
</tr>
<tr>
<td>&lt;15%</td>
<td>0.59 (0.01, 12.0)</td>
</tr>
<tr>
<td>15%–24%</td>
<td>1.36 (0.15, 16.9)</td>
</tr>
<tr>
<td>≥25%</td>
<td>1.0</td>
</tr>
<tr>
<td>Birth weight</td>
<td></td>
</tr>
<tr>
<td>&lt;2500 g</td>
<td>2.58 (0.03, 222)</td>
</tr>
<tr>
<td>≥2500 g</td>
<td>1.0</td>
</tr>
<tr>
<td>Height for age and gender percentile</td>
<td></td>
</tr>
<tr>
<td>&lt;10th</td>
<td>2.25 (0.15, 33.2)</td>
</tr>
<tr>
<td>≥10th</td>
<td>1.0</td>
</tr>
<tr>
<td>Triglyceride level</td>
<td></td>
</tr>
<tr>
<td>&gt;150 mg/dL</td>
<td>1.49 (0.02, 31.8)</td>
</tr>
<tr>
<td>≤150 mg/dL</td>
<td>1.0</td>
</tr>
</tbody>
</table>

http://www.pediatrics.org/cgi/content/full/109/5/e74
roviral therapy; the most common risk factor has been previous treatment with systemic corticosteroids. Similar to the adult studies, antiretroviral therapy was not an independent predictor of osteonecrosis in our study; the majority of cases and controls had been treated with antiretrovirals before the index case’s LCPD diagnosis and 4 of the cases were diagnosed before the availability of PIs. Also similar to data in infected adults, osteonecrosis was not associated with CD4 lymphocyte number, occurring in children with normal as well as low CD4 cell percentage.

Fifty percent of HIV-infected children with LCPD in PACTG 219 had received corticosteroid therapy before the development of disease; however, only 1 had received systemic steroids, whereas 2 had topical exposure only. The relationship of topical corticosteroids use and osteonecrosis is controversial. Two cases of osteonecrosis of the femur have been described in adults uninfected with HIV after topical administration corticosteroids for several years (approximately 3–4 years). It was speculated that long-term administration of topical steroids could result in an alteration of the skin penetration barrier, with transcutaneous absorption of the drugs leading to exposure that might be comparable to a high systemic dose of corticosteroids. However, in our cohort, 1 of the 2 children with LCPD who had been treated with topical corticosteroids had received only slightly >1 month of treatment. In addition, a similar percentage of cases and controls had received corticosteroid treatment, suggesting that steroid use is an unlikely explanation for the increased incidence of LCPD among HIV-infected children.

It is important to note that although each PACTG 219 visit includes a physical examination, the visits do not include orthopedic-targeted physical or laboratory evaluations either at the time of enrollment or during follow-up that would allow for an early diagnosis of LCPD. Data on orthopedic conditions were obtained through medical record review. However, the children are seen regularly for examinations, which could lead to more complete ascertainment of LCPD in this group than in the general population. Concern for potential ascertainment bias was the primary motivation for distinguishing between prevalent and incident cases.

The number of LCPD cases in our cohort was small, limiting the power to detect associations with covariates included in the case-control analysis and yielding wide 95% CIs for odds ratios. We tried to minimize confounding by matching on race, gender, and age, all known risk factors for LCPD in uninfected children. Additionally, we could evaluate only information available in the database, which included medical record review and laboratory evaluations performed for routine clinical care, and thus could not evaluate potential risk factors such as hypercoagulation disorders. Finally, the young age of the HIV-uninfected population in PACTG 219 made comparison of the infected and uninfected cohorts impossible, as the uninfected cohort is just now, at the median age of 3 years, entering into the period of higher risk for LCPD.

However, our data indicate that the increased incidence of osteonecrosis of the hip observed in HIV-infected adults also occurs in HIV-infected children, and that clinicians should be alert to this diagnosis in HIV-infected children presenting with hip pain or limp. Two of the children reported in our series have had significant morbidity from LCPD. Whether LCPD is attributable to HIV infection itself, HIV-associated complications that could predispose one to thrombosis, HIV therapies, or to the growth abnormalities in HIV-infected children is unknown and deserves additional investigation.

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