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High Rate of Coronary Artery Abnormalities in Adolescents and Young Adults Infected with Human Immunodeficiency Virus Early in Life

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Abstract

We completed a cross-sectional study of individuals infected with HIV in early childhood using cardiac MRI and MRA. Coronary artery abnormality (CAA) was defined by the presence of luminal narrowing and irregularity of the coronary vessel wall. More than 50% of participants (14/27) had evidence of CAA. Individuals had a high rate of CAA, suggesting possible early atherosclerosis.

Keywords

HIV; Pediatric; Coronary Artery Abnormality; Coronary MRI; Cardiovascular

INTRODUCTION

In the age of highly active antiretroviral therapy (HAART), children infected with human immunodeficiency virus (HIV) are reaching older ages. With this improved survival, deleterious outcomes in almost all organs, including the cardiovascular system, are being reported[1]. The increased cardiovascular disease (CVD) is attributed to traditional risk factors[2] and HIV specific factors including direct effects of HIV, microbial translocation, immune activation, co-infections and HAART [3],[4].

Recent studies in HIV-infected adults have looked at early sub-clinical CVD. Lo *et al*[5] found the rate of subclinical coronary artery atherosclerosis to be higher in HIV-infected men compared with age-matched controls. Data on the pediatric population are scant[1]. Until recently, technology to evaluate this younger population consisted mainly in using

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echocardiograms[6] or carotid ultrasound[7]. Although coronary computed tomography (CT) has provided a non-invasive method of investigating early atherosclerotic lesions in the adult population, its use is limited in children because of concerns about radiation exposure. The introduction of high field MR scanners (3 Tesla) [8],[9] provides an excellent opportunity to study the early cardiovascular changes in the younger population.

MATIERALS AND METHODS

Subjects and Data Collection

We performed a cross-sectional analysis of 27 individuals who acquired HIV early in life and who are followed longitudinally in an observational study at the National Institutes of Health (NIH). Enrollment for the cardiac imaging was from November 2008 to February 2009. The National Institute of Allergy and Infectious Diseases' institutional review board approved the protocol. Written informed consent was obtained from all patients, parents or legal guardians. Assent was obtained from minors when developmentally appropriate.

Study participants completed a detailed clinical evaluation including medical history, history of antiretroviral (ARV) exposure, opportunistic infections, co-morbidities and smoking (past and current). Participants also had a physical examination including height, weight and hip and waist circumference (obtained by registered dieticians using standardized techniques). Laboratory evaluation included fasting lipid profile, high sensitivity C-reactive protein (CRP), Pro-brain natriuretic peptide (proBNP), D-Dimer, Homocysteine, lymphocyte phenotype and HIV viral load.

All cardiac MRI/MRA studies were performed at the NIH under the supervision of a single radiologist (AMG) using a commercial 3T MRI scanner. Subjects received up to 0.3 mmol/kg gadolinium based contrast agent intravenously. MR images were evaluated using commercially available software (AZE, Tokyo, Japan). Each subject had three separate sequences to evaluate their coronary vessels. These included targeted high resolution approach (1), whole heart without (2) and with contrast (3). To ensure that the findings were not motion artifacts, only the lesions seen in the same location of the vessel on the three prescribed sequences were considered true findings. Coronary vessels were evaluated for abnormality based on the following classification: 0 – normal coronaries without irregular wall; 1- minimal coronary irregularity of the vessel wall without affecting the lumen diameter; 2- mild coronary irregularity of the vessel wall causing less than 25% narrowing of the vessel lumen; 3- moderate irregularity of the vessel wall causing 25% –50% narrowing of the vessel lumen. MRIs classified as a 2 or 3 were considered abnormal. This classification scale is a minor modification from that used by Kim et al.[8], which was chosen to capture all evidence of abnormality.

2D echocardiogram and EKG were performed at the NIH and interpreted by NIH cardiologists. All echo, EKG and MRI studies were confirmed by independent cardiologists from Children's National Medical Center (SC and RC).

Statistical Analyses

General characteristics are summarized using mean and standard deviation. Comparisons between subjects with and without coronary artery abnormalities (CAA) were made using Kruskal-Wallis tests and chi-square statistics for non-continuous variables. A multivariate regression model was used to identify possible independent predictors and included factors identified in univariate analysis as potentially important in CAA. All statistical analyses were performed using SAS JMP Statistical Software (Version 7.0, SAS Institute Cary, NC), and two-tailed alpha level of 0.05 was used to determine statistical significance.

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RESULTS

Twenty-seven subjects were able to complete MRI. Their characteristics are shown in Supplemental Digital Content 1 (Table). The mean age was 18.9±3.4 years with a range from 13–29 years, 41% subjects were male, 37% subjects were white, 44% were African American, 93% had acquired HIV perinatally, 100% had ARV exposure, 70% had undetectable HIV viral loads, 18% had history of ever smoking. Mean CD4 count was 652 copies/mL. Mean duration of ARV exposure was 15.0 years.

Seven subjects had previous known cardiac conditions, including one subject each with tetralogy of fallot repaired in infancy, resolved aortic insufficiency, a history of aortic septal defect, a history of viral pericarditis, cardiomyopathy of unknown origin and two subjects with Zidovudine related cardiomyopathy that had resolved. None of the subjects had cardiac symptoms at the time of evaluation.

Similar to previous cohorts, the study revealed a high percentage of traditional cardiac risk factors including 7.4% with high cholesterol (total fasting cholesterol > 200 mg/dL), 26% with elevated triglycerides (total fasting triglycerides > 150 mg/dL), and 37% with low HDL (HDL < 40 mg/dL). One subject was being treated for hypertension with medication and had controlled blood pressures during study visits.

More than half (14/27) of the subjects had CAA with luminal narrowing detected on MR angiography; 13 classified as level 2 and 1 classified as level 3. Based on the cardiologists' clinical recommendation, the subject classified with a level 3 had a coronary CT, which corroborated findings of atherosclerotic disease.

There was no association between previous cardiac conditions and CAA. Two of the 14 patients with CAA had a history of cardiac complications including viral pericarditis and Zidovudine-related cardiomyopathy. The remaining 12 patients with CAA did not have previous cardiac conditions. Two of the subjects with CAA (and none of the patients without abnormalities) had ejection fraction (EF) abnormalities (EF < 55 %).

Interestingly, there was no increase in years of protease inhibitor or total ARV exposure in subjects with CAA. However, subjects with abnormalities had greater duration of exposure to tenofovir (2.3 years vs. 0.84 years, p=0.005) and emtricitabine (1.2 years vs. 0.29 years, p=0.01). Although not statistically significant, subjects with CAA tended to have higher LDL cholesterol (92 mg/dL vs. 78 mg/dL, p=0.24), higher CRP (0.29 mg/dL vs. 0.12 mg/dL, p=0.20) and were more likely to have a history of smoking (29% vs. 8%, p=0.17). There was no difference in D-Dimer, homocysteine, proBNP, HIV viral load or CD4 count between those with and without CAA. In a multivariate regression analysis that included tenofovir years, emtricitabine years, LDL, CRP and smoking, only history of smoking was a significant predictor of CAA (p=0.03).

DISCUSSION

The high rate of CAA seen in adolescents and young adults who acquired HIV early in life suggests possible early atherosclerosis in this population. The advent of new, less invasive technology allows better understanding of early changes. Because of the novelty of the technology, normative values are unavailable. However, one would not expect a high rate of CAA in this population. Coronary artery calcium has been used as a measure of early, subclinical disease in a healthy young adult population with a similar age distribution (18–30 years), which identified an overall prevalence of 9.3% of patients with coronary artery calcium[10]. MRI technology has been validated for detecting severe CAD, but has not been

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validated for detecting pre-clinical or minimal disease. We did an internal validation by requiring each lesion to be seen in three sequences in the same location.

The changes seen most probably signify vessel wall thickening as a result of early plaque development. Inflammation plays an important role in plaque development, especially at the early stages and in HIV related vasculopathy[11]. Therefore, the exact etiology of wall thickening cannot be determined in this small study and can represent either inflammation or CAD

In this small cross-sectional study, causality cannot be established and interpretation of associations with individual ARV medications must be made with caution. Tenofovir DF and emtricitabine have not been previously reported as increasing the risk of CVD in HIV and their association does not persist in multivariate analyses. Smoking history, which has more physiologic relevance, appears to be a more relevant predictor of CAA. However, because of the small sample size, it is difficult to make conclusions about specific risk factors. These preliminary data do highlight the importance of examining sub-clinical disease. Studying early disease is critical to identifying modifiable risk factors and to understanding disease progression, which will aid in developing appropriate screening methods and interventions.

A considerable portion of the study participants had previous cardiac conditions. This may be related to the risk of acquiring HIV from surgery-related blood transfusions during the 1980s and the cardiotoxic effects of both untreated HIV and medications used in HIV treatment. However, the patients with prior cardiac conditions were not more likely to have CAA.

There are several limitations with the current study including a small sample size, lack of a control group and the use of novel MR technology. Despite these limitations, the current report is among the first to identify early atherosclerosis in the population of young adults and adolescents with the greatest lifetime exposure to HIV and its therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCESS

1. Hazra R, Siberry G, Mofenson L. Growing up with HIV: Children, Adolescents, and Young Adults with Perinatally Acquired HIV Infection. Annu Rev Med. 2010; 61:169–185. [PubMed: 19622036]
2. Hadigan C, Meigs J, Corcoran C, Rietschel P, Piecuch S, Basgoz N, et al. HIV/AIDS Major Article: metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infection and lipodystrophy. Clin Infec Dis. 2001; 32:130–139. [PubMed: 11118392]
3. Grunfeld C, Delaney JA, Wanke C, Currier JS, Scherzer R, Biggs ML, et al. Preclinical atherosclerosis due to HIV infection: carotid intima-medial thickness measurements from the FRAM study. J Acquir Immune Defic Syndr. 2009; 23:1841–1849.

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4. Lorenz MW, Stephen C, Harmjanz A, Staszewski S, Beuhler A, Bickel M, et al. Both long-term HIV infection and highly active antiretroviral therapy are independent risk factors for early carotid atherosclerosis. Atherosclerosis. 2008; 196:720–726. [PubMed: 17275008]

5. Lo J, Abbara S, Shturman L, Sonii A, Wei J, Rocha-Filho J, et al. Increased prevalence of subclinical coronary atherosclerosis detected by coronary computed tomography angiography in HIV-infected men. J Acquir Immune Defic Syndr. 2010; 24:243–253.

6. Fisher SD, Easley KA, Orav EJ, Colan SD, Kaplan S, Starc TJ, et al. Mild dilated cardiomyopathy and increased left ventricular mass predict mortality: the prospective P2C2 HIV Multicenter Study. Am Heart J. 2005; 150:439–447. [PubMed: 16169321]

7. Ross AC, O'Riordan MA, Storer N, Dogra V, McComsey GA. Heightened inflammation is linked to carotid intima-media thickness and endothelial activation in HIV-infected children. Atherosclerosis. 2010 in press.

8. Kim WY, Danias PG, Stuber M, Flamm SD, Plein S, Nagel E, et al. Coronary magnetic resonance angiography for the detection of coronary stenoses. N Engl J Med. 2001; 345:1863–1869. [PubMed: 11756576]

9. Gharib AM, Ho VB, Rosing DR, Herzka DA, Stuber M, Arai AE, et al. Coronary artery anomalies and variants: technical feasibility of assessment with coronary MR angiography at 3 T. Radiology. 2008; 247:220–227. [PubMed: 18372470]

10. Yan L, Daviglus M, Colangelo L, Kiefe C, Sidney S, Matthews K, et al. Education, 15-year risk factor progression, and coronary artery calcium in young adulthood and early middle age: the coronary artery risk development in young adults study. JAMA. 2006; 295:1793–1800. [PubMed: 16622141]

11. Sanz J, Fayad Z. Imaging of atherosclerotic cardiovascular disease. Nature. 2008; 451:953–957. [PubMed: 18288186]