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Elevated Aspartate Aminotransferase-to-Platelet Ratio Index in Perinatally HIV-infected Children in the United States

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Abstract

Elevated aspartate aminotransferase-to-platelet ratio index (APRI) may signal liver fibrosis. Among 397 US children with perinatal HIV infection, APRI at baseline was > 1.5 in 0.8% (95% confidence interval [CI], 0.2–2.2%) and > 0.5 in 6.5% (95%CI, 4.3–9.4%); incidence on study was 0.5 (95%CI, 0.2–1.2) and 6.4 (95%CI, 4.8–8.3) per 100 person-years, respectively. Long-term liver outcomes after perinatal HIV infection warrant further study.

Keywords

HIV; liver; APRI

Chronic liver disease has emerged as an important problem in adults with longstanding HIV infection [1,2]. The burden of clinically recognized liver disease appears to be much lower in HIV-infected children than that in adults [3,4]. APRI [aspartate aminotransferase (AST)-to-platelet ratio index] has been validated against liver biopsy as an indicator of liver fibrosis in adults with hepatitis C (HCV)-HIV coinfection and in children with viral hepatitis [5,6].

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In children with viral hepatitis, APRI > 0.5 and APRI > 1.5 have identified liver fibrosis on biopsy with specificity of 90% and 100% and sensitivity of 47% and 18%, respectively [6]. The purpose of this study was to characterize APRI as a marker of possible liver fibrosis in a U.S. cohort of perinatally HIV-infected children.

METHODS

The Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort study is an ongoing prospective cohort study designed to evaluate the impact of HIV-infection and antiretroviral therapy on youth with perinatal HIV-infection. Between March 2007 and December 2009, 451 infected youth from 15 study sites in the United States were enrolled if they were born to HIV-infected mothers, were 7 up to 16 years of age and had complete medical history of antiretroviral therapy use, plasma HIV RNA (viral load) concentrations, and lymphocyte subset measurements since birth. AMP was approved by the institutional review board at the Data and Operations Center (Harvard School of Public Health) and at each participating site. Written informed consent was obtained from each participant's parent or legal guardian. Assent was obtained from child participants according to local institutional review board guidelines. Demographic and clinical characteristics at enrollment and between study visits were collected primarily through medical chart abstraction. Only race and ethnicity were self-reported. APRI was calculated as [(AST/Upper Limit of Normal)/platelet count (10^9/L)] * 100, using local laboratory AST upper limit of normal. Covariates considered as potential predictors of incident APRI included: age, race, ethnicity, body mass index (BMI) for age z-score, reported diagnosis of hepatitis B (HBV) or C (HCV) virus infection, alanine aminotransferase (ALT), homeostatic model assessment of insulin resistance (HOMA-IR), fasting total cholesterol and triglycerides, viral load, CD4 count and nadir CD4 count at first APRI measurement; ever use and duration of protease inhibitor (PI)-based antiretroviral therapy (ART); ever use and duration of didanosine; and ever use and duration of hepatotoxic ART and non-ART medications which were defined based on clinician review (medication details in Table 1 footnote).

Prevalence of APRI>0.5 and >1.5 at the first APRI measurement (i.e., baseline) was defined as the number of children with APRI >0.5 or >1.5 divided by the number of children with at least one APRI measurement. Incident cases of APRI>0.5 and >1.5 were defined as the number of new cases of APRI >0.5 or >1.5 divided by the person-years at risk for either APRI>0.5 or >1.5 (i.e., excluding prevalent cases at baseline). Baseline predictors of incident APRI >0.5 were identified using Wilcoxon and Fisher's Exact tests as appropriate. A mixed-effects model with time as the independent variable and an assumed first order auto-regressive correlation structure was used to describe changes in APRI over the study follow-up period, including all study visits at which an APRI could be calculated.

RESULTS

Of 451 perinatally HIV-infected children participating in AMP, 402 had at least one AST measure recorded; 397 had a platelet value within 2 weeks of their AST making them eligible for inclusion. Participants were 52% female, 74% black race, and 23% Hispanic. At baseline, the mean BMI z-score was 0.4 and mean age was 12.4 years (Table). Four

participants (1%) reported HBV infection and four reported HCV infection. Most (368, 93%) were receiving ART; PI-containing ART was most common (285, 72%). The majority of participants had virologic suppression (65% with viral load ≤ 400 copies/mL) and high CD4 counts (mean 754 cells/mm^3).

At baseline, APRI exceeded 0.5 in 26 (6.5%, 95% confidence interval [CI]: 4.3–9.4%) participants and exceeded 1.5 in 3 (0.8%, 95% CI: 0.2–2.2%) participants (Table 1). Among 371 participants whose initial APRI was ≤ 0.5 at baseline, 55 developed an APRI > 0.5 while on study (860 person-years [PY] at risk; median [range] follow-up time, 2.5 [0–4.9] years) for an incidence of 6.4 (95% CI: 4.8–8.3) per 100 PY; among 394 subjects whose initial APRI was ≤ 1.5 at baseline, 5 developed an APRI > 1.5 on study (986 PY at risk; median [range] follow-up time, 2.9 [0–4.9] years) for an incidence of 0.5 per 100 person-years (95% CI: 0.2–1.2 per 100 PY). The only predictor of incident elevation in APRI was higher baseline ALT: mean ALT was 28.3 vs. 20.6 mU/mL (p=0.01) for those who did vs. those who did not have an incident APRI > 0.5. No other baseline factors predicted incident elevation in APRI. Among the 4 participants with HCV infection, one had APRI > 0.5 at baseline and one had incident APRI > 0.5 on study but none had APRI > 1.5. None of the 4 participants with HBV infection ever had APRI > 0.5; all four were receiving two ARV drugs with anti-HBV activity at the time of initial and follow-up APRI measurements. Among the 8 participants with an APRI > 1.5 at least once, 7 had at least 3 APRI measurements, of which 3 (43%) had ≥50% of APRI measurements > 1.5. Among the 81 participants with at least one APRI > 0.5, 76 had at least 3 APRI measurements, of which 22 (29%) had APRI > 0.5 on at least 50% of those measurements. There was a significant trend for small increases in APRI over time (slope = 0.0001/week. p = 0.04) among participants whose baseline APRI was ≤ 0.5.

DISCUSSION

This investigation of potential liver fibrosis in a cohort of US children with perinatal HIV infection revealed a low level of APRI elevation at baseline. However, incident APRI elevations continued to occur and APRI values appeared to increase throughout the study period. The small magnitude of the risk of APRI elevation is largely reassuring about the status of liver health in perinatally HIV-infected children but this optimistic interpretation is tempered by the relatively low sensitivity of these APRI cut-offs for detecting liver fibrosis in children [6]. In addition, the lack of APRI elevation risk associated with ARV treatment duration or specific ARV classes and agents affirms findings in studies of HIV mono-infected adults that chronic ARV treatment does not increase the risk of elevated APRI [8–10]. The 0.8% prevalence of APRI > 1.5 in this pediatric cohort appears lower than rates of 3.0–3.9% reported in several studies of HIV-infected adults [7–9] and much lower than the 8% rate observed in one adult study [10]. This lower prevalence among HIV-infected children is likely attributable to lower rates in HIV-infected children compared to HIV-infected adults of other factors that contribute to liver problems, such as viral hepatitis and alcohol use (only 36% of perinatal HIV AMP participants reported alcohol use [11]). The prevalence of APRI > 1.5 in this US pediatric cohort is also substantially lower than the 3.2% prevalence reported in a large group of children in Latin America [12]. In addition to possible differences in host genetic factors and environmental exposures, children in the US

PHACS cohort were older than children in the Latin American study and had received ART for a longer time. In the Latin American children, markers of ineffective HIV treatment also increased the risk of APRI elevation. Taken together, the two pediatric studies support the reassuring idea that longer and better ARV treatment lead to lower, not higher, risk of APRI elevation. Since liver diseases are often associated with progressive fibrosis, the observed signal of a small increase in APRI over time is of concern for these children who have long lives ahead of them, and careful follow-up is warranted.

While the finding of elevated APRI does not prove the presence of liver fibrosis in these HIV monoinfected children, APRI has been validated against liver biopsy findings for identifying liver fibrosis in adults with HIV-HCV co-infection [13] and in children with viral hepatitis[6]. Studies that use elastography or even liver biopsy in HIV-monoinfected children with persistently elevated APRI will be important for evaluating the risk and outcome of liver fibrosis and for validating the use of APRI in children for this purpose. While the dominant effect of HAART appears to be beneficial for liver outcomes, the potential for toxicity related to specific agents and comorbidities merits evaluation in long-term studies.

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Table 1

Baseline[1] demographic and clinical characteristics by APRI

		APRI			
		Prevalent		Incident	
Characteristic	**Total (N=397)**	**>1.5 (N=3)**	**>0.5 (N=26)**	**>1.5 (N=5)**	**>0.5 (N=55)**
Age (years)					
Mean (SD)	12.4 (2.7)	12.6 (4.2)	13.1 (2.5)	14.5 (3.1)	12.2 (2.8)
Median	12.6	11.3	13.5	16.0	12.7
Q1, Q3	10.3, 14.5	9.2, 17.3	11.0, 15.1	15.1, 16.1	9.2, 14.7
Female Sex, N (%)	208 (52)	1 (33)	14 (54)	4 (80)	31 (56)
Black Race, N (%)	293 (74)	3 (100)	20 (77)	2 (40)	40 (73)
Hispanic, N (%)	89 (23)	0 (0)	6 (23)	2 (40)	10 (18)
Mean (SD) BMI-for-age z-score	0.4 (1.1)	0.1 (1.4)	0.5 (1.2)	0.8 (0.9)	0.2 (1.0)
Ever Hepatitis B diagnosis, N (%)	4 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Ever Hepatitis C diagnosis, N (%)	4 (1)	0 (0)	1 (4)	0 (0)	1 (2)
Mean (SD) ALT, mU/mL	22.7 (17.0)	33.7 (31.6)	35.4 (21.9)	66.2 (99.5)	28.3 (32.7)
Mean (SD) AST, mU/mL	29.4 (13.2)	78.7 (73.0)	53.0 (31.5)	31.6 (15.4)	31.7 (11.3)
Mean (SD) AST/ULN	0.7 (0.3)	2.2 (1.7)	1.4 (0.7)	0.9 (0.5)	0.8 (0.2)
Mean (SD) Platelet, $10^3/mm^3$	280.7 (77.1)	121.0 (123.0)	187.4 (77.0)	244.2 (87.0)	252.9 (66.8)
Mean (SD) CD4 count, cells/mm^3	753.5 (368.8)	312.3 (277.8)	555.7 (329.1)	510.0 (314.8)	726.3 (330.4)
Mean (SD) Nadir CD4 count (cells/mm^3)	383.1 (256.5)	165.7 (145.4)	285.0 (272.7)	242.4 (131.9)	382.6 (263.2)
Viral load ≤400 copies/mL, N (%)	256 (65)	2 (67)	11 (42)	4 (80)	37 (67)
ART, N(%)					
PI-based	285 (72)	2 (67)	21 (81)	4 (80)	42 (76)
Non-PI based	83 (21)	1 (33)	4 (15)	0 (0)	10 (18)
None	29 (7)	0 (0)	1 (4)	1 (20)	3 (5)
DDI use, N (%)	82 (21)	1 (33)	6 (23)	0 (0)	10 (18)
Hepatotoxic ART use[2], N (%)	364 (92)	3 (100)	25 (96)	4 (80)	51 (93)
Mean (SD) duration of use (years)					
PI-based ART	6.8 (3.8)	5.9 (4.6)	7.3 (3.5)	9.2 (1.2)	6.4 (3.9)

		APRI			
		Prevalent		Incident	
Characteristic	**Total (N=397)**	**>1.5 (N=3)**	**>0.5 (N=26)**	**>1.5 (N=5)**	**>0.5 (N=55)**
Non-PI-based ART	3.5 (3.5)	4.6 (2.6)	3.8 (3.2)	3.3 (2.8)	3.3 (3.7)
DDI use	3.2 (3.5)	3.4 (2.9)	4.1 (3.9)	6.9 (4.6)	3.5 (4.1)
Hepatotoxic ART use[2]	10.2 (3.0)	10.5 (3.4)	11.0 (2.3)	12.5 (2.5)	9.7 (3.6)
Non-ARV hepatotoxic medication use[3], N (%)	126 (32)	1 (33)	12 (46)	1 (20)	20 (36)

[1]Baseline defined as date of the 1st aspartate aminotransferase-to-platelet ratio index (APRI) measurement.

[2]Hepatotoxic ART included: Abacavir, Stavudine, Zalcitabine, Didanosine, Zidovudine, Nevirapine, Efavirenz, Delavirdine, Amprenavir, Lopinavir/ritonavir, Nelfinavir, Ritonavir, Saquinavir, Tipranavir;

[3]Non-ARV hepatotoxic medications included: (des)loratadine, phenylpropanolamine, Cyproheptadine, amphotericin B, griseofulvin, ketoconazole, terbinafine, cefadroxil, cefprozil, cefpodoxime, cefdinir, loracarbef, clarithromycin, doxycycline, Trimethoprim-sulfamethoxazole, fluconazole, ceftazidime, ceftriaxone, cephalexin, erythromycin, isoniazid, acyclovir, ganciclovir, azithromycin, pentamidine, phenobarbital, vitamin B complex, clindamycin, linezolid, rifabutin, oseltamivir, ofloxacin, levofloxacin, moxifloxacin, sulfasalazine, sulfisoxazole, diaminodiphenylsulfone, atovaquone, cyclobenzaprine, atenolol, enalapril, fish oil, pravastatin, fenofibrate, atorvastatin, ezetimibe, nitrous oxide, ultane, ketorolac, naproxen, acetaminophen, divalproex, Levetiracetam, Topiramate, Anafranil/clomipramine, Venlafaxine, Duloxetine, Quetiapine, triazolam, Atomoxetine, hyperalimentation, Candesartan, docusate, ondansetron, omeprazole, ranitidine, methylprednisolone, testosterone, Phenazopyridine, vitamin E. BMI: Body Mass Index, ART: antiretroviral therapy, PI: Protease Inhibitor, DDI: didanosine, ARV: antiretroviral