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Proteinuria is Associated with Neurocognitive Impairment in Antiretroviral Therapy Treated HIV-infected Individuals

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Abstract

Background—Proteinuria is a marker of vascular dysfunction that predicted increased cardiovascular mortality, and was associated with neurocognitive impairment (NCI) in population-based studies. We examined associations between proteinuria and HIV-associated NCI.

Methods—Multivariable logistic regression was used to examine associations between NCI at the first neurocognitive assessment (baseline) and simultaneous, clinically significant proteinuria (as random spot urine protein-to-creatinine ratios [UP/Cr] \geq 200 mg/g) in a prospective multicenter observational cohort study. Generalized estimating equations were used to examine associations between baseline proteinuria and subsequent NCI among subjects without NCI at baseline. NCI was defined as a z-score, derived from the combination of normalized scores from the Trailmaking A & B and the Wechsler Adult Intelligence Scale-Revised Digit Symbol tests.

Results—1,972 subjects were included in this analysis. Baseline proteinuria was associated with increased odds of NCI (OR: 1.41 [95% C.I., 1.08 to 1.85]; $P=0.01$), and with subsequent NCI among subjects without NCI at baseline (OR=1.39 [95% C.I., 1.01 to 1.93], $P=0.046$) in multivariable models adjusted for risk factors and potential confounders. Similar associations were evident when these analyses were limited to visits at which time study subjects maintained plasma HIV RNA levels $<$ 200 copies/mL.

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Conflicts of Interest: David Clifford serves a consultant for Biogen, Idec, Millennium, Bristol Myers Squibb, Pfizer, Genzyme, Amgen, Quintiles, Genetech and AstraZeneca and received honoraria for lectures from Sun Biopharma; Robert Kalayjian is currently receiving a grant from Gilead (GS-US-292-0112). For the remaining authors none were declared.

Conclusions—The association between proteinuria and NCI observed in this study adds to a growing body of evidence implicating contributions by vascular disease to NCI in antiretroviral treated individuals. Studies examining interventions that improve vascular function are warranted.

INTRODUCTION

HIV associated neurocognitive disorders (HAND) encompass a spectrum of neurologic conditions ranging from asymptomatic neurocognitive impairment to HIV-associated dementia [1]. Antiretroviral therapy (ART) substantially improves neurocognitive function and was associated with dramatic declines in the incidence of HIV-associated dementia [2-7], but neurocognitive dysfunction that was predominately mild or asymptomatic could be detected in 22% to 59% of ART treated patients [4, 8, 9]. Neither plasma nor cerebrospinal fluid HIV RNA concentrations was associated with the presence or severity of neurocognitive impairment (NCI) in ART treated patients [4, 10], but associations between vascular disease and NCI are increasingly recognized [11-14].

Proteinuria is a marker of kidney injury and vascular dysfunction. Comprised predominately of albumin, proteinuria or albuminuria predicted increased risks of cardiovascular and all-cause mortality in population-based studies [15-18], and similar associations also were observed in large observational studies of HIV-infected individuals [19-22]. Herein, we explored the relationship between proteinuria and NCI in ART treated HIV-infected participants of a multicenter prospective observational study who underwent annual neurocognitive testing and urine protein measurements.

METHODS

Study Participants

Established in 2000, the AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) study is a multicenter observational cohort study that co-enrolled participants from ACTG randomized clinical trials of ART (parent clinical trial) for longitudinal follow-up [23]. Participants underwent neurocognitive testing soon after entry to ALLRT, and every 48 weeks later.

Neurocognitive impairment was assessed using normalized NPZ-3 scores, derived from the combination of Trailmaking A & B and the Wechsler Adult Intelligence Scale-Revised Digit Symbol tests. Raw scores for each of these three tests were normalized by age, sex and race/ethnicity (as black non-Hispanic, white non-Hispanic or Hispanic) as Z-scores (NPZ-3 score) [24]. NCI was defined as 1 standard deviation (SD) below zero on at least two normalized scores, or 2 SDs below zero on at least one normalized score. Written and verbal instructions were primarily given in English, while there was an option for bilingual and monolingual Spanish-speaking subjects to receive written and verbal instructions in Spanish.

Urine protein and creatinine concentrations were measured from random spot urine samples that were collected every 48 weeks and calculated as the ratio of urine protein-to-creatinine (UP/Cr). UP/Cr measurements were included if urine protein was measured 3 months before or after the first neurocognitive assessment(baseline); clinically significant

proteinuria was defined by a UP/Cr ratio ≥ 200 mg/g [25]. Glomerular filtration rates were estimated (eGFR) from simultaneously collected serum creatinine measurements using the CKD-Epidemiology equation [26].

All participants provided written informed consent at their local ACTG clinical trials site. This study was conducted with oversight from the ACTG and the MetroHealth Medical Center Institutional Review Board and adhered to the Declaration of Helsinki.

Statistical Analysis

The aims of this analysis were to examine the relationship between NCI at the time of the initial neurocognitive assessment in ALLRT (baseline) with simultaneous proteinuria, and to examine the relationship between subsequent NCI during follow-up and baseline proteinuria among participants who did not have NCI at the baseline visit.

Included in the baseline cross-sectional analysis were 1,972 participants who had their initial neurocognitive testing and a simultaneous UP/Cr at baseline as of June 2010. Multivariable logistic regression models were used to assess the association (odds ratios and 95% confidence intervals) between UP/Cr (≥ 200 vs. < 200 mg/g) and NCI, controlling for other potential confounders and risk factors including: eGFR, age, sex, race/ethnicity, education duration, injection drug use (as previous, current or never), smoking history, ART experience upon entry to the parent study, CD4 cell counts and plasma HIV RNA concentrations; and diagnoses of: cardiovascular disease (defined by a history of myocardial infarction, stroke and other cardiovascular diseases), hypertension (defined as a blood pressure $>140/90$ mmHg on more than one occasion and receipt of antihypertensive medications), hypercholesterolemia (defined as a fasting LDL cholesterol >160 mg/dL and receipt of lipid-lowering medications), diabetes (defined as diagnosis of any hyperglycemia and receipt of hypoglycemic agents), and grade ≥ 3 anemia or thrombocytopenia (using The Division of AIDS Toxicity Scale, defined as a hemoglobin < 4.61 mmol/L, or a platelet count $< 50 \times 10^9/L$). An adjusted final model retained UP/Cr, the demographic variables, injection drug use history, ART experience, and other variables from univariate models with unadjusted *P*-values < 0.2 . In a sensitivity analysis, only participants with baseline HIV RNA < 200 copies/mL were assessed. An additional analysis examined potential confounding effects by tenofovir, an antiretroviral drug with low central nervous system penetration that is specifically associated with increased risk of proteinuria.

One thousand three hundred seventy-two subjects with a normal baseline NPZ-3 score and at least one follow-up neurocognitive visit were included in a longitudinal analysis. To investigate the association between baseline UP/Cr and incident NCI over time, multivariable logistic regression models using generalized estimating equations that were similarly constructed as described above, were assessed. The models included all the previously listed variables, of which the following were time-updated: eGFR, CD4 cell counts, HIV RNA concentrations, grade ≥ 3 anemia or thrombocytopenia, and time-updated diagnoses of cardiovascular disease, hypertension, hypercholesterolemia and diabetes. In a sensitivity analysis, only time points where participants had HIV RNA < 200 copies/mL were assessed.

RESULTS

Characteristics of the population

Among the 1,972 participants included in this analysis, median time between entry to the parent clinical trial and the first neurocognitive assessment (i.e. the baseline evaluation) was 16 weeks (IQR, 8 to 24 weeks), median age was 40 years and 82% were men. Four hundred and one participants (20%) had a UP/Cr ≥ 200 mg/g at baseline but only 41 (2%) had an eGFR < 60 ml/min/1.73 m² (Table 1). Two hundred and twelve subjects (11%) were ART naive at the baseline evaluation while 1,683 (85%) subjects had recently initiated ART upon entry to their parent clinical trial. Median baseline CD4 count was 319 cells/ μ L, and 60% of subjects were virologically suppressed (to < 200 copies/mL) at baseline; 52% were past or current cigarette smokers, 11% had hypertension, 8% had a history of cardiovascular disease, and 4% and 3% had diabetes or hypercholesterolemia at baseline, respectively.

Baseline Cross-Sectional Analysis

NCI was detected in 481 of 1,972 (24%) subjects, of whom 116 (24%) had clinically significant proteinuria (UP/Cr ratio ≥ 200 mg/g), compared to 285 (19%) of 1,491 subjects with clinically significant proteinuria but without NCI (unadjusted OR 1.34 [95% C.I., 1.05 to 1.72], $P=0.02$). When proteinuria was assessed as a continuous variable it was negatively correlated with eGFR ($r = -0.13$, $P < 0.001$). Proteinuria as a categorical variable (UP/Cr ≥ 200 mg/g) remained significantly associated with increased odds of NCI in a fully adjusted model that included eGFR (OR 1.41 [95% C.I., 1.08 to 1.85], $P=0.01$; Table 2), wherein higher eGFR also was associated with increased odds of NCI (OR 1.08 [95% C.I., 1.01 to 1.16] per every 10 ml/min*1.73 m² eGFR increase; $P=0.02$). Proteinuria remained significantly associated with NCI in the same adjusted model when the highest vs. the lowest quartile of UP/Cr concentrations were compared (OR 1.55 [95% C.I., 1.13 to 2.14], $P=0.007$ for UP/Cr > 168 vs. ≤ 69 mg/g).

Additional factors associated with increased odds of NCI in the prevalent model included female sex (OR 1.55 [95% C.I., 1.18 to 2.05], $P=0.002$), Hispanic ethnicity (OR 2.67 [95% C.I., 2.00 to 3.55], $P < 0.001$ vs. black) and pharmacologically-treated diabetes (OR 1.89 [95% C.I., 1.14 to 3.13], $P=0.01$); increased odds was associated with a grade 3 anemia though not statistically significant (OR 4.89 [95% C.I., 0.85 to 28.22], $P=0.08$). A lower risk of NCI was associated with more years of formal education (OR 0.95 [95% C.I., 0.92 to 0.98] per year of education, $P=0.004$). When the analysis was restricted to include the 1,186 subjects with a baseline HIV RNA < 200 copies/mL, proteinuria (as UP/Cr ≥ 200 mg/g) was not statistically associated with increased odds of NCI (OR 1.34 [95% C.I., 0.94 to 1.92], $P=0.11$). In additional sensitivity analyses, current tenofovir-use was not associated with increased risk of NCI (OR 0.94 [95% C.I., 0.68 to 1.30], $P=0.70$) and a 'U-shaped' association was suggested when eGFR was analyzed as a categorical variable in unadjusted models (OR: 2.25 (1.13, 4.47), 1.38 (1.05, 1.81) and 2.04 (1.48, 2.81) for associations with eGFR ≤ 60 , 60 to 120, and > 120 ml/min/1.73 m², respectively).

Incident NCI among Subjects without NCI at Baseline

Among the 1,491 subjects without NCI at the initial assessment, 1,372 had at least one post-baseline neurocognitive assessment and were followed for a median of 3.3 years (IQR 2.4 to 4.2 years). NCI was subsequently detected in 250 subjects (18%) a median of 1.7 years (IQR, 0.9 to 2.7 years) after the baseline assessment. In multivariable longitudinal analysis baseline UP/Cr ≥ 200 mg/g was associated with increased odds of incident NCI (OR 1.39 [95% C.I., 1.01 to 1.93]; $P=0.045$; Table 2). Consistent with the baseline analyses, Hispanic ethnicity remained associated with increased odds of subsequent NCI (OR 2.70 [95% C.I., 1.82 to 4.00] vs. black, $P<0.001$); other significant correlates in this model included older age (OR 1.22 [95% C.I., 1.03 to 1.45] per each 10 years older, $P=0.02$) and a grade ≥ 3 thrombocytopenia (OR 7.66 [95% C.I., 1.85 to 31.75]; $P=0.005$).

When the longitudinal analysis was restricted only to assessments during which time subjects achieved viral suppression to HIV RNA < 200 copies/mL ($n=1,280$), baseline proteinuria ≥ 200 mg/g was significantly associated with increased odds of subsequent NCI (OR 1.45, [95% C.I., 1.02 to 2.08], $P=0.04$). In contrast to the cross-sectional, prevalent analysis, baseline eGFR was not associated with incident NCI risk among all subjects in this longitudinal cohort (OR 1.00 [95% C.I., 0.99 to 1.0], $P=0.28$), or in the subset of subjects with viral suppression during follow up (OR 1.00 [95% C.I., 0.99 to 1.01], $P=0.61$).

DISCUSSION

We identified an association between NCI and concurrent, clinically significant proteinuria (UP/Cr ≥ 200 mg/g) among ART-treated, HIV-infected participants of a large prospective multicenter observational study. Baseline proteinuria also was associated with subsequent NCI among subjects in whom NCI was not detected during the initial evaluation in a longitudinal analysis. The association between this level of proteinuria and NCI was evident in multivariable models adjusted for additional risk factors and potential confounders including eGFR and comorbidities, and when UP/Cr concentrations were categorized within quartiles.

As a marker of vascular dysfunction, numerous studies have identified strong and consistent associations between proteinuria or albuminuria with fatal cardiovascular events that were independent of the levels of glomerular filtration [15-18]. Similar associations also were evident in studies of HIV-infected individuals [19-22]. While it is possible that residual confounding from common risk factors that are shared between patients with both cardiovascular and kidney disease could contribute to these associations, this relationship also may imply common pathogenic mechanisms underlying both disease processes [27, 28]. One such common mechanism may involve disruption of the glycocalyx lining that is present on all endothelial cells, including fenestrated glomerular cells, which limits endothelial activation by preventing leukocyte and platelet adhesion while also preventing negatively charged proteins including albumin to escape from the capillary lumen. This lining can be disrupted by oxidative stress, hyperglycemia or laminar shear leading to albuminuria and endothelial inflammation [29]. Although we identified significant associations with proteinuria, albuminuria is a more specific marker for glomerular

dysfunction and may be a better marker of endothelial dysfunction than is proteinuria, while renal tubular dysfunction also contributes to proteinuria [30].

Albuminuria also was associated with an increased risk of NCI in the general population, and with increased risk of subsequent NCI in patients with diabetes [31-35]. Common microvascular changes in the brains and kidneys of patients with cognitive impairment and proteinuria may similarly imply common pathogenic mechanisms involving both disorders. Renin angiotensin blockade with angiotensin converting enzyme inhibitors or angiotensin-II receptor blockers (ARB) are consistently effective in lowering albuminuria [36]. In one analysis of two large clinical trials that included participants with vascular disease and diabetes, telmisartan-use (an ARB) was associated with significantly reduced odds of neurocognitive decline among subjects with baseline macroalbuminuria [37].

In HIV associated NCI, vascular risk factors have been increasingly recognized including associations with increased carotid intima-media thickness [11], a previous history of cardiovascular comorbidities [12-14], or elevated CD163 plasma concentrations, a marker of arterial inflammation [38]. HIV infection was associated with reduced cerebral blood flow by magnetic resonance imaging (MRI) [39], and with small vessel ischemic vascular disease as determined by periventricular leukoaraiosis by MRI [40] suggesting important contributions by vascular disease to HAND.

In the present analysis we also identified a significant association between NCI and increased eGFR in the cross-sectional (but not in the longitudinal analyses) that is consistent with a previous study from the Multicenter AIDS Cohort Study [11]. By contrast, lower eGFR was associated with cognitive impairment in studies from the general population [41, 42]. Many studies have described 'U-shaped' associations between cardiovascular outcomes and eGFR with adverse outcomes associated with both ends of the eGFR spectrum [43, 44]. Non GFR determinates of serum creatinine levels including muscle mass, diet, age and systemic illness may confound associations with creatinine-based GFR estimates, where it is hypothesized that serum creatinine may be lower than expected for the level of GFR [45]. Glomerular hyperfiltration was also more common among HIV infected subjects in a recent study from the Multicenter AIDS Cohort Study, and this was associated with indicators of hyperglycemia and hypertension [46]. It is possible that confounding or hyperfiltration may have contributed to the observed associations between higher eGFR and NCI in the present study. Because only 41 subjects (2%) had a baseline eGFR < 60 ml/min/1.73 m², our ability to detect associations between NCI and lower eGFR levels was limited in the present study.

Associations between years of formal education or ethnic minority status with HIV associated NCI are consistent with some, [3, 11, 12] but not all previous studies [8, 10] and may represent differences in available educational opportunities. Most English-speaking subjects were instructed in English, including those for whom Spanish may have been their primary language. Because we did not adjust for Spanish-dominant language or the degree of bilingualism, this may have introduced an important source of bias in the association with ethnicity that we observed. The validity of the neurocognitive testing and the normative adjustments that were used in this study are nevertheless supported by favorable

performance characteristics when compared to more comprehensive, reference standard neuropsychological testing [47].

Although all levels of hemoglobin and platelet counts were not routinely captured in the database of this study, a small number of subjects had grade 3 toxicities of each. These were respectively associated with NCI in the baseline and longitudinal analyses and are consistent with previous studies that reported associations between anemia, or thrombocytopenia with HIV-associated dementia complex [48, 49]. In addition, the association between diabetes and NCI in the baseline evaluation of the present analysis is consistent with a previous association between self-reported diabetes and NCI among older ART treated HIV-infected subjects in a multi-center study [14]. Our study enrolled predominantly treatment naïve individuals who recently started ART but the interval between ART initiation and the measurement of proteinuria varied across the cohort (median 8 weeks after ART initiation, IQR 8 to 24 weeks). Finally, proteinuria was previously associated with elevated plasma HIV RNA concentrations in individual receiving ART, and with heightened immune activation markers [50-52]. The finding of reduced significance in the baseline association between proteinuria and NCI among the group with HIV- RNA < 200 copies/mL may suggest possible contributions by incomplete viral suppression to the relationship between proteinuria and NCI.

Strengths of this analysis include the prospective longitudinal design with regular, simultaneous measurements of proteinuria and neurocognitive function in this large well characterized cohort of HIV-infected individuals on ART that allowed us to adjust for multiple potential confounding factors. We used a brief and simple battery of three tests to determine NCI that was administered by trained staff, but not by neuropsychologists. More comprehensive testing would be required to define more subtle degrees of impairment and to assess all the domains of neurocognitive function. We also cannot exclude residual confounding from unmeasured factors that could contribute to the observed association between proteinuria and NCI, however.

In conclusion, we observed a significantly increased risk of NCI in persons with elevated proteinuria in both cross-sectional and longitudinal analyses of this prospective observational study of ART treated HIV-infected participants. Because of the previous, strong associations from population-based studies between proteinuria and disease processes that are characterized by vascular dysfunction, these associations also suggest an important role of vascular disease in HAND, adding to a growing number of similar associations implicating vascular contributions to this morbidity. Studies examining the effects on HAND by interventions that reduce vascular dysfunction are warranted.

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Table 1

Demographics and baseline variables by baseline neurocognitive impairment status

Characteristic	Total (N=1,972)	Neurocognitive Impairment at Baseline		
		Normal (N=1,491)	Impaired (N=481)	P-Value
UP/Cr, median (IQR) mg/g	99 (69, 168)	97 (67, 161)	104 (73, 194)	0.009 (a)
UP/Cr 200 mg/g, n (%)	401 (20%)	285 (19%)	116 (24%)	0.02 (b)
eGFR, median (IQR) mL/min/1.73m ²	104.2 (89.4, 116.3)	103.2 (88.5, 114.9)	109.2 (92.4, 119.7)	<.001 (a)
eGFR < 60 mL/min/1.73m ² , n (%)	41 (2%)	27 (2%)	14 (3%)	0.14 (b)
Male sex, n (%)	1,616 (82%)	1,251 (84%)	365 (76%)	<.001 (b)
Race/Ethnicity				<.001 (b)
White Non-Hispanic	892 (45%)	735 (49%)	157 (33%)	
Black Non-Hispanic	659 (33%)	515 (35%)	144 (30%)	
Hispanic (Regardless of Race)	421 (21%)	241 (16%)	180 (37%)	
Years of education, median (IQR)	14 (12, 16)	14 (12, 16)	12 (11, 15)	<.001 (a)
Age, median (IQR) years	40 (33, 47)	40 (33, 47)	39 (32, 46)	0.10 (a)
Previous or Current Injection drug use, n (%)	184 (9%)	138 (9%)	46 (10%)	0.84 (b)
Antiretroviral Naive at Baseline, n (%)	212 (11%)	182 (12%)	30 (7%)	0.02 (b)
CD4 cell counts, median (IQR) cells/pl	319 (184, 454)	324 (191, 461)	296 (166, 426)	0.01 (a)
HIV RNA < 200 copies/mL, n (%)	1,186 (60%)	897 (60%)	289 (60%)	0.98 (b)
Grade 3 hemoglobin toxicity, n (%)	6 (<1%)	2 (<1%)	4 (1%)	0.03 (c)
Grade 3 thrombocytopenia, n (%)	5 (<1%)	5 (<1%)	0 (0%)	0.34 (c)
Smoking history, n (%)	1,026 (52%)	787 (53%)	239 (50%)	0.21 (b)
History of cardiovascular diseases, n (%)	150 (8%)	119 (8%)	31 (6%)	0.27 (b)
Pharmacologically-treated hypercholesterolemia, n (%)	52 (3%)	39 (3%)	13 (3%)	0.92 (b)
Pharmacologically-treated hypertension, n (%)	219 (11%)	170 (11%)	49 (10%)	0.46 (b)
Pharmacologically-treated diabetes, n (%)	82 (4%)	50 (3%)	32 (7%)	0.002 (b)
Hepatitis C antibody positive	168 (9%)	128 (9%)	40 (8%)	0.85 (b)

(a) Wilcoxon Test

(b) Chi-Square Test

(c) Fisher's Exact Test

Table 2

Associations between baseline proteinuria (urine protein/creatinine >200 mg/g at the initial neurocognitive assessment) and prevalent and incident neurocognitive impairment, estimated as odds ratios and 95 percent confidence intervals (CI) adjusting for diabetes and other baseline and longitudinal risk factors.

Variables	Prevalent NCI (Baseline) ¹		Incident NCI (Longitudinal) ²	
	N=1,972		N=1,372	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
UP/Cr at baseline (> 200 vs <200 mg/g)	1.41 (1.08, 1.85)	0.01	1.39 (1.01, 1.93)	0.046
eGFR at baseline (per 10 mL/min/1.73m ² increase)	1.08 (1.01,1.16)	0.02	-	
Age at baseline (per 10 year increase)	1.00 (0.87,1.14)	>0.90	1.22 (1.03, 1.45)	0.02
Sex (Female vs. Male)	1.55 (1.18,2.05)	0.002	1.39 (0.99, 1.95)	0.05
Race/Ethnicity				
White vs. Black	1.02 (0.78, 1.35)	0.87	1.09 (0.76, 1.55)	0.65
Hispanic vs. Black	2.67 (2.00, 3.55)	<0.001	2.70 (1.82, 4.00)	<0.001
Years of Education at baseline (per 1 year increase)	0.95 (0.92, 0.98)	0.004	1.01 (0.95,1.06)	0.85
Grade μ 3 Anemia at baseline	4.89 (0.85, 28.22)	0.08	-	
Grade μ 3 Thrombocytopenia at follow up (time-updated)	-		7.66 (1.85, 31.75)	0.005
Pharmacologically-treated Diabetes at baseline	1.89 (1.14, 3.13)	0.01	-	

¹. Based on logistic regression; model also included: previous or current injection drug use history and ART- experience at entry to ALLRT; baseline CD4 (>200 vs < 200 cells/ μ L).

².Based on logistic Generalized Estimating Equations regression modelling; model also included: previous or current injection drug use history and ART- experience at entry to ALLRT, hepatitis B and hepatitis C status, baseline HIV-RNA (> 200 vs < 200 copies/mL), HIV-RNA copies at follow-up and time-updated diagnosis of hypertension.