ORIGINAL COMMUNICATION

Microalbuminuria: a sentinel of neurocognitive impairment in HIV-infected individuals?

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Abstract

Background According to population-based studies, microalbuminuria is associated with subsequent cognitive decline over a 4–6-year period, because of cerebral small-vessel disease (CSVD). This prospective cross-sectional study (NCT02852772) was designed to evaluate whether a history of microalbuminuria is associated with subsequent cognitive decline in combined antiretroviral therapy (cART)-treated persons living with human immunodeficiency virus (PLHIVs).

Methods From our computerized medical database, we identified 30 PLHIVs (median age 52 years), immunovirologically controlled on cART, who had microalbuminuria in 2008 and had undergone, between 2013 and 2015, a comprehensive neuropsychological assessment (NPA) including seven domains (cases): information-processing speed, motor skills, executive functions, attention/working memory, learning/memory, reasoning and verbal fluency. Forty-nine PLHIVs matched for age (median age 48 years; $p = 0.19$), sex, and year of first HIV-seropositivity without microalbuminuria in 2008 were identified and underwent the same NPA between 2013 and 2015 (controls).

Results Cases performed less well than controls for information-processing speed ($p = 0.01$) and motor skills ($p = 0.02$), but no differences were found for the other cognitive domains and global z-scores. A multivariable linear-regression model adjusted for confounding factors confirmed the microalbuminuria effect for the information-processing-speed z score.

Conclusion cART-treated PLHIVs with a history of microalbuminuria subsequently had worse cognitive performances for the information-processing-speed domain, possibly because of CSVD. Our observations should be considered preliminary findings of a temporal link between microalbuminuria, CSVD, and subsequent cognitive impairment.

Keywords Cerebral small-vessel disease (CSVD) · HIV infection · Microalbuminuria · Neuropsychological assessment · Urine albumin/creatinine ratio (UACR)

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Introduction

Because the renal and cerebral microcirculations share common hemodynamic properties, characterized by high-flow and low-resistance end organs with tightly autoregulated perfusion, the concept of the kidney being an anatomical and functional brain surrogate is increasingly recognized [1, 2]. Kidney-damage markers are microalbuminuria and/or lower estimated glomerular filtration rate (eGFR) [2]. Magnetic resonance imaging-documented cerebral small-vessel disease (CSVD) and/or neurocognitive impairment could reflect brain damage [2]. Over a decade, a growing body of evidence has shown a significant relationship between those kidney-damage markers and cognitive decline [2–4], leading to the concept of reno-cerebrovascular disease, considered to be based on SVD due to endothelial dysfunction, accompanied by inflammation and oxidative stress [5, 6].

In the general population, microalbuminuria is associated with a vascular profile of cognitive impairment appearing within 4–6 years [7–9]. Independent of traditional vascular risk factors, microalbuminuria is also associated with CSVD, which is responsible for impaired information-processing speed, motor skills, and executive functioning [8–12]. CSVD affects up to 50% of middle-aged persons living with HIV (PLHIVs), despite combined antiretroviral therapy (cART)-controlled aviremia [13]. The increased risk of CSVD is not associated with exposure to any ART class [14]. Evidence supports a significant CSVD role in the development of milder forms of HIV-associated neurocognitive disorders (HAND) for cART-treated virus-suppressed PLHIVs, leading to the new paradigm of vascular-driven milder forms of HAND [15–17].

While a comprehensive neuropsychological assessment (NPA) is required to characterize cognitive functions and diagnose HAND, it is time-consuming, personnel intensive, and costly. Simpler and less expensive approaches may suffice to detect PLHIVs at risk of cognitive decline that will lead to a thorough NPA in this selected PLHIV sub-population.

We hypothesized that PLHIVs with microalbuminuria would have more neurocognitive impairment than those without. Herein, impairment evaluation was limited to three specific cognitive domains—information-processing speed, motor skills, and executive function—known to be sensitive to the more premature, subtle decline of cART-controlled PLHIVs [17–19]. To evaluate, in this preliminary study, microalbuminuria's role in cognitive function, we selected PLHIVs without severe diabetes mellitus and/or hypertension, hepatitis C virus (HCV) infection, past or ongoing neurological diseases (notably acquired immunodeficiency syndrome (AIDS)-defining neurological events), and/or alcohol or illicit drug addiction.

Methods

Study population

The prospective, cross-sectional ALCOVE study (NCT02852772) was designed to estimate the association between microalbuminuria assessed with the urine albumin/creatinine ratio (UACR) 5 years earlier and current cognitive impairment, regardless of suspected cognitive impairment signs or symptoms or subjective cognitive complaints. In 2008, three of us (FX-L, EP, GP) established a cohort to explore HIV-associated kidney disease; 694 PLHIV outpatients were enrolled, among 2750 followed in the Department of Infectious Disease, Tenon Hospital, Paris, France [20]. Among those 694 PLHIVs, 96 had microalbuminuria at inclusion. Between 2013 and 2015, we selected among the 96 microalbuminuric PLHIVs, all those complying with the following inclusion criteria (henceforth cases): ≥ 18 years old; known HIV-positivity for ≥ 5 years; current CD4+ T-cell count ≥ 350/µl; cART-controlled plasma-HIV load (plVL) < 40 copies/ml for at least 12 months; and 2008 UACR, assessed on a fresh morning urine sample, 3–30 mg/mmol. Exclusion criteria were: neurological and psychiatric diseases or prior/current neurological and psychiatric pathologies including AIDS-defining neurological events (i.e., stroke, seizure disorders, multiple sclerosis, dementia, traumatic brain injury with loss of consciousness), HCV infection, prior/current alcohol or illicit substance abuse (except for occasional cannabis or popper use, < 1/month), diabetes mellitus with microvascular complications, uncontrolled hypertension, absence of fasting glycemia and lipidemia testing for ≥ 1 year, HIV-associated nephropathy, insufficient command of French and/or eGFR < 15 ml/min/1.73 m^2. Two non-microalbuminuric PLHIVs from the same database were matched to each case for age (± 5 years), sex, and year of first HIV-seropositivity (± 5 years), with 2008 UACR assessed on a fresh morning urine sample, < 3 mg/mmol (henceforth controls).

Entry sociodemographic characteristics, lifestyle (tobacco, alcohol and drugs), blood pressure, HIV/AIDS history, other past/current neurological conditions, psychotropic drug use, cardiovascular risk factors, and all treatments were recorded.

This study was approved by the CPP Île-de-France VI, Groupe Hospitalier Pitié-Salpêtrière Ethics Committee, and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Neuropsychological assessment

Trained neuropsychologists, blinded to UACR, administered a comprehensive NPA covering seven cognitive domains

(information-processing speed, motor skills, executive functions, attention/working memory, learning/memory, reasoning and verbal fluency). The main stumbling block of the Frascati criteria [21] is that they label > 30% of a normative reference population as cognitively impaired, which yields an unreasonably high false-positive proportion of cognitively impaired participants in a study population, due to their lower-than-expected specificity [19, 22–25]. Because evidence is mounting in support of not using the HAND criteria in the modern cART era in resource-rich settings and the availability of updated standards, we chose to apply the validated, normative datasets threshold of impairment, as widely acknowledged in memory clinics [26]. Raw scores for each cognitive domain test, except the 9-hole peg test, were normalized to age, sex, and educational levels, yielding z scores for analyses. In addition, a specific multivariable-model analysis with age, sex, and educational level was run for the 9-hole peg test to compensate for its lack of a z score. Within-domain test scores were averaged to calculate domain-specific z scores and across domains to calculate a global z score. Hamilton Depression and Anxiety Rating Scales assessed depression and anxiety, and Cognitive Complaint Interview evaluated subjective cognitive complaints [27, 28].

Statistical analyses

Non-parametric Mann–Whitney U tests for continuous variables, expressed as median [interquartile range] and Fisher's exact tests for categorical variables, expressed as number (%), compared cases versus controls. Based on those comparisons of characteristics, multivariable linear-regression models using the NPA scores as dependent variables were adjusted for variables that differed between them. Variables achieving $p \leq 0.10$ in non-parametric analyses were included in the multivariable regression model. CDC stage C and CD4$^+$ T-cell nadir, two of the main variables associated with HAND in cART-treated aviremic PLHIVs, were also added to this model. Statistical analyses were computed with Statistica software (Statsoft, Inc, Maison Alfort, France).

Data-availability statement

Anonymized data will be shared on request by any qualified investigator provided that data transfer is in agreement with EU legislation on general data-protection regulations.

Results

Between November 2013 and January 2015, 31 cases and 60 controls were recruited. Nine patients dropped out, did not reply or missed their scheduled NPAs. Three PLHIVs were

excluded secondarily because of unreliable NPA (language difficulties), leaving 30 cases and 49 controls whose characteristics are reported in Table 1. Cases had lower anxiety scores, current CD4$^+$ T-cell counts, males having sex with males, and smoking rates than controls but were comparable for all other variables. Cases had significant cognitive impairment compared to controls for information-processing speed ($p = 0.01$) and motor skills ($p = 0.02$), but their other domains and global z scores were comparable. After Bonferroni correction for the three comparisons defined as our primary objective, only the information-processing-speed difference remained significant.

To confirm the microalbuminuria effect on information-processing speed and motor skills, we used multivariable linear-regression models with information-processing-speed z score and 9-hole peg test both hands score as dependent variables. These multivariable models were adjusted for the following variables: current tobacco smoker, hypertension, microalbuminuria, Centers for Diseases Control (CDC) stage C, 2008 eGFR, CD4$^+$ T-cell nadir, and the current CD4$^+$ T-cell count (Table 2). Because it was unknown for 63% of the cases, HIV-transmission route appeared less useful and was not retained. Presence of microalbuminuria was retained as being associated with lower information-processing-speed z scores but was no longer associated with poorer performance in the 9-hole peg test, even after including age, sex, and educational level for the latter, to compensate for its lack of a z score. CDC stage C was also associated with lower information-processing-speed z scores.

Discussion

We applied the exposed/non-exposed study design [29, 30], as was used for the general population [7], to our historical cohort of cART-treated PLHIVs, whose inclusion/exclusion criteria have been described elsewhere [20]. Indeed, it appeared to be the most cost-effective way to test, in a preliminary study, whether microalbuminuria detected 5 years earlier was significantly associated with PLHIVs' subsequent cognitive impairment. After adjustment for factors associated with HAND and/or microalbuminuria (i.e., age, educational level, hypertension, CD4$^+$ T-cell nadir), previously microalbuminuric cases had worse cognitive performances for the information-processing-speed domain than controls. Overall, our PLHIVs performed well in executive-functioning and memory domains, which agrees with recent studies on cART-controlled aviremic PLHIVs without severe comorbidities [18, 19, 22].

A UACR (≥ 22.6 mg/mmol)–HAND association was reported [31]. However, that study was hampered by an unusual definition of albuminuria, predominantly cART-naïve PLHIVs, with 40% immunovirologically uncontrolled

Table 1 Epidemiological, clinical and biological characteristics and neuropsychological assessment (NPA) performances of 79 HIV-infected patients

		UACR, mg/mmol		
	All patients	Controls, <3	Cases, 3–30	p
Parameter	(n=79)	(n=49)	(n=30)	Value[a]
Demographic				
Age, years	50 [46–56][b]	48 [45–55][b]	52 [47–58][b]	0.19
Age at HIV diagnosis, years	31 [27–36]	31 [25–36]	32 [28–35]	0.49
Males	54 (68)	35 (71)	19 (63)	0.45
Caucasian	43 (54)	27 (55)	16 (53)	0.88
Sub-Saharan–African origin	34 (43)	20 (41)	14 (47)	0.61
Current tobacco smoker	31/74 (42)	25 (51)	6/25 (24)	0.03
Cannabis user	5/74 (7)	5 (10)	0/25 (0)	0.16
HIV-transmission route				
MSM	34 (43)	28 (57)	6 (20)	0.001
Intravenous drug users	2 (3)	2 (4)	0 (0)	(MSM
Heterosexual exposure only	17 (22)	12 (24)	5 (17)	Vs.
Blood transfusion	1 (1)	1 (2)	0 (0)	others)
Unknown	25 (32)	6 (12)	19 (63)	
HIV infection				
Estimated HIV duration, years	19 [14–22]	17 [14–22]	20 [15–24]	0.64
CDC stage C	20 (25)	11 (22)	9 (30)	0.45
2008 CD4+ T cells/µl	557 [399–667]	582 [407–729]	484 [399–650]	0.23
Current CD4+ T cells/µl	679 [469–873]	739 [544–1030]	620 [445–770]	0.02
CD4+ T-cell nadir/µl	212 [129–350]	208 [151–310]	238 [114–400]	0.48
2008 undetectable HIV plVL	63 (80)	37 (76)	26 (87)	0.23
Current undetectable HIV plVL	79 (100)	49 (100)	30 (100)	1
On cART at 2008 UACR dosage	72 (91)	43 (88)	29 (97)	0.24
On cART at NPA testing	78 (99)	48 (98)	30 (100)	1
Renal parameters				
Hypertension	23 (29)	11 (22)	12 (40)	0.10

Table 1 (continued)

Current antihypertensive use	20 (25)	11 (22)	9 (30)	0.45
Diabetes	2 (3)	2 (4)	0 (0)	0.52
2008 UACR (mg/mmol)	1 [0.47–5]	0.59 [0.36–0.87]	5.59 [4.16–8.00]	<0.001
2008 eGFR, ml/min/1.73 m^2	89.5 [79.5–99.5]	92 [82–101]	82.5 [74.5–96.5]	0.09
Current eGFR, ml/min/1.73 m^2	90.5 [80–105]	94 [81–107]	90 [79–93]	0.18
2008 serum creatinine (mg/dl)	86.5 [78.5–94.5]	84.5 [77.5–91.5]	92 [80–98]	0.11
Current serum creatinine (mg/dl)	80.5 [72–94]	79 [72–92]	81 [72–95]	0.56
Current total cholesterol (mmol/l)	5.03 [4.34–5.67]	5.09 [4.39–5.82]	4.99 [4.16–5.62]	0.39
Current LDL cholesterol (mmol/l)	2.86 [2.28–3.56]	2.99 [2.28–3.46]	2.7 [2.48–3.61]	0.86
Current triglycerides (mmol/l)	1.21 [0.85–2.01]	1.2 [.86–2.1]	1.42 [0.82–2.01]	0.85
Current lipid-lowering–drug use	15 (19)	10 (20)	5 (17)	0.68
Cardiovascular history	5 (6)	2 (4)	3 (10)	0.36
Neuropsychological performances[c,d]				
Generalities				
Education, years	12 [11–17]	12 [11–17]	12 [11–15]	0.94
HAM-A	7 [4–10]	7 [5–10]	5.5 [3–8]	0.05
HAM-D	4 [1–5]	4 [2–6]	2.5 [1–5]	0.09
CCI	1 [0–4]	2 [0–4]	1 [1–4]	0.96
Information-processing speed, z-scores				
WAIS-IV digit-symbol coding	−0.95±1.07	−0.80±0.98	−1.20±1.17	0.04
WAIS-IV symbol search	−0.45±1.09	−0.27±1.16	−0.75±0.89	0.04
Trail-Making Test A (time)	−0.30±1.37	−0.01±1.07	−0.79±1.66	0.01
Domain z-score	−0.57±1.04	−0.36±0.95	−0.91±1.09	0.01
Executive functions, z-scores				
Trail-Making Test B (time)	−1.25±2.08	−1.04±1.99	−1.59±2.21	0.19
Trail-Making Test B perseverative errors	−0.59±1.91	−0.53±1.76	−0.69±2.15	0.77
WCST-128 perseverations	−0.27±1.14	−0.12±0.91	−0.53±1.43	0.14
WCST-128 conceptualization responses	−0.46±0.86	−0.30±0.71	−0.73±1.02	0.07
Stroop interference	0.11±0.85	−0.05±0.83	0.36±0.84	0.15
Domain z-score	−0.48±0.89	−0.39±0.83	−0.63±0.97	0.15
Motor skills				

Table 1 (continued)

9-hole peg test both hands	22.63±3.42	21.97±3.01	23.71±3.81	0.02
Attention/working memory, *z*-scores				
WAIS-IV digit span	−0.49±0.93	−0.52±0.99	−0.45±0.84	0.75
WAIS-IV LNS	−0.21±1.01	−0.23±1.04	−0.16±0.96	0.85
WMS-III spatial span	−0.33±0.93	−0.27±0.95	−0.43±0.91	0.47
Domain *z*-score	−0.36±0.80	−0.37±0.87	−0.36±0.69	0.96
Learning/memory, *z*-scores				
BVMT-R immediate recall	−0.82±1.52	−0.73±1.49	−0.96±1.58	0.55
WMS-IV logical memory: immediate recall	−0.39±0.96	−0.33±0.96	−0.47±0.97	0.55
BVMT-R delayed recall	−0.39±1.48	−0.42±1.44	−0.34±1.56	0.70
WMS-IV logical memory: delayed recall	−0.43±0.95	−0.45±1.01	−0.42±0.85	0.79
Domain *z*-score	−0.51±1.02	−0.49±1.05	−0.55±1.00	0.77
Reasoning, *z*-scores				
WAIS-IV matrix reasoning	−0.52±1.00	−0.35±1.05	−0.80±0.85	0.11
WAIS-IV similarities	0.73±1.67	0.92±1.71	0.41±1.59	0.21
Domain *z*-score	0.11±1.22	0.30±1.25	−0.19±1.14	0.09
Verbal fluency, *z*-scores				
Word-list generation (animal)	−0.94±1.13	−0.87±1.14	−1.06±1.12	0.38
Word-list generation (P letter)	−0.76±1.34	−0.75±1.45	−0.78±1.16	0.89
Domain *z*-score	−0.85±1.05	−0.81±1.08	−0.92±1.02	0.79
All domains *z*-score	−0.44±0.80	−0.35±0.78	−0.59±0.82	0.23

[a]Significantly different values are in bold type

[b]Values are median [interquartile range] or number (%)

[c]All test results are demographically corrected *z* scores, except the 9-hole peg test

[d]Values are expressed as median [interquartile range] or mean ± SD

BVMT-R Brief Visuospatial Memory Test-Revised, *cART* combined antiretroviral treatment, *CCI* Cognitive Complaint Interview, *CDC* Centers for Diseases Control, *eGFR* estimated glomerular filtration rate, *HAM-A* Hamilton Anxiety Rating Scale, *HAM-D* Hamilton Depression-Rating Scale, *LDL* low-density lipoprotein, *LNS* Letter-Number Sequencing, *MSM* males having sex with males, *PASAT* paced auditory serial addition, *plVL* plasma virus load, *Stroop* color and word test, *UACR* urine albumin/creatinine ratio, *WAIS-IV* Weschler Adult Intelligence Scale-4th edition, *WCST* Wisconsin Card-Sorting Test, *WMS-IV* Weschler Memory Scale 4th edition, *WMS-III* Weschler Memory Scale 3rd edition

individuals (plVL ≥ 200 copies/ml), who had only recently started cART, with potential factors contributing to HAND (e.g., current cocaine use and HCV coinfection) and insufficient NPA results and CD4 nadir. UACR ≥ 3 mg/mmol was shown to be a determinant of poorer cognitive performance by middle-aged, cART-controlled, aviremic PLHIVs compared to HIV-uninfected individuals [17].

Systemic SVD is considered the underlying pathophysiological mechanism, with renal SVD manifesting as microalbuminuria and brain involvement as cognitive decline, with hemodynamic similarities in the vascular beds of both end

Table 2 Multivariable analyses

Variables	z score information-processing speed		9-hole peg test both hands	
	β (95% CI)[a]	p value[b]	β (95% CI)[a]	p value[b]
Current tobacco smoker	0.19 (− 0.04;0.43)	0.11	− 0.00 (− 0.26;0.26)	0.98
Presence of hypertension	0.05 (− 0.18;0.27)	0.69	− 0.12 (− 0.37;0.13)	0.34
Presence of microalbuminuria	**− 0.32 (− 0.57;0.06)**	**0.01**	0.03 (− 0.25;0.31)	0.84
CDC stage C	**− 0.26 (− 0.50;0.04)**	**0.02**	− 0.17 (− 0.43;0.13)	0.18
2008 eGFR	− 0.20 (− 0.42;0.02)	0.07	− 0.09 (− 0.34;0.16)	0.47
Current CD4+ T-cell count	− 0.23 (− 0.48;0.01)	0.06	0.07 (− 0.21;0.34)	0.63
CD4+ T-cell count nadir	− 0.03 (− 0.27;0.20)	0.77	− 0.01 (− 0.27;0.26)	0.95

95% CI 95% confidence interval, *CDC* Centers for Diseases Control, *eGFR* estimated glomerular filtration rate

[a]β statistic values represent the standardized coefficients in multiple linear-regression models

[b]Significant p values are in bold type

organs [1, 2]. CSVD, which affects 50% of PLHIVs [13] and is a major contributor to HAND in multivariable analyses, seems even more important than HIV parameters [17]. Information-processing speed is one of the most affected domains in the general population with CSVD-related cognitive decline [32, 33] and PLHIVs with primary HAND [34]. Information-processing speed being the only deficiency found in our cART-controlled-aviremic cases might suggest CSVD [32]. Unfortunately, our study design did not include brain magnetic resonance imaging to explore the microalbuminuria–CSVD relationship, representing a clear limitation. However, our objective was not to show an association between microalbuminuria and CSVD in PLHIVs, and such imaging is technically demanding, costly and time-consuming, unlike inexpensive, safe, easy, and rapid microalbuminuria testing, especially relevant for low-resource countries.

Although UACR measurements without cognitive testing preceded the NPA by up to 5 years, our study should be considered cross-sectional. As for similar studies [35], our historical PLHIV cohort did not undergo cognitive testing at the time they were screened for microalbuminuria. A longitudinal study is needed to evaluate the temporal link between microalbuminuria, CSVD, and subsequent cognitive impairment. Also, our study-sample size was relatively small, so the absence of difference in other cognitive domains might be due to a lack of power. However, information-processing speed was the most affected domain, as attested by the two major tests used to assess it, i.e., Trail-Making Test B and Wechsler Memory Scale 4th edition, while language, memory and motor skill functions were preserved [36].

Our cohort is representative of PLHIVs in Northern Europe, where > 90% are successfully treated [17], but our findings may not be generalizable to more vulnerable PLHIVs. Nevertheless, the 2019 UNAIDS world epidemiological data showed that 79% of PLHIVs are aware of their seropositivity, 78% of PLHIVs knowing their HIV status

are cART-treated, and 86% of those cART-treated PLHIVs have a plVL below the detection threshold (unaids.org). Moreover, it was recently demonstrated that low detectability-threshold plVLs of 51–200 or 201–500 copies/ml were strongly associated with virological failure [37]. Hence, reporting results nowadays concerning virologically uncontrolled cART-treated PLHIVs is not really suitable. UACR, measured with a single-spot urine sample, correlated well with 24-h urinary albumin-excretion rates [38, 39].

Conclusion

Our observations should be considered preliminary to devising well-designed, prospective, longitudinal studies to confirm the temporal microalbuminuria–CSVD link with subsequent cognitive impairment. Indeed, microalbuminuria is a rapid inexpensive test, of particular interest in low-resources countries. Because the PLHIV CSVD rate is twice that of the general population, HIV infection could serve as a model to evaluate the microalbuminuria–cognitive decline relationship in the general population.

revised the manuscript for intellectual content; F-XL, EP designed the study; revised the manuscript for intellectual content; CL conducted the statistical analyses; interpreted the data; drafted the manuscript and revised it for intellectual content; GP interpreted the data and revised the manuscript for intellectual content.

Compliance with ethical standards

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