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Cocaine use and white matter hyperintensities in homeless and unstably housed women

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Abstract

OBJECTIVES.—Cocaine use has been linked to stroke in several studies. However, few studies have considered the influence of cocaine use on stroke mechanisms such as small vessel disease (SVD). We conducted a study to assess associations between the toxicology-confirmed use of multiple drugs, including cocaine, and a marker of SVD, white matter hyperintensities (WMH).

MATERIALS AND METHODS.—We conducted a nested case-control study (n=30) within a larger cohort study (N=245) of homeless and unstably housed women recruited from San Francisco community venues. Participants completed six monthly study visits consisting of an interview, blood draw, vital sign assessment and baseline brain MRI. We examined associations between toxicology-confirmed use of multiple substances, including cocaine, methamphetamine, heroin, alcohol and tobacco, and WMH identified on MRI.

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DISCLOSURES
The authors have no conflict of interest or disclosures.

RESULTS.—Mean study participant age was 53 years, 70% of participants were ethnic minority women and 86% had a history of cocaine use. Brain MRIs indicated the presence of WMH (i.e., Fazekas score>0) in 54% (18/30) of imaged participants. The odds of WMH were significantly higher in women who were toxicology-positive for cocaine (Odd Ratio=7.58, p=0.01), but not in women who were toxicology-positive for other drugs or had several other cerebrovascular risk factors.

CONCLUSIONS.—Over half of homeless and unstably housed women showed evidence of WMH. Cocaine use is highly prevalent and a significant correlate of WMH in this population, while several traditional CVD risk factors are not. Including cocaine use in cerebrovascular risk calculators may improve stroke risk prediction in high-risk populations and warrants further investigation.

Keywords

cocaine; stroke; small vessel disease; white matter hyperintensities; women

INTRODUCTION

Stroke is disproportionately common in low-income populations,[1–4] due in part to the high prevalence of risk factors like cardiovascular disease (CVD)[5–9] and substance use.[10–12] The links between stroke and alcohol or cigarette use are well-documented.[13–19] However, recent studies also show that stroke is associated with opiates,[20] all forms of amphetamine use,[21–23] and there is particularly strong evidence implicating cocaine as a risk factor for stroke.[24–28] While the evidence is consistent, few studies have considered the influence of cocaine use on mechanisms of stroke, such as cerebral small vessel disease (SVD). Whether prevalence differs in asymptomatic individuals who use substances like cocaine is an area of study that has received little attention.

SVD causes approximately 20%−30% of all strokes,[32, 33] more than doubles the future risk of a second stroke[34, 35] and increases risk of death or ischemic stroke in patients with atherosclerotic disease.[36] Few SVD studies consider the influence of drugs such as cocaine. Among the few that have, one retrospective study based on medical chart review reported that, among young (≤49 years), mostly male urban stroke patients presenting for care, microbleeds were more common among individuals reporting a history of drug use and those with a current positive cocaine toxicology.[37] In addition, significant associations between cocaine and white matter hyperintensities (WMH) have been reported in all-male[38] and mostly male samples.[39] Whether similar results would be observed in middle-aged populations that include more women is unclear. However, this is an important question because some studies suggest that women may have more severe and progressive SVD, possibly due to smaller arterial size and/or more frequent vascular remodeling.[40] This, combined with additional cerebrovascular insults from cocaine, could result in a greater risk of SVD. It is also unclear whether similar results would be observed in populations that have not presented for stroke care. This is important because silent disease progression is pronounced in people who use cocaine, and many remain asymptomatic until they present to an emergency department with an acute event.[41–43]

While abstinence is an important goal, our prior research with homeless and unstably housed women shows high rates of consistent use and high rates of initiating use predicted by homelessness and violence, paired with low quit rates.[44] We conducted a study to assess associations between toxicology-confirmed cocaine use and WMH detected on magnetic resonance imaging (MRI) in a community-recruited cohort of homeless and unstably housed women. The goal of the study was to gain a better understanding of stroke mechanisms in low-income women, which could facilitate stroke prevention and care strategies for this vulnerable population.

METHODS

Study Design

We conducted a nested neuroimaging sub-study within the "Polysubstance use and Health Outcomes Evaluation" [PULSE] cohort study. Cohort data were collected for the PULSE study between June 2016 and January 2019 and details have been described elsewhere.[45] In brief, we used community-based recruitment methods to obtain a cohort that reflected San Francisco's larger population of homeless and unstably housed women.[46] HIV-positive individuals were over-sampled on additional recruitment days to address specific aims of the main study. Participation included monthly study visits for six consecutive months, including interviews, vital sign assessment, and blood draws to assess drug toxicology. Informed consent was obtained from all study participants and each was reimbursed $45 for each PULSE study interview.

Study Participants

Individuals undergoing regular PULSE study interviews between July and October of 2018 were invited to participate in a neuroimaging sub-study. Sub-study participation involved brain MRI, and linkage of the MRI data with sociodemographic and drug use data from the PULSE study. Sub-study participants were reimbursed $65 for completing imaging and sub-study activities. Approval for all study procedures was obtained from the Committee on Human Research, University of California, San Francisco.

Study Outcome

The outcome of the study was WMH of presumed vascular origin. We chose WMH because they are among the most commonly observed and clinically applied markers of SVD[29], making them a sensitive and clinically relevant measure. We defined WMH by a Fazekas score, which indicated the burden of MRI-confirmed white matter microangiopathic change (0=absent, 1=mild, 2=moderate, 3=severe).[47, 48] No contrast or sedation were given for MRI examinations, and images were acquired on a 3T GE MR750 MRI scanner. The presence of lacunar infarcts and cerebral microbleeds were also characterized using subjective assessments of T2 FLAIR and susceptibility-sensitive T2*images, respectively. Assessments were made by a single neuro-radiologist who was unaware of participant substance use status to maintain consistency and impartiality.

The following 45-minute imaging protocol was used: (1) Volumetric 3D T1 BRAVO (TR/TE/TI=min/min/600ms, ASSET=2, FA=10°, 1.0mm isotropic), (2) Coronal 3D CUBE

T2 FLAIR (TR/TE=6000/116ms, ASSET=2, 1.0mm isotropic), (3) Axial 3D T2* SWAN (TR/TE=45/24ms, slice thickness 2.8mm, matrix 400×260; FOV 25.6cm; parallel), (4) Axial 3D TOF MRA (TR/TE=min/5.6ms, ASSET=2, FA=25°, slice thickness 0.7mm, 1×1 mm in-plane), (5) Axial diffusion tensor imaging (DTI, TR/TE=min/60 ms, b=1000, 30 gradient directions).

Study Exposures

Primary study exposures were toxicology-confirmed use of alcohol, nicotine/cotinine, cocaine/benzoylecgonine, methamphetamine and heroin at any one of six monthly follow-up visits. We tested hydrolyzed urine samples using a qualitative liquid chromatography-high resolution mass spectrometry (LC-HRMS) method. Data acquisition and generation of mass spectra took place using an SCIEX 5600 TripleTOF® LC-HRMS system. We used HRMS full scan mode with information-dependent acquisition of HRMS product ion spectra, which were searched against a mass spectral library for positive identification of each substance. This methodology has proven sensitive and specific for the detection of these compounds in urine[49]. In addition to single drugs, we considered two-drug combinations that included cocaine. All additional exposure variables were assessed at baseline, including age, race, BMI, HIV status, hypertension, LDL cholesterol, HDL cholesterol, self-reported blood pressure medication and self-reported history of stroke.

Analysis

Chi-square tests and logistic regression were used to assess associations between cocaine use and WMH. Simple and multivariable logistic regression using Firth's penalized likelihood adjustment for small sample sizes[50] was used to assess associations between study factors and any WMH. We decided a priori to minimize the number of variables included in multivariable analyses based on the recommendation of roughly one exposure variable per 10 individuals with the outcome.[51]

RESULTS

Among 245 women participating in the PULSE study, the neuroimaging sub-study recruited 30 individuals. Compared to the original PULSE study sample, a higher proportion of the sub-study sample was HIV-positive (63% vs. 27%, $p<0.001$). No other study factor differed by sample.

The median age of study participants was 57 years, 67% were ethnic minority women and 67% of women had hypertension at baseline (Table 1). The most commonly used drug was cocaine (67%). Large vessel findings included two participants with old large-territory ("cortical") infarcts (one large right MCA infarct and one very small right MCA branch infarct).

Evidence of WMH was observed in over half (54%) of participants. Based on its appearance (i.e., patchy, deep white matter lesions), the white matter disease observed was typical of microvascular ischemic disease (e.g., SVD). The lesions did not occur in typical places for demyelination (e.g., corpus callosum), trauma (also callosum, more at gray-white junctions) or other disorders. These findings, in conjunction with the tendency for vascular white

matter disease to occur frequently with microbleeds, supported our presumption of an etiological link between WMH and SVD.

The distribution of Fazekas scores to characterize WMH was as follows: 12 people (44%) had a score of 0 (no lesion), 5 (19%) had a score of 1 (mild WMH), 8 (29%) had a score of 2 (moderate WMH), and 2 (7%) had a score of 3 (severe WMH). Observed white matter changes in all subjects were typical of small-vessel microangiopathic changes, and did not fit a pattern to suggest demyelination or trauma, and subjects reported no current migraine headache. Lacunar infarcts were present in 4 individuals (13% of the sample), cerebral microbleeds were seen in 3 individuals (10% of the sample).

The unadjusted odds of WMH by toxicology-confirmed cotinine/nicotine, alcohol, methamphetamine and opiate use were non-significant (Table 2). However, the odds of any WMH among persons who were toxicology-positive for cocaine or benzoylecgonine at any study visit were 7.58 (p=0.01; 95% CI: 1.56–49.91). This association persisted, even after adjusting for age, race, BMI, hypertension, blood pressure medication use, history of stroke and HIV status (Table 3).

Among study participants, 21 (70%) used multiple substances concurrently (polysubstance use) (Table 4). Associations between WMH and each 2-drug combination that included cocaine (compared to neither or one drug only) were non-significant after adjusting for age.

DISCUSSION

Over half of community-recruited homeless and unstably housed women showed evidence of WMH, a marker of SVD. The odds of WMH were over seven-fold higher for individuals who were toxicology-positive for cocaine; however, associations between all other drugs and WMH were non-significant. In addition, polysubstance use was common in this population, but associations between WMH and all two-drug combinations including cocaine were non-significant. Results suggest that a sole focus on acute cerebrovascular effects of cocaine, such as infarction and sudden death,[52] may be shortsighted in populations like homeless and unstably housed women where cocaine use is common and may have chronic influences on subclinical conditions that act as mechanisms of stroke. Given that SVD increases risk, not only of stroke but also of dementia, vascular death, and all-cause mortality,[53, 54] results presented here suggest that including cocaine use in the risk assessment of serious conditions like SVD and stroke could improve their prediction in high-risk populations.

The significant association we found between toxicology-confirmed cocaine use and WMH in community-recruited women extends prior research showing significant associations between cocaine use and stroke in mostly male, young individuals who present for stroke care. It has been suggested that cerebral SVD is disproportionately common, more severe, and more progressive in women compared with men.[40] While no male study subjects were included for comparison in the current study, it is possible that cocaine use could exacerbate sex differences even further. Future research could help clarify sex differences and determine whether risk assessment tools could be improved by accounting for effect modification by --or possibly interaction between --sex and cocaine use.

An important limitation of this study was the use of WMH as a surrogate for SVD. Some other markers of SVD are infrequently found, making WMH a more sensitive measure and particularly strong candidate as the study outcome. In addition, SVD is a main mechanism behind age-related WMH, further strengthening its use as the study outcome. However, the etiology of SVD is less certain in younger populations like the one described here, and WMH were presumed to be of vascular origin. While justified, larger future studies may strengthen the etiological link of our findings by including multiple markers of vascular disease. Another important limitation was the small sample size, which reduced statistical power and generalizability. Also, HIV-positive persons were overrepresented, which may have limited the generalizability of study findings; however, HIV was not significantly associated with WMH, suggesting very minimal if any bias. In addition, medical record verification was unavailable for prior stroke. A third limitation was the absence of substance-using years, which could help elucidate associations with certain use patterns and/or possible threshold effects. Study strengths included recruiting a probability sample of community-recruited, middle-aged homeless and unstably housed women, which differs from traditional clinic-based research by including women both in and out of care, as well as women with and without symptomatic disease. Another strength is the study's inclusion of toxicology-confirmed drug use and WMH detected on MRI, rather than relying on chart review or self-report alone.

CONCLUSION

Cocaine is a well-established risk factor for stroke,[24–28] and high rates of silent cerebrovascular disease are reported in cocaine users.[41–43] This, combined with the high rate of WMH observed here and its significant associations with cocaine use, reinforce the contention that a failure to account for drug use in stroke-related research and clinical care has likely led to an underestimation of its influence.[55, 56] This is particularly problematic for homeless and unstably housed women, a population known to have high rates of crack cocaine use and low quit-rates.[44, 57] Including cocaine use in cerebrovascular risk calculators may improve stroke risk prediction in high-risk populations and warrants further investigation.

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Table 1.

Prevalence of Baseline Study Factors by SVD status in homeless and unstably housed women (N=30)

	N (%) or Median (IQR) SVD (Fazekas>0)	N (%) or Median (IQR) No SVD (Fazekas=0)	p-value
Age	59.4 (56.5–63.3)	51.8 (40.9–57.6)	0.004 *
Combined race/ethnicity			0.49
Non-Latina white	9 (56.3)	4 (28.6)	
Non-Latina Black	4 (25.0)	4 (28.6)	
Latina	2 (12.5)	4 (28.6)	
Non-Latina other	1 (6.3)	2 (14.3)	
BMI	27.4 (23.0–33.9)	35.4 (24.9–42.3)	0.08
Hypertension	12 (75.0)	8 (57.1)	0.26
LDL cholesterol (mg/dL)	83.5 (70.5–98.5)	56.5 (46.0–71.0)	0.08
HDL cholesterol (mg/dL)	54.0 (42.5–63.0)	56.5 (46.0–71.0)	0.56
Blood pressure medication use at baseline	7 (43.8)	4 (30.8)	0.37
History of stroke	4 (25.0)	2 (14.3)	0.40
HIV status	10 (62.5)	9 (64.4)	0.68
Toxicology-confirmed cotinine/nicotine use during the 6-month study period	9 (56.3)	7 (50.0)	0.51
Toxicology-confirmed alcohol use during the 6-month study period	10 (62.5)	7 (50.0)	0.38
Toxicology-confirmed cocaine use during the 6-month study period	14 (87.5)	6 (42.9)	0.02 *
Toxicology-confirmed methamphetamine use during the 6-month study period	4 (25.0)	1 (7.1)	0.21
Toxicology-confirmed heroin use during the 6-month study period	0 (0)	1 (7.1)	1.0
Use of 2+ substances (polysubstance use) during the 6-month study period	13 (81.3)	8 (57.1)	0.15

* = p-value below 0.05. Non-parametric Wilcoxon Rank Sum Test and Fishers Exact Chi-square Test were used for the continuous and categorical factors, respectively.

Table 2.

Associations between study factors and Small Vessel Disease in homeless and unstably housed women (N=30)

	Unadjusted Odds Ratio (95% CI)
Age	1.18 (1.05–1.40) *
Combined race/ethnicity	
Non-Latina white	Ref.
Non-Latina Black	2.11 (0.38–12.57)
Latina	0.56 (0.06–4.13)
Non-Latina other	0.60 (0.04–6.58)
BMI at baseline	0.92 (0.84–1.01)
Hypertension at baseline	2.12 (0.49–9.97)
LDL cholesterol (mg/dL)	0.99 (0.96, 1.01)
HDL cholesterol (mg/dL)	0.99 (0.95, 1.03)
Blood pressure medication use at baseline	1.67 (0.39–7.70)
History of stroke	1.80 (0.33–11.96)
HIV status	0.94 (0.22–3.97)
Toxicology-confirmed cotinine/nicotine use during the 6-month study period	1.27 (0.31–5.22)
Toxicology-confirmed alcohol use during the 6-month study period	1.62 (0.40–6.83)
Toxicology-confirmed cocaine use during the 6-month study period	7.58 (1.56–49.91) *
Toxicology-confirmed methamphetamine use during the 6-month study period	3.24 (0.51–35.71)
Toxicology-confirmed heroin use during the 6-month study period	0.27 (<0.01–5.55)
Use of 2+ substances (polysubstance use)	2.95 (0.65, 15.50)

* = 95% CI does not include 1

Table 3.

Associations between Cerebrovascular Risk Factors and Small Vessel Disease, Adjusted for Cocaine Use (N=30)

	Odds Ratio (95% CI) Adjusted for cocaine
Model 1: Age + Cocaine	
Age at baseline	1.16 (1.04–1.40) *
+ Cocaine Toxicology	6.49 (1.06–55.00) *
Model 2: Race/Ethnicity + Cocaine	
Combined race/ethnicity $\chi 2$	0.81 (3)
Non-Latina white	Ref.
Non-Latina Black	1.56 (0.23–10.16)
Latina	0.62 (0.06–5.57)
Non-Latina other	0.91 (0.05–14.18)
+ Cocaine Toxicology	5.15 (1.06–31.70) *
Model 3: BMI + Cocaine	
Baseline BMI	0.95 (0.86–1.05)
+ Cocaine Toxicology	5.39 (1.03–36.32) *
Model 4: HIV status + Cocaine	
HIV positive status	1.14 (0.23–5.86)
+ Cocaine Toxicology	7.21 (1.51–46.85) *
Model 5: Hypertension + Cocaine	
Baseline hypertension	1.07 (0.16–5.91)
+ Cocaine Toxicology	6.84 (1.31–49.78) *
Model 6: HDL + Cocaine	
Baseline HDL	0.98 (0.94, 1.02)
+ Cocaine Toxicology	8.63 (1.69, 62.63) *
Model 7: LDL + Cocaine	
Baseline LDL	0.99 (0.96, 1.02)
+ Cocaine Toxicology	6.85 (1.41, 44.66) *
Model 8: Medication + Cocaine	
Current Rx for heart rate/BP	2.23 (0.45–14.24)
+ Cocaine Toxicology	7.21 (1.41–52.77) *
Model 9: Stroke history + Cocaine	
History of stroke	1.27 (0.19–9.73)
+ Cocaine Toxicology	6.92 (1.43–45.26) *

* = 95% CI does not include 1

Table 4.

Toxicology-Confirmed Use of Multiple Substances (Polysubstance Use)* in Homeless and Unstably Housed Women (N=30)

	Use of this drug + Nicotine/cotinine # (%)	Use of this drug + Alcohol # (%)	Use of this drug + Cocaine # (%)	Use of this drug + Methamphetamine # (%)	Use of this drug + Heroin # (%)
Nicotine/cotinine	--				
Alcohol	12 (40.0)	--			
Cocaine	14 (46.7)	15 (50.0)	--		
Methamphetamine	3 (18.8)	4 (13.3)	5 (25.0)	--	
Heroin	1 (3.3)	0 (0)	0 (0)	0 (0)	--

* Drug combinations are not mutually exclusive