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Socioeconomic status does not predict cocaine use among ischemic stroke patients: A nested case-control study

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Abstract

Previous studies of cocaine use and stroke have focused on acute effects of cocaine in perceived high-risk populations. We characterized mechanisms and risk factors for cocaine use among ischemic stroke patients from a broad range of socioeconomic backgrounds to inform medical management decisions and prevention efforts. We studied consecutive adults admitted with acute ischemic stroke to our institution between January 2007 and December 2010 with a history or laboratory confirmation of cocaine use. Age, sex, and race-matched cocaine-negative controls were derived from the same study population. Demographics, risk factors, clinical and imaging data were compared between groups. Among 4073 acute ischemic stroke patients, 91 (2.2%) had a history of cocaine use and/or a positive toxicology screen (cases). Cocaine abusers did not differ from controls by occupation, income, or educational level ($P > 0.5$). Active tobacco use independently increased the odds of cocaine use among stroke patients (odds ratio 3.9, 95% confidence interval 2.0–7.5), as did the history of migraine (odds ratio 2.5, 95% confidence interval 1.1–5.9). Stroke subtype also predicted cocaine use among stroke patients (odds ratio 0.73, 95% confidence interval 0.58–0.93). Stroke patients with current or past cocaine use could not be distinguished from non-users by socioeconomic factors. Liberal use of toxicology screening among a much broader population of patients is needed for proper identification and management. Further study of causal mechanisms for cardioembolism in cocaine-associated stroke is warranted.

Keywords

Ischemic stroke, cocaine, drug abuse, toxicology, migraine, cardioembolism, cerebrovascular disease, epidemiology

Introduction

Cocaine use is a preventable risk factor for ischemic stroke. In 2008, 5.3 million Americans aged 12 years and older used cocaine.[1] Acutely, cocaine use is thought to cause ischemic stroke through a variety of mechanisms including hypertension, cardiac dysrhythmia, platelet dysfunction, and vasospasm or vasculopathy. Cocaine is associated with an earlier age of onset of ischemic stroke.[2] Prior studies of cocaine and ischemic stroke delineated the acute effects of cocaine ingestion, were restricted to younger persons, and were conducted in perceived "high-risk" populations.[3–8]

One exception to previous trends in describing "high-risk" groups was a study from Northern California's Kaiser Permanente system.[9] Subjects included were diagnosed with ischemic or hemorrhagic stroke and had relatively higher socioeconomic status. More than 50% of cocaine and amphetamine users were identified as whites, 44% were high school graduates, and 7% had college degrees. However, generalizability was limited by the study's restriction to women 15–44 years old. Controls were non-stroke patients, limiting inference about stroke mechanisms unique to cocaine use.

Given the narrow group of subjects sampled in previous investigations, we hypothesized that cocaine use is associated with ischemic stroke in patients from a broader range of socioeconomic backgrounds.

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Furthermore, we sought to characterize stroke mechanisms and risk factors among cocaine-associated stroke in order to better inform medical management decisions and prevention efforts.

Methods

Patient selection

Subjects were selected from an ongoing two-center prospective cohort study of consecutive subjects with ischemic stroke aged ≥18 years admitted to the Massachusetts General Hospital or Brigham and Women's Hospital Stroke Unit after presenting to the emergency department (ED) within 24 h of symptom onset from 1 January 2007 to 31 December 2010. Acute ischemic stroke (AIS) was defined as a clinical syndrome of any duration associated with a radiographically proven acute infarct consistent with a vascular pattern of involvement and without radiographic evidence of a demyelinating, neoplastic, or other structural disease, including vasospasm due to subarachnoid hemorrhage, or primary intracerebral hemorrhage. Diagnosis of acute cerebral ischemia was confirmed for all AIS subjects in this study by admission diffusion-weighted (DWI) magnetic resonance imaging (MRI) completed within 48 h after symptom onset.

Subjects were selected from the AIS cohort retrospectively. Those reporting either a history (more than two weeks since last use) of cocaine use or a toxicology screen positive for cocaine at the time of index stroke admission were defined as cocaine-associated stroke (cases). Subjects with toxicology screens positive for amphetamines ($n = 2$) were excluded. Age, sex, and race/ethnicity-matched controls were AIS subjects derived from the same cohort in 1:2 ratio. The Institutional Review Board at Massachusetts General Hospital approved all aspects of this study, and informed consent for collection of data was obtained for all subjects or their legal guardians.

Data collection and patient follow-up

All patients were evaluated by a neurologist in the ED, where the National Institutes of Health Stroke Scale (NIHSS) was determined. Clinical and demographic data, including tobacco use and comprehensive substance abuse history, were abstracted prospectively by patient or proxy interview and supplemented through chart review. Median income data by zip code were obtained from the US Census Bureau.[10] Vascular risk factors, including hypertension, hyperlipidemia, diabetes, coronary artery disease, and atrial fibrillation, were recorded based on the existing international guidelines as previously described.[11,12]

Ischemic stroke subtypes were assigned prospectively by stroke neurologists according to Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria.[13] Brain MRI scans obtained at the time of evaluation for AIS were reviewed by the investigator (CRF) blinded to the case–control status or outcomes. Ischemic stroke infarct volume was quantified on DWI MRI according to ABC/2 calculation (infarcts $\leq 5\,mm^3$ were recorded as $5\,mm^3$ for analysis).[14] Computed tomographic or MR angiographic evidence for cerebral vasculitis was determined by investigator review (CRF), and confirmed by chart abstraction of the diagnosis assigned by the primary team of stroke neurologists. Discharge NIHSS was determined by a stroke neurologist at the time of discharge.

Statistical analysis

All statistical analyses were performed using SAS version 9.2 (Cary, NC). Continuous numeric variables were expressed as mean ± standard deviation (SD) with the exception of DWI volume, which was expressed as the median ± interquartile range. Cases and controls were compared in univariate analysis using t test, Wilcoxon rank sum test, χ^2 test, or Fisher's exact test as appropriate. A multivariate logistic regression model inclusive of unmatched demographic variables and all variables that demonstrated nominal association with outcome (univariate $P < 0.20$) was used to determine independent predictors of cocaine-associated ischemic stroke. A separate analysis restricted to toxicology-positive "active" cocaine users was conducted in a similar fashion. The level of significance was set at $P < 0.05$ (two-tailed) for all analyses.

Results

Among 4073 AIS admissions during the study period, 91 (2.2%) had a history of cocaine use or positive toxicology screen. Characteristics of the 91 cases and 182 matched control subjects included in the analytical sample are described in Table 1. Mean age among cases was 50 years (SD ± 10.5), 74% were male, and 88% self-identified as White. Highest level of education for 70% of cases was high school, 25% completed college, five (5%) held masters, and one (1%) a doctoral degree. A small proportion of cases were unemployed (4%) or disabled (3%). Compared to controls, cases did not statistically differ by annual income ($49,499 ± 15,494 vs $51,818 ± 16,776), occupation, or educational level (all $P > .05$).

Compared to non-cocaine users, active tobacco use at the time of stroke was high (84% vs 6%, $P < 0.001$). History of migraine was reported more frequently among cocaine users (15%) than non-users (8%)

Table 1. Subject characteristics.

	Cocaine (+) ($n = 91$)	Cocaine (−) ($n = 182$)	*P* value
Age (years)	50 ± 10.5	50.2 ± 10.3	0.88
Male (%male)	67 (74)	134 (74)	1.00
White (%total)	78 (88)	157 (88)	0.99
Median income (US$)	49,499 ± 15,494	51,818 ± 16,776	0.43
College education	17 (19)	41 (22)	0.82
Occupation[a]	27 (30)	50 (27)	0.19
Carotid artery stenosis	2 (2)	6 (3)	0.72
Atrial fibrillation	4 (4)	13 (7)	0.44
Coronary artery disease	13 (4)	27 (5)	1.00
Current tobacco use	76 (84)	10 (6)	<0.01
Tobacco use intensity[b]	0.97 (0.7)	1.1 (0.73)	0.60
Hypertension	48 (52)	102 (57)	0.61
Hyperlipidemia	27 (30)	62 (34)	0.49
Diabetes mellitus type II	19 (20)	47 (26)	0.37
Migraine	14 (15)	14 (8)	0.06

Data are expressed as number (percent) or mean ± standard deviation.
[a]Most common occupational category of service/clerical results are displayed.
[b]Among current cigarette smokers, number of packs per day.

Table 2. Infarct characteristics and outcomes.

	Cocaine (+)	Cocaine (−)	*P* value
TOAST subtype			<0.01
Large-artery atherosclerosis	16 (18)	24 (13)	
Cardioembolism	39 (43)	50 (27)	
Small-artery occlusion	19 (21)	37 (20)	
Other determined etiology	13 (14)	62 (34)	
Undetermined etiology	4 (4)	9 (5)	
Stroke location			0.61
Anterior circulation	51 (56)	104 (57)	
Posterior circulation	38 (42)	70 (38)	
Multifocal	2 (2)	8 (4)	
IV tPA thrombolysis	11 (12)	31 (17)	0.37
Infarct volume (mm^3)	33.6 (5–20)	21.2 (5–20)	0.47
NIHSS on admission	2	3	0.30
NIHSS at discharge	2	2	0.87

Data are expressed as number (percent), median, or median (Q1–Q3).
IV tPA: intravenous plasminogen activator; NIHSS: National Institutes of Health Stroke Scale; TOAST: Trial of ORG 10172 in Acute Stroke Treatment criteria.

($P = 0.06$). Infarct characteristics and outcome measures are listed in Table 2. According to TOAST subtype, cardioembolism was more common among cocaine-associated cases (43%) than controls (27%), whereas strokes of other determined etiology were more prevalent among controls (34% vs 14%).

A multivariable analysis was performed using income, education, occupation, tobacco use, migraine, and TOAST subtype in the model. Current tobacco use (odds ratio [OR] 3.9, 95% confidence interval [CI] 2.0–7.5), history of migraine (OR 2.5, 95% CI 1.1–5.9), and TOAST stroke subtype (OR 0.73, 95% CI 0.6–0.9)

emerged as independent predictors of being in the cocaine-associated ischemic stroke group.

There were no statistically significant differences in vascular territory involved, infarct volume, or rates of IV thrombolysis, nor was there evidence of different stroke severity (admission NIHSS) or early outcomes (discharge NIHSS) between cases and controls. Cocaine use was not an independent predictor of stroke severity (OR 0.8, 95% CI 0.5–1.2) or early outcome (OR 0.9, 95% CI 0.6–1.5).

A subset analysis of toxicology confirmed "active" cocaine users ($n = 29$) with AIS were matched with non-cocaine users using controls ($n = 58$) from the same population. Median age of active cocaine users was 47 years (range 19–79). Association between cardioembolic stroke subtypes ($P < 0.004$) persisted. Active tobacco use again emerged as a robust predictor of cocaine-associated stroke (OR 12.9, 95% CI 3.7–44.4) in this subset.

Discussion

This nested case–control study of cocaine use and ischemic stroke from a hospital-based cohort was unable to detect socioeconomic differences between stroke patients who used cocaine and those who did not. The cohort represents the widest range of socioeconomic backgrounds studied to date, lending support to the importance of broad vascular risk factor and toxicology screening in stroke evaluation and prevention. Active tobacco use is a key risk factor identified in our analysis among stroke patients with both current and prior cocaine use. Among toxicology-positive (active) cocaine users, those who smoked tobacco had 12-fold increased odds of cocaine-associated stroke compared to non-cocaine users. Tobacco use among historical cocaine users nearly tripled the odds of being in the cocaine-associated stroke group.

Previous investigators have established cocaine as a common cause of stroke in younger individuals. A retrospective analysis of the International Classification of Disease (ICD-9) codes inclusive of ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage first established cocaine and other drugs as significant causes of stroke among persons aged 15–44.[15] Subsequent studies, such as the Baltimore Washington Cooperative Young Stroke Study, and others similarly restricted enrollment to ages less than 45.[5,9,16] Beyond age restriction, previous studies of cocaine and ischemic stroke sampled lower income urban populations.[3–5,7] An analysis of the National Health and Nutrition Examination Survey (NHANES III) data used a broader population at risk and identified black men and lower educational level as risk factors for cocaine use.[6] However, the study did not find a statistical association between cocaine use and stroke. High-risk groups exist, but sampling methods from prior studies have skewed perceptions of cocaine users at risk for stroke.

In this analysis, we demonstrate that income, educational level, and occupation did not differentiate stroke patients who used cocaine from those who did not. We derived cases from a large prospective registry of ischemic stroke patients representing a wider range of age and socioeconomic status. Control subjects were from the same cohort allowing for detailed comparison of stroke characteristics and common vascular risk factors. Our analysis included both historical and active cocaine users. Consistent with prior investigations, cocaine use is associated with early-onset stroke. We identified strokes among active cocaine users with ages ranging from 19 to 79 years, suggesting that toxicology screening should be considered at the time of emergency presentation in stroke patients of all ages. Mean age of stroke onset at our institution during the study period was 69 years, consistent with the US average of 70 years.[17] Both active and prior cocaine users in this study had strokes, on average, 19 years earlier, suggesting that even distant cocaine use may be a risk factor for early onset stroke.

Income and educational level of both active and historical cocaine users are the highest of any study published thus far. Demographic characteristics of our population limit evaluation of previously reported race and/or ethnicity-related risk of cocaine-associated strokes.[2,5,6,9] However, our findings fill a void left by prior investigations and reveal that cocaine-associated stroke is not limited to "high-risk" populations (70% held high school diplomas and 30% held college or graduate level degrees), which may reflect specifics of our catchment area.

Active tobacco use was the strongest risk factor for cocaine-associated stroke in this analysis. Tobacco as a risk factor for vascular disease is well established. The interaction of cocaine and tobacco use is less clear. Recent studies of tobacco smoke suggest that it impairs nitric oxide synthesis and vasodilation.[18] A synergy of cocaine and tobacco may alter vascular reactivity and lead to stroke. Endothelial dysfunction and platelet activation, among other mechanisms, play prominent roles in the pathophysiology of cocaine and tobacco use.[19,20] Our findings further reinforce the need for tobacco cessation among individuals with current or prior history of cocaine use as a means for stroke prevention.

TOAST classification revealed a predominance of cardioembolic events among cocaine users. Other studies of cocaine and stroke have also noted high rates of cardiac dysrhythmia.[7] The catecholamine surge associated with acute cocaine intoxication induces

contraction band necrosis and cardiac dysrhythmia.[21,22] Post mortem studies confirm these structural changes as predisposing to dysrhythmia.[23] Contraction band necrosis as a substrate, or marker, for risk of paroxysmal atrial fibrillation is not well understood. Extended Holter recordings may be useful in the evaluation of these patients. Consistent with other studies,[24] vasculitis was a very rare (one of 91 subjects) cause of stroke among cocaine users in our analysis.

Limitations of this study relate to flaws of retrospective review of prospectively ascertained subjects. Given the illicit nature of cocaine use, exposure is underestimated in our cohort. A substance abuse history was obtained prospectively from all members of the cohort, but toxicology screens were performed on only 63% of cases and 49% of controls ($P = 0.33$). Given that rates of toxicology screening were similar among age, race, and gender-matched groups, misclassification of undetected cocaine users would bias toward the null. Previous studies have suggested that route of cocaine administration may impact stroke risk.[25] We conducted separate analyses for active and historical users with similar findings. However, more detailed substance use histories, including route and frequency of cocaine use, would enhance inference of causal mechanisms between cocaine and ischemic stroke. Other substances of abuse may go undetected, confounding our estimates of a relationship between ischemic stroke and cocaine. Marijuana use has recently been associated with risk of stroke.[26] Active marijuana use was rare among both cases (8.7%) and controls (4.4%) in our cohort. NIHSS at the time of discharge did not differ between groups ($P = 0.87$). Long-term follow-up data, using a true stroke disability measure such as the modified Rankin Scale, would limit this potential source of type II error.

A population-based study in Texas attributed 2.4% of ischemic strokes in the state to cocaine use.[27] Our hospital-based cohort of relatively high socioeconomic status individuals, which included both prior and current users, found a similar proportion of 2.2%. Current American Heart Association and National Stroke Association education Web sites either do not mention cocaine as a risk factor for stroke or place a low emphasis on the risk.[28,29] If validated in future studies, cocaine use prevention campaigns should warn against both acute and long-term risk of stroke while targeting a broad range of socioeconomic groups.

Conclusions

Income, education level, and racial or ethnic background are poor predictors of cocaine-associated stroke. A wide range of socioeconomic status individuals are at risk, and liberal use of toxicology screening is needed to identify and manage these patients appropriately. Active tobacco use is a key risk factor for cocaine use among stroke patients. Cocaine's relation to migraine, cardioembolism, and cardiac pathophysiology warrants further study as future avenues for stroke prevention.

Ethical approval

None

Guarantor

CRF is the guarantor for all content presented in this article.

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Competing interests

CRF and AMA report no disclosures.

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Contributorship

CRF contributed to study concept/design, data preparation and interpretation, statistical analysis, drafting, and revising manuscript. AMA contributed to data preparation and analysis. NSR contributed to study design, statistical analysis, and manuscript revision.

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