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CLINICAL RESEARCH STUDY

The Association of Methamphetamine Use and Cardiomyopathy in Young Patients

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ABSTRACT

PURPOSE: Methamphetamine is the most widespread illegally used stimulant in the United States. Previously published case reports and series suggest a potential association between methamphetamine exposure and cardiomyopathy. The objective of this study is to demonstrate an association between methamphetamine use and cardiomyopathy.

SUBJECT AND METHODS: Case-control study based on chart review of discharges from a tertiary care medical center from January 2001 to June 2004. Patients were ≤45 years old. Cases included patients with a discharge diagnosis of either cardiomyopathy or heart failure. Controls included hospitalized patients who had an echocardiographic assessment of left ventricular function with ejection fraction ≥55% and no wall motion abnormalities.

RESULTS: One hundred and seven cases and 114 controls were identified. Both groups had similar gender distribution, length of hospital stay, rates of health insurance, prevalence of coronary artery disease, diabetes mellitus, hypertension, cigarette smoking, alcohol abuse, and marijuana and cocaine use. Cases were older than controls (mean age: 38 vs 35 years; $P=.008$), had higher body mass index (BMI) (mean BMI: 37 vs 30 kg/m^2; $P<.001$), and higher prevalence of renal failure (13% vs 4.4%; $P=.03$). Methamphetamine users had a 3.7-fold increased odds ratio [95% confidence interval, 1.8-7.8] for cardiomyopathy, adjusting for age, body mass index, and renal failure.

CONCLUSIONS: Methamphetamine use was associated with cardiomyopathy in young patients.

KEYWORDS: Cardiomyopathies; Congestive Heart Failure; Methamphetamine

PURPOSE

Methamphetamine, a synthetic amine and potent stimulant, is currently the most widespread stimulant that is illegally manufactured, distributed, and abused in the United States.[1] Commonly referred to as "speed", "crystal", "crank", "go", and "ice", the 2003 National Survey on Drug Use & Health reported the lifetime use of methamphetamines at 12.3 million, representing 5.2% of the population of age 12 years and older.[2] Furthermore, emergency department visits involving amphetamines or methamphetamines increased by 54% (from 25,245 to 38,961) between 1995 to 2002, with more than half the visits involving patients aged 18 to 34.[3] Available information from 1998 estimates the general prevalence of methamphetamine use in the State of Hawaii at 11.9%.[4]

Previous cellular, animal and autopsy studies, individual case reports and case series suggest that methamphetamine exposure is potentially associated with structural and functional changes of myocytes, as well as clinical manifestations of cardiomyopathy and congestive heart failure.[5-17]

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The purpose of this investigation is to examine the association of methamphetamine use and cardiomyopathy.

SUBJECTS AND METHODS

The study was approved by the Institutional Review Committee of the study institution. Medical records of patients admitted to a single, tertiary care medical center in Honolulu, Hawaii were retrospectively reviewed by a team of medical residents and medical students using a standardized data abstraction form. Cases were restricted to patients ≤45 years old discharged from the hospital between January 1, 2001 and June 30, 2004. Cases had a primary discharge diagnosis of either cardiomyopathy (ICD9: 425.2-425.9) or heart failure (ICD9: 428.0-428.9). Controls were restricted to patients ≤45 years old discharged between January 1, 2002 and June 30, 2004 without a primary or secondary diagnosis of either cardiomyopathy or heart failure. Controls were required to have an in-hospital echocardiogram that showed left ventricular ejection fraction (LVEF) ≥55%. Fifty percent of the controls also were required to have urine tested for toxicology. This was performed by cross referencing all eligible controls with a list generated by the clinical laboratory of all patients with urine tested for toxicology within the study period. Three cases and 24 controls with repeat hospitalizations and controls having primary discharge diagnoses related to trauma, obstetrics, or psychiatry were excluded from the analysis.

Patients were categorized into 4 ethnic groups (Caucasian, Asian, Pacific Islander, Others) based on self reporting during their hospital admission. African American and Hispanic patients were uncommon in Hawaii. Where a patient had multiple admissions during the study period, the data collected from the most recent hospitalization was used in the analysis. There was no overlap of subjects between the case and control group. Demographics, prevalence of comorbidities, cardiovascular risk factors, drug abuse and echocardiographic data were compared between cases and controls. Presence of diabetes mellitus, hypertension, and renal failure was determined from the documented medical history. Information on substance abuse was obtained during the chart review from the documented medical or nursing history, and/or from urine testing for toxicology (if performed). Either of the above, if present, would result in the patient being categorized as having a history of substance abuse. Urine toxicology was tested on a Beckman Coulter LX20 system and standard enzyme immunoassay reagents.

CLINICAL SIGNIFICANCE:

- Methamphetamine use is associated with cardiomyopathy.
- Methamphetamine-associated cardiomyopathy is more severe compared to other non-ischemic cardiomyopathies.
- In our study population, methamphetamine use was seen in 40% of young patients with cardiomyopathy.

Odds ratios (ORs) were used as the measure of association and were calculated using unconditional logistic regression. Normal theory approximation was used to determine the 95% confidence intervals (CI) for OR estimates. Significance testing of regression coefficients was based on Wald's statistic. Univariate factors associated with cardiomyopathy at the $\alpha<.05$ level of statistical significance were included in the multivariable logistic regression model. The Fisher's exact test was used for comparison of categorical variables and Student's t-test for continuous variables. A P-value of $<.05$ was considered to be statistically significant. Statistical analysis was performed using SAS statistical software version 9.1.3 (SAS Institute, Cary, NC).

RESULTS

A total of 143 discharges fulfilling criteria as cases and 143 discharges fulfilling criteria as controls were identified. Table 1 shows the frequency of diagnoses for hospitalization in the control group. The predominant diagnoses were cerebrovascular accident, chest pain and myocardial infarction, arrhythmia and infection. After excluding repeat hospitalizations (24 cases and 3 controls), control patients without echocardiographic data (n=3), and control patients with LVEF <55% (n=24), 107 cases and 114 controls were identified and used in the analysis. Table 2 shows the patient characteristics of both groups. There were no significant differences between cases and controls in gender distribution, mean length of hospital stay (9.2 vs 5.2 days; $P=.28$), rates of health insurance, prevalence of atherosclerotic heart disease, diabetes mellitus, hypertension, cigarette smoking,

Table 1 Frequency of Diagnoses for Hospitalization in the Control Group

Diagnosis	N (%)
Strokes and seizures	28 (20)
Chest pain and myocardial infarctions	27 (19)
Arrhythmias	22 (15)
Sepsis and other infections	16 (11)
Pneumonia and respiratory failure	12 (8)
Acute abdomen	8 (6)
Hypertension	4 (3)
Chronic and acute kidney failure	4 (3)
Valvular heart disease	4 (3)
Diabetes mellitus	3 (2)
Musculoskeletal disease	3 (2)
Pericardial disease	3 (2)
Malignancy	2 (1)
Other	7 (5)

Table 2 Patient Characteristics in the Case and Control Groups

Variable	Cases n (%)*	Controls n (%)*	OR [95% CI]
Age Group			
≤30	12 (11)	30 (26)	1.0 Referent
>30 to 40	50 (47)	40 (35)	3.1 [1.4-6.9]
>40	45 (42)	44 (39)	2.6 [1.2-5.6]
Sex			
Female	37 (35)	44 (39)	1.0 Referent
Male	70 (65)	69 (61)	1.2 [0.70-2.1]
BMI (Kg/m^2)			
Normal (18.5 to <25)	14 (15)	29 (26)	1.0 Referent
Underweight (<18.5)	2 (2.1)	4 (3.6)	1.0 [0.17-6.3]
Overweight (25 to <30)	19 (20)	34 (31)	1.2 [0.50-2.7]
Obesity (≥30)	59 (63)	43 (39)	2.8 [1.3-6.0]
Race			
Caucasian	22 (21)	35 (32)	1.0 Referent
Asian	31 (29)	37 (33)	1.3 [0.65-2.7]
Pacific Islander	49 (46)	36 (32)	2.2 [1.1-4.3]
Other	5 (4.7)	3 (2.7)	2.7 [0.58-12]
Health insurance (current)			
No	29 (27)	22 (19)	1.0 Referent
Yes	78 (73)	91 (81)	0.65 [0.35-1.2]
Cigarette smoking			
Never	58 (54)	72 (63)	1.0 Referent
Ever	49 (46)	42 (37)	1.4 [0.85-2.5]
Alcohol use (excludes social alcohol)			
No	82 (77)	95 (83)	1.0 Referent
Yes	25 (23)	19 (17)	1.5 [0.78-3.0]
Methamphetamine use			
Never	54 (57)	80 (80)	1.0 Referent
Ever	41 (42)	20 (20)	3.0 [1.6-5.7]
Cocaine use			
Never	96 (90)	101 (89)	1.0 Referent
Ever	11 (10)	13 (11)	0.89 [0.38-2.1]
Heroin use			
Never	105 (98)	106 (93)	1.0 Referent
Ever	2 (1.9)	8 (7.0)	0.25 [0.052-1.2]
Marijuana use			
Never	97 (91)	104 (91)	1.0 Referent
Ever	10 (9.4)	10 (8.8)	1.1 [0.43-2.7]
Diabetes mellitus			
No	81 (76)	97 (86)	1.0 Referent
Yes	26 (24)	16 (14)	1.9 [0.98-3.9]
Hypertension			
No	95 (89)	106 (94)	1.0 Referent
Yes	12 (11)	7 (6.2)	1.9 [0.72-5.1]
Atherosclerotic heart disease			
No	98 (92)	109 (96)	1.0 Referent
Yes	9 (8.4)	4 (3.5)	2.5 [0.75-8.4]
Renal failure			
No	93 (87)	109 (96)	1.0 Referent
Yes	14 (13)	5 (4.4)	3.3 [1.1-9.5]
Urine tested for toxicology†			
No	66 (62)	51 (45)	1.0 Referent
Yes	41 (38)	63 (55)	0.50 [0.29-0.86]

*Percentages may not add to 100% due to missing values.
†Obtained at any time during the admission

alcohol use, and marijuana or cocaine use. Mean LVEF in the cardiomyopathy group was 31% while the control group had a mean LVEF of 60%. Compared to controls, cases were older (mean age 38 vs 35 years; $P=.008$), had a higher mean BMI (37 vs 30 kg/m^2; $P<.001$), were more likely to be Pacific Islanders (46% vs 32%, OR=2.2, 95% CI, 1.1-4.3), and had a higher prevalence of renal failure (13% vs 4.4%; $P=.03$). Cases also were less likely than controls to have urine tested for toxicology (38% vs 55%, $P=.02$) during the admission. Cases were more likely than controls

to have a history of methamphetamine use (42% vs 20%, OR=3.0, 95% CI, 1.6-5.7).

Age- and race-adjusted multiple logistic regression analysis showed that methamphetamine use (OR=3.7, 95% CI, 1.8-7.8), BMI (normal OR=1.0; underweight OR=1.5, 95% CI, 0.21-10.3; overweight OR=1.3, 95% CI, 0.49-3.3; obese OR=2.7, 95% CI, 1.1-6.6), and renal failure (OR=4.5, 95% CI, 1.4-15) were independently associated with cardiomyopathy or heart failure (not shown in the table). These associations persisted even after the exclusion of patients with atherosclerotic heart disease from the total cohort. No substantive change in results was noted when the analysis was restricted only to either subjects who had urine toxicology screening or echocardiography performed.

Table 3 shows the characteristics of cardiomyopathy patients (cases) with and without evidence of methamphetamine use. The mean LVEF was significantly lower in the group with methamphetamines use compared with the group without methamphetamine use (26% vs 35%, $P=.009$, not shown in table). Cardiomyopathy patients with methamphetamine use had a greater prevalence of tobacco use (61% vs 31%, OR=3.4, 95% CI, 1.5-8.0) and were also more likely to have their urine tested for toxicology compared to the cardiomyopathy patients without methamphetamine use (85% vs 65%, OR=3.2, 95% CI, 1.1-8.9).

When the entire cohort of cases and controls was analyzed, patients with a positive history of methamphetamine use were more likely to have their urine tested for toxicology (78% vs 36%, OR=6.1, 95% CI, 3.0-12). Testing also was more likely to result in a positive test for methamphetamines (51% vs 5.1%, OR=20, 95% CI, 5.3-72). However, a positive history of methamphetamine use was not significantly associated with urine toxicology testing positive for any other drug (eg, cocaine or marijuana).

DISCUSSION

We observed an association between methamphetamine use and cardiomyopathy in patients ≤45 years old. To our knowledge, this is the first case-control study to show an association between methamphetamine exposure and cardiomyopathy. In our patient cohort, every 4 of 10 patients with cardiomyopathy and age ≤45 years used methamphetamine.

Our data suggests that cardiomyopathy patients with methamphetamine use have a significantly lower LVEF compared to cardiomyopathy patients without methamphetamine use. This finding suggests that young patients who use methamphetamines are not only at a higher risk of developing cardiomyopathy but also of developing a more severe form of cardiomyopathy.

Various cardiovascular manifestations of methamphetamine exposure have been previously reported in the medical literature. They include hypertension,[18] tachyarrhythmia,[19] vasospasm,[20] myocardial infarction,[21,22] aortic dissection,[23] pulmonary hypertension,[24] and sudden cardiac death.[16] Cardiomyopathy related to amphetamine or methamphetamine exposure have been previously reported in a number of individual case observations[11-14,17] and case series from Honolulu[5] and Sacramento.[6]

Evidence suggests that methamphetamine exposure leads to a high catecholamine state through several mechanisms. Methamphetamine stimulates the release of catecholamine, dopamine, and serotonin from the adrenal medulla and the sympathetic nerve terminals, resulting in activation of central and peripheral alpha and beta-adrenergic autonomic receptors. It also is a weak inhibitor of monoamine oxidase, the neuronal enzyme that inactivates norepinephrine and dopamine.[25] Catecholamine excess can conceivably result in cardiomyopathy through recurrent coronary vasospasm, tachycardia, hypertension, accelerated atherosclerosis and/or direct myocardial toxicity. Autopsy studies of methamphetamine users have shown contraction band necrosis in the myocardium, which also is seen in catecholamine toxicity and in the hearts of cocaine users.[9,15,16] Some observations suggest that myocardial pathology may be reversible with early cessation of exposure to methamphetamine.[11,13] The exact mechanism(s) through which methamphetamine exerts myocardial pathology remains to be elucidated.

Contrary to the widespread clinical belief, our results do not show an association between cardiomyopathy and cocaine use. The comparatively higher cost of cocaine may explain the relatively lower prevalence of cocaine compared with methamphetamine use in our study population (9.8% vs 31%). Cost also may be a factor in the frequency of cocaine use; however, frequency of use was not collected in our database. Accordingly, the lack of an association between cocaine use and cardiomyopathy conceivably could be attributable to the low incidence and/or frequency of cocaine use among our study participants.

The lack of an association between a history of methamphetamine use and positive urine testing for other specific illicit substances in this study is probably due to the low rates of substance use other than methamphetamines in our study population. The pattern of illicit substance use may differ in other populations and geographical areas.

Our study has limitations inherent to all hospital-based case-control studies using medical record review. It is prone to selection bias. However, we attempted to reduce the selection bias by including all eligible patients as cases. Controls were selected randomly by medical records personnel as long as they fulfilled selection criteria. Further, the duration and severity of substance abuse could not be quantified in our review of the medical records.

Another possible limitation of our results is the potential for bias in the control group in that patients admitted for other reasons may not have an adequate drug use history. Because history of drug use is inconsistently documented in medical records, a control group with a random selection of patients from medical records alone would underestimate the prevalence of drug use. On the other hand, if the entire control group consists of patients who had urine toxicology screening, the results would overestimate the prevalence of

Table 3 Characteristics of Cardiomyopathy Patients (Cases) With and Without Methamphetamine Use

Variable	Cardiomyopathy & methamphetamine use n (%)*	Cardiomyopathy & no methamphetamine use n (%)*	OR [95% CI]
Age Group			
≤30	3 (7.3)	9 (17)	1.0 Referent
>30 to 40	20 (49)	24 (44)	2.5 [0.60-10]
>40	18 (44)	21 (39)	2.6 [0.60-11]
Sex			
Female	15 (37)	17 (31)	1.0 Referent
Male	26 (63)	37 (69)	0.80 [0.34-1.9]
BMI (Kg/m^2)			
Normal (18.5 to <25)	8 (21)	5 (11)	1.0 Referent
Underweight (<18.5)	1 (2.6)	1 (2.2)	0.63 [0.003-12]
Overweight (25 to <30)	10 (26)	9 (20)	0.69 [0.17-2.9]
Obesity (≥30)	19 (50)	31 (67)	0.38 [0.11-1.3]
Race			
Caucasian	7 (17)	14 (26)	1.0 Referent
Asian	11 (27)	16 (30)	1.4 [0.42-4.5]
Pacific Islander	22 (54)	21 (39)	2.1 [0.71-6.2]
Other	1 (2.4)	3 (5.6)	0.67 [0.06-7.6]
Health insurance (current)			
No	10 (24)	14 (26)	1.0 Referent
Yes	31 (76)	40 (74)	1.1 [0.43-2.8]
Cigarette smoking			
Never	16 (39)	37 (69)	1.0 Referent
Ever	25 (61)	17 (31)	3.4 [1.5-8.0]
Alcohol use (excludes social alcohol)			
No	30 (73)	44 (81)	1.0 Referent
Yes	11 (27)	10 (19)	1.6 [0.61-4.3]
Cocaine use			
Never	35 (85)	50 (93)	1.0 Referent
Ever	6 (15)	4 (7.4)	2.1 [0.56-8.2]
Heroin use			
Never	39 (95)	54 (100)	1.0 Referent
Ever	2 (4.9)	0	–
Marijuana use			
Never	36 (88)	49 (91)	1.0 Referent
Ever	5 (12)	5 (9.3)	1.4 [0.37-5.1]
Diabetes mellitus			
No	32 (78)	40 (74)	1.0 Referent
Yes	9 (22)	14 (26)	0.80 [0.31-2.1]
Hypertension			
No	37 (90)	46 (85)	1.0 Referent
Yes	4 (10)	8 (15)	0.62 [0.17-2.2]
Atherosclerotic heart disease			
No	40 (98)	48 (89)	1.0 Referent
Yes	1 (2.4)	6 (11)	0.2 [0.02-1.7]
Renal failure			
No	36 (88)	45 (83)	1.0 Referent
Yes	5 (12.2)	9 (17)	0.69 [0.21-2.3]
Urine tested for toxicology†			
No	6 (15)	19 (35)	1.0 Referent
Yes	35 (85)	35 (65)	3.2 [1.1-8.9]

*Percentages may not add to 100% due to missing values.
†Obtained at any time during the admission

drug use. This is because urine toxicology screening is not a routine test and is performed when there is a clinical suspicion of drug use. Due to these competing concerns, approximately half of the patients in the control group were intended to have urine toxicology screening, in addition to having left ventricular ejection fraction ≥55% and absence of wall motion abnormalities by echocardiography. Since fewer cases than controls (38% vs 55%, $P=.02$) had urine tested for toxicology during admission, our results likely under-estimate the true effect size for methamphetamine use. It is conceivable that hospitalized methamphetamine users with cardiomyopathy represent patients with more

severe disease. If so, it would suggest that there are a larger proportion of non-hospitalized methamphetamine users with subclinical cardiomyopathy.

The temporal or cause-effect relationship between methamphetamine exposure and development of cardiomyopathy cannot be determined in a case control study. A prospective cohort or randomized investigation related to methamphetamine use has prohibitive costs and logistic considerations, and is challenging due to ethical concerns and characteristics of the population studied. Incentives to encourage participation in a prospective study, even if small, potentially can lead to further drug use.

Our study of young hospitalized patients at a single medical center may not be generalizable to the population as a whole. The prevalence of methamphetamine use in our study may be higher than the methamphetamine use in the general population. We selected adult patients with age $\leq$45 years for the study because ischemic cardiomyopathy is less prevalent in young patients compared to older patients. Inclusion of all age groups would have increased the generalizability of the findings but at the cost of a significantly larger sample size required to identify the fraction of patients whose cardiomyopathy is potentially related to methamphetamine use. Also, anecdotally, we have observed an increase in heart failure admissions in this age group and methamphetamine use has been suspected as a cause.

Our inclusion criteria did not encompass patients with diastolic dysfunction. Documentation of indices of diastolic dysfunction was variable during the study period. Nonetheless, our results reflect a general definition of cardiomyopathy.

Finally, our findings only applied to the smoked form of methamphetamine ("ice"), as this is the most common method of abuse in our study population.

CONCLUSIONS

Our data, if confirmed by other groups under varying demographic and study settings, lend support to the hypothesis that methamphetamine use may be a possible cause of unexplained cardiomyopathy in young patients. This would prompt obtaining a detailed history of substance use, especially of methamphetamine, and toxicology screening in young patients who present with cardiomyopathy or heart failure.

Given its widespread use, the health and socioeconomic impact of methamphetamine use on the society is potentially enormous. Future studies are required to better understand the socio-cultural and economic impact of methamphetamine abuse and to elucidate the pathophysiologic mechanisms underlying this addictive disease. Future research into the optimal management strategies of this preventable, potentially reversible, premature form of severe cardiomyopathy in young patients is important and imperative.

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