JACC: HEART FAILURE
VOL. 5, NO. 6, 2017

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2017.02.017

Clinical Characteristics, Histopathological Features, and Clinical Outcome of Methamphetamine-Associated Cardiomyopathy

Stephan Schürer, MD,[a] Karin Klingel, MD,[b] Marcus Sandri, MD,[a] Nicolas Majunke, MD,[a] Christian Besler, MD,[a] Reinhard Kandolf, MD,[b] Philipp Lurz, MD,[a] Michael Luck, MD,[a] Pia Hertel, MSc,[a] Gerhard Schuler, MD,[a] Axel Linke, MD,[a] Norman Mangner, MD[a]

ABSTRACT

OBJECTIVES This study aimed to assess characteristics including endomyocardial biopsy and outcome of patients with methamphetamine (MA)-associated cardiomyopathy in a series of patients treated in Germany.

BACKGROUND MA abuse is an increasing problem worldwide.

METHODS The cases of 30 consecutive MA-abusing patients with a left ventricular (LV) ejection fraction of <40% and endomyocardial biopsy performed at initial diagnosis were analyzed. Baseline characteristics were collected retrospectively, whereas follow-up was prospective. The primary endpoint was a composite of death, nonfatal stroke, and rehospitalization for heart failure.

RESULTS Patients were 30.3 ± 1.9 years of age, predominantly male (93.3%), and highly symptomatic; 83.3% had New York Heart Association functional class III or IV dyspnea. Echocardiography revealed marked LV dilatation (mean LV end-diastolic diameter 67.1 ± 7.4 mm) and impaired LV ejection fraction (mean 19 ± 6%). One-third of the patients had intraventricular thrombi. Endomyocardial biopsy revealed markers of inflammation and fibrosis; the fibrosis correlated with the duration of MA abuse. At follow-up, discontinuation of MA abuse together with medical therapy partially improved cardiac function (LV ejection fraction, 19 ± 6 vs. 43 ± 13; $p < 0.001$) and symptoms ($p = 0.056$), whereas patients with continued abuse did not show any improvement. The improvement in cardiac function was independently associated with the extent of fibrosis. The primary endpoint occurred more often in patients with continued MA abuse (57.1% vs. 13.0%; $p = 0.037$).

CONCLUSIONS MA-associated cardiomyopathy is characterized by severe heart failure and depressed cardiac function. The extent of myocardial fibrosis seems to predict the recoverability of LV function. Cessation of MA abuse is associated with improvement in cardiac function and symptoms, whereas continued MA abuse leads to ongoing heart failure and worse outcome. (J Am Coll Cardiol HF 2017;5:435–45) © 2017 by the American College of Cardiology Foundation.

Drug abuse and its consequences are burdens on many societies worldwide. The United Nations World Drug Report of 2015 estimated that approximately 250,000,000 people between the ages of 15 and 64 years used an illicit drug (global prevalence 5.2%) (1). Methamphetamine (MA) and related substances have become the second most frequently used drugs in the world. In 2013, there were approximately 33,900,000 users worldwide (1).

From the [a]Department of Internal Medicine/Cardiology, University of Leipzig, Heart Center Leipzig, Leipzig, Germany; and the [b]Department of Molecular Pathology, University of Tübingen, Tübingen, Germany. Dr. Linke has received speaker and consultant fees from Medtronic, St. Jude Medical, Edwards Lifesciences, Boston Scientific, Symetis, Bard, and Claret Medical; and has received stock option fees from Claret Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Schürer and Klingel contributed equally to this work.

Manuscript received November 2, 2016; revised manuscript received February 8, 2017, accepted February 10, 2017.

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

DCM = dilated cardiomyopathy

EMB = endomyocardial biopsy

LGE = late gadolinium-enhanced

LV = left ventricular

LVEF = left ventricular ejection fraction

MA = methamphetamine

MACM = methamphetamine-associated cardiomyopathy

Cardiac complications play a significant role in MA-related morbidity and include malignant hypertension, arrhythmias, aortic dissection, myocardial infarction secondary to vasospasm, stroke, and MA-associated cardiomyopathy (MACM) (2). Moreover, cardiovascular complications are the leading causes of death and were found in up to three-fourths of MA abusers in an Australian cohort (2). Various mechanisms (e.g., catecholamine excess and/or direct toxic effects of MA to the myocytes) are supposed to lead to cardiac complications, in particular MACM (3).

SEE PAGE 446

However, data on the characteristics of histopathological changes in the myocardium and the outcome of patients with MACM are rare. In particular, the reversibility of MACM after discontinuation of MA abuse has not been documented in detail (4–6). Thus we aimed to assess clinical characteristics, histopathological features, and clinical outcome in a well-defined cohort of patients presenting with MACM and to evaluate the impact of MA abuse discontinuation as opposed to uninterrupted MA abuse.

METHODS

PATIENTS AND FOLLOW-UP. Overall, 30 patients were recruited for this study: 15 patients from the Heart Center Leipzig in Leipzig, Germany; and 15 patients identified by the Department of Molecular Pathology at the University of Tübingen in Tübingen, Germany. The initial diagnosis of MACM was established between 2007 and 2016. For inclusion, patients had to have a left ventricular (LV) ejection fraction (LVEF) of <40% with endomyocardial biopsy (EMB) performed at the initial diagnosis. Baseline characteristics were collected retrospectively, whereas follow-up was prospective with visits in Leipzig for clinical and echocardiographic evaluation. Time from diagnosis until inclusion in this study was 23 ± 23 months, and prospective follow-up was 12 ± 7 months. Outcome data were available in all patients; however, echocardiographic data were available in only 27 patients (90%) because of the death of 1 patient and refusal by 2 patients. The local ethics committee approved the study, and all patients gave written informed consent at follow-up.

ENDPOINTS. The primary clinical endpoint was a composite of death, nonfatal stroke, and rehospitalization for heart failure. Secondary endpoints included the composite of death and rehospitalization for heart failure. Furthermore, the development of LVEF and symptoms were evaluated according to the status of continued or discontinued MA abuse at follow-up.

DIAGNOSTIC PROCEDURES. Every subject underwent a standardized 2-dimensional echocardiographic examination using commercial ultrasound systems and analyzed according to current recommendations (7). Diagnostic coronary angiography was performed according to local standards. EMB specimens were taken from the left ventricle, right ventricle, or both in 18, 9, and 3 patients, respectively.

ANALYSIS OF ENDOMYOCARDIAL BIOPSIES. EMB specimens were fixed in 4% buffered formaldehyde for immunohistological examination. Another sample was fixed in RNAlater (Ambion, Inc., Foster City, California) for detection of viral genomes by nested real-time polymerase chain reaction. Paraffin-embedded EMB specimens were stained with Masson's trichrome reflecting myocyte necrosis, as well as interstitial fibrosis, and were analyzed by light microscopy (8). The extent of myocardial fibrosis in EMB specimens was defined as an index, as described previously (8), and patients were classified as having no or mild, moderate, or severe fibrosis.

The analysis of inflammation was performed as described previously (9), and we refined the degree of inflammation according to a modified scheme as described (9) (grade 0 = no inflammation; grade 1 = single inflammatory cells [T lymphocytes and macrophages ≥14/mm^2]; grade 2 = a few foci of inflammation; grade 3 = several foci of inflammation; and grade 4 = pronounced inflammation).

To elucidate the effect of MA on inflammation and fibrosis, we compared the findings in patients with MACM with 31 age-, sex-, and LVEF matched patients with dilated cardiomyopathy (DCM).

STATISTICAL ANALYSIS. Categorical variables are expressed as numbers and percentages and were compared with the use of the Fisher exact test. Continuous variables are expressed as mean ± SD and were compared using the 2-sided, Student *t* test or the Mann-Whitney *U* test, as appropriate. Predictors of improvement of LVEF at follow-up were analyzed using a multiple linear regression model including 3 clinical meaningful factors that showed the highest predictor importance in an automatic linear modeling using the Akaike information criterion. Time-to-event curves were analyzed according to the method of Kaplan-Meier, and group comparisons were made by applying the log-rank test. Significance was accepted as $p < 0.05$. All analysis was performed with the use of SPSS software version 21 (IBM, Armonk, New York).