Chagas Disease Is an Independent Risk Factor for Stroke : Baseline Characteristics of a Chagas Disease Cohort

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Stroke 2005, 36:2015-2017: originally published online August 4, 2005
doi: 10.1161/01.STR.0000177866.13451.e4
Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0039-2499. Online ISSN: 1524-4628

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Baseline Characteristics of a Chagas Disease Cohort

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Background and Purpose—Chagas disease (CD) is frequently associated with cardioembolic stroke in South America. Our objective was to identify the predictors of stroke in a region where CD is endemic.

Method—We screened 305 consecutive cardiopathy patients. Significant predictors of stroke in univariable analyses were included in a multivariable model.

Results—Stroke was more frequent in CD (15.0%) compared with other cardiopathies (6.3%; $P=0.015$). Other predictors of stroke in univariable analyses were previous diabetes or cardioversion and use of amiodarone, antiplatelet agents, and warfarin. In multivariable analysis, remaining predictors of stroke were CD (odds ratio [OR], 1.09; 95% CI, 1.02 to 1.17), cardioversion (OR, 1.07; 95% CI, 1.02 to 1.13), and diabetes (OR, 1.12; 95% CI, 1.01 to 1.24).

Conclusions—In conclusion, CD is a risk factor for stroke, independent of systolic dysfunction or presence of cardiac arrhythmias. **(*Stroke*. 2005;36:2015-2017.)**

Key Words: cerebrovascular disorders ■ stroke ■ trypanosomiasis

Chagas disease (CD) affects 16 to 18 million people in Latin America.[1] In the United States, rare cases have been reported in immigrants, and vectors have been identified,[2,3] but prevalence is likely underestimated because screening for the disease in stroke patients is not routine practice.

Recently, an association between various infectious agents and stroke has been described.[4,5] In CD, stroke has been identified in patients without clinical signs of cardiopathy,[6] raising the possibility of other operative mechanisms. In the present study, we aimed to describe predictors of stroke in patients with various cardiopathies, in a region where CD is endemic.

Patients and Methods

We studied consecutive patients in a cardiomyopathy clinic. Patients were enrolled if they had clinical signs suggestive of cardiomyopathy and a transthoracic echocardiogram available within 1 year of study entry. After informed consent, patients underwent a standardized evaluation by a cardiologist, with the following collected prospectively: age, gender, history of diabetes or hypertension, alcohol abuse defined as daily alcohol use, current smoking status, history of coronary artery disease, coronary artery bypass grafting, permanent cardiac pacer use, cardiac arrest, medications currently used, electrocardiogram (ECG), echocardiographic data, and admission blood pressure. Additionally, cardiologists screened for stroke using the Questionnaire for Verifying Stroke-Free Status.[7] Patients with positive screening underwent an evaluation by a neurologist who confirmed stroke status. Cardiomyopathy was defined by the presence of low ejection fraction (EF) on echocardiogram (<40%) or a borderline-low EF (40 to 49%) plus signs of cardiac dilatation (left ventricle systolic diameter >45 mm and left ventricle diastolic diameter >55 mm). CD was confirmed by appropriate serologic assays. We then compared each variable between patients with or without stroke on enrollment. All patients are being followed in a cohort study, which was approved by the local research ethics committee.

For univariable analyses, Student *t* test was used for continuous variables, and Fisher exact test for categorical variables, with $P<0.05$ considered significant. Logistic regression was used for multivariable analysis, including variables with a possible association ($P<0.1$).

Results

We enrolled 305 patients between February 2002 and February 2003. Mean age was 53±12 years (179 males). CD was the main etiology of cardiopathy (52%). History of hypertension was the most frequent cerebrovascular risk factor (47.7%). Stroke was present in 32 (10.5%) patients, more commonly in CD (15.0%) than in other cardiopathies (6.3%; $P=0.015$). In 60 patients without evidence of systolic dysfunction (EF≥50%), stroke was present in 6 of 39 (15.4%) patients with CD and only 1 (4.8%) patient with other cardiopathies ($P=0.404$). Patients with CD had a similar frequency of atrial fibrillation and history of cardioversion as non-CD patients. Apical aneurysm with thrombus was only present in patients with CD.

Variables associated with stroke in univariable analyses (Table 1) were history of diabetes, CD, or cardioversion, and use of amiodarone, antiplatelet agents, and warfarin. Echo-

Received January 30, 2005; final revision received June 7, 2005; accepted June 14, 2005.

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Stroke **is available at http://www.strokeaha.org** **DOI: 10.1161/01.STR.0000177866.13451.e4**

TABLE 1. Univariable Predictors of Stroke

Variable	With Stroke (n=32)	Without Stroke (n=273)	P
Age, y	54±12	53±13	NS
Male gender, no. (%)	22 (69)	157 (58)	NS
Hypertension, no. (%)	17 (53)	126 (46)	NS
Diabetes, no. (%)	8 (25)	31 (11)	0.035
Coronary artery disease, no. (%)	5 (16)	29 (11)	NS
Cardiomyopathy, no. (%)	24 (75)	217 (79)	NS
Chagas disease, no. (%)	22 (69)	125 (46)	0.015
CABG, no. (%)	1 (3)	7 (3)	NS
Cardiac pacer, no. (%)	2 (6)	9 (3)	NS
Cardioversion, no. (%)	1 (3)	3 (1)	0.026
Cardiopulmonary arrest, no. (%)	1 (3)	2 (1)	NS
Alcohol abuse, no. (%)	6 (19)	50 (18)	NS
Current smoking, no. (%)	8 (25)	49 (18)	NS
Systolic blood pressure, mm Hg	113±23	124±25	NS
Diastolic blood pressure, mm Hg	77±14	81±14	NS
Echocardiogram			
Left atrium diameter, mm	42±8	42±8	NS
LVDD, mm	67±12	65±10	NS
LVSD, mm	54±12	53±11	NS
IVS, mm	7±3	7±3	NS
EF, %	39±11	39±13	NS
Apical aneurysm with thrombus, no. (%)	0 (0)	10 (4)	NS
Electrocardiogram			
Atrial fibrillation, no. (%)	4 (13)	11 (4)	0.060
Left bundle branch block, no. (%)	5 (16)	49 (18)	NS
Right bundle branch block, no. (%)	6 (19)	42 (15)	NS

LVDD indicates left ventricle diastolic diameter; LVSD, left ventricle systolic diameter; IVS, interventricular septum width; CABG, coronary artery bypass grafting; EF, ejection fraction.

cardiographic findings did not differ between patients with or without stroke.

In multivariable analysis (Table 2), remaining predictors of stroke were CD (odds ratio [OR], 1.09), cardioversion (OR, 1.07), and diabetes (OR, 1.12). Because medication use was probably consequence and not a cause of stroke in this population, we did not include these in the final analysis. If we excluded patients with concomitant CD and either hypertension or diabetes from the analysis (n=48), CD still showed a trend as a significant predictor of stroke (OR, 1.07; 95% CI, 0.99 to 1.15; $P=0.068$).

Discussion

CD remains an important cause of cardiopathy in South America. The presence of apical aneurysm and intracardiac thrombus are hallmarks of the disease, making CD a highly embolic condition.[8]

TABLE 2. Multivariable Predictors of Stroke

Variable	OR	95% CI	P
Diabetes mellitus	1.12	1.01–1.24	0.026
Cardioversion	1.07	1.02–1.13	0.006
CD	1.09	1.02–1.17	0.011

The main finding of our study was an independent association between CD and stroke. Previously, neurological manifestations of the chronic form of CD have been attributed to embolic phenomenon.[8] However, case series have reported stroke in patients with CD without clinical evidence of cardiopathy.[6] A case-control study also established CD as an independent risk factor for stroke but did not correct for presence or severity of cardiac disease.[9] In our patients, stroke was frequently present in patients without evidence of systolic dysfunction by echocardiogram, and the relationship between CD and stroke was independent of cardiac disease severity. When excluding important confounders for stroke risk such as hypertension and diabetes, CD still showed marginal significance ($P=0.068$) as an independent predictor for stroke, a hypothesis that should be confirmed in future studies.

The reason for an association between CD and stroke is speculative. Associations between chronic infections and stroke have been attributed to activation of inflammatory and coagulation cascade, endothelial dysfunction, and atherogenesis.[4,5] In CD, a chronic activation of the immune system

occurs, with persistent lymphomonocytic myocarditis and fibrosis.[10] In experimental CD, microvascular damage,[11,12] endothelial cell changes,[13] and hyperviscosity[14] have been demonstrated. We hypothesize that such chronic inflammation may explain, at least in part, our findings of stroke in patients without criteria for cardiomyopathy. However, we cannot fully exclude that CD patients with stroke could have intermittent cardiac arrhythmias undetected on clinical examination, history or EKG, or intracardiac thrombus undetected by transthoracic echocardiogram.

There are limitations to our study. First, our population is selected, including only patients with clinical signs of cardiomyopathy. Thus, no patients with latent, arrhythmic or gastrointestinal forms of CD were studied. Second, no data were collected regarding stroke subtypes, which might differ according to the cardiomyopathy etiology. In the present cohort, we are currently collecting data on carotid duplex sonography and neuroimaging, which will allow for a more complete classification.

Acknowledgments

J.O.-F. is supported in part by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) grant 304094/2002-1, and by National Institutes of Health grant R21TW006679-01.

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