Chagas Disease Predicts 10-Year Stroke Mortality in Community-Dwelling Elderly

The Bambu Cohort Study of Aging

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Background and Purpose—Previous case–control studies have suggested a causal link between Chagas disease, which is caused by the protozoan *Trypanosoma cruzi*, and stroke. We investigated the relationship between Chagas disease and long-term stroke mortality in a large community-based cohort of older adults.

Methods—Participants were 1398 (80.3% from total) residents aged ≥60 years in Bambu City, Brazil. The end point was death from stroke. Potential confounding variables included age, sex, conventional stroke risk factors, and high sensitive C-reactive protein.

Results—Participants of this study were followed from 1997 to 2007 leading to 9740 person-years of observation. The baseline prevalence of *T. cruzi* infection was 37.5% and the overall mortality rate from stroke was 4.62 per 1000 person-years. The risk of death from stroke among *T. cruzi*-infected participants was twice that of those noninfected (adjusted hazard ratio, 2.36; 95% CI, 1.25 to 4.44). A B-type natriuretic peptide level in the top quartile was a strong and independent predictor of stroke mortality among those infected (adjusted hazard ratio, 2.72; 95% CI, 1.25 to 5.91). The presence of both a high B-type natriuretic peptide level and electrocardiographic atrial fibrillation increased the risk of stroke mortality by 11.49 (95% CI, 3.19 to 41.38) in these individuals.

Conclusions—This study provides new evidence supporting a causal link between Chagas disease and stroke. The results also showed that B-type natriuretic peptide alone or in association with atrial fibrillation has prognostic value for stroke mortality in *T. cruzi* chronically infected older adults. **(*Stroke*. 2010;41:2477-2482.)**

Key Words: brain natriuretic peptide ■ Chagas disease ■ epidemiology ■ etiology ■ prognosis ■ risk factors ■ stroke mortality ■ *Trypanosoma cruzi*

Chagas disease (ChD), which is caused by the protozoan *Trypanosoma cruzi*, is an individual and public health issue in Latin American countries with approximately 8 million people infected.[1] As a consequence of immigration from endemic countries, ChD is also an emerging issue in North America and Europe[2] and an example in the era of globalization of how infectious diseases extend beyond endemic areas.[3] Approximately 30% of infected individuals develop chagasic cardiomyopathy with heart failure, heart block, ventricular arrhythmias, and cardioembolic phenomenon.[4] A chronic activation of the immune system occurs in ChD[5] and endothelial cell changes have also been demonstrated.[6] All of these mechanisms may predispose to stroke.

Stroke has been an unrecognized complication of ChD until recently.[3] Only in the last decade has evidence emerged from hospital-based case–control studies linking both conditions.[7–9] However, the strength of the association between ChD and stroke varies largely with multivariate ORs ranging from 1.1[8] to 7.2[9] and 16.2.[7] Case–control studies are prone to selection bias and to residual confounding mainly by conventional stroke risk factors and life-course socioeconomic factors,[10] which may partially explain the variation found.

Follow-up studies of hospitalized patients with chagasic cardiopathy showed that the incidence of stroke is low in these individuals: 1% for fatal stroke[11] and approximately 3% for clinical ischemic stroke[12,13] in follow-up periods ranging from 1 to 3 years. However, no previous cohort study has compared the risk of stroke in *T. cruzi*-infected and noninfected individuals.

B-type natriuretic peptide (BNP), which is released from cardiomyocytes in response to ventricular wall stretch, has emerged as a novel biomarker to predict cardiovascular events. A recent meta-analysis of cohort studies showed that the risk for stroke was almost double in individuals with high

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baseline BNP levels in relation to those with lower values.[14] Increased BNP levels are seen in patients with cardiomyopathy due to ChD, particularly in the presence of left ventricular dysfunction[15] Furthermore, a large community-based study showed that there was a graded and strong cross-sectional relationship between BNP levels and *T. cruzi* infection and that BNP was an independent predictor for 10-year all-cause mortality in *T. cruzi*-infected older adults[16] These raise the hypothesis that BNP is a predictor of stroke in ChD.

We used data from 10 years of follow-up of the Bambu Cohort Study of Aging in Brazil to (1) estimate the risk for death from stroke associated with *T. cruzi* infection; and (2) examine whether BNP level predicts this outcome among infected individuals.

Methods

Study Design and Population

The study was conducted in Bambu , a city of approximately 15 000 inhabitants, located in southeastern Brazil, which is an area long known to be endemic for ChD.[17] The intensive use of insecticides interrupted the household transmission of *T. cruzi* infection in the study area by 1970. As a consequence, by the mid-1990s, seropositive cases were no longer seen in young people, but the infection remained highly prevalent among elderly residents who had acquired the infection in their youth.[18]

The cohort study procedures have been described in detail elsewhere.[19] Briefly, the baseline cohort population consisted of all residents aged ≥60 years on January 1, 1997, who were identified by means of a complete census in the city. From a total of 1742 older residents, 1606 (92.2%) participated in the baseline survey. Baseline data collection was performed from February to May 1997, including standardized interviews, blood tests, blood pressure measurements, and electrocardiograms (ECGs). Cohort members undergo annual follow-up visits, which consist of an interview and verification of death certificates. Participants signed an informed consent and authorized death certificate verification. The Bambu Cohort Study of Aging was approved by the Ethics Board of the Fundação Oswaldo Cruz, Brazil.

Mortality Data Source

Deaths occurring from the study enrollment to December 31, 2007, were included in this analysis. Deaths were reported by next of kin during the annual follow-up interview and confirmed through the Brazilian System of Information on Mortality (Sistema de Informações sobre Mortalidade) with the permission of the Ministry of Health. Deaths certificates were obtained for 98.9% of individuals. Codes were assigned according to the *International Classification of Diseases, 10th Revision*. Deaths assigned to stroke (*International Classification of Diseases, 10th Revision*: I61, I63, I64, I66, and I69) were the outcome variable in this analysis.

Chagas Disease-Related Measures

Infection with *T. cruzi* was assessed at baseline by 3 different assays performed concurrently: a hemagglutination assay (Biolab Mérieux) and 2 enzyme-linked immunoabsorbent assays (Abbott and Wiener). The agreement (Cohen κ) among these assays was 0.989 ($P<0.001$). Infection was defined by seropositivity in all 3 examinations, and absence of infection was defined as consistent seronegativity. Individuals with inconsistent serological results in ≥1 assays were excluded from the analysis. Twelve-lead ECGs at baseline were digitally recorded (Hewlett Packard MI700A) using standardized procedures. ECGs were analyzed at the ECG Reading Center EPICARE (Wake Forest University) and classified according to the Minnesota code criteria.[20] Left and right complete bundle branch block (Minnesota code: 7.1, 7.2, 7.4, or 7.8) and frequent ventricular premature beats (Minnesota code: 8.1.2 or 8.1.3), leading alterations associated with ChD,[17,21] and atrial fibrillation (Minnesota code: 8.3.1), an alteration associated with stroke,[22,23] were included in this analysis.

The benefit and safety of treating chronic *T. cruzi* infection in old age is uncertain.[24] None of the cohort participants had a history of antitrypanosomal medication on entry into the cohort, and none received treatment during the period in which patients were followed. Treatment of the chronic phase of ChD is directed at the management of heart failure. Digoxin was the medication most commonly used for heart failure by cohort members and was considered in this analysis. Digoxin use was ascertained during the household interview by reviewing prescriptions and/or the medication packaging.

B-Type Natriuretic Peptide

Blood samples for measurement of BNP were collected at baseline in tubes containing ethylenediaminetetraacetic acid. BNP was measured using a microparticle-based immunoassay (MEIA/AxSYM; Abbott). The lower limits of detection and the average interassay coefficients of variation in this assay are <15 pg/mL and 12%, respectively. Subjects were asked to fast for 12 hours before phlebotomy (6:30 to 8:30 AM). Aliquots were stored at −80°C until used.

Other Measures

Other baseline measures considered in this study included: sociodemographic characteristics (age, sex, and number of complete years of schooling), conventional risk factors for stroke[22] (systolic blood pressure, diabetes mellitus, smoking, coronary heart disease, and left ventricular hypertrophy by ECG (Minnesota code: 3.1 and 4.1.x, 4.2, 5.1, 5.2), and high sensitive C-reactive protein, a nonspecific measure of inflammation. Systolic blood pressure was defined by the mean of 2 of 3 measures by using a standard protocol. Diabetes mellitus was defined as a fasting blood glucose level ≥126 mg/dL and/or current use of hypoglycemic medication. Current smokers were those who had smoked at least 100 cigarettes in their lifetime and were still smokers. Coronary heart disease was defined by a previous medical diagnosis of myocardial infarction or angina pectoris. The number of conventional stroke risk factors was defined by the sum (yes=1) of systolic blood pressure ≥140 mm Hg, diabetes mellitus, smoking, coronary heart disease, and left ventricular hypertrophy on ECG. High sensitive C-reactive protein was determined by immunoturbidimetry (Siemens).

Statistical Analysis

The analysis of the associations between baseline characteristics and *T. cruzi* infection was based on age- and sex-adjusted prevalence ratios and robust 95% CIs estimated by Poisson regression. Hazard ratios (HRs) and 95% CI for death from stroke were estimated by using Cox proportional hazards models after confirming that the assumption of proportionality was met. Population-attributable risks and 95% CI for death from stroke were estimated by means of univariate and multivariate Poisson regression. For the association between *T. cruzi* infection and death from stroke, a sensitivity analysis of the accuracy of death certificates was performed to quantify systematic errors in the way cause of death was classified. These analyses were based on 60% to 80% theoretical levels of sensitivity and specificity. Because we did not have statistical power for separate analyses for sex, all the analyses were for both men and women with sex as a covariate. Statistical analyses were conducted using STATA 11.0 statistical software (Stata Corp, College Station, Texas). All probability values were 2-tailed ($\alpha=0.05$).

Results

Of the 1606 cohort subjects enrolled, 1398 (87.1%) for whom complete data were available for all study variables were included in the analysis. Subjects were excluded from the analysis if serological tests for *T. cruzi* infection were not

Table 1. Baseline Characteristics of the Study Participants by *Trypanosoma cruzi* Infection, the Bambu Cohort Study, 1997

Characteristics	Total (n=1398)	*Trypanosoma cruzi* Infection		Age- and Sex-Adjusted Prevalence Ratio (95% CI)
		Yes (n=524)	No (n=874)	
Age, mean years (SD)	68.9 (7.0)	69.2 (6.9)	68.6 (7.0)	1.04 (0.99–1.09)
Female sex, %	60.8	67.9	56.5	1.37 (1.17–1.58)†
Schooling inferior to 4 years, %	63.7	84.0	51.5	2.95 (2.39–3.62)†
Systolic blood pressure, mean mm Hg (SD)	137.4 (22.4)	135.5 (22.9)	138.6 (22.0)	1.00 (0.91–1.00)*
Diabetes mellitus, %	14.3	10.5	16.6	0.69 (0.55–0.87)†
Smoking, %	17.1	16.8	18.4	1.04 (0.86–1.26)
Coronary heart disease, %	11.5	11.5	11.6	0.97 (0.74–1.27)
Left ventricular hypertrophy by ECG, %	3.2	1.7	4.0	0.54 (0.31–0.97)*
C-reactive protein, mg/L, median (interquartile range)	3.25 (1.42–6.70)	3.04 (1.40–6.35)	3.29 (1.41–6.40)	0.99 (0.97–1.01)
BNP, pg/dL, median (interquartile range)	80 (43–148)	121 (63–205)	64 (34–112)	1.06 (1.06–1.09)†
Use of digoxin %	14.3	20.8	10.4	1.57 (1.36–1.83)†
Atrial fibrillation by ECG, %	3.3	5.9	1.7	1.86 (1.49–2.31)†
Right bundle branch block by ECG, %	10.9	23.5	3.3	7.44 (4.95–11.17)†
Left bundle branch block by ECG, %	2.6	3.4	2.1	1.63 (0.84–3.16)
Frequent ventricular premature beats by ECG, %	6.4	10.1	4.2	1.65 (1.37–1.98)†

The prevalence ratios were computed for a 5-year increment for age, continuous for systolic blood pressure, and 10 percentile unit increments for C-reactive protein and BNP. All other variables compared presence versus absence.

*$P<0.05$.

†$P<0.01$.

performed (n=110), if the results were inconclusive (n=17), or if data for any other study variable was missing (n=81). Subjects included in the analysis were younger than those excluded (mean age [SD]=68.9 [7.0] versus 72.4 [9.3] years, respectively; $P<0.001$); female sex predominated in both groups (60.8% and 54.8%, respectively; $P=0.100$).

Six percent of the original cohort participants were lost to follow-up. Those who were lost were younger than those followed (mean age [SD]=67.3 [5.9] and 69.0 [7.2] years, respectively; $P=0.033$). Women were similarly represented in both groups (61.0% and 57.3%, respectively; $P=0.485$).

From a total of 512 deaths among cohort members during the study period, 45 were assigned to stroke (25 among *T. cruzi*-infected individuals). Participants of this study were followed for a mean period of 7.0 years, leading to 9740 person-years of observation (3479 person-years among infected). The 10-year cumulative incidence of death from stroke among *T. cruzi*-infected and noninfected individuals was 4.8% (25 of 524) and 2.3% (20 of 874), respectively.

Table 1 shows baseline participants characteristics according to *T. cruzi* infection status. The prevalence of *T. cruzi* infection was 37.5%. Age- and sex-adjusted prevalence ratios showed significant and positive associations between *T. cruzi* infection and female sex, low schooling level, BNP level, digoxin use, atrial fibrillation, right bundle branch block, and frequent ventricular premature beats. Negative and significant associations with *T. cruzi* infection were found for systolic blood pressure, diabetes mellitus, and left ventricular hypertrophy.

HRs for the association between baseline *T. cruzi* serology and death from stroke are shown in Table 2. The risk of death from stroke among *T. cruzi*-infected subjects was double the risk for noninfected individuals. The fully adjusted model yielded an adjusted HR for death from stroke of 2.35 (95% CI, 1.25 to 4.44). Population-attributable risk for death from stroke due to *T. cruzi* infection was 30.0% (95% CI, 3.5% to 49.3%) in the crude analysis and 29.9% (2.5% to 48.2%) in the fully adjusted analysis.

The results of a sensitivity analysis showed that the association between *T. cruzi* infection and subsequent death from stroke would persist even if the accuracy of the death certificate to correctly classify the cause of death was moderate to low. For theoretical levels of both sensitivity and specificity values of 80%, 70%, and 60%, the fully adjusted HRs were 1.91 (95% CI, 1.32 to 2.77), 1.63 (95% CI, 1.18 to 2.24), and 1.41 (95% CI, 1.19 to 1.68), respectively.

Table 2. HRs for 10-Year Stroke Mortality Among *Trypanosoma cruzi* Seropositive Individuals Compared With Seronegative Individuals, the Bambu Cohort Study, 1997–2007

Trypanosoma cruzi Infection	No. Deaths/Person-Years at Risk (Death Rate per 1000)	HR (95%CI) Adjusted for Age and Sex	HR (95% CI) Adjusted for Age, Sex, Schooling, and No. of Conventional Risk Factors	HR (95%CI) Adjusted for Age, Sex, Schooling, No. of Conventional Risk Factors, and C-reactive Protein Level
Noninfected	20/6261 (3.19)	1.0	1.0	1.0
Infected	25/3479 (7.58)	2.28 (1.26–4.12)	2.35 (1.25–4.42)	2.35 (1.25–4.44)

Table 3. HRs and 95% CIs for 10-Year Stroke Mortality Among *Trypanosoma cruzi*-Infected and Noninfected Individuals by Selected Baseline Characteristics, the Bambu Cohort Study, 1997–2007

Characteristics	Infected Age- and Sex-Adjusted HR (95% CI)	Noninfected Age- and Sex-Adjusted HR (95% CI)
Age	1.34 (1.00–1.82)	1,22 (0.88–1.70)
Female sex	1.31 (0.52–3.29)	0.59 (0.24–1.42)
Schooling inferior to 4 years	1.09 (0.49–2.41)	0.81 (0.37–1.37)
No. of conventional stroke risk factors	1.39 (0.87–2.22)	2.39 (1.49–3.83)†
C-reactive protein	1.03 (0.96–1.11)	1.03 (0.96–1.12)
BNP, pg/dL	1.08 (1.01–1.17)*	1,13 (1.04–1.23)†
Digoxin medication	1.00 (0.37–2.74)	1.16 (0.26–5.08)
Left bundle branch block by ECG	2.27 (0.17–9.52)	1.16 (0.26–5.08)
Right bundle branch block by ECG	1.79 (0.77–4.19)	2.39 (0.31–18.56)
Frequent ventricular premature beats by ECG‡	1.94 (0.65–5.81)	. . .
Atrial fibrillation by ECG‡	3.87 (1.26–11.91)†	. . .

The prevalence ratios were computed for a 5-year increment for age, continuous for systolic blood pressure, and 10 percentile unit increments for C-reactive protein and BNP. All other variables compared presence versus absence.

*$P<0.05$.

†$P<0.01$.

‡HR were not computed for the noninfected due to small numbers in the exposed group.

Among *T. cruzi*-infected individuals, ECG-documented atrial fibrillation showed the strongest predictive value for death from stroke followed by BNP level; age was at the borderline of the statistical significance. Among noninfected, the number of conventional risk factors and baseline BNP levels showed significant associations with the outcome. Other variables were not associated with death from stroke in either groups (Table 3).

Table 4 shows the results of the multivariate analysis of the separate and joint effect of baseline ECG-documented atrial fibrillation and BNP level on death from stroke with noninfected individuals as the reference group. Those infected, but lacking both risk factors, were not at increased risk of death from stroke. High BNP alone (top quartile) increased the risk of stroke death by 2.85 (95% CI, 1.31 to 6.19). Our results also suggest an increased risk associated with atrial fibrillation alone (HR, 4.97; 95% CI, 0.64 to 35.57), but the statistical power was insufficient for a conclusive result. The presence of both risk factors increased the risk of death from stroke 11.49-fold (95% CI, 3.19 to 41.38).

Discussion

This cohort study with 9740 person-years of follow-up provides epidemiological evidence of a strong association between ChD and death from stroke in community-dwelling elderly. *T. cruzi*-infected individuals were at twice the risk of death from stroke than individuals who were not infected independent of age, sex, schooling, conventional risk factors, and high sensitive C-reactive protein.

The predictive value of atrial fibrillation[22,23] and of increased BNP levels[14] for stroke has been well established in the context of nontransmissible diseases. Individuals infected with *T. cruzi* are more likely to present atrial fibrillation and increased BNP levels as observed in the baseline survey of this study. Also, a previous case–control study reported an association between atrial fibrillation on ECG and stroke in patients with chagasic cardiomyopathy.[25] Our results add to previous studies by showing that first, high BNP levels predicted death from stroke in *T. cruzi* chronically infected elderly; and second, the presence of both BNP and atrial fibrillation increased substantially the risk of stroke mortality in these individuals.

Two main mechanisms might explain stroke in ChD: cardioembolic phenomena and inflammation.[3,8,12,13,25] High sensitive C-reactive protein, a nonspecific marker of inflammation, was not found to be a predictor of stroke mortality in this study. Both the dysfunctional left atrial appendage observed in atrial fibrillation as well as the dilated ventricle observed in the left ventricular systolic dysfunction are sites of thrombus formation that predispose to cardioembolism.[12,26] Thus, the association between high BNP level (which is closely related with left ventricular systolic dysfunction in ChD[15]) and atrial fibrillation with deaths to stroke found in this study support the cardioembolic hypothesis of stroke in ChD. However, the absence of echocardio-

Table 4. HRs and 95% CIs for 10-Year Mortality Among *Trypanosoma cruzi*-Infected Individuals Compared With Noninfected Individuals by the Separate and Joint Effects of Baseline Plasma BNP and ECG Atrial Fibrillation, the Bambu Cohort Study of Aging, 1997–2007

Combinations of BNP Level and Atrial Fibrillation Among Infected	No. of Deaths/Person-Years at Risk (Death Rate per 1000)	HR (95%CI) Adjusted for Age, Sex, Schooling, No. of Conventional Risk Factors, and C-reactive Protein	*P*
Noninfected	20/6261 (3.20)	1.0	
Infected			
No AF and BNP in lower quartiles	10/2114 (4.73)	1.61 (0.73–3.58)	0.239
AF and BNP in lower quartiles	1/0067 (14.93)	4.97 (0.64–38.57)	0.125
No AF and BNP in top quartile	11/1222 (9.0)	2.85 (1.31–6.19)	0.008
AF and BNP in top quartile	3/0076 (39.47)	11.49 (3.19–41.38)	<0.001

AF indicates atrial fibrillation.

graphic evaluation in the study population precludes further conclusions.

Our results showed that use of digoxin did not attenuate the risk of stroke mortality. Our analysis did not confirm previous reports of an association between stroke in ChD and young age,[25] female sex,[9,25] and right and left bundle branch block on ECG.[25] We found a strong cross-sectional association between low schooling level (an indicator of socioeconomic status) and *T. cruzi* infection. Schooling, however, was not found to be associated with subsequent death from stroke. Among noninfected elderly, predictors of deaths from stroke were as expected, that is, number of conventional stroke risk factors[22] and increased BNP level.[14]

Strengths of this study include the community-based sample (and its size), the standardized and systematic measurement of parameters at baseline, continuous surveillance for mortality according to standardized criteria, and minimal loss of participants to follow-up. These allowed meaningful estimates of risks of mortality from stroke over a long period of time. This study has some limitations. Cause of death was obtained from death certificates and, thus, the outcome measure is subject to misclassification bias. However, it is unlikely that this would have affected the associations found for 2 reasons; first, a sensitivity analysis showed that the association between *T. cruzi* infection and death from stroke would remain significant even if the accuracy of death records were as low as 60%; and second, a previous study showed that neither baseline *T. cruzi* infection nor cardiovascular risk factors or diseases were associated with future deaths assigned to ill-defined conditions (*International Classification of Diseases, 10th Revision* codes R00 to R99) in the study population.[27] There were only 25 deaths to stroke among the infected cohort members indicating a low event rate. This potentially limits the statistical power to detect small effects in our analysis. Surveillance bias is unlikely because ChD is still an underrecognized risk factor for stroke.

The evidence from this and from previous studies[3,7–9] supports a causal link between *T. cruzi* infection and stroke. *T. cruzi* infection is not a sufficient cause for stroke, but when Bradford Hill's classic criteria for causality[28] are applied, 7 of 9 criteria are met: (1) strength of the association (strong association in this and in 2 previous case–control studies[7,9]); (2) consistency (association found in this cohort study and in 3 previous case–control studies[7–9]); (3) specificity (the association was limited to those who also had increased BNP levels and/or atrial fibrillation and persisted after adjustments for conventional risk factors); (4) temporality (this cohort study established a temporal sequence between *T. cruzi* infection and the outcome); (5) coherence (the association is in agreement with the natural history of ChD[3,4]); (6) plausibility (the association is biologically plausible); and (7) analogy (increased BNP levels and/or atrial fibrillation predicts stroke in nontransmissible diseases[14,22,23]). A dose–response relationship and experimental evidence were not accomplished. A dose–response relationship was not shown for any single infectious agent in previous studies.[10] Experimental evidence is seldom available for human populations.

Conclusions

Our results provide new evidence supporting a causal link between *T. cruzi* chronic infection and stroke. Our results also showed that BNP alone or in association with atrial fibrillation has prognostic value for stroke mortality in *T. cruzi* chronically infected elderly.

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Disclosures

None.

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