Chagas Disease: 101 Years of Solitude!
Time for Action

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See related article, pages 2477–2482.

O
ne hundred and one years ago, Carlos Chagas made the
description of American trypanosomiasis, better known as
Chagas disease, a neglected disease that still remains a major
public health problem with significant social and economic
implications in most Latin American countries.1,2

The severity of stroke associated with Chagas disease has not
been systematically studied and the role of the persistence
of low-grade parasitemia has not been established as a factor
that plays a role in the pathophysiology. The baseline inci-
dence of stroke in >2200 patients enrolled in the BENzi-
dazole Evaluation For Interrupting Trypanosomiasis (BENEFIT)
trial,3 a randomized placebo-controlled study evaluating the role
of benznidazole in patients with early Chagas cardiomyopathy,
is 5% with a 7% rate of atrial fibrillation at the time of enrolment
(unchanged data). Stroke is one of the composite primary
outcomes that BENEFIT is evaluating and this study will be the
first to determine whether antitypansomal therapy reduces
stroke among other clinically significant outcomes. Sadly, after
more than a century, several questions remain unanswered
regarding the course and recurrence of stroke in this overly
neglected population.

In this issue of Stroke, Lima-Costa and collaborators report
their experience derived from a case–control study (the Bambui study)
that determined the 10-year stroke mortality in a community of subjects ≥60 years of age infected with T. cruzi, 9740 person-years of follow-up provided evidence of a
strong association between Chagas disease and death from
stroke. In this cohort with a mean follow-up of 7.0 years, the
prevalence of T. cruzi infection was 37.5% and 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. Individuals had a very
high prevalence of T. cruzi infection and were at twice the
risk of death from stroke than individuals who were not infected.
These observations were independent of age, gender,
schooling, conventional risk factors and high sensitive
C-reactive protein.

Interestingly, high brain natriuretic peptide levels predicted
death from stroke in chronically infected patients (2.85 [95% CI, 1.31 to 6.19]). Atrial fibrillation was also found to be
associated with death from stroke in this population, albeit
not statistically significant (hazard ratio, 4.97; 95% CI, 0.64
to 35.57). Serological documentation alone was not associ-
ated with increased risk of death from stroke. The presence of
dysfunction, female gender, hypertension, and cardiac ar-
rhythmias have been demonstrated to be associated with
stroke in patients with Chagas disease.4 The prevalence of
apical aneurysm and mural thrombus in subjects with cardio-
myopathy has been estimated at 37% with 11.7% presenting
with stroke.5 Nonetheless, different studies have suggested
that stroke may occur in the absence of any of the risk factors
discussed, independent of systolic dysfunction or presence of
cardiac arrhythmias.6 In a few series, the diagnosis of
Chagas disease was established after presentation with stroke
in approximately 40% of the patients.7,8

The most feared clinical manifestation of Chagas disease is
the development of cardiomyopathy that occurs in approxi-
mately 30% of infected subjects. Clinical manifestations are
varied, including typical intraventricular conduction abnor-
malities, congestive heart failure, sudden cardiac death,
arhythmias and thromboembolism. Cerebral infarction has
been reported in up to 17.5% in autopsies of chagasic patients
with cardiomyopathy and its presence and complications
have been associated with death in 52% of the cases.9

Stroke from cardioembolic etiology has been reported to be
high compared with atherothrombotic strokes in patients
infected with T. cruzi. Carod-Artal et al reported, in a
case–control series, a prevalence of cardioembolism of
56.38% and 9.33% of chagasic patients and control subjects,
respectively (P=0.000), with atherothrombotic stroke in con-
trast occurring in 8.51% versus 20% (P=0.016) and small-
vessel stroke in 9.57% versus 34.67% (P=0.000).10

Several risk factors such as heart failure, mural thrombus,
left ventricular apical aneurysm, left ventricular systolic

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both risk factors (atrial fibrillation and high brain natriuretic peptide) increased substantially the risk of death from stroke by 11.49-fold (95% CI, 3.19 to 41.38). Two possible mechanisms could explain this strong association: cardioembolic phenomena and inflammation. Although the investigators have discussed the potential role of inflammation in this setting, high sensitive C-reactive protein levels were not found to be a predictor of stroke mortality, not entirely supporting the inflammation hypothesis. Nonetheless, the inflammation hypothesis cannot be completely discarded because other markers of inflammation and increased immune response were not reported and have been clearly associated with the progression of Chagas disease such as tumor necrosis factor-α and other markers. Adventitia of high brain natriuretic peptide, a manifestation of left ventricular systolic dysfunction, suggests a pathological link between heart failure and stroke in T. cruzi-infected individuals. Further studies are needed to prove this interesting finding because potentially prevention of progression of Chagas cardiomyopathy could lead to reduced stroke. The Bambuí study provides several new insights into our understanding of Chagas disease and the significant role of stroke in this population; however, this cohort may not be necessarily representative of the general Chagas population because the incidence of the disease is higher than in other regions, and this was an older cohort, potentially affecting the outcomes. Nonetheless, the authors should be commended for providing a “Framingham” type of study in a population that has been neglected long enough. This information should spark further research and potentially improve the prophylaxis of stroke in this population.

In summary, the study by Lima-Costa and collaborators provides new insight into the devastating consequences of Chagas disease and the high incidence of stroke. The role of atrial fibrillation and brain natriuretic peptide levels is important and clinicians both in endemic and nonendemic countries taking care of patients with stroke should keep in mind the diagnosis of Chagas disease. Finally, after 101 years of being neglected, it is time to promote further research and improve outcomes in this devastating disease. The time to act has arrived and clinical trials and studies like the Bambuí cohort will help change the course of the disease once and forever.

Disclosures

None.

References


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