Chagas Disease: 101 Years of Solitude!

Time for Action

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See related article, pages 2477–2482.

One 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 Approximately 8 million people in Latin America are affected3 and the Pan American Health Organization estimated that 109 million individuals were at risk and nearly 7.7 million individuals were infected in 2005.4,5 Globalization has led to a recent increased awareness of Chagas disease because it is becoming an emerging health problem in nonendemic areas.6–9 In the United States, >300,000 individuals are reportedly infected with Trypanosoma cruzi and Spain has reported that between 47,738 to 67,423 individuals are infected.7,8 Although the mortality rate related to Chagas disease has been decreasing, in 2006, this disease was responsible for 12,500 deaths.2

The most feared clinical manifestation of Chagas disease is the development of cardiomyopathy that occurs in approximately 30% of infected subjects. Clinical manifestations are varied, including typical intraventricular conduction abnormalities, congestive heart failure, sudden cardiac death, arrhythmias 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.10

Stroke from cardiomebolic 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 study, a prevalence of cardiomebolic stroke of 56.38% and 9.33% of chagasic patients and control subjects, respectively (P=0.000), with atherothrombotic stroke in contrast occurring in 8.51% versus 20% (P=0.016) and small-vessel stroke in 9.57% versus 34.67% (P=0.000).11

Several risk factors such as heart failure, mural thrombus, left ventricular apical aneurysm, left ventricular systolic dysfunction,12 female gender, hypertension, and cardiac arrhythmias have been demonstrated to be associated with stroke in patients with Chagas disease.11 The prevalence of apical aneurysm and mural thrombus in subjects with cardiomyopathy has been estimated at 37% with 11.7% presenting with stroke.13 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.14 In a few series, the diagnosis of Chagas disease was established after presentation with stroke in approximately 40% of the patients.12,15

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 incidence of stroke in >2200 patients enrolled in the BENznidazole Evaluation For Interrupting Trypanosomiasis (BENEFIT) trial,16 a randomized placebo-controlled study evaluating the role of benznidazole in patients with early Chagas cardiomypathy, is 5% with a 7% rate of atrial fibrillation at the time of enrolment (unpublished data). Stroke is one of the composite primary outcomes that BENEFIT is evaluating and this study will be the first to determine whether antitrypanosomal 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.17

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 significance (hazard ratio, 4.97; 95% CI, 0.64 to 35.57). Serological documentation alone was not associated with increased risk of death from stroke. The presence of...
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.18

The finding 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 Bambui 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 Bambui cohort will help change the course of the disease once and forever.

Disclosures
None.

References
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