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ORIGINAL ARTICLE

Epidemiology of concurrent Chagas disease and ischemic stroke in a population attending a multicenter quaternary rehabilitation network in Brazil

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Abstract

Background and purpose Chagas disease and ischemic stroke (IS) have a close but poorly understood correlation. In endemic settings, continued transmission over time has resulted in increasing prevalence of both asymptomatic infection and cardiomyopathy with increasing age. Latin America has made substantial progress towards Chagas disease control. Although several epidemiological studies have been conducted, information regarding epidemiology and distribution of IS in Chagas disease is still lacking.

Methods We retrospectively studied the electronic medical record data of all patients with both IS and Chagas disease admitted at SARAH Hospitals across Brazil from 2009 to 2013 to make epidemiological quantifications and statistical inferences.

Results A total of 279 patients with Chagas disease and IS were analyzed from 7729 IS-related admissions, indicating a median prevalence of 3.6% of Chagas disease in IS patients in our cohort. Mean age was 60 years, with female predominance (65%). Most of the cases were from Bahia (61%), followed by Minas Gerais (19%) and Goiás (9.7%). Low-income cities, with decreased access to healthcare, showed the highest number of cases. Distribution of vascular risk factors and outcome after stroke differed among the units. According to current guidelines, secondary prevention was inadequate in 60% of patients.

Conclusions Chagas disease was common in IS patients; prevalence of concurrent Chagas disease and IS was high in some regions of the country. However, the infection frequency seems to be reduced in the last few years. Public health issues for improving the treatment of Chagas disease and IS are urgently needed.

Keywords Chagas disease · Ischemic stroke · Epidemiology

Abbreviations

IS	Ischemic stroke
CT	Computed tomography
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
S S S - CCS	Stop Stroke Study Causative Classification System
TOAST	Trial of ORG 10172 in Acute Stroke Treatment

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Introduction

Chagas disease, described in 1909, is a chronic disease caused by the parasite *Trypanosoma cruzi* that primarily affects the heart and/or digestive system [1, 2]. Over 16 million people are infected worldwide, with most cases in South America; however, cases involving immigrants have also been described, raising concerns about possible blood-borne transmission [3]. There is growing concern regarding Chagas disease prevalence, especially in the developed world, considering the changes in migration flows [2]. In Brazil, although

infections transmitted via *Triatoma infestans* have been deemed eradicated since 2006, hematological and other means of transmission have been described. Since the start of the Bambui cohort study, progress has been made in describing the epidemiological and geographical distribution of Chagas disease in Brazil [4–6]. Old age and few new infections have been the mainstay of the findings [7–9].

The classical form of transmission of this infection is vector-borne, via *Triatoma infestans* [7]. It is important to notice that classical stercorarian transmission (through feces of an infected vector) is relatively inefficient; generally, incidence of *T. cruzi* infections is estimated to be < 1% per year. The highest estimated incidence of 4% per year is observed in the hyperendemic Bolivian Chaco [10]. There have also been concerns regarding other forms of contagion, such as consumption of contaminated açaí (a local fruit common in north Brazil) [9] and through work-related illnesses of piassaba (a plant also common in the northern region) gatherers [11]. Data also corroborates an increase in such alternative forms of infection [9].

Besides cardiac and digestive system involvement, stroke, especially ischemic, has been related to Chagas disease. Although the correlation between Chagas disease and ischemic stroke (IS) has been described and studied, establishing a causal relationship may be difficult in some situations [7, 8, 12, 13]. Data on the epidemiology of IS caused by or related to Chagas disease are scarce. Most studies have evaluated data from a single hospital. Knowledge about the population distribution of IS related to Chagas disease is of the utmost importance for developing preventive strategies.

Objective

The aim of this study was to describe the epidemiological and geographical distribution of IS in Chagas disease in patients attending multicenter, open access, quaternary rehabilitation hospital network spread across four of the five regions of Brazil and to infer the relevant statistical assessments for identifying eventual regional differences.

Methods

Our descriptive and analytic study, involving a historical cohort, aimed at describing the main characteristics of patients with Chagas disease and IS who were admitted between 2009 and 2013 in 7 rehabilitation centers spread across four of the five regions of Brazil (which is divided in 5 regions). Chagas disease was confirmed using two different serological tests (enzyme-linked immunosorbent and hemagglutination assays); IS was confirmed using neuroimaging (computed tomography [CT] and/or magnetic resonance imaging [MRI]). Exclusion criteria included conflicting serological results, absence of IS confirmation, and age < 18 years. Chagas disease serology was routinely performed in IS patients in most centers (2 centers in Brasilia; one center each in Salvador, São Luis, and Belo Horizonte); however, in the centers in Rio de Janeiro and Fortaleza, serology was only performed in the presence of some epidemiological data or at the physician discretion. There are other two centers (at Macapá and Belém, both in north Brazil), but they did not admit adult patients with stroke.

All patients admitted for the neurological rehabilitation service at SARAH network hospitals due to the aforementioned diagnoses from January 2009 to December 2013 were analyzed (inpatients and outpatients) and followed up until 2017.

Data recorded included vascular risk factors, age, sex, city of residence, neurological outcome (measured by the modified Rankin Scale [mRS]), statin use, secondary epilepsy, secondary prevention therapy, cognitive status after stroke, and etiological investigation, as detailed elsewhere [14].

Two independent neurologists classified stroke etiology using a computerized system according to the Stop Stroke Study Causative Classification System (SSS-CCS) Trial of ORG 10172 in Acute Stroke Treatment (TOAST), using the same methodology as in our previously published works [14–17].

We divided patients into two groups for analysis: one group based on place of birth and one group based on current residence. This classification was important due to migration flows and the possibility of error in the analysis regarding the location of infection and occurrence of IS. For vascular risk factors, etiological investigation, mRS score, and use of secondary prevention, we considered the current residence because admission and follow-up had occurred when the patient was residing at the current residence. For Chagas disease frequency and incidence of Chagas disease among all studied IS patients, we considered the place of birth because that is where the patient probably acquired the infection. The ethics committee of the SARAH Network of Hospitals approved our study protocol, and the requirement for patient consent was waived by the committee. This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) IBM ® version 23. Continuous variables were expressed as mean with standard deviation for normally distributed variables and as median and interquartile range for non-normally distributed variables.

For comparisons between variables pertaining to different regions\states of the country and to hospital units of our network, we used the chi-square test or the Shapiro-Wilk test of normality and the Student's *t* test, as appropriate. For the

distribution of cases according to years, we use the chi-square test for goodness-of-fit and the Fischer's exact test for prevalence distribution in our attended population according to age groups. For evaluating the geographical and spatial distribution of Chagas disease in IS patients, we used data analysis methods based on statistics and algorithms that were implemented on the TerraView 4.2.2 software. p values ≤ 0.05 were considered statistically significant.

Results

From a total 7729 IS-related admissions in the whole network, a total of 279 patients with Chagas disease and IS were analyzed, indicating a median prevalence of 3.6% in our cohort between 2009 and 2013 (Fig. 1). The prevalence corrected by age in every region of the country is shown in Table 1. Chagas disease prevalence in IS patients varied according to hospital units: 6%, Salvador; 5%, Belo Horizonte; 4%, Fortaleza; 3%, Brasilia and São Luis; and 0.2%, Rio de Janeiro ($p = 0.06$). Most of the cases were from the state of Bahia (61%), followed by Minas Gerais (19%) and Goiás (9.7%). Most cases (75%) did not present a history of acute infection symptoms. Table 2 illustrates the cities with the highest prevalences, all located in the same state and all low-income areas, except the capital city (Salvador). Salvador showed the highest prevalence; the top 32 cities with the highest prevalences of Chagas disease were from Bahia. Figure 2 (Supplemental material) illustrates the geographical distribution of patients with Chagas disease and IS attended in our hospitals across the country. Absolute frequencies were the highest in the northeast region (where the state of Bahia is located), followed by the southeast (mainly due to Minas Gerais), mid-west, and northern regions. However, the prevalence of IS by region was higher in the mid-west (9%), northeast (5%), north and southeast regions (1% each). We found that 45% of patients had changed residence some time in their lives, with most patients searching for better quality of life and access to healthcare; over 60% patients had developed IS in their place of birth.

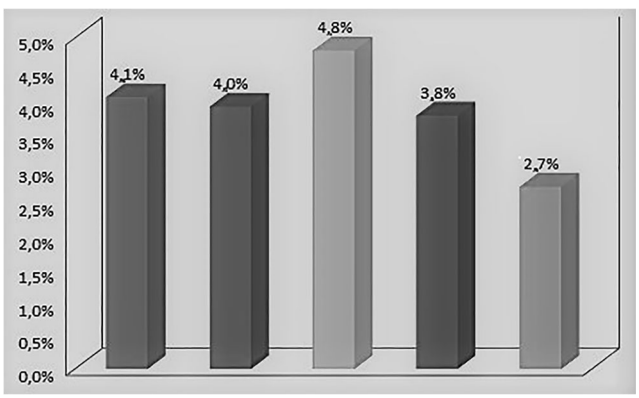

Fig. 1 Incidence of Chagas disease in all admitted ischemic stroke patients per year (p value, 0.048)

Overall, mean age was 60 years with female predominance (65%). Differences were observed in the distribution of vascular risk factors: high prevalence of obesity in the north and northeast regions, predominance of alcoholism in the north and southeast regions, and high prevalence of smoking in the northeast and southeast regions (Table 3). The outcome of stroke also differed among hospital units. The incidence of cognitive deficit was higher in the northeast and southeast regions than in other regions. The prevalence of death and epilepsy was also higher in the northeast region than in other regions. Anticoagulation therapy was used most frequently in the southeast region (22%) and used least frequently in the northeast region (13%) ($p = 0.009$); most patients received antiplatelet agents instead of anticoagulants after IS. According to current guidelines, 60% of patients in our cohort were using inadequate secondary prophylaxis [18]. Majority of the patients did not experience coronary events.

In patients with Chagas disease and cardioembolic etiology (53% of the cohort), cardiac changes, such as dilated cardiomyopathy, hypokinesis, and arrhythmias, were attributed to the disease. There was no significant difference in etiological diagnosis among the hospital units (Table 4) or macro-regions (Table 5). For etiological investigation, all patients underwent transthoracic echocardiography and electrocardiography, 64% underwent brain CT, 26% underwent brain MRI, and 10% underwent both brain CT and MRI. Twenty-four-hour Holter monitoring and non-invasive intracranial (angio CT and\or magnetic resonance angiography) vascular studies were performed in 20% and 30% of the population, respectively. Etiological investigations performed varied widely among hospital units; for example, intracranial vascular studies were performed in 65% of patients in the Brasilia unit but in no patients in the northeast region. The kappa coefficient of agreement between the two neurologists' etiological classification was 0.909 [14].

Discussion

Generally, Chagas disease has a high prevalence in IS patients, reaching up to 6% in some regions in our cohort. Consistent with the literature, we found a high prevalence of IS related to Chagas disease in low-income areas [19]. In very poor regions, the percentage of IS related to Chagas disease was up to 10% [9]. Consistent with other studies, we also found a low prevalence in young patients [11, 19].

There seemed to be a decrease in the incidence of IS related to Chagas disease in our cohort. This finding is consistent with recent data showing a decrease in Chagas disease incidence even in rural or isolated populations [20]. This decrease is probably related to public policies developed for fighting the

Table 1 Prevalence of ischemic stroke corrected by age groups in our population

Age	Midwest			Northeast			North			Southeast			
	n	*P*	Prevalence	*n*	*P*	Prevalence	*n*	*P*	Prevalence	*n*	*P*	Prevalence	*p* value
20–29	1	27	4%	2	64	3%	0	2	0%	1	69	1%	0.682
30–39	4	79	5%	5	143	3%	0	3	0%	2	139	1%	0.385
40–49	6	89	7%	19	381	5%	0	8	0%	2	295	1%	0.002
50–59	25	186	13%	45	774	6%	1	14	7%	2	661	0.3%	< 0.0001
≥ 60	36	419	9%	113	1907	6%	0	25	0%	15	1733	1%	< 0.001
Total IS	72	800		184	3269		1	52		22	2897		

n, number of cases; *P*, population; *IS*, ischemic stroke. Age measured in years

disease and vector, although intermediate vectors remain a challenge [21]. Latin America has made substantial progress towards Chagas disease control. The Pan American Health Organization has certified the interruption of transmission by domestic vectors in several countries in South America and Central America [11].

We observed significant differences in the distribution of vascular risk factors and in stroke outcomes, represented by the incidence of cognitive deficit, epilepsy, and death. This could possibly be explained by the socio-economic reality of the poorer regions (specifically the northeast of the country), including less access to healthcare.

Table 2 Cities with the highest frequencies of IS with CD according to patients' birthplaces

State	Cities	*n*	%
BA	Salvador	20	11.2%
BA	Castro Alves	11	6.1%
BA	Santo Amaro	9	5.0%
BA	Santo Antônio de Jesus	8	4.5%
BA	Feira de Santana	7	3.9%
BA	Maragogipe	6	3.4%
BA	Nazaré	6	3.4%
BA	São Felipe	6	3.4%
BA	Cachoeira	5	2.8%
BA	Candeias	5	2.8%
BA	São Gonçalo dos Campos	5	2.8%
BA	Coração de Maria	4	2.2%
BA	Muritiba	4	2.2%
BA	Cruz das Almas	3	1.7%
BA	Itanagra	3	1.7%
BA	Mundo Novo	3	1.7%
BA	Muniz Ferreira	3	1.7%
BA	Sapeaçu	3	1.7%
BA	Teodoro Sampaio	3	1.7%

BA, Bahia

There is also an important increase in the prevalence of IS with age. This is also described in the literature [22] and is possibly explained by vascular comorbidities being more common with increasing age. Unfortunately, there are no reliable sources of the incidence of Chagas disease infection in Brazil for comparison with our results. Only acute Chagas disease cases are reported (even so, with failures in noticing the disease) [23]. Since many patients present with no symptoms at the time of infection, it is impossible to infer the real incidence of chronic disease in the country.

According to a recent meta-analysis [22], prevalence of Chagas disease infection in Brazil ranged from 2% in the south and mid-west to 5% in the northeast and southeast regions; the north region had 2.9% prevalence. Our cohort showed a higher prevalence of IS in the mid-west and northeast regions, possibly due to migration flows to the mid-west region.

Another important finding of our study was that more than half of our patients were not receiving adequate secondary prophylaxis, according to current guidelines. This occurred in all regions but was more evident in the northeast region, especially in terms of anticoagulant use. Use of antiplatelet agents instead of anticoagulants in patients with Chagas disease and high embolic risk could have influenced the difference in stroke incidence and outcomes among regions. This could be related to difficulties in establishing correct etiological diagnosis and to social difficulties related to anticoagulant treatment. In the southeast region (richest region of the country), the proportion of anticoagulation use was high; however, given the small number of subjects, this could be related to better access to healthcare systems.

The following were the strengths of our study: (1) our study was performed in a quaternary multicenter rehabilitation network setting that ensures reasonable etiological investigation and follow-up of patients, with good coverage of the national territory. Thus, a considerable number of patients could be enrolled. (2) Our service involves a defined etiological investigation protocol for IS. (3) Patients from most regions of the country were able to attend our centers.

Table 3 Comparison of patient characteristics in each region according to residence of patients

	Midwest (72)	Northeast (184)	North (1)*	Southeast (22)	*p* value
Middle age, mean ± SD	59.1 ± 10.8	62.3 ± 12.6	59 (0)	59 ± 15.0	0.202
Male sex, *n* (%)	27 (37%)	60 (32%)	1 (100%)	9 (41%)	0.408
SAH, *n* (%)	51 (71%)	139 (76%)	1 (100%)	17 (77%)	0.778
DM, *n* (%)	10 (14%)	43 (23%)	0 (0%)	5 (23%)	0.369
Dyslipidemia, *n* (%)	41 (57%)	93 (51%)	1 (100%)	9 (41%)	0.411
Smoking, *n* (%)	32 (44%)	54 (29%)	1 (100%)	3 (14%)	0.007
Alcoholism, *n* (%)	33 (46%)	54 (29%)	0 (0%)	3 (14%)	0.021
Obesity, *n* (%)	6 (2%)	6 (3%)	0 (0%)	4 (18%)	0.026
Epilepsy, *n* (%)	17 (24%)	19 (10%)	0 (0%)	6 (27%)	0.011
Antiplatelet use[1], *n* (%)	51 (71%)	142 (77%)	1 (100%)	13 (59%)	0.204
Statin use, *n* (%)	44 (61%)	99 (54%)	1 (100%)	15 (68%)	0.363
Anticoagulant use[1], *n* (%)	19 (26%)	23 (13%)	0 (0%)	7 (32%)	0.009
Cognitive deficit, *n* (%)	14 (20%)	70 (38.0%)	0 (0.0%)	8 (36%)	0.022
Coronary artery disease, *n* (%)					
No	66 (92%)	180 (98%)	1 (100%)	21 (96%)	0.09
Yes, before IS	5 (7%)	4 (2%)	0 (0%)	0 (0%)	
Yes, after IS	1 (1%)	0 (0%)	0 (0%)	1 (5%)	
Death, *n* (%)	2 (3%)	25 (14%)	0 (0%)	1 (5%)	0.034
Initial mRs ≤ 3, *n* (%)	39 (54%)	87 (47%)	1 (100%)	10 (46%)	0.569
ESUS, *n* (%)	48 (67%)	108 (59%)	1 (100%)	15 (68%)	0.498

SAH, systemic arterial hypertension; *DM*, diabetes mellitus; *mRs*, modified Rankin Scale; *ESUS*, embolic stroke of undetermined source; *SD*, standard deviation

[1] After stroke (secondary prevention)

*There was only one patient residing in the north of the country; however, he was attended at the Brasília unit of our network

Table 4 Comparison of stroke etiology among the rehabilitation centers

		SSS TOAST1					Total
		Small vessel occlusion	Atherosclerosis of supra aortic large vessels	Cardioaortic	Other	Undetermined	
BHZ	*n*	2	1	15	0	4	22
	%	9%	5%	68%	0%	18%	100%
BSB	*n*	6	6	43	1	23	79
	%	8%	8%	54%	1%	29%	100%
FOR	*n*	1	0	5	0	0	6
	%	17%	0%	83%	0%	0%	100%
RIO	*n*	0	2	0	0	0	2
	%	0%	100%	0%	0%	0%	100%
SLS	*n*	0	0	2	0	1	3
	%	0%	0%	67%	0%	33%	100%
SSA	*n*	26	28	82	2	29	167
	%	16%	17%	49%	1%	17%	100%
Total	*n*	35	37	147	3	57	279
	%	13%	13%	53%	1%	20%	100%

Pearson chi-square, 30.6; *p*, 0.06

BHZ, Belo Horizonte; *SSA*, Salvador; *RIO*, Rio de Janeiro; *BSB*, Brasília (including 2 centers located in the same city); *FOR*, Fortaleza; *SLZ*, São Luis
Stop Stroke Study Causative Classification System (SSS-CCS) Trial of ORG 10172 in Acute Stroke Treatment (TOAST)

Table 5 Etiologies according to macro-regions[1]

			SSS TOAST1					Total
			Small vessel occlusion	Atherosclerosis of supra aortic large vessels	Cardioaortic	Other	Undetermined	
Regions	Midwest	*n*	6	6	43	1	23	79
		%	8%	8%	54%	1%	29%	100%
	Northeast	*n*	27	28	89	2	30	176
		%	15%	16%	51%	1%	17%	100%
	Southeast	*n*	2	3	15	0	4	24
		%	8%	13%	63%	0%	17%	100%
Total		*n*	35	37	147	3	57	279
		%	13%	13%	53%	1%	20%	100%

Pearson chi-square, 10.82; *p*, 0.212

[1] According to place of diagnosis, only one patient residing in the northern region had cardioaortic etiology but was diagnosed at the Brasilia (BSB) center

Following were the limitations of our study: (1) our study was retrospective in nature. (2) There was a prolonged time lapse between ictus and hospitalization, and therefore, some patients may have died before enrollment in our study. (3) Patients in the northern and southern areas of the country experienced difficulties while accessing our services. The evidence supporting increasing incidence of infection in the southern and northern regions [22–24] could lead to a selection bias. (4) The difference in protocols for serological investigation differed among centers and could have influenced the results; however, the geographical distribution of Chagas disease found in our study was consistent with the current literature [8–11, 13, 19].

Conclusions

Chagas disease was common in patients with IS and its prevalence was higher in the states of Bahia, Minas Gerais, and Goiás. Despite this, the frequency of infection seems to be decreasing in the last few years. Prevalence of Chagas disease among IS patients, prevention of stroke in patients with Chagas disease, and outcome after stroke clearly differ among different regions of the country. There is an urgent need for addressing public health issues for improving the treatment of Chagas disease and IS.

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Compliance with ethical standards

As stated in the Methods section of the manuscript, the ethics committee of the SARAH Network of Hospitals approved our study protocol and the requirement for patient consent was waived by the committee. This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Conflict of interest The authors declare that they have no conflict of interest.

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