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LETTER TO THE EDITORS

Chagas disease is independently associated with brain atrophy

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Abstract Chagas disease (CD) remains a major cause of cardiomyopathy and stroke in developing countries. Brain involvement in CD has been attributed to left ventricular dysfunction, resulting in chronic brain ischemia due to hypoperfusion and/or embolic infarcts. However, cognitive impairment in CD may occur independently of cardiac disease. Therefore, we aimed to investigate head computed tomography (CT) findings in patients with Chagas disease cardiomyopathy (CDC) in comparison with other cardiomyopathies (OC). We studied 73 patients with CDC ($n = 41$) or OC ($n = 32$) matched for age and gender. These patients underwent head CT, rated by an investigator blinded to all clinical information. Head CT was rated for the presence of lacunar or territorial infarcts, as well as for measuring the total volumes of the brain, cerebellum and ventricles. Total brain volume was smaller in CDC as compared to OC patients (1,135 ± 150 vs. 1,332 ± 198 cm^3, $P < 0.001$). Cerebellar and ventricular volumes did not differ between the groups. The prevalence of brain infarcts did not differ significantly between the groups. Chagas disease was the only independent predictor of brain atrophy in the multivariable analysis (OR = 1.38; 95% CI = 1.06–1.79, $P = 0.017$). Chagas disease is associated with brain atrophy independent of structural cardiac disease related to cardiomyopathy. Brain atrophy, rather than multiple infarcts, may represent the main anatomical substrate of cognitive impairment in Chagas disease.

Keywords Other cerebrovascular disease/stroke · All cognitive disorders/dementia · Computed tomography · Parasitic infections

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Chagas disease (CD) is a chronic infection caused by the parasite *Trypanosoma cruzi*, affecting primarily the heart and/or the digestive system [2]. A cerebral form of CD was initially suggested [3], but later refuted by other authors, attributing most brain involvement to cardioembolic stroke [6, 9, 10]. However, cases of active brain inflammation have been described in immune suppressed patients [10], and brain atrophy has been found pathologically [6]. Our objective was to compare computed tomography (CT) findings in patients with CD cardiomyopathy (CDC) and other cardiomyopathies (OC).

Patients and methods

A random sample of patients was evaluated from a university-based cardiomyopathy clinic. Patients were consecutively screened for inclusion and exclusion criteria and

written informed consent was obtained. For inclusion, a clinical diagnosis of congestive heart failure and an echocardiogram performed within 1 year of study entry were required. OC controls were matched to CDC cases by sex and age.

A full neurological examination including the NIH Stroke Scale (NIHSS) was performed by a certified investigator. Stroke history was not an exclusion criterion as long as the NIHSS score was zero. Patients underwent a structured interview with prospective collection of demographic data, cerebrovascular risk factors, medications currently used, and electrocardiographic and transthoracic echocardiographic data. Hypertension was defined by two blood pressure measurements above 140/90 mmHg or by previous anti-hypertensive medication use. Diabetes was defined by previous use of anti-diabetic medications. Coronary artery disease was defined by a history of myocardial infarction, angina or coronary artery revascularization or angioplasty procedures. New York Heart Association heart failure functional class, blood pressure and heart rate were obtained on admission. Both cardiomyopathy and its etiology were defined by the attending cardiologist and Chagas disease was confirmed by appropriate serology (hemaglutination or immune-fluorescence tests). Alcohol abuse was defined as any amount of daily alcohol use. The study was approved by the hospital ethics committee.

Head CT was acquired in axial cuts obtained from the base of the skull to the vertex with 5 mm intervals at the posterior fossa and 10 mm intervals at the supra-tentorial region. A blinded rater (J.O.-F.) evaluated head CT findings, quantifying the number of lacunar and territorial infarcts, while another blinded rater (P.S.O.R.) measured volumes of the brain, ventricles and cerebellum using ImageJ 1.34S software (available for download in http://rsbweb.nih.gov/ij/) [1]. Total volumes were calculated by multiplying the area of the specific region of interest on axial CT by the slice thickness. To calculate total brain volume, ventricular volumes were subtracted. Brain atrophy was defined as one standard deviation below the mean brain volume of the OC group.

For statistical analyses, the Mann-Whitney *U* test was used for continuous variables and the Fisher's exact test for categorical variables. Backward step-wise logistic regression was performed in order to correct for multiple confounding variables with any possible association with brain atrophy ($P < 0.1$ on univariable analysis).

Results

Seventy-three patients underwent CT between January 2003 and June 2005 (Table 1). Cardiomyopathy etiologies were Chagas disease in 41 (56%), hypertensive in 13 (18%), ischemic in 5 (7%), idiopathic dilated in 5 (7%), and other in 9 (12%). Patients with OC frequently had more cerebrovascular risk factors. CDC and OC groups were highly comparable in regard to age and sex, variables known to affect brain volume. Chronic alcohol use was rare in both groups, and two patients in the OC group were thought to have alcoholic dilated cardiomyopathy. Cardiac disease duration and severity were similar in both groups (mean ejection fraction of 44% in CDC vs. 42% in OC groups, $P = 0.647$). No patient was using corticosteroids or any other medication possibly associated with brain atrophy.

Table 1 Clinical and demographic characteristics of 73 patients undergoing head CT, with Chagas disease cardiomyopathy (CDC) and other cardiomyopathies (OC)

Variable	CDC ($n = 41$)	OC ($n = 32$)
Age, years, mean ± SD	56 ± 10	56 ± 10
Male sex, *n* (%)	15 (37)	13 (41)
Hypertension, *n* (%)*	23 (56)	27 (84)
Diabetes, *n* (%)	6 (14)	4 (13)
CAD, *n* (%)*	2 (5)	8 (25)
Alcohol abuse, *n* (%)	5 (15)	3 (10)
Stroke history, *n* (%)	14 (34)	9 (28)
Atrial fibrillation, *n* (%)	2 (5)	3 (9)
Intracardiac thrombus, *n* (%)	2 (5)	0 (0)
Warfarin use, *n* (%)	16 (39)	10 (31)
Duration of cardiomyopathy, months, mean ± SD	103 ± 85	80 ± 94
NYHA Heart Failure Functional Class, median (range)	II (I–IV)	II (I–IV)
Ejection fraction, %, mean ± SD	44 ± 13	42 ± 13
LVSD, mm, mean ± SD	47 ± 10	52 ± 11
LVDD, mm, mean ± SD*	60 ± 8	66 ± 10

CAD coronary artery disease, *LVSD* left ventricle systolic diameter, *LVDD* left ventricle diastolic diameter, *NYHA* New York Heart Association

* $P < 0.05$

Imaging results are shown in Table 2. The number of brain infarcts was similar in both groups; however, brain volumes were significantly lower in CDC patients as compared to OC patients (1,135 ± 150 vs. 1,332 ± 198 cm^3, $P < 0.001$). Volumes of the cerebellum and the lateral ventricles did not differ between the groups. In the multivariable analysis including age, sex, duration of cardiomyopathy, history of alcohol abuse, Chagas disease, left ventricle systolic and diastolic diameters, and ejection fraction, only Chagas disease was an independent predictor of brain atrophy (odds ratio = 1.38; 95% confidence interval = 1.06–1.79, $P = 0.017$).

Table 2 Computed tomography findings in 73 patients with Chagas disease cardiomyopathy (CDC) and other cardiomyopathies (OC)

Variable	CDC ($n = 41$)	OC ($n = 32$)	P-value
Brain volume, cm^3, mean ± SD	1,135 ± 150	1,332 ± 198	<0.001
Ventricle volume, cm^3, mean ± SD	49 ± 24	56 ± 24	0.203
Cerebellum volume, cm^3, mean ± SD	121 ± 38	120 ± 25	0.912
Brain atrophy, *n* (%)	30 (73)	15 (47)	0.001
Number of right-hemisphere territorial infarcts, median (range)	0 (0–1)	0 (0–1)	0.501
Number of right-hemisphere lacunar infarcts, median (range)	0 (0–2)	0 (0–1)	0.161
Number of left-hemisphere territorial infarcts, median (range)	0 (0–1)	0 (0–1)	0.501
Number of left-hemisphere lacunar infarcts, median (range)	0 (0–1)	0 (0–2)	0.410
Patients with territorial infarcts, *n* (%)	9 (22.0)	6 (18.8)	0.779
Patients with lacunar infarcts, *n* (%)	6 (14.4)	3 (9.4)	0.722

Discussion

This is the first study to investigate in vivo imaging of the brain in Chagas disease. One previous pathological series found brain infarcts and atrophy more frequently in 114 CD patients when compared to 38 patients with idiopathic dilated cardiomyopathy, but did not control for factors known to affect brain volume, such as age and sex [6]. Our study confirmed the finding of more frequent brain atrophy in patients with CD. The pathophysiology behind this brain atrophy is speculative. In pathological series, neuronal loss in the cerebellar Purkinje cell layer, thalamic nuclei and cortical laminar necrosis was thought to represent chronic ischemic changes from congestive heart failure [6, 9]. However, this interpretation does not explain our findings, since severity of cardiac disease was the same when comparing CDC to OC patients. An association between brain atrophy and systemic inflammation (high IL-6 and TNF-alfa levels) has been reported [7]. Both IL-6 and TNF-alfa production are associated with chronic Chagas disease [4, 5]. Thus, we hypothesize that chronic inflammation in Chagas disease may underlie the mechanism for a progressive form of brain atrophy [8].

Our study did not find more brain infarcts in patients with CDC. One possible explanation is that the number of infarcts detected in this predominantly stroke-free population was small, which increases the chance of a type II error. An alternative explanation is that non-contrast CT is an insensitive technique to detect small cortical, subcortical or peri-ventricular infarcts. Further studies using magnetic resonance imaging could better quantify small vessel disease, white matter disease and small cortical infarcts.

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