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SCIENTIFIC LETTER

Lack of correlation for anti–β1 autoantibodies and cardioelectric disorders in chagas cardiomyopathy

Ausencia de correlación ente anticuerpos β1 y trastornos electricos en cardiopatía chagásica

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Chagas' disease, caused by the parasite *Trypanosoma cruzi*, is one of the most pervasive endemic infections in Latin America, currently affecting approximately 7 million people[1]. Nearly 40% of patients eventually develop chronic Chagas' cardiomyopathy (CCC), which can manifest with conduction disorders, arrhythmias, congestive heart failure, stroke, and/or sudden death[1].

After the initial acute phase of the disease, hosts who are incompletely treated with anti-parasitic agents enter the indeterminate phase, characterized by low levels of parasitemia and the absence of signs or symptoms. Nearly two-thirds of people in the indeterminate phase remain in this state for over 10 years. Unfortunately, the other third progress to the chronic stage, wherein patients again experience the effects of antigenic stimulation.

Chronic Chagas' disease most commonly presents as a slowly evolving inflammatory cardiomyopathy. The presence of high levels of inflammatory mediators in patients with Chagas' disease suggests that the host's immune response to parasitic activity could play a key role in the perpetuation of myocardial inflammation. Patients with CCC have been found to produce anti-β1 and -ß2 adrenergic autoantibodies and anti-M2 cholinergic autoantibodies in the heart[2,3], through a phenomenon known molecular mimicry. The relationship between autoantibody titers and the degree of cardiac disease remains controversial.

The aim of this study was to evaluate whether patients with CCC and higher levels of anti-β1 autoantibodies had a significantly higher presence of cardiac arrhythmias or conduction disorders, which are considered clinical markers of CCC.

Ethics clearance was granted by the bioethics commission of Jorge Ramos Mejía Hospital in Buenos Aires, Argentina. The study population consisted of 65 patients with at least a 20-year history of positive serology for Chagas' disease to allow adequate time for manifestations of CCC to develop (Table 1). All patients had a left ventricular ejection fraction (LVEF) of either less than or equal to 35% or greater than or equal to 50%, as evaluated by Doppler echocardiography, to eliminate subjective differences in echocardiographic data. Patients with LVEF between 36% and 49%, or who had another established cause of cardiomyopathy, were excluded from the study.

The presence of arrhythmias and conduction disorders was evaluated using electrocardiograms (ECG), storage data from implantable cardioverter-defibrillators (ICD) and pacemaker interrogation, and 24-h Holter

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Table 1. Chronic Chagas' cardiomyopathy patients by serum anti-β1 autoantibody cutoff levels

Variables	Total (%)	Cut off < 800 (%)	Cut off ≥ 800 (%)	p	Cut off < 1000 (%)	Cut off ≥ 1000 (%)	p
n (patients)	65	25	40		41	24	
Age, (mean ± SD years)	59.98 ± 11.99	57.24 ± 11.48	61.70 ± 12.12	0.397	60.07 ± 12.95	59.83 ± 10.40	0.394
Female	32 (49.2)	13 (20.0)	19 (29.2)	0.724	20 (30.8)	12 (18.5)	0.924
NYHA I	47 (72.3)	19 (29.2)	28 (43.1)	0.721	30 (46.2)	17 (26.2)	0.302
LVEF ≤ 35%	25 (38.5)	10 (15.4)	15 (23.1)		16 (24.6)	9 (13.8)	
LVEF ≥ 50%	40 (61.5)	15 (23.1)	25 (38.5)		25 (38.5)	15 (23.1)	
Arrhythmia, total	20 (30.8)	8 (12.3)	12 (18.5)	0.865	12 (18.5)	8 (12.3)	0.732
– LVEF ≤ 35%	12 (18.5)	6 (9.23)	6 (9.23)		7 (10.8)	5 (7.69)	
– LVEF ≥ 50%	8 (12.3)	2 (3.08)	6 (9.23)		5 (7.69)	3 (4.62)	
Conduction disorders, total	37 (56.9)	11 (16.9)	26 (40.0)	0.133	20 (30.8)	17 (26.2)	0.102
– LVEF ≤ 35%	20 (30.8)	7 (10.8)	13 (20.0)		12 (18.5)	8 (12.3)	
– LVEF ≥ 50%	17 (26.2)	4 (6.15)	13 (20.0)		8 (12.3)	9 (13.8)	
LAFB	7 (10.8)	1 (1.54)	6 (9.23)		2 (3.08)	5 (7.69)	
RBBB	11 (16.9)	4 (6.15)	7 (10.8)		7 (10.8)	4 (6.15)	
RBBB + LAFB	8 (12.3)	4 (6.15)	4 (6.15)		5 (7.69)	3 (4.62)	
LBBB	9 (13.8)	1 (1.54)	8 (12.3)		4 (6.15)	5 (7.69)	

SD: standard deviation; NYHA: New York Heart Association classification of heart failure symptoms; LVEF: left ventricular ejection fraction; LAFB: left anterior fascicular block; RBBB: right bundle branch block; LBBB: left bundle branch block.

monitor registries. Arrhythmias of interest were sustained and non-sustained ventricular tachycardia and supraventricular tachycardia, including atrial flutter, atrial fibrillation, or atrial tachycardia. Conduction disorders of interest consisted of left anterior fascicular block (LAFB), right bundle branch block (RBBB), a composite of LAFB and RBBB, and left bundle branch block (LBBB).

Serum levels of anti-β1 receptor autoantibodies for all patients were measured using two different cutoff values: 1000ng/mL, as per the lab kit manufacturer's specifications, and 800ng/mL about Anti-β1 autoantibody receptor testing kit: blood was drawn into a BD Vacutainer tube (367983). The serum was transferred to Eppendorf tubes. Serum levels of anti-β1 autoantibodies were then measured using the Human Anti-β1 Adrenergic Receptor Antibodies Enzyme-Linked Immunosorbent Assay (ELISA) lab kit from MyBioSource. Two different cutoff values for autoantibody titers were analyzed in parallel: 1000 ng/mL, as per the manufacturer's specifications, and a cutoff value of 800 ng/mL). The number of patients with symptoms categorized as New York Heart Association (NYHA) class I was also recorded, as the previous literature suggests a correlation between circulating levels of cardiac autoantibodies and worsening heart failure symptoms, regardless of the etiology of cardiomyopathy[4].

Rates of cardiac manifestations found in each autoantibody cutoff group were expressed as percentages and compared using Chi-square tests and Cramér's V. Statistical significance was established at $p < 0.05$.

The mean age was 59.98 ± 11.99, of which 50.8% (n = 33) were men. About 38% (n = 25) had LVEF ≤ 35% with mean LV end-diastolic diameter (LVDD) 64 ± 5.06 mm. Patients with LVEF ≥ 50% (n = 40) had mean LVDD of 49 ± 6.24 mm. When the 800 ng/mL cutoff was applied, 61.5% (n = 40) of the total patients had anti-β1 autoantibody levels above this value. About 30% (n = 12) of these patients were found to have arrhythmias of interest vs. 32% (n = 8) of patients below the cutoff (p = 0.527). Conduction disorders were present in 65% (n = 26) of patients above the cutoff compared to 44% (n = 11) of patients below the cutoff (p = 0.961).

When applying cutoff level of 1000 ng/mL, 36.9% (n = 24) of all patients had autoantibody titers exceeding this value. Further analysis yielded no significant

differences in the presence of arrhythmias (33.3% (n = 8) of patients above cutoff, 29.3% (n = 12) of patients below cutoff, p = 0.693) or conduction disorders (70.8% (n = 17) of patients above cutoff, 48.8% (n = 20) of patients below cutoff, p = 0.102) between groups.

In a population of patients with CCC, we found no significant relationship between levels of the anti-β1 autoantibody and the presence of arrhythmias or conduction disorders.

Several studies have demonstrated a relationship between the prevalence of ventricular arrhythmias and serum anti-β1 autoantibody levels. Further, the anti-β1 autoantibody has been implicated in the development of heart failure and dilated cardiomyopathy of varying etiologies in multiple animal experiments, and these associations have also been demonstrated in some human studies[5,6]. However, robust data using human subjects with a focus on CCC are lacking[7,8]. Ours is the first clinical study to explore any potential association between anti-β1 autoantibody titers strictly in patients with CCC and the prevalence of cardiac arrhythmias and conduction disorders.

Our study is limited by a relatively small sample size and observation at a single timepoint. The future studies with larger populations over a longer duration may further elucidate any relationships between these autoantibodies and CCC to determine if autoantibody levels could serve as clinically useful markers of disease progression. Further, given pre-clinical *in vitro* experiments suggest immunoadsorption techniques can reduce reactivity between autoantibodies and β1 receptors[9], continued investigation of anti-β1 autoantibodies in CCC may yield fruitful targeted therapeutic options to directly reduce autoreactivity and disease progression.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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