Electrocardiographic Alteration among First Degree Relatives with Serologic Evidence of *Trypanosoma cruzi* Infection. A Sibship Study

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To analyze whether electrocardiographic alterations (ECGA) in patients with antibodies to Trypanosoma cruzi *showed a pattern of familial aggregation, a sample of 379 young adults (166 men and 213 women) distributed in sibships, were assessed for the presence of anti-*T.cruzi *antibodies, and subjected to a complete clinical examination and a standard resting electrocardiogram (ECG). Positive* T. cruzi *serology was detected in 165 individuals, 48 of them showing an abnormal ECG (overall prevalence 29%). One hundred and eleven seropositive individuals were distributed in 45 sibships, each of them constituted by more than one seropositive sib, with ECGA being present in 34 out of these patients. Seropositive subjects with ECGA were detected in 27 sibships. Since the index case within each sibship is counted exactly once, affected individuals selected at random as propositi were extracted to calculate the prevalence of ECGA among first degree relatives of probands. Abnormal ECGs were recorded in 7 out of 45 sibs yielding a prevalence that did not differ from estimations registered in the general population or seropositive sibs. Data from the present sample show no familial aggregation for the occurrence of ECGA in patients with* T.cruzi *infection.*

Key words: chronic chagasic cardiomyopathy - sibships - familial study

Chronic chagasic cardiomyopathy (CCC) mainly consisting of inflammatory and degenerative lesions of myocardial fibers and conducting tissues, is a frequent consequence of *Trypanosoma cruzi* infection and a leading cause of mortality and disability in endemic areas (Maguire et al. 1983). Clinical manifestations of CCC may appear years or decades after initial infection, and mostly reflects on heart enlargement together with disturbances of cardiac rhythm and/or conduction (Laranja et al. 1956).

Although *T. cruzi* infection is the essential cause for the occurrence of CCC, it is becoming clear that additional influences, i.e., risk factors, are likely to play a contributory role on the generation of chronic heart lesions in *T. cruzi* infected patients. In this setting, several factors such as race, sex, age, strain or zymodemes of the parasite, length of residence in high endemicity areas, and even life conditions in urban areas have been reported in the literature as exerting some influence on the establishment of CCC (Laranja et al. 1956, Numesmeia & Mendoza 1980, Puigbó et al. 1969, Maguire et al. 1982, a, b, Miles 1983, Tibayrenc & Desjeux 1983, Medrado-Faria et al. 1984, Dávila et al. 1987). In contrast to this background of information, scarce data exist as to whether CCC shows a pattern of familial aggregation. In a recent study, Zicker et al. (1990) have reported that *T. cruzi*-infected subjects were at a greater risk of showing ECGA when a history of cardiovascular disease was referred to be present among their siblings. Taking into account that the serological status of the latter individuals was unknown and CCC is not always symptomatic, an alternative approach may be to carry out studies in sibships constituted by subjects with serologic evidence of *T. cruzi* infection, aimed at analyzing whether heart involvement of chronic Chagas' disease are more likely to occur within families.

To address this question the present study was undertaken.

MATERIALS AND METHODS

Populations studied - The geographic location of the tested populations is shown in the Figure.

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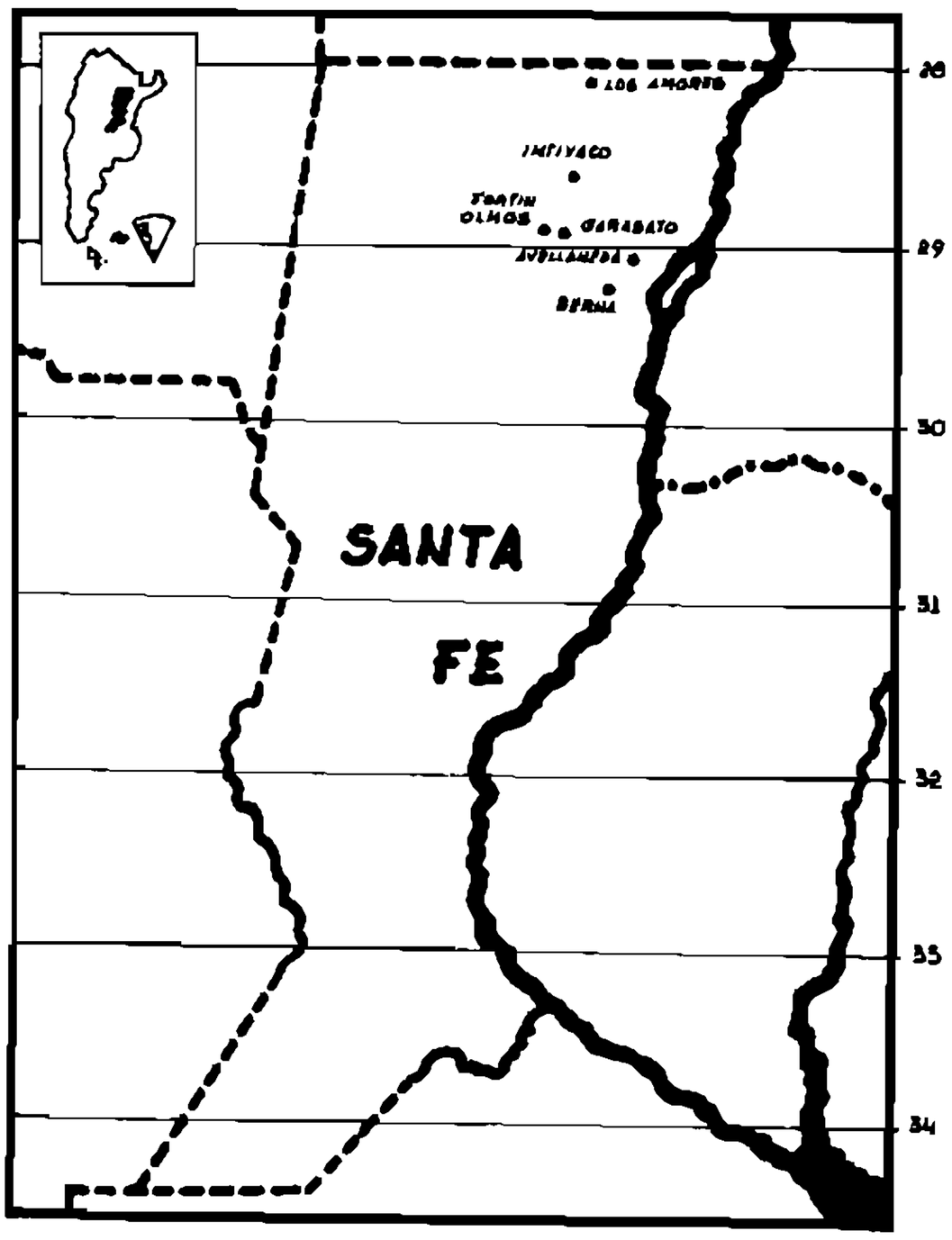

Santa Fe Province, Argentina. Geographic location of villages where the study was performed.

The zone corresponds to an endemic area of Chagas' disease, which is situated in Vera and General Obligado Departments of northern Santa Fe province (latitude 28° to 30° S). Young adults, both sexes, were admitted into the study if they had one or more siblings, and the latter also volunteered to participate in the investigation. Participants were permanent residents of six small villages (Los Amores, Intiyaco, Garabato, Fortin Olmos, Avellaneda, and Berna), who lived in substandard dwellings. Most of them had inhabited dwellings made of mud walls and palms roofs ("ranchos") during their childhood. The population, mainly of mixed Spanish and Indian origin, shared the same socioeconomic and environmental conditions, and was devoted to rural labors: wood cutting, fishing and hunting, with housekeeping as the main activity among women.

Serologic tests - Blood samples were obtained by venipuncture and sera were stored at -20° C until tested. Presence of antibodies to *T.cruzi* were assessed by indirect immunofluorescence and indirect hemagglutination tests. Results were considered positive when both serological methods yielded positive reactions. Cases with doubtful serology were excluded.

Clinical examination and electrocardiogram - Participants were subjected to a complete clinical examination, and special attention was paid to the presence of relevant concomitant cardiopathies (i.e.,valvular and congenital) that may result in biased ascertainment. The 12-lead ECG was recorded after 10 min of bed rest, at a paper speed of 25 mm/sec and a 30-second rhythm strip. Clinical examination and interpretation of ECG tracings was performed by an experienced cardiologist blinded to the serological results. Information was recorded in a standard questionnaire, in which data from personal interviews, like habits, were also registered.

Analysis of data - Prevalence rates were calculated from the results of serologic tests and ECG. Differences in age, sex, and prevalence of ECG alterations between people with positive or negative *T. cruzi* serology were analyzed by the Student's *t* test and chi square test. To ascertain familial aggregation, a method developed by Falconer (1965) for estimating heritability of multifactorial threshold traits was employed. Briefly, phenotypic variance of a trait is the sum of genetic variance plus environmental and genotype-environment interaction variance. Genetic variance, in turn, can be partitioned into two components, additive variance and dominance variance (Cavalli-Sforza & Bodmer 1971), where heritability represents the proportion of the total phenotypic variance of the trait that is due to additive genetic variation. The procedure requires knowledge only of the prevalence of the disease in question in the general population and in relatives of the index case or propositus. It is clear that an increased prevalence of the disease in question among the relatives of affected individuals as compared with the prevalence in the general population, constitutes a major indication of a genetic component as playing a role in the establishment of such a disease. Because family prevalence was calculated among first degree relatives, that is brothers or sisters of all index cases, each affected individual selected as propositus was not counted in the sibship when prevalence among relatives was estimated.

RESULTS

A total of 379 individuals, representing two balanced age groups of males (n=166) and females (n=213) with a mean general age of 33 ± 19 (s.d.) years, were studied. Serologic evidence of infection with *T. cruzi* was present in 165 of the participants yielding an overall prevalence of 43.5 %. Upon that, subjects were grouped according to serology and then analyzed for the caracteristics of both groups. Except for the fact that seropositive patients were a little older than seronegatives. Comparison between both groups revealed no major differences as to sex, blood pressure, and heart rate, which appeared within

the normal range (Table I). Nevertheless, an abnormal ECG was more frequently recorded in seropositive people and accounted for a statistical significant difference when compared with the seronegative ones (Table II, $p < 0.01$). Pathological ECG tracings were neither related to an increasing age nor sex. Since the total population was rather uniform as to the socioeconomic conditions, regardless of the serological status, no association between ECG abnormalities and variables like physical activity or habits could be established.

We then proceeded to select sibships composed by a minimum of two seropositive individuals. Accordingly, 45 sibships were chosen with the number of seropositive sibs ranging from 2 to 5. Thirty per cent of these persons (34/111) showed abnormal ECG and the frequency of the different pathological tracings corresponded fairly well to the distribution recorded in the general population of infected people. Eighteen of the selected sibships also had subjects with negative serology, and four of them (14.3%) presented minimal ECG alterations (3 incomplete right bundle branch block and 1 left ventricular hypertrophy). Patients with positive or negative *T. cruzi* serology showed no statistical differences with regard to sex, age, blood pressure, heart rate, and PR and QT intervals.

Next, we separated 27 sibships showing seropositive subjects with ECGA. Since the index

TABLE I

Characteristics of subjects according to *Trypanosoma cruzi* serology

	Seropositives	Seronegatives
Age	34.6 ± 14	32.6 ± 13[a]
Males	74	92
Females	91	122
Systolic blood pressure[b]	131 ± 29.6	129.8 ± 33
Diastolic blood pressure[b]	79 ± 16	78.5 ± 18
Heart rate (beats/min)	77 ± 14	75 ± 12

Values represent mean ± standard deviation
[a]: $p < 0.05$ student's t test
[b]: in mm Hg

TABLE II

List of abnormal ECG findings in patients with positive or negative *Trypanosoma cruzi* serology

Seropositive (n = 165)			Seronegative (n = 214)		
Abnormality	n	%	Abnormality	n	%
IRBBB	13	27.0	IRBBB	6	20.7
VE	7	14.6	CRBBB	5	17.2
LAH	6	12.5	LVH	5	17.2
CRBBB	4	8.3	LAH	3	10.3
LVH	4	8.3	VRD	2	6.9
VRD	3	6.2	VE	1	3.5
VCD	2	4.2	SVE	1	3.5
LPH	1	2.1	VRD LVH	3	10.3
SVE	1	2.1	IRBBB LAH	2	6.9
AF	1	2.1	CRBBB LAH VE	1	3.5
CRBBB LAH	2	4.2			
VE VCD	1	2.1			
CRBBB LVH	1	2.1			
VE LVH	2	4.2			
Overal prevalence of abnormal ECG		29.0			13.5[a]

IRBBB: incomplete right bundle branch block; CRBBB: complete right bundle branch block; VE: multifocal ventricular extrasystolia; LAH: left anterior hemiblock; LVH: left ventricular hypertrophy; VRD: ventricular repolarization disturbances; VCD: ventricular conduction defects; LPH: left posterior hemiblock; SVE: supraventricular extrasystolia; AF: atrial fibrilation.
[a]: $p<0.01$.

case within each sibship is counted exactly once, probands selected at random were extracted and the prevalence of ECGA among first degree relatives was calculated. As shown in Table III, ECGA were present in 7 out of 45 sibs yielding a prevalence that did not differ from the values registered either in the general population or sibs with positive serology. Prevalence among seropositive sibs did not change substantially even when extracting sibships 11, 23, 25, and 26, in which the index case presented ECGA of little relevance for CCC (7/34 = 20%). Overall prevalence of ECGA in seropositives upon exclusion of such borderline ECG tracings yielded a quite similar value (31/165 = 18.8%).

TABLE III

Distribution of ECGA in sibships with one or more affected individuals

Sibship number	Seropositives Proband	Seropositives Sibs, n	Seronegatives Sibs, n
1	CRBBB	1 NA	1 NA
2	IRBBB	2 NA	
3	VE	1 NA	
4	IRBBB	1 IRBBB, 2 NA	3 NA
5	VE	2 NA	1 NA
6	IRBBB	1 IRBBB	
7	VCD	2 NA	
8	VRD	1 NA	
9	VE	1 IRBBB	
10	CRBBB	2 NA	
11	LVH	1 NA	2 NA, 1 LVH
12	VE	1 NA	1 IRBBB, 1 NA
13	LAH	1 IRBBB, 2 NA	
14	LAH	1 NA	
15	LAH	1 VE LVH, 1 NA	
16	LPH	2 NA	
17	CRBBB	1 NA	
18	VE	1 VE LVH	
19	CRBBB LAH	3 NA	
20	AF	1 NA	
21	LAH	1 LAH, 1 NA	
22	CRBBB LAH	1 NA	
23	LVH	1 NA	
24	VE	1 NA	1 NA
25	IRBBB	3 NA	1 NA
26	LVH	4 NA	1 NA
27	CRBBB	1 NA	

IRBBB: incomplete right bundle branch block; CRBBB: complete right bundle branch block; VE: multifocal ventricular extrasystolia; LAH: left anterior hemiblock; LVH: left venticular hypertrophy; VRD: ventricular repolarization disturbances; VCD: ventricular conduction defects; LPH: left posterior hemiblock; SVE: supraventricular extrasystolia; AF: atrial fibrilation; NA: no alterations. Prevalence of ECGA among first degree relatives = 15% (7/45).

DISCUSSION

Familial aggregation has been described in cancer as well as other pathological disorders of chronic nature, but the proper significance of this phenomenon is not completely elucidated. While familial aggregation is likely to be the result of some genetic predisposition, the possibility exist, on the other hand, that shared cultural, socioeconomic, or other environmental factors may partly account for such an event.

Beyond the controversy, assessment of familial aggregation for heart involvement in chronic *T. cruzi* infection raises some particular issues that should be carefully taken into account when estimations are to be made. Firstly, participants should have firm evidence, at least serologic, of *T. cruzi* infection. Although some ECG abnormalities are more likely to occur in CCC, no pathological tracing can be considered as specific of Chagas' disease. Therefore, subjects must be evaluated for the presence of concomitant factors, i.e., other cardiomyopathies, that may lead to altered ECG. Another point that one should bear in mind deals with the extent of cardiac affectation, that is whether the study is addressed to evaluate only ECGA or more advanced stages of the CCC. Lastly, since ageing may result itself in ECGA, prevalence of the latter among relatives should be preferably ascertained in sibs. Data collected from the present sample give no support to the hypothesis of CCC as aggregating in families, even when ECGA of little significance were disregarded. Our results bear no relation with evidence presented by Zicker et al. (1990) who demonstrated that subjects with a sibling history of cardiovascular disease are more prone to show ECGA. In trying to establish reasons for such a discrepancy it should be considered first that the history of heart disease in those siblings cannot be directly linked to Chagas' disease as no information on their *T. cruzi* serology was reported. Yet, assuming that *T. cruzi* infection was actually present in a great proportion of them, it seems that in populations where CCC is more clinically evident (either because of different ethnical background, parasite strains and/or environmental conditions), familial aggregation may exist.

Heart involvement in chronic Chagas' disease may be regarded as a threshold trait in which genetic and non-genetic influences are likely to play a pathogenetic contributory role. The net balance arising from the complex interplay between individual genotype environment interactions may determine to a great extent the possibility of CCC showing a pattern of familial aggregation or not. According to the present findings one can conclude that such phenomenon is not noticeable in our population. Nevertheless, this concept cannot be extrapolated to other epidemiological situation.

The threshold model for the analysis of inheritance of all-or-none characters assumes the

existence of a continuos variate underlying them, where information on variances and covariances of such variate are obtained from the prevalence in the general population and in relatives of persons possessing the character.

If in another situation, evidence for CCC showing familial aggregation is found, regression of relatives of different degrees on propositi may help to elucidate the contribution of genetic factors in the establishment of chronic heart lesions.

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