EARLY ELECTROCARDIOGRAPHIC ABNORMALITIES IN Trypanosoma cruzi–SEROPOSITIVE CHILDREN

ANA LUCIA SAMPAIO SGAMBATTI DE ANDRADE, FABIO ZICKER, ANIS RASSI, ALEXANDRE GABRIEL RASSI, RENATO MAURICIO OLIVEIRA, SIMONNE ALMEIDA SILVA, SORAYA SGAMBATTI DE ANDRADE, AND CELINA MARIA TURCHI MARTELLI

Communicable Diseases Program, Pan American Health Organization, Washington, District of Columbia; Instituto de Patologia Tropical e Saúde Pública, Departamento de Medicina Tropical Saúde Coletiva e Dermatologia, e Faculdade de Medicina, Universidade Federal de Goiás, Goiânia, Goiás Brazil; Special Program for Research and Training in Tropical Diseases, World Health Organization, Geneva, Switzerland; Hospital São Salvador, Setor Oeste, Goiânia, Brazil

Abstract. As part of a major epidemiologic study on Chagas’ disease, we compared the prevalence of electrocardiographic (ECG) abnormalities among 141 school children 7–12 years of age and seropositive for Trypanosoma cruzi, and 282 age-, sex-, and school-matched seronegative children in an endemic area in Brazil. The prevalence of ECG abnormalities was 11.3% among seropositive children and 3.5% among seronegative children (odds ratio = 3.5, 95% confidence interval [CI] = 1.5–8.4). The prevalence rate of ECG alterations was 10.7% for seropositive males versus 8.9% for seropositive females. Complete right bundle branch block (CRBBB), which is highly suggestive of Chagas’ disease cardiopathy, was diagnosed in nine (6.4%) seropositive children and in only one (0.3%) seronegative child (odds ratio = 18.5, 95% CI = 2.3–146.5, attributable fraction = 58.3%). Five incident new cases of CRBBB were diagnosed after a 36-month follow-up of seropositive children who were enrolled in an independent clinical field trial. No case of frequent and/or multifocal ventricular premature beats was found in the cohort of children. The surprisingly high frequency of early ECG abnormalities, which indicates a rapid evolution from infection to disease, suggests the existence of endemic areas with a particular accelerated disease progression that was not described before. Under such conditions, a public health chemotherapy program focusing on the treatment of young seropositive children would be recommended.

The knowledge of the natural history of Chagas’ disease cardiopathy has been built on hospital-based observations and from a small number of population-based long-term investigations conducted in endemic areas.1–3 The comparison between studies and the understanding of evolving patterns of the disease, however, have been limited to some extent due to the geographic difference of vector species, levels of endemicity, and the lack of standard procedures for selecting and examining study participants.4

In endemic areas, infection by Trypanosoma cruzi occurs early in life; the prevalence rate of positive serology increases with age up to the fifth decade of life and decreases afterwards.5 Electrocardiographic (ECG) alterations are usually the first clinical evidence of disease progression, but the onset of these abnormalities is rarely detected, since they tend to be asymptomatic at the beginning and heart involvement is usually clinically detected in adult life.6,7

In cross-sectional observations the prevalence of ECG abnormalities increases with age at a peak at the fourth to fifth decade of life, while the differential risk of ECG abnormalities comparing seropositive with seronegative subjects decreases with age.8 Cardiopathy seems to occur in family clusters, but no single risk factor has been clearly associated with disease progression at individual or population levels.4 It is estimated that approximately 20–30% of seropositive subjects will develop heart disease during the course of their lives.9 The prevalence of heart disease in rural populations tends to be underestimated due to selective exclusion from the endemic communities of diseased individuals who migrate for medical treatment or have died.

We report here the results of an ECG cross-sectional survey carried out among seropositive and seronegative school children, and a subsequent ECG evaluation of a cohort of seropositive children, who enrolled into a three-year clinical follow-up in an endemic area in Brazil.10

METHODS

Study area and population. The study protocol was ethically and technically reviewed and approved by the Regional Medical Council in accordance with World Health Organization guidelines for biomedical research. Signed informed consent was obtained from the parents or guardians of each child. Participants were recruited from children attending 60 rural schools in three small municipalities (Posse, Guarani de Goias, and Simolandia) in the northern part of Goias State in central Brazil, where T. cruzi infection rates for children 7–12 years old ranged from 12% to 23%, as reported in a national survey, 1975–1980.11

From March to September 1991, a total of 1,900 school children were examined. Eluates of blood samples collected onto filter paper were processed for anti-T. cruzi antibodies simultaneously by indirect immunofluorescence, indirect hemagglutination, and ELISA. Details of this screening and methods used have been described elsewhere.12 The study included 141 of 153 children who were positive by all three tests on eluates and later confirmed by testing serum samples collected by venipuncture. An age- (7–9 and 10–12 years), sex-, and school-matched group of 282 seronegative children (two seronegative to one seropositive) were randomly selected from the screened population as a comparison group. This procedure was achieved by using a computer-generated stratified assignment into subgroups of age, sex, and school, and individually matching a seropositive child to the next two seronegative children in numerical order of screening.

Data collection. Parents of all children were interviewed to collect information on living conditions and child’s medical history. Anthropometric measures were recorded: height measured to the nearest 0.5 cm and weight to the nearest 100 grams. All participants were physically examined and...
no clinical evidence of Chagas’ disease was observed. Also, no clinical manifestation related to acute T. cruzi infection in the past was reported by parents during the interviews.

A standard ECG was recorded for all subjects at the beginning of the study. One hundred twenty-nine seropositive children of the 141 seropositive children who were also enrolled into a clinical trial had a second ECG at the end of a 36-month follow-up (the follow-up consisted of a clinical examination, T. cruzi serology every six months, and an ECG at the end of the third year). The ECG traces were interpreted by two independent cardiologist readers following a coding system adapted for Chagas’ disease. An ECG was classified as abnormal in the presence of at least one of the following: large Q or QS waves (code 1-1, 1-2), pattern of ventricular hypertrophy (tall precordial R waves) with ST segment and T wave alteration (3-1 to 3-4 and 5-1 to 5-4), A-V block (6-1 to 6-4), ventricular conduction defects (7-2, 1.7-7), complex arrhythmia (8-3-1 to 8-6-4), ventricular premature beats when present in 10% or more of recorded cycles or when multifocal or bigeminy (8-1-1, 8-1.2, 8-1.3), and sinus bradycardia (< 50 pm) (8-8-1) associated with extrasystoles or primary and diffuse changes in ventricular repolarization (5-1 to 5-4). Complete bundle branch block was defined as rR’ or R waves in V1 with a duration ≥ 0.12 sec.

All ECG traces with an abnormal report by any observer and a 10% random sample of normal ECGs from seropositive and seronegative children were double-read independently to ensure reliability of the results. The interviewers and the readers were kept blinded to the serologic result.

Statistical analysis. The seropositive and seronegative children were compared in relation to general characteristics, nutritional status, and prevalence of ECG alterations. Nutritional status was evaluated based on the National Center for Health Statistics (NCHS) standard. Stunting, wasting, and underweight were defined as a Z score < -2.0 respectively for height-for-age, weight-for-height, and weight-for-age. Boys > 11.5 years old and girls > 10.5 years old were not included in the nutritional evaluation because they were identified in the program and excluded from the analysis. Chi-square and Student’s t-tests were used to compare categorical and continuous variables, respectively. Conditional logistic regression was used to estimate crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of the association between seropositivity and ECG abnormality, examining the potential confounding effect of age, sex, and nutritional status. The population attributable-risk percent (PAR%) was calculated as PAR% = (p (RR – 1))/(p(RR – 1) + 1) × 100, where p is the prevalence of seropositivity (7.9%), as estimated in a previous population-based screening, and RR is the ratio between incidence rates of seropositive to seronegative children.

RESULTS

The seropositive and seronegative children did not differ statistically regarding age, sex, and place of origin distributions. Approximately 90% of them had lived in the study area and their families resided in the region for approximately 10–11 years. Seropositive children presented a higher proportion of stunting (19.9% versus 10.3%) and underweight (12.8% versus 4.6%) while the proportion of wasting (10.3% versus 20.1%) was higher in the seronegative children (Table 1).

Table 2 shows the ECG profile among the study population. An abnormal ECG was recorded in 11.3% of the seropositive and in 3.5% of seronegative children (adjusted OR = 3.5, 95% CI = 1.5–8.4, P < 0.001, and population attributable-risk = 58.3%). Complete right bundle branch block (CRBBB), which is highly suggestive of Chagas’ disease cardiopathy, was diagnosed in nine (6.4%) seropositive children, two of them associated with left anterior hemiblock (LAH), and in only one (0.3%) seronegative child (adjusted OR = 18.5, 95% CI = 2.3–146.5, P < 0.01). No statistical association was detected between malnutrition and ECG abnormalities. Other ventricular conduction defects were rare and no case of frequent and/or multifocal ventricular premature beats was found in the cohort of children. Three cases of A-V conduction disturbance (2.1%) were recorded in the seropositive group and none among the seronegative group.

### Table 1
Baseline characteristics of Trypanosoma cruzi-seropositive and -seronegative children

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Seropositive (n = 141)</th>
<th>Seronegative (n = 282)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age, years (SD)</strong></td>
<td>10.4 (1.6)</td>
<td>10.4 (1.7)</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td>60.3%</td>
<td>60.3%</td>
</tr>
<tr>
<td><strong>Anthropometric status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stunting</strong></td>
<td>19.9%*</td>
<td>10.3%*</td>
</tr>
<tr>
<td><strong>Wasting</strong></td>
<td>10.3%*</td>
<td>20.1%*</td>
</tr>
<tr>
<td><strong>Underweight</strong></td>
<td>12.8%*</td>
<td>4.6%*</td>
</tr>
</tbody>
</table>

* P < 0.01.
† 221 not included in the analysis because the National Center for Health Statistics does not calculate wasting for males > 11.5 years of age and females > 10.5 years of age.
New cases, three-year-follow-up

Electrocardiographic (ECG) conduction defects among Trypanosoma cruzi-seropositive and -seronegative children

<table>
<thead>
<tr>
<th>ECG pattern*</th>
<th>Seropositive No. (%)</th>
<th>Seronegative No. (%)</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>125 (88.7)</td>
<td>272 (96.5)</td>
<td>Reference</td>
</tr>
<tr>
<td>Abnormal</td>
<td>16 (11.3)</td>
<td>10 (3.5)</td>
<td>3.5 (1.5–8.4)</td>
</tr>
<tr>
<td>VC defects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRBBB</td>
<td>9 (6.4)</td>
<td>1 (0.3)</td>
<td>18.5 (2.3–146.5)</td>
</tr>
<tr>
<td>LAH</td>
<td>1 (0.7)</td>
<td>1 (0.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>LBBB</td>
<td>1 (0.7)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>AV block</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second degree A-V block</td>
<td>1 (0.7)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>First degree A-V block</td>
<td>2 (1.4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Atrial ectopic rhythm</td>
<td>2 (1.4)</td>
<td>7 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Septal fibrosis</td>
<td>0</td>
<td>1 (0.3)</td>
<td></td>
</tr>
</tbody>
</table>

* CRBBB = complete right bundle branch block; LAH = left anterior hemiblock; LBBB = left bundle branch block; A-V = atrioventricular, A-V B = second degree A-V block, first A-V B < first degree A-V block.
† Two seropositive children with both CRBBB and LAH.

Individual data from 16 children who presented ventricular conduction defects and/or A-V conduction disturbances are shown in Table 3. The median age of this case series was 11 years old and the male:female ratio was 2.2:1. The overall prevalence of ECG abnormalities was 10.7% (9 of 85) for seropositive males and 8.9% (5 of 56) for seropositive females. Five incident new cases of CRBBB were diagnosed among seropositive children who were enrolled into a clinical field trial with 36 months of follow-up. All of them were males who presented some degree of malnutrition. Figure 1 shows the ECG of one of those cases, an 11-year-old asymptomatic seropositive boy who had a normal ECG at the initial examination (Figure 1A) and presented a typical ECG pattern of CRBBB and LAH after a three-year-follow-up (Figure 1B).

**DISCUSSION**

This study was part of a major investigation on the epidemiology of Chagas’ disease among children and a baseline evaluation of a clinical trial with benznidazole during the early phase of the disease published elsewhere. 10,16 The data differ from previous publications on the epidemiology of Chagas’ disease because they involve a large number of children age-, sex-, and school-matched seronegative controls, a strict definition of seropositive children, and a blinded reading of ECGs. Well-standardized serologic and ECG methods, not always included in rapid epidemiologic assessment of Chagas’ disease endemicity, were used in this study.

The high prevalence rate of ECG abnormalities associated with T. cruzi-positive serology among children was an unexpected finding. Childhood Chagas’ disease heart morbidity is an uncommon event. The differential frequency of CRBBB between seropositive and seronegative children is an indication that Chagas’ disease was the specific etiology for this alteration. Prevalences of CRBBB as high as 16% have been reported, but in seropositive adults living in rural and also in urban areas of Brazil. 7,8,17

The epidemiology and clinical evolution of Chagas’ disease among children has not been extensively reported. In areas under vector control, the serologic screening of a defined age cohort of school children seems to be the recommended strategy for surveillance monitoring to detect residual transmission. 1,2,8 Most of the clinical epidemiologic studies on T. cruzi infection were conducted in the adult population. Longitudinal studies have indicated that Chagas’ disease heart manifestations develop mostly in the second decade after the infection. In the present study, the absence of premature ventricular beats in children contrasts with that in adults. 3 Ventricular conduction defects, such as branch blocks were more frequent instead, and they are considered
an unequivocal sign of disease progression, and known to be associated with increased mortality.\textsuperscript{2}

The detection of five new incident cases of CRBBB among a group of 129 children in a period of three years of follow-up denotes an area of rapid disease progression. The possible role of the exposure to reinfection, malnutrition, parasite strains, and vector species in the progression of Chagas’ disease morbidity is still unclear. The study area was free from vector infestation since 1991,\textsuperscript{10,19} and malnutrition was not statistically associated with ECG alterations, though it was found associated with \textit{T. cruzi} infection.\textsuperscript{20} Experimentally, it has been described that some \textit{T. cruzi} strains induce more cardiac damage than others.\textsuperscript{21} However, attempts to establish a relationship between parasite genetic markers and clinical manifestation have failed.\textsuperscript{22,23}

The data obtained in this study are unique and cause concern considering that such an epidemiologic and clinical situation still exists at the same time as a major success is claimed by the “Southern Cone Initiative” for the elimination of vectorial transmission of Chagas’ disease.\textsuperscript{19,24} A major effort is required to develop drugs for treatment of Chagas’ disease that would interrupt the course of the disease.

The ultimate control of Chagas’ disease has to consider not only the interruption of vectorial and transfusional transmission, but an adequate solution to prevent disease progression in a large number of infected patients. The surprisingly high frequency of early ECG abnormalities, which indicates a rapid evolution from infection to disease in children, suggests the existence of endemic areas with a particular accelerated disease progression that was never described before. In such conditions, a public health chemotherapy program focusing on the treatment of young individuals with current available drugs should be seriously considered.

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Authors’ addresses: Ana Lucia Sampaio Sgambatti de Andrade, Communicable Diseases Program, Pan American Health Organization, 525 Twenty-Third Street, NW, Washington, DC 20037. Fabio Zicker, Special Program for Research and Training in Tropical Diseases (TDR), World Health Organization, Avenue Appia 1211, Geneva 27, Switzerland. Anis Rassi, Faculdade de Medicina, Universidade Federal de Goiás, 1a. Avenida, S/No-Setor Universitário, CEP 74605-050 Goiânia/Go, Brazil. Alexandre Gabriel Rassi, Hospital São Salvador, Avenida A No. 333, Setor Oeste, CEP 74110-020 Goiânia/Go, Brazil. Renato Mauricio Oliveira, Simone Almeida Silva, Soraya Sgambatti de Andrade, and Celina Maria Turchi Martelli, Instituto de Patologia Tropical e Saúde Pública, Departamento de Medicina Tropical Saúde Coletiva e Dermatologia Universidade Federal de Goiás, Rua Delenda R Melo, S/N - Setor Universitário, CEP 74605-050 Goiânia/Go, Brazil.

Reprint requests: Ana Lucia Sampaio Sgambatti de Andrade, Communicable Diseases Program, Pan American Health Organization 525 Twenty-Third Street, NW, Washington, DC 20037.

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