Indeterminate Form of Chagas Disease

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Estimatives based on the last Brazilian sorological survey on Chagas disease showed that aproximately six million people would be infected and half of them could not show clinical or electrocardiographic abnormalities. It means that a significant number of individuals could be considered unable for physical work because a positive antibody test.

Forty percent of patients without sings or symptoms of Chagas disease from areas where endemic transmission occurs are 20 to 40 years old and therefore economically productive (Macêdo 1973, Castro 1978, Dias 1982).

Migration from rural areas to big cities looking for better working conditions contributed to increase the importance of Chagas disease as a social security problem because individuals with a positive antibody test were considered as candidates for retirement. Other problems are related to discriminatory practices against individuals who had a positive test during job applications. Goldbaum (1978) estimates that two to three percent of working population of State of São Paulo could be at risk of discriminatory practices because of Chagas disease. All this unfair picture was due to the lack of clear evaluation criteria of chagasic patiens and the apparent unpredictable evolution of Chagas disease described by Laranja (l979).

Working capacity of patients with the indeterminate phase living in a rural endemic area was evaluated by Macêdo (1973) and Macêdo et al. (1979) showing that chagasic patients had greater capacity to carry weight when compared with healthy controls despite difficulties to increase the cardiac frequency. Mathews (1973) suggested that chagasic patients could be classified in different groups based on performance during ergometric test.

Faria (1978), Macêdo (1973), Macêdo et al. (1979), Marins (1979), Siqueira et al. (1976), did not find any rythm disorder during ergometric test in patients with the indeterminate form. However Marins (1979), Macêdo et al. (1979), Bellini et al. (1979) and Pereira et al. (1987) showed that these chagasic patients had good working capacity despite difficulties to increase systolic pressure and cardiac frequency meaning that it does exist cardiac involvement not detected by electrocardiography.

Belini et al. (1979) described impaired capacity to increase systolic pressure using the ergometric test in 10 out of 52 individuals with positive antibody test without cardiac sings and symptoms.

Mathews (1973), Faria (1978), Macêdo et al. (1979) and Rassi et al. (1991) showed that chagasic patients with the indeterminate form had no differences in working capacity during ergometric tests when compared with healthy controls. All these evidences support that chagasic patients without symptoms, normal electrocardiographic and ergometric tests should be considered able to work.

Controversies about definition of the indeterminate form were resolved during the first meeting of applicated research in Chagas disease held in Araxá, Minas Gerais in 1985. Since then, the indeterminate form of Chagas disease was defined for patients who fulfilled the following criteria: (1) an antibody positive test and/or parasitological confirmed diagnosis; (2) abscence of signs and symptoms of disease; (3) normal conventional electrocardiographic studies; (4) normal radiological heart oesophagus and colon images.

This classification was extremely valuable for epidemiological studies and improved specificity using stringent criteria.

The definitions described above were supported by previous knowledge from classical cohort studies on disease evolution (Macêdo 1973, Prata 1975, Castro 1978, Dias 1982, Pereira 1983, Coura & Pereira 1984) and the standardized criteria for classification of clinical forms of Chagas disease defined in 1974 by a research council published by CNPq. These criteria included clinical evaluation, conventional electrocardiography with a 30 cm DII derivation, chest X rays and barium contrast studies of oesophagus and colon.

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Present knowledge permit us to affirm that using higher sensitivity tests it is possible to identify abnormalities in patients with the indeterminate form of the disease. However it does not diminish the validity of previous definitions for epidemiological studies under field conditions. Most of this work was developed to detect cardiac alterations and did not evaluate the gastrointestinal tract. It could be possible that some of these patients had the digestive form of disease and therefore they had not the indeterminate form.

Rezende (1956) showed that oesophageal alterations are usually early manifestations of disease when compared to cardiac abnormalities and considering that neural lesions are present in the acute phase (Köberle 1957) it could be plausible that oesophageal disease precede the cardiac involvement.

Macedo et al. (1974) studied the colinergic response to pilocarpine in 25 patients with the indeterminate phase compared to 25 healthy controls in São Felipe, Bahia. All 25 chagasic patients had a normal submaximal ergometric test (Macêdo et al. 1972). They showed that abnormal salivary secretion, diaphoresis and/or first degree atrioventricular block were present in 24% of the chagasic patients. Forty percent of chagasic patients had a greater increase of PR interval than controls. These data were similar to the response of individulas with megaoesophagus and evidence of alterations of AV conduction using conventional electrocardiography in previous studies (Vieira 1959, Godoy & Vieira 1964). These results indicated that pilocarpine test was useful to demonstrate early abnormalities in patients with the indeterminate form. Sosa (1977), and Decourt et al. (1981,1985), studied AV conduction through His bundle eletrogram in patients with the indeterminate form in association with pharmacological tests using atropine and propranolol detecting intraatrial and AV nodal dysfunction

Junqueira et al. (1979) did not find any abnormalities of vegetative system in chagasic patients with the indeterminate form using the atropine test and Valsava´s maneuver. Junqueira Jr (1979) evaluated the baroceptor reflex in these patients compared to controls showing the same response in both groups.

In other study Junqueira Jr and Veiga (1984) found some alterations of cardiac funtion and Manço et al. (1985) showed funcional abnormalities of autonomic nervous system in patients with the indeterminate form.

Other approaches disclosed abnormal deep tendom reflexes in patients with the indeterminate form. Castro et al. (1977), and Faria (1978) showed that these individuals have loss the achillean reflex. Fortes Rego et al. (1980) confirmed the same phenomenum in 28% of 50 patients from São Felipe, Bahia.

De Faria et al. (1979) studied the motor denervation finding a 60% reduction of the motor unit.

Developing of especialized methods of cardiological research such as His bundle eletrogram and angiography are demonstrating abnormalities in this clinical form. Grupi et al. (1976), Sosa (1977), Benchimol et al. (1979), Saad (1978), Pilleggi et al. (1978) used the His bundle eletrogram to demonstrate that patients with the indeterminate form had alterations of atril stimulus and sometimes AV block.

Hemodinamic approaches showed evidences of cardiac hypocontractility (Saad 1978, Garzon et al. 1979, Mady et al. 1982, Kuschnir et al. 1984, Barreto 1985, Sobral Sosa et al. 1988, Madoery & Madoery 1992).

Results from echocardiographic evaluation have been controversial, some authors have demonstrated abnormal dynamic function (Ortiz et al. 1976, Saad 1978, Friedman et al. 1979, Garzon et al. 1979, Alves et al. 1987, Sobral Sosa et al. 1988) while others did not find any alterations (Acquatella et al. 1979, Marins 1979, Rassi et al. 1991, Ianni 1995). Dynamic electrocardiography had similar controvesial results with some studies showing arrythmias and others normal findings compared with healthy controls (Almeida et al. 1982, Marin et al. 1982, Ortiz et al. 1976, ElufNeto 1984, Rassi et al. 1991).

Rassi et al. (1991) studied 103 chagasic patients with the indeterminate form compared with twenty healthy controls. All chagasic patients fulfilled the diagnostic criteria of Araxá meeting. Echocardiography, dynamic electrocardiography and ergometric test were performed in all individuals showing normal echocardiogram in 100%, 5% arrythmias in both groups during dynamic electrocardiography and 16% abnormal ergometric test in chagasic patients and in 10% of controls. This well controlled study confirm that chagasic patients with the indeterminate form of disease had similar performance when it is compared with normal population. I believe that most of time the use of different inclusion criteria could explain apparent controversies when researchers attempt to show abnormal function of patients with the indeterminate form.

Despite some research on evolution of this peculiar phase we do not know exactly what is the real prognosis of this type of affection.

Some important contributions came from animal models. Laranja et al. (1949) studied dogs with experimental infection with the indeterminate form. Animals were sacrificed 55 months after infection

and it was find focal lymphoplasmocitary myocarditis. Andrade and Andrade (1968) showed inflamatory lesions with vascular arteriolar necrosis in various organs with different evolutive phases in apparently healthy mouse model with more than 100 days infection. They suggested that this prolonged infection would correspond to the "latent phase" or indeterminate phase of human infection.

Lopes et al. (1980a) evaluated six dogs naturally infected in an endemic area without symptoms of disease. Five dogs showed histopathologic findings similar to human patients with the indeterminate form.

Necropsy studies of patients with the indeterminate form who died from accidental causes revealed scarce myocardial inflammatory sites randomly located (Lopes et al. 1978, 1980 ab, 1985, Chapadeiro 1979). Mady et al. (1982) firstly studied humans with the indeterminate form through endocardial biopsy. He evaluated 20 patients using right ventricle biopsy showing histopathological abnormalities in 60%.

Immunological research also revealed alterations in patients with this form of disease. Teixeira et al. (1979) demonstrated that T lymphocytes from these patients showed cytotoxic activity against myocardial cells identical to lymphocytes from patients with chagasic cardiomyopathy and Shikanai-Yasuda (1982) found association of anti EVI antibodies of IgM class with the indeterminate form. It suggests a relationship between these antibodies and cardiac lesions detected by vectocardiography.

Analysis of cohort studies developed in endemic areas are showing that the prognosis of the indeterminate form could be good in the short and medium time. In younger patients it is difficult to estimate a prognosis but we believe that evolution to clinical disease if it does happen would be in a period of 10 to 30 years based on studies of Prata (1968) and Dias (1982). Older patients who are classified with this form would show a lesser degree of evolutive potential as stated by Prata (1990) supported by studies of prevalence of the indeterminate form in individuals older than sixty. Details of cohort studies in endemic areas of São Felipe (Bahia), Mambaí (Goiás), Bambuí and Virgem da Lapa (Minas Gerais) have contributed to establish a prognosis of the indeterminate form. Dias (1982) studied patients who presented acute disease in Bambuí after a follow-up period of 10 to 15 years showing that many of them remained with the indeterminate form. He stated that despite this long period of time without disease these patients could develop clinical disease after 20 or 30 years. He believed that the type of evolution depended in part of the age when acute infection happened. Further analysis of Bambui´s cohort showed that 20 years after acute infection 50% of patients remained in the indeterminate form and 38% after 30 years.

In São Felipe, Macêdo (1980) showed that 78% of patients initially diagnosed with the indeterminate form did not have status alteration after 10 year follow-up and Castro (1993) showed that 72% of these patiens in a similar study remainded without alterations after 13 years follow-up. Coura and Pereira (1984) found similar figures in a shorter period of follow-up in two endemic areas of Minas Gerais.

Cohort studies developed in the endemic areas of São Felipe (Macêdo 1973), Mambaí (Castro 1978), Bambuí (Dias 1982) and Virgem da Lapa (Coura & Pereira 1984) showed that infected individuals younger than 10 had the indeterminate form in 63%, 71%, 80% and 100% respectively. Individuals between 20 and 29 years had a decrease of the indeterminate form prevalence to 44%, 58%, 39% e 42% respectively. All studies showed that 30% of patients older than 50 present this form concluding that 20 to 35 years after infection 40 to 50% will develop detectable cardiac or gastrointestinal disease diagnosed by conventional methods.

Mean time to develop oesophageal dysfunction after acute infection appears to be variable. Sometimes it appears early and megaoesophagus in children supports this fact. Rezende and Rassi (1958) reported two adult individuals with oesophageal dysfunction, one and three years after acute infection. All research suggest that the time to develop oesophageal disease is shorter than the time needed to develop myocardiopathy (Rezende 1956, Rezende & Rassi 1958).

Castro et al. (1994) studied the evolution of 55 chagasic patients during a follow-up period of 13 years. Thirty one (62%) who had the indeterminate form in 1975/1976 developed the digestive form of disease. Twenty four developed GI megaoesophagus, five GII, and two GIII. These findings supports observations of Rezende and Rassi (1958) who stated that oesophageal dysfunction precede the cardiac form of disease.

In São Felipe, 400 chagasic patients with the indeterminate form were evaluated by Macêdo (1980) after ten years of initial studies. Ninety six (24%) developed clinical disease. The frequency of this evolutive pattern was greater in younger individuals. Fifty percent in younger than 20, 40% between 20 and 40 years and 10% in older than 50. Sixty two (62.4%) individuals developed CI cardiopathy, 22 (23%) CII, six (6%) CIII, and one (1%) CIV. Cinco (5.2%) patients developed megaoesophagus. Mortality due to sudden death

was not observed in patients with the indeterminate form and this fact allow us to affirm that this patients had good prognosis ten years after initial diagnosis.

We know now that more sensitive methods will detect abnormalities in asymptomatic patients with Chagas disease in the indeterminate form but it remains unclear what do these alterations mean. Until now, we can not explain why some humans infected with *Trypanosoma cruzi* will never develop disease.

Castro (1993) failed to demonstrate association between blood parasite level and disease evolution. Macêdo and Silveira (1987) compared the evolution of chagasic patients with the indeterminate form who had been treated with specific drugs and placebo and did not find differences after a ten years follow-up period.

Actually we do not know what is the role of other factors such as the parasite virulence related to strain diversity, the inoculum effect, the immunogenetic pattern of human host and others characteristics which could determine the type of long term evolution of human infection with *T. cruzi*. Certainly recent advances in molecular biology applied to basic parasitology and immunology together with well controlled clinical cohort studies will answer some of these intricate questions.

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