THE INDETERMINATE FORM OF HUMAN CHRONIC CHAGAS' DISEASE A CLINICAL EPIDEMOLOGICAL REVIEW

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Data on the epidemiology and the natural history of the indeterminate form of human chronic Chagas' disease (IFCCD) are discussed, revealing its great importance in endemic areas of Brazil. The work shows that IFCCD presents a gradual and very slow course, causing a benign picture in the studied patients. Evolution patterns, prognostic and anatomo-pathological features are also discussed.

For practical purposes, the classical concept of IFCCD proved to be simple, operational and consistent, It is defined by the absence of symptoms and clinical findings in chronic infected patients with positive serology and/or parasitological examinations for Trypanosoma cruzi *coupled with normal electrocardiographic and radiological exams (heart, oesophagus and colon X-Rays). If a patient is submitted to more rigorous and sophisticated tests, these can reveal some alterations, generally small ones and unable to interfere with the prognosis of the infection.*

It is suggested that research lines specially related to the evolution ary factors and immunological involvement during this phase be adopted.

Key-words: Chagas' disease. Indeterminante form. Prognosis. Evolution factors.

The indeterminate form of human chronic Chagas' disease (IFCCD) has had very great epidemiological importance in endemic areas. In 1916, Carlos Chagas[11] introduced the term "indeterminante", to indicate "the absence of predominant clinical syndromes" while, in 1923, E. Villela[50] wrote that "the indeterminate form has no single description; it is recognized only as a temporary stage of the provisional classification of the cases that will be developing toward one of the clinical forms, or as a latent phase in which the lack of clinical signs will give the appearance of perfect health". Also called "laboratorial form" or "latent phase", or even "sub-clinical" form, IFCCD generally comprises more than half of the infected population in Brazilian endemic areas[18 29 32 38].

The general concept of IFCCD has an "operational" nature, as pointed out by the Laranja's et al. classic paper of 1956[29]. "The asymptomatic period, described as the chronic indeterminate form of the disease, comprises a long period, usually from 10 to 20 years, between the end of the acute stage and the establishment of the late heart disease of chronic infection. During the asymptomatic period individuals may be considered as belonging to the category of potential cardiac patients. In the endemic areas this group of asymptomatic chronic infection is the largest of the three groups of patients with *T. cruzi* infection. Although these patients are apparently healthy and asymptomatic, they most important from the epidemiological standpoint". With the more recent descriptions of the chronic digestive forms of the disease[22 42] this concept must incorporate the absence of the symptoms and signs of the major digestive "pathies", the oesophageal and colonic chagasic dysperistalsis[6 35 44].

The present concept earned general acceptance with the beginning of the longitudinal studies of Chagas'disease in endemic and non-endemic Brazilian areas in the sixties[13 21 31] and was formally discussed in official documents in 1971[35] and 1974[21]. In November 1984, a very distinguished group of Brazilian experts was brought together by the Conselho Nacional de Desenvolvimento Científico e Tecnológico to discuss IFCCD, and expressed the classical concept in the following terms[41]: "Considering the existing controversies on the validity of the concept of the so-called indeterminate forms of Chagas'disease, and also unfavourable repercussion for the patient from the medical, social and laboural points of view, the participants of the First Meeting of Applied Research on Chagas'Disease, taking place in Araxá (MG, Brazil), from December 13th to 15th 1984,

decided to establish the following as criteria for its characterisation:

    1. Serological and/or parasitological positivity;

    2. Absence of symptoms and/or signs of the disease;

    3. Normal conventional electrocardiogram;

    4. Normal heart, oesophagus and colon X-ray images.

The Group considered it convenient to maintain this concept of the indeterminate form in clinical evaluation and epidemiological studies, taking into account the good prognosis for the cases.

Finally, the Group emphasised that, when submitted to more sensitive examination methods, chagasic patients included in the criteria above can show some changes, but this fact does not invalidate the concept here expressed".

IFCCD normally shows its highest incidence in the first 10 or 15 years of the infection, immediately after the acute phase; this includes the younger group of patients in endemic areas[18 32]. It must be emphasised that the acute period of the disease passes unnoticed, with few or no symptom, in the great majority of the cases[18 20 29]. This "inapparent" form of acute Chagas' disease was described by G. Teixeira[48] in 1977, having A. Teixeira[47] detected immunosuppresive phenomena in these patients.

Nevertheless, this inapparent acute Chagas' disease must not be confused with IFCCD, since the patients present at least some fever and positive fresh blood examinations. As described by Laranja et al[29], the simplest criteria to distinguish the end of acute phase are the subsidence of the acute clinical manifestations and the reduction of the number of trypanosomes in the blood to such levels that can no longer be detected on fresh examination. One very important consideration about this transitional period between the end of the acute and the beginning of the chronic phase is the possibility of a parasitological cure for many patients, since adequate specific treatment may be performed at this time[9 17].

Generally, the IFCCD begins a few weeks or months after the acute phase, as shown by longitudinal studies. Among 317 symptomatic acute patients followed in Bambuí (MG, Brazil) the great majority of the cases passed to the chronic "latent" period in the first six months after the beginning of the infection; the fever and clinical picture disappeared first and the normalisation of ECG and cardiac X-rays were observed later. Nevertheless, in a few patients a persistent cardiac involvement could be observed after the acute episode, with ECG disturbances (PR enlargement or T wave disturbances) and/or persistent cardiac enlargement for several years, even in the absence of fever, cardiac failure of other important symptoms. In a few other cases it was noted that IFCCD had a very short duration (one or two years) after the acute phase, since heart of oesophagic chronic involvement were soon detected[18]. Finally, in another small group of patients, there was a variable period of between two and five years during which transient episodes of an acute heart involvement (chiefly electrocardiographic disturbances) alternated with typical IFCCD, until the establishment of persistent IFCCD or definite chronic form.

The general picture of the possible courses for human Chagas' disease can be summarised in Figure 1[12]. This shows both Chagas' and Villela's concept of IFCCD as a transitionary form of the disease, as well as the more recent view that some cases can remain permanently in this condition[5 19 29 32 38].

Figure 1   –   General frame of the natural history of Human Chagas' Disease
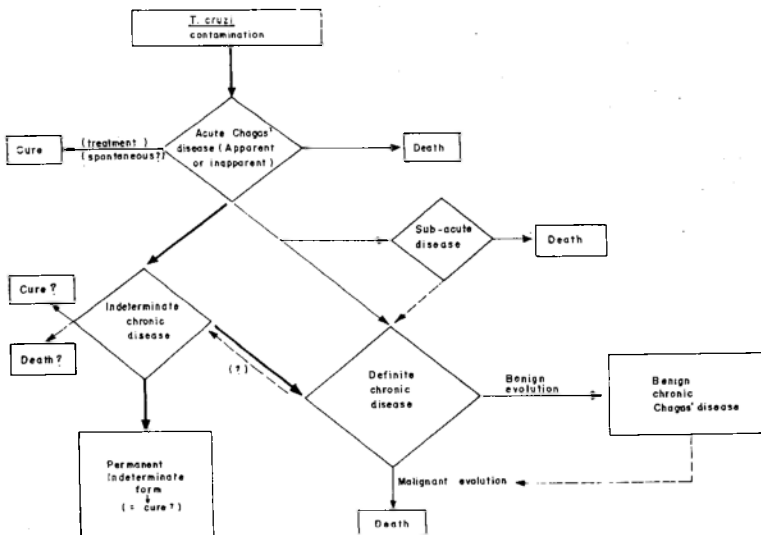
In the majority of patients IFCCD persists for 10 to 20 years after infection with *T. cruzi*[18 38]. Sometimes individuals remain indefinitely in this "latent" stage, and it is common to detect them living in endemic areas when over 70 years of age[22].

About 2-5% of patients with IFCCD evolve towards the symptomatic disease form each year. The more common evolution pattern is an incipient chagasic cardiopathy, or into the initial degrees of oesophagic involvement[18 22 32]. Table 1 summarises the main

It seems therefore that individuals whith less cardiac involvement during the acute phase have a tendency to remain free of cardiopathy during the chronic stage. These data agree with recent experimental works.

Schlemper Jr.[46] verified in white mice a positive correlation between the more severe chronic cardiopathy (especially with histological fibrosis) and the intensity of acute myocardial inflammation. Similary, Ramirez[39] observed more important chronic electrocardiographic disturbances in rabbits which had

Table 1 – *Main clinical forms of Chagas' disease in patients observed since the acute phase in Minas Gerais, Brasil[18].*

Years of disease	Number of patients	Detected clinical forms							
		Indeterminante		Cardiac		Oesophagopathy		Colopathy	
		Nọ	%	Nọ	%	Nọ	%	Nọ	%
10 – 20	68	41	60	23	34	7	10	5	7
21 – 30	73	29	40	36	49	13	18	16	22
31 – 40	31	10	32	18	58	6	19	8	26

clinical forms of chronic Chagas' disease in patients observed over several years in the endemic area of Bambuí, Brazil[18].

This Table shows that most young patients generally present IFCCD with more than 80% in this asymptomatic form in the first ten years after infection, i.e. people from 10 to 20 years of age, since the onset of the acute phase occurred in people between one and ten years old[18].

Still considering this longitudinal study, some factors related to the clinical picture may be observed[16 20]. Firstly the prevalence of ECG alterations during the chronic phase was significantly higher in the patients who displayed abnormal ECG's during the acute phase, than in those who had normal tracings during this early stage of the disease (Table 2).

Table 2 – *ECG in 82 patients with chronic Chagas' disease observed for 27 years in Bambui, MG, Brazil[18 21].*

ECG's in the acute phase	ECG's after 27 years	
	Normal	Altered
Normal (59=72%)	41 (69.5%)	18 (30.5%)
Altered (23 = 28%)	9 (39.1%)	14 (60.9%)
Total	50	32

p = 0.027

shown ECG alterations in the acute phase than in those that had no such changes.

The prevalence of digestive forms among patients who had a more severe acute phase was significantly higher than in those with more benign acute episode. A greater tendency to present chronic cardiopathy was observed in those patients whose acute phase occurred at lower ages (0-2 years)[18].

Another important factor in the natural history of Chagas' disease is the parasite strain involved. Several laboratories have shown different evolution patterns of the disease in animals experimentally infected with strains of *T. cruzi* of different virulence, including the degree of parasitic histotropism[6 22 34 35 43]. Nevertheless, it must be stressed that, in a particular endemic area, the expected tendency is generally that of a homogenous population of circulating parasites, as suggested by S. Andrade[2] and Dias[18]. These observations are still more important when one takes into account that, in areas in which the vector control programme started, acute cases became more and more rare and severe cases in young people disappeared[18 20]. It seems that, under strong vectorial transmission pressure, the incidence of severe acute cases in younger people is higher than in areas where the transmission rate is low; this observation may partly explain the different degrees of morbidity of the chronic disease in endemic areas[18].

The clinical evolution of patients with IFCCD is generally slow and benign. In the São Felipe project, Macêdo[32] has verified that, among 400 chagasic patients with this form, 96 (24%) progressed to another clinical form in a period of 10 years, as shown

in Table 3. This study was performed in an endemic area of Bahia State, Brazil, with a non-selected general population. The IFCCD group represented 50% of the chagasic patients of the area and was made up of individuals of both sexes, mostly young people (50% under 20 years of age).

Table 3 – *Clinical forms to which 400 individuals with the indeterminate chronic form of Chagas' disease in Bahia, Brazil evolved in 10 years of follow-up[32].*

Clinical Forms*	nº	%
Cardiac I	62	16
Cardiac II	22	6
Cardiac III	6	2
Cardiac IV	1	0
Oesophagic involvement	5	1
Without evolution	304	76

* Chronic cardiopathy classified according to the severity of cardiac disease; I is the initial and less severe degree[6] [31].

Data are also very similar in other endemic Brazilian areas[14] [18] and even in a longitudinal study performed in Buenos Aires[33].

In Minas Gerais State, Coura and Pereira[14] have determined the evolution of 76 cases followed for 6 years in the Northeast and 57 cases followed for 10 years in the West of the State (Table 4).

Table 4 – *Evolution of indeterminate form of Chagas' disease in two endemic areas in Minas Gerais, Brazil[14].*

	Percent evolution	
Evolution	Northeast	West
Initial heart disease	33	35
Severe cardiac involvement	3	5
Oesophagal dysperistalsis	6	5
Unaltered	58	54

The potential of IFCCD for determining the evolution into the symptomatic form seems to be higher among young male than among females patients up to 40 years[9] [18] [25]. According to Macedo, 50% of the indeterminate patients who evolved into the symptomatic form were in the age group between 10 and 20 years; 40% between 21 and 49 and only 10% were under 50 years old[32].

The long term evolution of patients with IFCCD is generally very favourable, and they usually die of causes other than Chagas' disease. Mortality data on these patients are available in some longitudinal studies such as those of Macêdo[32], Dias[18], Dias and Kloetzel[23] and Forichon[25] showing a very good *quod vitam* prognosis for the patient between five and ten years after the diagnosis, in any age group. For instance, in the São Felipe study only eight patients died amongst 400 individuals presenting the indeterminate form, seven of them due to non-chagasic causes and one because of acute chagasic myocarditis due to reinfection[32]. In the Bambuí study, none of the 37 patients followed up since the acute onset who died in the chronic phase was in the indeterminate form[18]. Forichon[25], still in Bambuí, verified that not more than 3% amongst 885 adult chagasic patients without cardiac involvement died during the following 10 years, whilst the general mortality reached 30% for female and 45% for male patients with chagasic chronic cardiopathy.

Similar data were obtained by Coura and Pereira[14] who followed 116 indeterminate patients for six years and 130 for ten years, with no deaths, in an endemic area of Minas Gerais. These data suggest once more, as did very early Carlos Chagas' and Laranja et al that the main cause of death from Chagas' disease is still the severe heart involvement. Therefore, since the most common evolution pattern of IFCCD is to initial benign cardiopathy (Table 3), it is easy to understand why the immediate and medium-term prognoses of patients are so good.

The general prevalence of IFCCD is about 50% among all chagasic people in endemic areas[14] [38]. Longitudinal and cross sectional specific studies must take into account the age groups of the population, since the major evolution potential belongs to the younger groups and also because it is sometimes very difficult to reach conclusions about Chagas' disease in older ages[18] [33]. In other words, because of the evolutive potential of some patients, those in IFCCD must be closely observed by the primary health services. Early detection of heart involvement makes the clinical management of chronic chagasic cardiopathy much easy[17] [26]. Unfortunately, it seems that specific treatment of patients in the indeterminate form results neither in cure (except for some young patients)[2] [40] nor in the interruption of the evolution course[8]. Manzullo and Darraidou[33] observed 185 chronic patients during eight years or more, part of them treated with Nifurtimox and the other part untreated. Both these groups had normal ECG's and X-rays at the beginning of the study, and electrocardiographic disturbances emerged at an annual rate of 6.6% and 6.7% respectively.

Race, sex, concomitant or intercurrent diseases, nutritional status and alcoholism are some general factors that must affect the natural history of the disease[2] [3] [6] [13] [18] [19] [20] [25] [38]. Work is a very important factor that was recently discussed by Faria et al[24]

who showed the very high exercise performance of adult rural workers with IFCCD (group I) in comparison with normal individuals and chagasic patients with complete right bundle branch block (groups II and III). Table 5 summarises these results.

The good work performance of individuals with IFCCD is generally accepted. The interference of work with the clinical course of this form is still not completely clear. It seems that some individuals can remain asymptomatic all their lives in endemic areas, in spite of very hard physical work[18 32]. But it is also true that high physical effort can interfere in cardiac equilibrium producing pathophysiologic changes in the myocardial units that, in chagasic hearts, could induce progressive degrees of cardiac failure[4 18 19 26 28].

The evolution towards the "clinical" forms is directly related to the duration of the disease. As Prata and Macedo[38] have observed "the longer this time the more chance there is of cardiopathy appearing".

Parasitemia *per se* does not appear to modify the course of chronic Chagas' disease, according to Castro[10] and Dias[18]. Nevertheless Pifano[37] states that cardiac involvement is more likely to appear in individuals with a high parasitemia, measured by xenodiagnosis.

Dias[16] and Macêdo[31] suggest that the clinical evolution may also be influenced by reinfections, but

Table 5 – *Chagas' disease and work. Exercise parameters for chagasic rural workers with the indeterminate form (Group I), and those with complete right bundle block (Group III) compared with non-chagasic (Group II) rural workers*[19].

	Group I	Group II	Group III
Number of individuals	28	28	9
Caucasoid/negroid	22/6	26/2	7/2
Smokers/non-smokers	15/13	13/15	4/5
Physical activity			
High/medium/low	22/5/1	23/4/1	6/1/2
Can ride a bicycle	25	25	8
Blood pressure, lung and Thryoid function test,			
Hematocrit	Normal	Normal	Normal
Other diseases	Absent	Absent	Absent
Cardiac area	Normal	Normal	Normal
EKG	Normal	Normal	RBBB
Serology to Chagas' disease	Positive	Negative	Positive
Age (years)	30.6 ± 6.8	30.1 ± 6.8	34.2 ± 4.1
Height (cm)	166.2 ± 4.9	168.1 ± 6.1	168.8 ± 8.5
Weight (kg)	58.5 ± 7.5	56.8 ± 8.8	57.0 ± 7.7
Fat %	11.5 ± 2.8	11.3 ± 2.2	10.9 ± 2.6
Lean body mass (kg)	51.6 ± 5.6	51.3 ± 5.3	50.7 ± 6.1
Health-Carter's somatotype	2.6 – 4.9 – 2.9	2.4 – 4.4 – 3.3	2.3 – 4.4 – 3.6
Maximal load attained (w)	204 ± 31	206 ± 49	189 ± 33*
Pulse (bpm) At rest	69 ± 10	72 ± 8	67 ± 13
Maximum	187 ± 12	188 + 8	165 ± 18*
Systolic blood pressure (mmHg)			
At rest	119 ± 13	188 ± 10	119 ± 12
Maximum	182 ± 12	181 ± 16	185 ± 35
Arrythmias			
At rest	5	3	6***
Exercise	8	9	7**
(N° of cases) Recovery	5	8	7**
Test Maximal	24*	28	7*
Sub-maximal	4*	0	2*
Less than sub-maximal	0	0	0
Symptoms Exercise	1	0	0
Recovery	0	0	0

*p < 0.05   **p < 0.01   ***p < 0.005

this factor did not appear to be important in the longitudinal study in Bambui[18].

As remarked above, the acute episode influences the clinical course of the chronic phase[3 18 22 39]. Andrade[2] stresses that IFCCD generally means a general picture of inactive scarce inflammatory foci remaining from the acute phase, with few possibilities of evolution. As suggested by Koberle[28] the autonomous denervation, chiefly occurring in the acute phase, can result in clinical chronic signs, which depend on the physiological balance between the involved functions and the number of neurons destroyed. In the chronic phase, the acute denervations is slowly increased by a slight chronic denervation and also by age-dependent physiological denervation[38 42]. The anatomical substrate of IFCCD was studied chiefly by Chapadeiro[12], Andrade[2] and Lopes et al[30]. Generally the digestive tract of the patients with this form presents some degree of intramural autonomous denervation, with or without scarce detectable chronic inflammatory foci[3 28 44]. General para-sympathetic denervation is nearly always present in Brazilian patients with IFCCD, but this condition is not frequently detectable in some other endemic countries such as Venezuela and Central America[18 44]. On the other hand, as stressed by Rezende[44], "the greatest variation in the level of denervation seen among infected individuals belonging to the same community or the same family, points to the existence of important immunological factors linked to the host".

In the heart, the systematic studies performed in asymptomatic individuals who have died in accidents can be summarised as follows[12 30]:

a) The volume and the weight of these hearts are within normal limits.

b) Macroscopically, about 90% of the hearts present thick white pericardic formations sometimes presented as little plaques, or as tendinous spots, or even as rosary-form nodes; microscopically these formations represent an active chronic pericarditis that can reach some autonomic nervous intracardiac ganglia or threads;

c) The myocardium generally presents a macroscopically normal aspect, but sometimes can become thin (10%) and, more rearely, shows wall aneurysms. The myocardial features in IFCCD commonly consist of lympho-plasmocytic infiltrations that are small and scarce, but sometimes can constitute larger foci with associated myocytolysis. There are frequent tiny fibrotic scars in some parts of the myocardium. In dogs that survived acute disease, Andrade[1] verified several degrees of cicatricial lesions in the myocardium, in the conducting tissue of the heart and in intra-cardiac vagal neurons. He concluded that "it was apparent that the destructive changes occurring during acute infection and involving structures that cannot regenerate will leave cicatricial areas in the heart and, presumably, elsewhere. Will such cicatricial lesions in the conducting tissue and autonomic nervous system be responsible for the positivity of the refined tests when cardiac function is explored in asymptomatic Chagas' patients?"

d) The inflammatory process is more evident in the region of the *vertex;*

e) The endocardium is generally normal, but in a few cases may be thickened because of fibroblastic proliferation;

f) The finding of amastigote forms of the parasite is exceptional.

As a more general conclusion, Lopes et al[30]. have stated that inflammatory lesions are always observed in all chagasic patients and that different levels of involvement in the heart of patients with IFCCD may explain at least in part, the clinical differences amongst the cases. These authors also stated that it is very difficult to establish the evolutive potential of the focal lesions observed in patients with IFCCD.

The long silent period between the acute infection and the late cardiac manifestations of chronic Chagas' disease still remains without an adequate explanation. When chronic myocarditis starts, it apparently assumes a self-perpetuating mechanism and progresses until the death of the host. Although it is not known the nature of the antigens[9] responsible for the main lesions, there is a general assumption that they result from mechanisms of hypersensitivity[1]. Andrade[1] thinks that all the markers of hypersensitivity are found in hosts that present either IFCCD or in chronic chagasic heart disease. "One is therefore tempted to suggest that diferences in the two conditions may lie in the state of immunological suppressive factors which, while they seem to be successful during the indeterminate stage, appear to have been overcome to allow for the development of chronic progressive myocarditis[1]. On the same subject, Ribeiro-dos-Santos and Rossi[45] stated that it was possible to detect in patients with IFCCD a M-immunoglobulin able to block the hypersensitivity reactions of homologous cells. These results "suggest that, in the chronic phase of Chagas' desease, hypersensitivity mechanisms (or even cellular auto-immune responses against myocardial factors) are started which, in normal conditions and immunological balance, would be blocked and unable to produce histological lesions". In other words, the organism in normal conditions would be able to modulate the auto-immune response while it is producing an anti-auto-immune reaction[17]. Some experimental studies with cyclophosphamide in dogs with IFCCD[1] show that the immunodepressive effect of the drug was able to induce some minor electrocardiographic disturbances, especially after Ajmaline administration, stressing the idea that such a pathogenetic

pathway depends on a delayed-type hypersensitive mechanism[1] [2].

In spite of the several evolutive possibilities of IFCCD[15] [19], or even the accumulated data about histological, haemodynamic and pharmacological disturbances that can be detected in some of these cases[15] [18] it must be stressed that classical definition of IFCCD is above all, a practical and operational concept based on two main considerations:

a) This concept is sufficiently simple to be useful in any kind of area or medical service. Besides serological diagnosis, it demands no more than a good clinical examination, a conventional ECG and simple x-ray apparatus able to perform chest examinations, oesophagic barium meal transit studies and simple contrast examinations of the colon[6] [31] [35] [44].

b) The concept itself is very consistent, since the patients labelled as "indeterminate" really present very good work performance and an immediately favourable clinical evolution in most of the reported cases[13] [14] [18] [24] [32] [33] [38].

Nevertheless, using "secondary" more sophisticated methods, cardiac and oesophagic abnormalities may appear in "indeterminated" patients[15] [38] [41]. Therefore, within the classical concept of IFCCD, two main groups of patients can be distinguished: those individuals whose results remain normal and those who show some alterations with "secondary" examinations. As stressed by Prata and Macêdo[38], it is difficult to determine whether these two groups have a different prognosis. Histopathological changes verified in cardiac biopsies[15], small and transient atrioventricular conduction abnormalities after vagolytic drug administration[38], echocardiographic[36], vectocardiographic[15], haemodynamic[15] and cardiac autonomic disturbances[27] are some alterations that can be detected in patients with IFCCD. Also incipient neuro-motor incordination may emerge in manometric oesophagic studies[43]. Psychological disturbances can also be detected in the "asymptomatic" patients, as pointed out by Vieira[49], since autonomic denervation occurs in the acute phase and the day life tensions can induce them to be hyperreactive (stressed) to the different environmental stimuli.

These considerations do not invalidate the classical concept of IFCCD, as mentioned in the Araxá document[41]. The really pertinent problems on the correct definition of the indeterminate form concern chiefly the operational aspects of the basic diagnosis, namely:

a) A consistent serologic diagnosis, involving, at least, two concordant serological tests;

b) A correct and detailed clinical examination, taking into account the basic aspects of the disease. Official guidelines for this examination have been published by WHO and CNPq[6] [35] and must be used both in individual and population studies;

c) The precise and homogeneous interpretation of the ECG, in order to eliminate the concessions in interpretation pointed by Decourt et al[15]. (The same considerations can be applied to the radiological examination, concerning both interpretation and technical aspects). TDR and other institutions are trying to standardise specific criteria and guidelines to make these examinations comparable in every area;

d) The consistent differential diagnosis with other prevalent diseases. For this it is very important to establish the real "chagasic component" of heart or digestive problems in individuals. For instance, young patients with IFCCD can be affected by idiopathic myocardiophaties, whilst old chagasic patients may present presbioesophagus, hypertensive or myocardic sclerotic lesions without any participation of Chagas' disease in such disturbances[17] [29]. In most epidemiologic and comparative studies the patients with other heart and/or digestive problems must be removed even it they are in IFCCD.

For practical purposes, the basic clinical examination of patients in IFCCD can be improved with minimal resources, even in field work. The various workshops of the TDR and the National Scientific Councils[6] [35], and the accummulated experience of the Brazilian longitudinal and crossectional studies suggest the following simple procedures for patient analysis:

Clinical Examination: Anamnesis must be reliable. Heart and digestive symptoms are often underrated by the patients and must be correctly explored. It is also important to distinguish when hypocondriac patients (or people that are hoping for social security benefits) are stressing some general and/or vague symptoms. Clinical signs of the main chronic syndromes must be looked for in detail, chiefly the initial heart failure and cardiac arrythmias, Apart from a long and detailed cardiac auscultation, observation of the pulse for one minute or more is useful in detecting incipient ectopic beats[17] [35]. Some ambulatorial non-invasive procedures such as the Valsalva and hyperventilation manoeuvers are also very useful in detecting cardiac arrythmias in apparently heathy individuals[17] [24].

Basal ECG: This is the most important auxiliary method in the study of human chronic Chagas' disease[5] [29] [35]. It is necessary to establish electrocardiographic normality, as well as to record a sufficient number of cardiac complexes to detect easily ectopic heart beats[33]. ECG may be accompanied either by Valsalva or hyperventilation manoeuvres or by simple pharmacological tests[38].

Effort tests: They probably constitute the best non-invasive procedure to explore heart function in

IFCCD. As verified by Faria et al[24], ergometric tests can detect heart function degeneration earlier than resting ECG, X-ray studies and clinical examinations. Several years of using the cycloergometric test has proved its safety, but it must be emphasised that risks do exist and the procedure must be performed carefully and by trained personnel[24].

Certainly the asymptomatic chagasic patients with a "negative" effort test will have much better prognosis *quod vitam* than those with increased readings. The value of ergometry is unquestionable in Chagas' disease. The use of this procedure must be stimulated both in research and clinical care services, in endemic countries.

The digestive forms of chronic Chagas' disease are usually detected by anamnesis plus contrasted X-ray examinations[17 35 44]. Nevertheless some problems can be present for IFCCD characterisation, since border-line oesophagic or colonic dysperistalsis can occur[18 43]. Incipient colopathy without "mega" seems to be very frequent in some endemic areas, with a progressive and very slow evolution, presenting transitory periods of constipation and with a radiological picture showing only some degree of sygmoid elongation[18]. Should these individuals be considered to be in the indeterminate form?

Autonomic denervation seems to appear in different degrees, in chagasic patients of different endemic areas[3 27 28 44]. Many patients with IFCCD may show signs of denervation when submitted to simple neurological tests[27 28]. Such neurological aspects might receive more attention and general research, but probably a low or moderate level of denervation will not interfere with the classical concept of IFCCD. As a matter of fact, denervation phenomena in chronic Chagas' infection generally progress very slowly or even remain stable, frequently being tolerated by the individual, with no clinical manifestations[18 28]. In terms of peripheral and central nervous systems, the usual neurological examinations are generally completely negative[17].

Final Remarks

The epidemiological importance of IFCCD and the related laboral and medical aspects constitute a reason to vigorously strengthen the research on this form of American Trypanosomiasis.

The multicentric investigation must be obviously standardised looking for epidemiological, operational, clinical, anatomical, therapeutical and immunological aspects.

The evolutionary aspects of the IFCCD must be investigated more completely including work on laboratory models, in order to clarify the risk factors, and the possible therapeutic avenues.

The clinical management of these patients shoud be more completely detailed, giving special attention to diagnostic aspects and operational procedures to be transferred to the primary health care system.

Laboral aspects of IFCCD also need more research, chiefly in order to determine up to what limit physical effort influences the natural history of the group.

Immunological and immunochemical studies must be stimulated along two main lines:

a) Attempts to discover a marker in the host able to indicate whether the disease is in evolution or not.

b) Attempts to clarify the mechanism and elements of the disease evolution, in order to establish the basis for the prevention of this evolution.

RESUMO

Analisam-se epidemiologia e a história natural da forma indeterminada da doença de Chagas (FCI), confirmando-se sua grande importância epidemiológica em áreas endêmicas da tripanosomose, no Brasil. Os dados mostram que a evolução da FCI é geralmente lenta, com bom prognóstico, discutindo-se alguns fatores evolutivos, o prognóstico e o substrato anatomopatológico desta entidade.

Sob o prisma prático, verifica-se que o conceito clássico da FCI se mostra simples, consistente e operacional: define-se no paciente crônico e assintomático, portador de provas sorológicas e/ou parasitológicas positivas para T. cruzi, *com exames clínico, eletrocardiográfico e radiológico (área cardíaca, esôfago e cólon) normais. Exames outros mais rigorosos e sofisticados podem demonstrar algumas alterações e anormalidades nestes pacientes, geralmente discretas e pouco interferentes no prognóstico.*

Fazem-se algumas sugestões de pesquisa sobre a FCI, principalmente com relação ao envolvimento imunológico e a fatores de evolução.

Palavras-chaves: *Doença de Chagas. Forma indeterminada. Prognóstico. Fatores de evolução.*

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