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Pathogenesis of cardiac neuro-myopathy in Chagas' disease and the role of the autonomic nervous system

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Introduction

Millions of people in Latin America are affected by Chagas' disease. Because of its lengthy evolution its symptoms begin to be noticed in the third decade when the person is in the fullness of life. From Mexico to Argentina, Chagas' disease is an endemic cardioneuromyopathy and the population exposed to the disease is about 65 million people [1].

The disease is transmitted: (a) by trypanosome infestation, the transmitting agent par excellence in endemic areas; (b) blood transfusion from a positive donor; (c) through the placenta.

Moreover, thousands of infected individuals have migrated to the U.S.A., Canada and Europe, but there are very few data on the spread of Chagas' disease in these countries [2]. In spite of its severity and its endemic distribution Chagas' disease, first described by Carlos Chagas in Brazil in 1909, has a poorly understood pathogenesis.

Over a period of 10 years we have carried out a systematic study of the involvement of the autonomic nervous system, by investigating the

baroreceptor reflex in Chagasic patients with or without congestive heart failure, and comparing them with patients with congestive heart failure of different aethiology and with normal subjects.

Material

Normal subjects

These were Argentinian volunteers who had negative Machado-Guerreiro and immunofluorescence tests for Chagas' disease and had no evidence or history of cardiovascular disease, chronic systemic diseases or acute viral or febrile diseases. ECG and chest X-ray examination were normal. Ten normal volunteers in Los Angeles were studied as controls for the non-Chagasic heart failure patients during norepinephrine measurement.

Chagasic patients

The patients (identified serologically) were divided into three groups: Group I, patients who were asymptomatic and had normal ECG and chest X-ray; Group II, patients who complained of weakness and palpitations, had abnormal ECG with arrhythmias, right bundle branch block and/or left anterior hemiblock with normal chest X-ray and no heart failure; Group III, patients

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who had abnormal ECG, severe cardiomegaly on chest X-ray and congestive heart failure (Class III-IV of the New York Heart Association) [3]. Four of them required pacemaker implantation because of complete AV block, and were used during norepinephrine measurement.

Non-Chagasic heart failure patients

Non-Chagasic patients from Argentina and Los Angeles had severe chronic congestive heart failure (Class III-IV of the New York Heart Association). The etiology of the heart failure was coronary artery disease or dilated cardiomyopathy. No patient had evidence of primary valvular disease, recent acute myocardial infarction or active ischemia. All patients gave informed consent to be studied.

Arterial blood pressure

The arterial blood pressure of Chagasic patients was compared with that of the general population of the same geographic area [4,5]. 115 Chagasic patients were studied with a male/female ratio of 1 to 1 and a mean age of 39 ± 13 years. The results were: (a) mean values of systolic blood pressure and diastolic blood pressure of Chagasic patients were significantly lower than those of the general population [4], (b) the systolic pressure in female patients in the age group of 30 to 40, did not exceed that in male patients, as usually happens in the general population [4]; (c) the correlations between blood pressure and body weight or age observed in the general population were not found in the Chagasic patients [4].

Basal heart rate [6]

The prevalence of slow heart rate was studied in 222 Chagasic patients, 55 patients with congestive heart failure of different origin and 50 normal subjects. In any decade of life the basal heart rate was always significantly lower in Chagasic patients with heart failure than in other patients or in normal subjects. For each decade (20-30-40-50-60) means and standard deviations were as follows. Normal subjects: 78 ± 6 ; 72 ± 4 ; 71 ± 5 ; 69 ± 8 ; 65 ± 4 . Chagasic patients group I: 67 ± 11 ; 69 ± 12 ; 70 ± 10 ; 58 ± 5 ; 66 ± 6 . Chagasic patients group II: 83 ± 12 ; 75 ± 15 ; 69 ± 9 ; 68 ± 8 ;

--; Chagasic patients group III: 53 ± 6 ; 66 ± 11 ; 62 ± 12 ; 60 ± 11 ; 58 ± 6 . Non-Chagasic heart failure patients: 91 ± 10 ; 88 ± 8 ; 93 ± 10 ; 87 ± 6 ; 80 ± 10 .

Tilting test [7]

Patients and normal subjects were studied during passive tilting. The results demonstrate that (a) all Chagasic patients responded with a significantly smaller rise in diastolic blood pressure (0-3.8 mmHg) than normal subjects (9-12 mmHg), and (b) Chagasic heart failure patients had a significantly lower heart rate than normal subjects and non-Chagasic heart failure patients (73.6 ± 11.3 ; 79.9 ± 7.6 ; 89.4 ± 13.4 beats/min, respectively).

Valsalva Manoeuvre [8]

(a) Straining phase: all Chagasic patients showed less tachycardia than normal subjects. Means and standard deviations for the percentage variations of R-R intervals in relation with basal condition were: normal subjects, $-27 \pm 4.3\%$; Chagasic patients groups I and II, $-14 \pm 6.9\%$; Chagasic patients group III, $-11.6 \pm 18\%$.

(b) Releasing phase: all Chagasic patients showed less bradycardia than normal subjects. Means and standard deviations for the percentage variations of R-R intervals in relation with basal condition were: normal subjects, $44.6 \pm 38\%$; Chagasic patients groups I and II, $17 \pm 11.1\%$; Chagasic patients group III, $1.7 \pm 5.4\%$.

Baroreceptor sensitivity index [9]

All Chagasic groups had a diminished response to phenylephrine by comparison to normal subjects. Systolic pressure was correlated with the immediately following pulse interval, measured by electrocardiography. The slope of the systolic pressure-pulse interval correlation was used to express baroreflex sensitivity [10]. As age and blood pressure act independently to reduce baroreflex sensitivity, a logarithmic formula was used to correct the influence of age and blood pressure [11]. The average value of the baroreceptor slope in normal subjects (15.5 ± 6.9 ms/mmHg) was significantly higher than that observed in Chagasic patients group I (10.2 ± 3.2

ms/mmHg), Chagasic patients group II: (7.4 ± 1.9 ms/mmHg) and Chagasic patients group III (4.1 ± 1.8 ms/mmHg). Deterioration of the baroreceptor reflex correlates with the degree of clinical involvement.

Hyperventilation test [12]

Immediately after hyperventilation the Chagasic patients of all the groups had a significantly smaller fall in systolic or diastolic blood pressure than the normal subjects. Once hyperventilation was stopped, blood pressure of normal subjects rapidly recovered and was within about 8 s back to near normal levels. In contrast, all patients with Chagas' disease showed a delayed recovery lasting 20 s or more.

Cold pressor test [13]

In Chagasic patients with congestive heart failure (Group III) the response was stronger than in normal subjects or in patients with heart failure of different etiology.

Autonomic blockade [14]

Chagasic patients of all three groups showed a smaller response to intravenous injection of atropine (0.04 mg/kg) than normal subjects. After 3 min, propranolol was given intravenously (0.2 mg/kg) and again patients with Chagas' disease showed a smaller response than normal subjects. Using the José formula [15,16], we found that observed and predicted intrinsic heart rates were similar in normal subjects, whereas in all the patients with Chagas' disease the observed heart rate was significantly lower than the predicted heart rate.

Norepinephrine plasma concentration and blood pressure during resting condition and after standing [17]

We measured plasma levels of norepinephrine by a radioenzymatic method [18]. Blood pressure and pulse rate were measured in order to determine whether the sympathetic involvement was (a) consistent with a blockade of the vascular α -receptor, yielding normal or high levels of norepinephrine with no rise or a small rise in diastolic blood pressure on standing, or (b) con-

sistent with blockade of vascular receptors and partial denervation, yielding a normal or low supine plasma level of norepinephrine and a drop of diastolic blood pressure on standing.

The results were as follows. (a) The systolic blood pressure fell slightly or did not change in response to standing. The diastolic blood pressure increased with standing in normal subjects, did not change in Chagas' patients of groups I and II, and fell with standing in patients of group III. (b) Heart rate increased with standing in normal subjects and in Chagas' patients of groups I and II, and did not change in patients of group III. (c) Plasma norepinephrine levels of normal subjects (supine position, 388 ± 46 ng/l (mean \pm SD); on standing, 585 ± 64 ng/l) were similar to those measured by other authors [19]. They increased significantly with standing in normal subjects and in Chagas' patients. There were no statistically significant differences across the groups, but norepinephrine levels were highest in patients of the second group. In contrast, the level of plasma norepinephrine was much increased (870 ± 128 ng/l) in patients with heart failure but without Chagas' disease.

Coughing reflex test [20]

As a reliable and quantitative index of the cardio-acceleratory capacity we used the coughing reflex test. In normal subjects coughing significantly increased the heart rate (from a basal rate of 67.3 to 103 beats/min) whereas in Chagas' patients there was only a modest increase (from 71.5 to 73 beats/min in group I and from 60.5 to 64.3 beats/min in group II).

Discussion

On the basis of our findings, the pathogenesis of Chagas' cardiac neuro-myopathy can be described as follows: *Trypanosoma cruzi*, once within the organism, by an unknown mechanism (autoimmunity, lymphocyte-mediated reactions, antibodies to laminins, antibodies to neurons, deposit of antigen-antibody in the endothelium, in muscle fibres and nerve endings [21-25] induces (a) progressive blockade of adrenergic receptors in the

vascular musculature in patients of groups I and II; and (b) partial denervation of the blood vessel wall in patients with heart failure (group III) which is added to the pre-existing adrenergic receptors blockade. The sequence blockade-denervation produced in the different clinical stages of Chagas' disease can be explained as follows:

Group I

The blockade of the receptors begins in a slow and progressive way. This slight blockade allows the infected subject to have a positive serology and at the same time to be asymptomatic, with normal ECG and chest X-ray. However, due to the presence of receptor blockade in both branches of the autonomic nervous system (sympathetic and parasympathetic), the patients show a lower arterial pressure than the general population, poor rise of diastolic blood pressure in response to tilting test and on standing, less tachycardia and less bradycardia than normal subjects during the straining and releasing phases of Valsalva Manoeuvre, diminished baroreceptor sensitivity index and hypo-reactivity to hyperventilation test, coughing reflex test and cold pressor test. Because of the adrenergic receptors blockade on standing position, the patients - while having a normal norepinephrine level - do not show a rise in diastolic blood pressure; in fact this tends to fall (normal subjects: 6.4 mmHg with 578 ng/l of norepinephrine; patients: -1.1 mmHg with 595 ng/l of norepinephrine). The results obtained through total pharmacological denervation in this group of Chagasic patients confirm our conclusions.

Group II

The adrenergic receptor blockade advances and the signs and symptoms of the patient's nerve and muscle impairment become apparent: tiredness, weakness, dizziness, hypotension, palpitations, biliary lithiasis [26]. The abnormalities observed in group I increase significantly and new abnormalities appear which account for the symptoms in this stage of the disease. In any organ adreno-receptor blockade induces an increase of the contents of neurotransmitter. In these patients, plasma norepinephrine levels are higher than in normal

subjects and in patients of group I; however, the same blockade that determines the rise in norepinephrine prevents it to act on the receptors. Consequently, despite the high plasma level of norepinephrine, the patients are unable to raise diastolic blood pressure on standing as normal subjects do. The high plasma level of norepinephrine could explain the appearance of cardiac arrhythmias [27].

Group III

This is the last stage of Chagas' disease. The severity of the adrenergic receptor blockade increases, but now denervation is added. The abnormalities in the physiological tests requiring a free receptor increase; however, because of the denervation there is no increase in norepinephrine levels, unlike the case in patients with heart failure but without Chagas' disease. With low levels of plasma norepinephrine and with a blockade of adrenergic receptors, diastolic blood pressure on standing falls to -4.75 compared with the values in horizontal position. The cold pressor test shows hyperreaction, a sign of denervation (Cannon's law).

The hypoactivity of the sympathetic nervous system - so different from the hyperactivity of non-Chagasic heart failure patients - is present in this group of patients with unique characteristics: low heart rate, absence of sweating, asthenia and abulia. The reduced sympathetic activity might explain the high prevalence of sudden death attributed to this pathology, since it has been demonstrated that there is a close relationship between low sympathetic activity and sudden death [28].

Indeed, the cardiac neuropathy and myopathy in Chagas' disease is an excellent model for comparative research on other dysautonomias.

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