CENTRAL NERVOUS SYSTEM INVOLVEMENT IN CHAGAS' DISEASE. AN UPDATING.

José Eymard Homem PITTELLA.

SUMMARY

A review was made of the available literature on central nervous system (CNS) involvement in Chagas' disease. Thirty-one works concerning the acute nervous form and 17 others dealing with the chronic nervous form, all presenting neuropathologic studies, were critically analysed. Based on this analysis, an attempt was made to establish the possible natural history of CNS involvement in Chagas' disease. Among others, the following facts stand out: 1) the initial, acute phase of Trypanosoma cruzi infection is usually asymptomatic and subclinical; 2) only a small percentage of cases develop encephalitis in the acute phase of Chagas' disease; 3) the symptomatic acute forms accompanied by chagasic encephalitis are grave, with death ensuing in virtually all cases as a result of the brain lesions per se or of acute chagasic myocarditis, this being usually intense and always present; 4) individuals with the asymptomatic acute form and with the mild symptomatic acute form probably have no CNS infection or, in some cases, they may have discrete encephalitis in sparse foci. In the latter case, regression of the lesions may be total, or residual inflammatory nodules of relative insignificance may persist. Thus, no anatomical basis exists that might characterize the existence of a chronic nervous form of Chagas' disease; 5) reactivation of the CNS infection in the chronic form of Chagas' disease is uncommon and occurs only in immunosuppressed patients.

KEY WORDS: Chagas' disease; Chagasic encephalitis; Acute nervous form; Immunosuppression

INTRODUCTION

Since Chagas' disease was first described, it has been known that the central nervous system (CNS) may be affected by Trypanosoma cruzi. Although rare, the cases of chagasic encephalitis in the acute form of the disease are well documented, most of the patients-being children under 2 years of age. On the other hand, reactivation of chronic Chagas' disease with involvement of the CNS, nevertheless also uncommon, has been reported in immunosuppressed patients, particularly in the last few years. That a chronic nervous form caused directly by T. cruzi existed was also postulated by CHAGAS, based on the presence of encephalitis in the acute cases. According to CHAGAS, the chronic nervous form was consequent upon the lesions observed in the acute form, i.e., it represented a sequela of encephalitis. The author later admitted, however, that the majority of the cases with the chronic nervous form were probably evolutive forms of the histopathologic lesions. Yet, the pathological documentation presented by CHAGAS and the other authors who studied the chronic nervous form was too scarce to allow definitive conclusions to be made as to whether or not an anatomical substrate exists that could characterize a chronic nervous form as proposed by CHAGAS. Recent works based on the histopathological study of the brains of a large number of patients have denied the existence of such anatomical basis. However, other recent publications, although describing very discrete, insignificant focal inflammatory changes in the CNS of a few chronic chagasic patients, such changes being identical to those observed in the control group, still questions the existence of a morphological basis for the chronic nervous form.

Laboratory of Neuropathology, Departament of Pathology, Federal University of Minas Gerais Medical School, Belo Horizonte, Minas Gerais, Brazil.

Address for Correspondence: José Eymard Homem Pittella - Departamento de Anatomia Patológica e Medicina Legal - Faculdade de Medicina da Universidade Federal de Minas Gerais, Av. Alfredo Balena 190. 30130-100 Belo Horizonte, Minas Gerais, Brazil.

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A review of the literature concerning CNS involvement in Chagas' disease confirmed by pathological studies shows that 43 works based on case studies 1,6,8,9,11-13,15-17,19,21,23,26,28,37,39,43,45,51-53,59,61, in addition to 8 reviews 14,17,24,25,27,36,40, are available. Numerous works have been published on CNS involvement in Chagas' disease in the past few years. However, the latest reviews on the subject, in addition to being partial, date back to 16 and 17 years ago, respectively 25. In view of this, we have decided to analyse the above mentioned literature and attempt to situate CNS involvement within the general picture of Chagas' disease. Where pertinent, reference will also be made to a few clinical works. The acute nervous form and the chronic nervous form of Chagas' disease will be considered separately, here. Finally, a possible natural history of CNS involvement in Chagas' disease will be proposed.

Acute Nervous Form

Of the 43 published works on CNS involvement in Chagas' disease in which case studies are presented, 31 are concerned with the acute nervous form 11,12,13,15-17,19,21,23,26,31-34,36,37,40,43,45,50-53,58,61. Forty-four cases of the acute nervous form of Chagas' disease are reported, most of the authors presenting one or two cases each. Only RUBIO & HOWARD 24, CARDOSO 17, MENESES et al. 25, and QUEIROZ 26,29 used a larger number of cases: three, four, four and five, respectively. Of these 31 works, 13 are reports on the appearance of the acute nervous form in immunosuppressed patients 12,16,21,23,31,33,37,40,41,46,47,53,55. Altogether, 18 immunosuppressed chagasic patients with CNS involvement were studied. Of these, 9 had the acquired immunodeficiency syndrome (AIDS) 15,21,23,40,45,53, 4 had received renal grafts 31,35,47,55. 3 had leukemia 16,37,41, one had Hodgkin's disease 34, and one had hypogammaglobulinemia 39.

Most of the patients were children under two years of age, including 5 congenital cases. A few cases were described in older children, and in three adults over 60 years of age. Immunosuppressed individuals predominated in the group aged 11 to 45.

The fundamental finding in the acute nervous form of Chagas' disease is encephalitis in multiple foci, characterized by nodular arrangement of the inflammatory exudate; forming glial or microglial nodules that resemble granulomas (nodular encephalitis). Parasites in the form of amastigotes are identified in the great majority of the cases, both within the inflammatory foci and/or externally to them, inside glial cells. In the first situation, the number of parasites is in inverse proportion to the intensity of the inflammatory process 50, i.e., it is abundant in recent inflammatory foci and reduced or non-existent in older inflammatory foci 74. Other cells such as microglia, histiocytes, macrophages and endothelial cells may also contain parasites 15,27,34,36,42,49,54,60. Neurons parasitized by amastigotes were described by two authors only 60, both in review works, with no case studies being mentioned. The finding of neurons parasitized by amastigotes is systematically denied by other authors 15,19,42,45. Neuronal changes, when present, are untypical and of a degenerative nature, affecting only cells located close to the inflammatory focus 11,15,36,45,49,50,61. Morphologically preserved neurons may even be observed within the inflammatory foci and adjacent to the nests of amastigotes 11,42,45. Chagasic encephalitis is invariably associated with acute chagasic myocarditis, the latter being usually intense, with marked perimysitis, such association being responsible for the severity and high mortality rate of the acute nervous and cardiac forms 11,15,17,24,27,34,36,37,49,50,54,56,59,61. In addition to these cases of more severe CNS damage in the acute form, other cases are described in which more sparsely distributed inflammatory lesions, with or without parasites, are present 15,34,49,50,61, as well as cases in which no evidence of CNS involvement is found 15,26,34,54.

CNS involvement in immunosuppressed chagasic patients differs from the neuropathological picture described above in three aspects: the encephalitis in multiple foci tends to acquire a necrotizing feature; numerous amastigotes are always present; some patients have the tumoral form, characterized by the presence of single or multiple necrotic-hemorrhagic nodular lesions, usually located in the cerebral hemispheres. The tumoral form of chagasic encephalitis was first described by QUEIROZ 28 in a 62-year-old male with no evidence of Chagas' disease in other organs.

Chronic Nervous Form

In the available literature on the so-called chronic nervous form of Chagas' disease there are 17 works based on case studies 1,6,7,9,13,15,28.
chronic chagasic patients, with neurons often being selectively affected\textsuperscript{46}, it would be fair to postulate that neuronal loss in some brain structures such as observed in the chronic form of Chagas' disease might be consequent on the hypoxemia resulting from congestive heart failure and cardiac arrhythmias.

Possible Natural History of CNS Involvement in Chagas' Disease

Our analysis of the available literature on the acute and chronic nervous forms of Chagas' disease allows us to establish the following observations concerning the possible natural history of CNS involvement in Chagas' disease:

1) the initial, acute phase of T. cruzi infection is usually asymptomatic, subclinical and goes undiagnosed in 66 to 99\% of the infected individuals, usually babies and children\textsuperscript{5,10,18,22,57,58} (Asymptomatic Acute Form);

2) only a small percentage (not yet determined) of patients develop myocarditis and encephalitis in the acute phase of Chagas' disease\textsuperscript{58} (Symptomatic Acute Cardiac and Nervous Forms, respectively). The mortality rate among these patients is approximately 10\%\textsuperscript{52}, which may be reduced if specific treatment is initiated in due time\textsuperscript{18}. The symptomatic acute forms accompanied by chagasic encephalitis are grave, with death ensuing in virtually all cases as a consequence of the cerebral lesions or of acute chagasic myocarditis, this being usually intense and invariably present\textsuperscript{4,11,15,17,26,27,32,34,36,37,49,50,54,56,59,61}.

3) the intensity of the parasitism and inflammatory lesions in the CNS may vary in the acute nervous form, with cases of more severe brain involvement being nearly as frequent as those with more sparsely distributed inflammatory lesions with or without parasites\textsuperscript{31,34,49,50,54}. In these cases, death occurs as a result of complications which are not related to the nervous system, such as congestive heart failure secondary to acute chagasic myocarditis;

4) individuals with the asymptomatic acute form and those with the mild symptomatic acute form probably have no CNS infection\textsuperscript{58} or, in some cases, discrete encephalitis in sparse foci may be present, in which case there may be total regression of the lesions or small, paucicellular in-
flammatory nodules without parasites may persist, these being relatively insignificant and interpreted as of a residual nature. This latter possibility is corroborated by the frequent finding of *T. cruzi* in the cerebrospinal fluid during the acute phase, even in patients with no neurological symptoms. Besides, in most patients with the symptomatic acute form, all clinical manifestations, including neurological signs and symptoms usually disappear spontaneously.

5) reactivation of CNS infection in the chronic form of Chagas' disease is uncommon and occurs only in immunosuppressed patients (for example: AIDS, transplantation, leukemia, lymphomas, etc.), constituting the reactivated acute nervous form. In these cases, focal encephalitis tends to acquire a necrotizing feature, sometimes with a mass effect (tumoral form).

RESUMO

Envolvimento do sistema nervoso central na doença de Chagas'. Revisão atual.

Fez-se revisão da literatura publicada a respeito do envolvimento do sistema nervoso central (SNC) na doença de Chagas. A análise crítica dos 31 trabalhos existentes sobre a forma aguda nervosa e de outros 17 sobre a forma crônica nervosa, todos em estudo neuropatológico, permitiu estabelecer uma possível história natural do envolvimento do SNC na doença de Chagas, destacando-se entre outros fatores os seguintes: 1) a fase inicial, aguda, da infecção pelo *Trypanosoma cruzi* é usualmente assintomática, subclínica; 2) somente uma pequena percentagem de casos desenvolve encefalite na fase aguda da doença de Chagas; 3) as formas agudas sintomáticas acompanhadas de encefalite chagásica são graves, com morte em virtualmente todos os casos, resultante do próprio acometimento cerebral ou da miocardite chagásica aguda, geralmente intensa, sempre presente; 4) os indivíduos com a forma aguda assintomática e a forma aguda sintomática leve provavelmente não apresentam infecção do SNC ou, em alguns casos, exibem encefalite discreta, em focos esparso, com involução total das lesões ou, então, com persistência de nódulos inflamatórios residuais relativamente insignificantes, não hendo, portanto, base anatomica que possa caracterizar a existência da forma crônica nervosa da doença de Chagas; 5) reativação da infecção no SNC na forma crônica da doença de Chagas é incomum e ocorre somente em pacientes imunossuprimidos.

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