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

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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[11,50,54]. On 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 five years[40,43,53]. That a chronic nervous form caused directly by **T. cruzi** existed was also postulated by CHAGAS[13-15], based on the presence of encephalitis in the acute cases[13]. 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[14]. Yet, the pathological documentation presented by CHAGAS and the other authors who studied the chronic nervous form was to 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[45,46,51]. However, other recent publication, 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[39].

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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 [1,6,8,9,11-13,15-17,19-21,23,26,28-37,39-43,45-51,53-56,59,61], in addition to 8 reviews[2,4,7,14,25,27,38,60], 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[4,25]. 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 cases studies are presented, 31 are concerned with the acute nervous form[11,12,15-17,19-21,23,26,31-34,36,37,40-43,45-50,53-56,61]. 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[54], CARDOSO[11], MENESES et al.[40], and QUEIROZ[49,50] 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[12,16,21,23,31,33,37,40,41,43,47,53,55]. Altogether, 18 immunosuppressed chagasic patients with CNS involvement were studied. Of these, 9 had the acquired immunodeficiency syndrome (AIDS)[12,21,23,40,43,53], 4 had received renal grafts[31,33,47,55], 3 had leukemia[16,37,41], one had Hodgkin's disease[41], and one had hypogammaglobulinemia[33].

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 exsudate; 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[61], i.e., it is abundant in recent inflammatory foci and reduced or non-existent in older inflammatory foci[7,14]. Other cells such as microglia, histiocytes, macrophages and endothelial cells may also contain parasites[19,27,34,36,42,48,54,60]. Neurons parasitized by amastigotes were described by two authors only[7,60], both in review works, with no case studies being mentioned. The finding of neurons parasitized by amastigotes is systematically denied by other authors[11,19,42,45]. Neuronal changes, when present, are unspecific and of a degenerative nature, affecting only cells located close to the inflammatory foci[11,19,36,45,49,50,61]. 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 parasitism, such association being responsible for the severity and high mortality rate of the acute nervous and cardiac forms[4,11,15,17,26,27,32,34,36,37,49,50,54,56,59-61]. 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[11,34,49,50,54], 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[48] 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-

[30,35,39,45,46,49,51,59] and 6 reviews[2,7,14,25,38,60]. A critical analysis of these works permits dividing them into four groups, according to the materials and methods used and the results obtained.

Group 1[45,46,51] comprises works in which a large number of chronic chagasic patients were studied (31, 50 and 114, respectively) and adequate methodology was used, including an immunohistochemical study made by one author to demonstrate **T. cruzi** amastigotes in histologic sections of the brain[46]. The results of these works point to the low frequency and relative insignificance of the residual lesions from the acute form, thus providing no anatomical basis that would allow establishing the existence of a chronic nervous form of Chagas' disease. Similar results were obtained by MENESES *et al.*[39] who studied a reduced number of cases; to these authours, however, the existence of a morphological basis for the chronic nervous form of Chagas' disease is still questionable.

Group 2 includes works which, whether describing very few or single cases[6,13,15,28,30] or dealing with a larger series of cases[59], fail to provide details on the methods used for examination of the CNS, provide too brief neuropathological descriptions or contain no illustrations[6,13,15,59].

Group 3 comprises works which, in addition to using no control group and, in some instances, being restricted to the study of single cases, report unspecific neuropathological changes of a degenerative, inflammatory and/or cicatricial nature, for which reason other causal factors cannot be excluded in explaining the lesions observed[1,29] (and case no. 2 described by CHAGAS)[13].

Group 4 refers to works in which a varying number of cases were studied using quantitative methods, the results of which showed a reduction in the number of Purkinje cells in the cerebellum[1,8] and in the number of neurons in the dorsal nucleus of the vagus[35], nucleus of the hypoglossal[35] and supraoptic nucleus of the hypothalamus[9]. Different interpretations were offered by the authors for these findings: 1) "reliquat" from the acute phase[8]; 2) other factors besides the hypoxemia that accompanies congestive heart failure[35], and; 3) the action of a neurotoxin[9]. However, considering that degenerative neuronal phenomena in the acute nervous form of Chagas' disease are occasional and of a focal nature (see **Acute Nervous Form**) and that ischemic cerebral changes are frequently present in chronic chagasic patients, with neurons often being selectively affected[44], 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[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[58] (**Symptomatic Acute Cardiac and Nervous Forms**, respectively). The mortality rate among these patients is approximately 10%[32], which may be reduced if specific treatment is initiated in due time[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[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[11,34,49,50,54]. 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[50] 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[45,46]. 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 [24]. Besides, in most patients with the **symptomatic acute form**, all clinical manifestations, including neurological signs and symptoms usually disappear spontaneously[3,5,52].

5) reactivation of CNS infection in the chronic form of Chagas' disease is uncommon and occurs only in immunosuppressed patients (for example: AIDS[12,21,23,40,43,53], transplantations[31,33,47,55], leukemias[16,37,41], lymphomas[41] 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 com estudo neuropatológico, permitiu estabelecer uma possível história natural do envolvimento do SNC na doença de Chagas, destacando-se entre outros fatos 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 esparsos, com involução total das lesões ou, então, com persistência de nódulos inflamatórios residuais relativamente insignificantes, não havendo, portanto, base anatômica 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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