

# Chagas disease as a mechanistic model for testing a novel hypothesis

## A doença de Chagas como um modelo mecanicista para testar uma nova hipótese

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### ABSTRACT

The association between depression and cardiovascular disease is well documented. Nevertheless, the process through which they are linked remains unknown, as does the direction of this relationship. Studies have suggested both that depression is a risk factor for heart disease and that heart disease is a risk factor for depression. A number of studies have established that a relationship exists between depression and inflammation, with alterations in the levels of inflammatory markers (IL-1, IL-6, TNF-alpha and others). Depressive symptoms have also been identified in many diseases characterized by inflammatory processes e.g. rheumatoid arthritis, bronchial asthma, diabetes, tuberculosis and cardiovascular diseases. In this brief viewpoint, we explain and propose how to use Chagas disease, a disorder characterized by inflammatory processes and leading to cardiovascular and autonomic problems, as a model for studying the directionality of the relationship between heart disease and depression.

**Key-words:** Chagas disease. Depression.

### RESUMO

A associação entre depressão e doença cardiovascular está bem documentada. Não obstante, o processo pelo qual está associada permanece desconhecido, assim como o sentido desta associação. Estudos têm sugerido que tanto a depressão é um fator de risco para a doença cardiovascular quanto esta o é para a depressão. Uma série de trabalhos tem estabelecido que uma relação existe entre depressão e inflamação, com alterações evidenciadas por marcadores de inflamação (IL-1, IL-6, TNF alfa e outros). Sintomas de depressão também têm sido identificados em diversas doenças caracterizadas por processos inflamatórios, tais como artrite reumatoide, asma brônquica, diabete, tuberculose e doenças cardiovasculares. Nesta breve opinião é explicitado e proposto como empregar a doença de Chagas, um agravo caracterizado por processos inflamatórios e indutor de problemas cardiovasculares e autonômicos, como um modelo de estudo da direcionalidade da relação entre doença cardíaca e depressão.

**Palavras-chaves:** Doença de Chagas. Depressão.

The association between depression and cardiovascular disease is well documented<sup>13</sup>. Cross-sectional and prospective analyses have shown that a prior history of depression is associated with an increased risk of developing heart disease, and of increased morbidity among those that do.

Research<sup>1</sup> has also suggested that heart disease may precede the onset of depression<sup>8,9</sup>. However, the processes through which depression and cardiovascular disease are linked remain unknown.

A number of studies have established that a relationship exists between depression and inflammation<sup>24</sup>. Various studies on depression have found alterations in the levels of inflammatory

markers (IL-1, IL-6, tumor necrosis factor [TNF- $\alpha$ ]<sup>20,29</sup> and others). Depressive symptoms have also been identified in many diseases characterized by inflammatory processes, e.g. rheumatoid arthritis<sup>18,30</sup>, asthma<sup>27</sup>, diabetes<sup>19</sup>, tuberculosis<sup>1</sup> and cardiovascular disease<sup>31,35</sup>.

The direction of this relationship remains unclear. Studies have suggested both that depression is a risk factor for heart disease and that heart disease puts people at risk of depression. The robust comorbidity between the two conditions has led us to propose a third mechanism: that depression and cardiovascular disease are outcomes from the same process, and thus that there is no directionality to the relationship. To this end, we propose

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to use Chagas disease, a disorder characterized by inflammatory processes and leading to cardiovascular outcomes, as a model for studying the relationship between heart disease and depression.

### WHY CHAGAS DISEASE?

Chagas disease presents complex disease progression that can be broken down, for most patients, into acute, indeterminate and chronic stages. Once the individual has survived the acute phase, the disease may be asymptomatic and may go undetected for many years. During this indeterminate stage, the disease is not inactive, but gradually develops via the cardiovascular system, where it produces microvascular changes, cardiac muscle remodeling and cardiac dysautonomia<sup>23</sup>. In the chronic stage, the clinical outcomes are sudden death, complex arrhythmia, ventricular aneurysms, heart failure, thromboembolism and stroke<sup>23</sup>.

The pathology of Chagas disease can be almost completely explained as a systemic parasitic stressor initiating a cascade of immunological processes. Our model shows how these processes account for Chagas pathology and, when applied to the body as a whole, how they would also provoke changes in the brain consistent with neurocognitive dysfunction and depression. In this paper, we propose using Chagas disease as a model for neurocognitive/mood changes in relation to inflammation, which, if our theory is correct, we predict should be present.

### A PROPOSED MECHANISM

Immune system stimulation can be triggered by many types of stressors, including parasitic stressors, as in Chagas disease. When there is stress, the body recognizes, evaluates and adapts to the adverse events by initiating a cascade of events meant both to eradicate the stressor and to return the body to homeostatic balance. When the stress becomes chronic, the persistence of these processes becomes maladaptive and, as has been proposed, initiates a series of established biological events that lead to outcomes in the neurocognitive and cardiovascular spheres.

Macrophages, the first phase of the inflammatory response, trigger the release of cytokines, which are hormone-like messengers that initiate other changes in the body. In the liver, acute phase reactants (APRs), which include fibrinogen and prothrombin, are produced<sup>11</sup>. When converted, respectively, to fibrin and thrombin forms, they provide a meshwork for thrombus formation<sup>2</sup>. Adhesion molecules, which are normally stimulated to resolve an acute condition through attracting white blood cells, are produced in excess, resulting in increased adhesiveness of the vascular wall, and promoting the accumulation of a pathological number of macrophages and lymphocytes<sup>3 12</sup>. Cytokines also increase the concentration of various lipids such as triglycerides, cholesterol and free fatty acids<sup>10</sup>. Increases in intracellular calcium in conjunction with platelet agonists like thromboxane A2 cause further platelet aggregation<sup>5 15</sup>. In situations of chronic inflammation, all these factors lead to atherosclerosis and vascular remodeling.

Within cells, cytokines stimulate the activity of cyclooxygenase, thereby leading to synthesis of thromboxane A2 (TXA2), prostacyclin (PGI2), and prostaglandins (PGE2). Prostaglandins are potential inducers of intracellular oxidative stress – composed of nitric oxide and free radicals – which leads to cell degeneration and death<sup>14</sup>. Oxidative stress inhibits mitochondrial function in cells throughout the brain and the body<sup>17</sup>. Additionally, in neuronal populations, cytokines and glucocorticoids in conjunction with neopterin (an APR) can alter the metabolism of tryptophan from normal production of 5HTP (serotonin) to the kynurenine pathway and the synthesis of quinolinic acid<sup>21</sup>. Increased production of this NMDA agonist, coupled with increased calcium in the presence of arginine, escalates nitric oxide synthesis and causes neuron damage from oxidative stress, thus leading to apoptosis in neuronal, astrocytic, and microglial cells<sup>7 16</sup>.

When cellular damage by oxidative stress and apoptosis damages or kills serotonergic neurons, the subsequent decrease in serotonin can have further effects on the vasculature. Lower levels of plasma-bound 5HT induce platelet receptor upregulation, which in turn increases platelet reactivity and the aggregation response<sup>6 34</sup>. Lower levels of 5HT may also promote HPA axis hyperactivity, thereby increasing glucocorticoid levels and reducing the sensitivity to the feedback loop that is intended to return the body to homeostasis<sup>32</sup>. In turn, corticosteroids can activate the sympathetic nervous system, thus increasing heart rate and blood pressure and putting more pressure on the cardiovascular system.

In summary, the total effect of the stressor is the cumulative result of a series of biochemical events that result in immune, neurohumoral and cardiovascular system dysfunction, as well as changes in the brain. Especially because the latter changes affect serotonergic neurons, they may manifest as neurocognitive dysfunction and depression. These biochemical events are all linked together in a self-perpetuating cycle of interlinked systems with positive feedback, with expression in the brain and heart and with a parasitic stressor as the initiator. The full execution of the pathways described above would hinge on an individual's susceptibility to pathological processes, which is associated with his genetic endowment and/or to prenatal/perinatal environmental exposure such as low birth weight or hypoxia<sup>4 28</sup>. Depression would be consequent to these brain changes. If correct, this model explains the perceived directionality of causation on which the first two paradigms are founded, and resolves the apparent contradiction that they pose.

### IMPLICATIONS AND CONCLUSION

Chagas disease pathology is accompanied by many of the inflammation-induced changes described above. Microvascular changes are extensive in Chagas disease. Increases in blood-borne oxidative stress markers as well as mitochondrial dysfunction caused by oxidative stress are both associated with the progression of Chagas disease<sup>25 35</sup>. Increases in oxidative stress markers have also been associated with neuron degeneration and development of dysautonomia in other diseases<sup>33</sup>.

Chagas disease provides a unique model to test our hypothesis. The initiator of the inflammatory process is known and well

defined, and not dependent on lifestyle choices such as diet, smoking, etc. Additionally, the various stages of this disease - acute, indeterminate and chronic - make it ideal for studying its covariance with neurocognitive and depressive symptoms. A search through previous literature yielded only one related study: Mangone et al in 1994 suggested that Chagas patients may be impaired in their orientation, attention, nonverbal reasoning, information processing, learning and sequencing<sup>22</sup>. Additionally, according to Oliveira Jr<sup>26</sup>, the frequent occurrence of progressive and often severe cardiopathy in Chagas patients contributes by augmenting any preexisting depression.

A study of this magnitude on a disorder that has not been given its due international medical attention will do much to bring recognition to this disease, which human migration is spreading beyond its typical geographic boundaries.

Demonstration of a common biological mechanism for depression and heart disease will provide further opportunities for both preventative and ameliorative treatment of both conditions. Additionally, by addressing the psychological impact of disease, doctors can increase the chances of recovery, insofar as depression and neurocognitive dysfunction are associated with noncompliance with drug treatment.

This hypothesis has the potential to significantly alter the way we think about depression. Depression is currently treated as an illness rather than a symptom of an underlying biological process. If inflammation can be identified as a cause of depression, it will improve diagnosis and treatment as well as provide insights into other diseases in which depression is a symptom.

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