Brain-derived neurotrophic factor is up regulated in chronic Chagas disease

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Chagas disease is caused by the parasite Trypanosoma cruzi, and is a serious public health concern in Latin America. Chagasic chronic cardiomyopathy (CCC) is the most significant clinical manifestation of the disease, due to its potential severity. CCC is characterized by extreme clinical variability, making the prediction of the progress of cardiac dysfunction a challenge for many researchers [1,2].

Brain Derived Neurotrophic Factor (BDNF) is a neurotrophin first recognized by its action on neuronal targets [3]. Growing evidence has implicated BDNF in several nonneuronal phenomena, and circulating levels of the factor have been proposed as a peripheral marker for a variety of disorders, including those pertaining to the cardiovascular system [4–6].

We assessed BDNF serum levels in chronic chagasic patients in order to correlate with the degree of cardiac dysfunction. Patients were recruited from an outpatient reference center for Chagas Disease treatment (Centro de Tratamento e Referência em Doenças Infecciosas e Parasitárias, in Belo Horizonte, MG, Brazil). Informed consent was obtained from all subjects. The protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as re-acted in a priori approval by our institutional human ethics committee, protocol number 001.97.

Healthy subjects formed the control group (C) which was comprised of 18 men and 8 women, aged 22–55 years (mean ± SD = 36.5 ± 9.4 years). Chagasic patients where divided into 3 groups: asymptomatic (A), non-dilated cardiopathic (ND), and dilated cardiopathic (D). These 3 groups were segregated based on ventricular dysfunction and conduction defects, assessed by electrocardiogram (ECG) and echocardiogram tests. Group A was comprised of asymptomatic patients whose ECG showed no alteration or discrete or minor alterations. None of the patients in this group had conduction defects. Patients in group ND had considerable ECG alterations and were characterized by advanced conduction defects and/or severe arrhythmia, but with no ventricular enlargement. Group D included patients with signs of heart enlargement and global systolic dysfunction. The principal clinical characteristics of the chagasic patients are depicted in Table 1.

BDNF serum levels were determined by ELISA (Enzyme Linked Immuno Sorbent Assay), using kit and protocol from R&D Systems (Minneapolis, MN, USA). Nonparametric Mann–Whitney and Spearman rank correlation tests were performed, with significance levels at 0.001% and 0.05%.

Serum levels of BDNF were significantly higher in all groups of chagasic patients when compared to those in the control group (median [interquartile range]: 597.6 [249.9–5964] pg/mL). Groups A and ND presented similar BDNF levels (5353 [2003–7054] pg/mL and 5782 [3163–7995] pg/mL, respectively). In contrast, Group D presented lower BDNF levels (3584 [1205–7309] pg/mL) than those of groups A and ND (Fig. 1a). The Spearman Rank test showed a positive correlation between BDNF levels and ejection fraction (r = 0.3137, p = 0.0431), and a negative correlation between BDNF levels and ventricular dilatation index (r = −0.3146, p = 0.0424) in chagasic patients (Fig. 1b and c).

A role for BDNF has been established in the modulation of the heart autonomic nervous system [5,7]. Chagasic patients, even the asymptomatic ones, are considered to have dyssautonomia which does not always manifest as an alteration of heart rate and atrioventricular conduction [8,9]. Thus, autonomic denervation could account for, at least partially, the high levels of BDNF observed in chagasic patients. Denervated cardiomyocytes could be among the cells contributing to the elevation of BDNF levels, since it is known that these cells secrete neurotrophic factors, including BDNF [10,11]. In some conditions of autonomic denervation, including T. cruzi infection, cardiomyocytes are stimulated to secrete neurotrophic factors, as demonstrated for Nerve Growth Factor and Glial Derived Neurotrophic Factor [12–14]. It is important to consider that in chagasic patients with severe cardiomyopathy there is an appreciated fibrosis [8,15]. This could result in a decrease in the number of cardiomyocytes available for BDNF synthesis, and explain, at least partially, the lower serum levels of BDNF in patients with dilated cardiomyopathy. Inflammatory cells could be another important source of BDNF in chagasic patients, as these cells are considered a major source of BDNF and this neurotrophin production is increased upon antigen stimulation [16]. Finally, we cannot discard other possible sources of circulating BDNF such as vascular smooth muscle cells which can secrete BDNF [5].

Table 1  Clinical data from control (healthy) and chagasic patients.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Group C</th>
<th>Group A</th>
<th>Group ND</th>
<th>Group D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>26</td>
<td>11</td>
<td>15</td>
<td>29</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>36.5 ± 9.4</td>
<td>41.1 ± 7.5</td>
<td>50.7 ± 10.3</td>
<td>50.8 ± 10.3</td>
</tr>
<tr>
<td>Range</td>
<td>22–55</td>
<td>28–52</td>
<td>27–60</td>
<td>36–70</td>
</tr>
<tr>
<td>Male/female</td>
<td>18/08</td>
<td>10/01</td>
<td>09/06</td>
<td>21/08</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>64.5 ± 6.5</td>
<td>59.3 ± 8.6</td>
<td>41.6 ± 9.5</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>49–70</td>
<td>35–67</td>
<td>18–56</td>
<td></td>
</tr>
<tr>
<td>Left Ventricular Dilatation Index (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>50.0 ± 5.2</td>
<td>53.3 ± 4.7</td>
<td>62.4 ± 4.9</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>42–61</td>
<td>35–67</td>
<td>54–74</td>
<td></td>
</tr>
</tbody>
</table>

C = control subjects; A = asymptomatic chagasic patients; ND = non-dilated cardiopathic chagasic patients; D = dilated cardiopathic chagasic patients.

⁎ p < 0.05.

⁎⁎ p < 0.0001.

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In conclusion elevated levels of serum BDNF are associated with Chagas disease. More, there is a significant correlation between serum BDNF levels and two clinical variables routinely used to evaluate cardiac function, ventricle enlargement and low ejection fraction. The underlying mechanism as to how remains unclear, but a relationship between BDNF serum levels and both cardiac autonomic denervation and inflammatory processes is supported. Although not directly associated to the severity of disease, serum BDNF levels could, to some degree, predict the evolution of patients to the dilated form of the disease. To confirm this, a longitudinal study involving a greater number of chagasic patients in varying stages of the disease is necessary.

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References