RESÚMENES DE PUBLICACIONES

CHAGAS DISEASE REACTIVATION IN RHEUMATOLOGIC PATIENTS: ASSOCIATION WITH IMMUNOSUPPRESSIVE THERAPY AND HUMORAL RESPONSE

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Evidence for Chagas disease reactivation (CDR) in rheumatologic patients under rheumatologic treatments (RTs) is scarce. To screen and follow-up patients with rheumatic diseases and concomitant Chagas disease, under RT to detect CDR and to describe a possible relationship between CDR and specific RT. An observational, longitudinal, prospective, consecutive study was carried out between 2018 and 2020. Included patients were evaluated during the follow-up for clinical and laboratorial manifestations of CDR. Direct blood parasitological examination (Strout method) and polymerase chain reaction (PCR) were employed to diagnose CDR. The dynamic of anti-*T. cruzi*–specific antibodies was also assessed by IHA and ELISA (total IgG and Anti-SAPA). Fifty-one patients were included (86% women). Rheumatoid arthritis was the predominant disease (57%). Classic DMARDs (86.3%) and corticosteroids (61%) were the most frequent RT. CDR was developed in 6 patients (11.7%), exhibiting both positive Strout and PCR. Symptomatic reactivation of CD (fever, asthenia, arthralgias, myalgias) occurred in two patients who had previously been diagnosed with it. Regardless of the different RT, all patients who experienced CDR had previously received more than ≥ 20 mg/day of prednisone equivalent. Despite immunosuppression, patients with CDR exhibited increased levels of specific anti-*T. cruzi* and anti-SAPA antibodies, which decreased after anti-parasitic treatment. CDR is possible in rheumatologic patients, especially after receiving high doses of corticosteroids. Since CDR symptoms may mimic rheumatic disease activity, monitoring of Chagas disease is highly recommended before, during and after immunosuppression.

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LEVELS OF ANTI-B13 ANTIBODIES OVER TIME IN A COHORT OF CHRONIC INFECTED BY TRYPANOSOMA CRUZI. ITS RELATIONSHIP WITH SPECIFIC TREATMENT AND CLINICAL STATUS

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The immunodominant B13 protein of *Trypanosoma cruzi* is found on the surface of trypomastigotes and exhibits cross-reactivity with the human cardiac myosin heavy chain; for which antibodies against this parasitic antigen may be involved in the development of disease pathology. In a cohort of chronically *T. cruzi*-infected adults, undergoing trypanocidal treatment, or not, we, therefore, decided to evaluate the levels of anti-B13 antibodies (ELISA-B13) and its eventual relationship with heart complaints. Two hundred twenty-eight serum samples from 76 chronically infected adults with an average follow-up of 24 years were analyzed. Thirty of them had received trypanocidal treatment. Among treated patients, anti-B13 Ab levels in successive samples showed a significant decrease in reactivity as the years after treatment increased (ANOVA test, p = 0.0049). At the end of the follow-up, 36.7% became nonreactive for ELISA B13.

Untreated patients did not have significant variations in the level of anti-B13 antibodies during follow-up. None of the treated patients had electrocardiographic changes compatible with chronic chagasic cardiomyopathy, whereas 21.7% of those undergoing no treatment did show such kind of pathological electrocardiogram tracings. ELISA-B13 was reactive in all cases with heart involvement. Among untreated patients, there were no significant differences in anti-B13 antibodies when comparing individuals without proven pathology with those with chronic chagasic cardiomyopathy. Although treatment with trypanocidal drugs was followed by decreased anti-B13 antibody levels, such assessment was unhelpful in differentiating the evolution of chronic chagasic heart disease.

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TRYPANOCIDAL THERAPY AMONG CHILDREN INFECTED WITH CHRONIC INFECTION BY TRYPANOSOMA CRUZI. SEROLOGICAL AND ELECTROCARDIOGRAPHIC CHANGES OVER A MEAN TWENTY-FIVE-YEARS FOLLOW-UP PERIOD

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This study compared the serological and electrocardiographic evolution among patients with chronic *T. cruzi* infection treated during childhood or left untreated. A retrospective cohort study was conducted during a mean follow-up period of 25 years in 82 patients: half of them underwent treatment (nifurtimox 8, benznidazole 33) before being 15 years old, whereas the other half remained untreated. During the follow-up, negative seroconversion occurred in 92.7% of the treated children, while all the untreated ones remained positive for conventional serology. At baseline, 2 patients from each group had electrocardiographic abnormalities. During the study period, 4/41 (9.75%) and 9/41 (21.95%) of treated and untreated patients displayed an altered electrocardiogram, respectively. In multivariate analyses, the probability of developing electrocardiographic abnormalities was significantly reduced among treated patients (OR = 0.18, 95% CI = 0.04-0.79; p = 0.023). Electrocardiographic abnormalities attributable to Chagas cardiomyopathy were seen in 3 patients from the untreated group (complete right bundle branch block + left anterior fascicular block, frequent ventricular extrasystole, and left anterior fascicular block). The remarkable seronegativization seen in Benznidazole and Nifurtimox recipients underlines the parasiticidal effect of both compounds. Such demonstration along with the fact that CCC-related alterations were only present in the untreated group, reinforces the view of trypanocidal treatment in chronically *T. cruzi*-infected children as decreasing the risk for cardiomyopathy development.

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ENHANCED MIGRATORY CAPACITY OF T LYMPHOCYTES IN SEVERE CHAGASIC PATIENTS IS CORRELATED WITH VLA-4 AND TNF-α EXPRESSION

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Trypanosoma cruzi infection in humans leads to progression to chronic chagasic myocarditis (CCM) in 30% of infected individuals, paralleling T cell inflammatory infiltrates in the heart tissue. T-cell trafficking into the hearts of CCM patients may be modulated by in situ expression of chemotactic or haptotactic molecules, as the chemokine CXCL12, the cytokine tumor necrosis factor-alpha (TNF-a), and extracellular matrix proteins (ECM), such as fibronectin. Herein we evaluated the expression of fibronectin, CXCL12, and TNF-α in the myocardial tissue of *T. cruzi* seropositive (asymptomatic or with CCM), as well as seronegative individuals as healthy controls. Hearts from CCM patients exhibited enhanced expression of these three molecules. CXCL12 and TNF-α serum levels were also increased in CCM individuals. We then evaluated T lymphocytes from chronic chagasic patients by cytofluorometry, in terms of membrane expression levels of molecules involved in cell activation and cell migration, respectively, HLA-DR and the VLA-4 (very late antigen-4, being one integrin-type fibronectin receptor). Indeed, the expression of HLA-DR and VLA-4 was enhanced on T lymphocytes from chagasic patients, especially in the CCM group. To further approach the dynamics of T cell migratory events, we performed fibronectin-, TNF-α, and CXCL12-driven migration. Peripheral blood mononuclear cells (PBMCs) and T cells from CCM patients presented an ex vivo enhanced migratory capacity driven by fibronectin alone when this ECM protein was placed in the membrane of transwell migration chambers. When TNF-α was previously placed upon fibronectin, we observed a further and significant increase in the migratory response of both PBMCs and T lymphocytes. Overall, these data suggest the existence in patients with chronic Chagas disease of a cardiac inflammatory infiltrate vector that promotes the recruitment and accumulation of activated T cells, driven in part by enhanced tissue expression of fibronectin and TNF-α, as well as the respective corresponding VLA-4 and TNF receptors.

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INCREASED LEVELS OF CIRCULATING LPS DURING TUBERCULOSIS PREVAILS IN PATIENTS WITH ADVANCED PULMONARY INVOLVEMENT

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Our earlier studies in tuberculosis (TB) patients indicate that in those where the process evolves to a larger pulmonary involvement, the immune endocrine response may promote an unfavorable environment. Chronic infectious diseases, and their persistent proinflammatory response, may affect mucosal barriers integrity favoring the translocation of gastrointestinal bacteria, leading to an increase of circulating lipopolysaccharides (LPS). Consequently, we quantified LPS levels in TB patients, with different degrees of pulmonary involvement, and controls (Co) and analyzed the possible relationship between LPS and inflammatory mediators i.e., C reactive protein (CRP), interleukin 6 (IL-6) and Interferon gamma (IFN-γ), Erythrocyte Sedimentation Rate (ESR), steroid hormones (Cortisol and Dehydroepiandrosterone,

DHEA), and inflammatory transcripts from peripheral blood mononuclear cells (IL-1β, IL-6, IFN-γ). LPS was assessed by the Limulus amoebocyte lysate assay and the ELISA technique was used to quantify hormones and cytokines in the plasma samples. Cytokine transcripts from PBMC were evaluated by qRT-PCR. Nonparametric tests were used. LPS levels were increased in TB patients, as did levels of CRP, IL-6, IFN-γ, cortisol and ESR. Severe patients had the highest amounts of circulating LPS; with moderate and severe cases showing much higher levels of CRP, ESR, IL-6, IFN-γ and cortisol/DHEA ratio, as an endocrine imbalance. Only in PBMC from severe cases was mRNA for IL-1β increased. Correlation analysis showed that levels of LPS from severe patients were positively associated with IL-6 and IFN-γ plasma concentrations and with IL-1β transcripts, while IL-6 had a positive correlation with the cortisol/DHEA ratio. The higher levels of circulating LPS during progressive TB may emerge as a contributing factor for the persistence of the greater immune endocrine imbalance distinctive of advanced disease, which might suggest a vicious cycle among LPS, inflammation and endocrine imbalance.

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